Studies with 2-(Acetonylthio)benzothiazole: Novel Synthesis of Pyridazin-6(1*H*)-one, Pyridazin-6(1*H*)-imine, and Phthalazine Derivatives of Antimicrobial and Antifungal Activities

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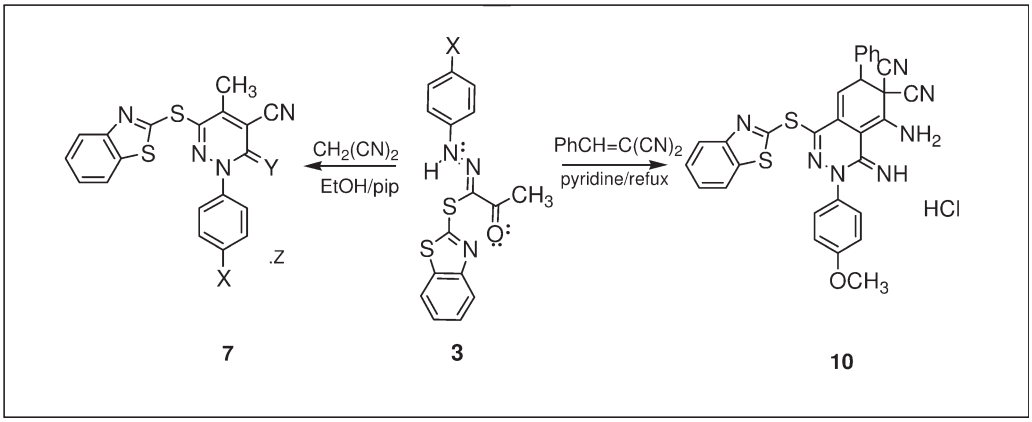

A novel series of (*Z*)-1-(arylhydrazono)-1-(benzothiazol-2′-ylthio)propan-2-ones have been prepared and their utility as building blocks in the synthesis of novel derivatives of Pyridazin-6(1*H*)-ones, pyridazin-6(1*H*)-imines, and phthalazine incorporating a benzothiazole residue are investigated. All of the title compounds were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, NOE, and mass spectrometry. The synthesized compounds are screened for their antibacterial as well as antifungal activity. All the tested compounds showed high to moderate activity against the selected microorganisms.

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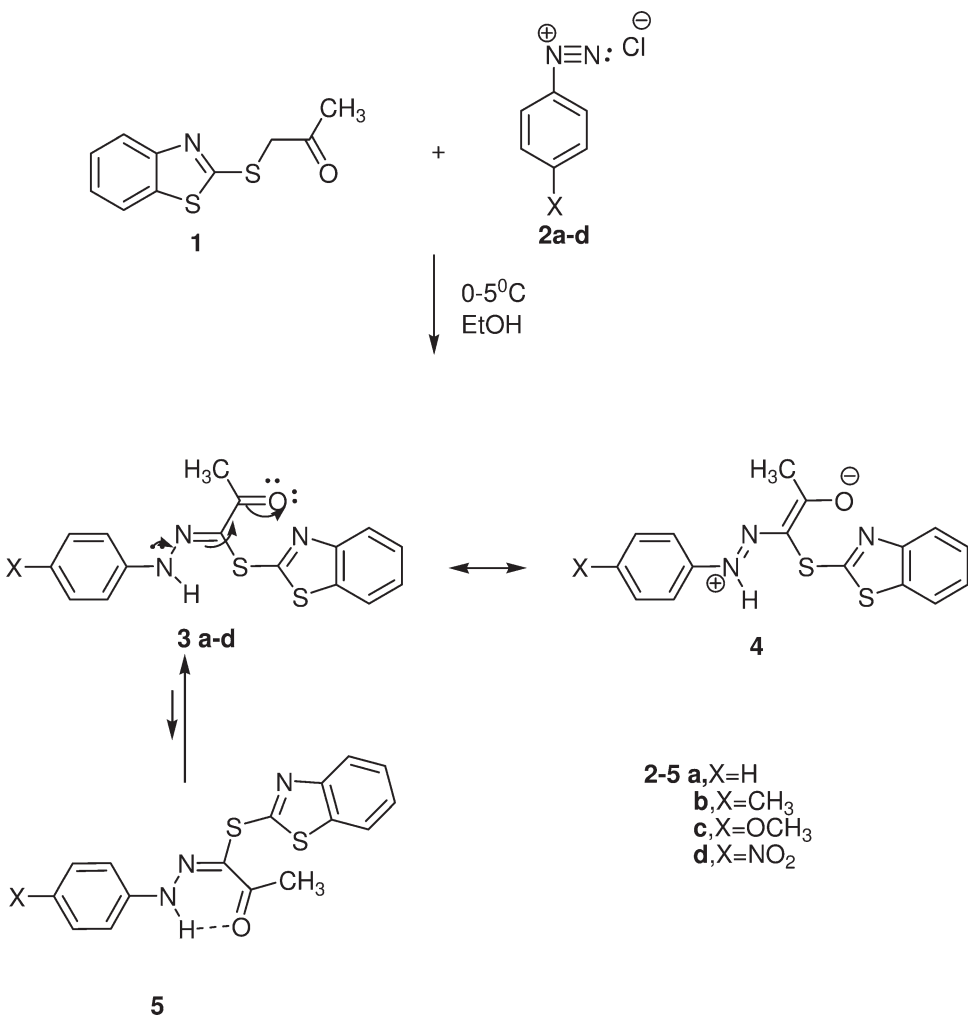
INRODUCTION

Aryl hydrazones are highly reactive intermediates in organic synthesis. They are extensively used for the synthesis of functionalized pyridazines [1–6]. Several publications have pointed out that pyridazines exhibit a wide spectrum of the biological activities and pharmacological properties, such as reduction of the blood pressure [7], analgesic [8], anti-inflammatory [9], antibacterial, and anticonvulsant [10]. On the other hand, 2–mercaptobenzothiazole and its derivatives have also been reported to have potent biological activities, such as antimicobaterial activity [11] and cyclooxygenase inhibitors [12]. As part of our recent research programmed dealing with synthesis of heterocyclic system, particularly those containing a 2–mercaptobenzothiazole moiety [13]. It is thought of interest to accommodate 2–mercaptobenzothiazole with pyridazin-6(1*H*)one, or pyridazin-6(1*H*)imine or phthalazine moieties in one single molecular framework by using hitherto unreported (*Z*)-1-(arylhydrazono)-1-(benzothiazol-2′-ylthio)propan-2-one (**3**) and screen them for antibacterial as well as antifungal activity.

RESULT AND DISCUSSION

The key intermediates (Z)-1-(arylhydrazono)-1-(benzothiazol-2′-ylthio)propan-2-one (**3a–c**) are prepared in excellent yield according to known method [3] by coupling of 1-(benzothiazol-2′-ylthio)propan-2-one **1** [13] with aryl diazonium salts **2a–d** in ethanoic sodium hydroxide solution. The reaction carried out at 0 to 5°C with relatively long reaction time of 2 h. The color of hydrazones **3a–d** range from red to yellow in excellent yield. The structures of *S*-alkylated hydrazones **3a–d** were deduced from their elemental analysis and spectra data. The mass spectrum of **3a** revealed a molecular ion peaks with *m*/*z* 327 (M^+). The structure of hydrazone **3** was assigned as nonhydrogen bonded (*Z*)-conformation basis on their IR spectra of **3a–d**. It was believed that due to the resonance effect involving the delocalization of the hydrazone lone pair of electrons to the carbonyl group created a delicate balance between the structures **3 and 4**. This effect increases the carbonyl bond length and reduces the frequencies of absorption at ν_{max} about 1690 cm^{-1}. It is considered lower than the isolated carbonyl group in compound **1**, which revealed carbonyl

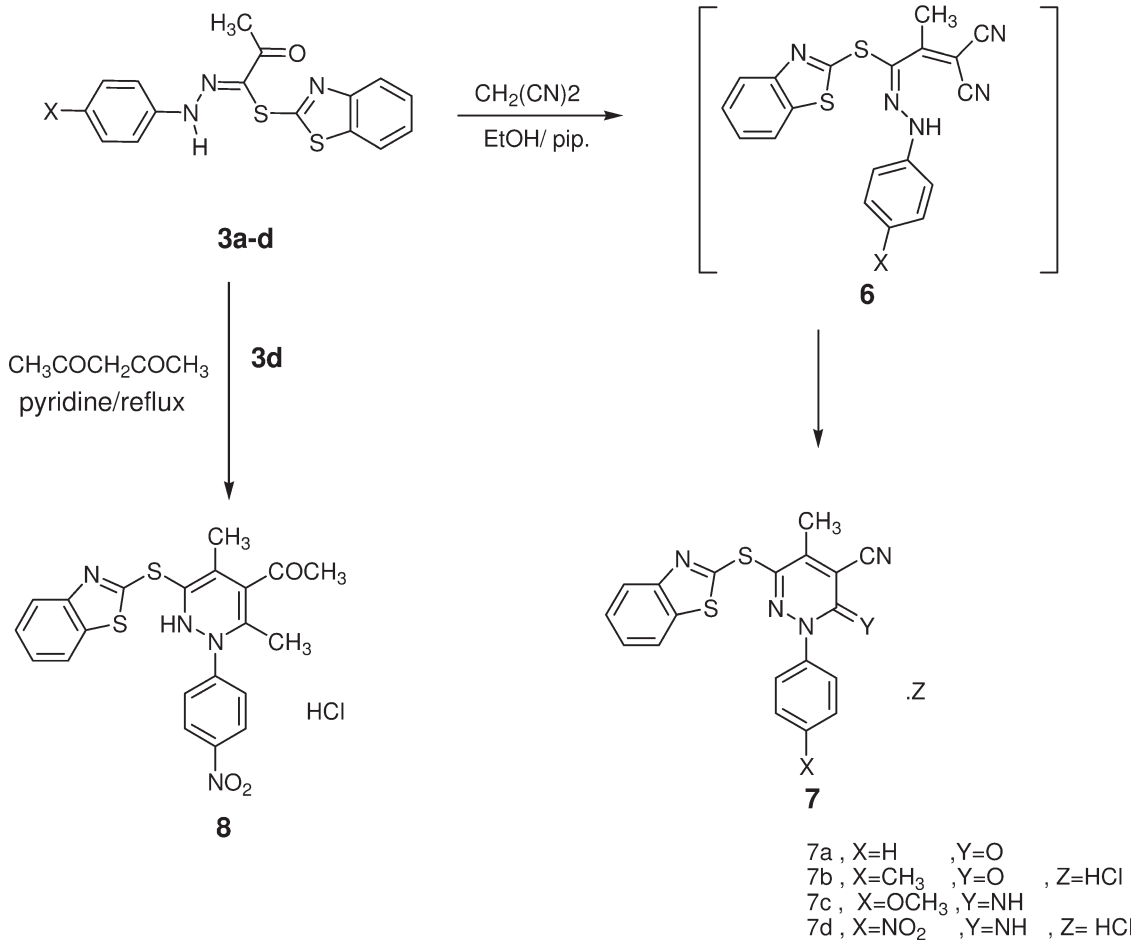
Scheme 1



stretching band at ν_{max}1720 cm^{-1} [13]. Under the influence of both the conjugated C=N group and hydrogen bonding, one might expected the absorption of carbonyl group should be lower frequency at ν_{max} about 1625 cm^{-1} for the (*E*)-conformer. Moreover, the ^{13}C NMR spectra show a larger downfield shift of carbonyl signal δ_c 189 ppm for the (*Z*)-conformation. The ^{1}H NMR spectra of **3a–d** showed, in addition to an aromatic multiple, singlet signals for methyl at δ_H 2.32 ppm and NH hydrazone's which appears at low field signals at δ_H about. 13.75 ppm. The latter signal underwent ready H/D exchange upon addition of deuterium oxide. If the product is (*E*)–conformer, one would expected that NH-hydrazone proton appear at higher field. Firm evidence of this conclusion was obtained from nuclear Overhauser effect (NOE) experiments for **3d**; on irradiating the methyl proton at δ_H 2.32 ppm has no effect on aromatic and NH protons (Scheme 1).

The reactivity of (*Z*)-*S*-alkylated hydrazones **3a–d** toward methylene carbonitriles was investigated. Treatment of compounds **3a–d** with malononitrile in refluxing ethanol and the presence of a catalytic amount of piperidine afforded in each case the corresponding pyridazin-6(*1H*)-one (**7a–b**) and pyridazin-6(*1H*)-imine (**7c–d**) derivatives in excellent yield. The structures of the isolated products **7a–d** were confirmed on the basis of their elemental analysis and spectral data. The mass spectrum of **7c** revealed a molecular ion peak with *m*/*z* 405. The IR spectra of **7a–d** showed, a strong absorption band at ν_{max} about 2205cm^{-1} corresponding to nitrile functional group. The absence of carbonyl ketone group absorption in their IR spectra indicates that carbonyl ketone group is involved in the reaction. The ^{1}H NMR spectra also indicated the disappearance of hydrazone NH proton. Moreover, ^{13}C NMR spectra for **7a–b** and **7c–d** revealed highest frequency signal at δ_c about

Scheme 2

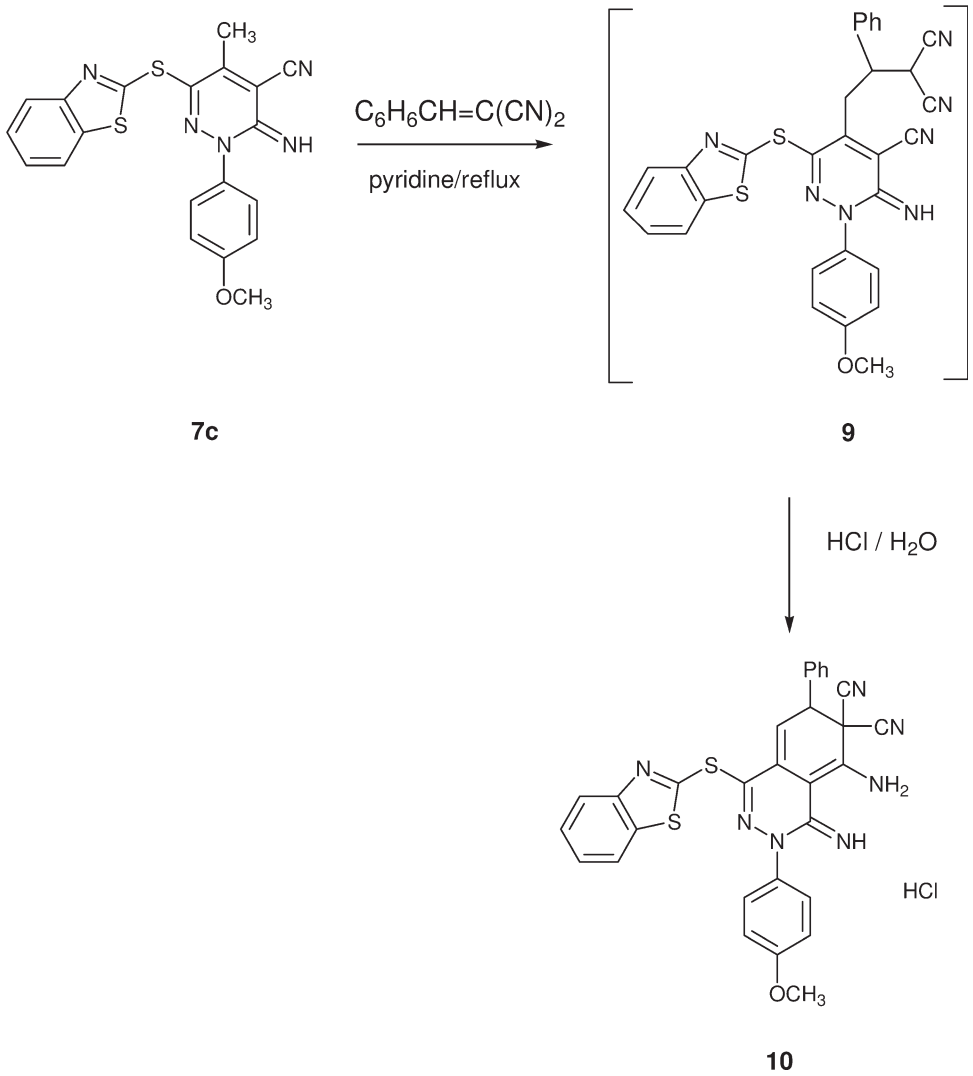


164 and 155 ppm assignable to the amide carbonyl and imine carbons, respectively. The formation of compound **7** is considered most likely based on its similarity to well established behavior, which was assumed to proceed *via* condensation of malononitrile with carbonyl group hydrazone *via* formation of intermediate **6** and subsequence cyclization into pyridazine derivatives **7** [4] (*cf*. Scheme 2).

Treatment of *S*-alkylated hydrazone **3d** with acetyl acetone in pyridine under reflux gives the 1,2-dihydropyridazine **8** in good yield. The structure of 1,2-dihydropyridazine **8** was confirmed on the basis of elemental analysis and spectral data. The ^{13}C NMR spectrum of the reaction product revealed highest frequency signal at δ_c 198.8 ppm assignable to the an acetyl carbon and three signals at lower frequency at δ_c 25.0, 27.1, and 29.8 ppm corresponding three methyl groups. Moreover, the ^{1}H NMR spectrum revealed the presence of one D_2O exchangeable proton attributed to the NH function at δ_H 8.24 ppm.

On the other hand, treatment of **7c** with benzylidenemalonitrile in refluxing pyridine afforded tetrahydrophthalazine derivative **10** similar to that which have been reported [3,14]. The mass spectrum of compound **10** revealed a molecular ion peak with *m*/*z* 559 (M^+-HCl). The ^{1}H NMR spectrum of tetrahydrophthalazine derivative **10** was revealed the presence of both NH_2 and NH groups, which readily underwent H/D exchange upon addition of deuterium oxide. However, the absence of methyl singlet δ_H 2.39 ppm in the ^{1}H NMR spectrum indicate that methyl group in pyridazin-6-(1*H*)-imine **7c** is involved in the reaction. Moreover, the ^{13}C NMR spectrum for **10** is characterized by two signals at δ_C 113.2 and 114.2 ppm corresponding to the two CN groups. In addition two lowest frequency signals at δ_C 25.0 and 38.9 ppm corresponding to the two sp^3 carbon. The signal at δ_C 25.0 corresponding to the carbon coupled with proton (C-7). The formation of **10** is considered most likely based on its similarity to well established behavior, which was assumed to proceed *via* initial Michael addition of the methyl group under basic condition in compound **7c** to an activated double bond in benzylidenemalononitrile *via* formation of intermediate **9** and subsequence cyclization to form adduct **10**. The formed adduct did not aromatize by losing

Scheme 3



7c **9** **10**

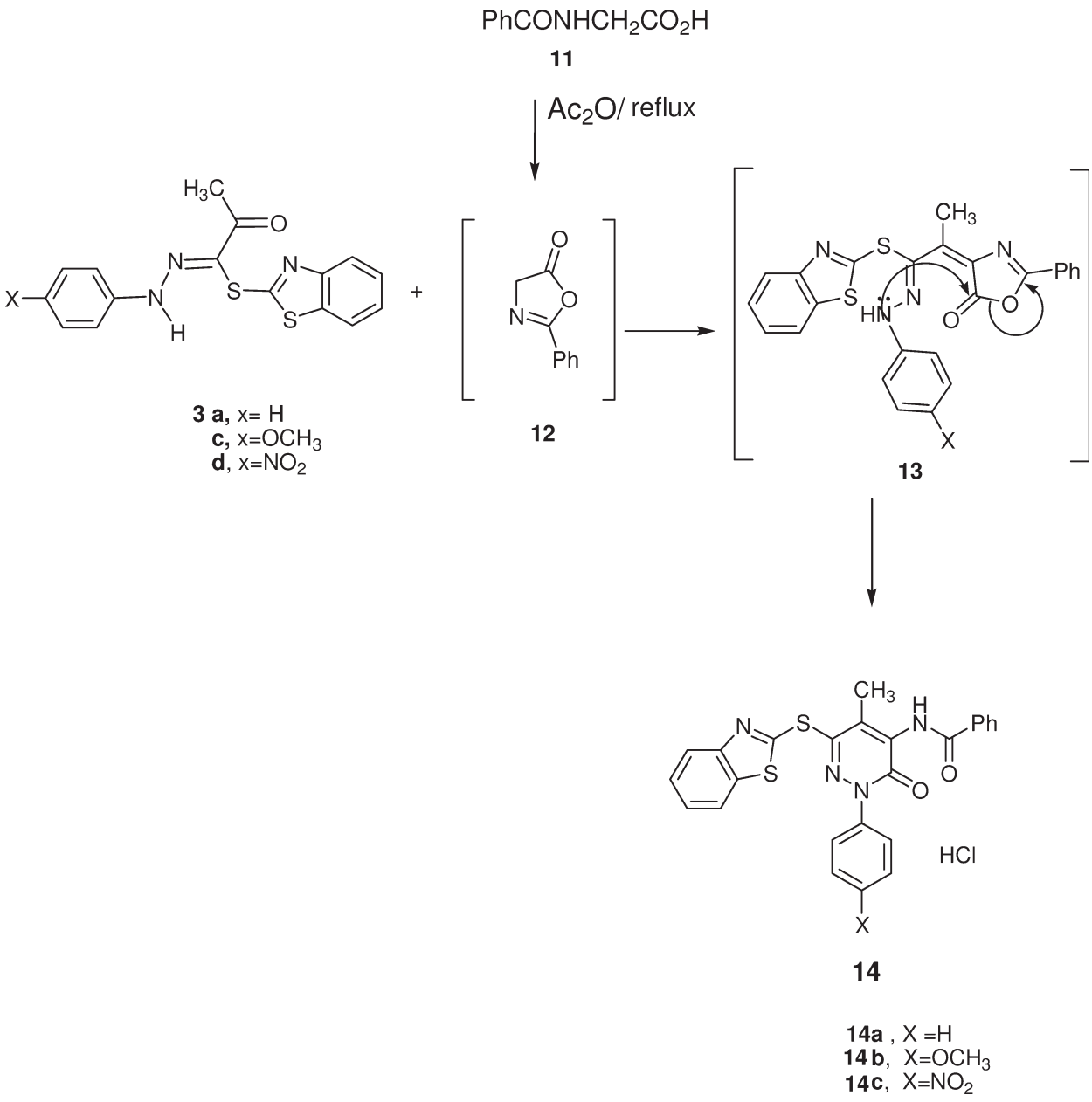
hydrogen cyanide. Perhaps in this case, **10** is more stable than the product that would be obtained by elimination of hydrogen cyanide [3,14] (*cf*. Scheme 3).

Treatment of each of the (*Z*)-*S*-alkylated hydrazones **3a**, **3c**, and **3d** with hippuric acid in refluxing acetic anhydride afforded color crystalline products identified as 1-aryl-5-benzamido-(3-benzothiazol-2,-ylthio)-4-methyl-6-oxo-1,6-dihydropyridazine hydrochloride **14a–c** on the basis of spectral data (Scheme 4). The mass spectrum of **14c** reveals a molecular ion peak at *m/z* 515(M^+-HCl). The H^1 NMR spectra of compounds **14a–c** were free from the hydrazone NH proton of **3** at δ_H 13.75 ppm. The spectra revealed the presence of D_2O exchangeable proton attributed to the NH function of benzamido group at δ_H 8.05 ppm. Also, it revealed, in addition to aromatic signals, one up field signal at δ_H about 2.23 ppm corresponding to methyl group. Moreover, ^{13}C NMR spectra revealed highest frequency signals at δ_c 162 and 172ppm, described to ring carbonyl and amide carbonyl groups, respectively. The formation of the product **14** is considered most likely based on its similarity to the well-established behaviors of hydrazones towards hippuric acid [4,6]. This was assumed to proceed *via* initial cyclization of hippuric acid would generate *in situ* the oxazolone **12**. The oxazolone condenses with each **3a, 3c, and 3d** to form the phenyl hydrazones **13**. The intermediate **13** then rearrange into the pyridazinones **14** *via* attack of nuclophilic nitrogen of hydrazone moiety at the ring carbonyl group (*cf*. Scheme 4).

BIOLOGICAL ACTIVITY

The biological activities of some newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger* and *Penicillium digitatum*, whereas the antibacterial activity was tested against

Scheme 4



Escherichia *coli, Bacillus subtilis, and Staphylococcus aureus*. Most of the tested sample showed strongly antibacterial and fungicidal activity (Table 1).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra (KBr) were recorded on a Jasco FT/IR-6300. ^{1}H, ^{13}C NMR spectra and NOE experimenter were recorded on a Brucker 400 MHz spectrometer in DMSO–d_6 or $CDCl_3$ as solvent using TMS as an internal standard, chemical shifts are reported as δ unit (ppm)and TMS = 0.00 ppm. Mass spectra were measured on GC/MS INCOL XL Finnegan MAT instrument. Microanalyses were performed on a Vario Micro Cube. Abbreviation: Ac_2O = acetic anhydride, EtOH = ethanol, DMF = *N*,*N*-dimethylformamide, DMSO-d_6 = dimethyl-d_6-sulfoxide, TMS = tetramethylsilane, $CDCl_3$ = deuteriochloroform.

General procedure for synthesis of 3a–d. A cold solution of *p*-aryl diazonium chloride **2a–d** (10 mmoles) was prepared by adding of a solution sodium nitrite (0.69 g into 3 mL H_2O) to a cold solution of aryl amine **2a–d** (10 mmoles in 3 mL HCl) with stirring as described earlier [3]. The result of solution of the aryl diazonium salt was then added to cold of **1** (2.23 g, 10 mmoles) in EtOH (100 mL) containing sodium hydroxide (0.20 g, 10 mmoles). The mixture was stirred at 5°C for 2 h. The solid products, so formed, were collected by filtration and recrystallised from EtOH.

Table 1

In vitro antimicrobial and fungicidal activity of some newly synthesized compounds.

Compound	*Escherichia coli*	*Bacillus subtilis*	*Staphylococcus aureus*	*Aspergillus niger*	*Penicillium sp*
3d	+	+	NT	−	−
7a	−	+++	++	+	+++
7b	−	++	−	−	+++
8	++	+++	+++	+	−
10	+	+++	−	−	+++
14c	−	−	NT	−	−

Inactive = −(no inhibition zone); slightly active = +(inhibition zone 7.5–9.0 mm); moderately active = ++(inhibition zone active 9.5–11.0 mm); highly active = +++(inhibition zone 11–17.5 mm); TN, not tested.

(Z)-1-(Benzothiazol-2′-ylthio)-1-(phenylhydrazono)propan-2-one (3a). Compound **3a** was obtained as orange crystal, 2.32g (71%), mp. 191–192°C. IR: ν 3429 (NH), 1686 (C=O) cm^{-1}; ^1H NMR (DMSO–d_6): δ 2.32 (s, 3H, CH_3), 7.12–8.00 (m, 9H, aromatic and benzothiazole protons), 13.81 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO–d_6): δ 25.0 (CH_3), 115.3, 118.3, 121.8, 121.9, 124.2, 125.4, 129.4, 134.8, 141.3, 148.3, 152.5, 156.8 (aromatic and benzothiazole carbons), 189.8 (C=O) ppm; ms: m/z 327(M^+). *Anal*. Calcd. for $C_{16}H_{13}N_3OS_2$ (327.42): C, 58.69; H, 4.00; N, 12.83. Found: C, 58.73; H, 4.00; N, 12.78.

(Z)-1-(Benzothiazol-2′-ylthio)-1-(p-methylphenylhydrazono) propan-2-one (3b). Compound **3b** was obtained as red crystal, 2.48 g (73%), mp.107–109°C. IR: ν 3439 (NH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) :δ 2.39 (s, 3H, *p*-CH_3), 2.55 (s, 3H, CH_3), 6.94–7.83 (m, 8H, aromatic and benzothiazole protons), 13.77 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR(DMSO-d_6): δ 18.0 (*p*-CH_3), 25.0 (CH_3), 118.4, 121.8, 121.9, 124.4, 125.8, 128.3, 129.4, 135.9, 140.3, 148.1, 152.6, 157.7(aromatic and benzothiazole carbons), 189.2 (C=O) ppm; ms: m/z 341 (M^+). *Anal*. Calcd. for $C_{17}H_{15}N_3OS_2$ (341.45): C, 59.79; H 4.42 ; N 12.30. Found: C 59.68; H, 4.68; N, 12.48.

(Z)-1-(Benzothiazol-2′-ylthio)-1-(p-methoxyphenylhydrazono)-propan-2-one (3c). Compound **3c** was obtained as yellow crystal, 2.42g (68%), mp.101–103°C. IR: ν 3431 (NH), 1685 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.53 (s, 3H, CH_3), 3.81 (s, 3H, *p*-OCH_3), 7.09–7.86 (m, 8H, aromatic & benzothiazole protons), 13.77 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 25.4 (CH_3), 56.0 (*p*-OCH_3), 114.6, 118.7, 125.7, 125.9, 127.6, 128.9, 131.4, 141.3, 147.1, 152.6, 157.4, 159.1 (aromatic and benzothiazole carbons), 189.8(C=O) ppm. *Anal*. Calcd. for $C_{17}H_{15}N_3O_2S_2$ (357.45): C, 57.12; H, 4.22; N, 11.75. Found: C 56.90; H, 4.15; N, 11.86.

(Z)-1-(Benzothiazol-2′-ylthio)-(p-nitrophenylhydrazono)propan-2-one (3d). Compound **3d** was obtained as yellow crystal, 3.0 g (81%), mp.119–120°C. IR: ν 3107 (NH), 1692 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.23–8.30 (m, 8H, aromatic and benzothiazole protons), 13.73 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}CNMR(DMSO-d_6): δ 26.1 (CH_3), 119.5, 122.1, 122.9, 123.2, 125.3, 125.6, 134.6, 143.5, 145.6, 149.5, 154.5, 156.5 (aromatic and benzothiazole carbons), 189.2 (C=O) ppm. *Anal*. Calcd. for $C_{16}H_{12}N_4O_3S_2$ (372.29): C, 51.61; H, 3.24; N, 15.04. Found: C, 51.49; H, 3.02; N, 15.27.

General procedure for synthesis of 7a–d. To a suspension of each compounds **3a–d** (10 mmoles) in EtOH (20 mL), malononitrile (0.66 g, 10 mmoles) and 2–3 drops of piperidine were added. The reaction was refluxed for 1 h, left to cool at room temperature, then poured onto ice-cold water and acidify with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from the EtOH.

3-(Benzothiazol-2′-ylthio)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-5-carbonitrile (7a). Compound **7a** was obtained as pale brown crystal, 3.04 g (81%), mp. 96–98°C. IR: ν 1621 (ring C=O), 2207(CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 6.83–7.89 (m, 9H, aromatic and benzothiazole protons) ppm; ^{13}C NMR (DMSO-d_6): δ 24.9 (CH_3), 115.9, 119.6, 121.0, 122.1, 122.9, 124.2, 125.5, 125.7, 130.0, 135.6, 148.2, 152.4, 154.6, 156.9, 158.6 (aromatic, benzothiazole carbons and CN), 162.3 (ring C=O) ppm. *Anal*. Calcd. for $C_{19}H_{12}N_4OS_2$ (376.45): C, 60.62; H, 3.21; N, 14.88. Found: C 60.38, H, 3.13; N, 14.65.

3-(Benzothiazol-2′-ylthio)-4-methyl-1-(p-methylphenyl)-6-oxo-1,6-dihydropyridazine-5-carbonitrile hydrochloride (7b). Compound **7b** was obtained as brown crystal, 3.23 g (76%), mp. 84–86°C. IR: ν 1631 (ring C=O), 2204 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3),: 2.51 (s, 3H, *p*-CH_3), 7.26–8.27 (m, 8H, aromatic and benzothiazole protons) ppm; ^{13}C NMR (DMSO-d_6): δ 18.0, 21.7 (2 CH_3), 111.0, 115.1, 121.1, 121.4, 121.8, 124.5, 125.6, 126.4, 129.4, 130.7, 134.8, 141.3, 146.1, 152.5, 153.7 (aromatic, benzothiazole carbons and CN), 164.9 (ring C=O) ppm. ms: *m/z* 390 (M^+-HCl). *Anal*. Calcd. for $C_{20}H_{15}ClN_4OS_2$ (426.94): C, 56.27; H, 3.54; N 13.12. Found: C, 56.15; H, 3.80; N, 13.21.

3-(Benzothiazol-2′-ylthio)-6-imino-1-(p-methoxyphenyl)-4-methyl-1,6-dihydropyridazine-5-carbonitrile (7c). Compound **7c** was obtained as pale green, 3.16 g (78%), mp.120–122°C. IR: ν 3431–3321(NH), 2206 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 3.84 (s, 3H, *p*-OCH_3), 7.00–7.91 (m, 8H, aromatic and benzothiazole protons), 8.05 (br.s, 1H, NH, D_2O exchangeable) ppm;^{13}C NMR ($CDCl_3$): δ 26.2 (CH_3), 55.6 (*p*-OCH_3), 114.0, 116.2, 115.7, 117.8, 121.6, 121.9, 124.2, 126.5, 133.3, 142.2, 146.9, 148.1, 151.9, 152.8 (aromatic, benzothiazole carbons and CN), 154.5 (C-6), 157.4(*ipso*-OCH_3) ppm; ms:*m/z* 405 (M^+). *Anal*. Calcd. for $C_{20}H_{15}N_5OS_2$ (405.48): C, 59.24; H 3.73; N 17.27. Found: C, 59.39; H, 4.00; N, 17.43.

3-(Benzothiazol-2′-ylthio)-6-imino-4-methyl-1-(p-nitrophenyl)-1,6-dihydropyridazine-6-carbonitrile hydrochloride (7d). Compound **7d** was obtained as pale red crystal, 3.14 g (69%), mp.135–137°C. IR: ν 3444–3454 (NH), 2229(CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 7.25–8.30 (m, 8H, aromatic and benzothiazole protons), 10.42 (br.s, ^1H, NH, D_2O exchangeable) ppm; ^{13}C NMR(DMSO-d_6): δ 25.7(CH_3), 111.7,

116.1, 117.5, 121.5, 121.9, 122.8, 125.3, 126.8, 135.3, 136.2, 143.8, 144.4, 147.9, 149.25, 153.6 (aromatic, benzothiazole carbons and CN), 156.3 (C-6) ppm; ms:*m*/*z* 420 (M^+-HCl). *Anal*. Calcd. for $C_{19}H_{13}Cl\ N_6O_2S_2$ (456.92): C, 49.94; H 2.87; N 18.39. Found: C, 49.75, H, 2.98: N, 18.58.

5-Acetyl-3-(benzothiazol-2′-ylthio)-4,6-dimethyl-1-(p-nitrophenyl)-1,2-dihydropyridazine hydrochloride (8). A mixture of **3d** (3.72 g, 10 mmoles) and acetyl acetone (1.00g, 10 mmoles) in pyridine (20 mL) was refluxed for 3 h. The reaction mixture poured onto ice-cold water and acidified with HCl (10%). The solid product, so formed, was collected by filtration and recrystallized from EtOH as pale yellow crystals, 2.64 g (71%), mp. 96–98. IR: ν 3447 (NH), 1670 (C=O) cm^{-1}; ^1H NMR(DMSO-d_6): δ 2.28 (s, 6H, $2CH_3$), 2.39 (s, 3H,$COCH_3$), 7.37–8.25 (m, 9H, aromatic, benzothiazole protons & NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 25.0, 27.1, 29.8 ($2CH_3$ and $COCH_3$), 111.4, 113.3, 115.5, 122.3, 122.7, 123.0, 124.6, 125.4, 134.5, 135.6, 137.9, 139.7, 142.1, 148.5, 153.8 (aromatic and benzothiazole carbons), 198.8(C=O) ppm. *Anal*. Calcd. for $C_{21}H_{19}ClN_4O_3S_2$ (474.48): C, 53.10; H, 4.03; N, 11.79. Found: C, 53.29; H, 3.82; N, 11.76.

5-Amino-1-(benzothiazol-2′-ylthio)-4-imino-3-(p-methoxyphenyl)-7-phenyl-3,4-dihydrophthalazine-6,6(7H)-dicarbonitrile hydrochloride (10). A solution of **7c** (3.57 g,10 mmoles) in pyridine (20 mL) was treated with benzylidenemalononitrile (1.54 g, 10 mmoles). The reaction mixture was refluxed for 4 h then poured onto ice-cold water and acidify with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from EtOH as green crystal, in 75% yield, mp.150–152°C. IR: ν 3436–3198 (NH, NH_2), 2205(2CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.44(m, 1H, H-7), 3.73(s, 3H, *p*-OCH_3), 7.00–8.55 (m, 16H, aromatic, benzothiazole protons & NH_2, D_2O exchangeable), 10.52 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 25.0 (C-7), 38.9 (C-6), 52.4 (*p*-OCH_3), 101.7, 113.2, 114.2, 117.0, 118.3, 121.2, 122.0, 123.4, 125.4, 126.4, 127.1, 128.3, 130.4, 134.4, 135.3, 138.2, 140.6, 148.3, 149.5, 150.1, 152.1(aromatic, benzothiazole carbons & 2CN), 156.0, 156.8 (C-4 & *ipso*- OCH_3) ppm; ms:*m*/*z* 559 (M^+- HCl). *Anal*. Calcd. for $C_{30}H_{22}ClN_7OS_2$ (596.13): C, 60.44; H 3.71; N 16.44. Found: C, 60.57; H, 3.76; N, 16.34.

General procedure for the synthesis of 14a-c. A solution of each compounds **3a**, **3c,** and **3d** (10 mmoles) and hippuric acid (1.79 g, 10mmoles) in Ac_2O (20 mL) was refluxed for 2 h. The reaction mixture was poured into ice-cold water and acidified with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from a proper solvent.

5-Benzamido-3-(benzothiazol-2′-ylthio)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine hydrochloride (14a). This compound was recrystallized from EtOH to give brown crystals, in 69% yield, mp 168–170°C. IR: ν 3430 (NH), 1686 (amide C=O), 1622 (ring CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 7.03–7.92 (m,14H, aromatic and benzothiazole protons), 8.03 (br.s,1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 24.9 (CH_3), 119.2, 121.0, 121.8, 123.2, 125.4, 126.4, 126.8, 127.9, 128.5, 128.7, 129.0, 135.7, 138.1, 147.2, 148.3, 149.1, 150.1, 153.4 (aromatic and benzothiazole carbons), 161.6 (ring C=O), 172.0 (amide C=O) ppm. *Anal*. Calcd. for $C_{25}H_{19}\ ClN_4O_2S_2$ (507.03): C, 59.22; H, 3.77; N, 11.04. Found: C, 59.27; H, 3.89; N, 11.22.

5-Benzamido-3-(benzothiazol-2′-ylthio)-1-(p-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine hydrochloride (14b). This compound was recrystallized from EtOH to give orange crystals, in 74% yield, mp. 90–92°C. IR: *v* 3432 (NH), 1684 (amide C=O), 1607(ring CO) cm^{-1}; ^1H NMR(DMSO-d_6): δ 2.39 (s, 3H, CH_3), 4.20 (s, 3H, *p*-OCH_3), 7.02–7.98 (m, 13H, aromatic and benzothiazole protons), 8.05 (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 26.2(CH_3), 56.3 (*p*-OCH_3), 118.5, 115.9, 121.1, 121.9, 122.6, 123.2, 123.7, 124.0, 124.8, 126.5, 133.3, 136.3, 136.4, 142.1, 146.7, 151.9, 154.5, 157.5(aromatic and benzothiazole carbons), 162.9(ring C=O), 171.0ppm (amide C=O). *Anal*. Calcd. for $C_{26}H_{21}ClN_4O_3S_2$ (537.05): C, 58.14; H, 3.94; N, 10.43. Found: C, 58.36; H, 4.13; N, 10.30.

5-Benzamido-3-(benzothiazol-2′-ylthio)-4-methyl-1-(p-nitrophenyl)-3-oxo-1,6-dihydropyridazine hydrochloride (14c). This compound was recrystallized from a mixture of EtOH/ DMF (1:2) to give yellowish brown crystals, in 63% yield, mp.75–77°C. IR: *v* 3444 (NH), 1670 (amide C=O), 1622 (ring CO) cm^{-1}; ^1H NMR(DMSO-d_6): δ 2.23 (s,3H, CH_3), 7.11–8.2 (m, 13H, aromatic and benzothiazole protons), 8.31 ppm (br.s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 24.9 (CH_3), 119.9, 122.3, 122.7, 123.2, 124.0, 124.6, 125.4, 127.3, 128.5, 131.0, 132.1, 133.4, 135.7, 144.9, 145.1, 148.7, 151.8, 155.3 (aromatic and benzothiazole carbons), 162.3(ring C=O), 172.0 (amide C=O) ppm; ms:*m*/*z* 515 (M^+ -HCl). *Anal*. Calcd. for $C_{25}H_{18}\ ClN_5O_4S_2$ (551.94): C, 54.40; H, 3.29; N, 12.69. Found: C, 54.48; H, 3.41; N, 12.81.

BIOLOGICAL TESTING

The newly synthesized compounds were tested against the specified microorganism, using 400 μg /mL (w/v) solutions in sterile dimethyl sulfoxide (DMSO). A solution of the tested compound (0.01 mol) was poured aseptically in a well of 0.01 mL diameter made by a Cork borer in the nutrient agar for fungal test. After placing the same volume in wells of all tested microorganism nutrient agar plates were incubated at 37°C for 24 h and sabaurdies dextrose agar were incubated at 25°C for 48 h. The activities were expressed as inhibition zones (mm, diameter, as clear areas) as antibacterial and antifungal effect. The least concentration, which showed inhibitory effect on any specify microorganism, was considered as the minimum inhibitory concentration (MIC) that was determined using streptomycin (50 μg/mL) as the references.

Acknowledgment. This work was financed by University of Kuwait, Research Grant SC 07/04. We are grateful to the Faculty of Science, Chemistry Department, SAF facility for the analytical and spectral measurement (Project GS 01/01, GS 03/01, GS 01/ 05 & GS 01/ 03). The authors are also grateful to Dr. S. A. Abdel-Gahny for the biological activity tests.

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Efficient and One-Pot Catalytic Synthesis of 2-Imidazolines and Bis-Imidazolines with *p*-Toluenesulfonic Acid under Solvent Free Conditions

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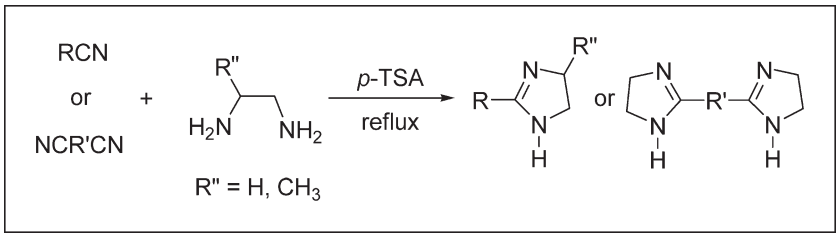

A practical, efficient, and inexpensive method for the synthesis of 2-imidazoline from the reaction of nitriles with ethylenediamine or 1,2-propanediamine using *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate under reflux conditions is reported. This catalyst can be successfully applied for the chemoselective conversion of dicyanobenzenes to corresponding mono- and bis-imidazolines. The applications of these catalysts are feasible because of easy preparation, easy handling, stability, inexpensive, good activity, and eco-friendly.

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INTRODUCTION

2-Imidazolines are very important moieties because of their extensive utilities in chemistry, biochemistry, and pharmacology [1]. These heterocycles exhibit several pharmaceutical activities such as antidiabetic [2], antihypertensive [3], antidepressive [4], anticancer [5], anti HIV-1 [6], antitumor [7], and anti-Alzheimer [8] activities. These compounds are also used as catalysts [9] and synthetic intermediates [10]. Various reaction conditions including homogeneous and/or heterogeneous catalysts have been used for this purpose. Several publications have been described for the preparation of 2-substituted imidazolines from different precursors such as carboxylic acids [11], esters [12], nitriles [13], amides [14], aziridines [15], aldehydes [16], orthoesters [17], hydroximoylchlorides [18], hydroxy amides [19], mono- or disubstituted (chlorodicyanovinyl)benzene [20], and *N-tert*-butoxycarbonyl-protected α-amino acids [21]. However, many of the synthetic protocols reported have certain limitations, such as needing anhydrous conditions, the applications of stoichiometric amounts of catalysts, organic solvents and metals and expensive reagents, harsh reaction conditions and prolonged reaction times. Therefore, the development of an efficient, simple and environmentally benign catalytic procedure for the synthesis of these heterocycles is still in high demand.

The application of 1,2-diamines is the first class synthesis methods of imidazolines. The highlighted advantage of this method is the easy introduction of chirality by using enantiopure 1,2-diamines [22]. A good source of C-1 for preparation of imidazolines is nitriles. Some novel conditions have been developed for this reaction, using Lewis acids, Brönsted acids, or other small molecules as catalysts, such as HCl [13d], CuCl [13e], thioacetamide [23], sulfur [13i], $ZrOCl_2$ [13j], silica sulfuric acid [24], 12-tungstophosphoric acid [25], and carbon disulfide [13k].

We have found that *p*-toluenesulfonic acid (*p*-TSA) and pyridinium *p*-toluenesulfonate (PPTS) as inexpensive and common organic chemicals are efficient catalysts for the synthesis of 2-imidazolines and bis-imidazolines.

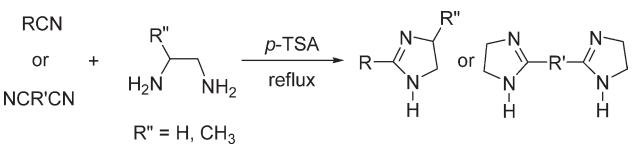
Crystalline pyridinium *p*-toluenesulfonate can easily be prepared from pyridine and *p*-toluenesulfonic acid monohydrate [26]. It is soluble in methylene chloride, chloroform, ethanol, and acetone, and slightly soluble in benzene but insoluble in ether. It is noteworthy that pyridinium *p*-toluenesulfonate is a weaker acid (pH 3.0 in 1.0*M* aqueous solution) than acetic acid (pH 2.4 in 1.0*M* aqueous solution). Consequently, this catalyst is mild enough to be used on complex systems containing sensitive polyfunctional groups.

In this work, we wish to report an efficient synthesis of imidazolines and bisimidazolines using catalytic amounts of a Brønsted acid, such as *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate.

RESULTS AND DISCUSSION

In this article, we describe an efficient method for the synthesis of 2-imidazolines and bis-imidazolines by the

Scheme 1



reaction of ethylenediamine or 1,2-propanediamine with nitriles in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) or pyridinium *p*-toluenesulfonate (PPTS) under reflux condition (Scheme 1).

Synthesis of 2-imidazolines catalyzed by *p*-toluenesulfonic acid. The results from the reaction of ethylenediamine or 1,2-propanediamine and various nitriles in the presence of optimized amount of *p*-toluenesulfonic acid are shown in Table 1. As shown in entries 1–17, the reactions using various aromatic nitriles proceeded well to give the corresponding 2-imidazolines and bis-imidazolines in good to excellent yields.

Typically, benzonitrile (**4**), ethylenediamine, and *p*-TSA were mixed and exposed to heating for 35 min. Cold water was added and the mixture was extracted by $CHCl_3$. Removal of the solvent and recrystallization of the crude product from cyclohexane gave the corresponding 2-imidazoline in 92% yield.

Surprisingly, it was observed that both mono- and bis-imidazolines can be obtained by this catalytic system. As shown in Table 1, mono-imidazolines were produced from dinitriles in 90–92% yields with shorter reaction times (50–60 min). Increasing of the reaction times to 100–110 min, produced bis-imidazolines in 85–87% yields. The preparation of mono-imidazolines from dinitrile compounds is of great interest because the remaining nitrile group can be converted to other functional groups [28].

As it has been reported, catalytic synthesis of bis-imidazolines from the reaction of dinitriles with ethylenediamine in the presence of supported tungstophosphoric was not successful [25], whereas in the presence of *p*-TSA, the corresponding bis-imidazolines were synthesized from dinitriles in the good yields (entries 11, 13; Table 1).

One advantage of this method is large scale applicability so that imidazolines and bis-imidazolines were prepared on a 100 mmol scale, and the results were comparable with the small scale experiments.

A plausible mechanism is shown in Scheme 2. The nitrile is first activated by the catalyst to give **1** then ethylenediamine attacks **1** to produce **2** and in final cyclization of **2** gives product and releases of the catalyst for the next catalytic cycle.

Synthesis of 2-imidazolines catalyzed by pyridinium *p*-toluenesulfonate. As shown in Table 2, in the presence of pyridinium *p*-toluenesulfonate, the synthesis of 2-imidazoline was performed in longer time with slightly reduced yields in comparison with *p*-TSA. For example, in the presence of *p*-TSA, the reaction of benzonitrile was completed in 35 min, whereas PPTS catalyst carried out the reaction in 85 min with 85% yield. These results show that PPTS probably can be used in the synthesis of imidazolines containing sensitive groups.

CONCLUSIONS

A simple and efficient procedure for the synthesis of 2-imidazolines and bis-imidazolines has been developed. Mild reaction conditions, absence of solvent, moderate reaction times, easy and quick isolation of the products, good to excellent yields (75–92%), inexpensive and easily preparation of the catalyst, and large scale applicability are the main advantages.

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. All of the products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were recorded on a Jasco IR-680 spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker-Arance AQS 300 MHz or a Bruker 400 Ultrasheilld (400 MHz) spectrometers.

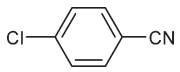
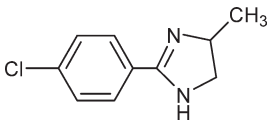
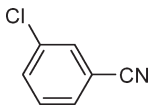
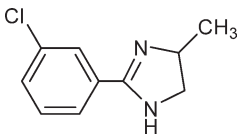
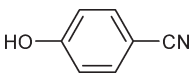
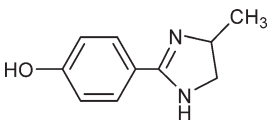
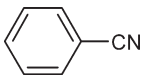
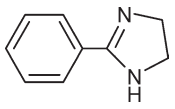
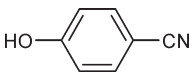
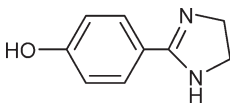
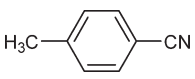
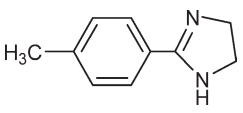
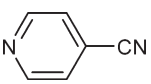
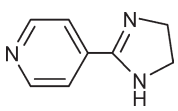
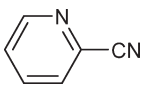
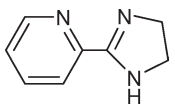
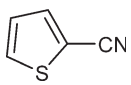
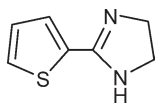
General procedure for the preparation of 2-imidazolines and bis-imidazolines. A mixture of nitrile (10 mmol), ethylenediamine or 1,2-propanediamine (40 mmol), and *p*-toluenesulfonic acid (3 mmol) or pyridinium *p*-toluenesulfonate (4 mmol) was heated under reflux for 45–220 min. After completion of the reaction as indicated by TLC (eluent:EtOAc/MeOH, 4:1), cold water was then added after the reaction mixture cooled down to room temperature. After stirred, the mixture was extracted by 15 mL (3×5) $CHCl_3$ and solvent evaporated. The crude products were recrystallized from suitable solvents (**4** was recrystalised from cyclohexane; **12** and **14** were recrystallized from methanol and others were recrystallized from *n*-hexane) gave the pure products in 75–95% yields based on the starting nitrile (Table 1). Spectroscopic data of new compounds:

2-(4-Chlorophenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 1). Mp:150–152°C; $R_f = 0.464$ (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3100 (NH), 2953, 1600, 1583, 1479, 1368, 1331, 831; ^{1}H NMR (400 MHz, DMSO) δ(ppm) : 1.27 (d, 3H, CH_3), 3.33 (m, 2H, CH_2), 3.92 (m, 1H, CH), 4.25 (s, 1H, NH), 7.55–7.85 (dd, 4H, ArH). ^{13}C NMR (400 MHz, DMSO) δ(ppm): 22.23, 56.47, 57.34, 126.92, 128.77, 129.6, 138.55, 162.06. Anal. Calcd. for $C_{10}H_{11}ClN_2$: C 61.70, H 5.70, N 14.39; found: C 61.6, H 5.8, N 14.3.

2-(3-Chlorophenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 2). Mp:147–149°C; $R_f = 0.500$ (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3120 (NH), 2962, 1592, 1542, 1490; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 1.14 (d, 3H, CH_3), 3.18 (t, 1H, CH_2), 3.37 (s, 1H, NH), 3.75 (t, 1H, CH_2), 3.97 (m, 1H, CH), 7.43–7.91 (m, 4H, ArH). ^{13}C NMR (400

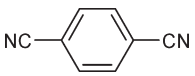
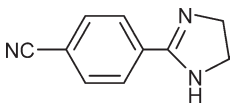
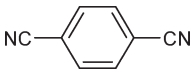
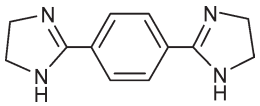
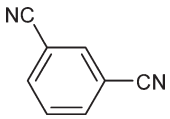
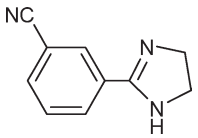
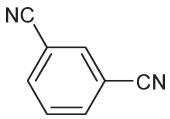
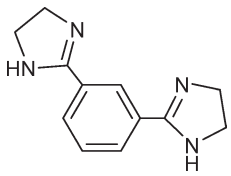
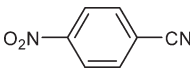
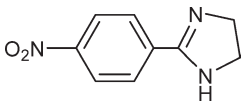
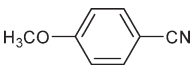
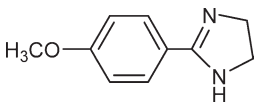
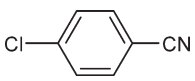
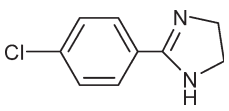
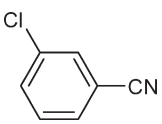
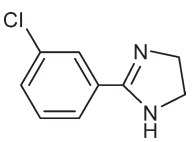
Table 1

Synthesis of imidazolines and bis-imidazolines in the presence of *p*-TSA.

Entry	Substrate	R''	Product[a]	Time (min)	Yield[b] (%)	Mp (°C) found	Mp (°C) reported
1		CH_3		90	75	150–152	–
2		CH_3		30	90	147–149	–
3		CH_3		75	80	148–150	–
4		H		35	92	100–101	101–102
5		H		60	92	300–302	–
6		H		75	92	177–179	175–176
7		H		100	85	134–135	136–137
8		H		140	85	101–102	94
9		H		105	90	175–178	178

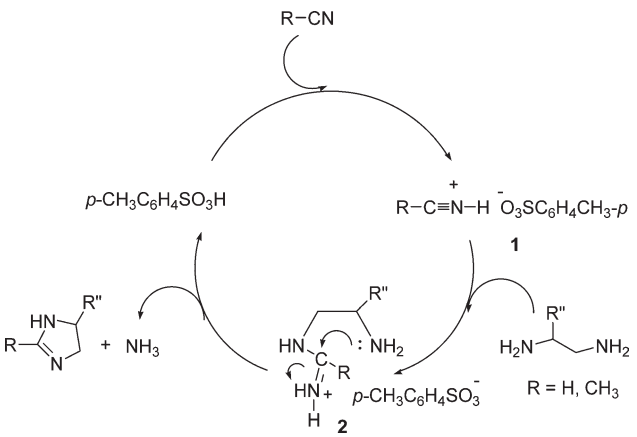
(*Continued*)

Table 1
(*Continued*)

Entry	Substrate	R''	Product[a]	Time (min)	Yield[b] (%)	Mp (°C) found	Mp (°C) reported
10		H		50	92	204–205	202
11		H		100	85	312–314	318
12		H		60	90	132–134	133–134
13		H		110	87	242–243	244
14		H		180	72	230–232	231
15		H		80	80	139–140	138–140
16		H		50	87	186–188	185–187
17		H		25	92	136–137	134–136

[a] Characterized by spectral analysis and comparison with these reported in the literature [13, 16, 25, 27].
[b] Yields refer to isolated and purified products.

Scheme 2



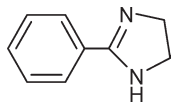
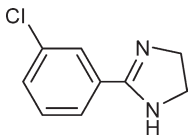
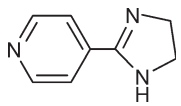
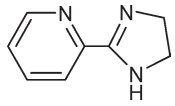
MHz, DMSO) δ(ppm): 22.11, 56.75, 57.99, 123.36, 124.47, 125.82, 127.29, 130.36, 133.20, 161.42. Anal. Calcd. for $C_{10}H_{11}ClN_2$: C 61.70, H 5.70, N 14.39; found: C 61.8, H 5.8, N 14.5.

2-(4-Hydroxyphenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 3). Mp:148–150°C; R_f = 0.587 (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3350 (b, OH), 3188 (NH), 2998, 1591, 1184, 856; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 1.19 (d, 3H, CH_3), 3.23 (dd, 1H,CH_2), 3.80 (t, 1H, CH_2), 4.23(m, 1H, CH), 4.42 (s, 1H, NH), 4.72 (s, 1H, OH), 6.70 (d, 2H, ArH), 7.64 (d, 2H, ArH). ^{13}C NMR (400 MHz, DMSO) δ(ppm): 21.81, 53.42, 54.67, 114.25, 116.72, 130.20, 163.20, 165.57. Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16, H 6.86, N 15.90; found: C 68.2, H 6.8, N 15.8.

2-(4-Hydroxyphenyl)-4,5-dihydro-1H-imidazole (Table 1, entry 5). Mp:300–302°C; R_f = 0.536 (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3323 (b, OH), 3201 (NH), 1613, 1592, 1503, 1186, 853; ^{1}H NMR (400 MHz, DMSO) δ(ppm) : 3.55 (s, 4H, $2CH_2$), 3.40 (s, 1H, NH), 6.70 (d, 2H, ArH), 7.61 (d, 2H, ArH), 8.31 (s, 1H, OH). Anal. Calcd. for $C_9H_{10}N_2O$: C 66.65, H 6.21, N 17.27; found: C 66.5, H 6.3, N 17.2.

Table 2

Synthesis of some imidazolines in the presence of pyridinium *p*-toluenesulfonate.

		PPTS		*P*-TSA	
Entry	Product	Time (min)	Yield (%)	Time (min)	Yield (%)
1		85	85	35	90
2		80	78	25	92
3		270	80	100	85
4		360	82	140	85

Acknowledgment. The partial support of this work by Yasouj University is acknowledged.

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Synthesis of 2,3-Diaryl-3,4-dihydro-2*H*-1,3-benzoxazines and Their Fungicidal Activities

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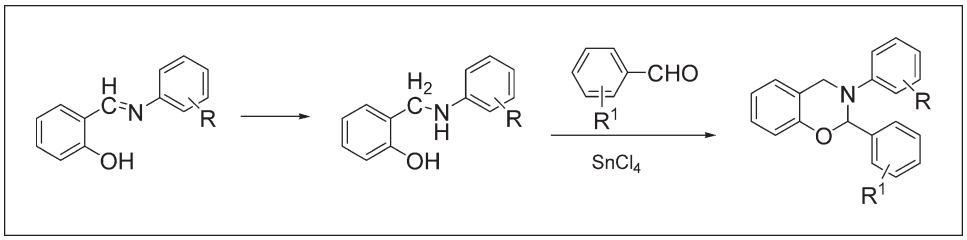

A series of novel 2,3-diaryl-3,4-dihydro-*2H*-1,3-benzoxazines have been prepared in high yields from *o*-arylaminomethylphenols and aromatic aldehydes in the presence of $SnCl_4$ for the first time, and their fungicidal activities were investigated too. Some of the products showed good fungicidal activities against *Rhizoctonia solani* justified by 100% activity of compound **1b**.

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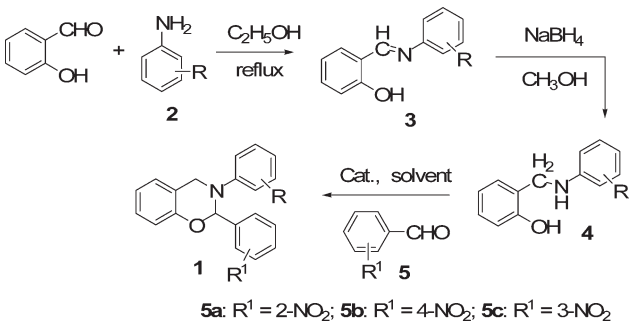
INTRODUCTION

As 3,4-dihydro-2*H*-1,3-benzoxazines and 3,4-dihydro-2*H*-1,3-oxazine containing compounds have been reported to show different antimicrobial properties [1], such as bactericidal, fungicidal, and many pharmacological features [2] such as antitumour, antituberculosis, and anthelmintic activity, these types of compounds have been an important subject of researches. In addition, *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines are potential intermediates for the preparation of phenol-formaldehyde resins [3]. Hence, the synthesis of these compounds including the synthesis of benzoxazine monomers containing special functional group has attracted great interest. Several methods have been reported for the preparation of these compounds in the literature. For example, an important method was developed by Burke et al. [4], using Mannich-type condensation of phenols with primary amines and two equivalents of formaldehyde. Condensations of *o*-aminomethylphenol with aldehydes or ketones provided another route [5]. Reactions of primary amines with oxygen-containing dihalocompounds established a way to prepare 3,4-dissymmetric-substituted 3,4-dihydro-1,3-benzoxazines [6]. Recently, rhodium-catalyzed reactions of 2-(alkenyloxy)benzylamines have been developed as a new way to generate 3,4-dihydro-1,3-benzoxazines, which involves an allylic cleavage followed by regioselective carbonylation at the internal carbon atom [7]. However, some drawbacks existed in previous methods. Hence, both the preparation of novel 3,4-dihydro-1,3-benzoxazines and the development of efficient method are still of great importance. On the other hand, the reported biological studies of dihydro-1,3-benzoxazines were mainly focused on the pharmacological activities. To the best of our knowledge, few papers about the pesticidal activities of dihydro-2*H*-1,3-benzoxazines and the preparation of 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzoxazines have been reported. Hence, herein, we present our results of the synthesis of 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzoxazines mediated by $SnCl_4$ (Scheme 1) and the preliminary fungicidal activities of the products.

RESULTS AND DISCUSSION

The intermediate Schiff bases **3** were smoothly prepared in 84 to 99% yields (Table 1) by condensation reactions of substituted anilines **2** with salicylaldehyde, and followed by reduction with $NaBH_4$ affording *o*-arylaminomethylphenols **4** in 90 to 94% yields (Table 1) [8,9]. It was found that only *E* isomer of Schiff base **3** was formed [9], possibly due to the stability and a hydrogen bond between the hydroxyl group and the nitrogen atom [9,10]. Then, reaction of *o*-aminomethyl phenol **4c** with 3-nitrobenzaldehyde **5c** in the presence of *p*-toluenesulfonic acid (TsOH) [**2g**,11] was performed under reflux by removing the water of condensation

Scheme 1. Synthesis of 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzoxazines **1**.



with chloroform azeotropically to prepare 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzoxazine **1a**, the reaction gave the desired product in only 11% yield along with an unknown white solid (Table 2, entry 1). We next attempted a mixed solvent of chloroform and cyclohexane, (v:v = 1:7) taking into account the higher azeotropic ability of cyclohexane, the yield raised to 18% (entry 2), but still far away from satisfaction. Here, it should be noted that the addition of chloroform was to increase the solubility of reactants. In literature, Lewis acid $SnCl_4$ was reported as an effective catalyst for many reactions, such as acetalization and ketalization of aldehydes or ketones [12]. Therefore, we tried $SnCl_4$ (20 mol %) as catalyst, to our delight, it turned out that the reaction of **4c** with **5c** in chloroform/cyclohexane (v:v = 1:7) gave product **1a** in 95% yield at 85°C (entry 3). To the best of our knowledge, this is the first time to use $SnCl_4$ as catalyst for the zaz-acetalization of aromatic aldehyde with *o*-aminomethylphenol to prepare dihydro-1,3-benzoxazine. But, the yield decreased when the amount of the catalyst was increased to 25 mol % (entry 4). Thus, we employed 20 mol % of $SnCl_4$ for the synthesis of compounds **1b–1o**. Generally, under these conditions, **1b–1o** were prepared in 60 to 80% yields (entries 3–18). Compounds possessing an electron-releasing group on the phenyl group bond to the nitrogen atom gave higher yields than those with an electro-withdrawing group. Electron-releasing group increases the electron density of the nitrogen and hence increases its nucleophilicity. Moreover, it was observed that, for compounds containing a methyl group on the benzene ring connected with the nitrogen atom, the yield mainly depended on the position of the methyl group in the order of *para* > *meto* > *ortho* regardless of the nature of the aryl group at position-2 of the oxazine ring. The last two cases may be attributed to the steric hindrace.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and elemental analysis. For compound **1b**, strong absorptions at 1530 and 1337 cm^{-1} are attributed to the antisymmetrical and symmetrical stretch vibration absorption of the NO_2 group, and 1585 and 1610 cm^{-1} for νC=C bond. δ = 6.85 observed in ^{1}H-NMR corresponds to OCHN proton of benzoxazine ring. The downfield shift of OCHN proton is due to the strong electron negative of nitrogen and oxygen atoms. Particularly, the proton of NCH_2 group absorbs as two doublets at 4.00 and 4.19 instead of a singlet. These data strongly suggested the formation of benzoxazine ring. In addition, the spectroscopic data-based structure was further confirmed by X-ray crystallographic analysis of **1b** (Fig. 1) [13]. It can be seen clearly from the structure, in solid state, the conformation of oxazine ring is a half-chair form with two trans-axial orientation of both the *N*-aryl and 2-aryl group. It apparently indicated that the nitrogen atom adopted sp^3 hybrid orbital.

According to SOP procedure [14], fungicidal activities of the prepared compound **1a–1o** against *Gibberella zeae, Phytophythora capsici, Alternaria alternate*, *Botrytis cinerea*, and *Sclerotonia sclerotiorum* were evaluated using the mycelium growth rate test in concentration of 25 mg/L, which was expressed as inhibition rate (%), and their activities against *Rhizoctonia solani* using the leaf-disc culture in concentration of 500 mg/L, which was expressed as control efficacy (%). The results are summarized in Table 3. In principle, it can be seen that most of the compounds showed moderate to good activity. For the tested compounds, the activity against *Rhizoctonia solani* was the best as shown by compound **1b** (100%) and **1e, 1g, and 1n** (80% for three compounds). Moreover, compounds possessing an electron-releasing group on the phenyl group bond to the nitrogen atom showed higher activities against *Rhizoctonia solani* than those with an electro-withdrawing group. For other fungus, there was not apparent structure-activity relationship. The insecticidal activities of the compounds **1** are in progress.

EXPERIMENTAL

All solvents were dried by standard procedure. Aromatic aldehydes and substituted anilines were commercially

Table 1

The results of the preparation of Schiff base **3** and *o*-aminomethylphenol **4**.

Entry	R	Product 3	Yield[a] (%)	Product 4	Yield[b] (%)
1	2-CH_3	**3a**	90	**4a**	91
2	3-CH_3	**3b**	84	**4b**	94
3	4-CH_3	**3c**	98	**4c**	94
4	4-Cl	**3d**	98	**4d**	90
5	4-OCH_3	**3e**	93	**4e**	92
6	H	**3f**	91	**4f**	91

[a] Isolated yield for reaction carried out in refluxing ethanol for 3 h.
[b] Isolated yield for reaction carried out in methanol at 0°C for 40 min.

Table 2

The results of the preparation of compound **1**.

Entry	R	R^1	Conditions[a]	Product	Yield[b] (%)
1	4-CH_3	3-NO_2	TsOH (20 mol %), $CHCl_3$, reflux, 5 h	**1a**	11[c]
2	4-CH_3	3-NO_2	TsOH (20 mol %), reflux, 5 h, $CHCl_3/C_6H_{12}$	**1a**	18
3	4-CH_3	3-NO_2	$SnCl_4$(20 mol %), 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1a**	95
4	4-CH_3	3-NO_2	$SnCl_4$ (25 mol %), 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1a**	85
5	4-CH_3	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1b**	80
6	4-CH_3	4-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1c**	67
7	3-CH_3	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1d**	69
8	3-CH_3	3-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1e**	68
9	3-CH_3	4-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1f**	65
10	2-CH_3	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1g**	63
11	2-CH_3	3-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1h**	65
12	2-CH_3	4-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1i**	64
13	4-Cl	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1j**	69
14	4-Cl	4-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1k**	60
15	H	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1l**	66
16	H	3-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1m**	61
17	4-CH_3O	2-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1n**	73
18	4-CH_3O	3-NO_2	$SnCl_4$, 85°C, 5 h, $CHCl_3/C_6H_{12}$	**1o**	70

[a] The mole ratio of *n* (aromatic aldehyde **5**): *n* (aminomethyl phenol **4**) = 1.3:1 for all reactions. The amount of $SnCl_4$: 20 mol % based on aminomethyl phenol except for the cases marked in the table. C_6H_{12}: cyclohexane; $CHCl_3$:C_6H_{12} = 1:7 (v:v).
[b] Isolated yield.
[c] An unknown white solid also formed.

available. Infrared spectra were recorded on a PE-2000 FT-IR. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Avance-500 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to Me_4Si (0, ^{1}H) or $CDCl_3$ (77.0, ^{13}C). Mass spectra were obtained with Thermo Finnigan LCQ Advantage spectrometer. Elemental analysis was measured on PE 2400 II CHNS instrument. Melting points were determined on a WRS-1B digital melting point instrument and without correction. Thin-layer chromatography (TLC) was run on precoated silica gel plates (Merck 60F_{254}). Column chromatography was carried out using flash silica gel. X-ray crystallographic analysis was performed on a Bruker Smart CCD diffractometer equipped with a graphite monochromator Mo Kα radiation (λ = 0.71073 Å).

Schiff bases **3a–f** and corresponding *o*-arylaminomethyl phenols **4a–f** were prepared according to the method described in references [8,9].

General procedure for the synthesis of 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzoxazines 1a-1o. Under nitrogen, into a 250-mL three-necked flask equipped with a Dean-stark, 2-((*p*-toluidino)methyl)phenol **4c** (1.07 g, 5 mmol), 3-nitrobenzaldehyde (0.98 g, 6.5 mmol), mixed solvent of chloroform and cyclohexane (150 mL, v:v = 1:7), and $SnCl_4$ (0.26 g, 20 mol %) were added and mixed with stirring. The solution was heated at 85°C for 5 h (checked by TLC), and the water of condensation was removed by azeotropic distillation. Then, triethyl amine was added to make solution at pH = 8, followed by addition of ethyl acetate (100 mL), and washed sequentially with water (2 × 100 mL) and saturated brine (2 × 100 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The obtained yellow oil was purified by flash column chromatography (silica gel, PE-EtOAc) affording the product **1a** (1.64 g, 95% yield) as a yellow solid.

2-(3-Nitrophenyl)-3-*p*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1a). Yield 95%, m.p.: 123.6–125.5°C; IR (KBr): 3093, 3070, 3022, 2978, 2857, 1611, 1583, 1528, 1513, 1490, 1457, 1380, 1346, 1272, 1265, 1227, 1197, 1149, 1127, 1108, 1083, 1033, 995, 956, 941, 923, 893, 821, 811, 805, 752, 734, 711, 694, 670, 594 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.27 (s, 3H, CH_3), 4.25 (d, *J* = 17.0 Hz, 1H, CH_2), 4.35 (d, *J* = 17.0 Hz, 1H, CH_2), 6.56 (s, 1H, CH), 6.86 (d, *J* = 8.0 Hz, 2H), 7.02–7.03 (m, 1H), 7.07–7.12 (m, 4H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 8.15–8.17 (m, 1H), 8.45 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 20.68, 47.20, 87.61, 117.09, 120.14, 121.01 (2C), 121.16, 122.29, 123.23, 126.67, 128.37, 129.69, 129.91 (2C), 132.58, 133.09, 141.64, 146.95, 148.70, 152.39; MS (EI, 70 ev) *m/z* (%): 346 (30) [M^+], 240 (100), 223 (6), 193 (8), 165 (4), 118 (14), 107 (4), 91 (25), 77 (9), 65 (9), 51 (4); Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 72.53; H 5.22; N 8.06.

2-(2-Nitrophenyl)-3-*p*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1b). Yield 80%, m.p.:152.6–153.0°C; IR (KBr): 3083, 3021, 2972, 2920, 1610, 1585, 1530, 1513, 1486, 1456, 1437, 1386, 1363, 1337, 1292, 1276, 1268, 1224, 1198, 1144, 1109, 1034, 1024, 1015, 978, 961, 935, 852, 839, 820, 782, 757, 736, 714, 687, 679, 632, 589 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.25 (s, 3H, CH_3), 4.00 (d, *J* = 17.0 Hz, 1H, CH_2), 4.19 (d, *J* = 17.0 Hz, 1H, CH_2), 6.85 (s, 1H, CH), 6.86–6.88 (m, 1H), 7.00–7.06 (m, 6H), 7.17–7.20 (m, 1H), 7.44–7.47 (m, 2H), 7.61–7.63 (m, 1H), 7.72–7.74 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 20.74, 47.12, 85.52, 116.72, 120.45, 120.86 (2C), 121.13, 124.45, 126.72, 128.41, 128.76, 129.21, 129.80 (2C), 131.84, 132.76, 132.99, 146.74, 149.08, 152.60; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 73.11; H 5.26; N 8.05.

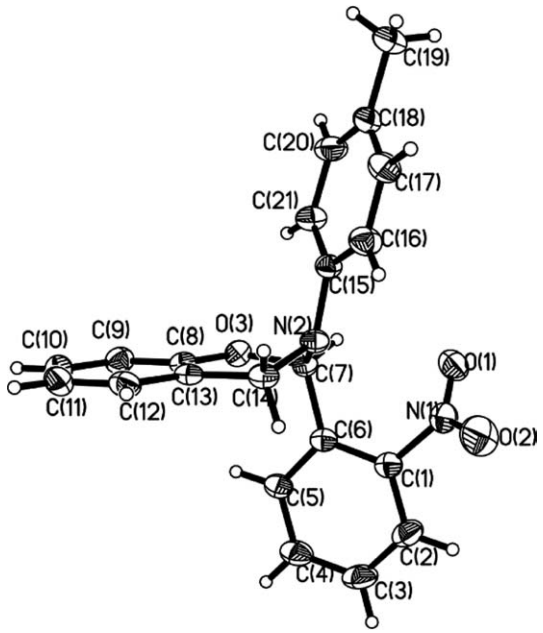


Figure 1. ORTEP diagram of compound **1b**.

2-(4-Nitrophenyl)-3-*p*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1c). Yield 67%, m.p.: 93.7–96.9°C; IR (KBr): 2920, 2859, 1614, 1583, 1516, 1490, 1455, 1442, 1386, 1343, 1318, 13002, 1224, 1205, 1144, 1109, 1033, 1014, 976, 960, 940, 905, 854, 829, 812, 760, 739, 712, 696, 589 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.27 (s, 3H, CH_3), 4.22 (d, J = 17.0 Hz, 1H, CH_2), 4.34 (d, J = 16.5 Hz, 1H, CH_2), 6.57 (s, 1H, CH), 6.86–6.88 (m, 2H), 6.99 (d, J = 3.5 Hz, 1H), 7.06–7.10 (m, 4H), 7.16–7.19 (m, 1H), 7.74 (d, J = 8.5 Hz, 2H), 8.18–8.21 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 20.64, 47.13, 87.72, 116.94, 120.10, 120.73 (3C), 121.14, 123.83, 123.99, 126.67, 127.92, 128.29, 129.87 (2C), 132.44, 146.41, 145.85, 147.69, 152.38; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 72.54; H 5.28; N 8.12.

2-(2-Nitrophenyl)-3-*m*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1d). Yield 69%, m.p.: 138.1–139.0°C; IR (KBr): 3072, 2947, 2906, 2862, 1606, 1586, 1535, 1489, 1456, 1445, 1378, 1340, 1301, 1273, 1236, 1216, 1199, 1169, 1140, 1109, 1036, 983, 958, 937, 852, 837, 782, 772, 756, 737, 690, 634, 597 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H, CH_3), 4.01 (d, J = 17.0 Hz, 1H, CH_2), 4.23 (dd, J = 1.0 Hz, J = 1.0 Hz, 1H, CH_2), 6.80(d, J = 7.5 Hz, 1H), 6.85–6.87 (m, 2H), 6.93–6.95 (m, 1H), 6.98 (s, 1H, CH), 7.01 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.17–7.20 (m, 1H), 7.43–7.48 (m, 2H), 7.61–7.62 (m, 1H), 7.73–7.74 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 21.72, 46.79, 85.03, 116.76, 117.27, 120.41, 121.05 (2C), 121.13, 123.91, 124.47, 126.66, 128.41, 128.78, 129.02, 129.22, 131.83, 132.99, 139.02, 149.10, 152.44; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 73.12; H 5.28; N 8.06.

2-(3-Nitrophenyl)-3-*m*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1e). Yield 68%, m.p.: 101.3–102.0°C; IR (KBr): 3092, 3025, 2979, 2918, 1602, 1585, 1529, 1488, 1475, 1380, 1348, 1314, 1271, 1238, 1219, 1181, 1123, 1113, 1087, 1046, 1032, 994, 958, 970, 942, 899, 891, 806, 776, 753, 735, 696, 688, 671, 599 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.32 (s, 3H, CH_3), 4.26 (d, J = 17.0 Hz, 1H, CH_2), 4.37 (d, J = 17.0 Hz, 1H, CH_2), 6.63 (s, 1H, CH), 6.82–6.89 (m, 3H), 7.00–7.04 (m, 3H), 7.15–7.19 (m, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.89–7.91 (m, 1H), 8.15–8.17 (m, 1H), 8.44 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 21.65, 46.56, 86.98, 117.11, 117.24, 120.05, 121.07, 121.13, 122.20, 123.22, 123.54, 126.60, 128.35, 129.17, 129.72, 133.04, 139.24, 141.60, 148.64, 149.36, 152.15; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 72.53; H 5.20; N 8.05.

2-(4-Nitrophenyl)-3-*m*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1f). Yield 65%, m.p.: 126.2–126.9°C; IR (KBr): 3042, 2976, 2876, 1607, 1584, 1554, 1541, 1512, 1489, 1456, 1378, 1350, 1306, 1239, 1221, 1189, 1169, 1128, 1110, 1038, 981, 956, 857, 826, 783, 767, 752, 739, 694, 609 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.32 (s, 3H, CH_3), 4.24 (d, J = 16.0 Hz, 1H, CH_2), 4.38 (d, J = 7.0 Hz, 1H, CH_2), 6.65 (s, 1H, CH), 6.83 (t, J = 7.5 Hz, 1H), 6.85 (t, J = 5.0 Hz, 2H), 7.00 (dd, J

Table 3

Fungicidal activities of compounds **1a–1o**.

Compound	*Gibberella zeae* (%)	*Phytophythora capsici* (%)	*Alternaria alternate* (%)	*Botrytis cinerea* (%)	*Rhizoctonia solani* (%)	*Sclerotonia sclerotiorum* (%)
1a	10.3	37.4	17.5	13.6	50.0	0
1b	30.9	28.0	10.5	19.0	100	59.8
1c	30.9	28.0	0	13.6	0	0
1d	39.2	33.6	14.0	6.8	50.5	56.1
1e	30.9	9.3	35.1	27.2	80.0	0
1f	30.9	37.4	10.5	20.4	0	0
1g	20.6	28.0	14.0	33.3	80.0	0
1h	20.6	28.0	10.5	33.3	0	0
1i	20.6	28.0	7.0	27.2	60.0	0
1j	30.9	31.8	42.1	47.6	0	75
1k	41.2	37.4	38.6	47.6	10.0	28.0
1l	30.9	31.8	17.5	23.1	50.0	0
1m	24.7	22.4	3.5	13.6	70.0	0
1n	51.5	37.4	45.6	27.2	80.0	56.1
1o	10.3	18.6	0	13.6	0	0

= 7.0 Hz, *J* = 3.5 Hz, 3H), 7.16–7.20 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 8.19 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 21.69, 46.66, 87.22, 117.07, 117.12, 120.16, 120.92, 121.21, 123.53(2C), 123.91, 126.69, 127.95(2C), 128.36, 129.25, 139.31, 146.51, 147.81, 149.36, 152.32; MS (ESI): 347[M+H]$^+$. Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 73.60; H 5.21; N 8.13.

2-(2-Nitrophenyl)-3-*o*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1g). Yield 63%, m.p.: 164.3–165.3°C; IR (KBr): 3079, 3025, 2948, 2913, 1608, 1597, 1588, 1527, 1458, 1439, 1365, 1338, 1300, 1274, 1228, 1207, 1187, 1142, 1118, 1057, 1035, 1021, 977, 955, 937, 855, 841, 827, 780, 760, 737, 725, 714, 684, 663, 634, 592 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.20 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 6.76 (d, *J* = 12.0 Hz, 1H), 6.83–6.86 (m, 1H), 6.98 (s, 1H, CH), 6.99–7.01 (dd, *J* = 7.4 Hz, *J* = 0.9 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.20–7.23 (m, 1H), 7.43–7.51 (m, 3H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.78 (dd, *J* = 1.5 Hz, *J* = 1.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 17.93, 47.84, 85.79, 116.61, 119.57, 121.08, 122.95, 124.92 (2C), 126.64, 127.06, 128.47, 128.77, 129.13, 131.19, 132.11, 133.17, 133.37, 148.11, 148.79, 152.44; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 72.51; H 5.21; N 8.05.

2-(3-Nitrophenyl)-3-*o*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1h). Yield 65%, m.p.: 85.0–86.1°C; IR (KBr): 3023, 2933, 2885, 1598, 1585, 1533, 1490, 1456, 1434, 1386, 1380, 1349, 1336, 1227, 1215, 1188, 1149, 1082, 1033, 986, 959, 893, 807, 764, 755, 742 724, 695, 673, 588 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.51 (s, 3H, CH_3), 4.14 (d, *J* = 17.0 Hz, 1H, CH_2), 4.25 (d, *J* = 17.0 Hz, 1H, CH_2), 6.34 (s, 1H, CH), 6.86–6.92 (m, 2H), 7.05–7.13 (m, 3H), 7.20–7.25 (m, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 8.16–8.18 (m, 1H), 8.54–8.55 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 18.59, 47.37, 87.92, 117.08, 119.86, 121.15, 122.35, 123.10, 123.31, 125.03, 126.69, 126.86, 128.23, 129.57, 131.07, 133.13, 133.17, 141.43, 148.11, 148.52, 152.28; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09%. Found: C 73.12; H 5.28; N 8.06.

2-(4-Nitrophenyl)-3-*o*-tolyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1i). Yield 64%, m.p.: 128.5–129.8°C; IR (KBr): 3074, 2955, 2886, 1607, 1584, 1520, 1486, 1456, 1380, 1345, 1333, 1228, 1214, 1183, 1140, 1106, 1033, 1019, 1011, 975, 953, 932, 858, 837, 763, 752, 742, 723, 709, 601 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.50 (s, 3H, CH_3), 4.12 (d, *J* = 16.5 Hz, 1H, CH_2), 4.23 (d, *J* = 17.0 Hz, 1H, CH_2), 6.35 (s, 1H, CH), 6.86–6.92 (m, 2H), 7.05–7.11 (m, 3H), 7.22–7.26 (m, 2H), 7.36–7.38 (m, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 8.22–8.23 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 18.59, 47.40, 88.16, 116.97, 119.89, 121.17, 123.19, 123.75, 124.25, 125.02, 126.73, 126.88, 128.03, 128.21, 130.44, 131.08, 133.04, 146.32, 147.61, 148.18, 152.35; MS (ESI): 347[M+H]$^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82; H 5.24; N 8.09. Found: C 72.51; H 5.20; N 8.04.

3-(4-Chlorophenyl)-2-(2-nitrophenyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1j). Yield 69%, m.p.: 140.7–141.3°C; IR (KBr): 3035, 2936, 2875, 1609, 1592, 1522, 1494, 1457, 1384, 1361, 1342, 1304, 1276, 1224, 1203, 1113, 1098, 1034, 1020, 1008, 980, 949, 936, 855, 826, 782 750, 740, 727, 645, 596 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.99 (d, *J* = 17.0 Hz, 1H, CH_2), 4.22 (d, *J* = 17.0 Hz, 1H, CH_2), 6.85 (s, 1H, CH), 6.87–6.91 (m, 1H), 7.00 (d, *J* = 9.5 Hz, 2H), 7.06–7.09 (m, 2H), 7.17–7.22 (m, 3H), 7.44–7.49 (m, 2H), 7.59–7.62 (m, 1H), 7.73–7.77 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 46.95, 85.09, 116.67, 119.81, 121.28, 121.98 (2C), 124.49, 126.60, 128.25, 128.57, 128.61, 129.14 (2C), 129.33, 131.94, 132.40, 147.54, 148.77, 152.28; MS (ESI): 367 [M+H]$^+$; Anal. Calcd. for $C_{20}H_{15}ClN_2O_3$: C 65.49; H 4.12; N 7.64. Found: C 65.75; H 4.10; N 7.68.

3-(4-Chlorophenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1k). Yield 60%, m.p.: 135.9–137.6°C; IR (KBr): 3075, 3057, 2938, 2973, 2891, 2851, 1605, 1593, 1583, 1516, 1496, 1487, 1455, 1373, 1348, 1331, 1288, 1224, 1199, 1182, 1131, 1112, 1034, 1005, 963, 930, 902, 855, 830, 819, 800, 753, 743, 724, 711, 642, 624, 602, 559 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.24 (d, *J* = 17.0 Hz, 1H, CH_2), 4.34 (d, *J* = 1 7.0 Hz, 1H, CH_2), 6.56 (s, 1H, CH), 6.89–6.94 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.11–7.12 (m, 2H), 7.17–7.19 (m, 1H), 7.20–7.24 (m, 2H), 7.72–7.74 (m, 2H), 8.19–8.21 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 47.24, 87.23, 117.02, 119.61, 121.39, 121.90 (3C), 123.90 (2C), 126.66, 127.84, 127.90 (2C), 128.53, 129.29 (2C), 145.83, 147.78, 152.12; MS (EI, 70 ev) *m*/*z* (%): 366 (35) [M$^+$], 260 (100), 213 (17), 178 (4%), 138 (10), 111 (12), 78 (7), 51 (5); Anal. Calcd. for $C_{20}H_{15}ClN_2O_3$: C 65.49; H 4.12; N 7.64. Found: C 65.15; H 4.08; N 7.60.

2-(2-Nitrophenyl)-3-phenyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1l). Yield 66%, m.p.: 130.9–131.7°C; IR (KBr): 3023, 2948, 2860, 1598, 1585, 1535, 1496, 1486, 1455, 1396, 1365, 1273, 1223, 1136, 1110, 1036, 981, 957, 853, 783, 756, 735, 717, 694, 591 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.04 (d, *J* = 17.0 Hz, 1H, CH_2), 4.26 (d, *J* = 17.0 Hz, 1H, CH_2), 6.89 (s, 1H, CH), 6.92–6.94 (m, 1H), 6.96–7.03 (m, 2H), 7.11 (s, 1H), 7.16–7.23 (m, 3H), 7.25–7.28 (m, 2H), 7.46–7.49 (m, 2H), 7.63–7.65 (m, 1H), 7.75-–7.77 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 46.78, 85.24, 116.75, 120.36, 120.55 (3C), 121.20, 123.12, 124.50, 126.69, 128.47, 128.79, 129.26 (3C), 131.88, 132.87, 149.08, 152.50; MS(EI, 70 ev) *m*/*z* (%) = 332 (29) [M$^+$], 315 (22), 284 (4), 226 (10), 209 (72), 196 (12), 181 (12), 179 (28), 151 (19), 152 (36), 134 (7), 120 (6), 104 (20), 92 (23), 77 (100), 65 (9), 51 (41); Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C 72.28; H 4.85; N 8.43. Found: C 71.95; H 4.82; N 8.39.

2-(3-Nitrophenyl)-3-phenyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1m). Yield 61%, m.p.: 90.3–91.8°C; IR (KBr): 3030, 2962, 2875, 1605, 1502, 1488, 1456, 1398, 1364, 1252, 1227, 1138, 1127, 1085, 994, 957, 893, 783, 757, 735, 713, 694, 592 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.04(d, *J* = 17.0 Hz, 1H, CH_2), 4.26 (d, *J* = 17.0 Hz, 1H, CH_2), 6.62 (s, 1H, CH), 6.82–6.92 (m, 3H), 7.02–7.06 (m, 3H), 7.16–7.20 (m, 2H), 7.25–7.28 (m, 1H), 7.51–7.55 (m, 2H), 7.66–7.76 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 47.02, 87.23, 116.90, 120.45, 120.62 (3C), 121.41, 123.22, 125.00, 126.73, 128.51, 129.02, 129.28 (3C), 132.11, 132.90, 149.09, 152.78; MS (ESI): 333 [M+H]$^+$; Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C 72.28; H 4.85; N 8.43. Found: C 72.65; H 4.81; N 8.38.

3-(4-Methoxyphenyl)-2-(2-nitrophenyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1n). Yield 73%, m.p.: 165.-166.9°C; IR (KBr): 3076, 2968, 1607, 1579, 1531, 1509, 1488, 1456, 1388, 1364, 1299, 1270, 1242, 1225, 1199, 1145, 1108, 1034, 1022, 975, 960, 854, 830, 783, 758, 737, 685, 631, 589 cm^{-1}; ^{1}H-

NMR ($CDCl_3$, 500 MHz): δ 3.75 (s, 3H, OCH_3), 4.01 (d, J = 17.0 Hz, 1H, CH_2), 4.17(d, J = 17.0 Hz, 1H, CH_2), 6.77–6.79 (m, 2H), 6.87–6.92 (m, 2H), 6.94 (s, 1H, CH), 7.04 (d, J = 8.0 Hz, 1H), 7.09–7.11 (m, 2H), 7.21–7.25 (m, 1H), 7.46–7.48 (m, 2H), 7.64–7.66 (m, 1H), 7.75–7.76 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 47.48, 55.29, 85.96, 114.17 (2C), 116.59, 120.41, 121.06, 123.18 (2C), 124.28, 126.64, 128.27, 128.59, 129.06, 131.75, 132.77, 142.48, 148.95, 152.63, 155.92; MS (ESI): 363 $[M+H]^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 69.60; H 5.01; N 7.73. Found: C 69.31; H 4.98; N 7.69.

3-(4-Methoxyphenyl)-2-(3-nitrophenyl)-3,4-dihydro-2*H*-benzo[e][1,3]oxazine (1o). Yield 70%, m.p.: 103.2–106.1°C; IR (KBr): 3070, 3093, 2950, 2832, 1610, 1582, 1528, 1512, 1488, 1456, 1345, 1252, 1227, 1197, 1179, 1127, 1085, 1038, 994, 957, 893, 826, 783, 757, 735, 712, 694, 670 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.77 (s, 3H, OCH_3), 4.26 (d, J = 17.0 Hz, 1H, CH_2), 4.34 (d, J = 17.0 Hz, 1H, CH_2), 6.48 (s, 1H, CH), 6.81–6.83 (m, 2H), 6.90–6.91 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 7.16–7.18 (m, 2H), 7.20–7.23 (m, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.17–8.1 9(m, 1H), 8.49 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 47.99, 55.36, 88.17, 114.31(2C), 116.96, 120.10, 121.10, 122.22, 123.12, 123.34(2C), 126.60, 128.25, 129.54, 133.07, 141.41, 142.61, 148.50, 152.44, 155.77; MS(EI, 70 ev) m/z (%) = 362 (72) $[M^+]$, 345(17), 256(100), 239(38), 227(7), 209(11), 196(19), 183(8), 168(48), 152(10), 1D40(19), 135(30), 122(51), 106(25), 92(20), 77(41), 64(19); Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 69.60; H 5.01; N 7.73. Found: C 69.85; H 5.05; N 7.69.

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Facile Routes for the Preparation of 3,4-Disubstituted 1,3-Oxazolidines and 1,2,5-Trisubstituted Imidazolidin-4-ones

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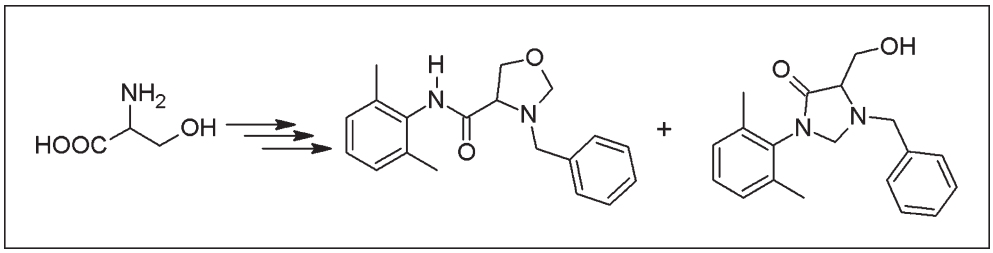

Facile, alternative synthetic routes to (*RS*)-, (*R*)-, and (*S*)-3-benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (**6**), a chiral oxazolidine derivative of tocainide, are reported. The synthetic routes described herein also afforded (*RS*)-, (*R*)-, and (*S*)-**11**, which present the imidazolidin-4-one core and belong to a class of compounds interesting for their biological activities. All the final compounds and intermediates were fully characterized. Enantiomeric excesses of homochiral **6** and **11** were determined by capillary electrophoresis analysis using 2-hydroxypropyl-β-cyclodextrin or highly sulfated γ-cyclodextrin as chiral selectors.

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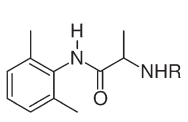
INTRODUCTION

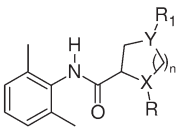
Tocainide, 2-amino-*N*-(2,6-dimethylphenyl)-propanamide (**1a**, Fig. 1), is a well-known sodium channel blocker belonging to class Ib antiarrhythmic drugs. It was once used in the treatment of symptomatic life-threatening ventricular arrhythmias [1,2]. It has also a marked analgesic effect in trigeminal neuralgia in humans [3,4] and antinociceptive effect in rats as well [5]. Finally, by virtue of its ability to block sodium channels in a use-dependent manner, that is, with an increased potency in conditions of high-frequency discharges of action potentials, tocainide has been proposed as a clinically useful antimyotonic drug [6]. In fact, myotonic syndromes are hereditary disorders of skeletal muscle due to genetic defects in sodium or chloride channels whose main result is an abnormal membrane hyperexcitability that triggers muscle stiffness. Due to the wide spectrum of pharmacological activity, the use of tocainide as antimyotonic is hindered by unwanted side effects [7]. A few years ago, a comprehensive model of the sodium channel was reported, showing that the increase in lipophilicity and molecular size of antiarrhythmic drugs can reinforce hydrophobic interactions with the binding site during use-dependent block [8,9]. Therefore, we started a program aimed at the development of new antimyotonic drugs, using tocainide as a lead compound. We found that potency and use-dependent behavior were found to be strongly increased by constraining the amino terminal group of **1a** in both a rigid α- and β-proline cycle (**2a** and **3a**). A further improvement was still achieved by introducing a benzyl moiety on the amino group of tocainide (**1b**) and proline-derived compounds (**2b** and **3b**) [10–12].

Thus, the preparation of the corresponding imidazolidine derivative **4**, which combines α-and β-proline features, may be envisaged. Nevertheless, it is commonly known that the imidazolidine ring is quite unstable; thus, we designed, synthesized, and tested on voltage-gated skeletal muscle sodium channels the corresponding piperazine analogue **5** [13]. This compound behaved as sodium channel blocker and was much more potent than tocainide both in tonic and phasic block experiments [13]. Herein, on the basis of isosteric relationships, we report the synthesis of the oxazolidine analogue **6**. It is noteworthy that, in the final step of the synthesis of **6,** we observed the formation of a new compound, deriving from a different intramolecular condensation reaction (see results and discussion), bearing an imidazolidin-4-one core (**11**). It is already known that imidazolidin-4-



1a (R = H, tocainide)

1b (R = Bn)



2a: n = 1, X = N, Y = CH, R = R_1 = H

2b: n = 1, X = N, Y = CH, R = Bn, R_1 = H

3a: n = 1, X = CH, Y = N, R = R_1 = H

3b: n = 1, X = CH, Y = N, R = H, R_1 = Bn

4: n = 1, X = Y = N, R = H, R_1 = Bn

5: n = 2, X = Y = N, R = H, R_1 = Bn

6: n = 1, X = N, Y = O, R = Bn

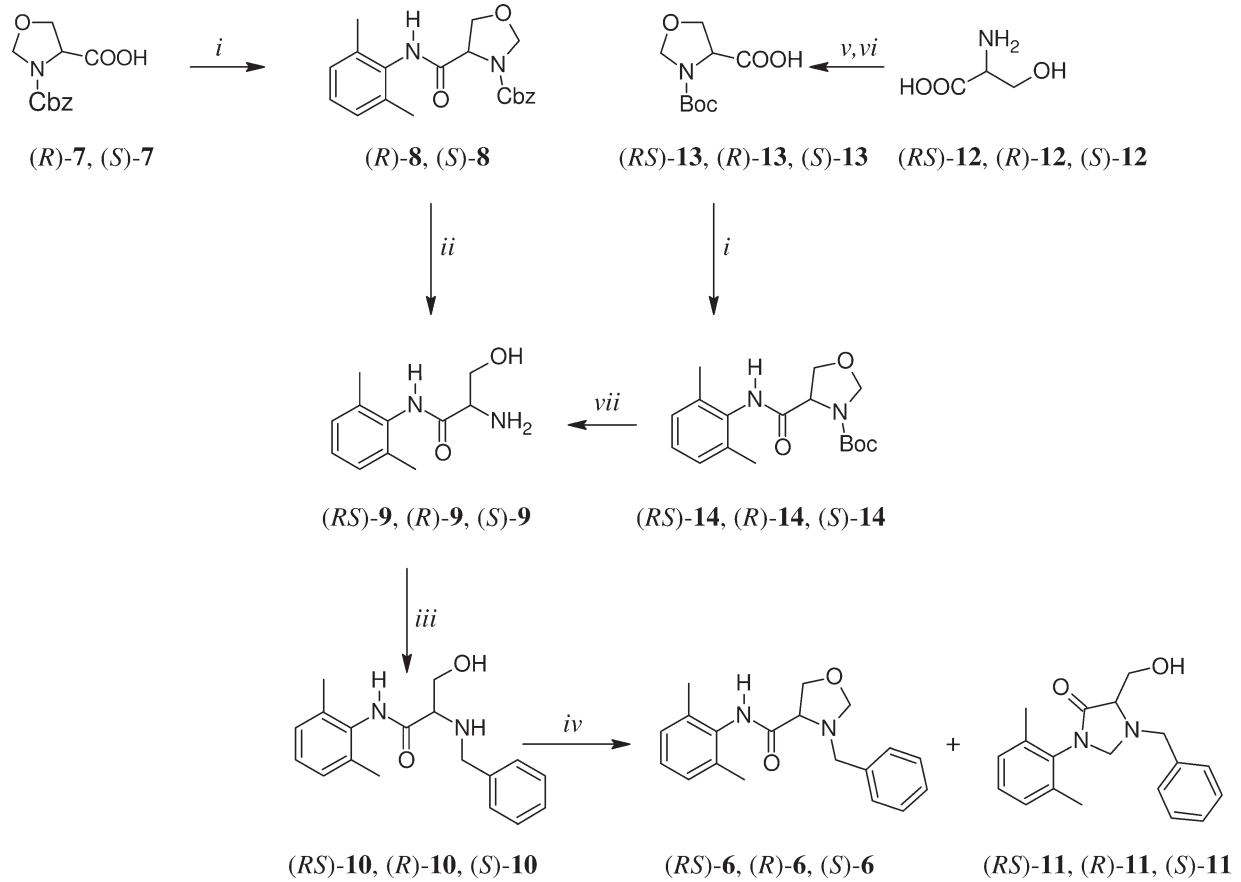
Figure 1. Structures of tocainide and its analogues.

ones represent an interesting class of compounds with respect to biological activity [14–16]. Through manipulation of the substituents around the imidazolidin-4-one core, molecules with a variety of biological properties have been discovered. Several examples include compounds that exhibit antibacterial activity [17,18]. Recently, imidazolidin-4-one was suggested as an attractive scaffold in the β-secretase (BACE-1) active site, a promising drug target for Alzheimer disease-modifying therapy [19,20]. The structural diversity of substituted imidazolidin-4-ones makes this compound class versatile for drug discovery research and necessitates the development of efficient and versatile syntheses of such molecules [21,22].

RESULTS AND DISCUSSION

The synthesis of (*R*)- and (*S*)-3-benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (**6**) was obtained by following two alternative routes (Scheme 1). The former starts from homochiral commercially available 3-(benzyloxycarbonyl)-4-oxazolidinecarboxylic acids (**7**), which were reacted with 2,6-dimethylaniline, in the presence of IIDQ (2-isobutoxy-1-isobutoxycarbonyl-1,2-diihydroquinoline) to give homochiral benzyl

Scheme 1. Synthesis of 3-benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (**6**) and 1-benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-ones (**11**). Reagents and conditions: (i) 2,6-dimethylaniline, IIDQ, Et_3N, $CHCl_3$, reflux, (ii) Et_3SiH, $PdCl_2$, Et_3N, CH_2Cl_2, reflux; (iii) benzyl bromide, K_2CO_3, dioxane/water, reflux; (iv) HCHO, 2*N* NaOH, dioxane, 0°C; (v) HCHO, 2*N* NaOH, 0°C; (vi) NH_2OH, HCl, aq. NaOH/acetone, Boc_2O, room temperature; (vii) conc HCl, EtOAc, room temperature.



(*R*)-**7**, (*S*)-**7**

(*R*)-**8**, (*S*)-**8**

(*RS*)-**13**, (*R*)-**13**, (*S*)-**13**

(*RS*)-**12**, (*R*)-**12**, (*S*)-**12**

(*RS*)-**9**, (*R*)-**9**, (*S*)-**9**

(*RS*)-**14**, (*R*)-**14**, (*S*)-**14**

(*RS*)-**10**, (*R*)-**10**, (*S*)-**10**

(*RS*)-**6**, (*R*)-**6**, (*S*)-**6**

(*RS*)-**11**, (*R*)-**11**, (*S*)-**11**

4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3-carboxylates (**8**) according to our previously reported procedure [13]. Deprotection of **8** with triethylsilane and palladium chloride [23] brought to the opening of the oxazolidine ring giving homochiral 2-amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamides (**9**), which were converted into their *N*-benzyl derivatives **10** by reaction with benzyl bromide. 1,3-Oxazolidine enantiomers **6** were then obtained by treatment of homochiral **10** with formaldehyde by modifying a literature procedure [24]. It is noteworthy that, in this reaction, a different intramolecular reaction also occurred resulting in the formation of the imidazolidin-4-one derivatives [1-benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-one] **11** along with compounds **6**. Compounds **6** and **11** possess the same molecular weight and retention times as assessed from GC-MS and LC-MS but differ in their physical properties (**6** and **11** being solid and oil, respectively) and have different R_f values by TLC, thus they were isolated by flash chromatography on silica gel. Ee values of **6** and **11** enantiomers were evaluated by capillary electrophoresis using 2-hydroxypropyl-β-cyclodextrin or highly sulfated γ-cyclodextrin as chiral selectors. Ee values were 98% and ≥99% for (*R*)- and (*S*)-**6**, respectively. It is noteworthy that, the intramolecular reaction that led to **11** occurred with a partial racemization, being ee values 80% and 86% for (*R*)- and (*S*)-**11**, respectively. The alternative route for the synthesis of homochiral **6** and **11** starts from homochiral D- and L-serine (**12**), which were easily converted into homochiral 3-(*tert*-butoxycarbonyl)-1,3-oxazolidine-4-carboxylic acids (**13**) following a procedure reported in the literature [25]. Compounds **13** underwent the same condensation reaction described above affording homochiral **14**. Deprotection of (*R*)- and (*S*)-**14** gave (*R*)- and (*S*)-**9**. The synthesis of racemic **6** and **11** was performed as above described for the enantiomers, starting from DL-serine, since racemic **7** is not commercial.

CONCLUSIONS

Alternative entries to (*RS*)-, (*R*)-, and (*S*)-**6**, a 2,6-oxazolidinylxylidide analogue of tocainide, have been proposed. The synthetic routes described herein brought also to the formation of a new imidazolidin-4-one derivative, 1-benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-one, in its racemic and homochiral forms [(*RS*)-, (*R*)-, and (*S*)-**11**]. The routes described herein also provided new hydroxyl derivatives (**9**,**10**) of tocainide (**1a**) and benzyltocainide (**1b**). The higher polarity of these compounds with respect to that of the parent compounds may be also useful to meet the need of thorough metabolic studies, considering that both tocainide (**1a**) and benzyltocainide (**1b**) act as potent voltage-gated sodium channel blockers [10–12]. All the final compounds and intermediates were fully characterized by routine spectroscopic analyses and enantiomeric excesses of **6** and **11** enantiomers were determined by capillary electrophoresis analysis using 2-hydroxypropyl-β-cyclodextrin or highly sulfated γ-cyclodextrin as chiral selectors. Pharmacological investigations on the newly synthesized compounds will be useful to better study the interaction of LA-like drugs with the binding site in voltage-gated sodium channels (for compounds **6**) and to analyze various potential biological properties (for the imidazolidin-4-one derivatives **11**), as above described and to explore their therapeutic potential usefulness.

EXPERIMENTAL

General. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Compounds **13** were prepared as previously described [25]. Melting points were determined on a Gallenkamp apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 300-MHz spectrometer (ASPECT 3000), operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR), and δ 77.3 (^{13}C NMR); DMSO-d_6, δ 2.50 (^1H NMR) and δ 40.2 (^{13}C NMR); CD_3OD, δ 3.30 (^1H NMR) and δ 47.8 (^{13}C NMR). *J* values are given in Hz. GC-MS was performed on a Hewlett–Packard 6890-5973 MSD at low resolution. LC-MS was performed on an Agilent 1100 series LC-MSD Trap System VL spectrometer. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer. GC was performed on a Varian 3800 gas chromatograph equipped with a flame ionization detector and a Jew Scientific DB-5 capillary column (30 m, 0.25 mm i. d., 0.25 μm film thickness). Electrophoretic runs were performed by CZE on a P/ACE™ MDQ Capillary Electrophoresis System (Beckman Coulter). A fused silica capillary of 60 cm (effective length 50 cm) and 0.05 mm i.d. (Quadrex Corp.) thermostated at 20°C was used as a separation tube. The samples (0.1 mg/mL) were pressure injected (0.5 psi/5 s) and detected at 214 nm. Phosphate buffer, in the presence of 2-hydroxypropyl-β-cyclodextrin or highly sulfated γ-cyclodextrin as chiral selectors, was used as background electrolyte. Optical rotations were measured on a Perkin–Elmer (Norwalk, CT) Mod 341 spectropolarimeter. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck, Darmstadt, Germany) as described by Still et al. [26]. TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F_{254}, Merck, Darmstadt, Germany).

(+)-(*R*)-Benzyl-4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3-carboxylate [(*R*)-8]. IIDQ (0.42 mL, 1.4 mmol), 2,6-dimethylaniline (0.16 mL, 1.3 mmol), and Et_3N (0.25 mL, 1.8 mmol) were added successively to a stirred solution of (*R*)-**7** (0.30 g, 1.2 mmol) in $CHCl_3$ (37 mL). The mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the residue was taken up with EtOAc. The organic layer was washed three times with a solution of 2*N* HCl and twice with a solution of 2*N* NaOH, and then dried over anhydrous Na_2SO_4. The evaporation of the solvent under reduced pressure gave 0.25 g (62%) of a white solid, which was recrystallized from $CHCl_3$/hexane to give 0.17 g (40%) of white crystals: mp 170–172°C; $[\alpha]_D^{20} = +111$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1710 (C=O) cm^{-1}; ^1H NMR δ 2.12 (s, 6H, C*H*$_3$), 4.21 (br t, *J* = 8.0 Hz, 1H, OC*H*H), 4.41 (br s, 1H, OCH*H*), 4.56–4.64 (m, 1H, C*H*), 4.94–5.04 (m, 1H, OC*H*HN), 5.06–5.14 (m, 1H, OCH*H*N), 5.21 (s, 2H, C*H*$_2$-Ph), 7.00–7.16 (m, 3H, Ar), 7.28–7.42 (m, 5H, Ar), 7.79 ppm (br s, 1H, N*H*); ^{13}C NMR δ 18.4 (2C), 59.1 (1C), 68.4 (1C), 70.8 (1C), 80.1 (1C), 127.8 (3C), 128.4 (3C), 128.6 (2C), 128.9 (2C), 133.1 (1C), 135.6 (1C), 154.8 (1C), 168.4 ppm (1C); GC-MS MS (70 eV, electron impact) *m*/*z* (%) 354 (M^+, 18), 91 (100). Anal. Calcd for ($C_{20}H_{22}N_2O_4$): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.53; H, 6.20; N, 7.88.

(−)-(*S*)-Benzyl-4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3-carboxylate [(*S*)-8]. Prepared as reported above for (*R*)-**8**. White crystals, 64% yield: mp 172–173°C ($CHCl_3$/hexane); $[\alpha]_D^{20} = -105$ (*c* 1.9, $CHCl_3$). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

***(RS)*-2-Amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*RS*)-9].** To a stirred solution of (*RS*)-**14** (3.50 g, 10.9 mmol) in EtOAc (120 mL), 37% HCl (28 mL) was added. The reaction mixture was kept at room temperature for 1 h, then the solvent was evaporated and the water was azeotropically removed giving the hydrochloride salt as a white solid [(*RS*)-**9**, HCl], which was recrystallized from MeOH/Et_2O to give 2.15 g (86%) as white crystals. (*RS*)-**9**, as free amine (white solid), was recovered by extraction of a sample of the corresponding hydrochloride salt.

***(RS)*-9.** IR (KBr): 3253 (NH + OH), 1657 (C=O) cm^{-1}; ^1H NMR δ 2.0–2.30 (m overlapping s at 2.22, exch D_2O, 3H, NH_2 + OH), 2.22 (s overlapping m at 2.0–2.30, 6H, C*H*$_3$), 3.64 (t, *J* = 5.1 Hz, 1H, C*H*), 3.79 (dd, *J* = 10.7, 5.5 Hz, 1H, C*H*H), 4.01 (dd, *J* = 10.7, 5.0 Hz, 1H, CH*H*), 7.0–7.2 (m, 3H, Ar), 8.92 ppm (br s, exch D_2O, 1H, N*H*CO).

***(RS)*-9·HCl.** Melting point 244–245°C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 2.14 (s, 6H, C*H*$_3$), 3.91 (br s, 2H, C*H*$_2$), 4.09 (br s, 1H, C*H*), 5.60 (br s, exch D_2O, 1H, O*H*), 6.95–7.15 (m, 3H, Ar), 8.28 (br s, exch D_2O, 2H, N*H*$_2$), 9.94 ppm (br s, exch D_2O, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 18.2 (2C), 59.0 (1C), 59.8 (1C), 129.1 (2C), 129.7 (1C), 132.5 (1C), 137.5 (2C), 166.5 ppm (1C). Anal. Calcd for $C_{11}H_{16}N_2O_2$·HCl (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 54.16; H, 6.81; N, 11.52.

***(R)*-2-Amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*R*)-9]**

Method A. A suspension of (*R*)-**14** (92 mg, 0.26 mmol), triethylsilane (0.17 mL, 1.04 mmol), triethylamine (25 μL, 0.18 mmol), and $PdCl_2$ (13.8 mg, 0.078 mmol) in dichloromethane (1 mL) was heated at reflux for 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ether several times. The combined organic phases were washed with water and then brine, dried, and concentrated *in vacuo* to give 22 mg (38%) of a white solid.

Method B. Prepared in 60% yield as reported above for (*RS*)-**9**.

*(+)(R)-**9**.* $[\alpha]_D^{20} = +22.3$ (*c* 2, MeOH); IR (KBr): 3253 (NH + OH), 1657 (C=O) cm^{-1}; ^1H NMR δ 2.10–2.30 (m overlapping s at 2.22, exch D_2O, 3H, NH_2 + OH), 2.22 (s overlapping m at 2.10–2.30, 6H, C*H*$_3$), 3.65 (t, *J* = 5.1 Hz, 1H, C*H*), 3.79 (dd, *J* = 10.7, 5.2 Hz, 1H, C*H*H), 4.02 (dd, *J* = 10.7, 5.0 Hz, 1H, CH*H*), 7.0–7.15 (m, 3H, Ar), 8.92 ppm (br s, exch D_2O, 1H, N*H*CO).

*(−)(R)-**9** HCL.* $[\alpha]_D^{20} = -34.9$ (*c* 2, MeOH); mp > 250°C (MeOH/Et_2O); ^1H NMR (CD_3OD) δ 2.23 (s, 6H, C*H*$_3$), 6.45 (dd, *J* = 11.4, 6.5, 1H, C*H*), 4.16 (dd, *J* = 11.4, 4.3 Hz, 1H, C*H*H), 4.26 (dd, *J* = 6.6, 4.1 Hz, 1H, CH*H*), 7.05–7.15 ppm (m, 3H, Ar); ^{13}C NMR (CD_3OD) δ 17.3 (2C), 55.2 (1C), 60.8 (1C), 127.6 (3C), 128.0 (2C), 135.7 (1C), 166.0 ppm (1C). Anal. Calcd for $C_{11}H_{16}N_2O_2$·HCl·1.33H_2O (268.72): C, 49.16; H, 7.38; N, 10.42. Found: C, 49.54; H, 7.66; N, 10.73.

***(S)*-2-Amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*S*)-9].** Prepared in 40% (*Method A*) and 86% (*Method B*) as above reported for (*R*)-**9**.

*(−)-(S)-**9**.* $[\alpha]_D^{20} = -24.3$ (*c* 2, MeOH). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

*(+)-(S)-**9**·HCl.* $[\alpha]_D^{20} = +33.5$ (*c* 2, MeOH); mp > 250°C (MeOH/Et_2O). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer. Anal. Calcd for $C_{11}H_{16}N_2O_2$·HCl (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 53.65; H, 7.02; N, 11.49.

***(RS)*-2-(Benzylamino)-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*RS*)-10].** To a stirring solution of (*RS*)-**9** (0.90 g, 4.44 mmol) in dioxane (50 mL), a solution of K_2CO_3 (1.75 g, 12.6 mmol) in H_2O (50 mL) was added. The reaction mixture was heated to 70°C, and then a solution of benzyl bromide (0.83 g, 0.58 mL, 4.88 mmol) in dioxane (15 mL) was added dropwise. The heating was continued for 45 min. Then, dioxane was removed under reduced pressure and the aqueous residue was taken up with EtOAc and extracted twice with 2*N* HCl. The aqueous phase was made alkaline with 2*N* NaOH and extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 0.50 g (38% yield) of (*RS*)-**10** as a white solid.

***(RS)*-10.** mp 119–120°C; IR (KBr): 3272 (NH + OH), 1664 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.13 (s, 6H, C*H*$_3$), 3.26 (t, *J* = 5.6 Hz, 1H, C*H*), 3.35 (br s, 1H, N*H*), 3.50–3.75 (m overlapping 2d at 7.39, 2H, C*H*$_2$OH), 3.79 (2d overlapping m at 3.50–3.75, *J* = 13.2 Hz, 2H, benzylic protons), 4.91 (br s, exch D_2O, 1H, O*H*), 7.00–7.10 (m, 3H, Ar), 7.18–7.45 (m, 5H, Ar), 9.32 ppm (br s, exch D_2O, 1H, N*H*CO); GC-MS (70 eV, electron impact) *m*/*z* (%) 298 (M^+, <1), 91 (100).

(+)-(R)-2-(Benzylamino)-N-(2,6-dimethylphenyl)-3-hydroxypropanamide [(R)-10]. Prepared in 30% yield as reported above for (*RS*)-**10**. White solid, $[\alpha]_D^{20} = +38.8$ (*c* 1.2, MeOH); mp 119–120°C; IR (KBr): 3275 (NH + OH), 1663 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.13 (s, 6H, C*H*$_3$), 2.55 (br s, 1H, exch D_2O, N*H*), 3.26 (t, *J* = 5.6 Hz, 1H, C*H*), 3.62 (q overlapping d, *J* = 5.7 Hz, 2H, C*H*$_2$OH), 3.78 (2d, *J* = 13.5

Hz, 2H, benzylic protons), 4.90 (br t, exch D_2O, 1H, O*H*), 6.95–7.10 (m, 3H, Ar), 7.20–7.42 (m, 5H, Ar), 9.31 ppm (br s, exch D_2O, 1H, N*H*CO).

***(−)-(S)*-2-(Benzylamino)-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*S*)-10].** Prepared in 32% yield as reported above for (*RS*)-**10**. White solid, $[\alpha]_D^{20} = -30.6$ (*c* 1, MeOH); mp 119–120°C. All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

***(RS)*-3-Benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamide [(*RS*)-6].** To a stirred suspension of (*RS*)-**10** (0.30 g, 1 mmol) in a mixture of dioxane (7 mL) and 2*N* NaOH (11.5 mL) at 0°C, a solution of aqueous formaldehyde 37% (6.9 mL) was added. Then, the dioxane was removed under reduced pressure and the aqueous residue was extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash chromatography (EtOAc/petroleum ether 7:3) gave (*RS*)-**6** as white needles, which were recrystallized from EtOAc/petroleum ether to give 48 mg (23%) of white crystals: mp 145–147°C; IR (KBr): 3240 (NH), 1665 (C=O) cm^{-1}; ^1H NMR δ 2.10 (s, 6H, CH_3), 3.79 (dd, *J* = 8.2, 5.0 Hz, 1H, C*H*HCH), 3.94 (d, *J* = 7.7 Hz, 2H, benzylic protons), 3.97–4.06 (m, 1H, CH*H*CH), 4.34 (t, *J* = 8.5 Hz, 1H, C*H*), 4.44 (d, *J* = 6.0 Hz, 1H, NC*H*HO), 4.57 (d, *J* = 6.0 Hz, 1H, NCH*H*O), 7.0–7.15 (m, 3H, Ar), 7.25–7.45 (m, 5H, Ar), 8.79 ppm (br s, 1H, N*H*); GC-MS (70 eV) *m*/*z* (%) 310 (M^+, <1), 91 (100); LC-MS *m*/*z* (%): 311 ($M^+ + H$). Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.51; H, 7.11; N, 8.98.

***(+)-(R)*-3-Benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamide [(*R*)-6].** Prepared in 22% yield as reported above for (*RS*)-**6**. White crystals: $[\alpha]_D^{20} = +1.1$ (*c* 1.5, $CHCl_3$); 98% ee (capillary electrophoresis, BGE: phosphate buffer 0.050*M* at pH 3.5; chiral selector: 2-hydroxypropyl-β-cyclodextrin (40 mg/mL); voltage: 20 kV); mp 182–183°C; ^1H NMR δ 2.11 (s, 6H, CH_3), 3.79 (dd, *J* = 8.5, 5.0 Hz, 1H, C*H*HCH), 3.94 (d, *J* = 7.7 Hz, 2H, benzylic protons), 3.98–4.06 (m, 1H, CH*H*CH), 4.34 (t, *J* = 8.5 Hz, 1H, C*H*), 4.45 (d, *J* = 6.0 Hz, 1H, NC*H*HO), 4.57 (d, *J* = 6.0 Hz, 1H, NCH*H*O), 7.02–7.15 (m, 3H, Ar), 7.25–7.45 (m, 5H, Ar), 8.79 ppm (br s, 1H, N*H*); GC-MS (70 eV, electron impact) *m*/*z* (%) 310 (M^+, <1), 91 (100). Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.20; H, 7.27; N, 8.99.

***(−)-(S)*-3-Benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamide [(*S*)-6].** Prepared in 22% yield as reported above for (*RS*)-**6**. White crystals: $[\alpha]_D^{20} = -1.5$ (*c* 2, $CHCl_3$); ≥99% ee (capillary electrophoresis using the conditions described for the *R*-enantiomer); mp 144–147°C. All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer. Anal. Calcd for $C_{19}H_{22}N_2O_2 \cdot 0.25\ H_2O$ (314.89): C, 72.47; H, 7.20; N, 8.90. Found: C, 72.80; H, 7.02; N, 8.98.

***(RS)*-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(*RS*)-11].** It was obtained in 21% yield in mixture with (*RS*)-**6**. Slightly yellowish oil; IR (neat): 3429 (OH), 1700 (C=O) cm^{-1}; ^1H NMR δ 2.19 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.92 (br s, exch. D_2O, 1H, O*H*), 3.50–3.56 (m, 1H, C*H*), 3.76 (d overlapping d at 3.78, *J* = 12.9 Hz, 1H, C*H*HPh), 3.78 (d overlapping d at 3.76, *J* = 11.0 Hz, 1H, C*H*HCH), 3.98 (br d, *J* = 11.0 Hz, 1H, CH*H*CH), 4.13 (d overlapping dd at 4.17, *J* = 12.9 Hz, 1H, CH*H*Ph), 4.17 (dd overlapping d at 4.13, *J* = 5.5, 1.9 Hz, 1H, NC*H*HN), 4.31 (dd, *J* = 5.5, 1.4 Hz, 1H, NCH*H*N), 7.02–7.18 (m, 3H, Ar), 7.26–7.38 ppm (m, 5H, Ar); GC-MS (70 eV, electron impact) *m*/*z* (%) 310 (M^+, <1), 91 (100); LC-MS *m*/*z* (%): 311 ($M^+ + H$).

***(−)-(R)*-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(*R*)-11].** It was obtained in 43% yield in mixture with (*R*)-**6**. Slightly yellowish oil; $[\alpha]_D^{20} = -30.9$ (*c* 1, $CHCl_3$); 80% ee (capillary electrophoresis, BGE: phosphate buffer 0.025*M* at pH 5.9; chiral selector: highly sulfated γ-cyclodextrin (24 mg/mL); voltage: 10 kV); IR (neat): 3421 (OH), 1699 (C=O) cm^{-1}; ^1H NMR δ 2.21 (apparent d, 6H, CH_3), 2.92 (br d, *J* = 9.6 Hz, exch. D_2O, 1H, O*H*), 3.50–3.56 (m, 1H, C*H*), 3.76 (d overlapping d at 3.78, *J* = 12.9 Hz, 1H, C*H*HPh), 3.78 (d overlapping d at 3.76, *J* = 11.0 Hz, 1H, C*H*HCH), 3.92–4.06 (m, 1H, CH*H*CH), 4.13 (d overlapping dd at 4.17, *J* = 12.9 Hz, 1H, CH*H*Ph), 4.17 (dd overlapping d at 4.13, *J* = 5.5, 1.9 Hz, 1H, NC*H*HN), 4.31 (dd, *J* = 5.5, 1.4 Hz, 1H, NCH*H*N), 7.02–7.18 (m, 3H, Ar), 7.24–7.38 ppm (m, 5H, Ar); GC-MS (70 eV, electron impact) *m*/*z* (%) 310 (M^+, <1); LC-MS *m*/*z* (%): 311 ($M^+ + H$).

***(+)-(S)*-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(*S*)-11].** It was obtained in 41% yield in mixture with (*RS*)-**6**. Slightly yellowish oil; $[\alpha]_D^{20} = +33.8$ (*c* 1.9, $CHCl_3$). 86% ee (capillary electrophoresis using the conditions described for the *R*-enantiomer). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

***(RS)*-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate [(*RS*)-14].** Prepared in 72% yield as reported above for (*R*)-**8**. White crystals: mp 158–159°C (EtOAc/EP); IR (KBr): 3224 (NH), 1654, 1710 (C=O) cm^{-1}; ^1H NMR δ 1.51 (s, 9H, *t*-Bu), 2.22 (s, 6H, CH_3), 4.21 (apparent t, 1H, C*H*HO), 4.41 (br s, 1H, C*H*), 4.48–4.60 (m, 1H, CH*H*O), 4.84–4.94 (br s, 1H, C*H*HN), 4.98–5.08 (m, 1H, CH*H*N), 7.02–7.17 (m, 3H, Ar), 7.99 ppm (br s, 1H, N*H*); ^{13}C NMR δ 18.5 (2C), 28.5 (3C), 58.8 (1C), 70.7 (1C), 80.1 (1C), 82.5 (1C), 127.7 (2C), 128.4 (1C), 133.3 (2C), 135.6 (1C), 154.3 (1C), 168.8 ppm (1C); GC-MS (70 eV, electron impact) *m*/*z* (%) 320 (M^+, 7), 57 (100).

(+)-(*R*)-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate [(*R*)-14]. Prepared in 66% yield as reported above for (*R*)-**8**. White crystals: $[\alpha]_D^{20} = +111.3$ (*c* 2, $CHCl_3$); mp 170–171°C (EtOAc/EP). IR (KBr): 3204 (NH), 1658, 1712 (C=O) cm^{-1}; ^1H NMR δ 1.52 (s, 9H, *t*-Bu), 2.22 (s, 6H, CH_3), 4.21 (apparent t, 1H, C*H*HO), 4.41 (br s, 1H, C*H*), 4.48–4.60 (m, 1H, CH*H*O), 4.82–4.94 (m, 1H, C*H*HN), 4.98–5.10 (m, 1H, CH*H*N), 7.02–7.16 (m, 3H, Ar), 7.92 ppm (br s, 1H, N*H*); ^{13}C NMR δ 18.5 (2C), 28.5 (3C), 58.8 (1C), 70.6 (1C), 80.1 (1C), 82.4 (1C), 127.7 (2C), 128.4 (1C), 133.4 (2C), 135.6 (1C), 154.2 (1C), 168.8 ppm (1C); GC-MS (70 eV, electron impact) *m*/*z* (%) 320 (M^+, 4), 57 (100).

(−)-(*S*)-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate [(*S*)-14]. Prepared in 46% yield as reported above for (*R*)-**8**. White crystals: $[\alpha]_D^{20} = -111.2$ (*c* 2, $CHCl_3$); mp 173–174°C (EtOAc/EP). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

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Triton B Catalyzed Three-Component, One-Pot Synthesis of 2-Amino-2-chromenes at Ambient Temperature

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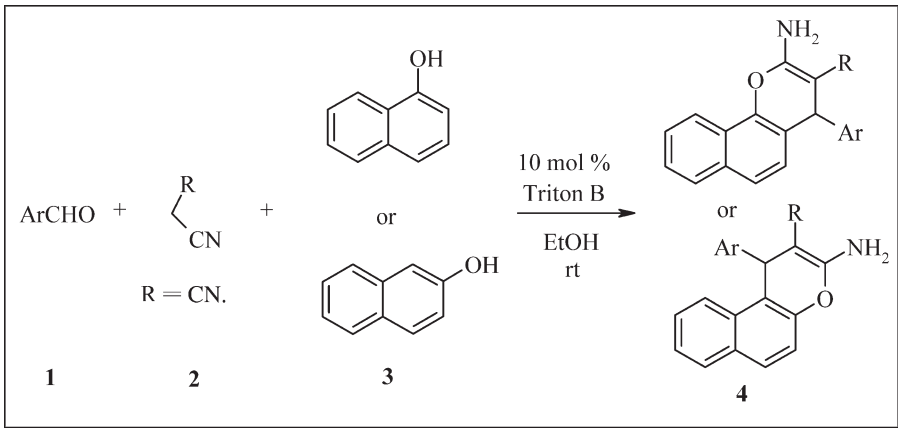

A one-pot, three-component synthesis of 2-amino-2-chromenes is described at ambient temperature by the reaction of an aldehyde and malononitrile or ethyl cyanoacetate with α-naphthol or β-naphthol in ethanol in presence of a catalytic amount of Triton B.

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INTRODUCTION

Multicomponent reactions are gaining importance both in academia and industry [1–4] due to their atom economy, simple procedure, selectivity, time and energy saving as well as environmental friendliness. 2-amino-chromenes are widely employed as pigments [5], cosmetics, and potential biodegradable agrochemicals [6] and represent an important class of compounds being the main components of many natural products. These compounds have been of interest to the medicinal chemist for many years [7]. Fused chromenes are biologically active compounds with a wide spectrum of activities such as antimicrobial [8a], mutagenicitical [8b], antiviral [9,10] antiproliferative [11] sex pheromonal [12], antitumora [13], and central nervous system activities [14]. The most straight forward synthesis of this heterocyclic nucleus involves the multicomponent reactions of an aldehyde, malononitrile and an activated phenol in the presence of piperidine [15] using acetonitrile or ethanol as solvent. Several methods with modified procedures have been reported [16] but, most of the reported methods require prolonged reaction times at reflux temperature, reagents in stoichiometric amounts, works only with α-naphthol, and generate moderate yields of the product. Therefore there is a still demand for the development of an effective catalyst for the synthesis of 2-aminochromenes, which equally works with α-and β-naphthol.

Initially we tried the reaction of aromatic aldehyde with malononitrile and α-naphthol using proline as a catalyst in aq. ethanol, but trace amounts of the product was isolated at reflux temperature. Then we screened other catalysts such as $CeCl_3.7H_2O/NaI$, PMA/SiO_2, which were failed to give the desired products.

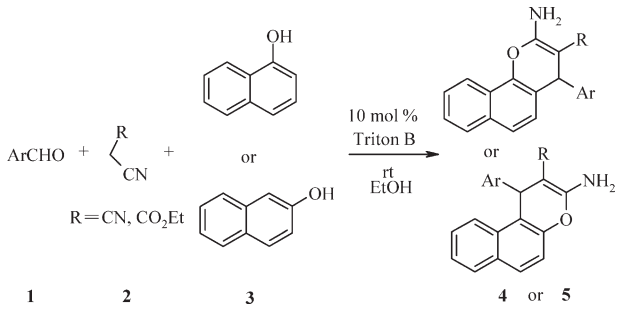
Benzyltrimethylammonium hydroxide (Triton B) has been used in the preparation of dithiocarbamates using alcoholic tosylates [17], dihydroxy-dithioethers [18] and in alkylation of mono Michael products [19].

RESULTS AND DISCUSSION

When *p*-nitro benzaldehyde **1b**, ethyl cyanoacetate **2**, α-naphthol **3**, and 10 mol % Triton B were added together and stirred at ambient temperature in EtOH, the reaction proceeded rapidly and was complete within 1 h to give the corresponding product **4b** in 92% yield (Scheme 1).

The structure of the product was confirmed by spectral data and compared with the authentic sample. To study the generality of this method the optimized

Scheme 1



procedure was used for the synthesis of a variety of 2-amino-2-chromenes. Aromatic aldehydes having electron-withdrawing groups reacted fast with malononitrile and α-naphthol giving high yields of products when compared to aldehydes containing electron-donating groups. It should be noted that under similar conditions, ethyl cyanoacetate also found to give better yields (Table 1, entries a-e). Encouraged by these results, we carried out the reaction of aromatic aldehyde and malononitrile with β-naphthol, which was found to react equally as α-naphthol giving high yields of products. The results of the study are shown in Table 2. The structures of all compounds were confirmed by IR, ^{1}H NMR and mass spectroscopy. The ^{1}H NMR of **4** displayed a singlet at δ 5.20 (H-4) and a broad singlet due to —NH_2 at δ 6.40 (D_2O exchangeable). Signals at δ 40 (C-4) and at 160 (C-2) in the ^{13}C NMR spectrum confirmed the formation of the product.

The change in mol% of Triton B did not much alter the yield of product. Also, when the reaction was run in EtOH/H_2O mixture, at room temperature the intermediate was isolated and at 100°C a 30% yield of the product formation was observed. The present reaction was studied with other catalysts such as ammonium molybdate and amberlite 400. The reaction using ammonium molybdate as catalyst in different media gives low yields of products and requires longer reaction time. However using amberlite 400, the reaction does not proceed at r. t., but gives low yield of product at higher temperature and results are shown in Table 3.

Mechanism of the reaction. As the mechanism for the formation of the product is well known that it represents a cascade reaction in which the benzylidene malononitrile is produced by Knoevenagel condensation of malononitrile to the aromatic aldehyde by loss of water. The second step requires a catalyst which involves the phenol ortho C-alkylation by reaction with the electrophilic C=C double bond and the nucleophilic addition of the phenolic OH group on the CN moiety [16l].

In conclusion, we have developed a highly efficient reaction protocol at room temperature for the synthesis of a variety of 2-amino-2-chromenes via Triton B catalyzed three component coupling of α- or β-naphthol, aromatic aldehyde and malononitrile or ethyl cyanoacetate.

EXPERIMENTAL

All reactions were monitored by thin layer chromatography (TLC) using silica-coated plates. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator. ^{1}H NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) in $CDCl_3$. Chemical shift values were reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on LC-MSD (Agilent Technologies). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical, India. Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates.

General procedure. A mixture of aldehyde (1.0 mmol), ethyl cyanoacetate /malononitrile (1.0 mmol) and α-naphthol/ β-naphthol (1.0 mmol) and Triton B (10 mol %) stirred in EtOH at room temperature for specified time (tables). Precipitated solid was filtered and recrystallized from MeOH.

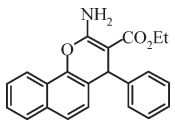
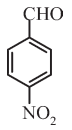
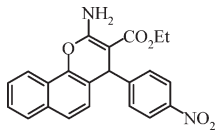
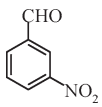
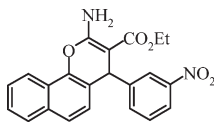
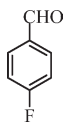
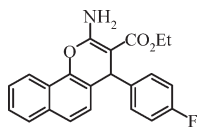
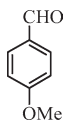
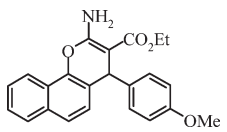
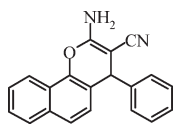
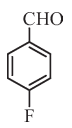
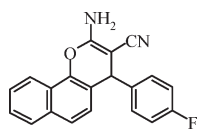
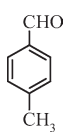
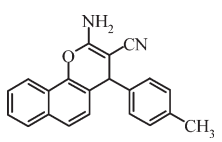
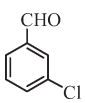
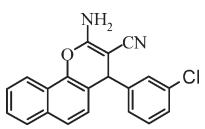
Spectral data. ***Ethyl 2-amino-4-(3-nitrophenyl)-4H-benzo[h]chromene-3-arboxylate (4c).*** Yellow solid, mp: 198–200°C; IR (KBr): 3416.0, 3289.9, 3084.4, 2924.3, 2854.7, 1672.4, 1603.6 and 1522.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.26-8.22 (m, 2H, Ar-**H**), 8.03 (dd, J = 8.3, 2.2 Hz, 1H, Ar-**H**), 7.78 (d, J = 8.3 Hz, 1H, Ar-**H**), 7.61-7.48 (m, 4H, Ar-**H**), 7.38 (t, J = 8.3 Hz, 1H, Ar-**H**), 7.09 (d, J = 8.3 Hz, 1H, Ar-**H**), 6.52 (brs, 2H, -N**H**$_2$), 5.20 (s, 1H, -C**H**-), 4.12 (m, 2H, -OC**H**$_2$-), 1.23 (t, J = 6.8 Hz, 3H, -C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100MHz) δ: 168.8, 159.9, 149.5, 147.9, 143.3, 134.2, 133.1, 129.0, 127.6, 126.6, 126.5, 126.1, 124.4, 123.2, 122.9, 121.3, 120.8, 118.9, 78.1, 59.7, 40.8, 14.4.; ESMS m/z: 413.0; HRMS m/z calc.: 413.1113; found: 413.1099 (M^++Na).

Ethyl 2-amino-4-(4-fluorophenyl)-4H-benzo[h]chromene-3-carboxylate (4d). Pale yellow solid, mp: 206–208°C.; IR (KBr): 3385.5, 3288.7, 3050.8, 2980.3, 2904.9, 1671.3, 1603.1 and 1505.1 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.17 (d, J = 8.0 Hz, 1H, Ar-**H**), 7.72 (dd, J = 7.3, 2.2 Hz, 1H, Ar-**H**), 7.55-7.39 (m, 3H, Ar-**H**), 7.24-7.14 (m, 2H, Ar-**H**), 7.07 (d, J = 8.8 Hz, 1H, Ar-**H**), 6.86 (t, J = 8.8 Hz, 2H, Ar-**H**), 6.45 (brs, 2H, -N**H**$_2$), 5.00 (s, 1H, -C**H**-), 4.08 (dq, J = 6.6, 2.2 Hz, 2H, -OC**H**$_2$-), 1.18 (t, J = 6.6 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 162.9, 159.9, 159.6, 143.4, 143.3, 143.1, 132.9, 129.4, 129.3, 127.6, 126.5, 126.3, 124.1, 123.3, 120.7, 120.4, 115.0, 114.7, 79.0, 59.5, 40.1, 14.3.; ESMS m/z: 386.0; HRMS m/z calc.: 386.1168; found: 386.1172 (M^++Na).

Ethyl 3-amino-1-phenyl-1H-benzo[f]chromene-2-carboxylate (5a). Pale yellow solid, mp: 166–168°C.; IR (KBr): 3402.3, 3295.5, 3052.9, 2991.8, 2963.2, 1671.5 and 1616.7 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 200MHz) δ: 7.98 (d, J = 8.0 Hz, 1H, Ar-**H**), 7.76-7.67 (m, 2H, Ar-**H**), 7.46-6.98 (m, 8H, Ar-**H**), 6.30 (brs, 2H, -N**H**$_2$), 5.53 (s, 1H, -C**H**-), 4.30-4.12 (m, 2H, -OC**H**$_2$-), 1.37 (t, J = 7.3 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 169.1, 160.0, 159.9, 147.1, 146.4, 131.1, 131.0, 128.6, 128.3, 128.0, 127.9, 126.8, 126.1, 124.6, 123.5, 119.2, 119.1, 116.6, 80.3, 59.6, 37.1, 14.5.; ESMS m/z: 368.0; HRMS m/z calc.: 368.1262; found: 368.1260 (M^++Na).

Table 1

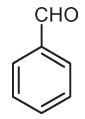
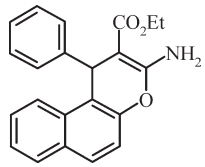
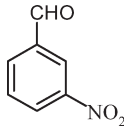
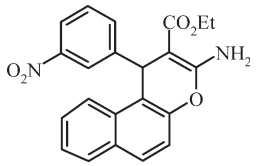
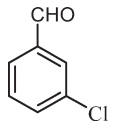
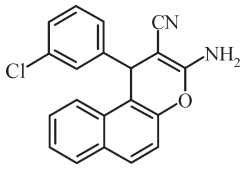
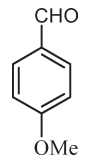
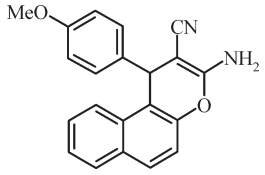
Triton B catalyzed synthesis of 2-amino-2-chromenes.[a,b,c]

Entry	Aldehyde **3**	*R*	Product **4**	Time (h)	Yield (%)
a		CO_2Et		1.50	88
b		CO_2Et		1.00	92
c		CO_2Et		1.00	92
d		CO_2Et		1.25	90
e		CO_2Et		3.00	80
f		CN		1.25	87[16c]
g		CN		1.00	90[16j]
h		CN		3.00	80[16j]
i		CN		1.25	90[16l]

[a] New products were characterized by IR, ^1H NMR, ^{13}C and mass spectral data.
[b] Known products were compared with authentic samples.
[c] Isolated pure products.

Table 2

Triton B catalyzed synthesis of 2-amino-2-chromenes.[a,b,c]

Entry	Aldehyde **3**	*R*	Product **5**	Time (h)	Yield (%)
a		CO_2Et		1.50	87
b		CO_2Et		1.00	92
c		CN		1.00	90
d		CN		3.00	80[16d]

[a] New products were characterized by IR, ^1H NMR, ^{13}C and mass spectral data.
[b] Known compounds were compared with authentic samples.
[c] Isolated pure products.

Table 3

Comparsion of various catalysts at various temperature.

Entry	Catalyst	Solvent	Temp.	Time (h)	Yield (%)
a	Triton B(10 mol%)	EtOH	r. t.	1.0	92
b	”	EtOH:H_2O (1:1)	r. t.	6.0	–[b]
c	”	”	100°C	3.0	30
d	$(NH_4)_2MoO_4$(10 mol %)	EtOH	r. t.	3.0	85
e	”	EtOH:H_2O (1:1)	r. t.	6.0	–[a]
f	”	”[b]	100°C	0.5	88
g	”	H_2O[b]	”	3.0	62
h	”	”	r. t.	12.0	–[a]
i	”	DMF	”	12.0	10
j	”	”	100°C	3.0	30
k	”	PEG 400	”	2.0	74
l	”	”	r. t.	6.0	35
m	Amberlite 400 (10 mol %)	EtOH	”	6.0	–[a]
n	”	”	100°C	3.0	68

[a] Intermediate was formed.
[b] Catalytic amount of TBAI was used.

Ethyl 3-amino-1-(3-nitrophenyl)-1H-benzo[f]chromene-2-carboxylate (5b). Yellow solid, mp: 188–190°C.; IR (KBr): 3463.0, 3312.7, 3072.7, 2976.6, 2930.0, 1675.7, 1595.5 and 1523.4 cm-^{1}.; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.28 (s, 1H, Ar-**H**), 7.94 (dd, J = 8.3, 1.5 Hz, 1H, Ar-**H**), 7.85 (d, J = 8.3 Hz, 1H, Ar-**H**), 7.76 (d, J = 9.0 Hz, 2H, Ar-**H**), 7.48-7.24 (m, 5H, Ar-**H**), 6.37 (brs, 2H, -N**H**$_2$), 5.66 (s, 1H, -C**H**-), 4.30-4.14 (m, 2H, -OC**H**$_2$-), 1.40 (t, J = 7.5 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 168.2, 159.9, 148.4, 147.9, 147.0, 134.2, 131.2, 130.5, 129.4, 129.0, 128.6, 127.1, 124.9, 123.0, 122.9, 121.2, 117.3, 116.6, 79.06, 59.8, 37.0, 14.4.; ESMS *m*/*z*: 413.0; HRMS *m*/*z* calc.: 413.1113; found: 413.1124 (M^++Na).

3-amino-1-(3-chlorophenyl)-1H-benzo[f]chromen-2-yl cyanide (5c). Yellow solid, mp: 202–204°C; IR (KBr): 3410.3, 3302.5, 2924.0, 2853.7, 2187.5, 1655.2 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 200MHz) δ: 7.85-7.76 (m, 2H, Ar-**H**), 7.68-7.61 (m, 2H, Ar-**H**), 7.42-7.34 (m, 2H, Ar-**H**), 7.31-7.17 (m, 2H, Ar-**H**), 7.15-7.06 (m, 2H, Ar-**H**), 6.32 (s, 2H, -N**H**$_2$), 5.18 (s, 1H, -C**H**-).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 160.0, 149.5, 143.2, 133.8, 133.0, 129.4, 129.1, 128.2, 127.8, 127.6, 126.4, 126.3, 126.2, 126.0, 124.2, 123.3, 120.8, 119.8, 59.5, 40.7.; ESMS *m*/*z*: 355.0; HRMS *m*/*z* calc.: 355.0614; found: 355.0609 (M^++Na).

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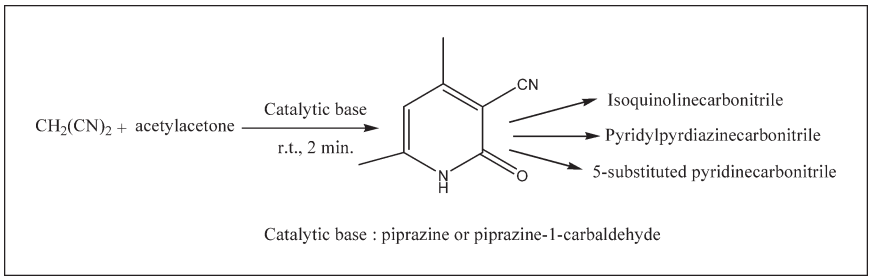

Rapid synthesis of 3-cyano-4,6-dimethyl-2-pyridone **3**, using piprazine as a catalyst was reported. X-ray data of the 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile exhibited its oxo form. Synthesis of isoquinolinecarbonitrile and pyridylpyridazine using compound **3** was investigated. Reactivity of the synthesized pyridone toward different organic reagents was also studied.

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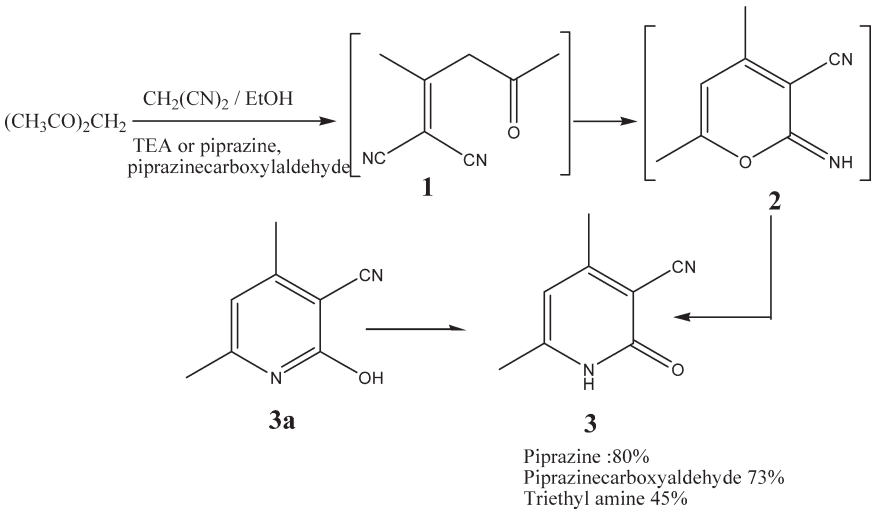
INTRODUCTION

2-Pyridones are biologically interesting molecules, and their chemistry have received considerable attention [1–6]. Over the last decade, natural products with this structure have emerged as potent antitumor and antiviral agents [7]. Recent studies have shown the usefulness of 2-pyridones as intermolecular connectors between building blocks in material science. Thus, despite the large number of methods known for their synthesis, new procedures are continuously being developed [8]. Many catalysts have been used in the synthesis of 2-pyridone from 1,3-diketones, such as zeolites [9], lipase enzymes [10–12], and triethylamine [13]. Microwave irradiation in preparing *N*-substituted pyridones has also been reported recently [14]. In this article, piprazine, piprazinecarboxyaldehyde, and triethylamine were used as a base catalyst. Piprazine was found to be the most efficient of the three catalysts.

RESULTS AND DISCUSSION

In this article, treatment of acetylacetone with malononitrile in presence of triethylamine afforded 3-cyano-4,6-dimethyl-2-pyridine **3** (Scheme 1), a 45% yield. The formation of **3** is assumed to proceed via initial condensation of malononitrile and acetylacetone to yield **1**

Scheme 1



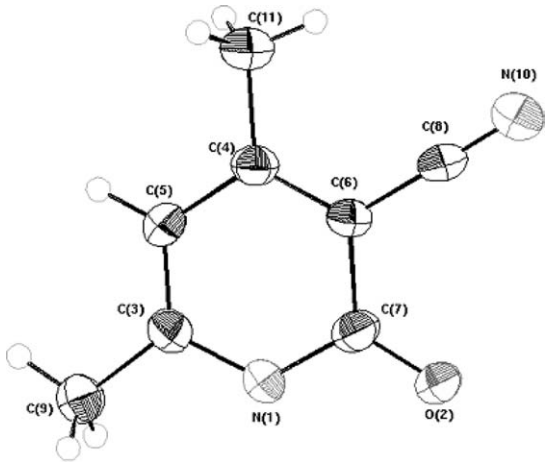


Figure 1. ORTEP diagram of compound **3**.

(Scheme 1), which then cyclizes into **2** (Scheme 1). The latter undergoes a Dimorth-like rearrangement to yield the final isolable product **3**. Higher yield (80%) of **3** was obtained on replacing triethylamine with piprazine. Although **3** may also exist in the form of structure **3a**, the oxo form **3** is the predominant as evidenced from X-ray analysis (Deposit number CCDC 668767) [15]. The crystal structure of compound **3** is shown in Figure 1.

X-ray crystallography. X-ray quality crystals of the title compound **3** were obtained by slow crystallization from dimethyl formamide [15]. The data was collected with the maXus computer programs on a Bruker Nonius instrument [16–20].

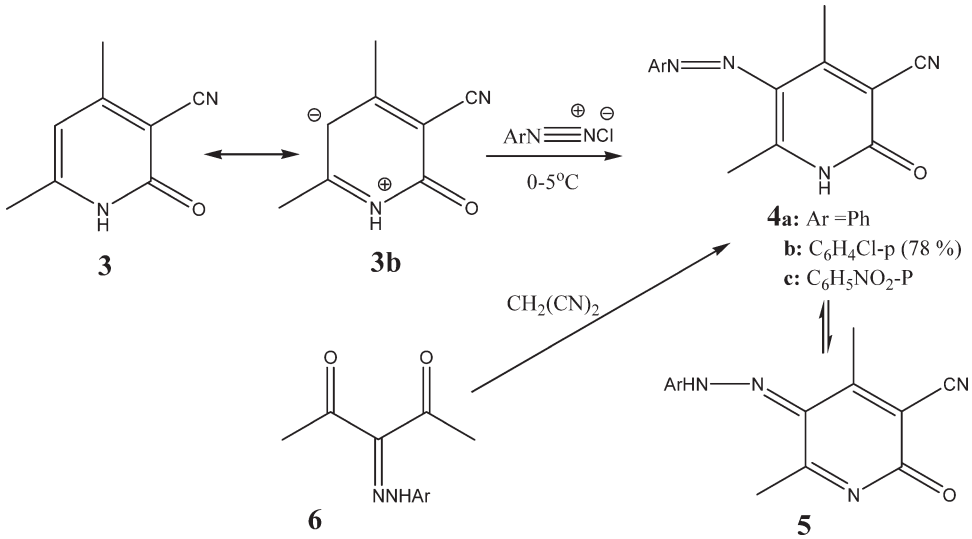
Interestingly, compound **3** was coupled with aryldiazonium chloride to yield 3-cyano-4,6-dimethyl-5-(aryldiazenyl)-2-pyridone **4** or its tautomer 3-cyano-4,6-dimethyl-5-(arylhydrazono)-2-pyridone **5** (Scheme 2). Although **4** may also exist as **5**, Nuclear Overhauser Effect (NOE) difference experiments indicate that the molecule exists solely as **4**. Irradiation of NH at δ 12.23 ppm enhanced methyl group at δ 2.54 ppm and *vice versa*. If the hydrazone form **5** exists, enhancement of aryl protons should have been observed. The formation of **4** provides evidence for the contribution of the charge-separated resonance form (**3b**) to the structure, and thus **3** behaves as typical enamines. Compounds **4a–c** could also be obtained when 3-(substituted arylazo)-2,4-pentanedione **6** was treated with malononitrile or cyanoacetamide in a basic medium as shown in Scheme 2 [21].

Consistent with this finding, compound **3** was brominated at C-5 to give the 5-bromo-3-cyano-4,6-dimethyl-2-pyridone **7**, through refluxing **3** with *N*-bromosuccinimide (Scheme 3). The structure of the product **7** was confirmed based on its elemental analysis and spectral data.

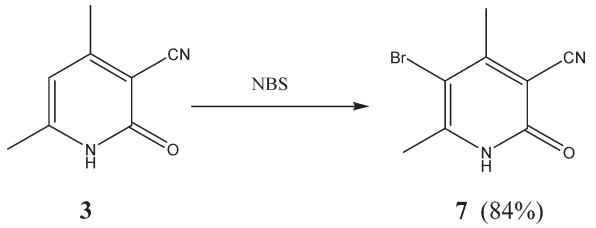
Typical to alkyl heteroaromatic carbonitriles, compound **3** reacted with arylidenemalononitrile **8** or benzoylacetonitrile **9** in a basic medium to yield 8-amino-3-methyl-1-oxo-6-aryl-1,2-dihydroisoquinoline-7-carbonitrile **10** (Scheme 4). Compound **10** is formed most likely via intermediates **11** and **12** (Scheme 4). Although in case of benzoylacetonitrile, the reaction is believed to proceed through the condensation of the carbonyl group in benzoylacetonitrile with the methyl group to form nonisolated intermediate **13**, followed by the addition of active methylene to the cyano group, and subsequent cyclization to dihydroisoquinolinecarbonitrile derivatives **10a** (Scheme 4).

Compound **3** is condensed with chloroacetonitrile to yield *N*-alkylated compound **3**-cyano-1-(cyanomethyl)-1,2-dihydro-4,6-dimethyl-2-pyridone **14**, rather than *O*-alkylated analog 2-(cyanomethoxy)-4,6-dimethylnicotinonitrile **15** (Scheme 5). The *N*-alkylated product **14** is

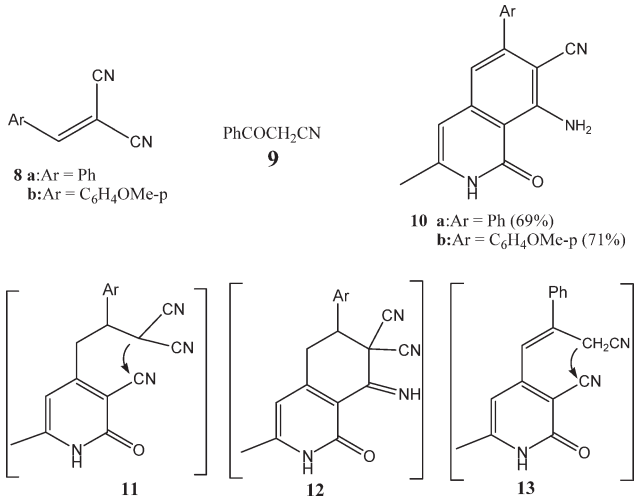
Scheme 2



Scheme 3



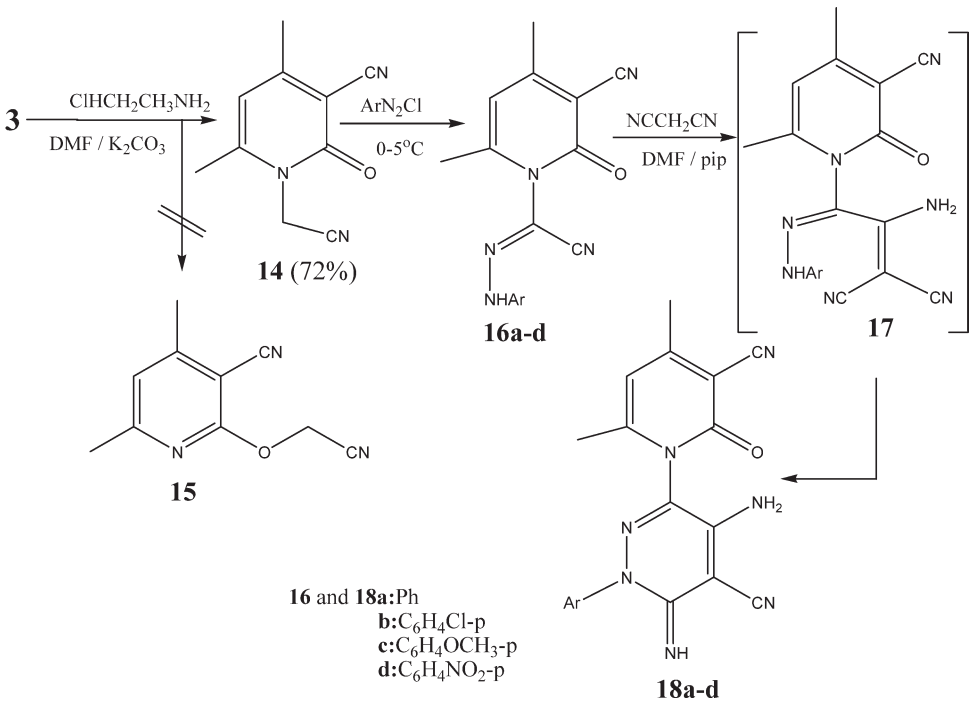
Scheme 4



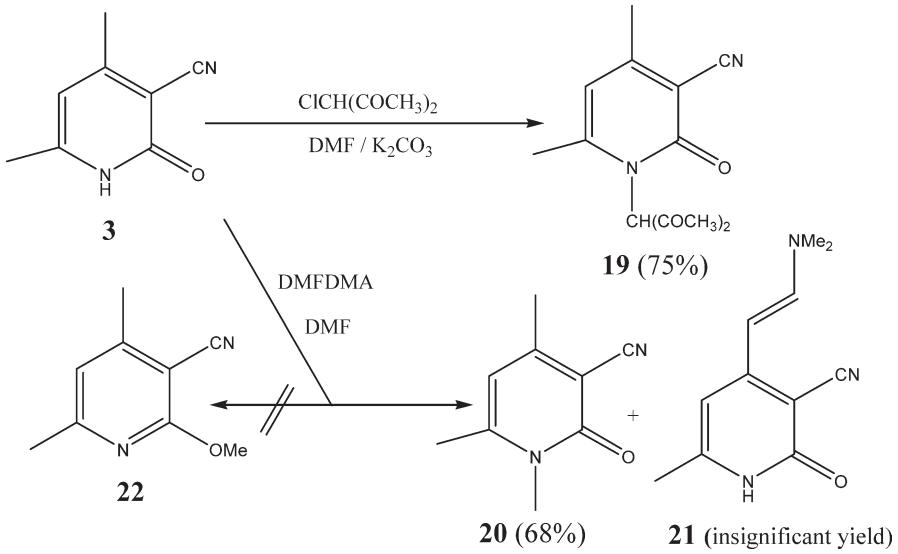
coupled with aromatic diazonium salts to yield 3-cyano-1-((2-arylhydrazono)cyanomethyl)-4,6-dimethyl-2-pyridone **16a–d** (Scheme 5). The latter reacted with malononitrile, in a similar way to that reported for arylhydrazononitriles, to yield 5-amino-6-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-imino-2-aryl-2,3-dihydropyridazine-4-carbonitrile **18a–d** via nonisolated intermediate **17** (Scheme 5).

Similarly, compound **3** is reacted with α-chloroacetylacetone to yield the *N*-alkylation product 3-cyano-1,2-dihydro-1-(2,4-dioxopentan-3-yl)-4,6-dimethyl-2-pyridone, **19** (Scheme 6). The structure of the latter was established based on elemental analysis and spectral data. Thus, IR revealed the disappearance of the NH band, whereas ^{1}H-NMR showed the dihydropyridine-H at δ 6.12 ppm. In contrast to the known behavior of alkylheteroaromatic carbonitriles condensing **3** with DMFDMA afforded 3-cyano-4-(2-(dimethylamino)vinyl)-6-methyl-2-pyridone **21** in low yield (Scheme 6), identified from gas chromatography-mass spectrometry (GC/MS), which showed *m/z* 203; rather methylation of **3** took place in good yield. Alkylation of pyridones with N,N-dimethylformamide dimethylacetal (DMFDMA), has been reported recently [22]. The alkylation product can, thus, be assigned as structures 3-cyano-1,4,6-trimethyl-2-pyridone **20**, or its isomeric form 2-methoxy-4,6-dimethylnicotinonitrile **22** (Scheme 6). Again, NOE difference experiments established the structure as **20**, as irradiating methyl group at δ 2.32 ppm enhanced other methyl group at δ 2.41 ppm indicating that both are especially proximal as would be the case in **20** (*cf.* Scheme 6).

Scheme 5



Scheme 6



Treating compound **19** with a nucleophilic reagents, for example, hydrazine hydrate or phenylhydrazine has afforded the compound, which may have either 3-cyano-1,2-dihydro-1-(4,6-dimethyl-1,2-dihydro-2-pyridone-3-carbonyl)-4,6-dimethyl-2-pyridone **23** or 3-cyano-1-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4,6-dimethyl-1,2-dihydro-2-pyridone **24** (Scheme 7). The latter structure (**24**) was ruled out based on mass spectrometry (MS) data (*m*/*z* 297), which is in agreement with structure **23** (Scheme 7).

The following Scheme 8 illustrates the pathway for the formation of product **23**, which is believed to be formed via the addition of nitrogen nucleophile to the carbon electrophile of the cyano group in the other molecule to give the imine form, which is then converted to the keto form under the reaction condition.

CONCLUSIONS

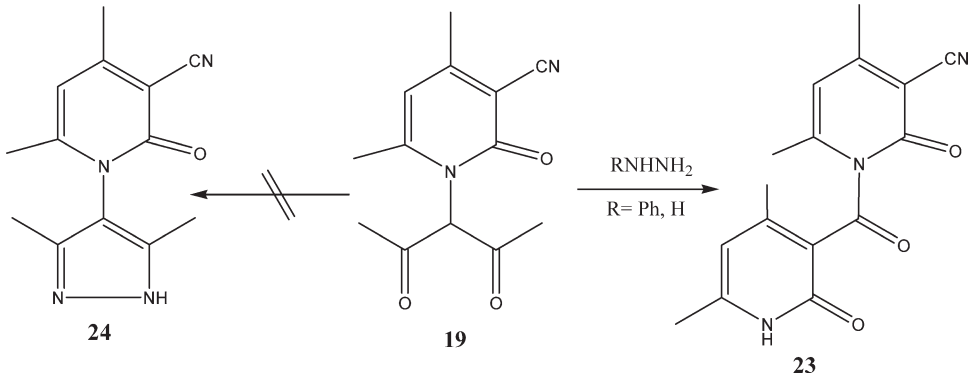
In summary, using piprazine as a catalyst for the synthesis of 3-cyano-4,6-dimethyl-2-pyridone was found to be more efficient than the use of piprazinecarboxyaldehyde or triethylamine. Bromination at C-5 of 3-cyano-4,6-dimethyl-2-pyridone is investigated. Also, reactivity of C-5 toward nitrogen electrophiles (aryldiazonium salt) has been investigated to provide evidence for the contribution of the charge separated resonance form typical to enamines. Alkylation of NH in the pyridone ring with chloroacetylacetone and chloroacetonitrile has also been studied.

EXPERIMENTAL

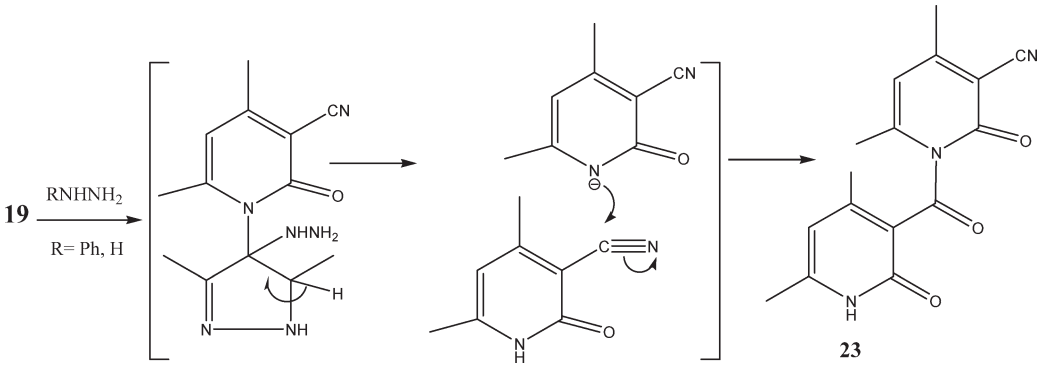
All melting points are uncorrected. IR spectra were recorded in KBr with an IR spectrophotometer Shimadzu 408. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian EM-390 MHz spectrometer using tetramethylsilane (TMS) as internal standard reference, and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt.

3-Cyano-1,2-dihydro-4,6-dimethyl-2-pyridone (3). To a solution of malononitrile (0.01 mol) in ethanol (50 mL), triethylamine or piprazine or piprazinecarboxyaldehyde (0.01 mol)

Scheme 7



Scheme 8



and acetylacetone (0.01 mol) were added. The solid product, so formed, after 2, 8, and 12 min (in case of piprazine, piprazine-1-carbaldehyde, and triethylamine, respectively), was left for 2h at room temperature and then collected by filtration, washed thoroughly with water, and then dried over sodium sulfate anhydrous.

Compound **3** was obtained as pale yellow crystals (80% in case of piprazine, 73% in case of piprazinecarboxyaldehyde, and 45% in case of triethylamine) from DMF/EtOH, m.p. 294°C; IR: 3434 (NH), 2218 (CN), 1658 cm^{-1} (CO); ^{1}H-NMR: δ 12.32 (br, 1H, NH, D_2O-exchange), 6.16 (s, 1H, pyridine-H), 2.30, 2.22 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 163.01 (CO), 116.11 (CN), 153.22, 152.13, 117.21, 112.31(pyridine carbons), 22.12, 18.43 (methyl carbons). MS: *m*/*z* 148 (M^+, 100%); Anal. Calcd. requires for $C_8H_8N_2O$ (148.16): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.95; H, 5.36; N, 18.99.

3-Cyano-4,6-dimethyl-5-(phenyldiazenyl)-2-pyridone (4a), 3-cyano-5-(4-chlorophenyl-diazenyl)-4,6-dimethyl-2-pyridone (4b), and 3-cyano-5-(4-nitrophenyldiazenyl)-4,6-dimethyl-2-pyridone (4c). A mixture of **3** (0.01 mol) in DMF or pyridine (30 mL), sodium hydroxide (1.0 g), the appropriate arene diazonium chloride (0.01 mol) [prepared by adding sodium nitrite (0.02 mol) to the appropriate primary aromatic amine (0.01 mol) in concentrated HCl (2 mL) at 0–5°C while stirring] was added dropwise while cooling at 0 to 5°C and stirring. The reaction mixture was left in fridge for 3h. The solid product formed was filtered off and washed many times with water and then crystallized from proper solvent.

All the obtained compounds **4a–c** are in agreement with analysis with the literature data [21,23], melting point of **4a** 283 to 284°C lit. M.p. 285°C [21], **4b** > 300°C; **4c** > 300°C lit. M.p. > 280°C [21].

Compound **4b** was obtained as yellow crystals 78% from EtOH, m.p. > 300°C; IR: 3423 (NH), 2214 cm^{-1} (CN); ^{1}H-NMR: δ 12.10 (br, 1H, NH, D_2O-exchange), 7.84–7.66 ppm (dd, 4H, C_6H_4, J = 7.3 Hz), 2.54, 2.45 (s, 6H, 2Me). MS: *m*/*z* 286 (M^+, 100%); Anal. Calcd. requires for $C_{14}H_{11}ClN_4O$ (286.72): C, 58.65; H, 3.87; N, 19.54. Found: C, 58.62; H, 3.78; N, 19.75.

5-Bromo-3-cyano-4,6-dimethyl-2-pyridone (7). To a solution of **3** (0.01 mol) in DMF/EtOH mixture (1:1, 50 mL), *N*-bromosuccinimide (0.01 mol) was added. The reaction mixture was refluxed for 3h. Excess solvent was evaporated under vacuum. Ice–cold water was then added. The solid product formed was collected by filtration.

Compound **7** was obtained as yellow crystals 84% from DMF/EtOH, m.p. 198°C; IR: 3445 (NH), 2224 cm^{-1} (CN); ^{1}H-NMR: δ 10.82 (br, 1H, NH, D_2O-exchange), 2.29, 2.21 (s, 6H, 2Me). ^{13}C-NMR: δ 179.86 (CO), 116.13 (CN), 161.41, 159.97, 151.35, 107.89 (pyridine carbons), 23.46, 21.51 (methyl carbons). MS: *m*/*z* 227, 228, 229 (M^+, M^{+1}, M^{+2}); Anal. Calcd. requires for $C_8H_7BrN_2O$ (227.06): C, 42.32; H, 3.11; N, 12.34. Found: C, 42.63; H, 3.29; N, 12.21.

8-Amino-3-methyl-1-oxo-6-phenyl-1,2-dihydroisoquinoline-7-carbonitrile (11a) and 8-amino-6-(4-methoxphenyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-7-carbonitrile (11b). ***Method A.*** To a solution of **3** (0.01 mol), arylidenemalononitrile (0.01 mol) in DMF (30 mL), triethylamine (0.5 mL) was added. The reaction mixture was refluxed for 5 h. The reaction mixture was poured onto ice–cold water. The resulting precipitated solid was collected by filtration and crystallized from proper solvent.

Method B. To a solution of **3** (0.01 mol), benzoylacetonitrile (0.01 mol) in DMF (30 mL), triethylamine (0.5 mL) was added. The reaction mixture was refluxed for 5 h. The reaction mixture was poured onto cold water. The resulting precipitated solid was collected by filtration and crystallized from proper solvent.

Compound **11a** was obtained as pale brown crystals 69% from DMF/EtOH, m.p. 265–266°C; IR: 3345–3223 (NH and NH_2), 2218 (CN), 1664 cm^{-1} (CO); ^{1}H-NMR: δ 12.13, 10.43 (br, 3H, NH and NH_2, D_2O-exchange), 7.20–7.45 (m, 6H, aromatic protons), 6.16 (s, 1H, pyridine-H), 2.29 ppm (s, 3H, Me). ^{13}C-NMR: δ 163.23 (CO), 156.12, 144.51, 142.13, 118.31, 112.02 (pyridine carbons), 148.31, 146.53, 141.64, 140.01, 132.12, 128.12, 112.11, 109.39 (aromatic carbons), 115.64 (CN), 21.14 ppm (Me). MS: *m*/*z* 275 (M^+, 100%); Anal. Calcd. requires for $C_{17}H_{13}N_3O$ (275.30): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.00; H, 4.67; N, 15.36.

Compound **11b** was obtained as brown crystals 71% from DMF/EtOH, m.p. 216–218°C; IR: 3345–3223 (NH and NH_2), 2214 (CN), 1661 cm^{-1} (CO); ^{1}H-NMR: δ 11.43, 10.34 (br, 3H, NH and NH_2, D_2O-exchange), 7.20, 6.88 (d, 4H, C_6H_4, J = 8.8 Hz), 7.32 (s, 1H, isoquinoline-H), 6.14 (s, 1H, pyridine-H), 3.75 (s. 3H, OMe), 2.29 ppm (s, 3H, Me). MS: *m*/*z* 305 (M^+, 100%); Anal. Calcd. requires for $C_{18}H_{15}N_3O_2$ (305.33): C, 70.81; H, 4.95; N, 13.76. Found: C, 70.68; H, 4.61; N, 13.66.

3-Cyano-1-(cyanomethyl)-1,2-dihydro-4,6-dimethyl-2-pyridone (14). A mixture of **3** (0.01 mol) and chloroacetonitrile (0.01 mol) in DMF (30 mL) containing potassium carbonate

(0.14 g) was refluxed for 3 h. The reaction mixture was left aside at room temperature overnight then poured onto ice–cold water. The solid product, so formed, was filtered off, washed by water (3 × 10), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was crystallized from DMF/EtOH

Compound **14** was obtained as deep yellow crystals 72%, m.p. 213–217°C; IR: 2210, 2217 (CN), 1656 cm^{-1} (CO); ^{1}H-NMR: δ 6.06 (s, 1H, pyridine-H), 4.12 (s, 2H, CH_2), 2.34 2.23 ppm (s, 6H, 2Me). ^{13}C NMR: δ 157.76 (CO), 154.02, 149.13, 115.35, 111.21 (pyridine carbons), 116.21, 114.90 (CN), 32.23 (CH_2), 19.45, 15.04 ppm (2Me). MS: *m*/*z* 187 (M^+, 100%); Anal. Calcd. requires for $C_{10}H_9N_3O$ (187.20): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.26; H, 4.75; N, 22.34.

3-Cyano-1-((2-phenylhydrazono)cyanomethyl)-4,6-dimethyl-2-pyridone (16a), 3-cyano-1-((2-*p*-chlorophenylhydrazono)cyanomethyl)-4,6-dimethyl-2-pyridone (16b), 3-cyano-1-((2-*p*-methoxyphenylhydrazono)cyanomethyl)-4,6-dimethyl-2-pyridone (16c), and 3-cyano-1-((2-*p*-nitrophenylhydrazono)cyanomethyl)-4,6-dimethyl-2-pyridone (16d). A mixture of **14** (0.01 mol) in DMF (30 mL), sodium acetate (2.0 g), the appropriate arene diazonium chloride (0.01 mol) [prepared by adding sodium nitrite (0.02 mol) to the appropriate primary aromatic amine (0.01 mol) in concentrated HCl (2 mL) at 0 to 5°C while stirring] was added dropwise while cooling at 0 to 5°C and stirring. The solid product formed was filtered off, wash many times with water, and the solvent was evaporated *in vacuo*, and then the residue was crystallized from proper solvent.

Compound **16a** was obtained as deep yellow crystals 74% from acetone/water (1:1), m.p. 242–243°C; IR: 3322 (NH), 2216, 2211 (CN), 1656 cm^{-1} (CO); ^{1}H-NMR: δ 11.12 (br, 1H, NH, D_2O-exchange), 7.33–6.14 (m, 5H, C_6H_5), 6.16 (s, 1H, pyridine-H), 2.33, 2.21 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 162.11 (CO), 154.29 (imine carbon), 118.31, 116.01 (2CN), 154.29, 143.42, 115.34, 109.55 (pyridine carbons), 143.12, 129.51, 118.72, 116.43 (aromatic carbons), 23.45, 21.49 ppm (methyl carbons). MS: *m*/*z* 291 (M^+, 100%); Anal. Calcd. requires for $C_{16}H_{13}N_5O$ (291.11): C, 65.97; H, 4.50; N, 24.04. Found: C, 65.84; H, 4.55; N, 23.98.

Compound **16b** was obtained as yellow crystals 69% from acetone/water (1:1), m.p. 230–232°C; IR: 3422 (NH), 2216, 2212 (CN), 1657 cm^{-1} (CO); ^{1}H-NMR: δ 11.11 (br, 1H, NH, D_2O-exchange), 7.12, 6.44 (dd, 4H, C_6H_4, J = 8.6 Hz), 6.14 (s, 1H, pyridine-H), 2.32, 2.20 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 162.23(CO), 154.56 (imine carbon), 118.19, 114.93 (2CN), 153.45, 142. 38, 116.54, 111.29 (pyridine carbons), 142.34, 130.37, 123.43, 118.27 (aromatic carbons), 23.42, 21.15 ppm (methyl carbons). MS: *m*/*z* 325 (M^+, 100%); Anal. Calcd. requires for $C_{16}H_{12}ClN_5O$ (325.75): C, 58.99; H, 3.71; N, 21.50. Found: C, 59.04; H, 3.75; N, 21.56.

Compound **16c** was obtained as yellow crystals 75% from acetone/water (1:1), m.p. 221–223°C; IR: 3422 (NH), 2218, 2212 (CN), 1658 cm^{-1} (CO); ^{1}H-NMR: δ 11.23 (br, 1H, NH, D_2O-exchange), 7.22, 6.23 (dd, 4H, C_6H_4, J = 8.9 Hz), 6.16 (s, 1H, pyridine-H), 3.63 (s, 3H, MeO), 2.34, 2.23 ppm (s, 6H, 2Me). MS: *m*/*z* 321 (M^+, 100%); Anal. Calcd. requires for $C_{17}H_{15}N_5O_2$ (321.33): C, 63.54; H, 4.71; N, 21.79. Found: C, 63.44; H, 4.75; N, 21.53.

Compound **16d** was obtained as yellow crystals 75% from acetone/water (1:1), m.p. > 250°C; IR: 3422 (NH), 2218, 2211 (CN), 1659 cm^{-1} (CO); ^{1}H-NMR: δ 11.13 (br, 1H, NH, D_2O-exchange), 7.32, 6.33 (dd, 4H, C_6H_4, J = 8.7 Hz), 6.06 (s, 1H, pyridine-H), 2.32, 2.20 ppm (s, 6H, 2Me). MS: *m*/*z* 336 (M^+, 100%); Anal. Calcd. requires for $C_{16}H_{12}N_6O_3$ (336.30): C, 57.14; H, 3.60; N, 24.99. Found: C, 57.22; H, 3.54; N, 25.01.

5-Amino-6-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-imino-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (18a), 5-amino-2-(4-chlorophenyl)-6-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-imino-2,3-dihydropyridazine-4-carbonitrile (18b), 5-amino-6-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-imino-2-(4-methoxyphenyl)-2,3-dihydropyridazine-4-carbonitrile (18c), and 5-amino-6-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-imino-2-(4-nitrophenyl)-2,3-dihydropridazine-4-carbonitrile (18d). To a solution of **16** (0.01 mol) and malononitrile (0.01 mol) in DMF (30 mL), piperidine (5–10 drops) was added. The reaction mixture was refluxed for 3 h. The solid product, so formed, was collected by filtration and crystallized from proper solvent.

Compound **18a** was obtained as brown crystals 72% from DMF/EtOH, m.p. char over 250°C; IR: 3345–3221 (NH and NH_2), 2220, 2212 (CN), 1657 cm^{-1} (CO); ^{1}H-NMR: δ 11.13, 10.42 (br, 3H, NH and NH_2, D_2O-exchange), 7.22- 6.37 (m, 5H, C_6H_5), 6.14 (s, 1H, pyridine-H), 2.29, 2.21 ppm (s, 6H, 2Me). ^{13}C NMR: δ 161.96 (CO), 153.93, 143.77, 115.15, 112.21 (pyridine carbons), 165.32, 155.12, 154.20, 79.38 (pyridazine carbon), 145.31, 128.65, 119.98, 116.24 (aromatic carbons), 116.09, 115.94 ppm (2CN). MS: *m*/*z* 357 (M^+, 100%); Anal. Calcd. requires for $C_{19}H_{15}N_7O$ (357.37): C, 63.86; H, 4.23; N, 27.44. Found: C, 64.01; H, 4.54; N, 27.64.

Compound **18b** was obtained as yellow crystals 69% from DMF/EtOH, m.p. char over 250°C; IR: 3345–3223 (NH and NH_2), 2221, 2210 (CN), 1657 cm^{-1} (CO); ^{1}H NMR: δ 11.15, 10.41 (br, 3H, NH and NH_2, D_2O-exchange), 7.32, 6.33 (dd, 4H, C_6H_4, J = 8.6 Hz), 6.16 (s, 1H, pyridine-H), 2.31, 2.22 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 162.34 (CO), 154.34, 142.92, 116.41, 109.61, 107.25 (pyridine carbons), 164.93, 153.23, 145.32, 78.98 (pyridazine carbon), 143.45, 130.17, 124.83, 118.37 (aromatic carbons), 116.39, 115.94 (2CN), 14.64, 20.61 ppm (2Me). MS: *m*/*z* 391 (M^+, 100%); Anal. Calcd. requires for $C_{19}H_{14}ClN_7O$ (391.81): C, 58.24; H, 3.60; N, 25.02. Found: C, 58.34; H, 3.56; N, 25.32.

Compound **18c** was obtained as yellow crystals 75% from EtOH, m.p. char over 250°C; IR: 3345–3223 (NH and NH_2), 2221, 2211 (CN), 1657 cm^{-1} (CO); ^{1}H-NMR: δ 11.23, 10.53 (br, 3H, NH and NH_2, D_2O-exchange), 7.02, 6.35 (dd, 4H, C_6H_4, J = 8.9 Hz), 6.14 (s, 1H, pyridine-H), 3.67 (s,3H, OMe), 2.32, 2.21 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 162.32 (CO), 153.61, 143.34, 115.35, 112.02 (pyridine carbons), 164.34, 154.84, 152.92, 79.31 (pyridazine carbon), 151.07, 139.16, 118.13, 115.01 (aromatic carbons), 116.09, 115.79 (2CN), 56.02 (OMe), 14.14, 21.06 ppm (2Me). MS: *m*/*z* 387 (M^+, 100%); Anal. Calcd. requires for $C_{20}H_{17}N_7O_2$ (387.39): C, 62.01; H, 4.42; N, 25.31. Found: C, 62.20; H, 4.37; N, 25.34.

Compound **18d** was obtained as brown crystals 68% from DMF/EtOH, m.p. char over 250°C; IR: 3345–3223 (NH and NH_2), 2219, 2211 (CN), 1658 cm^{-1} (CO); ^{1}H-NMR: δ 11.23, 10.50 (br, 3H, NH and NH_2, D_2O-exchange), 7.87, 6.72 (dd, 4H, C_6H_4, J = 8.7 Hz), 6.16 (s, 1H, pyridine-H), 2.40, 2.32 ppm (s, 6H, 2Me). ^{13}C-NMR: δ 164.23 (CO), 157.17, 144.21,

115.54, 110.20 (pyridine carbons), 164.66, 155.21, 152.72, 90.21 (pyridazine carbon), 152.11, 140.24, 124.3, 117.7 (aromatic carbons), 116.12, 115.36 (2CN), 14.23, 21.06 ppm (2Me). MS: *m*/*z* 402 (M^+, 100%); Anal. Calcd. requires for $C_{19}H_{14}N_8O_3$ (402.37): C, 56.72; H, 3.51; N, 27.85. Found: C, 56.64; H, 3.50; N, 28.02.

3-Cyano-1,2-dihydro-1-(2,4-dioxopentan-3-yl)-4,6-dimethyl-2-pyridone (19). A mixture of **3** (0.01 mol) and 3-chloro-2,4-pentandione (0.01 mol) in DMF (30 mL) containing potassium carbonate (0.14 g) was refluxed for 3 h. The reaction mixture was left aside at room temperature overnight then poured into ice–cold water. The solid product, so formed, was filtered off and washed with water.

Compound **19** was obtained as deep yellow crystals 75% from MeOH, m.p. 176°C; IR: 2215 (CN), 1654–1640 cm^{-1} (CO); ^{1}H-NMR: δ 6.12 ppm (s, 1H, pyridine-H), 5.12 (br, 1H, CH), 2.44, 2.37, 2.32, 2.24 ppm (s, 12H, 4Me). MS: *m*/*z* 246 (M^+, 100%); Anal. Calcd. requires for $C_{13}H_{14}N_2O_3$ (246.26): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.43; N, 11.53.

3-Cyano-1,4,6-trimethyl-2-pyridone (20). To a solution of **6** (0.01 mol) in DMF (30 mL), DMF DMA (0.01 mol) was added. The reaction mixture was refluxed for 5 h. The solvent was then evaporated *in vacuo*. The residue was triturated with ice–cold water; the solid product, so formed, was collected by filtration.

Compound **20** was obtained as yellow crystals 68% from DMF/EtOH, m.p. 185°C; IR: 2210 (CN), 1655 cm^{-1} (CO); ^{1}H-NMR: δ 6.06 ppm (s, 1H, pyridine-H), 2.41, 2.39, 2.32 (s, 9H, 3Me). ^{13}C-NMR: δ 163.01 (CO), 116.11 (CN), 153.20, 152.23, 117.22, 112.33 (pyridine carbons), 24.11, 22.12, 18.43 (methyl carbons). MS: *m*/*z* 162 (M^+, 100%); Anal. Calcd. requires for $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.32; H, 6.38; N, 17.53.

Compound **21** is agreement in analysis with the literature data22.

3-Cyano-1,2-dihydro-1-(4,6-dimethyl-1,2-dihydro-2-pyridone-3-carbonyl)-4,6-dimethyl-2-pyridone. A mixture of **19** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in a dry dioxane (30 mL) was refluxed for 3 h.23 The solvent was evaporated and then dissolved in methanol. Filtration of the mixture gave mother liquor, which evaporated to give the product.

Compound **23** was obtained as pale brown crystals 63% from DMF, m.p. > 250°C; IR: 3422 (NH), 2217 (CN), 1686, 1656 cm^{-1} (CO); ^{1}H-NMR: δ 12.12 (br, 1H, NH, D_2O-exchange), 6.06 (s, 2H, 2pyridine-H), 2.45, 2.35, 2.31, 2.22 ppm (s, 12H, 4Me). ^{13}C-NMR: δ 163.01 (CO), 160.22 (CO), 116.23 (CN), 159.54, 149.32, 133601, 135.32, 112.11, 132.33, 131.60, 131.15. (pyridine carbons), 23.46, 22.89, 21.52, 2051 (methyl carbons). MS: *m*/*z* 297 (M^+, 100%); Anal. Calcd. requires for $C_{16}H_{15}N_3O_3$ (297.31): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.54; H, 5.05; N, 14.31.

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An Efficient One-Pot Synthesis of Diarylpyrazolo [1,5-*a*]pyrimidine from Isoflavones

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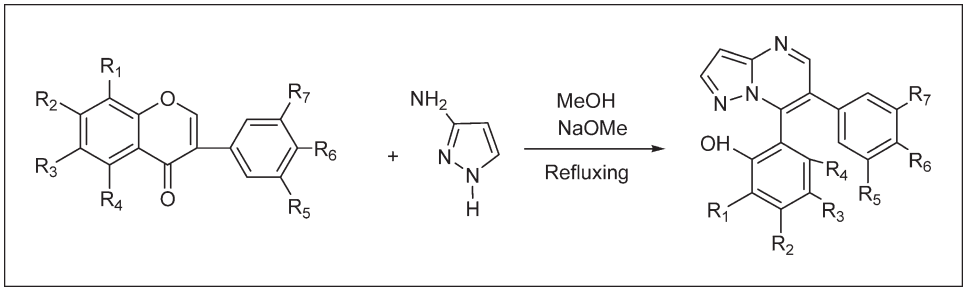

Direct synthetic methods of 6,7-diphenylpyrazolo[1,5-*a*]pyrimidine derivatives have been developed. Cyclocondensation of isoflavones with 3-aminopyrazole in the presence of sodium methoxide as alkali promoter gave 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines in moderate to good yields.

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INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidine, although virtually unknown as natural products, are an important pharmaceutical targets (Scheme 1) [1]. They and related fused heterocycles are of interest as potential bioactive molecules. Pyrazolo[1,5-*a*]pyrimidines exhibited biological activities, such as cSRC kinase inhibitors involved with ischemic brain pathology [2], cyclin dependent kinase 1 inhibitor [3], HIV reverse transcriptase inhibitors [4], CCR1 antagonists [5], protein kinase inhibitors [6], cGMP degradation inhibitors, or herbicidal and fungicidal activities [7].

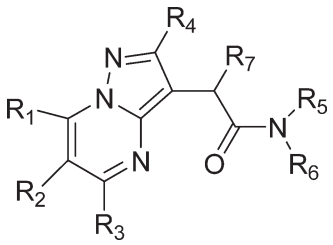
Numerous methods for the synthesis of pyrazolo[1,5-*a*]pyrimidine have been reported in the last 20 years, which involved the reaction between aminopyrazoles and 1,3-bise-lectrophilic compounds, such as β-dicarbonyl, alkoxymethylene-β-dicarbonyl [8], and β-enaminone compounds [9]. It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent which readily react with amidines [10], guanidine [11], sulfocarbamides [12], and hydrazine [13] to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles, 4,5-biphenyl-2-pyrimidinylguanidine and 2, 3-diarylpyrimido[1,2-*a*] benzimidazole by using one-step reaction of hydrazine [14], biguanidine [15], and 2-aminobenzimidazole [16] with isoflavones respectively. Herein, we report a new strategy for the preparation of the unknown class of 6,7-diphenylpyrazolo [1,5-*a*]pyrimidines from isoflavones.

RESULTS AND DISCUSSION

We designed the cyclocondensation of isoflavone **1**, which can generate a 1,3-dicarbonal equivalent in the presence of alkali, with 3-aminopyrazoles **2** to synthesize 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines **3** (Scheme 2). Thus, treatment of ipriflavone (7-isopropoxyisoflavone) **1a** with 3-aminopyrazole **2** (1.1 equiv) in refluxed ethanol in the presence of sodium hydroxide (3 equiv) for 12 h afforded 6-phenyl-7-(2-hydroxy-4-isopropoxyphenyl) pyrazolo[1,5-*a*]pyrimidine **3a** [38%] (Table 1, entry 1). We then turned our attention to optimize the conditions of the cyclocondensations between isoflavone **1a** and 3-aminopyrazole **2** (Table 1). Thus when NaOH (5*M*) was used as base, **3a** obtained in 38% yield (entry 1). It was also found that Et_3N was ineffective in providing the desired condensation product (entry 2). A comparative reactivity study of bases in the reaction showed that NaOMe proved to be most effective for the cyclocondensation (entry 3). Further study with varying NaOMe equivalents revealed that 3.0 equiv of base is necessary to obtain a high yield of **3a** (entries 3–6). MeOH was a solvent of choice, since reactions in THF, DMF, or EtOH gave lower yields (entries 6–10). Compound **3a** was obtained in high yield when ratio of **1a**:**2** (1:1.3) were used (entry 12).

Next, the condensation of a variety of structurally divergent isoflavones **1** with **2** were performed to illustrate this concise and general method for the synthesis of **3**.

Scheme 1



The wide range of isoflavones (**1a–1t**) reacted efficiently with **2** under the basic conditions to afford the respective products **3** (12–45 h) in moderate to excellent yields (Table 2). All products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. Single crystal X-ray diffraction analysis of **3a** (Fig. 1) was used to corroborate the postulated structures unequivocally, which added additional evidence for the structures identification. The reaction has a general character and isoflavone **1** with various substituent on the both aryl rings (e.g. alkoxy groups) gave **3** in high yields (Table 2). The yields, however, decrease when the number of the hydroxyl group on the aryl rings increase. For example, isoflavones, **1a, 1b**, **1d**, **1f**, **1i**, **1k**, **1l**, **1m**, **1q**, and **1t** (Table 2, entries 1, 2, 4, 6, 9, 11–13, 17, 20), which do not contain hydroxyl group gave **3** in about 80% yields. Isoflavone with one hydroxyl group, **1c**, **1e**, **1j**, **1o**, and **1s** (Table 2, entries 3, 5, 10, 15, 19) afforded **3** in about 65% yield while isoflavone with two free hydroxyl groups such as **1g** and **1h** (Table 2, entries 7, 8) gave desired products in about 60% yields. Consideration of Genistein (4′,5,7-trihydroxyisoflavon) (Table 2, entry 14) with **2** produced **3n** (45%) was well but in lower yield.

The yields of **3** are directly dependant on the number of free hydroxyl group present on the engaged isoflavone. Because the hydroxyls at isoflavones **1** under the basic conditions would be oxyanions, which possess stronger electron donability than alkoxy and benzyoxyl groups, they might prevent condensation of the reaction.

Further experimentation and mechanistic studies are required to fully understand the regioselective of the cyclocondensation of isoflavone **1** with pyrazoles **2**. As reported [17], isoflavone may undergo ring opening reaction in the presence of alkali to form a α,β-unsaturated ketone intermediate **5** (Scheme 3). Attack of the primary amine group from the 3-aminoprazole **2** on the β-carbon in **5**, followed by the ring closure reaction between produce **3**. Additionally, the choice of base is very important for the cyclocondensations of aminopyrazoles with isoflavone. Intermediate **5** was showed to undergo conversion to ketone **6** [18] at high concentration of base by elimination of $HC(OMe)_3$ molecule. On the other hand, the isoflavone ring would be hard to open and produce intermediate **5** in the lower concentration of base.

CONCLUSIONS

In summary, we have developed a useful method for the construction of fused 6,7-diphenylpyrazolo[1,5-*a*] pyrimidines derivatives by the cyclocondensation of 3-aminopyrazole with isoflavone in methanol and the presence of sodium methoxide. It is an efficient and regioselective approach toward the synthesis 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines. The yields of pyrazolo[1,5-*a*] pyrimidine derivatives are excellent, most between 70–80%. On the basis of the present investigation, we are now carrying out research on the applications of 6,7-diphenylpyrazolo[1,5-*a*] pyrimidines in pharmacology.

EXPERIMENTAL

Melting points were measured on X-5 micro melting point apparatus, which is uncorrected. IR spectra were recorded on Fourier transform Infrared Spectrometer. The ^{1}H-NMR spectra were recorded at 300.00 MHz on Bruker DRX-300 Advance spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm) downfield from Me_4Si which was used as the internal standard for all NMR spectra. ^{1}H-NMR spectra are reported in order: multiplicity and approximate coupling constant (*J* value) in hertz (Hz), number of protons; signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), and br s (broad signal). The ^{13}C-NMR spectra were recorded at 75.00 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The MS instrument is LTQ ESI-MS. The elemental analyses were performed with an Elementar Analysensyteme GmbH Vario EL III. All the products are

Scheme 2. The designed cyclocondensation route of isoflavones 1 with aminopyrazoles 2.

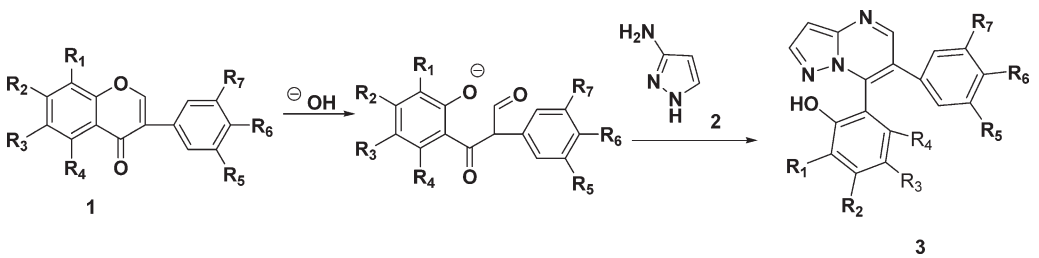
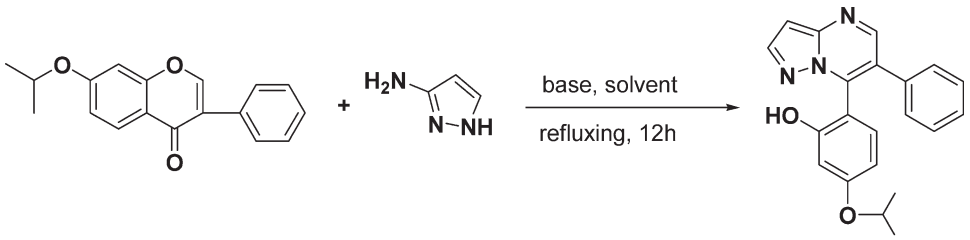


Table 1

Optimization of cyclocondensation of isoflavone **1a** with 3-aminepyrazole **2**[a].



1a **2** **3a**

Entry	Solvent	Base	Molar ratios (eq.) **1a**/**2**/base	**3a** Yield/%[b]
1[c]	EtOH	NaOH	1/1.1/3	38
2	EtOH	Et_3N	1/1.1/3	0
3	EtOH	NaOMe	1/1.1/2	53
4	EtOH	NaOMe	1/1.1/3	70
5	EtOH	NaOMe	1/1.1/4	64
6	EtOH	NaOMe	1/1.1/5	45
7	THF	NaOMe	1/1.1/3	30
8[d]	DMF	NaOMe	1/1.1/3	25
9	MeOH	NaOMe	1/1.2/3	75
10	MeOH	NaOMe	1/1.3/3	88
11	MeOH	NaOMe	1/1.4/3	85
12	MeOH	NaOMe	1/1.5/3	89

[a] All reactions were carried out with isoflavone **1a** (2 mmol) and 3-aminopyrazole **2** and different kind of base until the formation in appropriate solvents (20 mL) was completed as monitored by TLC(24 h, refluxing).
[b] Isolated yield based on isoflavone.
[c] Reactions with EtOH, MeOH, and THF as solvent were carried out under the boiling point.
[d] The reaction with DMF as solvent was carried at 100°C.

new compounds, which were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectra. X-Ray crystallography dates were given by Bruker Smart-1000 CCD diffactometer. All other commercially obtained reagents were used as received. Thin-layer chromatography (TLC): silica gel 60 GF_{254} plate; and the eluant of column chromatography is the mixture of petroleum ether and ethyl acetate at volume ratio of 1:1.

General procedure for the synthesis of diarylpyrazolo[1,5-*a*]pyrimidine 3. The isoflavone **1a–1t** (2 mmol), 3-aminepyrazol **2** (2.6 mmol), and sodium methoxide (6, 8, 10, and 12 mmol were used for 0, 1, 2, and 3 free hydroxyl group of **1**) were refluxed in methanol (40 mL) for 12–45 h. All reactions were monitored by TLC, which showed the disappearances of the starting materials. The reaction mixture was then concentrated to 10 mL by using rotary evaporator, the condensate was poured into a 10% HCl (15 mL) and a light yellow precipitate formed. This precipitate was collected by filtration and washed with distilled water until the pH value of the filtrate was 7. Finally, the precipitate was recrystallized from absolute ethanol or purified on silica gel column chromatography ($CHCl_3$:CH_3OH = 20:1), **3** were obtained.

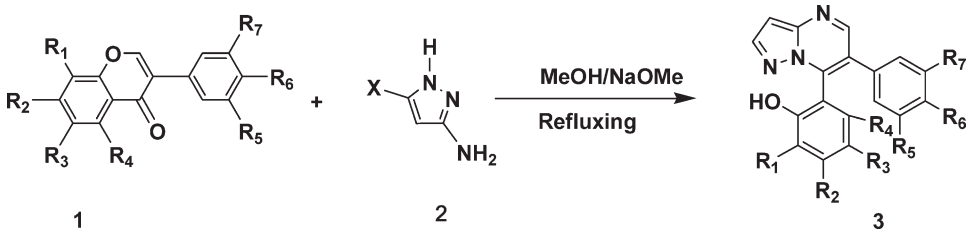
6-Phenyl-7-(2-hydroxyl-4-isopropoxyphenyl)pyrazolo[1,5-*a*]pyrimidine(3a). m. p. 248–250°C; IR (KBr), ν (cm^{-1}): 3314, 2977, 1684, 1610, 1519, 1423, 1386, 1235, 1113, 993, 837, 796, 699; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.26 (d, 6H), 4.53 (m, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 6.80 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.31 (s, 5H), 8.14 (s, 1H), 8.61 (s, 1H), 9.73 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 21.8, 69.3, 96.1, 102.7, 106.2, 110.3, 122.1, 127.3, 128.2, 129.3, 131.6, 135.3, 142.6, 144.3, 147.7, 150.5, 156.9, 159.7. ESI-MS: *m*/*z* (rel intensity) 368 (M+Na, 52), 346 (M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found C, 73.10; H, 5.58; N, 12.20.

6-Phenyl-7-(2-hydroxyl-4-methoxy-6-methyphenyl)pyrazolo[1,5-*a*]pyrimidine (3b). m. p. 242.0–242.2°C; IR (KBr), ν (cm^{-1}): 3489, 3240, 3172, 3056, 2997, 1595, 1513, 1453, 1335, 1283, 1197, 1160, 1132, 1039, 831; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.71 (s, 3H), 3.72 (s, 3H), 6.28 (s, 2H), 6.81 (d, J = 1.9 Hz, 1H), 7.32 (s, 5H), 8.13 (d, J = 1.9 Hz, 1H), 8.63 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 19.0, 54.9, 96.1, 98.7, 106.2, 110.7, 122.6, 127.6, 128.2, 128.8, 135.3, 138.2, 141.9, 144.4, 147.7, 150.4, 156.6, 160.9. EIMS: *m*/*z* (rel intensity) 354 (M+Na, 38), 332 (M + 1, 100). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.173; N, 12.68; Found C, 72.55; H, 5.21; N, 12.72.

6-(4-Methoxyphenyl)-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3c). m. p. 245.0–245.7°C; IR (KBr), ν (cm^{-1}): 3142, 2958, 2836, 1709, 1605, 1506, 1458, 1209, 1238, 1179, 836; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.73 (s, 3H,), 6.22 (d, J = 8.2 Hz, 2H), 6.35 (s, 1H), 6.76 (s, 1H), 6.86 (d, 2H), 7.22 (d, J = 8.2Hz, 2H), 8.10 (s, 1H), 8.57 (s, 1H), 9.54 (s, 1H), 9.56 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6 / TMS, δ (ppm)]: 55.5, 96.5, 103.1, 107.1, 109.6, 114.2, 122.2,

Table 2

Synthesis of 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines 3 by the cyclocondensations of aminopyrazoles **2** with isoflavones **1**[a].



1 2 3

Entry	Substrate	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Product/yield[b]/time **3**		
1	**1a**	H	*i*-OPr	H	H	H	H	H	**3a**	88	12
2	**1b**	H	OMe	H	Me	H	H	H	**3b**	79	13
3	**1c**	H	OH	H	H	H	OMe	H	**3c**	65	24
4	**1d**	H	OMe	H	OMe	H	OMe	H	**3d**	86	15
5	**1e**	H	OH	H	H	H	H	H	**3e**	61	20
6	**1f**	H	OMe	H	H	H	OMe	H	**3f**	82	12
7	**1g**	H	OH	H	H	H	OH	H	**3g**	58	32
8	**1h**	H	OH	H	H	*i*-Pr	OH	*i*-Pr	**3h**	62	35
9	**1i**	H	OMe	H	H	H	H	H	**3i**	76	13
10	**1j**	H	OMe	H	H	H	OH	H	**3j**	74	22
11	**1k**	Br	*i*-OPr	H	H	H	H	H	**3k**	82	14
12	**1l**	H	OMe	H	H	*i*-Pr	OMe	*i*-Pr	**3l**	77	16
13	**1m**	H	OMe	OMe	OMe	H	OMe	H	**3m**	86	18
14	**1n**	H	OH	H	OH	H	OH	H	**3n**	45	42
15	**1o**	H	OMe	H	H	*i*-Pr	OH	*i*-Pr	**3o**	80	28
16	**1p**	H	OMe	H	OMe	*i*-Pr	OMe	*i*-Pr	**3p**	76	18
17	**1q**	Br	OMe	H	H	H	OMe	H	**3q**	77	15
18	**1r**	H	OH	H	OH	*i*-Pr	OH	*i*-Pr	**3r**	48	45
19	**1s**	H	OMe	H	H	Br	OH	Br	**3s**	70	26
20	**1t**	H	OEt	H	H	H	OMe	H	**3t**	83	13

[a] Reaction conditions. For a detailed experimental operation, see Experimental section. **1** (2 mmol), **2** (2.6 mmol), $NaOCH_3$ (**3**: 6, 8, 10, and 12 mmol were used for 0, 1, 2, and 3 free hydroxyl group of **1**), 70°C.
[b] Isolated yield after silica gel chromatography.

128.0, 131.0, 131.9, 143.2, 144.5, 148.1, 151.2, 157.3, 159.0, 160.2; ESI-MS: *m/z* (rel intensity) 437 (95), 356 (M + Na, 40), 437.12 (51), 334 (M + 1, 100), 318 (13), 274 (25). Anal. Calcd for C19H15N3O3: C, 68.46; H, 4.54; N, 12.61; Found C, 68.52; H, 4.61; N, 12.71.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4,6-dimethoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (3d). m. p. 248.6–249.3°C; IR (KBr), ν (cm^{-1}): 3129, 3011, 2955, 2837, 1605, 1509, 1462, 1370, 1201, 1167, 1114, 1029, 935, 825; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.51 (s, 3H), 3.69(s, 3H), 3.73 (s, 3H), 6.06 (s, 1H), 6.11(s, 1H), 6.75 (s, 1H), 6.89 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 8.07 (s, 1H), 8.56 (s, 1H), 9.69 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 55.5, 89.9, 93.7, 95.8, 100.3, 113.6, 123.0, 127.6, 129.8, 139.9, 143.9, 147.6, 150.3, 156.8, 158.7, 158.9, 162.2; ESI-MS: *m/z* (rel intensity) 400 (M + Na, 68), 378 (M + 1, 100), 274 (22). Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13; Found C, 66.86; H, 5.12; N, 11.18.

6-Phenyl-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3e). m.p. 240.7–242.5°C; IR (KBr), ν (cm^{-1}): 3132, 2971, 1611, 1536, 1456, 1264, 1168, 1521, 1447, 1247, 1203, 1100, 1021, 834; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 6.23 (s, 1H), 6.37 (d, J = 7.4 Hz, 1H), 6.78 (s, 1H), 6.86 (d, J = 7.4 Hz, 1H), 7.25 (m, 5H), 8.12 (s, 1H), 8.60 (s, 1H), 9.58 (s, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 160.3, 157.3, 151.0, 148.5, 135.9, 132.0, 129.8, 128.7, 127.7, 126.7, 125.1, 122.5, 108.8, 107.1, 103.1, 96.5. ESI-MS: *m/z* (rel intensity) 388 (63), 365 (40), 346 (63), 330 (M + Na, 11), 304 (M + 1, 26), 274(52). Anal Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85; Found C, 71.21; H, 4.26; N, 13.77.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3f). m. p. 247.8–248.5°C; IR (KBr), ν (cm^{-1}): 3142, 2962, 2889, 1614, 1504, 1449, 1319, 1250, 1202, 1087, 1034, 833; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.73 (s, 6H), 6.38–6.45 (m, 2H), 6.78 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.00 (d, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.11 (s, 1H), 8.60 (s, 1H), 9.82 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.1, 101.2, 104.8, 110.7, 113.7, 121.8, 127.3, 130.5, 131.5, 142.2, 144.1, 147.6, 150.7, 156.8, 158.5, 161.3; ESI-MS: *m/z* (rel intensity) 370 (M+Na, 60), 348 (M + 1, 100). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10; Found C, 66.09; H, 4.81; N, 11.89.

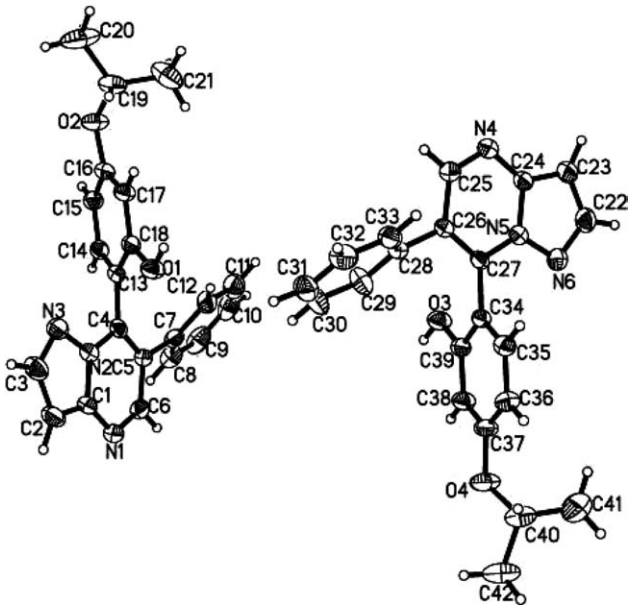


Figure 1. Single-crystal X-ray structural analysis of 3a.

6-(4-Hydroxylphenyl)-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3g). m. p. 240.6–240.8°C; IR (KBr), ν (cm^{-1}): 3138, 2923, 1611, 1545, 1505, 1455, 1251, 1179, 1110, 837; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 6.21(d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.68 (d, J = 7.6 Hz, 2H), 6.75 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 7.09 (d, J = 7.6 Hz, 2H), 8.09 (s, 1H), 8.55 (s, 1H), 9.73 (bs, 3H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 160.1, 157.3, 157.2, 151.2, 148.0, 144.4, 143.0, 131.9, 130.9, 126.3, 122.6, 115.6, 109.7, 107.0, 103.0, 96.4; ESI-MS: *m*/*z* (rel intensity) 437 (100), 346 (M + Na, 22), 319 (M + 1, 73), 274 (60), 267 (43). Anal. Calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16; Found C, 67.69; H, 3.99; N, 13.01.

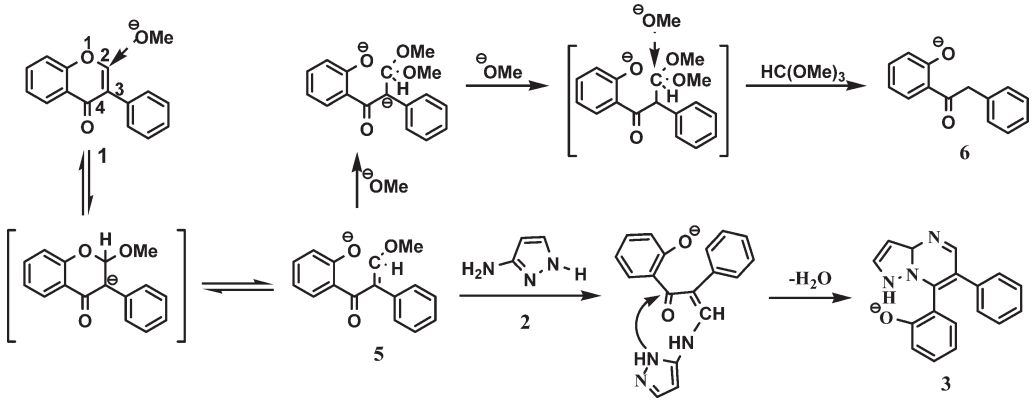
6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2,4-dihydroyphenyl)pyrazolo[1,5-*a*]pyrimidine (3h). m. p. 244.2–245.9°C; IR (KBr), ν (cm^{-1}): 3140, 2956, 2869, 2833, 1622, 1496, 1306, 1251, 1190, 1156, 955, 788; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.20 (m, 12H), 3.2 (m, 2H), 6.19 (s, 1H), 6.37 (s, 1H), 6.74 (s, 1H), 6.95 (s, 2H), 8.06–8.10 (m, 2H), 8.64 (s, 1H), 9.49–9.55 (d, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 159.4, 156.7, 150.6, 149.8, 147.2, 143.9, 142.5, 134.9, 130.9, 126.1, 124.2, 122.5, 109.7, 106.5, 102.3, 95.8, 25.9, 22.7; ESI-MS: *m*/*z* (rel intensity) 477 (22), 437 (12), 426 (9), 404 (M+1, 100), 274 (20). Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41; Found C, 71.39; H, 6.19; N, 10.37.

6-Phenyl-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]-pyrimidine (3i). m. p. 240.3–240.8°C; IR (KBr), ν (cm^{-1}): 3135, 2959, 1615, 1537, 1497, 1273, 1200, 1164, 1112, 829; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.67 (s, 3H), 6.42 (m, 2H), 6.80 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.25 (m, 5H), 8.12 (s, 1H), 8.60 (s, 1H), 9.81 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.5, 96.6, 101.6, 105.3, 110.8, 122.6, 127.8, 128.7, 129.8, 132.1, 135.7, 143.1, 144.7, 148.5, 151.0, 157.5, 161.9; ESI-MS: *m*/*z* (rel intensity) 444 (100), 437 (50), 424 (30), 402 (76), 360 (38), 318(M + 1, 44), 274(19). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24; Found C, 72.00; H, 4.82; N, 13.41.

6-(4-Hydroxyphenyl)-7-(2-hydroxy-4-methoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (3j). m. p. 242.2–244.2°C; IR (KBr), ν (cm^{-1}): 3272, 3118, 2936, 2665, 1596, 1495, 1442, 1382, 1316, 1235, 1204, 1172, 829; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.74 (s, 3H), 6.42 (m, 2H), 6.69 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.97 (d, 1H), 7.11 (d, J = 8.3 Hz, 2H), 8.10 (s, 1H), 8.57 (s, 1H), 9.53 (s, 1H), 9.77 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.0, 101.2, 104.8, 110.9, 115.1, 122.2, 125.6, 130.0, 130.5, 131.5, 142.1, 143.9, 147.5, 150.8, 156.8, 161.3; ESI-MS: *m*/*z* (rel intensity) 437 (39), 432 (22), 356 (M + Na, 34), 334 (M + 1, 100), 318 (26), 276 (68), 274 (43) . Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61; Found C, 68.53; H, 4.61; N, 12.70.

6-Phenyl-7-(2-hydroxyl-3-bromo-4-isopropoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3k). m. p. 210.2–210.9°C; IR (KBr), ν (cm^{-1}): 3140, 2980, 2901, 1607, 1486, 1445, 1403, 1323, 1258, 1192, 1105, 1102, 971, 839; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.06 (s, 12H), 3.12–3.20 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H), 6.41 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 6.76 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.07 (s, 2H) 8.09 (s, 1H), 8.67 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.0, 157.5, 153.9, 151.0, 148.1, 144.6, 142.8, 141.3, 131.7, 131.2, 125.7, 122.5, 111.7, 105.4, 101.8, 96.5, 62.3, 55.6, 26.3, 24.2; ESI-MS: *m*/*z* (rel intensity) 437 (M + Na, 57), 424 (M − 1, 19), 368 (38), 346 (100), 274

Scheme 3. Proposed mechanism for the formation of 3.



(19). Anal. Calcd for $C_{21}H_{18}BrN_3O_2$: C, 59.45; H, 4.28; N, 9.90; Found C, 59.41; H, 4.22; N, 9.84.

6-(3,5-Diisopropyl-4-methoxylphenyl)-7-(2-hydroxy-4-methoxyphenyl)pyrazolo[1,5-*a*] pyrimidine(3l). m. p. 204.3–206.8°C; IR (KBr), ν (cm^{-1}): 3452, 3140, 2956, 2873, 1642, 1623, 1496, 1468, 1306, 1078, 1014, 971, 892; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.06 (s, 12H), 3.16 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H,), 6.41 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 6.76 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.07 (s, 2H), 8.09 (s, 1H), 8.67 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.0, 157.5, 153.9, 151.0, 148.1, 144.6, 142.8, 141.3, 131.7, 131.2, 125.7, 122.5, 111.7, 105.4, 101.8, 96.5, 62.3, 55.6, 26.3, 24.2; ESI-MS: *m*/*z* (rel intensity) 454 (M+Na, 34), 432 (M + 1, 100). Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74; Found C, 71.20; H, 6.52; N, 9.49.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4,5,6-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3m). m. p. 240.2–241°C; IR (KBr), ν (cm^{-1}): 3136, 2976, 2930, 1616, 1509, 1429, 1296, 1249, 1185, 1115, 1032, 830; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.33 (t, J = 6.9 Hz, 3H), 3.74 (s, 3H), 4.00 (q, J = 6.9 Hz, 3H), 6.40 (m, 2H), 6.76 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.98 (s, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.09 (s, 1H), 8.57 (s, 1H), 9.64 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 15.1, 55.6, 63.5, 96.5, 102.3, 105.9, 111.2, 114.3, 122.3, 127.9, 131.0, 132.0, 142.8, 144.5, 148.1, 151.2, 157.3, 159.1, 161.2 ESI-MS: *m*/*z* (rel intensity) 437 (19), 390(35), 384 (M + Na, 80), 362(M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found C, 71.01; H, 5.06; N, 11.59.

6-(4-Hydroxylphenyl)-7-(2,4,6-trihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3n). m. p. 204.2–210.9°C; IR (KBr), ν (cm^{-1}): 3143, 2936, 2838, 1613, 1509, 1467, 1366, 1256, 1185, 1096, 1034, 994, 826; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.43 (s, 3H), 3.71 (m, 9H), 6.32 (d, J = 9.1 Hz, 1H), 6.91 (m, 2H), 7.28–7.33 (m, 2H), 8.12 (d, 1H, J = 9.1 Hz), 8.61 (s, 1H), 9.58 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 158.8, 154.9, 151.6, 151.2, 150.4, 147.5, 143.9, 139.4, 134.0, 130.0, 127.3, 122.6, 113.7, 104.3, 96.0, 95.5, 60.4, 60.1, 55.6, 55.0; ESI-MS: *m*/*z* (rel intensity) 430(M+Na, 76), 408 (M + 1, 100). Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31; Found C, 64.79; H, 5.00; N, 10.22.

6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2-hydroxy-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3o). m. p. 246.5–247.2°C; IR (KBr), ν (cm^{-1}): 3546, 3133, 2962, 2580, 1612, 1535, 1467, 1312, 1238, 1202, 1105, 1025, 788; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.05 (s, 12H), 3.23 (m, 2H), 3.71 (s, 3H), 6.45 (d, 1H, J = 8.5 Hz), 6.50 (s, 1H), 6.76 s, 1H), 6.93 (m, 3H), 8.08 (s, 1H), 8.13 (s, 1H), 8.68 (s, 1H), 9.81 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 161.4, 157.0, 150.7, 150.1, 147.4, 143.9, 141.9, 134.9, 131.2, 126.0, 124.2, 122.6, 111.4, 104.9, 101.3, 95.8, 55.1, 26.0, 22.7; ESI-MS: *m*/*z* (rel intensity) 440 (M + Na, 22), 418 (M + 1, 100). Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06; Found C, 71.89; H, 649; N, 9.98.

6-(3,5-Diisopropyl-4-methoxyphenyl)-7-(2-hydroxyl-4,6-dimethoxyphenl)pyrazolo[1,5-*a*]pyrimidine (3p). m. p. 242.0–243.7°C; IR (KBr), ν (cm^{-1}): 3148, 2962, 2872, 1627, 1502, 1463, 1356, 1304, 1249, 1196, 1159, 1004, 939, 808; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 0.85 (s, 12H), 2.96 (m, 2H), 3.24 (s, 3H), 3.49 (s, 3H), 3.57 (s, 3H), 5.86 (s, 1H), 5.89 (s, 1H), 6.53 (s, 1H), 6.83 (s, 2H), 7.86 (s, 1H), 8.41 (s, 1H), 9.54 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.4, 158.5, 157.1, 153.4, 150.0, 147.5, 143.9, 140.7, 140.1, 131.1, 124.8, 124.5, 123.9, 123.1, 95.8, 94.9, 93.8, 90.0, 61.9, 55.4, 55.2, 25.9, 24.7, 23.6; ESI-MS: *m*/*z* (rel intensity) 488 (38), 484 (M + Na, 60), 462 (M + 1, 100).Anal. Calcd for $C_{27}H_{31}N_3O_4$: C, 70.26; H, 6.77; N, 9.10; Found C, 70.12; H, 6.47; N, 8.95.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-3-bromo-4-methoxyphenyl)pyrazolo[1,5-*a*] pyrimidine (3q). m. p. 202.8–204.3°C; IR (KBr), ν (cm^{-1}): 3488, 2940, 1600, 1490, 1451, 1396, 1250, 1205, 1049, 829, 787; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.86 (d, 6H), 6.80 (s, 1H), 6.52 (s, 1H), 6.90 (s, 1H, J = 8.4 Hz), 7.08 (s, 1H), 7.24 (s, 1H, J = 8.4 Hz), 7.36–7.48 (d, 2H), 8.13 (s, 1H,), 8.59 (s, 1H), 10.15 (d, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 56.6, 96.7, 96.9, 100.9, 112.8, 114.3, 122.5, 130.4, 131.0, 134.0, 134.4, 144.7, 145.0, 151.0, 151.3, 157.0; ESI-MS: *m*/*z* (rel intensity) 505 (22), 453 (27), 426 (M + 1, 100). Anal. Calcd for $C_{20}H_{16}BrN_3O_3$: C, 56.35; H, 3.78; N, 9.86; Found C, 56.41; H, 3.84; N, 9.97.

6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2,4,6-trihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3r). m. p. 248.4–249.6°C; IR (KBr), ν (cm^{-1}): 3207, 2962, 1876, 1648, 1565, 1443, 1295, 1191, 1158, 833; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.15 (d, 12H, J = 6.2 Hz), 3.30 (m, 2H), 6.00 (s, 1H), 6.09 (s, 1H), 6.62 (s, 1H), 7.21 (s, 2H), 7.87 (s, 1H), 8.01 (s, 1H), 8.07 (s, 1H), 10.30 (s, 1H), 13.32 (s, 1H), 15.03 (s, 1H); ^{13}C-NMR[75 MHz, DMSO-d_6/TMS, δ (ppm)]: 179.4, 163.7, 162.5, 150.1, 148.5, 142.7, 141.1, 134.7, 131.1, 125.1, 123.7, 119.9, 107.1, 101.9, 98.0, 91.6, 26.2, 23.0. ESI-MS: *m*/*z* (rel intensity) 462 (32), 442 (M + Na, 44), 420 (M + 1, 100), 346 (50). Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02; Found C, 68.81; H, 6.21; N, 10.15.

6-(4-Hydroxyl-3,5-dibromophenyl)-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3s). m. p.185.1–189.5°C; IR (KBr), ν (cm^{-1}): 3466, 2922, 1601, 1543, 1466, 1299, 877, 785; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.84 (s, 3H), 6.46 (d, 1H, J = 7.8 Hz), 6.80 (s, 1H), 7.09 (s, 1H, J = 7.8 Hz), 7.48 (d, 2H), 8.14 (s, 1H,), 8.63 (s, 1H), 9.98 (t, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.3, 100.3, 101.1, 105.5, 111.4, 119.8, 129.1, 131.5, 132.9, 134.0, 140.8, 142.5, 144.4, 147.7, 150.2, 156.6, 161.6; ESI-MS: *m*/*z* (rel intensity) 491 (M + 1, 19), 477 (100), 431 (40). Anal. Calcd for $C_{19}H_{13}Br_2N_3O_3$: C, 46.46; H, 2.67; N, 8.56; Found C, 46.52; H, 2.71; N, 8.84.

6-(4-Methoxyphenyl)-7-(2-hydroy-4-ethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin (3t). m. p. 240.2–241°C; IR (KBr), ν (cm^{-1}): 3136, 2976, 2930, 1616, 1509, 1429, 1296, 1249, 1185, 1115, 1032, 830; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.33 (t, J = 6.9 Hz, 3H), 3.74 (s, 3H), 4.00 (q, J = 6.9 Hz, 3H), 6.40 (m, 2H), 6.76 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.4 Hz), 7.23 (d, J = 8.6 Hz, 2H), 8.09 (s, 1H), 8.57 (s, 1H), 9.64 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 15.1, 55.6, 63.5, 96.5, 102.3, 105.9, 111.2, 114.3, 122.3, 127.9, 131.0, 132.0, 142.8, 144.5, 148.1, 151.2, 157.3, 159.1, 161.2; ESI-MS: *m*/*z* (rel intensity) 437 (19), 390(35), 384 (M + Na, 80), 362(M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found C, 71.01; H, 5.06; N, 11.59.

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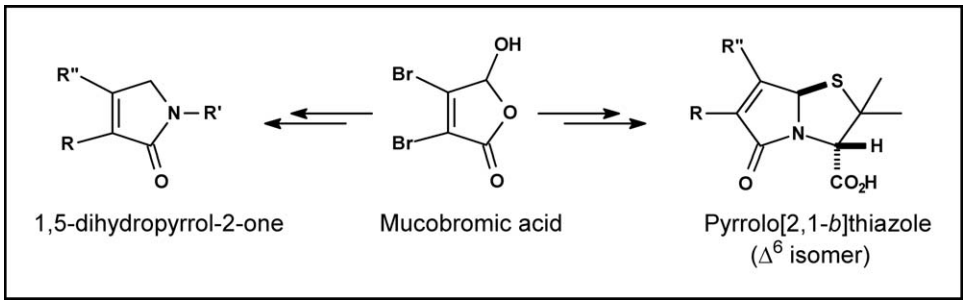

A modular synthesis of selectively-substituted pyrrolo[2,1-*b*]thiazoles (Δ^6 isomeric form) has been implemented, involving a distinctive bicyclization reaction of a mucobromic acid derivative followed by a Suzuki-Miyaura coupling. A novel process of Δ^6 to Δ^7 isomerization of the pyrrolothiazole structure was uncovered that appears to involve a 1,4-addition-1,2-elimination mechanism. Preparation of 1,5-dihydropyrrol-2-one structures, selectively substituted at the 3- and 4-positions, was also achieved using the mucobromic acid synthon in a reductive amination process.

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INTRODUCTION

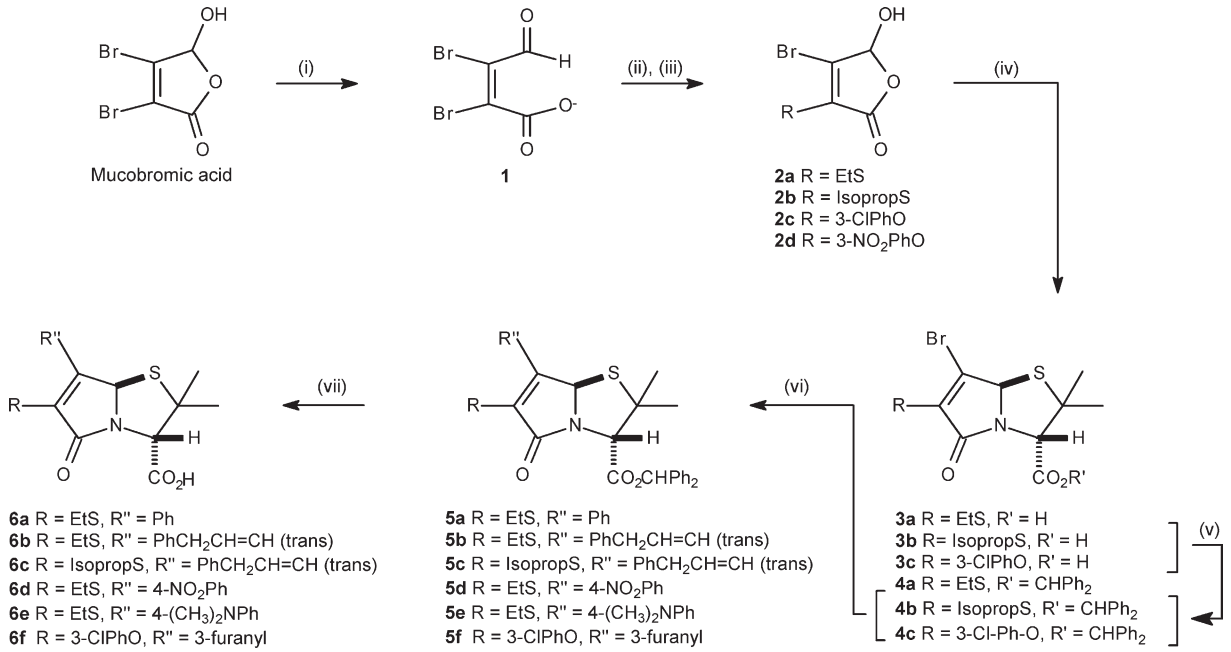
Pyrrolo[2,1-*b*]thiazole and 1,5-dihydropyrrol-2-one structures are important synthetic targets given the range of biological and other properties that they show [1,2]. As part of our research on development of serine protease inhibitors a modular synthesis of the above structures was required that allowed for ready variation of the substituent groups R, R′, and R″. Herein we report on a modular synthesis based on mucobromic acid, which is a cheap multifunctional building block [3–5].

RESULTS AND DISCUSSION

The first step in the modular synthesis (Scheme 1) was introduction of substituent R via a 1,4-addition-elimination reaction on the anionic ring-opened form of mucobromic acid. Thiols and phenols are suitable for this reaction as the corresponding thiolate and phenoxide nucleophiles are readily formed in aqueous base [6] here ethyl and isopropyl mercaptan as well as 3-chloro and 3-nitrophenol were used. Formation of the pyrrolo[2,1-*b*]thiazole structure was achieved by a bicyclization reaction of the muco derivative with D-penicillamine. This type of reaction was first reported by Wasserman et al. [7] and was later exploited by Moore and Arnold, who verified by X-ray crystallography that a single stereoisomer of the bicyclic product was formed. [8] The bicyclic structure **3** was converted to its benzhydryl ester **4** to facilitate its purification and for optimal formation of the subsequent Suzuki-Miyaura products **5a–f**. The R′ substituents (aryl, heteroaryl, and alkenyl groups) were introduced by a Suzuki-Miyaura coupling [9] using commercially available boronic acids or boronic acid pinacol esters.

A mechanism for the bicyclization with D-penicillamine is given in Scheme 2 together with data (this work) on the relative thermodynamic stability of the diastereomeric products **B** and **B′**: the stereochemical outcome appears to be controlled by an unfavorable endocyclic interaction between the 3-carboxyl group and the γ-lactam carbonyl that occurs in **B′** but not in **B**. The facile formation of structure type **B**, involving H_2O as a leaving group in a weakly acidic aqueous medium at ambient temperature, attests to the strong thermodynamic driving force for cyclization of structure type **A**. During the synthetic work, it was found that the bicyclization reaction did not proceed well where the halogen of muco structure **2** was replaced by nonelectron-withdrawing groups. The reaction rate and yield of the bicyclization was much lower (27–32%) when cysteine was used in place of penicillamine [10]. This difference may be as a result of a faster thiazolidine ring formation step with penicillamine due to a gem-dimethyl effect

Scheme 1. (i) KOH_{aq}, (ii) RSH or ArOH, KOH_{aq}, (iii) HCl_{aq}, (iv) D-penicillamine, EtOH/H_2O 1:1, HOAc (1.2 equiv.), (v) Diphenyldiazomethane, (vi) Suzuki-Miyaura coupling, (vii) $AlCl_3$ in CH_2Cl_2/$EtNO_2$, −80°C, 1 h.

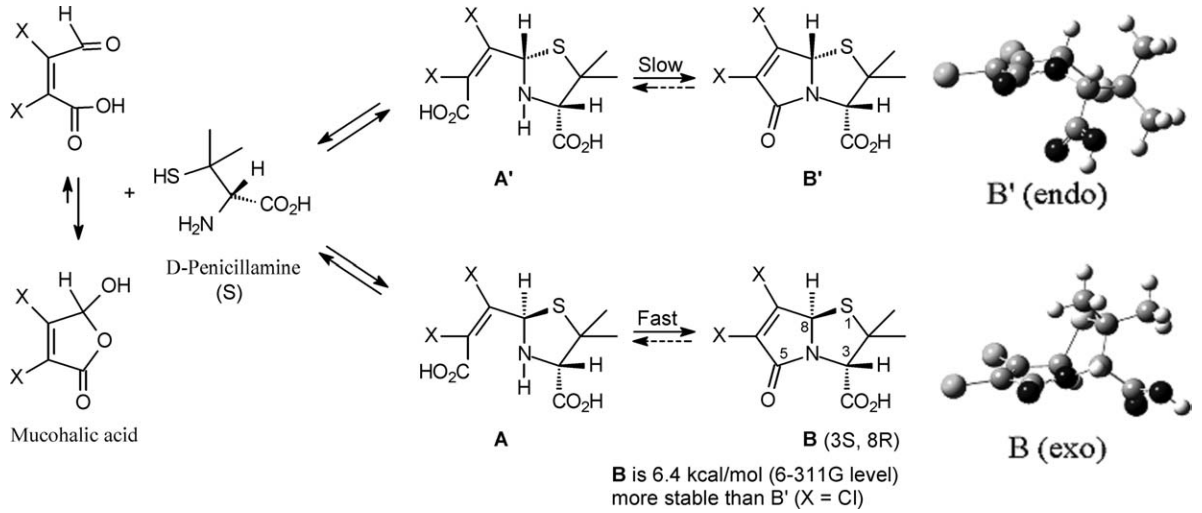


[11], making the bicyclization path dominant over competing side reactions.

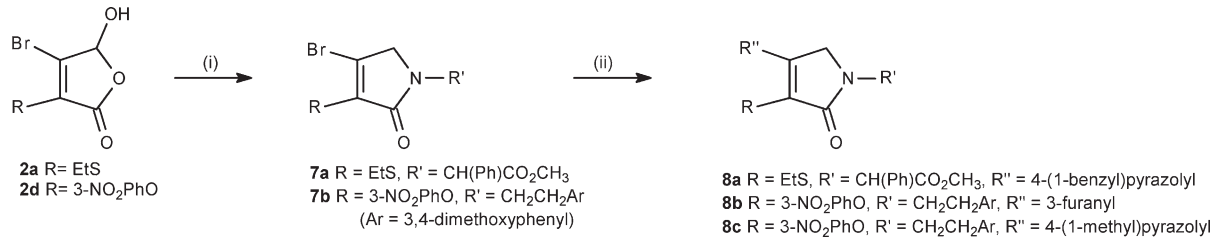
Muco synthons **2a** and **2d** were also used to prepare a set of 1,5-dihydropyrrol-2-ones (**8a–c**, Scheme 3) by reductive amination followed by Suzuki-Miyaura coupling. (R)-phenylglycine methyl ester was used for the preparation of **7a** and 2-(3,4-dimethoxyphenyl)ethylamine was used for **8b** and **8c**. This reaction occurs via imine formation with the neutral ring-opened form of the mucoderivative, which is present in very low equilibrium concentration with the ring-closed form [5]. Hydride addition to the imine leads directly to cyclization—here again the facile ring closure, involving water as a leaving group in a weakly acidic medium at ambient temperature, indicates the strong thermodynamic driving force for the formation of the unsaturated γ-lactam unit. In the reductive amination step with **2a,** a small amount of the desbromo reduction product was formed, which was removed prior to the coupling step.

Isomerisation of Δ^6 to the Δ^7 isomer. In previous work, we had found that, in at least one case, the Δ^7 isomer was thermodynamically more stable than the Δ^6 isomer. Thus, in the rearrangement reaction of a modified penicillin with MeOH/Et_3N (Scheme 4), the

Scheme 2. Mechanism of the bicyclization reaction between D-penicillamine and a mucohalic acid.

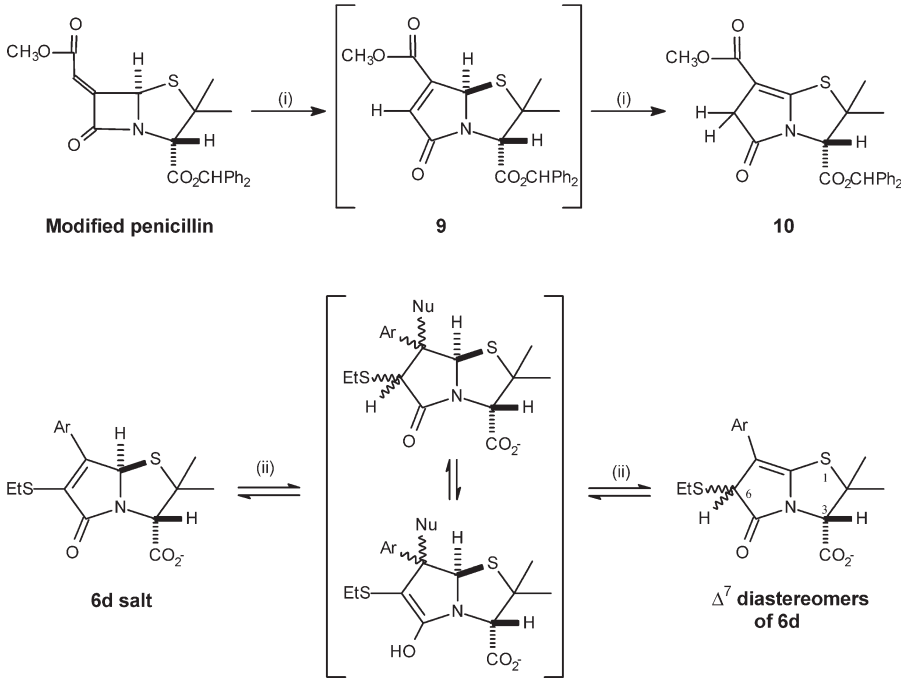


Scheme 3. (i) Reductive amination; (ii) Suzuki-Miyaura coupling



quantitatively isolated product was the Δ^7 pyrrolothiazole **10**, which must have been derived from the initially-formed Δ^6 isomer **9** [12]. The most likely isomerization mechanism under those reaction conditions is via deprotonation of the bridgehead hydrogen H-8. This process was found to lack general applicability. In this work, an alternative isomerization process was uncovered with the carboxylate salt of **6d**. The ^{1}H NMR spectrum of **6d** in D_2O buffer (50 m*M* phosphate, pH 7.2) containing 10% DMSO-d6 indicated the presence of ~1% each of two structures, which were not present in the free acid **6d** in $CDCl_3$. Unexpectedly, the ^{1}H NMR spectrum (D_2O) of the solids recovered after freeze-drying showed the presence of ~10% of each of the new structures with the remainder being, largely, unreacted **6d**. Indeed, the material recovered after freeze-drying twice from phosphate buffer/10%DMSO contained ~30% of each of the new structures (Fig. 1); this value rose to 41% when phosphate buffer/20% DMSO was used. Two further freeze-drying cycles from H_2O to maximize removal of DMSO did not alter the composition, however, on standing for several days at 4°C the solid material—a DMSO solvate by its ^{1}H NMR spectrum—was found to contain, largely, the Δ^7 isomers but no **6d**. The new structures did not correspond to the γ-lactam ring-opened form of **6d**. In previous work, we had shown that a signature of such ring-opened structures is the significant upfield shift of the resonance of a gem-dimethyl group [12], which was absent here, and in addition, **6d** was found to remain unchanged after 20 h at 21°C in D_2O buffer (50 m*M* phosphate, pH 7.2). The new resonances were consistent with two Δ^7 diastereomers (6-R and 6-S epimers) derived from the **6d** salt: two new sets of resonances were clearly observed for the aromatic hydrogens and for H-3, and the new resonances for the methylene hydrogens of the ethylsulfanyl unit at

Scheme 4. Mechanisms of Δ^6 to Δ^7 isomerization of selected pyrrolo-thiazole structures. Top route: Deprotonation of bridgehead hydrogen H-8: (i) CH_3OH/NEt_3; Lower route: 1,4 addition-1,2 elimination, (ii) aqueous phosphate buffer/20% DMSO (with freeze-drying), Ar = *p*-nitrophenyl, Nu = nucleophile-cum-leaving group.



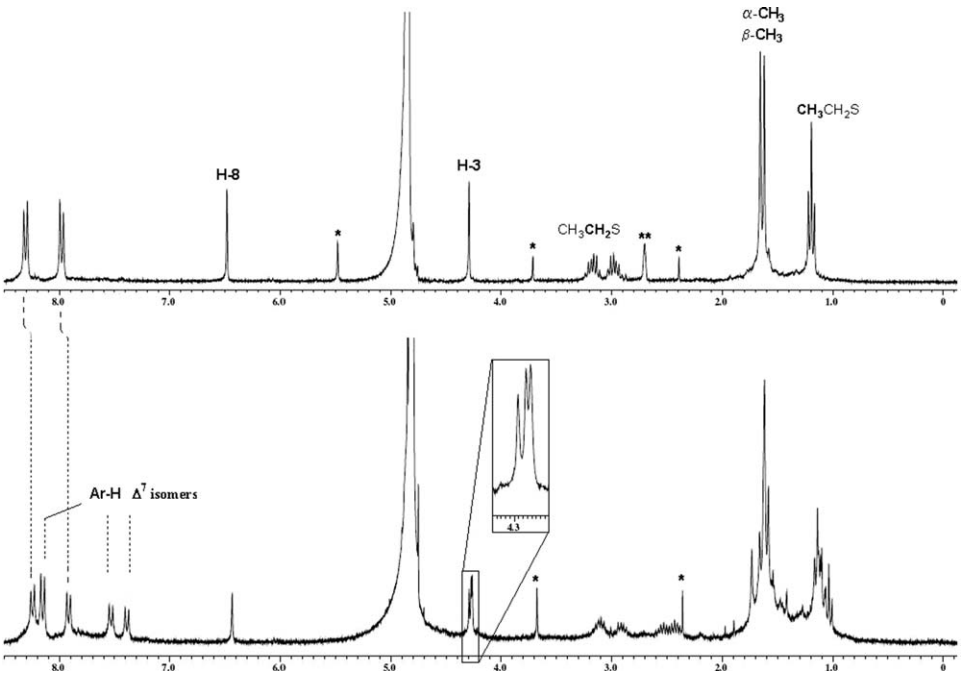


Figure 1. Top: ^{1}H NMR spectrum of the *p*-nitrophenyl derivative **6d** in D_2O phosphate buffer/10%DMSO-d6. Bottom: ^{1}H NMR spectrum in D_2O of the material recovered after two stages of freeze-drying from phosphate buffer/10% DMSO showing ~30% of each of the Δ^7 isomers. * = solvent impurities, ** = DMSO-d6. Note that a small displacement of chemical shift values is observed between D_2O buffer/10% DMSO-d6 and pure D_2O as solvent.

2.45 ppm were characteristic of those of a dialkyl sulfide such as diethyl sulfide. The initial observation in the D_2O buffer system showed a diminution in the intensity of the H-8 resonance of **6d** without the obvious appearance of a new peak indicating deuterium incorporation in the new structures. High-resolution mass

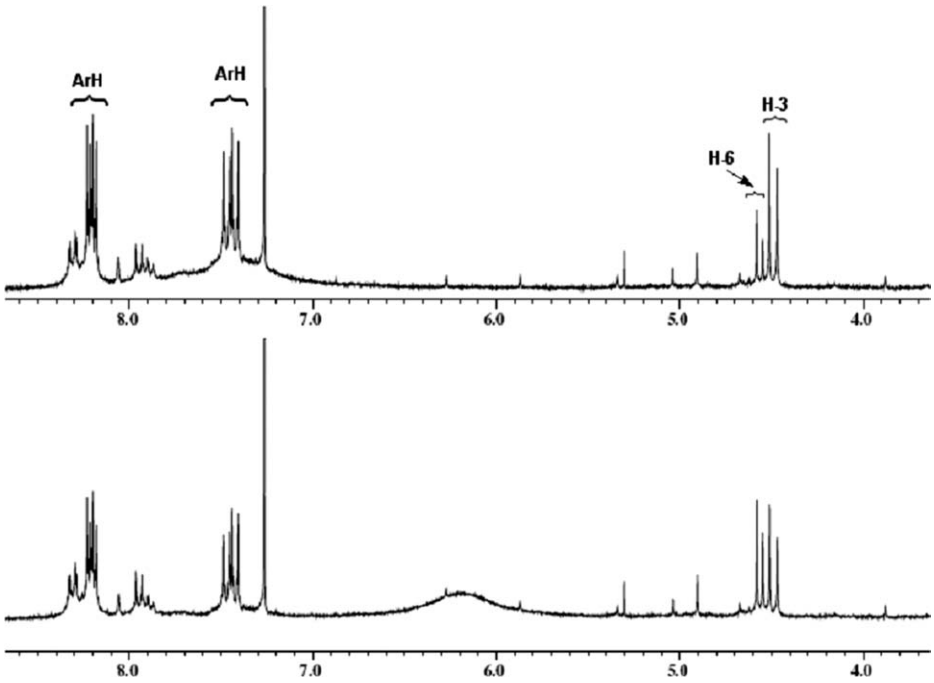


Figure 2. A portion of the ^{1}H NMR spectrum in $CDCl_3$ of the recovered free acids (crude) of each Δ^7 isomer of **6d**. (Bottom): before exchange with D_2O; (Top): after partial exchange with D_2O.

spectral analysis of this sample gave peaks at 393.0573 and at 394.0641, which correspond respectively, to the molecular weights of the Δ^6 isomer (calcd. 393.0579) and of the Δ^7 isomer containing one deuterium (calcd. 394.0642). The crude free acids of the Δ^7 isomers were recovered from an acidified aqueous solution (pH 3.5) of the solids by extraction with dichloromethane. The ^{1}H NMR spectrum (Fig. 2) of these clearly showed singlets, ~40:60, respectively, for each H-3 at 4.47 and 4.51, and at 4.55 and 4.58 ppm for each H-6; these latter hydrogens were characterized by being exchanged for deuterium on addition of D_2O. The enhancing effect of divalent sulfur on the kinetic acidity of α-hydrogens is well established [13].

The most likely mechanism of isomerization is via 1,4-addition-1,2-elimination as shown in Scheme 4, with phosphate dianion as the nucleophile-cum-leaving group. For an example of a reaction where phosphate di-anion has been shown to act as a nucleophile-cum-leaving group see [14]. The finding that a similar isomerization occurred with the phenyl derivative **6a** but not with the *N*,*N*-dimethyl derivative **6e** supports a 1,4 addition step. In the freeze-drying process water is removed faster than DMSO so that the frozen solution becomes enriched in DMSO, which may enhance the activity of the buffer nucleophiles [15] this may also be the case with the solid DMSO solvate. Isomerization of the earlier-stage synthon **3a** was unsuccessful under these conditions.

CONCLUSIONS

A concise modular synthesis of selectively-substituted pyrrolo[2,1-*b*]thiazoles (Δ^6 isomeric form) has been implemented, involving a distinctive bicyclization step with a mucobromic acid derivative. A novel process of Δ^6 to Δ^7 isomerization of these pyrrolothiazoles was uncovered that appears to involve a 1,4-addition-1,2-elimination mechanism, which is accelerated by repeated freeze-drying from a phosphate buffer/DMSO mixture. The synthesis of related monocyclic 3,4-disubstituted 1,5-dihydropyrrol-2-ones was also elaborated by reductive amination of the mucobromic acid derivative.

EXPERIMENTAL

1,4-Addition-elimination–general procedure. To a solution of mucobromic acid (1.00 g, 3.88 mmol) in water (4 mL) containing potassium hydroxide (256 mg, 4.56 mmol) was added the required alkyl mercaptan (5.82 mmol), or substituted phenol (4.27 mmol), in water (3.5 mL) containing potassium hydroxide (392 mg, 5.82 mmol). The mixture was allowed to stir at room temperature for 3 h. The pH was lowered to <2 using 1*M* HCl and extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to leave a brown (**2a** and **2b**) or orange (**2c**) to bright orange (**2d**) oil.

4-Bromo-3-ethylsulfanyl-5-hydroxy-5*H*-furan-2-one (2a). 568 mg, 2.38 mmol, 61%; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7 0.42 Hz, C**H$_3$**—CH_2), 3.23 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H$_{2A}$**S (diastereotopic)) overlapping with 3.29 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H$_{2B}$**S (diastereotopic)), 5.97 (s, 1H, **H**-5); ^{13}C NMR (67.5 MHz, $CDCl_3$, DEPT) δ15.49 (**C**$H_3$$CH_2$S), 25.01 ($CH_3$**C**$H_2$), 97.70 (**C**H(OH)O), 131.11, 139.27 (**C**-3, **C**-4), 166.53 (**C**=O); ESI-HRMS for $C_6H_7O_3SBr$: $[M - H]^-$ calcd: 236.9221, found: 236.9256 and 238.9241. This material was used directly in the bicyclization reaction (see below) without further purification.

4-Bromo-5-hydroxy-3-isopropylsulfanyl-5*H*-furan-2-one (2b). (754 mg, 2.98 mmol, 50%); ^{1}H NMR (270 MHz, $CDCl_3$) δ1.32 (d, 6H, J = 6.93 Hz (C**H$_3$**)$_2$CHS, diastereotopic methyl groups with coincident chemical shifts), 4.22 (sept, 1H, J = 6.68 Hz, (CH_3)$_2$C**H**S), 6.00 (s, 1H **H**-5); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.59, 23.96 ((**C**H_3)$_2$CHS (diastereotopic methyl groups)), 35.82 ((CH_3)$_2$**C**HS), 97.82 (**C**H(OH)O), 131.43, 141.27 (**C**-3, **C**-4), 166.83 (**C**=O); EI-HRMS for $C_7H_9O_3SBr$: $[M]^+$ calcd: 251.9459, found: 251.9456 and 253.9453. This material was used directly in the bicyclization reaction (see below) without further purification.

4-Bromo-3-(3-chlorophenoxy)-5*H*-furan-2-one (2c). Purification by silica gel column chromatography using 1:1 dichloromethane/hexane containing 5% acetic acid, followed by washing with water to remove acetic acid, gave **2c** as a colorless gum (590 mg, 1.93 mmol, 50%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.10 (s, 1H, **H**-5), 6.96 (ddd, 1H, J = 8.18, 2.47, 0.99 Hz, Ar**H**), 7.07 (app t, 1H, J = 2.23 Hz, Ar**H**), 7.17 (ddd, 1H, J = 7.92, 1.98, 0.99 Hz, Ar**H**), 7.28 (t, 1H, J = 8.16 Hz, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 96.24 (**C**H(OH)O), 115.93, 118.15, 123.02 (**C**-3/**C**-4), 125.07, 130.42, 134.90 (**C**-3/**C**-4), 142.34, 154.26 (Ar**C**), 164.52 (**C**=O); ESI-HRMS for $C_{10}H_6O_4BrCl$: $[M + Na]^+$ calcd: 326.9036, found: 326.9046 and 328.9040.

4-Bromo-3-(3-nitrophenoxy)-5*H*-furan-2-one (2d). Purification by silica gel column chromatography using 1:1 dichloromethane/hexane containing 5% acetic acid, followed by washing with water to remove acetic acid, gave **2d** as a pale yellow gum (637 mg, 2.02 mmol, 52%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.17 (s, 1H, **H**-5), 7.44 (ddd, 1H, J = 8.16, 2.47, 1.24 Hz, Ar**H**), 7.56 (t, 1H, J = 8.16 Hz, Ar**H**), 7.88 (app t, 1H, J = 1.98 Hz, Ar**H**), 8.05 (ddd, 1H, J = 8.16, 1.98, 0.99 Hz, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 96.26 (**C**H(OH)O), 112.75, 119.81, 124.0, 124.54 (**C**-3/**C**-4), 130.63, 142.36 (**C**-3/**C**-4), 148.87, 154.39 (Ar**C**), 163.61 (**C**=O); ESI-HRMS for $C_{10}H_6O_6Br$: $[M + H]^+$ calcd: 337.9276, found: 337.9290 and 339.9274.

Bicyclization–general procedure. To a solution of D-penicillamine (315 mg, 2.11 mmol) and sodium chloride (144 mg) in water (3 mL) containing acetic acid (144 μL, 2.52 mmol) was added a solution of the required muco derivative **2a-2c** (1.92 mmol) in ethanol (3 mL). The mixture was stirred at room temperature overnight and was then extracted with dichloromethane (10 mL). The organic layer was dried, filtered and concentrated by rotary evaporation to yield the free acid as a yellow solid.

(3S,7aR)-7-Bromo-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*] thiazole-3-carboxylic acid (3a). A yellow solid (459 mg, 1.31 mmol, 68%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.42 Hz, C**H$_3$**CH_2S), 1.59 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 3.14 (dq, 1H, J = 13.5, 7.42 Hz,

$CH_3C\mathbf{H_{2A}}S$ (diastereotopic)) overlapping with 3.25 (dq, 1H, J = 13.5, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$ (diastereotopic)), 4.66 (s, 1H, **H**-3), 5.87 (s, 1H, **H**-8). This material was converted into its benzhydryl ester (see below) without further purification.

(3S,7aR)-7-Bromo-6-isopropylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo [2,1-*b*]thiazole-3-carboxylic acid (3b). A yellow solid (458 mg, 1.25 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (d, 3H, J = 6.68 Hz, $(C\mathbf{H_{3A}})_2$CHS (diastereotopic)) overlapping with 1.31 (d, 3H, J = 6.68 Hz, $(C\mathbf{H_{3B}})_2$CHS (diastereotopic)), 1.58 (s, 3H, α-C$\mathbf{H_3}$), 1.62 (s, 3H, β-C$\mathbf{H_3}$), 4.09 (sept, 1H, J = 6.68 Hz, $(CH_3)_2C\mathbf{H}$S), 4.68 (s, 1H, **H**-3), 5.90 (s, 1H, **H**-8). This material was converted into its benzhydryl ester (see below) without further purification.

(3S,7aR)-7-Bromo-6-(3-chlorophenoxy)-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid (3c). A pale yellow oil (611 mg, 1.46 mmol, 76%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.66 (s, 6H, α-C$\mathbf{H_3}$, β-C$\mathbf{H_3}$), 4.62 (s, 1H, **H**-3), 5.96 (s, 1H, **H**-8), 6.93 (ddd, 1H, J = 7.92, 2.47, 0.99 Hz, **H**ArCl), 7.05 (app t, 1H, J = 2.24 Hz, **H**ArCl), 7.11 (ddd, 1H, J = 7.92, 2.47, 0.99 Hz, **H**ArCl), 7.25 (t, 1H, J = 7.92 Hz, **H**ArCl). This material was converted into its benzhydryl ester (see below) without further purification.

Benzyhydryl ester formation–general procedure. To the required pyrrolothiazole acid **3a-3c** in dichloromethane at room temperature was added dropwise a solution of diphenyldiazomethane (∼0.65*M*) in dichloromethane (prepared by oxidation of benzophenone hydrazone with activated MnO_2) until a pale pink color persisted and the evolution of nitrogen gas was no longer observable (2–3 h). The solution was concentrated by rotary evaporation to yield a yellow solid, which was purified by silica gel column chromatography as indicated below.

(3S,7aR)-7-Bromo-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*] thiazole-3-carboxylic acid benzhydryl ester (4a). Purification using 3:1 dichloromethane/hexane gave **4a** as a pale yellow solid (438 mg, 0.84 mmol, 49%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3H, α-C$\mathbf{H_3}$), 1.29 (t, J = 7.42 Hz, 3H, C$\mathbf{H_3}CH_2$S), 1.50 (s, 3H, β-C$\mathbf{H_3}$), 3.13 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}$S (diastereotopic)) overlapping with 3.25 (dq, 1H, J = 13.50, 7.72 Hz, $CH_3C\mathbf{H_{2B}}$S (diastereotopic)), 4.79 (s, 1H, **H**-3), 5.89 (s, 1H, **H**-8), 6.98 (s, 1H, C**H**$(Ph)_2$), 7.26–7.39 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ15.62 (**C**H_3CH_2S), 25.03 (α-**C**H_3), 26.11 (CH_3**C**H_2S), 32.13 (β-**C**H_3), 60.70, 68.76, 72.26 (**C**-2, **C**-3, **C**-8), 78.48 (**C**$H(Ph)_2$), 126.92, 127.73, 128.12, 128.39, 128.55, 128.59, 132.58, 138.97, 139.05, 139.09 (Ar**C**, **C**-6, **C**-7), 167.49, 169.53 (2× **C**=O); ESI-HRMS for $C_{24}H_{24}NO_3Br$: [M + Na]$^+$ calcd: 540.0283, found: 540.0291 and 542.0333.

(3S,7aR)-7-Bromo-6-isopropylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo [2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (4b). Purification using 3:1 dichloromethane/hexane gave **4b** as a yellowish solid (488 mg, 0.92 mmol, 33%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3H, α-C$\mathbf{H_3}$) overlapping with 1.28 (d, 3H, J = 6.93 Hz, $(C\mathbf{H_{3A}})_2$CHS (diastereotopic)) overlapping with 1.30 (d, 3H, J = 6.93 Hz, $(C\mathbf{H_{3B}})_2$CHS (diastereotopic)), 1.49 (s, 3H, β-C$\mathbf{H_3}$), 4.13 (sept, 1H, J = 6.80 Hz, $(CH_3)_2C\mathbf{H}$S), 4.81 (s, 1H, **H**-3), 5.92 (s, 1H, **H**-8), 6.98 (s, 1H, C**H**$(Ph)_2$), 7.30–7.37 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.19, 24.27 ($(CH_3)_2$CHS (diastereotopic methyl groups)), 26.10 (α-**C**H_3), 32.22 ($(CH_3)_2$**C**H), 35.63 (β-**C**H_3), 60.71, 68.77, 72.32 (**C**-2, **C**-3, **C**-8), 78.47 (**C**H-Ar_2), 126.92, 127.69, 128.11, 128.38, 128.54, 128.58, 132.90, 139.05, 139.09, 140.92 (Ar**C**, **C**-6, **C**-7), 167.48, 169.67 (2× **C**=O); ESI-HRMS for $C_{25}H_{26}NO_3S_2Br$: [M + H]$^+$ calcd: 532.0616, found: 532.0595 and 534.0617.

(3S,7aR)-7-Bromo-6-(3-chlorophenoxy)-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (4c). Purification using 1:1 dichloromethane/hexane gave **4c** as a pale yellow solid (535 mg, 0.92 mmol, 63%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 3H, α-C$\mathbf{H_3}$), 1.53 (s, 3H, β-C$\mathbf{H_3}$), 4.76 (s, 1H, **H**-3), 5.95 (s, 1H, **H**-8), 6.92 (dd, 1H, J = 8.16, 2.47 Hz, **H**ArCl), 6.98 (s, 1H, C**H**Ph_2), 7.05 (app t, 1H, J = 2.23 Hz, **H**ArCl), 7.11 (dd, 1H, J = 8.16, 2.23 Hz, **H**ArCl), 7.25 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.29–7.38 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 26.23 (α-**C**H_3), 32.06 (β-**C**H_3), 60.80, 68.39, 69.10 (**C**-2, **C**-3, **C**-8), 78.68 (**C**HPh_2), 115.32, 117.79, 122.42, 124.49, 126.94, 127.77, 128.19, 128.47, 128.60, 128.65, 130.38, 135.06, 139.97, 139.03, 144.31, 155.33 (Ar**C**, **C**-6, **C**-7), 165.92, 167.33 (2× **C**=O); ESI-HRMS for $C_{28}H_{23}NO_4SClBr$: [M + Na]$^+$ calcd: 606.0117, found: 606.0129 and 608.0104.

Reductive Amination–General Procedure. (R)-(4-Bromo-3-ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl)-phenylacetic acid methyl ester (7a). To a stirred solution of **2a** (412 mg, 1.72 mmol) and phenyl glycine methyl ester hydrochloride (416 mg, 2.06 mmol) in chloroform (5 mL) was gradually added sodium triacetoxyborohydride (547 mg, 2.58 mmol). The solution color lightened during addition from dark to pale yellow. After stirring for 10 min at room temperature the mixture was diluted with chloroform (10 mL) and washed twice with DIW (10 mL). The organic extracts were combined, dried, filtered, and concentrated by rotary evaporation to leave a yellow solid. Purification by silica gel column chromatography using 1:1 hexane/ethylacetate gave **7a** as a pale yellow glassy solid (238 mg, 0.643 mmol, 35%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (t, J = 7.42 Hz, 3H, (C$\mathbf{H_3}CH_2$S), 3.15 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}$S(diastereotopic)) overlapping with 3.21 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}$S(diastereotopic)), 3.58 (d, J = 18.80 Hz, 1H, **H**-5_A), 3.79 (s, 3H, OC$\mathbf{H_3}$), 4.44 (d, J = 18.80 Hz, 1H, **H**-5_B), 6.06 (s, 1H, C**H**C(O)), 7.23–7.44 (m, 5H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.47 (**C**H_3CH_2S), 25.22 (CH_3**C**H_2S), 52.58, 54.08, 57.82 (**C**-5, O**C**H_3, N**C**H(Ph)), 128.47, 129.01, 129.23, 131.56, 133.57, 134.63, 140.52 (Ar**C**, **C**-3, **C**-4), 167.13, 170.47 (2× **C**=O); ESI-HRMS for $C_{15}H_{16}BrNO_3S$: [M + H]$^+$ calcd: 370.0113, found: 370.0103 and 372.0041.

(R)-(3-Ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl)-phenylacetic acid methyl ester (desbromo structure). An off-white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.42 Hz, C$\mathbf{H_3}CH_2$S), 2.89 (q, 2H, J = 7.42 Hz, $CH_3C\mathbf{H_2}$S (diastereotopic methylene hydrogens with coincident chemical shifts), 3.51 (dd, 1H, J = 19.55, 2.47 Hz, **H**-5_A), 3.77 (s, 3H, OC$\mathbf{H_3}$), 4.35 (dd, 1H, J = 19.55, 2.47 Hz, **H**-5_B), 6.12 (s, 1H, C**H**C(O)), 6.51 (t, 1H, J = 2.47, **H**-4), 7.20–7.39 (m, 5H, Ar**H**); ESI-HRMS for $C_{15}H_{17}NO_3S$: [M]$^+$ calcd: 291.0929, found: 291.0927.

4-Bromo-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (7b). Prepared as for **7a** but using **2d** with 2-(3,4-dimethoxyphenyl)ethylamine hydrochloride, in dichloroethane with a 12 h reaction time; purification by silica gel column chromatography using ethylacetate/hexane 1:1 then 3:1 gave **7b** as a yellow oil (239 mg, 0.516 mmol, 30%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.89 (t, 2H, J = 7.17 Hz, $NCH_2C\mathbf{H_2}$), 3.71 (t, 2H, J = 7.17 Hz, $NC\mathbf{H_2}CH_2$), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H,

OCH_3), 3.91 (s, 2H, C**H**$_2$NC(O)), 6.73–6.86 (m, 3H, **H**Ar(-$OCH_3)_2$), 7.305 (ddd, 1H, J = 8.16, 2.47, 0.99 Hz, **H**ArNO_2), 7.50 (t, 1H, J = 8.16 Hz, **H**ArNO_2), 7.80 (app t, 1H, J = 2.47 Hz, **H**ArNO_2), 7.98 (ddd, 1H, J = 8.16, 2.23, 0.99 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 34.12 (NCH_2**C**H_2), 44.56, 52.98 (N**C**H_2CH_2, **C**H_2NC(O); 55.90 (2 × O**C**H_3), 111.43, 111.64, 117.71, 114.89, 118.58, 120.61, 123.21, 130.20, 130.38, 144.72, 147.92, 148.95, 149.14, 155.67 (Ar**C**, **C**-3, **C**-4), 162.97 (**C**=O); ESI-HRMS for $C_{20}H_{19}N_2O_6Br$: [M + H]$^+$ calcd: 463.0505, found: 463.0490 and 465.0471.

Suzuki-Miyaura Coupling–general Procedure. To a solution of the required benzhydryl ester **4a–4c**, or the muco derivatives **7a** and **7b**, (0.498 mmol) in degassed 1:1 toluene/water (4 mL each) was added the required boronic acid (0.747 mmol), cesium fluoride (151 mg, 0.996 mmol), $PdCl_2(PPh_3)_2$ (8.74 mg, 0.01245 mmol), and benzyldimethylhexadecyl ammonium chloride (4.93 mg, 0.01245 mmol). The mixture was heated to reflux under N_2 for 2–48 h during which time the color changed from yellow-brown to either pink or brown; reaction progress was monitored by ^{1}H NMR spectroscopy. The mixture was allowed to cool to room temperature, quenched with 0.5*M* HCl (50 mL) and diluted with toluene (20 mL) and separated. The aqueous layer was re-extracted with toluene (20 mL), the organic extracts were combined, washed with DIW (30 mL), dried, filtered, and concentrated by rotary evaporation to yield a red orange gel, which was purified by silica gel column chromatography as indicated below.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-phenyl-2,3,5,7a-tetrahydro pyrrolo [2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5a). The reaction time is 2.5 h; purification using 3:1 dichloromethane/hexane gave **5a** as a pale yellow solid (121 mg, 0.235 mmol, 47%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.32 (s, 3H, α-C**H**$_3$), 1.54 (s, 3H, β-C**H**$_3$), 3.12 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.28 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.83 (s, 1H, **H**-3), 6.30 (s, 1H, **H**-8), 7.01 (s, 1H, C**H**(Ar)$_2$), 7.25–7.48 (m, 13H, Ar**H**), 7.70–7.80 (m, 2H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.39 (**C**H_3CH_2S), 26.11, 26.44 (α-**C**H_3, CH_3**C**H_2S), 31.82 (β-**C**H_3), 61.12, 67.94, 68.81 (**C**-2, **C**-3, **C**-8), 78.40 (**C**HPh$_2$), 126.95, 127.82, 128.09, 128.20, 128.38, 128.58, 128.60, 128.65, 130.02, 131.80, 139.23, 139.30, 154.19 (Ar**C**, **C**-6, **C**-7), 168.02, 172.07 (2 × **C**=O); ESI-HRMS for $C_{30}H_{29}NO_3S_2$: [M + H]$^{+1}$ calcd: 516.1667, found: 516.1660.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-((E)-3-phenylpropenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5b). Three h reaction time; purification using 1:1 hexane/ethyl acetate gave **5b** as a pale yellow solid (144 mg, 0.259 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S) overlapping with 1.26 (s, 3H, α-C**H**$_3$), 1.50 (s, 3H, β-C**H**$_3$), 3.00 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)) overlapping with 3.11 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 3.58 (d, 2H, J = 6.93 Hz, ArC**H**$_2$CH = CH), 4.70 (s, 1H, **H**-3), 5.89 (s, 1H, **H**-8), 6.14 (dt, 1H, J = 16.08, 6.93 Hz, $ArCH_2$C**H**=CH—), 6.69 (d, 1H, J = 15.83 Hz, $ArCH_2$CH=C**H**—), 6.96 (s, 1H, C**H**(Ph)$_2$), 7.16–7.36 (m, 15H, Ar**H**); ESI-HRMS for $C_{33}H_{33}NO_3S_2$: [M + H]$^{+1}$ calcd: 556.1980, found: 556.1969.

(3S,7aR)-6-Isopropylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenylpropenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5c). The reaction time is 2.5 h; purification using 3:1 dichloromethane/hexane gave **5c** as a yellow solid (317 mg, 0.556 mmol, 60%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.80 Hz, (C**H**$_{3A}$)$_2$CHS(diastereotopic) overlapping with 1.25 (s, 3H, α-C**H**$_3$) overlapping with 1.27 (d, 3H, J = 6.80 Hz (C**H**$_{3B}$)$_2$CHS (diastereotopic)), 1.49 (s, 3H, β-C**H**$_3$), 3.57 (d, 2H, J = 6.93 Hz, ArC**H**$_2$CH=CH), 3.88 (sept, 1H, J = 6.68 Hz, $(CH_3)_2$C**H**S), 4.73 (s, 1H, **H**-3), 5.93 (s, 1H, **H**-8), 6.15 (dt, 1H, J = 15.83, 7.17 Hz, $ArCH_2$C**H**=CH), 6.72 (d, 1H, J = 15.83 Hz, $ArCH_2$CH=C**H**), 6.96 (s, 1H, C**H**(Ph)$_2$), 7.15–7.38 (m, 15H, Ar**H**); ESI-HRMS for $C_{34}H_{35}NO_3S_2$: [M + H]$^{+1}$ calcd: 570.2137, found: 570.2133.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-7-(4-nitrophenyl)-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5d). Twenty-four h reaction time; purification using 3:1 dichloromethane/hexane gave **5d** as a yellow glassy solid (125 mg, 0.223 mmol, 40%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.33 (s, 3H, α-C**H**$_3$), 1.56 (s, 3H, β-C**H**$_3$), 3.23 (dq, 1H, J = 13.50, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.41 (dq, 1H, J = 13.50, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.81 (s, 1H, **H**-3), 6.30 (s, 1H, **H**-8), 7.02 (s, 1H, C**H**(Ph)$_2$), 7.28–7.39 (m, 10H, Ar**H**), 7.86 (d, 2H, J = 8.91 Hz, **H**ArNO_2), 8.29 (d, 2H, J = 8.91 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.54 (**C**H_3CH_2S), 26.03, 26.42 (CH_3**C**H_2S, α-**C**H_3), 31.73 (β-**C**H_3), 61.64, 67.90, 68.47 (**C**-2, **C**-3, **C**-8), 78.58 (**C**H(Ph)$_2$), 123.82, 126.90, 127.81, 128.16, 128.47, 128.59, 128.62, 128.84, 131.56, 137.78, 139.06, 139.11, 147.73, 149.86 (Ar**C**, **C**-6, **C**-7), 167.72, 170.83 (2 × **C**=O); ESI-HRMS for $C_{30}H_{28}N_2O_5S_2$: [M − H]$^-$ calcd: 559.1361, found: 559.1378.

(3S,7aR)-7-(4-Dimethylaminophenyl)-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5e). Two h reaction time; purification using 3:1 hexane/ethyl acetate gave **5e** as an orange-red glassy solid (312 mg, 0.559 mmol, 67%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.31 (s, 3H, α-C**H**$_3$), 1.51 (s, 3H, β-C**H**$_3$), 3.03 (s, 6H, N(C**H**$_3$)$_2$ overlapping with 3.04 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.17 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.83 (s, 1H, **H**-3), 6.28 (s, 1H, **H**-8), 6.70 (d, 2H, J = 9.15 Hz, $N(CH_3)_2$Ar**H**), 7.00 (s, 1H, C**H**(Ph)$_2$), 7.29–7.42 (m, 10H, Ar**H**), 7.81 (d, 2H, J = 9.15 Hz, $N(CH_3)_2$Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.25 (**C**H_3CH_2S), 26.41, 26.64 (CH_3**C**H_2S, α-**C**H_3), 32.08 (β-**C**H_3), 39.99 (N(**C**H_3)$_2$, 60.57, 67.89, 68.89 (**C**-2, **C**-3, **C**-8), 78.20 (**C**H(Ph)$_2$), 111.32 (**C**-7), 119.26, 120.06, 126.94, 127.76, 127.92, 128.39, 128.52, 128.55, 129.90, 139.30, 139.37, 151.31, 156.43 (Ar**C**, **C**-6, **C**-7), 168.25, 173.22 (2× **C**=O); ESI-HRMS for $C_{32}H_{34}N_2O_3S_2$: [M − H]$^-$ calcd: 557.1933, found: 557.1906.

(3S,7aR)-6-(3-Chlorophenoxy)-7-furan-3-yl-2,2-dimethyl-5-oxo-2,3,5,7a-tetra hydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5f). Three h reaction time; purification using 3:1 hexane/ethylacetate gave **5f** as a yellow oil (116 mg, 0.199 mmol, 40%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.34 (s, 3H, α-C**H**$_3$), 1.58 (s, 3H, β-C**H**$_3$), 4.72 (s, 1H, **H**-3), 6.11 (s, 1H, **H**-8), 6.62 (d, 1H, J = 1.73 Hz, furanyl), 6.93 (ddd, 1H, J = 8.16, 2.47, 0.99 Hz, **H**ArCl), 6.99 (s, 1H, C**H**Ph$_2$), 7.04–7.09 (m, 2H, **H**ArCl), 7.22 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.27–7.40 (m, 10H, Ar**H**), 7.45 (d, 1H, J = 1.73 Hz, furanyl), 7.74 (s, 1H, furanyl); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 26.43 (α-**C**H_3), 31.79 (β-**C**H_3), 61.30, 64.97, 67.44 (**C**-2, **C**-3, **C**-8), 78.52 (**C**H(Ph)$_2$), 108.58, 114.37, 116.84, 123.81, 126.94, 127.80, 128.14, 128.43, 128.58, 128.63, 135.04, 135.17, 138.51, 139.08, 139.17, 156.18 (Ar**C**, **C**-

furanyl, **C**-6, **C**-7), 167.79, 167.83 (2 × **C**=O); ESI-HRMS for $C_{32}H_{26}NO_5SCl$: $[M + Na]^+$ calcd: 594.1118, found: 594.1133.

[4-(1-Benzyl-1*H*-pyrazol-4-yl)-3-ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl]-phenylacetic acid methyl ester (8a). Forty-eight h reaction time using the boronic acid pinacol ester with **7a**; purification using 1:1 hexane/ethylacetate gave **8a** as a brown oil (129 mg, 0.288 mmol, 45%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, J = 7.42 Hz, 3H, C**H$_3$**CH$_2$S), 3.08 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.16 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic)), 3.74 (d, 1H, J = 18.06 Hz, **H**-5$_A$), 3.79 (s, 3H, OC**H$_3$**), 4.61 (d, J = 18.31 Hz, 1H, **H**-5$_B$), 5.31 (s, 2H, PhC**H$_2$**N), 6.18 (s, 1H, C**H**C(O)), 7.15–7.41 (m, 10H, Ar**H**), 7.86 (s, 1H, C=C**H**—N), 8.05 (s, 1H, C—C**H**=N); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.46 (**C**H$_3$CH$_2$S), 26.29 (CH$_3$**C**H$_2$S), 49.31, 52.41, 56.25, 57.68 (**C**-5, O**C**H$_3$, (Ph)**C**H$_2$N) (**C**HC(O)), 115.62, 120.95 (**C**=**C**), 127.54, 127.75, 128.24, 128.41, 128.68, 128.85, 128.96, 129.09, 129.18, 134.27, 135.71, 138.42, 145.52 (Ar**C**, **C**-3, **C**-4, N=**C**), 170.08, 170.89 (2 × **C**=O); ESI-HRMS for $C_{25}H_{25}N_3O_3S$: $[M - H]^-$ calcd: 448.1695, found: 448.1692.

4-Furan-3-yl-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (8b). Three h reaction time using the boronic acid with **7b**; purification using 1:3 hexane/ethylacetate gave **8b** as a pale yellow solid (135 mg, 0.30 mmol, 60%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.92 (t, 2H, J = 7.42 Hz, NCH$_2$C**H$_2$**), 3.75 (t, 2H, J = 7.42 Hz, NC**H$_2$**CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 3.90 (s, 3H, NC**H$_3$**), 4.08 (s, 2H, C**H$_2$**NC(O)), 6.56 (d, 1H, J = 1.98 Hz, furanyl), 6.76–6.85 (m, 3H, **H**Ar(OCH$_3$)$_2$), 7.315 (ddd, 1H, J = 8.41, 2.27, 0.74 Hz, **H**ArNO$_2$), 7.44 (d, 1H, J = 1.98 Hz, furanyl), 7.49 (t, 1H, J = 8.41 Hz, **H**ArNO$_2$), 7.70 (s, 1H, furanyl), 7.81 (app t, 1H, J = 2.47 Hz, **H**ArNO$_2$), 7.95 (ddd, 1H, J = 8.41, 2.23, 0.74 Hz, **H**ArNO$_2$); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 34.23 (NCH$_2$**C**H$_2$), 44.48, 48.59 (N**C**H$_2$CH$_2$, **C**H$_2$NC(O); 55.88 (2 x O**C**H$_3$), 108.13, 111.07, 111.34, 111.69, 116.28, 118.06, 120.62, 122.60, 127.83, 130.25, 130.72, 139.28, 141.49, 144.18, 147.77, 149.05, 156.39 (Ar**C**, **C**-furanyl, **C**-3, **C**-4), 164.87 (**C**=O); ESI-HRMS for $C_{24}H_{22}N_2O_7$: $[M + H]^+$ calcd: 451.1505, found: 451.1501.

4-(1-Methyl-1*H*-pyrazol-4-yl)-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (8c). Twenty-four h reaction time using the boronic acid pinacol ester with **7b**; purification using ethylacetate then methanol gave **8c** as a pale yellow oil (173 mg, 0.373 mmol, 75%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.92 (t, 2H, J = 7.17 Hz, NCH$_2$C**H$_2$**), 3.74 (t, 2H, J = 7.17 Hz, NC**H$_2$**CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 3.90 (s, 3H, NCH$_3$), 4.09 (s, 2H, C**H$_2$**NC(O)), 6.76–6.84 (m, 3H, **H**Ar(OCH$_3$)$_2$), 7.31 (ddd, 1H, J = 8.41, 2.27, 0.74 Hz, **H**ArNO$_2$), 7.49 (t, 1H, J = 8.41 Hz, **H**ArNO$_2$), 7.59 (s, 1H, pyrazole), 7.60 (s, 1H, pyrazole), 7.81 (app t, 1H, J = 2.47 Hz, **H**ArNO$_2$), 7.95 ((ddd, 1H, J = 8.16, 2.23, 0.74 Hz, **H**ArNO$_2$); ESI-HRMS for $C_{24}H_{24}N_4O_6$: $[M + H]^+$ calcd: 465.1774, found: 465.1785.

Benzhydryl removal–general procedure. The required benzhydryl ester (0.6748 mmol) was dissolved in dichloromethane (15 mL) and cooled under nitrogen to −84°C (liquid N_2/ethylacetate slurry). A solution of aluminum trichloride (222 mg, 1.664 mmol) in nitroethane (1.39 mL) was added in one portion to the cooled pyrrolothiazole solution at which point the solution changed color from pale to intense yellow. The reaction mixture was allowed to stir at −84°C for 1 h at which point ethyl acetate (70 mL) and 5% sodium carbonate (45 mL) were added successively while maintaining the temperature at −84°C. The reaction mixture was allowed to warm to room temperature at which point the aqueous layer was separated and filtered through celite before being extracted with ethyl acetate (20 mL). The aqueous portion was layered with ethyl acetate (30 mL) and the pH lowered to 2.2 using 1*M* HCl. The organic extract was separated and the aqueous portion extracted with a further portion of ethyl acetate (30 mL). The organic extracts were combined, dried, filtered, and concentrated by reduced pressure to yield a solid, which was further dried under vacuum.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-phenyl-2,3,5,7a-tetrahydro pyrrolo[2,1-*b*] thiazole-3-carboxylic acid (6a). A pale yellow solid (166 mg, 0.475 mmol, 70%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S), 1.65 (s, 3H, α-CH$_3$), 1.70 (s, 3H, β-CH$_3$), 3.11 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.24 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic)), 4.66 (s, 1H, **H**-3), 6.27 (s, 1H, **H**-8), 7.42–7.47 ((m, 3H, Ar**H**)), 7.73–7.76 (m, 2H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.30 (**C**H$_3$CH$_2$S), 26.28, 26.80 (α-**C**H$_3$, CH$_3$**C**H$_2$S), 30.79 (β-**C**H$_3$), 60.73, 68.00, 68.82 (**C**-2, **C**-3, **C**-8), 127.03, 128.24, 128.66, 130 0.18, 131.53 (Ar**C**, **C**-7) 154.31 (**C**-6), 172.36, 172.76 (2 × **C**=O); ESI-HRMS for $C_{17}H_{19}NO_3S_2$: $[M - H]^-$ calcd: 348.0728, found: 348.0733.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenyl-propenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6b). A pale yellow solid (27.2 mg, 0.0698 mmol, 27%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S), 1.60 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 2.99 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.07 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic), 3.58 (d, 2H, J = 6.93 Hz, PhC**H$_2$**CH=CH—), 4.52 (s, 1H, **H**-3), 5.85 (s, 1H, **H**-8), 6.21 (dt, 1H, J = 16.08, 6.93 Hz, PhCH$_2$C**H**=CH), 6.70 (d, 1H, J = 16.08 Hz, PhCH$_2$CH=C**H**), 7.18–7.44 (m, 5H, Ar**H**); ESI-HRMS for $C_{20}H_{23}NO_3S_2$: $[M - H]^-$ calcd: 388.1041, found: 388.1039.

(3S,7aR)-6-Isopropylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenyl-propenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6c). A pale yellow solid (44 mg, 0.109 mmol, 19%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 6.68 Hz, (C**H$_{3A}$**)$_2$CHS (diastereotopic)) overlapping with 1.26 (d, 3H, J = 6.68Hz, (C**H$_{3B}$**)$_2$CHS (diastereotopic)), 1.59 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 3.58 (d, 2H, J = 6.93 Hz, Ph-C**H$_2$**CH=CH), 3.82 (sept, 1H, J = 6.68 Hz, (CH$_3$)$_2$C**H**S), 4.53 (s, 1H, **H**-3), 5.87 (s, 1H, **H**-8), 6.22 (dt, 1H, J = 7.17, 16.08 Hz, Ph-CH$_2$C**H**=CH), 6.72 (d, 1H, J = 15.83 Hz, Ph-CH$_2$CH=C**H**), 7.17–7.36 (m, 5H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.21, 24.06, (**C**H$_3$)$_2$CHS (diastereotopic methyl groups)), 26.64, 30.81, 36.77 (α-**C**H$_3$, β-**C**H$_3$, (CH$_3$)$_2$**C**HS), 39.70 (Ar**C**H$_2$C=C), 60.51, 66.74, 67.52 (**C**-2, **C**-3, **C**-8), 123.03 (ArCH$_2$**C**H=CH), 126.44, 126.61, 128.58, 128.68, 138.35, 139.20 (Ar**C**, **C**-7, ArCH$_2$CH=**C**H), 157.64 (**C**-6), 171.97, 173.18 (2 × **C**=O); ESI-HRMS for $C_{21}H_{25}NO_3S_2$: $[M - H]^-$ calcd: 402.1198, found: 402.1190.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-7-(4-nitrophenyl)-5oxo-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6d). An orange solid (48.7 mg, 0.123 mmol, 55%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S),

1.66 (s, 3H, α-CH_3), 1.71 (s, 3H, β-CH_3), 3.24 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}S$ (diastereotopic)), 3.38 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$ (diastereotopic)), 4.67 (s, 1H, **H**-3), 6.27 (s, 1H, **H**-8), 7.89 (d, 2H, J = 9.15 Hz, **H**ArNO_2), 8.31 (d, 2H, J = 9.15 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.51 ($\mathbf{C}H_3CH_2S$), 26.14, 26.73 (α-$\mathbf{C}H_3$, $CH_3\mathbf{C}H_2S$), 30.86 (β-$\mathbf{C}H_3$), 61.13, 67.92, 68.46 (**C**-2, **C**-3, **C**-8), 123.86, 128.91, 131.71, 137.57, 147.85, 149.79 (Ar**C**, **C**-6, **C**-7), 171.43, 171.88 (2 × **C**=O); ESI-HRMS for $C_{17}H_{18}N_2O_5S_2$: $[M - H]^-$ calcd: 393.0579, found: 393.0591.

(3S,7aR)-7-(4-Dimethylaminophenyl)-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a -tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6e). An orange-red solid (122 mg, 0.311 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, $C\mathbf{H_3}CH_2S$), 1.64 (s, 3H, α-$C\mathbf{H_3}$), 1.72 (s, 3H, β-$C\mathbf{H_3}$), 3.05 (s, 6H, $N(C\mathbf{H_3})_2$ overlapping with 3.04 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}S$) overlapping with 3.14 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$)), 4.57 (s, 1H, **H**-3), 6.20 (s, 1H, **H**-8), 6.72 (d, 2H, J = 8.91 Hz, $N(CH_3)_2Ar\mathbf{H}$), 7.86 (d, 2H, J = 8.91 Hz, $N(CH_3)_2Ar\mathbf{H}$); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.21 ($\mathbf{C}H_3CH_2S$), 26.61, 26.86 (α-$\mathbf{C}H_3$, $CH_3\mathbf{C}H_2S$), 30.19 (β-$\mathbf{C}H_3$), 40.00 ($N(\mathbf{C}H_3)_2$, 59.89, 68.09, 68.58 (**C**-2, **C**-3, **C**-8), 111.34, 118.95, 120.02, 130.10, 151.51, 156.76 (Ar**C**, **C**-6, **C**-7), 170.82, 174.84 (2 × **C**=O); ESI-HRMS for $C_{19}H_{24}N_2O_3S_2$: $[M - H]^-$ calcd: 391.1150, found: 391.1135.

(3S,7aR)-6-(3-Chlorophenoxy)-7-furan-3-yl-2,2-dimethyl-5-oxo-2,3,5,7a-tetra hydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6f). A pale yellow solid (64 mg, 0.154 mmol, 45%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.66 (s, 3H, α-$C\mathbf{H_3}$), 1.70 (s, 3H, β-$C\mathbf{H_3}$), 4.56 (s, 1H, **H**-3), 6.08 (s, 1H, **H**-8), 6.65 (d, 1H, J = 1.98 Hz, furanyl), 6.94 (ddd, 1H, J = 8.16, 2.23, 0.74, **H**ArCl), 7.06–7.11 (m, 2H, **H**ArCl), 7.24 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.48 (d, J = 1.98 Hz, furanyl), 7.78 (s, 1H, furanyl); ESI-HRMS for $C_{19}H_{16}NO_5SCl$: $[M - H]^-$ calcd: 404.0359, found: 404.0376.

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Novel Synthetic Protocol toward Pyrazolo[3,4-*h*]-[1,6]naphthyridines *via* Friedlander Condensation of New 4-Aminopyrazolo[3,4-*b*]pyridine-5-carbaldehyde with Reactive α-Methylene Ketones

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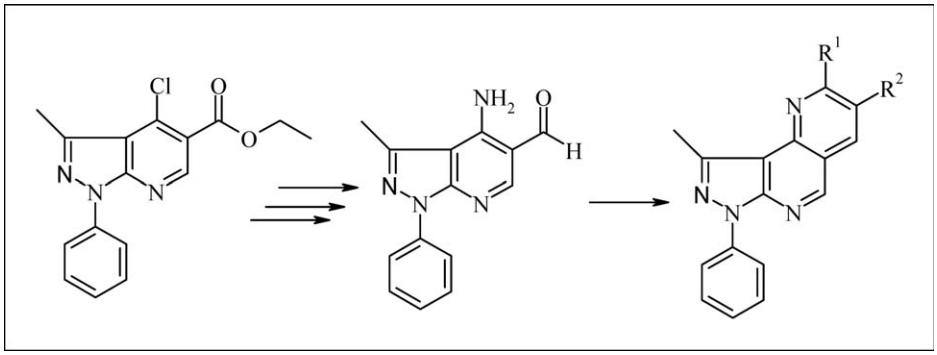

Novel pyrazolo[3,4-*h*][1,6]naphthyridine derivatives **6**, **8**, **9**, **11**, **13**, and **15** have been synthesized by Friedlander condensation of new 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (*o*-aminoaldehyde) **4** with active methylene ketones, such as symmetric acetone **5a**, monoalkylketones **5b**–**k**, unsymmetrical dialkyl ketones **7a**–**b**, *p*-bromophenylacetonitrile **10**, β-ketoester **12a**, β-ketoamide **12b**, or diethyl malonate **14**, respectively.

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INTRODUCTION

Pyrazole derivatives and heterocycle-annelated pyrazoles have wide spectrum of interesting agricultural and various biological activities [1–4]. Naphthyridine derivatives constitute an important class of compounds possessing diverse types of biological properties [5–8]. The synthetic approach of some pyridine derivatives from tetracyanopropenes is an important part of cyanocarbon chemistry, and the synthesis of 1,6-naphthyridine derivatives has been widely dealt in the literature [9–13] as part of a general study on cyclization of dinitriles. Several reports are dedicated to naphthyridines chemistry [14–16].

Considering this literature prompted us to synthesize pyrazolo[3,4-*h*][1,6]naphthyridines by Friedlander condensation of *o*-aminoaldehyde with reactive α-methylene ketones.

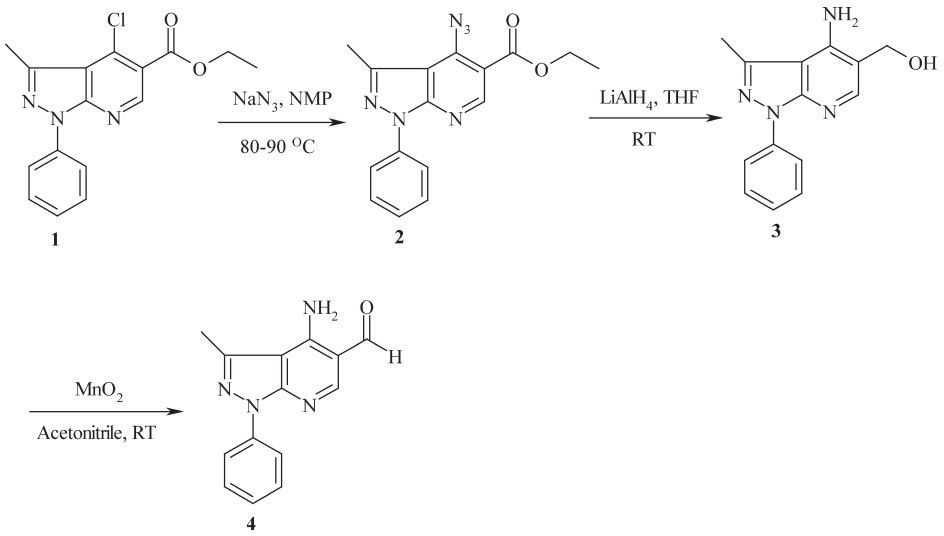
We now report a novel synthetic route for the synthesis of pyrazolo[3,4-*h*][1,6]naphthyridines, which involve annelation of a pyridine ring onto the performed pyrazolo[3,4-*b*]pyridine ring *via* Friedlander condensation, which may have biological activities. In our earlier communication [17], pyrazolo[3,4-*h*][1,6]naphthyridines has been synthesized in low yield (50%) by annelation of pyridine ring onto pyrazolo[3,4-*b*]pyridine nucleus, in which amino and ester functionality were ortho to each other. In this work, we have synthesized a new pyrazolo[3,4-*b*]pyridine in which ester group was replaced by aldehyde and Friedlander condensation performed on it, with reactive α-methylenes to obtain title compounds in high yield (66–81%).

RESULTS AND DISCUSSION

o-Aminoaldehydes [18] have fascinating potentiality for annelation of heterocyclic ring structures, which provide a synthetic entry in heterocyclic systems fused to a pyridine or pyrimidine nucleus by Friedlander condensation reactions. These are also the key intermediates for the synthesis of various biologically active heterocycles [19,20]. The annelation of pyridine ring onto pyrazolopyridine nucleus involves the 4 + 2 cyclocondensation reaction [21].

The required 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (*o*-aminoaldehyde) **4** was achieved in three steps. Thus, the chloroester **1**, synthesized by literature method [22], yielded an azido derivative **2** by SN^2 displacement of the chloro group by azido with sodium azide in *N*-methyl pyrrolidine at

Scheme 1



80–90°C in 77% yield. A stretching vibration in the IR spectrum of **2** was observed at 2144 cm^{-1}. The synchronous reduction of both azido group and ester group of **2** ortho to each other in one pot by lithium aluminum hydride (LAH) in dry tetrahydrofuran at room temperature yielded the ortho amino alcohol **3** in 84% yield. This type of one-pot reduction of azido and ester groups is not known in literature. This on oxidation with manganese(IV)oxide (without protecting amino group [23,24]) in acetonitrile at room temperature furnished desired *o*-aminoaldehyde **4** in 94% yield. In this step, expected N-oxide was not formed as revealed by spectral and analytical data (Scheme 1). Compounds **2**, **3**, and **4** were characterized by IR, ^{1}H-, ^{13}C NMR, mass spectroscopy, and elemental analysis; *e.g.*, the IR spectrum of **4** showed carbonyl stretching bands at 1654 cm^{-1}, the ^{1}H NMR spectrum showed down field singlet at δ 8.43 corresponding to H-2 and singlet at δ 9.75 due to aldehydic proton. The ^{13}C NMR spectrum of the compound exhibits peak at δ 195.56 for an aldehydic carbon. The mass spectral analysis showed an ion with *m/z* 252 (M^+), which supports the proposed structure **4**.

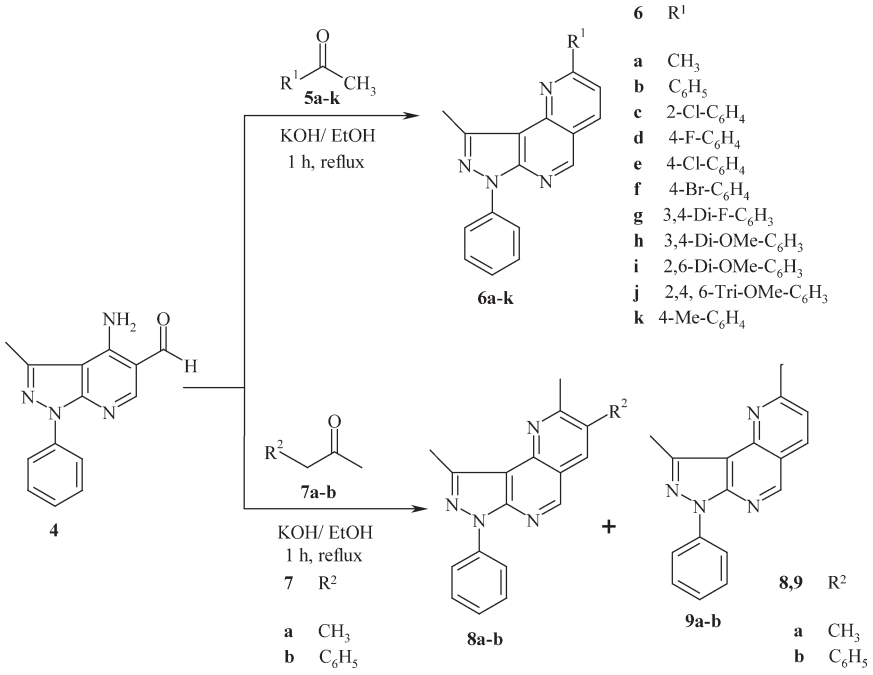
The Friedlander condensation of *o*-aminoaldehyde such as 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde 4 with ketones is described to take place either with strong bases or acids as catalysts, in special cases the ring closure can be observed without a catalyst at higher temperatures (*e.g.*, under microwave irradiation) [21]. We obtained the best results when a mixture of the appropriate *o*-aminoaldehyde **4** and the corresponding ketones **5** or **7** was brought to reaction in refluxing ethanolic potassium hydroxide solution. A Friedlander cyclocondensation of *o*-aminoaldehyde **4a** with acetone **5a** or acetophenones **5b–k** afforded 2,9-dimethyl and 2-aryl-9-methyl-7-phenyl-7*H*-pyrazolo[3,4-*h*][1,6]naphthyridine **6a–k** in 66–81% yield (Scheme 2).

When unsymmetric dialkyl ketones **7a–b** were used as condensation partner, instead of symmetric ketone **5a** or monoalkylketones **5b–k**, they yielded an expected mixture of two isomers **8** and **9** in 3:1 ratio, under similar reaction conditions.

The 3-substituted isomer **8** was formed by attack of the aldehyde moiety at the benzyl CH_2 group of the ketone **7**, whereas the condensation on the α-methyl group of **7** formed the 3-unsubstituted isomer **9**. These mixtures were separated by column chromatography using *n*-hexane/ethyl acetate (9:1) as the eluent and were characterized by spectral and analytical data. The structural assignment of **8a** and **9a** could easily be performed by ^{1}H NMR because **8a** showed two methyl singlets at 2.69 and 3.02 δ, together with the singlet of 4-H at 7.93 ppm of the newly annelated pyridine ring, whereas **9a** showed triplet at δ 1.42 and quartet at δ 2.78 patterns for ethyl group together with two doublets at δ 7.31 and δ 8.19 assigned to the *ortho*-coupled protons at H-3 and H-4 position in newly annelated pyridine ring. The other signals in both compounds appeared nearly at same δ values. The molecular ion peak **8a** and **9a** observed in both cases the same mass of 288 (M^+) in the mass spectra (Scheme 2).

As mentioned earlier, the Friedlander condensation can be catalyzed by various reagents [21]. When we extended synthetic investigation to CH-acidic compounds, such as *p*-bromophenylacetonitrile **10**, β-ketoester **12a**, β-ketoamide **12b**, and diethyl malonate **14**, we found that already piperidine as base was sufficiently strong to catalyze the condensation reaction. This method provided a versatile method for the synthesis of various substituted pyrazolo[3,4-*h*][1,6]naphthyridines and pyrazolo[3,4-*h*][1,6]naphthyridione. The

Scheme 2



cyclocondensation of **4** with *p*-bromophenylacetonitrile **10**, β-ketoester **12a**, β-ketoamide **12b**, and diethyl malonate **14** afforded pyrazolo[3,4-*h*][1,6]naphthyridine-3-carbonitrile **11**, ethyl-pyrazolo[3,4-*h*][1,6]naphthyridine-3-carboxylate **13a**, pyrazolo[3,4-*h*][1,6]naphthyridine-3-carboxamide **13b**, and 3-carbethoxy-pyrazolo [3,4-*h*][1,6]naphthyridin-2-one **15**, respectively, in 63–79% yield (Scheme 3). Compounds **11**, **13a-b**, and **15** were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analysis.

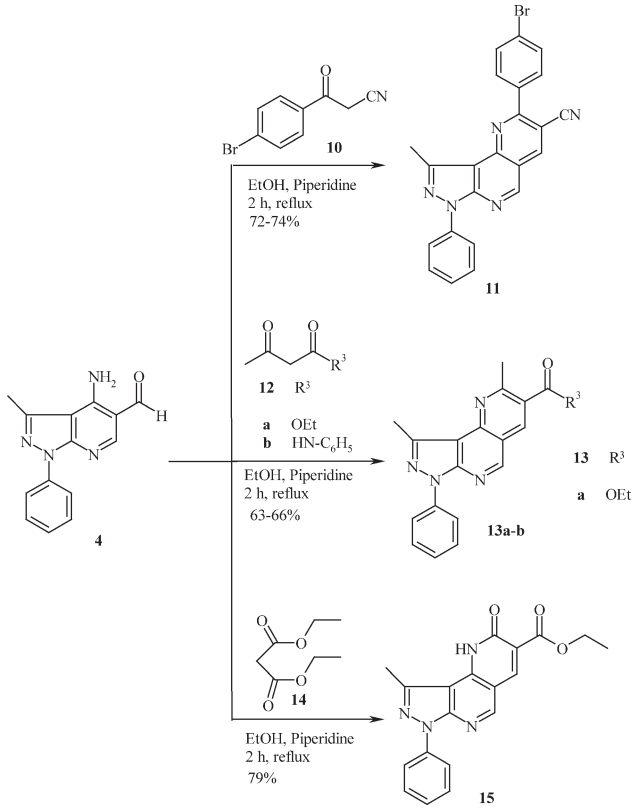
In conclusion, the reactions herein report new synthetic routes toward novel pyrazolo[3,4-*h*][1,6]naphthyridines and pyrazolo[3,4-*h*][1,6]naphthyridione by Friedlander condensation reaction of new 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **4** with reactive α-methylene ketones.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB595 in open capillary tubes and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Varian XL-300 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded using a Shimadzu IR-408, a Shimadzu FTIR instrument with potassium bromide discs. Mass spectrum was recorded on Shimadzu GC-MS QP mass spectrometer with an ionization potential of 70 eV. Elemental analyses were obtained on a Hosli CH-Analyzer and are within ±0.3 of the theoretical percentage.

All the reactions were monitored by thin layer chromatography on 0.2-mm silica gel F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagents-grade chemicals were either commercially available and were used without further purification or prepared by standard literature procedures.

Scheme 3



Ethyl-4-azido-3-methyl-1-phenyl-1*H*-pyrazolo[3.4-*b*]pyridine-5-carboxylate (2). A mixture of **1** (7.25 g, 23 mmol) and sodium azide (1.69 g, 26 mmol) was heated in *N*-methylpyrrolidine (60 mL) at 80–90°C for 6 h. The solvent was distilled out by vacuum distillation. The reaction mass was quenched with water (30 mL) and extracted in chloroform (50 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ethyl acetate = 1:4) to furnish **2** as a colorless solid, 5.9 g (77%), mp 178–179°C; IR: 2991, 2922, 2144, 1727, 1585, 1498, 1189, 769 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, J = 6.8 Hz, CH_3), 2.75 (s, 3H, CH_3), 4.37 (q, 2H, J = 6.8 Hz, CH_2), 7.28 (t, 1H, J = 7.2 Hz, Ar—H), 7.48 (t, 2H, J = 7.2 Hz, Ar—H), 8.11 (d, 2H, J = 7.2 Hz, Ar—H), 8.91 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 12.49, 13.54, 54.66, 98.97, 102.63, 119.88 (2 C's), 124.29; 127.20 (2 C's), 136.24, 140.51, 150.55, 151.35, 151.87, 166.41; MS: *m/z* 322 (M^+, 100), 307 (19), 280 (34), 231 (15), 129 (23), 77 (32); Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.79; H, 4.45; N, 25.89.

4-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl-methanol (3). A solution of **2** (4.83 g, 15 mmol) in tetrahydrofuran (15 mL) was added slowly into the dispersed LAH (46 mmol) in tetrahydrofuran (20 mL) at 0°C; after addition the reaction mass was allowed to come at 25°C and stirred it for 4 h. The reaction mass was quenched with saturated sodium sulfate solution (20 mL) at 0°C and extracted in ethyl acetate (2 × 20 mL). The combined organic layer was washed with water (2 × 15 mL), then dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated under reduced pressure; the crude solid was taken in ethanol, filtered, and dried under high vacuum to provide **3** as a colorless solid, 3.31 g (84%); mp 173–174°C; IR: 3479, 3369, 3302, 3056, 2964, 1611, 1505, 1204, 772 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 4.53 (d, 2H, J = 5.4 Hz, CH_2), 5.04 (t, 1H, J = 5.4 Hz, OH, D_2O exchangeable), 6.29 (bs, 2H, NH_2, D_2O exchangeable), 7.19 (t, 1H, J = 7.2 Hz, Ar—H), 7.45 (t, 2H, J = 7.2 Hz, Ar—H), 8.01 (s, 1H, Ar—H), 8.26 (d, 2H, J = 7.2 Hz, Ar—H); ^{13}C NMR (DMSO-d_6): δ 13.52, 59.93, 113.65, 117.35, 119.67 (2 C's), 124.75, 127.31 (2 C's), 138.68, 142.57, 149.85, 150.11, 162.47; MS: *m/z* 254 (M^+, 100), 237 (24), 221 (18), 129 (21), 77 (34); Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.01; H, 5.46; N, 22.19.

4-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (4). Manganese(IV)dioxide (2.5 g) was added into the solution of **3** (4.06 g, 16 mmol) in acetonitrile (40 mL) at 25°C for 20 h. The reaction mass was filtered through celite and evaporated acetonitrile under reduced pressure to yield **4** as a colorless solid, 3.92 g (94%); mp 173–174°C; IR: 3435, 3094, 2931, 2723, 1654, 1599, 1502, 1219, 765 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.64 (s, 3H, CH_3), 6.65 (bs, 2H, NH_2), 7.29 (t, 1H, J = 7.8 Hz, Ar—H), 7.49 (t, 2H, J = 7.8 Hz, Ar—H), 8.08 (d, 2H, J = 7.8 Hz, Ar—H), 8.43 (s, 1H, Ar—H), 9.75 (s, 1H, CH=O). ^{13}C NMR (DMSO-d_6): δ 17.64, 106.26, 112.67, 123.73 (2 C's), 128.68 (2 C's), 131.71, 141.48, 146.83, 153.98, 155.24, 161.26, 195.56; MS: *m/z* 252 (M^+, 100), 236 (28), 223 (36), 208 (18), 133 (16), 77 (26); Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.66; H, 4.79; N, 22.21. Found: C, 66.84; H, 4.65; N, 22.06.

General procedure for the synthesis of compounds 6a–k. A mixture of **4** (0.1 g, 0.396 mmol), **5a–k** (0.396 mmol), and ethanolic potassium hydroxide solution (5 mL, 2%) was heated under reflux for 1 h. The mixture was cooled to room temperature and the obtained solid was collected by suction filtration and washed with ethanol to furnish compound **6** in 66–81% yield.

2,9-Dimethyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6a). This compound was obtained as a colorless solid, 0.072 g (66%); mp 157–158°C; IR: 3035, 2923, 1604, 1508, 1438, 1307, 1221, 767 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 7.39 (d, 1H, J = 7.2 Hz, Ar—H), 7.34 (t, 1H, J = 7.8 Hz, Ar—H), 7.54 (t, 2H, J = 7.8 Hz, Ar—H), 8.19 (d, 1H, J = 7.2 Hz, Ar—H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 8.97 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.09, 24.23, 108.32, 116.21, 119.01, 120.16 (2 C's), 124.35, 127.26 (2 C's), 134.45, 137.56, 142.86, 145.50, 148.34, 150.73, 162.56; MS: *m/z* 274 (M^+, 100%), 259 (37), 183 (25), 167 (14), 91 (26), 77 (42); Anal. Calcd. for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.59; H, 5.03; N, 20.57.

9-Methyl-2,7-diphenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6b). This compound was obtained as a pale yellow solid, 0.093 g (70%); mp 158–159°C; IR: 3062, 2925, 1591, 1500, 1435, 1320, 1226, 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.16 (s, 3H, CH_3), 7.35 (t, 1H, J = 7.8 Hz, Ar—H), 7.51–7.62 (m, 5H, Ar—H), 8.01 (d, 1H, J = 8.4 Hz, Ar—H), 8.25 (d, 2H, J = 7.8 Hz, Ar—H), 8.35 (d, 2H, J = 8.2 Hz, Ar—H), 8.42 (d, 1H, J = 8.4 Hz, Ar—H), 9.08 (s, 1H, Ar—H); MS: *m/z* 336 (M^+, 100), 244 (23), 259 (39), 167 (19), 91 (23), 77 (28); Anal. calcd. for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.65. Found: C, 78.68; H, 4.96; N, 16.75.

2-(2-Chlorophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6c). This compound was obtained as a pale yellow solid, 0.105 g (71%); mp 164–165°C; IR: 3064, 2934, 1609, 1503, 1433, 1310, 1220, 772 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.06 (s, 3H, CH_3), 7.33 (t, 1H, J = 7.2 Hz, Ar—H), 7.42–7.59 (m, 5H, Ar—H), 7.87 (m, 1H, Ar—H), 7.95 (d, 1H, J = 8.4 Hz, Ar—H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 8.44 (d, 1H, J = 8.4 Hz, Ar—H), 9.01(s, 1H, Ar—H); MS: *m/z* (%) 372 (M + 2, 34), 370 (M^+, 100), 335 (23), 279 (18), 259 (26), 91 (28), 77 (32); Anal. Calcd. for $C_{22}H_{15}ClN_4$: C, 71.25; H, 4.08; N, 15.11. Found: C, 71.02; H, 3.96; N, 15.29.

2-(4-Fluorophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6d). This compound was obtained as a pale yellow solid, 0.106 g (75%); mp 188–189°C; IR: 3079, 2920, 1594, 1504, 1406, 1308, 1228, 759 cm^{-1}; ^1H NMR ($CDCl_3$ + *d*-CF_3COOD): δ 3.21 (s, 3H, CH_3), 7.39 (t, 2H, J = 8.2 Hz, Ar—H), 7.52–7.75 (m, 5H, Ar—H), 8.23 (m, 2H, Ar—H), 8.31 (d, 1H, J = 8.4 Hz, Ar—H), 9.05 (d, 1H, J = 8.4 Hz, Ar—H), 9.52 (s, 1H, Ar—H); MS: *m/z* 354 (M^+, 100%), 339 (17), 263 (19), 259 (22), 244 (28), 91 (20), 77 (26); Anal. calcd. for $C_{22}H_{15}FN_4$: C, 74.56; H, 4.27; N, 15.81. Found: C, 74.75; H, 4.19; N, 15.92.

2-(4-Chlorophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6e). This compound was obtained as a pale yellow solid, 0.112 g (76%); mp 236–237°C; IR: 3052, 2924, 1610, 1500, 1457, 1317, 1230, 753 cm^{-1}; ^1H NMR (DMSO-d_6 + *d*-CF_3COOD): δ 2.89 (s, 3H, CH_3), 7.29–7.38 (m, 5H, Ar—H), 7.57 (d, 2H, J = 7.2 Hz, Ar—H), 7.96 (d, 1H, J = 8.4 Hz, Ar—H), 8.04 (d, 2H, J = 8.4 Hz, Ar—H), 8.72 (d, 1H, J = 8.7 Hz, Ar—H), 9.16 (s, 1H, Ar—H); MS: *m/z* 370 (M^+, 100), 372 (M + 2, 38), 259 (18), 91 (21), 77 (36); Anal.

Calcd. for $C_{22}H_{15}ClN_4$: C, 71.25; H, 4.08; N, 15.11. Found: C, 71.42; H, 4.14; N, 15.26.

2-(4-Bromophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6f). This compound was obtained as a pale yellow solid, 0.119 g (72%); mp 240–241°C; IR: ν 3072, 2923, 1608, 1501, 1423, 1229, 756 cm^{-1}; ^1H NMR (DMSO-d_6 + d-CF_3COOD): δ 2.87 (s, 3H, CH_3), 7.29–7.34 (m, 3H, Ar—H), 7.49 (t, 4H, J = 8.4 Hz, Ar—H), 7.78 (d, 1H, J = 8.7 Hz, Ar—H), 8.04 (d, 2H, J = 8.4 Hz, Ar—H), 8.82 (d, 1H, J = 8.7 Hz, Ar—H), 9.17 (s, 1H, Ar—H); MS: m/z 414 (M^+, 100), 416 (M + 2, 86), 399 (22), 323 (15), 259 (21), 155 (18), 91 (24), 77 (27); Anal. Calcd. for $C_{22}H_{15}BrN_4$: C, 63.63; H, 3.64; N, 13.49. Found: C, 63.77; H, 3.52; N, 13.28.

2-(3,4-Difluorophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6g). This compound was obtained as a pale yellow solid, 0.112 g (76%); mp 201–202°C; IR: 3041, 2931, 1604, 1515, 1439, 1236, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.14 (s, 3H, CH_3), 7.31–7.40 (m, 2H, Ar—H), 7.56 (t, 2H, J = 8.2 Hz, Ar—H), 7.93 (d, 1H, J = 8.4 Hz, Ar—H), 8.06 (m, 1H, Ar—H), 8.22–8.25 (m, 3H, Ar—H), 8.45 (d, 1H, J = 8.4 Hz, Ar—H), 9.08 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 15.27, 110.31, 117.73, 117.96, 119.82 (2 C's), 122.08, 123.94, 124.31, 126.47, 129.23 (2 C's), 135.83, 137.61, 139.37, 143.23, 144.73, 147.34, 147.92, 150.41, 152.54, 158.44; MS: m/z 372 (M^+, 100), 357 (21), 281 (19), 259 (24), 91 (21), 77 (29); Anal. Calcd. for $C_{22}H_{14}F_2N_4$: C, 70.96; H, 3.79; N, 15.05. Found: C, 70.83; H, 3.71; N, 15.25.

2-(3,4-Dimethoxyphenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6h). This compound was obtained as a colorless solid, 0.124 g (79%); mp 208–209°C; IR: 3054, 2930, 1595, 1499, 1448, 1234, 1131, 771 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.15 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.04 (d, 1H, J = 8.4 Hz, Ar—H), 7.35 (t, 1H, J = 7.8 Hz, Ar—H), 7.56 (t, 2H, J = 7.8 Hz, Ar—H), 7.85 (d, 1H, J = 8.4 Hz, Ar—H), 7.96 (d, 1H, J = 8.7 Hz, Ar—H), 8.14 (d, 1H, J = 2.1 Hz, Ar—H), 8.25 (d, 2H, J = 7.8 Hz, Ar—H), 8.37 (d, 1H, J = 8.4 Hz, Ar—H), 9.05 (s, 1H, Ar—H); MS: m/z 396 (M^+, 100), 365 (46), 335 (31), 305 (15), 259 (21), 91 (18), 77 (33); Anal. Calcd. for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.58; H, 5.19; N, 14.29.

2-(2,6-Dimethoxyphenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6i). This compound was obtained as a colorless solid, 0.127 g (81%); mp 215–216°C; IR: 3062, 2941, 1602, 1501, 1425, 1219, 1154, 783 cm^{-1}; ^1H NMR (DMSO-d_6 + d-CF_3COOD): δ 2.84 (s, 3H, CH_3), 3.69 (s, 6H, 2 × OCH_3), 6.79 (d, 2H, J = 8.4 Hz, Ar—H), 7.31 (t, 1H, J = 7.8 Hz, Ar—H), 7.40 (t, 1H, J = 8.4 Hz, Ar—H), 7.52 (t, 2H, J = 7.8 Hz, Ar—H), 7.62 (d, 1H, J = 8.4 Hz, Ar—H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 8.65 (d, 1H, J = 8.4 Hz, Ar—H), 9.28 (s, 1H, Ar—H); MS: m/z 396 (M^+, 100), 365 (54), 335 (17), 259 (24), 168 (19), 77 (27); Anal. Calcd. for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.87; H, 5.17; N, 13.94.

9-Methyl-7-phenyl-2-(2,4,6-trimethoxyphenyl)-7H-pyrazolo[3,4-h][1,6]naphthyridine (6j). This compound was obtained as a colorless solid, 0.127 g (75%); mp 142–143°C; IR: 3067, 2941, 1607, 1505, 1455, 1227, 1127, 754 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.07 (s, 3H, CH_3), 3.79 (s, 6H, 2 × OCH_3), 3.91 (s, 3H, OCH_3), 6.30 (s, 2H, Ar—H), 7.33 (t, 1H, J = 7.5 Hz, Ar—H), 7.52–7.59 (m, 3H, Ar—H), 8.23 (d, 2H, J = 7.5 Hz, Ar—H), 8.32 (d, 1H, J = 8.4 Hz, Ar—H), 9.08 (s, 1H, Ar—H); ^{13}C NMR (DMSO-d_6): δ 14.62, 55.42, 55.90 (2 C's), 91.45 (2 C's), 117.77, 118.10, 121.17 (2 C's), 124.53, 126.01, 129.09 (2 C's), 130.89, 136.05, 138.19, 139.05, 143.67, 146.29, 149.58, 150.23, 151.62 (2 C's), 155.27; MS: m/z 426 (M^+, 100), 365 (27), 335 (24), 318 (18), 259 (19), 91 (21), 77 (32); Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.54; H, 5.10; N, 12.96.

9-Methyl-7-phenyl-2-p-tolyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (6k). This compound was obtained as a colorless solid, 0.099 g (71%); mp 204–205°C; IR: ν 3018, 2919, 1596, 1501, 1457, 1230, 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 7.28 (t, 1H, J = 8.1 Hz, Ar—H), 7.33 (d, 2H, J = 8.4 Hz, Ar—H), 7.52 (t, 2H, J = 8.1 Hz, Ar—H), 7.89 (d, 1H, J = 8.4 Hz, Ar—H), 8.16–8.22 (m, 4H, Ar—H), 8.29 (d, 1H, J = 8.4 Hz, Ar—H), 8.98 (s, 1H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.32, 19.64, 115.24, 116.78, 120.17 (2 C's), 124.38, 125.85, 127.27 (2 C's), 128.90 (2 C's), 129.14 (2 C's), 133.99, 135.20, 137.57, 138.96, 142.95, 145.64, 148.52, 150.66, 158.97; MS: m/z 350 (M^+, 100), 335 (31), 182 (24), 91 (20), 77 (28); Anal. Calcd. for $C_{23}H_{18}N_4$: C, 78.83; H, 5.18; N, 15.99. Found: C, 79.02; H, 5.07; N, 15.76.

General procedure for the synthesis of compounds 8a–b and 9a–b. A mixture of **4** (0.1 g, 0.396 mmol), corresponding ketone **7a–b** (0.396 mmol), and ethanolic potassium hydroxide solution (5 mL, 2%) was heated under reflux for 1 h. The mixture was cooled to room temperature and the solid precipitated was filtered by suction. It contained two compounds according to TLC analysis (R_f values: 0.89 and 0.65 in ethyl acetate/n-hexane = 3:7). This mixture was separated by column chromatography (18 mm × 300 mm, eluent n-hexane/ethyl acetate = 9:1); detection by TLC analysis (254 nm).

2,3,9-Trimethyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (8a). This compound was obtained as a colorless solid, 0.065 g (57%); mp 163–164°C; IR: 3041, 2931, 1605, 1510, 1439, 1277, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.69 (s, 3H, CH_3), 3.02 (s, 6H, 2 × CH_3), 7.31 (t, 1H, J = 7.4 Hz, Ar—H), 7.53 (t, 2H, J = 7.4 Hz, Ar—H), 7.93 (s, 1H, Ar—H), 8.24 (d, 2H, J = 7.4 Hz, Ar—H), 8.91 (s, 1H, Ar—H); MS: m/z 288 (M^+, 100), 197 (26), 91 (23), 77 (36); Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.14; H, 5.68; N, 19.62.

2,9-Dimethyl-3,7-diphenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (8b). This compound was obtained as a colorless solid, 0.072 g (52%); mp 171–172°C; IR: 3054, 2927, 1596, 1504, 1432, 1249, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.89 (s, 6H, 2 × CH_3), 7.28–7.40 (m, 6H, Ar—H), 7.50 (t, 2H, J = 7.8 Hz, Ar—H), 7.86 (s, 1H, Ar—H), 8.18 (d, 2H, J = 7.8 Hz, Ar—H), 8.89 (s, 1H, Ar—H); MS: m/z 350 (M^+, 100), 259 (23), 91 (21), 77 (35); Anal. Calcd. for $C_{23}H_{18}N_4$: C, 78.83; H, 5.18; N, 15.99. Found: C, 79.01; H, 5.26; N, 15.74.

2-Ethyl-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (9a). This compound was obtained as a colorless solid, 0.023 g (20%); mp 139–140°C; IR: 3048, 2933, 1592, 1506, 1418, 1234, 764 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (t, 3H, J = 5.4 Hz, CH_3), 2.78 (q, 2H, J = 5.4 Hz, CH_2), 3.04 (s, 3H, CH_3), 7.31 (d, 1H, J = 7.2 Hz, Ar—H), 7.34 (t, 1H, J = 7.8 Hz, Ar—H), 7.56 (t, 2H, J = 7.8 Hz, Ar—H), 8.19 (d, 1H, J = 7.2 Hz, Ar— H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 8.97 (s, 1H, Ar—H); MS: m/z 288 (M^+, 100), 273 (42), 182 (28), 91 (19), 77 (30); Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.17; H, 5.68; N, 19.27.

2-Benzyl-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (9b). This compound was obtained as a colorless solid, 0.03 g (22%); mp 157–158°C; IR: 3061, 2920, 1600, 1499, 1426, 1219, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.16 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 7.35 (t, 1H, J = 7.8 Hz, Ar—H), 7.51–7.62 (m, 5H, Ar—H), 8.01 (d, 1H, J = 8.4 Hz, Ar—H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 8.35 (d, 2H, J = 8.1 Hz, Ar—H), 8.42 (d, 1H, J = 8.4 Hz, Ar—H), 9.08 (s, 1H, Ar—H); MS: m/z 350 (M^+, 100), 273 (29), 259 (21), 244 (18), 91 (23), 77 (34); Anal. Calcd. for $C_{23}H_{18}N_4$: C, 78.83; H, 5.18; N, 15.99. Found: C, 78.96; H, 5.11; N, 16.23.

General procedure for the synthesis of compounds 11, 13a,b, and 15. A mixture of **4** (0.1 g, 0.396 mmol) and **10**, **12**, or **14** (0.396 mmol) was refluxed in ethanol (3 mL) in the presence of catalytic amount of piperidine for 2 h. Upon cooling to room temperature, a solid product precipitated, which was collected by filtration and washed with cold ethanol to yield the compounds **11**, **13**, and **15** in 63–79% yield.

2-(4-Bromophenyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine-3-carbonitrile (11). This compound was obtained as a colorless solid, 0.13 g (73%); mp 289–290°C; IR: 3056, 2954, 2259, 1610, 1505, 1438, 1237, 756 cm^{-1}; ^1H NMR (DMSO-d_6 + d-CF_3COOD): δ 2.87 (s, 3H, CH_3), 7.29 (t, 1H, J = 7.8 Hz, Ar—H), 7.31 (d, 2H, J = 8.2 Hz, Ar—H), 7.48 (t, 2H, J = 7.8 Hz, Ar—H), 7.53 (d, 2H, J = 8.2 Hz, Ar—H), 8.13 (d, 2H, J = 7.8 Hz, Ar—H), 8.80 (s, 1H, Ar—H), 9.14 (s, 1H, Ar—H); MS: m/z 441 (M+2, 75), 439 (M^+, 100), 348 (24), 233 (19), 91 (23), 77 (31); Anal. Calcd. for $C_{23}H_{14}BrN_5$: C, 62.74; H, 3.20; N, 15.91. Found: C, 62.96; H, 3.28; N, 16.06.

Ethyl-2,9-dimethyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine-3-carboxylate (13a). This compound was obtained as a colorless solid, 0.090 g (66%); mp 127–128°C; IR: 3062, 2947, 1727, 1606, 1495, 1435, 1251, 1157, 765 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.39 (t, 3H, J = 5.4 Hz, CH_3), 2.94 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.39 (q, 2H, J = 5.4 Hz, CH_2), 7.38 (t, 1H, J = 7.2 Hz, Ar—H), 7.58 (t, 2H, J = 7.2 Hz, Ar—H), 8.21 (d, 2H, J = 7.2 Hz, Ar—H), 9.18 (s, 1H, Ar—H), 9.43 (s, 1H, Ar—H); MS: m/z 346 (M^+, 100), 317 (41), 301 (27), 255 (19), 91 (16), 77 (26); Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.22; H, 5.13; N, 15.99.

2,9-Dimethyl-N,7-diphenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine-3-carboxamide (13b). This compound was obtained as a pale yellow solid, 0.098 g (63%); mp 179–180°C; IR: 3381, 3207, 3056, 2924, 1665, 1610, 1509, 1455, 1266, 780 cm^{-1}; ^1H NMR (DMSO-d_6 + d-CF_3COOD): δ 2.78 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 6.97 (t, 1H, J = 7.8 Hz, Ar—H), 7.08 (t, 2H, J = 7.8 Hz, Ar—H), 7.24–7.29 (m, 5H, Ar—H), 7.43 (d, 2H, J = 7.8 Hz, Ar—H), 7.87 (s, 1H, NH), 9.21 (s, 1H, Ar—H), 9.23(s, 1H, Ar—H); MS: m/z 393 (M^+, 100), 301 (15), 273 (17), 210 (22), 91 (21), 77 (29); Anal. Calcd. for $C_{24}H_{19}N_5O$: C, 73.27; H, 4.87; N, 17.80. Found: C, 73.10; H, 4.96; N, 17.94.

Ethyl-9-methyl-2-oxo-7-phenyl-2,7-dihydro-3H-pyrazolo[3,4-h][1,6]naphthyridine-3-carboxylate (15). This compound was obtained as a colorless solid, 0.109 g (79%); mp 144–145°C; IR: 3215, 3061, 2949, 1755, 1671, 1595, 1502, 1436, 1230, 790 cm^{-1}; ^1H NMR (DMSO-d_6 + d-CF_3COOD): δ 1.44 (t, 3H, J = 7.2 Hz, CH_3), 3.06 (s, 3H, CH_3), 4.50 (q, 2H, J = 7.2Hz, CH_2), 7.53–7.63 (m, 5H, Ar—H), 8.27 (s, 1H, NH), 9.09 (s, 1H, Ar—H), 9.24(s, 1H, Ar—H); MS: m/z 348 (M^+, 100), 303 (29), 257 (23), 172 (17), 91 (25), 77 (31); Anal. calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.33; H, 4.75; N, 16.23.

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Synthesis of Benzo[3,4-*h*][1,6]naphthyridines *via* Friedländer Condensation with Active Methylenes

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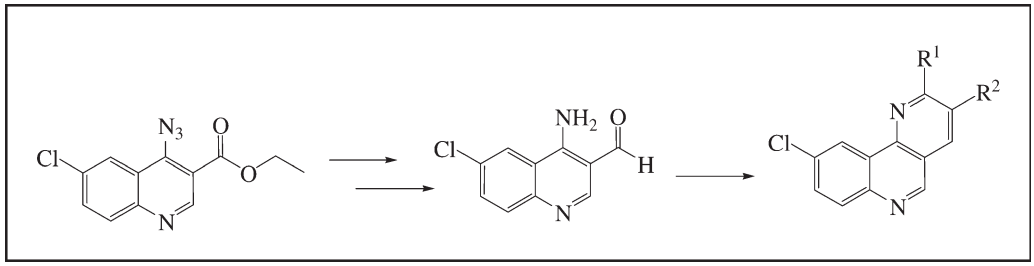

Novel 4-amino-6-chloroquinoline-3-carbaldehyde has been synthesized by synchronous reduction by lithium aluminiumhydride and finally oxidation with MnO_2. Friedländer condensation of it with reactive methylenes furnished novel benzo[3,4-*h*][1,6]naphthyridine derivatives.

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INTRODUCTION

The construction of ring structures from orthoaminoaldehyde as a starting material has wide applicability for the annulation of heterocyclic systems. This construction method predominates the direction of ring growth (angular vs. linear) and generally permits the direct and regiospecific introduction of functional groups and/or substituents in the newly formed heterocyclic ring. Among numerous possibilities for ortho joined functionalities those containing carbon and nitrogen are of particular interest, because the numerous combinations of their different oxidation states and easy accessibility of simple derivatives provide them with exceptional versatility in hetero annulation reaction. From literature, it was noted that o-aminobenzaldehyde, the first and best known member of this class of compounds has been utilized for synthesis of various heterocycles [1–17]. Annulation reaction of heterocyclic aminoaldehydes provide a synthetic entry into heterocyclic systems fused to pyridine [18–21], pyrazole [22–25], and quinoline nucleus [26,27]. The functionalized quinolines and their benzo/hetero-fused analogous present in numerous natural products along with the wide spectrum of physiological activities [28]. In our earlier communication, we have reported the synthetic utility of heterocyclic o-aminoaldehyde in which annulation of heterocyclic system on to pyrazole and pyrazolopyridine nuclei was performed [29–31].

These literature reports and our continuous interest in this area prompted us to report the novel synthesis of orthoaminoformylquinoline and study of Friedländer condensation of it with various reactive methylenes. In this communication we have synthesized benzo[3,4-*h*][1,6]naphthyridines, which may have potential biological activities such as antimalarials [32], antagonists of 5-HT_4 receptor [33], reported earlier.

Godard and Queguiner reported synthesis of 4-aminoquinoline-3-carbaldehyde by following sequence of reaction [34]. In their sequence, the anhydride **I** was treated with NH_3 to furnish carboxamide **II**. The alkaline hydrolysis of **II** with KOH yielded aminoacid **III**, which was esterified with MeOH/ H_2SO_4 to yield orthoaminoester **IV**. The lithium aluminiumhydride reduction of **IV** yielded primary alcohol **V** and finally oxidation with MnO_2 furnished a orthoaminoaldehyde **1a** (Fig. 1).

We have adopted different strategy for synthesis of 4-amino-6-chloroquinoline-3-carbaldehyde **1b** (heterocyclic orthoaminoaldehyde). Chloro-ester **A** was synthesized in the beginning by reported method [35], starting with p-chloroaniline. Then SN^2 displacement of chloro functionality at position 4 was achieved with NaN_3 in DMF at room temperature to yield **B** quantitatively. The synchronous reduction of both azido and ester group in **B** by lithium aluminiumhydride in dry THF at 0–5°C yielded the ortho amino alcohol **C** in 79% yield. Finally, oxidation of **C** with manganese (IV) oxide, without protecting amino group [34,36], in dichloromethane at room temperature furnish desire target molecule 4-amino-6-chloroquinoline-3-carbaldehyde **1b** in 71% yield. In this step, expected N-oxide was not formed as revealed by spectral and analytical data. The

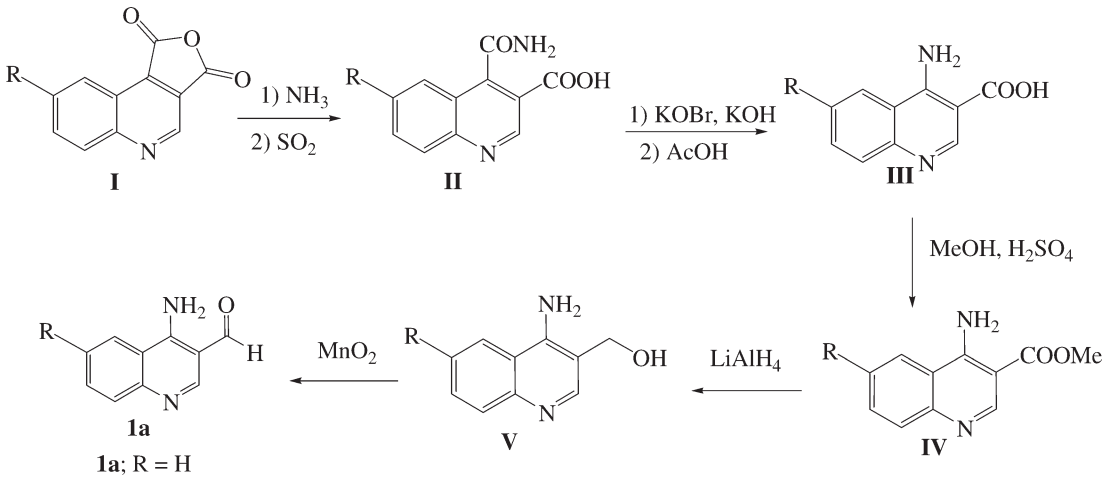


Figure 1. Godard method for synthesis of 4-aminoquinoline-3-carbaldehyde.

intermediates **B**, **C**, and **1b** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis (Scheme 1).

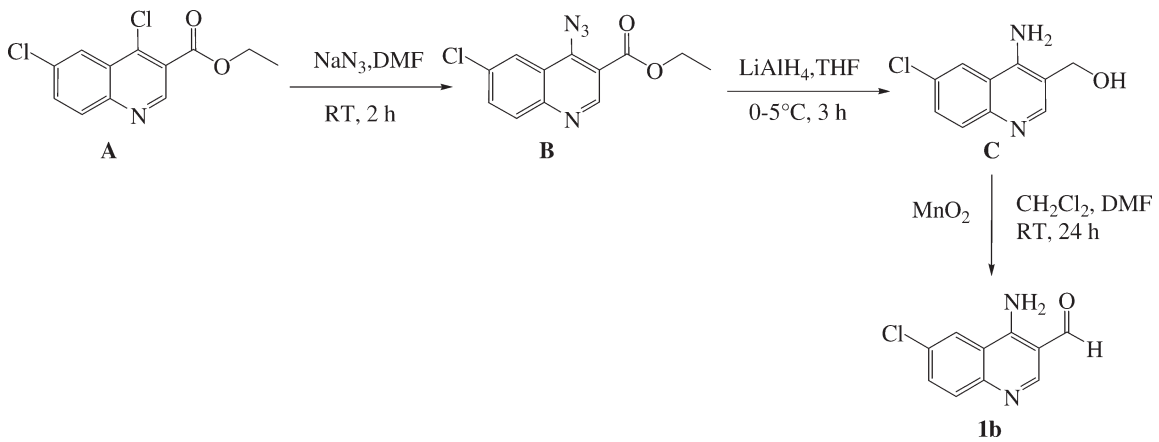
In our approach, the yields of intermediates **B**, **C**, and **1b** are excellent. This method is versatile and scalable. Compound **1b** in hand reacted with alkyl and/or aryl ketones **2a–k** in DMF at reflux using potassium hydroxide (KOH) as a base to yield benzo[*h*] naphthyridines **3a–k** in 68–80% yield. Analogously **1b** when reacted with unsymmetric dialkyl ketones **4a–b**, instead of expected mixture of two isomer [29], only single isomer **5a–b** were obtained in good yield. However, reaction of **1b** with malononitrile **6** under similar reaction condition was unsuccessful. This condensation was achieved by refluxing a mixture of **1b**, malononitrile and piperidine in ethanol to yield benzo naphthyridine **7**, having nitrile and amino functionality ortho to each other, in 78% yield (Scheme 2).

Compounds **3**, **5**, and **7** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis.

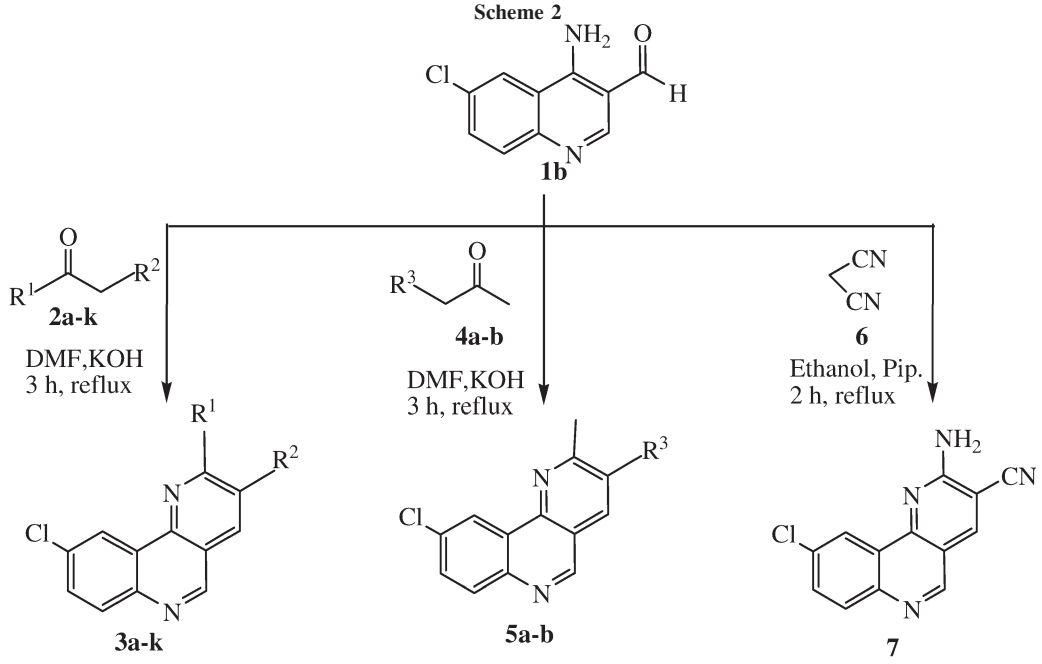
The Friedländer condensation can be catalyzed by various reagents [37]. When we extend our synthetic investigation to CH-acidic compounds such as benzoylacetonitrile **8a–d**, β-ketoester **10a**, β-ketoamide **10b**, and diethyl malonate **12**, we found that already piperidine as base was sufficient strong to catalyze the condensation reaction. Thus, cyclocondensation of **1b** with **8a–d**, **10a–b**, and **12**, afforded 9-Chloro-2-arylbenzo[*h*][1,6]-naphthyridine-3-carbonitriles **9a–d**, Ethyl 9-Chloro-2-methylbenzo[*h*][1,6]naphthyridine-3-carboxylate **11a**, 9-Chloro-2-methyl-N-phenylbenzo[*h*][1,6]naphthyridine-3-carboxamide **11b** and Ethyl 9-Chloro-1,2-dihydro-2-oxobenzo[h][1,6]naphthyridine-3-carboxylate **13**, respectively, in 75–85% yield (Scheme 3). Compounds **9**, **11**, and **13** were characterized by IR, ^{1}H, and ^{13}C NMR, mass spectroscopy and elemental analysis.

In conclusion herein, we report novel and scalable route towards orthoaminoformylquinoline **1b**. A series of novel benzo[3,4-*h*][1,6]naphthyridines and benzo[3,4-

Scheme 1



Scheme 2



2,3	R^1	R^2
a	CH_3	H
b	C_6H_5	H
c	C_6H_5	CH_3
d	2-Cl-C_6H_4	H
e	4-Cl-C_6H_4	H
f	4-F-C_6H_4	H
g	4-Br-C_6H_4	H
h	3,4-di-OMe-C_6H_3	H
i	2,6-di-OMe-C_6H_3	H
j	4-Me-C_6H_4	H
k	3,5-di-CF_3-C_6H_3	H

5	R^3
a	CH_3
b	C_6H_5

h][1,6]naphthyridone was synthesized by Friedländer condensation reaction of 4-amino-6-chloroquinoline-3-carbaldehyde **1b** with reactive methylene compounds.

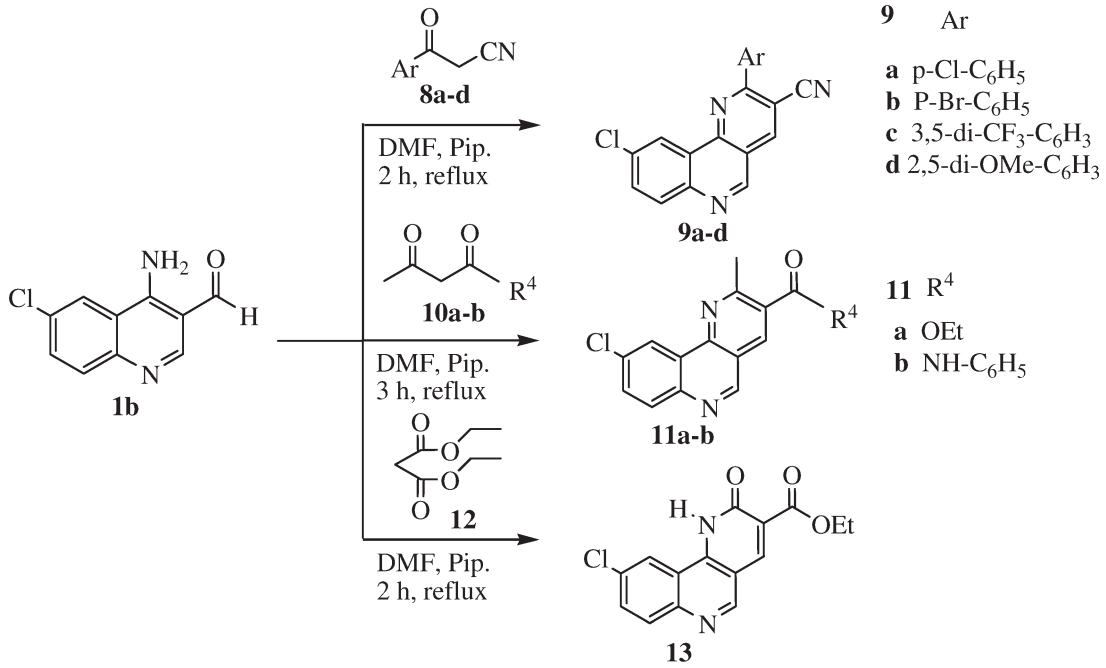
EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB595 in open capillary tubes and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on a Varian XL-300 spectrometer using tetramethylsilane as the internal standard. IR spectra were recorded using a Shimadzu IR-408, a Shimadzu FTIR instrument with potassium bromide discs. Mass spectrum was recorded on Shimadzu GC-MS QP mass spectrometer with an ionization potential of 70 eV. Elemental analyses were obtained on a Hosli CH-Analyzer and are within ±0.3 of the theoretical percentage.

All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagents were either commercially available and were used without further purification or prepared by standard literature procedures.

Ethyl 4-Azido-6-chloroquinoline-3-carboxylate (B). A mixture of **A** [35] (0.246 g, 1 mmol) and sodium azide (0.065 g, 1 mmol) in DMF (2 mL) was stirred at RT for 2 h. After completion of the reaction (TLC check), the solvent was distilled out by vacuum distillation. The reaction mass was quenched in ice cold water (10 mL) and extracted with three fraction of ethyl acetate (12 mL × 3). The organic layer was dried over sodium sulphate and solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, and dried to furnish **B** as colorless solid; (0.182 g, 74%), mp 292–293°C; ir (potassium bromide): 3086(w), 2920(m), 2134(m), 1770(s), 1563(s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 6.9 Hz, 3H), 4.45 (q, J = 6.9 Hz, 2H), 7.73 (dd, J = 8.5, 2.2 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.02, 60.3, 124.5, 128.6, 129.4, 131.7, 133.1, 133.9, 138.4, 146.2, 146.9, 166.2; ms: *m/z* (%) 276 (M^+,100), 278 (M+2, 32); Anal. Calcd. for $C_{12}H_9ClN_4O_2$ (276.68): C, 52.09; H, 3.28; N, 20.25. Found: C, 52.25; H, 3.37; N, 20.43.

Scheme 3



(4-Amino-6-chloroquinolin-3-yl)methanol (C). A solution of **B** (0.276 g, 1 mmol) in tetrahydrofuran (2 mL) was added slowly into the dispersed lithium aluminium hydride (0.144 g, 4 mmol) in tetrahydrofuran (2 mL) at 0–5°C, after addition, the reaction mass was allowed to stand at RT and further stirred for 3 h. After completion of reaction (TLC check), the reaction mass was quenched in saturated sodium sulphate solution (2–3 mL) at 0–5°C and extracted in three fraction of ethyl acetate (5 mL × 3). The combined organic layer was washed with water (5 mL × 3), then dried over anhydrous sodium sulphate, filtered, and the solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (8:2) to give **C** as colorless solid; (0.218 g, 79%); mp 221–222°C; ir (potassium bromide): 3443(m), 3354(m), 3248(s), 2895(w), 1660(s), 1564(s), 1500(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.56 (d, J = 5.4 Hz, 2H, CH_2), 5.13 (t, J = 5.4 Hz, 1H, OH), 6.62 (s, 2H, NH_2), 7.55 (d, J = 9 Hz, 1H), 7.76 (d, J = 9 Hz, 1H), 8.36 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 56.3, 116.7, 119.4, 122.9, 129.7, 130.5, 131.1, 146.4, 149.2, 151.9; ms: *m/z* (%) 208 (M^+,100), 210 (M+2, 33); Anal. Calcd. For $C_{10}H_9ClN_2O$ (208.64): C, 57.57; H 4.35; N, 13.43. Found: C, 57.63; H, 4.46; N, 13.51.

4-Amino-6-chloroquinoline-3-carbaldehyde (1b). To the solution of **C** (0.208 g, 1 mmol) in dichloromethane (2 mL), manganese (IV) dioxide (0.170 g, 2 mmol) was added. The reaction mixture was stirred at 25°C for 24 h. After completion of the reaction (TLC check), the reaction mass was filtered through celite and solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to give **1b** as pale brown needles; (0.147 g, 71%); mp 319–320°C; ir (potassium bromide): 3323(m), 3093(m), 2926(m), 2783(w), 1714(s), 1657(s), 1589(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.77 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 8.67 (s, 1H), 8.73 (s, 1H), 8.91 (s, 2H, NH_2), 9.96 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6): δ 115.2, 121.5, 123.7, 130.7, 131.8, 133.0, 142.6, 145.3, 159.9, 193.0; ms: *m/z* (%) 206 (M^+, 100), 208 (M+2, 31); Anal. Calcd. For $C_{10}H_7ClN_2O$ (206.63): C, 58.13; H, 3.41; N, 13.56. Found. C, 58.23; H, 3.47; N, 13.62.

General procedure for the synthesis of compounds 3a–k. A mixture of **1b** (0.206 g, 1 mmol) and **2a–k** (1 mmol) in DMF with catalytic amount of KOH was heated under reflux for 3 h, after completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (7:3) to furnish compounds **3a–k** in 68–80% yield.

9-Chloro-2-methylbenzo[h][1,6]naphthyridine (3a). Pale yellow solid; (0.148 g, 72%); mp 282–283°C; ir (potassium bromide): 3111(w), 3040(w), 2833(m), 2830(m), 2905(m), 1671(s), 1659(w), 1561(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.47 (s, 3H), 7.73 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 8.4 Hz, 1H), 9.24 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 24.2, 119.9, 121.4, 122.7, 125.3, 125.9, 130.1, 130.8, 131.1, 133.8, 135.3, 145.6, 156.2; ms: *m/z* (%) 228 (M^+, 100), 230 (M+2, 34); Anal. Calcd. For $C_{13}H_9ClN_2$ (228.66): C, 68.28; H, 3.97; N, 12.25. Found. C, 68.34; H, 4.1; N, 12.31.

9-Chloro-2-phenylbenzo[h][1,6]naphthyridine (3b). Colorless solid; (0.154 g, 75%); mp 298–299°C; ir (potassium bromide): 3022(w), 2979(m), 1668(m), 1639(w), 1567(m), 1559(m), 1518(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.66 (m, 3H, Ar—H), 7.81 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 8.46 (m, 3H), 8.71 (d, J = 8.4 Hz, 1H), 9.12 (s, 1H), 9.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 121.2, 123.9, 126.7 (2 C's), 128.0, 128.1, 128.3, 128.9 (2 C's), 130.0, 131.6, 132.7, 133.4, 136.1, 136.9, 144.7, 148.2, 154.3; ms: *m/z* (%) 290 (M^+, 100), 292 (M+2, 35); Anal. Calcd. For $C_{18}H_{11}ClN_2$ (290.75): C, 74.36; H, 3.81; N, 9.63. Found. C, 74.48; H, 3.79; N, 9.77.

9-Chloro-3-methyl-2-phenylbenzo[h][1,6]naphthyridine (3c). Pale yellow solid; (0.164 g, 80%); mp 294–295°C; ir (potassium bromide): 3093(w), 2973(w), 1643(s), 1631(m), 1612(m), 1582(m), 1567(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H), 7.22–7.56 (m, 5H), 7.84 (d, J = 7.4 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 8.37 (s, 1H), 8.82 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.5, 121.7, 124.0, 126.9, 128.6, 129.1, 129.7, 130.1, 130.3, 132.0, 132.4, 132.9, 133.1, 135.2, 135.3, 137.3, 146.6, 150.1, 160.8; ms: *m/z* (%) 304 (M^+, 100), 306 (M+2, 32); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88; H, 4.30; N, 9.19. Found. C, 74.91; H, 4.43; N, 9.24.

9-Chloro-2-(2-chlorophenyl)benzo[h][1,6]naphthyridine (3d). Colorless solid; (0.140 g, 68%); mp 276–277°C; ir (potassium bromide): 2985(m), 2822(w), 2818(m), 1691(m), 1637(w), 1583(w), 1501(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.44 (m, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H,), 8.12 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 6.7 Hz, 1H), 8.42 (d, J = 6.7 Hz, 1H), 9.27 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 120.5, 123.3, 124.9, 126.8, 127.5, 127.9, 128.2, 129.1, 130.3, 131.1, 131.9, 132.4, 132.7, 134.0, 134.7, 145.1, 149.1, 152.7; ms: *m/z* (%) 324 (M^+, 100), 326 (M+2, 31), 328 (M+4, 18); Anal. Calcd. For $C_{18}H_{10}Cl_2N_2$ (325.19): C, 66.48; H, 3.10; N, 8.16. Found. C, 66.52; H, 3.19; N, 8.27.

9-Chloro-2-(4-chlorophenyl)benzo[h][1,6]naphthyridine (3e). Pale yellow solid; (0.142 g, 69%); mp 269–270°C; ir (potassium bromide): 3012(m), 2921(m), 2817(w), 1658(m), 1649(s), 1486(m), 1422(w), 1583(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.37 (d, J = 7.9 Hz, 2H), 7.91 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H,), 8.52 (d, J = 7.9 Hz, 2H), 8.65 (d, J = 7.2 Hz, 1H), 9.00 (s, 1H), 9.24 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 118.3, 123.0, 127.2, 127.9, 128.9 (2 C's) 130.0, 130.7, 130.9, 131.2, 133.3, 134.1, 134.7, 143.8 (2 C's) 147.2, 154.0, 157.1; ms: *m/z* (%) 324 (M^+,100), 326 (M+2, 36), 328 (M+4, 13); Anal. Calcd. For $C_{18}H_{10}Cl_2N_2$ (325.19): C, 66.48; H, 3.10; N, 8.16. Found. C, 66.49; H, 3.21; N, 8.29.

9-Chloro-2-(4-fluorophenyl)benzo[h][1,6]naphthyridine (3f). Colorless solid; (0.150 g, 73%); mp 297–298°C; ir (potassium bromide): 2989(m), 2817(w), 1631(m), 1604(m), 1588(m), 1563(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.55 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.4 Hz, 1H), 7.93 (d, J = 7.4 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 8.4 Hz, 2H), 8.90 (s, 1H), 9.26 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 113.4 (2 C's), 120.7, 122.9, 125.6, 125.8, 129.1(2 C's), 129.9, 131.1, 131.9, 132.0, 133.7, 135.1, 144.6, 147.9, 154.1, 159.3; ms: *m/z* (%) 308 (M^+, 100), 310 (M+2, 33); Anal. Calcd. For $C_{18}H_{10}ClFN_2$ (308.74): C, 70.03; H, 3.26; N, 9.07. Found. C, 70.11; H, 3.37; N, 9.19.

2-(4-Bromophenyl)-9-chlorobenzo[h][1,6]naphthyridine (3g). Pale yellow solid; (0.150 g, 73%); mp 267–268°C; ir (potassium bromide): 3005(w), 2918(m), 1645(m), 1623(w), 1522(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H,), 8.56 (d, J = 7.5 Hz, 2H), 8.53 (d, J = 7.6 Hz, 1H), 9.08 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 117.7, 123.5, 126.9, 128.0, 129.0 (2 C's) 131.0, 131.2, 131.3, 131.4, 134.0, 134.2, 134.6, 144 (2 C's) 147.0, 154.4, 159.8; ms: *m/z* (%) 368 (M^+, 78), 370 (M+2, 95), 372 (M+4, 19); Anal. Calcd. For $C_{18}H_{10}BrClN_2$ (369.64): C, 58.49; H, 2.73; N, 7.58. Found. C, 58.58; H, 2.75; N, 7.69.

9-Chloro-2-(3,4-dimethoxyphenyl)benzo[h][1,6]naphthyridine (3h). Pale yellow solid; (0.154 g, 75%); mp 294–295°C; ir (potassium bromide): 3018(m), 2963(w), 1683(w), 1669(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.67 (s, 6H), 7.06 (d, J = 7.5 Hz, 1H), 7.30 (dd, J = 7.2,2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 7.4 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.75 (d, J = 7.4 Hz, 1H), 9.11 (s, 1H), 9.23 (s, 1H); ms: *m/z* (%) 350 (M^+, 100), 352 (M+2, 34); Anal. Calcd. For $C_{20}H_{15}ClN_2O_2$ (350.80): C, 68.48; H, 4.31; N, 7.99. Found. C, 68.53; H, 4.42; N, 8.1.

9-Chloro-2-(2,6-dimethoxyphenyl)benzo[h][1,6]naphthyridine (3i). Colorless solid; (0.158 g, 77%); mp 297–298°C; ir (potassium bromide): 2981(m), 2897(w), 1676(m), 1632(m), 1548(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.79 (s, 6H), 7.43 (m, 3H, Ar—H), 8.3 1(d, J = 8.2 Hz, 1H), 8.42 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 7.8 Hz, 1H), 9.10 (s, 1H), 9.17 (s, 1H); ms: *m/z* (%) 350 (M^+, 100), 352 (M+2, 36); Anal. Calcd. For $C_{20}H_{15}ClN_2O_2$ (350.80): C, 68.48; H, 4.31; N, 7.99. Found. C, 68.50; H, 4.37; N, 8.2.

9-Chloro-2-p-tolylbenzo[h][1,6]naphthyridine (3j). Colorless solid; (0.156 g, 76%); mp 297–298°C; ir (potassium bromide): 2981(m), 2978(w), 2896(m), 1635(m), 1618(m), 1512(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.37 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H), 8.91 (s, 1H), 9.13 (s, 1H); ms: *m/z* (%) 304 (M^+, 100), 306 (M+2, 31); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88; H, 4.30; N, 9.19. Found. C, 74.91; H, 4.33; N, 9.27.

2-(3,5-Bis(trifluoromethyl)phenyl)-9-chlorobenzo[h][1,6]-naphthyridine (3k). Colorless solid; (0.154 g, 75%); mp 283–284°C; ir (potassium bromide): 3012(m), 2937(m), 1683(w), 1662(s), 1544(m), 1537(w); ^1H NMR (DMSO-d_6): δ 7.87 (m, 1H), 8.16 (m, 2H), 8.65 (dd, J = 2.7,8.4 Hz, 1H), 8.80 (dd, J = 2.7,8.4 Hz,1H), 8.93 (s,2H), 9.01 (s, 1H), 9.44 (s, 1H); ms: m/z (%) 426 (M^+, 100), 428 (M+2, 33); Anal. Calcd. For $C_{20}H_9ClF_6N_2$ (426.74): C, 56.33; H, 2.11; N, 6.57. Found. C, 56.31; H, 2.17; N, 6.56.

General procedure for the synthesis of compounds 5a and b. A mixture of **1b** (0.206 g, 1 mmol) and corresponding ketones **4a–b** (1 mmol) in DMF with catalytic amount of KOH was heated under reflux for 3 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure, the crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to furnish **5a–b** in 76–79% yield.

9-Chloro-2,3-dimethylbenzo[h][1,6]naphthyridine (5a). Pale yellow solid; (0.160 g, 78%); mp 302–303°C; ir (potassium bromide): 3012(w), 2982(m), 2811(m), 1683(m), 1661(w), 1537(m), 1518(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H), 2.71 (s, 3H), 7.86 (d, J = 6.6 Hz, 1H), 8.10 (d, J = 6.6 Hz, 1H), 8.32 (s, 1H) 8.96 (s, 1H), 9.30 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 16.3, 18.1, 120.7, 126.6, 127.8, 130.1, 131.3, 132.6, 133.1, 133.2, 135.0, 145.7, 150.0, 159.1; ms: m/z (%) 242 (M^+, 100), 244 (M+2, 37); Anal. Calcd. For $C_{14}H_{11}ClN_2$ (242.70): C, 69.28; H, 4.57; N, 11.54. Found. C, 69.37; H, 4.58; N, 11.63.

9-Chloro-2-methyl-3-phenylbenzo[h][1,6]naphthyridine (5b). Pale yellow solid; (0.156 g, 76%); mp 291–292°C; ir (potassium bromide): 3314(m), 3017(m), 2983(w), 1683(m), 1676(w), 1560(w), 1553(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ

2.60 (s, 3H), 7.22–7.56 (m, 5H), 8.07 (d, J = 7.4 Hz, 1H), 8.29 (d, J = 7.4 Hz, 1H), 8.45 (s, 1H), 9.03 (s, 1H), 9.25 (s, 1H); ms: m/z (%) 304 (M^+, 100), 306 (M+2, 32); Anal. Calcd. For $C_{19}H_{13}ClN_2$ (304.77): C, 74.88: H, 4.30; N, 9.19. Found. C, 74.93; H, 4.48; N, 9.21.

2-Amino-9-chlorobenzo[*h*][1,6]naphthyridine-3-carbonitrile (7). A mixture of **1b** (0.206 g, 1 mmol) and malononitrile **6** (0.066 g, 1 mmol) in ethanol with catalytic amount of piperidine was heated under reflux for 2 h. After completion of reaction (TLC check), separated solid was collected by filtration and recrystallized from DMF to furnish compound **7** as colorless needles; (0.160 g, 78%); mp 279–280°C; ir (potassium bromide): 3406(s), 3315(w), 3084(m), 2962(w), 2744(w), 2218(m), 1660(s), 1599(s), 1489(s) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.86 (d, J = 8.7 Hz, 1H), 7.88 (s, 2H, NH_2), 8.02 (d, J = 8.7 Hz, 1H), 8.75 (s, 1H), 8.89 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 95.2, 119.6, 120.5, 127.3, 127.9, 129.1, 131.2, 133.1, 135.9, 142.7, 146.8, 149.6, 163.0; ms: m/z (%) 254 (M^+, 100), 256 (M+2, 35); Anal. Calcd. For $C_{13}H_7ClN_4$ (254.67): C, 61.31: H, 2.77; N, 22.00. Found. C, 61.36; H, 2.86; N, 22.09.

General procedure for the synthesis of compounds 9a–d. A mixture of **1b** (0.206 g, 1 mmol) and corresponding benzoylacetonitrile **8a–d** (1 mmol) in DMF with catalytic amount of piperidine was heated under reflux for 2 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (8:2) to furnish compounds **9a–d** in 75–85% yield.

9-Chloro-2-(4-chlorophenyl)benzo[h][1,6]naphthyridine-3-carbonitrile (9a). Pale brown solid; (0.170 g, 83%); mp 297–298°C; ir (potassium bromide): 3002(w), 2987(m), 2811(m), 2217(m), 1678(s), 1657(m), 1583(w), 1559(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.62 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 7.6 Hz, 2H), 8.23 (d, J = 8.2 Hz, 1H), 8.54 (s, 1H), 8.81 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 91.9, 117.6, 122.2, 123.8, 126.7, 129.1, 129.3, 129.7, (2 C's), 130.1, 131.8, 132.6, 133.1, 133.3, 135.5, 140.3, 144.2, 149.1, 164.4; ms: m/z (%) 349 (M^+, 100), 351 (M+2, 36), 353 (M+4, 14); Anal. Calcd. For $C_{19}H_9Cl_2N_3$ (350.20): C, 65.16; H, 2.59; N, 12.00. Found. C, 65.21; H, 2.66; N, 12.11.

2-(4-Bromophenyl)-9-chlorobenzo[h][1,6]naphthyridine-3-carbonitrile (9b). Pale brown solid; (0.166 g, 81%); mp 297–298°C; ir (potassium bromide): 2963(m), 2917(m), 2221(m), 1682(w), 1667(m), 1591(m), 1551(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.75 (d, J = 7.5 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 7.5 Hz, 2H), 8.33 (d, J = 8.4 Hz, 1H), 8.64 (s, 1H), 8.81 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 90.0, 118.0, 123.2, 126.4, 126.8, 130.2, 130.3, 130.7, (2 C's), 131.1, 131.7, 132.9, 134.1, 134.3, 135.7, 141.0, 143.2, 150.1, 165.3; ms: m/z (%) 394 (M^+, 81), 396 (M+2, 97), 398 (M+4, 22); Anal. Calcd. For $C_{19}H_9BrClN_3$ (394.65): C, 57.82; H, 2.30; N, 10.65. Found. C, 57.83; H, 2.41; N, 10.72.

2-(3,5-Bis(trifluoromethyl)phenyl)-9-chlorobenzo[h][1,6]-naphthyridine-3-carbonitrile (9c). Colorless solid; (0.164 g, 80%); mp 291–292°C; ir (potassium bromide): 3012(m), 2969(m), 2219(m), 1673(w), 1656(m), 1569(m), 1533(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.76 (s, 1H), 8.03 (s, 2H), 8.14 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 7.5 Hz, 1H), 8.64 (s, 1H), 8.83 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 89.5, 105.3, 124.1, 124.3, 124.9, 125.7, 126.8, 128.2, 128.8 (2 C's), 131.1, 132.2 (2 C's), 132.9 133.0, 134.7, 138.2, 140.1, 144.3, 147.9, 163.8; ms: m/z (%) 451 (M^+, 100), 453 (M+2, 31); Anal. Calcd. For $C_{21}H_8ClF_6N_3$ (451.75): C, 55.87; H, 1.77; N, 9.31. Found. C, 55.83; H, 1.90; N, 9.28.

9-Chloro-(2,5-dimethoxyphenyl)benzo[h][1,6]naphthyridine-3-carbonitrile (9d). Pale yellow solid; (0.175 g, 85%); mp 293–294°C; ir (potassium bromide): 2986(m), 2947(w), 2218(m), 1683(w), 1669(w), 1527(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.65 (s, 6H), 7.01–7.35 (m, 3H, Ar—H), 8.01 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.59 (s, 1H), 8.73 (s, 1H), 9.10 (s, 1H); ms: m/z (%) 375 (M^+, 100), 377 (M+2, 33); Anal. Calcd. For $C_{21}H_{14}ClN_3O_2$ (375.81): C, 69.12; H, 3.75; N, 11.18. Found. C, 69.17; H, 3.81; N, 11.27.

General procedure for the synthesis of compounds 11a and b. A mixture of **1b** (0.206 g, 1 mmol) and corresponding diketone **10a–b** (1 mmol) in DMF with catalytic amount of piperidine was heated under reflux for 3 h. After completion of the reaction (TLC check), solvent was evaporated under reduced pressure. The crude solid was washed with methanol, filtered, dried under high vacuum, and recrystallized from ethanol: DMF (6:4) to furnish compound **11a–b** in 77–79% yield.

Ethyl 9-Chloro-2-methylbenzo[h][1,6]naphthyridine-3-carboxylate (11a). Colorless solid; (0.158 g, 77%); mp 297–298°C; ir (potassium bromide): 3161(w), 3073(m), 2981(m), 2935(m), 1767(s), 1661(s), 1624(m), 1510(m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.33 (s, 3H), 3.78 (t, J = 6.9 Hz, 3H), 4.35 (q, J = 6.9 Hz, 2H, OCH_2), 7.92 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.54 (s, 1H), 8.86 (s, 1H), 9.14 (s, 1H); ms: m/z (%) 300 (M^+, 100), 302 (M+2, 33); Anal. Calcd. For $C_{16}H_{13}ClN_2O_2$ (300.74): C, 63.90; H, 4.36; N, 9.31. Found. C, 63.97; H, 4.49; N, 9.30.

9-Chloro-2-methyl-N-phenylbenzo[h][1,6]naphthyridine-3-carboxamide (11b). Pale yellow solid; (0.150 g, 73%); mp 271–272°C; ir (potassium bromide): 3336(s), 3152(m), 3017(w), 2880(m), 1693(s), 1642(s), 1624(m), 1517(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.36 (s, 3H, CH_3), 7.34 (m, 5H, Ar—H), 8.01 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.34 (s, 1H), 8.80 (s, 1H), 9.14 (s, 1H), 11.80 (s, 1H, NH); ms: m/z (%) 347 (M^+, 100), 349 (M+2, 35); Anal. Calcd. For $C_{20}H_{14}ClN_3O$ (347.80): C, 69.07; H, 4.06; N, 12.0. Found. C, 69.14; H, 4.01; N, 12.06.

Ethyl 9-Chloro-1,2-dihydro-2-oxobenzo[*h*][1,6]naphthyridine-3-carboxylate (13). Colorless solid; (0.152 g, 74%); mp 247–248°C; ir (potassium bromide) 3398(w), 3167(m), 3072(m), 2980(s), 1741(m), 1699(s), 1662(s), 1604(s), 1500(w) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.33 (t, J = 6.9 Hz, 3H, CH_3), 4.34 (q, J = 6.9 Hz, 2H, OCH_2), 7.83 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 8.71 (s, 1H), 9.00 (s, 1H), 9.16 (s, 1H), 12.8 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.1, 60.9, 110.4, 116.9, 122.4, 123.4 131.5, 131.6, 131.8, 142.0, 143.1, 146.2, 151.5, 159.2, 163.6; ms: m/z (%) 302 (M^+, 100), 304 (M+2, 34); Anal. Calcd. For $C_{15}H_{11}ClN_2O_3$ (302.71): C, 59.52; H, 3.66; N, 9.25. Found. C, 59.41; H, 3.67; N, 9.19.

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An Efficient Synthesis of Pyrazolo[3,4-*b*]quinolin-5(6*H*)-one Derivatives in Ionic Liquid

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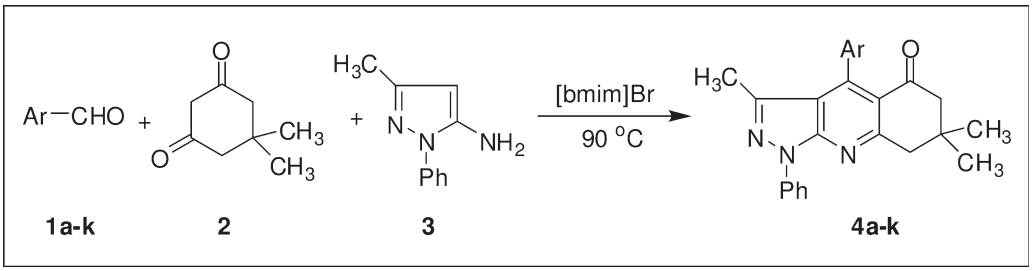

A series of 4-aryl-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-ones were synthesized via the three-component reaction of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexandione and 5-amino-3-methyl-1-phenylpyrazole in ionic liquid without using any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, short reaction time, and environmentally benign procedure.

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INTRODUCTION

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, antiinflammatory, and antitumor properties. In particular, condensed pyrazole are known for various biological activities, *e. g.* pyrazolo[3,4-*b*]quinolines have exhibited potential antiviral [1], antimalarial [2], and serum cholesterol lowering activities. A number of methods are available for the synthesis of pyrazolo[3,4-*b*]quinolines[3], the most efficient and commonly used method involves the reaction of aromatic aldehyde, 1,3-dicarbonyl compound and aminopyrazole in organic solvent such as EtOH [4]. All the reported methods of their synthesis have limitations of poor yields, difficult workups, and effluent pollution.

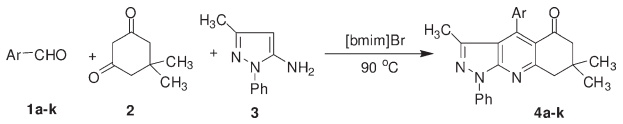
Multicomponent reactions (MCRs) in which multiple reactions are combined into one synthetic operation have been used extensively to form carbon–carbon bonds in the synthetic chemistry [5]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade there has been tremendous development in three- and four-component reactions and great efforts continue to be made for developing new MCRs [6].

Room temperature ionic liquids, especially those based on 1-alkyl-3-methylimidazolium cations, have shown great promise as an attractive alterative to conventional organic solvents, and more attention has been currently focused on organic reactions promoted by ionic liquids [7]. They are nonvolatile, recyclable, nonexplosive, easily operable, and thermally robust [8]. There are many reports concerning the applications of ionic liquid in organic reactions, such as Friedel-Crafts reactions [9], Diels-Alder reactions [10], Heck reactions [11], Pechmann condensatios [12], Biginelli reactions [13], Beckmann rearrangements [14], and other reactions [15]. As part of our current studies on the developments of new routes to heterocyclic system in ionic liquid [16], we herein described a facile synthesis of pyrazolo[3,4-*b*]quinolin-5(6*H*)-one derivatives by the three-component reaction of aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexandione and 5-amino-3-methyl-1-phenylpyrazole in ionic liquid without using any catalyst (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimal reaction solvent, the reaction of 4-hydroxybenzaldehyde (**1a**) 5,5-dimethyl-1,3-cyclohexandione (**2**)

Scheme 1



and 5-amino-3-methyl-1-phenylpyrazole (**3**) was examined using a variety of ionic liquids 3-butyl-1-methylimidazolium bromide ([bmim]Br), [bmim]BF_4, 3-propyl-1-methylimidazolium bromide ([pmim]Br), and conventional reaction solvents; DMF, acetic acid, acetone, and ethanol, at different reaction temperature for the synthesis of the pyrazolo[3,4-b]quinolin-5(6*H*)-one (**4a**). The results are summarized in Table 1.

It can be seen from the Table 1 that the best result was obtained when the reaction was carried out in [bmim]Br at 90°C (Table 1, entry 1). [bmim]Br was chosen as the solvent for all further reactions as it is environmentally friendly and the toxic organic reagents can be avoided. Under these optimized reaction conditions, a series of pyrazolo[3,4-*b*]quinolin-5(6*H*)-one derivatives **4** were synthesized. The results are summarized in Table 2.

As shown in Table 2, this protocol could be applied to the aromatic aldehydes with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl and alkoxyl groups). The products were different from those literature reported. The reaction of 5-amino-3-methyl-1-phenylpyrazole with dimedone and aromatic aldehyde in ethanol afforded 4-aryl-7,7-dimethyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b] quinolin-5-one[4a]. The structures of the products were established on the spectroscopic data (IR, ^{1}H NMR, and HRMS).

Though the detailed mechanism of this reaction has not been clarified yet, the formation of **4** can be explained by the possible mechanism presented in Scheme 2. The reaction occurs via an initial formation of the α,β-unsaturated ketone, from the condensation of aldehyde and 5,5-dimethyl-1,3-cyclohexanedione as shown in Scheme 2, which suffers nucleophilic attack to give the Michael adduct [A]. The intermediate [A] then isomerizates, cyclizes, dehydrates and subsequently losses a hydrogen molecule to afford the fully aromatized compound. This type of hydrogen loss is well documented [17].

In summary, we have developed an efficient three-component reaction of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione and 5-amino-3-methyl-1-phenylpyrazole for the synthesis of pyrazolo[3,4-*b*]quinolne-5(6*H*)-one derivatives using ionic liquid as solvent. Compared to the previous methods, this new protocol has the advantages of easier work-up, milder reaction conditions, short reaction time, and environmentally benign procedure.

Table 1

Solvent optimization for the synthesis of **4a**.

Entry	Solvent	Reaction temperature (°C)	Reaction time (h)	Isolated yield (%)
1	[bmim]Br	90	2	98
2	[bmim]BF_4	90	2	94
3	[pmim]Br	90	2	93
4	DMF	100	8	20
5	HOAc	100	8	52
6	acetone	Reflux	8	n. r.
7	ethanol	Reflux	8	39

Table 2

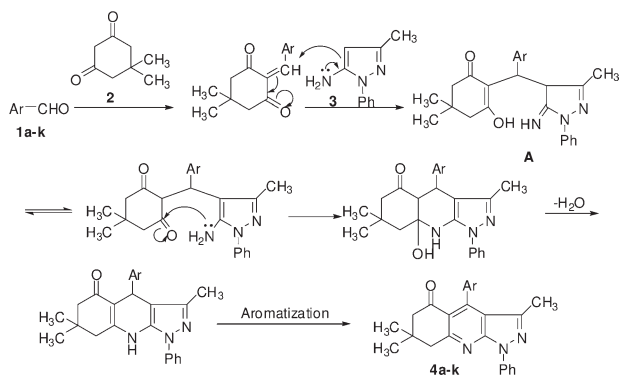
The synthesis of **4a-k** in ionic liquid [bmim]Br.

Entry	Ar	Time (h)	Yield (%)
4a	4-HOC_6H_4	2	98
4b	4-$CH_3C_6H_4$	1.5	95
4c	4-FC_6H_4	2	95
4d	4-ClC_6H_4	2	94
4e	4-BrC_6H_4	2.5	93
4f	2-NO_2-5-ClC_6H_3	3.5	90
4g	3,4-$Cl_2C_6H_3$	4	78
4h	2,4-$Cl_2C_6H_3$	4.5	79
4i	4-$CH_3OC_6H_4$	3	85
4j	3,4-$OCH_2OC_6H_3$	4	68
4k	4-$(CH_3)_2NC_6H_4$	3	86

EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on a FTIR Temsor 27 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR was determined on Bruker DPX-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using Micromass TOF-

Scheme 2



MS instrument. Starting materials used were obtained from Alfa Aesar and used without further purification. Ionic liquids were prepared according to the stardard method [18].

General procedure for the synthesis of pyrazolo[3,4-*b*]quinolne-5-one derivatives 4. A dry 50 mL flask was charged with aromatic aldehyde **1** (1 mmol), 5,5-dimethyl-1,3-cyclohexandione **2** (1 mmol), 5-amino-3-methyl-1-phenyl-pyrazole **3** (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 90°C for 1.5–4.5 h to complete the reaction (monitored by TLC), then 5 mL water was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from the mixture of DMF and ethanol to give **4**.

4-(4-Hydroxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4a). Mp: 277–279°C; IR (potassium bromide): 3304, 2957, 1666, 1613, 1594, 1571, 1557, 1512, 1472, 1455, 1433, 1385, 1265, 1124, 820, 758, 688 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.07 (s, 6H, 2 × CH_3), 1.87 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.19 (s, 2H, CH_2), 6.84 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 7.35 (t, J = 7.6 Hz, 1H, ArH), 7.57 (t, J = 7.6 Hz, 2H, ArH), 8.24 (d, J = 8.4 Hz, 2H, ArH), 9.60 (s, 1H, OH); HRMS [Found: *m*/*z*: 397.1790 (M^+); Calcd for $C_{25}H_{23}N_3O_2$: M 397.1790].

4-(4-Methylphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4b). Mp: 184–186°C; IR (potassium bromide): 3021, 2953, 1677, 1591, 1560, 1499, 1470, 1455, 1438, 1415, 1386, 1367, 1355, 1305, 1263, 1232, 1180, 908, 803, 752, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.06 (s, 6H, 2 × CH_3), 1.83 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.43 (s, 2H, CH_2), 3.15 (s, 2H, CH_2), 7.04 (d, J = 8.0 Hz, 2H, ArH), 7.19–7.23 (m, 3H, ArH), 7.44 (t, J = 7.6 Hz, 2H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 395.2012 (M^+); Calcd for $C_{26}H_{25}N_3O$: M 395.1998].

4-(4-Fluorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4c). Mp. 172–174°C; IR (potassium bromide): 3062, 2955, 1679, 1596, 1562, 1509, 1470, 1455, 1381, 1308, 1260, 1232, 1093, 912, 848, 814, 753, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.08 (s, 6H, 2 × CH_3), 1.83 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 7.27–7.38 (m, 5H, ArH), 7.58 (t, J = 8.0 Hz, 2H, ArH), 8.24 (d, J = 7.6 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 399.1735 (M^+); Calcd for $C_{25}H_{22}FN_3O$: M 399.1747].

4-(4-Chlorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4d). Mp: 180–183°C; IR (potassium bromide): 2955, 1680, 1595, 1558, 1509, 1489, 1455, 1386, 1264, 1234, 982, 910, 859, 844, 810, 791, 752, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.08 (s, 6H, 2 × CH_3), 1.84 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 7.32–7.39 (m, 3H, ArH), 7.52–7.60 (m, 4H, ArH), 8.24 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 415.1434 (M^+); Calcd for $C_{25}H_{22}^{35}ClN_3O$: M 415.1451].

4-(4-Bromophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4e). Mp: 188–189°C; IR (potassium bromide): 2954, 1679, 1591, 1558, 1511, 1498, 1486, 1455, 1386, 1367, 1305, 1263, 981, 909, 858, 842, 806, 751, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.08 (s, 6H, 2 × CH_3), 1.84 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 7.27 (d, J = 8.0 Hz, 2H, ArH), 7.37 (t, J = 7.2 Hz, 1H, ArH), 7.58 (t, J = 7.6 Hz, 2H, ArH), 7.67 (d, J = 8.0 Hz, 2H, ArH), 8.24 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 459.0961 (M^+); Calcd for $C_{25}H_{22}^{79}BrN_3O$: M 459.0946].

4-(5-Chloro-2-nitrophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4f). Mp: 193–194°C; IR (potassium bromide): 3077, 2959, 1677, 1599, 1573, 1519, 1479, 1458, 1389, 1378, 1296, 1261, 986, 926, 845, 762, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.02 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.44 (d, J = 16.4 Hz, 1H, CH), 2.59 (d, J = 16.4 Hz, 1H, CH), 3.23 (s, 2H, CH_2), 7.39 (t, J = 7.6 Hz, 1H, ArH), 7.60 (t, J = 7.6 Hz, 2H, ArH), 7.72 (s, 1H, ArH), 7.88 (dd, J_1 = 1.2 Hz, J_2 = 8.8 Hz, 1H, ArH), 8.25 (d, J = 8.0 Hz, 2H, ArH), 8.38 (d, J = 8.8 Hz, 1H, ArH); HRMS [Found: *m*/*z*: 460.1327 (M^+); Calcd for $C_{25}H_{21}^{35}ClN_4O_3$: M 460.1302].

4-(3,4-Dichorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4g). Mp: 179–181°C; IR (potassium bromide): 3063, 2954, 1685, 1597, 1567, 1508, 1468, 1383, 1355, 1291, 1265, 985, 925, 884, 863, 809, 791, 755, 690 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.09 (s, 6H, 2 × CH_3), 1.89 (s, 3H, CH_3), 2.53 (s, 2H, CH_2), 3.22 (s, 2H, CH_2), 7.32∼7.40 (m, 2H, ArH), 7.59 (t, J = 7.6 Hz, 2H, ArH), 7.68 (d, J = 1.6 Hz, 1H, ArH), 7.74 (d, J = 8.4 Hz, 1H, ArH), 8.23 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 449.1093 (M^+); Calcd for $C_{25}H_{21}^{35}Cl_2N_3O$: M 449.1062].

4-(2,4-Dichorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4h). Mp: 127–129°C; IR (potassium bromide): 3052, 2957, 1677, 1592, 1562, 1508, 1484, 1383, 1291, 1264, 985, 910, 860, 846, 813, 778, 755, 693 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.06 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 2.55 (s, 2H, CH_2), 3.24 (s, 2H, CH_2), 7.36–7.43 (m, 2H, ArH), 7.56–7.61 (m, 3H, ArH), 7.81 (d, J = 1.6 Hz, 1H, ArH), 8.24 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 449.1082 (M^+); Calcd for $C_{25}H_{21}^{35}Cl_2N_3O$: M 449.1062].

4-(4-Methoxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4i). Mp: 138–140°C; IR (potassium bromide): 3021, 2953, 1677, 1591, 1560, 1499, 1455, 1386, 1305, 1263, 982, 908, 803, 752, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.08 (s, 6H, 2 × CH_3), 1.81 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 7.16 (d, J = 8.0 Hz, 2H, ArH), 7.27 (d, J = 8.0 Hz, 2H, ArH), 7.36 (t, J = 7.6 Hz, 1H, ArH), 7.58 (t, J = 8.0 Hz, 2H, ArH), 8.24 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 411.1926 (M^+); Calcd for $C_{26}H_{25}N_3O_2$: M 411.1947].

4-(3,4-Methylenedioxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4j). Mp: 175–177°C; IR (potassium bromide): 3059, 2955, 1672, 1621, 1598, 1557, 1506, 1489, 1381, 1365, 1291, 1255, 987, 934, 907, 886, 876, 810, 788, 752 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.07 (s, 6H, 2 × CH_3), 1.93 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.19 (s, 2H, CH_2), 6.12 (d, J = 8.0 Hz, 2H, OCH_2O), 6.72 (d, J = 7.6 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 7.00 (d, J = 8.0 Hz, 1H, ArH), 7.36 (t, J = 7.2 Hz, 1H, ArH), 7.58 (t, J = 7.6 Hz, 2H, ArH), 8.24 (d, J = 8.0 Hz, 2H, ArH); HRMS [Found: *m*/*z*: 425.1727 (M^+); Calcd for $C_{26}H_{23}N_3O_3$: M 425.1739].

4-(4-Dimethylaminophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4k). Mp: 194–196°C; IR (potassium bromide): 2954, 1687, 1612, 1598, 1567, 1514, 1506, 1490, 1473, 1385, 1364, 1283, 1260, 983, 947, 816, 804, 766, 692 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.07 (s, 6H, 2 × CH_3), 1.92 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 2.99 (s, 6H, $(CH_3)_2N$), 3.18 (s, 2H, CH_2), 6.78 (d, J = 8.4 Hz, 2H, ArH), 7.09 (d, J = 8.4 Hz, 2H, ArH), 7.35 (t, J = 7.6 Hz, 1H,

ArH), 7.57 (t, $J = 7.6$ Hz, 2H, ArH), 8.25 (d, $J = 8.0$ Hz, 2H, ArH); HRMS [Found: *m*/*z*: 424.2246 (M^+); Calcd for $C_{27}H_{28}N_4O$: M 424.2263].

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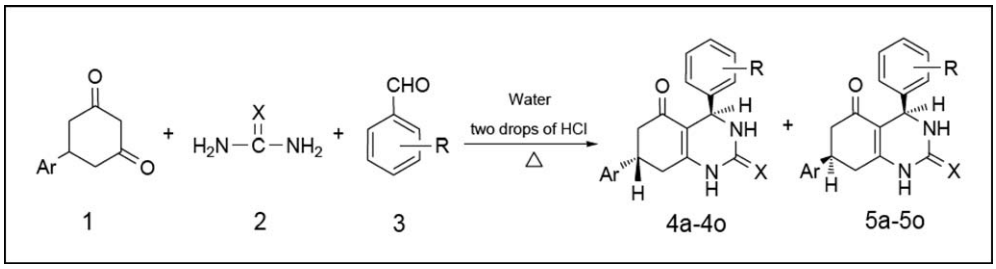

A green and convenient approach to the synthesis of novel 4,7-diaryl-2-oxo(thio)-1,2,3,4,5,6,7,8-octahydroquinazoline-5-one derivatives from appropriate aromatic aldehydes and 5-aryl-1,3-cyclohexanedione with urea or thiourea in the presence of dilute HCl as catalyst in water is described. This method provides several advantages such as environmental friendliness, low cost, high yields, and simple workup procedure. The structures of all compounds were characterized by elemental analysis, IR, MS, and ^{1}H NMR. The crystal and molecular structure of 4-(4′-chlorophenyl)-7-(4′-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione **5m** have been determined by single crystal X-ray diffraction analysis. The crystal of compound **5m** belongs to monoclinic with space group $P\text{-}2_1/c$, $a = 1.4353$ (4) nm, $b = 1.4011$ (4) nm, $c = 0.9248$ (3) nm, $\alpha = 90.00°$, $\beta = 101.242$ (6)°, $\gamma = 90.00°$, $Z = 4$, $V = 1.8241$ (9) nm^3, $R_1 = 0.0448$, and $wR_2 = 0.1022$.

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INTRODUCTION

Recently, much attention has been focused on the synthesis of octahydroquinazolinone due to their significant biological activities, such as against staphylococcus aureus, escherichiacoli, pseudomonas aeruginosa [1], and calcium antagonist activity [2,3]. Many methods have been developed for the preparation of quinazolinone derivatives which include the three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol [4,5], or using microwaves [6], ionic liquids [7], or refluxing at high temperature with many catalysts [8–14]. However, many of these reagents or catalysts are expensive, harmful, and difficult to handle especially on a large scale.

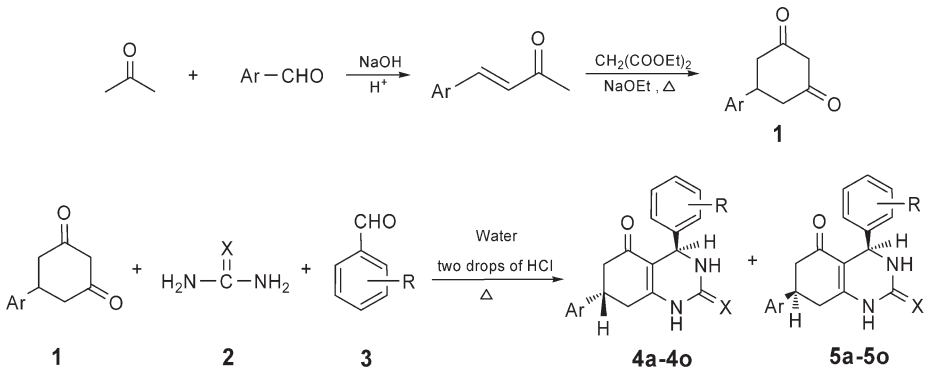
In this article, we report a clean and highly efficient route for the one-pot synthesis of the title compounds using dilute HCl as catalyst in water. This novel method is not only environmental friendliness but also consistently gives the corresponding products in good yields. We also obtained the single crystal **5m**, and the three-dimensional structure was confirmed by the X-ray diffraction analysis.

RESULTS AND DISCUSSION

The synthetic pathway is shown in Scheme 1. The 5-aryl-1,3-cyclohexanedione were obtained from aromatic aldehyde, acetone, and diethyl malonate according to the literature [15] method with slightly modification. The 4,7-diaryl-2-oxo(thio)-1,2,3,4,5,6,7,8-octahydroquinazoline-5-one derivatives were obtained by the Biginelli condensation reaction of 5-aryl-1,3-cyclohexanedione with urea or thiourea and substituted benzaldehydes using two drops of concentrated HCl as catalyst in water. As shown in Table 1, the reaction proceeded smoothly to afford the corresponding products in good yields. All aromatic aldhydes containing electron-withdrawing groups (such as halide) or electron-donating groups (such as methoxy) were used and reacted well to give the corresponding product in good yields under these conditions, so we conclude that the nature of the substituents on the aromatic ring had no obvious effect on the reaction.

Taking the reaction of benzaldehyde for example, we investigated the effect of the amount of catalyst on the reaction, which plays a crucial role in the success of the

Scheme 1



a: Ar=C_6H_5, X=O, R=H; b: Ar=C_6H_5, X=O, R=2-Cl; c: Ar=C_6H_5, X=O, R=4-Cl;
d: Ar=C_6H_5, X=O, R=3-OCH_3; e: Ar=C_6H_5, X=O, R=4-OCH_3; f: Ar=C_6H_5, X=S, R=H;
g: Ar=C_6H_5, X=S, R=2-Cl; h: Ar=C_6H_5, X=S, R=4-Cl; i: Ar=C_6H_5, X=S, R=3-OCH_3;
j: Ar=C_6H_5, X=S, R=4-OCH_3; k: Ar=4-$OCH_3C_6H_4$, X=O, R=H; l: Ar=4-$OCH_3C_6H_4$, X=O, R=2-Cl;
m: Ar=4-$OCH_3C_6H_4$, X=O, R=4-Cl; n: Ar=4-$OCH_3C_6H_4$, X=O, R=4-OCH_3; o: Ar=4-$OCH_3C_6H_4$, X=S, R=H;

reaction in terms of the rate and the yields. It was found that the reaction could not be carried out without the catalyst, and with two drops of concentrate HCl(about 0.1 mL) in 20 mL water at 70–80°C for 2 h, the reaction could afford the corresponding product in good yields. But with the catalyst increased, the yields show a decreasing trend. These data indicated that two drops of concentrate HCl in 20 mL water is quite suitable for this reaction.

The data of ^{1}H NMR, MS, and IR shown in the experimental section are in accordance with the chemical structures of the target compounds. In the ^{1}H NMR spectrum of compound **4f**, the single proton peak at δ 5.20 was the characteristic absorption proton peak of the 4-H, two broad single peaks at δ 7.88 and δ 9.66 were observed. They disappeared after D_2O exchange and therefore were attributed to the two *N*-H of the amino group. Because of the existence of intramolecular hydrogen bond between one proton of the amino group and the oxygen atom of the carbonyl group nearby (Table 3), its proton peak was drifted to δ 9.66.

The structures of these compounds were further supported by their IR spectra. Server typical absorption bands at 1711 cm^{-1} for (C═O), 3275 cm^{-1} for (*N*═H) were observed.

Table 1

Synthesis of 4,7-diaryl-2-oxo(thio)-1,2,3,4,5,6,7,8-octahydroquinazoline-5-one.

Entry	Ar	X	R	M.P. (°C)	Yield (%)	Approximate ratio (4:5)[a]
4a	C_6H_5	O	H	278–279	50	–
5a	C_6H_5	O	H	278–280	26	–
4b+5b	C_6H_5	O	2-Cl	280–282	80	5:3
4c+5c	C_6H_5	O	4-Cl	282–284	77	5:2
4d+5d	C_6H_5	O	3-OCH_3	280–281	85	2:1
4e	C_6H_5	O	4-OCH_3	270–272	57	–
5e	C_6H_5	O	4-OCH_3	272–274	26	–
4f	C_6H_5	S	H	250–251	50	–
5f	C_6H_5	S	H	251–252	29	–
4g+5g	C_6H_5	S	2-Cl	242–244	84	3:1
4h+5h	C_6H_5	S	4-Cl	250–251	81	7:3
4i+5i	C_6H_5	S	3-OCH_3	244–245	80	3:2
4j+5j	C_6H_5	S	4-OCH_3	247–248	86	2:1
4k+5k	4-$OCH_3C_6H_4$	O	H	252–254	88	2:1
4l+5l	4-$OCH_3C_6H_4$	O	2-Cl	259–260	86	7:3
4m	4-$OCH_3C_6H_4$	O	4-Cl	286–287	56	–
5m	4-$OCH_3C_6H_4$	O	4-Cl	284–286	28	–
4n+5n	4-$OCH_3C_6H_4$	O	4-OCH_3	254–256	83	3:2
4o+5o	4-$OCH_3C_6H_4$	S	H	234–235	81	5:3

[a] It was speculated from the integration area of the special position H in the ^{1}H NMR spectrum.

Table 2

Crystallographic data for crystallographic data for complex **5m.**

Empirical formula	C_{21} H_{19} Cl N_2 O_3
Formula weight	382.83
Wavelength (nm)	0.071073
Crystal system	Monoclinic
Space group	$P2_1/c$
a (nm)	1.4353(4)
b (nm)	1.4011(4)
c (nm)	0.9248(3)
α (°)	90.00
β (°)	101.242(6)
γ (°)	90.00
Volume (nm^3)	1.8241(9)
Z	4
Calculated density (g cm^{-3})	1.394
Absorption coefficient (mm^{-1})	0.234
F (000)	800
Final R indices [I > 2sigma (I)]	$R_1 = 0.0448$, $wR_2 = 0.1022$
R indices (all data)	$R_1 = 0.0769$, $wR_2 = 0.1162$

CRYSTAL STRUCTURE

A summary of the crystal data and structure refinement is presented in Table 2. A perspective view of compound **5m** with atomic numbering scheme was shown in Figure 1. In compound **5m**, The dihedral angle between the bond lengths and bond angles are generally normal in the phenyl and quinoline ring and the quinoline ring [C(7), C(8), C(9), C(10), C(11), C(12), C(13), C(14), N(1), N(2)] with plane equation 4.0780 (0.0027) x + 10.7892 (0.0071) y + 4.6691 (0.0053) z = 8.9674, The benzene ring a [C(1), C(2), C(3), C(4), C(5), C(6)] with plane equation 10.4240 (0.0095) x + 3.3441 (0.0130) y − 7.1571 (0.0059) z = 11.7828 is 88.76°. The benzene ring b [C(15), C(16), C(17), C(18), C(19), C(20)] is coplanar with the conjunction C(14), whose plane equation is − 2.5083 (0.0140) x + 11.9234 (0.0087) y − 4.1769 (0.0084) z = 0.8635. The dihedral angles between the benzene ring b and quinoline ring plane is 59.09°. The packing diagram of the **5m** in a unit cell was shown in Figure 2. X-ray analysis reveals that there are intramolecular and intermolecular hydrogen bonds in the crystal. The intermolecular hydrogen bond N(1)–H(1)···O(2) is 2.861(4) Å, the structural analysis indicates that these molecular interactions play the role of further stabilizing the structure. The bond lengths and bond angles of primary hydrogen bonds were listed in Table 3.

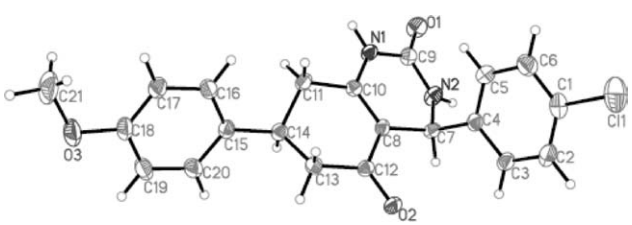


Figure 1. Molecular structure of compound **5m**.

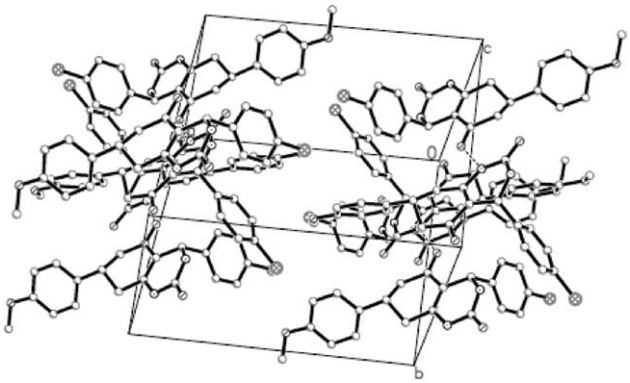


Figure 2. Packing diagram of compound **5m** in unit-cell.

CONCLUSIONS

In summary, we have described a general and highly efficient procedure for the one-pot preparation of 4,7-diaryl-2-oxo(thio)-1,2,3,4,5,6,7,8-octahydroquinazoline-5-one derivatives catalyzed by two drops of concentrate HCl in water. It is possible to apply tenets of green chemistry to the generation of interesting products using aqueous media methods that are less expensive and less toxic than those with organic solvent. Catalyst is very cheap, nontoxic and used in very small amount. Moreover, the procedure offers several advantages including high yields, low-cost, operational simplicity, cleaner reactions, and minimal environmental effects, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

Melting points were determined on an electro-thermal apparatus and the temperature was not calibrated. Microanalysis was performed by the Perkin–Elmer 2400 Microanalytical Service. Infrared spectra were recorded as thin films on KBr using a Perking-Elmer 1700 spectrophotometer. The NMR spectra were recorded by a Bruker ARX-300 spectrometer. Sample solutions were prepared in $CDCl_3$ or DMSO containing TMS as an internal reference. Mass spectra were recorded by JMS-DX300 at 70 eV.

All chemical reagents were commercially available and purified with standard methods before use. 5-aryl-1,3-cyclohexanedione were obtained from aromatic aldehyde, acetone, and

Table 3

Inter and intramolecular interaction distances (Å) for the compound **5m**.

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry
N(1)–H(1)···O(2)	0.900	1.98	2.861	165.68	*x*, *y*, *z*

diethyl malonate according to the literature [15] method with slightly modification. A mixture of an 5-aryl-1,3-cyclohexanedione (**1**, 5 mmol), urea or thiourea(**2**, 5 mmol), aromatic aldehyde (**3**, 5 mmol) and two drops of 37% HCl (0.1 mL) in water (20 mL) were stirred at 70–80°C for 2 h. Then the mixture was cooled to room temperature; solid was filtered off and washed with water. The crude products were purified by recrystallization from ethanol (95%).

Data of compounds are shown below. ***4a.*** ^{1}H NMR (DMSO, 300 MHz) δ: 2.26–2.60 (m, 3H, 6-H + 8-H), 2.70–2.83 (m, 1H, 6-H), 3.41–3.47 (m, 1H, 7-H), 5.13 (s, 1H, 4-H), 6.85–7.32 (m, 10H, Ph-H), 7.72 (s, 1H, 3-NH), 9.50 (s, 1H, 1-NH); IR (KBr) ν: 3240, 1712, 1671, 1619, 1507 cm^{-1}; MS (70eV) *m/z* (%): 319.17 (M + 1, 100); Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C 75.45, H 5.70, N 8.80; found C 75.37, H 5.62, N 8.87.

5a. ^{1}H NMR (DMSO, 300 MHz) δ: 2.36–2.66 (m, 3H, 6-H + 8-H), 2.71–2.86 (m, 1H, 6-H), 3.41–3.47 (m, 1H, 7-H), 5.16(s, 1H, 4-H), 6.80–7.33 (m, 10H, Ph-H), 7.78 (s, 1H, 3-NH), 9.56 (s, 1H, 1-NH); IR (KBr) ν: 3243, 1715, 1671, 1629, 1508 cm^{-1}; MS (70eV) *m/z* (%): 319.17 (M + 1, 100); Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C 75.45, H 5.70, N 8.80; found C 75.53, H 5.65, N 8.67.

4b + 5b. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.25–2.79 (m, 4H, 6-H + 8-H), 3.37–3.47 (m, 1H, 7-H), 5.58 and 5.62 (each s, 1H, 4-H), 7.07–7.49 (m, 9H, Ph-H), 7.71 and 7.75 (each s, 1H, 3-NH), 9.60 and 9.62 (each s, 1H, 1-NH); IR (KBr) ν: 3255, 1693, 1632, 1500 cm^{-1}; MS (70eV) *m/z* (%): 352.50 (M, 100); Anal. Calcd. for $C_{20}H_{17}ClN_2O_2$: C 68.09, H 4.86, N 7.94; found C 68.21, H 4.77, N 7.81.

4c + 5c. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.61–2.86 (m, 4H, 6-H + 8-H), 3.32–3.47 (m, 1H, 7-H), 5.45 and 5.52 (each s, 1H, 4-H), 7.07–7.49 (m, 9H, Ph-H), 8.13 and 8.17 (each s, 1H, 3-NH), 9.50 and 9.52 (each s, 1H, 1-NH); IR (KBr) ν: 3310, 1720, 1678, 1614, 1491 cm^{-1}; MS (70eV) *m/z* (%): 351.17 (M-1, 100); Anal. Calcd. for $C_{20}H_{17}ClN_2O_2$: C 68.09, H 4.86, N 7.94; found C 68.15, H 4.95, N 7.82.

4d + 5d. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.46–2.84 (m, 4H, 6-H + 8-H), 3.38–3.53 (m, 1H, 7-H), 5.43 and 5.53 (each s, 1H, 4-H), 6.71–7.49 (m, 9H, Ph-H), 8.00 and 8.03 (each s, 1H, 3-NH), 9.00 and 9.05 (each s, 1H, 1-NH); IR (KBr) ν: 3325, 1711, 1674, 1621, 1489 cm^{-1}; MS (70eV) *m/z* (%): 347.17 (M-1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04; found C 72.48, H 5.70, N 8.13.

4e. ^{1}H NMR (DMSO, 300 MHz) δ: 2.36–3.10 (m, 4H, 6-H + 8-H), 3.39–3.50 (m, 1H, 7-H), 3.70 (s, 3H, -OCH_3), 5.13 (s, 1H, 4-H), 6.76–7.38 (m, 9H, Ph-H), 7.73 (s, 1H, 3-NH), 9.51 (s, 1H, 1-NH); IR (KBr) ν: 3215, 1715, 1638, 1598, 1510 cm^{-1}; MS (70eV) *m/z* (%): 349.49 (M + 1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04; found C 72.25, H 5.65, N 7.92.

5e. ^{1}H NMR (DMSO, 300 MHz) δ: 2.36–2.86 (m, 4H, 6-H + 8-H), 3.41–3.47 (m, 1H, 7-H), 5.16 (s, 1H, 4-H), 6.80–7.33 (m, 9H, Ph-H), 7.78 (s, 1H, 3-NH), 9.56 (s, 1H, 1-NH); IR (KBr) ν: 3218, 1715, 1628, 1600, 1511 cm^{-1}; MS (70eV) *m/z* (%): 349.49 (M + 1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04; found C 72.48, H 5.68, N 8.12.

4f. ^{1}H NMR (DMSO, 300 MHz) δ: 2.27–2.83 (m, 4H, 6-H + 8-H), 3.10–3.30 (m, 1H, 7-H), 5.20 (s, 1H, 4-H), 7.20–7.40 (m, 9H, Ph-H), 7.88 (s, 1H, 3-NH), 9.66 (s, 1H, 1-NH); IR (KBr) ν: 3275, 1711, 1680, 1624, 1509 cm^{-1}; MS (70eV) *m/z* (%): 334.18 (M-1, 100); Anal. Calcd. for $C_{20}H_{18}N_2OS$: C 71.83, H 5.42, N 8.38; found C 71.75, H 5.50, N 8.24.

5f. ^{1}H NMR (DMSO, 300 MHz) δ: 2.38–2.86 (m, 4H, 6-H + 8-H), 3.36–3.48 (m, 1H, 7-H), 5.18 (s, 1H, 4-H), 7.18–7.41 (m, 9H, Ph-H), 7.83 (s, 1H, 3-NH), 9.60 (s, 1H, 1-NH); IR (KBr) ν: 3276, 1709, 1683, 1624, 1512 cm^{-1}; MS (70eV) *m/z* (%): 334.18 (M-1, 100); Anal. Calcd. for $C_{20}H_{18}N_2OS$: C 71.83, H 5.42, N 8.38; found C 71.95, H 5.51, N 8.22.

4g + 5g. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.60–2.99 (m, 3H, 6-H + 8-H), 3.47–3.66 (m, 1H, 6-H), 3.69–3.96 (m, 1H, 7-H), 5.44 and 5.54 (each s, 1H, 4-H), 6.56–7.41 (m, 9H, Ph-H), 9.70 and 9.76 (each s, 1H, 3-NH), 12.40 and 12.47 (each s, 1H, 1-NH); IR (KBr) ν: 3293, 1693, 1632, 1500 cm^{-1}; MS (70eV) *m/z* (%): 368.50 (M, 100); Anal. Calcd. for $C_{20}H_{17}ClN_2OS$: C 65.12, H 4.65, N 7.59; found C 65.32, H 4.47, N 7.53.

4h + 5h. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.60–3.08 (m, 4H, 6-H + 8-H), 3.33–3.56 (m, 1H, 7-H), 5.44 and 5.51 (each s, 1H, 4-H), 7.12–7.57 (m, 9H, Ph-H), 12.08 and 12.11 (each s, 1H, 3-NH), 12.40 and 12.45 (each s, 1H, 1-NH); IR (KBr) ν: 3276, 1695, 1640, 1502 cm^{-1}; MS (70eV) *m/z* (%): 369.19 (M + 1, 100); Anal. Calcd. for $C_{20}H_{17}ClN_2OS$: C 65.12, H 4.65, N 7.59; found C 65.05, H 4.53, N 7.67.

4i + 5i. ^{1}H NMR (DMSO, 300 MHz) δ: 2.34–2.90 (m, 4H, 6-H + 8-H), 3.27–3.47 (m, 1H, 7-H), 3.79 (s, 1H, -OCH_3), 5.21 and 5.24 (each s, 1H, 4-H), 6.76–7.36 (m, 9H, Ph-H), 9.70 and 9.76 (each s, 1H, 3-NH), 10.65 and 10.72 (each s, 1H, 1-NH); IR (KBr) ν: 3301, 1680, 1624, 1501 cm^{-1}; MS (70eV) *m/z* (%): 365.04 (M + 1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C 69.20, H 5.53, N 7.69; found C 69.08, H 5.50, N 7.77.

4j + 5j. ^{1}H NMR (DMSO, 300 MHz) δ: 2.30–2.96 (m, 4H, 6-H + 8-H), 3.43–3.49 (m, 1H, 7-H), 3.71 (s, 1H, -OCH_3), 5.13 and 5.17 (each s, 1H, 4-H), 6.77–7.43 (m, 9H, Ph-H), 9.66 and 9.73 (each s, 1H, 3-NH), 10.61 and 10.68 (each s, 1H, 1-NH); IR (KBr) ν:3255, 1644, 1609, 1562, 1510 cm^{-1}; MS (70eV) *m/z* (%): 364.15 (M, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C 69.20, H 5.53, N 7.69; found C 69.32, H 5.47, N 7.58.

4k + 5k. ^{1}H NMR (DMSO, 300 MHz) δ: 2.25–2.85 (m, 4H, 6-H + 8-H), 3.10–3.30 (m, 1H, 7-H), 3.70 (s, 1H, -OCH_3), 5.17 and 5.18 (each s, 1H, 4-H), 6.80–7.32 (m, 10H, Ph-H), 7.75 and 7.80 (each s, 1H, 3-NH), 9.79 and 9.55 (each s, 1H, 1-NH); IR (KBr) ν: 3270, 1714, 1606, 1597, 1514 cm^{-1}; MS (70eV) *m/z* (%): 347.34 (M-1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04; found C 72.32, H 5.87, N 8.12.

4 l + 5 l. ^{1}H NMR (DMSO, 300 MHz) δ: 2.22–2.88 (m, 4H, 6-H + 8-H), 3.22–3.44 (m, 1H, 7-H), 3.72 (s, 1H, —OCH_3), 5.59 and 5.60 (each s, 1H, 4-H), 6.84–7.40 (m, 8H, Ph-H), 7.66 and 7.69 (each s, 1H, 3-NH), 9.56 and 9.62 (each s, 1H, 1-NH); IR (KBr) ν: 3291, 1717, 1636, 1596, 1498 cm^{-1}; MS (70eV) *m/z* (%): 383.12 (M + 1, 100); Anal. Calcd. for $C_{21}H_{19}ClN_2O_3$: C 65.88, H 5.00, N 7.32; found C 65.93, H 4.90, N 7.23.

4m. ^{1}H NMR (DMSO, 300 MHz) δ: 2.34–2.82 (m, 4H, 6-H + 8-H), 3.27–3.40 (m, 1H, 7-H), 3.72 (s, 1H, —OCH_3), 5.20 (s, 1H, 4-H), 6.85–7.27 (m, 8H, Ph-H), 7.80 (s, 1H, 3-NH), 9.57 (s, 1H, 1-NH); IR (KBr) ν:3331, 1723, 1611, 1600, 1509 cm^{-1}; MS (70eV) *m/z* (%): 381.26 (M-1, 100); Anal. Calcd. for $C_{21}H_{19}ClN_2O_3$: C 65.88, H 5.00, N 7.32; found C 65.82, H 5.07, N 7.25.

5m. ^{1}H NMR (DMSO, 300 MHz) δ: 2.40–2.75 (m, 4H, 6-H + 8-H), 3.35–3.43 (m, 1H, 7-H), 3.70 (s, 1H, -OCH_3), 5.18 (s, 1H, 4-H), 6.80–7.37 (m, 8H, Ph-H), 7.78 (s, 1H, 3-NH), 9.54

(s, 1H, 1-NH); IR (KBr) ν: 3335, 1723, 1610, 1603, 1512 cm^{-1}; MS (70eV) *m*/*z* (%): 381.26 (M-1, 100); Anal. Calcd. for $C_{21}H_{19}ClN_2O_3$: C 65.88, H 5.00, N 7.32; found C 65.81, H 5.08, N 7.22.

4n + 5n. ^{1}H NMR (DMSO, 300 MHz) δ: 2.34–2.82 (m, 4H, 6-H + 8-H), 3.35–3.43 (m, 1H, 7-H), 3.69 (s, 1H, —OCH_3), 3.72 (s, 1H, —OCH_3), 5.15 and 5.18 (each s, 1H, 4-H), 6.74–7.27 (m, 8H, Ph-H), 7.73 and 7.79 (each s, 1H, 3-NH), 9.48 and 9.54 (each s, 1H, 1-NH); IR (KBr) ν: 3341, 1712, 1637, 1608, 1515 cm^{-1}; MS (70eV) *m*/*z* (%): 377.33 (M-1, 100); Anal. Calcd. for $C_{22}H_{22}N_2O_4$: C 69.83, H 5.86, N 7.40; found C 69.92, H 5.78, N 7.31.

4o + 5o. ^{1}H NMR (DMSO, 300 MHz) δ: 2.28–2.87 (m, 3H, 6-H + 8-H), 3.16–3.31 (m, 1H, 6-H), 3.37–3.46 (m, 1H, 7-H), 3.71 (s, 1H, -OCH_3), 5.21 and 5.23 (each s, 1H, 4-H), 6.81–7.37 (m, 8H, Ph-H), 9.67 and 9.73 (each s, 1H, 3-NH), 10.60 and 10.67 (each s, 1H, 1-NH); IR (KBr) ν: 3358, 1701, 1595, 1567, 1502 cm^{-1}; MS (70eV) *m*/*z* (%): 365.14 (M + 1, 100); Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C 69.20, H 5.53, N 7.69; found C 69.33, H 5.46, N 7.75.

Determination of crystal structure. A colorless transparent crystal of size 0.30 mm × 0.20 mm × 0.15 mm was selected for the crystal structure measurement. The X-ray diffraction intensities were recorded by a Bruker SMART APEX CCD automatic diffractometer with graphite-monochromatized Mo Kα radiation (λ = 0.071073 nm) at 291(2)K. In the range of $2.05 < \theta < 25.99$, 9632 independent reflections were obtained. The structures were solved by direct methods using SHELXL-97 program. All the nonhydrogen atoms were refined on F^2 anisotropically with the full-matrix least squares method. Hydrogen atoms were added according to the theoretical methods.

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Synthesis and Antioxidant Activity of Novel 15-Alkyl/aryl-13, 17-dihydro-15λ^5-dibenzo [e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-selones/thiones/ones

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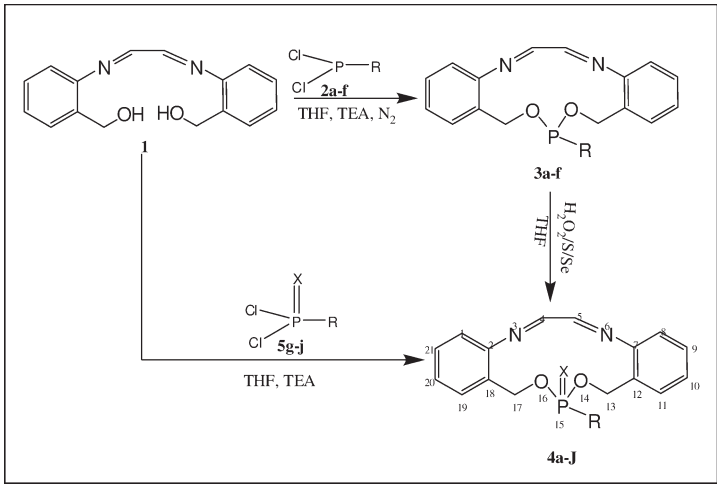

A new class of phosphorus macrocycles were synthesized from 2-[(E)-2-2 [(hydroxymethyl) phenyl] imino ethylidene) amino] phenyl methanol **1** with various phenylphosphorodichloridates, phenyldichlorophosphine, and ethyldichlorophosphite in the presence of triethylamine at 0–10°C under N_2 atmosphere in THF. All the title compounds were confirmed by analytical and spectral data (IR, ^{1}H-, ^{13}C-, ^{31}P-NMR, and mass). The title compounds exhibited promising anti-oxidant activity.

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INTRODUCTION

Phosphorus-containing macrocycles are elegant molecules with phosphate moiety have been attracted in supra-molecular and synthetic organic chemistry [1]. Their derivatives are important class of pesticides, herbicides, antibiotic, and antiviral agents [2]. The importance of these molecules as phosphorus analogues of crown ethers is derived from the potential catalytic activity and ion carrying properties. The design of host molecules capable of binding neutral organic molecules as guests is an area of rapidly expanding interest [3]. Cram and coworkers [4], Lehn and coworkers [5], Vogtle and coworkers [6], Diederich and coworkers [7], and others have made significant advances in this field of host-guest complexation [8]. They are expected to function as good hosts in the host-guest chemistry. This particular property enables them to carry certain metal-ion species and drug molecules in the living system. The versatile behavior of phosphorus compounds in addition to the complexity and low yield of multistage macrocyclic synthesis presumably explain the slow development of the corresponding phosphorus macrocyclic chemistry. Most of the studies were concerned with the incorporation of phosphorus (III) or (V) in crown ether links or with the substitution of some oxygen atoms of crown ethers by phosphorus leading to species possessing one or more P—C, P—O, P—S, or, much more scarcely, P—N bonds [9]. An increasing interest has been paid for several years to the chemistry of heterocyclic rings containing phosphorus due to their unique physical properties, specific chemical reactivity, and biological properties [10,11]. Novel phosphorus molecular hosts containing nitrogen and oxygen atoms were reported from our research group [12,13]. Macrocycle phosphates were well known for their insecticidal activities [14] and are known to degrade hydrolytically and enzymatically to nontoxic residues. Discovery of their fungicidal properties became an important development [15]. Antioxidants are widely studied for their capacity to protect

organisms and cells from damage induced by oxidative stress during metabolism. Many disease manifestations such as cancer, emphysema, cirrhosis, atherosclerosis, and arthritis have been correlated with oxidative tissue damage. Particularly, oxidation was essential to many living organisms for the production of energy to fuel biological processes. However, oxygen centered free radicals and other reactive oxygen species (ROS), which were continuously, produced *in vivo*, result in cell death and tissue damage [16]. ROS play an important role in some pathogenesis of serious diseases, such as neurodegenerative disorders, cancer, liver cirrhosis, cardiovascular diseases, atherosclerosis, cataracts, diabetes, and inflammation [17]. Compounds that can scavenge free radicals have great potential in ameliorating these diseases [18]. Generally, phosphorus antioxidants are used in combination with different substituted phenols and other stabilizers.

In view of these and various applications of phosphorus-macroheterocycles, we herein report the synthesis of novel 13-membered heterocycles containing N, O, and P in the ring and their antioxidant properties.

RESULTS AND DISCUSSION

The title compounds such as oxides, sulfides, and selenides (**4a–f**) were prepared through a two-step synthetic route involving condensation of (**1**) with dichlorophenyl phosphine and ethyldichloro phosphite in the presence of triethylamine under nitrogen atmosphere in dry THF to form the corresponding trivalent phosphorus intermediates (**3a** and **3d**). They were further converted to the corresponding oxide, sulfide, and selenide by reaction with H_2O_2, sulfur, and selenium, respectively, under reflux condition in dry tetrahydrofuran. Alternatively, a few of the title compounds (**4g–j**) were synthesized by the condensation of (**1**) with various phenyl phosphorodichloridates in equimolar quantities in the presence of TEA in dry THF at 35–40°C. The chemical structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-, ^{13}C-, ^{31}P-NMR, and mass spectral data.

The disappearance of absorption band and signal corresponding to the —OH group in both in IR and ^{1}H-NMR spectra and the appearance of new bands in the region 1250–1220 cm^{-1}, 820–730 cm^{-1}, and 700–625 cm^{-1} ascribable to P=O, P=S, and P=Se stretching vibrations, respectively. A sharp absorption band in the region 1590–1658 cm^{-1} is due to C=N [19]. ^{1}H-NMR spectra display multiplet in the region δ 6.74–7.49 for aromatic and azomethyne protons and another multiplet in the region δ 4.70–4.90 is assigned to methylene-oxy protons. The endocyclic methyleneoxy carbons (C-13, C-17) gave doublets at δ 68.0–66.3 (d, J = 13.5 Hz), whereas in compounds (**4d–f**) the exocyclic carbons (methyleneoxy) also gave doublets at δ 64.5–63.2 (d, J = 12.0 Hz). The imine carbons (C-4, C-5) resonated as singlets at δ 164.2–161.5. ^{13}C-NMR chemical shifts of the P—C aryl carbons of **4a–c** appeared at δ 130.2, 127.6, and 133.0, respectively. ^{31}P-NMR chemical shifts of compounds **4a–j** appeared in the region 72.30–16.50 ppm depending on the heteroatom linked to phosphorus atom (P=Se, P=S, and P=O) (Scheme 1).

CONCLUSIONS

An elegant synthesis of 13-membered phosphorus heterocycles containing N, O, and P with moderate yields is accomplished and their antioxidant activity was evaluated. They exhibited promising antioxidant activity.

EXPERIMENTAL

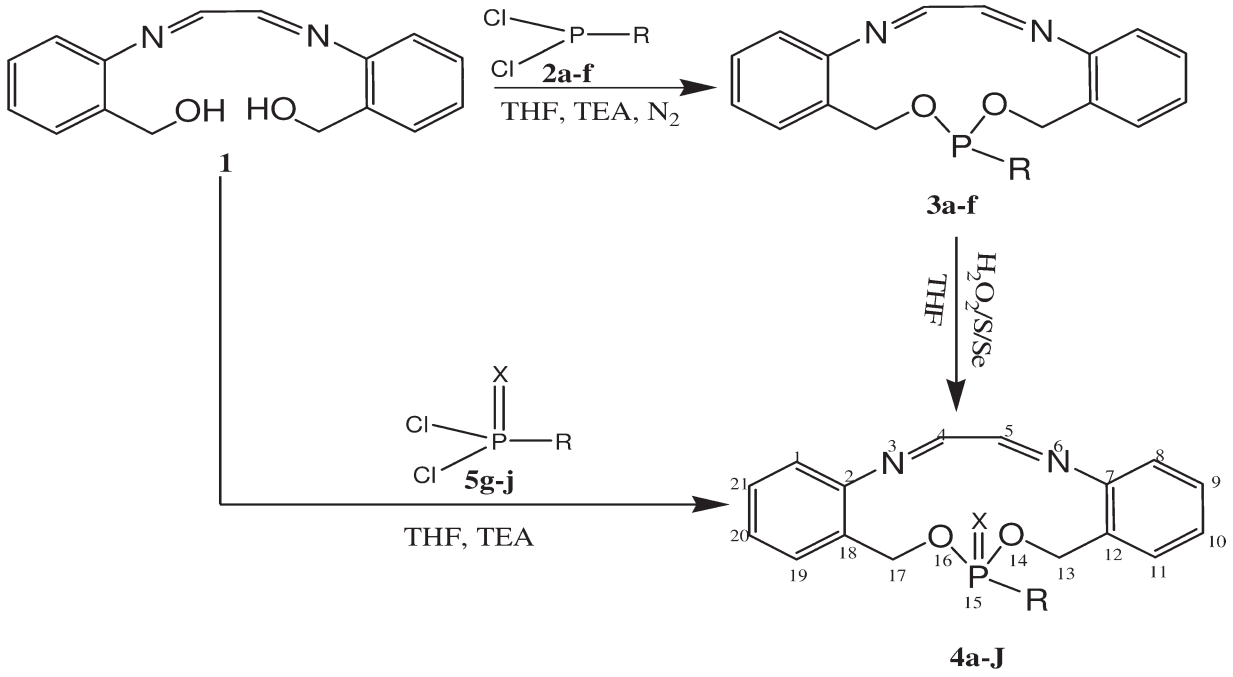
Chemicals were obtained from Sigma-Aldrich, Lancaster used as such without further purification. All solvents (AR or Extra pure grade) used for spectroscopic and other physical studies were further purified by literature methods [20]. All operations were performed under nitrogen atmosphere using standard glassware. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a FT-IR 200 double beam spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 300 MHz spectrometer operating at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 121.5 MHz for ^{31}P, respectively. The ^{1}H and ^{13}C chemical shifts were referenced to tetramethylsilane and ^{31}P chemical shifts to 85% H_3PO_4. LC mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer.

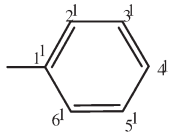
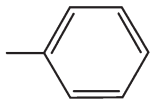
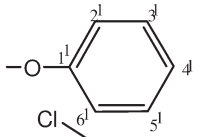
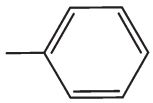
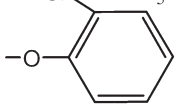
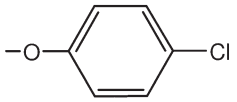
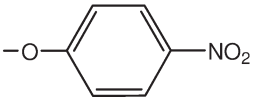
2-[(E)-2-2[(hydroxymethyl) phenyl] imino ethylidene) amino] phenyl methanol (**1**) was prepared following literature method [21].

Synthesis of title compounds (4a–f) via intermediates (3a and 3d). A solution of dichlorophenylphosphine/dichloroethylphosphite **2** (0.02 mol) in 10 mL of dry THF was added dropwise to a stirred solution of **1** (0.02 mol) in 20 mL of dry THF, triethylamine (0.04 mol) at 0°C over a period of 20 min. After stirring for 2 h at 30–35°C, formation of the intermediates **3a/3d** was ascertained by TLC analysis (ethyl acetate:hexane, 4:6, R_f 0.7). To the cooled (0–5°C) solution of **3a/3d** in the same vessel, equimolar quantity of selenium/sulfur/H_2O_2 (0.02 mol) in 10 mL of dry THF was added. The reaction mixture was further stirred at room temperature for 2 h, later at reflux temperature for 2 h. TLC analysis was used to ascertain the completion of the reaction. Triethylamine hydrochloride was separated by filtration and the solvent from the filtrate was removed in a rota-evaporator. The residue was purified by column chromatography (ethyl acetate:hexane, 3:7) to afford the title compounds **4a–f**.

Synthesis of title compounds (4g–j). Phenyl phosphorodichloridate **5** (0.02 mol) in dry THF (10 mL) was added dropwise to a stirred solution of **1** (0.02 mol) and triethylamine (0.04 mol) in 20 mL of dry THF at 0–5°C during 20 min. After completion

Scheme 1



Compound	R	X	Compound	R	X
4a		Se	4f	-O-CH_2-CH_3	O
4b		S	4g		O
4c		O	4h		O
4d	-O-CH_2-CH_3	Se	4i		O
4e	-O-CH_2-CH_3	S	4j		O

of the addition, the reaction temperature was slowly raised to 35–40°C and stirred for 4 h. Progress of the reaction was monitored by TLC (ethyl acetate:hexane, 4:6, R_f 0.6). On separation of triethylamine hydrochloride by filtration and evaporation of the filtrate in a rota-evaporator, a solid residue was obtained. It was purified by column chromatography (ethyl acetate:hexane, 3:7) to yield the title compound **4g**. Other members **4h–j** were prepared by adopting the above procedure.

15-Phenyl-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-selone (4a). Yield 79%, mp 170–172°C; ^{1}H-NMR (DMSO-d_6): δ 6.61–7.40 (15H, m, Ar—H, —N=CH—), 4.74–4.93 (4H, m, —OCH_2—); ^{13}C-NMR data: 161.2 (C-4, C-5), 141.8 (C-2, C-7), 131.4 (C-2^1, C-6^1), 130.1 (C-1^1), 129.6 (C-4^1), 127.8 (C-3^1, C-5^1), 127.1 (C-12, C-18), 124.6 (C-9, C-21), 120.5 (C-11, C-19), 119.9 (C-10, C-20), 117.2 (C-1, C-8), 66.4 (d, J = 13.5 Hz, C-13, C-17); ^{31}P-NMR data: δ 68.70; IR (KBr) cm^{-1}: 1658 (C=N), 1424 (P—$C_{aromatic}$), 1015 (P—O—$C_{aliphatic}$), 635 (P=Se); EIMS *m/z* 454 [55, M^+ +1], Anal. Calcd. for $C_{22}H_{19}N_2O_2PSe$: C, 58.27; H, 4.10; N, 6.18. Found: C, 58.29; H, 4.24; N, 6.13.

15-Phenyl-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-thione (4b). Yield 74%,

mp 159–160°C; ^{1}H-NMR (DMSO-d_6): δ 6.60–7.02 (15H, m, Ar—H, —N=CH—), 4.73–4.92 (4H, m, —OCH_2—); ^{13}C-NMR data: 160.9 (C-4, C-5), 141.8 (C-2, C-7), 131.2 (C-2^1, C-6^1), 129.2 (C-1^1), 128.2 (C-4^1), 127.6 (C-3^1, C-5^1), 127.3 (C-12, C-18), 124.2 (C-9, C-21), 120.1 (C-11, C-19), 119.5 (C-10, C-20), 117.5 (C-1, C-8), 66.4 (d, J = 12.7 Hz, C-13, C-17); ^{31}P-NMR data: δ 50.71; IR (KBr) cm^{-1}: 1628 (C=N), 1475 (P—$C_{aromatic}$), 1030 (P—O—$C_{aliphatic}$), 710 (P=S); Anal. Calcd. for $C_{22}H_{19}N_2O_2PS$: C, 65.02; H, 4.67; N, 6.89. Found: C, 65.03; H, 4.74; N, 7.09.

15-Phenyl-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4c). Yield 77%, mp 160–162°C; ^{1}H-NMR (DMSO-d_6): δ 6.76–7.99 (15H, m, Ar—H, —N=CH—), 4.72–4.87 (4H, m, —OCH_2—); ^{13}C-NMR data: 161.5 (C-4, C-5), 141.4 (C-2, C-7), 131.8 (C-1^1), 131.4 (C-4^1), 130.4 (C-2^1, C-6^1), 128.6 (C-3^1, C-5^1), 127.4 (C-12, C-18), 124.5 (C-9, C-21), 120.3 (C-11, C-19), 119.7 (C-10, C-20), 117.4 (C-1, C-8), 67.9 (d, J = 12.5 Hz, C-13, C-17); ^{31}P-NMR data: δ 27.40; IR (KBr) cm^{-1}: 1658 (C=N), 1494 (P—$C_{aromatic}$), 1256 (P=O), 1067 (P—O—$C_{aliphatic}$); Anal. Calcd. for $C_{22}H_{19}N_2O_3P$: C, 67.69; H, 4.87; N, 7.17. Found: C, 67.58; H, 4.96; N, 7.23.

15-Ethoxy-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-selone (4d). Yield 75%, mp 170–172°C; ^{1}H-NMR (DMSO-d_6): δ 6.55–7.90 (10H, m, Ar—H, —N=CH—), 4.53–4.79 (6H, m, —OCH_2—), 1.18 (3H, t, J = 6.7 Hz, —CH_3); ^{13}C-NMR data: 161.6 (C-4, C-5), 142.2 (C-2, C-7), 127.6 (C-12, C-8), 124.3 (C-9, C-21), 120.2 (C-11, C-19), 119.8 (C-10, C-20), 117.3 (C-1, C-8), 66.5 (d, J = 13.0 Hz, C-13, C-17), 65.8 (d, J = 11.8 Hz —OCH_2), 14.3 (s, —CH_3); ^{31}P-NMR data: δ 72.32; IR (KBr) cm^{-1}: 1640 (C=N), 995 (P—O—$C_{aliphatic}$), 650 (P=Se); Anal. Calcd. for $C_{18}H_{19}N_2O_3PSe$: C, 51.30; H, 4.51; N, 6.65. Found: C, 51.37; H, 4.62; N, 6.72.

15-Ethoxy-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-thione (4e). Yield 79%, mp 155–157°C; ^{1}H-NMR (DMSO-d_6): δ 6.50–7.85 (10H, m, Ar—H, —N=CH—), 4.67–4.83 (6H, m, —OCH_2—), 1.31 (3H, t, J = 7.0 Hz, —CH_3); ^{13}C-NMR data: 162.3 (C-4, C-5), 142.2 (C-2, C-7), 128.5 (C-12, C-8), 124.5 (C-9, C-21), 121.2 (C-11, C-19), 120.1 (C-10, C-20), 118.4 (C-1, C-8), 55.1 (d, J = 12.7 Hz, C-13, C-17), 61.5 (d, J = 11.2 Hz —OCH_2), 15.5 (s,—CH_3); ^{31}P-NMR data: δ 52.50; IR (KBr) cm^{-1}: 1618 (C=N), 1020 (P—O—$C_{aliphatic}$), 735 (P=S); CIMS m/z 375 [90, M^+ +1]. Anal. Calcd. for $C_{18}H_{19}N_2O_3PS$: C, 57.75; H, 5.08; N, 7.48. Found: C, 57.65; H, 5.15; N, 7.56.

15-Ethoxy-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4f). Yield 75%, mp 156–158°C; ^{1}H-NMR (DMSO-d_6): δ 6.63–7.87 (10H, m, Ar—H, —N=CH—), 4.56–4.77 (6H, m, —OCH_2—), 1.46 (3H, t, J = 7.3 Hz, —CH_3); ^{13}C-NMR data: 162.0 (C-4, C-5), 141.5 (C-2, C-7), 128.0 (C-12, C-8), 124.8 (C-9, C-21), 120.7 (C-11, C-19), 119.5 (C-10, C-20), 117.7 (C-1, C-8), 66.7 (d, J = 12.7 Hz, C-13, C-17), 64.4 (d, J = 11.5 Hz —OCH_2), 16.0 (s,—CH_3); ^{31}P-NMR data: δ 20.10; IR (KBr) cm^{-1}: 1630 (C=N), 1280 (P=O), 1070 (P—O—$C_{aliphatic}$); EIMS m/z 359 [66, M^+ +1]. Anal. Calcd. for $C_{18}H_{19}N_2O_3P$: C, 60.33; H, 5.30; N, 7.82. Found: C, 60.40; H, 5.37; N, 7.90.

15-Phenoxy-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4g). Yield 78%, mp 158–160°C; ^{1}H-NMR (DMSO-d_6): δ 6.86–7.98 (15H, m, Ar—H, —N=CH—), 4.64–4.97 (4H, m,—OCH_2—); ^{13}C-NMR data: 162.4 (C-4, C-5), 143.2 (C-1^1), 142.4 (C-2, C-7), 130.6 (C-12, C-18), 126.1 (C-3^1, C-5^1), 125.1 (C-9, C-21), 120.6 (C-11, C-19), 120.1 (C-4^1), 118.6 (C-2^1, C-6^1), 117.5 (C-10, C-20), 116.5 (C-1, C-8), 63.4 (d, J = 12.2 Hz, C-13, C-17); ^{31}P-NMR data: δ 20.50; IR (KBr) cm^{-1}: 1613 (C=N), 1250 (P=O), 1065 (P—O—$C_{aliphatic}$), 1220, 950 (P—O—$C_{aromatic}$); Anal. Calcd. for $C_{22}H_{19}N_2O_4P$: C, 65.02; H, 4.67; N, 6.89. Found: C, 65.06; H, 4.74; N, 6.76.

15-(2-Chlorophenoxy)-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4h). Yield 81%, mp 162–164°C; ^{1}H-NMR (DMSO-d_6): δ 6.93–7.56 (14H, m, Ar—H, —N=CH—), 4.62–4.81 (4H, m, —OCH_2—); ^{13}C-NMR data: 161.1 (C-4, C-5), 142.1 (C-1^1), 142.0 (C-2, C-7), 130.4 (C-2^1), 128.6 (C-3^1, C-5^1), 126.7 (C-12, C-18), 124.8 (C-9, C-21), 124.1 (C-4^1), 120.9 (C-11, C-19), 119.4 (C-10, C-20), 118.2 (C-1, C-8), 115.6 (C-6^1), 64.2 (d, J = 12.4 Hz, C-13, C-17); ^{31}P-NMR data: δ 21.00; IR (KBr) cm^{-1}: 1625 (C=N), 1260 (P=O), 1080 (P—O—$C_{aliphatic}$), 1210, 968 (P—O—$C_{aromatic}$); LCMS m/z 440 [25, M^+], 442 [8, M +2]. Anal. Calcd. for $C_{22}H_{18}N_2O_4PCl$: C, 59.94; H, 4.08; N, 6.35. Found: C, 59.68; H, 4.03; N, 6.40.

15-(4-Chlorophenoxy)-13, 17-dihydro-15λ^5-dibenzo[e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4i). Yield 81%, mp 173–175°C; ^{1}H-NMR (DMSO-d_6): δ 7.01–7.99 (14H, m, Ar—H, —N=CH—), 4.92–4.98 (4H, m, —OCH_2—); ^{13}C-NMR data: 161.5 (C-4, C-5), 142.2 (C-1^1), 141.1 (C-2, C-7), 130.6 (C-3^1, C-5^1), 128.4 (C-2^1, C-6^1), 126.2 (C-12, C-18), 125.3 (C-4^1), 124.1 (C-9, C-21), 120.7 (C-11, C-19), 118.0 (C-10, C-20), 117.2 (C-1, C-8), 65.3 (d, J = 12.0 Hz, C-13, C-17); ^{31}P-NMR data: δ 20.20; IR (KBr) cm^{-1}: 1637 (C=N), 1265 (P=O), 1073 (P—O—$C_{aliphatic}$), 1219, 950 (P—O—$C_{aromatic}$); LCMS m/z 440 [30, M^+], 442 [10, M +2]; Anal. Calcd. for $C_{22}H_{18}N_2O_4PCl$: C, 59.94; H, 4.08; N, 6.35. Found: C, 59.69; H, 4.05; N, 6.45.

15-(4-Nitrophenoxy)-13, 17-dihydro-15λ^5-dibenzo [e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-one (4j). Yield 76%, mp 168–170°C; ^{1}H-NMR (DMSO-d_6): δ 6.54–8.06 (14H, m, Ar—H, —N=CH—), 4.85–4.90 (4H, m, —OCH_2—); ^{13}C-NMR data: 161.8 (C-4, C-5), 142.8 (C-1^1), 141.6 (C-2, C-7), 140.1 (C-4^1), 130.4 (C-2^1, C-6^1), 128.6 (C-3^1, C-5^1), 127.5 (C-12, C-18), 124.6 (C-9, C-21), 120.2 (C-11, C-19), 118.9 (C-10, C-20), 117.8 (C-1, C-8), 67.4 (d, J = 12.8 Hz, C-13, C-17); ^{31}P-NMR data: δ 16.50; IR (KBr) cm^{-1}: 1645 (C=N), 1256 (P=O), 1075 (P—O—$C_{aliphatic}$), 1209, 958 (P—O—$C_{aromatic}$); Anal. Calcd. for $C_{22}H_{18}N_3O_6P$: C, 58.53; H, 3.99; N, 9.31. Found: C, 58.45; H, 4.10; N, 9.42%.

EVALUATION OF ANTIOXOIDATACTIVITY

DPPH radical scavenging activity. The hydrogen atom or electron donation ability of the compound was measured from the bleaching of the purple-colored methanol solution of 2,2-diphenly-1-picrylhydrazyl (DPPH). The DPPH free radical is a stable free radical, which has been widely accepted as a tool for estimating free radical scavenging activity of antioxidants [22]. This spectrophotometric assay uses the stable radical DPPH as a reagent. One milliliter of various concentrations of the extract (25, 50, 75, and 100 μg/mL) in

Table 1

DPPH radical scavenging activity of **4a–j.**

	DPPH (% of inhibition) (μg/mL)			
Compounds	25	50	75	100
BHT	30.15	39.31	51.14	57.44
4a	11.8	18.89	24.3	32.94
4b	3.5	5.15	9.16	15.29
4c	2.48	3.50	4.19	6.87
4d	2.67	3.62	6.1	8.0
4e	14.0	19.1	26.3	43.32
4f	6.9	10.2	13.3	18.7
4g	8.77	15.64	18.12	29.19
4h	9.16	17.36	18.32	29.41
4i	18.2	26.8	36.21	41.17
4j	11.6	18.31	23.66	29.58

Table 3

H_2O_2 scavenging activity of **4a–j.**

	H_2O_2 (% of inhibition) (μg/mL)			
Compounds	25	50	75	100
BHT	33.4	59.1	76.7	77.22
4a	59.7	69.3	73.8	74.7
4b	51.2	63.5	68.5	69.0
4c	44.3	58.6	67.6	68.5
4d	44.4	62.5	68.1	68.8
4e	60.9	70.5	75.0	76.1
4f	51.3	63.9	70.4	69.4
4g	53.0	68.2	71.2	69.8
4h	57.8	68.6	72.8	74.0
4i	65.7	71.0	76.5	77.8
4j	58.1	69.1	73.3	74.3

methanol were added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. The per cent of inhibition (*I*%) of free radical production from DPPH was calculated by using the following equation.

$$\mathrm{I}\% = \left[\left(\mathrm{A\ control} - \mathrm{A\ sample}\right)/\mathrm{A\ blank}\right] \times 100$$

Where *A* control is the absorbance of the control reaction (containing all reagents except the test compound) and *A* sample is the absorbance of the test compound. Tests were carried out in triplicate and the results are presented in Table 1.

The antioxidant activity of these compounds was expressed as IC_{50} (inhibitory concentration, 50%). DPPH forms a stable molecule on accepting an electron or a hydrogen and thus found application in the determination of radical scavenging and antioxidant activity. In the case of 15-alkyl/aryl-13, 17-dihydro-15λ^5-dibenzo [e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-selones/thiones/ones, **4i** showed the highest DPPH scavenging activity with IC_{50} of 0.11 mg/mL when compared with other compounds. The remaining compounds exhibited DPPH radical scavenging activity in the following order: **4e** (IC_{50} 0.115 mg/mL) > **4a** (IC_{50} 0.151 mg/mL) > **4j** (IC_{50} 0.169 mg/mL) > **4h** (IC_{50} 0.17 mg/mL) > **4g** (IC_{50} 0.171 mg/mL) > **4f** (IC_{50} 0.267 mg/mL) > **4b** (IC_{50} 0.327 mg/mL) > **4d** (IC_{50} 0.625 mg/mL) > **4c** (IC_{50} 0.727 mg/mL).

Table 2

Reducing power of **4a–j.**

	Reducing power (% of inhibition) (μg/mL)			
Compounds	25	50	75	100
BHT	0.284	0.424	0.586	0.697
4a	0.143	0.177	0.206	0.231
4b	0.12	0.134	0.153	0.171
4c	0.093	0.108	0.119	0.124
4d	0.119	0.125	0.132	0.148
4e	0.157	0.181	0.214	0.262
4f	0.122	0.136	0.163	0.18
4g	0.136	0.167	0.189	0.215
4h	0.14	0.168	0.195	0.218
4i	0.165	0.186	0.226	0.283
4j	0.142	0.174	0.201	0.225

Reducing power. The reducing power was determined according to the method of Oyaizu [23]. Different concentrations of the compound (25, 50, 75, and 100 μg/mL) prepared in methanol were mixed with phosphate buffer (2.5 mL, 0.2*M*, pH 6.6) and potassium ferricyanide [$K_3Fe(CN)_6$] (2.5 mL, 1%). The mixture was incubated at 50°C for 20 min and 2.5 mL of trichloroaceticacid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer of the solution (2.5 mL) was mixed with distilled water (2.5 mL) and $FeCl_2$ (0.5 mL, 0.1%) and the absorbance was measured at 700 nm. Increased absorbance of the reaction mixture indicated increased reducing power. Butylated hydroxy toluene (BHT) was used as a standard. In this method, also the compound **4i** showed the highest reducing power followed by **4e** > **4a** > **4j** > **4h** > **4g** > **4f** > **4b** > **4d** > **4c**. The free radical scavenging activity and reducing power of the methanolic test compounds were significantly related to their total phenolic content, and the results are presented in Table 2. The methanolic diluted test compounds exhibited the highest radical scavenging activity and ferric reducing power with the greatest amount of phenolic content. The presence of polyphenolic compounds in test compounds which are dissolved in methanol might be responsible for this high-antioxidant activity.

H_2O_2 scavenging activity. The H_2O_2 scavenging ability of the compounds were determined according to

the method of Ruch et al. [24]. A solution of H_2O_2 (40 m*M*) was prepared in phosphate buffer (pH 7.4). 25, 50, 75, and 100 μg/mL concentrations of the compound in 3.4 mL phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 m*M*). The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated by using the following equation

$$\% \text{ of scavenging} = \left[\left(\text{A control} - \text{A sample}\right)/\text{A blank}\right] \times 100$$

Where *A* control is the absorbance of the control reaction (containing all reagents except the test compound) and *A* sample is the absorbance of the test compound. Tests were carried out in triplicate, and the results are presented in Table 3.

The hydroxyl radical is the most ROS that attacks almost every molecule in the body. It initiates the peroxidation of cell membrane lipids yielding malondialdehyde, which is mutagenic and carcinogenic. Even though the 15-alkyl/aryl-13, 17-dihydro-15λ^5-dibenzo [e, k] [1, 3, 7, 10, 2] dioxadiazaphosphacyclotridecin-15-selones/thiones/ones known to scavenge the hydroxyl radical, the compound **4i** showed significant hydroxyl radical scavenging activity with IC_{50} of 0.0190 when compared with other compounds. The remaining compounds exhibited hydroxyl radical scavenging activity in the following order, respectively: **4e** (IC_{50} 0.0205 mg/mL) > **4a** (IC_{50} 0.0209 mg/mL) > **4j** (IC_{50} 0.0215 mg/mL) > **4h** (IC_{50} 0.0216 mg/mL) > **4g** (IC_{50} 0.0235 mg/mL) > **4f** (IC_{50} 0.0243 mg/mL) > **4b** (IC_{50} 0.0244 mg/mL) > **4d** (IC_{50} 0.0281 mg/mL) > **4c** (IC_{50} 0.0282 mg/mL).

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A Novel Route to 4-Oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones *via* Efficient Cross-Claisen Condensation

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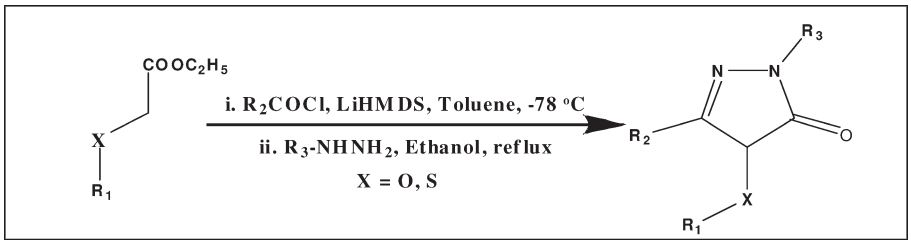

α-Oxy/thio substituted β-keto esters were synthesized through an efficient cross-Claisen condensation of oxy/thio substituted acetic acid ethyl esters with acid chlorides, which in turn converted *in situ* into 4-oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones by the addition of hydrazine and its derivatives. This method has been found to be extremely fast, general, and useful toward the synthesis of inaccessible pyrazolones and synthetically demanding 4-oxy/thio substituted pyrazolones.

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INTRODUCTION

A considerable interest has been shown to develop new methods for the synthesis of heterocyclic systems. Particularly, 2,3-pyrazol-1(5*H*)-ones have been reported as pharmaceuticals and useful intermediates in the synthesis of heterocycles [1,2]. Some of the aryloxy pyrazolone derivatives are in clinical practice for the treatment of a variety of disorders caused by human immunodeficiency virus and other genetic ailments caused by retroviruses such as acquired immune deficiency syndrome [3]. To date, synthesis of these compounds have been somewhat limited by the available chemistry. The reaction of β-keto esters with hydrazine and its derivatives is a general and most prevalent method to obtain pyrazolones [4], other synthetic methods which do not require β-keto esters have also been reported [5], but these methods tend to have serious drawbacks such as step intensive, usage of sensitive palladium catalysts, and carbon monoxide. So these factors confer that usage of β-keto esters as an intermediate is the broadest and most efficient way to synthesize pyrazolones. To synthesize 4-oxy/thio substituted pyrazolones indeed, α-oxy/thio substituted β-keto esters are still in need. The reported methods to synthesize α-oxy/thio substituted β-keto esters have serious drawbacks such as step intensive, time consuming, and usage of imidazoles [6]. There is a single-step reaction protocol for the self-Claisen condensation [7], which has main limitation in varying the substituents. Hence, there is a need to develop an efficient procedure for cross-Claisen condensation.

RESULTS AND DISCUSSION

This work focused on the cross-Claisen condensation between oxy/thio substituted acetic acid ethyl ester and acid chlorides. We hypothesized that an ester enolate might react in a smooth manner with strong electrophile acid chloride, if proper conditions have maintained to slow down the side reactions such as, self-Claisen condensation and *O*-alkylation. However, there have been very few reports on the application of cross-Claisen condensation between different esters [8] or between esters and acid chlorides, and some successful results were also been reported in the reactions using hydroxyl esters [9]. A nucleophilic reaction of an ester enolate with acid imidazolide has been widely used to synthesis β-keto esters [10], but it would rather be expensive to use imidazolide or active ester in an industrial setting.

Recently, Tanabe and coworkers [11] reported an efficient Ti-crossed Claisen esters and acid chlorides to provide a variety of β-keto esters; this method also suffers by the usage of imidazoles and costlier $TiCl_4$. Hence, we indent to improve the efficiency of traditional cross-Claisen condensation by changing the equivalence of base, acid chloride, reaction time, sequence of addition of reactants, temperature, and solvents choosing compound **1** as representative example. The results of every

Table 1

Yield of the reaction optimized with different equivalent of reactants.

Method	Cross condensed product (%)[a]	Self-condensed product (%)[a]
A	05	81
B	13	68
C	10	54
D	23	35
E	47	22
F	64	09

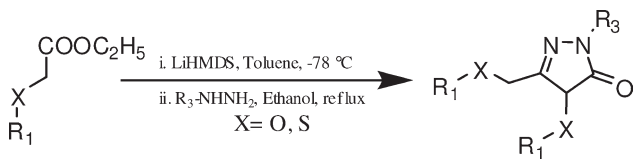
[a] Isolated yield.

change accomplished have been represented as different methods A–I (detailed procedure given in Experimental Section). The yield of cross- and self-condensed products were given in Table 1.

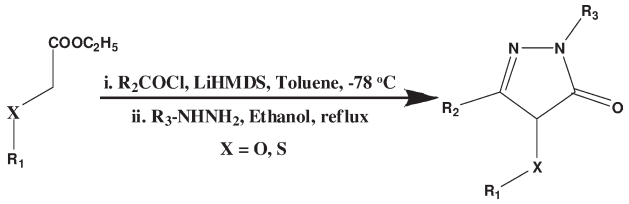
Our initial attempt to synthesize pyrazolone by method A resulted in undesirable self-condensed pyrazolone as major product (Scheme 1) and the desired cross-condensed pyrazolone (Scheme 2) as a minor product (5%). Then the yield of cross-condensed product was optimized with reference to the compound **1** by changing the equivalence of base, acid chloride, time, and order of addition of reactants (methods A–F), and the results were given in Table 1. After finding the suitable composition of equivalence of base, acid chloride, and the order of additions (method F), the reaction condition was optimized by carrying out the experiment at different temperatures (Table 2) and then with different bases and solvents (Table 3).

As expected, the yield of self-condensed product was increased with increasing the temperature. The results shown in Table 3 clearly revealed that the lithium enolate was reacting smoothly with stronger electrophilic acid chloride compared with other enolates (sodium and potassium). The reaction between lithium enolate and the acid chloride was favored in toluene than in tetrahyrofuran (THF). The side reactions were slowed down in a hydrocarbon solvent like toluene which disfavored the possible formation of the intermediates with charges and hence the ester enolate react with the acid chloride. The attempt to improve the yield by carrying out the experiment in two steps was failed, as we could not isolate the β-keto esters as very pure [only 70–80% of purity was recorded using liquid chromatography-mass spectroscopy (LC-MS)] in step 1, and the overall yield of the condensation of β-keto esters with hydrazine hydrate also observed as moderate (∼ 60%). Finally, in method F, we could achieve the maximum yield.

Scheme 1



Scheme 2



The above experiments clearly revealed that the usage of more than 3 equiv. of base avoided the self-condensation. The highly active oxyacetic acid ethyl ester undergoes self-Claisen condensation quickly than the other bulky, sterically hindered esters such as *t*-butyl, benzyl, and *iso*-propyl in the solution phase (solvated) [12], and hence to avoid the self-condensation, the time lag should be avoided between the addition of base and acid chloride (not more than 2 min). Hence, the attention toward rapid addition of base and acid chloride was indeed. Various new derivatives of pyrazolones from β-keto ester intermediates were synthesized to test the generality of this method and their results are given in Table 4. It revealed that yields were generally good, although conditions are not optimized for each of the reactions.

In few cases, the hydrazides of corresponding acetic acid ethyl esters were observed in crude LCMS. Many functional groups were tolerated with less or no side products. Mainly, electrophile-containing enolizable α-protons were successfully coupled with the ester enolates to form β-keto esters. Particularly, cyano functionality was retained in compound **5**. Steric effect could be observed in case of compound **8**, pyrazolone formation was affected sterically by the presence of tetrazole ring (β-keto ester and the corresponding hydrazide was observed in LCMS). Among the substituted hydrazines, highly nucleophilic methyl hydrazine worked well under these conditions and phenyl hydrazine did not react with β-keto esters in the same conditions due to its less nucleophilicity. However, the conditions of less

Table 2

Yield of the reaction optimized at different temperatures.

Method	Temperature (°C)	Cross-condensed product (%)[a]	Self-condensed product (%)[a]
G	−50	62	13
H	−20	57	15
I	0	48	21

[a] Isolated yield.

Table 3

Effect of solvent and base on the yield.

Base	Solvent	Yield (%)[a]
LiHMDS (1.0*M* THF)	Toluene	64
NaHMDS (1.0*M* THF)	Toluene	47
KHMDS (1.0*M* THF)	Toluene	38
LDA (1.0*M* THF)	Toluene	31
NaOMe	THF	14
KO^{t}Bu	THF	07
LiHMDS (1.0*M* THF)	THF	38

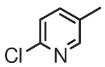
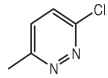
[a] Isolated yield.

nucleophilic phenyl hydrazines with the β-keto esters were successful when we do the reaction in two steps (see general procedure, method J).

In summary, an efficient, extremely rapid method that is hitherto unreported to synthesize α-oxy/thio substituted β-keto esters from oxy/thio substituted acetic acid esters and acid chlorides through efficient cross-Claisen condensation has been developed. The β-keto esters were treated with hydrazine *in situ* to get new derivatives of 4-oxy/thio substituted pyrazolones in good yield. As this method is successful with different oxy/thio acetic acid ethyl esters and acid chlorides, it can be

Table 4

List of 4-oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones prepared by method F.

Product	X	R_1	R_2	R_3	Yield (%)[a]
1	O	—Ph	—CH_3	—H	64
2	O	—CH_3	—4Cl—Ph	—H	57
3	O	—CH_2—3Br—Ph	—CH_2CH_3	—H	60
4	O	—4OCH_3—Ph	—CH_2CH_3	—H	57
5	O	—4CN—Ph	—CH_3	—H	48
6	S	—Ph	—$(CH_2)_4CH_3$	—H	74
7	S	—CH_2Ph	—Cylopropyl	—H	54
8	O	—Ph	—2—Tetrazolo5—clorophenyl	—H	0[b]
9	O	—4Cl—Ph	—Ph	—H	52
10	S	—Ph		—H	51
11	O	—Ph	—CH_2CH_3	—H	57
12	O	—Ph	—CH_2OCH_3	—H	54
13	O	—CH_2—3Br—Ph	—CH_3	—H	58
14	O	—4OCH_3—Ph	—CH_3	—H	62
15	S	—Ph	—CH_3	—H	67
16	S	—Ph	—Isobutyl	—H	74
17	S	—Ph	—CH $(CH_3)_2$	—H	71
18	S	—CH_2Ph	—CH_2CH_3	—H	61
19	S	—CH_2Ph	—CH_2OCH_3	—H	58
20	S	—4Cl—Ph	—Isobutyl	—H	78
21	O	—Ph	—4Cl—Ph	—H	59
22	O	—Ph	—CH $(CH_3)_3$	—H	58
23	O	—Ph	—Isobutyl	—CH_3	64
24	O	—Ph	—CH_3	—Ph	0[c]
25	O	—Ph	—CH_3	—4F—Ph	0[c]
26	S	—Ph	—CH_3	—CH_3	60
27	O	—Ph	—CH_2CH_3	—CH_3	77[c]
28	O	—Ph	—Isobutyl	—4F—Ph	52[d]
29	S	—Ph	—CH_3	—4F—Ph	58[d]
30	O	—Ph	—CH_2CH_3	—CH_2CF_3	49[d]
31	O	—Ph	—CH_3	—4F—Ph	60[d]
32	S	—Ph	—Isobutyl	—4F—Ph	51[d]
33	O	—Ph	—CH_2CH_3	—4F—Ph	61[d]
34	S	—Ph	— $(CH_2)_4CH_3$		29[c],[d]
35	S	—Ph	—CH_2CH_3	—4F—Ph	40[c],[d]

[a] Isolated yield.
[b] Only β-keto ester and the corresponding hydrazide was observed in crude LCMS.
[c] Percentage of product in crude LCMS.
[d] Prepared by method J.

regarded as useful method for the synthesis of previously inaccessible pyrazolones as well as pharmaceutically demanding pyrazolones. At present, we are adopting this method to synthesize other heterocycles, which originate from β-keto esters.

EXPERIMENTAL

All the reagents were purchased from Aldrich and used as received. Lithium hexamethyl disilylamide (LiHMDS) solutions were kept under nitrogen atmosphere after opening. Acid chlorides were freshly prepared and used. Dry toluene, AcOH, and EtOH were supplied by Spectrochem. All chemistry was performed under a nitrogen atmosphere using standard techniques. Melting points were determined by Buchi B-545 apparatus. All the NMR spectra were recorded using Bruker AMX 400 or Bruker DPX 300 Instrument with 5-mm PABBO BB-1H tubes. ^{1}H-NMR spectra recorded using $\sim$ 0.03*M* solutions in d_6-DMSO at 300 or 400 MHz with tetramethyl silane (TMS) as internal reference. ^{13}C-NMR spectra were recorded using $\sim$ 0.05*M* solutions in d_6-DMSO at 75 or 100 MHz with TMS as internal reference. In many cases, pyrazolones were recorded in the enol form whenever d_6-DMSO was used as solvent. IR spectra were recorded using NICOLET 6700 FTIR (Thermo scientific). MALDI experiment was carried out using laser beam (intensity, 350 nm) in Bruker autoflex III smart beam. LCMS were obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Column chromatography was performed using a silica gel (230–400 mesh).

General procedure to synthesis pyrazolones (method F). LiHMDS (19.4 mL, 1.0*M* in THF, 19.4 mmol) was added quickly to the solution of phenoxyacetic acid ethyl ester (1 g, 5.5 mmol) in toluene (15 mL) using syringe at −78°C with agitation and the formed anion is allowed to stand for $\sim$ 2 min. Then, acetyl chloride (1 mL, 13.8 mmol) was added in a lot with stirring. The reaction mixture was removed from acetone-dry ice bath and stirred for 10 min, then 2 mL of AcOH was added with stirring. EtOH (15 mL) and hydrazine hydrate (1.5 mL, 44 mmol) were added to the reaction mixture, refluxed for 10 min. Then, the reaction mixture was concentrated to dryness under reduced pressure and redissolved in EtOAc, the organic layer was washed with saturated brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using MeOH:EtOAc (1:99). Yield of the product was 676 mg (64%). Yield of the unwanted self-condensed product was 140 mg (9%).

Method A. LiHMDS (5.5 mL, 1.0*M* in THF, 5.5 mmol) was added slowly to the solution of phenoxy acetic acid ethyl ester (1 g, 5.5 mmol) in toluene (15 mL) at −78°C with stirring (30 min), followed by acetyl chloride (0.39 mL, 5.5 mmol) in dropwise at the same temperature. Resulting solution was slowly (10 min) warmed to −20°C, then quenched with AcOH (2 mL) and EtOH (15 mL). Hydrazine hydrate (1.5 mL, 4.4 mmol) was added and refluxed for 10 min. The resulting light brown solution was concentrated directly and the obtained residue was redissolved in EtOAc, washed with brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using MeOH:EtOAc (1:99). Yield of the product was 90 mg (8%). Yield of the unwanted self-condensed product was 1.26 g (81%).

Method B. The LiHMDS in THF was taken as 11.1 mmol and other additions, conditions were followed as such in method A. Yield of the product was 144 mg (13%). Yield of the unwanted self-condensed product was 1.12 g (72%).

Method C. Phenoxy acetic acid ethyl ester (1 g, 5.5 mmol) in toluene was added slowly to the solution of LiHMDS (5.5 mL, 1.0*M* in THF, 5.5 mmol) in toluene (10 mL) at −78°C over a period of 10 min and the mixture stirred at this temperature for 30 min, then acetyl chloride (0.39 mL, 5.5 mmol) was added slowly to reaction mixture over a period of 5 min at the same temperature. The resulting solution was slowly (10 min) warmed to −20°C, then quenched with AcOH (2 mL) and EtOH (15 mL). Hydrazine hydrate (1.5 mL, 44 mmol) was added and refluxed for 10 min. The resulting light brown solution was concentrated to dryness and redissolved in EtOAc, the separated organic layer was washed with brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using MeOH:EtOAc (1:99). Yield of the product was 105 mg (10%). Yield of the unwanted self-condensed product was 1.06 g (68%).

Method D. LiHMDS (5.5 mL, 1.0*M* in THF, 5.5 mmol) was added quickly to the solution of phenoxy acetic acid ethyl ester (1 g, 5.5 mmol) in toluene (15 mL) using syringe at −78°C with stirring, and the formed anion is allowed to stand for $\sim$1 min, then acetyl chloride (0.39 mL, 5.5 mmol) was added in a lot with stirring. Reaction mixture was removed from acetone-dry ice bath, stirred for 10 min, and then added 2 mL of AcOH with stirring. EtOH (15 mL) and hydrazine hydrate (1.5 mL, 44 mmol) were added and refluxed for 10 min. Reaction mixture was concentrated to dryness under reduced pressure and redissolved in EtOAC, the organic layer washed with brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using MeOH:EtOAc (1:99). Yield of the product was 242 mg (23%). Yield of the unwanted self-condensed product was 548 mg (35%).

Method E. LiHMDS (11.1 mL, 1.0*M* in THF, 11.1 mmol) was added quickly using syringe to the solution of phenoxy acetic acid ethyl ester (1 g, 5.5 mmol) in toluene (15 mL) at −78°C with stirring, and the formed anion is allowed to stand for $\sim$ 1 min, then acetyl chloride (0.8 mL, 11.1 mmol) added in a lot with stirring. Reaction mixture was removed from acetone-dry ice bath and stirred for 10 min, then 2 mL of AcOH was added with stirring. EtOH (15 mL) and hydrazine hydrate (1.5 mL, 44 mmol) were added and refluxed for 10 min. Reaction mixture was concentrated to dryness under reduced pressure and redissolved in EtOAc, then organic layer washed with brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using MeOH:EtOAc (1:99). Yield of the product was 496 mg (47%). Yield of the unwanted self-condensed product was 344 mg (22%).

In methods G, H, and I, the reaction was carried out at −50, −20, and 0°C, respectively. The additions and other conditions were followed as such given in method F.

General procedure to synthesize *N*-substituted pyrazolones: (Method J). LiHMDS (19.4 mmol, 1*M* solution in THF) was added quickly using syringe to the solution of an ester (5.5 mmol) in toluene (15 mL) at −30°C with stirring, the formed anion is allowed to stand for $\sim$ 2 min, then acid chloride (13.8 mmol) was added in one portion with stirring. Reaction mixture was removed from acetone-dry ice bath and continues the stirring for 10 min, then quenched with water,

and extracted with EtOAc (2 × 100 mL). Then, combined organic layer was dried over Na_2SO_4, concentrated at rotary evaporator. The obtained crude product was taken in the mixture of EtOH (20 mL) and AcOH (2 mL), to this substituted hydrazine (10 mmol) was added and refluxed overnight. Reaction was monitored by thin layer chromatography (TLC); reaction mixture was concentrated to dryness. See specific compounds for purification details.

3-Methyl-4-phenoxy-1H-pyrazol-5(4H)-one (1) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid. m.p. 221.7–222.8°C; IR (KBr): ν 3738, 2571, 2296, 1588 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.12 (brs, 1H), 7.27 (t, J = 7.4 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 7.8 Hz, 2H), 1.96 (s, 3H), 1.36 (brs, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 159.1, 152.9, 130.8, 129.3, 121.9, 120.5, 115.1, 9.27; LC-MS: *m/z* 190.3 (M+); Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.18; N, 14.63.

3-(4-Chlorophenyl)-4-methoxy-1H-pyrazol-5(4H)-one (2) This compound was obtained according to above general procedure of method F. Purified by preparative high performance liquid chromatography (HPLC) [MeCN: trifluoro acetic acid (TFA)], pale brown solid. m.p. 147.8–148.9°C; IR (KBr): ν 3292, 2944, 2360, 1736, 1656 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (brs, 2H), 7.73 (d, J = 6.8 Hz, 2H), 7.49 (d, J = 7.0 Hz, 2H), 3.70 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 152.7, 131.1, 129.5, 128.8, 128.3, 126.7, 126.2, 60.4; LC-MS: *m/z* 224.8 (M+); Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47. Found: C, 53.55; H, 4.24; N, 12.50.

3-Ethyl-4-(3-bromophenylmethoxy)-1H-pyrazol-5(4H)-one (3) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 220.1–221.7°C; IR (KBr): ν 2969, 2927, 2722, 2130, 1783, 1715 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.90 (brs, 1H), 9.70 (brs, 1H), 7.56 (s, 1H), 7.49 (d, J = 6.7 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 152.8, 141.1, 135.0, 131.0, 130.9, 130.8, 127.4, 124.3, 121.9, 73.9, 17.2, 13.3; LC-MS: *m/z* 297.1 (M+), Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.43. Found: C, 48.62; H, 4.32; N, 9.39.

3-Ethyl-4-(4-methoxyphenyoxy)-1H-pyrazol-5(4H)-one (4) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid, m.p. 256.3–257.5°C; IR (KBr): ν 2937, 2833, 2702, 1621, 1536 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30 (brs, 1H), 9.70 (brs, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.78 (d, J = 9.3 Hz, 2H), 3.68 (s, 3H), 2.35 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 154.3, 153.3, 153.0, 136.1, 120.6, 115.9, 114.9, 55.8, 17.4, 13.0; LC-MS: *m/z* 234.9 (M+); Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.38; H, 5.94; N, 12.09.

3-Methyl-4-(4-cyanophenyoxy)-1H-pyrazol-5(4H)-one (5) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 281.3–282.8°C; IR (KBr); ν 2677, 2221, 1596, 1497 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.50 (brs, 1H), 9.80 (brs, 1H), 7.76 (d, J = 4.8 Hz, 2H), 7.01 (d, J = 9.6 Hz, 2H), 1.97 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 162.5, 152.4, 134.7, 134.6, 119.3, 116.8, 116.3, 104.4, 9.21; LC-MS: *m/z* 215.9 (M+); Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.44; H, 4.35; N, 19.64.

3-Pentyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (6) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid. m.p. 182.1–183.5°C; IR (KBr) ν 3061, 2953, 2923, 2854, 1587 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.00 (brs, 1H), 10.00 (brs, 1H), 7.21 (t, J = 7.7 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 7.3 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 1.46 (m, 2H), 1.21 (m, 4H), 1.13 (t, J = 5.0 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.8, 149.0, 139.8, 129.2, 125.3, 125.0, 87.0, 31.1, 28.2, 25.0, 22.1, 14.2. LC-MS: *m/z* 263.0 (M+); Anal. Calcd. for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68. Found: C, 64.00; H, 6.98; N, 10.55.

3-Cyclopropyl-4-(phenylmethylthio)-1H-pyrazol-5(4H)-one (7) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 231.0–231.9°C; IR (KBr) ν 3066, 2955, 2923, 2868, 1583 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.20 (brs, 1H), 9.77 (brs, 1H), 7.24–7.17 (m, 3H), 7.11 (d, J = 6.7 Hz, 2H), 3.69 (s, 2H), 1.58–1.51 (m, 1H), 0.66 (t, J = 2.2 Hz, 2H), 0.58 (t, J = 5.0 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.4, 149.3, 139.0, 129.3, 128.5, 127.0, 90.5, 7.2, 7.1; LC-MS: *m/z* 246.9 (M+); Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.53; H, 5.65; N, 11.49.

4-(4-Chlorophenoxy)-3-phenyl-1H-pyrazol-5(4H)-one (9) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 226.7–227.8°C; IR (KBr) ν 3447, 3203, 2281, 1614, 1525 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD): δ 7.66 (m, 2H), 7.40–7.38 (m, 3H), 7.22 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 164.6, 149.2, 139.3, 133.4, 131.7, 130.8, 129.9, 128.8, 128.5, 127.8, 88.7; LC-MS: *m/z* 300.9 (M+); Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.80; H, 3.87; N, 9.77. Found: C, 62.85; H, 3.69; N, 9.77.

3-(6-Chloropyridine-2-yl)-4-(phenylthio)-1H-pyrazol-5 (4H)-one (10) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), off white semisolid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.00 (brs, 1H), 10.50 (brs, 1H), 8.70 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 8.0 Hz, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H); LC-MS: *m/z* 303.0 (M+).

3-Ethyl-4-phenoxy-1H-pyrazol-5(4H)-one (11) This compound was obtained according to above general procedure of method F. Purified by column chromatography (acetone:EtOAc, 1:4), white solid. m.p. 196.2–197.3°C; IR (KBr): ν 3787, 2977, 2698, 1620 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30 (s, 1H), 9.70 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 6.96 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 2.35 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.3, 152.9, 136.2, 130.2, 121.8, 119.9, 115.1, 17.4, 13.0; LC-MS: *m/z* 204.3 (M+); Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.09; H, 5.92; N, 13.72. Found: C, 64.17; H, 5.88; N, 13.64.

3-Methoxymethyl-4-phenoxy-1H-pyrazol-5(4H)-one (12) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 146.4–147.2°C; IR (KBr):

ν 3206, 2930, 2550, 2361, 1587 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 9.80 (s, 1H), 7.27 (t, J = 7.4 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 4.16 (s, 2H), 3.15 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.1, 152.3, 131.3, 129.7, 122.0, 121.3, 115.2, 62.8, 57.76; LC-MS: m/z 220.1 (M+); Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.08; H, 5.319; N, 12.68.

3-Methyl-4-(3-bromophenylmethoxy)-1H-pyrazol-5(4H)-one (13) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid. m.p. 183.6–184.7°C; IR (KBr): ν 2966, 2923, 2871, 2557, 2361, 1588 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.80 (brs, 1H), 9.60 (brs, 1H), 7.57 (s, 1H), 7.50 (d, J = 5.9 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 4.81 (s, 2H), 1.90 (s, 3H); ^{13}C-NMR (75 MHz. DMSO-d_6): δ 152.8, 141.2, 131.0, 130.9, 130.85, 129.4, 127.4, 125.12, 121.9, 73.9, 9.2; LC-MS: m/z 283.8 (M+); Anal. Calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.54; H, 3.84; N, 9.82.

3-Methyl-4-(4-methoxyphenyoxy)-1H-pyrazol-5(4H)-one (14) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid. m.p. 201.0–202.7°C; IR (KBr): ν 2833, 2701, 1621, 1572 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.20 (brs, 1H), 9.70 (brs, 1H), 6.25 (d, J = 7.2 Hz, 2H), 6.80 (d, J = 6.7 Hz, 2H), 3.67 (s, 3H), 1.90 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 154.4, 153.1, 152.9, 130.7, 121.4, 116.0, 114.9, 55.8, 9.26; LC-MS: m/z 220.9 (M+); Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.07; H, 5.55; N, 12.68.

3-Methyl-4-phenylthio-1H-pyrazol-5(4H)-one (15) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 292.3–294.1°C; IR (KBr): ν 3007, 2656, 1575, 1478 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.00 (brs, 1H), 7.22 (t, J = 7.7 Hz, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.3 Hz, 2H), 2.08 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.7, 145.0, 139.5, 129.3, 125.2, 125.1, 87.3, 10.7; LC-MS: m/z 206.9 (M+); Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.18; H, 4.76; N, 13.45.

3-Isobutyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (16) This compound was obtained according to above general procedure of method F. Purified by column chromatography (Pet. ether:-EtOAc, 1:1), pale yellow solid. m.p. 198.1–198.4°C; IR (KBr) ν 3061, 2954, 2866, 2591, 1590 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.00 (brs, 1H), 10.00 (brs, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 2.36 (d, J = 7.6 Hz, 2H), 1.85 (m, 1H), 0.90 (d, J = 4.4 Hz, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.8, 147.9, 139.7, 129.1, 125.2, 124.9, 87.5, 34.2, 28.2, 22.6; LC-MS: m/z 248.9 (M+); Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.80; H, 6.41; N, 11.20.

3-Isopropyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (17) This compound was obtained according to above general procedure of method F. Purified by column chromatography (Pet. ether:-EtOAc, 1:1), white solid. m.p. 216.1–217.2°C; IR (KBr): ν 3054, 2970, 2735, 1604 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.00 (brs, 1H), 10.00 (brs, 1H), 7.23 (t, J = 7.6 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 2.96 (m, 1H), 1.15 (d, J = 9.6 Hz, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.8, 154.0, 139.8, 129.2, 125.1, 125.0, 85.6, 25.8, 21.9; LC-MS: m/z 233.8 (M+); Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H; 6.02; N, 11.96. Found: C, 61.44; H; 5.98; N, 12.06.

3-Ethyl-4-(benzylthio)-1H-pyrazol-5(4H)-one (18) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:9), white solid. m.p. 226.9–227.8°C; IR (KBr): ν 3061, 3024, 2930, 1576 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.50 (brs, 1H), 9.80 (brs, 1H), 7.25–7.08 (m, 3H), 7.07 (d, J = 6.6 Hz, 2H), 3.66 (s, 2H), 2.10 (q, J = 8.0 Hz, 2H), 0.84 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 162.5, 149.4, 139.1, 129.2, 128.4, 126.9, 89.4, 18.1, 13.3; LC-MS: m/z 234.9 (M+); Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.50; H, 6.06; N, 11.88.

3-Methoxymetyl-4-(benzylthio)-1H-pyrazol-5(4H)-one (19) This compound was obtained according to above general procedure of method F. Purified by column chromatography (Pet. ether:-EtOAc, 1:1), white solid. m.p. 226.6–227.9°C; IR (KBr): ν 3058, 2982, 2817, 2362, 1577 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.31–7.17 (m, 3H), 7.07 (d, J = 7.6 Hz, 2H), 3.79 (s, 2H), 3.69 (s, 2H), 3.13 (s, 3H); ^{13}C-NMR (100 MHz, CD_3OD): δ 164.3, 148.3, 140.7, 130.7, 129.7, 128.3, 93.1, 65.7, 59.0, 41.3; LC-MS: m/z 251.0 (M+); Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.51; H, 5.68; N, 11.04. Found: C, 57.51; H, 5.68; N, 11.04.

3-Isobutyl-4-(4-chlorophenylthio)-1H-pyrazol-5(4H)-one (20) This compound was obtained according to above general procedure of method F. Purified by column chromatography (Pet. ether:-EtOAc, 1:1), off white solid. m.p. 227–228°C; IR (KBr): ν 2956, 2869, 1701, 1603 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.00 (brs, 1H), 10.00 (brs, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 6.8 Hz, 2H), 2.36 (d, J = 6.8 Hz, 2H), 1.85 (m, 1H), 0.78 (d, J = 6.4 Hz, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 162.7, 147.9, 138.9, 129.5, 129.1, 126.8, 87.1, 34.2, 28.2, 22.6; LC-MS: m/z 282.6 (M+); Anal. Calcd. for $C_{13}H_{15}ClN_2OS$: C, 55.21; H, 5.35; N, 9.91. Found: C, 55.11; H, 5.24; N, 9.84.

3-(4-Chlorophenyl)-4-phenoxy-1H-pyrazol-5(4H)-one (21) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 208.2–209.9°C; IR (KBr): ν 3915, 3787, 3661, 2740, 1589 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.20 (brs, 1H), 10.10 (brs, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 10.7 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.7 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 158.3, 132.8, 130.1, 129.4, 126.8, 122.4; LC-MS: m/z 287.2 (M+); Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.87; H, 3.78; N, 9.66.

3-Tert-butyl-4-phenoxy-1H-pyrazol-5(4H)-one (22) This compound was obtained according to above general procedure of method F. Purified by preparative HPLC, brown semisolid. IR (KBr): ν 2964, 2868, 2716, 1599, 1562 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.00 (brs, 2H), 7.26 (t, J = 7.4 Hz, 2H), 6.94 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 2H), 1.16 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.0, 153.1, 142.7, 129.8, 121.8, 119.0, 115.1, 31.7, 29.2; LC-MS: m/z 232.3 (M+); Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.09; H, 6.89; N, 12.186.

3-Isobutyl-1-methyl-4-phenoxy-1H-pyrazol-5(4H)-one (23) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH: CH_2Cl_2, 2:98), pale brown solid. m.p. 141.4–142.7°C; IR

(KBr): ν 3188, 2956, 2870, 1693, 1588 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD): δ 7.27 (t, J = 7.5 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.92 (d, J = 7.6 Hz, 2H), 3.48 (s, 3H), 2.31 (d, J = 7.3 Hz, 2H), 1.89 (m, 1H), 0.96 (d, J = 6.3 Hz, 6H); ^{13}C-NMR (100 MHz, CD_3OD): δ 160.2, 142.7, 130.8, 123.4, 116.3, 34.9, 32.0, 29.2, 22.0; LC-MS: *m/z* 247.0 (M+); Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37; O, 12.29. Found: C, 68.15; H, 7.26; N, 11.297.

1,3-Dimethyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (26) This compound was obtained according to above general procedure of method F. Purified by column chromatography (MeOH:CH_2Cl_2, 2:98), pale brown solid. m.p. 170.5–171.8°C; IR (KBr): ν 3065, 2918, 2359, 1583 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30 (brs, 1H), 7.25 (t, J = 8.0 Hz, 3H), 7.09 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 3.15 (brs, 3H), 1.98 (brs, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.6, 149.8, 139.6, 129.4, 125.1, 125.1, 49.1, 33.9, 12.6; LC-MS: *m/z* 220.2 (M+); Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; Found: C, 60.07; H, 5.41; N, 12.68.

1-(4-Flurophenyl)-3-isobutyl-4-phenoxy-1H-pyrazol-5(4H)-one (28) This compound was obtained according to above general procedure of method J. Purified by column chromatography (MeOH:EtOAc, 1:9), white solid. m.p. 198–199.4°C; IR (KBr): ν 3077, 2954, 2922, 2867, 1590 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.69 (m, 2H), 7.27 (m, 4H), 7.01 (m, 3H), 2.39 (d, J = 7.1 Hz, 2H), 1.98 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.8, 144.4, 144.1, 135.9, 130.0, 123.0, 122.3, 121.5, 116.0, 115.3, 35.5, 27.5, 22.8; LC-MS: *m/z* 325.5 (M+); Anal. Calcd. for $C_{19}H_{19}FN_2O_2$: C, 69.92; H, 5.87; N, 8.58. Found: C, 69.81; H, 5.82; N, 8.47.

1-(4-Flurophenyl)-3-methyl-4-(phenylthio)-1H-pyrazol-5 (4H)-one (29) This compound was obtained according to above general procedure method of J. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 202.1–202.6°C; IR (KBr): ν 3067, 2447, 1583 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.57 (brs, 1H), 7.74 (m, 2H), 7.30 (m, 4H), 7.01 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 1.98 (brs, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 161.5, 159.1, 152.4, 138.8, 135.1, 129.5, 125.4, 123.4, 116.3, 116.4, 12.8; LC-MS: *m/z* 299.7 (M+); Anal. Calcd. for $C_{16}H_{13}FN_2OS$: C, 63.98; H, 4.36; N, 9.33. Found: C, 64.07; H, 4.25; N, 9.26.

3-Ethyl-1-(4-(2,2,2-trifluoroethyl)phenyl)-4-phenoxy-1H-pyrazol-5(4H)-one (30) This compound was obtained according to above general procedure of method J. Purified by column chromatography (MeOH:EtOAc, 1:99), white solid. m.p. 189.7–190.4°C; IR (KBr): ν 2976, 2500, 1583, 1489 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.37 (brs, 1H), 7.30 (t, J = 8.3 Hz, 3H), 6.99 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 4.69 (brs, 2H), 2.25 (q, J = 7.4 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.5, 145.6, 144.4, 129.6, 129.3, 128.0, 125.2, 122.4, 121.8, 119.6, 117.0, 114.9, 114.7, 47.5, 19.2; LC-MS: *m/z* 285.9 (M+); Anal. Calcd. for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79; Found: C, 54.46; H, 4.51; N, 9.88.

1-(4-Flurophenyl)-3-methyl-4-phenoxy-1H-pyrazol-5(4H)-one (31) This compound was obtained according to above general procedure of method J. Purified by column chromatography (MeOH:EtOAc, 1:99), pale yellow solid. m.p. 190.2–191.7°C; IR (KBr): ν 3084, 2922, 2687, 1721, 1632 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.75 (d, J = 4.5 Hz, 2H), 7.30 (d, J = 7.5 Hz, 4H), 7.01(t, J = 6.9 Hz, 1H), 6.94 (d, J = 8.3 Hz, 2H), 2.48 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.7, 158.2, 140.9, 129.6, 129.4, 21.9, 115.8, 115.5, 114.8, 10.9; LC-MS: *m/z* 284.5 (M+); Anal. Calcd. for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.55; H, 4.76; N, 9.735.

1-(4-Fluorophenyl)-3-isobutyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (32) This compound was obtained according to above general procedure of method J. Purified by column chromatography (30% EtOAc in Pet. ether), white solid. m.p. 219.4–220.6°C, IR (KBr): ν 3061, 3026, 2652, 1736, 1577 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.20 (brs, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.28 (m, 4H), 7.08 (m, 3H), 2.35 (d, J = 3.1 Hz, 2H), 1.92 (m, 1H), 0.84 (d, J = 6.6 Hz, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 161.5, 159.1, 155.0, 139.0, 135.2, 129.4, 125.4, 125.3, 123.5, 116.3, 116.1, 55.4, 36.1, 27.8, 22.8; LC-MS: *m/z* 320.8 (M+); Anal. Calcd. for $C_{19}H_{19}FN_2OS$: C, 66.64; H, 5.59; N, 8.18. Found: C, 66.57; H, 5.51; N, 8.22.

3-Ethyl-1-(4-fluorophenyl)-4-phenoxy-1H-pyrazol-5(4H)-one (33) This compound was obtained according to above general procedure of method J. Purified by column chromatography (30% EtOAc in Pet. ether), white solid. m.p. 168.3–169.5°C; IR (KBr): ν 3066, 2980, 2880, 2777, 2702, 2627, 1623 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.58 (brs, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.2 Hz, 3H), 7.00 (m, 3H), 2.34 (brs, 2H), 1.60 (brs, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.8, 146.3, 135.9, 130.1, 123.1, 122.3, 119.2, 166.2, 116.0, 115.5, 115.2, 19.8, 12.5; LC-MS: *m/z* 298.6 (M+); Anal. Calcd. for $C_{17}H_{15}FN_2O$: C, 68.45; H, 5.07; N, 9.39. Found: C, 68.33; H, 5.15; N, 9.21.

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A Novel CAN-SiO_2-Mediated One-Pot Oxidation of 1-Keto-1,2,3,4-tetrahydrocarbazoles to Carbazoloquinones: Efficient Syntheses of Murrayaquinone A and Koeniginequinone A

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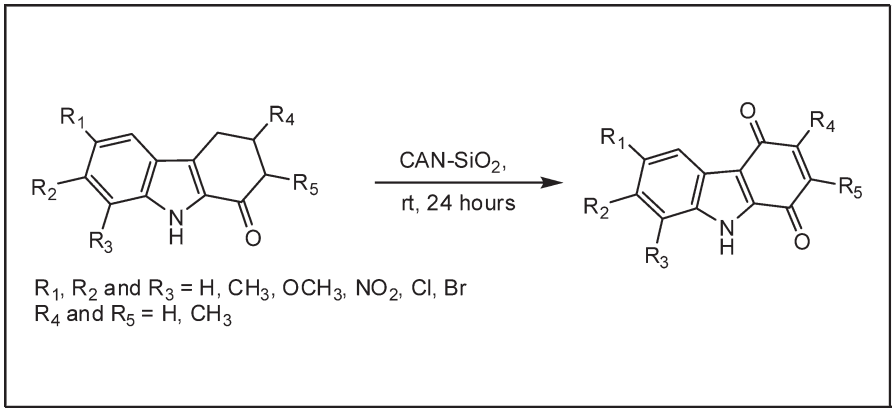

One-pot oxidations of substituted 1-keto-1,2,3,4-tetrahydrocarbazoles (**1**) to carbazole-1,4-quinones (**2**) are efficiently carried out by CAN-SiO_2-mediated reaction. This generalized protocol was successfully extended to the synthesis of two naturally occurring carbazoloquinones: murrayaquinone A (**2b**) and koeniginequinone A (**2g**). A plausible mechanism for this novel reaction involves formation of a 9-hydroxy-2,3,4,9-tetrahydro-1*H*-carbazole-1-one followed by rearrangement to 1-hydroxycarbazole derivatives, which are further oxidized by cerium (IV) to carbazoloquinones.

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INTRODUCTION

As part of a larger project in our laboratory, we faced the problem of synthesizing, in quantity, the carbazole-1,4-quinone (**2a**). To date, there is only one report [1] for direct oxidation of 1-keto-1,2,3,4-tetrahydrocarbzoles to carbazole-1,4-quinones and each cited example uses 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In our hands, however, this method proved unsuccessful in the transformation of **1a** into **2a** (Scheme 1).

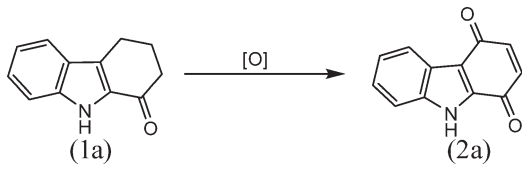
This failure motivated us to study the similar oxidation of 1-keto-1,2,3,4-tetrahydrocarbzoles by using the time-honored single-electron oxidant, CAN [2–4]. A survey of the literature [5] revealed that CAN, a single-electron oxidant is a reagent of choice for the synthesis quinones.

It is worth mentioning that substituted 1-keto-1,2,3,4-tetrahydrocarbazoles have been extensively used as an intermediate in the synthesis of naturally occurring carbazole alkaloids [6]. Cabazole-1,4-quinones are present in a large group of alkaloids that includes murrayaquinones A and B [7,8], pyrrayaquinones A and B [9], and koeniginequinones A and B [10]. Murrayaquinone A is known to have cardiotonic activity on guinea-pig papillary muscle [11]. Further carbazole-1,4-quinones [12] have been used as intermediates in the synthesis of a novel class of antibiotics, carbazomycines G and H [13].

In addition to the aforementioned oxidations [1] using DDQ, there are several reported syntheses of carbazole-1,4-quinones from 1- or 4-oxygenated carbazoles [10,14–16] *via* oxidation with Fremy's salt. A Japanese team [17] has developed a facile palladium (II) assisted intramolecular ring closure of arylamino-1,4-benzoquinones to carbazole-1,4-quinones. Knolker and coworkers [18,19] have taken advantage of this oxidative cyclization to obtain koeniginequinones A and B and carbazomycines G and H. Chowdhury *et al*. [20] have reported a photochemical oxidation of 3-methyl carbazole to obtain murrayaquinone A. Recently, Mal *et al*. [21] have developed a new strategy using [4 + 2] cycloaddition to obtain carbazole quinones from furoindolone and Michael acceptors.

Considering the importance of carbazole-1,4-quinones and the easy availability of 1-keto-1,2,3,4-tetrahydrocabazoles, we have studied the oxidation of 1-keto-1,2,3,4-tetrahydrocarbazole (**1a**) with CAN and CAN/DDQ

Scheme 1. Attempted oxidation of **1a** to **2a**.



under different conditions. However, because it could not be accomplished satisfactorily in solution phase, we had to carry out this reaction on a solid support.

RESULTS AND DISCUSSION

The strong oxidizing power of cerium (IV) salts often leads to undesired over oxidized products [22]. The concept of moderating the effect of reagents by immobilizing them on an inorganic solid support has achieved considerable popularity in organic syntheses [23,24]. Taking advantage of the moderated activity of CAN when it is immobilized on silica gel, we oxidized **1a** in solid phase under solvent-free conditions and obtained **2a** in moderate yield.

Using this finding as a starting point, a new and environmentally safe method for the oxidation of substituted 1-keto-1,2,3,4-tetrahydrocarbazoles (**1**) to carbazole-1,4-quinones (**2**) in single step using CAN-SiO_2 has been developed. The analysis of our observations and characterization of the products is the subject of this communication. Finally, we extend the scope of the reaction to the synthesis of the naturally occurring carbazoloquinones: murrayaquinone A (**2b**) and koeniginequinone A (**2g**) (Fig. 1).

The required substituted 1-keto-1,2,3,4-tetrahydrocarbazoles (**1**) were prepared through Fischer indole cyclization [25] of substituted cyclohexane-1,2-dione-1-phenylhydrazones obtained by Japp-Klingemann procedure from diazonium salts and 1,3-dicarbonyl compounds. CAN was dissolved in acetonitrile and then mixed with requisite amount of silica gel (see Experimental Section). Solvent was then evaporated and replaced by a solution of the substituted 1-keto-1,2,3,4-tetrahydrocarbazole (**1**). After re-evaporation, the mixture was kept at room temperature overnight [monitored by thin layer chromatography (TLC)], and the product was isolated and purified (Scheme 2). The results are summarized in Table 1.

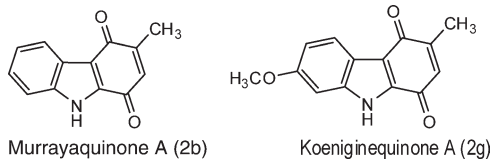
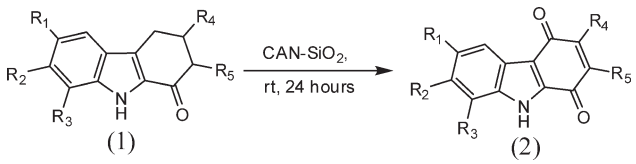


Figure 1. Representative carbazoloquinones.

Scheme 2. CAN-SiO_2-mediated oxidation to obtain carbazole-1,4-quinones.



The apparently favorable effect of 3-substitution on yields in the oxidation reaction of **1** provoked to also examine the effect of 2-substitution. However, no perceptible change was observed when compared with that of 3-methyl isomer. Again, presence of an electron-donating methoxy group in the benzene moiety of **1** lowers the yield of **2**, probably because of over oxidation [22]. However, this observation prompted us to investigate the oxidations of 1-keto-1,2,3,4-tetrahydrocarzoles (**1**) with electron-withdrawing group in the phenyl ring. On the basis of this insight, we successfully synthesized several carbazole-1,4-quinones with electron-withdrawing group (Table 1). It is worth mentioning that, with carbazole-1,4-quinones containing electron-withdrawing group on the phenyl ring, optimum yields are formed by heating the reaction for at least 4 h in an oil bath maintained at ca. 150°C or by microwave irradiation for 20 s at the power level 80% of 720 W.

It was noted by TLC that a compound with R_f 0.65 (solvent system, benzene–chloroform–diethyl amine 14:5:1) formed alongside quinone **2t** (R_f 0.26). The less polar by-product was isolated by column chromatography and identified as 9-hydroxy-6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) for which there is a good literature precedent [26] and the reaction is assumed to proceed as in Scheme 3.

The key steps of the reaction sequence shown above (Scheme 3) are the oxidation of **1t** to **3** followed by 1,4-elimination of a water molecule and subsequent 1,5-shift of the hydrogen atom to afford a 1-hydroxycarbazole, which is oxidized further by CAN to the final product, a 1,4-carbazoloquinone **2t**. Further identification of **3** was established through *O*-acetylation and *O*-methylation to obtain 6-methoxy-3,7-dimethyl-1-oxo-3,4-dihydro-1*H*-carbazol—9(2*H*)-yl acetate (**13**) and 6,9-dimethoxy-3,7-dimethyl-1-oxo-3,4-dihydro-1*H*-carbazol-1-one (**14**), respectively.

We then turned our attention to the conversion of **3** to a 1-hydroxycarbazole under several solid acid catalyzed conditions using SiO_2, acidic Al_2O_3, SiO_2-NH_4Cl, montmorillonite-K10, and montmorillonite-KSF. However, all these attempts were unsuccessful and in each case, the unreacted starting material **3** was almost completely recovered. Finally, we tried the CAN-SiO_2-mediated oxidation on **3** and obtained the desired 1,4-carbazoloquinone **2t**. This observation led to the idea that Ce (IV) may

Table 1

CAN-SiO_2 mediated oxidation of 1-keto-1,2,3,4-tetrahydrocarbazoles (1) to carbazole-1,4-quinones (2).

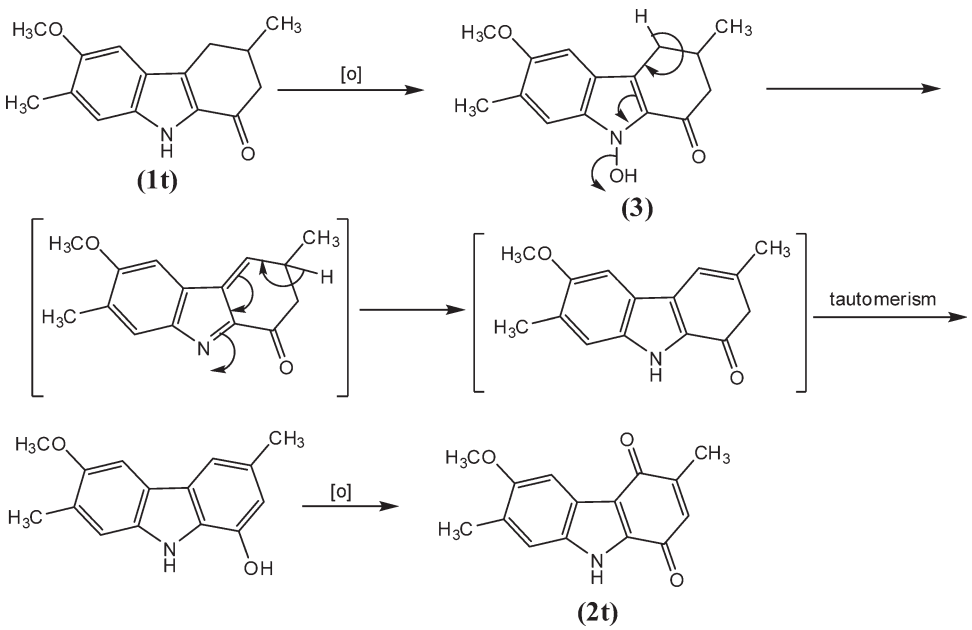
Entry	Substrate	Product	Yield (%)[a]	References
1	1a. $R_1 = R_2 = R_3 = R_4 = R_5 = H$	2a	55	26
2	1b. $R_1 = R_2 = R_3 = R_5 = H$, $R_4 = CH_3$	2b	62	1,8,14,15,17,18
3	1c. $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = H$	2c[b]	50	–
4	1d. $R_1 = R_4 = CH_3$, $R_2 = R_3 = R_5 = H$	2d	60	17
5	1e. $R_1 = R_3 = R_4 = CH_3$, $R_2 = R_5 = H$	2e[b]	54	–
6	1f. $R_1 = OCH_3$, $R_2 = R_3 = R_5 = H$, $R_4 = CH_3$	2f	50	17
7	1g. $R_1 = R_3 = R_5 = H$, $R_2 = OCH_3$, $R_4 = CH_3$	2g	56	10,17,18
8	1h. $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = CH_3$	2h	58	17
9	1i. $R_1 = R_5 = CH_3$, $R_2 = R_3 = R_4 = H$	2i	54	17
10	1j. $R_1 = R_3 = R_5 = CH_3$, $R_3 = R_4 = H$	2j[b]	52	–
11	1k. $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$, $R_5 = CH_3$	2k	50	17
12	1l. $R_1 = NO_2$, $R_2 = R_3 = R_4 = R_5 = H$	2l[b]	88	–
13	1m. $R_1 = NO_2$, $R_2 = R_3 = R_5 = H$, $R_4 = CH_3$	2m[b]	92	–
14	1n. $R_1 = Cl$, $R_2 = R_3 = R_4 = R_5 = H$	2n[b]	81	–
15	1o. $R_1 = Cl$, $R_2 = R_3 = R_5 = H$, $R_4 = CH_3$	2o	85	17
16	1p. $R_1 = Cl$, $R_2 = R_3 = R_4 = H$, $R_5 = CH_3$	2p	85	17
17	1q. $R_1 = Br$, $R_2 = R_3 = R_4 = R_5 = H$	2q[b]	83	–
18	1r. $R_1 = Br$, $R_2 = R_3 = R_5 = H$, $R_4 = CH_3$	2r[b]	89	–
19	1s. $R_1 = Br$, $R_2 = R_3 = R_4 = H$, $R_5 = CH_3$	2s[b]	88	–

[a] yields are reported after isolation in pure form.
[b] spectral data of these unknown compounds are incorporated in the Experimental Section.

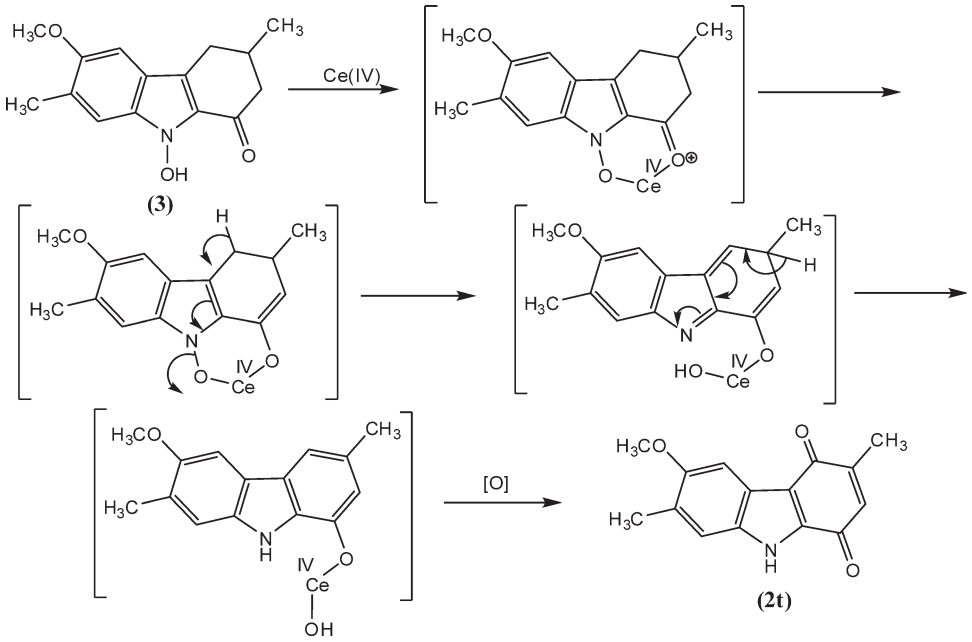
participate in the process by forming a complex as shown in Scheme 4. The ability of Ce (IV) to complex with aromatic OH groups is previously documented in literature [27].

To synthesize the starting compound 6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1t**), the amine hydrochloride **9** was prepared from *o*-cresol (Scheme 5) using a method different from that reported in literature [28]. *o*-Cresol (**4**) was converted to the nitroso derivative [29] **5** which on reduction with H_2S, NH_3 furnished the corresponding amine **6**. The amine **6** on acetylation furnished the acetyl derivative **7** which on methylation with CH_3I and $NaOC_2H_5$ gave **8**. Compound **8** on hydrolysis with concentrated hydrochloric acid (HCl) in ethanol afforded the required amine hydrochloride **9**. Diazotization of **9** followed by coupling with 2-(hydroxymethylene)-5-methylcyclohexanone (**10**) under Japp-Klingemann conditions furnished 2-(4-methoxy-3-

Scheme 3. Plausible mechanistic details for the oxidation of 1-keto-1,2,3,4-tetrahydrocarbazoles.



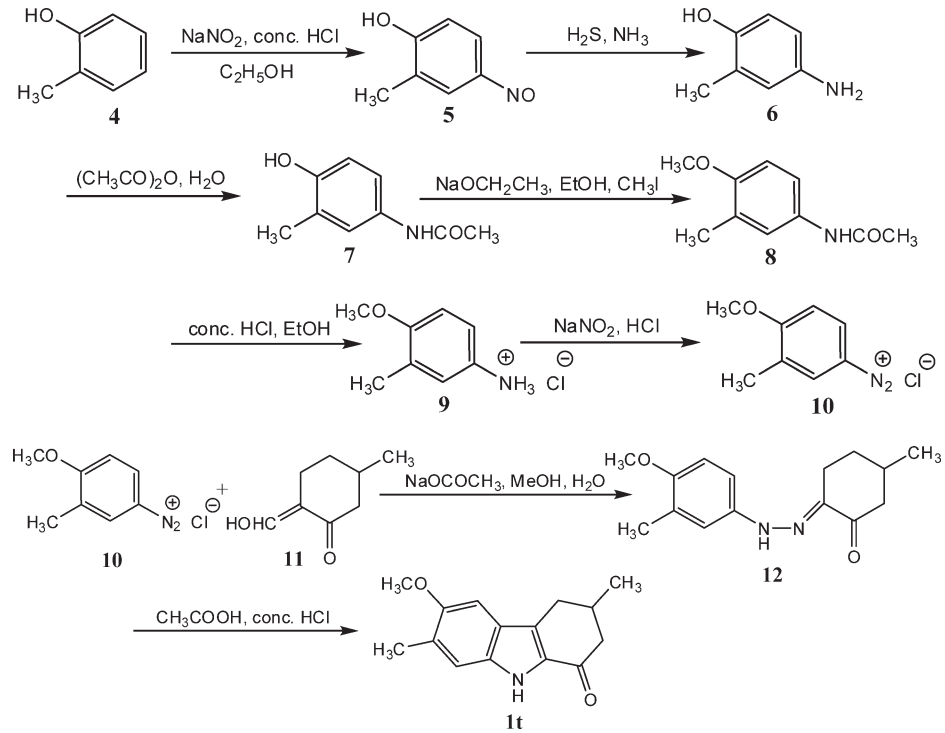
Scheme 4. Plausible mechanism for Ce (IV)-mediated pathway for the conversion of **3** to **2t**.



methylphenyl)hydrazono-5-methylcyclohexanone (**11**), which was cyclized to **1t**.

The presence of a carbazole-1,4-quinone moiety **2a–t** was confirmed by their UV and IR spectra [8] and the presence of two carbonyl signals at around δ 180 in the ^{13}C-NMR spectrum. In the ^{1}H-NMR spectrum, the C-5 proton was deshielded at around δ 7.20–8.20 due to the carbonyl moiety at 4-C. In addition, the C-5 proton of **2e**, **2j**, and **2t** showed unexpected lower intensity in ^{1}H-NMR spectra. Moreover, Nuclear Overhauser Effect (NOE) analysis [8,30] suggested orientation of the 6-*O*-methyl group toward C-5 hydrogen.

Scheme 5. Synthesis of 6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one.



In summary, we have developed a very simple, inexpensive, nontoxic, and eco-friendly one-pot oxidation of substituted 1-keto-1,2,3,4-tetrahydrocarbazoles to carbazole-1,4-quinones and applied it to the synthesis of the naturally occurring carbazoloquinones murrayaquinone A (**2b**) and koeniginequinone A (**2g**). The method is fairly general, although product yields are higher when the phenyl ring of the 1-keto-1,2,3,4-tetrahydrocarbazole starting material contains an electron-withdrawing substituent. Isolation of 9-hydroxy-6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) during the CAN-SiO_2 oxidation of 6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1t**) as an intermediate product, followed by its subsequent oxidation to 6-methoxy-3,7-dimethyl-1*H*-carbazole-1,4(9*H*)-dione (**2t**) suggested a plausible mechanism for the reaction. The present study expands the application of CAN-SiO_2-mediated oxidation in synthetically useful transformations.

EXPERIMENTAL

General methods and materials. Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from a commercial source and used without further purification. All reaction mixtures and column eluents were monitored by TLC using commercial aluminum TLC plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. IR spectra were recorded in KBr discs on Schimadzu FTIR-8300 and NMR spectra were recorded on Bruker AV 500. Results of attached proton test—^{13}C-NMR experiments are shown in parentheses where (+) denotes CH_3 or CH and (−) denotes CH_2 or C. High-resolution mass spectra (HRMS) were performed on Qtof Micro YA263.

Typical experimental procedure for CAN-SiO_2-mediated oxidation of 1b to murrayaquinone A (2b). Ceric ammonium nitrate (15 mmol) was dissolved in dry acetonitrile (30 mL) and then mixed with silica gel (35 gm). Solvent was then evaporated at room temperature and the reagent was impregnated with the solution of **1b** (2.5 mmol) in dichloromethane (20 mL) followed by evaporation of solvent in air. The mixture was then kept over night at room temperature. After the reaction, the mixture was extracted with dichloromethane (3 × 50 mL). The solvent was evaporated to dryness and the residue was chromatographed over silica gel by eluting successively with hexane and hexane–dichloromethane (2:3). The eluent furnished a red-colored solid which was purified by crystallization from dichloromethane–hexane to yield murrayaquinone A (**2b**), m.p. 242–243°C (lit. m.p. [1] 240–241°C).

6-Methyl-1H-carbazole-1,4(9H)-dione (2c). m.p. 238°C (dec.); UV (MeOH): 224 (sh), 255.5, 388; IR (KBr): ν = 3178, 2928, 1662,1636 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz) 2.41 (s, 3H, Ar—CH_3), 6.69 (s, 1H × 2, C_2—H & C_3—H), 7.20 (s, 1H, C_7—H), 7.41 (s, 1H, C_8—H), 7.80 (s, 1H, C_5—H), 12.76 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 21.20 (+), 113.46 (+), 114.92 (+), 120.93 (+), 123.61 (−), 128.32 (−), 133.28 (−), 135.28 (+), 135.28 (+), 135.84 (−),138.72 (−),179.77 (−), 183.11 (−); HRMS *m/z* calcd for $C_{13}H_9NO_2Na$ $[M + Na]^+$ 234.0531; found 234.0581.

3,6,8-Trimethyl-1H-carbazole-1,4(9H)-dione (2e). m.p. 236°C (dec.); UV (MeOH): 219 (sh), 258.7, 378.5; IR (KBr): ν = 3324, 2920, 1669,1647 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 1.99 (s, 3H, Ar—CH_3), 2.12 (s, 3H, Ar—CH_3), 2.25 (s, 3H, C_3—CH_3), 6.52 (s, 1H, C_2—H), 7.10 (s, 1H, C_7—H), 7.60 (s, 1H, C_5—H), 13.16 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 15. 42 (+), 15.74 (+), 16.42 (+), 113.28 (+), 114.42 (−), 124.12 (+), 126.99 (−), 128.84 (−), 131.42 (−), 136.29 (−), 137.28 (+), 141.74 (−), 148.21 (−), 179.47 (−), 181.14 (−); HRMS *m/z* calcd for $C_{15}H_{13}NO_2Na$ $[M + Na]^+$ 262.0844; found 262.0846.

2,6,8-Trimethyl-1H-carbazole-1,4(9H)-dione (2j). m.p. 239°C (dec.); UV (MeOH): 223 (sh), 257.7, 370.5; IR (KBr): ν = 3313, 2929, 1662, 1651 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 1.98 (s, 3H, Ar—CH_3), 2.28 (s, 3H, Ar—CH_3), 2.55 (s, 3H, C_2—CH_3), 6.56 (s, 1H, C_3—H), 7.18 (s, 1H, C_7—H), 7.25 (s, 1H, C_5—H), 13.25 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 14.79 (+), 16.42 (+), 16.87 (+), 113.53 (+), 114.30 (−), 124.16 (+), 127.01 (−), 128.99 (−), 135.05 (−), 136.51 (+), 137.24 (−), 141.82 (−143.86 (−), 179.77 (−), 181.42 (−); HRMS *m/z* calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$ 240.1024; found 240.1028.

6-Nitro-1H-carbazole-1,4(9H)-dione (2l). m.p. 233°C (dec.); UV (MeOH): 246.5, 375; IR (KBr): ν = 3244, 2956, 2928, 1728, 1649 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 6.80 (d, J = 6.0, 1H, C_2—H), 6.82 (d, J = 6.0, 1H, C_3—H), 7.52 (dd, J_{13} = 15.5, J_{24} = 26, 1H, C_7—H), 8.40 (d, J = 8, 1H, C_8—H), 8.65 (d, J = 7.5, 1H, C_5—H), 10.64 (s, 1H, N—H, exch.); ^{13}C-NMR ($CDCl_3$, 125 MHz): 117.06 (−), 123.47 (+), 123.84 (+), 126.88 (−), 129.97 (−), 131.14 (+), 134.26 (−), 135.32 (+), 136.33 (−), 139.02 (+), 179.11 (−), 182.85 (−); HRMS *m/z* calcd for $C_{12}H_6N_2O_4Na$ $[M + Na]^+$ 265.0225; found 265.0235.

3-Methyl-6-nitro-1H-carbazole-1,4(9H)-dione (2m). m.p. 230°C (dec.); UV (MeOH): 246.5, 283, 371; IR (KBr): ν = 3298, 2958, 2920, 1726, 1649 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.20 (s, 3H, C_3—CH_3), 6.63 (s, 1H, C_2—H), 7.50 (dd, J_{13} = 7.5, J_{24} = 7.5, 1H, C_7—H), 8.38 (d, J = 7.5, 1H, C_8—H), 8.66 (d, J = 7.5, 1H, C_5—H), 10.56 (s, 1H, N—H, exch.); ^{13}C-NMR ($CDCl_3$, 125 MHz): 15.23 (+), 117.06 (−), 122.95 (+), 123.34 (+), 128.04 (−), 129.5 (−), 131.42 (+), 132.20 (+), 135.32 (−), 136.30 (−), 148.70 (−), 179.11 (−), 182.85 (−); HRMS *m/z* calcd for $C_{13}H_8N_2O_4Na$ $[M + Na]^+$ 279.0382; found 279.0382.

6-Chloro-1H-carbazole-1,4(9H)-dione (2n). m.p. 248°C (dec.); UV (MeOH): 225.5, 258.7, 383; IR (KBr): ν = 3201, 2991, 1666, 1635 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 6.76 (s, 1H × 2, C_2—H & C_3—H), 7.52 (d, J = 8.5, 1H, C_7—H), 7.54 (d, J = 8.5, 1H, C_8—H), 7.95 (s, 1H, C_5—H), 13.08 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 114.69 (−), 115.53 (+), 120.42 (+), 124.06 (−), 126.56 (+), 128.43 (−), 135.48 (+), 135.77 (−), 136.40 (−), 138.67 (+), 179.66 (−), 182.80 (−); HRMS *m/z* calcd for $C_{12}H_7NO_2Cl$ $[M + H]^+$ 232.0165; found 232.0168.

6-Bromo-1H-carbazole-1,4(9H)-dione (2q). m.p. 254°C (dec.); UV (MeOH): 224, 259, 388; IR (KBr): ν = 3200, 2987, 1664, 1637 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 6.78 (s, 1H × 2, C_2—H & C_3—H), 7.53 (s, 1H × 2, C_7—H & C_8—H), 8.14 (s, 1H, C_5—H), 13.11 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 114.55 (−), 115.91 (+), 116.48 (−), 123.54 (+), 124.66 (−), 129.09 (+), 135.55 (+), 136.02 (−), 136.25 (−),

138.70 (+), 179.70 (−), 182.88 (−); HRMS *m/z* calcd for $C_{12}H_6NO_2BrNa$ $[M + Na]^+$ 297.9479; found 297.9482.

3-Methyl-6-bromo-1H-carbazole-1,4(9H)-dione (2r). m.p. 257°C (dec.); UV (MeOH): 225.5, 258.7, 322, 392; IR (KBr): ν = 3205, 2985, 1667, 1640 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 2.03 (s, 3H, C_3—CH_3), 6.57 (s, 1H, C_2—H), 8.06 (s, 1H, C_7—H), 8.20 (s, 1H × 2, C_5—H & C_8—H), 12.94 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 15.49 (+), 114.49 (−), 116.31 (+), 124.13 (+), 124.84 (−), 129.31 (+), 131.65 (+), 135.98 (−), 136.32 (−), 139.37 (−), 147.89 (−), 179.66 (−), 182.53 (−); HRMS *m/z* calcd for $C_{13}H_8NO_2BrNa$ $[M + Na]^+$ 311.9636; found 311.9638.

2-Methyl-6-bromo-1H-carbazole-1,4(9H)-dione (2s). m.p. 258°C (dec.); UV (MeOH): 224, 258.7, 325, 397; IR (KBr): ν = 3203, 2983, 1668, 1645 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): 2.02 (s, 3H, C_2—CH_3), 6.56 (s, 1H, C_3—H), 7.43—7.53 (m, 1H × 2, C_7—H & C_8-H), 8.18 (s, 1H, C_5—H), 12.97 (s, 1H, N—H, exch.); ^{13}C-NMR (DMSO-d_6, 125 MHz): 15.19 (+), 114.65 (−), 115.74 (+), 124.03 (+), 124.35 (−), 124.50 (−), 128.81 (+), 134.66 (+), 136.35 (−), 139.44 (−), 144.20 (−), 179.85 (−), 182.83 (−); HRMS *m/z* calcd for $C_{13}H_9NO_2Br$ $[M + H]^+$ 289.9816; found 289.9816.

Preparation and oxidation of 6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (1t). ***2-Methyl-4-nitrosophenol (5).*** To a solution of *o*-cresol (**4**, 10.8 gm, 0.1 mol) in 95% ethanol (80 mL), concentrated HCl (75 mL) was added. The mixture was cooled to 0°C and to the stirred solution sodium nitrite (10.5 gm, 0.15 mol) was added in portions of about 1 gm each while maintaining the reaction temperature at 0–5°C. Initially, a brown precipitate appeared which turned greenish within half an hour. The reaction mixture was then poured in ice water (400 mL). The light yellow solid (yield 7.5 gm) was collected by filtration and washed with cold water (100 mL). This crude product was used in the next step without further purification.

4-Amino-2-methylphenol (6). The crude nitroso derivative (**5**, 30 gm) was dissolved in a mixture of 28% aqueous ammonia (300 mL) and water (400 mL). The brown solution was then filtered and H_2S was passed until light yellow amino compound (**6**) was precipitated out. The reaction mixture was kept over night in refrigerator for complete crystallization of **6** (22 g, 81%), m.p. 173°C (lit. m.p. [31] 175.4°C). IR: 3390 (—OH), 3300 (—NH_2), and 1600, 1555, 1500 cm^{-1} (aromatic).

4-Acetamido-2-methylphenol (7). 4-Amino-2-methylphenol (**6**, 24.6 gm, 0.20 mol) was suspended in water (60 mL) and acetic anhydride (24 mL, 0.25 mol) was added with vigorous stirring. The mixture was warmed at about 60–65°C for 30 min. On cooling, a solid was separated out which was collected by filtration and washed with cold water. The acetyl derivative **7** was crystallized from water with charcoal treatment to yield colorless needle-shaped crystals (27.75 gm, 84%), m.p. 178°C (lit. m.p. [28] 179°C). IR: 3315 (—OH), 3285 (—NH), 1652 (C=O), and 1605, 1542, 1500 cm^{-1} (aromatic).

4-Methoxy-3-methylacetanilide (8). Clean sodium (1.5 gm, 0.065 mol) was placed in absolute alcohol (40 mL). After the dissolution of sodium, the mixture was cooled and 4-acetamido-2-methylphenol (10 gm, 0.06 mol) was added. Iodomethane (15.6 gm, 0.11 mol) was added slowly to the mixture under reflux using pressure equalizer. After 1-h reaction, mixture was poured in ice water (100 mL), cooled in ice bath, and crude methylated product was thus separated out. The crude product was leached with 1% NaOH solution (150 mL), filtered, and washed with ice cooled water (100 mL). Compound **8** was crystallized from MeOH-H_2O to furnish colorless needles (8 gm, 75%), m.p. 105°C (lit. m.p. [32] 103–3.5°C). IR: 3310 (—NH), 1654 (C=O), and 1560, 1510 cm^{-1} (aromatic).

4-Methoxy-3-methylaniline hydrochloride (9). 4-Methoxy-3-methylacetanilide (**7**, 35.8 gm, 0.20 mol) was dissolved in ethanol (100 mL) by boiling and concentrated HCl (100 mL) was added dropwise under reflux during 1 h. After 3 h, the solution was cooled when the crystals of amine hydrochloride (**9**) separated out, which was collected by filtration to furnish colorless crystals (27.8 gm, 80%), IR: 3440–3400 (—NH_3^+) and 1600, 1540, 1510 cm^{-1} (aromatic).

2-(4-Methoxy-3-methylphenyl)hydrazono-5-methylcyclohexanone (12). 2-Hydroxymethylene-5-methylcyclohexanone [10] (**11**, 16.20 gm, 0.12 mol) in methanol (150 mL) was added to an aqueous solution of sodium acetate (26 gm, 100 mL of water). To this a solution of 4-methoxy-3-methylphenyldiazonium chloride [10] (**10**, prepared from 20.8 gm, 0.12 mol of 4-methoxy-3-methylaniline hydrochloride) was added during 1 h under mechanical agitation when red crystals of **12** were obtained. Filtration and crystallization from methanol–dichloromethane yielded reddish brown crystals (**12**, 26.50 gm, 85%), m.p. 111–112°C. MS: *m/z* 260 (M^+); IR: 3450 (—NH), 1630 (C=O), and 1600, 1510 cm^{-1} (aromatic).

6-Methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (1t). 2-(4-Methoxy-methyl phenyl)hydrazono-5-methylcyclohexanone (**12**, 5.2 gm, 0.02 mol) was refluxed with glacial acetic acid (30 mL) containing concentrated HCl (7 mL) for 5 min and the hot reaction mixture was poured in ice water (200 mL). The solid thus obtained was collected by filtration, washed with water, dried, and then chromatographed over silica gel (50 gm) and the column was eluted with hexane–dichloromethane (2:1). The eluent gave a colorless solid which on crystallization from dichloromethane–hexane furnished colorless crystals (**1t**, 3.2 gm, 66%), m.p. 248°. IR (KBr): ν = 3255, 2997, 2829, 1648 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 500 MHz): 1.15 (d, J = 3.50 Hz, 3H, C_3—CH_3), 2.25 (s, 3H, Ar—CH_3), 2.29–2.54 (m, 3H, C_2—2H & C_3—1H), 3.06 (d, J = 15.30 Hz, 2H, C_4—2H), 3.82 (s, 3H, Ar—OCH_3), 6.97 (s, 1H, C_8—H), 7.15 (s, 1H, C_5—H), 11.22 (br, 1H, N—H, exch); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 125 MHz): 17.22 (+), 21.06 (+), 29.29 (−), 32.47 (+), 46.16 (−), 55.11 (+), 99.29 (+), 113.59 (+), 122.39 (−), 126.82 (−), 127.37 (−), 130.47 (−), 133.36 (−), 152.39 (−), 189.15 (−); HRMS *m/z* calcd for $C_{15}H_{17}NO_2Na$ $[M + Na]^+$ 266.1156; found 266.1176.

9-Hydroxy-6-methoxy-3,7-dimethyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (3) and 6-Methoxy-3,7-dimethyl-1H-carbazole-1,4(9H)-dione (2t). The immobilized CAN-SiO_2 reagent was impregnated with the solution of **1u** (603 mg, 2.5 mmol) in dichloromethane–acetonitrile mixture (1:1, 80 mL) followed by evaporation of solvent in air. The mixture was then kept over night at room temperature. After the reaction, the mixture was extracted with dichloromethane (4 × 50 mL). The solvent was evaporated to dryness and the residue so obtained was chromatographed over silica gel (15 gm) by eluting successively with hexane and mixtures of hexane and dichloromethane in the ratio 1:1 followed by 2:3. The eluent from hexane–dichloromethane (1:1) furnished a reddish brown-colored solid which was purified by crystallization from dichloromethane–hexane to yield **3** (100 mg, 16%), m.p. 206°C; UV

(MeOH): 233 (sh), 316.5; IR (KBr): ν = 3244, 2959, 2928, 2871, 1649 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18 (d, J = 4.11 Hz, 3H, C_3—CH_3), 1.81 (s, 1H, N—OH), 2.37–2.54 (m, 1H, & C_3—1H), 2.46 (s, 3H, Ar—CH_3), 2.66 (d, J = 10.23, 2H, C_2—2H), 2.91 (d, J = 14.43 Hz, 2H, C_4—2H), 3.90 (s, 3H, Ar—OCH_3), 7.26 (s, 1H, C_8—H), 7.45 (s, 1H, C_5—H); ^{13}C-NMR ($CDCl_3$, 75 MHz): 17.03 (+), 21.28 (+), 29.66 (−), 32.61 (+), 46.12 (−), 62.75 (+), 116.37 (+), 117.33 (+), 125.95 (−), 132.79 (−), 132.88 (−), 135.50 (−), 136.47 (−), 145.59 (−), 191.97 (−); HRMS m/z calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$ 260.1286; found. 260.1258. Further the eluent from hexane–dichloromethane (2:3) provide a red-colored solid which on crystallization from dichloromethane–hexane yielded **2t** (350 mg, 55%), m.p. 222°C (dec.); UV (MeOH): 222, 258.5, 378.5; IR (KBr): ν = 3323, 2924, 1724, 1651, 1616 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz) 2.03 (s, 3H, Ar—CH_3), 2.43 (s, 3H, C_3—CH_3), 3.81 (s, 3H, Ar—OCH_3), 6.67(s, 1H, C_2—H), 7.47 (s, 1H, C_8—H), 7.58 (s, 1H, C_5—H); ^{13}C-NMR (DMSO-d_6, 125 MHz): 15.72 (+), 16.31 (+), 62.58 (+), 113.22 (−), 113.39 (−), 117.54 (+), 131.55 (+), 131.65 (−), 134.68 (−), 137.55 (−), 138.16 (+), 146.08 (−), 148.24 (−), 179.48 (−), 181.28 (−); HMQC spectrum: δ_H (ppm):7.58 (C_5—H) δ_C (ppm): 118.41 (C_5); HRMS m/z calcd for $C_{15}H_{13}NO_3Na$ $[M + Na]^+$ 278.0793; found 278.0794.

6-Methoxy-3,7-dimethyl-1-oxo-3,4-dihydro-1H-carbazol—9(2H)-yl acetate (13). A mixture **3** (130 mg, 0.5 mmol), dry acetic anhydride (4.0 mL, 4.4 gm, 43 mmol), 4-(dimethylamino)pyridine (50.0 mg), and dry pyridine (two drops) was heated on water bath for 8 h. The reaction mixture was cooled and poured in ice water (50 mL), the whole mixture was extracted with ether (4 × 25 mL), the combined ether extract was washed with 5% $NaHCO_3$ solution until the evolution of carbon dioxide ceased, and then the organic phase was washed with brine solution (50 mL). Ether layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed over silica gel (10 gm) and elution with hexane–dichloromethane (3:2) furnished a light yellow-colored solid which on crystallization yielded **13** (120 mg, 80%), m.p. 123°C; UV (MeOH): 237 (sh), 320; IR (KBr): ν = 2956, 2929, 1716, 1678 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.12 (d, J = 5.1 Hz, 3H, C_3—CH_3), 2.18–2.47 (m, 1H, C_3—1H), 2.44 (s, 3H, Ar—CH_3), 2.53 (s, 3H, $OCOCH_3$), 2.65 (d, J = 14.15, 2H, C_2—2H), 2.77 (d, J = 13.74 Hz, 2H, C_4—2H), 3.82 (s, 3H, Ar—OCH_3), 7.32 (s, 1H, C_8—H), 8.11 (s, 1H, C_5—H); ^{13}C-NMR ($CDCl_3$, 75 MHz): 17.25 (+), 20.86 (+), 27.55 (+), 29.82 (−), 31.17 (+), 46.83 (−) 62.75 (+), 116.79 (−), 119.78 (+), 128.65 (+), 133.47 (−), 133.57 (−), 135.55 (−), 135.65 (−), 146.73 (−), 171.95 (−), 189.38 (−).

6,9-Dimethoxy-3,7-dimethyl-1-oxo-3,4-dihydro-1H-carbazol-1-one (14). The compound **3** (100 mg, 0.38 mmol) was dissolved in dry benzene–*N*,*N*-dimethylformamide (DMF) mixture (2:1, 15 mL). After cooling the solution to 0°C, 60% sodium hydride in paraffin (60 mg, 1.5 mmol) was added to it. The reaction mixture was cooled in ice bath and iodomethane (600 mg, 4.2 mmol) was added with stirring. The stirring was continued for 7 h. The reaction mixture was poured in ice water (50 mL) and the whole mixture was extracted with dichloromethane (4 × 25 mL). The combined dichloromethane extract was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4, and evaporated, and the residue was chromatographed over silica gel (8.5 gm) and elution with hexane–dichloromethane (3:2) furnished a light yellow-colored solid which was crystallized to obtain **14** (90 mg, 85%), m.p. 143°C; UV (MeOH): 240 (sh), 325; IR (KBr): ν = 2968, 2933, 1681 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) 1.18 (d, J = 5.4 Hz, 3H, C_3—CH_3), 2.41 (s, 3H, Ar—CH_3), 2.50 (q, 1H, C_3—1H), 2.71 (d, J = 14.15, 2H, C_2—2H), 2.75 (d, J = 13.74 Hz, 2H, C_4—2H), 3.82 (s, 3H, Ar—OCH_3), 3.97 (s, 3H, N—OCH_3), 7.19 (s,1H, C_8—H), 7.23 (s, 1H, C_5—H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 17.26 (+), 20.22 (+), 29.33 (+) , 31.79 (−), 46.89 (−) 62.80 (+), 65.73 (+), 94.85 (+), 114.47 (+), 114.90 (−), 122.73 (−), 130.49 (−), 131.64 (−), 137.10 (−), 145.02 (−), 198.19 (−).

Oxidation of 3. The CAN-SiO_2 reagent was soaked with the solution of **3** (130 mg, 0.5 mmol) in dichloromethane (7 mL) and solvent was removed. The mixture was then kept over night at room temperature. The reaction mixture was then extracted with dichloromethane (2 × 50 mL). The solvent was removed and the residue so obtained was chromatographed over silica gel (10 gm) by eluting successively with hexane and hexane–dichloromethane (2:3). The eluent provided a red-colored solid which was crystallized from dichloromethane–hexane to yield **2t** (100 mg, 78%).

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Synthesis and Antimicrobial and Pharmacological Properties of New Thiosemicarbazide and 1,2,4-Triazole Derivatives

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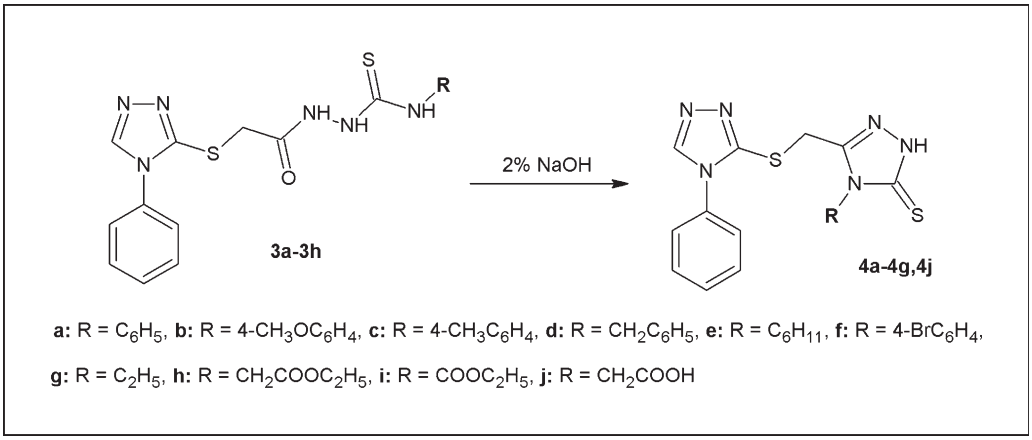

Reaction of 4-phenyl-4*H*-1,2,4-triazole-3-thione with ethyl bromoacetate has led to the formation of ethyl [(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetate **1**, the structure of which was confirmed by X-ray analysis. In the next reaction with 80% hydrazide hydrate, appropriate hydrazide **2** was obtained, which in reaction with isothiocyanates was converted to new acyl derivatives of thiosemicarbazides **3a–3h**. The cyclization of these compounds in alkaline media has led to formation of new derivatives of 5-{[(4-phenyl-4*H*-1,2,4-triazole-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thiones **4a–4g**, **4j**. The structure of the compounds was confirmed by elementary analysis and IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra. Compounds **3a–3h** and **4a–4g** were screened for their antimicrobial activities, and the influence of the compounds **4a, 4b**, and **4e–4g** on the central nervous system of mice in behavioral tests was examined.

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INTRODUCTION

Cyclization of thiosemicarbazide derivatives leads to 1,2,4-triazole derivatives in alkaline media [1,2], where as in acidic media [3,4] to 1,3,4-thiadiazole derivatives.

In previous papers [2–5], it was stated that the reaction of cyclization was affected not only by pH of the medium but also by the nature of substituents in thiosemicarbazide derivatives. The course of cyclization in alkaline and acidic media for thiosemicarbazide derivatives of formic, benzoic, and nicotinic acids was investigated [5].

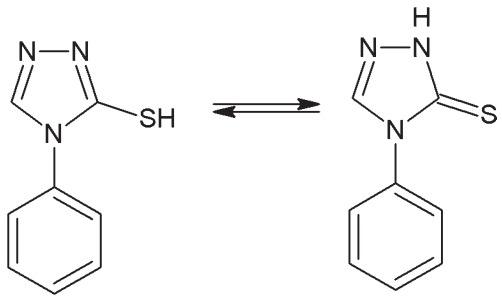
Cyclization of thiosemicarbazide derivatives of formic and nicotinic acids in alkaline and in acidic media leads to 1,2,4-triazole derivatives. In the cyclization reaction of benzoic acid thiosemicarbazide derivatives in the presence of alkaline media 1,2,4-triazole system was obtained, whereas in acidic media 1,3,4-thiadiazole derivatives were obtained [5].

4-Phenyl-4*H*-1,2,4-triazole-3-thione, which can exist in two tautomeric forms (Scheme 1), was a starting material for synthesis.

In various reactions, depending on the conditions used, this compound can lead either to the S- or N-derivatives. In this article, the reaction of 4-phenyl-4*H*-1,2,4-triazole-3-thione with ethyl bromoacetate was investigated. Based on the results of the previous papers [5,6], the elemental and spectral analysis as well as the X-ray crystallography, it was revealed and confirmed that reaction leads to the formation of S-derivative **1** (Fig. 1).

This compound was converted to hydrazide **2**, then in reaction with isothiocyanates appropriate

Scheme 1. Thiol/thione tautomerism forms of 4-phenyl-4*H*-1,2,4-triazole-3-thiol.



thiosemicarbazide derivatives were obtained **3a–3h**. Cyclization of these compounds in alkaline media leads to new derivatives of 1,2,4-triazole **4a–4g**.

The reactions were performed according to Scheme 2, and the substituents are presented in Table 1.

Depending on the nature of substituents, the 1,2,4-triazole derivatives show various pharmacological activities. Some of them, obtained in previous papers and investigated on experimental animals, had potential action on central nervous system (CNS) [7]. Others

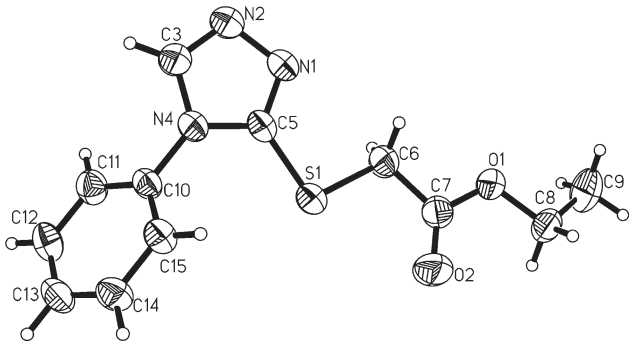


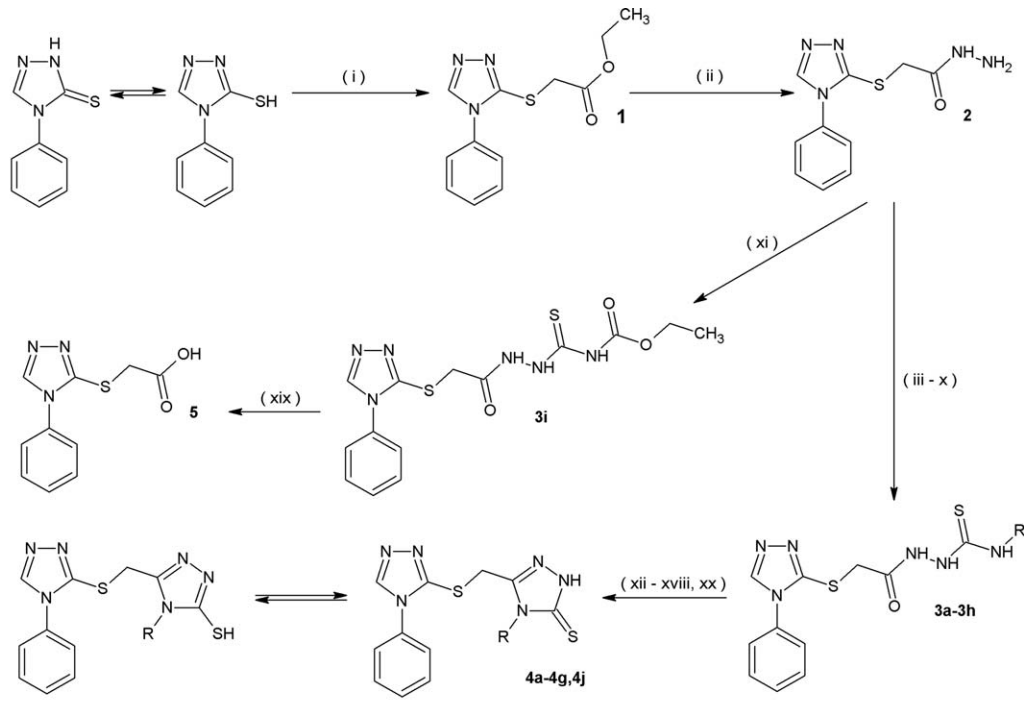
Figure 1. Molecular structure with atom numbering scheme for compound **1**. Displacement ellipsoids are drawn at the 50% probability level.

show analgesic [8], antifungal [9], antibacterial [10–12], antiphlogistic [13], and antituberculous [14,15] action.

Pharmacological experiments (on CNS on mice) were carried out for compounds **4a**, **4b**, and **4e–4g**.

All tested compounds were screened for *in vitro* antibacterial activity by the agar well diffusion method, and for agents **3d**, **3f**, **3g**, and **3h** showing potential inhibitory effect on the growth of bacteria minimal inhibitory

Scheme 2. Synthesis of new thiosemicarbazide and 1,2,4-triazole derivatives.

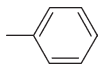
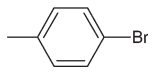
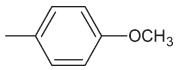
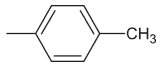
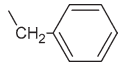
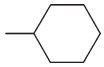


a: R = C_6H_5, **b:** R = 4-$CH_3OC_6H_4$, **c:** R = 4-$CH_3C_6H_4$, **d:** R = $CH_2C_6H_5$, **e:** R = C_6H_{11}, **f:** R = 4-BrC_6H_4, **g:** R = C_2H_5, **h:** R = $CH_2COOC_2H_5$
i: R = $COOC_2H_5$, **j:** R = CH_2COOH

Reagents and conditions: (i) NaOEt then $BrCH_2COOC_2H_5$, mix at 25°C for 4h, left at 25°C for 12 h and heat at boiling point for 2 h (65.9%);
(ii) EtOH then 80% $NH_2NH_2 \cdot H_2O$, left at 25°C for 24 h (78%); (iii) C_6H_5NCS, 50°C, 12 h (91.5%);
(iv) 4-$CH_3OC_6H_4NCS$, 50°C, 12 h (88.9%); (v) 4-$CH_3C_6H_4NCS$, 80°C, 12 h (88.5%); (vi) $C_6H_5CH_2NCS$, 40°C, 12 h (93.9%);
(vii) $C_6H_{11}NCS$, 70°C, 12 h, (84,5%); (viii) 4-BrC_6H_4NCS, 95°C, 12 h (79.2%); (ix) C_2H_5NCS, 50°C, 12 h (76.3%);
(x) $C_2H_5OOCCH_2NCS$, 40°C, 12 h (65.2%); (xi) $C_2H_5OOCNCS$, 45°C, 12 h (75,1%); (xii-xx) 2% NaOH, heat at boiling point for 2 h (77.8-95.1%).

Table 1

Substituents of compounds **3a–4j**.

Compounds	R	Compounds	R
3a, 4a		**3f, 4f**	
3b, 4b		**3g, 4g**	C_2H_5
3c, 4c		**3h**	$CH_2COOC_2H_5$
3d, 4d		**3i**	$COOC_2H_5$
3e, 4e		**4j**	CH_2COOH

concentration (MIC) values were estimated by microdilution technique [16,17].

RESULTS AND DISCUSSION

4-Phenyl-4*H*-1,2,4-triazole-3-thione was the starting material for synthesis of new derivatives, which consist of two 1,2,4-triazole systems connected with *S*-methylene group.

This compound was obtained (using the method described earlier) by cyclization of 1-formyl-4-phenyl thiosemicarbazide in alkaline media. Reaction with ethyl bromoacetate in the presence of sodium ethanolate gave ethyl [(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetate **1** (Fig. 1), which was converted to hydrazide **2** on reaction with 80% hydrazine hydrate.

Reactions of hydrazide **2** with aliphatic, aromatic, ethoxycarbonyl, and ethoxycarbonylmethyl isothiocyanates were carried out by heating substrates in an oil bath; temperatures were selected experimentally ($t = 40$–$95°C$).

New thiosemicarbazide derivatives **3a–3g** in cyclization reaction with 2% aqueous solution of sodium hydroxide leads to a new group of 5-{[4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazol-3(2*H*)-thione **4a–4g** derivatives.

The cyclization of thiosemicarbazide in alkaline media, which contain ethoxycarbonylmethyl group **3h**, was accompained by hydrolysis of ester group and led to formation of 4-carboxymethyl-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione **4j**.

The hydrolysis was also observed in the case of cyclization of 4-ethoxycarbonyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide **3i** in alkaline media, which led to formation of [(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetic acid **5**. This compound was described earlier [18,19], but it was obtained in a different way.

The test of cyclization of 1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}-1-phenyl thiosemicarbazide **3a** in acidic media (acetic acid) gave the derivative with 1,2,4-triazole system **4a**.

The structure of the obtained compounds was confirmed by elementary analysis, IR, and ^{1}H-NMR spectra. Some of them were also submitted to ^{13}C-NMR and MS spectral analysis.

In the IR spectra of 1,2,4-triazole system **4a–4g, 4j**, the following characteristic absorption bands were observed: 1513–1530 cm^{-1} corresponding to C—N group and in the range of 1608–1624 cm^{-1} corresponding to C=N group.

^{1}H-NMR spectra of the thiosemicarbazide derivatives **3a–3i** show three proton signals typical for the NH group in the δ 8.30–10.45 ppm range. Whereas for the new compounds of 1,2,4-triazole system **4a–4g**, **4j** one proton signal of the NH group was observed in the δ 13.63–13.99 ppm range.

Table 2

Antinociceptive activity compounds **4a**, **4b**, **4e** and **4f** in the writhing syndrome test in mice.

Compound	Part of LD_{50}	Mean writhing number	Inhibition (%)
Control **4a**	–	47.9 ± 4.7	–
	0.025	41.4 ± 6.2	14
	0.05	15.5 ± 4.5**	68**
	0.1	12.0 ± 5.0**	75**
Control **4b**	–	57.2 ± 5.1	–
	0.00625	58.2 ± 6.2	–
	0.0125	26.4 ± 8.4**	54**
	0.025	28.1 ± 5.6**	51**
	0.05	10.0 ± 4.4**	82.5**
	0.1	10.9 ± 4.3**	81**
Control **4e**	–	64.8 ± 5.9	–
	0.0125	62.0 ± 6.5	4
	0.025	47.8 ± 8.8*	26*
	0.05	29.1 ± 5.5**	55**
	0.1	5.6 ± 1.8**	91**
Control **4f**	–	46.8 ± 2.6	–
	0.0125	40.7 ± 2.3	13**
	0.025	35.5 ± 4.3*	24*
	0.05	34.3 ± 5.9*	27*
	0.1	25.9 ± 3.2**	44**

Compounds were given 30 min before the test.
% of inhibition obtained by comparison with control group.
* $P < 0.05$ *vs*. the control group.
** $P < 0.001$.

Table 3

The influence of assayed **3d, 3f, 3g, 3h** compounds on the growth of gram-positive bacteria recorded as the average diameter of the growth inhibition zone (including 8 mm of the well) in the agar well diffusion technique and on the basis of MIC values in the broth microdilution method (OD_{600}).

	3d		3f		3g		3h	
Species	Zone of growth inhibition (mm)	MIC (mg/L)	Zone of growth inhibition (mm)	MIC (mg/L)	Zone of growth inhibition (mm)	MIC (mg/L)	Zone of growth inhibition (mm)	MIC (mg/L)
Staphylococcus aureus ATCC 25923	8	>1000	17	500	17	500	16	1000
Staphylococcus aureus ATCC 6538	8	>1000	15	125	8	>1000	8	>1000
Staphylococcus epidermidis ATCC 12228	15	>1000	17	250	17	500	16	1000
Bacillus subtilis ATCC 6633	25	1000	8	500	54	500	32	1000
Bacillus cereus ATCC 10876	17	>1000	16	250	11	>1000	9	>1000
Micrococcus luteus ATCC 10240	22	1000	30	125	50	250	50	250

^{13}C-NMR spectra were performed for compounds **3a**, **3f**, **3g**, **4a**, **4f**, and **4g**, whereas MS spectra for **3f**, **3g**, **4a**, **4f**, and **4g** compounds.

The behavioral study showed that the compounds **4a**, **4b**, **4e**, and **4f** weakly affected the CNS of mice. Compound **4g** was without effect. The compounds **4a**, **4b**, **4e**, and **4f** showed antinociceptive properties (Table 2). The most active compounds were **4b** in doses of 0.0125–0.1 LD_{50} and **4e** in doses of 0.025–0.1 lethal dose $(LD)_{50}$. These doses induced a decrease (by 54–81% and 26–91%, respectively) in a number of mice exhibiting pain reactivity in the ''writhing syndrome'' test. In the remaining tests, none of the compounds produced a statistically significant effect. In our research, we have shown that the antinociceptive activity of **4b** (4-(4-methoxyphenyl)-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione) and **4e** (5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-methyl}-4-cyclohexyl-4*H*-1,2,4-triazole-3(2*H*)-thione) is interesting and should be examined in more detail.

Among Gram-positive species of bacteria, the most sensitive to all of the assayed compounds was *Micrococcus luteus* American Type Culture Collection (ATCC) 10240 (growth inhibition zone from 22 to 50 mm, MIC = 125–1000 mg/L). The growth of *Staphylococcus aureus* ATCC 25923, *S. aureus* ATCC 6538, and *Staphylococcus epidermidis* ATCC 12220 were totally or partially inhibited by the following compounds: **3f** (inhibitory zone from 15 to 17 mm, MIC 125–500 mg/L), **3g** (inhibitory zone from 8 to 17 mm, MIC 500–1000 mg/L), and **3h** (inhibitory zone from 8 to 16 mm, MIC = 1000 or >1000 mg/L), similarly growth of *Bacillus subtilis* ATCC 6633 and *B. cereus* ATCC 10876 by compounds **3d** (inhibitory zone from 17 to 25 mm, MIC = 1000 or >1000 mg/L), **3g** (inhibitory zone from 11 to 54 mm, MIC = 500 or >1000 mg/L), and **3h** (inhibitory zone from 9 to 32 mm, MIC = 1000 or >1000 mg/L). For comparison, MIC values for reference strains of tested bacteria were 0.015–0.49 mg/L for gentamicin and 0.49–1.95 mg/L for cefuroxime.

It was found that the most effective compound against Gram-positive microorganisms was **3f** with diameter of the growth inhibition zone from 8 to 30 mm at 5000 mg/L concentration and MIC values from 125 to 500 mg/L (Table 3). No activity of the tested compounds against Gram-negative bacteria or fungi was found.

Our results should be of value to further detailed studies on the biological activity of this group of compounds. Especially **3f** agent described in this article could be regarded as leading structure at seeking of the compounds with increased antibacterial activity against potentially pathogenic or opportunistic Gram-positive bacteria, including Staphylococci (coagulase-positive *S. aureus* and coagulase-negative *S. epidermidis*).

EXPERIMENTAL

Chemistry. Melting points were determined in Fisher-Johns (Pittsburgh, PA) blocks and presented without any corrections. The IR spectra (ν, cm^{-1}) were recorded in KBr tablets using a Specord IR-75 spectrophotometer (Germany). The ^{1}H-NMR spectra were recorded on a Bruker Avance 300 apparatus (Bruker BioSpin GmbH, Rheinstetten/Karlsruhe, Germany) in dimethyl sulfoxide (DMSO)-d_6 with tetramethylsilane (TMS) as internal standard. The ^{13}C-NMR spectra were recorded on a Bruker Avance 300. Chemical shifts are given in ppm (δ scale). The MS spectra were recorded on a ThermoFinnigan Trace TSQGC MS apparatus (Waltham, MA). Chemicals were purchased from Merck Co. (Whitehouse Station, NJ) or Lancaster (Windham, NH) and used without further purification.

The purity of obtained compounds was checked by thin layer chromatography (TLC) on aluminum oxide 60 F_{254} plates (Merck Co.), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system with UV visualization ($\lambda = 254$ nm).

Ethyl [(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetate (1). Sodium [0.23 g (0.01 mol)] was added to 5 mL of anhydrous ethanol, placed in a three-necked flask equipped with reflux condenser closed with a tube of $CaCl_2$ and mercury stirrer. The content was mixed till sodium dissolved completely and then 1.77 g (0.01 mol) of 4-phenyl-4*H*-1,2,4-triazole-3-thione was added. Then 1.22 mL ethyl bromoacetate was added drop by drop. The content of the flask was mixed for 4 h and left at room temperature for 12 h. Then 10 mL anhydrous ethanol was added and heated for 1 h. The mixture was filtered off inorganic compounds. After cooling, the precipitate was filtered off and crystallized from ethanol.

Yield: 1.73 g, (65.9%). m.p.: 66–68°C. For $C_{12}H_{13}N_3O_2S$ (263.31) calculated: C: 54.76%, H: 4.97%, N: 15.96%; found: C: 54.73%, H: 4.95%, N: 15.95%. IR (KBr): 3098 (CH_{ar}), 2913, 1417 (CH_{al}), 1735 (C=O), 1556 (C=N). ^{1}H-NMR (DMSO-d_6): 1.17 (t, 3H, CH_3, $J = 7.2$ Hz); 4.09 (s, 2H, CH_2); 4.06–4.13 (q, 2H, CH_2, $J = 7.2$ Hz); 7.51–7.65 (m, 5H, $5CH_{ar}$); 8.87 (s, 1H, CH).

[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetohydrazide (2). Hydrazine hydrate (0.63 mL of 80%) was added to 2.63 g (0.01 mol) of compound **1** in 5 mL of anhydrous ethanol. The mixture was left at room temperature for 24 h. The precipitate of hydrazide **2** was filtered off, dried, and crystallized form ethanol.

Yield: 1.94 g, (78%). m.p 132–134°C. For $C_{10}H_{11}N_5OS$ (249.29) calculated: C: 48.14%, H: 4.44%, N: 28.08%; found: C: 48.16%, H: 4.41%, N: 28.05%. ^{1}H-NMR (DMSO-d_6): 3.89 (s, 2H, CH_2); 4.29 (s, 2H, NH_2); 7.51–7.61 (m, 5H, $5CH_{ar}$); 8.86 (s, 1H, CH); 9.33 (s, 1H, NH).

Derivatives of 1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetyl}thiosemicarbazide (3a–3i)

General procedure. A mixture of hydrazide (**2**) 2.49 g (0.01 mol) and 0.01 mol appropriate isothiocyanate was heated in an oil bath at 40–95°C for 12 h. The product was washed with diethyl ether to remove unreacted isothiocyanate and with water to remove unreacted hydrazide (**2**). Then it was filtered off, dried, and crystallized from ethanol.

1-{[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}-4-phenyl thiosemicarbazide (3a). Yield: 3.51 g, (91.5%). Temperature of reaction: 50°C for 12 h. m.p.: 168–170°C. For $C_{17}H_{16}N_6OS_2$ (384.48) calculated: C: 53.06%, H: 4.19%, N: 21.85%; found: C: 53.09%, H: 4.20%, N: 21.87%. ^{1}H-NMR (DMSO-d_6): 3.99 (s, 2H, CH_2); 7.13–7.65 (m, 10H, $10CH_{ar}$); 8.90 (s, 1H, CH); 9.74, 9.76, 10.43 (3s, 3H, 3NH). ^{13}C-NMR: 34.8 (CH_2); 125.2, 125.4, 128.0, 129.6, 129.9 ($6\times CH_{ar}$); 133.2, 139.0 ($2\times C_{ar}$); 145.4 ($CH_{triazole}$); 149.2 (N=C—S—); 166.9 (C=O); 180.8 (C=S).

1-{[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}-4-(4-methoxyphenyl)thiosemicarbazide (3b). Yield: 3.68 g, (88.9%). Temperature of reaction: 50°C for 12 h. m.p.: 174–176°C. For $C_{18}H_{18}N_6O_2S_2$ (414.50) calculated: C: 52.11%, H: 4.37%, N: 20.27%; found: C: 52.10%, H: 4.39%, N: 20.28%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.74 (s, 3H, CH_3); 3.98 (s, 2H, CH_2); 6.90–7.35 (dd, 4H, 4-$CH_3OC_6H_4$, $J = 6$ Hz); 7.52–7.61 (m, 5H, $5CH_{ar}$); 8.89 (s, 1H, CH); 9.63, 9.65, 10.38 (3s, 3H, 3NH).

1-{[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}-4-(*p*-tolyl)thiosemicarbazide (3c). Yield: 3.52 g, (88.5%). Temperature of reaction: 80°C for 12 h. m.p.: 188–190°C. For $C_{18}H_{18}N_6OS_2$ (398.50) calculated: C: 54.2%, H: 4.55%, N: 21.1%; found: C: 54.18%, H: 4.56%, N: 21.11%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.28 (s, 3H, CH_3); 3.98 (s, 2H, CH_2); 7.11–7.38 (dd, 4H, 4-$CH_3C_6H_4$, $J = 9$ Hz); 7.52–7.62 (m, 5H, $5CH_{ar}$); 8.89 (s, 1H, CH); 9.67, 9.70, 10.41 (3s, 3H, 3NH).

4-Benzyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide (3d). Yield: 3.73 g (93.9%). Temperature of reaction: 40°C for 12 h. m.p.: 164–166°C. For $C_{18}H_{18}N_6OS_2$ (398.50) calculated: C: 54.2%, H: 4.55%, N: 21.1%; found: C: 54.18%, H: 4.53%, N: 21.09%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.96 (s, 2H, CH_2); 4.79 (s, 2H, CH_2); 7.18–7.64 (m, 10H, $10CH_{ar}$); 8.86 (s, 1H, CH); 8.81, 9.51, 10.37 (3s, 3H, 3NH).

4-Cyclohexyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide (3e). Yield: 3.29 g, (84.5%). Temperature of reaction: 70°C for 12 h. m.p.: 166–168°C. For $C_{17}H_{22}N_6OS_2$ (390.53) calculated: C: 52.24%, H: 5.67%, N: 21.51%; found: C: 54.26%, H: 5.65%, N: 21.50%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.07–1.76 (m, 10H, $5CH_2$); 3.86 (s, 2H, CH_2); 4.08 (s, 1H, CH); 7.52–7.69 (m, 5H, $5CH_{ar}$); 8.94 (s, 1H, CH); 9.26, 9.52, 10.16 (3s, 3H, 3NH).

4-(4-Bromophenyl)-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide (3f). Yield: 3.67 g, (79.2%). Temperature of reaction: 95°C for 12 h. m.p.: 178–180°C. For $C_{17}H_{15}N_6BrOS_2$ (463.37) calculated: C: 44.02%, H: 3.25%, N: 18.13%; found: C: 44.0%, H: 3.26%, N: 18.15%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.97 (s, 2H, CH_2); 7.51–7.62 (m, 9H, $9CH_{ar}$); 8.90 (s, 1H, CH); 9.81, 9.88, 10.45 (3s, 3H, 3NH). ^{13}C-NMR: 34.7 (CH_2); 125.2, 125.4, 129.6, 129.9, 130.8 ($5\times CH_{ar}$); 117.5, 133.1, 138.4 ($3\times C_{ar}$); 145.4 ($CH_{triazole}$); 149.2 (—N=C—S—); 166.9 (C=O); 180.8 (C=S). MS *m/e* (%): 463 (M^{+}, 0.1); 287 (0.7); 249 (3.1); 213 (80); 190 (7); 176 (100); 157 (16); 134 (20); 104 (12); 91 (27); 77 (35).

4-Ethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide (3g). Yield: 2.56 g, (76.3%). Temperature of reaction: 50°C for 12 h. m.p.: 171–173°C. For $C_{13}H_{16}N_6OS_2$ (336.43) calculated: C: 46.37%, H: 4.79%, N: 24.97%; found: C: 46.38%, H: 4.80%, N: 24.98%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.11 (t, 3H, CH_3, $J = 6$ Hz); 3.50–3.59 (q, 2H, CH_2, $J = 6.6$ Hz); 3.90 (s, 2H, CH_2); 7.53–7.65 (m, 5H, $5CH_{ar}$); 8.94 (s, 1H, CH); 8.30, 9.32, 10.25 (3s, 3H, 3NH). ^{13}C-NMR: 14.6 (CH_3); 34.1 (—S—CH_2—); 38.6 (—CH_2—CH_3); 125.3, 129.7, 129.9 ($3\times CH_{ar}$); 133.1 (C_{ar}); 145.5 ($CH_{triazole}$); 149.5 (—N=C—S—); 166.7 (C=O); 181.2 (C=S). MS *m/e* (%): 336 (M^{+}, 1); 321 (0.5); 257 (3); 249 (2); 218 (20); 204 (7); 190 (6); 176 (100); 149 (7); 135 (5); 104 (10); 91 (18); 87 (24); 77 (30).

4-Ethoxycarbonylmethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl} thiosemicarbazide (3h). Yield: 2.57 g (65.2%). Temperature of reaction: 40°C for 12 h. m.p.: 109–112°C. For $C_{15}H_{18}N_6O_3S_2$ (394.47) calculated: C: 45.67%, H: 4.60%, N: 21.30%; found: C: 45.65%, H: 4.61%, N: 21.28%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.19 (t, 3H, CH_3, $J = 7.2$ Hz); 3.97 (s, 2H, CH_2); 4.07–4.14 (q, 2H, CH_2); 4.24 (d, 2H, CH_2); 7.46–7.65 (m, 5H, $5CH_{ar}$); 8.91 (s, 1H, CH); 8.86, 9.68, 10.46 (3s, 3H, 3NH).

4-Ethoxycarbonyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide (3i). Yield: 2.85 g, (75.1%). Temperature of reaction: 45°C for 12 h. m.p.: 172–174°C. For $C_{14}H_{16}N_6O_3S_2$ (380.44) calculated: C: 44.16%, H: 4.23%, N:

22.08%; found: C: 44.15%, H: 4.21%, N: 22.07%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.23 (t, 3H, CH_3, J = 6.9 Hz); 4.09 (s, 2H, CH_2); 4.14–4.21 (q, 2H, CH_2, J = 6.9 Hz); 7.51–7.64 (m, 5H, $5CH_{ar}$); 8.89 (s, 1H, CH); 9.96, 11.06, 11.37 (3s, 3H, 3NH).

Derivatives of 5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4a–4g, 4j)

General procedure. A mixture of thiosemicarbazide (**3a–3h**; 0.01 mol) and 20 mL of 2% aqueous solution of sodium hydroxide was refluxed for 2 h. Then, the solution was neutralized with diluted hydrochloric acid, and the formed precipitate was filtered off and crystallized from ethanol.

5-{[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4-phenyl-4*H*-1,2,4-triazole-3(2*H*)-thione (4a). Yield: 3.12 g, (85.3%). m.p.: 160–162°C. For $C_{17}H_{14}N_6S_2$ (366.46) calculated: C: 55.68%, H: 3.85%, N: 22.93%; found: C: 55.69%, H: 3.85%, N: 22.91%. IR (KBr, cm^{-1}): 3110 (CH_{ar}); 2918, 1458 (CH_{al}); 1608 (C=N); 1513 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.12 (s, 2H, CH_2); 7.25–7.58 (m, 10H, $10CH_{ar}$); 8.89 (s, 1H, CH); 13.83 (s, 1H, NH). ^{13}C-NMR: 27.8 (CH_2); 128.2, 129.1, 129.3, 129.5, 129.6, 129.7 ($6\times CH_{ar}$); 133.1 ($2\times C_{ar}$); 145.8 ($CH_{triazole}$); 147.1 (CH_2—C); 148.0 (C—S); 168.2 (C=S). MS *m/e* (%): 366 (M^+, 0.2); 266 (0.15); 222 (0.04); 190 (0.54); 176 (75); 149 (14); 135 (8); 104 (9); 91 (28); 77 (100).

5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole-3(2*H*)-thione (4b). Yield: 3.58 g, (90.1%). m.p.: 168–170°C. For $C_{18}H_{16}N_6OS_2$ (396.49) calculated: C: 54.48%, H: 4.06%, N: 21.19%; found: C: 54.48%, H: 4.08%, N: 21.17%. IR (KBr, cm^{-1}): 3095 (CH_{ar}); 2922, 1461 (CH_{al}); 1618 (C=N); 1515 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.81 (s, 3H, CH_3); 4.10 (s, 2H, CH_2); 7.03 (d, 2H, $2CH_{ar}$, 4-$CH_3OC_6H_4$, J = 9 Hz); 7.16 (d, 2H, $2CH_{ar}$, 4-$CH_3OC_6H_4$, J = 9 Hz); 7.35–7.59 (m, 5H, $5CH_{ar}$); 8.89 (s, 1H, CH); 13.77 (s, 1H, NH).

5-{[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4-(4-tolyl)-4*H*-1,2,4-triazole-3(2*H*)-thione (4c). Yield: 3.52 g, (92.7%). m.p.: 166–168°C. For $C_{18}H_{18}N_6S_2$ (380.49) calculated: C: 56.77%, H: 4.23%, N: 22.08%; found: C: 56.78%, H: 4.22%, N: 22.08%. IR (KBr, cm^{-1}): 3095 (CH_{ar}); 2922, 1459 (CH_{al}); 1610 (C=N); 1526 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.37 (s, 3H, CH_3); 4.10 (s, 2H, CH_2); 7.10–7.32 (dd, 4H, $4CH_{ar}$, 4-$CH_3C_6H_4$, J = 8.1 Hz); 7.34–7.58 (m, 5H, $5CH_{ar}$); 8.89 (s, 1H, CH); 13.80 (s, 1H, NH).

4-Benzyl-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4d). Yield: 3.61 g, (95.1%). m.p.: 130–132°C. For $C_{18}H_{16}N_6S_2$ (380.49) calculated: C: 56.77%, H: 4.23%, N: 22.08%; found: C: 56.77%, H: 4.22%, N: 22.07%. IR (KBr, cm^{-1}): 3088 (CH_{ar}); 2926, 1459 (CH_{al}); 1615 (C=N); 1529 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.31 (s, 2H, CH_2); 5.26 (s, 2H, CH_2); 7.19–7.56 (m, 10H, $10CH_{ar}$); 8.90 (s, 1H, CH); 13.83 (s, 1H, NH).

4-Cyclohexyl-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4e). Yield: 3.32 g, (89.4%). m.p.: 102–104°C. For $C_{17}H_{20}N_6S_2$ (372.51) calculated: C: 54.76%, H: 5.38%, N: 22.55%; found: C: 54.75%, H: 5.37%, N: 22.55%. IR (KBr, cm^{-1}): 3100 (CH_{ar}); 2918, 1455 (CH_{al}); 1610 (C=N); 1527 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.06–1.75 (m, 10H, $5CH_2$); 3.58 (s, 2H, CH_2); 4.44 (s, 1H, CH); 7.37–7.64 (m, 5H, $5CH_{ar}$); 8.95 (s, 1H, CH); 13.95 (s, 1H, NH).

4-(4-Bromophenyl)-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4f). Yield: 3.72 g, (83.6%). m.p.: 147–149°C. For $C_{17}H_{13}BrN_6S_2$ (445.46) calculated: C: 45.8%, H: 2.93%, N: 18.86%; found: C: 45.8%, H: 2.92%, N: 18.88%. IR (KBr, cm^{-1}): 3088 (CH_{ar}); 2924, 1470 (CH_{al}); 1624 (C=N); 1527 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.14 (s, 2H, CH_2); 7.23 (d, 2H, $2CH_{ar}$, 4-BrC_6H_4, J = 8.7 Hz); 7.35–7.59 (m, 5H, $5CH_{ar}$); 7.72 (d, 2H, $2CH_{ar}$, 4-BrC_6H_4, J = 8.7 Hz); 8.89 (s, 1H, CH); 13.87 (s, 1H, NH). ^{13}C-NMR: 27.8 (CH_2); 125.4, 129.5, 129.7, 130.4, 132.3 ($5\times CH_{ar}$); 122.9, 132.4, 133.0 ($3\times C_{ar}$); 145.8 ($CH_{triazole}$); 147.0 (CH_2—C); 147.9 (C—S); 168.1 (C=S). MS *m/e* (%): 445 (M^+, 0.03); 366 (0.01); 287 (0.01); 268 (0.2); 257 (0.03); 213 (0.07); 190 (0.17); 176 (75); 149 (15); 135 (9); 104 (10); 91 (28); 77 (100).

4-Ethyl-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4g). Yield: 2.93 g, (94.5%). m.p.: 184–186°C. For $C_{13}H_{14}N_6S_2$ (318.42) calculated: C: 48.98%, H: 4.43%, N: 26.38%; found: C: 48.99%, H: 4.44%, N: 26.39%. IR (KBr, cm^{-1}): 3101 (CH_{ar}); 2922, 1463 (CH_{al}); 1612 (C=N); 1530 (C—N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.36 (t, 3H, CH_3, J = 9 Hz); 4.15–4.22 (q, 2H, CH_2, J = 7.2 Hz); 4.53 (s, 2H, CH_2); 7.37–7.61 (m, 5H, $5CH_{ar}$); 9.00 (s, 1H, CH); 13.63 (s, 1H, NH). ^{13}C-NMR: 13.1 (CH_3); 27.4 (—S—CH_2—); 38.5 (—CH_2—CH_3); 125.8, 129.6, 129.7 ($3\times CH_{ar}$); 133.1 (C_{ar}); 145.9 ($CH_{triazole}$); 147.3 (CH_2—C); 148.1 (C—S); 166.7 (C=S). MS *m/e* (%): 318 (M^+, 25); 302 (1); 290 (2); 258 (2.5); 218 (3); 204 (12); 190 (3); 176 (100); 149 (9); 135 (6); 104 (8); 91 (11); 77 (25).

4-Carboxymethyl-5-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl}-4*H*-1,2,4-triazole-3(2*H*)-thione (4j). Yield: 2.71 g, (77.8%). m.p.: 123–125°C. For $C_{13}H_{12}N_6O_2S_2$ (348.40) calculated: C: 44.81%, H: 3.47%, N: 24.12%; found: C: 44.82%, H: 3.47%, N: 24.11%. ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.26 (s, 2H, CH_2); 4.64 (s, 2H, CH_2); 7.35–7.62 (m, 5H, $5CH_{ar}$); 8.84 (s, 1H, CH); 10.52 (s, 1H, OH); 13.83 (s, 1H, NH).

[(4-Phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetic acid (5). Compound **5** was obtained using the same method described earlier for derivatives **4a–4g**, **4j**. That is, a mixture of thiosemicarbazide (**3i**; 0.01 mol) and 20 mL of 2% aqueous solution of sodium hydroxide was refluxed for 2 h. Then, the solution was neutralized with diluted hydrochloric acid and the formed precipitate was filtered off and crystallized from ethanol.

Yield: 1.88 g, (80.2%). m.p.: 184–186°C. For $C_{10}H_9N_3O_2S$ (235.26) calculated: C: 51.0%, H: 3.58%, N: 17.87%; found: C: 51.0%, H: 3.6%, N: 17.9%. ^{1}H-NMR (DMSO-d_6): 4.04 (s, 2H, CH_2); 7.49–7.64 (m, 5H, $5CH_{ar}$); 8.86 (s, 1H, CH); 12.91 (s, 1H, OH).

X-ray crystallography. Crystal data for compound **1**: space group, $P2_1/n$, a = 7.726(1) Å, b = 19.313(3) Å, c = 9.222(2) Å, β = 113.92(2)°, V = 1257.9(4) Å^3, Z = 4, d_{calc} = 1.390 g cm^{-3}, μ = 0.255 mm^{-1}.

A crystal with approximate dimensions of 0.41 × 27 × 0.14 mm^3 was mounted on a glass fiber in a random orientation. Single-crystal diffraction data were measured at room temperature in the ω/2θ mode on the Oxford Diffraction Xcalibur diffractometer using the graphite-monochromated MoK_α radiation. The stability of intensities was monitored by measurement of three standards for every 100 reflections. Crystal structure was solved by direct methods using SHELXS97 [20] and refined by the full-matrix least-squares on F^2 using the SHELXL97 [21]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were positioned geometrically and allowed to ride on their parent

atoms, with $U_{iso}(H) = 1.2\ U_{eq}(C)$. Final discrepancy factors are $R_1 = 0.0438$, $wR_2 = 0.0954$ for $I > 2\sigma(I)$, GOOF = 1.019, $\Delta\rho_{min,\ max} = -0.22/0.21$ e Å^{-3}.

Pharmacology. The experiments were carried out on male Albino-Swiss mice weighing 20–24 g. The animals were housed in colony cages with free access to food (standard laboratory pellets, Bacutil Motycz, Poland) and tap water and maintained in the natural light–dark cycle. The tested groups, consisting of eight animals, were randomly assigned. The experiments were performed between 8:00 a.m. and 2:00 p.m. The investigated compounds (**4a**, **4b**, **4e**, **4f**, and **4g**) were administered intraperitoneally (i.p.) in doses equivalent to 0.00625, 0.0125, 0.025, 0.05, and 0.1 of their LD_{50} as suspensions in 1% Tween 80 in a volume 10 cm^3/kg at 30 min before tests. Control mice received the equivalent volume of solvent. The Bioethical Committee of Lublin Medical University approved all experimental procedures applied in this study. The following behavioral tests were performed.

Chimney test. The effect of above investigated compounds in a dose of 0.1 of their LD_{50} on motoring impairment was quantified with the chimney test [22]. All animals were pertained 24 h before the test. The mice were inserted into a plastic tube (25 cm long, 3 cm in inner diameter). When the mouse reached the end, the tube was positioned upright, and motor impairment was indicated when the animal was unable to climb backward up the tube within 60 s. It was quantified as the percentage of animals that failed to complete the test.

Body temperature. The rectal body temperature in mice (Ellab thermometer) was recorded 15, 30, 45, 60, 90, and 120 min after the administration of the investigated compounds in a dose of 0.1 of their LD_{50}.

Hole board test. To determine the effects of the compounds on the explorative activity, the hole board test of Boissier *et al*. [23] was taken. The mice were placed on the board 30 min after administration of compounds in a dose of 0.1 of their LD_{50}. The number of holes explored was counted for 5 min.

Four plate test. Anxiolytic activity was measured by the ''four plate'' test in mice according to Aron *et al*. [24]. Thirty minutes after the injection of compounds in a dose of 0.1 of their LD_{50}, the number of punished crossings was counted for 1 min.

Passive avoidance task. The passive avoidance task is considered to be a measure of long-term memory in rodents [25]. On the first day, 30 min after injection of compounds in a dose of 0.1 of their LD_{50}, the animals were placed in an illuminated box (10 × 13 × 15 cm^3) connected to a dark box (25 × 20 × 15 cm^3), equipped with an electric grid floor. Having entered the dark box, the mice were punished by an electric foot shock (0.6 mA, 2 s). Animals not entering the dark box within 60 s were excluded from the subsequent experiment. The next day (24 h later), animals were again placed individually in the illuminated box and observed up to 3 min. The time from placement in the illuminated box to entry into the dark box was taken as an indication of the degree of long-term memory impairment. In the control group, the animals did not enter the dark compartment within 3 min.

Forced swimming test. Thirty minutes after the injection of compounds in a dose of their LD_{50}, the mice were individually placed and forced to swim in a glass cylinder (27 × 16 cm^2) containing 15 cm of water (25°C). A mouse was considered immobile when it floated in the water in an upright position and made only small movements to keep its head above water. The total immobility time of mice was measured during the last 4 min of the 6-min test [26].

Thiopental sleeping time. Thiopental (75 mg/kg i.p.) was given 30 min after the injection of the all compounds in a dose of 0.1 of their LD_{50}. The sleeping time of mice (from disappearance to return of the righting reflex) was measured.

Antinociceptive activity. Pain reactivity was measured by the writhing syndrome test in mice according to Witkin *et al*. [27]. Thirty minutes after the injection of compounds, **4a** (0.025–0.1 LD_{50}), **4b** (0.00625–0.1 LD_{50}), **4e** and **4f** (0.0125–0.1 their LD_{50}), **4g** (0.1 LD_{50}), the animals were injected with 0.6% acetic acid. The number of writhing episodes was counted for 30 min.

Pentetrazole-induced seizures. Thirty minutes after administration of compounds in a dose of 0.1 their LD_{50}, the animals were injected subcutaneously (sc) with pentetrazole (110 mg/kg) and were observed during 30 min. The number of mice developing clonic and tonic seizures as well as mortality was recorded in that period.

Head twitches. Head-twitch responses induced by L-5-hydroxytryptophan (L-5-HTP) were measured in mice according to Corne *et al*. [28]. The compounds in a dose of 0.1 of their LD_{50} were injected 30 min before L-5-HTP (165 mg/kg). The number of head-twitch episodes of mice was counted during 60 min after the injection of L-5-HTP.

Microbiology. The reference strains of ATCC, including six Gram-positive bacteria (*S. aureus* ATCC 25923, *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12220, *B. subtilis* ATCC 6633, *B. cereus* ATCC 10876, *M. luteus* ATCC 10240), four Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, and *Pseudomonas aeruginosa* ATCC 9027), and three strains of yeasts belonging to *Candida* spp. (*C. albicans* ATCC 10231, *C. albicans* ATCC 2091, *C. parapsilosis* ATCC 22019) were used.

Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of McFarland standard 0.5 (150 × 10^6 colony forming units per mL). All stock solutions of the tested compounds were dissolved in DMSO. The medium containing DMSO at the final concentrations and without any of tested compounds served as control, and no microbial growth inhibition was observed. Gentamicin and cefuroxime were used as control antimicrobial agents. Mueller-Hinton agar or Mueller-Hinton agar supplemented with 2% glucose was used for examination of antibacterial or antifungal activity, respectively.

In the first step, all tested compounds were screened for *in vitro* antimicrobial activity by the agar well diffusion method based on the appearance of the growth inhibition zone surrounding the well ($d = 8$ mm) containing the tested chemicals at 5000 mg/L concentration (80 μL/well separately). The sterile swabs were used to spread the microbial suspensions onto the medium surface. The plates were preincubated at room temperature for 1.5 h to allow the diffusion of solution into the medium and then were incubated at 37°C for 18 h (for bacteria) or at 30°C for 24–48 h (for fungi).

Subsequently, MIC of the compounds **3d**, **3f**, **3g**, and **3h**, showing some antibacterial activity using the agar well diffusion method, was estimated by microdilution technique [optical density $(OD)_{600}$] and Mueller-Hinton broth containing from 1.95 to 1000 mg/L of the tested agents. MIC is usually defined as the lowest concentration of compound at which there was no visible growth of tested microorganisms. Microdilution

broth technique was developed using 96-well microplates, which were inoculated with a 1:10 diluted microbial suspension of optical density of 0.5 McFarland standard. About 20 μL of bacterial suspension was put into 180 μL of medium containing twofold dilution of the tested compounds. After incubation (at 37°C for 18 h), the optical density (OD_{600}) measurements were determined for bacterial culture in broth medium, and the MIC values were determined by comparison with the bacterial growth in control (compound free) medium.

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Synthesis and Antifungal Evaluation of Novel Dicyanoderivatives of Rhodanine

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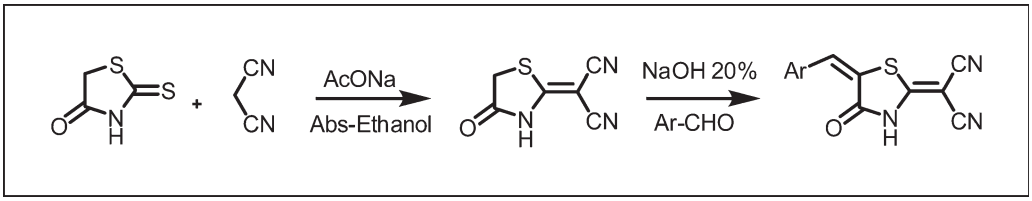

This work describes the synthesis and antifungal evaluation of 5-arylidene-(*Z*)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones **5** obtained from the reaction of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** and benzaldehydes **4**. The starting material **3** was synthesized by a condensation reaction of rhodanine **1** and malononitrile **2**. The structures of the obtained products were established by IR, NMR, mass spectrometry, and elemental analysis.

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INTRODUCTION

Rhodanine (2-thioxo-1,3-thiazolidin-4-one, **1**) has given place to a very important group of heterocyclic compounds for drug discovery programs. Arylidene derivatives of rhodanine have attracted great interest for the synthetic organic chemists because of the broad biological activities shown by these compounds, with demonstrated antiviral [1], antimicrobial [2], cardiac [3], anti-inflammatory [4], and antifungal activities [5]. Additionally, rhodanine derivatives can potentially be used in the treatment of diabetes, obesity, Alzheimer's disease, cystic fibrosis, thrombocytopenia, cancer, sleep, mood, and central nervous system disorders as well as chronic inflammation [6]. We have previously prepared some of these compounds to determine their antifungal activity [5(a)], and most recently [5(b)], arylidene derivatives containing the α,β-unsaturated carbonyl moiety have been used as bielectrophiles in cyclocondensation reactions with heterocyclic amines [7].

As an ongoing work, here we provide a simple and efficient method for the synthesis of new arylidene derivatives of rhodanine **5a–i**, by converting rhodanine into its dicyanoderivative **3** and its subsequent condensation reaction with aromatic aldehydes **4a–i** (Scheme 1).

RESULTS AND DISCUSSION

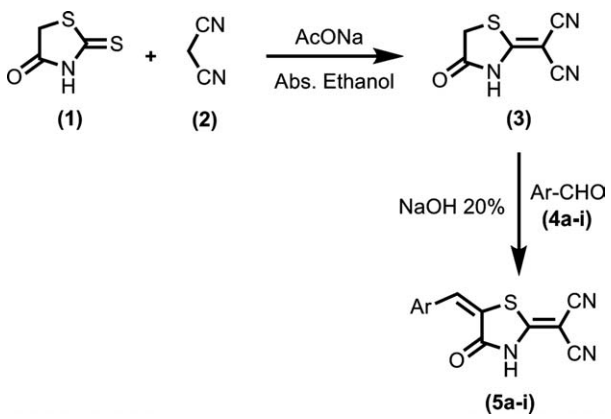
To prepare the 5-arylidene-(*Z*)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones **5a–i**, a mixture of equimolar amounts of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** and benzaldehydes **4a–i** and aqueous 20% sodium hydroxide (0.3 mL) and ethanol (10 mL) was stirred at room temperature during 12–20 h (Scheme 1, Table 1). The starting material **3** was prepared previously by the reaction of rhodanine **1**, malononitrile **2**, and sodium acetate in absolute ethanol.

The formation of compounds **5** as the unique reaction products was confirmed from the thin layer chromatography (TLC) monitoring and by their spectroscopic data (IR, 1D- and 2D NMR, high-resolution mass spectrometry, and elemental analysis).

Previously it has been reported that although arylalkylidenerhodanines may exist in both *Z* and *E* isomeric forms, the thermodynamically more stable *Z* isomer is the preferred [8–11]. In such reports, configuration on the exocyclic double bond was determined on the basis of NMR spectra. The ^{1}H-NMR signals of the methine-group hydrogens appeared in the range of 7.30–7.70 ppm for *Z* isomers and 6.60–7.10 ppm for *E* isomers. Our experimental NMR data showed the methine protons in the range 7.44–7.60 ppm, confirming that our compounds **5** were obtained in the single *Z* isomeric form.

The main vibration bands in the IR spectra for compounds **5a–i** correspond to: NH at 3401–3459 cm^{-1}, C≡N (only one band) at 2211–2220 cm^{-1}, and C=O at 1639–1671 cm^{-1}.

Scheme 1. Synthesis of dicyanoarylidenerhodanine derivatives **5**.



The ^{1}H- and ^{13}C-NMR spectra of products show that the number of protons and carbon atoms agrees with the proposed structures **5**. The NH signal is not observed in the ^{1}H-NMR spectra of all compounds **5**. For example, in the ^{1}H-NMR spectrum of compound **5c** (Fig. 1), it is observed a singlet at 7.50 ppm (1H) assigned to H-5′, and it is also observed two doblets at 7.61 and 7.57 ppm (2H) assigned to H*m* and H*o*, respectively, whereas the most relevant signals in the ^{13}C-NMR spectra correspond to the two CN groups at 116.8 and 118.2 ppm, the C-5′ carbon atom at 126.8 ppm, and the C=O function at 180.8 ppm. Moreover, the unambiguous assignment of the above signals was performed through HSQC and HMBC experiments.

On the other hand, compounds **5a–i** were tested for antifungal properties with the microdilution technique following the guidelines of Clinical and Laboratory Standards Institute against a panel of yeasts (*Candida albicans*, *Saccharomyces cerevisiae*, and *Cryptococcus neoformans*), *Aspergillus* spp. (*A. niger*, *A. fumigatus*, and *A. flavus*) and dermatophytes in a similar way as previously reported for some other rhodanine derivatives [5(a)].

Results showed that any of compounds **5** assayed displayed antifungal activity below of 250 μg/mL. These findings constitute an important data for our current purposes of structure–activity relationship (SAR) study on the antifungal properties of arylidenerhodanines. In fact, as we have reported previously, [5(a)] compounds **6a–d** (Fig. 2, Table 2) showed moderate to strong antifungal activity against yeasts, *Aspergillus* spp. as well as dermatophytes, being the clinically relevant *C. albicans* and *C. neoformans* particularly sensitive toward compounds **6b** and **6c** [5(a)]. Contrary to the observed above, any of the analog compounds **5a–d** displayed antifungal activity below of 250 μg/mL. This finding clearly indicates that the dicyano substituent in C-2 led to a loss of the antifungal activity of arylidenerhodanines.

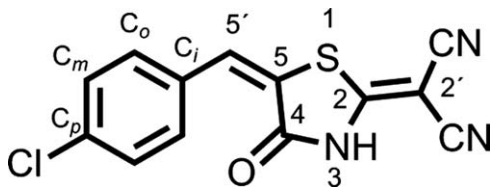


Figure 1. Numbering of structure **5c**.

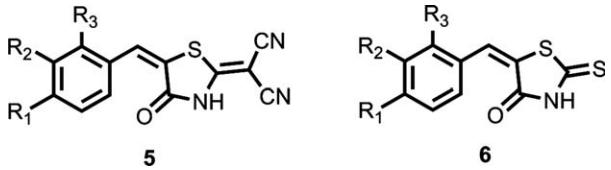


Figure 2. Structures of dicyanorhodanines **5** and rhodanines **6**.

CONCLUSIONS

In conclusion, we have developed a novel procedure to synthesize new dicyanoarylidenerhodanine derivatives, which were evaluated for antifungal properties against a panel of human opportunistic and pathogenic fungi with standardized procedures. Results demonstrated the versatility and high regioselectivity of the process and added interesting data for the SAR study on the arylidenerhodanine derivatives.

EXPERIMENTAL

General procedures. Melting points were taken in open capillaries on a Thomas Hoover melting point apparatus (Thomas Hoover Capillary Apparatus, Philadelphia, PA) and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and TMS as internal standard (Bruker BioSpin GmbH, Rheinstetten, Germany). High-resolution mass spectra (HRMS) were recorded in a Waters Micromass Auto-Spec NT spectrometer (Waters, Manchester, UK) (STIUJA, Servicios Técnicos de Investigación de la Universidad de Jaén).

Experimental procedures. ***Synthesis of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (3) [12].*** A mixture of rhodanine **1** (1 mmol), malononitrile **2** (1.2 mmol), sodium acetate (1.2 mmol), and absolute ethanol (15 mL) was refluxed for 12 h. The precipitate formed was filtered off and washed with water and ice-cooled ethanol. The solid was purified by recrystallization from ethanol, 74% yield; m.p. 225–227°C; IR (KBr) cm^{-1}, 3445 (N—H), 2212 and 2196 (2C≡N), 1647 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.79 (s, 2H, CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 39.2 (C-5), 46.4 (C-2′), 117.7 (C≡N), 119.0 (C≡N), 188.7 (C-2), 188.9 (C=O); HRMS (EI): $C_6H_3N_3OS$ requires: 164.9997. Found: 164.9998. Anal. Calcd. for $C_6H_3N_3OS$: C, 43.63; H, 1.83; N, 25.44. Found: C, 43.71; H, 1.87; N, 25.35.

General procedure for the synthesis of 5-arylidene-(Z)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones 5a–i. A mixture of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** (1 mmol), aldehyde **4** (1 mmol), ethanol (15 mL), and aqueous 20% sodium

Table 1

Synthesis of dicyanoarylidenerhodanine analogs **5**.

Entry	Compound	Ar	m.p. (°C)	Yield (%)	r.t. (h)[a]
1	**3**	–	225–227	74	12
2	**5a**	C_6H_5	334–336	45	13
3	**5b**	4-F—C_6H_4	323–325	85	15
4	**5c**	4-Cl—C_6H_4	341–343	60	20
5	**5d**	4-Br—C_6H_4	>350	85	18
6	**5e**	4-NO_2—C_6H_4	>350	80	14
7	**5f**	4-CH_3—C_6H_4	342–343	59	13
8	**5g**	4-OCH_3—C_6H_4	>350	63	13
9	**5h**	3,4,5-$(CH_3O)_3$—C_6H_2	343–345	74	16
10	**5i**	3,4-(OCH_2O)—C_6H_3	>350	81	18

[a] r.t.(h) refers to the reaction times in hours for the conversion of **3–5**.

hydroxide (0.3 mL) was stirred at room temperature for 12–20 h. The precipitate formed was filtered off, washed with water and ice-cooled ethanol. The solids were purified by recrystallization from ethanol.

*(Z)-5-Benzylidene-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5a**)*. This compound was obtained according to general procedure as a yellow powder, 45% yield; m.p. 334–336°C; IR (KBr) cm^{-1}, 3459 (N—H), 2214 (2C≡N), 1651 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.52 (s, 1H, =CH), 7.59 (d, 2H, J = 7.63 Hz, H*o*), 7.52 (dd, 2H, J = 7.63, and 7.36 Hz, H*m*), 7.41 (t, 1H, J = 7.36 Hz, H*p*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.2 (C-2′), 116.9 (C≡N), 118.3 (C≡N), 128.2 (C-5′), 134.9 (C-5), 129.8 (C*o*), 130.0 (C*i*), 129.5 (C*m*), 129.6 (C*p*), 180.0 (C-2), 181.0 (C=O); HRMS (EI): $C_{13}H_7N_3OS$ requires: 253.0310. Found: 253.0320. Anal. Calcd. for $C_{13}H_7N_3OS$: C, 61.65; H, 2.79; N, 16.59. Found: C, 61.78; H, 2.84; N, 16.67.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-fluorobenzylidene)-1,3-thiazol-4-one (**5b**)*. This compound was obtained according to general procedure as a yellow powder, 85% yield; m.p. 323–325°C; IR (KBr) cm^{-1}, 3456 (N—H), 2214 (2C≡N), 1656 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.51 (s, 1H, =CH), 7.65 (dd, 2H, J = 8.75, and 5.50 Hz, H*o*), 7.35 (dd, 2H, J = 8.75 Hz, and 7.35 Hz, H*m*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.2 (C-2′), 116.9 (C≡N), 118.3 (C≡N), 127.1 (C-5′), 131.5 (C-5), 132.2 (d, C*o*, $^3J_{C-F}$ = 8.7 Hz), 129.7 (C*i*), 116.7 (d, C*m*, $^2J_{C-F}$ = 21.9 Hz), 162.6 (d, C*p*, $^1J_{C-F}$ = 248.5 Hz), 179.9 (C-2), 181.0 (C=O); HRMS (EI): $C_{13}H_6FN_3OS$ requires: 271.0216. Found: 271.0208. Anal. Calcd. for $C_{13}H_6FN_3OS$: C, 57.56; H, 2.23; N, 15.49. Found: C, 57.65; H, 2.30; N, 15.40.

*(Z)-5-(4-Chlorobenzylidene)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5c**)*. This compound was obtained according to general procedure as a yellow powder, 60% yield; m.p. 341–343°C; IR (KBr) cm^{-1}, 3448 (N—H), 2215 (2C≡N), 1648 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.50 (s, 1H, =CH), 7.61 (d, 2H, J = 7.96 Hz, H*m*), 7.57 (d, 2H, J = 7.96 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 49.4 (C-2′), 116.8 (C≡N), 118.2 (C≡N), 126.8 (C-5′), 134.1 (C-5), 129.7 (C*o*), 130.7 (C*i*), 131.6 (C*m*), 133.8 (C*p*), 179.7 (C-2), 180.8 (C=O); HRMS (EI): $C_{13}H_6ClN_3OS$ requires: 286.9920. Found: 286.9923. Anal. Calcd. for $C_{13}H_6ClN_3OS$: C, 54.27; H, 2.10; N, 14.60. Found: C, 54.20; H, 2.02; N, 14.52.

*(Z)-5-(4-Bromobenzylidene)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5d**)*. This compound was obtained according to general procedure as a yellow powder, 85% yield; m.p. >350°C; IR (KBr) cm^{-1}, 3446 (N—H), 2218 (2C≡N), 1671 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.47 (s, 1H, =CH), 7.70 (d, 2H, J = 8.54 Hz, H*m*), 7.47 (d, 2H, J = 8.54 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.4 (C-2′), 116.8 (C≡N), 118.2 (C≡N), 126.8 (C-5′), 130.9 (C-5), 131.7 (C*o*), 122.8 (C*i*), 132.6 (C*m*), 134.2 (C*p*), 179.7 (C-2), 180.9 (C=O); HRMS (EI): $C_{13}H_6BrN_3OS$ requires: 330.9415. Found: 330.9458. Anal. Calcd. for $C_{13}H_6BrN_3OS$: C, 47.01; H, 1.82; N, 12.65. Found: C, 47.10; H, 1.89; N, 12.58.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-nitrobenzylidene)-1,3-thiazol-4-one (**5e**)*. This compound was obtained according to general procedure as a brown powder, 80% yield; m.p.

Table 2

Comparative antifungal activity (MICs in μg/mL) of compounds **6a–d** from Ref. 5(a) with their current dicyanoarylidenerhodanine analogs **5a–d**.

					MICs[a] (μg/mL) for compounds **6** [5a]			MICs (μg/mL) for compounds **5**
Entry	Compound	R_1	R_2	R_3	Yeasts	*Aspergillus* spp.	Dermatophytes	All fungi assayed
1	**6a/5a**	H	H	H	62.5–125	62.5–125	3.9–7.8	>250
2	**6b/5b**	F	H	H	7.8	250	7.8–32	>250
3	**6c/5c**	Cl	H	H	15.6–250	125–250	62.5	>250
4	**6d/5d**	Br	H	H	62.5–(>250)	>250	>250	>250

[a] Minimum inhibitory concentration.

>350°C; IR (KBr) cm^{-1}, 3406 (N—H), 2214 (2C≡N), 1661 (C=O), 1498, 1286 (NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.60 (s, 1H, =CH), 8.33 (d, 2H, J = 8.88 Hz, H*m*), 7.84 (d, 2H, J = 8.54 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 49.2 (C-2′), 116.5 (C≡N), 117.9 (C≡N), 125.6 (C-5′), 134.4 (C-5), 130.8 (C*o*), 141.5 (C*i*), 124.7 (C*m*), 147.2 (C*p*), 179.4 (C-2), 180.5 (C=O); HRMS (EI): $C_{13}H_6N_4O_3S$ requires: 298.0161. Found: 298.0159. Anal. Calcd. for $C_{13}H_6N_4O_3S$: C, 52.35; H, 2.03; N, 18.78. Found: C, 52.26; H, 1.98; N, 18.86.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-methylbenzylidene)-1,3-thiazol-4-one (**5f**).* This compound was obtained according to general procedure as a yellow powder, 59% yield; m.p. 342–343°C; IR (KBr) cm^{-1}, 3441 (N—H), 2213 (2C≡N), 1650 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 2.34 (s, 3H, CH_3), 7.47 (s, 1H, =CH), 7.48 (d, 2H, J = 8.04 Hz, H*m*), 7.32 (d, 2H, J = 8.04 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 21.5 (CH_3), 47.9 (C-2′), 117.0 (C≡N), 118.5 (C≡N), 128.3 (C-5′), 128.7 (C-5), 130.2 (C*o*), 139.7 (C*i*), 130.0 (C*m*), 132.1 (C*p*), 180.0 (C-2), 181.2 (C=O); HRMS (EI): $C_{14}H_9N_3OS$ requires: 267.0466. Found: 267.0461. Anal. Calcd. for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72. Found: C, 62.84; H, 3.31; N, 15.65.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-methoxybenzylidene)-1,3-thiazol-4-one (**5g**).* This compound was obtained according to general procedure as a yellow powder, 63% yield; m.p. > 350°C; IR (KBr) cm^{-1}, 3401 (N—H), 2212 (2C≡N), 1645 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.81(s, 3H, OCH_3), 7.47 (s, 1H, =CH), 7.54 (d, 2H, J = 8.76 Hz, H*o*), 7.08 (d, 2H, J = 8.76 Hz, H*m*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 55.8 (CH_3O), 47.6 (C-2′), 117.1 (C≡N), 118.6 (C≡N), 128.2 (C-5′), 127.2 (C-5), 131.7 (C*o*), 127.4 (C*i*), 115.2 (C*m*), 160.5 (C*p*), 179.9 (C-2), 181.3 (C=O); HRMS (EI): $C_{14}H_9N_3O_2S$ requires: 283.0415. Found: 283.0414. Anal. Calcd. for $C_{14}H_9N_3O_2S$: C, 59.35; H, 3.20; N, 14.83. Found: C, 59.28; H, 3.29; N, 14.76.

*(Z)-2-(1,1-Dicyanomethylene)-5-(3,4,5-trimethoxybenzylidene)-1,3-thiazol-4-one (**5h**).* This compound was obtained according to general procedure as a yellow powder, 74% yield; m.p. 343–345°C; IR (KBr) cm^{-1}, 3451 (N—H), 2220 (2C≡N), 1663 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.73 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.48 (s, 1H, =CH), 6.90 (s, 2H, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 56.5 (2OCH_3-*m*), 60.7 (OCH_3-*p*), 48.0 (C-2′), 117.0 (C≡N), 118.3 (C≡N), 128.6 (C-5′), 129.1 (C-5), 107.6 (C*o*), 130.6 (C*i*), 153.6 (C*m*), 139.2 (C*p*), 179.7 (C-2), 181.0 (C=O); HRMS (EI): $C_{16}H_{13}N_3O_4S$ requires: 343.0627. Found: 343.0615. Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.06; H, 3.90; N, 12.16.

*(Z)-2-(1,1-Dicyanomethylene)-5-(3,4-methylendioxybenzylidene)-1,3-thiazol-4-one (**5i**).* This compound was obtained according to general procedure as a yellow powder, 81% yield; m.p. > 350°C; IR (KBr) cm^{-1}, 3421 (N—H), 2211 (2C≡N), 1639 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 6.10 (s, 2H, —OCH_2O—), 7.44 (s, 1H, =CH), 7.12 (d, 1H, J = 1.64 Hz, H*o*), 7.14 (dd, 1H, J = 8.10 and 1.64 Hz, H*o*′), 7.05 (d, 1H, J = 8.10 Hz, H*m*′); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 47.7 (C-2′), 102.2 (OCH_2O), 117.0 (C≡N), 118.5 (C≡N), 128.3 (C-5′), 127.9 (C-5), 109.3 (C*o*), 125.0 (C*o*′), 129.2 (C*i*), 148.7 (C*m*), 109.4 (C*m*′), 148.5 (C*p*), 179.8 (C-2), 181.1 (C=O); HRMS (EI): $C_{14}H_7N_3O_3S$ requires: 297.0208. Found: 297.0204. Anal. Calcd. for $C_{14}H_7N_3O_3S$: C, 56.56; H, 2.37; N, 14.13. Found: C, 56.49; H, 2.30; N, 14.21.

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An Efficient One-Pot Synthesis of Pyrazolo[3,4-*b*]pyridinone Derivatives Catalyzed by L-Proline

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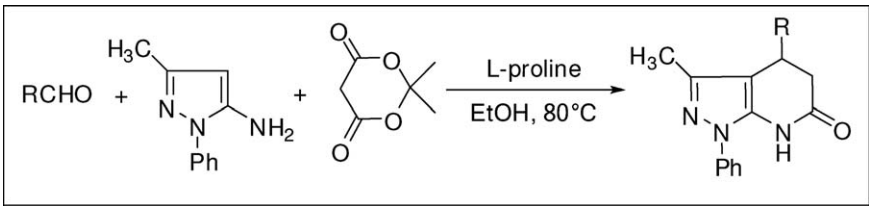

A series of 3-methyl-1,4-disubstituted-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-ones was synthesized *via* the three-component reaction of aldehyde, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and Meldrum's acid catalyzed by L-proline. This protocol has the advantages of easier work-up, milder reaction conditions, and high yields.

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INTRODUCTION

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, anti-inflammatory, and antitumor properties [1–4]. In particular, condensed pyrazoles are known for various biological activities, *e.g.*, pyrazolo[3,4-*b*]pyridines are useful for treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhaged stress, drug and alcohol withdrawal symptoms, drug addition, and infertility [5]. Pyrazolo[3,4-*b*]pyridine derivatives are generally prepared by reaction of 5-aminopyrazole and substituted α,β-unsaturated nitriles or benzylidene derivatives of Meldrum's acid in organic solvent (*i.e.*, ethanol) using triethylamine as catalyst [6–8], but most of them suffer from drawbacks such as lower yields, and using organic solvent.

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon bonds in synthetic chemistry [9]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus, avoiding the complicate purification operations and allowing savings of both solvents and reagents. In the past decade, there have been tremendous development in three- and four-component reactions and great efforts continue to be made to develop new MCRs [10,11].

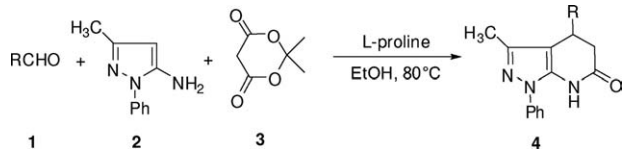
The replacement of current chemical process with more environmentally benign alternatives is an increasingly attractive goal in organic synthesis. Recently, organic reaction catalyzed by small organic molecules has been studied more and more extensively. A lot of small organic molecules, for instance, cinchona alkaloids, L-proline, and its derivatives have been used in various transformations with excellent yields [12,13]. Direct catalytic asymmetric aldol [14], Mannich [15,16], Michael [17–19], Diels–Alder [20], α-amination reactions [21], and Knoevenagel type reaction [22] using L-proline as catalyst have also been reported. Recently, L-proline and its derivatives have been used in multicomponent unsymmetric Biginelli [23,24] and Hantzsch reactions [25] and other MCR [26,27]. As a consequence of our interest in organic synthesis catalyzed by L-proline, we would like to describe a mild and highly efficient protocol for the synthesis of pyrazolo[3,4-*b*]pyridinone derivatives catalyzed by L-proline.

RESULTS AND DISCUSSION

When the mixture of aldehyde **1**, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2**, Meldrum's acid **3**, and catalytic amount of L-proline were stirred for 1–3 h at 80°C in ethanol solution, the desired products **4** were obtained in good yields (Scheme 1), and the results are summarized in Table 1.

As shown in Table 1, this protocol could be applied not only to the aromatic aldehydes with electron-withdrawing groups (such as halide and nitro groups) but also to aromatic aldehydes with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the electronic nature of the

Scheme 1



substituents of aromatic aldehydes has no significant effect on this reaction.

The structures of the compounds **4** were identified by their spectroscopy analysis. Thus, the infrared (IR) spectra of compounds **4** measured in potassium bromide pellets show one band of the elongation vibrations of the C=O group at 1678–1692 cm^{-1} and NH groups at 3112–3356 cm^{-1}. In the ^1H NMR spectra of compounds **4** measured in dimethyl-d_6 sulfoxide, the CH_3 proton signals at 1.76–2.07 ppm, the CH_2 proton signals at 2.58–2.75 and 2.96–3.43 ppm, the CH proton signals at 4.10–4.61 ppm, the NH proton signals at 10.30–10.69 ppm, and the aromatic proton signals at 6.64–8.22 ppm were observed.

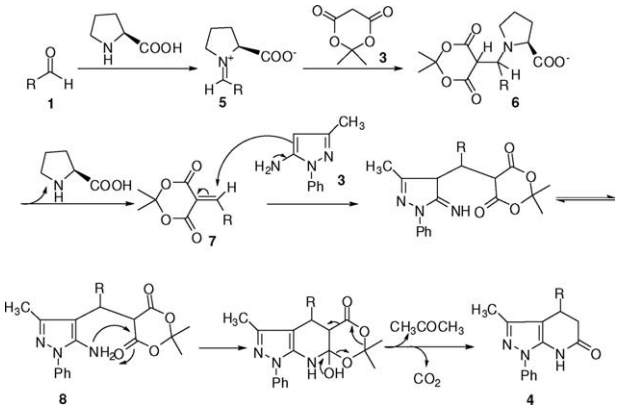
Although the detailed mechanism of above reaction remains not to be fully clarified, the formation of compounds **4** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded *via* a reaction sequence of condensation, addition, cyclization, and elimination. We suggest that L-proline catalyzes the formation of iminium ion **5** in a reversible reaction with aldehydes **1**. The higher reactivity of the iminium ion compared with the carbonyl species could facilitate Knoevenagel condensation between aldehydes **1** and Meldrum's acid **3** *via* intermediate **6**, and after the elimination of L-proline, **7** might be produced as an intermediate. Then, intermediate **7** is attacked *via* Michael addition of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** to give the intermediate **8**, which is followed by the cycloaddition and losing of acetone and carbon dioxide to form the desired products **4**.

Table 1

Synthesis of pyrazolo[3,4-*b*]pyridinone derivatives **4** catalyzed by L-proline.

Entry	R	Time (h)	Isolated yield (%)	Mp (°C)
4a	4-$CH_3OC_6H_4$	1.5	94	182–184
4b	4-ClC_6H_4	2	91	206–208
4c	4-$NO_2C_6H_4$	2	95	217–219
4d	4-BrC_6H_4	1.5	96	216–218
4e	2-Thiophenyl	2	92	153–155
4f	4-$(Me)_2NC_6H_4$	2	82	148–149
4g	2-ClC_6H_4	1.5	83	169–171
4h	2-NO_2-5-ClC_6H_3	1.5	93	228–229
4i	3-ClC_6H_4	2	98	127–129
4j	2,4-$Cl_2C_6H_3$	1	97	167–168
4k	2-$NO_2C_6H_4$	1.5	88	174–176
4l	3,4-$(MeO)_2C_6H_3$	2	86	140–141

Scheme 2



In conclusion, we have developed an efficient synthesis of 3-methyl-1,4-disubstituted-4,5-dihydro-1*H*-pyrazolo [3,4-*b*]pyridine-6(7*H*)-ones *via* the three-component reaction of aldehyde, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and Meldrum's acid catalyzed by L-proline. This protocol has the advantages of easier work up, milder reaction conditions, and high yields.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was determined on Varian-400 MHz spectrometer in dimethyl sulfoxide (DMSO)-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard tetramethylsilane (TMS). High resolution mass spectra (HRMS) data were obtained using time-of-flight mass spectrometry (TOF-MS) instrument.

General Procedure for the Synthesis of 3-methyl-1,4-disubstituted-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-ones 3. A dry 50 mL flask was charged with aldehyde **1** (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1 mmol), Meldrum's acid **3** (1 mmol), L-proline (0.1 mmol), and ethanol (2 mL). The mixture was stirred at 80°C for 1–3 h to complete the reaction [monitored by thin layer chromatography (TLC)] and then 50 mL H_2O was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give pure **4**.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4a). Mp: 182–184°C; IR (potassium bromide): 3135, 3043, 1678, 1596, 1513, 1340, 1257, 1183, 1024 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.88 (s, 3H, CH_3), 2.61 (dd, J_1 = 4.8 Hz, J_2 = 15.6 Hz, 1H, CH_2), 2.97 (dd, J_1 = 7.2 Hz, J_2 = 15.6 Hz, 1H, CH_2), 3.72 (s, 3H, CH_3O), 4.16 (dd, J_1 = 4.8 Hz, J_2 = 7.2 Hz, 1H, CH), 6.88 (d, *J* = 8.8 Hz, 2H, ArH), 7.11 (d, *J* = 8.4 Hz, 2H, ArH), 7.34 (t, *J* = 7.2 Hz, 1H, ArH), 7.46–7.53 (m, 4H, ArH), 10.51 (s, 1H, NH). HRMS [Found: *m/z* 333.1476 (M^+); Calcd for $C_{20}H_{19}N_3O_2$: M 333.1477].

4-(4-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4b). Mp: 206–208°C (209–210°C; ref. [8]); IR (potassium bromide): 3142, 3050, 1684, 1595, 1546, 1495, 1385, 1328, 1170, 1085, 1013 cm^{-1}; ^1H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.64 (dd, $J_1 = 4.8$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 3.03 (dd, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.26 (dd, $J_1 = 4.8$ Hz, $J_2 = 6.8$ Hz, 1H, CH), 7.23 (d, $J = 8.4$ Hz, 2H, ArH), 7.35 (t, $J = 7.2$ Hz, 1H, ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH), 7.47–7.54 (m, 4H, ArH), 10.57 (s, 1H, NH).

3-Methyl-4-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4c). Mp: 217–219°C (223–224°C; ref. [8]); IR (potassium bromide): 3112, 2998, 1688, 1595, 1516, 1496, 1384, 1352, 1175, 1119 cm^{-1}; ^1H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.69 (dd, $J_1 = 4.8$ Hz, $J_2 = 16.0$ Hz, 1H, CH_2), 3.11 (dd, $J_1 = 7.6$ Hz, $J_2 = 16.0$ Hz, 1H, CH_2), 4.45 (dd, $J_1 = 4.4$ Hz, $J_2 = 8.0$ Hz, 1H, CH), 7.36 (t, $J = 6.8$ Hz, 1H, ArH), 7.49–7.55 (m, 6H, ArH), 8.22 (d, $J = 8.4$ Hz, 2H, ArH), 10.65 (s, 1H, NH).

4-(4-Bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4d). Mp: 216–218°C; IR (potassium bromide): 3143, 3048, 1683, 1596, 1545, 1496, 1457, 1327, 1169, 1070 cm^{-1}; ^1H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.63 (dd, $J_1 = 4.4$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 3.43 (dd, $J_1 = 6.8$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.25 (dd, $J_1 = 5.2$ Hz, $J_2 = 6.4$ Hz, 1H, CH), 7.17 (d, $J = 8.0$ Hz, 2H, ArH), 7.35 (t, $J = 7.6$ Hz, 1H, ArH), 7.47–7.54 (m, 6H, ArH), 10.57 (s, 1H, NH); HRMS [Found: *m/z* 381.0474 (M^+); Calcd for $C_{19}H_{16}^{79}BrN_3O$: M 381.0477].

3-Methyl-1-phenyl-4-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4e). Mp: 153–155°C; IR (potassium bromide): 3141, 3051, 1692, 1598, 1563, 1500, 1364 cm^{-1}; ^1H NMR (DMSO-d_6): 2.07 (s, 3H, CH_3), 2.73 (dd, $J_1 = 2.8$ Hz, $J_2 = 15.2$ Hz, 1H, CH_2), 3.11 (dd, $J_1 = 6.8$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.52 (dd, $J_1 = 3.2$ Hz, $J_2 = 6.8$ Hz, 1H, CH), 6.90 (d, $J = 2.4$ Hz, 1H, ArH), 6.97 (t, $J = 4.8$ Hz, 1H, ArH), 7.34–7.38 (m, 2H, ArH), 7.47–7.53 (m, 4H, ArH), 10.60 (s, 1H, NH). HRMS [Found: *m/z* 309.0937 (M^+); Calcd for $C_{17}H_{15}N_3OS$: M 309.0936].

4-(4-(Dimethylamino)phenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4f). MP: 148–149°C; IR (potassium bromide): 3143, 3054, 1687, 1601, 1521, 1355, 1226, 1071 cm^{-1}; ^1H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.60 (dd, $J_1 = 4.4$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 2.86 (s, 6H, 2 × CH_3), 2.96 (dd, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.10 (t, $J = 6.0$ Hz, 1H, CH), 6.69 (d, $J = 8.0$ Hz, 2H, ArH), 7.01 (d, $J = 8.4$ Hz, 2H, ArH), 7.34 (t, $J = 6.8$ Hz, 1H, ArH), 7.46–7.53 (m, 4H, ArH), 10.48 (s, 1H, NH). HRMS [Found: *m/z* 346.1794 (M^+); Calcd for $C_{21}H_{22}N_4O$: M 346.1794].

4-(2-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4g). Mp: 169–171°C; IR (potassium bromide): 3225, 3161, 3058, 1683, 1602, 1538, 1456, 1348, 1264, 1197, 1037 cm^{-1}; ^1H NMR (DMSO-d_6): 1.86 (s, 3H, CH_3), 2.61 (dd, $J_1 = 4.4$ Hz, $J_2 = 16.0$ Hz, 1H, CH_2), 3.11 (dd, $J_1 = 7.6$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.61 (dd, $J_1 = 4.4$ Hz, $J_2 = 7.6$ Hz, 1H, CH), 7.03 (dd, $J_1 = 4.0$ Hz, $J_2 = 6.0$ Hz, 1H, ArH), 7.28–7.32 (m, 2H, ArH), 7.37 (t, $J = 7.2$ Hz, 1H, ArH), 7.48–7.53 (m, 3H, ArH), 7.56 (d, $J = 7.6$ Hz, 2H, ArH), 10.65 (s, 1H, NH). HRMS [Found: *m/z* 337.0980 (M^+); Calcd for $C_{19}H_{16}^{35}Cl\ N_3O$: M 337.0982].

4-(5-Chloro-2-nitrophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4h). Mp: 228–229°C; IR (potassium bromide): 3356, 3065, 1692, 1598, 1501, 1457, 1345, 1202, 1169, 1104, 1068 cm^{-1}; ^1H NMR (DMSO-d_6): 1.79 (s, 3H, CH_3), 2.75 (dd, $J_1 = 6.0$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 3.12 (dd, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.70 (t, $J = 6.4$ Hz, 1H, CH), 7.33 (d, $J = 2.4$ Hz, 1H, ArH), 7.37 (t, $J = 7.2$ Hz, 1H, ArH), 7.50 (d, $J = 8.4$ Hz, 1H, ArH), 7.55 (t, $J = 8.0$ Hz, 3H, ArH), 7.65 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1H, ArH), 8.06 (d, $J = 8.8$ Hz, 1H, ArH), 10.69 (s, 1H, NH). HRMS [Found: *m/z* 382.0826 (M^+); Calcd for $C_{19}H_{15}^{35}Cl\ N_4O_3$: M 382.0833].

4-(3-Chlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4i). Mp: 127–129°C; IR (potassium bromide): 3230, 3154, 3053, 1688, 1598, 1559, 1501, 1479, 1355, 1224, 1161, 1073 cm^{-1}; ^1H NMR (DMSO-d_6): 1.91 (s, 3H, CH_3), 2.67 (dd, $J_1 = 4.0$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 3.05 (dd, $J_1 = 7.2$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 4.29 (t, $J = 6.0$ Hz, 1H, CH), 7.19 (d, $J = 7.2$ Hz, 1H, ArH), 7.27 (s, 1H, ArH), 7.32 (d, $J = 8.0$ Hz, 1H, ArH), 7.38 (t, $J = 7.6$ Hz, 2H, ArH), 7.50 (d, $J = 7.6$ Hz, 2H, ArH), 7.55 (d, $J = 8.4$ Hz, 2H, ArH), 10.60 (s, 1H, NH). HRMS [Found: *m/z* 337.0983 (M^+); Calcd for $C_{19}H_{16}^{35}Cl\ N_3O$: M 337.0982].

4-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4j). Mp: 167–168°C; IR (potassium bromide): 3203, 3061, 1692, 1603, 1540, 1500, 1464, 1380, 1200, 1163, 1103, 1048 cm^{-1}; ^1H NMR (DMSO-d_6): 1.88 (s, 3H, CH_3), 2.58 (dd, $J_1 = 3.6$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 3.12 (dd, $J_1 = 7.6$ Hz, $J_2 = 16.0$ Hz, 1H, CH_2), 4.58 (dd, $J_1 = 4.0$ Hz, $J_2 = 7.6$ Hz, 1H, CH), 7.03 (d, $J = 8.4$ Hz, 1H, ArH), 7.36–7.42 (m, 2H, ArH), 7.50 (d, $J = 8.0$ Hz, 1H, ArH), 7.55 (t, $J = 8.0$ Hz, 3H, ArH), 7.70 (s, 1H, ArH), 10.69 (s, 1H, NH). HRMS [Found: *m/z* 371.0589 (M^+); Calcd for $C_{19}H_{15}^{35}Cl_2N_3O$: M 371.0592].

3-Methyl-4-(2-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4k). Mp: 174–176°C; IR (potassium bromide): 3227, 3051, 1683, 1603, 1528, 1457, 1345, 1204, 1070 cm^{-1}; ^1H NMR (DMSO-d_6): 1.76 (d, $J = 12.4$ Hz, 3H, CH_3), 2.62–2.70 (m, 1H, CH_2), 3.08–3.17 (m, 1H, CH_2), 4.60–4.66 (m, 1H, CH), 7.27–7.39 (m, 2H, ArH), 7.47–7.56 (m, 5H, ArH), 7.64–7.70 (m, 1H, ArH), 7.94–7.99 (m, 1H, ArH), 10.68 (d, $J = 11.2$ Hz, 1H, NH). HRMS [Found: *m/z* 348.1224 (M^+); Calcd for $C_{19}H_{16}N_4O_3$: M 348.1222].

4-(3,4-Dimethoxyphenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (4l). Mp: 140–141°C; IR (potassium bromide): 3220, 3056, 1684, 1598, 1517, 1458, 1383, 1244, 1148, 1026 cm^{-1}; ^1H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.68 (dd, $J_1 = 3.6$ Hz, $J_2 = 15.6$ Hz, 1H, CH_2), 2.96 (dd, $J_1 = 7.2$ Hz, $J_2 = 16.0$ Hz, 1H, CH_2), 3.72 (s, 6H, 2 × OCH_3), 4.16 (t, $J = 5.2$, 1H, CH), 6.64 (d, $J = 8.4$ Hz, 1H, ArH), 6.87 (d, $J = 8.8$ Hz, 2H, ArH), 7.35 (t, $J = 6.8$ Hz, 1H, ArH), 7.47–7.54 (m, 4H, ArH), 10.50 (s, 1H, NH). HRMS [Found: *m/z* 363.1583 (M^+); Calcd for $C_{21}H_{21}N_3O_3$: M 363.1583].

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Synthesis of Some New Azole, Pyrimidine, Pyran, and Benzo/Naphtho[*b*]furan Derivatives Incorporating Thiazolo[3,2-*a*]benzimidazole moiety

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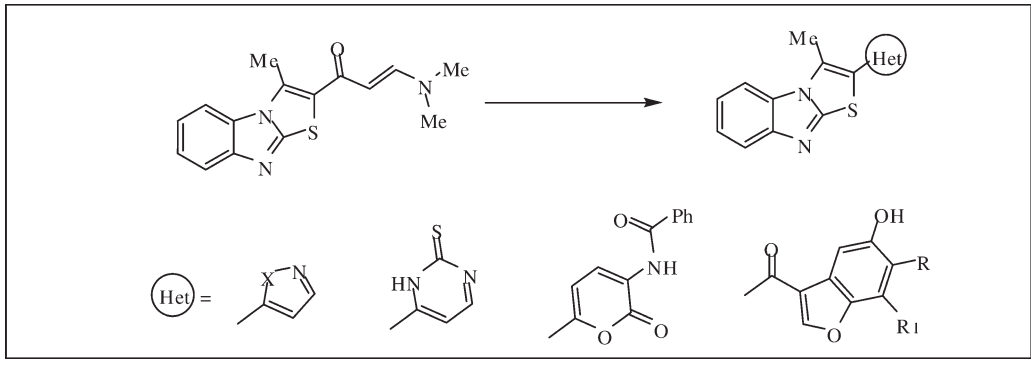

Reaction of *E*-3-(*N*,*N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**1**) with some *N*-nucleophiles, such as anilines **2a-c**, 4-amino-*N*-pyridin-2-yl-benzenesulfonamide (**4a**), 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (**4b**), hydrazine, hydroxylamine, thiourea, and guanidine afforded the corresponding arylaminoprop-2-en-1-one derivatives **3a-c**, **5a,b**, the pyrazole, isoxazole, pyrimidinethione and aminopyrimidine derivatives **7a**, **7b**, **9a**, and **9b**, respectively. The utility of compound **1**, as a versatile building block, for the synthesis of the pyranone **13**, benzo[*b*]furan **17a**, and naphtho[1,2-*b*]furan **17b** was also explored via its reaction with 2-benzamidoacetic acid (**10**), 1,4-benzoquinone (**14a**), and 1,4-naphthoquinone (**14b**), respectively.

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INTRODUCTION

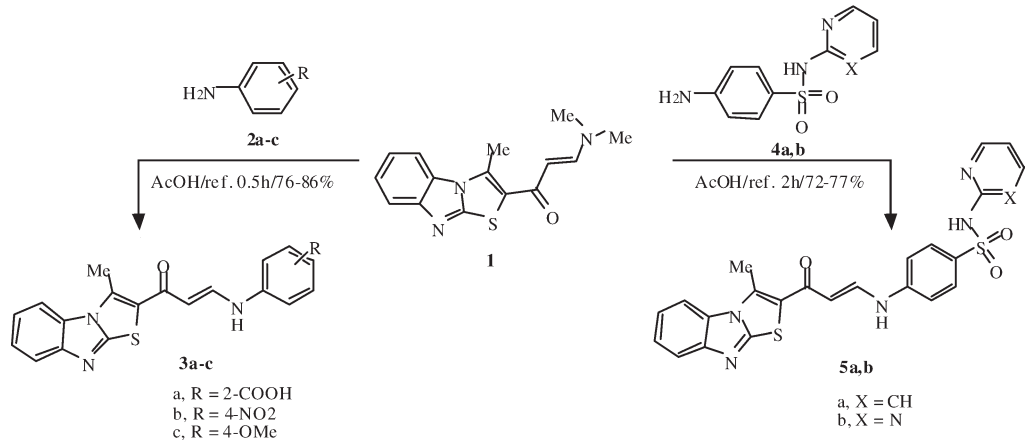
Thiazolo[3,2-*a*]benzimidazoles have been reported to possess interesting biological and pharmacological activities where several derivatives of this fused ring system are used as antibacterial [1–3], anti-inflammatory [4], antiulcer [5,6], and antiviral [7,8] agents. Moreover, certain thiazolo[3,2-*a*]benzimidazoles, such as 6-amino-*N*-cyclohexyl-*N*,3-dimethyl-thiazolo[3,2-*a*]benzimidazole-2-carboxamide (YM-298,198) has been reported as potent selective and noncompetitive metabotropic glutamate receptor type 1 (mGluR1) antagonist [9,10]. On the other hand, tilomisole (WY-18,251) was largely studied [11,12] demonstrating its anti-inflammatory [13] and immunomodulatory [14] activities. Additionally, the gastric antisecretory activity of thiazolo[3,2-*a*]benzimidazol-1-oxide (WY-26,769) was reported [15]. Also, some of these derivatives are used for treatment of cancer [16], cerebral infarction [17], neurogenic pain [18], and bone diseases [19].

As a part of our ongoing research program directed towards developing new approaches to a variety of heterocyclic ring systems for biological screening [20–37] specially those containing thiazolo[3,2-*a*]benzimidazole moiety [20,29,37], we report herein on the utility of *E*-3-(*N*,*N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**1**) [20] for the synthesis of title compounds.

RESULTS AND DISCUSSION

Recently, we have reported the synthesis of the enaminone **1** by the reaction of 1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)ethanone with [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (Gold's reagent) [20] or with dimethylformamide dimethylacetal (*DMF-DMA*) [29]. Treatment of **1** with aniline derivatives **2a-c** gave the corresponding acyclic secondary amines **3a-c** (Scheme 1). The structures of the

Scheme 1



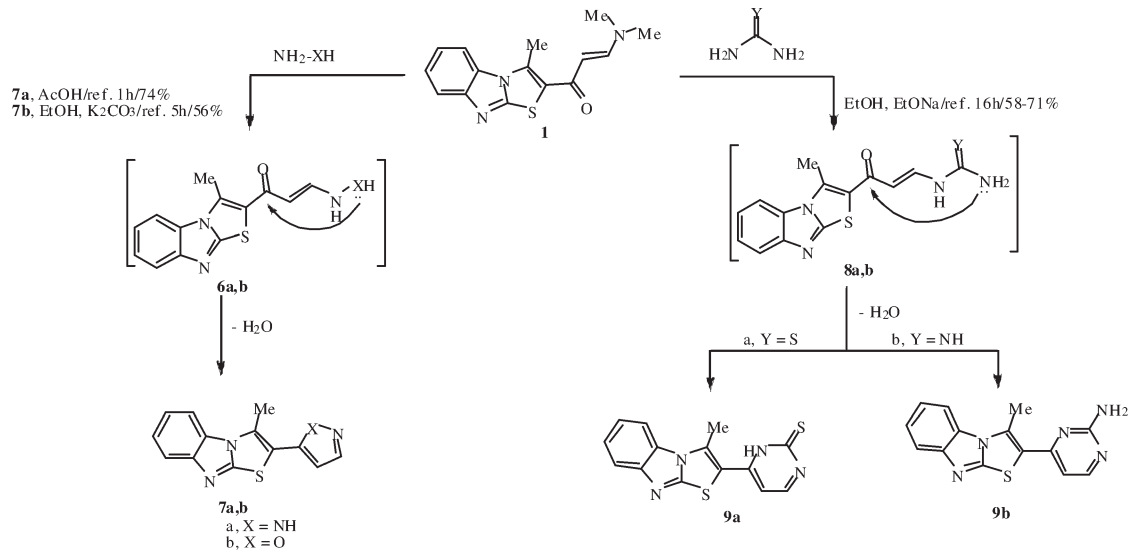
later products were assigned on the basis of their analytical and spectral data. For example, the IR spectra of the reaction products exhibited, in each case, NH absorption band in the region 3333–3179 cm^{-1}. Their mass spectra revealed, in each case, molecular ion peaks at the corresponding *m*/*z* value. The enaminone **1** reacted also with 4-amino-*N*-pyridin-2-yl-benzenesulfonamide (**4a**) and 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (**4b**), in refluxing acetic acid to afford the corresponding sulfonamide derivatives **5a**, and **5b**, respectively (Scheme 1). The IR spectra of the reaction products showed, in each case, two absorption bands corresponding to 2NH functions in the region 3233–3105 cm^{-1}, in addition to a carbonyl absorption band in the region 1643–1639 cm^{-1}. Their mass spectra revealed, in each case, a peak corresponding to the molecular ion and their ^{1}H NMR spectra were free of signals characteristic for the dimethylamino protons [*cf.* Experimental part].

The enaminone **1** reacted also with hydrazine and afforded a white product that was identified as 3-methyl-2-(2*H*-pyrazol-3-yl)thiazolo[3,2-*a*]benzimidazole (**7a**) (Scheme 2). The ^{1}H-NMR spectrum of later product revealed a pair of doublet signals duo to pyrazole protons at δ 6.65 and 7.62 with $J = 2.4$ Hz, in addition to D_2O-exchangeable broad singlet at δ 13.82 due to pyrazole NH proton.

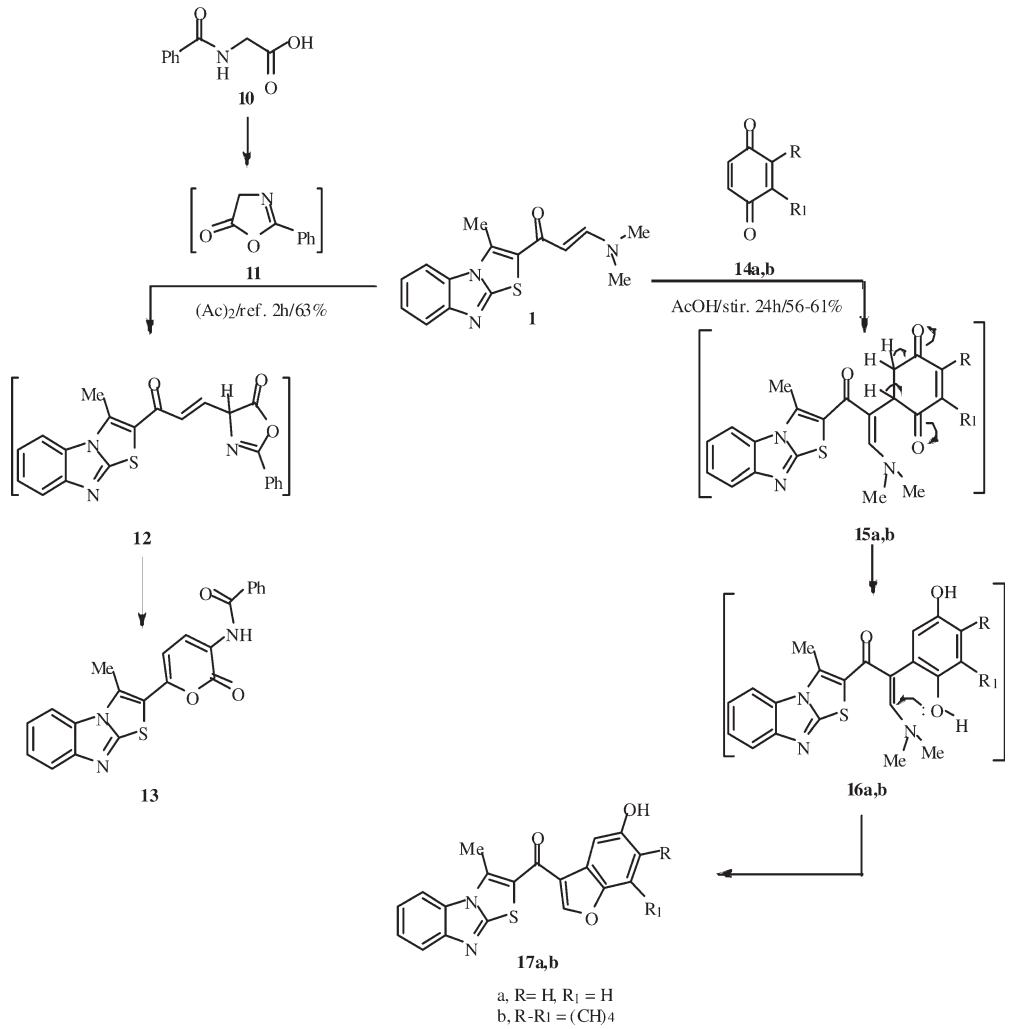
When compound **1** was treated with hydroxylamine in refluxing ethanol, it afforded a single product identified as 2-(isoxazol-5-yl)-3-methylthiazolo[3,2-*a*]benzimidazole (**7b**) (Scheme 2).

Treatment of compound **1** with thiourea in refluxing ethanol, in the presence of sodium ethoxide, afforded the pyrimidine-2-thione derivative **9a** (Scheme 2). Compound **9a** is assumed to be formed *via* the addition of the NH_2 group of thiourea to the activated exocyclic double bond in compound **1** with subsequent elimination

Scheme 2



Scheme 3



of dimethylamine molecule to give the nonisolable intermediate **8a**, which underwent intramolecular cyclization to form the final product **9a** *via* loss of a water molecule. Compound **1** reacted also with guanidine and gave the corresponding pyrimidine derivative **9b** (Scheme 2). The structures of compounds **9a** and **9b** were deduced from their elemental analyses and ^{1}H NMR data. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values [*cf*. Experimental part].

Treatment compound with 2-benzamidoacetic acid (**10**) in refluxing acetic anhydride led to the formation of *N*-[6-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)-2-oxo-2*H*-pyran-3-yl]benzamide (**13**) (Scheme 3). The ^{1}H NMR spectrum of compound **13** showed two doublets corresponding to pyran protons at δ 6.83 and 7.81 with $J = 7.8$ Hz, in addition to a broad D_2O-exchangeable signal at δ 9.61 due to NH proton. Compound **13** was assumed to be formed according to the following sequence; 2-benzamidoacetic acid (**10**) undergoes intramolecular cyclization *in situ* under the reaction conditions into the oxazolone intermediate **11**, which then reacts with the enaminone **1**, yielding the nonisolable intermediate **12**, that further rearranges into the final pyranone structure **13** (Scheme 3).

When the enaminone **1** was treated with *p*-benzoquinone (**14a**) in acetic acid at room temperature, it afforded a single product that was formulated as the benzo[*b*]furan derivative **17a** on the basis of its elemental analysis and spectral data. For example, its IR spectrum showed a broad band at 3475 cm^{-1} due to OH group and revealed a carbonyl absorption band at 1636 cm^{-1}. Its ^{1}H NMR spectrum showed a characteristic downfiled singlet signal at δ 8.90 due to the furan ring proton and revealed a broad D_2O-exchangeable signal at δ 9.55 due to OH proton. Compound **17a** is suggested to be formed *via* an initial addition of the electron-rich C2 of the enaminone **1** to the activated electron-poor double bond of the quinone **14a** to form the

intermediate **16a**, which undergoes intramolecular cyclization into the final product *via* elimination of dimethylamine (Scheme 3).

In a similar manner, the enaminone **1** reacted with 1,4-naphthoquinone (**14b**) and afforded 2-(5-hydroxynaphtho[1,2-*b*]furan-3-oyl)-3-methylthiazolo[3,2-*a*]benzimidazole (**17b**) (Scheme 3).

The proposed reaction sequence of the enaminone **1** with *p*-benzoquinone (**14a**) and 1,4-naphthoquinone (**14b**) is analogous to Nenitzescu reaction of enaminones with quinones, which has proven to be highly efficient method for the synthesis of 5-hydroxyindole-based derivatives with a wide range of substituents at various positions of the ring system [38–49].

In conclusion, the utility of *E*-3-(*N,N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**1**) was explored, as a versatile synthon, in rapid and efficient experiments for the synthesis of the title compounds from simple and accessible materials.

EXPERIMENTAL

Melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were obtained from the microanalytical unit, Cairo University, Cairo, Egypt, their results were found to be in good agreement with the calculated values. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in deuterated dimethylsulfoxide [D_6] DMSO. Mass spectra were measured on a Varian MAT CH-5 spectrometer (70 eV). *E*-3-(*N,N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**1**) [20,29] was prepared according to reported methods. 4-Amino-*N*-(pyridin-2-yl)benzenesulfonamide (**4a**), 4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide (**4b**), 2-benzamidoacetic acid (**10**), 1,4-bezoquinone (**14a**), and 1,4-naphthoquinone (**14b**) were obtained commercially.

General procedure for the synthesis of the enaminones 3a-c and 5a,b A mixture of *E*-3-(*N,N*-dimethylamino)-1-(3-methylthiazolo[3,2-*a*]benzimidazol-2-yl)prop-2-en-1-one (**1**) [20] (1.43 g, 5 mmol) and the appropriate amine [2-aminobenzoic acid (**2a**), 4-nitroaniline (**2b**), 4-methoxyaniline (**2c**), 4-amino-*N*-(pyridin-2-yl)benzenesulfonamide (**4a**) or 4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide (**4b**)] (5 mmol) in acetic acid (20 mL) was refluxed for 0.5 h (2 h in case of **4a** and **4b**). The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from DMF/H_2O afforded the corresponding derivatives **3a-c** and **5a,b**.

(E)-2-(3-(3-Methylbenzo[d]thiazolo[3,2-a]imidazol-2-yl)-3-oxoprop-1-enylamino)benzoic acid (3a). Yellow crystals, yield (76%); mp 290–292°C; IR (KBr) ν_{max}/cm^{-1}: 3450 (OH), 3115 (NH), 1693, 1630 (2C=O), 1605 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.01 (s, 3H, CH_3), 6.39 (d, 1H, J = 12.3 Hz, —CO—CH=), 7.27–8.14 (m, 9H), 10.84 (br. s, 1H, NH, D_2O-exchangeable) 11.96 (br. s, 1H, OH, D_2O-exchangeable); MS *m/z* (%): 378 (M$^+$+1, 16.4%), 377 (M$^+$, 100%), 240 (17.2%), 77 (8.5%). Anal. Calcd for $C_{20}H_{15}N_3O_3S$: C, 63.65; H, 4.01; N, 11.13; S, 8.50%. Found: C, 63.38; H, 3.92; N, 11.30; S, 8.73%.

(E)-1-(3-Methylbenzo[d]thiazolo[3,2-a]imidazol-2-yl)-3-(4-nitrophenylamino)prop-2-en-1-one (3b). Orange crystals, yield (86%); mp 270–272°C; IR (KBr) ν_{max}/cm^{-1}: 3124 (NH), 1643 (C=O), 1546 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.15 (s, 3H, CH_3), 6.38 (d, 1H, J = 12.0 Hz, —CO—CH=), 7.30–8.28 (m, 9H), 10.90 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 379 (M$^+$+1, 4.9%), 378 (M$^+$, 100%), 241 (18.2%), 135 (43.0%), 77 (7.4%). Anal. Calcd for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.73; N, 14.81; S, 8.47%. Found: C, 60.57; H, 3.49; N, 14.95; S, 8.33%.

(E)-3-(4-Methoxyphenylamino)-1-(3-methylbenzo[d]-thiazolo[3,2-a]imidazol-2-yl)prop-2-en-1-one (3c). Yellow fine crystals, yield (77%); mp 181–183°C; IR (KBr) ν_{max}/cm^{-1}: 3134 (NH), 1633 (C=O), 1569 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.12 (s, 3H, CH_3), 3.75 (s, 3H, —OCH_3), 6.1 (d, 1H, J = 12.3 Hz, —CO—CH=), 6.94–8.07 (m, 9H), 10.20 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 365 (M$^+$+2, 18.5%), 364 (M$^+$+1, 4.0%), 363 (M$^+$, 100%), 319 (53.5%), 242 (26.9%), 133 (30.9%), 77 (15.0%). Anal. Calcd for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56; S, 8.82%. Found: C, 65.84; H, 4.86; N, 11.54; S, 8.94%.

(E)-4-(3-(3-Methylbenzo[d]thiazolo[3,2-a]imidazol-2-yl)-3-oxoprop-1-enylamino)-N-(pyridin-2-yl)benzenesulfonamide (5a). Yellow fine crystals, yield (77%); mp 268–270°C; IR (KBr) ν_{max}/cm^{-1}: 3225, 3115 (2NH), 1628 (C=O), 1593 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.12 (s, 3H, CH_3), 6.24 (d, 1H, J = 12.3 Hz, —CO—CH=), 6.86–8.21 (m, 13H, 12 Ar—H), 10.50 (br. s, 1H, NH, D_2O-exchangeable), 11.70 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 490 (M$^+$+1, 5.7%), 489 (M$^+$, 7.2%), 240 (26.3%), 187 (43.8%), 184 (100%), 106 (18.4%). Anal. Calcd for $C_{24}H_{19}N_5O_3S_2$: C, 58.88; H, 3.91; N, 14.30; S, 13.10%. Found: C, 58.54; H, 3.73; N, 14.62; S, 13.33%.

(E)-4-(3-(3-Methylbenzo[d]thiazolo[3,2-a]imidazol-2-yl)-3-oxoprop-1-enylamino)-N-(pyridin-2-yl)benzenesulfonamide (5b). Yellow fine crystals, yield (72%); mp 277–279°C; IR (KBr) ν_{max}/cm^{-1}: 3233, 3105 (2NH), 1639 (C=O), 1578 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.13 (s, 3H, CH_3), 6.24 (d, 1H, J = 12.3 Hz, —CO—CH=), 7.03–8.52 (m, 12H), 10.50 (br. s, 1H, NH, D_2O-exchangeable), 11.69 (br. s, 1H, NH, D2O-exchangeable); MS *m/z* (%): 491 (M$^+$+1, 3.0%), 490 (M$^+$, 12.4%), 240 (16.8%), 186 (76.8%), 185 (100%), 150 (15.1%), 108 (29.9%), 92 (47.2%), 65 (70.8%). Anal. Calcd for $C_{23}H_{18}N_6O_3S_2$: C, 56.31; H, 3.70; N, 17.13; S, 13.07%. Found: C, 56.50; H, 3.53; N, 17.00; S, 12.88%.

3-Methyl-2-(2H-pyrazol-3-yl)thiazolo[3,2-a]benzimidazole (7a). A mixture of the enaminone (**1**) (1.43 g, 5 mmol) and hydrazine hydrate (1 mL, 99%) in acetic acid (20 mL) was refluxed for 1 h, then left to cool. The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from EtOH afforded the pyrazole derivative **7a** as white powder in 74% yield, mp 243–245°C; IR (KBr) ν_{max}/cm^{-1}: 3125 (NH), 1624 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.96 (s, 3H, CH_3), 6.65 (d, 1H, J= 2.4 Hz, pyrazole), 7.23–7.55 (m, 2H, Ar—H), 7.62 (D, 1H, J = 2.4 Hz, pyrazole), 7.7–8.03 (m, 2H, Ar—H), 9.82 (br. s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 256 (M$^+$+2, 28.1%), 255 (M$^+$+1, 100%), 254 (M$^+$, 50.4%), 65 (22.5%). Anal. Calcd for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03; S, 12.61%. Found: C, 61.64; H, 4.12; N, 21.85; S, 12.80%.

2-(Isoxazol-5-yl)-3-methylthiazolo[3,2-a]benzimidazole (7b). A mixture of the enaminone **1** (2.85 g, 10 mmol), hydroxylamine hydrochloride (10 mmol), and anhydrous potassium carbonate (0.5 g) in absolute ethanol (25 mL) was refluxed for 5 h, then left to cool. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, dried, and finally recrystallized from ethanol to afford the isoxazole derivative **7b** as white powder in 56% yield, mp 191–193°C; IR (KBr) ν_{max}/cm^{-1}: 1616 (C=N); ^1H NMR (DMSO-d_6): δ 3.01 (s, 3H, CH_3), 6.66 (d, 1H, J = 2.7 Hz, isoxazole), 7.24–7.7.57 (m, 2H, Ar—H), 7.68 (d, 1H, J = 2.7 Hz, isoxazole), 7.73–8.01 (m, 2H, Ar—H); MS *m*/*z* (%): 256 (M^++1, 3.6%), 255 (M^+, 100%), 240 (45.2%), 118 (M^+, 16.4%). Anal. Calcd for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46; S, 12.56%. Found: C, 61.40; H, 3.53; N, 16.67; S, 12.38%.

Reaction of 1 with thiourea and guanidine. The enaminone **1** (2.85 g, 10 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and absolute ethanol (50 mL)] then thiourea (0.076 g, 10 mmol) or guanidine nitrate (0.12 g, 10 mmol) was added. The reaction mixture was refluxed for 16 h, then left to cool and poured into crushed ice and neutralized with diluted hydrochloric acid in case of thiourea. The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from EtOH/DMF afforded the pyrimidine derivatives **9a** and **9b**, respectively.

6-(3-Methylthiazolo[3,2-a]benzimidazol-2-yl)pyrimidine-2(1H)-thione (9a). Yellow crystals, yield (71%); mp 266–268°C; IR (KBr) ν_{max}/cm^{-1}: 3190 (NH), 1608 (C=N); ^1H NMR (DMSO-d_6): δ 3.04 (s, 3H, CH_3), 7.12–8.08 (m, 6H, Ar—H), 8.65 (br. s, 1H, NH, D_2O-exchangeable); MS *m*/*z* (%): 299 (M^++1, 4.2%), 298 (M^+, 14.0%), 240 (100%), 188 (11.3%), 118 (16.1%), 111 (5.8%), 56 (18.2%). Anal. Calcd for $C_{14}H_{10}N_4S_2$: C, 56.35; H, 3.38; N, 18.78; S, 21.49%. Found: C, 56.03; H, 3.44; N, 18.53; S, 21.20%.

2-Amino-4-(3-methylthiazolo[3,2-a]benzimidazol-2-yl)pyrimidine (9b). Yellow powder, yield (58%); mp >300°C; IR (KBr) ν_{max}/cm^{-1}: 3240, 3126 (NH_2), 1608 (C=N); ^1H NMR (DMSO-d_6): δ 3.02 (s, 3H, CH_3), 6.75 (br. s, 2H, NH, D_2O-exchangeable), 7.20–8.07 (m, 6H, Ar—H); MS *m*/*z* (%): 283 (M^++2, 3.1%), 282 (M^++1, 8.6%), 281 (M^+, 6.4%), 242 (100%), 188 (6.0%), 94 (3.3%), 51 (14.8%). Anal. Calcd for $C_{14}H_{11}N_5S$: C, 59.77; H, 3.94; N, 24.89; S, 11.40%. Found: C, 60.13; H, 3.68; N, 24.66; S, 11.25%.

N-[6-(3-Methylthiazolo[3,2-a]benzimidazol-2-yl)-2-oxo-2H-pyran-3-yl]benzamide (13). A solution of the enaminone **1** (2.85 g, 10 mmol) and 2-benzamidoacetic acid (**10**) (1.7 g, 10 mmol) in acetic anhydride (20 mL) was heated under reflux for 2 h. The reaction mixture was concentrated in *vacuo* and the solid product obtained upon cooling was filtered off, washed with water, and recrystallized from DMF/H_2O to afford the pyran derivative **13** as yellow powder in 63% yield, mp >300°C; IR (KBr) ν_{max}/cm^{-1}: 3109 (NH), 1717, 1670 (2C=O), 1628(C=N); ^1H NMR (DMSO-d_6): δ 3.03 (s, 3H, CH_3), 6.83 (d, 1H, J = 7.8 Hz, pyran), 7.31–7.74 (m, 5H, Ar—H), 7.81 (d, 1H, J = 7.8 Hz, pyran), 7.85–8.22 (m, 4H, Ar-H), 9.61 (br. s, 1H, NH, D_2O-exchangable); MS *m*/*z* (%): 402 (M^++1, 43.6%), 401 (M^+, 100%), 314 (46.1%), 264 (20.0%), 211 (42.8%), 109 (61%), 77 (34.5%). Anal. Calcd for $C_{22}H_{15}N_3O_3S$: C, 65.82; H, 3.77; N, 10.47; S, 7.99%. Found: C, 66.11; H, 3.91; N, 10.25; S, 8.07%.

General procedure for the synthesis of the furan derivatives 17a,b. To a stirred solution of the enaminone **1** (2.85 g, 10 mmol) in acetic acid (50 mL), 1,4-benzoquinone **14a** or 1,4-naphthoquinone **14b** (10 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated in *vacuo*, and solid product obtained was filtered off, washed with EtOH, dried and recrystallized from EtOH/DMF to afford the corresponding furan derivatives **17a** and **17b**, respectively.

a2-(5-Hydroxybenzofuran-3-oyl)-3-methylthiazolo[3,2-a]benzimidazole (17a). White powder, yield (61%); mp 268–270°C; IR (KBr) ν_{max}/cm^{-1}: 3475 (OH), 1636 (C=O), 1543 (C=N); ^{13}C NMR (DMSO-d_6): δ 14.9 (—CH_3), 106.3, 112.2, 112.6, 114.9, 118.7, 120.1, 121.2, 121.3, 124.3, 125.1, 130.2, 137.6, 148.3, 149.1, 153.9, 154.0, 154.9, 180.6 (C=O); ^1H NMR (DMSO-d_6): δ 3.01 (s, 3H, CH_3), 6.88–8.10 (m, 7H, Ar—H), 8.90 (s, 1H, furan), 9.55 (br. s, 1H, OH, D_2O-exchangeable); MS *m*/*z* (%): 349 (M^++1, 26.5%), 348 (M^+, 53.9%), 264 (18.0%), 201 (21.6%), 144 (100%), 118 (44.8%), 77 (65%). Anal. Calcd for $C_{19}H_{12}N_2O_3S$: C, 65.51; H, 3.47; N, 8.04; S, 9.20%. Found: C, 65.35; H, 3.35; N, 8.22; S, 9.04%.

2-(5-Hydroxynaphtho[1,2-b]furan-3-oyl)-3-methylthiazolo[3,2-a]benzimidazole (17b). White powder, yield (56%); mp 290–292°C; IR (KBr) ν_{max}/cm^{-1}: 3414 (OH), 1670 (C=O), 1620 (C=N); ^1H NMR (DMSO-d_6): δ 3.03 (s, 3H, CH_3), 7.31–8.29 (m, 9H, Ar—H), 8.99 (s, 1H, furan), 10.27 (br. s, 1H, OH, D_2O-exchangeable); MS *m*/*z* (%): 400 (M^++2, 18.1%), 399 (M^++1, 46.2%), 398 (M^+, 100%), 331 (68.5%), 245 (99%), 210 (37.6%), 98 (10.2%). Anal. Calcd for $C_{23}H_{14}N_2O_3S$: C, 69.33; H, 3.54; N, 7.03; S, 8.05%. Found: C, 69.62; H, 3.52; N, 6.86; S, 7.93%.

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A Convenient and Efficient Synthesis of Heteroaromatic Hydrazone Derivatives *via* Cyclization of Thiosemicarbazone with ω-Bromoacetophenone

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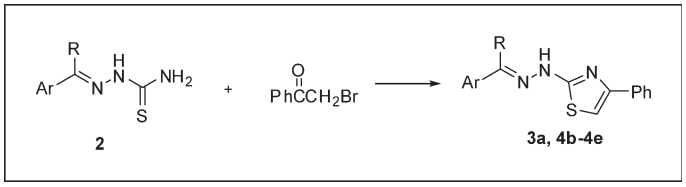

The synthesis of hydrazone derivatives containing thiazole unit was achieved with condensation of thiosemicarbazones and ω-bromoacetophenone at room temperature. This mild, convenient, and efficient method affords the desired products with good to excellent yields. Their structures have been determined by X-ray diffractional analysis, ^{1}H-NMR, MS, elemental analysis, and IR. Thiosemicarbazones were prepared by the condensation of thiosemicarbazide with aldehydes or ketones.

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INTRODUCTION

Thiosemicarbazones and their derivatives are important compounds in organic and medicinal chemistry due to their biological properties including antitumor [1], antifungal [2], antibacterial [3], antimalarial [4], antifilarial [5], antiviral, and anti-HIV activities [6]. Thiosemicarbazones, especially those derived from heteroaromatic aldehydes or ketones have been extensively studied. It is found that their structural pi-delocalization of charge and configurational flexibility of their molecular chain can give rise to a variety of reaction manners.

As part of our studies on thiocarbonyl chemistry [7], the reactivity of heteroaromatic aldehyde- and ketone-derived thiosemicarbazones were further investigated. Chemical compounds with biological activity are often derived from heterocyclic structures. Heterocycles are an important class of scaffolds that are found in natural products such as vitamins, hormones, antibiotics, as well as pharmaceuticals, herbicides, and dyes. Herein, we report an efficient and convenient method to synthesize a new class of thiosemicarbazones that contain thiazole heterocyclic ring. These novel compounds were expected to exhibit biological activity in the near future. The structures of products have also been fully characterized by infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance (^{1}H-NMR), mass spectrometry (MS), elemental analysis, and single-crystal X-ray diffraction analysis.

RESULTS AND DISCUSSION

Initially, thiosemicarbazones **2a** were synthesized by treating heterocyclic thioaldehydes **1a** with potassium hydroxide and an equimolar quantity of thiosemicarbazide in the cosolvent of anhydrous ethanol and dimethylsulfoxide (DMSO) [8]. The desired thiosemicarbazones **2b**–**2e** also can be readily formed under the acid or neutral condition. The results are summarized in Table 1.

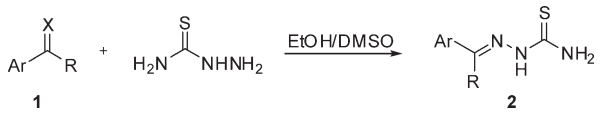
The structures of **2a**–**2e** were unambiguously characterized by spectroscopy (^{1}H-NMR, IR, and MS), elemental analysis, and further confirmed by X-ray diffractional analysis [9] of **2a**. The Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing and cell packing diagram are given in Figure 1.

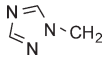
Subsequently, we treat heteroaromatic thiosemicarbazones **2a** with ω-bromoacetophenone in anhydrous ethanol. To our surprise, a novel compound (**3a**) with thiazole scaffold was formed. The reaction proceeds smoothly at room temperature and good yield (62%) was obtained. Single-crystal X-ray diffraction analysis [10] of **3a** was measured, and the ORTEP drawing and cell packing diagram are given in Figure 2.

Then, we examine whether the same reaction system can be applied to other heteroaromatic thiosemicarbazones (entries 2–5). It is found that both heteroaromatic aldehyde-derived and heteroaromatic ketone-derived thiosemicarbazones can be smoothly converted to the desired products with good to excellent yields (61–90%). The results were summarized in Table 2. It is

Table 1

Results of reactions of thiosemicarbazide with aldehydes, thioaldehydes, and ketones.



Entry	Ar	R	X	Solvent	Time (h)	Product	Yield (%)
1	2-Phenylindolizin-3-yl	H	S	EtOH/DMSO	6	**2a**	78
2	Furan-2-yl	H	O	EtOH/H_2O	2	**2b**	70
3	Thiophen-2-yl	H	O	EtOH/H_2O	5	**2c**	73
4	Indol-3-yl	H	O	EtOH/H_2O	3	**2d**	88
5	Phenyl		O	EtOH	4	**2e**	70

noteworthy that the present reaction was accomplished under mild conditions and the method is operationally simple with satisfactory yields. The structures of **3a, 4b–4e** have been characterized by spectroscopic (^{1}H-NMR, IR, and MS) and elemental analysis.

A plausible mechanism was proposed in Scheme 1. The bromine of ω-bromoacetophenone was substituted to form imide salt **5**. The protolysis reaction of **5** gave **6** followed by cyclization leading to 4-hydroxyl-4,5-dihydrothiazole salt **7**. The salt releases H_2O to afford thiazole salt **3a** and **4** followed by losing HBr to form thiazole ring. Since indolizinyl moiety has the strong conjugation ability, 3-formyl-2-phenylindolizine thiosemicarbazone (**2a**) can react with ω-bromoacetophenone to afford thiazole salt **3a**. When referred to other thiosemicarbazone (**2b–2e**), the final step is to release HBr to give products (**4b–4e**) with thiazole rings.

To conclude, in the present study, we report a convenient and efficient method to synthesize a series of novel thiosemicarbazone derivatives that contain thiazole heterocyclic ring. Given the fact that many thiosemicarbazone derivatives have exhibited biological activity, we anticipate that these new compounds described in the present report would be valuable for pharmaceutical research.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Nicolet FTIR 5DX spectrometer in KBr with absorption in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker ACF-300 spectrometer, *J* values are in hertz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. Mass spectra were obtained on a ZAB-HS mass spectrometer at 70 eV. Elemental analytical were performed on a Foss Heraeus CHN-O-Rapid analyzer.

Preparation of 3-formyl-2-phenylindolizine thiosemicarbazone (2a). A solution of 2-phenyl-3-thioformylindolizine (**1a**; 0.24 g, 1 mmol) and thiosemicarbazide (0.09 g, 1 mmol) in anhydrous ethanol (50 mL) was stirred, after adding potassium hydroxide (0.06 g, 1.1 mmol), DMSO (5 mL) was added dropwise. The mixture was refluxed at 80°C for 6 h [monitored by thin layer chromatography (TLC)], the resulting mixture was cooled and poured into ice water, filtered, purified by alumina chromatography eluted with the mixture of petroleum ether and ethyl acetate in gradient to afford **2a**.

General procedure for preparation of thiosemicarbazone (2b–2d). 'A solution of 2-formylfuran (**1b**; 0.29 g, 3 mmol) and thiosemicarbazide (0.27 g, 3 mmol) in 50% ethanol (20 mL) was stirred, 0.8-mL glacial acetic acid was added. The mixture was refluxed at 80°C for 2 h (monitored by TLC), the resulting mixture was cooled and poured into ice water, filtered, purified by recrystallization from anhydrous ethanol to afford **2b**. Under

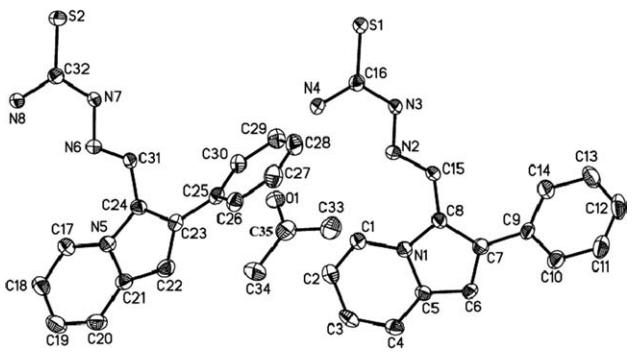


Figure 1. Molecular structure of **2a**.

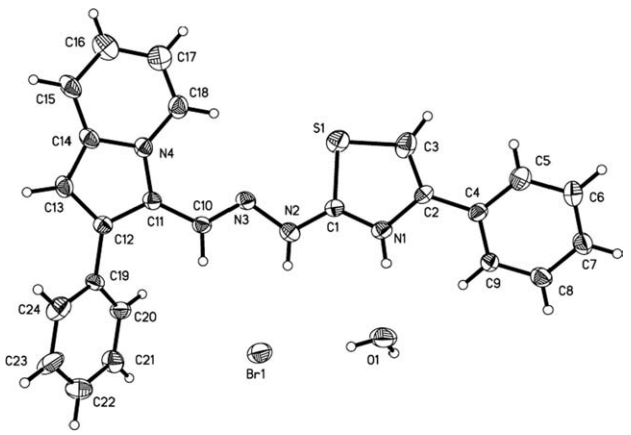
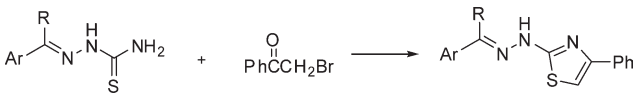


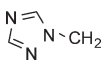
Figure 2. Molecular structure of **3a**.

Table 2

Reactions of heteroaromatic thiosemicarbazones **2** with ω-bromoacetophenone.



2 **3a, 4b-4e**

Entry	Ar	R	Time (min)	Product	Yield (%)
1	2-Phenylindolizin-3-yl	H	12	**3a**	62
2	Furan-2-yl	H	30	**4b**	87
3	Thiophen-2-yl	H	20	**4c**	66
4	Indol-3-yl	H	30	**4d**	90
5	Phenyl		30	**4e**	61

these conditions, reaction of **1b**–**1d** was similarly conducted to give the corresponding thiosemicarbazone **2b**–**2d**.

1-Phenyl-2-[1,2,4]triazol-1-ylethanone thiosemicarbazone (2e). A solution of 1-phenyl-2-[1,2,4]triazol-1-ylethanone (0.56 g, 3 mmol) and thiosemicarbazide (0.27 g, 3 mmol) in anhydrous ethanol (20 mL) was stirred, 0.2-mL glacial acetic acid and catalyst levels pyridine was added. The mixture was refluxed at 80°C for 4 h (monitored by TLC), the resulting mixture was cooled and poured into ice water, filtered, purified by recrystallization from anhydrous ethanol to afford **2e**.

General procedure for the cyclization of 2 and ω-bromoacetophenone to prepare 3a or 4b–4e. A solution of 2-phenyl-3-thioformylindolizine thiosemicarbazone **(2a**; 0.12 g, 0.40 mmol), ω-bromoacetophenone (0.085 g, 0.40 mmol) in anhydrous ethanol (10 mL) was stirred at room temperature, until all the thiosemicarbazone had disappeared (monitored by TLC). The deposit was filtered, purified by recrystallization from 95% ethanol to afford **3a**. Under these conditions, reaction of **2b**–**2e** was similarly conducted to give the corresponding cyclization compound **4b**–**4e**.

3-Formyl-2-phenylindolizine thiosemicarbazone (2a). Yellow crystals, Yield 78%, m.p. 155°C; IR (KBr): 3510, 3384, 3232, 3139, 3027.8, 1600, 1583, 1537, 1500, 1454, 1096, 834 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.41 (br, s, 1H, —NH_2), 6.67 (s, 1H, indolizin-3-yl C_1—H), 6.86–6.90 (m, 2H, indolizin-3-yl C_6—H, —NH_2), 7.04–7.10 (m, 1H, indolizin-3-yl C_7—H), 7.44–7.58 (m, 6H, Ph, indolizin-3-yl C_8—H), 8.10 (s, 1H, =CH—), 9.14 (s, 1H, —NH—), 9.21 (d, J = 7.0 Hz, 1H, indolizin-3-yl C_5—H). Anal. Calcd for $C_{16}H_{14}N_4S$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.45; H, 4.95; N, 19.10. MS (EI): *m*/*z* 276 (58.9), 249 (24.7), 218 (51.3), 193 (100), 165 (35.3), 115 (29.6), 83 (30.8), 51 (28.9).

2-Formylfuran thiosemicarbazone (2b). Yellowish brown crystals, yield 70%, m.p. 154–156°C (lit. 152–154°C) [8].

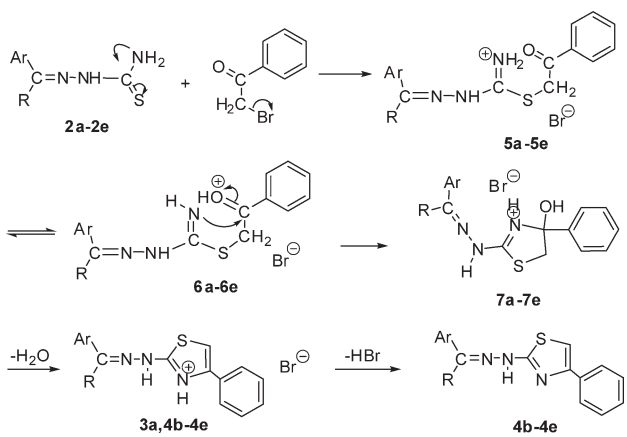
2-Formylthiophene thiosemicarbazone (2c). Light brown crystals, yield 73%, m.p. 184–186°C (lit. 185–186°C) [8].

3-Formyl-1H-indole thiosemicarbazone (2d). Light pink crystals, yield 88%, m.p. 232–234°C; IR (KBr): 3448, 3311, 3230, 3145, 3039, 1613, 1582, 1550, 1518, 1441, 1200, 751 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.10–7.21 (m, 2H, indol-3-yl C_6-H, indol-3-yl C_7—H), 7.42 (br, s, 1H, —NH_2), 7.43 (d, J = 7.9 Hz, 1H, indol-3-yl C_8—H), 7.82 (d, J = 2.7 Hz, 1H, indol-3-yl C_2—H), 8.03 (br, s, 1H, —NH_2), 8.23 (d, J = 7.7 Hz, 1H, indol-3-yl C_5—H), 8.31(s, 1H, =CH—), 11.18 (s, 1H, —NH—), 11.61 (s, 1H, indol-3-yl nitrogen proton). Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.04; H, 4.59; N, 25.69. Found: C, 55.10; H, 4.55; N, 25.62. MS (EI): *m*/*z* 218 (M^+, 2.4), 201 (16), 143 (61.2), 142 (100), 115 (28.9), 89 (10.9).

1-Phenyl-2-[1,2,4]triazol-1-ylethanone thiosemicarbazone (2e). Colorless crystals, yield 70%, m.p. 157–159°C ; IR (KBr): 3373, 3264, 3173, 3073, 2986, 1644, 1619, 1603, 1510, 1492, 1448, 1270, 844, 745, 676 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.73 (s, 2H, —CH_2—), 7.37–7.95 (m, 5H, PhH), 8.11 (s, 1H, —NH_2), 8.52 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 8.65 (s, 1H, —NH_2), 8.68 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 10.96 (s, 1H, —NH—). Anal. Calcd for $C_{11}H_{12}N_6S$: C, 50.77; H, 4.62; N, 32.31. Found: C, 50.85; H, 4.67; N, 32.30. ; MS (EI): *m*/*z* 243 (1.4), 178 (15.9), 103 (100), 77 (44.2), 69 (10.5).

N-(4-phenyl-thiazol-2-yl)-3-formyl-2-phenylindolizine hydrazone hydrobromic acid (3a). Green crystals, yield 62%, m.p. 122–124°C; IR (KBr): 3333, 2853, 1625, 1590, 1533, 1496, 1456, 764, 697 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H, indolizin-3-yl C_1—H), 6.90–7.01 (m, 1H, indolizin-3-yl C_6—H), 7.10–7.21 (m, 1H, indolizin-3-yl C_7—H), 7.37–7.88 (m, 12H, indolizin-3-yl C_8—H, phenyl and thiazole ring proton); 8.41 (s, 1H, =C—H), 9.31 (d, J = 8.2 Hz, 1H, indolizin-3-yl C_5—H), 12.61 (s, 1H, —NH—), 13.87 (s, 1H, —N^+H—). Anal. Calcd for $C_{24}H_{21}BrN_4OS$: C, 58.42; H, 4.26; N, 11.36. Found:

Scheme 1



C, 58.50; H, 4.42; N, 11.26. MS (EI): *m/z* 394 [(M-HBr-H_2O)$^+$, 2.9], 219 (92), 218 (100), 192 (2.2), 176 (96.6), 134 (56.6).

N-(4-phenyl-thiazol-2-yl)-2-formylfuran hydrazone (4b). Brownish yellow crystals, yield 87%, m.p. 136–138°C; IR (KBr): 3117, 3141, 3065, 1619, 1603, 1561, 1486, 760, 691 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.59–6.62 (m, 1H, furan-2-yl C_4—H), 6.81 (d, J = 3.3 Hz, 1H, furan-2-yl C_3—H), 7.23–7.93 (m, 9H, thiazole ring and phenyl proton, furan-2-yl C_5—H, =C—H, —NH—). Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.45; H, 4.09; N,15.61. Found: C, 62.53; H, 4.05; N,15.77. MS (EI): *m/z* 269 (M^+, 16.8), 176 (100), 134 (62.6).

N-(4-phenyl-thiazol-2-yl)-2-formylthiophene hydrazone (4c). Light brown crystals, yield 66%, m.p. 202–203°C; IR (KBr): 3302, 3099, 3055, 1602, 1561, 1521, 1505, 1490, 768, 748, 740, 722, 706, 683 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 1H, thiazole ring proton), 7.00–7.90 (m, 8H, thiophen-2-yl and phenyl proton), 7.97 (s, 1H, —CH=N—), 8.20 (br, s, 1H, —NH—). Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 58.95; H, 3.86; N, 14.74.Found: C, 59.01; H, 3.96; N, 14.65. MS (EI): *m/z* 285 (M^+, 15.8), 176 (100), 134 (83.5), 110 (4.4), 77 (2.5).

N-(4-phenyl-thiazol-2-yl)-2-formyl-1H-indole hydrazone (4d). Light purple crystals, yield 90%, m.p. 185–187°C; IR (KBr): 3292, 3103, 2943, 1625, 1608, 1574, 1531, 1491, 749, 735 675 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.15–7.52 (m, 8H, thiazole ring and phenyl proton, indol-3-yl C_6—H, indol-3-yl C_7—H), 7.78 (s, 1H, —NH—), 7.85–7.95 (m, 2H, indol-3-yl C_8—H, indol-3-yl C_2—H), 8.23–8.35 (m, 2H, indol-3-yl C_5—H, =CH—), 11.61 (s, 1H, indol-3-yl nitrogen proton). Anal. Calcd for $C_{18}H_{14}N_4S$: C, 67.92; H, 4.40; N, 17.61. Found: C, 67.93; H, 4.32; N, 17.66. MS (EI): *m/z* 318 (M^+, 0.5), 176 (100), 142 (59.6), 134 (38.4), 115 (7.4), 89 (5.2).

N-(4-phenyl-thiazol-2-yl)-ω-(1, 2, 4-triazol-1-yl)acetophenone hydrazone (4e) Light yellow crystals, yield 61%, m.p. 212–214°C; IR (KBr): 3165, 3096, 3081, 2656, 1598, 1583, 1503, 1444, 749, 688 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.74 (s, 2H, —CH_2—); 7.33–7.89 (m, 11H, thiazole ring and phenyl proton), 7.97 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 8.74 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton). Anal. Calcd for $C_{19}H_{16}N_6S$: C, 58.95; H, 3.86; N, 14.74. Found: C, 59.01; H, 3.96; N, 14.65. MS (EI): *m/z* 291 (22.7), 262 (18.8), 176 (9.4), 134 (59.9), 103 (100), 77 (66.5), 69 (13.9).

Acknowledgments. The authors are grateful to the National Natural Science Foundation of China (No. 20672090), the Six Kinds of Professional Elite Foundation of Jiangsu Province (No. 07-A-024), the Science and Technology Critical Project Foundation of Lianyungang Municipality (CG0803-2), and the Natural Science Foundation of Jiangsu Education Department (08KJB150002).

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[9] Crystal data for **2a**: $2(C_{16}H_{14}N_4S)\cdot C_2H_6CO$; M = 646, Yellow single crystals, 0.20 × 0.20 × 0.30 mm^3, triclinic, space group $P1$, a = 11.572 (8), b = 11.845 (8), c = 13.173 (8) Å, α = 92.56 (3), β = 110.61 (4), γ = 102.57 (4)°, V = 1635 (2) Å^3, Z = 2, D_c = 1.318 mg m^{-3}. F (000) = 682, μ (MoKα) = 0.206 mm^{-1}. Intensity data were collected on Bruker SMART APEX II with graphite monochromated MoKα radiation (λ = 0.71073 Å) using ω scan mode with 1.9° < θ < 25.0°. 5671 unique reflections were measured and 4302 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0533 and wR = 0.1168.

[10] Crystal data for **3a**: $C_{24}H_{21}BrN_4OS$; M = 493, Blackish green single crystals, 0.42 × 0.36 × 0.20 mm^3, monoclinic, space group $P2_1/n$, a = 6.1679 (12), b = 11.1657 (18), c = 32.640 (4) Å, α = 90, β = 91.708 (2), γ = 90°, V = 2246.9 (6) Å^3, Z = 4, D_x = 1.459 mg m^{-3}. F (000) = 1008, μ (MoKα) = 1.946 mm^{-1}. Intensity data were collected on Bruker SMART APEX II with graphite monochromated MoKα radiation (λ = 0.71073 Å) using ω scan mode with. 1.93° < θ < 25.01°. 3904 unique reflections were measured and 2795 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0661 and wR = 0.1554.

Green and Efficient Synthesis of Pyrazolo[3,4-*b*]quinolin-5-ones Derivatives by Microwave-Assisted Multicomponent Reaction in Hot Water Medium

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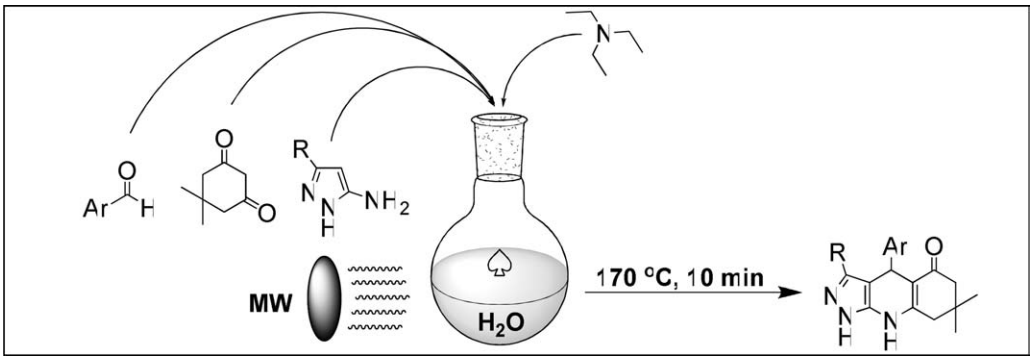


Novel simple, efficient, and eco-friendly synthetic procedure for preparation of pyrazolo[3,4-b]quinolin-5-ones based on three-component microwaves-assisted heterocyclization reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium was developed. The new method allows obtaining target heterocycles in good and excellent yields and with high degree of purity.

J. Heterocyclic Chem., **48**, 365 (2011).

INTRODUCTION

The concept of ''green chemistry'' is now widely adopted to meet the fundamental scientific challenges of protecting the human health and environment with simultaneously achieving commercial viability [1,2]. One of the key areas of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents.

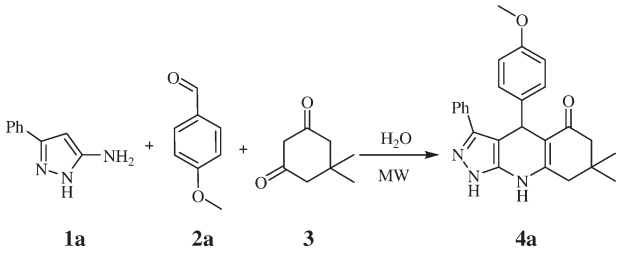
Among alternative media, water is very benign and, compared with organic solvents, is abundant, nontoxic, and eco-friendly. In many examples of ''aqueous reactions,'' organic cosolvents are employed to increase the solubility of organic reactants in water [3]. However, chemical processing in pure water is also possible under ''superheated conditions'' (>100°C) in sealed vessels, as the so-called near-critical water (150–300°C) possesses properties very different from those of ambient liquid water [4]. Therefore, water has become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of the expensive solvents but also for some unique reactivity and selectivity [5].

In the most chemical processes, major adverse effects toward the environment are due to the consumption of energy for heating. To overcome this problem, it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, to facilitate chemical reactions. Recently, the combination of these two prominent green chemistry principles, ''microwaves'' and ''water,'' has become very popular and received substantial interest [6].

Nitrogen-containing heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids as well as pharmaceuticals, herbicides, and dyes [7]. Developing efficient, selective, and eco-friendly synthetic methods for applications in complex organic preparations of heterocyclic compounds is the ultimate goal of several research groups. For example, there were reported green and efficient synthesis of several fused pyrimidine derivatives by microwave-assisted reactions in water [8], three-component, aqueous one-pot synthesis of fused pyrazoles [9(a)], synthesis of benzimidazoles in ''hot water'' [9(b)], environmentally benign aqueous microwave Biginelli protocol [10], and an approach to pyrano[2,3-c]pyrazoles in aqueous media [11].

Recently, much attention has been devoted to pyrazolo-annelated heterocycles because this fragment is a key moiety in numerous biologically active compounds,

Scheme 1



among them are prominent drug molecules such as Viagra, Celebrex, Analginum, and many others [12]. Interested in biological activity of a significant number of compounds containing condensed pyrazole ring system, in broad program of developing efficient, selective, and eco-friendly synthetic methods, we started exploring the use of water as reaction medium in combination with microwave irradiation as a useful, environmentally benign alternative.

Here, we report direct synthesis of well-known substituted pyrazolo[3,4-b]quinolin-5-ones using high-temperature water and microwave heating *via* one-pot three-component reaction of 3-substituted 5-aminopyrazols, aromatic aldehydes, and dimedone. In earlier publications [13], it was shown that direction of this treatment sufficiently depended on conditions and, thereby, such multicomponent reaction is a challenge object for development of eco-friendly synthetic methodology based on application of hot water medium.

RESULTS AND DISCUSSION

The algorithm of choosing appropriate reaction parameters, being of crucial importance for successful organic synthesis, includes search for optimal medium and catalytic system, temperature regime, reaction time, activation method, etc. To elaborate efficient microwave-assisted synthesis of target pyrazolo[3,4-b]quinolinones **4** in water medium the three-component reaction of 3-phenyl-1*H*-pyrazol-5-amine **1a**, 4-metoxybenzaldehyde **2a**, and dimedone **3** was selected as a model treatment for searching optimal reaction conditions (Scheme 1).

First, different types of acidic and basic catalysts were screened at the fixed temperature (130°C) and the constant microwave (MW) power of 375 W. It was established (Table 1) that multicomponent reaction of equimolar mixture of **1a**, **2a**, and **3** in water under MW heating was the most efficient in the presence of 1.2 equivalents Et_3N, whereas application of other basic or acidic catalysts gave worse results. Moreover, in the case of HOAc, HCl, NaOH, and K_2CO_3, a sufficient resinification of the reaction mixture was observed.

However, when the catalyst was absent, only starting materials were quantitatively isolated. To optimize the reaction temperature, the synthesis of **4a** was performed in water with 1.2 equivalents of Et_3N at 130–200°C with an increment of 10°C. It was established that within a range 130–170°C, the yield of quinolinone **4a** raised up with increasing the temperature (Table 2). The temperature growth allowed also shortening the reaction time from 15 to 10 min without influence on yield and purity. However, no significant changes in the yield of **4a** were observed, when the reaction temperature was raised from 170 to 200°C. Therefore, the temperature of 170°C was chosen as the most suitable to carry out the multicomponent reaction studied in the water medium.

Table 1

Screening of the catalyst type for the synthesis of **4a** (MW, H_2O, 130°C).

Entry	Catalyst	Time (min)	Yield (%)
1	None	10	40
2	HOAc	10	43
3	p-TSA	10	46
4	HCl	10	36
5	NaOH	10	30
6	K_2CO_3	10	42
7	Et_3N	10	65
8	Piperidine	10	55

With the application of the elaborated optimized reaction conditions (H_2O/Et_3N, MW, 170°C, 10 min), a 21-membered library of pyrazolo[3,4-*b*]quinolin-5-ones **4a–u** was easily synthesized by the three-component treatment of equimolar amounts of pyrazol-5-amines **1a–c**, aldehydes **2a–g**, and dimedone **3** (Scheme 2 and Table 3). The reaction products were isolated in good and excellent yields as stable crystalline solids.

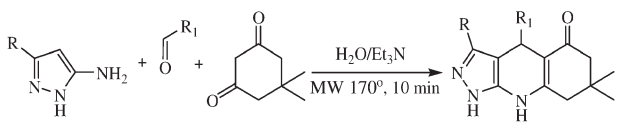
It was established that wide range of aromatic aldehydes containing diverse types of substituents can be efficiently used in the new microwave-assisted eco-friendly protocol to produce target heterocycles **4** in excellent yields and purity. However, when the aliphatic aldehydes were applied, no product of heterocyclization was isolated from the reaction mixture.

Table 2

Temperature optimization for the synthesis of **4a** (MW, H_2O).

Entry	*T* (°C)	Time (min)	Yield (%)
1	130	15	65
2	140	15	68
3	150	13	70
4	160	13	77
5	170	10	82
6	180	10	80
7	190	10	80
8	200	10	78

Scheme 2



1a-c **2a-g** **3** **4a-u**

CONCLUSION

Thus, the simple, efficient, and eco-friendly synthetic method was developed for preparation of pyrazolo[3,4-*b*]quinolin-5-ones by microwaves-assisted multicomponent heterocyclization reaction of 5-aminopyrazoles, aromatic aldehydes, and dimedone in hot-water medium in the presence of triethylamine. All target heterocyclic compounds were obtained in good to excellent yields and purity of >95%.

EXPERIMENTAL

The near-critical water microwave-assisted experiments were carried out in a MARS multimode reactor from CEM Corporation (Matthews, NC) equipped with fiber-optic temperature probe.

General procedure for the synthesis of 4a–u. Pyrazol-5-amine **1a–c** (1.0 mmol), aldehyde **2a–g** (1.0 mmol), dimedone **3** (1.0 mmol), triethylamine (1.2 mmol), and 3 mL of water were placed in 10 mL Xpress vial which then was capped. The mixture was irradiated at 170°C (375 W) for 10 min with intensive magnetic stirring. After cooling to room temperature, 3 mL of EtOH-H_2O mixture (1:1) was added to the crude reaction mixture and stirred for 10 min. The precipitate was collected by filtration, washed with EtOH–H2O (1:1), and dried at room temperature to produce the desired pyrazoloquinolinone **4a–u**. In all the cases, the reaction gave a single product whose structure was proven by spectroscopic methods (^{1}H NMR, ^{13}C NMR, and MS). The spectral and analytical data were identical to previously published [13].

Table 3

Synthesis of compounds **4a-u**.

Compound	*R*	R^1	Yield (%)
4a	Ph	4-$CH_3OC_6H_4$	82
4b	Ph	4-$CH_3C_6H_4$	83
4c	Ph	4-BrC_6H_4	83
4d	Ph	4-ClC_6H_4	90
4e	Ph	4-$C_2H_5OC_6H_4$	84
4f	Ph	Ph	80
4g	Ph	3,4-$(CH_3O)_2C_6H_3$	76
4h	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	80
4i	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	80
4j	4-$CH_3C_6H_4$	4-BrC_6H_4	85
4k	4-$CH_3C_6H_4$	4-ClC_6H_4	86
4l	4-$CH_3C_6H_4$	4-$C_2H_5OC_6H_4$	86
4m	4-$CH_3C_6H_4$	Ph	82
4n	4-$CH_3C_6H_4$	3,4-$(CH_3O)_2C_6H_3$	74
4o	CH_3	4-$CH_3OC_6H_4$	86
4p	CH_3	4-$CH_3C_6H_4$	86
4q	CH_3	4-BrC_6H_4	86
4r	CH_3	4-ClC_6H_4	82
4s	CH_3	4-$C_2H_5OC_6H_4$	77
4t	CH_3	Ph	75
4u	CH_3	3,4-$(CH_3O)_2C_6H_3$	77

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Synthesis and Structure Characterization of New [1,2,4]Triazolo[5,4-*d*][1,5]benzothiazepine Derivatives Through 1,3-Dipolar Cycloaddition Reaction

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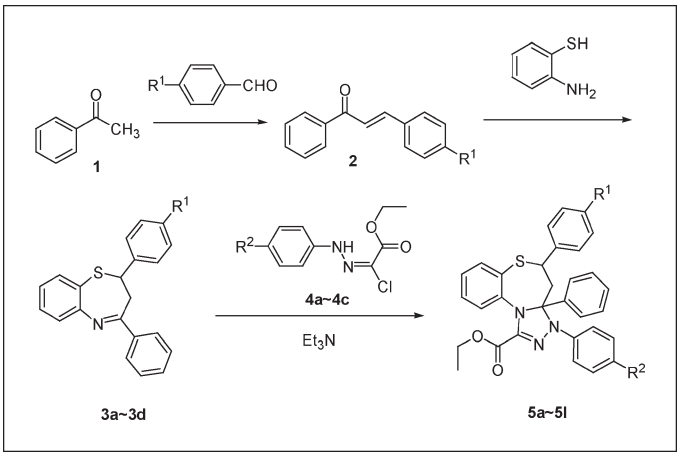

Reaction of 1,5-benzothiazepines **3**, obtained from chalcones **2** and *o*-aminobenzenthiol, with the (phenylhydrazino) chloromethylenecarboxylates **4** in the presence of Et_3N leads to a series of new [1,2,4]triazolo[5,4-*d*][1,5]benzothiazepine derivatives **5**. Their structures were established using spectroscopic methods and that of compound **5d** was confirmed using X-ray diffraction analysis.

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INTRODUCTION

The synthesis of benzothiazepine derivatives has attracted considerable attention of organic and medicinal chemists because of their broad spectrum of biological activities, such as cardiovascular modulator, coronary vasodilators, ACE inhibitors, anti-HIV, antihypertensive, antidepressant, and antibacterial and anticancer activity [1,2]. Recently, progress has been made into fix an additional heterocycle on the heptatomic nucleus of 1,5-benzothiazepine for the preparation of fused ring compounds. The presence of the conformational preferences of the seven-membered ring is possibly correlated with biological activity, and the fusion of a heterocyclic nucleus to the thiazepine system could induced an increase of the ring inversion barrier and consequently modify the activity profile [3,4].

Furthermore, 1,2,4-triazole derivatives have been reported to exhibit antifungal, anti-inflammatory, and antimicrobial activity [5]. For example, itraconazole and fluconazole are clinically used as antimicrobial drugs [6,7]. In addition, a 1,2,4-triazole is a key subunit in the structure of a potential anticancer and anti-HIV agents [8,9].

Inspired by the biological profile of 1,5-benzothiazepine and 1,2,4-triazole derivatives and in continuation of our interest in the synthesis of new 1,5-benzothiazepine derivatives [10,11], we reported herein the reaction of 1,5-benzothiazepines **3** with the nitrileimines **4** through 1,3-dipolar cycloaddition to afford a new series of [1,2,4]triazolo[5,4-*d*][1,5]benzothiazepine derivatives **5**. (Table 1). It was thought worthwhile to synthesize the title compounds with both active pharmacophores in a single molecular framework, which may have potential biological and medical applications.

RESULTS AND DISCUSSION

The synthetic route used is shown in Scheme 1. The chalcones **2** were readily prepared by condensation of aryl aldehydes with acetophenone. The reaction of **2** with *o*-aminobenzenthiol, in methanol in the presence of acetic acid at reflux temperature for 4 h, to get the required 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines **3** in good to excellent yields. 1,3-Dipolar cycloaddition reaction of **3** with nitrileimines, generated *in situ* from

Table 1

Physical and analytical data of compounds **5**.

Entry	Comp.	R^1	R^2	mp (°C)	Yield (%)	Molecular formula	Analysis % (Calcd./Found) C	H	N
1	**5a**	H	H	237–238	25	$C_{31}H_{27}N_3O_2S$	73.64	5.38	8.31
							73.61	5.40	8.33
2	**5b**	H	Cl	199–200	31	$C_{31}H_{26}ClN_3O_2S$	68.94	4.85	7.78
							68.92	4.86	7.80
3	**5c**	H	CH_3	189–190	30	$C_{32}H_{29}N_3O_2S$	73.96	5.62	8.09
							73.98	5.61	8.07
4	**5d**	Cl	H	217–218	26	$C_{31}H_{26}ClN_3O_2S$	68.94	4.85	7.78
							68.95	4.82	7.79
5	**5e**	Cl	Cl	254–255	32	$C_{31}H_{25}Cl_2N_3O_2S$	64.81	4.39	7.31
							64.79	4.40	7.34
6	**5f**	Cl	CH_3	215–216	29	$C_{32}H_{28}ClN_3O_2S$	69.36	5.09	7.58
							69.32	5.11	7.59
7	**5g**	OCH_3	H	178–179	21	$C_{32}H_{29}N_3O_3S$	71.75	5.46	7.84
							71.77	5.45	7.82
8	**5h**	OCH_3	Cl	244–245	27	$C_{32}H_{28}ClN_3O_3S$	67.42	4.95	7.37
							67.40	4.96	7.39
9	**5i**	OCH_3	CH_3	221–222	33	$C_{33}H_{31}N_3O_3S$	72.11	5.68	7.64
							72.10	5.67	7.67
10	**5j**	NO_2	H	179–180	22	$C_{31}H_{26}N_4O_4S$	67.62	4.76	10.18
							67.61	4.75	10.21
11	**5k**	NO_2	Cl	230–231	31	$C_{31}H_{25}ClN_4O_4S$	63.64	4.31	9.58
							63.66	4.30	9.55
12	**5l**	NO_2	CH_3	170–171	28	$C_{32}H_{28}N_4O_4S$	68.07	5.00	9.92
							68.08	4.99	9.94

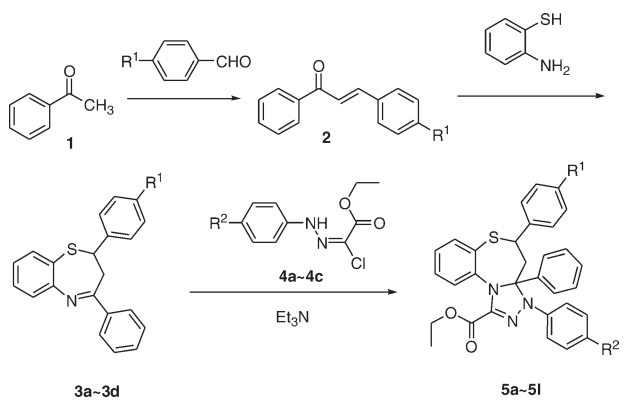
(phenylhydrazino) chloromethylenecarboxylates **4** in the presence of Et_3N, to yield the target compounds **5a–5l**.

The structures of the title compounds have been characterized by IR, ^{1}H-NMR, MS, and elemental analysis. For example, the infrared spectra of these compounds showed a characteristic absorption band at 1730 cm^{-1} because of the presence of the ester-carbonyl group. Also, their ^{1}H-NMR spectra revealed multiplet between δ 7.60 and 6.60 ppm because of the aromatic protons, the signal for ethoxycarbonyl CH_2 and CH_3 appeared at δ 4.19–4.21 ppm and 1.19–1.20 ppm, respectively, and three distinct double doublets in the ABX system (a CH proton and tow anisochronous protons of a CH_2) appeared at δ 2.65–4.56 ppm, as has been observed in 2,3-dihydro-1,5-benaothiazepine. In MS spectra, the compounds exhibit a stable molecular ion, and the base peak is the [M-(EtOCO+$R_1C_6H_5CH{=}CH_2$)] ion in all the compounds analyzed. The relative abundance of the main fragmentation in the compounds has some common features. The most important ions are as follows: M^+, [M-77], [M-($R_1C_6H_5CH{=}CH_2$)], and [M-(EtO-CO+$R_1C_6H_5CH{=}CH_2$)]. The main fragmentation was consistent with the assigned structures.

Subsequently, the absolute configuration of the reaction products **5** has been further elucidated from X-ray diffraction analysis of a single crystal. The general view of the molecule **5d** and its principal characteristics are given in Figure 1. The higher occupancy in the three-dimensional packing arrangement is shown in Figure 2. The crystal data and structure refinement of **5d** are listed in Table 2. Selected bond distances and angles of **5d** are tabulated in Table 3.

Figure 1 is the stereostructure of compound **5d**. There is a five-membered ring in the molecule, resulting from the cycloaddition reaction. All atoms [N(1), C(7), N(2), N(3), and C(17)] in the ring are nearly coplanar with similar bond angles [N(1)—C(7)—N(2) 114.71(19)°, C(7)—N(2)—N(3) 106.34(17)°, N(2)—N(3)—C(17) 111.98(15)°, N(3)—C(17)—N(1) 97.98(15)°, and

Scheme 1



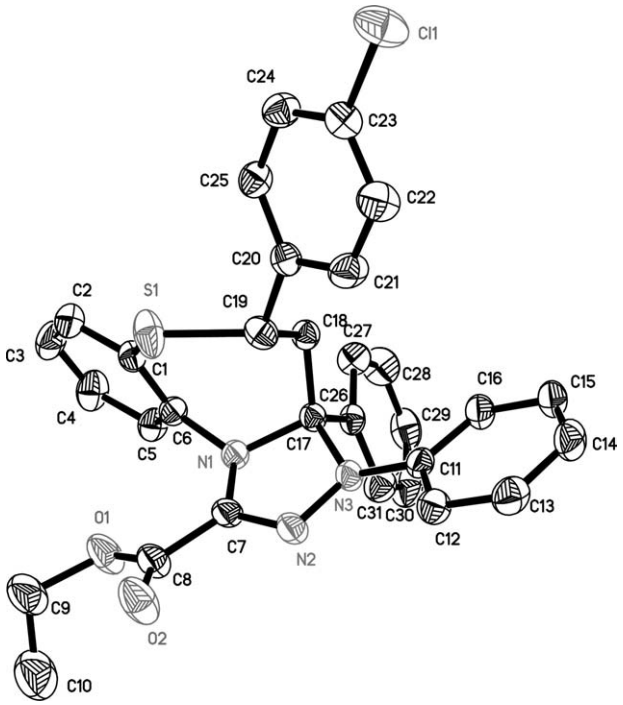


Figure 1. The molecular structure of the title compound **5d**.

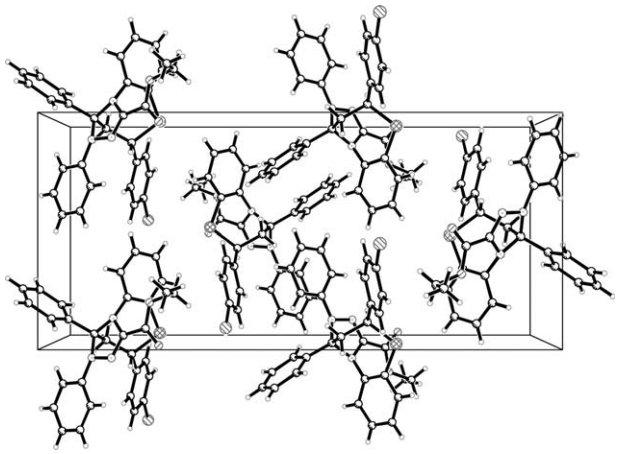


Figure 2. Packing of molecules in a unit cell of **5d**.

C(17)—N(1)—C(7) 107.28(16)°], indicating the ring is stable. The five-membered ring is characterized by the endocyclic torsion angles [enumerated clockwise and starting with C(7)—N(2)—N(3)—C(17)]: 7.5(3)°, 1.3(3)°, −9.4(3)°, 12.1(2)°, and −12.1(2)°. The five-membered ring plane adopts an envelope conformation with atom C(17) deviating from the plane defined by N(3), N(2), C(7), and N(1) of 0.0737 Å. The bond length of N(2)—C(7), 1.281(3) Å, indicates that it is a double bond.

There is also a seven-membered ring in the molecule. 1,5-Benzothiazepine ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with S(1)—C(1)—C(6)—N(1)): −1.9(3)°, 41.8(2)°, 11.2(2)°, −82.5(2)°, 56.0(2)°, 43.8(2)°, and −76.0(3)°. N(1), S(1), C(17), and C(19) are coplanar, whereas C(1), C(6), and C(18) are all below the plane, with their deviations being −0.4046, −0.2090, and −0.6481 Å. Therefore, the seven-membered ring adopts a boat-like conformation.

CCDC-769643 (for **5d**) contains the supplementary crystallographic data for this article. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html.

In conclusion, we have achieved an efficient one-step synthesis of new [1,2,4]triazolo[5,4-*d*][1,5]benzothiazepines **5a–5l** by way of highly regioselective 1,3-dipolar cycloaddition of the (phenylhydrazino) chloromethylenecarboxylates **4a–4c** to 2,4-diary-2,3-dihydro-1,5-benzothiazepines **3a–3d**.

EXPERIMENTAL

All reagents were of commercial availability. Reactions were monitored by thin-layer chromatography (TLC). Melting points were measured on a mettler FP-5 capillary melting point

Table 2

Crystal data and structure refinement for compound **5d**.

Empirical Formula	$C_{31}H_{26}ClN_3O_2S$	V (Å^3)	2643.3(3)
Formula weight	540.06	Z	4
Temperature	293(2) K	D_c (mg/m^3)	1.357
Wavelength	0.71073 A	Crystal size (mm)	0.72 × 0.45 × 0.10
Crystal system	Orthorhombic	θ range (°)	3.10–27.48
Space group	$P2(1)2(1)2(1)$	μ (mm^{-1})	0.258
a (Å)	9.7747(7)	Reflections collected	26123
b (Å)	11.0448(8)	Independent reflection	6060 [R(int) = 0.0353]
c (Å)	24.4840(17)	Data/restraints/parameters	6060/0/344
α (°)	90	Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0445$, $wR_2 = 0.1125$
β (°)	90	R indices (all data)	$R_1 = 0.0628$, $wR_2 = 0.1309$
γ (°)	90		

Table 3

Selected bond lengths (Å) and angles (°) of compounds **5d**.

N(1)—C(7)	1.388(3)	C(1)—S(1)—C(19)	107.30(10)
N(2)—C(7)	1.281(3)	C(7)—N(1)—C(6)	124.45(18)
N(2)—N(3)	1.392(2)	C(7)—N(1)—C(17)	107.28(16)
N(1)—C(17)	1.495(3)	N(2)—N(3)—C(11)	116.82(17)
N(3)—C(17)	1.493(3)	N(2)—C(7)—N(1)	114.71(19)
O(1)—C(8)	1.320(3)	O(2)—C(8)—C(7)	123.4(2)
O(2)—C(8)	1.206(3)	C(7)—N(2)—N(3)	106.34(17)
C(7)—C(8)	1.485(3)	O(2)—C(8)—O(1)	124.7(2)
C(17)—C(26)	1.322(3)	C(17)—C(18)—C(19)	112.36(18)

apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox 55 FTIR spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian Inova-400 spectrophotometer using TMS as an internal standard. EI-MS spectra were recorded with an Agilent 5975 apparatus. X-ray crystal structure was obtained using R-AXIS SPIDER X-ray diffraction. Chalcones **2** were obtained according to the known procedure [12]. The (phenylhydrazino) chloromethylenecarboxylates **4a–4c** (**4a**: R^2 = H; **4b**: R^2 = Cl; **4c**: R^2 = CH_3) were obtained according to the known procedure [13].

General procedure for the preparation of the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines (3a–3d). Chalcones **2** (6 mmol) and *o*-aminobenzenthiol (6 mmol) were dissolved in 25 mL hot methanol [14]. After the mixture had cooled to room temperature and piperidine (five drops) was added, yellow solid appeared in 0.5 h, then a little methanol was added and the slurry heated until all material dissolved. Glacial acetic acid (2 mL) then was added, and the mixture was stirred under reflux for 4 h and allowed to stand overnight at a room temperature. The yellow precipitate formed was filtered, dried, and crystallized from anhydrous ethanol and benzene to give **3** as yellow crystals. Purity of the compounds was checked by TLC.

3a: Yield 86%, mp 113–115°C (lit. [14], 114–115°C), yellow crystals.

3b: Yield 72%, mp 137–139°C (lit. [15], 128°C), yellow crystals.

3c: Yield 81%, mp 128–130°C (lit. [15], 127–128°C), yellow crystals.

3d: Yield 43.2%, mp 201–202°C (lit. [16], 140°C; lit. [17], 185°C), yellow crystals.

General procedure for the preparation of the ethyl 3a,4-dihydro-3a-phenyl-3,5-diaryl-5H-[1,2,4]triazolo[5,4-*d*][1,5] benzothiazepine-1-carboxylate (5a-5l). To a stirred solution of 1,5-benzothiazepine derivatives **3** (1 mmol) and the (phenylhydrazino) chloromethylenecarboxylates **4** (1.5 mmol) in CH_2Cl_2 (20 mL), a solution of triethylamine (0.5 mL) in the same solvent (5 mL) was added dropwise over a few minutes. The reaction mixture was kept under stirring at room temperature for 3 days. After the removal of the solvent under reduced pressure, ethyl acetate was added to the residue and the triethylamine hydrochloride was filtered. The solvent was then evaporated off and the residue subjected to silica gel column chromatography with ethyl acetate/light petroleum (V:V = 1:8) as an eluent. A series of compounds **5** were cultured from ethyl acetate and light petroleum.

Ethyl 3a,4-dihydro-3,3a,5-triphenyl-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5a). This compound was obtained as yellow crystals in 25% yield, mp 237–238°C. IR(KBr) υ: 3051, 1730, 758 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 19H, Ar-H), 4.55 (dd, 1H, H-5x, J_{ax} = 1.56 Hz, J_{bx} = 11.52 Hz), 4.20 (q, 2H, O—*CH*$_2$—CH_3), 2.86 (dd, 1H, H-4a, J_{ax} = 1.56 Hz, J_{ab} = 16 Hz), 2.71 (dd, 1H, H-4b, J_{bx} = 11.52 Hz, J_{ab} = 16 Hz), 1.19 (t, 3H, O—CH_2—*CH*$_3$). MS: *m/z* 505 (M^+). Anal. Calcd. for $C_{31}H_{27}N_3O_2S$: C, 73.64; H, 5.38; N, 8.31; Found: C, 73.61; H, 5.40; N, 8.33.

Ethyl 3a,4-dihydro-3-(4-chlorophenyl)-3a,5-diphenyl-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5b). This compound was obtained as yellow crystals in 31% yield, mp 199–200°C. IR(KBr) υ: 3047, 1725, 763 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 18H, Ar-H), 4.52 (dd, 1H, H-5x, J_{ax} = 1.60 Hz, J_{bx} = 11.60 Hz), 4.21 (q, 2H, O—*C*H_2—CH_3), 2.87 (dd, 1H, H-4a, J_{ax} = 1.60 Hz, J_{ab} = 16 Hz), 2.77 (dd, 1H, H-4b, J_{bx} = 11.60 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—C*H*$_3$). MS: *m/z* 539 (M^+). Anal. Calcd. for $C_{31}H_{26}ClN_3O_2S$: C, 68.94; H, 4.85; N, 7.78; Found: C, 68.92; H, 4.86; N, 7.80.

Ethyl 3a,4-dihydro-3-(4-methylphenyl)-3a,5-diphenyl-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5c). This compound was obtained as yellow crystals in 30% yield, mp 189–190°C. IR(KBr) υ: 3043, 1721, 762 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 18H, Ar-H), 4.55 (dd, 1H, H-5x, J_{ax} = 1.43 Hz, J_{bx} = 11.77 Hz), 4.20 (q, 2H, O—*CH*$_2$—CH_3), 2.88 (dd, 1H, H-4a, J_{ax} = 1.43 Hz, J_{ab} = 16 Hz), 2.72 (dd, 1H, H-4b, J_{bx} = 11.77 Hz, J_{ab} = 16 Hz), 2.22 (s, 3H, Ar-CH_3), 1.20 (t, 3H, O—CH_2—C*H*$_3$). MS: *m/z* 519 (M^+). Anal. Calcd. for $C_{32}H_{29}N_3O_2S$: C, 73.96; H, 5.62; N, 8.09; Found: C, 73.98; H, 5.61; N, 8.07.

Ethyl 3a,4-dihydro-3,3a-diphenyl-5-(4-chlorophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5d). This compound was obtained as yellow crystals in 26% yield, mp 217–218°C. IR(KBr) υ: 3055, 1730, 765 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 18H, Ar-H), 4.53 (dd, 1H, H-5x, J_{ax} = 1.45 Hz, J_{bx} = 11.35 Hz), 4.20 (q, 2H, O—*CH*$_2$—CH_3), 2.86 (dd, 1H, H-4a, J_{ax} = 1.45 Hz, J_{ab} = 16 Hz), 2.70 (dd, 1H, H-4b, J_{bx} = 11.35 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—*CH*$_3$). MS: *m/z* 539 (M^+). Anal. Calcd. for $C_{31}H_{26}ClN_3O_2S$: C, 68.94; H, 4.85; N, 7.78; Found: C, 68.95; H, 4.82; N, 7.79.

Ethyl 3a,4-dihydro-3-(4-chlorophenyl)-3a-phenyl-5-(4-chlorophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5e). This compound was obtained as yellow crystals in 32% yield, mp 254–255°C. IR(KBr) υ: 3062, 1733, 763 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 17H, Ar-H), 4.51 (dd, 1H, H-5x, J_{ax} = 1.54 Hz, J_{bx} = 11.68 Hz), 4.19 (q, 2H, O—*CH*$_2$—CH_3), 2.84 (dd, 1H, H-4a, J_{ax} = 1.54 Hz, J_{ab} = 16 Hz), 2.69 (dd, 1H, H-4b, J_{bx} = 11.68 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—*CH*$_3$). MS: *m/z* 573 (M^+). Anal. Calcd. for $C_{31}H_{25}Cl_2N_3O_2S$: C, 64.81; H, 4.39; N, 7.31; Found: C, 64.79; H, 4.40; N, 7.34.

Ethyl 3a,4-dihydro-3-(4-methylphenyl)-3a-phenyl-5-(4-chlorophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5f). This compound was obtained as yellow crystals in 29% yield, mp 215–216°C. IR(KBr) υ: 3107, 1730, 762 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.59–6.60 (m, 17H, Ar-H), 4.54 (dd, 1H, H-5x, J_{ax} = 1.42 Hz, J_{bx} = 11.40 Hz), 4.20 (q, 2H, O—*CH*$_2$—CH_3), 2.85 (dd, 1H, H-4a, J_{ax} = 1.42 Hz, J_{ab}

= 16 Hz), 2.73 (dd, 1H, H-4b, J_{bx} = 11.40 Hz, J_{ab} = 16 Hz), 2.20 (s, 3H, Ar-CH_3), 1.19 (t, 3H, O—CH_2—CH_3). MS: *m/z* 553 (M^+). Anal. Calcd. for $C_{32}H_{28}ClN_3O_2S$: C, 69.36; H, 5.09; N, 7.58; Found: C, 69.32; H, 5.11; N, 7.59.

Ethyl 3a,4-dihydro-3,3a-diphenyl-5-(4-methoxyphenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5g). This compound was obtained as yellow crystals in 21% yield, mp 178–179°C. IR(KBr) υ: 3072, 1730, 765 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 18H, Ar-H), 4.56 (dd, 1H, H-5x, J_{ax} = 1.54 Hz, J_{bx} = 11.26 Hz), 4.21 (q, 2H, O—CH_2—CH_3), 3.73 (s, 3H, OCH_3), 2.86 (dd, 1H, H-4a, J_{ax} = 1.54 Hz, J_{ab} = 16 Hz), 2.70 (dd, 1H, H-4b, J_{bx} = 11.26 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—CH_3). MS: *m/z* 535 (M^+). Anal. Calcd. for $C_{32}H_{29}N_3O_3S$: C, 71.75; H, 5.46; N, 7.84; Found: C, 71.77; H, 5.45; N, 7.82.

Ethyl 3a,4-dihydro-3-(4-chlorophenyl)-3a-phenyl-5-(4-methoxyphenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5h). This compound was obtained as yellow crystals in 27% yield, mp 244–245°C. IR(KBr) υ: 3110, 1736, 763 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 17H, Ar-H), 4.55 (dd, 1H, H-5x, J_{ax} = 1.62 Hz, J_{bx} = 11.10 Hz), 4.20 (q, 2H, O—CH_2—CH_3), 3.72 (s, 3H, OCH_3), 2.85 (dd, 1H, H-4a, J_{ax} = 1.62 Hz, J_{ab} = 16 Hz), 2.72 (dd, 1H, H-4b, J_{bx} = 11.10 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—CH_3). MS: *m/z* 569 (M^+). Anal. Calcd. for $C_{32}H_{28}ClN_3O_3S$: C, 67.42; H, 4.95; N, 7.37; Found: C, 67.40; H, 4.96; N, 7.39.

Ethyl 3a,4-dihydro-3-(4-methylphenyl)-3a-phenyl-5-(4-methoxyphenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5i). This compound was obtained as yellow crystals in 33% yield, mp 221–222°C. IR(KBr) υ: 3102, 1720, 762 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53–6.60 (m, 17H, Ar-H), 4.56 (dd, 1H, H-5x, J_{ax} = 1.52 Hz, J_{bx} = 11.29 Hz), 4.20 (q, 2H, O—CH_2—CH_3), 3.74 (s, 3H, OCH_3), 2.85 (dd, 1H, H-4a, J_{ax} = 1.52 Hz, J_{ab} = 16 Hz), 2.74 (dd, 1H, H-4b, J_{bx} = 11.29 Hz, J_{ab} = 16 Hz), 2.22 (s, 3H, Ar-CH_3), 1.19 (t, 3H, O—CH_2—CH_3). MS: *m/z* 549 (M^+). Anal. Calcd. for $C_{33}H_{31}N_3O_3S$: C, 72.11; H, 5.68; N, 7.64; Found: C, 72.10; H, 5.67; N, 7.67.

Ethyl 3a,4-dihydro-3,3a-diphenyl-5-(4-nitrophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5j). This compound was obtained as yellow crystals in 22% yield, mp 179–180°C. IR(KBr) υ: 3118, 1731, 764 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 18H, Ar-H), 4.52 (dd, 1H, H-5x, J_{ax} = 1.48 Hz, J_{bx} = 11.42 Hz), 4.19 (q, 2H, O—CH_2—CH_3), 2.87 (dd, 1H, H-4a, J_{ax} = 1.48 Hz, J_{ab} = 16 Hz), 2.70 (dd, 1H, H-4b, J_{bx} = 11.42 Hz, J_{ab} = 16 Hz), 1.20 (t, 3H, O—CH_2—CH_3). MS: *m/z* 550 (M^+). Anal. Calcd. for $C_{31}H_{26}N_4O_4S$: C, 67.62; H, 4.76; N, 10.18; Found: C, 67.61; H, 4.75; N, 10.21.

Ethyl 3a,4-dihydro-3-(4-chlorophenyl)-3a-phenyl-5-(4-nitrophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5k). This compound was obtained as yellow crystals in 31% yield, mp 230–231°C. IR(KBr) υ: 3075, 1733, 762 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.57–6.60 (m, 17H, Ar-H), 4.50 (dd, 1H, H-5x, J_{ax} = 1.68 Hz, J_{bx} = 11.36 Hz), 4.19 (q, 2H, O—CH_2—CH_3), 2.86 (dd, 1H, H-4a, J_{ax} = 1.68 Hz, J_{ab} = 16 Hz), 2.70 (dd, 1H, H-4b, J_{bx} = 11.36 Hz, J_{ab} = 16 Hz), 1.19 (t, 3H, O—CH_2—CH_3). MS: *m/z* 584 (M^+). Anal. Calcd. for $C_{31}H_{25}ClN_4O_4S$: C, 63.64; H, 4.31; N, 9.58; Found: C, 63.66; H, 4.30; N, 9.55.

Ethyl 3a,4-dihydro-3-(4-methylphenyl)-3a-phenyl-5-(4-nitrophenyl)-5H-[1,2,4]triazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (5l). This compound was obtained as yellow crystals in 28% yield, mp 170–171°C. IR(KBr) υ: 3097, 1745, 764 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.60 (m, 17H, Ar-H), 4.54 (dd, 1H, H-5x, J_{ax} = 1.51 Hz, J_{bx} = 11.29 Hz), 4.20 (q, 2H, O—CH_2—CH_3), 2.85 (dd, 1H, H-4a, J_{ax} = 1.51 Hz, J_{ab} = 16 Hz), 2.72 (dd, 1H, H-4b, J_{bx} = 11.29 Hz, J_{ab} = 16 Hz), 2.20 (s, 3H, Ar-CH_3), 1.20 (t, 3H, O—CH_2—CH_3). MS: *m/z* 564 (M^+). Anal. Calcd. for $C_{32}H_{28}N_4O_4S$: C, 68.07; H, 5.00; N, 9.92; Found: C, 68.08; H, 4.99; N, 9.94.

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Design and Synthesis of New Imidazolinone Derivatives as Potential Antifungal Agents

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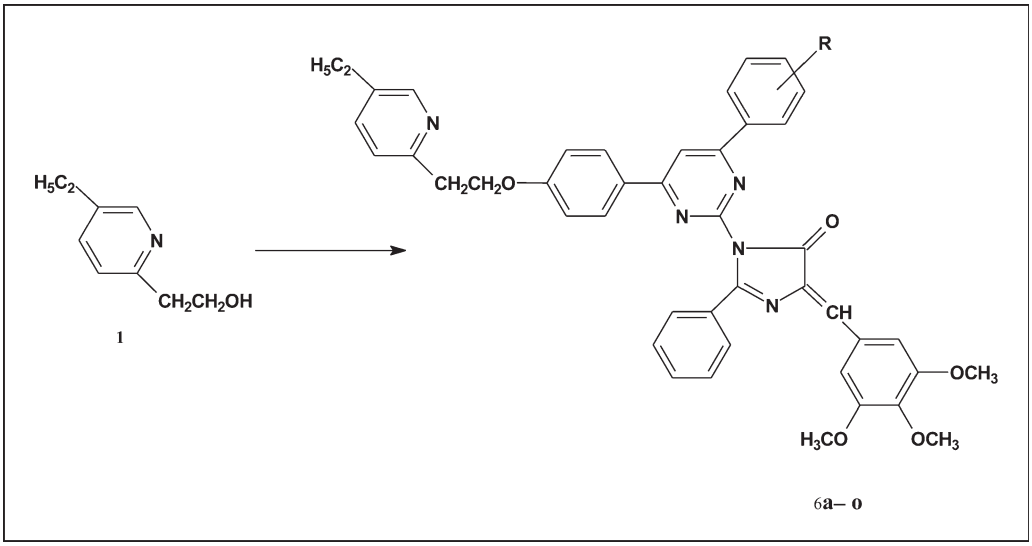

A new series of chalcones, pyrimidines, and imidazolinone is described; chalcones (**4a–o**) were prepared from the lead 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde. Pyrimidines (**5a–o**) were prepared from the reaction of chalcones and guanidine nitrate in alkali media. Imidazolinones (**6a–o**) were synthesized from the reaction of pyrimidine and oxazolone derivatives (prepared by Erlenmeyer azlactone synthesis). The structures of the synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}H-NMR, and ^{13}C-NMR spectral data. All the products were screened against different strains of bacteria and fungi. Most of these compounds showed better inhibitory activity in comparison with the standard drugs.

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INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. Nitrogen and oxygen containing five- and six-membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry.

The basic nucleus imidazole emerges from the drug intermediate azlactone. The azlactones possess oxazolone moiety. They are also of great importance to produce penicillin type of drug intermediates and also useful to produce synthetic hormonal compounds. Imidazole is a planer five-membered heterocyclic ring system with three carbon and two nitrogen atoms in 1 and 3 positions; imidazolones are keto dihydro imidazoles and are known as oxoimidazoline; a five-membered heterocyclic ring system having nitrogen atoms in 1 and 3 positions and carbonyl at 5 position. Oxoimidazoline, also known as imidazolinone, is reported to exhibit a wide variety of antibacterial [1,2], antifungal [3], and antimicrobial activities [4–7]. They have also been reported to possess fungicidal activities [8], herbicidal activities [9], vasodilator activities [10], anticonvulsant agents [11], and antitumor agent [12].

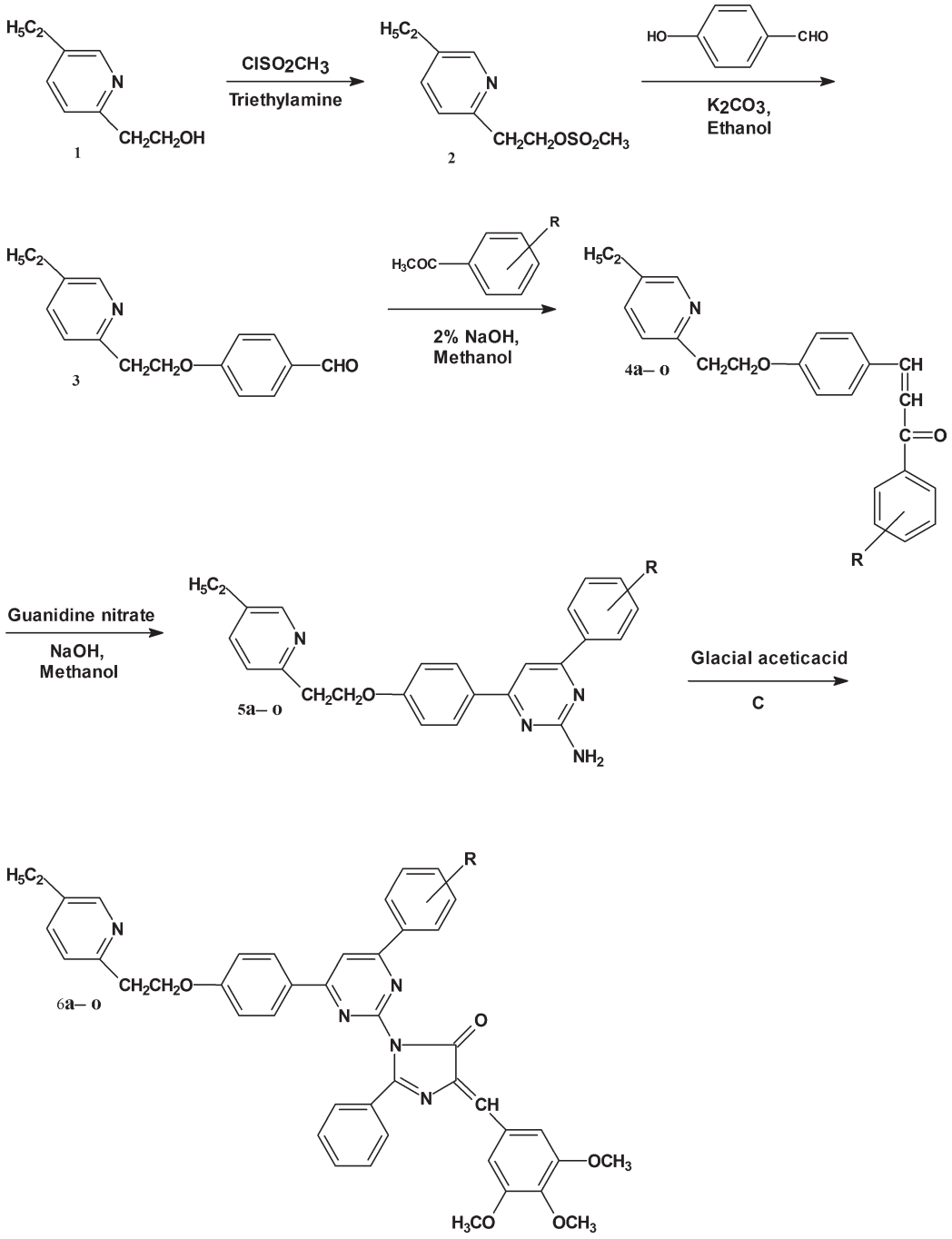
Recently, we have prepared chalcones, pyrimidines, and amide derivatives and studied their antibacterial and antifungal activities [13,14]. In continuation of our work on chalcones and pyrimidines, we planned to attach oxazolones with amino group of pyrimidine and to synthesize imidazolinone derivatives.

Hence, with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of imidazolinone heterocycles by incorporating the chalcone and pyrimidine moieties in a single molecular framework.

RESULTS AND DISCUSSION

Chemistry. The synthesis of chalcones, pyrimidines, and imidazolinone derivatives was performed following the steps shown in Scheme 1. In the initial step,

Scheme 1. Synthesis of compounds **5a–o** and **6a–o**.



chalcones **4a–o** were synthesized by condensing 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde with appropriate aromatic acetophenones in diluted methanolic sodium hydroxide solution at room temperature. The compounds **5a–o** were synthesized by the reaction of an appropriate chalcone with guanidine nitrate and sodium ethoxide solution. Compounds **6a–o** were prepared from the reaction of pyrimidines and oxazolones. The purity of the compounds was determined by thin layer chromatography (TLC) and elemental analyses. Spectral data (IR, ^{1}H-NMR, and ^{13}C-NMR) of all the newly synthesized compounds were in full agreement with the proposed structures.

The synthesis of **4a–o** was confirmed by the IR and NMR spectra. In the IR spectrum, the sharp band of —C=O was observed at 1662 cm^{-1}, —CH=CH— of chalcone was observed at 1599 cm^{-1}, the asymmetric and symmetric band of C—O—C ether linkage in the structure were observed at 1223 and 1036 cm^{-1}. The

^{1}H-NMR spectra exhibited one doublet at δ 7.11 attributed to the =CH—CO— protons and two protons with triplet at δ 4.32 confirmed that —CH_2—O—. In the ^{13}C-NMR spectra of chalcones, the higher field resonances at δ 190.0 ppm were attributed to the carbonyl group present in chalcone. The structures of compounds **5a–o** and **6a–o** were also established by using IR and NMR spectroscopy. The IR spectra of pyrimidine showed disappearance of —C=O band at 1662 cm^{-1} and appearance of asymmetric and symmetric new broad bands at 3355 cm^{-1} and 3220 cm^{-1} for —NH_2, respectively. A signal at δ 5.15 and δ 7.85 for the —NH_2 and —CH of pyrimidine ring, respectively, was observed, and the ^{13}C-NMR spectra of pyrimidine —CH appeared at δ 103.2. The sharp band of —C=O in imidazolinone was observed at 1797 cm^{-1} and another band of —C=N was observed at 1656 cm^{-1}. The ^{1}H-NMR spectra showed a signal at 7.30 with singlet that determined the —CH group of imidazolinone, and the ^{13}C-NMR spectra carbon of —C=O appeared at 170.4.

From the above spectral analysis, we have confirmed the conversion of chalcones to pyrimidines and the conversion of pyrimidines to imidazolinones derivatives.

Antimicrobial activity. ***Methods.*** All microbial type culture collection (MTCC) cultures were collected from the Institute of Microbial Technology, Chandigarh, and tested against the known drugs ampicillin and greseofulvin. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 colony-forming unit per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test on standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and kept for incubation at 37°C overnight. The tubes were then incubated overnight. The minimum inhibition concentrations (MIC) of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic, a reduced number of colonies indicating a partial or slow bactericidal activity, and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/mL concentration, as a stock solution. In primary screening, 500, 250 and 125 μg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125, and 1.5625 μg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [15]. Antibacterial activity was screened against two Gram-positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two Gram-negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441) bacteria, in which ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323, in which greseofulvin was used as a standard antifungal agent.

Antibacterial activity. The minimal bactericidal concentrations (MBCs) of the tested compounds are shown in Table 1. The different compounds **4a–o**, **5a–o**, and **6a–o** were tested in *in vitro* against two Gram-positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 443) and two Gram-negative (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441) bacteria. From the screening data, chalcones, **4b**, **4f**, and **4h** showed MBC value in the range between 62.5 and 100 μg/mL while ampicillin has standard MBC value of 100 μg/mL against *E. coli* which indicates that these compounds have excellent activity, while other chalcones **4c**, **4d** and **4o** possessed MBC value in the range of 125–150 μg/mL against *E. coli*, and **4h** exhibited very good activity against *P. aeruginosa*. Compounds **4f** and **4h** displayed excellent activity in the range of 100–150 μg/mL while remaining **4b**, **4d** and **4n** were equivalent against *S. aureus* when compared with ampicillin. Compound **4h** have MBC value of 150 μg/mL, which was comparatively good against *S. pyogenus*. The remaining chalcones possessed moderate to poor activity against all four bacterial species. In the pyrimidine derivatives, compound **5b** possessed MBC value of 62.5 μg/mL against *E. coli* and MBC value of 150 μg/mL against *P. aeruginosa*, which was comparable with ampicillin. Compound **5e** exhibited MBC value of 150 μg/mL against *P. aeruginosa*. Compound **5h** showed MBC value of 100 μg/mL against *S. aureus* and MBC value of 100 μg/mL against *S. pyogeneus*. Compound **5i** possessed MBC value of 62.5 μg/mL against *E. coli* and MBC value of 150 μg/mL against *S. aureus*, which showed that this compound is as active as ampicillin. Compound **5l** showed MBC value of 100 μg/mL against *P. aeruginosa* and MBC

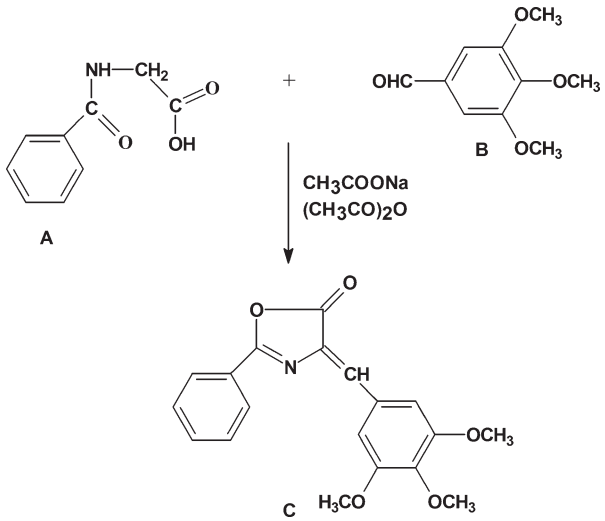
Table 1

Antimicrobial activities of compounds **4a–o**, **5a–o**, and **6a–o**.

		Minimal bactericidal concentration (μg/mL)				Minimal fungicidal concentration (μg/mL)		
		Gram negative		Gram positive				
Compound	R	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
4a	2,4-Cl,5-F	200	250	1000	1000	1000	500	500
4b	4-OCH_3	100	150	250	250	1000	1000	1000
4c	2,4-Cl	150	500	500	500	500	500	1000
4d	4-OH	150	200	250	250	500	500	1000
4e	2,6-Cl,5-F	500	250	500	1000	1000	500	500
4f	4-CH_3	100	150	100	250	1000	1000	1000
4g	-H	500	1000	1000	1000	200	500	500
4h	4-F	62.5	100	150	150	250	>1000	>1000
4i	2,4-F	250	250	500	500	1000	1000	1000
4j	4-Br	500	500	500	250	1000	>1000	>1000
4k	3,4-Cl	500	500	1000	1000	1000	>1000	>1000
4l	4-Cl	500	250	500	250	1000	500	500
4m	3-OCH_3	500	500	1000	1000	500	500	500
4n	3-F	250	500	250	500	500	1000	1000
4o	3,4-F	125	250	500	500	1000	1000	1000
5a	2,4-Cl,5-F	150	250	500	500	500	500	1000
5b	4-OCH_3	62.5	150	250	250	500	>1000	>1000
5c	2,4-Cl	500	500	250	500	500	>1000	>1000
5d	4-OH	250	200	500	500	500	500	1000
5e	2,6-Cl,5-F	250	150	1000	1000	500	500	500
5f	4-CH_3	200	200	250	250	500	500	500
5g	-H	250	250	500	500	500	500	500
5h	4-F	250	250	100	100	500	250	250
5i	2,4-F	62.5	150	150	200	500	1000	1000
5j	4-Br	250	250	200	200	1000	1000	1000
5k	3,4-Cl	250	250	250	250	1000	500	500
5l	4-Cl	250	100	150	250	500	500	500
5m	3-OCH_3	250	250	500	500	1000	500	500
5n	3-F	500	500	250	250	500	1000	1000
5o	3,4-F	250	500	500	250	200	200	200
6a	2,4-Cl,5-F	250	250	500	1000	>1000	>1000	>1000
6b	4-OCH_3	500	250	250	250	500	500	500
6c	2,4-Cl	250	200	250	500	1000	500	500
6d	4-OH	100	100	500	500	500	500	500
6e	2,6-Cl,5-F	250	500	500	500	500	>1000	>1000
6f	4-CH_3	200	250	500	1000	500	1000	1000
6g	-H	200	250	1000	1000	500	>1000	>1000
6h	4-F	100	150	200	200	1000	500	500
6i	2,4-F	100	250	250	500	1000	>1000	>1000
6j	4-Br	200	250	250	250	200	200	200
6k	3,4-Cl	250	200	250	250	500	1000	1000
6l	4-Cl	150	250	1000	150	500	1000	>1000
6m	3-OCH_3	200	250	1000	1000	1000	1000	1000
6n	3-F	1000	500	500	250	1000	500	1000
6o	3,4-F	1000	1000	250	250	1000	1000	1000
Gentamycin		0.05	1	0.25	0.5	–	–	–
Ampicillin		100	100	250	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Ciprofloxacin		25	25	50	50	–	–	–
Norfloxacin		10	10	10	10	–	–	–
Nystatin		–	–	–	–	100	100	100
Greseofulvin		–	–	–	–	500	100	100

value of 150 μg/mL against *S. aureus*. The remaining pyrimidines displayed moderate to poor activities against all four bacterial species. For the imidazolinone derivatives, compounds **6h** and **6i** showed MBC value of 100 μg/mL against *E. coli*. Compound **6d** showed MBC value of 100 μg/mL against *E. coli* and *P. aeruginosa*, which was as active as ampicillin; against *S. aureus*, compounds **6b**, **6c**, **6i**, **6j**, **6k**, and **6o** gave MBC value of 250 μg/mL, which

Scheme 2. Synthesis of oxazol-5(4H)-one.



shows that these compounds are as active as ampicillin. Compound **6h** is said to be more active when it was tested against *S. aureus*. Imidazolinones are moderately active against *S. pyogeneus*.

Antifungal activity. Minimal fungicidal concentrations (MFCs) of the synthesized compounds are shown in Table 1. For *in vitro* antifungal activity, three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282, and *A. clavatus* MTCC 1323 were used and compared with greseofulvin. Most of the compounds possessed very good antifungal activity against *C. albicans* when they were compared greseofulvin; their MFC values were in the range between 100 and 500 μg/mL. For chalcones, compounds **4g** and **4h** showed excellent activities of 200–250 μg/mL; **4c**, **4d**, **4m**, and **4n** possessed very good activity of 500 μg/mL, which is similar to greseofulvin (500 μg/mL) against *C. albicans*, whereas chalcones possessed moderate to poor activity against *A. niger* and *A. clavatus*. For pyrimidines, compound **5o** possessed good activity of 200 μg/mL against *C. albicans*, which showed that this compound is more active when compared with greseofulvin (500 μg/mL); whereas for imidazolinone derivatives, compound **6j** displayed excellent activity of 200 μg/mL against *C. albicans*, *A. niger*, and *A. clavatus*, which indicates that this compound is very active when compared with greseofulvin; while rest of the compounds **6b**, **6d**, **6e**, **6f**, **6g**, **6k**, and **6l** possessed MFC value of 500 μg/mL against *C. albicans*, which have similar values like greseofulvin.

CONCLUSION

Chalcones and pyrimidine derivatives possessed very good activity against all four bacterial species, but the observed results for fungicidal species are satisfactory. In the case of imidazolinone derivatives, compounds **6b**, **6d**, **6e**, **6f**, **6g**, **6k**, and **6l** are said to be as active as greseofulvin when they were tested with *C. albicans*. Compound **6j** displayed excellent activity of 200 μg/mL against *C. albicans*. From these results, it is concluded that the imidazolinone derivatives showed good antifungal activity rather than antibacterial activity.

EXPERIMENTAL

Laboratory chemicals were supplied by Rankem India Ltd., New Delhi, India and Ficher Scientific UK Ltd., Loughborough, Leicestershire. Melting points were determined by the open-tube capillary method and are uncorrected. The purity of the compounds was determined by TLC plates (silica gel G) in the solvent system, *i.e.*, toluene:ethyl acetate (75:25). The spots were observed by exposure to iodine vapors or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FTIR spectrometer (KBr pellets). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in $CDCl_3$. Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.

Procedure for the synthesis of 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde (3). 4-[2-(5-Ethylpyridin-2-yl)ethoxy]-benzaldehyde (3) was synthesized by the method described in refs. 16 and 17.

General preparation of the compounds 4a–o. Chalcones were synthesized and characterized by the method described in ref. 13.

General preparation of the compounds 5a–o. Pyrimidines were synthesized and characterized by the method described in ref. 13.

General process of oxazol-5(4H)-one (Erlenmeyer azlactone synthesis) (C). A mixture of 3,4,5-trimethoxy benzaldehyde (0.33 mol), hippuric acid (0.33 mol), and potassium acetate (0.33 mol) in acetic anhydride (0.83 mol) was refluxed with stirring for 15 min [reaction progress was monitored by TLC using isohexane:ethyl acetate (3:1) as eluent]. The mixture was then cooled and neutralized by the addition of solid potassium carbonate. The solid product was separated by filtration, dried, and purified from ethanol (as shown in Scheme 2).

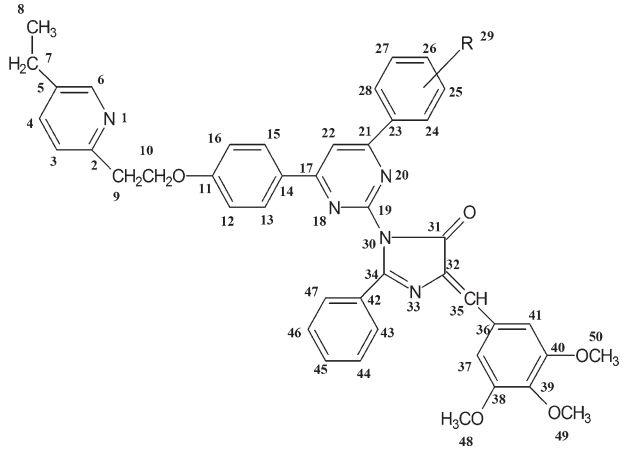


Figure 1. Imidazolinones **6a–o**.

General preparation of the compounds 6a–o. A mixture of **5a–o** (0.01 mol) and an appropriate oxazolone (0.01 mol) in 50 mL acetic acid was refluxed for 6–8 h [reaction progress was monitored by TLC using toluene–ethyl acetate (7.5:2.5) as eluent]. After completion of reaction, the resulted mixture was cooled and poured into ice cold water and the formed precipitate was filtered and washed with water till pH neutral. The raw product was crystallized from ethanol (Fig. 1).

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-dichloro-5-fluoro phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6a). This compound was obtained as brown solid, yield 54%, m.p. 115–119°C, R_f: 0.62; IR (KBr): Ar-H 3063, CH_2 2952, 2834, C=O of imidazolinone 1797, C=N imidazolinone 1655, C=N of pyrimidine 1613, C—O—C 1223, 1035, C—F 973, C—Cl 744 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.20 (t, 3H, J = 7.63 Hz, —CH_3), 2.51 (q, 2H, J = 7.62 Hz, —CH_2—), 3.26 (t, 2H, J = 6.71 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.35 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.76–8.33 (m, 17H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.2 (C_8), 25.2 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.3 (C_{22}), 103.8–150.4 (C_{36}–C_{41}), 108.4 (C_{35}), 114.8–157.3 (C_{11}–C_{16}), 122.3–157.3 (C_2–C_6), 126.3–130.0 (C_{42}–C_{47}), 118.7–1161.4 (C_{23}–C_{28}), 130.4 (C_{32}), 160.2 (C_{21}), 163.6 (C_{17}), 164.2 (C_{34}), 169.5 (C_{19}), 170.8 (C_{31}). Anal. Calcd for $C_{44}H_{36}N_5O_5Cl_2F$: C, 65.67; H, 4.51; N, 8.70. Found: C, 65.63; H, 4.50; N, 8.68.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-methoxy phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6b). This compound was obtained as brown solid, yield 65%, m.p. 110–112°C, R_f: 0.64; IR (KBr): Ar-H 3064, CH_2 2951, 2833, C=O of imidazolinone 1792, C=N imidazolinone 1655, C=N of pyrimidine 1614, C—O—C 1223, 1032 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.53 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.3 (C_7), 37.2 (C_9), 55.8 (C_{29}), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.5–150.7 (C_{36}–C_{41}), 108.2 (C_{35}), 114.5–157.6 (C_{11}–C_{16}), 122.1–157.4 (C_2–C_6), 126.5–130.1 (C_{42}–C_{47}), 114.8–160.6 (C_{23}–C_{28}), 130.2 (C_{32}), 160.6 (C_{21}), 163.3 (C_{17}), 164.3 (C_{34}), 169.1 (C_{19}), 170.3 (C_{31}). Anal. Calcd for $C_{45}H_{41}N_5O_6$: C, 72.27; H, 5.53; N, 9.36. Found: C, 72.25; H, 5.51; N, 9.34.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-dichloro phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6c). This compound was obtained as yellow solid, yield, 58%, m.p. 113–115°C, R_f: 0.59; IR (KBr): Ar-H 3059, CH_2 2950, 2832, C=O of imidazolinone 1791, C=N imidazolinone 1654, C=N of pyrimidine 1615, C—O—C 1225, 1034, C—Cl 743 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.21 (t, 3H, J = 7.64 Hz, —CH_3), 2.55 (q, 2H, J = 7.62 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.84 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.32 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.1 (C_8), 25.6 (C_7), 37.6 (C_9), 56.4 (C_{48}–C_{50}), 67.3 (C_{10}), 103.7 (C_{22}), 103.2–150.4 (C_{36}–C_{41}), 108.2 (C_{35}), 115.0–157.2 (C_{11}–C_{16}), 122.1–157.4 (C_2–C_6), 126.6–130.4 (C_{42}–C_{47}), 127.4–135.7 (C_{23}–C_{28}), 130.8 (C_{32}), 160.1 (C_{21}), 163.7 (C_{17}), 164.5 (C_{34}), 169.4 (C_{19}), 170.6 (C_{31}). Anal. Calcd for $C_{44}H_{37}N_5O_5Cl_2$: C, 67.18; H, 4.74; N, 8.90. Found: C, 67.12; H, 4.71; N, 8.91.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-hydroxy phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6d). This compound was obtained as yellow solid, yield 57%, m.p. 215–217°C, R_f: 0.61; IR (KBr): Ar-H 3065, OH 3354, CH_2 2953, 2833, C=O of imidazolinone 1795, C=N imidazolinone 1652, C=N of pyrimidine 1612, C—O—C 1224, 1032 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.17 (t, 3H, J = 7.63 Hz, —CH_3), 2.54 (q, 2H, J = 7.63 Hz, —CH_2—), 3.24 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 19H, pyridine, pyrimidine, and Ar-H), 9.85 (s, 1H, —OH); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.7 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.7 (C_{22}), 103.6–150.4 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.6 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.5–130.8 (C_{42}–C_{47}), 116.4–158.5 (C_{23}–C_{28}), 130.6 (C_{32}), 160.2 (C_{21}), 163.6 (C_{17}), 164.1 (C_{34}), 169.5 (C_{19}), 170.9 (C_{31}). Anal. Calcd for $C_{44}H_{39}N_5O_6$: C, 72.02; H, 5.36; N, 9.54. Found: C, 72.04; H, 5.35; N, 9.52.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,6-dichlouro-5-flouro phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6e). This compound was obtained as brown solid, yield 56%, m.p. 103–105°C, R_f: 0.60; IR (KBr): Ar-H 3058, CH_2 2958, 2837, C=O of imidazolinone 1789, C=N imidazolinone 1653, C=N of pyrimidine 1617, C—O—C 1223, 1035, C—F 972, C—Cl 745 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.16 (t, 3H, J = 7.63 Hz, —CH_3), 2.50 (q, 2H, J = 7.63 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 17H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.8 (C_8), 25.8 (C_7), 37.2 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.5–150.4 (C_{36}–C_{41}), 108.7 (C_{35}), 115.1–157.1 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.3–130.6 (C_{42}–C_{47}), 118.3–161.4 (C_{23}–C_{28}), 130.1 (C_{32}), 160.7 (C_{21}), 163.4 (C_{17}), 164.5 (C_{34}), 169.0 (C_{19}), 170.6 (C_{31}). Anal. Calcd for $C_{44}H_{36}N_5O_5Cl_2F$: C, 65.67; H, 4.51; N, 8.70. Found: C, 65.61; H, 4.50; N, 8.73.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-methyl phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6f). This compound was obtained as dark brown solid, yield 61%, m.p. 200–203°C, R_f: 0.65; IR (KBr): Ar-H 3063, CH_2 2953, 2835, C=O of imidazolinone 1797, C=N imidazolinone 1656, C=N of pyrimidine 1614, C—O—C 1222, 1034 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.34 (s, 3H, —CH_3), 2.51 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.70 Hz, —CH_2), 3.80 (s, 3H, —OCH_3), 4.32 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.76–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.3 (C_8), 25.4 (C_{29}), 25.7 (C_7), 37.3 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.8–149.2 (C_{36}–C_{41}), 108.5 (C_{35}), 114.9–158.9 (C_{11}–C_{16}), 123.3–155.4 (C_2–C_6), 127.0–130.2 (C_{42}–C_{47}), 128.1–137.23 (C_{23}–C_{28}), 130.2 (C_{32}), 158.9 (C_{21}), 160.8 (C_{17}), 163.5 (C_{34}), 165.5 (C_{19}), 170.0 (C_{31}). Anal. Calcd for $C_{45}H_{41}N_5O_5$: C, 73.85; H, 5.65; N, 9.57. Found: C, 73.80; H, 5.62; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(1-phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6g). This compound was obtained as brown solid, yield 55%, m.p. 102–104°C R_f: 0.59; IR (KBr): Ar-H 3064, CH_2 2957, 2836, C=O of imidazolinone 1795, C=N imidazolinone 1655, C=N of pyrimidine 1615, C—O—C 1229, 1033 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.24 (t,

3H, J = 7.61 Hz, —CH_3), 2.53 (q, 2H, J = 7.61 Hz, —CH_2—), 3.26 (t, 2H, J = 6.70 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.78–8.37 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.6 (C_7), 37.4 (C_9), 56.3 (C_{48}–C_{50}), 67.6 (C_{10}), 103.5 (C_{22}), 103.5–150.3 (C_{36}–C_{41}), 108.7 (C_{35}), 114.8–157.6 (C_{11}–C_{16}), 122.4–157.3 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 127.5–133.0 (C_{23}–C_{28}), 130.4 (C_{32}), 160.1 (C_{21}), 163.5 (C_{17}), 164.2 (C_{34}), 169.6 (C_{19}), 170.1 (C_{31}). Anal. Calcd. for $C_{44}H_{39}N_5O_5$: C, 73.62; H, 5.48; N, 9.76. Found: C, 73.65; H, 5.45; N, 9.75.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-fluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6h). This compound was obtained as brown solid, yield 52%, m.p. 125–128°C, R_f: 0.60; IR (KBr): Ar-H 3068, CH_2 2955, 2832, C=O of imidazolinone 1793, C=N imidazolinone 1653, C=N of pyrimidine 1617, C—O—C 1226, 1038, C—F 974 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.16 (t, 3H, J = 7.63 Hz, —CH_3), 2.56 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.70 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.78–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.8 (C_8), 25.2 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.5 (C_{10}), 103.8 (C_{22}), 103.2–150.8 (C_{36}–C_{41}), 108.4 (C_{35}), 114.9–157.5 (C_{11}–C_{16}), 122.4–157.2 (C_2–C_6), 126.1–130.3 (C_{42}–C_{47}), 116.0–162.9 (C_{23}–C_{28}), 130.1 (C_{32}), 160.7 (C_{21}), 163.6 (C_{17}), 164.4 (C_{34}), 169.3 (C_{19}), 170.3 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5F$: C, 71.82; H, 5.21; N, 9.52. Found: C, 71.81; H, 5.23; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-difluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6i). This compound was obtained as brown solid, yield 60%, m.p. 95–99°C, R_f: 0.59; IR (KBr): Ar-H 3066, CH_2 2953, 2833, C=O of imidazolinone 1795, C=N imidazolinone 1654, C=N of pyrimidine 1614, C—O—C 1225, 1035, C—F 975 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.20 (t, 3H, J = 7.63 Hz, —CH_3), 2.55 (q, 2H, J = 7.63 Hz, —CH_2—), 3.25 (t, 2H, J = 6.71 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.74–8.30 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.2 (C_8), 25.5 (C_7), 37.6 (C_9), 56.3 (C_{48}–C_{50}), 67.6 (C_{10}), 103.2 (C_{22}), 103.6–150.4 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.3 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 111.6–164.5 (C_{23}–C_{28}), 130.6 (C_{32}), 160.8 (C_{21}), 163.2 (C_{17}), 164.2 (C_{34}), 169.3 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5F_2$: C, 70.11; H, 4.95; N, 9.29. Found: C, 70.13; H, 4.92; N, 9.27.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-bromophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6j). This compound was obtained as brown solid, yield 61%, m.p. 130–132°C, R_f: 0.63; IR (KBr): Ar-H 3065, CH_2 2954, 2835, C=O of imidazolinone 1794, C=N imidazolinone 1656, C=N of pyrimidine 1612, C—O—C 1225, 1033, C—Br 864 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.63 Hz, —CH_3), 2.55 (q, 2H, J = 7.63 Hz, —CH_2—), 3.24 (t, 2H, J = 6.72 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.36 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.4 (C_7), 37.1 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.3 (C_{22}), 103.7–150.6 (C_{36}–C_{41}), 108.4 (C_{35}), 114.7–157.1 (C_{11}–C_{16}), 122.5–157.8 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 123.1–132.1 (C_{23}–C_{28}), 130.5 (C_{32}), 160.4 (C_{21}), 163.4 (C_{17}), 164.3 (C_{34}), 169.5 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5Br$: C, 66.33; H, 4.81; N, 8.79. Found: C, 66.30; H, 4.80; N, 8.77.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3,4-dichlorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6k). This compound was obtained as brown solid, yield 65%, m.p. 83–85°C, R_f: 0.66; IR (KBr): Ar-H 3060, CH_2 2952, 2834, C=O of imidazolinone 1798, C=N imidazolinone 1658, C=N of pyrimidine 1610, C—O—C 1220, 1035, C—Cl 749 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.22 (t, 3H, J = 7.63 Hz, —CH_3), 2.50 (q, 2H, J = 7.63 Hz, —CH_2—), 3.20 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.30 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.1 (C_7), 37.6 (C_9), 56.4 (C_{48}–C_{50}), 67.8 (C_{10}), 103.0 (C_{22}), 103.1–150.2 (C_{36}–C_{41}), 108.2 (C_{35}), 114.9–157.2 (C_{11}–C_{16}), 122.7–157.3 (C_2–C_6), 126.5–130.5 (C_{42}–C_{47}), 127.0–133.8 (C_{23}–C_{28}), 130.5 (C_{32}), 160.2 (C_{21}), 163.4 (C_{17}), 164.2 (C_{34}), 169.4 (C_{19}), 170.7 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5Cl_2$: C, 67.18; H, 4.74; N, 8.90. Found: C, 67.12; H, 4.72; N, 8.88.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-chlorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6l). This compound was obtained as dark yellow solid, yield 67%, m.p. 115–118°C, R_f: 0.54; IR (KBr): Ar-H 3063, CH_2 2951, 2834, C=O of imidazolinone 1794, C=N imidazolinone 1653, C=N of pyrimidine 1615, C—O—C 1227, 1035, C—Cl 743 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.23 (t, 3H, J = 7.64 Hz, —CH_3), 2.56 (q, 2H, J = 7.64 Hz, —CH_2—), 3.26 (t, 2H, J = 6.72 Hz, —CH_2), 3.84 (s, 3H, —OCH_3), 4.33 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.31 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.4 (C_8), 25.7 (C_7), 37.7 (C_9), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.4 (C_{22}), 103.4–150.6 (C_{36}–C_{41}), 108.4 (C_{35}), 114.8–157.6 (C_{11}–C_{16}), 122.7–157.4 (C_2–C_6), 126.4–130.0 (C_{42}–C_{47}), 128.9–134.3 (C_{23}–C_{28}), 130.6 (C_{32}), 160.2 (C_{21}), 163.4 (C_{17}), 164.2 (C_{34}), 169.5 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5Cl$: C, 70.25; H, 5.09; N, 9.31. Found: C, 70.24; H, 5.02; N, 9.32.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3-methoxyphenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6m). This compound was obtained as yellow solid, yield 52%, m.p. 114–116°C, R_f: 0.61; IR (KBr): Ar-H 3062, CH_2 2952, 2831, C=O of imidazolinone 1796, C=N imidazolinone 1658, C=N of pyrimidine 1617, C—O—C 1221, 1036 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.17 (t, 3H, J = 7.64 Hz, —CH_3), 2.53 (q, 2H, J = 7.64 Hz, —CH_2—), 3.26 (t, 2H, J = 6.72 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.33 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.73–8.36 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.3 (C_7), 37.2 (C_9), 55.8 (C_{29}), 56.4 (C_{48}–C_{50}), 67.2 (C_{10}), 103.2 (C_{22}), 103.3–150.6 (C_{36}–C_{41}), 108.7 (C_{35}), 114.2–157.5 (C_{11}–C_{16}), 122.5–157.3 (C_2–C_6), 126.1–130.3 (C_{42}–C_{47}), 112.2–161.1 (C_{23}–C_{28}), 130.4 (C_{32}), 160.3 (C_{21}), 163.2 (C_{17}), 164.1 (C_{34}), 169.4 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{45}H_{41}N_5O_6$: C, 72.27; H, 5.53; N, 9.36. Found: C, 72.25; H, 5.55; N, 9.34.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3-fluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6n). This compound was obtained as brown solid, yield 51%, m.p. 100–103°C, R_f: 0.62; IR (KBr): Ar-H 3067, CH_2 2955, 2835, C=O of imidazolinone 1795, C=N imidazolinone 1654, C=N of pyrimidine 1613, C—O—C 1224, 1032, C—F 974 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.51 (q, 2H, J = 7.61 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.35 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.34 (m,

19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.3 (C_8), 25.6 (C_7), 37.4 (C_9), 56.4 (C_{48}–C_{50}), 67.3 (C_{10}), 103.7 (C_{22}), 103.3–150.6 (C_{36}–C_{41}), 108.3 (C_{35}), 114.4–157.4 (C_{11}–C_{16}), 128.5–157.2 (C_2–C_6), 126.3–130.2 (C_{42}–C_{47}), 115.5–163.4 (C_{23}–C_{28}), 130.5 (C_{32}), 160.2 (C_{21}), 163.5 (C_{17}), 164.5 (C_{34}), 169.3 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5F$: C, 71.82; H, 5.21; N, 9.52. Found: C, 71.84; H, 5.22; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3,4-difluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6o). This compound was obtained as brown solid, yield 62%, m.p. 180–182°C, R_f: 0.60; IR (KBr): Ar-H 3063, CH_2 2957, 2836, C=O of imidazolinone 1796, C=N imidazolinone 1652, C=N of pyrimidine 1612, C—O—C 1224, 1037, C—F 972 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.21 (t, 3H, J = 7.63 Hz, —CH_3), 2.54 (q, 2H, J = 7.62 Hz, —CH_2—), 3.21 (t, 2H, J = 6.72 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.40 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.8 (C_7), 37.8 (C_9), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.8 (C_{22}), 103.4–150.6 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.4 (C_{11}–C_{16}), 122.3–157.3 (C_2–C_6), 126.3–130.2 (C_{42}–C_{47}), 117.5–149.5 (C_{23}–C_{28}), 130.4 (C_{32}), 160.7 (C_{21}), 163.6 (C_{17}), 164.3 (C_{34}), 169.4 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5F_2$: C, 70.11; H, 4.95; N, 9.29. Found: C, 70.09; H, 4.94; N, 9.27.

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Synthesis of Vinylindoles and Vinylpyrroles by the Peterson Olefination or by Use of the Nysted Reagent

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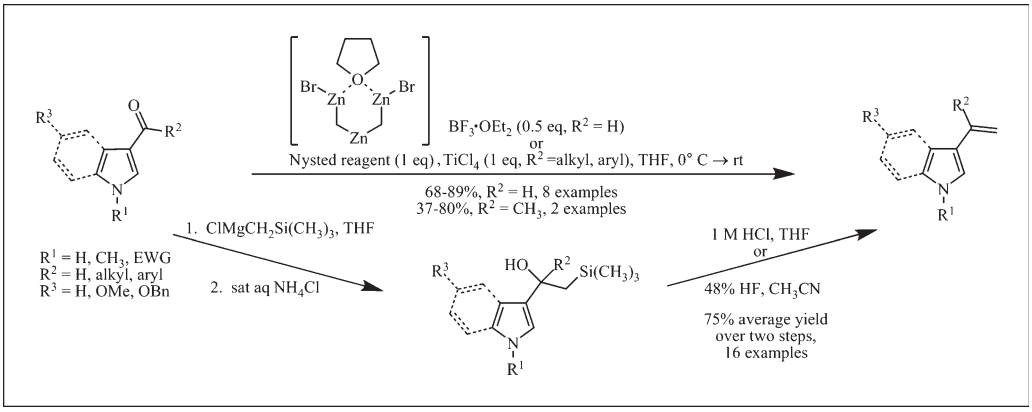

Vinylindoles and vinylpyrroles were prepared from their corresponding aldehydes or ketones using the Peterson olefination, or by use of the Nysted reagent, a commercially available gem-dimetallic compound. The two methods provide efficient and convenient access to these useful heterocyclic 1,3-diene systems.

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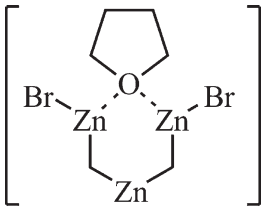
INTRODUCTION

There is great interest in the chemistry of indoles and carbazoles [1] as some of these compounds, both natural and synthetic [2], exhibit pharmacological activity. Vinylindoles and vinylpyrroles have been shown to act as dienes in regio- and stereo-controlled [4+2]-cycloadditions with electron-deficient alkenes or alkynes, and, therefore, represent valuable synthons for highly functionalized indole and carbazole ring systems [3].

The methylenation of carbonyl compounds is an important reaction in organic synthesis and various reagents have been used for this transformation, namely, phosphorus ylides [4], transition metal-carbene complexes [5], the Tebbe complex and related compounds [6], and gem-dimetallic compounds [7]. In addition to these reagents, combinations of gem-dihaloalkanes and low-valent metal salts have been used in the alkylidenation of aldehydes, ketones, and esters [8–10], although the reactive species generated by the above reagent systems have not been completely clarified. Among the synthetic methods available for making vinylindoles and vinylpyrroles, reliable standard methods are the Knoevenagel, Perkin, and Aldol condensations [11], the Cram modification of the Cope reaction [12], Wittig and Horner-Wadsworth-Emmons olefinations [13], reduction/dehydration [3i,14], base-mediated enolization followed by subsequent trapping [15], Michael addition with electron-deficient acetylenes and ethylenes [16], and Pd-catalyzed vinylation [17]. However, some of the drawbacks that may be encountered using these reagents and methods include low yields, harsh reaction conditions, and tedious workup procedures. Therefore, it is desirable to develop additional practical methods for the synthesis of these heterocyclic 1,3-diene systems.

The Peterson olefination involves generation of β-hydroxysilanes from carbonyl compounds and α-silylcarbanions, followed by exposure to either acidic or basic conditions to give alkenes, the driving force of the reaction being formation of the strong Si—O bond [18]. Although there is an example of the generation of 2-(3-indolyl)vinyltributylphosphonium salts [19] and also of the generation of 3-(2-(trimethylsilyl)vinyl)indoles [20] using the Peterson olefination, there is only a single example of the synthesis of a vinylindole with an unsubstituted olefin using this procedure [21], and to the best of our knowledge there are zero examples of the synthesis of vinylindoles with alkyl-substituted olefins or of any vinylpyrrole using this procedure.

The Nysted reagent **1** (Fig. 1) [22] is a commercially available reagent possessing two gem-dimetallic methylenating units in one molecule, and its utility for the methylenation of carbonyl compounds and also toward



1

Figure 1. Nysted reagent **1**.

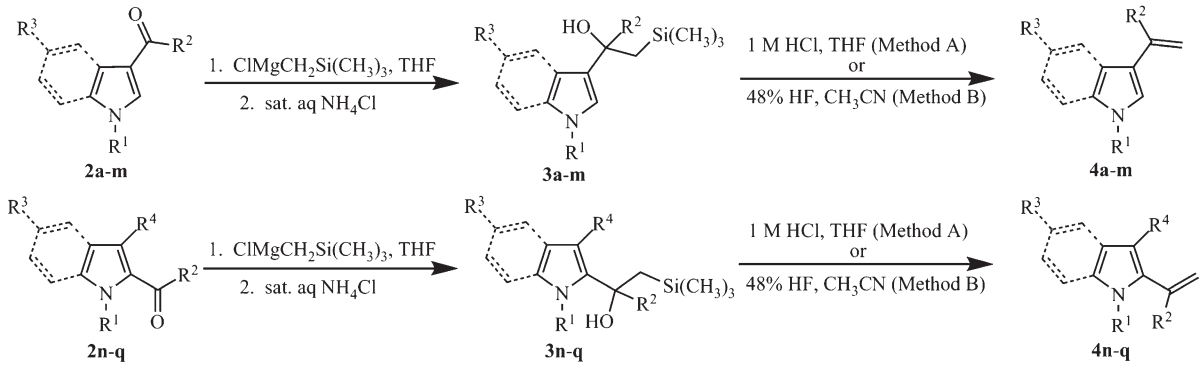
the methylenation of ketones using $TiCl_4$-mediated conditions were demonstrated soon after its introduction [23]. The precise reactivity of the Nysted reagent and the mechanistic role of $TiCl_4$ still remain to be clarified. Matsubara *et al*. have reported the use of **1** for the olefination of aldehydes and ketones [24]. They found that the reagent is suitable for the chemoselective methylenation of aldehydes under $BF_3{\bullet}OEt_2$-mediated conditions, whereas ketones require $TiCl_4$, $TiCl_3$, or a combination of $TiCl_2$ and $BF_3{\bullet}OEt_2$. There are numerous recent examples of methylenation with the Nysted reagent **1** during target-driven syntheses [25]. Although there is an example of the formation of a 3-vinylfuran using **1** [26], to the best of our knowledge there are no examples of the use of **1** to generate vinylindoles or vinylpyrroles.

We present here several examples using the Peterson olefination to make vinylindoles and vinylpyrroles in which the vinyl group is either unsubstituted or has an alkyl substituent. We also give what we believe to be the first examples of vinylindole and vinylpyrrole formation using the Nysted reagent.

RESULTS AND DISCUSSION

The Peterson olefination. Vinyl compounds **4a–g**, **i–m**, and **o–q** were successfully formed from carbonyl compounds **2a–g**, **i–m**, and **o–q** using the Peterson olefination at 75% average yield over two steps. The results are summarized in Scheme 1. Aldehyde **2h** was converted to the β-silanol **3h**, but, upon subsequent treatment

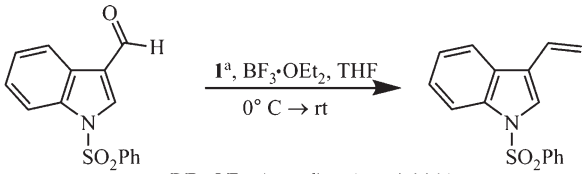
Scheme 1. Vinylindoles and vinylpyrroles from the Peterson olefination.



Carbonyl (2.0 mmol)	Heterocycle	R^1	R^2	R^3	R^4	β-Hydroxysilanes, **3**[a] Time, h	Yield %[b]	Elimination method[c]	Time, h	Product	Yield %[d]	References
2a	indole	SO_2Ph	H	H	-	2	87	A	2	**4a**	82	13b,17a,27
2b	indole	Ts	H	H	-	2	87	A	2	**4b**	94	13c
2c	indole	Bz	H	H	-	2	90	A	1	**4c**	79	-
2d	indole	Boc	H	H	-	2	97	A	1	**4d**	84	13d,28,29
2e	indole	SO_2Ph	H	OMe	-	2	90	A	1	**4e**	85	39
2f	indole	SO_2Ph	H	OBn	-	2	99	A	1	**4f**	92	-
2g	indole	Ms	H	H	-	2	99	A	2	**4g**	78	-
2h	indole	CH_3	H	H	-	2	85	A	-	**4h**	-	12b,13b,c
2h	indole	CH_3	H	H	-	2	85	B	-	**4h**	-	12b,13b,c
2i	indole	SO_2Ph	CH_3	H	-	18	97	A	2	**4i**	56	13a,b
2j	indole	SO_2Ph	$C(CH_3)_3$	H	-	48	99	A	48	**4j**	-	-
2j	indole	SO_2Ph	$C(CH_3)_3$	H	-	48	99	B	0.5	**4j**	86	-
2k	indole	SO_2Ph	Ph	H	-	24	96	A	4	**4k**	62	13e,31
2k	indole	SO_2Ph	Ph	H	-	24	96	B	0.5	**4k**	85	13e,31
2l	indole	SO_2Ph	4-FPh	H	-	24	85	A	4	**4l**	61	-
2l	indole	SO_2Ph	4-FPh	H	-	24	85	B	0.5	**4l**	79	-
2m	pyrrole	SO_2Ph	CH_3	-	-	24	93	A	3	**4m**	54	-
2n	indole	SO_2Ph	H	H	H	1.5	99	A	1	**4n**	-	13f,17b
2o	indole	SO_2Ph	H	H	CH_3	1.5	95	A	1	**4o**	88	-
2p	pyrrole	SO_2Ph	H	-	H	1	94	A	1	**4p**	86	3i
2q	pyrrole	Boc	H	-	H	1	92	A	1	**4q**	94	13g,29,32

[a] Satisfactory ^{1}H-NMR, ^{13}C-NMR, and IR were obtained. [b] Isolated, crude yield. [c] Method A: 1 M HCl, THF; method B: 48% HF, CH_3CN; see flow charts above. [d] Yield after purification by column chromatography.

Scheme 2. Methylenation of aldehyde **2a** with **1** and $BF_3 \bullet OEt_2$.



$BF_3 \cdot OEt_2$ (mmol)	**4a**, Yield %
-	48
0.05	32
0.10	57
0.15	72
0.50	79

[a] **1** (1.0 mmol), **2a** (1.0 mmol), THF (25 mL).

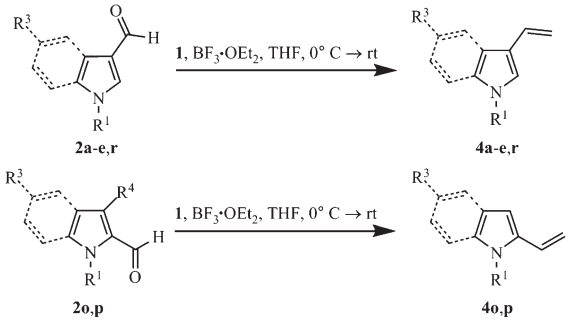
with either aqueous 1*M* HCl or aqueous 48% HF only a putative cycloadduct was observed by TLC, and the vinylindole **4h** was not isolated. It can be rationalized that the unshared electron pair on the unprotected nitrogen allowed elimination of the silylol, which was followed by acid-catalyzed dimerization of two of the resulting vinylindole molecules [33]. Problems were also experienced in attempting to synthesize **4n** by this strategy, which is not surprising as it is well-known that 2-vinylindoles dimerize under either acidic or thermal conditions [34]. The steric presence of a methyl group at the 3-position of the indole nucleus, however, allowed facile preparation of the 2-vinylindole **4o** as a stable crystalline solid.

Even in sterically demanding cases, the Peterson olefination performs quite admirably, although extended reaction times are required. Additionally, the elimination seems to occur more efficiently in the presence of aqueous 48% HF than aqueous 1*M* HCl [35]. For example, the β-silanol **3j** with aqueous 1*M* HCl was recovered unchanged even after prolonged exposure (48 h), whereas with aqueous 48% HF it gave the 3-vinylindole **4j** within 30 min at room temperature.

The practical advantages of this approach to vinylindoles and vinylpyrroles are high yields so long as an appropriate protecting group is used to attenuate the reactivity of the electron-rich heterocycle, easy workup conditions and purification (the main by-products are volatile silanols), gentle reaction conditions, and insensitivity to steric hindrance.

The Nysted reagent. Methylenation of aldehyde **2a** was examined first (Scheme 2). The reaction conditions were optimized by varying the amount of $BF_3 \bullet OEt_2$ and keeping the amount of Nysted reagent fixed at 1 equiv., as it has previously been demonstrated that the use of excess Nysted reagent does not dramatically improve yields of methylenated product [24]. An improvement in yield was observed with increasing amounts of added $BF_3 \bullet OEt_2$; however, as found by Matsubara *et al.* [24], the gains in yield seemed to plateau around 0.5 equiv. $BF_3 \bullet OEt_2$.

Scheme 3. Methylenation of aldehydes **2a–e**, **o**, **p**, and **r**.



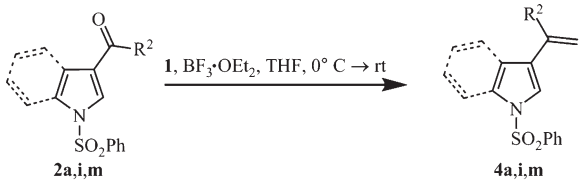
Aldehyde (1.0 mmol)	Heterocycle	**1** (mmol)	R^1	R^3	R^4	Product	Yield %
2a	indole	1.0	SO_2Ph	H	-	**4a**	79
2a	indole	2.0	SO_2Ph	H	-	**4a**	83
2b	indole	1.0	Ts	H	-	**4b**	75
2c	indole	1.0	Bz	H	-	**4c**	71
2d	indole	1.0	Boc	H	-	**4d**	85
2e	indole	1.0	SO_2Ph	OMe	-	**4e**	86
2o	indole	1.0	SO_2Ph	H	CH_3	**4o**	89
2r	pyrrole	1.0	SO_2Ph	-	-	**4r**	80
2p	pyrrole	1.0	SO_2Ph	-	H	**4p**	87

Aldehydes **2b–e**, **o**, **p**, and **r** were methylenated using the most efficient reaction conditions described above for **2a**. Good to excellent yields were obtained for all of the aldehydes studied (Scheme 3). In addition, it was confirmed that the use of excess Nysted reagent (2 equiv.) for the olefination of **2a** did not significantly improve the yield of **4a**.

The methylenation of ketones with the Nysted reagent was also examined (Scheme 4). In the cases where $BF_3 \bullet OEt_2$ or no mediator was used to catalyze the methylenation of **2i**, no olefin was obtained. In the presence of $TiCl_4$, however, olefins **4i** and **4m** were obtained from the corresponding ketones in fair to good yields, depending on the amount of Nysted reagent and $TiCl_4$ used.

As $BF_3 \bullet OEt_2$ mediated methylenation of aldehyde **2a**, but not ketone **2i**, the chemoselectivity of the Nysted reagent **1** was studied briefly (see Scheme 4, last two

Scheme 4. Methylenation using **1** in the presence of $TiCl_4$.



(1.0 mmol)	Heterocycle	**1** (mmol)	Mediator (mmol)	R^2	Product	Yield %
2i	indole	1.0	none	CH_3	**4i**	0
2i	indole	1.0	$BF_3 \cdot OEt_2$ (0.5)	CH_3	**4i**	0
2i	indole	0.5	$TiCl_4$ (0.5)	CH_3	**4i**	37
2i	indole	0.5	$TiCl_4$ (1.0)	CH_3	**4i**	51
2i	indole	1.0	$TiCl_4$ (1.0)	CH_3	**4i**	76
2m	pyrrole	1.0	$TiCl_4$ (1.0)	CH_3	**4m**	68
2a+2i[a]	indole	2.0	$BF_3 \cdot OEt_2$ (0.5)	H + CH_3	**4a+4i**	75/0
2a+2i[a]	indole	2.0	$TiCl_4$ (1.0)	H + CH_3	**4a+4i**	61/80

[a] 1.0 mmol **2a** combined with 1.0 mmol of **2i** was used

entries). Thus, an equimolar mixture of **2a** and **2i** was allowed to react with 1 equiv. **1** and 0.5 equiv. $BF_3 \bullet OEt_2$. After 2 h at room temperature, **4a** was isolated in 75% yield, whereas **2i** was recovered unchanged. In contrast, when $TiCl_4$ (1.0 equiv.) was used instead of $BF_3 \bullet OEt_2$ to mediate the reaction, **4a** was isolated in 61% yield, whereas **4i** was isolated in 80% yield.

CONCLUSIONS

In summary, we have developed convenient and efficient procedures for the preparation of vinylpyrroles and vinylindoles from the corresponding ketones and aldehydes in good to excellent yields by using either the Nysted reagent or the Peterson olefination. The Nysted reagent is chemoselective for the methylenation of aldehydes in the presence of ketones when the appropriate reaction mediator ($BF_3 \bullet OEt_2$) is used. The Peterson olefination performs well under sterically demanding conditions. The mild conditions, relatively short reaction times, and convenient workup procedures make these particular routes to vinylpyrroles and vinylindoles an attractive alternative to other olefination procedures. Moreover, as vinylpyrroles and vinylindoles represent useful synthons to highly functionalized indoles and carbazoles, the application of this methodology to the synthesis of indole and carbazole alkaloids is currently under investigation.

EXPERIMENTAL

General methods. Reagents were purchased from Aldrich Chemical Company and were used as received, unless otherwise noted. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone. Brine refers to saturated aqueous NaCl solution. TLC analyses were performed on plastic-backed plates precoated with 0.2 mm silica with F_{254} indicator. Column chromatography was performed with silica gel (230-400 mesh). Solvent ratios used in TLC and column chromatography are reported by volume. Melting points are uncalibrated. For ^1H and ^{13}C NMR spectra, chemical shifts (δ) were referenced to the solvent, and for ^{19}F NMR spectra, they were referenced to $CFCl_3$. ^{13}C NMR spectra were proton-decoupled. Infrared spectra were recorded on a 4000 FT-IR spectrometer; only the most intense and/or diagnostic peaks are reported. Elemental analyses were performed at M-H-W Laboratories, Phoenix, AZ. Aldehydes and ketones were prepared according to published procedures [36].

5-Benzyloxy-1-phenylsulfonyl-1H-indole-3-carboxaldehyde (2f). Aqueous 50% potassium hydroxide (12 mL) and phenylsulfonyl chloride (4.2 g, 23.8 mmol) were added to a solution of 5-benzyloxyindole-3-carboxaldehyde (3.0 g, 11.9 mmol, prepared by formylation [37] of 5-benzyloxyindole [38,39]) and tetrabutylammonium hydrogen sulfate (0.05 g, 0.14 mmol) in benzene (40 mL) at rt. After being stirred for 2.5 h, the mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (2 × 100 mL), brine (100 mL), dried over $MgSO_4$, and the solvents were removed using a rotating evaporator, giving a brown oil. Addition of cold EtOH (10 mL) caused the brown oil to crystallize, giving **2f** (3.01 g, 65%) as a tan solid: mp 129–131°C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.84 (s, 1H), 8.08 (dd, J = 7.5, 1.5 Hz, 2H), 7.89 (d, J = 7.2 Hz, 1H), 7.75–7.59 (m, 4H), 7.44–7.25 (m, 5H), 7.11 (dd, J = 9.0, 2.4 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 187.25, 156.83, 139.45, 137.32, 136.78, 135.85, 130.66, 129.44, 128.90, 128.33, 123.12, 127.63, 127.36, 122.05, 116.30, 114.66, 105.69, 104.99, 70.14; HR-EI MS: $C_{22}H_{17}NO_4S$ [M]+, calcd. 391.0878, found 391.0876. Anal. Calcd. for $C_{22}H_{17}NO_4S$: C, 67.50; H, 4.38; N, 3.58; S, 8.19. Found: C, 67.61; H, 4.21; N, 3.69; S, 8.25.

2,2-Dimethyl-1-(3-(1-phenylsulfonyl-1H-indolyl))-1-propanone (2j). Aqueous 50% KOH (25 mL) and phenylsulfonyl chloride (8.83 g, 0.050 mol) were added sequentially to a solution of 3-pivaloylindole [40] (5.00 g, 0.025 mol) and tetrabutylammonium hydrogen sulfate (0.11 g, 0.3 mmol) in benzene (100 mL) at rt. After being stirred for 1.5 h, the mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL), washed with brine (100 mL), dried over $MgSO_4$, and the solvents were removed using a rotating evaporator, giving a golden yellow oil. Trituration with EtOH (10 mL) followed by drying gave **2j** as white crystals (7.24 g, 85%): mp 93–95 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.16 (dd, J = 6.9, 1.0 Hz, 2H), 7.96 (d, J = 8.1 Hz, 1H), 7.69–7.57 (m, 3H), 7.39–7.31 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 202.58, 136.98, 135.69, 133.84, 130.86, 130.56, 129.40, 127.71, 126.36, 125.18, 123.36, 117.64, 113.31, 44.68, 28.25; HR-EI MS: $C_{19}H_{19}NO_3S$ $[M]^+$, calcd. 341.1086, found 341.1080. Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found: C, 66.96; H, 5.55; N, 4.08; S, 9.34.

3-(4-Fluorobenzoyl)-1-phenylsulfonyl-1H-indole (2l). 3-(4-Fluorobenzoyl)indole [40] (5.98 g, 0.025 mol) was treated with phenylsulfonyl chloride (8.83 g, 0.050 mol) as in the procedure described above for **2j**, with recrystallization from EtOH giving **2l** as tan crystals (8.55 g, 90%): mp 108–110°C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.15 (d, J = 7.2 Hz, 3H), 8.00–7.95 (m, 3H), 7.70 (dd, J = 7.5, 7.2 Hz, 1H), 7.58 (dd, J = 8.1, 7.2 Hz, 2H), 7.41 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 189.03, 166.84, 163.51, 136.79, 135.77, 135.71, 135.67, 134.63, 134.56, 132.36, 132.24, 130.54, 128.49, 127.92, 126.56, 125.38, 122.87, 119.66, 116.42, 116.13, 113.55; ^{19}F (282 MHz, DMSO-d_6) δ -117.19; HR-EI MS: $C_{21}H_{14}FNO_3S$ $[M]^+$, calcd. 379.0678, found 379.0680. Anal. Calcd. for $C_{21}H_{14}FNO_3S$: C, 66.48; H, 3.72; N, 3.69; O, 12.65; S, 8.45. Found: C, 66.39; H, 3.75; N, 3.71; O, 12.64; S, 8.33.

3-Ethenyl-1-phenylsulfonyl-1H-indole (4a) (General procedures for the synthesis of compounds 4a–q (Peterson Olefination) and 4a–e,o,p,r (Nysted)) [13b,17a,27]. *Using the Peterson olefination.* Formation of the β-silanol **3a**: (Trimethylsilyl)methylmagnesium chloride (3.0 mmol, 1*M* solution in Et_2O, 1.5 equiv.) diluted with THF (5 mL) was added dropwise to a solution of 1-phenylsulfonylindole-3-carboxaldehyde **2a** (0.571 g, 2.0 mmol) in THF (10 mL) at rt under N_2. The reaction was monitored by TLC (SiO_2, CH_2Cl_2) and was shown to be

complete when 2,4-DNP stain (for preparation, see ref. 41) indicated the absence of the aldehyde, in 2–48 h (typically in no more than 2 h). The reaction solution was quenched with saturated aqueous NH_4Cl (15 mL) and stirred at rt for 30 min. It was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. The solution was filtered, and the solvents were evaporated using a rotating evaporator, giving the crude β-silanol **3a** (0.725 g, 97 %) as a viscous, yellow oil, which was carried on to the dehydration/desilylation step without further purification. Formation of the olefin **4a**: For method A, aqueous 1*M* HCl (10 mL) was added to a solution of the crude **3a** (0.725 g, 1.9 mmol) in THF (10 mL) and the two liquid phases were stirred at rt. After 0.5–48 h, TLC (SiO_2, CH_2Cl_2) indicated the elimination to be complete (typically in no more than 2 h). The reaction solution was poured slowly into saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were removed using a rotating evaporator giving the crude vinylindole **4a** as a pale golden-yellow oil. Flash chromatography (SiO_2, hexanes/CH_2Cl_2 3:1) gave analytically pure **4a** as a white crystalline solid (0.45 g, 82%): mp 64–65°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (m, 4H), 7.88 (d, J = 7.8 Hz, 1H), 7.70 (m, 1H), 7.60 (dd, J = 8.1, 7.2 Hz, 2H), 7.40 (ddd, J = 8.1, 7.5, 1.2 Hz, 1H), 7.32 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 6.86 (dd, J = 17.7, 11.4 Hz, 1H), 5.93 (dd, J = 18.0, 1.0 Hz, 1H), 5.37 (dd, J = 11.4, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.34, 135.24, 135.17, 130.35, 128.90, 127.95, 127.20, 125.69, 125.48, 124.40, 121.20, 121.10, 116.24, 113.83; HR-EI MS: $C_{16}H_{13}NO_2S$ $[M]^+$, calcd. 283.0667, found 283.0668. Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94; S, 11.32. Found: C, 67.64; H, 4.67; N, 5.01; S, 11.29.

Using the Nysted reagent. Nysted reagent **1** [22] (11.5 g of a 20 wt % suspension in THF, 5.0 mmol, 1 equiv.) was added under N_2 to THF (15 mL) at 0°C. A solution of BF_3•Et_2O (0.35 g, 2.5 mmol, 0.5 equiv.) in THF (5 mL) was added dropwise and the milky gray suspension was stirred at 0°C for 10 min. A solution of 1-phenylsulfonylindole-3-carboxaldehyde **2a** (1.43 g, 5.0 mmol) in THF (15 mL) was added by syringe and the mixture was warmed slowly to room temperature and kept there for 3 h after which the milky gray suspension had turned gray-black. TLC (silica gel, CH_2Cl_2) indicated completion of the reaction, so the mixture was poured into a beaker containing aq 1*M* HCl (50 mL). The resulting dark gray suspension was stirred until the HCl dissolved all of the Nysted reagent zinc metal. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (100 mL), saturated aq $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotating evaporator, giving an amber oil. Purification by column chromatography (silica gel, hexanes/CH_2Cl_2, 3:1, v/v) gave the 3-ethenylindole (**4a**) as a white crystalline solid (1.12 g, 79%). Analytical data matched that listed above for **4a**.

3-Ethenyl-1-(4-methylphenylsulfonyl)-1H-indole (4b) [13c]. Preparation using the Peterson and Nysted procedures was as described for **4a**. Data for **4b**: white crystalline solid (Peterson: 0.488 g, 82% over two steps; Nysted: 1.115 g, 75%); mp 97–98°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.30 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 7.25 (ddd, J = 8.7, 7.2, 1.2 Hz, 1H), 7.20 (dd, J = 8.4, 1.0 Hz, 2H), 6.77 (dd, J = 18.0, 11.1 Hz, 1H), 5.78 (dd, J = 18.0, 1.0 Hz, 1H), 5.35 (dd, J = 11.1, 1.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.09, 135.54, 135.14, 129.96, 129.06, 127.60, 126.89, 124.97, 124.14, 123.57, 121.01, 120.49, 115.39, 113.78, 21.59; IR (KBr) cm^{-1} 1670, 1630, 1598, 1448, 1372, 1178, 960; HR-EI MS: $C_{17}H_{15}NO_2S$ $[M]^+$, calcd. 297.0823, found 297.0826. Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.61; H, 4.99; N, 4.74; S, 10.96.

1-Benzoyl-3-ethenyl-1H-indole (4c). Preparation using the Peterson and Nysted procedures was as described for **4a**. Data for **4c**: golden yellow oil (Peterson: 0.351 g, 71% over two steps; Nysted: 0.878 g, 71%); R_f 0.75 (silica gel, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (dd, J = 6.9, 1.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.2 Hz, 2H), 7.73–7.32 (m, 6H), 6.82 (dd, J = 18.0, 11.4 Hz, 1H), 5.85 (d, J = 18.0 Hz, 1H), 5.30 (d, J = 11.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.58, 136.75, 134.43, 132.58, 129.55, 129.47, 129.23, 128.98, 128.69, 127.13, 125.62, 124.72, 120.79, 119.92, 116.53, 115.64; IR (neat NaCl plates) cm^{-1} 3054, 1683, 1633, 1601, 1580, 1548, 1451, 1417, 1351, 1255, 1225; HR-EI MS: $C_{17}H_{13}NO$ $[M]^+$, calcd. 247.0997, found 247.0988. Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.44; H, 5.35; N, 5.77.

1,1-Dimethylethyl 3-ethenyl-1H-indole-1-carboxylate (4d) [13d,28,29]. Preparation using the Peterson and Nysted procedures was as described for **4a**. Data for **4d**: pale yellow oil (Peterson: 0.487 g, 82% over two steps; Nysted: 1.034 g, 85%); R_f 0.73 (silica gel, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 7.2, 1.0 Hz, 1H), 7.77 (s, 1H), 7.32 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.24 (ddd, J = 8.7, 7.8, 1.2 Hz, 1H), 6.82 (dd, J = 18.0, 11.4 Hz, 1H), 5.83 (dd, J = 18.0, 1.2 Hz, 1H), 5.27 (dd, J = 11.4, 1.2 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.37, 135.79, 128.61, 128.56, 125.10, 124.95, 123.50, 120.59, 119.08, 115.38, 114.91, 84.29, 28.06; HR-EI MS: $C_{15}H_{17}NO_2$ $[M]^+$, calcd. 243.1259, found 243.1259. Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.21; H, 7.01; N, 5.65.

3-Ethenyl-5-methoxy-1-phenylsulfonyl-1H-indole (4e) [30]. Preparation using the Peterson and Nysted procedure was as described for **4a**. Data for **4e**: pale yellow solid (Peterson: 0.483 g, 77% over two steps; Nysted 1.347 g, 86%); mp 127–129°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97-7.92 (m, 3H), 7.84 (d, J = 9 Hz, 1H), 7.65 (dd, J = 8.7, 1.2 Hz, 1H), 7.55 (dd, J = 8.4, 8.1 Hz, 2H), 7.27 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 9.0, 2.4 Hz, 1H), 6.82 (dd, J = 18.0, 11.4 Hz, 1H), 5.86 (dd, J = 18.0, 1.0 Hz, 1H), 5.31 (dd, J = 11.4, 1.0 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.95, 137.29, 135.09, 130.30, 130.12, 129.74, 127.81, 127.11, 125.88, 121.30, 116.11, 114.72, 114.35, 103.73, 55.99; IR (KBr) cm^{-1} 3107, 3067, 1610, 1593, 1566, 1473, 1448, 1373, 1292, 1222, 1174, 1119, 1095, 1036, 984; HR-EI MS: $C_{17}H_{15}NO_3S$ $[M]^+$, calcd. 313.0773, found 313.0774. Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found: C, 64.98; H, 4.75; N, 4.58; S, 10.17.

5-Benzyloxy-3-ethenyl-1-phenylsulfonyl-1H-indole (4f). Preparation using the Peterson procedure was as described for **4a**. Data for **4f**: white crystals (0.709 g, 91% over two steps); mp 142–143°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (m, 2H),

7.86 (d, J = 9.0 Hz, 1H), 7.69–7.54 (m, 3H), 7.45–7.27 (m, 6H), 7.05 (dd, J = 9.0, 2.4 Hz, 1H), 6.80 (dd, J = 18.0, 11.4 Hz, 1H), 5.85 (d, J = 18.0 Hz, 1H), 5.31 (d, J = 11.7 Hz, 1H), 5.11 (s, 2H); ^{13}C (75 MHz, DMSO-d_6) δ 156.01, 137.57, 137.29, 135.12, 130.33, 130.02, 129.86, 128.91, 128.33, 128.23, 127.83, 127.13, 126.06, 121.24, 116.13, 114.99, 114.75, 105.01, 70.22; HR-EI MS: $C_{23}H_{19}NO_3S$ $[M]^+$, calcd. 389.1086, found 389.1060. Anal. Calcd. For $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60; S, 8.23. Found: C, 71.05; H, 4.99; N, 3.44; S, 8.19.

3-Ethenyl-1-methanesulfonyl-1H-indole (4g). Preparation using the Peterson procedure was as described for **4a**. Data for **4g**: off-white solid (0.341 g, 77% over two steps); R_f 0.70 (SiO_2, CH_2Cl_2); mp 57–59°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 7.41 (dd, J = 8.7, 7.8 Hz, 1H), 7.34 (dd, J = 8.1, 7.5 Hz, 1H), 6.88 (dd, J = 17.7, 11.1 Hz, 1H), 5.90 (dd, J = 18.0, 1.0 Hz, 1H), 5.34 (dd, 11.4, 1.0 Hz, 1H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6) δ 135.46, 128.58, 128.27, 125.45, 125.38, 124.00, 121.10, 119.69, 115.55, 113.57, 41.38; IR (neat, NaCl plates) 1636, 1604, 1448, 1362, 1269, 1219, 1173, 1124, 970 cm^{-1}; HR-EI MS: $C_{11}H_{11}NO_2S$ $[M]^+$, calcd. 211.0510, found 211.0491. Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.77; H, 5.22; N, 6.39; S, 14.38.

3-(1-Methylethenyl)-1-phenylsulfonyl-1H-indole (4i) [13a,b]. Preparation using the Peterson procedure was the same as described for **4a**. The Nysted procedure and molar quantities used for the synthesis of compound **4a** was followed, except that: (1) The BF_3•Et_2O solution in THF was replaced by $TiCl_4$ (0.55 mL, 0.95 g, 5.0 mmol) which was added by syringe; and (2) The reaction mixture was kept at rt for 4 h instead of 3 h. The product **4i** was obtained as a white crystalline solid (Peterson: 0.321 g, 54% over two steps; Nysted: 1.130 g, 76%): R_f 0.71 (silica gel, CH_2Cl_2); mp 97–98°C; ^{1}H and ^{13}C NMR ($CDCl_3$) data matched those in the literature[13a,b]; HR-EI MS: $C_{17}H_{15}NO_2S$ $[M]^+$, calcd. 297.0824, found 297.0839. Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.49; H, 5.05; N, 4.58; S, 10.69.

3-(2,2-Dimethyl-1-methylenepropyl)-1-phenylsulfonyl-1H-indole (4j). Preparation using the Peterson procedure described for **4a**, with the exception that method B was used in which 48% aqueous HF (8 drops) was added in place of HCl, and rather than THF the crude **3j** was dissolved in CH_3CN (5 mL). Data for **4j**: white crystalline solid (0.577 g, 85% over two steps); mp 59–61°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97–7.93 (m, 3H), 7.59 (dd, J = 7.5, 1.5 Hz, 1H), 7.54–7.49 (m, 3H), 7.36–7.29 (m, 2H), 7.20 (ddd, J = 8.1, 7.8, 1.0 Hz, 1H), 5.35 (d, J = 1.2 Hz, 1H), 4.83 (d, J = 1.2 Hz, 1H), 1.00 (s, 9H); ^{13}C (75 MHz, DMSO-d_6) δ 149.42, 137.41, 134.99, 134.35, 132.19, 130.20, 127.10, 125.31, 124.22, 124.11, 123.29, 121.09, 115.07, 113.66, 36.36, 29.52; HR-EI MS: $C_{20}H_{21}NO_2S$ $[M]^+$, calcd. 339.1293, found 339.1292. Anal. Calcd. for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13; O, 9.43; S, 9.45. Found: C, 70.71; H, 6.09; N, 3.98; S, 9.41.

3-(1-Phenylethenyl)-1-phenylsulfonyl-1H-indole (4k) [13e, 31]. Preparation using the Peterson procedure was conducted in two ways: as described for **4a**, with the use of method A, and also as described for **4a** but with the exception that method B was used, as described for **4j**. Recrystallization from MeOH gave the analytical sample of **4k** as a white solid (Method A: 0.431 g, 60% over two steps; Method B: 0.589 g, 82% over two steps): R_f 0.69 (SiO_2, CH_2Cl_2); mp 111–112°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (dd, J = 7.8, 1.2 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.66 (dd, J = 7.2, 1.2 Hz, 1H), 7.56 (ddd, J = 7.8, 7.2, 1.2 Hz, 2H), 7.38–7.26 (m, 5H), 7.13 (m, 2H), 5.61 (s, 1H), 5.60 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) 140.69, 140.35, 137.28, 135.22, 135.13, 130.35, 129.61, 128.98, 128.70, 127.71, 127.32, 125.70, 125.55, 124.14, 123.78, 121.45, 116.61, 113.96; HR-EI MS: $C_{22}H_{17}NO_2S$ $[M]^+$, calcd. 359.0980, found 359.0981. Anal. Calcd. For $C_{22}H_{17}NO_2S$: C, 73.51; H, 4.77; N, 3.90; S, 8.92. Found C, 73.62; H, 4.92; N, 3.96; S, 8.74.

3-(1-(4-Fluorophenyl)ethenyl)-1-phenylsulfonyl-1H-indole (4l). Preparation using the Peterson procedure was conducted in two ways: as described for **4a**, with the use of method A, and as described for **4a** but with the exception that method B was used, as described for **4j**. Data for **4l**: white crystalline solid (Method A: 0.393 g, 52% over two steps; Method B: 0.377 g, 50% over two steps); R_f 0.82 (SiO_2, CH_2Cl_2); mp 98–99°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (dd, J = 7.5, 1.5 Hz, 2H), 7.97 (d, J = 8.4, 1H), 7.73–7.67 (m, 2H), 7.56 (dd, J = 7.8, 7.2 Hz, 2H), 7.35–7.28 (m, 3H), 7.19–7.10 (m, 4H), 5.59 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.16, 160.91, 139.60, 137.27, 136.80, 136.75, 135.24, 135.11, 130.37, 129.82, 129.71, 129.47, 127.34, 125.78, 125.58, 124.20, 123.59, 121.40, 116.68, 115.98, 115.69, 113.97; ^{19}F NMR (282 MHz, DMSO-d_6) δ −124.17; HR-EI MS: $C_{22}H_{16}FNO_2S$ $[M]^+$, calcd. 377.0886, found 377.0898. Anal. Calcd. for $C_{22}H_{16}FNO_2S$: C, 70.01; H, 4.27; F, 5.03; N, 3.71; S, 8.50. Found: C, 70.19; H, 4.38; F, 5.15; N, 3.77; S, 8.45.

3-(1-Methylethenyl)-1-phenylsulfonyl-1H-pyrrole (4m). Preparation using the Peterson procedure was the same as described for **4a**. The Nysted procedure and molar quantities used for the synthesis of compound **4a** were used, with the exceptions noted above for compound **4i**, giving **4m** (Peterson: 0.247 g, 50% over two steps; Nysted: 0.841 g, 68%) as a white crystalline solid: R_f 0.68 (silica gel, CH_2Cl_2); mp 58–60°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.64–7.46 (m, 3H), 7.11 (m, 2H), 6.45 (m, 2H), 5.51 (dd, J = 1.5, 1.2 Hz, 1H), 5.19 (dd, J = 1.5, 1.2 Hz, 1H), 2.14 (s, 3H); HR-EI MS: $C_{13}H_{13}NO_2S$ $[M]^+$, calcd. 247.0667, found 247.0691. Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; S, 12.97. Found: C, 63.26; H, 5.24; N, 5.78; S, 12.85.

2-Ethenyl-3-methyl-1-phenylsulfonyl-1H-indole (4o). Preparation using the Peterson and Nysted procedure was as described for **4a**. Data for **4o**: pale yellow solid (Peterson: 0.500 g, 84% over two steps; Nysted: 1.323 g, 89%); mp 131–133°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, J = 8.1 Hz, 1H), 7.80 (dd, J = 8.1, 1.2 Hz, 2H), 7.70 (m, 1H), 7.61–7.56 (m, 3H), 7.45 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.36 (ddd, J = 8.7, 7.5, 0.9 Hz, 1H), 7.17 (dd, J = 17.7, 11.7 Hz, 1H), 5.79 (dd, J = 11.7, 1.8 Hz, 1H), 5.58 (dd, J = 17.7, 1.8 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.73, 135.99, 135.08, 134.81, 131.97, 130.25, 127.58, 126.92, 126.15, 124.71, 121.72, 120.40, 119.51, 115.19, 10.70; HR-EI MS: $C_{17}H_{15}NO_2S$ $[M]^+$, calcd. 297.0823, found 297.0819. Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.85; H, 5.14; N, 4.69; S, 10.87.

2-Ethenyl-1-phenylsulfonyl-1H-pyrrole (4p) [3i]. Preparation using the Peterson and Nysted procedures was as described for **4a**. Data for **4p**: white crystalline solid (Peterson: 0.378 g,

81% over two steps; Nysted: 1.015 g, 87%); mp 67–68°C; ^{1}H NMR data (300 MHz, $CDCl_3$) matched those in the literature [3i]; ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.06, 134.13, 133.85, 129.22, 126.81, 125.44, 123.26, 115.21, 112.44, 111.89; HR-EI MS: $C_{12}H_{11}NO_2S$ $[M]^+$, calcd. 233.0510, found 233.0506.

1,1-Dimethylethyl 2-Ethenyl-1H-pyrrole-1-carboxylate (4q) [13g,29,32]. Preparation using the Peterson procedure was as described for **4a**, giving **4q** as a yellow oil (0.332 g, 86% over two steps): spectral data for **4q** matched those in the literature[13g].

3-Ethenyl-1-phenylsulfonyl-1H-pyrrole (4r) [3i]. Preparation using the Nysted procedure was as described for **4a**. Data for **4r**: white crystalline solid (0.933 g, 80%); mp 40–41°C; ^{1}H NMR data ($CDCl_3$) matched those in the literature [3i]; ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.91, 133.66, 129.42, 128.20, 127.79, 126.83, 121.77, 118.45, 113.52, 111.06; HR-EI MS: $C_{12}H_{11}NO_2S$ $[M]^+$, calcd. 233.0510, found 233.0513.

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Synthesis and Antiviral Activity of Novel Pyrazole Amides Containing α-Aminophosphonate Moiety

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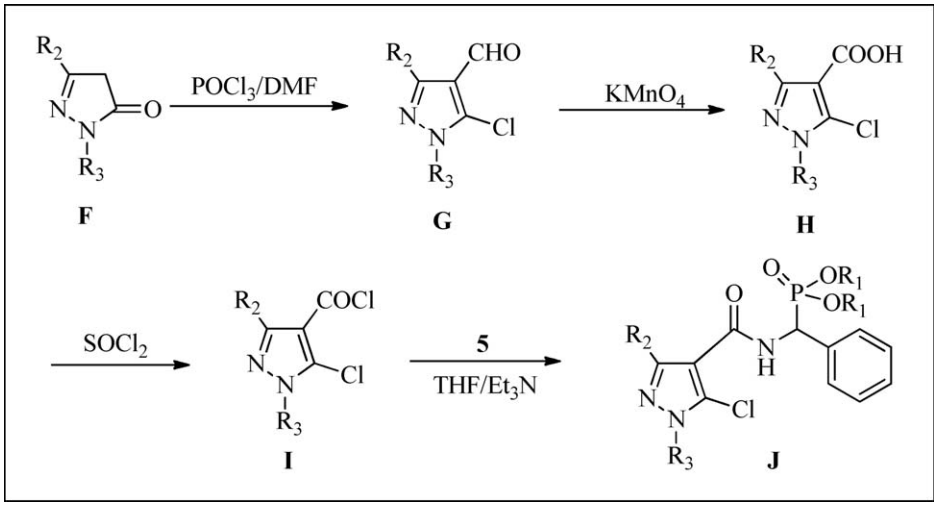

A series of novel pyrazole amides **J1–J15** containing an α-aminophosphonate moiety were synthesized and subsequently characterized by spectral (IR, ^{1}H-, ^{13}C-, ^{31}P-, and ^{19}F-NMR) data and elemental analysis. The racemic sample of **J1** was further separated into its enantiomers under normal-phase condition on two immobilized polysaccharide-based chiral stationary phases (Chiralpak IA and Chiralpak IC). The synthesized compounds revealed certain degree of antiviral activity in the bioassay. The title compounds (**J3**, **J10**, and **J12**) showed some curative activities (39.9%, 41.8%, 50.1%, respectively) against tobacco mosaic virus at 0.5 mg/mL.

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INTRODUCTION

Pyrazole amide derivatives occupy an important position in medicinal and pesticide chemistry due to their diverse bioactivities. Not only they display prominent antagonist, anti-inflammatory, and inhibitory activities as drugs [1–3] but are also used as potent insecticides, fungicides, and herbicides in pesticide science [4–6]. Considerable attention has been paid in recent years to the synthesis of these compounds [7]. Amongst the active compounds, as shown in Figure 1, Furametpyr (Sumitomo Chemical Co., 1997) and Penthiopyrad (Mitsubishi Chemical Co., 2005) are known for their ability to protect certain plants from severe antifungal infection. Another important class of compounds that belongs to α-aminophosphonic acid group has enormous application as growth regulators, fungicides, plant virucides, and herbicides [8–10]. A great deal of research has been directed for the development of suitable synthetic techniques to access biologically active α-aminophosphonates and their derivatives [11–15]. In our continued endeavor to develop environment-friendly antiviral agents, we had earlier prepared a large number of substituted aryl aminophosphonate derivatives containing amide, thiourea, and cyanoacrylate moieties [16–24]. As different aminophosphonates and their derivatives display varying activities, we envisioned that screening of properly substituted pyrazole amide derivatives bearing various α-amiophosphonate moieties might lead to lead structures having superior antiviral activities against tobacco mosaic virus (TMV) (Fig. 2). Keeping these considerations in mind, herein we report preparation of new pyrazole amide derivatives bearing α-aminophosphonate moieties (Scheme 1) and their subsequent evaluation as antiviral agents. To the best of our knowledge, this is the first report on the synthesis and antiviral studies of compounds where aminophosphontes are incorporated into parent pyrazole amide unit.

RESULTS AND DISCUSSION

The title compounds **J** can be synthesized by the reaction of the appropriate amine with carboxylic acid

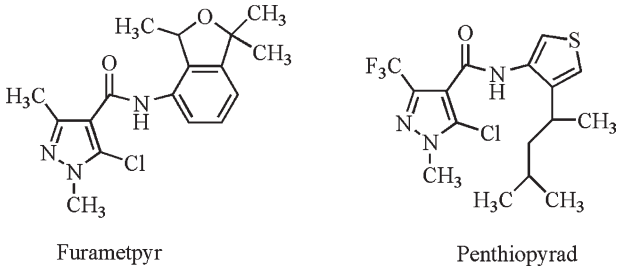


Figure 1. The structures of commercial fungicides.

or by treating the amine with acyl chloride. In the first approach, a controlled addition of 1,3-dicyclohexylcarbodiimide into the mixture of amine and acid is necessary as the reaction is exothermic and tends to get violent. By carefully controlling the reaction temperature at 0°C, the desired product could be prepared but in much lower yield. Using the second method, however, the title compounds **J** could be obtained in 45–80% yield from a reaction of acyl chloride and amine in presence of triethylamine. The base was required as the resulting phosphonates are susceptible to acidolysis by liberated HCl. This later approach was preferred over the former due to the ease of preparation, higher yield and reactivity, and shorter reaction time. The entire synthetic route to access the target compound is shown in Scheme 1. The key intermediate **5** was first synthesized from appropriate dialkyl phosphite and benzaldehyde. The imine **3** was generated in two steps. Addition of *p*-toluenesulfonic acid into **3** is highly exothermic and may cause an undesired side reaction. Controlling the reaction temperature near 0°C during its addition is the most important factor in the synthesis of α-aminobenzylphosphonate **5**. The 5-pyrazolones **F** were subjected to Vilsmeier–Haack chloroformylation using *N*,*N*-dimethylformamide (DMF) and an excess of phosphorus oxychloride ($POCl_3$) to yield the corresponding 5-chloro-4-formylpyrazoles **G**, which were further oxidized by potassium permanganate and then chlorinated with thionyl chloride ($SOCl_2$) to provide the intermediate **I**.

To optimize the reaction conditions for the preparation of compound $\mathbf{J_1}$ bearing an asymmetric carbon atom adjacent to the phosphonate moiety, the reaction was carried out in different solvents, such as tetrahydrofuran (THF), dichloromethane (DCM), chloroform, DMF, and acetonitrile. A maximum yield of 70% was achieved when the reaction mixture was stirred in the presence of triethylamine for 0.5 h in THF. The effect of solvent system is summarized in Table 1.

Having established the most suitable condition for the preparation of $\mathbf{J_1}$, we carried out semipreparative enantioseparation of this racemate. This was done to confirm if the individual enantiomers differed in their antiviral bioactivity. The sample was dissolved in a mobile phase consisting of *n*-hexane/isopropyl alcohol (IPA)/DCM (80/15/5, v/v/v) and *n*-hexane/IPA/DCM (80/15/5, v/v/v) at 6.5 mg/mL with an injection volume of 2 mL, flow rate 3.0 mL/min, and detection wavelength 230 nm. The two fractions collected in the order of their elution were assigned as F1 and F2, respectively. After semipreparative separation, the first-eluting enantiomer (F1) and the second-eluting enantiomer (F2) were analyzed by analytical IA column to ascertain their enantiomeric excess (e.e.) values. The analytical samples were dissolved in EtOH at an approximate concentration of 0.5 mg/mL and injection volume of 5 μL. The mobile phase was composed of *n*-hexane/EtOH (90/10, v/v), flow rate was set at 1.0 mL/min and detection wavelength was fixed at 230 nm. Temperature was always kept at 25°C except for those experiments where effect of temperature was studied. The holdup time was determined from the elution of an unretained marker (toluene). The analytical assessment of enantiomeric excess values showed that the collected fractions were practically enantiopure with e.e. exceeding 99% (Fig. 3). Optical rotation values were measured on a WZZ-ZS automatic polarimeter and the data are presented in Table 2.

The main characteristic of the ^{1}H-NMR spectra of $\mathbf{J_1}$–$\mathbf{J_{15}}$ is the appearance of chemical shift in the region 5.38–5.80 ppm as a doublet of a doublet due to the presence of **CH** proton adjacent to phosphorus center and NH group. The typical carbon resonance at 158.3–161.1 ppm in the ^{13}C-NMR spectra was indicative of a carbonyl group, whereas the IR stretching frequencies at 3225–3290 and 1636–1667 cm^{-1} confirmed an amide linkage. The phosphorus resonance at δ_P 20.5–23.1 ppm

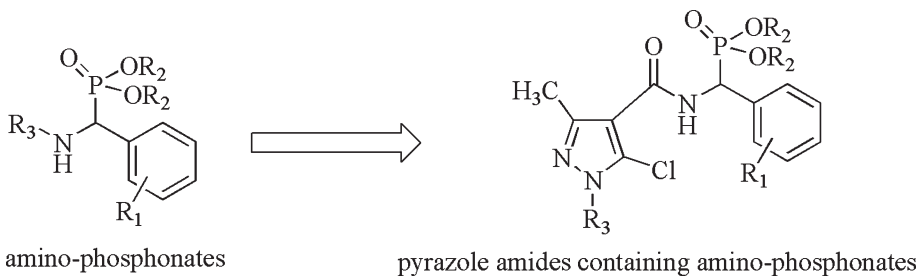
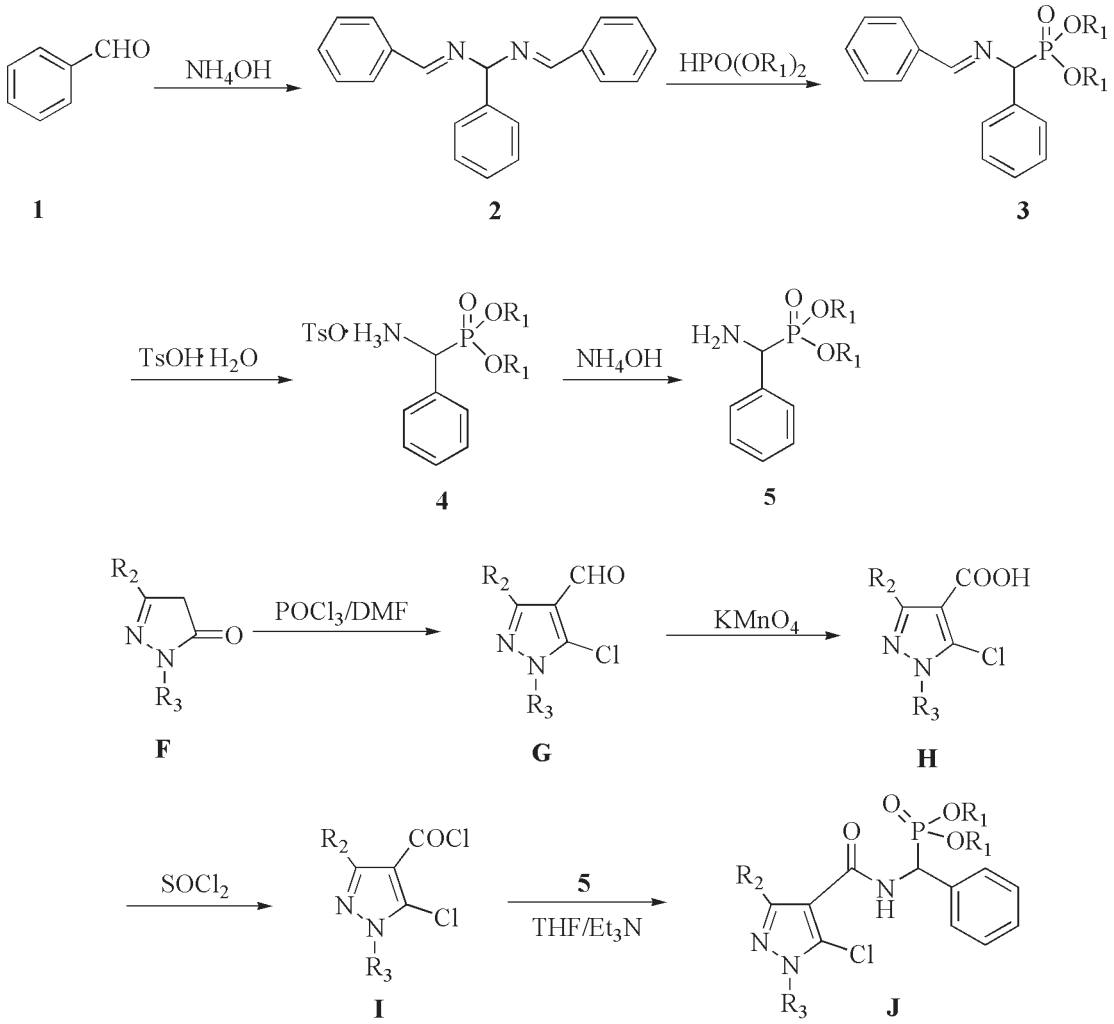


Figure 2. Structural features of aminophosphonates versus pyrazole amides containing aminophosphonates.

Scheme 1. Synthetic route to pyrazole amide analogues $\mathbf{J_1}$–$\mathbf{J_{15}}$ containing α-aminophosphonate.



$\mathbf{J_1}$: R_1=Et, R_2=CH_3, R_3=CH_3; $\mathbf{J_2}$: R_1=*n*-Pr, R_2=CH_3, R_3=CH_3; $\mathbf{J_3}$: R_1=*i*-Pr, R_2=CH_3, R_3=CH_3;
$\mathbf{J_4}$: R_1=*n*-Bu, R_2=CH_3, R_3=CH_3; $\mathbf{J_5}$: R_1=$CH_2CH_2OCH_3$, R_2=CH_3, R_3=CH_3;
$\mathbf{J_6}$: R_1=Et, R_2=CF_3, R_3=CH_3; $\mathbf{J_7}$: R_1=*n*-Pr, R_2=CF_3, R_3=CH_3; $\mathbf{J_8}$: R_1=*n*-Pr, R_2=CF_3, R_3=CH_3;
$\mathbf{J_9}$: R_1=*n*-Bu, R_2=CF_3, R_3=CH_3; $\mathbf{J_{10}}$: R_1=$CH_2CH_2OCH_3$, R_2=CF_3, R_3=CH_3;
$\mathbf{J_{11}}$: R_1=Et, R_2=CF_3, R_3=Ph; $\mathbf{J_{12}}$: R_1=*n*-Pr, R_2=CF_3, R_3=Ph; $\mathbf{J_{13}}$: R_1=*i*-Pr, R_2=CF_3, R_3=Ph;
$\mathbf{J_{14}}$: R_1=*n*-Bu, R_2=CF_3, R_3=Ph; $\mathbf{J_{15}}$: R_1=$CH_2CH_2OCH_3$, R_2=CF_3, R_3=Ph;

in the ^{31}P-NMR spectra of $\mathbf{J_1}$–$\mathbf{J_{15}}$ reveals the presence of phosphorus center coupled to adjacent **CH**. The presence of trifluoromethyl group was confirmed by the appearance of a singlet at −61.4 to −61.6 ppm in the ^{19}F-NMR spectra of the title compounds.

The antiviral activities of compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$ against TMV were assayed by the reported method [25]. The results of bioassay *in vivo* against TMV are given in Table 2. Ningnanmycin, perhaps the most successful registered plant antiviral agent in China, was used as reference antiviral agent. The data provided in Table 3 indicated that the title compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$ had curative rates of 29.4–50.1%, albeit lower than that of the commercial reference (52.8%). Amongst them, the title compounds ($\mathbf{J_3}$, $\mathbf{J_{10}}$, and $\mathbf{J_{12}}$) showed higher curative activities (39.9%, 41.8%, 50.1%, respectively) compared to the rest against TMV at 0.5 mg/mL. From the data in Table 3, it may be observed that the compounds with electron-donating groups in pyrazole ring display higher activity than those with electron-withdrawing ones.

In summary, a series of novel pyrazole amides containing α-aminophosphonate moiety were obtained from the reaction of acyl chloride and amine in THF in the presence of deacidification reagent triethylamine. The

Table 1

Effect of different solvents for synthesis of $\mathbf{J_1}$.

No	Solvent	Yield (%)
1	THF	70
2	CH_2Cl_2	58
3	$CHCl_3$	60
4	DMF	53
5	CH_3CN	57

Volume: 20 mL; reaction time: 0.5 h; temperature: 25°C.

racemic sample of $\mathbf{J_1}$ was separated into its enantiomers under conventional normal phase condition on two immobilized polysaccharide-based chiral stationary phases (Chiralpak IA and Chiralpak IC). Some of the title compounds displayed certain degree of antiviral activity against TMV.

EXPERIMENTAL

Melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disk. The ^{1}H-, ^{13}C-, ^{31}P-, and ^{19}F-NMR (solvent $CDCl_3$) spectral analyses were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. The analytical HPLC of the compounds was performed on Agilent 1200 series Apparatus composed of a quarternary pump, an autosampler, a DAD detector, a vacuum degasser, a column oven and Agilent Chemstation software. The two columns used were Chiralpak IA-amylose tris-(3,5-dimethylphenylcarbamate) immobilized on silica-gel and Chiralpak IC-cellullose tris-(3,5-dichlorophenylcarbamate) immobilized on 5-μm silica-gel (both the columns of 250 mm × 4.6 mm i.d., 5 μm, Daicel Chemical Industries). Semipreparative HPLC was carried out by Agilent 1100 series consisting of a preparative pump, a DAD detector, and a manual injector with a 10-mL sample loop. Semipreparative Chiralpak IA column (250 mm × 10 mm i.d., 5 μm) was also purchased from Daicel Chemical Industries. Optical rotation values were measured on a WZZ-ZS automatic polarimeter. Analytical TLC was performed on silica gel GF_{254}. Column chromatographic purification was carried out using silica gel. The solvents *n*-hexane, DCM, IPA, and ethanol (EtOH) were of HPLC grade and purchased from Jiangsu Hanbang Science and Technology Co. (Jiangsu, China). All other reagents were of analytical reagent grade or chemically pure. The solvents were dried, deoxygenated, and redistilled before use.

Table 2

Enantiomeric excess values and some physical constants of the first (F1) and the second (F2) fractions collected after semipreparation.

	First fractions (F1)		Second fractions (F2)	
Compound	e.e. (%)	$[\alpha]_D^{20}$	e.e. (%)	$[\alpha]_D^{20}$
$\mathbf{J_1}$	100	−41.7	100	+37.5

Determination of enantiomeric excess: column: 230 nm; flow rate: 1 mL/min; injection volume: 5 μL; detection: mobile phase: *n*-hexane/EtOH (90/10, v/v), Chiralpak IA column (250 mm × 10 mm i.d., 5 μm); optical rotation measurement: temperature, 25°C; solvent, DCM.

Intermediate **I** was prepared according to the reported methods [26–28], α-aminobenzylphosphonate **5** was made by following the literature procedure [29].

General procedure for the preparation of compounds $\mathbf{J_1}$–$\mathbf{J_{15}}$. A mixture of intermediate **5** (1.5 mmol) and triethylamine (1.5 mmol) in THF (10 mL) was stirred at room temperature and then the system was cooled down to 0°C. The intermediate **I** (1 mmol) in THF (10 mL) was slowly added into the above mixture, heated up to 25°C, and stirred for another 0.5 h. The triethylamine hydrochloride generated was removed by filtration; the solvent was evaporated to afford a crude product which was further purified by column chromatography on silica using a mixture of petroleum ether/ethyl acetate (1/1, v/v) as an eluant to give the target compounds in 45–80% yields. The physical and spectral data for $\mathbf{J_1}$–$\mathbf{J_{15}}$ are provided below.

Diethyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_1). Yellow solid; yield, 70%; mp: 118–120°C; IR (KBr): ν 3248 (NH), 3061, 3030, 2986, 2926, 2909, 1659 (C═O), 1549, 1495, 1474, 1450, 1261, 1234 (P═O), 1150, 1147, 1120 (P─O─C), 976, 762, 721, 700, 561 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.11 (t, J = 7.15 Hz, 3H, CCH_3), 1.31 (t, J = 6.88 Hz, 3H, CCH_3), 2.44 (s, 3H, pyrazole-CH_3), 3.70–3.78 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.92–3.40 (m, 1H, OCH_2), 4.07–4.19 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 23.80 Hz, 1H, NCHP), 7.12–7.15 (br, 1H, NH), 7.27–7.32 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.1, 150.9, 135.3, 128.8, 128.2, 128.0, 126.6, 110.9, 63.6, 63.1,

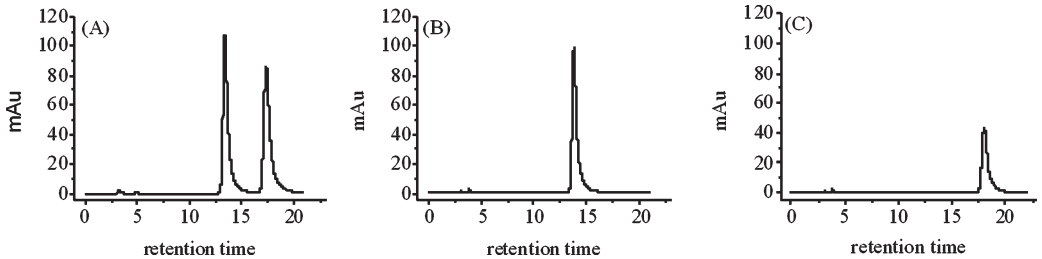


Figure 3. A: Analytical chromatogram of compound $\mathbf{J_1}$. B: Purity determination of the single fraction F1 of compound $\mathbf{J_1}$ collected on a semipreparative scale. C: Purity determination of the single fraction F2 of compound $\mathbf{J_1}$ collected on a semipreparative scale. Column: IA column (250 mm × 4.6 mm i.d., 5 μm); injection volume: 5 μm; detection: 230 nm; flow rate: 1.0 mL/min; mobile phase: *n*-hexane/EtOH (90:10, v/v).

Table 3

The curative effect of the new compounds against TMV *in vivo*.

Compound	Concentration (mg/mL)	Curative effect (%)
J_1	0.500	29.4
J_2	0.500	34. 7
J_3	0.500	39.9
J_4	0.500	36.4
J_5	0.500	36.3
J_6	0.500	24.6
J_7	0.500	34.0
J_8	0.500	38.0
J_9	0.500	31.3
J_{10}	0.500	41.8
J_{11}	0.500	33.5
J_{12}	0.500	50.1
J_{13}	0.500	28.4
J_{14}	0.500	37.4
J_{15}	0.500	35.2
Ningnamycin	0.500	52.8

50.7, 49.5, 36.4, 16.5, 16.2, 14.5; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{17}H_{23}ClN_3O_4P$ (399.11): C, 51.07; H, 5.80; N, 10.51. Found: C, 51.05; H, 6.12; N, 10.35.

Dipropyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)-(phenyl)methyl)phosphonate (J_2). Yellow solid; yield, 63%; mp: 125–127°C; IR (KBr): ν 3240 (NH), 3059, 3030, 2967, 2931, 2911, 1645 (C═O), 1539, 1470, 1456, 1402, 1377, 1246 (P═O), 1228, 1146, 1145, 1107 (P─O─C), 976, 762, 700, 543 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.93 (t, J = 7.42 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.63–1.71 (m, 2H, CCH_2C), 2.44 (s, 3H, pyrazole-CH_3), 3.59–3.65 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.83–3.88 (m, 1H, OCH_2), 3.97–4.07 (m, 2H, OCH_2), 5.61–5.67 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.13–7.15 (br, 1H, NH), 7.27–7.31 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.9, 135.4, 128.7, 128.2, 128.0, 126.6, 110.9, 68.9, 68.5, 50.7, 49.5, 36.4, 24.0, 23.9, 14.5, 11.1, 9.9; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{19}H_{27}ClN_3O_4P$ (427.14): C, 53.34; H, 6.36; N, 9.82. Found: C, 53.70; H, 6.65; N, 9.73.

Diisopropyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_3). Yellow solid; yield, 56%; mp: 98–100°C; IR (KBr): ν 3250 (NH), 3061, 3030, 2978, 2934, 2911, 1651 (C═O), 1523, 1506, 1496, 1456, 1454, 1380, 1375, 1303, 1234 (P═O), 1179, 1144, 1103 (P─O─C), 993, 898, 769, 700, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.75 (d, J = 5.75 Hz, 3H, CCH_3), 1.07 (d, J = 6.30 Hz, 6H, CCH_3), 1.15 (d, J = 6.30 Hz, 6H, CCH_3), 2.25 (s, 3H, pyrazole-CH_3), 3.50 (s, 3H, NCH_3), 4.26–4.32 (m, 1H, OCH), 4.50–4.55 (m, 1H, OCH), 5.38–5.44 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.11–7.13 (br, 2H, ArH and NH), 7.14–7.17 (t, J = 7.18 Hz, 2H, ArH), 7.47 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 160.9, 150.3, 135.6, 128.4, 128.2, 128.0, 127.9, 126.4, 110.9, 72.3, 71.6, 51.2, 49.9, 36.1, 24.1, 24.0, 23.0, 14.2; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 20.5; Anal. Calc. for: $C_{19}H_{27}ClN_3O_4P$ (427.14): C, 53.34; H, 6.36; N, 9.82. Found: C, 53.69; H, 6.74; N, 9.44.

Dibutyl((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)-(phenyl)methyl)phosphonate (J_4). Yellow solid; yield, 44%; mp: 78–80°C; IR (KBr): ν 3290 (NH), 3061, 3030, 2957, 2932, 2872, 1636 (C═O), 1522, 1506, 1456, 1361, 1450, 1248 (P═O), 1148, 1165, 1130 (P─O─C), 989, 903, 781, 700, 640, 543 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.43 Hz, 3H, CCH_3), 0.89 (t, J = 7.45 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.33–1.45 (m, 4H, CCH_2C), 1.59–1.65 (m, 2H, CCH_2C), 2.44 (s, 3H, pyrazole-CH_3), 3.62–3.68 (m, 1H, OCH_2), 3.82 (s, 3H, NCH_3), 3.86–3.92 (m, 1H, OCH_2), 4.00–4.11 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.13–7.16 (br, 1H, NH), 7.27–7.31 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.47 (d, J = 8.00 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.9, 135.4, 128.8, 128.2, 128.0, 126.6, 110.9, 67.1, 66.7, 50.7, 49.4, 36.4, 32.6, 32.3, 18.7, 18.6, 14.5, 13.6; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.4; Anal. Calc. for: $C_{21}H_{31}ClN_3O_4P$ (455.17): C, 55.32; H, 6.85; N, 9.22. Found: C, 55.54; H, 7.14; N, 8.86.

Bis(2-methoxyethyl)((5-chloro-1,3-dimethyl-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_5). Yellow solid; yield, 46%; mp: 76–78°C; IR (KBr): ν 3254 (NH), 3061, 3030, 2978, 2929, 2889, 2821, 1650 (C═O), 1521, 1456, 1367,1338, 1296, 1253 (P═O), 1200, 1132, 1197, 1155, 1134 (P─O─C), 972, 842, 772, 700, 565 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.44 (s, 3H, pyrazole-CH_3), 3.28 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.36–3.41 (m, 1H, CH_2O), 3.42–3.45 (m, 1H, CH_2O), 3.54–3.55 (m, 2H, CH_2O), 3.81 (s, 3H, NCH_3), 3.87–3.93 (m, 1H, OCH_2), 4.04–4.11 (m, 1H, OCH_2), 4.14–4.21 (m, 2H, OCH_2), 5.69–5.75 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.21–7.24 (br, 1H, NH), 7.28–7.31 (m, 1H, ArH), 7.36 (t, J = 6.90 Hz, 2H, ArH), 7.47 (d, J = 7.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 161.0, 150.7, 135.2, 128.7, 128.2, 128.0, 126.8, 111.1, 71.4, 66.1, 65.7, 58.8, 50.9, 49.6, 36.3, 14.4; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 23.1; Anal. Calc. for: $C_{19}H_{27}ClN_3O_6P$ (459.13): C, 49.62; H, 5.92; N, 9.14. Found: C, 49.37; H, 6.28; N, 8.94.

Diethyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_6). Yellow solid; yield, 80%; mp: 132–134°C; IR (KBr): ν 3237 (NH), 3061, 3030, 2986, 2926, 2909, 1645 (C═O), 1553, 1497, 1474, 1452, 1242 (P═O), 1213, 1175, 1163, 1148, 1045, 1026 (P─O─C), 974, 958, 700, 561 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.12 (t, J = 7.15 Hz, 3H, CCH_3), 1.31 (t, J = 6.88 Hz, 3H, CCH_3), 3.70–3.78 (m, 1H, OCH_2), 3.93 (s, 3H, NCH_3), 3.95–4.00 (m, 1H, OCH_2), 4.08–4.19 (m, 2H, OCH_2), 5.59–5.65 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.31–7.33 (m, 1H, ArH), 7.37 (t, J = 7.15 Hz, 2H, ArH), 7.46 (d, J = 6.85 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 134.5, 129.9, 128.8, 128.4, 128.0, 123.4, 121.3, 119.2, 112.9, 63.7, 63.1, 51.1, 49.9, 37.4, 16.4, 16.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.6; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{17}H_{20}ClF_3N_3O_4P$ (453.08): C, 45.00; H, 4.44; N, 9.26. Found: C, 45.18; H, 4.71; N, 9.06.

Dipropyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_7). Yellow solid; yield, 62%; mp: 113–115°C; IR (KBr): ν 3230 (NH), 3059, 3020, 2970, 2939, 2987, 1667 (C═O), 1560, 1497, 1456, 1319, 1244 (P═O), 1219, 1180, 1126, 1070, 1022 (P─O─C), 997, 762, 707, 559 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.93 (t, J = 7.18 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.63–1.71 (m, 2H, CCH_2C), 3.59–3.65 (m, 1H, OCH_2), 3.83–3.88 (m, 1H, OCH_2), 3.92 (s, 3H, NCH_3), 3.97–4.07 (m, 2H, OCH_2), 5.60–5.66 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.29–

7.33 (m, 1H, ArH), 7.36 (t, J = 7.15 Hz, 2H, ArH), 7.46 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.2, 139.9, 134.8, 129.9, 128.8, 128.4, 128.0, 123.4, 121.3, 119.2, 112.8, 68.9, 68.5, 51.1, 49.9, 37.3, 23.9, 23.7, 14.5, 10.0, 9.8; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{19}H_{24}ClF_3N_3O_4P$ (481.1): C, 47.36; H, 5.02; N, 8.72. Found: C, 47.53; H, 4.82; N, 8.65.

Diisopropyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_8). Yellow solid; yield, 80%; mp: 130–132°C; IR (KBr): ν 3226 (NH), 3061, 3030, 2987, 2934, 1676 (C=O), 1658, 1555, 1506, 1496, 1456, 1379, 1238 (P=O), 1219, 1177, 1140, 1103 (P—O—C), 999, 989, 769, 700, 569 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.90 (d, J = 6.30 Hz, 3H, CCH_3), 1.24 (d, J = 6.30 Hz, 6H, CCH_3), 1.31 (d, J = 6.30 Hz, 3H, CCH_3), 3.90 (s, 3H, NCH_3), 4.43–4.46 (m, 1H, OCH), 4.63–4.69 (m, 1H, OCH), 5.49–5.55 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.01–7.03 (br, 1H, NH), 7.29–7.33 (m, 1H, ArH), 7.33 (t, J = 7.15 Hz, 2H, ArH), 7.44 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.1, 139.9, 135.1, 130.0, 128.6, 128.2, 128.1, 123.4, 121.3, 119.2, 112.9, 72.8, 71.9, 51.9, 50.6, 37.4, 24.3, 24.1, 23.9, 23.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 19.8; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{19}H_{24}ClF_3N_3O_4P$ (481.1): C, 47.36; H, 5.02; N, 8.72. Found: C, 47.48; H, 4.48; N, 8.84.

Dibutyl((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-arboxamido)(phenyl)methyl)phosphonate (J_9). Yellow solid; yield, 61%; mp: 80–82°C; IR (KBr): ν 3209 (NH), 3040, 3032, 2961, 2935, 1670 (C=O), 1560, 1496, 1456, 1385, 1321, 1248 (P=O), 1219, 1177, 1130, 1026, 1005 (P—O—C), 986, 891, 708, 700, 563 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.15 Hz, 3H, CCH_3), 0.91 (t, J = 7.15 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.33–1.45 (m, 4H, CCH_2C), 1.60–1.65 (m, 2H, CCH_2C) 3.62–3.68 (m, 1H, OCH_2), 3.86–3.91 (m, 1H, OCH_2), 3.92 (s, 3H, NCH_3), 4.00–4.11 (m, 2H, OCH_2), 5.59–5.65 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.07–7.09 (br, 1H, NH), 7.30–7.32 (m, 1H, ArH), 7.36 (t, J = 7.45 Hz, 2H, ArH), 7.46 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.3, 140.2, 139.9, 134.8, 129.8, 128.8, 128.3, 128.0, 123.5, 121.3, 119.2, 112.9, 67.3, 66.7, 51.1, 49.9, 37.3, 32.5, 32.3, 18.7, 18.5, 13.6, 13.5; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.6; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.4; Anal. Calc. for: $C_{21}H_{28}ClF_3N_3O_4P$ (509.15): C, 49.47; H, 5.54; N, 8.24. Found: C, 49.63; H, 5.58; N, 8.08.

Bis(2-methoxyethyl)((5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{10}). Yellow solid; yield, 56%; mp: 94–96°C; IR (KBr): ν 3238 (NH), 3057, 3032, 2929, 2895, 1666 (C=O), 1551, 1490, 1452, 1317, 1238 (P=O), 1213, 1175, 1132, 1099, 1064, 1041 (P—O—C), 979, 962, 727, 698, 579 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.29 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.36–3.41 (m,1H, CH_2O), 3.42–3.45 (m, 1H, CH_2O), 3.55 (t, J = 4.30 Hz, 2H, CH_2O), 3.93 (s, 3H, NCH_3), 3.94–3.99 (m, 1H, OCH_2), 4.05–4.12 (m, 1H, OCH_2), 4.14–4.25 (m, 2H, OCH_2), 5.69–5.75 (dd, J = 9.15 Hz, J = 21.20 Hz, 1H, NCHP), 7.26–7.29 (br, 1H, NH), 7.30–7.33 (m, 1H, ArH), 7.37 (t, J = 7.43 Hz, 2H, ArH), 7.47 (d, J = 7.45 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 140.2, 139.9, 134.6, 129.7, 128.8, 128.3, 128.0, 123.5, 121.3, 119.2, 113.1, 71.4, 66.2, 65.8, 58.8, 51.4, 50.2, 37.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.1; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5; Anal. Calc. for: $C_{19}H_{14}ClF_3N_3O_4P$ (509.15): C, 44.41; H, 4.71; N, 8.18; Found: C, 45.03; H, 4.53; N, 7.81.

Diethyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{11}). Yellow solid; yield, 68.0%; mp: 152–154°C; IR (KBr): ν 3244 (NH), 3068, 3030, 2983, 2931, 2906, 1674 (C=O), 1545, 1490, 1411, 1388, 1315, 1247 (P=O), 1217, 1182, 1024, 1033 (P—O—C), 993, 974, 771, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.12 (t, J = 7.18 Hz, 3H, CCH_3), 1.33 (t, J = 7.15 Hz, 3H, CCH_3), 3.71–3.79 (m, 1H, OCH_2), 3.93–4.00 (m, 1H, OCH_2), 4.09–4.20 (m, 2H, OCH_2), 5.63–5.69 (dd, J = 9.15 Hz, J = 20.60 Hz, 1H, NCHP), 7.18–7.21 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 141.5, 141.2, 136.7, 134.6, 130.1, 129.6, 128.9, 128.5, 128.1, 125.7, 121.3, 119.2, 114.0, 63.8, 63.1, 51.2, 50.0, 16.2, 16.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5; Anal. Calc. for: $C_{22}H_{22}ClF_3N_3O_4P$ (515.10): C, 51.22; H, 4.30; N, 8.15; Found: C, 51.40; H, 3.93; N, 7.86.

Dipropyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{12}). Yellow solid; yield, 79%; mp: 142–144°C; IR (KBr): ν 3244 (NH), 3067, 3030, 2972, 2940, 2899, 2881, 1681 (C=O), 1455, 1385, 1315, 1238 (P=O), 1215, 1174, 1120, 1139, 1012 (P—O—C), 995, 765, 702, 569 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.79 (t, J = 7.45 Hz, 3H, CCH_3), 0.94 (t, J = 7.45 Hz, 3H, CCH_3), 1.45–1.52 (m, 2H, CCH_2C), 1.66–1.71 (m, 2H, CCH_2C), 3.58–3.64 (m, 1H, OCH_2), 3.83–3.89 (m, 1H, OCH_2), 3.99–4.09 (m, 2H, OCH_2), 5.64–5.70 (dd, J = 9.15 Hz, J = 20.65 Hz, 1H, NCHP), 7.18–7.20 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 134.7, 130.2, 129.6, 128.8, 128.4, 128.1, 125.7, 121.3, 119.2, 113.9, 69.2, 68.6, 51.2, 50.0, 23.9, 10.1, 9.9; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_4P$ (543.13): C, 53.00; H, 4.82; N, 7.73; Found: C, 53.23; H, 4.54; N, 7.49.

Diisopropyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{13}). Yellow solid; yield, 73%; mp: 126–128°C; IR (KBr): ν 3251 (NH), 3065, 3030, 2980, 2938, 1674 (C=O), 1545, 1489, 1387, 1332, 1315, 1238 (P=O), 1213, 1148, 1099, 1078, 1016 (P—O—C), 991, 770, 694, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.92 (d, J = 6.30 Hz, 3H, CCH_3), 1.27 (t, J = 6.30 Hz, 6H, CCH_3), 1.35 (d, J = 5.70 Hz, 3H, CCH_3), 4.44–4.50 (m, 1H, OCH), 4.67–4.73 (m, 1H, OCH), 5.55–5.61 (dd, J = 9.15 Hz, J = 20.65 Hz, 1H, NCHP), 7.13–7.16 (br, 1H, NH), 7.30–7.54 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 135.1, 130.1, 129.6, 128.8, 128.3, 128.1, 125.8, 121.3, 119.2, 113.9, 72.8, 71.9, 52.0, 50.8, 31.0, 24.4, 21.0, 29.2, 23.1; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 19.7; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.5. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_4P$ (543.13): C, 53.00; H, 4.82; N, 7.73; Found: C, 53.21; H, 4.72; N, 7.58.

Dibutyl((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamido)(phenyl)methyl)phosphonate (J_{14}). Yellow solid; yield, 78%; mp: 179–181°C; IR (KBr): ν 3225 (NH), 3065, 3032, 2961, 2933, 1674 (C=O), 1558, 1497, 1385, 1332, 1315, 1246, 1224 (P=O), 1186, 1153, 1035, 1006 (P—O—C), 764, 698, 567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.82 (t, J = 7.15 Hz, 3H, CCH_3), 0.91 (t, J = 7.45 Hz, 3H, CCH_3), 1.18–1.26 (m, 2H, CCH_2C), 1.35–1.46 (m, 4H, CCH_2C), 1.62–1.67 (m, 2H, CCH_2C), 3.61–3.67 (m, 1H, OCH_2), 3.87–3.93 (m, 1H, OCH_2), 4.02–4.14 (m, 2H, OCH_2),

5.63–5.69 (dd, $J = 9.15$ Hz, $J = 20.65$ Hz, 1H, NCHP), 7.16–7.18 (br, 1H, NH), 7.31–7.56 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.4, 141.6, 141.3, 136.7, 134.7, 130.2, 129.6, 128.8, 128.4, 128.1, 125.7, 121.3, 119.2, 113.9, 67.4, 66.8, 51.2, 50.0, 32.6, 32.5, 18.7, 18.6, 13.6; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 21.5; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{26}H_{30}ClF_3N_3O_4P$ (571.16): C, 54.60; H, 5.29; N, 7.35; Found: C, 54.37; H, 5.12; N, 7.01.

Bis(2-methoxyethyl)((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carbo-xamido)(phenyl)methyl)phosphonate (J15). Yellow solid; yield, 59%; mp: 112–114°C; IR (KBr): ν 3230 (NH), 3069, 3030, 3001, 2930, 2885, 1670 (C═O), 1557, 1490, 1390, 1339, 1315, 1252, 1219 (P═O), 1184, 1099, 1069, 1037 (P─O─C), 993, 980, 775, 696 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.29 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.37–3.41 (m, 1H, CH_2O), 3.45–3.48 (m, 1H, CH_2O), 3.56 (t, 2H, $J = 4.78$ Hz, CH_2O), 3.96–4.01 (m, 1H, OCH_2), 4.07–4.12 (m, 1H, OCH_2), 4.16–4.26 (m, 2H, OCH_2), 5.74–5.80 (dd, $J = 9.15$ Hz, $J = 21.20$ Hz, 1H, NCHP), 7.31–7.56 (m, 11H, ArH and NH); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 158.5, 141.6, 141.2, 136.7, 134.5, 130.2, 129.6, 128.8, 128.3, 128.0, 125.7, 121.3, 119.2, 113.2, 71.4, 66.2, 65.8, 58.3, 50.3; ^{31}P-NMR ($CDCl_3$, 200 MHz) δ: 22.0; ^{19}F-NMR ($CDCl_3$, 470 MHz) δ: −61.6. Anal. Calc. for: $C_{24}H_{26}ClF_3N_3O_6P$ (575.12): C, 50.05; H, 4.55; N, 7.30; Found: C, 50.00; H, 4.93; N, 7.40.

Antiviral biological assay. ***Purification of tobacco mosaic virus.*** Using Gooding's method [30], the upper leaves of *Nicotiana tabacum L* inoculated with TMV were selected and were ground in phosphate buffer, then filtered through double layer pledget. The filtrate was centrifuged at 10,000 × *g*, treated twice with PEG and centrifuged again. The whole experiment was carried out at 4°C. Absorbance values were estimated at 260 nm using an ultraviolet spectrophotometer.

$$\text{Virus concentration} = (A_{260} \times \text{dilution ratio})/E_{1\text{ cm}}^{0.1\%,\ 260\text{ nm}} \quad (1)$$

Curative effect of compounds against TMV *in vivo*. Growing leaves of *Nicotiana tabacum L* of the same ages were selected. The TMV (concentration of 6×10^{-3} mg/mL) was dipped and inoculated on the whole leaves. Then the leaves were washed with water and dried. The compound solution was smeared on the left side and the solvent was smeared on the right side for control. The local lesion numbers were then counted and recorded 3–4 days after inoculation [25]. For each compound, three repetitions were measured. The inhibition rate of the compound was then calculated according to the following formula (''av'' means average).

$$\text{Inhibition rate}(\%) = \frac{\text{av local lesion numbers of control(not treated with compound)} - \text{av local lesion numbers smeared with drugs}}{\text{av local lesion numbers of control (not treated with compound)}} \times 100\% \quad (2)$$

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Microwave-Assisted Expeditious Synthesis of Novel Benzo[*b*][1,8]-naphthyridine-3-carbonitriles

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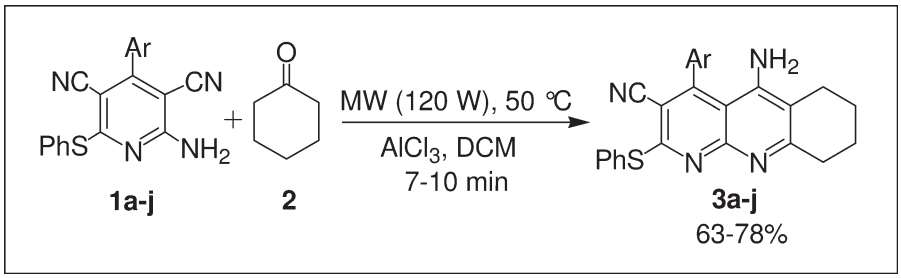

A rapid and facile method for the synthesis of novel 5-amino-2-sulfanyl tetrahydrobenzo[*b*][1,8]-naphthyridine-3-carbonitrile derivatives has been developed by the treatment of 2-amino-3,5-dicarbonitrile-6-sulfanyl pyridines with cyclohexanone in the presence of anhydrous aluminium chloride in dry dichloromethane under controlled microwave irradiation.

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INTRODUCTION

Naphthyridine derivatives are compounds of current interest due to their diverse biological activities including anti-tumor [1], anti-inflammatory [1d,2,3], antifungal [3], antibacterial [4], anticonvulsant [5], antihypertensive [6], and antiproliferative [7]. They also act as potential inhibitors of platelet aggregation, protein tyrosine kinases, topoisomerase I, and human immunodeficiency virus-1 (HIV-1) integrase [8–11] and are used for the diagnosis and treatment of human diseases such as acquired immune deficiency syndrome (AIDS) and allergies [12]. Recently, naphthyridines have been reported as label-free aptamer-based sensor using abasic site-containing DNA and nucleobase-specific fluorescence ligands [13]. 1,8-Naphthyridine-3-carbonitriles have been particularly identified as a new class of serotonin 5-HT_3 receptor antagonists [14]. Because of their biological and pharmacological importance, the synthesis of naphthyridine derivatives has attracted a great deal of current attention and a number of reports for the synthesis of such systems have appeared [14,15]. However, to the best of our knowledge, there exists no report on the synthesis of 5-amino-2-sulfanyl tetrahydrobenzo[*b*][1,8]-naphthyridine-3-carbonitriles, which may be much potent and useful products for further synthetic as well as biological studies.

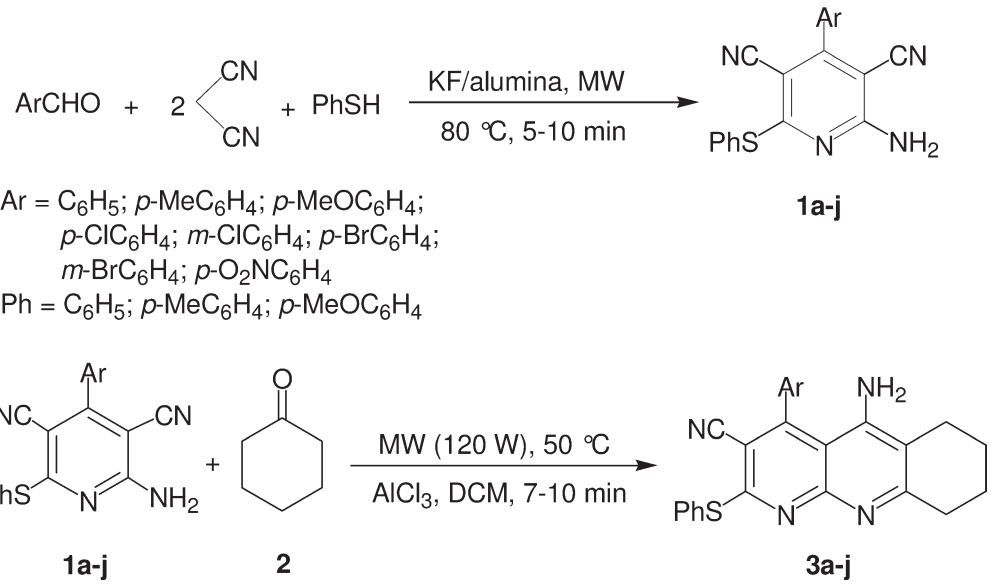
Microwave (MW) irradiation has evolved as a powerful method to perform organic synthesis with great success, particularly in the light of the current paradigm shift to ''Green Chemistry.'' It provides chemical processes with special attributes, such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimization of reactions, and several eco-friendly advantages [16].

RESULTS AND DISCUSSION

Because of our interest on MW-assisted synthesis of heterocyclic compounds [17], we report herein an aluminum chloride catalyzed, expeditious procedure for the construction of novel 5-amino-2-sulfanyl tetrahydrobenzo[*b*][1,8]-naphthyridine-3-carbonitrile derivatives **3a–j** by the reaction of 2-amino-3,5-dicarbonitrile-6-sulfanyl pyridines **1a–j** with cyclohexanone **2** in dichloromethane under MW irradiation in reasonably good yield (63–78%; Scheme 1). The starting substrates, 2-amino-3,5-dicarbonitrile-6-sulfanyl pyridines **1a–j**, were prepared *via* a three-component reaction of aromatic aldehyde, malononitrile, and thiophenol using KF/alumina as catalyst in ethanol under controlled MW conditions [17a].

To screen the experimental conditions, a model reaction of 2-amino-4-phenyl-6-phenylsulfanylpyridine-3,5-dicarbonitrile **1a** with cyclohexanone **2** was carried out using various Lewis acids under conventional heating as well as under MW irradiation. The results are summarized in Table 1. When the reaction was carried out using anhydrous $AlCl_3$ (1.5 equiv) in DCM (2 mL), the desired naphthyridine **3a** was formed in 56% yield under conventional heating at reflux in 1.0 h and 74% yield under

Scheme 1



MW at 50°C in 7 min (Table 1, entry 5). Decreasing the molar proportion of $AlCl_3$ decreases the yield of the product considerably (Table 1, entries 1-4); however, an increase in the molar proportion (2.0 equiv) of $AlCl_3$ does not improve the product yield further (Table 1, entry 6). Switching to other Lewis acids such as $FeCl_3$, $ZnCl_2$, I_2, $InCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, and Montmorillonite K 10 gave rise to very low yield or no formation of the product (Table 1, entries 10–16). It is worthwhile to mention that no anticipated product is formed in solvents such as ethanol, methanol, and acetonitrile (Table 1, entries 7–9).

Thus, it is concluded from the Table 1 that $AlCl_3$ in DCM (2 mL) under MW irradiation (120 W, 50°C) affords the optimum yield of the product with considerable reduction in reaction time. Further, increase of MW power and temperature did not improve the product yield.

Table 1

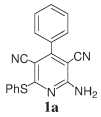
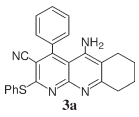
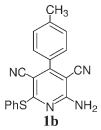
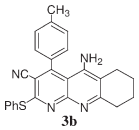
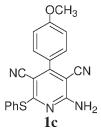
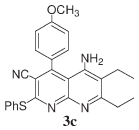
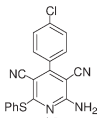
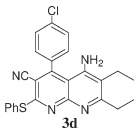
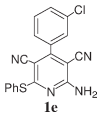
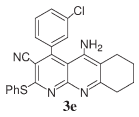
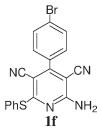
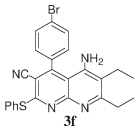
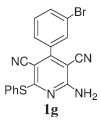
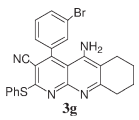
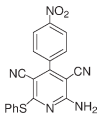
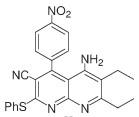
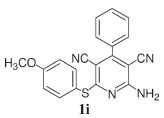
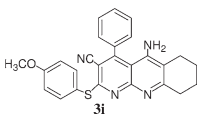
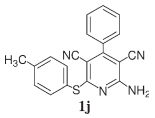
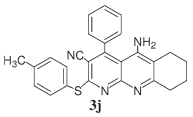
Optimization of reaction conditions for **3a**.

		Reaction conditions			
		Reflux		MW	
Entry	Lewis acid	Time (h)	Yield (%)	Time (min)	Yield (%)
1	$AlCl_3$ (0.5 equiv)	1.5	Trace	10	17
2	$AlCl_3$ (1.0 equiv)	1.5	20	10	42
3	$AlCl_3$ (1.1 equiv)	1.0	25	10	47
4	$AlCl_3$ (1.3 equiv)	1.0	41	7	63
5	$AlCl_3$ (1.5 equiv)	1.0	56	7	74
6	$AlCl_3$ (2.0 equiv)	1.0	55	7	74
7	$AlCl_3$ (1.5 equiv)[a]	2.0	–	10	–
8	$AlCl_3$ (1.5 equiv)[b]	2.0	–	10	–
9	$AlCl_3$ (1.5 equiv)[c]	2.0	–	10	–
10	$FeCl_3$(1.5 equiv)	1.5	30	8	53
11	$ZnCl_2$(2.0 equiv)	2.0	23	10	47
12	I_2 (1.0 equiv)	2.0	–	10	–
13	$InCl_3$ (20 mol %)	2.0	–	10	–
14	$Yb(OTf)_3$ (20 mol %)	1.5	–	10	–
15	$Sc(OTf)_3$ (20 mol %)	1.5	–	10	–
16	Montmorillonite K 10 (1.5 equiv)	2.0	–	10	–

[a] Reaction carried out in ethanol.
[b] Reaction carried out in methanol.
[c] Reaction carried out in acetonitrile.

Table 2

MW-assisted synthesis[a] of 5-amino-2-sulfanyl tetrahydrobenzo[*b*][1,8]-naphthyridine-3-carbonitriles.

Entry	Pyridine derivatives	Product	Time (min)	Yield[b] (%)	Mp (°C)
1	 **1a**	 **3a**	7	74	243–244
2	 **1b**	 **3b**	7	77	295–296
3	 **1c**	 **3c**	7	78	274–275
4	 **1d**	 **3d**	8	74	264–265
5	 **1e**	 **3e**	10	70	234–235
6	 **1f**	 **3f**	8	71	267–268
7	 **1g**	 **3g**	10	68	228–230
8	 **1h**	 **3h**	10	63	216–217
9	 **1i**	 **3i**	7	76	240–241
10	 **1j**	 **3j**	7	75	257–258

[a] MW heating (120 W, 50°C) using substituted pyridines (1 mmol) and cyclohexanone (1.2 mmol).
[b] Isolated yield based on recrystallization.

Under the optimized set of reaction conditions (Table 1, entry 5), various substituted pyridines **1** were allowed to undergo reaction with cyclohexanone **2** in a molar ratio of 1:1.2 with $AlCl_3$ (1.5 equiv) in dry DCM (2 mL) using safe pressure regulation 10-mL pressurized vial with ''snap-on'' cap under MW (120 W, 50°C) heating for 7–10 min. The results are given in Table 2. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, the mixture was poured into an ice-cold water contained in

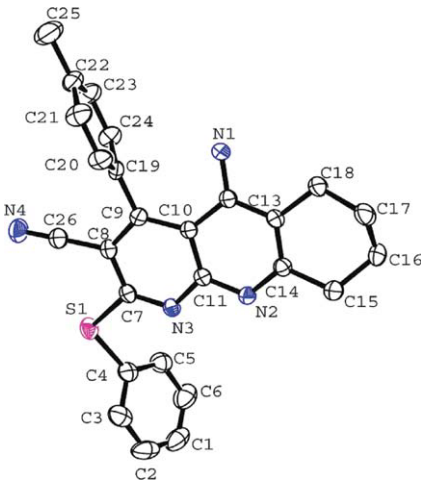


Figure 1. ORTEP diagram of compound **3b**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

a beaker and was extracted with DCM (3× 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The resultant solid was purified by recrystallization from ethanol to obtain pure product **3** in moderate to good yield.

All the products **3a–j** are new and have been fully characterized on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analyses. Single crystal X-ray analysis of one product, **3b**, conclusively confirmed the structures of these compounds. An Oak Ridge thermal ellipsoid plot (ORTEP) diagram of **3b** is shown in Figure 1 [18].

From the molecular structure, it is clear that the condensation of substituted pyridine derivatives and cyclohexanone results in the formation of products with three fused rings. Two of them are heteroaromatics having bond lengths 1.308–1.443 Å, which is in conformity with the reported range; whereas the third one is aliphatic having bond length 1.509–1.527 Å, corresponding to C—C single bond.

A mechanistic rationalization for this reaction is provided in Scheme 2. The reaction is initiated by the nucleophilic addition of NH_2 at the electrophilic carbonyl carbon followed by loss of water to give imine. Thus, the imine formed undergoes tautomerism to enamine, which then nucleophilically attacks at the cyano group with subsequent aromatization to provide the product **3**. The role of $AlCl_3$ is assumed to enhance the elecrtophilicity of the carbonyl and cyano carbons.

CONCLUSIONS

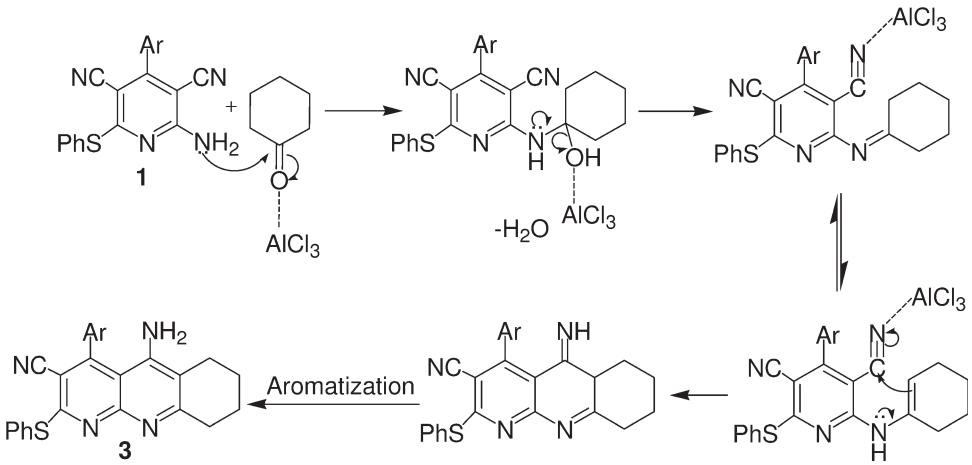
In conclusion, an expeditious synthesis of novel 5-amino-2-sulfanyl tetrahydrobenzo[*b*][1,8]-naphthyridine-3-carbonitriles in high purity and in good yields has been developed *via* cyclocondensation of 2-amino-3,5-dicarbonitrile-6-sulfanyl pyridines with cyclohexanone in dichloromethane using anhydrous $AlCl_3$ as catalyst under MW irradiation.

EXPERIMENTAL

Aluminum chloride (powder) and cyclohexanone were procured from E. Merck, Germany. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FT-NMR spectrometer; chemical shifts are given in δ ppm, relative to tetramethylsilane (TMS) as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc., Model CE-440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected. The X-ray diffraction measurements were carried out at 293 K on a CrysAlispro Oxford Diffractometer equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ = 0.71073 Å). The MW irradiation was effected using the CEM's Discover BenchMate single-mode MW synthesis system using safe pressure regulation 10-mL pressurized vials with ''snap-on'' cap.

General procedure for the synthesis of 3a–j. Substituted pyridine **1** (1 mmol), cyclohexanone **2** (1.2 mmol), anhydrous

Scheme 2



$AlCl_3$ (1.5 mmol), and dry DCM (2 mL) were mixed in a sealed pressure regulation 10-mL pressurized vial with ''snap-on'' cap. The mixture was irradiated in a single-mode MW synthesis system at 120 W power and 50°C temperature for 7–10 min. After completion of reaction (TLC), the mixture was poured into a beaker containing ice cold water and was extracted with DCM (3× 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The resultant solid was recrystallized from ethanol to yield pure product **3a–j**.

5-Amino-4-phenyl-2-phenylsulfanyl-6,7,8,9-tetrahydrobenzo-[b][1,8]-naphthyridine-3-carbonitrile (3a). Yellow solid; IR (KBr): 3432, 3350, 2928, 2210, 1617, 1531 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.45–7.71 (m, 10H, ArH), 4.39 (s, 2H, NH_2), 2.97 (t, *J* = 5.4 Hz, 2H, CH_2), 2.30 (t, *J* = 5.4 Hz, 2H, CH_2), 1.84–1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.3, 161.4, 154.7, 154.3, 149.6, 136.1, 135.6, 130.4, 129.8, 129.5, 127.9, 115.0, 112.1, 105.9, 104.3, 34.0, 23.4, 22.2, 18.4; Anal. Calcd. for $C_{25}H_{20}N_4S$: C, 73.50; H, 4.93; N, 13.71; Found: C, 73.41; H, 4.98; N, 13.75.

5-Amino-4-(4-methylphenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3b). Yellow solid; IR (KBr): 3467, 3346, 2921, 2217, 1621, 1539, 1510 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69–7.72 (m, 2H, ArH), 7.40–7.47 (m, 5H, ArH), 7.31–7.34 (m, 2H, ArH), 4.45 (s, 2H, NH_2), 2.95 (t, *J* = 5.7 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.30 (t, *J* = 5.7 Hz, 2H, CH_2), 1.83–1.85 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.3 (C), 161.2 (C), 154.9 (C), 154.6 (C), 149.6 (C), 140.6 (C), 135.4 (CH), 133.1 (C), 130.5 (CH), 129.4 (CH), 128.1 (C), 127.8 (CH), 115.2 (C), 112.0 (C), 106.3 (C), 104.6 (C), 34.2 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 22.2 (CH_2), 21.5 (CH_3); Anal. Calcd. for $C_{26}H_{22}N_4S$: C, 73.90; H, 5.25; N, 13.26; Found: C, 74.01; H, 5.16; N, 13.32.

5-Amino-4-(4-methoxyphenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3c). Light yellow solid; IR (KBr): 3478, 3339, 2920, 2218, 1630, 1548, 1507 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69–7.71 (m, 2H, ArH), 7.45–7.47 (m, 3H, ArH), 7.36 (d, *J* = 8.4 Hz, 2H, ArH), 7.11 (d, *J* = 8.4 Hz, 2H, ArH), 4.49 (s, 2H, NH_2), 3.91 (s, 3H, OCH_3), 2.95 (t, *J* = 5.4 Hz, 2H, CH_2), 2.31 (t, *J* = 5.4 Hz, 2H, CH_2), 1.84–1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.1 (C), 161.5 (C), 154.6 (C), 154.3 (C), 148.7 (C), 140.3 (C), 135.2 (CH), 133.2 (C), 130.7 (CH), 129.3 (CH), 128.3 (C), 127.5 (CH), 115.1 (C), 112.0 (C), 109.5 (C), 106.4 (C), 55.1 (CH_3), 34.0 (CH_2), 24.1 (CH_2), 23.5 (CH_2), 22.1 (CH_2); Anal. Calcd. for $C_{26}H_{22}N_4OS$: C, 71.21; H, 5.06; N, 12.78; Found: C, 71.32; H, 5.13; N, 12.71.

5-Amino-4-(4-chlorophenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3d). Yellow solid; IR (KBr): 3470, 3343, 2951, 2221, 1628, 1544, 1492 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.59–7.71 (m, 4H, ArH), 7.39–7.48 (m, 5H, ArH), 4.34 (s, 2H, NH_2), 2.96 (t, *J* = 5.7 Hz, 2H, CH_2), 2.32 (t, *J* = 5.7 Hz, 2H, CH_2), 1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7, 159.9, 154.1, 152.6, 149.2, 135.8, 134.6, 133.9, 129.4, 129.0, 128.8, 114.4, 112.0, 105.4, 38.6, 33.6, 22.9, 21.6; Anal. Calcd. for $C_{25}H_{19}ClN_4S$: C, 67.79; H, 4.32; N, 12.65; Found: C, 67.66; H, 4.39; N, 12.60.

5-Amino-4-(3-chlorophenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3e). Light yellow solid; IR (KBr): 3438, 3341, 3036, 2219, 1628, 1547, 1522 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56–7.70 (m, 3H, ArH), 7.54 (s, 1H, ArH), 7.36–7.47 (m, 5H, ArH), 4.39 (s, 2H, NH_2), 2.96 (t, *J* = 5.7 Hz, 2H, CH_2), 2.33 (t, *J* = 5.7 Hz, 2H, CH_2), 1.84–1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.8, 161.3, 154.8, 152.4, 149.2, 137.9, 135.9, 135.3, 131.1, 130.6, 129.5, 128.2, 127.8, 126.2, 114.9, 112.4, 105.8, 104.3, 34.3, 23.5, 22.3, 22.2; Anal. Calcd. for $C_{25}H_{19}ClN_4S$: C, 67.79; H, 4.32; N, 12.65; Found: C, 67.91; H, 4.24; N, 12.69.

5-Amino-4-(4-bromophenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3f). Brown solid; IR (KBr): 3468, 3348, 3216, 2988, 2215, 1628, 1536, 1501 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68–7.77 (m, 4H, ArH), 7.32–7.47 (m, 5H, ArH), 4.38 (s, 2H, NH_2), 2.95 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 2.30–2.32 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.5, 158.7, 155.2, 152.2, 148.7, 135.5, 134.8, 132.7, 129.6, 128.5, 115.1, 112.8, 104.9, 34.8, 33.7, 22.7, 22.1; Anal. Calcd. for $C_{25}H_{19}BrN_4S$: C, 61.60; H, 3.93; N, 11.49; Found: C, 61.68; H, 3.98; N, 11.45.

5-Amino-4-(3-bromophenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3g). Light yellow solid; IR (KBr): 3438, 3336, 2218, 1623, 1547, 1488 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.67–7.76 (m, 3H, ArH), 7.59 (s, 1H, ArH), 7.41–7.52 (m, 5H, ArH), 4.41 (s, 2H, NH_2), 2.94 (t, *J* = 5.4 Hz, 2H, CH_2), 2.31 (t, *J* = 5.4 Hz, 2H, CH_2), 1.84-1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.8, 161.4, 154.8, 152.3, 149.2, 138.1, 133.6, 131.3, 129.5, 127.8, 126.6, 123.9, 114.8, 112.4, 105.8, 34.2, 33.5, 23.5, 22.2; Anal. Calcd. for $C_{25}H_{19}BrN_4S$: C, 61.60; H, 3.93; N, 11.49; Found: C, 61.47; H, 3.85; N, 11.55.

5-Amino-4-(4-nitrophenyl)-2-phenylsulfanyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3h). Yellow solid; IR (KBr): 3426, 3318, 3076, 2222, 1637, 1541, 1518 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.41–8.50 (m, 4H, ArH), 7.46–7.57 (m, 5H, ArH), 5.55 (s, 2H, NH_2), 2.98 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 1.86 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 162.3, 161.1, 154.5, 152.6, 148.7, 135.8, 135.5, 129.8, 129.6, 129.3, 124.9, 124.4, 112.2, 105.7, 104.7, 33.8, 22.6, 22.4, 18.5; Anal. Calcd. for $C_{25}H_{19}N_5O_2S$: C, 66.21; H, 4.22; N, 15.44; Found: C, 66.29; H, 4.15; N, 15.49.

5-Amino-2-(4-methoxyphenylsulfanyl)-4-phenyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3i). Yellow solid; IR (KBr): 3434, 3330, 3048, 2209, 1628, 1551, 1437 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44–7.62 (m, 5H, ArH), 6.95–7.01 (m, 4H, ArH), 4.38 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.95 (t, *J* = 5.7 Hz, 2H, CH_2), 2.29 (t, *J* = 5.7 Hz, 2H, CH_2), 1.83–1.85 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.7 (C), 158.9 (C), 155.1 (C), 154.6 (C), 148.4 (C), 141.0 (C), 136.3 (CH), 133.5 (C), 130.2 (CH), 129.6 (CH), 127.9 (C), 126.7 (CH), 115.6 (C), 111.9 (C), 109.7 (C), 105.1 (C), 55.4 (CH_3), 34.1 (CH_2), 23.9 (CH_2), 23.3 (CH_2), 22.3 (CH_2); Anal. Calcd. for $C_{26}H_{22}N_4OS$: C, 71.21; H, 5.06; N, 12.78; Found: C, 71.10; H, 4.98; N, 12.84.

5-Amino-2-(4-methylphenylsulfanyl)-4-phenyl-6,7,8,9-tetra-hydrobenzo[b][1,8]-naphthyridine-3-carbonitrile (3j). Orange solid; IR (KBr): 3450, 3326, 3047, 2921, 2214, 1617, 1547, 1463 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56–7.61 (m, 5H, ArH), 7.26–7.44 (m, 4H, ArH), 4.40 (s, 2H, NH_2), 2.93 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.29 (m, 2H, CH_2), 1.84 (m, 4H, 2× CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.1 (C),

159.8 (C), 155.1 (C), 153.3 (C), 149.4 (C), 141.2 (C), 136.7 (CH), 133.8 (C), 130.4 (CH), 129.7 (CH), 129.1 (C), 128.8 (CH), 115.5 (C), 111.7 (C), 109.6 (C), 106.4 (C), 34.6 (CH_2), 24.5 (CH_2), 23.7 (CH_2), 22.1 (CH_2), 20.8 (CH_3); Anal. Calcd. for $C_{26}H_{22}N_4S$: C, 73.90; H, 5.25; N, 13.26; Found: C, 73.81; H, 5.32; N, 13.31.

X-ray crystallographic data for compound 3b. Empirical formula, $C_{26}H_{22}N_4S$; formula weight, 422.54; crystal color, yellow color; crystal dimensions, 0.25 × 0.23 × 0.22 mm^3; monoclinic space group = P 21/c, a = 11.4944(18) Å, b = 14.559(2) Å, c = 13.214(4) Å, $\alpha = 90°$, $\beta = 95.261(17)$, $\gamma = 90°$, V = 2202.2(8) $Å^3$, T = 293(2) K, Z = 4, d = 1.274 Mg/m^{-3}, $\mu = 0.168$ mm^{-1}, 12929 observed reflections, final R_1 = 0.0576, wR_2 = 0.1485 and for all data R_1 = 0.0883, wR_2 = 0.1631 [18].

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Eco-Friendly Synthesis of Quinoxaline Derivatives by Grinding Under Solvent-Free Conditions

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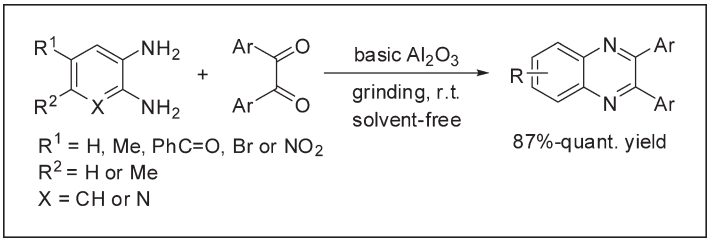

An efficient and facile synthesis of quinoxaline derivatives in excellent isolated yields by the condensation of 1,2-diamines and 1,2-diketones on grinding under solvent-free conditions at ambient temperature has been developed. The important features of this method are that it is reasonably fast, very clean, high yielding, simple workup, and environmentally benign.

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INTRODUCTION

Quinoxaline derivatives have become increasingly important in the past few years because they have been proven to be extremely useful intermediates for the preparation of new biological materials [1]. Quinoxaline ring is a part of a number of antibiotics such as echinomycin, levomycin, and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors [2]. Therefore, a variety of synthetic strategies have been developed for the preparation of quinoxaline derivatives [3]. One of the most common methods is the condensation of 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid [4]. Later, many improved methods have been reported for the synthesis of quinoxaline derivatives in the presence of various catalysts, such as Zn/L-proline [5], bismuth(III) triflate [6], metal hydrogen sulfates [7], gallium(III) triflate [8], molecular iodine [9], silica-bonded S-sulfonic acid [10], cerium(IV) ammonium nitrate [11], stannous chloride [12], zirconium tetrakis(dodecylsulfate) [13], amidosulfonic acid [14], montmorillonite K-10 [15], polyanilinesulfate salt [16], niobium pentachloride [17], Wells-Dawson heteropolyacid [18], ionic liquid [19], and ZrO_2/M_xO_y (M = Al, Ga, In, and La) mixed metal oxides supported on MCM-41 mesoporous molecular sieves [20]. The condensation has also been accomplished under catalyst-free conditions, but needs for the microwave heating [21] in industry. Recently, we reported an efficient catalyst-free protocol for the synthesis of quinoxaline derivatives under ultrasound irradiation [22]. All these facts have strengthened our resolve to find newer eco-friendly methods.

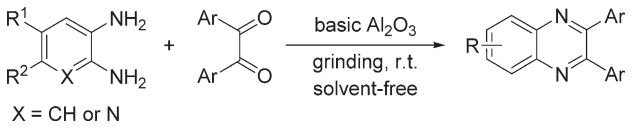
In recent years, significant articles have appeared reporting solid-state reactions by grinding [23]. Most of these reactions are carried out at room temperature in a completely solvent-free environment using only a mortar and pestle, and therefore the common merit of these processes is that they are efficient, economical, and environmentally friendly.

Aiming at the development of green and efficient organic methodologies, we recently reported some organic reactions carried out in ionic liquids [24] or under solvent-free conditions [25]. Herein, we report a green, efficient and convenient procedure for the synthesis of quinoxaline derivatives by the condensation of 1,2-diketones and 1,2-diamines on grinding at room temperature under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, initial studies were concentrated on treatment of 1,2-phenylenediamine (**1a**) with benzil (**2a**) as a model reaction (Scheme 2). Different reaction media were tested to find the optimal conditions. As shown in Table 1, basic Al_2O_3 was

Scheme 1



determined to be the more suitable medium, which afforded the desired product diphenylquinoxaline (**3a**) with excellent yield for 10 min (Table 1, entry 5). In contrast, the yield was decreased to some extent when the reactions were carried using no media, silica gel, neutral Al_2O_3, or acid Al_2O_3 at room temperature (Table 1, entries 1–5). Furthermore, the present route to **3a** was successfully applied to a large-scale reaction. For instance, the reaction of **1a** (5 mmol) with **2a** (5 mmol) using basic Al_2O_3 (5 g) as reaction medium provided the desired product **3a** in 97% (Table 1, entry 5).

With optimal conditions in hand, the reaction of a variety of structurally diverse 1,2-diketones and various 1,2-diamines was examined to explore the scope of the reaction, and the results are summarized in Table 2. It was observed that electron-donating groups on the phenyl ring of 1,2-diamine favored the formation of product to give excellent yields (Table 2, entries 5–10). In contrast, electron-withdrawing groups associated with 1,2-phenylenediamines slightly decreased the reactivity of the substrate, and a relatively long reaction time was required (Table 2, entry 11). However, 1,2-diamines containing strong electron-withdrawing group (—NO_2) on the benzene ring, such as 4-nitrobenzene-1,2-diamine, afforded the corresponding products **3l** in slightly lower yield, even the reaction time increased to 25 min (Table 2, entry 12).

To check the versatility of this method, we have also subjected other than heterocyclic 1,2-diamine such as 5-bromopyridine-2,3-diamine and obtained the products in high yield (Table 2, entry 13). Moreover, we also examined the condensation of heterocyclic 1,2-diketone such as 1,2-di(furan-2-yl)ethane-1,2-dione with various 1,2-diamine. Similarly, the corresponding products **3n** and **3o** were obtained in excellent yields (Table 2, entries 14 and 15).

Finally, we investigated the recycling of reaction media in a subsequent reaction, for example, the reaction of 1,2-phenylenediamine (**1a**) with benzil (**2a**). The basic Al_2O_3 was reused for five runs without any appreciable loss of activity (Scheme 3).

Scheme 2

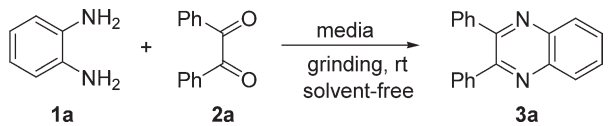


Table 1

Effect of reaction conditions.

Entry	Media	Time (min)	Yield (%)[a]
1	–	15	32
2	Silica gel	10	75
3	Neutral Al_2O_3	10	92
4	Acid Al_2O_3	10	81
5	Basic Al_2O_3	10	98, 99[c]
6	Basic Al_2O_3	5	85
7	Basic Al_2O_3	15	98

[a] Reactions conditions: **1a** (108 mg, 1 mmol), **2a** (210 mg,1 mmol), and media (500 mg) on grinding at room temperature under solvent-free conditions.
[b] Isolated yields after column chromatography.
[c] **1a** (0.54 g, 5 mmol), **2a** (1.05 g, 5 mmol), and basic Al_2O_3 (5 g).

In summary, we developed a highly efficient and facile method for the quinoxalines from various 1,2-diketones and 1,2-diamines on grinding under solvent-free conditions at room temperature. High yields, short reaction times, and neat conditions are the notable advantages of this method. It also has a good aspect of green chemistry as the basic Al_2O_3 media can be easily recovered and reused for five runs without any appreciable loss of activity, which makes this method a useful and attractive strategy in view of economic and environmental advantages.

EXPERIMENTAL

Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were recorded on an AVATAR 370 FI-Infrared Spectrophotometer. NMR spectroscopy was performed on a Bruker-300 spectrometer or Bruker-500 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal standard at room temperature. Mass spectra were measured with a Thermo Finnigan LCQ-Advantage. Elemental analyses were carried out using a Carlo-Erba EA1112 instrument.

General procedure for the synthesis of quinoxaline derivatives (3). The following components were added to the glass mortar: basic Al_2O_3 (200–300 mesh, 500 mg), 1,2-diketone 1 (1 mmol), and 1,2-diamine 2 (1 mmol). Then, the mixture was ground at room temperature with a glass pestle in the glass mortar. After 10 min, a mixture example was taken out and dissolved in ethyl acetate to monitor the progress of the reaction using TLC. After completion of the reaction, the mixture was transferred by ethyl acetate. The Al_2O_3 was collected by filtration, which precipitated from the organic phase, and the product was left in the organic phase. The recovered Al_2O_3 could be reused in the next batch after it was dried in oven. The crude product was subjected to column chromatography over silica gel using hexane/ethyl acetate as an eluent to obtain pure product.

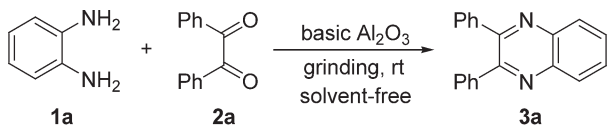
Table 2

Solvent-free synthesis of quinoxaline derivatives by grinding.

Entry	R^1	R^2	X	Ar	Time (min)	Product	Yield (%)[a]	Mp (°C)	Mp (°C) [Lit.]
1	H	H	CH	Ph	10	**3a**	98	120–122	128–129 [8]
2	H	H	CH	*p*-(Me)-C_6H_4	10	**3b**	95	143–144	141–142 [17]
3	H	H	CH	*p*-(OMe)-C_6H_4	10	**3c**	94	146–147	146–148 [22]
4	H	H	CH	*p*-(Br)-C_6H_4	10	**3d**	96	189–191	190–192 [17]
5	Me	H	CH	Ph	10	**3e**	Quant.	112–114	116–117 [17]
6	Me	H	CH	*p*-(OMe)-C_6H_4	10	**3f**	99	120–122	121–123 [22]
7	Me	H	CH	*p*-(Br)-C_6H_4	10	**3g**	98	184–185	183–184 [17]
8	Me	Me	CH	Ph	10	**3h**	Quant.	171–173	172–174 [11]
9	Me	Me	CH	*p*-(OMe)-C_6H_4	10	**3i**	97	125–127	Not reported [16b]
10	Me	Me	CH	*p*-(Br)-C_6H_4	10	**3j**	96	174–176	–
11	PhC=O	H	CH	Ph	20	**3k**	95	139–140	140–142 [8]
12	NO_2	H	CH	Ph	25	**3l**	87	185–187	188–190 [8]
13	Br	H	N	Ph	20	**3m**	93	150–152	154–155 [22]
14	H	H	CH	2-Furyl	10	**3n**	98	130–131	131–132 [22]
15	Me	H	CH	2-Furyl	10	**3o**	99	112–114	116–118 [8]

[a] Reactions were carried out on a 1-mmol scale by grinding at room temperature under solvent-free conditions.
[b] Isolated yields after column chromatography.

Scheme 3



1a 2a 3a

Run 1, 98%; run 2, 98%; run 3, 97%; run 4, 96% and run 5, 96%

2,3-Bis(4-bromophenyl)-6,7-dimethylquinoxaline (3j). This compound was obtained as colorless needles, mp 174–176°C; IR: 1716, 1673, 1587, 1483.6, 1446, 1420, 1392, 1364, 1224, 1207, 1073, 1010, 971, 872, 831 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 2H), 7.46 (d, J = 6.2 Hz, 4H), 7.34 (d, J = 8.4 Hz, 4H), 2.49 (s, 6H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 150.9, 141.1, 140.2, 138.0, 131.6, 131.5, 128.2, 123.4, 20.5. Anal. Calcd. for $C_{22}H_{16}Br_2N_2$: C, 56.44; H, 3.44; N, 5.98. Found: C, 56.35; H, 3.51; N, 6.06.

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Biaryl Sulfonamides from *O*-Acetyl Amidoximes: 1,2,4-Oxadiazole Cyclization under Acidic Conditions

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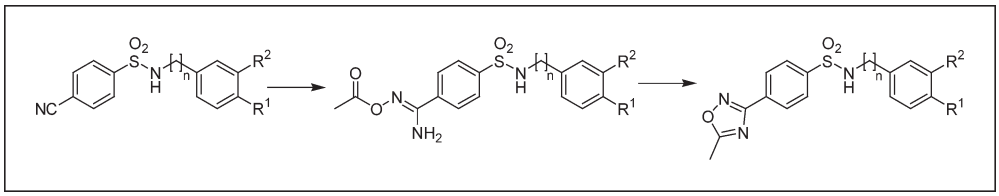

A series of 4-cyanobenzenesulfonamides (**1a–h**) was converted to the corresponding *O*-acetylated amidoximes (**2a–h**). The reaction of **1a** was exemplarily investigated with respect to the formation of a byproduct, which was identified as 1,2,4-oxadiazole derivative **3a**. This observation led to the development of an improved procedure for the preparation of **2a–h**. Compounds **2** could be transformed to 1,2,4-oxadiazoles **3a–h** in high yields and purity upon heating in acetic acid.

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INTRODUCTION

The 1,2,4-oxadiazole heterocycle has been found in a large number of compounds which display biological activity. Among a series of 5-alkyl-1,2,4-oxadiazol-3-yl-benzenesulfonamides, a 5-*n*-pentyl derivative was a particularly potent β_3 adrenergic receptor agonist [1]. The 1,2,4-oxadiazole moiety has been incorporated in selective SH2 inhibitors of tyrosine kinase ZAP-70 [2], novel 5-HT_3 antagonists [3], and histamine H_3 receptor antagonists [4].

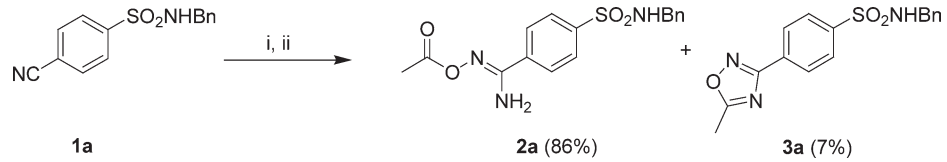
Because of their increased hydrolytic stability, oxadiazoles are often considered as ester bioisosteres in drug discovery research. For example, replacement of the methyl esters in arecoline or azabicyclo derivatives by 3- and 5-methyl-1,2,4-oxadiazole resulted in potent muscarinic agonists [5,6]. As benzodiazepine-receptor ligands, oxadiazoles have also been found to be metabolically stable alternatives to esters [7–9], and oxadiazoles related to disoxaril with antirhinoviral activity were identified [10]. The use of 1,2,4-oxadiazoles as amide mimetics has frequently been reported, for example to improve the *in vivo* efficacy of benzodiazepine receptor ligands [11] and to develop new inhibitors of palmitoyl-CoA oxidation [12]. The carboxamide-oxadiazole replacement led to A_{2B}-selective xanthine-based adenosine receptor antagonist [13] and to rimonabant-related CB1 cannabinoid-receptor antagonists [14]. Moreover, 1,2,4-oxadiazoles have been reported as dipeptidomimetics and successfully used in the design of pseudopeptides as μ- and δ-opioid and NK_1 receptor ligands [15,16].

The typical synthetic route to 1,2,4-oxadiazoles includes the *O*-acylation of easily accessible amidoximes [17], followed by their intramolecular condensation. For the first step, acid chlorides [18], esters [19], or symmetrical anhydrides [15] have been used, or carboxylic acids have been coupled to amidoximes in the presence of CDI, DCC, EDC, or BOP-Cl [20,21]. The 1,2,4-oxadiazoles were then obtained after thermal condensation of the *O*-acylated amidoxime precursors [22]. Numerous conditions for the dehydration step have been published, mostly involving heating in solvents such as DMF [23,24], diglyme [20], pyridine [15], or water [25]. Sodium acetate-catalyzed cyclodehydration was performed to produce series of enantiopure 1,2,4-oxadiazole-containing, Fmoc-protected β^3- and α-amino acids [26,27]. Cyclization could also proceed at room temperature, provided the presence of a strong basic reagent like TBAF [28]. Direct cyclization has also been reported, for example when reacting benzamidoxime with succinic anhydride under solvent-free conditions [29] or with acyl chlorides in pyridine [30]. However, da Costa Leite et al. heated aryl amidoximes in acetic acid as solvent and observed a product mixture of 3,5-bis(aryl)-1,2,4-oxadiazoles and 3-aryl-5-methyl-1,2,4-oxadiazoles [31].

RESULTS AND DISCUSSION

In the course of our studies related to the inhibition of serine proteases, we have designed benzamidines containing a sulfonamide structure as amide bioisostere

Scheme 1. Conditions: (i) $H_2NOH \times HCl$, DIPEA, EtOH, 87°C, 1 h; (ii) Ac_2O (3 equiv), AcOH, room temperature, 1 h.



1a **2a** (86%) **3a** (7%)

with strong hydrogen bonding donor–acceptor properties [32,33]. To take advantage of the preference of trypsin-like enzymes for arginine, the benzamidine substructure was chosen as a well-known arginine mimetic [34,35]. Thus, we were interested in a straightforward synthesis of a library of benzamidines from carbonitriles, which includes the formation of amidoximes, their *O*-acetylation and final reduction. These three steps were analyzed with respect to side products to develop a one-pot procedure to benzamidines. The first two steps were combined and the representative sulfonamide-containing nitrile **1a** was reacted with hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine (DIPEA) in refluxing ethanol. The crude product was directly dissolved in acetic acid [36] and treated with acetic anhydride (Scheme 1). Monitoring the reaction by TLC, a second product with unexpected low polarity was observed. The byproduct was separated from the desired *O*-acetylated substance **2a** by column chromatography and was then recrystallized. NMR spectroscopy showed a downfield shift of the methyl protons of 0.54 ppm and an upfield shift of the methyl carbon of 7.7 ppm, relative to the signals of **2a**. The NH_2 resonance and the N═C─N carbon signal at 155.6 ppm disappeared, whereas a new signal at 178.1 ppm was observed. Finally, the structure was confirmed by X-ray crystallography [37] to be the dehydrated 1,2,4-oxadiazole **3a** (Fig. 1, Table 1).

The cyclodehydration of *O*-acylated amidoximes at room temperature in the absence of a base has not been described in literature yet. It was not possible to complete the dehydration of **2a**, neither by increasing the reaction time nor by operating at higher temperatures, which even led to decomposition. Therefore, suitable conditions should be established to (i) convert *O*-acetylated amidoximes **2** to corresponding 1,2,4-oxadiazoles **3** and (ii) produce the benzamidine precursors **2** free of heterocyclic impurities. The corresponding reactions are depicted in Scheme 2.

Upon reaction with different amines, in dichloromethane and the presence of pyridine [38], the commercially available 4-cyanobenzenesulfonyl chloride was converted to eight cyano-substituted sulfonamides **1a–h** (Table 2). The corresponding *O*-acetylated amidoximes **2a–h** were obtained in good yields (Table 2) by a procedure combining the reaction with hydroxylamine and the *O*-acetylation. When performing the acetylation at room temperature using three equivalents of acetic anhydride and acetonitrile as the solvent, instead of acetic

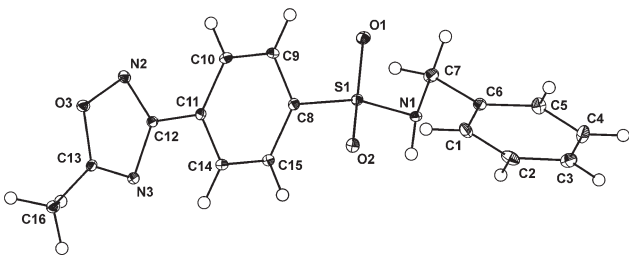


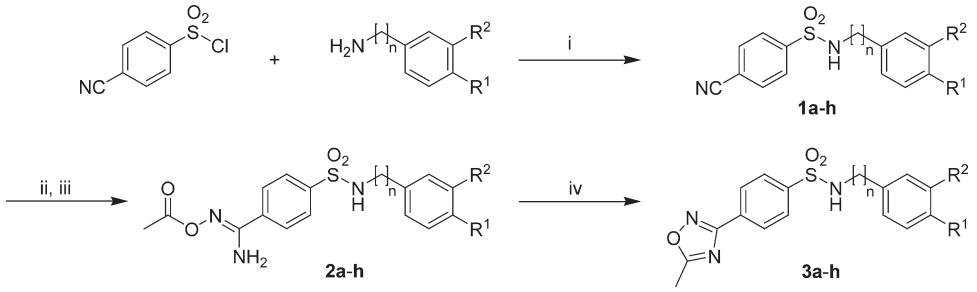
Figure 1. Molecular plot of **3a** showing the atom-labeling scheme and displacement ellipsoids at 30% probability level for the non-H atoms. H atoms are depicted as small circles of arbitrary radii [37].

Table 1

Crystallographic data of **3a.**

Empirical formula	$C_{16}H_{15}N_3O_3S$
Formula weight	329.37
Temperature	163(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 11.7210(3)$ Å; $\alpha = 105.463(2)°$ $b = 11.9411(2)$ Å; $\beta = 98.7490(10)°$ $c = 16.9507(5)$ Å; $\gamma = 92.208(2)°$
Volume	2252.16(10) $Å^3$
Z, Calculated density	6, 1.457 Mg/m^3
Absorption coefficient	0.235 mm^{-1}
F(000)	1032
Crystal size	0.42 mm × 0.33 mm × 0.19 mm
θ range for data collection	2.34–27.48°
Limiting indices	h, k, l −15/15, −15/15, −22/2
Reflections collected/unique	40076/10139 [R(int) = 0.0399]
Completeness to θ	98.1% ($\theta_{max} = 27.48°$)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9567 and 0.9078
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	10139/0/628
Goodness-of-fit on F^2	0.996
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0360$, $\omega R_2 = 0.0882$
R indices (all data)	$R_1 = 0.0563$, $\omega R_2 = 0.0956$
Largest diff. peak and hole	0.265 and −0.569 e/$Å^{-3}$

Scheme 2. Conditions: (i) pyridine, CH_2Cl_2, room temperature, 24 h; (ii) $H_2NOH \times HCl$, DIPEA, EtOH, 87°C, 1 h; (iii) Ac_2O (3 equiv), MeCN, room temperature, 1 h; (iv) AcOH, 80°C, 6 h.



acid, no heterocyclized byproducts were observed. The series of *O*-acetylated amidoximes **2** will be used for further transformation to benzamidines to become part of a library of potential serine protease inhibitors. Their biological evaluation is in progress and will be reported in due course.

The final 1,2,4-oxadiazoles **3a–h** were prepared from **2a**–**h** in acetic acid at 80°C (Table 2). Crystallization from ethyl acetate/hexane afforded the products in excellent purity. When compared with the initial experiment noted above, this procedure resulted in a complete conversion and yields of >78%. The use of purified material **2** in the cyclodehydration step seems favorable for the desired course of the reaction. An exemplary compound, **2a**, was cyclized in acetic acid at 120°C. This time, the product formation was completed after 1 h and the product, **3a**, was obtained in the same yield (80%) after recrystallization. The structural elucidation for **3a**–**h** was based on elemental analysis, ^{1}H- and ^{13}C-NMR data. Signals of both oxadiazole carbons, C-3 and C-5, appeared about 11 ppm downfield shifted, compared with the corresponding carbons in compounds **2**. Oxadiazole cyclizations, including the one presented herein, are useful methods for the introduction of heterocyclic biphenyl-analogous building blocks in the design of bioactive compounds, for example, inhibitors of cysteine cathepsins [39].

EXPERIMENTAL

Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany), Merck-Schuchardt (Hohenbrunn, Germany) or Sigma (Steinheim, Germany). Thin-layer chromatography was carried out on Merck aluminum sheets, silica gel 60 F_{254}. Preparative column chromatography was performed on Merck silica gel 60, 70–230 mesh. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts δ are given in ppm referring to the signal center using the solvent peak for reference: DMSO-d_6 2.49 ppm/39.7 ppm. The NMR signals were assigned by ^{1}H, ^{13}C correlation spectra (HMQC, HMBC) using standard pulse sequences. Elemental analyses were carried out with a Vario EL apparatus.

General procedure for the synthesis 4-cyanobenzenesulfonamides (1a–1h). A mixture of 4-cyanobenzenesulfonyl chloride (605 mg, 3 mmol), amine (3.3 mmol) and pyridine

Table 2

Conversion of 4-cyanobenzenesulfonamides to *O*-acetylated amidoximes and corresponding 1,2,4-oxadiazoles.

R^1	R^2	*n*	Nitrile	Yield (%)[a]	*O*-Acetyl-amidoxime	Yield (%)[a,b]	1,2,4-Oxadiazole	Yield (%)[a]
H	H	1	**1a**	71	**2a**	83	**3a**	80
OMe	H	1	**1b**	97	**2b**	77	**3b**	94
H	OMe	1	**1c**	67	**2c**	77	**3c**	84
OMe	OMe	1	**1d**	46	**2d**	91	**3d**	79
H	H	0	**1e**	45	**2e**	92	**3e**	87
OMe	H	0	**1f**	75	**2f**	75	**3f**	85
H	OMe	0	**1g**	92	**2g**	74	**3g**	90
OMe	OMe	0	**1h**	88	**2h**	95	**3h**	88

[a] Yields after recrystallization.
[b] No formation of 1,2,4-oxadiazole, monitored by TLC.

(736 mg, 9.3 mmol) was stirred for 24 h at room temperature in dry dichloromethane (10 mL). The solvent was removed under reduced pressure, acetic acid (1 mL) was added and the oily residue was purified by flash-column chromatography (dichloromethane). The product was obtained after recrystallization.

N-Benzyl-4-cyanobenzenesulfonamide (1a). Using benzylamine (354 mg, 3.3 mmol) as the amine component, the product **1a** was obtained following the general procedure after recrystallization from ethanol/water. Yield 580 mg (71%). Colorless solid, mp 138–140°C, ref. 40, 141–142°C; ^{1}H-NMR (DMSO-d_6): δ 4.04 (s, 2H, CH_2), 7.17–7.27 (m, 5H, phenyl-H), 7.90 (d, 2H, J = 8.8 Hz, phenyl-H), 8.01 (d, 2H, J = 8.8 Hz, phenyl-H), 8.45 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 46.3 (CH_2), 114.8 (C_q), 117.9 (CN), 127.4 (3× CH, Ph), 127.8 (2× CH, Ph), 128.4 (2× CH, Ph), 133.4 (2× CH, Ph), 137.3 (C_q), 145.2 (C_q).

4-Cyano-N-(4-methoxybenzyl)benzenesulfonamide (1b). Using 4-methoxybenzylamine (453 mg, 3.3 mmol), the product **1b** was obtained following the general procedure after recrystallization from toluene. Yield 880 mg (97%). Colorless solid, mp 128–131°C; ^{1}H-NMR (DMSO-d_6): δ 3.70 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.78 (d, 2H, J = 8.6 Hz, phenyl-H), 7.08 (d, 2H, J = 8.8 Hz, phenyl-H), 7.87 (d, 2H, J = 8.5 Hz, phenyl-H), 8.00 (d, 2H, J = 8.5 Hz, phenyl-H), 8.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 45.9 (CH_2), 55.2 (CH_3), 113.8 (2× CH, Ph), 114.7 (C_q), 117.9 (CN), 127.3 (2× CH, Ph), 129.1 (C_q), 129.2 (2× CH, Ph), 133.4 (2× CH, Ph), 145.3 (C_q), 158.7 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59%; H, 4.67%; N, 9.27%. Found C, 59.71%; H, 4.70%; N, 9.18%.

4-Cyano-N-(3-methoxybenzyl)benzenesulfonamide (1c). Using 3-methoxybenzylamine (453 mg, 3.3 mmol), the product **1c** was obtained after recrystallization from toluene. Yield 610 mg (67%). Colorless needles, mp 124–127°C; ^{1}H-NMR (DMSO-d_6): δ 3.67 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 6.71 (dd, 1H, J = 1.9 Hz, J = 1.9 Hz, phenyl-H), 6.74–6.77 (m, 2H, phenyl-H), 7.15 (dd, 1H, J = 7.9 Hz, J = 7.9 Hz, phenyl-H), 7.88 (d, 2H, J = 8.2 Hz, phenyl-H), 8.00 (d, 2H, J = 8.5 Hz, phenyl-H), 8.44 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 46.2 (CH_2), 55.1 (CH_3), 112.9, 113.3 (2× CH, Ph), 114.8 (C_q), 117.9 (CN), 119.9, 129.4, 127.3, 133.3 (6× CH, Ph), 138.8 (C_q), 145.2 (C_q), 159.3 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59%; H, 4.67%; N, 9.27%. Found C, 59.61%; H, 4.72%; N, 9.12%.

4-Cyano-N-(3,4-dimethoxybenzyl)benzenesulfonamide (1d). Using 3,4-dimethoxybenzylamine (552 mg, 3.3 mmol), the product **1d** was obtained following the general procedure after recrystallization from ethyl acetate/toluene. Yield 460 mg (46%). Pink solid, mp 171–175°C; ^{1}H-NMR (DMSO-d_6): δ 3.64, 3.69 (each s, 6H, CH_3), 3.98 (s, 2H, CH_2), 6.67 (dd, 1H, J = 8.2 Hz, J = 1.9 Hz, phenyl-H), 6.72 (d, 1H, J = 1.9 Hz, phenyl-H), 6.77 (d, 1H, J = 8.2 Hz, phenyl-H), 7.86 (d, 2H, J = 8.8 Hz, phenyl-H), 7.98 (d, 2H, J = 8.8 Hz, phenyl-H), 8.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 46.2 (CH_2), 55.5, 55.7 (CH_3), 111.7, 111.8 (2× CH, Ph), 114.7 (C_q), 117.9 (CN), 120.2, 127.4 (3× CH, Ph), 129.5 (C_q), 133.3 (2× CH, Ph), 145.3 (C_q), 148.2 (C_q), 148.7 (C_q). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82%; H, 4.85%; N, 8.43%. Found C, 57.99%; H, 4.86%; N, 8.34%.

4-Cyano-N-phenyl-benzenesulfonamide (1e). Using aniline (307 mg, 3.3 mmol), the product **1e** was obtained following the general procedure after recrystallization from ethyl acetate/hexane. Yield 349 mg (45%). White powder, mp 110–111°C; ^{1}H-NMR (DMSO-d_6): δ 7.03–7.09 (m, 3H, phenyl-H), 7.24 (dd, 2H, J = 8.7 Hz, J = 7.6 Hz, phenyl-H), 7.88 (d, 2H, J = 8.8 Hz, phenyl-H), 8.02 (d, 2H, J = 8.9Hz, phenyl-H), 10.49 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 115.5 (C_q), 117.7 (CN), 120.8, 124.8, 127.5, 129.4, 133.6 (9× CH, Ph), 137.1 (C_q), 143.7 (C_q). Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45%; H, 3.90%; N, 10.85%. Found C, 59.87%; H, 3.83%; N, 10.49%.

4-Cyano-N-(4-methoxyphenyl)benzenesulfonamide (1f). Using *p*-anisidine (406 mg, 3.3 mmol), the product **1f** was obtained following the general procedure after recrystallization from toluene. Yield 650 mg (75%). White powder, mp 148–149°C, ref. 41, 188–191°C; ^{1}H-NMR (DMSO-d_6): δ 3.66 (s, 3H, CH_3), 6.81 (d, 2H, J = 9.2 Hz, phenyl-H), 6.95 (d, 2H, J = 9.2 Hz, phenyl-H), 7.81 (d, 2H, J = 8.5 Hz, phenyl-H), 8.01 (d, 2H, J = 8.8 Hz, phenyl-H), 10.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.3 (CH_3), 114.6 (2× CH, Ph), 115.3 (C_q), 117.2 (CN), 124.1, 127.6 (4× CH, Ph), 129.4 (C_q), 133.5 (2× CH, Ph), 143.7 (C_q), 157.1 (C_q). Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32%; H, 4.20%; N, 9.72%. Found C, 58.48%; H, 4.32%; N, 9.65%.

4-Cyano-N-(3-methoxyphenyl)benzenesulfonamide (1g). Using *m*-anisidine (406 mg, 3.3 mmol), the product **1g** was obtained following the general procedure after recrystallization from toluene. Yield 800 mg (92%). Yellow crystals, mp 99–103°C; ^{1}H-NMR (DMSO-d_6): δ 3.66 (s, 3H, CH_3), 6.61–6.67 (m, 3H, phenyl-H), 7.13 (dd, 1H, J = 8.6 Hz, J = 8.4 Hz, phenyl-H), 7.90 (d, 2H, J = 8.9 Hz, phenyl-H), 8.03 (d, 2H, J = 8.8 Hz, phenyl-H), 10.50 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.2 (CH_3), 106.4, 109.9, 112.5 (3× CH, Ph), 115.5 (C_q), 117.7 (CN), 127.6, 130.3, 133.6 (5× CH, Ph), 138.4 (C_q), 143.6 (C_q), 159.9 (C_q). Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32%; H, 4.20%; N, 9.72%. Found C, 58.49%; H, 4.25%; N, 9.58%.

4-Cyano-N-(3,4-dimethoxyphenyl)benzenesulfonamide (1h). Using 4-aminoveratrole (505 mg, 3.3 mmol), the product **1h** was obtained following the general procedure after recrystallization from toluene. Yield 730 mg (76%). Dark pink crystals, mp 135–140°C; ^{1}H-NMR (DMSO-d_6): δ 3.63, 3.66 (each s, 6H, CH_3), 6.53 (dd, 1H, J = 8.7 Hz, J = 2.2 Hz, phenyl-H), 6.66 (d, 1H, J = 2.5 Hz, phenyl-H), 6.80 (d, 1H, J = 8.5 Hz, phenyl-H), 7.84 (d, 2H, J = 8.8 Hz, phenyl-H), 8.02 (d, 2H, J = 8.9 Hz, phenyl-H), 10.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.6, 55.87 (CH_3), 107.1, 112.2, 114.3 (3× CH, Ph), 115.3 (C_q), 117.7 (CN), 127.6 (2× CH, Ph), 129.8 (C_q), 133.5 (2× CH, Ph), 143.6 (C_q), 146.1 (C_q), 149.0 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_4S$: C, 56.59%; H, 4.43%; N, 8.80%. Found C, 56.89%; H, 4.51%; N, 8.69%.

Conversion of 1a to a mixture of 2a and 3a. A mixture of *N*-benzyl-4-cyanobenzenesulfonamide **1a** (545 mg, 2 mmol), hydroxylamine-hydrochloride (278 mg, 4 mmol) and DIPEA (517 mg, 4.08 mmol) in dry ethanol (17 mL) was refluxed for 1 h. The solvent was removed and the oily residue was dissolved in acetic acid (8 mL). After addition of acetic anhydride (613 mg, 6 mmol), the solution was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 2:1) to obtain **2a** (598 mg, 86%) and **3a** (46 mg, 7%). Compound **3a** was recrystallized from ethyl acetate/hexane.

General procedure for the synthesis of *N*-acetoxy-benzimidamides (2a–2h). A mixture of hydroxylamine-hydrochloride (2 equiv) and the 4-cyanobenzenesulfonamide (1 equiv) was refluxed in ethanol (25 mL) in the presence of DIPEA (2 equiv) for 1 h. Afterward, the solvent was removed *in vacuo*. The residue was dissolved in acetonitrile (20 mL), and acetic anhydride (3 equiv) was added. After 1 h, the solvent was evaporated, and the *N*-acetoxy-benzimidamide was isolated after recrystallization from ethyl acetate/hexane as a colorless solid.

***N*-Acetoxy-4-(*N*′-benzylsulfamoyl)benzimidamide (2a).** Following the general procedure, product **2a** was afforded from **1a** (429 mg, 1.58 mmol). Yield 455 mg (83%). White solid, mp 168–170°C; ^{1}H-NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.95 (s, 2H, NH_2), 7.20–7.30 (m, 5H, phenyl-H), 7.86 (d, J = 8.8 Hz, 2H, phenyl-H), 7.89 (d, J = 8.8 Hz, 2H, phenyl-H), 8.23 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.3 (CH_2), 126.7, 127.3, 127.7, 127.7, 128.4 (9× CH), 135.4 (C_q), 137.7 (C_q), 142.5 (C_q), 155.6 (N═C─N), 168.5 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.32%; H, 4.93%; N, 12.10%. Found C, 55.03%; H, 5.28%; N, 11.71%.

***N*-Acetoxy-4-(*N*′-(4-methoxybenzyl)sulfamoyl)benzimidamide (2b).** Following the general procedure, product **2b** was afforded from **1b** (756 mg, 2.5 mmol). Yield 727 mg (77%). Colorless solid, mp 165–166°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2), 6.82 (d, J = 8.9 Hz, 2H, phenyl-H), 6.94 (s, 2H, NH_2), 7.13 (d, J = 8.6 Hz, 2H, phenyl-H), 7.83 (d, J = 8.8 Hz, 2H, phenyl-H), 7.88 (d, J = 8.9 Hz, 2H, phenyl-H), 8.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 45.8 (CH_2), 55.2 (OCH_3), 113.8, 126.6, 127.6, 129.1 (8× CH, Ph), 129.4 (C_q), 135.3 (C_q), 142.5 (C_q), 155.6 (N═C─N), 158.6 (C_q), 168.4 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_5S$: C, 54.10%; H, 5.07%; N, 11.13%. Found C, 53.97%; H, 5.13%; N, 11.07%.

***N*-Acetoxy-4-(*N*′-(3-methoxybenzyl)sulfamoyl)benzimidamide (2c).** Following the general procedure, product **2c** was afforded from **1c** (346 mg, 1.14 mmol). Yield 333 mg (77%). White solid, mp 118–120°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2), 6.77–6.81 (m, 3H, phenyl-H), 6.94 (s, 2H, NH_2), (7.18 (dd, J = 7.6 Hz, J = 8.8 Hz, 1H, phenyl-H), 7.85 (d, J = 8.5 Hz, 2H, phenyl-H), 7.89 (d, J = 8.6 Hz, 2H, phenyl-H), 8.22 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.2 (CH_2), 55.1 (OCH_3), 112.9, 113.1, 119.8, 126.7, 127.7, 129.5 (8× CH, Ph), 135.4 (C_q), 129.2 (C_q), 142.5 (C_q), 155.5 (N═C─N), 159.4 (C_q), 168.5 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_5S$: C, 54.10%; H, 5.07%; N, 11.13%. Found C, 54.06%; H, 5.16%; N, 10.89%.

***N*-Acetoxy-4-(*N*′-(3,4-dimethoxybenzyl)sulfamoyl)benzimidamide (2d).** Following the general procedure, product **2d** was afforded from **1d** (341 mg, 1.03 mmol). Yield 380 mg (91%). White solid, mp 137–138°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.65, 3.69 (each s, 6H, OCH_3), 3.93 (s, 2H, CH_2), 6.72 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H, phenyl-H), 6.76 (d, J = 1.9 Hz, 1H, phenyl-H), 6.81 (d, J = 8.2 Hz, 1H, phenyl-H), 6.93 (s, 2H, NH_2), 7.83 (d, J = 8.9 Hz, 2H, phenyl-H), 7.88 (d, J = 8.5 Hz, 2H, phenyl-H), 8.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.2 (CH_2), 55.5, 55.7 (OCH_3), 111.7, 111.8, 120.0, 126.7, 127.6 (7× CH, Ph), 129.8 (C_q), 135.4 (C_q), 142.6 (C_q), 148.2 (C_q), 148.7 (C_q), 155.5 (N═C─N), 168.5 (CO). Anal. Calcd. for $C_{18}H_{21}N_3O_6S$: C, 53.06%; H, 5.20%; N, 10.31%. Found C, 53.00%; H, 5.29%; N, 10.05%.

***N*-Acetoxy-4-(*N*′-phenylsulfamoyl)benzimidamide (2e).** Following the general procedure, product **2e** was afforded from **1e** (280 mg, 1.08 mmol). Yield 333 mg (92%). Colorless needles, mp 166–167°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 6.91 (s, 2H, NH_2), 7.02 (tt, 1H, J = 7.4 Hz, J = 1.0 Hz, phenyl-H), 7.01–7.11 (m, 2H, phenyl-H), 7.22 (dd, 2H, J = 7.6 Hz, J = 8.5 Hz, phenyl-H), 7.80, (d, J = 8.9 Hz, 2H, phenyl-H), 7.84 (d, 2H, J = 8.5 Hz, phenyl-H), 10.33 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 120.4, 124.4, 126.9, 127.8, 129.3 (9× CH, Ph), 135.9 (C_q), 137.6 (C_q), 141.3 (C_q), 155.5 (N═C─N), 168.4 (CO). Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.04%; H, 4.54%; N, 12.60%. Found C, 54.01%; H, 4.57%; N, 12.37%.

***N*-Acetoxy-4-(*N*′-(4-methoxyphenyl)sulfamoyl)benzimidamide (2f).** Following the general procedure, product **2f** was afforded from **1f** (625 mg, 2.17 mmol). Yield 590 mg (75%). White crystalline solid, mp 150–152°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.80 (d, J = 9.2 Hz, 2H, phenyl-H), 6.91 (s, 2H, NH_2), 6.97 (d, J = 9.2 Hz, 2H, phenyl-H), 7.72 (d, J = 8.6 Hz, 2H phenyl-H), 7.83 (d, J = 8.8 Hz, 2H, phenyl-H), 9.96 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.3 (OCH_3), 114.5, 123.8, 126.9, 127.7 (8× CH, Ph), 129.9 (C_q), 135.7 (C_q), 141.2 (C_q), 155.5 (N═C─N), 156.8 (C_q), 168.4 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88%; H, 4.72%; N, 11.56%. Found C, 52.67%; H, 4.79%; N, 11.38%.

***N*-Acetoxy-4-(*N*′-(3-methoxyphenyl)sulfamoyl)benzimidamide (2g).** Following the general procedure, product **2g** was afforded from **1g** (641 mg, 2.22 mmol). Yield 600 mg (74%). White solid, mp 120–121°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 6.60 (ddd, J = 8.5 Hz, J = 2.4 Hz, J = 0.6 Hz, 1H, phenyl-H), 6.65–6.67 (m, 2H, phenyl-H), 6.91 (s, 2H, NH_2), 7.12 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, phenyl-H), 7.82 (d, J = 8.5 Hz, 2H, phenyl-H), 7.85 (d, J = 8.8 Hz, 2H, phenyl-H), 10.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.1 (OCH_3), 106.0, 109.4, 112.2, 126.9, 127.8, 130.2 (8× CH, Ph), 136.0 (C_q), 138.8 (C_q), 141.2 (C_q), 155.5 (N═C─N), 159.8 (C_q), 168.4 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88%; H, 4.72%; N, 11.56%. Found C, 52.48%; H, 4.75%; N, 11.40%.

***N*-Acetoxy-4-(*N*′-(3,4-dimethoxyphenyl)sulfamoyl)benzimidamide (2h).** Following the general procedure, product **2h** was afforded from **1h** (430 mg, 1.35 mmol). Yield 504 mg (95%). White crystalline solid, mp 116–118°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.63 (each s, 6H, OCH_3), 6.54 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, phenyl-H), 6.69 (d, J = 2.2 Hz, 1H, phenyl-H), 6.79 (d, J = 8.5 Hz, 1H, phenyl-H), 6.91 (s, 2H, NH_2), 7.76 (d, J = 8.5 Hz, 2H, phenyl-H), 7.84 (d, J = 8.5 Hz, 2H, phenyl-H), 9.97 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.6, 55.7 (OCH_3), 106.9, 112.3, 113.9, 127.0, 127.7 (7× CH, Ph), 130.4 (C_q), 135.8 (C_q), 141.2 (C_q), 146.4 (C_q), 149.0 (C_q), 155.5 (N═C─N), 168.4 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_6S$: C, 51.90%; H, 4.87%; N, 10.68%. Found C, 50.73%; H, 5.17%; N, 10.38%.

General procedure for the preparation of 1,2,4-oxadiazoles (3a–3h). Compound **2** was stirred in acetic acid (15 mL) for 6 h at 80°C. The solvent was removed under reduced pressure, and the corresponding 1,2,4-oxaziazole was obtained after recrystallization from ethyl acetate/hexane.

N-Benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3a). Following the general procedure, compound **3a** was prepared from **2a** (348 mg, 1.0 mmol). Yield 263 mg (80%). Colorless solid, mp 158–159°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 7.17–7.28 (m, 5H, phenyl-H), 7.94 (d, 2H, J = 8.6 Hz, phenyl-H), 8.14 (d, J = 8.5 Hz, 2H, phenyl-H), 8.32 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.3 (CH_2), 127.3, 127.5, 127.7, 127.8, 128.3 (9× CH, Ph), 129.7 (C_q), 137.6 (C_q), 143.5 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.34%; H, 4.59%; N, 12.76%. Found C, 58.41%; H, 4.75%; N, 13.01%.

N-(4-Methoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3b). Following the general procedure, compound **3b** was prepared from **2b** (377 mg, 1.0 mmol). Yield 338 mg (94%). Colorless solid, mp 152–153°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.96 (d, J = 6.3 Hz, 2H, CH_2), 6.79 (d, J = 8.5 Hz, 2H, phenyl-H), 7.12 (d, J = 8.5 Hz, 2H, phenyl-H), 7.92 (d, J = 8.9 Hz, 2H, phenyl-H), 8.14 (d, J = 8.9 Hz, 2H, phenyl-H), 8.22 (t, J = 6.3 Hz, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 45.9 (CH_2), 55.2 (OCH_3), 113.8, 127.5, 127.8, 129.1 (8× CH, Ph), 129.4 (C_q), 129.7 (C_q), 143.5 (C_q), 158.6 (C_q), 166.9 (N═C─N), 178.1 (O─C═N). Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81%; H, 4.77%; N, 11.69%. Found C, 56.83%; H, 4.77%; N, 11.49%.

N-(3-Methoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3c). Following the general procedure, compound **3c** was prepared from **2c** (199 mg, 527 μmol). Yield 160 mg (84%). Colorless solid, mp 152–154°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.03 (d, J = 6.0 Hz, 2H, CH_2), 6.73–6.80 (m, 3H, phenyl-H), 7.15 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.0 Hz, 1H, phenyl-H), 7.93 (d, J = 8.6 Hz, 2H, phenyl-H), 8.12 (d, J = 8.5 Hz, 2H, phenyl-H), 8.31 (t, J = 6.0 Hz, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.2 (CH_2), 55.1 (OCH_3), 112.9, 113.1, 119.9, 127.5, 127.8, 129.4 (8× CH, Ph), 129.7 (C_q), 139.1 (C_q), 143.5 (C_q), 159.3 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81%; H, 4.77%; N, 11.69%. Found C, 56.70%; H, 4.78%; N, 11.39%.

N-(3,4-Dimethoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl) benzenesulfonamide (3d). Following the general procedure, compound **3d** was prepared from **2d** (390 mg, 957 μmol). Yield 294 mg (79%). Colorless solid, mp 170–171°C; ^{1}H-NMR (DMSO-d_6): δ 2.68 (s, 3H, CH_3), 3.63, 3.66 (each s, 6H, OCH_3), 3.98 (s, 2H, CH_2), 6.71 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H, phenyl-H), 6.75 (d, J = 1.9 Hz, 1H, phenyl-H), 6.78 (d, J = 8.2 Hz, 1H, phenyl-H), 7.91 (d, J = 8.5 Hz, 2H, phenyl-H), 8.12 (d, J = 8.8 Hz, 2H, phenyl-H), 8.22 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.2 (CH_2), 55.4, 55.7 (OCH_3), 111.7, 111.8, 120.0, 127.5, 127.7 (7× CH, Ph), 129.6 (C_q), 129.7 (C_q), 143.5 (C_q), 148.2 (C_q), 148.7 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{18}H_{19}N_3O_5S$: C, 55.52%; H, 4.92%; N, 10.97%. Found C, 55.34%; H, 5.14%; N, 10.46%.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-phenyl-benzenesulfonamide (3e). Following the general procedure, compound **3e** was prepared from **2e** (382 mg, 1.15 mmol). Yield 315 mg (87%). Colorless solid, mp 175–176°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.03 (tt, J = 7.6 Hz, 1.3 Hz, 1H, phenyl-H), 7.08–7.10 (m, 2H, phenyl-H), 7.22 (dd, J = 7.3 Hz, J = 8.6 Hz, 2H, phenyl-H), 7.91 (d, J = 8.8 Hz, 2H, phenyl-H), 8.13 (d, J = 8.8 Hz, 2H, phenyl-H), 10.38 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 120.6, 124.6, 127.8, 128.0, 129.4 (9× CH, Ph), 130.3 (C_q), 137.5 (C_q), 142.1 (C_q), 166.8 (N═C─N), 178.2 (N═C─O). Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13%; H, 4.16%; N, 13.33%. Found C, 57.22%; H, 4.28%; N, 13.09%.

N-(4-Methoxyphenyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3f). Following the general procedure, compound **3f** was prepared from **2f** (190 mg, 523 μmol). Yield 154 mg (85%). Colorless solid, mp 174–177°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.80 (d, J = 9.2 Hz, 2H, phenyl-H), 6.97 (d, J = 9.2 Hz, 2H, phenyl-H), 7.83 (d, J = 8.5 Hz, 2H, phenyl-H), 8.12 (d, J = 8.2 Hz, 2H, phenyl-H), 10.01 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.3 (OCH_3), 114.5, 124.0, 127.8, 127.8 (8× CH, Ph), 129.8 (C_q), 130.1 (C_q), 142.0 (C_q), 156.9 (C_q), 166.8 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64%; H, 4.38%; N, 12.17%. Found C, 55.52%; H, 4.37%; N, 12.06%.

N-(3-Methoxyphenyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3g). Following the general procedure, compound **3g** was prepared from **2g** (406 mg, 1.12 mmol). Yield 350 mg (90%). Colorless solid, mp 162–164°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.59–6.61 (m, 1H, phenyl-H), 6.67–6.68 (m, 2H, phenyl-H), 7.12 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, phenyl-H), 7.93 (d, J = 8.2 Hz, 2H, phenyl-H), 8.14 (d, J = 8.5 Hz, 2H, phenyl-H), 10.40 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.2 (OCH_3), 106.2, 109.6, 112.4, 127.8, 128.0, 130.2 (8× CH, Ph), 130.3 (C_q), 138.7 (C_q), 142.0 (C_q), 159.9 (C_q), 166.7 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64%; H, 4.38%; N, 12.17%. Found C, 55.88%; H, 4.38%; N, 12.06%.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-(3,4-dimethoxyphenyl)-benzenesulfonamide (3h). Following the general procedure, compound **3h** was prepared from **2h** (490 mg, 1.25 mmol). Yield 411 mg (88%). Brown crystals, mp 186–187°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.62, 3.65 (s, 6H, OCH_3), 6.55 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, phenyl-H), 6.68 (d, J = 2.2 Hz, 1H, phenyl-H), 6.97 (d, J = 8.9 Hz, 1H, phenyl-H), 7.86 (d, J = 8.5 Hz, 2H, phenyl-H), 8.13 (d, J = 8.9 Hz, 2H, phenyl-H), 10.02 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.6, 55.7 (OCH_3), 107.1, 112.2, 114.2, 127.8, 127.9 (7× CH, Ph), 130.2 (C_q), 130.2 (C_q), 142.0 (C_q), 146.6(C_q), 149.0 (C_q), 166.8 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{17}H_{17}N_3O_5S$: C, 54.39%; H, 4.56%; N, 11.19%. Found C, 54.21%; H, 4.70%; N, 10.99%.

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Synthesis of an Isomer of the Renieramycin Skeleton from L-Tyrosine

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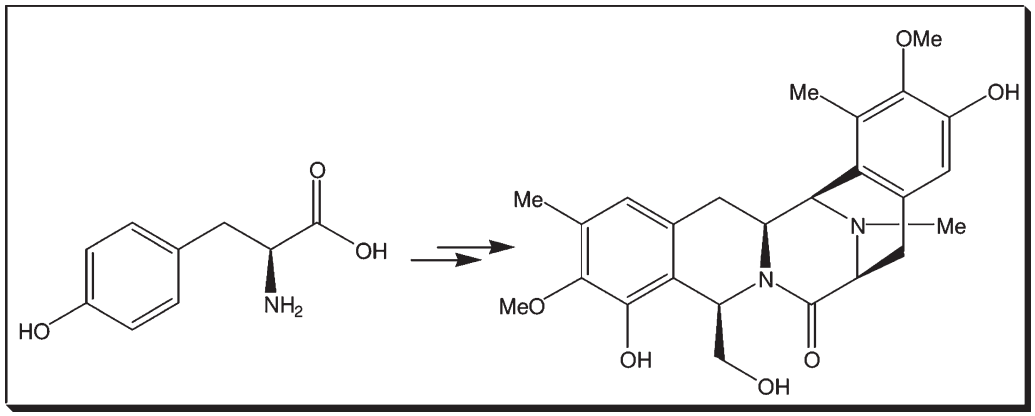

A new approach that tried to obviate the use of bromine protection groups was studied to synthesize (−)-renieramycin G from L-tyrosine. It was found that the first intermolecular Pictet–Spengler reaction proceeded successfully to give the correct tetrahydroisoquinoline precursor **6**. However, the second intramolecular Pictet–Spengler cyclization step failed to give the desired product, and an isomer of the skeleton of the renieramycins was obtained *via* 12 steps starting from L-tyrosine.

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INTRODUCTION

Members of the tetrahydroisoquinoline family of alkaloids including saframycins, ecteinascidins, renieramycins, quinocarcins, and lemonomycin display a wide range of biological properties such as antitumor and antimicrobial activities [1]. Renieramycins are marine natural products that are structurally and biologically related to the isoquinoline natural products. Renieramycin G (Fig. 1) was isolated in 1992 by Davidson [2] from the Fijian sponge *Xestospongia caycedoi*. Several studies on the total synthesis of the renieramycin natural products have been reported [3–5].

The stereospecific intramolecular Pictet–Spengler cyclization is one of the key steps for the construction of the pentacyclic skeleton of the bistetrahydroisoquinoline alkaloids. Organic acids such as HCOOH, $MeSO_3H$, CF_3SO_3H, and CF_3COOH have been used to realize the cyclization [6–23]. Previous research in our group mainly focused on the study of new approaches to construct the pentacyclic skeleton and the discovery of simplified derivatives of the bistetrahydroisoquinoline alkaloids [24]. Recently, our group reported a new approach for the total synthesis of (−)-renieramycin G using L-tyrosine as the chiral starting material [25]. Now as a continuation of this research, we investigated a more efficient synthetic route of (−)-renieramycin G, which tried to avoid the use of the bromine protection groups in the two benzene rings.

RESULTS AND DISCUSSIONS

The synthesis of amino acid **4** (Scheme 1) and the key 1,2,3,4-tetrahydroisoquinoline precursor **6** (Scheme 2) basically followed our published procedures. The difference was that the use of the bromine protecting groups on the benzene rings was obviated. The Baeyer–Villiger oxidation of **1** using *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform at room temperature, followed by hydrolysis of the resulting formate intermediate, provided phenol **2**. The N-acetyl group of **2** was removed with $SOCl_2$ in methanol, and the resulting free amine was reprotected as the corresponding Boc carbamate to afford compound **4**. Finally, hydrolysis of the methyl ester with LiOH provided amino acid **4**. Amino ester **2** was reduced to the corresponding alcohol by $LiBH_4$ in 91% yield. The N-acetyl group was removed

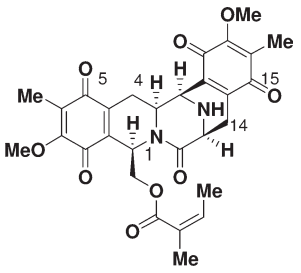


Figure 1. Structure of (−)-renieramycin G.

with 6 N aqueous HCl in CH_3OH to give amino alcohol **5** in 90% yield. The highly diastereoselective Pictet–Spengler cyclization reaction between amino alcohol **5** and benzyloxyacetaldehyde at −10°C regioselectively provided (1*R*,3*S*)-1,2,3,4-tetrahydroisoquinoline **6** in 87% yield. No product from the cylization occurring para to the hydroxyl group on the benzene ring was found. The stereochemistry of compound **6** was verified through the analysis of the stereochemistry of (−)-MY 336a, which was obtained from the hydrogenation of compound **6** [26]. Thus it proved that the intermolecular Pictet–Spengler reaction was successful without the bromine blocking group.

Next, 1,2,3,4-tetrahydroisoquinoline **6** was coupled with **4** through the action of bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) to afford amide **7**. Then, silylation of compound **7** with *tert*-butyldimethylsilyl chloride (TBSCl) and subsequent cleavage of TBS group selectively provided the primary alcohol **8**. Oxidation of compound **8** with Dess–Martin periodinane provided hemiaminal as a single diastereomer. Cleavage of the aryl TBS ether using tetrabutylammonium fluoride (TBAF) afforded compound **9** (Scheme 3).

With **9** in hand, we then investigated the key intramolecular Pictet–Spengler reaction to construct the pentacyclic skeleton. However, the pentacyclic product **10** was not obtained from the treatment of **9** with HCOOH, CF_3SO_3H, or $MeSO_3H$. Finally, treatment of compound **9** with trifluoroacetic acid (TFA) at room temperature provided pentacyclic compound **10** with the Boc group having been removed simultaneously. Without purification, crude compound **10** was N-methylated to give product **11** through the reductive methylation. The characteristic nuclear Overhauser effects (NOEs) between 5-H and 6-CH_3, and between 15-H and 16-OH in compound **11** confirmed that 15-H was ortho to 16-OH (Scheme 3). Thus it was confirmed that the intramolecular Pictet–Spengler cyclization occurred para instead of ortho to the hydroxyl group of the right benzene ring. It is supposed that the relatively strong condition of this reaction (CF_3CO_2H/r.t.) other than the mild one of the first intermolecular Pictet–Spengler reaction (acetic acid/−10°C) failed to give the desired product.

CONCLUSION

In conclusion, we studied a new approach for the total synthesis of (−)-renieramycin G without the use of the bromine protection groups. The first intermolecular Pictet–Spengler reaction proceeded smoothly to give the desired tetrahydroisoquinoline product. However, the second intramolecular Pictet–Spengler reaction did not give the correct cyclization product, and an isomer of the skeleton of renieramycin natural products was obtained through 12 steps for the longest linear route.

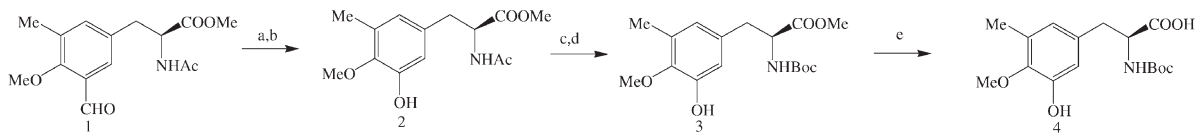
EXPERIMENTAL

General. ^{1}H-NMR spectra were recorded on a Bruker AM 600 or 300 instrument (Bruker BioSpin Corporation, MA) at 24°C in the indicated solvent and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C-NMR spectra were recorded at 150 or 75 MHz spectrometer at 24°C in the solvent indicated and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS were carried out by Agilent LC/MSD TOF (Agilent Technologies, CA). Optical rotations were measured on a Perkin Elmer Polarimeter 341LC (PerkinElmer Incorporation, MA) using 10-cm cells and the sodium D line (589 nm) at 20°C and concentration was indicated. All reagents were obtained from commercial suppliers unless otherwise stated.

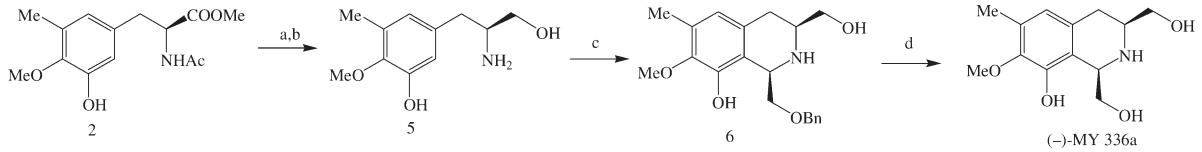
Synthesis of compound 4. To a solution of **3** (1.56 g, 4.6 mmol) in CH_3OH (10 mL), a solution of lithium hydroxide (0.44 g, 18.4 mmol, 4 equiv.) in water (5 mL) was added. The solution was stirred at room temperature for 4 h. The methanol was removed *in vacuo*, and the aqueous phase was acidified to pH 1.5. The aqueous phase was extracted with EtOAc (50 mL × 2), and the combined organic extracts were washed with brine and dried over Na_2SO_4. The organic phase was concentrated, and the residue was purified by flash column chromatography (EtOAc) to afford **4** (1.39 g, 93%) as a white solid. m.p.: 77–80°C.

^{1}H-NMR (300 MHz, dimethyl sulfoxide-d_6): σ 12.53 (s, 1H), 9.04 (s, 1H), 7.03 (d, J = 9.7 Hz, 1H), 6.55 (s, 1H), 6.46 (s, 1H), 4.02 (m, 1H), 3.63 (s, 3H), 2.85 (dd, J = 13.8, 4.2 Hz, 1H), 2.68 (dd, J = 13.2, 9.9 Hz, 1H), 2.13 (s, 3H), 1.34 (s, 9H).

Scheme 1. Reagents and conditions. (a) *m*-chloroperoxybenzoic acid, $CHCl_3$, rt, 6 h; (b) 12 N aq HCl, CH_3OH, 10 h, 91%; (c) $SOCl_2$, CH_3OH, reflux, 24 h, 94%; (d) Boc_2O, Et_3N, CH_2Cl_2, 91%; and (e) LiOH, CH_3OH–H_2O, 93%.



Scheme 2. Reagents and conditions. (a) $LiBH_4$, THF, 24 h, 91%; (b) 6 N aq HCl, CH_3OH, reflux, 6 h, 87%; (c) $BnCH_2CHO$, HOAc, 4 Å molecular sieves, CH_2Cl_2–CF_3CH_2OH, −10°C, 87%; and (d) H_2 (50 psi), $Pd(OH)_2$, CH_3OH, 12 h, 86%.



Synthesis of compound 6. To a solution of compound **5** (0.63 g, 3.0 mmol), acetic acid (0.45 g, 0.44 mL, 7.5 mmol, 2.5 equiv.), and the 4 Å molecular sieves (0.6 g) in CH_2Cl_2–CF_3CH_2OH (7:1, v/v, 12 mL), a solution of benzyloxyacetaldehyde (495 mg, 3.3 mmol, 1.1 equiv.) in dichloromethane (4 mL) was added slowly *via* syringe over 60 min at −10°C. After being stirred at −10°C for 8 h, the reaction mixture was diluted with dichloromethane and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography ($CHCl_3$:CH_3OH:NEt_3 = 100:1:0.2) to afford compound **6** (0.89 g, 87%) as a white solid. $[\alpha]_D^{20}$: −115.2 (c 0.5, CH_3OH). m.p: 109–111°C. HRMS calcd. for $C_{20}H_{26}NO_4$ ($M + H^+$) 344.1856 Da, Found 344.1885 Da.

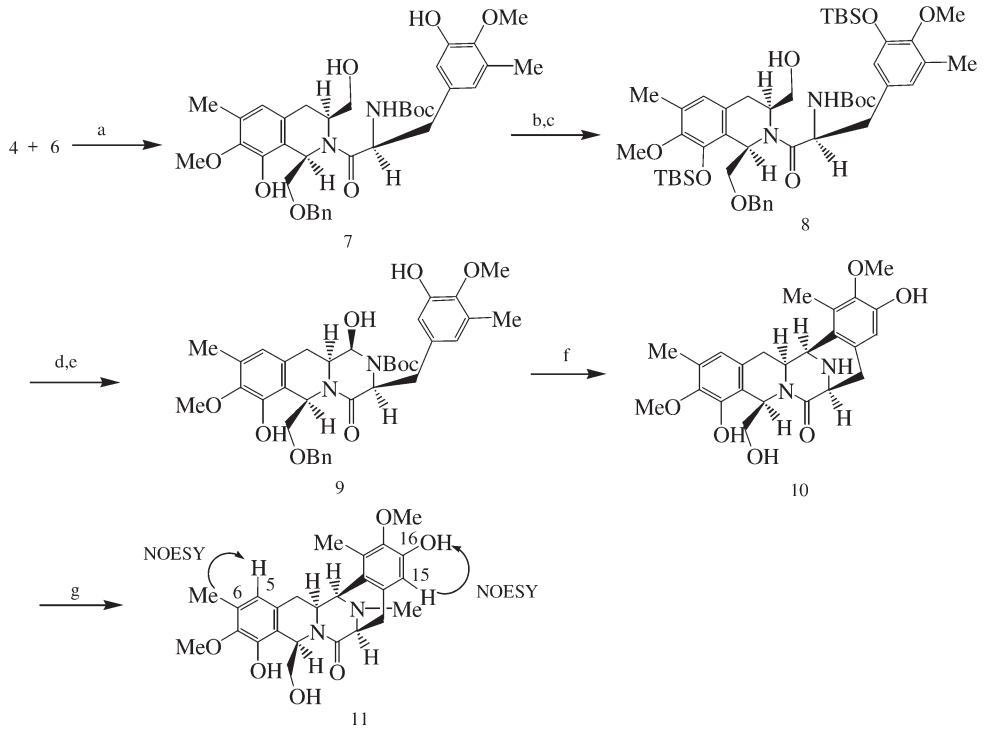
^{1}H-NMR (300 MHz, dimethyl sulfoxide-d_6): δ 8.65 (s, 1H), 7.32 (m, 5H), 6.37 (s, 1H), 4.70 (t, 1H), 4.49 (dd, J = 17.1, 12.6 Hz, 2H), 4.31 (brd, 1H), 4.13 (dd, J = 8.7, 2.7 Hz, 1H), 3.59 (s, 3H), 3.46 (m, 1H), 3.42 (d, J = 8.4 Hz, 1H), 3.36 (m, 1H), 3.33 (s, 1H), 2.68 (m, 1H), 2.42 (brd, J = 15 Hz, 1H), 2.28 (dd, J = 14.1, 11.1 Hz, 1H), 2.14 (s, 3H). ^{13}C-NMR (75 MHz, dimethyl sulfoxide-d_6): δ 146.7, 143.8, 138.7, 132.6, 128.1, 128.0, 127.3, 127.2, 120.9, 73.8, 72.0, 65.2, 59.9, 54.9, 53.9, 53.0, 33.0, 15.3.

Synthesis of compound 7. To a solution of tetrahydroisoquinoline **6** (1.16 g, 3.37 mmol) and triethylamine (1.17 mL, 8.42 mmol, 2.5 equiv.) in CH_2Cl_2 (70 mL) at 0°C, *N*-Boc amino acid **4** (1.20 g, 3.71 mmol, 1.1 equiv.) was added followed by BOPCl (0.94 g, 3.71 mmol, 1.1 equiv.) in portions. The mixture was aged for 6 h at room temperature. Water (40 mL) and 2*M* HCl were added to pH 1.5, and the organic phase was separated. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography ($CHCl_3$) to provide **7** (1.64 g, 75%) as a white solid. HRMS calcd. for $C_{36}H_{46}N_2O_9$ ($M + H^+$) 651.3281 Da, Found 651.3282 Da.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.29 (m, 5H), 6.67–6.26 (m, 3H), 6.18 (m, 1H), 5.93 (d, J = 5.1 Hz, 1H), 5.56 (d, J = 7.2 Hz, 1H), 5.28 (d, J = 7.2 Hz, 1H), 5.93 (dd, J = 7.5 Hz, 1H), 4.98 (m, 1H), 4.67 (m, 1H), 4.48 (m, 1H), 4.43 (m, 1H), 3.94 (m, 1H), 3.88 (m, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.54 (m, 1H), 3.45(m, 1H), 3.10–2.74 (m, 4H), 2.23 (s, 3H), 2.22 (s, 3H), 1.42–1.34(s, 9H).

Synthesis of compound 8. To a solution of compound **7** (0.786 g, 1.21 mmol) in CH_2Cl_2 (45 mL), TBSCl (1.002 g, 5.4

Scheme 3. Reagents and conditions. (a) BOPCl, Et_3N, CH_2Cl_2, 88%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 88%; (c) HCOOH, THF, H_2O, 92%; (d) Dess–Martin periodinane, CH_2Cl_2, 94%; (e) TBAF, THF, 2 h, 90%; (f) CF_3COOH, 82%; and (g) HCHO, $NaBH_3CN$, HOAc, CH_3OH, 83%.



mmol, 4 equiv.), triethylamine (1.9 mL, 7.26 mmol, 6 equiv.), and 4-dimethylamino pyridine (DMAP) (111 mg, 0.6 mmol, 0.5 equiv.) were added. The solution was stirred for 24 h and quenched with saturated aqueous NH_4Cl (30 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL × 2). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in *n*-hexane) to provide a yellow oil (694 mg, 88%).

The yellow oil (546 mg, 0.55 mmol) was dissolved in THF–HCO_2H–H_2O (6:3:1; 20 mL), the solution was stirred for 2 h at room temperature. The solution was concentrated by rotary evaporation, and the residue was dissolved in EtOAc (50 mL). Then, the organic phase was washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration of the solution by rotary evaporation, the residue was purified by column chromatography (10% EtOAc in *n*-hexanes) to provide **8** (445 mg, 92%) as a white solid.

^{1}H-NMR (300 MHz, dimethyl sulfoxide-d_6): δ 7.23 (m, 5H), 6.63 (s, 1H), 6.55 (s, 1H), 6.47 (s, 1H), 6.07 (m, 1H), 4.87 (brs, 1H), 4.65 (brd, J = 5.7 Hz, 1H), 4.50 (d, J = 12.6 Hz, 1H), 4.46 (d, J = 10.5 Hz, 1H), 4.35 (brs, 1H), 3.88 (brs, 1H), 3.61 (m, 2H), 3.57 (s, 3H), 3.54 (m, 2H), 3.50 (s, 3H), 2.86 (m, 2H), 2.74 (d, J = 4.8 Hz, 2H), 2.17 (s, 3H), 2.15 (s, 3H), 1.32 (s, 9H), 0.96 (s, 9H), 0.94 (s, 9H), 0.12 (s, 6H), 0.11(s, 6H).

Synthesis of compound 9. To a solution of compound **8** (298 mg, 0.34 mmol) in CH_2Cl_2 (25 mL) at 0°C, Dess–Martin periodinane (228 mg, 0.51 mmol, 1.5 equiv.) was added, and the solution was stirred for 2 h at room temperature. The reaction was quenched with two drops of 2-propanol. The solution was washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography (5% EtOAc in *n*-hexanes) to provide **12** (271 mg, 91%) as a white solid.

The white solid (245 mg, 0.28 mmol) was dissolved in THF (25 mL). To this solution, tetrabutylammonium fluoride (TBAF) was added (1.0*M* in THF, 0.84 mL, 0.84 mmol, 3.0 equiv.) at 0°C, and the solution was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography (1% CH_3OH in CH_2Cl_2) to provide **9** (181 mg, 90%) as a white solid. HRMS calcd. For $C_{36}H_{45}N_2O_9$ ($M + H^+$) 649.3125 Da, Found 649.3148 Da.

^{1}H-NMR (300 MHz, dimethyl sulfoxide-d_6): δ 8.94 (s, 3H), 7.24 (m, 5H), 6.64 (s, 1H), 6.60 (d, J = 4.8 Hz, 1H), 6.56 (s, 1H), 6.52 (s, 1H), 5.77 (m, 1H), 5.66 (m, 1H), 4.49 (d, J = 12.6 Hz, 2H), 4.38 (d, J = 12.6 Hz, 1H), 3.75 (dd, J = 9.9, 5.4 Hz, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.59 (m, 1H), 3.12 (d, J = 12.6, 1H), 3.04 (d, J = 9.6 Hz, 2H), 2.62 (d, J = 12.3, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 1.07 (s, 9H).

Synthesis of compound 11. To trifluoroacetic acid (TFA) (2 mL, 23 mmol), compound **9** was added (20 mg, 0.23 mmol) in one portion, and the mixture was stirred for 1 h at room temperature under argon atmosphere. Then, the reaction mixture was poured into 3 mL of ice-water, basified with saturated aqueous $NaHCO_3$ with stirring, and the whole mixture was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in MeOH (3 mL). To the solution, HCHO (0.22 mL, 37%), $NaBH_3CN$ (25 mg, 0.40 mmol), and CH_3COOH (0.4 mL) were added, and the mixture was stirred at room temperature for 2 h and concentrated. The residue was dissolved in EtOAc (20 mL), and saturated aqueous $NaHCO_3$ was added. Then the organic layer was separated and washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4 for 10 h. The organic layer was concentrated under reduced pressure, and the resultant residue was purified by flash column chromatography (EtOAc:-CH_3OH:Et_3N = 100:2:0.2) to afford compound **11** (8 mg, 47.7%). $[\alpha]_D^{20}$: −115.4 (c 4.8, CH_3OH). HRMS calcd. for 15 ($M + H^+$) 545.2646 Da, Found 545.2668 Da.

^{1}H-NMR (600 MHz, dimethyl sulfoxide-d_6): δ 9.01 (s, 1H, 16-OH), 8.86 (s, 1H, 8-OH), 7.20 (dd, 2H, Bn-H, J = 7.2), 7.16 (t, 1H, Bn-H, J = 7.2), 6.81 (d, 2H, Bn-H, J = 7.2), 6.49 (s, 1H, 5-H), 6.49 (s, 1H, 15-H), 5.55 (dd, 1H, 1-H, J = 3.6), 4.30 (d, 1H, 11-H, J = 3.0), 3.848 (m, 1H, 3-H), 3.82 (brs, 2H, 22-H), 3.625 (d, 1H, 21-H, J = 7.2), 3.59 (s, 3H, 17-H), 3.57 (s, 3H, 7-H), 3.39 (dd, 1H, 21-H, J = 10.2, 3.6), 3.30 (m, 1H, 14-H), 3.03 (dd, 1H, 14-H, J = 16.8, 7.2), 2.79 (m, 1H, 13-H), 2.79 (m, 1H, 4-H), 2.37 (dd, 1H, 4-H, J = 13.8), 2.21 (s, 3H, N-CH_3), 2.15 (s, 3H, 6-CH_3), 2.07 (s, 3H, 16-CH_3); ^{13}C-NMR (150 MHz, dimethyl sulfoxide-d_6): δ 70.61, 146.54, 145.85, 144.25, 144.16, 138.58, 132.89, 130.09, 129.11, 128.80, 127.97, 126.89, 126.68, 123.44, 119.83, 119.28, 114.12, 72.36, 71.08, 61.81, 59.90, 59.04, 53.18, 50.02, 48.84, 34.46, 31.99, 30.67, 15.44, 13.43.

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Microwave-Mediated Synthesis and Antibacterial Activity of Some Novel 2-(Substituted Biphenyl) Benzimidazoles *via* Suzuki-Miyaura Cross Coupling Reaction and Their *N*-Substituted Derivatives

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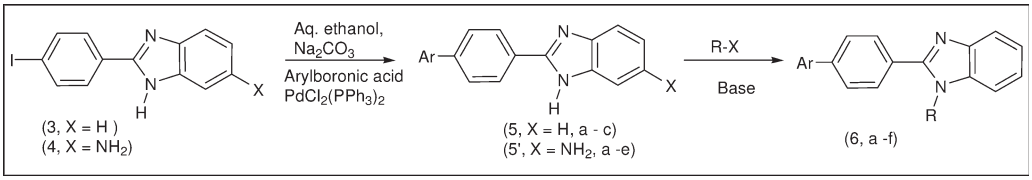

A series of some novel 2-(substituted biphenyl) benzimidazoles and their *N*-substituted derivatives were synthesized *via* microwave-mediated Suzuki-Miyaura coupling of 2-(4-iodophenyl)-1*H*-benzimidazole or 2-(4-iodophenyl)-6-amino-1*H*-benzimidazole and arylboronic acids. The method reported herein offers advantageous shorter reaction times, higher yields and is applicable to a large set of substrates. All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Salmonella typhimurium* bacterial species.

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INTRODUCTION

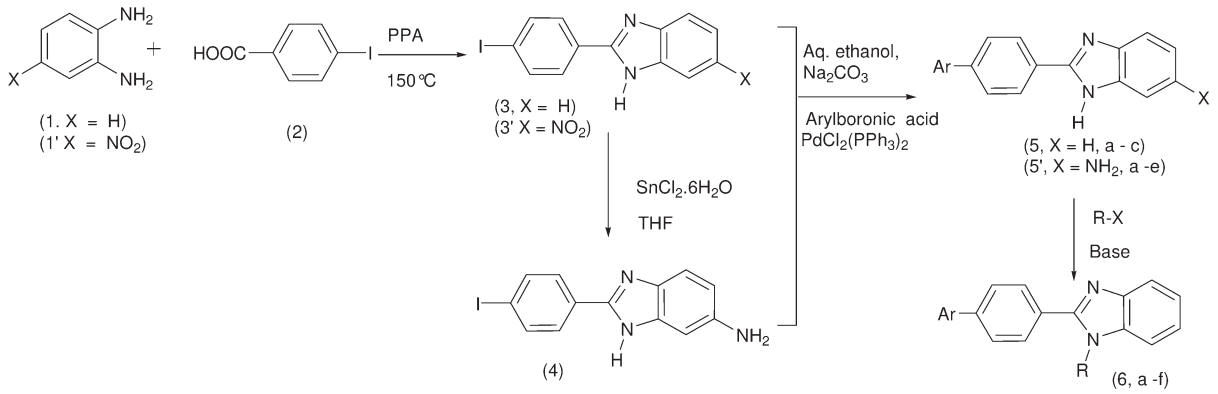
Various substituted benzimidazoles are important compounds because of their varied biological activities [1–10]. These classes of compounds, which act as angiotensin II AT1 receptor blockers and used in the treatment of hypertension, are Sartans [11] that possess biphenyl moiety as an integral part. Losartan potassium is commercially known as Covance, Lorzaar and Losaprex; Telmisartan as Kinzalmono, Micardis and Pritor; Candesartan cilexetil as Amias, Atacand and Blopress; Olmesartan medoxomil as Benevas, Benicar and Olmetec and Irbesartan as Aprovel, Avapro and Karvea. Bifonazol having biphenyl as an integral part exhibits antifungal and antimycotic activity [12]. Fluoro substituted biphenyls like Diflunisal and Flurbiprofen sodium exhibit anti-inflammatory activity and Diflunisal [13] is commercially known as Dolobid and Flurbiprofen sodium as Ocufen [14].

The Suzuki-Miyaura cross coupling reaction has emerged as one of the most powerful platform for carbon–carbon bond formation because of its mild reaction conditions and its compatibility with a broad range of functional groups [15]. Suzuki-Miyaura cross coupling reactions on the multifunctional molecules requires protection and deprotection, which unnecessarily increases the number of steps in organic synthesis, thereby decreasing the yields and increases pollution level and time wastage [16–18]. Therefore organic chemists are engaged in efforts to find new reagents with increased selectivity.

Green chemistry is destined to be a global goal in the near future. In the course of studies on green chemistry one of our goals has been to design microwave-mediated synthetic methods in aqueous medium and make them more ecofriendly and consistent with higher atom economy. Microwave (MW) irradiation is widely used to promote chemical reactions and a number of reviews have advocated the use of MW technology in organic synthesis [19,20]. Microwave activation as a nonconventional energy source is becoming a very popular and useful technique in organic chemistry. The combination of solvent-free reaction conditions and microwave irradiation leads to significantly reduced reaction times, enhanced conversions and sometimes higher selectivity with several advantages for the ecofriendly approach, termed green chemistry [21].

Looking the importance of microwave irradiation in organic synthesis, we nicely demonstrated the use of microwave conditions for Suzuki-Miyaura cross coupling of unprotected halogen-substituted benzimidazoles. The synthesized compounds were tested for their antibacterial action against two different bacterial species namely, *Staphylococcus aureus* and *Salmonella*

Scheme 1



Compd. No.	Arylboronic acid
5a	2-Methoxyphenylboronic acid
5b	4-Trifluoromethanephenylboronic acid
5c	2-[2,3-dihydro-1-methyl-2-triphenylmethyl-1*H*-5-isoindolyl]-1,3,6,2-dioxazaborocane
5'a	Phenylboronic acid
5'b	4-Chlorophenylboronic acid
5'c	2-Methoxyphenylboronic acid
5'd	4-Trifluoromethanephenylboronic acid
5'e	2-[2,3-dihydro-1-methyl-2-triphenylmethyl-1*H*-5-isoindolyl]-1,3,6,2-dioxazaborocane

Compd. No.	R-X
6a	Ethyl chloroformate
6b	Methanesulfonyl chloride
6c	Benzyl bromide
6d	4-Fluorobenzyl bromide
6e	3,5-Difluorobenzyl bromide
6f	4-Chlorobenzyl bromide

typhimurium in comparison with Cephalexin as a reference standard.

RESULT AND DISCUSSION

All the reactions were carried out under both microwave irradiation and conventional methods.

The condensation *o*-phenylenediamine (OPDA) (**1**) or 4-nitrobenzene 1,2-diamine (**1′**) with 4-iodobenzoic acid (**2**) in presence of polyphosphoric acid (PPA) was carried out in microwave oven at 100 W for 5–10 minutes at 150°C to obtain the 2-(4-iodophenyl)-1*H*-benzimidazole **(3)** or 2-(4-iodophenyl)-6-nitro-1*H*-benzimidazole **(3′)**. The reduction of (**3′**) using $SnCl_2.6H_2O$ in ethyl acetate and tetrahydrofuran yielded 2-(4-iodophenyl)-6-amino-1*H*-benzimidazole **(4)**.

Suzuki-Miyaura coupling of compounds **3**, **4** ideally, the approach should allow access to the free NH and NH_2 benzimidazoles utilizing readily available components and catalysts directly without the need for subsequent deprotection to obtain a series of novel 2-(substituted biphenyl)-1*H*-benzimidazoles **(5**, **a-c)**, or 2-(substituted biphenyl)-6-amino-1*H*-benzimidazoles **(5′**, **a-e)**.

The Suzuki-Miyaura coupling product **5b** was then alkylated or acylated at the benzimidazole -NH with different electrophilic reagents leading to functionalized derivatives (**6**, **a-f)** (Scheme 1). The structure of synthesized compounds was confirmed by IR, ^{1}H-NMR, Mass, and ^{13}C-NMR.

EXPERIMENTAL

Melting points were recorded on a MRVIS series, Lab India Instrument and are uncorrected. The monitoring of reaction and checking of purity of the product were done using precoated silica gel plates and visualization using iodine chamber/UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a (Varian Mercury Vx) SWBB 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm from internal TMS standard. The solvents for NMR spectra were CD_3OD. Mass spectra were recorded from

an HP 1100 LC/MSD mass spectral instrument (positive and negative APCI ion source, 50–200 V, nitrogen). Elemental analysis was carried out on a Perkin-Elmer Series-II CHNS/O Analyzer 2400. All microwave reactions were carried out in Biotage (Initiator^{TM} Eight) microwave synthesizer. Arylboronic acid, *o*-phenylenediamine, 4-nitrobenzene-1,2-diamine, and 4-iodobenzoic acid were obtained from S. D. Fine Chem, Mumbai, India. Palladium catalyst was obtained from Aldrich, India.

Synthesis of compounds 3 and 3′ *via* microwave irradiation method. A mixture of *o*-phenylenediamine (**1**) (1.29 g, 12 mmole) or 4-nitrobenzene-1,2-diamine (**1′**) (1.83 g, 12 mmole), 4-iodobenzoic acid (**2**) (2.47 g, 10 mmole) and polyphosphoric acid (PPA) (20 g) were stirred and irradiated in microwave oven at 100 W for 10 min at 150°C in sealed vessel (monitored by TLC, Hexane: Ethyl acetate, 7:3). The reaction mixture was then cooled to room temperature and neutralized with aqueous ammonia solution. The product was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with 5*N* HCl (10 mL) and sodium bicarbonate solution (5%, 10 mL), water (10 mL) and then organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain crude product, which was recrystallized from ethyl acetate to afford an off-white solid 2-(4-iodophenyl)-1*H*-benzimidazole **(3)** or 2-(4-iodophenyl)-6-nitro-1*H*-benzimidazole **(3′)**.

General procedure for the synthesis of compounds 3 and 3′. A mixture of *o*-phenylenediamine (**1**) (1.29 g, 12 mmole) or 4-nitrobenzene-1, 2-diamine (**1′**) (1.83 g, 12 mmole), 4-iodobenzoic acid (**2**) (2.47g, 10 mmole), and PPA (20 g) was stirred at 150°C for 6 h (monitored by TLC, Hexane: Ethyl acetate, 7:3). The reaction mixture was then cooled to room temperature and neutralized with aqueous ammonia solution. The product was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with 5*N* HCl (10 mL) and sodium bicarbonate solution (5%, 10 mL), water (10 mL) and then organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain crude product, which was recrystallized from ethyl acetate to afford an off-white solid 2-(4-iodophenyl)-1*H*-benzimidazole **(3)** or 2-(4-iodophenyl)-6-nitro-1*H*-benzimidazole **(3′)**.

Synthesis of 2-(4-iodophenyl)-6-amino-1*H*-benzimidazole (4). A solution of compound **3′** (3.65 g, 10 mmole) dissolved in tetrahydrofuran (15 ml) and water (15 mL). Stannous chloride hexahydrate (10 g, 36 mmole) was added in the reaction mass room temperature. After complete addition, the mixture was stirred at room temperature for 30 min. Thereafter, the solution was allowed to the 40–45°C and stirring continued for 2 h (monitored by TLC, Hexane: Ethyl acetate 1:1). The mixture was again cooled to room temperature and then ethyl acetate (50 mL), and aqueous ammonia solution (20 mL) was added at same temperature. The ethyl acetate layer was separated, dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to obtain the crude product, which was recrystallized from ethyl acetate to afford a white solid of 2-(4-iodophenyl)-6-amino-1*H*-benzimidazole **(4)**.

Synthesis of compound 4 by alternative method. A solution of compound **3′** (3.65 g, 10 mmole) dissolved in methanol (20 mL). Palladium carbon (5%, 0.5 g) was added under nitrogen atmosphere. The reaction was hydrogenated in an autoclave at 60 psig pressure for 3 h (monitored by TLC, Hexane: Ethyl acetate 1:1). After completion of reaction the mixture was filtered and solvent was evaporated under reduced pressure to obtain the crude product, which was recrystallized from ethyl acetate to afford a white solid **4**.

Synthesis of compounds (5, a-c) and (5′, a-e) *via* microwave irradiation method. To the solution of compound **3** (3.19 g, 10 mmole) or **4** (3.35 g, 10 mmole) in ethanol (20 mL), arylboronic acids (12 mmole), aqueous sodium carbonate solution 10% (20 mmole) and bis(triphenylphosphine)palladium(II)dichloride (0.87 g, 0.125 mmole) were irradiated in microwave oven at 100 W for 5–15 min at 80°C in sealed vessel (monitored by TLC, Hexane: Ethyl acetate, 7:3). After completion of reaction, the mixture was cooled to room temperature and filtered through celite. The filtrate was extracted with ethyl acetate (25 mL × 2), and the organic layer was washed with water (25 mL × 2) and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded crude products which were subjected to column chromatography (silica gel) using hexane and ethyl acetate mixture (9:1) to isolate the pure products (**5**, **a-c**) or (**5′**, **a-e**), respectively.

Synthesis of compounds (5, a-c) and (5′, a-e) by conventional heating method. To the solution of compound **3** (3.19 g, 10 mmole) or **4** (3.35 g, 10 mmole) in ethanol (50 mL), arylboronic acids (12 mmole), 10% aqueous sodium carbonate solution (20 mmole) and bis(triphenylphosphine)palladium(II)-dichloride (0.87 g, 0.125 mmole) were added and the mass was refluxed for 8–10 h (monitored by TLC, Hexane: Ethyl acetate, 7:3). After completion of reaction, the mixture was cooled to room temperature and filtered through celite. The filtrate was extracted with ethyl acetate (50 mL × 2), and the organic layer was washed with water (25 mL × 2) and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded crude products which were subjected to column chromatography (silica gel) using hexane and ethyl acetate mixture (9:1) to isolate the pure products **(5**, **a-c)** or **(5′**, **a-e)**.

Synthesis of compounds 6a and 6b *via* microwave irradiation method. To a solution of compound **5b** (3.38 g, 10 mmole) in pyridine (10 mL), ethyl chloroformate (1.62 g, 15 mmole)or methane sulfonyl chloride (1.7 g, 15 mmole) were irradiated in microwave oven at 100 W for 5–10 min at 45–50°C in sealed vessel (monitored by TLC, Hexane: Ethyl acetate, 1:1). After completion of reaction the mixture was cooled to room temperature, then a solution of 2*N* HCl was added to neutralize the reaction mixture. The solid was then extracted with ethyl acetate (50 mL), which was washed with aqueous sodium bicarbonate (5%, 25 mL), water (50 mL × 2), and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to give the crude product, which was recrystallized from ethyl acetate to afford compound **6a** or **6b**.

Synthesis of compounds 6a and 6b by conventional method. To a solution of compound **5b** (3.38 g, 10 mmole) in pyridine (25 mL), ethyl chloroformate (1.62 g, 15 mmole) or methane sulfonyl chloride (1.7 g, 15 mmole) was added slowly at 0°C. After complete addition, the reaction mixture was allowed to attain room temperature and stirred for 6–8 h at same temperature (monitored by TLC, Hexane Ethyl acetate, 1:1). A solution of 2N HCl was then added to neutralize the reaction mixture. The solid was then extracted with ethyl acetate (50 mL), which was washed with aqueous sodium bicarbonate (5 %, 25 mL), water (50 mL × 2), and dried over anhydrous sodium sulphate. Solvent was evaporated under

Table 1

Physical and yield comparison data of synthesized compounds

Sr. No.	Compd. No.	Molecular formula	M.P. (°C)	Microwave irradiation		Conventional heating	
				Time (min)	Yield (%)	Time (h)	Yield (%)
1	**3**	$C_{13}H_9IN_2$	289–290	10	85	6	75
2	**3′**	$C_{13}H_8IN_3O_2$		10	87	6	80
3	**5a**	$C_{20}H_{16}N_2O$	215–216	10	90	8	82
4	**5b**	$C_{20}H_{13}F_3N_2$	203–205	10	91	10	85
5	**5c**	$C_{41}H_{33}N_3$	150–152	15	87	9	82
6	**5′a**	$C_{19}H_{15}N_3$	250–254	10	92	8	78
7	**5′b**	$C_{19}H_{14}ClN_3$	220–221	15	90	10	75
8	**5′c**	$C_{20}H_{17}N_3O$	280–281	10	90	9	87
9	**5′d**	$C_{20}H_{14}N_3F_3$	285–286	10	91	9	78
10	**5′e**	$C_{41}H_{34}N_4$	230–231	15	85	10	78
11	**6a**	$C_{23}H_{17}N_2O_2F_3$	80–81	10	90	6	75
12	**6b**	$C_{21}H_{15}N_2O_2SF_3$	240–245	15	90	10	85
13	**6c**	$C_{27}H_{19}N_2F_3$	185–186	10	92	8	90
14	**6d**	$C_{27}H_{18}N_2F_4$	85–86	15	90	10	87
15	**6e**	$C_{27}H_{17}N_2F_5$	105–108	10	89	8	83
16	**6f**	$C_{27}H_{18}ClN_2F_3$	78–80	10	93	9	87

reduced pressure to give the crude product, which was recrystallized from ethyl acetate to afford compound **6a** or **6b**.

Synthesis of compounds (6, c-f) *via* microwave irradiation method. To a solution of compound **5b** (3.38 g, 10 mmole) in acetonitrile (20 mL), aqueous sodium hydroxide solution (10%, 20 mmole) was added and the mixture was stirred for 15 min. Various benzyl bromides (15 mmole) were added and irradiated in microwave oven at 100 W for 5–10 min at 50–55°C in sealed vessel (monitored by TLC, Hexane: Ethyl acetate, 1:1). After the completion of the reaction, acetonitrile from the reaction mixture was evaporated under reduced pressure and water (50 mL) was added to residue to separate solid. The solid was then extracted with ethyl acetate (20 mL), the extract was washed with water (25 mL × 2), and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to afford the crude products, which were recrystallized from ethanol to yield pure compounds **(6, c-f)**.

Synthesis of compounds (6, c-f) by conventional method. To a solution of compound **5b** (3.38 g, 10 mmole) in acetonitrile (50 mL), aqueous sodium hydroxide solution (5%, 25 mL) was added and the mixture was stirred for 15 min. Various benzyl bromides (15 mmole) were then added slowly with stirring to the reaction mixture at 0–10°C. After complete addition, the reaction mixture was allowed to attain room temperature and stirred for 8–10 h (monitored by TLC, Hexane: Ethyl acetate, 7:3). After the completion of the reaction, acetonitrile from the reaction mixture was evaporated under reduced pressure and water (50 mL) was added to residue to separate solid. The solid was then extracted with ethyl acetate (50 mL), the extract was washed with water (50 mL × 2), and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to afford the crude products, which were recrystallized from ethanol to yield pure compounds **(6, c- f)**. (Table 1)

BIOLOGICAL ACTIVITY

All the compounds prepared herein were screened for their antibacterial activities against *Staphylococcus aureus* (Gram positive) and *Salmonella typhimurium* (Gram negative) bacteria strains in comparison with Cephalexin as reference standard and the results are summarized in Tables 2 and 3. Most of the compounds tested were found to have good antibacterial activity against *Staphylococcus aureus* NCIM 5021 and *Salmonella typhimurium* NCIM 2501 when compared to standard.

CONCLUSION

We report a simple, rapid, efficient, economic, and environment-friendly method for the synthesis of some novel 2-(substituted biphenyl-2-yl)-1*H*-benzimidazoles and their *N*-substituted derivatives using microwave-mediated Suzuki-Miyaura coupling reaction. The advantage of the microwave irradiation shorter reaction times with an excellent yield compared to conventional method and also tested their antibacterial activity. The compounds 5a, 5b, 5′b, 5′c, 5′c, 5′d, 6c, 6d, and 6e showed completely inhibited the growth of both test bacterial species, namely, *S. aureus* and *S. typhi,* however, 6c, 6d, and 6e showed better antibacterial activity against *S. typhi*.

2-(4-Iodophenyl-1*H*-benzimidazole (3). IR (KBr): 3300, 2970, 1458, 1410, 1326, 1074, 834, 816 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.22–7.26 (m, 2H, Ar—H), 7.62–7.63 (m, 2H, Ar—H), 7.78 (d, J = 8.4 Hz, 2H, Ar—H), 8.17 (d, J = 8.4 Hz, 2H, Ar—H), 13.08 (bs, 1H, —NH); *Anal*. Calcd. for $C_{13}H_9IN_2$: C, 48.77; H, 2.83; N, 8.75; Found: C, 48.64; H, 3.10; N, 8.57.

2-(2-Methoxybiphenyl-4-yl)-1*H*-benzimidazole (5a). IR (KBr): 3421, 2962, 1740, 1621, 1596, 1427, 1261, 1161, 1099, 799, 741 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 3.82 (s, 3H, OCH_3), 7.01–7.10 (m, 2H, Ar—H), 7.24–7.27 (m,

Table 2

Antibacterial activity of synthesized compounds against *staphylococcus aureus*.

Comp. No.	Concentrations (μg/mL) 1	10	100	200	500	Approx. MIC (μg/mL)
5a	++	++	+	−−	−−	200
5b	++	++	+	−−	−−	200
5c	++	++	++	+	−−	500
5′a	++	++	++	+	−−	500
5″b	++	++	P	−−	−−	200
5′c	++	++	−−	−−	−−	100
5′d	++	+	−−	−−	−−	100
5′e	++	++	++	+	−−	500
6a	++	++	+	−−	−−	200
6b	++	++	++	+	−−	500
6c	++	++	+	−−	−−	200
6d	++	+	−−	−−	−−	100
6e	++	P	−−	−−	−−	100
6f	++	++	P	−−	−−	200
Cephalexin	++	−−	−−	−−	−−	10

−−, Total inhibition, no growth of organism; P, poor growth compared to controls; +, medium growth compared to controls; ++, confluent growth, no inhibition.

2H, Ar—H), 7.32–7.59 (m, 3H, Ar—H), 7.60–7.68 (m, 3H, Ar—H), 8.08–8.11 (m, 2H, Ar—H); ms: m/z 301.28 (M^++1); *Anal*. Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33; Found: C, 80.12; H, 5.15; N, 9.48.

2-(4-Ttrifluoromethylbiphenyl-4-yl)-1*H*-benzimidazole (5b). IR (KBr): 2924, 1618, 1449, 1428, 1333, 1262, 1159, 1079, 799 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 7.21–7.24 (m, 2H, Ar—H), 7.49–7.64 (m, 4H, Ar—H), 7.78–7.92 (m, 4H, Ar—H), 8.14–8.16; (m, 2H, Ar—H); ms: m/z 339.30 (M^++1); *Anal*. Calcd. for $C_{20}H_{13}F_3N_2$: C, 71.00; H, 3.87; F, 16.85; N, 8.28; Found: C, 71.14; H, 4.02; N, 8.06.

2-(1-Methyl-2-tritylisoindolin-4-yl)phenyl-1*H*-benzimidazole (5c). IR (KBr): 2924, 2854, 1747, 1594, 1463, 1377, 1314, 1276, 1156, 1032, 901, 848, 825, 768, 749, 708, 638.cm^{-1}; ^{1}H-NMR (CD_3OD): δ 1.44 (d, J = 6.6 Hz, 3H, —CH), 4.08–4.13, 4.53–4.54 (2H, —CH_2), 4.38–4.43 (m, 1H, —CH), 6.85 (d, J = 7.8 Hz, 2H, Ar—H), 6.94 (s, 1H, Ar—H), 7.02 (d, J = 6.9Hz, 2H, Ar—H), 7.06–7.16 (m, 4H, Ar—H), 7.25 (d, J = 3Hz,

Table 3

Antibacterial activity of synthesized compounds against *Salmonella typhimurium*.

Comp. No.	Concentrations (μg/mL) 1	10	100	200	500	Approx. MIC (μg/mL)
5a	++	++	+	P	−−	500
5b	++	++	+	−−	−−	200
5c	++	++	++	++	p	500
5′a	++	++	++	++	−−	500
5′b	++	++	+	P	−−	500
5′c	++	++	+	−−	−−	200
5′d	++	++	+	−−	−−	200
5′e	++	++	++	+	−−	500
6a	++	++	++	P	−−	500
6f	++	++	++	+	−−	500
6b	++	++	++	+	−−	500
6c	++	++	P	−−	−−	200
6d	++	++	+	−−	−−	200
6e	++	++	P	−−	−−	500
Cephalexin	++	++	P	−−	−−	200

−−, Total inhibition, no growth of organism; P, poor growth compared to controls; +, medium growth compared to controls; ++, confluent growth, no inhibition.

2H, Ar—H), 7.44–7.55 (m, 8H, Ar—H), 7.58–7.70 (m, 2H, Ar—H), 7.81 (s, 2H, Ar—H), 7.97 (s, 1H, Ar—H), 8.07 (d, 8.4Hz, 2H, Ar—H); ms: m/z Fragments 326.33 2-(1R)-2,3-dihydro-1-methyl-1*H*-5-isoindol, 243.25- triphenylmethyl; *Anal*. Calcd. for $C_{41}H_{33}N_3$: C, 86.74; H, 5.86; N, 7.40; Found: C, 86.64; H, 5.98; N, 7.52.

2-(Biphenyl-4-yl)-6-amino-1*H*-benzimidazole (5′a). IR (KBr): 3421, 3320, 3205, 1635, 1476, 1476, 1419, 1363, 1123, 813, 770, 728 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 6.76 (d, J = 8.1 Hz, 1 H, Ar—H), 6.93 (s, 1H, Ar—H), 7.35–7.47 (m, 4H, Ar—H), 7.66 (d, J = 7.8Hz, 2H, Ar—H), 7.75 (d, J = 7.8 Hz, 2H, Ar—H), 8.08 (d, J = 8.1Hz, 2H, Ar—H); *Anal*. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73; Found: C, 79.86; H, 5.38; N, 14.62.

2-(4-Chlorobiphenyl-4-yl)-6-amino-1*H*-benzimidazole (5′b). IR (KBr): 3396, 1902, 1635, 1475, 1436, 1403, 1261, 1180, 1091 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 6.61–6.68 (m, 1H, Ar—H), 7.30–7.35 (m, 3H, Ar—H), 7.45–7.65 (m, 5H, Ar—H), 7.98 (d, J = 9 Hz, 2H, Ar—H); ^{13}C-NMR (CD_3OD): δ 114.80, 117.65, 127.89, 127.89, 128.37, 128.37, 129.36, 129.36, 129.40, 129.40, 129.45, 129.89, 129.95, 130.03, 134.90, 139.72, 141.10, 145.18, 151.46, 157.46 (aromatic carbons); ms: m/z 320.37 (M^++1); *Anal*. Calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14; Found: C, 71.28; H, 4.54; N, 13.31.

2-(2-Methoxybiphenyl-4-yl)-6-amino-1*H*-benzimidazole (5′c). IR (KBr): 3391, 2036, 1612, 1509, 1471, 1392, 1259, 1239, 1181, 1124, 1057, 1025, 835, 762 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 3.83 (s, 3H, OCH_3), 7.06–7.16 (m, 2H, Ar—H), 7.4 (d, J = 7.8Hz, 2H, Ar—H), 7.58 (d, J = 8.7Hz, 1H, Ar—H), 7.85–7.98 (m, 4H, Ar—H), 8.18 (d, J = 8.4 Hz, 2H, Ar—H); ^{13}C-NMR (CD_3OD): δ 56.10 (OCH_3), 109.56, 112.8, 116.69, 121.67, 122.21, 122.47, 128.83, 128.83, 129.57, 131.40, 131.57, 131.57, 132.17, 132.68, 133.60, 133.63, 145.51, 146.45, 157.98 (aromatic carbons); ms: m/z 316.22 (M^++1); *Anal*. Calcd. for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32; Found: 76.32; H, 5.30; N, 13.44.

2-(4-Trifluoromethylbiphenyl-4-yl)-6-amino-1*H*-benzimidazole (5′d). IR (KBr): 3399, 2712, 1634, 1571, 1473, 1367, 1337, 1261, 1122, 807, 826, 699 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 7.51 (d, J = 8.1Hz, 1H, Ar—H), 7.62–7.67 (m, 2H, Ar—H), 7.79 (s, 1H, Ar—H), 7.88–8.01 (m, 5H, Ar—H), 8.2 (d, J = 8.1Hz, 2H, Ar—H); ^{13}C-NMR (CD_3OD): δ 109.70, 116.81, 122.60, 122.68, 123.25, 124.87, 126.55, 129.79, 129.79, 131.40, 130.05, 130.05, 131.27, 132.11, 132.79, 133.75, 133.80, 145.56, 146.39, 157.42 (aromatic carbons); ms: m/z 354.34 (M^++1); *Anal*. Calcd. for $C_{20}H_{14}N_3F_3$: C, 67.98; H, 3.99; 13; N, 11.89; Found: C, 68.04; H, 4.18; 13; N, 11.74.

2-(1-Methyl-2-tritylisoindolin-4-yl)phenyl-6-amino-1*H*-benzimidazole (5′e). IR (KBr): 2925, 2854, 2727,. 1747, 1594, 1463, 1377, 1156, 1023, 722, 540 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 1.39 (d, J = 6.8 Hz, 3H, —CH), 3.99–4.05, 4.35–4.45 (2H, —CH_2), 4.50–4.56 (m, 1H, —CH), 4.99 (s, 1H, —NH), 6.51(d, J = 8.7Hz, 1H, Ar—H), 6.57(d, J = 7.8Hz, 1H, Ar—H), 6.71 (m, 1H, Ar—H), 6.91 (d, J = 7.8Hz, 2H, Ar—H), 7.07–7.20 (m, 2H, Ar—H), 7.29 (d, J = 8.7Hz, 2H, Ar—H), 7.43–7.47 (m, 6H, Ar—H), 7.50–7.56 (m, 6H, Ar—H), 7.62–7.79 (m, 2H, Ar—H), 8.04 (d, J = 8.1Hz, 2H, Ar—H); ms: m/z 583.25 (M^++1); *Anal*. Calcd. for $C_{41}H_{34}N_4$: C, 84.50; H, 5.88; N, 9.61; Found: C, 84.61; H, 5.76; N, 9.74.

2-(4-Ttrifluoromethylbiphenyl-4-yl)-1-(ethylcarboxylate)-1*H*-benzimidazole (6a). IR (KBr): 2936, 1739, 1476,1 452, 1398, 1377,1338, 1283, 1214, 1065, 1007, 854 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 1.15–1.26 (m, 3H, —CH_3), 4.35–4.42 (m, 2H, CH_2), 7.39–7.47 (m, 2H, Ar—H), 7.64–7.69 (m, 3H, Ar—H), 7.71–7.74 (m, 4H, Ar—H), 7.96–8.08 (m, 2H, Ar—H), 8.1 (d, J = 2.1Hz, 1H, Ar—H); ms: m/z 411.04 (M^++1); *Anal*. Calcd. for $C_{23}H_{17}N_2O_2F_3$: C, 67.31; H, 4.18; F, 13.89; N, 6.83; Found: C, 67.22; H, 4.11; F, 13.97; N, 6.72.

2-(4-Trifluoromethylbiphenyl-4-yl)-1-(methylsulfonyl)-1*H*-benzimidazloe (6b). IR (KBr): 3420, 2627, 1633, 1518, 1458, 1436, 1334, 1264, 1239, 1149, 1037, 796, 751 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 2.7 (s, 3H, —CH_3), 7.63–7.66 (m, 2H, Ar—H), 7.71–7.76 (m, 2H, Ar—H), 7.84–7.87 (m, 2H, Ar—H), 7.88–8.09 (m, 4H, Ar—H), 8.26 (d, J = 8.4 Hz, 2 H, Ar—H); ms: m/z Fragment 339.2 (fragment of without methane sulfonyl group); *Anal*. Calcd. for $C_{21}H_{15}N_2O_2SF_3$: C, 60.57; H, 3.63; N, 6.73; Found: C, 60.66; H, 3.72; N, 6.64.

2-(4-Trifluoromethylbiphenyl-4-yl)-1-benzyl-1*H*-benzimidazole (6c). IR (KBr): 2958, 1600, 1509, 1470, 1452, 1389, 1271, 1222, 1190, 1168, 1006, 836 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 5.68 (s, 2H, CH_2), 7.04–7.09 (m, 2H, Ar—H), 7.18–7.22 (m, 2H, Ar—H), 7.72–7.80 (m, 7H, Ar—H), 7.93–8.03 (m, 6H, Ar—H); ms: m/z 429.25 (M^++1); *Anal*. Calcd. for $C_{27}H_{19}N_2F_3$: C, 75.69; H, 4.47; N, 6.54; Found: C, 75.71; H, 4.36; N, 6.65.

2-(4-Trifluoromethylbiphenyl-4-yl)-1-(4-fluorobenzyl)-1*H*-benzimidazole (6d). IR (KBr): 2922, 2853, 1747, 1610, 1494, 1460, 1406, 1377, 1337, 1264, 1162, 1122, 1097, 1075, 1035, 978, 900, 851, 805, 764 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 5.69 (s, 2H, CH_2), 7.05 (d, J = 6.9 Hz, 2H, Ar—H), 7.16–7.21(m, 3H, Ar—H), 7.27–7.39 (m, 3H, Ar—H), 7.62–7.67 (m, 3H, Ar—H), 7.73–7.79 (m, 3H, Ar—H), 7.94 (d, J = 8.7 Hz, 2H, Ar—H); ms: m/z 447.28 (M^++1); *Anal*. Calcd. for $C_{27}H_{18}N_2F_4$: C, 72.64; H, 4.06; N, 6.27; Found: C, 72.76; H, 4.18; N, 6.20.

2-(4-Trifluoromethylbiphenyl-4-yl)-1-(3,5-difluorobenzyl)-1*H*-benzimidazole (6e). IR (KBr): 2924, 2854, 1731, 1611, 1520, 1458, 1438, 1332, 1161, 1126, 804, 751 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 5.58 (s, 2H, —CH_2), 6.83 (d, J = 8.1Hz, 1H, Ar—H), 6.96–7.01 (m, 1H, Ar—H), 7.14–7.23 (m, 1H, Ar—H), 7.29–7.37 (m, 2H, Ar—H), 7.41–7.44 (m, 1H, Ar—H), 7.64–7.69 (m, 2H, Ar—H), 7.75–

7.86 (m, 5H, Ar—H), 7.96 (s, 2H, Ar—H); ms: m/z 465.35 (M^++1); *Anal*. Calcd. for $C_{27}H_{17}N_2F_5$: C, 69.83; H, 3.69; N, 6.03; Found: C, 69.72; H, 3.58; N, 6.13.

2-(4-Trifluoromethylbiphenyl-4-yl)-1-(4-chlorobenzyl)-1*H*-benzimidzloe (6f). IR (KBr): 2926, 1898, 1611, 1406, 1334, 1263, 1164, 1097, 1014, 801 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 5.63, (s, 2H, —CH_2), 7.04 (d, J = 7.8 Hz, 1H, Ar—H), 7.16 (d, J = 7.8 Hz, 1H, Ar—H), 7.30–7.39 (m, 7H, Ar—H), 7.68–7.85 (m, 5H, Ar—H), 7.96–8.0 (m, 2H, Ar—H); ms: m/z 463.12 (M^++1); *Anal*. Calcd. for $C_{27}H_{18}ClN_2F_3$: C, 70.06; H, 3.92; N, 6.05 Found: C, 70.14; H, 3.81; N, 5.82.

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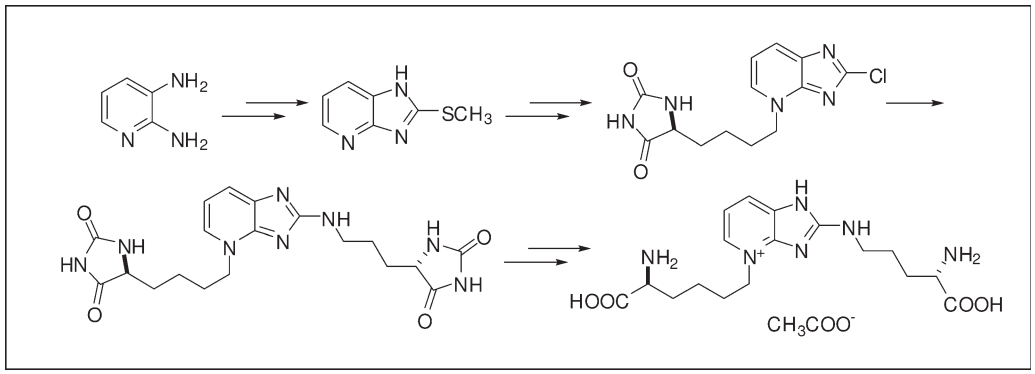

Pentosidine, a fluorescent advanced glycation endproduct that serves as a biomarker of diabetic complications, kidney dysfunction, oxidative stress, and aging and age-related diseases, was synthesized from 2,3-diaminopyridine and benzyloxycarbonyl (Cbz) protected chiral amino acids N^{α}-Cbz-lysine and N^{δ}-Cbz-ornithine. Regioselective alkylation of 2-(methylthio)imidazo[4,5-*b*]pyridine, chlorination of methylthio group, and amination of 2-chloro-imidazo[4,5-*b*]pyridine are the key steps. Hydantoin protection of amino acids was used and the deprotection under acidic condition was achieved in the presence of glycine.

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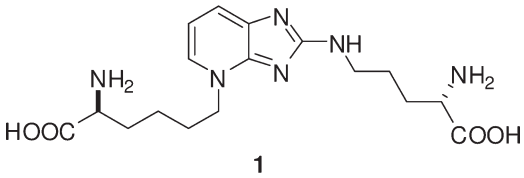
INTRODUCTION

Pentosidine (**1**) is one of the fluorescent advanced glycation endproducts (AGEs) that have been isolated and structurally characterized [3]. It was reported that pentosidine elevates in diabetes mellitus, and in patients with end-stage renal failure and kidney dysfunction [4]. A significant elevation of pentosidine was found in rheumatoid arthritis and in osteoarthritis as well [5]. Carbonyl stress, oxidative stress and aging progress the formation and accumulation of pentosidine [6]. During the aging process, pentosidine accumulates in the extracellular matrix and causes insolubility and protease resistance of extracellular matrix proteins [7]. Pentosidine level increases in disorders of pentose metabolism during aging and in age-related diseases such as Alzheimer's disease [8]. Ophthalmology research shows that pentosidine elevates in the aging vitreous body of eyes and in diabetic retinopathy [9]. Emerging evidence shows that pentosidine increases along with the deterioration of bone quality in terms of collagen crosslink formation in bone collagen and proteoglycan, and the stiffness of the cartilage [10]. Recent research shows that pentosidine levels may be associated with heart failure [11], alcohol misuse [12], and other drug abuse [13]. Because its characteristic fluorescence allows it to be seen and measured easily, pentosidine has become an indispensable biomarker in kidney dysfunction, end-stage renal disease, diabetes, and diabetic complications (including diabetic eye complications, such as diabetic retinopathy), rheumatoid arthritis, bone collagen deterioration, oxidative stress, and age-related diseases [14].

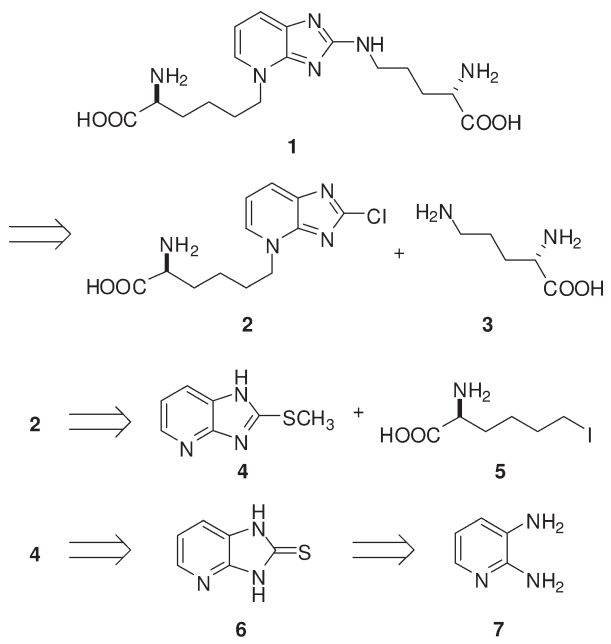


1

1a, CF_3CO_2H salt of **1**
1b, HCl salt of **1**
1c, CH_3CO_2H salt of **1**

In contrast to its extensive applications as a biomarker in biological and clinical research, synthesis of pentosidine has received little attention. Until now only two synthetic approaches have been reported. The first synthesis of pentosidine, reported by Monier and Sell, was

Scheme 1



achieved biochemically through incubation of ribose, lysine, and arginine [3a,15]. The synthesis served to confirm its structure and propose possible mechanism of its formation, but suffered complicated purification and extremely low yield (0.02%). Shioiri and coworkers obtained 5.1 mg of pentosidine trifluoroacetic acid salt (**1a**) using asymmetric alkylation of a chiral Schiff base to provide a lysine-like fragment, intramolecular guanylation with mercury (II) chloride, and quaternization accompanied by removal of the trityl group as key steps [16]. Because of the increasing importance of pentosidine in biological and clinical research, we have developed an alternate entry to this biomarker. In this article, we describe the details of our approach to this unique AGE crosslink.

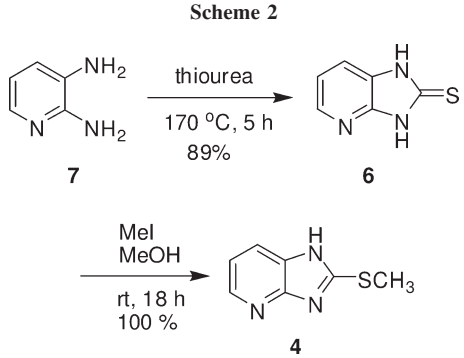
RESULTS AND DISCUSSION

Based on the synthesis of pentosidine framework we have previously reported [17], our plan for the synthesis of pentosidine is shown in retrosynthetic format in Scheme 1 and is centered on the construction of the key intermediate imidazo[4,5-*b*]pyridine core **4.** Pentosidine (**1**) should be available by consecutive introduction of amino acid subunit **3** (for lysine portion of pentosidine) and subunit **5** (for arginine portion of pentosidine) to the central piece **4** by a regioselective alkylation and an amination, respectively. We anticipated that the two subunits **3** and **5** could be obtained from chiral amino acids.

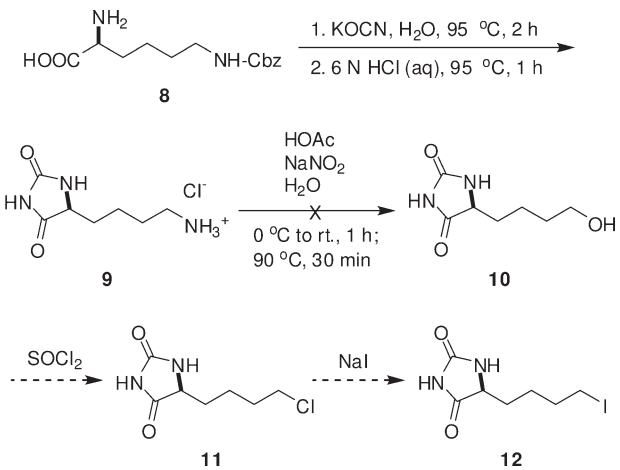
Chiral fragments developed from natural amino acids have been used in many asymmetric syntheses of natural products [18]. We envisioned that the amino acid subunit **3** could be generated from lysine and the subunit **5** from onithine. To make amino acid subunit fragments which could be incorporated through either an alkylation reaction or an amination reaction, the α-amino and carboxy groups of the amino acids needed to be protected. Of the several methods available for protecting amino acids, we decided to employ hydantoin derivatization. Hydantoins have been used as precursors of amino acids in many syntheses and serve as important amino acid surrogates for the production of pharmaceuticals (e.g., semisynthetic penicillins and cephalosporins), agrochemicals, and fine chemicals [19]. The conversion of hydantoins to amino acids could be achieved through hydrolysis [20,21] or biocatalysis [22]. Another reason for selecting hydantoin protection is that our synthesis involves some harsh reaction conditions, such as chlorination in 12*N* HCl [17], and hydantoin is the only protecting group that can survive all the reaction conditions involved in the synthesis.

As planned in Scheme 1, our synthesis began with the preparation of the key intermediate imidazo[4,5-*b*]pyridine core **4** (Scheme 2) [17]. The reaction of 2,3-diaminopyridine (**7**) with thiourea afforded 1*H*-imidazo[4,5-*b*]pyridine-2(3H)-thione (**6**) [17,23] and S-methylation of **6** gave 2-(methylthio)imidazo[4,5-*b*]pyridine (**4**) [17].

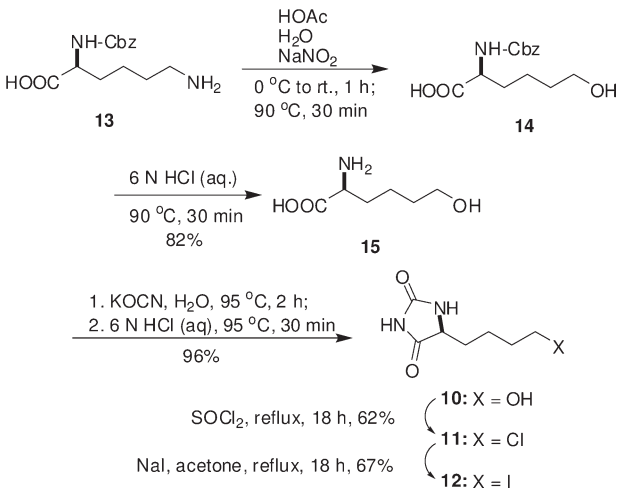
Scheme 2



Scheme 3



Scheme 4

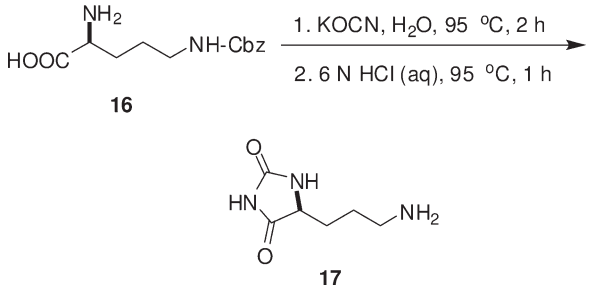


It was conjectured that the preparation of the hydantoin protected lysine subunit fragment **12** could be fulfilled by conversion of commercially available N^{ε}-Cbz-lysine (**8**) to the hydantoin compound **9** through Urech hydantoin synthesis (Scheme 3) [24], followed by a key conversion of **9** to **10** through diazotization and hydroxylation [25], a nucleophilic substitution of alcohol **10** to form **11** [26] and an alteration of chloride **11** into iodide **12** [27]. Although transformation of alkylamines into alcohols through diazonium intermediates has been reported to be achievable in good yield [25], the transformation of 5-(4-aminobutyl)hydantoin (**9**) to 5-(4-hydroxybutyl)-hydantoin (**10**) was not successful, with recovery of unchanged amino compound **9**.

We chose an alternate strategy involving transformation of amino to hydroxy group prior to hydantoin derivatization (Scheme 4) [25]. The conversion of N^{α}-Cbz-lysine (**13**) into alcohol **14** through diazotization and hydroxylation was accomplished in good yield [25]. L-6-hydroxynorleucine (**15**), obtained from **14** after deprotection, was then transformed into the hydantoin **10** through Urech hydantoin synthesis [24]. The alcohol **10** was converted into the chloride **11** via a nucleophilic substitution using $SOCl_2$ [26], and then into iodide **12** by refluxing with NaI in acetone [27]. It is worth mentioning that although the yields of both the conversion of **10** to **11** using thionyl chloride and the conversion of **11** to **12** were moderate, the both conversions could be forced to quantitative by prolonged refluxing (>168 h).

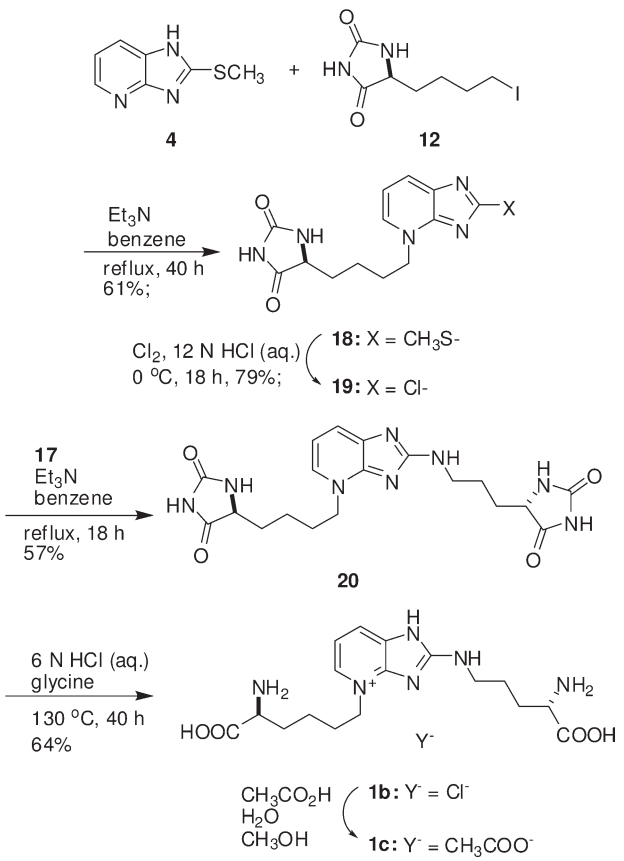
The amination reagent required for elaboration of the arginine portion of pentosidine corresponds to the ornithine subunit fragment **17**, which was prepared from N^{δ}-Cbz-ornithine (**16**) through Urech hydantoin synthesis followed by the removal of Cbz protective group (Scheme 5) [24].

Scheme 5

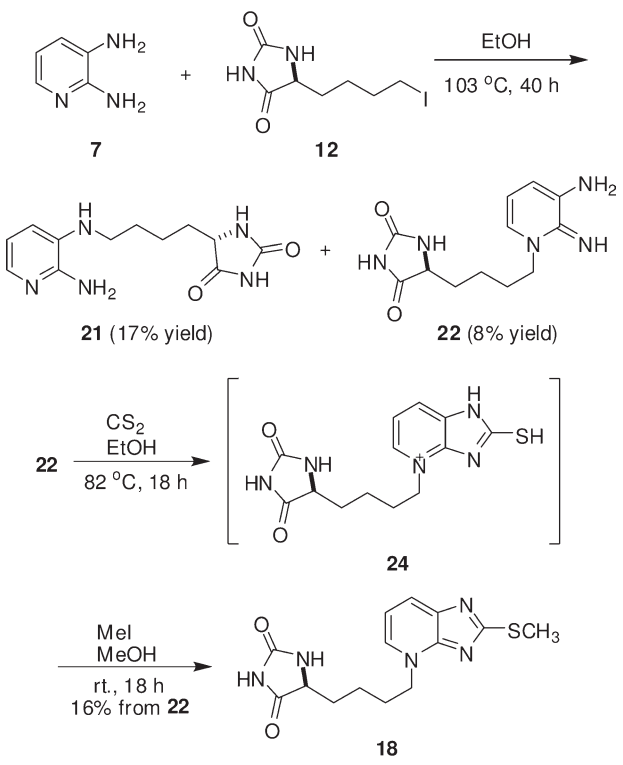


After we had prepared the key intermediate **4** and the amino acid subunit fragments **12** and **17**, their assembly started from the alkylation of imidazo[4,5-*b*]pyridine core **4** with iodide **12** in benzene in the presence of Et_3N to give pyridine *N*-alkylated imidazopyridine **18** [28] for pyridine nitrogen is more nucleophilic than the imidazole nitrogens at positions 1 or 3 (Scheme 6) [28]. Compound **18** was then transformed into 2-chloroimidazopyridine **19** through chlorination in hydrochloric acid [29]. The ornithine subunit fragment **17** was then introduced through amination of chloride **19** in the presence of Et_3N, resulting in the dihydantoin-protected pentosidine (**20**) [30].

Scheme 6



Scheme 7



Deprotection of hydantoins to amino acids could be achieved through basic hydrolysis [20], acidic hydrolysis [21], and biocatalytic means [22]. Although hydrolysis of the hydantoin protecting group under basic conditions is straightforward [20], it can lead to unwanted racemization. Acidic hydrolysis is favored because hydantoins and amino acids do not undergo racemization under such conditions [21]. The biocatalytic conversion of hydantoins to amino acids has been recognized in recent decades for potential application in the industrial production of amino acids [22]. The biocatalysis reaction involves two consecutive hydrolysis steps, catalyzed by both a hydantoinase and an *N*-carbamoylamino acid amidohydrolase (NCAAH). During the process, an L-selective hydantoinase converts a 5-monosubstituted hydantoin to an L-*N*-carbamoylamino acid and an L-selective NCAAH then converts the *N*-carbamoylamino acid to an L-amino acid. It seemed to us that the biocatalytic conversion is the most favored for the deprotection of dihydantoin-protected pentosidine **20**.

Because our work was halted due to the death of Professor Sayre and the consequent laboratory closing [31], we were unable to explore the preparation of amino acids via biocatalysis with hydantoinase and NCAAH. Prior to that we found removal of the hydantoin protecting groups required refluxing in 6*N* HCl in the presence of glycine. Pentosidine is stable in concentrated acid and was first obtained after refluxing in 6*N* HCl for 36 h [3a]. Only small amount of pentosidine formed during hydrolysis of **20** when glycine was absent. We still do not know how glycine facilitates the hydrolysis, a hydantoin change reaction could be a plausible explanation [32]. Purification of crude HCl salt of pentosidine (**1b**) with a mixed eluent of $CH_3OH/H_2O/CH_3CO_2H$ afforded its CH_3CO_2H salt (**1c**). Comparison of NMR, FAB-MS, and LC-MS data of our synthesized **1c** with the pentosidine CF_3CO_2H salt (**1a**) isolated by Sell and Monnier showed the consistency of synthesized and isolated compounds [3a]. We have also noted that the specific rotation value of our pentosidine CH_3CO_2H salt (**1c**) is $[\alpha]_D^{24} = +11.5°$ (c 0.2, CH_3OH), which differs from the value $[\alpha]_D^{24} = +16.5°$ (c 0.3, CH_3OH) of its CF_3CO_2H salt (**1a**) [15]. Considering UV and fluorescent properties of pentosidine are highly dependent on pH value [3,17], the difference of specific rotation values could be attributed to the different counterions in the two salt forms.

While pentosidine **1** could be obtained from the synthesis shown in Scheme 6, evidence for the regiochemistry of alkylation in **18**, and for structural assignment of **19**, **20**, and **1** that were obtained in subsequent steps, was not fully discussed. We assigned **18** as pyridine *N*-alkylated product on the basis of the regiochemistry of the alkylation reaction used to synthesize pentosidine framework [17]. To provide conclusive evidence for our structural assignment of **18**, **19**, **20**, and **1**, an unambiguous synthesis was used (Scheme 7). The regiochemistry of intermediate **18** in Scheme 6 was proven through comparison of its NMR spectrum to the spectrum of **18** obtained according to Scheme 7. In Scheme 7, direct alkylation of diaminopyridine (**7**) with iodide **12** gave a mixture of two isomeric products **21** and **22** [33]. The distinction of **22** from **21** could be made on the basis of both proton chemical shift and characteristic couplings. The chemical shift for the methylene group neighboring N in **21** is δ 3.17, but δ 4.22 in the case of **22.** Transformation of the pyridine *N*-alkylated isomer **22** afforded intermediate **18** [17,23,34]. The consistency of NMR spectra for the two individual samples of **18**, and the NMR spectrum of a mixture of the two samples (in 1:1 ratio), added conclusive evidence that imidazopyridine **18** obtained through this route is identical with the product obtained from the synthesis shown in Scheme 6.

In summary, pentosidine, an important biological marker for diabetic complications and oxidative damage has been synthesized. The regiochemistry of the targets and intermediates was established by an unambiguous synthesis. Our approach to the biomarker is more efficient than those reported in literature, especially in obtaining lysine subunit fragment through a procedure with fewer steps. The hydantoin-protected pentosidine

provides a platform for the future research on biocatalysis to generate pentosidine enantiomerically.

EXPERIMENTAL

All commercial reagents and solvents were used without purification. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.1 MHz) were recorded on Varian Gemini 300 or Gemini 200 instruments using TMS as internal standard. In the ^{13}C-NMR data, attached proton test (APT) designations are given as (+) or (−) following the chemical shift. High-resolution mass spectra (HRMS) were obtained at 20 eV on a Kratos MS-25A instrument. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets, and UV light was used for visualization. Flash column chromatography was done using E. Merck silica gel 60 (230–400 mesh). Solvent removal was accomplished with a rotary evaporator operating at vacuum (40–50 Torr).

1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (6). A mixture of 2,3-diaminopyridine (**3**) (2.18 g, 20.0 mmol) and thiourea (7.6 g, 100.0 mmol) was heated at 170 °C for 5 h. The reaction mixture was extracted with boiling ethanol (5 × 20 mL), leaving crystals that were collected by filtration. A second crop of crystals was obtained from the cooled filtrate after standing overnight. The combined yield of pure **6** was 2.7 g (89%). **6**: ^{1}H-NMR (DMSO-d_6) δ 7.13 (dd, J = 7.9, 5.0 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 5.0 Hz, 1H), 12.70 (s, 1H, NH), 13.12 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 116.2 (−), 118.1 (−), 125.4 (+), 142.3 (−), 146.4 (+), 169.8 (+). HRMS calcd for $C_6H_5N_3S$ (M^+) 151.0204, found 151.0204.

2-(Methylthio)-1*H*-imidazo[4,5-*b*]pyridine (4). A solution of **6** (2.26 g, 15.0 mmol) and methyl iodide (8.52 g, 60.0 mmol) in MeOH (30.0 mL) was stirred at room temperature for 18 h. Evaporation of the solvent and CH_3I under reduced pressure gave pure **4** (3.32 g, 100 %): ^{1}H-NMR (CD_3OD) δ 2.75 (s, 3H), 7.20 (dd, J = 7.9, 4.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 4.9 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 15.0 (−), 119.1 (−), 127.4 (−), 134.1 (+), 134.5 (−), 150.3 (+), 166.4 (+); HRMS calcd for $C_7H_7N_3S$ (M^+) 165.0361, found 165.0363.

5-(4-Aminobutyl)hydantoin hydrochloride (9). A mixture of *N*ε-Cbz-L-lysine **8** (841.0 mg, 3.0 mmol) and potassium cyanate (260.0 mg, 3.20 mmol) in water (20.0 mL) was stirred at 95°C for 2 h, then cooled to room temperature, acidified by adding 12*N* HCl (20.0 mL), and then stirred at 95°C for 1 h. Evaporation to dryness under reduced pressure afforded crude product **9** which was sufficiently pure for the next reaction step: ^{1}H-NMR (D_2O) δ 1.46 (m, 2H), 1.70 (m, 2H), 1.84 (m, 2H), 2.99 (t, J = 7.5 Hz, 2H), 4.29 (dd, J = 6.3, 4.8 Hz, 1H); ^{13}C-NMR (D_2O) δ 20.9 (+), 26.5 (+), 30.0 (+), 39.3 (+), 58.6 (−), 159.4 (+), 178.9 (+); FAB HRMS calcd for $C_7H_{14}N_3O_2$ (M + H) $^+$ 172.1086, found 172.1093.

L-6-Hydroxynorleucine (15). To a solution of N^{α}-Cbz lysine (**13**) (5.60 g, 20.0 mmol) in a mixed solvent of acetic acid (20.0 mL) and water (4.0 mL) was added a solution of $NaNO_2$ (2.76 g, 40.0 mmol) in water (4.0 mL) at 0°C dropwise. The mixture was stirred at room temperature for 1 h, at 90°C for 30 min, and then cooled to room temperature. After an aqueous 6*N* HCl (120.0 mL) was added, the reaction mixture was stirred at 90°C for another 30 min, and evaporated to give a residue which was diluted with a mixed solvent of (MeOH/ H_2O = 4:1, 40.0 mL), neutralized to pH 7.5 with 2*N* NaOH solution, and concentrated. The resulting crude was subjected to chromatography (DCM/MeOH = 1:5) to provide **15** (2.40 g, 82%): ^{1}H-NMR (D_2O) δ 1.46 (m, 2H), 1.62 (m, 2H), 1.91(m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.76 (t, J = 4.1 Hz, 1H); ^{13}C-NMR (D_2O) δ 21.8 (+), 31.2 (+), 31.9 (+), 55.7 (−), 62.2 (+), 175.7 (+); $[\alpha]_D^{20}$ = + 6.35° (c 0.2, H_2O); HRMS calcd for $C_7H_{12}N_2O_3$ (M^+) 147.0895, found 172.0889.

5-(4-Hydroxybutyl)hydantoin (10). A mixture of L-6-hydroxynorleucine (**15**) (2.38 g, 16.23 mmol) and potassium cyanate (1.76 g, 22.0 mmol) in water (100 mL) was stirred at 90°C for 2 h, then cooled to room temperature, acidified by adding 12*N* HCl (100.0 mL), and then stirred at 95°C for 30 min. The reaction mixture was concentrated, diluted with a mixed solvent of (MeOH/ H_2O = 4:1, 60.0 mL), neutralized to pH 7.5 with 2*N* NaOH solution, and concentrated to give a residue which was subjected to chromatography (CH_2Cl_2/CH_3OH = 6:1) to afford **10** (2.68 g, 96%): ^{1}H-NMR (CD_3OD) δ 1.40–1.88 (m, 6H), 3.56 (t, J = 6.4 Hz, 2H), 4.09 (dd, J = 6.9, 5.1 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 22.1 (+), 32.5 (+), 33.2 (+), 59.8 (−), 62.6 (+), 160.0 (+), 178.3 (+); HRMS calcd for $C_7H_{12}N_2O_3$ (M^+) 172.0848, found 172.0868.

5-(4-Chlorobutyl)hydantoin (11). A solution of **10** (2.66 g, 15.45 mmol) in thionyl chloride (100 mL) was heated at reflux for 18 h and evaporated to result in a residue which was diluted with a mixed solvent of (MeOH/ H_2O = 4:1, 40.0 mL), neutralized to pH 7.5 with 2 N NaOH solution, and concentrated. The residual crude was subjected to chromatography (CH_2Cl_2/CH_3OH = 6:1) to give **11** (1.83 g, 62%): ^{1}H-NMR (CD_3OD) δ 1.42 (m, 2H), 1.58 (m, 2H), 1.81 (m, 2H), 3.57 (t, J = 6.4 Hz, 2H), 4.10 (dd, J = 6.9, 5.1 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 23.1 (+), 32.0 (+), 33.3 (+), 45.5 (+), 59.7 (−), 160.0 (+), 178.1 (+); HRMS calcd for $C_7H_{11}N_2O_2Cl$ (M^+) 190.0509, found 190.0507.

5-(4-Iodobutyl)hydantoin (11). A solution of 5-(4-chlorobutyl)hydantoin (**11**) (1.79 g, 9.40 mmol) and NaI (4.68 g, 31.2 mmol) in acetone (100 mL) was refluxed for 18 h and then concentrated to give a residue which was subjected to chromatography (CH_2Cl_2/CH_3OH = 9:1) to afford **12** (1.78 g, 67%): ^{1}H-NMR (CD_3OD) δ 1.51 (m, 2H), 1.70 (m, 2H), 1.82 (m, 2H), 3.23 (t, J = 6.9 Hz, 2H), 4.29 (dd, J = 6.7, 4.7 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 6.4 (+), 26.6 (+), 31.5 (+), 34.3 (+), 59.7 (−), 160.0 (+), 178.1 (+); FAB HRMS calcd for $C_7H_{11}IN_2NaO_2$ ($(M + Na)^+$ 304.9763, found 304.9763.

5-(3-Aminopropyl)hydantoin (17). A suspension of N^{δ}-Cbz-L-ornithine (**16**) (266.3 mg, 1.0 mmol) and potassium cyanate (87.0 mg, 1.07 mmol) in water (10 mL) was stirred at 95°C for 2 h, then cooled to room temperature, acidified by adding 12*N* HCl (20 mL), then stirred at 95 °C for 1 h. The reaction mixture was concentrated, diluted with a mixed solvent of (MeOH/ H_2O = 4:1, 20.0 mL), neutralized to pH 7.5 with 2*N* NaOH solution, and concentrated to afford a residue which was subjected to chromatography (CH_2Cl_2/MeOH = 3:2) to provide **17** (151 mg, 96%): ^{1}H-NMR (CD_3OD) δ 1.75–1.93 (4H), 3.00 (t, J = 6.7 Hz, 2H), 4.70 (dd, J = 6.3, 4.7 Hz, 1H); ^{13}C-NMR (D_2O) δ 22.7 (+), 28.0 (+), 39.7 (+), 58.6 (−), 159.5 (+), 178.5 (+); HRMS calcd for $C_6H_{11}N_3O_2$ (M^+) 157.0851, found 157.0835.

4-[4-(5-Hydantoin)butyl]-2-methylthio-4*H*-imidazo[4,5-*b*] pyridine (18). A suspension of 5-(4-iodobutyl)hydantoin (**12**) (1.69 g, 6.0 mmol) and 2-(methylthio)-1*H*-imidazo[4,5-

b]pyridine (**4**) (495.1 mg, 3.0 mmol) in benzene (60 mL) with triethylamine (0.5 mL, 3.6 mmol) was stirred and heated in an oil bath (90°C) for 40 h. After removing the solvent under reduced pressure, the residue was dissolved in a mixture of MeOH (20 mL) and H_2O (20 mL) and adjusted to pH 9.5. Upon evaporation of the solvent under reduced pressure, flash chromatography (EtOAc/MeOH = 3:1) of the residue afforded **18** (584.0 mg, 61%): ^{1}H-NMR (CD_3OD) δ 1.45 (m, 2H), 1.75 (m, 2H), 1.92 (m, 2H), 2.67 (s, 3H), 4.09 (dd, J = 6.8, 4.6 Hz, 1H), 4.53 (t, J = 7.2 Hz, 2H), 7.09 (dd, J = 7.7, 6.7 Hz, 1H), 7.89 (d, J = 6.7 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 14.6 (−), 22.9 (+), 30.2 (+), 32.1 (+), 54.8 (+), 59.5 (−), 114.6 (−), 125.6 (−), 131. 4 (−), 145.3 (+), 154.3 (+), 159.9 (+), 173.1 (+), 178.0 (+); FAB HRMS calcd for $C_{14}H_{18}N_5O_2S$ $(M+1)^+$ 320.1181, found 320.1175.

4-[4-(5-Hydantoin)butyl]-2-chloro-4*H*-imidazo[4,5-*b*]pyridine (19). Chlorine was introduced into a solution of **18** (200.0 mg, 0.62 mmol) in 12*N* HCl (60 mL) with stirring at 0°C for 18 h. After evaporation to dryness under reduced pressure, the residue was dissolved in water (20 mL) and neutralized to 7.8 with NH_4OH. Water was removed under reduced pressure and the residue was extracted with CH_2Cl_2/MeOH (8:1). The organic extract was dried (Na_2SO_4) and evaporated to give a residue, which was subjected to chromatography (CH_2Cl_2/CH_3OH= 8:1) to furnish **19** (151.0 mg, 79%): ^{1}H-NMR (CD_3OD) δ 1.49 (m, 2H), 1.79 (m, 2H), 2.00 (m, 2H), 4.09 (dd, J = 6.9, 4.7 Hz, 1H), 4.64 (t, J = 7.5 Hz, 2H), 7.32 (dd, J = 7.8, 6.3 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 8.19 (d, J = 6.3 Hz, 1H); ^{13}C-NMR (CD_3OD) δ 22.6 (+), 30.3 (+), 32.0 (+), 55.3 (+), 59.5 (−), 116.0 (−), 129.7 (−), 134.1 (−), 143.9 (+), 152.6 (+), 159.7 (+), 159.9 (+), 178.0 (+); FAB HRMS calcd for $C_{13}H_{15}N_5O_2Cl$ $(M+1)^+$ 308.0914, found 308.0917.

4-[4-(5-Hydantoin)butyl]-2-[3-(5-hydantoin)propylamino]-4*H*-imidazo[4,5-*b*]pyridine (20). A suspension of **19** (138.4 mg, 0.48 mmol) and **17** (151.0 mg, 0.96 mmol) in benzene (20 mL) with triethylamine (0.334 mL, 242 mg g, 2.40 mmol) was stirred and heated in an oil bath (90°C) for 18 h. After removing solvent under reduced pressure, the residue was dissolved in MeOH (20 mL) and H_2O (20 mL) and adjusted to pH 9.5. Concentration under reduced pressure left behind a residue which was purified by chromatography (CH_2Cl_2/MeOH = 3:1) to provide **24** (117.2 mg, 57%): ^{1}H-NMR (CD_3OD) δ 1.40–1.98 (10H), 3.46 (t, J = 4.9 Hz, 2H), 4.08 (dd, J = 6.8, 5.2 Hz, 1H), 4.15 (dd, J = 5.9, 4.7 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 6.89 (dd, J = 6.4, 5.9 Hz, 1H), 7.42 (d, J = 5.9 Hz, 1H), 7.54 (d, J = 6.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6) δ 21.4 (+), 25.1 (+), 28.2 (+), 28.9 (+), 30.7 (+), 41.6 (+), 51.8 (+), 57.5 (2C) (−), 110.6 (−), 115.4 (−), 124.9 (−), 145.9 (+), 155.5 (+), 157.6 (2C) (+), 170.2 (+), 176.1 (+), 176.2 (+) (two peaks are missing due to overlap); FAB HRMS calcd for $C_{19}H_{25}N_8O_4$ $(M + 1)^+$ 429.2000, found 429.2008.

Acetic acid salt of pentosidine (1c). A mixture of **20** (107.5 mg, 0.25 mmol) and glycine (75.1 mg, 1.0 mmol) in 6 N HCl (45 mL) was refluxed under N_2 for 40 h and evaporated under reduced pressure to result in crude HCl salt of pentosidine (**1a**) which was subjected to chromatography (CH_3OH/H_2O/HOAc = 7:2:1) to provide **1c** (70.2 mg, 64%): $[\alpha]_D$ = +11.5° (c 0.2, CH_3OH); ^{1}H-NMR (D_2O) δ 1.4–1.6 (m, 2H), 1.8–2.1 (m, 8H), 2.08 (s, 3H, CH_3COO^-), 3.57 (t, J = 6.1 Hz, 2H), 3.96 (t, J = 6.3 Hz, 1H), 4.02 (t, J = 6.3 Hz, 1H), 4.55 (t, J = 7.1 Hz, 2H), 7.22 (dd, J = 7.7, 6.5 Hz, 1H), 7.78 (d, J = 7.7 Hz. 1H), 7.93 (d, J = 6.5 Hz, 1H); ^{13}C-NMR δ 21.0(+) (CH_3COO^-), 22.0 (+), 25.1(+), 28.3(+), 28.8(+), 30.5(+), 39.5(+), 42.6(+), 53.7(−), 53.8(−), 115.8(−), 120.2(−), 132.4(+), 132.7(−), 152.2(+), 160.3(+), 171.7(+), 172.3(+), 177.0(−) (CH_3COO^-); FAB HRMS calcd for $C_{17}H_{27}N_6O_4$ $(M + 1)^+$ 379.2094, found 379.2083.

2-Amino-3-[4-(5-hydantoin)butyl]aminopyridine (21) and 3-amino-1-[4-(5-hydantoin)butyl]-2-pyridone imine (22). A mixture of **7** (436.0 mg, 4 mmol) and **12** (1.35 g, 4.8 mmol) in EtOH (16.0 mL) was stirred at 100°C in a high pressure reaction vessel for 40 h, and then concentrated under reduced pressure to result in a residue which was diluted with a mixed solvent of MeOH (30 mL) and H_2O (30 mL), basified to pH 10 with 2*N* aqueous solution of NaOH, and concentrated. The residual crude was subjected to chromatography (EtOAc/MeOH = 4:1) to afford **21** (180.1 mg, 17% yield) and **22** (84.2 mg, 8%). **21**: ^{1}H-NMR (CD_3OD) δ 1.55 (m, 2H), 1.75 (m, 2H), 1.85 (m, 2H), 3.17 (t, J = 6.7 Hz, 2H), 4.12 (dd, J = 6.2, 5.6 Hz, 1H), 6.77 (dd, J = 7.7, 6.0 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 5.9 Hz, 1H); **22**: ^{1}H-NMR (CD_3OD) δ 1.50 (m, 2H), 1.75 (m, 2H), 1.85 (m, 2H), 4.12 (dd, J = 6.2, 5.6 Hz, 1H), 4.22 (t, J = 7.3 Hz, 2H), 6.77 (dd, J = 7.2, 6.4 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 6.3 Hz, 1H).

Preparation of 18 from 22. A mixture of **22** (71.8 mg, 0.27 mmol) in EtOH (4 mL) and CS_2 (4 mL) was stirred at 80°C in for 18 h and concentrated under reduced pressure. The resulting residue was mixed with a solution of methyl iodide (428 mg, 3 mmol) in MeOH (2 mL), stirred at room temperature for 18 h, evaporated to dryness under reduced pressure. The crude residue was dissolved in MeOH (10 mL) and H_2O (10 mL), basified to pH 9.5 with 2*N* aqueous solution of NaOH, and concentrated to furnish a residue which was subjected to chromatography (EtOAc/MeOH = 3:1) to furnish **18** (13.8 mg, 16%). ^{1}H-NMR, ^{13}C-NMR, and HRMS are identical with those of **18** prepared from **4** and **15**.

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Selective Substitution Reactions of Methoxycarbonylamino-1-(1-benzotriazolyl)alkanes with Active Methylene Compounds

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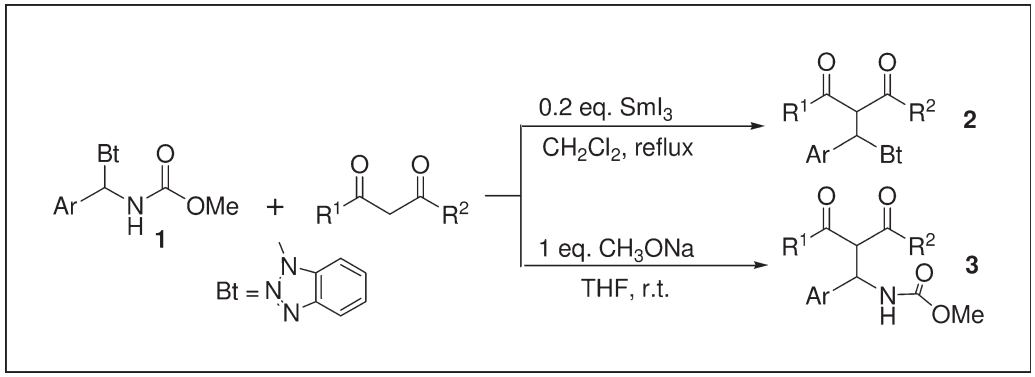

Benzotriazole adducts methoxycarbonylamino-1-(1-benzotriazolyl)alkanes **1** were derived from the condensation of an aldehyde, benzotriazole, and methylcarbamate. The leaving tendency of methoxycarbonylamino group (MeOCONH) and benzotriazole group (Bt) was investigated by treatment of the adducts with active methylene compounds under either Lewis acid-catalyzed or basic conditions. In the presence of SmI_3, MeOCONH take priority over Bt in the leaving process, whereas in the presence of MeONa, the Bt was substituted in preference. Thus, the tunable substitution of the two leaving groups could be used for different synthetic purposes.

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INTRODUCTION

Benzotriazole is a useful synthetic auxiliary due to the readily introduction and good leaving ability of the benzotriazolyl (Bt). A large number of benzotriazole derivatives have been reported as key intermediates for the synthesis of various compounds [1].

Benzotriazole derivatives of type Bt—C—OR was reported to be ionized [2] either by Bt—C bond scission to form alkyleneonium cations C^+—OR and Bt^- or by C—O bond scission to give RO^- anion and a benzotriazole stabilized carbocation Bt=C^+, depending on the substituents in the molecules. Recently, the selective substitution of Bt or amido group in *N*-(α-benzotriazolylalkyl)amides (Bt—C—NHCOR type) were achieved by using different Lewis acid catalysts. Promoted by $AlCl_3$ [3a] or SmI_3 [3b], the Bt could be substituted selectively by active methylene compounds. However, in the presence of $Dy(OTf)_3$, selective substitution of the amido group (—NHCOR) in the same substrates was found [3c]. The Bt in 1-(benzotriazole-1-yl)alkyl ester [4a] (Bt—C—OCOR type) could be selectively substituted by C-nucleophiles such as cyanide anion [4b] and the carbonanion from organozinc reagents [4c]. Interestingly, the acyloxy (—OCOR) in the same substrates could be selectively removed via SmI_2-mediated reduction [4d]. Nevertheless, examples concerning such conditions-dependent selectivity are limited and more examples for the selective scission of either Bt or the other concurrent leaving group are required so as to make it more applicable in organic synthesis.

RESULTS AND DISCUSSION

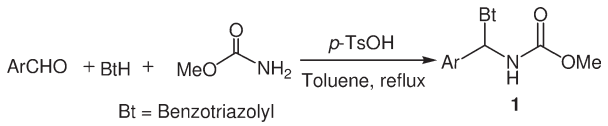
As a part of our continuing work in benzotriazole chemistry, we wish to report the selective substitution reactions of methoxycarbonylamino-1-(1-benzotriazolyl) alkanes **1** with active methylene compounds.

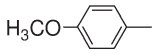
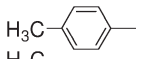
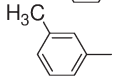
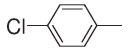
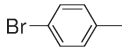
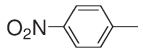
The substrates methoxycarbonylamino-1-(1-benzotriazoly)alkanes **1** could be facilely prepared by the condensation of an aldehyde, benzotriazole, and methylcarbamate (Table 1). They were obtained in moderate to good yields (Table 1, entries 1–8).

With compounds **1** in hand, we then tried to investigate the substitution reaction with active methylene compounds.

Table 1

Synthesis of Methoxycarbonylamino-1-(1-benzotriazoly)alkanes **1**.[a]



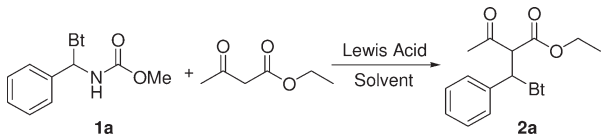
Entry	Ar	Compounds 1	Time (h)	Yields (%)[b]
1		**1a**	24	83
2		**1b**	24	56
3		**1c**	24	61
4		**1d**	24	60
5		**1e**	24	58
6		**1f**	24	72
7		**1g**	24	68
8		**1h**	24	70

[a] Reaction conditions: aldehyde (10 mmol), benzotriazole (10 mmol), methyl methyl-carbamate (10 mmol), toluene (30 mL), *p*-TsOH (0.1 mmol), reflux.
[b] Isolated yield.

Methyl *N*-(1-benzotriazol-1-phenylmethyl)carbamate **1a** and ethyl acetoacetate were initially used as the model substrates. The first attempt was performed in THF with SmI_3 (20 mol %) as the catalyst under reflux (Table 2, entry 1). Interestingly, in contrast with the previous results [3b], the major product now obtained was β,β-dicarbonyl derivatives **2a** (35% yield), where the methoxycarbonylamino (—NHCOOMe) was replaced and the Bt was reserved. We then tested other Lewis acid catalysts such as $AlCl_3$, and metal triflates (Table 2, entries 2–4).

Table 2

Substitution of **1a** with ethyl acetoacetate under different conditions.[a]

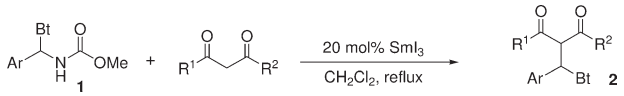


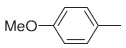
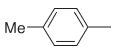
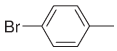
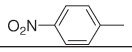
Entry	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	SmI_3 (0.2)	THF	Reflux	1	35
2	$AlCl_3$ (1.0)	THF	Reflux	12	19
3	$Zn(OTf)_2$ (0.2)	THF	Reflux	12	Trace
4	$Cu(OTf)_2$ (0.2)	THF	Reflux	12	Trace
5	SmI_3 (0.2)	CH_3CN	Reflux	1	37
6	SmI_3 (0.2)	Toluene	70	4	40
7	SmI_3 (0.2)	Dioxane	Reflux	2	48
8	SmI_3 (0.2)	CH_2Cl_2	Reflux	1	67
9	SmI_3 (0.2)	CH_2Cl_2	Room temperature	5	36

[a] Reaction conditions: acetoacetate (1.1 mmol), **1** (1 mmol), solvent (10 mL).
[b] Isolated yield.

Table 3

SmI_3-catalyzed nucleophilic substitution reaction of methoxycarbonyl-amino-1-(1-benzotriazoly)alkanes **1** with 1,3-dicarboyl compounds.[a]



Entry	Ar in 1	R^1	R^2	Time (h)	Products	Yields (%)[b]
1		Me-	EtO-	1	**2a**	67
2		Me-	MeO-	10	**2b**	70
3		Me-	Me-	24	**2c**	40
4		EtO-	EtO-	10	**2d**	58
5		Me-	MeO-	8	**2e**	63
6		Me-	EtO-	4	**2f**	54
7		Me-	EtO-	10	**2g**	59
8		Me-	MeO-	10	**2h**	60
9		Me-	MeO-	10	**2i**	65
10		EtO-	EtO-	10	**2j**	53
11		Me-	EtO-	10	–	–[c]
12		Me-	Me-	10	–	–[c]

[a] Reaction conditions: **1** (1 mmol), active methylene compounds (1 mmol), SmI_3 (0.2 mmol), solvent (10 mL), reflux.
[b] Isolated yield.
[c] Complete decomposition of compound **1**.

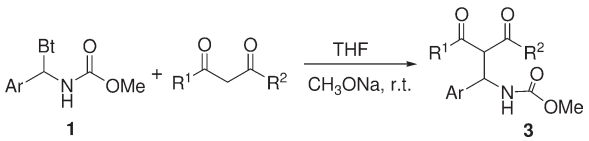
However, these acid catalysts did not give encouraging results and serious decomposition of substrate **1** to the original aldehyde, benzotriazole, and methyl carbamate was observed. Fortunately, screening of the solvents (Table 2, entries 5–8) and examination of the temperature (Table 2, entries 8–9) showed that refluxing in CH_2Cl_2 with 20 mol % of SmI_3 could afford **2a** in improved yield (67% yield) (Table 2, entry 8).

After the reaction conditions were optimized, various methoxycarbonylamino-1-(1-benzotri-azoly)alkanes **1** and active methylene compounds were used as the substrates to examine the scope and limitations. The results were summarized in Table 3. We were pleased to find a variety of active methylene compounds could smoothly react with **1** (Table 3, entries 1–10). Both β-keto esters and malonates were good C-nucleophiles for the reaction, whereas the substitutions with a β-diketone required longer reaction time and gave a lower yield (Table 3, entry 3). Compounds **1** bearing electron-donating groups (such as methyl and methoxy) on the phenyl ring could afford the desired products **2** in moderate yields (Table 3, entries 1–10). However, electron-withdrawing groups (such as bromo and nitro groups) led to the rapid decomposition of compounds **1**, and the desired products **2** could not be obtained in these cases (Table 3, entry 11 and entry 12).

Because Bt is also a good leaving group, it could be anticipated that the Bt might be substituted under suitable conditions. Recent studies showed that the Bt in benzyloxycarbonylamino-1-(1-benzotriazoly)alkanes could be smoothly substituted by *tert*-butyl acetates using lithium diisopropyl amine (LDA) as a base [5]. The above results inspired us to envision a selective substitution of Bt in **1** by the active methylene compounds via forming an enolate under proper basic conditions. We

Table 4

MeONa-promoted nucleophilic substitution of methyl (1H-benzotriazolylaryl)methylcarbamate with 1,3-dicarboyl compounds.[a]



Entry	Ar	R^1	R^2	Time (min)	Product 3	Yields (%)[b]
1		Me-	EtO-	45	**3a**	77
2		Me-	EtO-	60	**3b**	83
3		Me-	EtO-	35	**3c**	86
4		Me-	EtO-	40	**3d**	72
5		Me-	EtO-	120	**3e**	64
6		EtO-	EtO-	210	**3f**	65

[a] Reaction conditions: **1** (1 mmol), active methylene compounds (1 mmol), CH_3ONa (1 mmol), solvent (10 mL), room temperature.
[b] Isolated yields.

found that this substitution could proceed successfully in the presence of MeONa. Generally, moderate to good yield of the expected β-amino acid derivatives **3** could be obtained within 3.5 h despite the electronic effect (Table 4).

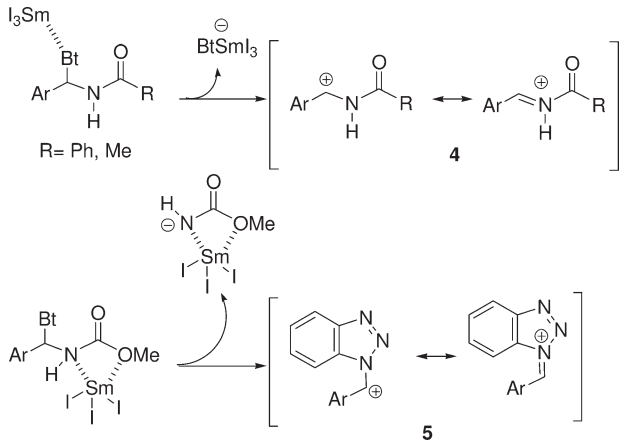
Very recently, the reaction between *N*-(α-amidoalkyl)-benzotriazoles and 1,3-diketones-dervied potassium enolates was used for the preparation of the β-amido β-diketones by the loss of Bt [6]. Combination with Katritzky's research [5a] and ours, it could be concluded that Bt is a better leaving group than either amido or alkoxycarbonylamino because the enolates consistently substitute the Bt in the three types of substrates. In the base conditions, the above reactions proceeded more probably via S_N2 mechanism. However, in the presence of SmI_3, the benzotriazole derivatives should ionize either to the benzotriazole anion and cation **4** [5b] or to the alkoxycarbonylamino anion and cation **5** [2] depending upon the substrate structures (Scheme 1). In contrast with the Bt—C—NHCOR stucutre [3b], which tended to ionize to cation **4** in the presence of SmI_3, good chelation may exist for the Bt—C—NHCOOMe moeity because samarium salt was reported to coordinate well with both O— and N— donors [7]. Hence, the leaving ability of —NHCOOMe was effectively enhanced until an alternative ionization mode to form cation **5** predominated. Attack of cation **5** with active methylene compounds afforded product **2**.

In summary, selective substitution of either NHCOOMe or Bt in *N*-(α-benzotriazol-1-ylalkyl) methylcarbamates was achieved by performing the reaction under different conditions. With SmI_3 as the Lewis acid catalyst, NHCOOMe could be selectively substituted by the active methylenyl group, and the benzotriazole derivatives could be obtained in moderate to good yields; whereas using MeONa as the base, the Bt was substituted preferentially and the β-amino acid derivatives were prepared under mild conditions. The tunable leaving tendency of the two leaving groups may be useful for other synthetic purposes.

EXPERIMENTAL

Methylene chloride was distilled from calcium hydride immediately before use. Melting points are uncorrected. ^{1}H-NMR

Scheme 1. Proposed mechanism for the selective substitution of —NHCOOMe with SmI_3 as a catalyst.



(400 MHz) spectra were recorded on a Bruker AV400 NMR instrument as $CDCl_3$ solutions using tetramethyl silane (TMS) as internal standard. Chemical shifts (σ) are reported in parts per million (ppm) and coupling constants J are given in hertz. IR spectra were recorded in film or using KBr disks with a Nicolet Nexus 670 FTIR spectrometer. Mass spectra were recorded on a HP 5989B MS spectrometer (70 eV). Elemental analyses were performed on a Vario-ELIII instrument. Compounds **1** were prepared using the method analogous to that for the preparation of benzyloxycarbonylamino-1-(1-benzotriazolyl)alkanes [8].

General procedure for the preparation of β,β-dicarbonyl benzotriazole derivatives 2. An oven-dried 50 mL flask was charged with samarium powder (0.03 g, 0.2 mmol), anhydrous THF (10 mL), and I_2 (0.076 g, 0.3 mmol). The mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. Then anhydrous CH_2Cl_2 (10 mL), 1,3-dicarbonyl compounds (1 mmol) and *N*-(1-benzotriazol-1-ylalky1)carbamate derivatives **1** (1 mmol) were added. The mixture was stirred under reflux until the disappearance of **1** was observed [reaction monitored by thin-layer chromatography (TLC)]. The reaction was quenched with aq. HCl (0.1*M*, 3 mL) and extracted with diethyl ether (3× 10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (5 mL), then with brine, and were dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by preparative TLC on silica gel using ethyl acetate/petroleum ether (1/4, v/v) as eluent to give the corresponding benzotriazole derivatives **2**.

General procedure for the preparation of 3. A mixture of **1** (1 mmol), active methylene compounds (1 mmol), and CH_3ONa (1 mmol) in THF (5 mL) was stirred until the disappearance of **1** (monitored by TLC). Then the reaction was quenched with H_2O and extracted with ethyl acetate (3× 10 mL). The combined organic extracts were washed with saturated Na_2CO_3, then with brine, and were dried over anhydrous Na_2SO_4, then filtrated and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel to give product **3**.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(phenyl) methylcarbamate (1a). White solid, mp 120–122°C (123–124°C) [8]. See Table 1, entry 1.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(4-methoxy-phenyl)-methylcarbamate (1b). White solid, mp 156–158°C. IR (KBr): 3414, 3193, 1715, 1546, 1400, 1252 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.4 Hz, 1H), 7.63–7.57 (m, 2H), 7.45–7.37 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 6.8 Hz, 2H), 6.50 (s, 1H), 3.77(s, 3H), 3.68 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.2, 156.0, 145.9, 132.5, 128.0, 127.8, 127.7, 124.3, 120.1, 114.4, 109.8, 67.1, 55.4., 52.9. Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.62; H, 5.15; N, 17.90. See Table 1, entry 2.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(p-tolyl)-methylcarbamate (1c). White solid, mp 154–157°C. IR (KBr): 3413, 3212, 1732, 1532, 1400, 1241 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 9.6 Hz, 1H), 7.58–7.36 (m, 4H), 7.15 (m, 4H), 6.35 (s, 1H), 3.71 (s, 3H), 2.32 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.1, 146.0, 139.4, 129.8, 127.8, 126.7, 126.2, 124.3, 120.1, 118.5, 109.8, 67.3, 52.5, 21.1. Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.62; H, 5.45; N, 18.94. See Table 1, entry 3.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(m-tolyl)-methylcarbamate (1d). White solid, mp 168–170°C. IR (KBr): 3337, 3131, 1702, 1530, 1400, 1234 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.0 Hz, 1H), 7.63–7.60 (m, 2H), 7.47–7.36 (m, 2H), 7.26–7.06 (m, 4H), 6.42 (s, 1H), 3.70 (s, 3H), 2.30 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.8, 145.9, 139.1, 130.1, 129.0, 127.9, 126.9, 126.7, 124.3, 123.3, 120.1, 118.5, 109.8, 66.9, 52.9, 21.4. Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.05; H, 5.42; N, 18.87. See Table 1, entry 4.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(o-tolyl-methylcarbamate (1e). White solid, mp 153–156°C. IR (KBr): 3290, 3133, 1718, 1531, 1400, 1246 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.50–7.27 (m, 3H), 7.26–7.14 (m, 4H), 6.39 (s, 1H), 3.70 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.9, 146.0, 135.8, 134.1, 132.4, 131.2, 129.5, 127.8, 126.7, 125.8, 124.3, 120.1, 109.8, 65.2, 53.0, 19.2. Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.98; H, 5.43; N, 18.96. See Table 1, entry 5.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(4-chloro-phenyl)-methylcarbamate (1f). White solid, mp 154–156°C. IR (KBr): 3295, 3023, 1718, 1549, 1400, 1250 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2H), 7.65 (s, 1H), 7.43–7.41 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.40 (s, 1H), 3.74 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.3, 145.5, 134.8, 132.4, 128.3, 127.8, 127.1, 124.5, 123.7, 118.6, 109.2, 73.0, 53.2. Anal. Calcd. for $C_{15}H_{13}ClN_4O_2$: C, 56.88; H, 4.14; N, 17.69. Found: C, 57.06; H, 4.13; N, 17.73. See Table 1, entry 6.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(4-bromo-phenyl)-methylcarbamate (1g). White solid, mp 158–160°C. IR (KBr): 3272, 3019, 1720, 1535, 1400, 1241 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89–7.87 (m, 2H), 7.65 (s, 1H), 7.47 (d, J = 8.4Hz, 2H), 7.42–7.40 (m, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6,45 (s,1H), 3.74 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.2, 144.3, 135.4, 132.2, 128.1, 127.8, 127.0, 124.5, 123.7, 118.5, 109.5, 73.6, 53.1. Anal. Calcd. for $C_{15}H_{13}BrN_4O_2$: C, 49.88; H, 3.63; N, 15.51. Found: C, 49.73; H, 3.64; N, 15.55. See Table 1, entry 7.

Methyl (1H-benzo[d][1,2,3]triazol-1-yl)(4-nitro-phenyl)methylcarbamate (1h). White solid, mp 147–150°C. IR (KBr): 3278, 3043, 1717, 1545, 1400, 1239 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 9.6 Hz, 1H), 7.66–7.42 (m, 5H), 6.61 (d, J = 9.6 Hz, 1H), 3.73 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.2, 147.6, 137.5, 134.1, 130.9, 128.5, 127.7, 124.8, 124.2, 120.3, 109.4, 66.1, 53.3. Anal. Calcd. for $C_{15}H_{13}N_5O_4$: C, 55.05; H, 4.00; N, 21.40. Found: C, 55.21; H, 4.01; N, 21.34. See Table 1, entry 8.

Ethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)-methyl)-3-oxobutanoate (2a). White solid, mp 137–139°C. IR (KBr): 3414, 1743, 1717, 1618, 1400 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.4 Hz, 1H), 7.48–7.45 (m, 3H), 7.42–7.40 (m, 1H), 7.30–7.28 (m, 4H), 6.43 (d, J = 11.2 Hz, 1H), 5.45 (d, J = 11.2 Hz, 1H), 4.06–4.03 (m, 2H), 2.40 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.2, 165.5, 146.1, 135.9, 132.9, 129.1, 129.0, 128.9, 127.9, 127.6, 124.3, 119.8, 109.9, 64.1, 62.1, 61.0, 30.3, 13.8. Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.78; H, 5.66; N, 12.43. MS (ES): *m/z* 337.9, ([M + Na]$^+$) (ES): ([M + Na]$^+$): 359.8. See Table 3, entry 1.

Methyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)-methyl)-3-oxobutanoate (2b). White solid, mp 103–106°C. IR (KBr): 3129, 1745, 1720, 1617, 1401 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.49–7.27 (m, 8H), 6.44 (d, *J* = 11.2 Hz, 1H), 5.46 (d, *J* = 11.2 Hz, 1H), 3.60 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.2, 165.9, 146.5, 136.0, 129.1, 129.0, 127.8, 127.7, 124.3, 119.9, 109.9, 63.9, 61.0, 53.0, 30.4.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.49–7.27 (m, 8H), 6.41 (d, *J* = 11.2 Hz, 1H), 5.46 (d, *J* = 11.2 Hz, 1H), 3.60 (s, 3H), 2.12 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.2, 166.4, 146.5, 135.7, 129.1, 129.0, 127.7, 127.6, 124.2, 119.8, 109.9, 109.7, 63.4, 61.2, 53.0, 31.9. Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.65; H, 5.31; N, 13.03. MS (ES): *m/z* 323.7, ($[M + Na]^+$) (ES): ($[M + Na]^+$): 345.7. See Table 3, entry 2.

3-((1H-Benzo[d][1,2,3]triazol-1-yl)(phenyl)methyl)-pentane-2,4-dione (2c). White solid, mp 146–148°C. IR (KBr): 3131, 1743, 1721, 1696, 1406 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 2 H), 7.50–7.47 (m, 2H), 7.36–7.30 (m, 5H), 6.72 (d, *J* = 11.6 Hz, 1H), 5.53 (d, *J* = 11.6 Hz, 1H), 2.23 (s, 3H), 2.09 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.6, 199.4, 144.3, 135.8, 129.3, 129.1, 127.7, 126.6, 118.2, 109.6, 72.9, 68.6, 30.8, 29.4. Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.46; H, 5.56; N, 13.65. MS (ES): *m/z* 307, ($[M + Na]^+$). (ES): ($[M + Na]^+$): 329.7. See Table 3, entry 3.

Diethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)-methyl)-malonate (2d). White solid, mp 105–108°C. IR (KBr): 3132, 1745, 1721, 1400 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.56–7.50 (m, 3H), 7.45–7.43 (m, 1H), 7.34–7.30 (m, 4H), 6.39 (d, *J* = 11.6 Hz, 1H), 5.17 (d, *J* = 11.6 Hz, 1H), 4.09–4.00 (m, 4H), 1.07 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3, 166.2, 146.1, 135.4, 133.0, 129.2, 128.9, 128.0, 127.6, 124.2, 120.0, 109.7, 62.2, 62.1, 61.6, 57.2, 13.8, 13.7. Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.61; H, 5.66; N, 11.45. MS (ESI): *m/z* 367.8, ($[M + Na]^+$) (ESI): 389.9. See Table 3, entry 4.

Methyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(4-meth-oxyphenyl)methyl)-3-oxobutanoate (2e). White solid, mp 102–104°C. IR (KBr): 3135, 1744, 1719, 1401 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.46–7.26 (m, 5H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 11.2 Hz, 1H), 5.42 (d, *J* = 11.2 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.4, 166.0, 159.9, 146.1, 132.8, 129.0, 127.9, 127.6, 124.3, 119.8, 114.2, 110.0, 64.0, 62.1, 55.2, 53.1, 30.5.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.46–7.26 (m, 5H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.34 (d, *J* = 11.2 Hz, 1H), 5.42 (d, *J* = 11.2 Hz, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 2.13 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.4, 166.5, 159.9, 145.9, 132.8, 129.1, 127.9, 127.6, 124.2, 119.8, 114.4, 109.8, 63.4, 60.7, 55.3, 53.0, 30.5. Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.88; H, 5.44; N, 11.87. MS (ES): *m/z* 352.9, ($[M + Na]^+$) (ES): 386.9. See Table 3, entry 5.

Ethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(p-tolyl)-methyl)-3-oxobutanoate (2f). White solid, mp 124–127°C. IR (KBr): 3130, 1743, 1717, 1400 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42–7.27 (m, 4H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.40 (d, *J* = 11.2 Hz, 1H), 5.43 (d, *J* = 11.2 Hz, 1H), 4.08–4.04 (m, 2 H), 2.40 (s, 3H), 2.27 (s, 3H), 1.10 (d, *J* = 11.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.4, 165.5, 138.9, 133.0, 129.5, 127.7, 127.6, 124.2, 119.8, 110.0, 64.1, 62.1, 60.8, 30.4, 21.1, 13.8. Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.54; H, 6.04; N, 12.01. MS (ES): *m/z* 353, ($[M + Na]^+$) (ESI): 389.9. See Table 3, entry 6.

Ethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(m-tolyl)-methyl)-3-oxobutanoate (2g). Colorless oil. IR (KBr): 3435, 1745, 1721, 1608 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.55–7.41 (m, 2H), 7.31–7.06 (m, 5H), 6.37 (d, *J* = 11.2 Hz, 1H), 5.44 (d, *J* = 11.2 Hz, 1H), 4.07–4.00 (m, 2H), 2.40 (s, 3H), 2.28 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.3, 165.5, 146.1, 138.7, 135.8, 132.9, 129.9, 128.7, 128.3, 127.6, 125.0, 124.2, 119.8, 109.9, 64.1, 62.1, 61.1, 30.3, 21.4, 13.8.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.55–7.41 (m, 2H), 7.31–7.06 (m, 5H), 6.35 (d, *J* = 11.2 Hz, 1H), 5.44 (d, *J* = 11.2 Hz, 1H), 4.07–4.00 (m, 2H), 2.28 (s, 3H), 2.15 (s, 3H), 1.03 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.2, 165.8, 145.9, 138.9, 135.7, 129.8, 128.9, 128.3, 127.6, 125.0, 124.2, 119.8, 109.7, 63.8, 62.1, 60.9, 31.8, 21.3, 13.7. Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.45; H, 6.01; N, 11.98. MS (ES): *m/z* 351.9, ($[M + Na]^+$) (ESI): 373.8. See Table 3, entry 7.

Methyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(m-tolyl)-methyl)-3-oxobutanoate (2h). White solid, mp 122–125°C. IR (KBr): 3130, 1748, 1717, 1400 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02–8.00 (m, 1H), 7.55–7.39 (m, 2H), 7.32–7.16 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.43–6.36 (m, 1H), 5.45 (d, *J* = 11.2 Hz, 1H), 3.62 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.2, 166.0, 146.1, 138.8, 135.9, 129.9, 128.7, 128.1, 127.6, 124.9, 124.3, 119.8, 110.0, 63.9, 61.0, 53.0, 30.5, 21.4.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00–8.02 (m, 1H), 7.55–7.39 (m, 2H), 7.32–7.16 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.43–6.36 (m, 1H), 5.45 (d, *J* = 11.2 Hz, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.3, 166.5, 146.1, 139.0, 135.6, 130.0, 129.0, 128.3, 128.1, 127.6, 124.9, 124.2, 119.8, 109.8, 63.4, 61.2, 52.9, 31.9, 21.4. Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.80; H, 5.67; N, 12.44. MS (ES): *m/z* 337.9, ($[M + Na]^+$) (ESI): 359.7. See Table 3, entry 8.

Methyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(o-tolyl)-methyl)-3-oxobutanoate (2i). White solid, mp 98–101°C. IR (KBr): 3434, 1745, 1720, 1450 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.8 Hz, 1H), 7.53–7.30 (m, 4H), 7.18–7.15 (m, 3H), 6.75 (d, *J* = 11.2 Hz, 1H), 5.51 (d, *J* = 11.2 Hz, 1H), 3.56 (s, 3H), 2.64 (s, 3H), 2.38 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.3, 166.0, 146.0, 136.2, 133.9, 132.8, 131.0, 129.0, 127.9, 127.6, 126.9, 124.2, 119.9, 109.8, 63.9, 56.5, 52.9, 30.4, 19.7.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.8 Hz, 1H), 7.53–7.30 (m, 4H), 7.18–7.15 (m, 3H), 6.70 (d, *J* = 11.2 Hz, 1H), 5.50 (d, *J* = 11.2 Hz, 1H), 3.58 (s, 3H), 2.63 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.1, 166.7, 146.0, 136.2, 134.0, 132.7, 131.2, 129.0, 127.9, 127.6, 127.0, 124.2, 119.9, 109.6, 63.2, 56.5, 53.0, 32.0, 19.8. Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.53; H, 5.69; N, 12.45. MS (ES): *m/z* 337.8, ($[M + Na]^+$) (ES): 359.8. See Table 3, entry 9.

Diethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(o-tolyl)-methyl)-malonate (2j). Colorless oil. IR (KBr): 3440, 1748, 1716, 1400 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.53–7.31 (m, 3H), 7.17–7.02 (m, 3H), 6.73 (d, J = 10.0 Hz, 1H), 5.19 (d, J = 10.0 Hz, 1H), 4.14–3.69 (m, 4H), 2.49 (s, 3H), 1.04–0.97 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.6, 166.1, 145.8, 136.2, 133.6, 133.0, 130.9, 129.0, 128.3, 127.6, 126.8, 124.1, 119.9, 109.7, 62.2, 62.0, 57.2, 57.1, 19.8, 13.9, 13.6. Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02; Found: C, 66.40; H, 6.06; N, 11.00. MS (ES): *m/z* 381.8, ($[M + Na]^+$) (ESI): 404.0. See Table 3, entry 10.

Ethyl 2-((4-bromophenyl)(methoxycarbonyl)methyl)-3-oxobutanoate (3a). IR (KBr): 3306, 1749, 1716, 1694 cm^{-1}; Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.19–7.16 (m, 2H), 6.15 (m, 1H), 5.40 (m, 1H), 4.17–4.04 (m, 2H), 4.00 (m, 1H), 3.63 (s, 3H), 2.16 (s, 3H), 1.20–1.13 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.9, 167.8, 156.5, 138.7, 131.8, 128.0, 121.8, 63.9, 62.0, 53.9, 52.5, 29.0, 13.9.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.19–7.16 (m, 2H), 6.40 (m, 1H), 5.52 (m, 1H), 4.17–4.04 (m, 2H), 3.93 (m, 1H), 3.62 (s, 3H), 2.30 (s, 3H), 1.20–1.13 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.2, 166.5, 156.5, 138.7, 131.8, 128.4, 121.8, 62.8, 61.8, 53.9, 52.4, 29.0, 13.9. Anal. Calcd. for $C_{15}H_{17}BrO_5$: C, 50.44; H, 4.80; Found: C, 50.61; H, 4.79. See Table 4, entry 1.

Ethyl 2-((methoxycarbonyl)(4-methoxyphenyl)-methyl)-3-oxobutanoate (3b). IR (KBr): 3316, 1744, 1713, 1697 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2H), 6.85–6.82 (m, 2H), 6.10 (d, J = 0.8 Hz, 1H), 5.38 (m, 1H), 4.13–4.06 (m, 2H), 4.00 (d, J = 0.8 Hz, 1H), 3.77 (s, 3 H), 3.65 (s, 3H), 2.30 (s, 3H), 1.19–1.14 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.9, 167.5, 159.0, 156.5, 131.6, 127.4, 114.0, 63.4, 61.8, 55.2, 53.9, 52.4, 28.8, 13.9.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H), 6.85–6.82 (m, 2H), 6.30 (m, 1H), 5.50 (s, 1H), 4.13–4.06 (m, 2H), 3.90 (m, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 2.17 (s, 3H), 1.19–1.14 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.9, 169.0, 159.0, 156.5, 131.5, 127.4, 114.0, 64.3, 61.6, 55.2, 53.9, 52.4, 28.8, 13.9. Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; Found: C, 62.25; H, 6.55. See Table 4, entry 2.

Ethyl 2-((methoxycarbonyl)(o-tolyl)methyl)-3-oxobutanoate (3c). IR (KBr): 3334, 1740, 1717, 1692 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23–7.12 (m, 4H), 6.06 (d, J = 9.2, 1H), 5.68 (m, 1H), 4.12–4.04 (m, 2H), 3.97 (d, J = 7.6 Hz, 1H), 3.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.8, 167.1, 156.2, 137.8, 134.8, 130.8, 127.8, 126.4, 125.6, 62.8, 61.7, 52.3, 50.7, 29.0, 19.3, 13.8.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24–7.13 (m, 4H), 6.49 (m, 1H), 5.68 (m, 1H), 4.12–4.04 (m, 2H), 3.84 (d, J = 5.2 Hz, 1H), 3.60 (s, 3H), 2.49 (s, 3H), 2.26 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5, 167.1, 156.2, 137.7, 134.8, 130.8, 127.8, 126.4, 126.0, 62.9, 61.6, 52.3, 50.1, 30.2, 19.2, 13.9. Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90; Found: C, 65.90; H, 6.88. See Table 4, entry 3.

Ethyl 2-((methoxycarbonyl)(m-tolyl)methyl)-3-oxobutanoate (3d). IR (KBr): 3339, 1745, 1716, 1701 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.17–7.04 (m, 4H), 6.18 (s, 1H), 5.40 (s, 1H), 4.09–4.01 (m, 3H), 3.62 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 1.15–1.09 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.1, 167.2, 156.3, 139.3, 138.3, 128.6, 127.0, 123.5, 123.2, 63.4, 61.8, 54.4, 52.3, 29.0, 21.4, 13.9.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.17–7.04 (m, 4H), 6.40 (s, 1H), 5.54 (s, 1H), 4.09–4.01 (m, 3H), 3.60 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 1.15–1.09 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.2, 168.3, 156.3, 139.4, 138.3, 128.5, 127.3, 123.5, 123.2, 64.2, 61.5, 53.3, 52.2, 30.4, 21.4, 13.9. Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90; Found: C, 65.85; H, 6.91. See Table 4, entry 4.

Ethyl 2-((methoxycarbonyl)(4-nitrophenyl)methyl)-3-oxobutanoate (3e). IR (KBr): 3349, 1732, 1715, 1698 cm^{-1}. Major: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17–8.13 (m, 2H), 7.51–7.48 (m, 2H), 6.33 (d, J = 0.8 Hz, 1H), 5.50 (m, 1H), 4.14–4.01 (m, 3H), 3.63 (s, 3H), 2.32 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.3, 167.8, 166.5, 156.4, 147.4, 147.0, 127.7, 123.9, 63.4, 62.4, 53.8, 52.9, 30.7, 13.9.

Minor: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17–8.13 (m, 2H), 7.51–7.48 (m, 2H), 6.50 (m, 1H), 5.60 (m, 1H), 4.14–4.01 (m, 3H), 3.61 (s, 3H), 2.17 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.5, 167.8, 166.5, 156.4, 147.3, 146.8, 127.4, 123.8, 63.4, 62.3, 53.8, 52.6, 29.0, 13.9. Anal. Calcd. for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33; Found: C, 55.82; H, 5.29; N, 4.34. See Table 4, entry 5.

Diethyl 2-((methoxycarbonyl)(4-nitrophenyl)-methyl)-malonate (3f). IR (KBr): 3358, 1715, 1710, 1700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.5 (m, 1H), 5.6 (m, 1H), 4.21–4.03 (m, 4H), 3.90 (m, 1H), 3.64 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.5, 166.4, 156.6, 147.5, 146.7, 127.5, 123.8, 62.3, 62.0, 56.2, 53.6, 52.5, 13.9, 13.8. Anal. Calcd. for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96; Found: C, 54.29; H, 5.43; N, 3.95. See Table 4, entry 6.

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The Formation of 3-Ferrocenylpyrazole-4-Carboxylates and Alkylhydrazine Insertion Products from α-Ferrocenylmethylidene-β-Oxocarboxylates

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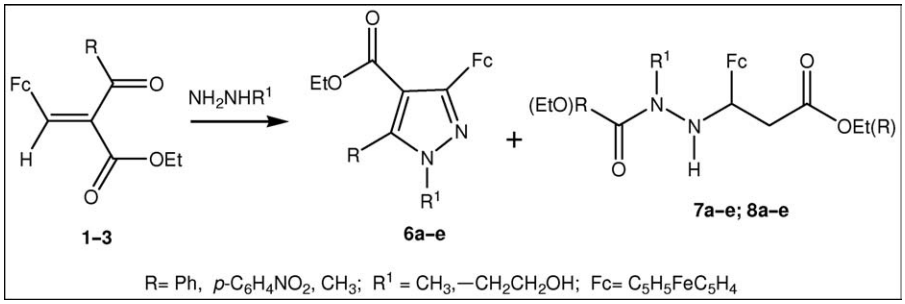

The reactions of α-ferrocenylmethylidene-β-oxocarboxylates (**1**, **2**, **3a**, and **3b**) with *N*-methyl- and *N*-(2-hydroxyethyl)hydrazines (**5a**, **5b**) afford ethyl 1-alkyl-5-aryl(methyl)-3-ferrocenylpyrazole-4-carboxylates (**6a–e**) (∼50%) and *N*-alkylhydrazine insertion products, *viz*., ethyl (*N*′-acyl-*N*′-alkylhydrazino)-3-ferrocenylpropanoates (**7a–e**) (∼20%) and 1-acyl-2-(*N*′-alkyl-*N*′-ethoxycarbonylhydrazino)-2-ferrocenylethanes (**8a–e**) (∼10%). The structures of the compounds obtained were established based on the spectroscopic data and X-ray diffraction analysis (for pyrazoles **6a** and **6b**).

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INTRODUCTION

Recently, we have reported [1] that the reactions of 2-ferrocenylmethylidene-1,3-diketones with *N*-methylhydrazine afford insertion products, *viz*., 1-(*N*′-acyl-*N*′-methylhydrazino)-2-acyl-1-ferrocenylethanes (∼40–58%), together with small amounts of fragmentation products with the loss of one acyl group rather than the expected ferrocenylpyrazole derivatives (Scheme 1).

This type of the insertion reactions was described for the first time despite the fact that it is the reactions of 1,3-dicarbonyl compounds with hydrazines that underlie the classic version of the synthesis of pyrazole derivatives. Numerous pyrazoles, including those with high-biological activities [2–18], have been synthesized by this reaction. In the case of ferrocenylpyrazoles, the respective α,β-unsaturated ketones (chalcones) are the most accessible starting compounds. Their reactions with hydrazines afford unstable 4,5-dihydropyrazoles whose mild oxidation, e.g., with arenecarbaldehydes, result in mono- and poly-cyclic ferrocenylpyrazoles [19,20]. A drawback of this approach is the impossibility of ring functionalization, e.g., with carboxylate groups.

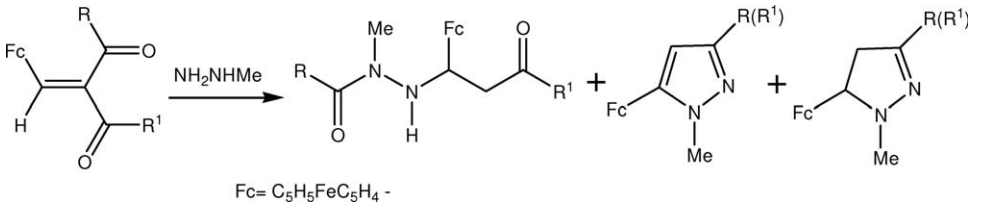
In our opinion, α-ferrocenylmethylidene-β-oxocarboxylates might serve as useful starting compounds for the synthesis of ferrocenylpyrazolecarboxylates provided: (i) it is the enone fragments that react preferentially with hydrazines, (ii) the —COOR group is retained in these reactions, (iii) the formation of the hydrazine insertion products is reduced to minimum or they are absent at all, and (iv) fragmentation of the starting 1,3-dicarbonyl compounds under the action of hydrazines is suppressed.

The goal of this work is the detailed analysis of reactions of α-ferrocenylmethylidene-β-oxocarboxylates with *N*-methyl- and *N*-(2-hydroxyethyl)hydrazines aimed at elucidating the possibility of their use in the synthesis of alkyl ferrocenylpyrazolecarboxylates.

RESULTS AND DISCUSSION

The starting α-ferrocenylmethylidene-β-oxocarboxylates (**1, 2, 3a**, and **3b**) were prepared by coupling of

Scheme 1



ferrrocenecarbaldehyde with ethyl benzoylacetate (**4a**), ethyl (*p*-nitrobenzoyl)acetate (**4b**), and ethyl acetoacetate (**4c**) [21–23] (Scheme 2).

The structure of ethyl 2-ferrocenylmethylidene-2-(*p*-nitrobenzoyl)acetate (**2**) was established based on the data from mass spectrometry, elemental analysis, and ^{1}H-NMR spectroscopy. According to the NMR data, compound **2** is formed as a single geometric isomer. Its ^{1}H-NMR spectrum contains characteristic signals for the protons for one ferrocene residue, one aryl and one ethyl group, and one singlet for the olefinic proton. *E*-configuration was assigned to this compound by analogy with ethyl *E*-2-ferrocenylmethylidene-2-benzoylacetate (**1**) [22]. Ethyl 2-(ferrocenylmethylidene)acetoacetates were obtained as two (*E*- and *Z*-) geometric isomers, **3a** and **3b** [21], in a ~2:1 ratio (^{1}H-NMR data) and separated by column chromatography on alumina.

The starting compounds **1**, **2**, **3a**, and **3b**, unlike 2-ferrocenylmethylidene-1,3-diketones [1], react with *N*-alkylhydrazines **5a,b** at ambient temperature to yield ethyl 1-alkyl-5-aryl(methyl)-3-ferrocenylpyrazole-4-carboxylates (**6a–e**) (~50%) and the insertion products, *viz*., ethyl (*N*′-acyl-*N*′-alkylhydrazino)-3-ferrocenylpropanoates (**7a–e**) (~20%) and 1-acyl-2-(*N*′-alkyl-*N*′-ethoxycarbonylhydrazino)-2-ferrocenylethanes (**8a–e**) (~10%) (Scheme 3).

The configuration of compounds **3a,b** (*E*- or *Z*-) did not virtually affect the yields of pyrazole **6e** and the insertion products **7e** and **8e** (~2:1, ^{1}H-NMR data).

In addition, fragmentation products were also isolated from the reaction mixtures, *viz*., ethyl *trans*-3-ferrocenylacrylate (**9**, 5–7%) and carbohydrazides **10a–e** (~5%). All the compounds synthesized (**6–10**) were separated by column chromatography on alumina and isolated in the individual state.

3-Ferrocenylpyrazole-4-carboxylates **6a–e** are storage-stable yellow crystalline substances. Their ^{1}H-NMR spectra contain characteristic signals for the protons of ferrocenyl, aryl, ethyl, and *N*-methyl/*N*-(2-hydroxyethyl) groups. The presence in the ^{13}C-NMR spectra of the required quantity of signals for the carbon atoms bearing no protons, methyl, methylene, and methine groups, and carbon atoms of the aryl and ferrocenyl substituents additionally corroborate their structures. A characteristic feature of the ^{13}C-NMR spectra of pyrazoles **6a–e** is the high-field position of the signals for C_{ipsoFc} ($\delta \sim 75$ ppm) as compared with those of the insertion products **7a–e** and **8a–e** ($\delta \sim 83$–87 ppm).

The spatial structures of compounds **6a** and **6b** were also determined by X-ray diffraction analysis of single crystals obtained by crystallization from dichloromethane–hexane (1:1). The general view of the molecules **6a** and **6b** are given in Figure 1(a,b) and their principal characteristics are listed in Table 1. These require no special comments.

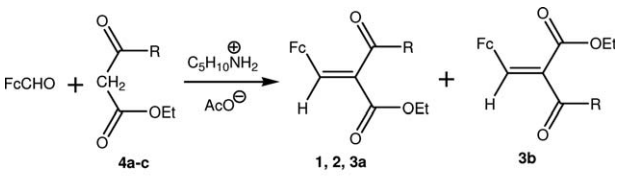
The structures of compounds **7a–e** and **8a–e** were elucidated based on spectroscopic data (IR, ^{1}H- and ^{13}C-NMR, mass spectrometry) and elemental analysis.

The ^{1}H-NMR spectra of these compounds contain characteristic ABM signals for the protons of the —CH_2—CH— fragment, singlets and triplets of the signals for the CH_3 groups, singlets for the protons of the NH and OH groups (**7b**,**d**,**e**; **8b**,**d**,**e**), and signals for the protons of the ferrocenyl, aryl, and methylene fragments. The ^{13}C-NMR spectra of compounds **7a–e** and **8a–e** contain the signals for the carbon atoms of the C=O and —COOEt groups, one ferrocene fragment with one signal for C_{ipsoFc}, and the corresponding amount of signals for the Me, Ar, CH_2, and CH groups.

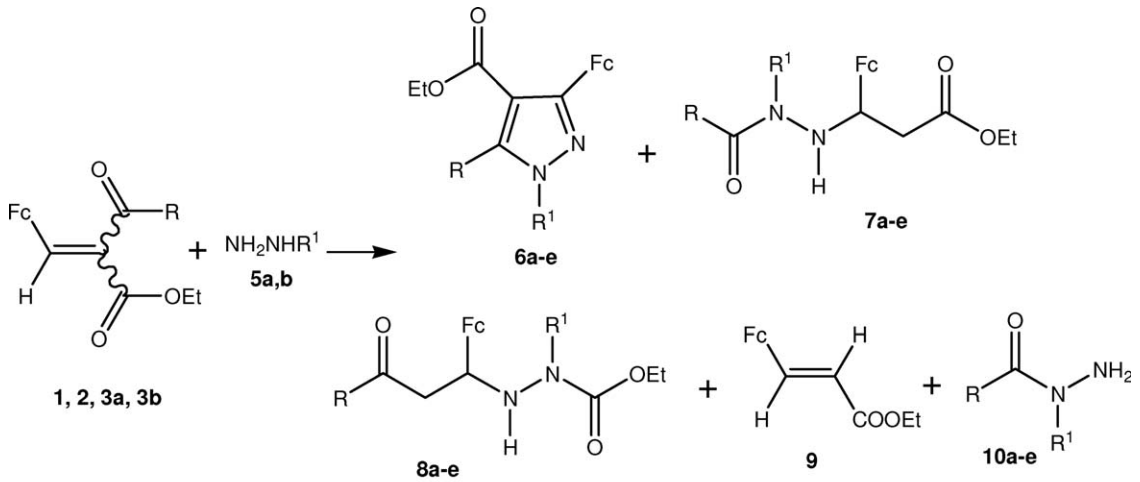
The assignment of the isomeric insertion products to either **7** or **8** type is based on the data from ^{1}H-NMR spectroscopy including 1D NOE experiments that have revealed the —COOEt group either to be (compounds **7a–e**), or not to be (compounds **8a–e**), adjacent to the —CH_2—CH— fragments.

Thus, the results obtained demonstrate that the reactions of α-ferrocenylmethylidene-β-oxocarboxylates with *N*-alkylhydrazines proceed in several pathways leading to (i) formation of tetrasubstituted pyrazoles **6a–e**, (ii) insertion of *N*-alkylhydrazines into the molecules of the

Scheme 2



Scheme 3



R= Ph, R^1 = CH_3 (**1, 5a, 6a-8a, 10a**)
R= Ph, R^1 = -CH_2CH_2OH (**1, 5b, 6b-8b, 10b**)
R= *p*-$C_6H_4NO_2$, R^1 = CH_3 (**2, 5a, 6c-8c, 10c**)
R= *p*-$C_6H_4NO_2$, R^1 = -CH_2CH_2OH (**2, 5b, 6d-8d, 10d**)
R= CH_3, R^1 = -CH_2CH_2OH (**3a, 3b, 5b, 6e-8e, 10e**)

starting compounds, and (iii) *N*-alkylhydrazine-induced fragmentation of the 1,3-dicarbonyl compounds **1–3**. In neither case, the reaction of alkylhydrazines with the β-oxocarboxylate system, which would result in (ferrocenylmethylidene)pyrazolones, took place. A putative mechanism of the formation of pyrazoles is presented in Scheme 4.

The two nucleophilic sites of *N*-alkylhydrazines attack simultaneously or sequentially the carbon atoms in positions 2 and 4 of the chalcone system C═C─C═O of the starting compounds **1–3** to afford hydroxypyrazolidine intermediates **11a–e**. Their intramolecular transformations including dehydration to dihydropyrazoles **12a–e** and oxidative dehydrogenation under the reaction conditions result ultimately in pyrazoles **6a–e**.

The oxidative dehydrogenation of ferrocene derivatives has been observed by us earlier. Thus, the Diels–Alder adducts of diferrocenylbuta-1,3-dienes to *N*-phenylmaleimide smoothly produce *N*-phenyl(diferrocenyl)phthalimides [24]. The formation of the insertion products **7a–e** and **8a–e** is presented in Scheme 5.

In our opinion, the reaction starts from the nucleophilic addition of the free amino group of the *N*-alkylhydrazine to the activated double bond Fc─CH═C of the 1,3-dicarbonyl compounds **1–3** (the Michael addition) leading to intermediates **13a–e**. Subsequent nucleophilic attack by the ─NHR^1 fragment on the carbon atoms of the carbonyl and carboxylate groups is accompanied by fragmentation of intermediates **13a–e** leading ultimately to the insertion products **7a–e** and **8a–e** *via* enols **14a–e** and **15a–e**, respectively. The formation of ethyl *trans*-3-ferrocenylacrylate **9** and carbohydrazides **10a–e** can be explained by the standard base-induced fragmentation of the starting β-oxocarboxylates (Scheme 6).

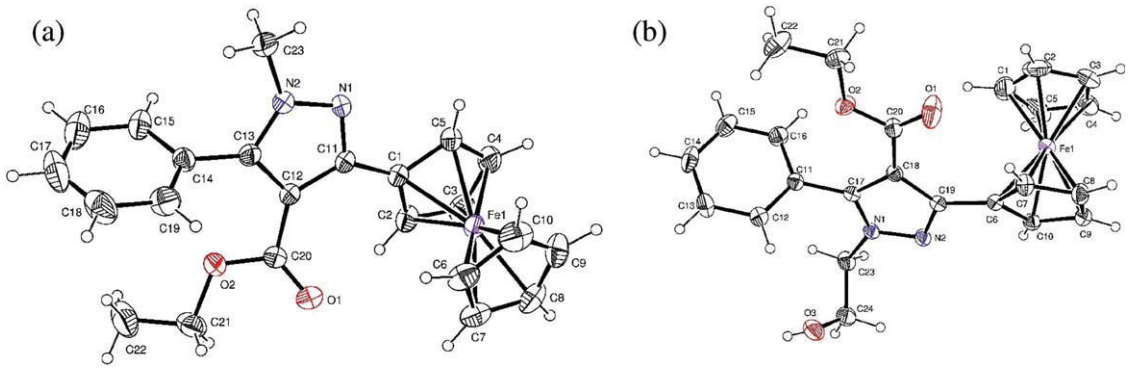


Figure 1. (a) Crystal structure of **6a** and (b) crystal structure of **6b**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Selected bond lengths and bond angles for compounds **6a** and **6b**.

Bond lengths (Å)		Bond angles (°)	
6a			
N(1)—N(2)	1.367(5)	C(11)—N(1)—N(2)	105.6(3)
N(1)—C(11)	1.311(5)	C(13)—N(2)—N(1)	113.4 (3)
N(2)—C(13)	1.361(5)	N(1)—N(2)—C(23)	118.6(3)
C(11)—C(12)	1.426(6)	N(2)—C(13)—C(12)	104.5(3)
C(12)—C(13)	1.402(6)	C(13)—C(12)—C(11)	106.3(4)
C(13)—C(14)	1.481(5)	C(1)—C(11)—N(1)	117.5(4)
C(11)—C(1)	1.457(6)	N(1)—C(11)—C(12)	110.0(4)
C(12)—C(20)	1.475(6)	C(14)—C(13)—C(12)	134.0(4)
C(23)—N(2)	1.452(5)	C(13)—C(12)—C(20)	124.1(4)
C(20)—O(1)	1.193(6)	O(1)—C(20)—C(12)	127.3(4)
6b			
N(1)—N(2)	1.3625(17)	C(17)—N(1)—N(2)	112.85(12)
N(1)—C(17)	1.3416(19)	C(23)—N(1)—N(2)	117.31(12)
N(2)—C(19)	1.3236(19)	N(1)—N(2)—C(19)	105.63(12)
C(19)—C(18)	1.425(2)	N(2)—C(13)—C(12)	104.5(3)
C(18)—C(17)	1.400(2)	N(2)—C(19)—C(6)	116.32(13)
C(19)—C(6)	1.475(2)	C(17)—C(18)—C(19)	104.92(13)
C(18)—C(20)	1.461(2)	N(2)—C(19)—C(18)	110.53(13)
C(17)—C(11)	1.483(2)	C(18)—C(17)—N(1)	106.06(13)
C(23)—N(1)	1.459(2)	N(2)—N(1)—C(23)	117.31(12)
C(20)—O(1)	1.195(2)	O(1)—C(20)—C(18)	125.10(15)

The high regioselectivity of all the reactions of α-ferrocenylmethylidene-β-oxocarboxylates with *N*-alkylhydrazines is noteworthy. This is connected with the uniqueness of the attacks by two nucleophilic sites: in all cases, the NH_2 group adds to the FcCH=C double bond of the starting compounds, whereas the —NHR group attacks one of the carbonyl groups.

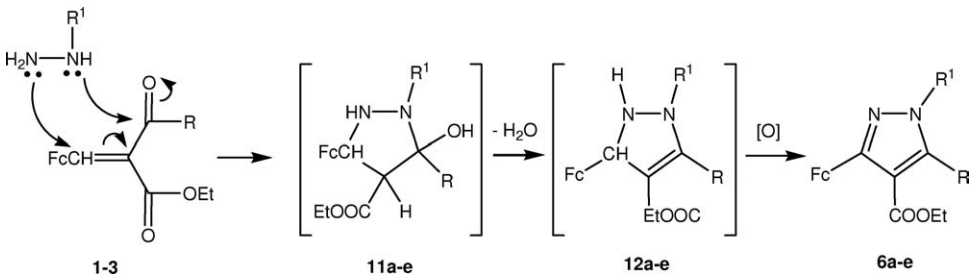
The one-step synthesis of tetrasubstituted functionalized ferrocenylpyrazoles based on the reaction of α-ferrocenylmethylidene-β-oxocarboxylates with *N*-alkylhydrazines is described for the first time. These compounds are of interest as potential building blocks for the preparation of diverse pyrazolecarboxylates and of the insertion products, *viz*., β-ferrocenyl-β-hydrazinopropionates and (ethoxycarbonyl)hydrazino-substituted ferrocene derivatives. The synthetic potential of this type of reactions, applied to arylmethylidene analogs as well, deserves indisputably more detailed studies.

EXPERIMENTAL

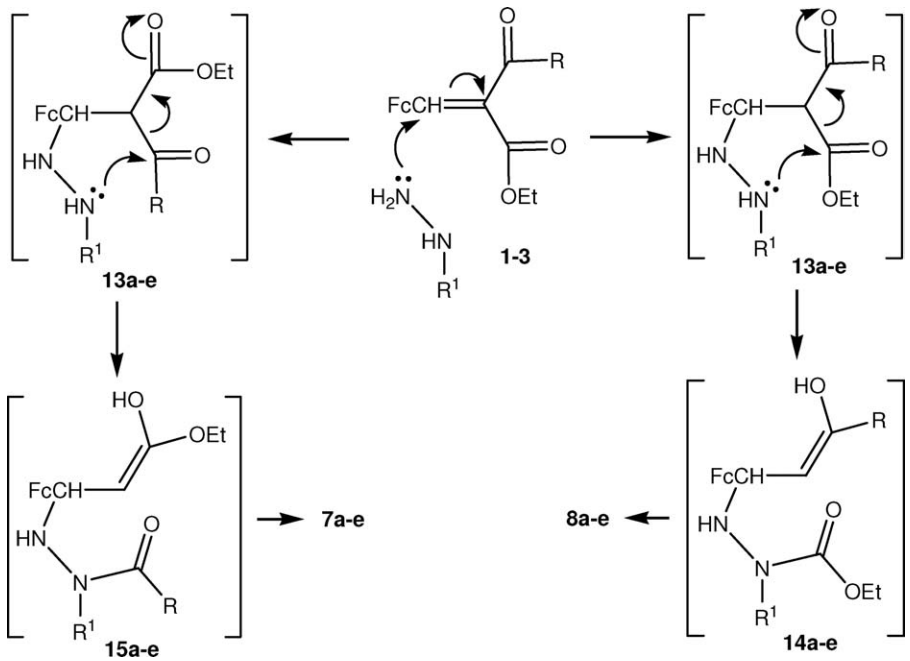
All the solvents were dried according to the standard procedures and were freshly distilled before use [25]. Column chromatography was carried out on alumina (Brockmann activity III). The ^{1}H- and ^{13}C-NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz) for solutions in $CDCl_3$, with Me_4Si as the internal standard. The IR spectra were measured with an FTIR spectrophotometer (Spectrum RXI Perkin-Elmer instruments) using KBr pellets. The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV). Elementar Analysensysteme LECO CHNS-900 was used for elemental analyses. The following reagents were purchased from Aldrich: ferrocenecarbaldehyde, 99%; ethyl acetoacetate, 99+%; ethyl benzoylacetate, 90%; ethyl *p*-nitrobenzoylacetate, %; *N*-methylhydrazine, 98%; *N*-(2-hydroxyethyl)hydrazine, tech. 90%. Ethyl (***E***)-2-ferrocenylmethylidene(-benzoyl)acetate (**1**) and -(*p*-nitrobenzoyl)acetate (**2**), ethyl ***E***- and ***Z***-2-ferrocenylmethylideneacetoacetates (**3a**) and (**3b**) were prepared by condensation of ferrocenecarbaldehyde with ethyl benzoyl-, *p*-nitrobenzoyl-, and acetoacetates **4a–c**, respectively, in benzene in the presence of piperidinium acetate [20,21,26,27]. The physical and ^{1}H-NMR spectroscopic characteristics of compounds **1**, **3a**, and **3b** were in accord with the literature data [20,21,26,27].

Condensation of ferrocenecarboxaldehyde with ethyl *p*-nitrobenzoylacetate (4b). A mixture of FcCHO (2.15 g, 10 mmol), ethyl *p*-nitrobenzoylacetate (**4b**) (3.55 g, 15 mmol), piperidine (0.5 mL), pyridine (0.5 mL), and AcOH (1 mL) in dry benzene (100 mL) was refluxed for 12 h. The reaction mixture was washed with 5% HCl to remove the amines and the organic layer was concentrated to dryness. Diethyl ether (100 mL) was added to the residue, the precipitate was filtered off and dried on a filter to give ethyl (*E*)-2-ferrocenylmethylidene(*p*-nitrobenzoyl)acetate **2**, yield 5.33 g (81.2%), violet powder, m.p. 162–164°C. Subsequent chromatography on Al_2O_3 (hexane/dichloromethane, 4:1) gave 4.94 g (76%) of compound **2**, violet crystals, m.p. 168–169°C; ir: 818, 845, 1102 (Fc); 1478, 1543, 1663, (C=C, =CH—, —NO_2); 1690, 1716 (C=O, COOEt); 3030 (C—H) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.16 (t, 3H, J = 7.2 Hz, CH_3), 4.17 (q, 2H, J = 7.2 Hz, CH_2), 4.20 (s, 5H, C_5H_5), 4.25 (m, 2H, C_5H_4), 4.39 (m, 2H, C_5H_4), 7.87 (s, 1H, CH=), 8.10 (d, 2H, J = 9.0 Hz, C_6H_4), 8.31 (d, 2H, J = 9.0 Hz, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.13 (CH_3), 61.15 (CH_2), 70.95, 71.81 (C_5H_4), 69.89 (C_5H_5), 79.16 (C_{ipso}Fc), 126.54, 131.07 (C_6H_4), 136.21 (CH=), 129.14, 139.78, 148.74 (3C), 165.06, 194.32 (2C=O) ppm; ms: *m*/*z* 433 (M^+). Anal. Calcd. for $C_{22}H_{19}FeNO_5$: C, 60.99; H, 4.42; Fe, 12.99; N, 3.23. Found: C, 61.04; H, 4.38; Fe, 13.02; N, 3.37.

Scheme 4



Scheme 5



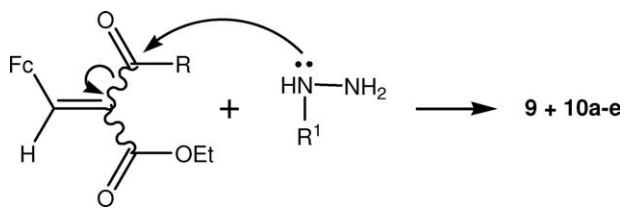
Reactions of α-ferrocenylmethylidene-β-oxocarboxylates 1, 2, 3a, and 3b with *N*-alkylhydrazines (5a,b). A mixture of the 1,3-dicarbonyl compound (10 mmol) and *N*-alkylhydrazine (20 mmol) in ethanol (50 mL) was stirred for 10 h at ambient temperature and then water (200 mL) was added to the yellow-brown reaction mixture. The oily residue was separated from the aqueous layer by decantation and dissolved in dichloromethane (50 mL). The solution was mixed with Al_2O_3 (activity III) (20 g) and the solvent was evaporated in air. This sorbent was applied onto a column with Al_2O_3 (the height of alumina is about 30 cm) and the reaction products were eluted from the column first with petroleum ether and then with a 1:6 ethyl acetate—petroleum ether solvent system. The elution order is as follows: (i) ethyl *E*-3-ferrocenylacrylate (**9**) [28,29]; (ii) carbohydrazides **10a** [30,31], **10b** [32], **10c** [33], **10d** [34], **10e** [35]; (iii) the insertion products **7a–e**; (iv) the insertion products **8a–e**; and (v) pyrazoles **6a–e**.

Ethyl 3-ferrocenyl-1-methyl-5-phenylpyrazole-4-carboxylate (6a). Yield 2.24 g (54%), yellow crystals, mp 187–188°C; ir: 820, 1001, 1027, 1105, 1164 (Fc); 1434, 1473, 1529, 1661 (C═C, ═CH─, C═N); 1684, 1712 (C═O, COOEt); 2878, 2922, 2913,3090 (C─H) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.95 (t, 3H, J = 7.2 Hz, CH_3), 3.68 (s, 3H, CH_3), 4.05 (q, 2H, J = 7.2 Hz, CH_2), 4.13 (s, 5H, C_5H_5), 4.30 (m, 2H, C_5H_4), 5.01 (m, 2H, C_5H_4), 7.35 (m, 2H, C_6H_5), 7.46 (m, 3H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.64, 37.12 (2 CH_3), 59.75 (CH_2), 69.46 (C_5H_5), 68.59, 69.11 (C_5H_4), 110.80 (C_{ipso} Fc), 128.15, 128.92, 129.65 (C_6H_5), 130.31 (C_{ipso}), 128.60, 146.67, 150.48 (3C), 163.74 (C═O) ppm; ms: *m/z* 414 (M^+). Anal. Calcd. For $C_{23}H_{22}FeN_2O_2$: C, 66.68; H, 5.36; Fe, 13.48; N, 6.76. Found C, 66.74; H, 5.27; Fe, 13.51; N, 6.63.

Ethyl 3-(*N*′-benzoyl-*N*′-methylhydrazino)-3-ferrocenylpropanoate (7a). Yield 0.84 g (20%), yellow powder, mp 193–194°C; ir: 818, 1002, 1012, 1053, 1061, 1101, 1149 (Fc); 1241, 1302, 1369 (NH); 1460, 1520, 1601 (C═C); 1657 (─N─C═O); 1713 (COOEt); 2921, 2961, 3053 (C─H), 3319 (NH) cm^{-1}; ^{1}H-NMR (300 $CDCl_3$): δ 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.52 (s, 3H, CH_3), 2.92 (dd, 1H, J = 9.0, 16.2 Hz, CH_2), 3.05 (dd, 1H, J = 3.3, 16.2 Hz, CH_2), 4.35 (dd, 1H, J = 3.3, 9.0 Hz, CH), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 4.17 (s, 5H, C_5H_5), 4.11 (m, 2H, C_5H_4), 4.28 (m, 2H, C_5H_4), 6.55 (bs, 1H, NH), 7.40 (m, 3H, C_6H_5), 7.64 (m, 2H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.17, 38.14 (2CH_3), 43.28, 60.86 (2CH_2), 62.05 (CH), 68.91 (C_5H_5), 66.66, 68.39, 68.72, 69.94 (C_5H_4), 82.63 (C_{ipso} Fc), 126.89, 128.52, 131.49 (C_6H_5), 133.76 (C_{ipso}), 165.42, 172.17 (2C═O) ppm; ms: *m/z* 434 (M^+). Anal. Calcd. for $C_{23}H_{26}FeN_2O_3$: C, 63.61; H, 6.03; Fe, 12.86; N, 6.45. Found: C, 63.56; H, 5.89; Fe, 12.74; N, 6.32.

1-Benzoyl-2-(*N*′-ethoxycarbonyl-*N*′-methylhydrazino)-2-ferrocenylethane (8a). Yield 0.39 g (9%), yellow powder, mp 203–204°C; ir: 820, 1003, 1015, 1064, 1103, 1162(Fc); 1477, 1520, 1610 (C═C); 1661, 1713 (PhC═O, N─COOEt); 2921, 2933, 3029 (C─H); 3321 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7.2 Hz, CH_3), 2.83 (m, 1H, CH_2), 2.90 (m, 1H, CH_2), 3.00 (s, 3H, CH_3), 4.40 (m, 1H, CH), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 4.15 (s, 5H, C_5H_5), 4.18 (m, 2H, C_5H_4), 4.22 (m, 2H, C_5H_4), 6.17 (bs, 1H, NH), 7.38–7.42 (m, 5H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.9, 39.46 (2CH_3), 40.65, 53.36 (2CH_2), 60.45 (CH), 68.33 (C_5H_5), 66.20, 67.58, 67.63, 67.87 (C_5H_4), 87.80 (C_{ipso} Fc), 127.30, 127.98, 129.88 (C_6H_5), 134.91 (C_{ipso}), 170.48,

Scheme 6



171.68 (2C=O) ppm; ms: *m*/*z* 434 (M^+). Anal. Calcd. for $C_{23}H_{26}FeN_2O_3$: C, 63.61; H, 6.03; Fe, 12.86; N, 6.45. Found: C, 63.72; H, 6.07; Fe, 12.71; N, 6.41.

Ethyl 3-ferrocenyl-1-(2-hydroxyethyl)-5-phenylpyrazole-4-carboxylate (6b). Yield 2.18 g (49%), yellow crystals, mp 176–179°C; ir: 824, 1002, 1032, 1060, 1073, 1104, 1169 (Fc); 1433, 1482, 1527, 1689 (C=C, C=N, =C—H); 1711 (COOEt); 2900, 2938, 2980, 3095 (C—H); 3481 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.95 (t, 3H, *J* = 7.2 Hz, CH_3), 2.10 (bs, 1H, OH), 4.00 (m, 4H, 2 CH_2), 4.05 (q, 2H, *J* = 7.2 Hz, CH_2), 4.13 (s, 5H, C_5H_5), 4.31 (m, 2H, C_5H_4), 4.98 (m, 2H, C_5H_4), 7.36 (m, 2H, C_6H_5), 7.46 (m, 3H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.64 (CH_3), 50.76, 59.93, 61.79 ($3CH_2$), 69.46 (C_5H_5), 68.73, 69.34 (C_5H_4), 110.80 (C_{ipso} Fc), 128.21, 129.17, 129.36 (C_6H_5), 144.73 (C_{ipso}), 129.28, 147.03, 151.21(3C), 163.65 (C=O) ppm; ms: *m*/*z* 444 (M^+). Anal. Calcd. for $C_{24}H_{24}FeN_2O_3$: C, 64.89; H, 5.44; Fe, 12.57; N, 6.30. Found: C, 64.93; H, 5.32; Fe, 12.65; N, 6.21.

Ethyl 3-[*N*′-benzoyl-*N*′-(2-hydroxyethyl)hydrazino]-3-ferrocenylpropanoate (7b). Yield 1.02 g (20%), yellow powder, mp 182–184°C; ir: 821, 1001, 1019, 1054, 1064, 1101, 1153 (Fc); 1437, 1461, 1524, 1589 (C=C, =C—H); 1662 (N—C=O); 1719 (COOEt); 2923, 2956, 3064 (C—H); 3341–3488 (NH, OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.33 (t, 3H, *J* = 7.2 Hz, CH_3), 2.26 (bs, 1H, OH), 2.85 (dd, 1H, *J* = 10.5, 15.9 Hz, CH_2), 3.01 (dd, 1H, *J* = 3.3, 15.9 Hz, CH_2), 3.79–3.96 (m, 4H, 2 CH_2), 4.13 (m, 2H, C_5H_4), 4.18 (s, 5H, C_5H_5), 4.22 (m, 2H, C_5H_4), 4.26 (q, 2H, *J* = 7.2 Hz, CH_2), 4.44 (dd, 1H, *J* = 3.3, 10.5 Hz, CH), 6.66 (bs, 1H, NH), 7.47 (m, 3H, C_6H_5), 7.65 (m, 2H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.11 (CH_3), 37.54, 58.17 (CH_2—CH_2), 59.99, 60.84 (2 CH_2), 61.56 (CH), 68.93 (C_5H_5), 66.33, 67.89, 68.66, 69.07 (C_5H_4), 82.34 (C_{ipso} Fc), 126.93, 128.59, 131.92 (C_6H_5), 132.54 (C_{ipso}), 167.41, 171.72 (2C=O) ppm; ms: *m*/*z* 464 (M^+). Anal. Calcd. for $C_{24}H_{28}FeN_2O_4$: C, 62.08; H, 6.08; Fe, 12.03; N, 6.03. Found: C, 62.14; H, 5.97; Fe, 12.11; N, 5.95.

1-Benzoyl-2-[*N*′-ethoxycarbonyl-*N*′-(2-hydroxyethyl)hydrazino]-2-ferrocenyl-ethane (8b). Yield 0.46 g (10%), yellow powder, mp 192–193°C; ir: 820, 1001, 1018, 1063, 1100, 1167 (Fc); 1457, 1481, 1520, 1608 (C=C, =C—H); 1665, 1723 (PhC=O, N—COOEt); 2908, 2923, 3042 (C—H); 3323 - 3489 (NH, OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz, CH_3), 1.88 (bs, 1H, OH), 2.78 (dd, 1H, *J* = 6.0, 9.3 Hz, CH_2), 2.97 (dd, 1H, *J* = 3.6, 9.3 Hz, CH_2), 3.41 (m, 2H, CH_2), 3.64 (m, 2H, CH_2), 4.46 (dd, 1H, *J* = 3.6, 6.0 Hz, CH), 4.12 (q, 2H, *J* = 7.2 Hz, CH_2), 4.25 (s, 5H, C_5H_5), 4.29 (m, 4H, C_5H_4), 6.13 (bs, 1H, NH), 7.38 (m, 3H, C_6H_5), 7.44 (m, 2H, C_6H_5) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.14 (CH_3), 39.37, 53.30, 60.88, 60.92 ($4CH_2$), 61.81 (CH), 68.63 (C_5H_5), 66.29, 67.96, 68.33, 68.37 (C_5H_4), 87.39 (C_{ipso} Fc), 127.73, 128.37, 130.28 (C_6H_5), 136.02 (C_{ipso}), 172.08, 177.32 (2C=O) ppm; ms: *m*/*z* 464 (M^+). Anal. Calcd. for $C_{24}H_{28}FeN_2O_4$: C, 62.08; H, 6.08; Fe, 12.03; N, 6.03. Found: C, 62.02; H, 6.13; Fe, 12.14; N, 6.09.

Ethyl 3-ferrocenyl-1-methyl-5-(*p*-nitrophenyl)pyrazole-4-carboxylate (6c). Yield 2.29 g (50%), yellow crystals, mp 214–215°C; ir: 819, 1001, 1030, 1062, 1071, 1103, 1173 (Fc); 1479, 1527, 1564, 1673 (C=C, C=N, =C—H, —NO_2); 1711 (COOEt); 2903, 2921, 2978, 3095 (C—H) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.01 (t, 3H, *J* = 6.3 Hz, CH_3), 3.69 (s, 3H, CH_3), 4.10 (q, 2H, *J* = 6.3 Hz, CH_2), 4.13 (s, 5H, C_5H_5), 4.32 (m, 2H, C_5H_4), 4.97 (m, 2H, C_5H_4), 7.58 (d, 2H, *J* = 9.0 Hz, C_6H_4), 8.35 (d, 2H, *J* = 9.0 Hz, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.79, 37.39 ($2CH_3$), 60.09 (CH_2), 69.46 (C_5H_5), 68.72, 69.21 (C_5H_4), 111.19 (C_{ipso} Fc), 123.40, 130.97 (C_6H_4), 129.76 (C_{ipso}), 136.97, 144.31, 148.13, 151.19 (4C), 163.06 (C=O) ppm; ms: *m*/*z* 459 (M^+). Anal. Calcd. for $C_{23}H_{21}FeN_3O_4$: C, 60.15; H, 4.61; Fe, 12.16; N, 9.15. Found: C, 60.08; H, 4.58; Fe, 12.04; N, 9.11.

Ethyl 3-[*N*′-methyl-*N*′-(*p*-nitrobenzoyl)hydrazino]-3-ferrocenylpropanoate (7c). Yield 1.01 g (21%), yellow powder, mp 179–181°C; ir: 810, 1001, 1021, 1042, 1104, 1164 (Fc); 1457, 1488, 1518, 1549, 1603 (C=C, —NO_2, =C—H); 1661 (N—C=O); 1727 (COOEt); 2987, 3053 (C—H), 3332 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, *J* = 7.2 Hz, CH_3), 2.56 (s, 3H, CH_3), 2.90 (dd, 1H, *J* = 9.6, 16.5 Hz, CH_2), 3.08 (dd, 1H, *J* = 2.7, 16.5 Hz, CH_2), 4.38 (dd, 1H, *J* = 2.7, 9.6 Hz, CH), 4.12 (q, 2H, *J* = 7.2 Hz, CH_2), 4.18 (s, 5H, C_5H_5), 4.15 (m, 2H, C_5H_4), 4.26 (m, 2H, C_5H_4), 6.79 (bs, 1H, NH), 7.81 (d, 2H, *J* = 8.7, C_6H_4), 8.25 (d, 2H, *J* = 8.7, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.03, 39.56 ($2CH_3$), 43.89, 60.97 ($2CH_2$), 62.34 (CH), 69.13 (C_5H_5), 67.84, 68.21, 68.94, 69.76 (C_5H_4), 84.34 (C_{ipso} Fc), 128.45, 130.43 (C_6H_4), 132.11 (C_{ipso}), 149.98 (C), 162.67, 176.81 (2C=O) ppm; ms: *m*/*z* 479 (M^+). Anal. Calcd. for $C_{23}H_{25}FeN_3O_5$: C, 57.63; H, 5.26; Fe, 11.65; N, 8.76. Found: C, 57.58; H, 5.15; Fe, 11.72; N, 8.68.

1-(*N*′-Ethoxycarbonyl-*N*′-methylhydrazino)-1-ferrocenyl-2-(*p*-nitrobenzoyl)ethanes (8c). Yield 0.49 g (10%), yellow powder, mp 198–199°C; ir: 814, 839 1002, 1021, 1043, 1104, 1160 (Fc); 1461, 1489, 1517, 1603(C=C, —NO_2, =C—H); 1663, 1718 (PhC=O, N—COOEt); 2982, 3045 (C—H), 3324 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.30 (t, 3H, *J* = 6.0 Hz, CH_3), 2.42 (dd, 1H, *J* = 9.6, 16.2 Hz, CH_2), 2.92 (dd, 1H, *J* = 3.0, 16.2 Hz, CH_2), 2.96 (s, 3H, CH_3), 4.29 (dd, 1H, *J* = 3.0, 9.6 Hz, CH), 4.19 (q, 2H, *J* = 6.0 Hz, CH_2), 4.18 (s, 5H, C_5H_5), 4.00 (m, 1H, C_5H_4), 4.04 (m, 1H, C_5H_4), 4.24 (m, 2H, C_5H_4), 6.13 (bs, 1H, NH), 7.36 (d, 2H, *J* = 7.8, C_6H_4), 8.03 (d, 2H, *J* = 7.8, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.97, 38.67 ($2CH_3$), 43.78, 60.85 ($2CH_2$), 61.48 (CH), 68.98 (C_5H_5), 68.69, 69.35 (C_5H_4), 83.12 (C_{ipso} Fc), 127.67, 129.46 (C_6H_4), 131.19 (C_{ipso}), 149.67 (C), 162.56, 175.34 (2C=O) ppm; ms: *m*/*z* 479 (M^+). Anal. Calcd. for $C_{23}H_{25}FeN_3O_5$: C, 57.63; H, 5.26; Fe, 11.65; N, 8.76. Found: C, 57.71; H, 5.34; Fe, 11.82; N, 8.75.

Ethyl 3-ferrocenyl-1-(2-hydroxyethyl)-5-(*p*-nitrophenyl)-pyrazole-4-carboxylate (6d). Yield 2.49 g (51%), yellow crystals, mp 231–233°C; ir: 812, 822, 1005, 1031, 1075, 1106, 1166, 1176 (Fc); 1461, 1483, 1514, 1559, 1604, 1686 (C=C, C=N, —NO_2, =C—H); 1715 (COOEt); 2903, 2939, 2984, 3097 (C—H); 3458 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (t, 3H, *J* = 7.2 Hz, CH_3), 3.50 (bs, 1H, OH), 4.00 (m, 4H, $2CH_2$), 4.08 (q, 2H, *J* = 7.2 Hz, CH_2), 4.13 (s, 5H, C_5H_5), 4.33 (m, 2H, C_5H_4), 4.97 (m, 2H, C_5H_4), 7.61 (d, 2H, *J* = 8.7 Hz, C_6H_4), 8.34 (d, 2H, *J* = 8.7 Hz, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 13.78 (CH_3), 51.16, 60.22 ($2CH_2$), 61.38 (CH_2), 69.50 (C_5H_5), 68.83, 69.43 (C_5H_4), 111.20 (C_{ipso} Fc), 123.39, 131.28 (C_6H_4), 144.89 (C_{ipso}), 131.28, 131.34, 136.45,148.21(4C), 162.97 (C=O) ppm; ms: *m*/*z* 489 (M^+). Anal. Calcd. for $C_{24}H_{23}FeN_3O_5$: C, 58.91; H, 4.74; Fe, 11.42; N, 8.58. Found: C, 58.84; H, 4.72; Fe, 11.32; N, 8.64.

Ethyl 3-[*N*′-(2-hydroxyethyl)-*N*′-(*p*-nitrobenzoyl)hydrazino)]-3-ferrocenylpropanoate (7d). Yield 1.02 g (20%), yellow powder, mp 203–204°C; ir: 820, 1001, 1014, 1055, 1063, 1106, 1152(Fc); 1437, 1461, 1520, 1563, 1612 (C=C, —NO_2,

=C—H); 1662 (N—C=O); 1719 (COOEt); 2928, 2960, 3064 (C—H); 3318–3480 (NH, CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 2.28 (bs, 1H, OH), 2.84 (dd, 1H, J = 10.5, 16.2 Hz, CH_2), 3.06 (dd, 1H, J = 3.3, 16.2 Hz, CH_2), 3.78 (m, 4H, $2CH_2$), 4.13 (m, 2H, C_5H_4), 4.17 (s, 5H, C_5H_5), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 4.26 (m, 2H, C_5H_4), 4.46 (dd, 1H, J = 3.3, 10.5 Hz, CH), 6.68 (bs, 1H, NH), 7.58 (d, 2H, J = 8.7 Hz, C_6H_4), 8.12 (d, 2H, J = 8.7 Hz, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.05 (CH_3), 37.59, 58.11 (CH_2—CH_2), 59.94, 60.72 ($2CH_2$), 61.63 (CH), 68.90 (C_5H_5), 66.23, 67.81, 68.69, 69.03 (C_5H_4), 82.42 (C_{ipso} Fc), 126.85, 131.29 (C_6H_5), 142.73 (C_{ipso}),148.21 (C), 167.78, 187.45 (2C=O) ppm; ms: m/z 509 (M^+). Anal. Calcd. for $C_{24}H_{27}FeN_3O_6$: C, 56.60; H, 5.34; Fe, 10.97; N, 8.24. Found: C, 56.65; H, 5.23; Fe, 10.88; N, 8.31.

1-[*N*′-Ethoxycarbonyl-*N*′-(2-hydroxyethyl)hydrazino]-1-ferrocenyl-2-(*p*-nitroben-zoyl)ethane (8d). Yield 0.5 g (10%), yellow powder, mp 193–195°C; ir: 820, 1004, 1017, 1068, 1105, 1166 (Fc); 1459, 1488, 1522, 1573, 1610 (C=C, —NO_2, =C—H); 1667, 1723 (PhC=O, N—COOEt); 2934, 3045 (CH); 3314–3489 (NH, CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.2 Hz, CH_3), 1.99 (bs, 1H, OH), 2.83 (dd, 1H, J = 5.7, 9.6 Hz, CH_2), 2.98 (dd, 1H, J = 3.6, 9.6 Hz, CH_2), 3.40 (m, 2H, CH_2), 3.58 (m, 2H, CH_2), 4.41 (dd, 1H, J = 3.6, 5.7 Hz, CH), 4.12 (q, 2H, J = 7.2 Hz, CH_2), 4.19 (s, 5H, C_5H_5), 4.32 (m, 4H, C_5H_4), 6.15 (bs, 1H, NH), 7.62 (d, 2H, J = 8.7 Hz, C_6H_4), 8.31 (d, 2H, J = 8.7 Hz, C_6H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.21 (CH_3), 39.47, 53.42 (CH_2—CH_2), 60.74, 60.97 ($2CH_2$), 61.84 (CH), 68.56 (C_5H_5), 66.69, 67.87, 68.21, 68.43 (C_5H_4), 87.22 (C_{ipso} Fc), 127.95, 132.20 (C_6H_4), 143.05 (C_{ipso}), 150.11 (C), 166.87, 176.32 (2C=O) ppm; ms: m/z 509 (M^+). Anal. Calcd. for $C_{24}H_{27}FeN_3O_6$: C, 56.60; H, 5.34; Fe, 10.97; N, 8.24. Found: C, 56.48; H, 5.41; Fe, 11.03; N, 8.19.

Ethyl 3-ferrocenyl-1-(2-hydroxyethyl)-5-methylpyrazole-4-carboxylate (6e). Yield 1.295 g (51%), yellow crystals, mp 142–143°C; ir: 820, 1002, 1042, 1068, 1106, 1161 (Fc); 1432, 1497, 1514, 1556, 1620 (C=C, C=N, =C—H); 1708 (COOEt); 2957, 2980–3203 (CH); 3448 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.37 (t, 3H, J = 7.2 Hz, CH_3), 2.04 (bs, 1H, OH), 2.49 (s, 3H, CH_3), 4.02 (t, 2H, J = 5.7 Hz, CH_2), 4.10 (t, 2H, J = 5.7 Hz, CH_2), 4.32 (q, 2H, J = 7.2 Hz, CH_2), 4.07 (s, 5H, C_5H_5), 4.26 (m, 2H, C_5H_4), 4.89 (m, 2H, C_5H_4) ppm; ^{13}C-NMR ($CDCl_3$): δ 11.37, 14.32 (2 CH_3), 50.14, 59.94, 61.24 ($3CH_2$), 69.35 (C_5H_5), 68.36, 69.41 (C_5H_4), 109.54 (C_{ipso} Fc), 124.89, 143.94, 150.83(3C), 164.06 (C=O) ppm; ms: m/z 382 (M^+). Anal. Calcd. for $C_{19}H_{22}FeN_2O_3$: C, 59.70; H, 5.80; Fe, 14.61; N, 7.33. Found: C, 59.79; H, 5.69; Fe, 14.68; N, 7.31.

Ethyl 3-[*N*′-acetyl—*N*′-(2-hydroxyethyl)hydrazino]-3-ferrocenylpropanoate (7e). Yield 0.81 g (20%), yellow oil; ir: 814, 1001, 1020, 1046, 1061, 1101, 1150 (Fc); 1434, 1456, 1522, 1567 (C=C, =C—H); 1660 (N—C=O); 1712 (COOEt); 2943–3054 (CH); 3319–3469 (NH, OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.2 Hz, CH_3), 1.97 (s, 3H, CH_3), 3.5 (bs, 1H, OH), 2.89 (dd, 1H, J = 3.9, 6.0 Hz, CH_2), 3.03 (dd, 1H, J = 4.5, 6.0 Hz, CH_2), 4.13 (dd, 1H, J = 3.9, 6.0 Hz, CH), 4.28 (q, 2H, J = 7.2 Hz, CH_2), 4.12 (s, 5H, C_5H_5), 3.82 (m, 4H, $2CH_2$), 4.19 (m, 2H, C_5H_4), 4.34 (m, 2H, C_5H_4), 6.51 (bs, 1H, NH) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.23, 14.78 ($2CH_3$), 55.13, 61.44 ($2CH_2$), 61.73, 61.78 ($2CH_2$), 65.38 (CH), 68.53 (C_5H_5), 67.94, 68.62, 68.88, 69.54 (C_5H_4), 85.58 (C_{ipso} Fc), 146.45, 170.08 (2C=O) ppm; ms: m/z 402 (M^+). Anal. Calcd. for $C_{19}H_{26}FeN_2O_4$: C, 56.73; H, 6.52; Fe, 13.88; N, 6.96. Found: C, 56.69; H, 6.39; Fe, 13.79; N, 6.78.

1-Acetyl-2-[*N*′-ethoxycarbonyl-*N*′-(2-hydroxyethyl)hydrazino]-2-ferrocenylethane (8e). Yield 0.4 g (10%), yellow oil; ir: 817, 1001, 1019, 1060, 1103, 1162 (Fc); 1459, 1476, 1522, 1608 (C=C, =C—H); 1661, 1719 (PhC=O, N—COOEt); 2937–3029 (CH); 3321–3431 (NH, OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.36 (t, 3H, J = 7.2 Hz, CH_3), 1.94 (s, 3H, CH_3), 3.58 (bs, 1H, OH), 2.85 (dd, 1H, J = 4.5, 9.9 Hz, CH_2), 3.07 (dd, 1H, J = 3.6, 9.9 Hz, CH_2), 3.94 (dd, 1H, J = 3.6, 4.5 Hz, CH), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 4.11 (s, 5H, C_5H_5), 4.17 (m, 4H, $2CH_2$), 3.86 (m, 2H, C_5H_4), 4.30 (m, 2H, C_5H_4), 6.08 (bs, 1H, NH) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.20, 14.56 ($2CH_3$), 55.41, 61.32 ($2CH_2$), 61.67, 61.84 ($2CH_2$), 65.31 (CH), 68.68 (C_5H_5), 68.07, 68.55, 68.92, 69.76 (C_5H_4), 85.18 (C_{ipso} Fc), 146.88, 170.35 (2C=O) ppm; ms: m/z 402 (M^+). Anal. Calcd. for $C_{19}H_{26}FeN_2O_4$: C, 56.73; H, 6.52; Fe, 13.88; N, 6.96. Found: C, 56.79; H, 6.67; Fe, 13.80; N, 7.03.

Determining the crystal structure. The unit cell parameters and the X-ray diffraction intensities were recorded on a Siemens P4 diffractometer. The structures of compounds **6a** and **6b** were solved by the direct method (SHELXS-97 [36]) and refined using full-matrix least-squares on F^2.

Crystal data for $C_{23}H_{22}FeN_2O_2$ (6a). M = 414.28 g mol^{-1}, monoclinic $P2_1/n$, a = 12.3299(18), b = 8.2116(10), c = 19.813(2) Å, α = 90, β = 98.371(11), γ = 90°, V = 1984.7(4) $Å^3$, T = 293(2) K, Z = 4, ρ = 1.385 mg/m^3, λ (Mo—Kα) = 0.71073 Å, $F(000)$ = 864, absorption coefficient 0.780 mm^{-1}, index ranges $-1 \le h \le 16$, $-1 \le k \le 11$, $-27 \le l \le 26$, scan range $1.83 \le \theta \le 29.00°$, 5184 independent reflections, R_{int} = 0.0252, 6606 total reflections, 255 refinable parameters, final R indices [$I > 2\sigma(I)$] R_1 = 0.0742, wR_2 = 0.2259, R indices (all data) R_1 = 0.1197, wR_2 = 0.2743, goodness-of-fit on F^2 1.006, largest difference peak and hole 0.736/−0.814 $eÅ^{-3}$.

Crystal data for $C_{24}H_{24}FeN_2O_3$ (6b). M = 444.30 g mol^{-1}, monoclinic $P2_1/n$, a = 10.5320(2), b = 13.5040(2), c = 14.8420(3) Å, α = 90, β = 90.150(2), γ = 90°, V = 2110.88(7) $Å^3$, T = 293(2) K, Z = 4, ρ = 1.398 mg/m^3, λ (Mo—Kα) = 0.71073 Å, $F(000)$ = 928, absorption coefficient 0.742 mm^{-1}, index ranges $-13 \le h \le 12$, $-15 \le k \le 16$, $-16 \le l \le 18$, scan range $3.02 \le \theta \le 26.07°$, 4164 independent reflections, R_{int} = 0.0259, 16587 total reflections, 275 refinable parameters, final R indices [$I > 2\sigma(I)$] R_1 = 0.0279, wR_2 = 0.0716, R indices (all data) R_1 = 0.0392, wR_2 = 0.0737, goodness-of-fit on F^2 1.032, largest difference peak and hole 0.247/−0.219 $eÅ^{-3}$.

Supplementary material. CCDC-761350 (for **6a**) and CCDC-761351 (for **6b**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data Centre).

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[29] Ethyl *trans*-3-ferrocenylacrylate (**9**): Yield 5–7%, orange crystals, m.p. 69–70°C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (t, $J = 7.2$ Hz, 3H, CH_3), 4.21 (q, $J = 7.2$ Hz, 2H, CH_2), 4.15 (s, 5H, C_5H_5), 4.39 (m, 2H, C_5H_4), 4.48 (m, 2H, C_5H_4), 6.00 (d, $J = 15.9$ Hz, 1H, CH=), 7.55 (d, $J = 15.9$ Hz, 1H, CH=).

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[31] *N*′-methylbenzhydrazide (**10a**): Yield 6%, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.95$ (s, 3H, CH_3), 5.02 (bs, 2H, NH_2), 7.50 (m, 3H, C_6H_5), 7.89 (m, 2H, C_6H_5) ppm.

[32] *N*′-(2-hydroxyethyl)benzhydrazide (**10b**): Yield 5%, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.12$ (bs, 1H, OH), 3.04–3.29 (m, 4H, $2CH_2$), 5.04 (bs, 2H, NH_2), 7.43 (m, 3H, C_6H_5), 7.74 (m, 2H, C_6H_5). $C_8H_{10}N_2O_2$ (180): calcd. C 60.00, H 6.70, N 15.54; found C 60.15; H 6.52, N 15.61. MS: *m*/*z* 180 $[M]^+$.

[33] *N*′-methyl-*p*-nitrobenzhydrazide (**10c**): Yield 6%, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 3.04$ (s, 3H, CH_3), 5.14 (bs, 2H, NH_2), 7.39 (d, $J = 8.4$ Hz, 2H, C_6H_4); 8.37 (d, $J = 8.4$ Hz, 2H, C_6H_4) ppm. $C_8H_9N_3O_3$ (195): calcd. C 49.23, H 4.65, N 21.52; found C 49.15, H 4.55, N 21.61. MS: *m*/*z* 195 $[M]^+$.

[34] *N*′-(2-hydroxyethyl)-*p*-nitrobenzhydrazide (**10d**): Yield 6%, colorless oil. ^{1}H-NMR 300 MHz, $CDCl_3$): $\delta = 2.07$ (bs, 1H, OH), 3.03–3.38 (m, 4H, $2CH_2$), 5.11 (bs, 2H, NH_2), 7.41 (d, $J = 8.7$ Hz, 2H, C_6H_4); 8.42 (d, $J = 8.7$ Hz, 2H, C_6H_4) ppm. $C_9H_{11}N_3O_4$ (225): calcd. C 48.00, H 4.93, N 18.65; found C 48.04, H 4.87, N 18.60. MS: *m*/*z* 225 $[M]^+$.

[35] *N*′-(2-hydroxyethyl)acethydrazide (**10e**): Yield 6%, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3H, CH_3), 2.13 (bs, 1H, OH), 2.87–3.08 (m, 4H, $2CH_2$), 5.09 (bs, 2H, NH_2) ppm. $C_4H_{10}N_2O_2$ (118): calcd. C 40.67, H 8.53, N 23.70; found C 40.73, H 8.59, N 23.64. MS: *m*/*z* 118 $[M]^+$.

[36] Sheldrick, G. M. SHELXS-97, Program for the Refinement of Crystal Structures; University of Göttingen: Germany, 1994.

Efficient 2,4,6-Trichloro-1,3,5-triazine-Catalyzed Synthesis of 2-Arylbenzothiazoles and Bisbenzothiazoles by Condensation of 2-Aminithiophenol with Aldehydes under Mild Conditions

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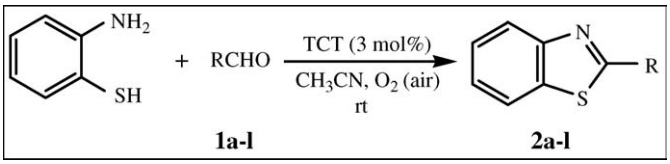

2,4,6-Trichloro-1,3,5-triazine efficiently catalyzed the condensation reactions between 2-aminothiophenol and aromatic aldehydes to afford 2-arylbenzothiazolles in good-to-excellent yields. Simple and mild reaction conditions, the use of a cheap catalyst and easy work up, and isolation are notable features of this method.

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INTRODUCTION

2-Arylbenzothiazoles have been investigated extensively by organic chemists due to their medicinal properties such as antitumor [1], antiviral, and antimicrobial drugs [2]. Also, some benzothiazoles have been found in some organisms [3]. Therefore, there is interest in developing methods for their synthesis.

Numerous methods are available for the synthesis of 2-arylbenzothiazoles and the important ones include the reaction of *o*-aminothiophenols with carboxylic acids [4], the potassium ferricyanide cyclization of thioacylbezanilides (Jacobson's method) [5], the palladium-catalyzed reaction of aryl halides with *o*-aminothiophenol in the presence of carbon monoxide [6], the ceric ammonium nitrate mediated reaction of thiophenols with aromatic nitriles [7], and flash vacuum pyrolysis and photolysis of 2-methylthio-*N*-(arenylidene)aniline [8].

On the other hand, the most general synthetic approaches for synthesis of 2-arylbenzothiazoles involve condensation of 2-aminothiophenols with aldehydes using various oxidants such as MnO_2/SiO_2 [9], *p*-TsOH or graphite on the surface of solid mineral supports under microwave irradiation [10], I_2/DMF [11], 1-phenyl-3-methylimidazolium bromide by microwave irradiation [12], activated carbon (Shirasagi KL or Darco® KB) under oxygen atmosphere [13], O_2 or H_2O_2 in the presence of $Sc(OTf)_3$ [14], tungstophosphoric acid impregnates zirconium phosphate [15], electrooxidation [16], Dowex 50W [17], and direct condensation of 2-aminothiophenol with aromatic aldehydes under microwave irradiation [18].

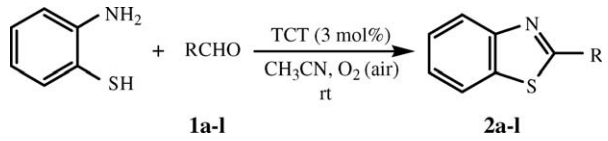
RESULTS AND DISCUSSION

In development of benzothiazoles synthetic methodologies [19] and as a part of our research interest toward the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions [20], we report here a facile synthesis of 2-arylbenzothiazoles in the presence of oxygen and a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) at room temperature (Scheme 1).

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) has been used in organic synthesis because it is stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent [21].

In the initial exploratory experiments, we optimized the reaction condition by testing several parameters, such as different amounts of TCT and different solvents. As a test case, the reaction of 2-aminothiophenol (1.2 mmol) with benzaldehyde (1 mmol) was carried out in the presence of TCT in CH_3CN to afford the 2-phenylbenzothiazoles (**2a**). In the experiments carried out to establish the optimal amount of TCT, the reaction with a 3 mol % catalyst loading gave 87% yield after 3 h. Increasing the amount of the catalyst (5, 7, and 10 mol %) did not

Scheme 1



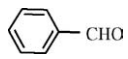
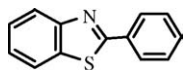
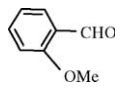
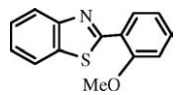
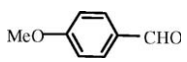
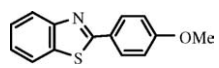
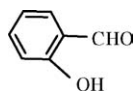
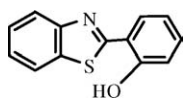
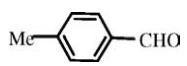
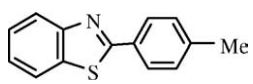
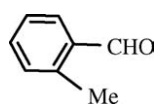
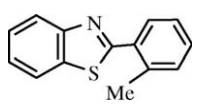
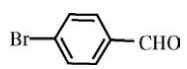
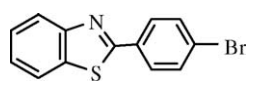
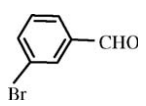
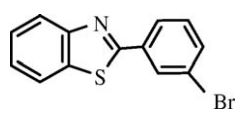
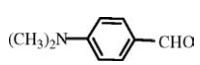
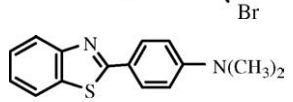
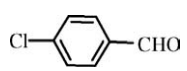
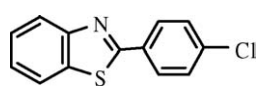
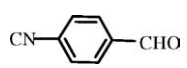
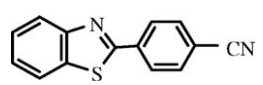
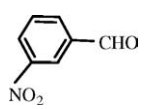
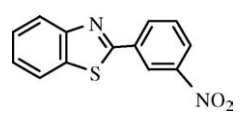
1a-l **2a-l**

change the isolated yield and the time reaction (3 h). The solvent effect in this reaction was also studied, and it was found that CH_3CN gave the best results among H_2O, MeOH, $CHCl_3$, CH_2Cl_2, and EtOH solvents. Similarly, by adopting optimized reaction conditions, the various 2-arylbenzothiazoles were prepared by condensation of 2-aminothiophenol with aromatic aldehydes (**1a–l**) in presence of 3 mol % TCT in CH_3CN (Table 1).

The present conversion did not precede under perfectly anhydrous reaction conditions. The proposed mechanism for the TCT-catalyzed synthesis of 2-arylbenzothiazoles may tentatively be visualized to occur via a tandem sequence of reactions as depicted in

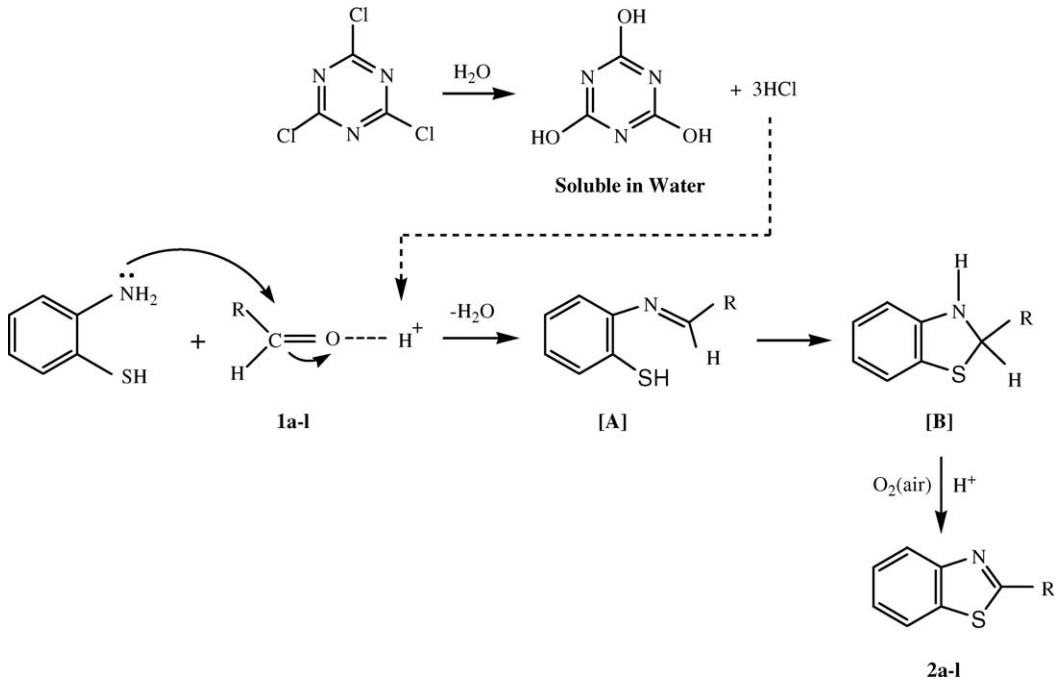
Table 1

The results of the reaction of 2-aminothiophenol with various aldehydes by TCT (3 mol %) in CH_3CN at room temperature.

Entry	Aldehyde (**1a–l**)	2-Arylbenzothiazole (**2a–l**)	Time (h)	Yield (%)[a]	Observed mp (°C)	References
1			3	87	111–112	112–114 [17]
2			3	84	103–105	101–103 [17]
3			2.5	80	119–120	120–121 [17]
4			3.5	84	127–128	127–128 [22a]
5			4	78	82–84	85 [22a]
6			4.5	80	52–54	53–54 [22a]
7			2.5	86	132–133	132 [17]
8			3	84	82–83	83–84 [17]
9			30[b]	80	157–159	160–161 [17]
10			2.5	80	116–118	115–117 [17]
11			2	90	161–162	162–164 [10]
12			3	86	179–180	181–182 [17]

[a] The yields refer to those of isolated products characterized by spectroscopic (IR, ^1H, ^{13}C-NMR) data.
[b] Reaction time is min.

Scheme 2



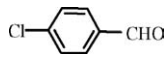
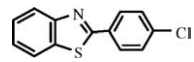
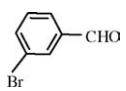
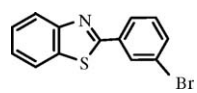
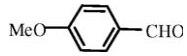
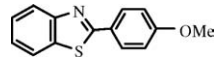
(Scheme 2) involving TCT [20e], which reacts with ''incipient'' moisture and releases 3 mol of HCl and cyanuric acid (removable by washing with water) as a by-product. The *in situ* generated HCl acts as a protic acid and activates the carbonyl oxygen to promote the condensation of 2-aminothiophenol with aldehydes to form adduct **[A]**, which then undergoes cyclization to give adduct **[B]**, followed by oxidation with oxygen (air) to form 2-arylbenzothiazoles (**2a–l**).

On the basis of previously reported mechanism for the synthesis of 2-arylbenzothiazoles in the presence of various catalytic amounts [9,13,17,18,20a,21a], and because of our observation in during the synthesis of 2-arylbenzothiazoles using TCT, we assume that HCl is generated from TCT as the active catalyst in the reaction medium. To confirm our assumption, we replaced the TCT by 10 mol % of HCl. A test reaction was performed between 4-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) in the presence of HCl (10 mol %) at 70°C without solvent. It was found that the generation of 2-(4-chlorophenyl) benzothiazole occurred in 54% after 5 h. To show the accessibility of the present work in comparison with the reported results with TCT, we summarized some of the results for the preparation of 2-arylbenzothiazoles using HCl in Table 2.

It is important to mention that, when the reaction of 2-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) was carried out in the presence of TCT (3

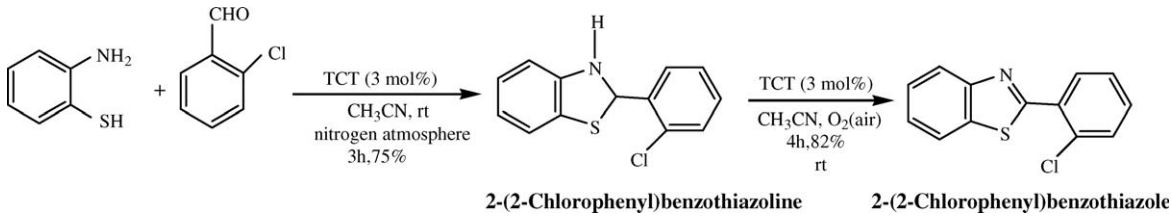
Table 2

Synthesis of 2-arylbenzothiazoles by HCl (10 mol %).

Entry	Aldehyde	2-Arylbenzothiazole	Time (h)	Yield (%)[a]	Observed mp (°C)	References
1			5[b]	54	115–116	115–117 [17]
2			20[c]	52	84–86	83–84 [17]
3			15[c]	48	120–121	120–121 [17]

[a] The yields refer to those of isolated products characterized by spectroscopic (IR, ^{1}H, ^{13}C-NMR) data.
[b] Reaction carried out under solvent-free condition at 70°C.
[c] Reaction carried out in EtOH at room temperature.

Scheme 3



2-(2-Chlorophenyl)benzothiazoline **2-(2-Chlorophenyl)benzothiazole**

mol %) under nitrogen atmosphere (in the absence of oxygen), the reactions stopped at the 2-(2-chlorophenyl)-benzothiazoline (mp 75–77°C, lit. 76°C [17]) stage, which never proceeded to benzothiazoles. The isolated 2-(2-chlorophenyl)benzothiazoline (1 mmol) reacted with TCT (3 mol %) in the presence of O_2 (air) to afford the corresponding 2-(2-chlorophenyl)benzothiazole (mp 82–83°C, lit. 81–83°C [10]). This surely proves that aerial oxygen is not essential for 2-arylbenzothiazoline **[B]** formation, though it is absolutely essential for the oxidation step leading to the formation of 2-arylbenzothiazoles (Scheme 3).

Having successfully performed the reactions of 2-aminothiophenol with a wide range of aldehydes, we focused our attention on examining the reaction of 2-aminothiophenol with 1,4-benzenedicarbaldehydes to TCT in CH_3CN at room temperature (Scheme 4). Finally, we have developed this synthetic method for the preparation of additional extended bisbenzothiazole derivatives in a 2:1 molar ratio of 2-aminothiophenol to 1,4-benzenedicarbaldehyde with 10 mol % TCT in CH_3CN. The reaction proceeded smoothly for 3 h at room temperature using the present protocol, and the desired product **2m** was obtained in 94% isolated yield, mp 258–260°C (lit. 258°C) [23].

In conclusion, we developed a new application for 2,4,6-trichloro-1,3,5-triazine. By using this catalyst, a series of 2-arylbenzothiazoles and bisbenzothiazoles were obtained in high yields via condensation of 2-aminiothiophenol with aldehydes under mild condition. Simple workup and easy isolation under mild reaction conditions are the best features of the present methodology.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr). ^{1}H-NMR spectra were obtained using JEOL FT NMR 90 MHz spectrometer in $CDCl_3$ using TMS as an internal reference. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected.

Typical experimental procedure for the synthesis of 2-arylbenzothiazoles by condensation 2-aminothiophenol with aldehydes using 2,4,6-trichloro-1,3,5-triazine. To a stirred solution of 2-aminothiophenol (1.2 mmol) in CH_3CN (5 mL), an aldehyde (**1a–l**, 1 mmol) and 3 mol % TCT were added. The reaction mixture was stirred at room temperature until the reaction was complete, as judged by TLC (eluent:hexane-EtOAc = 5:1) analysis. After completion, the solvent was evaporated and the residue was washed with water to give the crude products (**2a–l**). The residue was then recrystalized from (EtOH, 5 mL) to afford the pure product.

Selected physical and spectroscopic data of isolated the products. ***2-Phenylbenzothiazole (2a).*** Mp 111–112°C (lit. 112–114°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.41–8.08 (m, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 121.53, 123.23, 125.09, 126.22, 127.52, 128.91, 130.83, 133.64, 135.08, 154.19, 167.93; IR (KBr): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766 cm^{-1}.

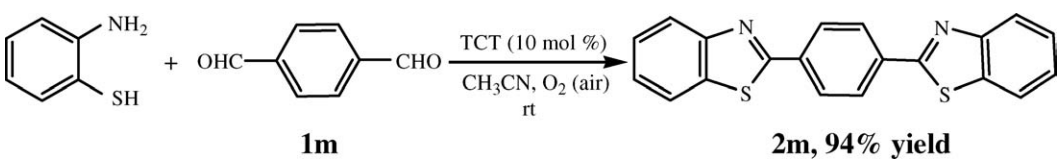
2-(4-Methoxyphenyl)benzothiazole (2c). Mp 119–120°C (lit. 120–121°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.82 (s, 3H, OMe), 7.00–7.95 (m, 8H, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 55.45 (OCH_3), 114.43, 121.53, 122.90, 124.81, 126.21, 129.16, 134.91, 154.38, 162,02, 167.85; IR (KBr): 3023, 2996, 2900, 2836, 1605, 1521, 1485, 1260, 832 cm^{-1}.

2-(4-Methylphenyl)benzothiazole (2e). Mp 84–86°C (lit. 85°C [22a]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.30–8.01 (m, 8H, H—Ar); IR (KBr): 3024, 2905, 1609, 1521, 1484, 1456, 1434, 1384, 1312, 760 cm^{-1}.

2-(4-Cyanophenyl)benzothiazole (2k). Mp 161–162°C (lit. 162–164°C [10]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.37–7.96 (m, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 113.93, 118.08, 121.66, 123.68, 125.96, 126.69, 127.68, 132.50, 137.20, 153.88, 165.09; IR (KBr): 3061, 2226, 1606, 1514, 1479, 1432, 1405, 764 cm^{-1}.

2-(3-Nitrophenyl)benzothiazoles (2l). Mp 179–180°C (lit. 181–182°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.44–8.30 (m, 7H, H—Ar), 8.85 (s, 1H); IR (KBr): 3058, 1611, 1576, 1529, 1459, 1433, 1347, 761 cm^{-1}.

Scheme 4



1m **2m, 94% yield**

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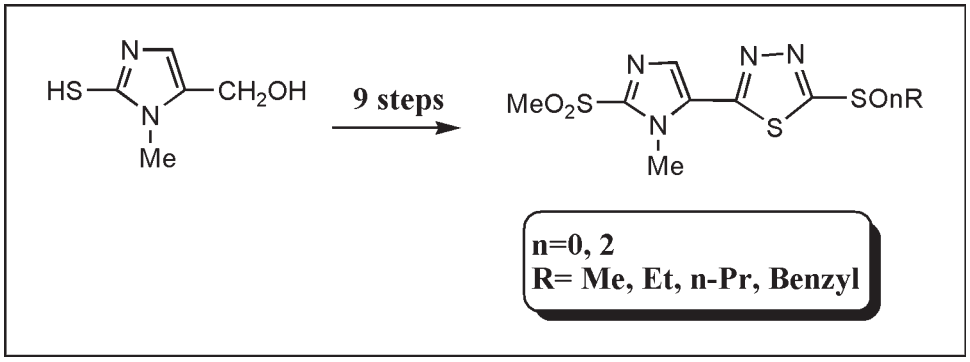

Starting from 5-hydroxymethyl-2-mercapto-1-methyl-1*H*-imidazole (1), a series of 2-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-5-alkylthio and 5-alkylsulfonyl-1,3,4-thiadiazole derivatives (**9a–d** and **10a–d**) were prepared as potential antimicrobial agents. The structure of the obtained compounds was confirmed by NMR, IR, Mass spectroscopy, and elemental analysis.

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INTRODUCTION

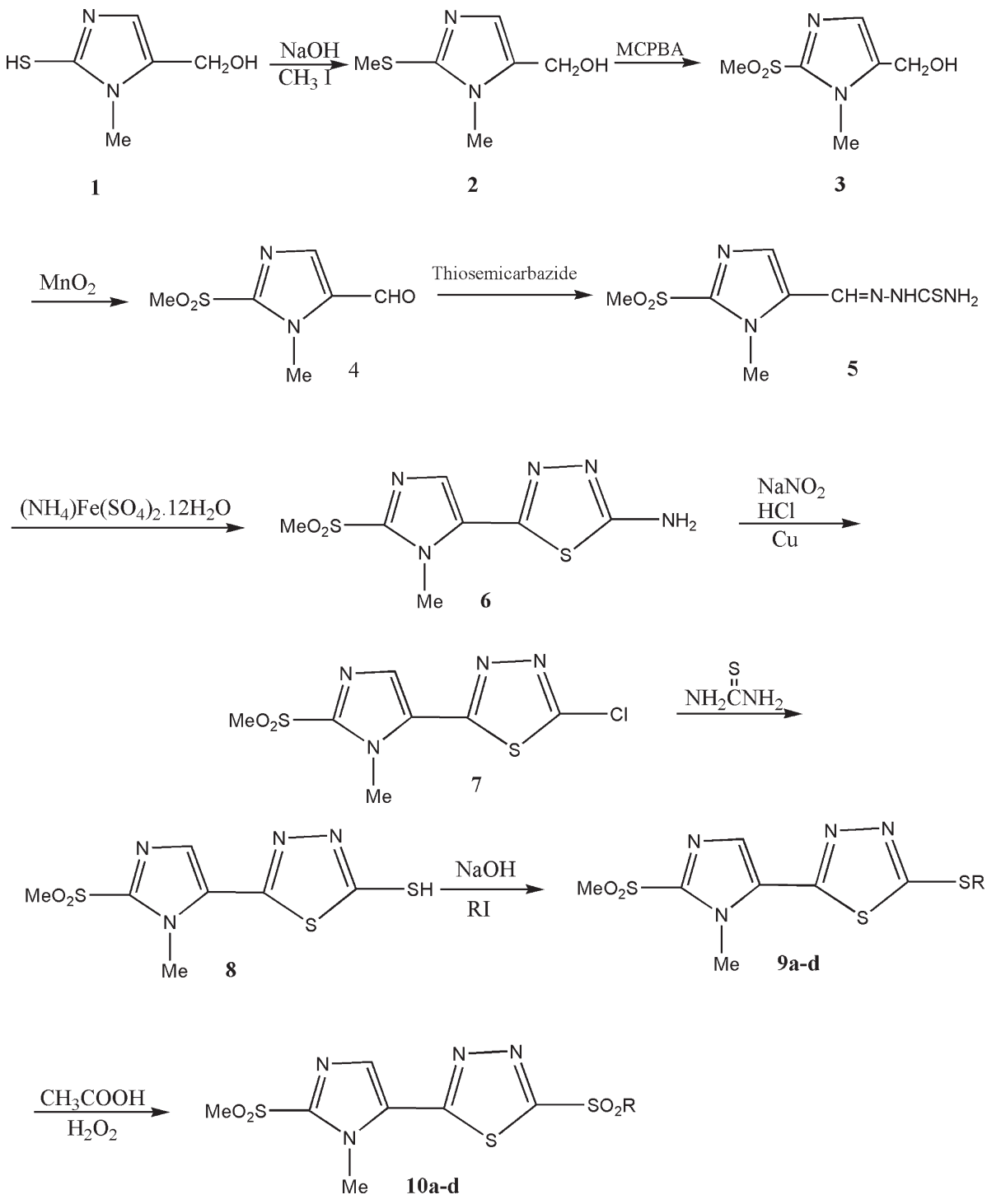
The treatment of microbial infections has become an important and challenging problem because of the emergence of multidrug-resistant organisms. During recent years, there have been intense investigations of different classes of thiadiazole compounds many of which are known to possess interesting biological properties such as antibacterial, antituberculosis, and anticonvulsant activities [1–3]. Imidazole nucleus has a vital rule and substituted imidazoles are known to possess several biological activities, and their antimicrobial properties have been largely described [4–6]. As a part of an extensive search for finding new antimicrobial agents, we have recently reported several classes of broad-spectrum antibacterial agents from 1,3,4-thiadiazole series [7–9]. Furthermore, substituted 1,3,4-thiadiazol-2-sulfides, sulfoxides, and sulfones have parasiticidal and antifungal properties [10,11]. Based on these findings, in continuation of our research program on 1,3,4-thiadiazole derivatives [12,13], herein we would like to report the synthesis of novel 2-substituted-5-alkylthio and 5-alkylsulfonyl-1,3,4-thiadiazole derivatives (**9a–d** and **10a–d**) containing 1-methyl-2-methylsulfonylimidazole moiety as possible drugs effecting microbial infections.

RESULTS AND DISCUSSION

The synthetic pathway for the target compounds is shown in Scheme 1. Reaction of 5-hydroxymethyl-2-mercapto-1-methylimidazole (**1**) with methyl iodide afforded 5-hydroxymethyl-2-methylthio-1-methylimidazole (**2**) [14]. Oxidation of alkylthio group with *m*-chloroperbenzoic acid gave compound **3** [15]. Oxidation of hydroxyl group at 5 position of compound **3** with activated manganese (IV) oxide yielded the desired aldehyde **4** [16].

Reaction of compound **4** with thiosemicarbazide in refluxing ethanol afforded thiosemicarbazone **5**. Oxidative cyclization of compound **5** with ammonium iron (III) sulfate dodecahydrate afforded 5-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole-2-amine (**6**). Diazotization of **6** using $NaNO_2$ in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole (**7**). Reaction of compound **7** with excess of thiourea gave 5-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole-2-thiol (**8**). Alkylation of compound **8** with appropriate alkyl halide gave the corresponding alkylthio-1,3,4-thiadiazoles **9a–d**. Subsequent oxidation of the sulfides **9a–d** with hydrogen peroxide in glacial acetic acid gave

Scheme 1



alkylsulphonyl derivatives **10a–d**. The structure of all compounds was identified according to their ^{1}H-NMR, IR, and Mass spectroscopy.

According to the observed antimicrobial properties of alkylthio and alkylsulfonyl-1,3,4-thiadiazoles such as antifungal [10] and anti-Helicobacter pylori activities [17], these novel 2-substituted-5-alkylthio and 5-alkylsulfonyl-1,3,4-thiadiazole derivatives (**9a–d** and **10a–d**) containing 1-methyl-2-methylsulfonylimidazole moiety have possibility to possess some biological properties such as antibacterial, antituberculosis, and antifungal activities based on their structures.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were obtained using a Nicolet FT-IR magna 550 spectrograph. The ^{1}H-NMR was obtained on a Bruker 80 MHz. Mass spectra were obtained on a Finnigan MAT-TSQ 70 spectrometer at 70 eV. Elemental analyses for compounds **9a–d** and **10a–d** were within ±0.4% of theoretical value for C, H and N.

1-Methyl-2-methylsulfonyl-1*H*-imidazol-5-carbaldehyde thiosemicarbazone (5). To a stirring mixture of compound **4** (4.7 g, 25 mmol) and thiosemicarbazide (2.46 g, 27 mmol) in ethanol (20 mL), three drops of hydrochloric acid 37% was added, and the mixture was refluxed for 2 h. After cooling, the precipitate was filtered, washed with methanol, and crystallized from ethanol–water 50:50 to give **5** as pale yellow powder, (yield = 82%), mp 242–243°C; IR (KBr): 1325, 1165 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6): δ 3.43 (s, 3H, CH_3S), 4.01 (s, 3H, CH_3N), 7.70 (bs, 2H, NH_2), 8.01 (s, 1H, H-C_4 imidazole), 8.41 (s, 1H, NH), 11.49 (s, 1H, CH); ms: *m/z* 261 (M^+, 100), 244 (39), 202 (36), 186 (68), 182 (21), 122 (30). Anal. Calcd. For $C_7H_{11}N_5O_2S_2$: C, 32.17; H, 4.24; N, 26.80. Found: C, 31.85; H, 4.23; N, 26.61.

5-(1-Methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole-2-amine (6). To a mixture of compound **5** (5.20 g, 20 mmol) and ammonium iron sulfate dodecahydrate (24.1 g, 50 mmol), water (250 mL) was added and refluxed for 1 h. Then, water (500 mL) and ammonium iron sulfate dodecahydrate (48.2 g, 100 mmol) were added again, and the mixture was refluxed for 3 h. The cold reaction mixture was filtered, and the filtrate was concentrated under the vacuum and extracted with ethyl acetate. Ethyl acetate was evaporated, and final compound was crystallized from ethanol to give **6** as a white powder, (yield = 75%), mp 223–226°C; IR (KBr): 1311, 1137 (SO_2), 3421, 3277 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$, DMSO-d_6): δ 3.4 (s, 3H, CH_3S), 4.40 (s, 3H, CH_3N), 6.92 (bs, 2H, NH_2), 7.50 (s, 1H, H-C_4 imidazole); ms: *m/z* 259 (M^+, 100), 217 (15), 172 (27), 138 (21), 96 (15), 74 (21). Anal. Calcd. For $C_7H_9N_5O_2S_2$: C, 32.42; H, 3.50; N, 27.01. Found: C, 32.24; H, 3.19; N, 27.31.

2-Chloro-5-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole (7). Compound **6** (1.56 g, 6 mmol) and sodium nitrite (138 g, 20 mmol) were robbed for 10 min. This mixture was added slowly to a mixture of hydrochloric acid 37% (4.48 mL) and water (1.92 mL) containing copper powder (0.08 g) at 0°C. The mixture was stirred in an ice-bath for 1 h and then at room temperature for 2 h. The resulting mixture was heated at 60°C for 15 min. The product was extracted with chloroform. The solvent was removed, and the residue was crystallized from ethanol to give compound **7** (yield = 50%), mp 155–159°C; IR (KBr): 1320, 1150 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6): δ 3.53 (s, 3H, CH_3SO_2), 4.21 (s, 3H, CH_3N), 7.92 (s, 1H, H-C_4 imidazole); ms: *m/z* 280 (M^+ + 2, 15), 278 (M^+, 42), 217 (36), 172 (58), 138 (51), 97 (58). Anal. Calcd. For $C_7H_7ClN_4O_2S_2$: C, 30.16; H, 2.53; N, 20.10. Found: C, 29.98; H, 2.52; N, 20.10.

5-(1-Methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-1,3,4-thiadiazole-2-thiol (8). Compound **7** (1.4 g, 5 mmol) and excess of thiourea (1.52 g, 20 mmol) in ethanol (15 mL) was stirred at room temperature for 3 days. The precipitate was filtered and gave compound **8** which was crystallized from ethanol (yield = 64%), mp 227–230°C; IR (KBr): 3093 cm^{-1} (CH-imidazole); ^{1}H NMR (DMSO-d_6): δ 3.50 (s, 3H, CH_3S), 4.11 (s, 3H, CH_3N), 7.72 (s, 1H, H-C_4-imidazole); ms: *m/z* 276 (M^+, 36), 200 (14), 76 (50). Anal. Calcd. For $C_7H_8N_4O_2S_3$: C, 30.42; H, 2.92; N, 20.27. Found: C, 30.60; H, 3.23; N, 20.29.

General procedure for the synthesis of 2-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-5-alkylthio-1,3,4-thiadiazoles (9). To a stirred solution of compound **8** (1 mmol) in methanol (5 mL), 1.0*N* solution of sodium hydroxide (1 mL) was added, and the mixture was stirred for 5 min. After addition of excess amounts of alkyl halide (3 mmol), the mixture was stirred overnight. Methanol was removed under reduced pressure, water was added to the residue, and the product was extracted with chloroform and crystallized from ethanol.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-methylthio-1,3,4-thiadiazole (9a). (yield = 42%), mp 189–191°C; IR (KBr): 1372, 1132 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 3H, CH_3S), 3.44 (s, 3H, CH_3SO_2), 4.33 (s, 3H, CH_3N), 7.42 (s, 1H, H-C_4 imidazole); ms: *m/z* 290 (M^+, 100), 218 (42), 173 (78), 138 (72), 98 (43), 92 (85), 89 (82). Anal. Calcd. For $C_8H_{10}N_4O_2S_3$: C, 33.09; H, 3.47; N, 19.29. Found: C, 33.12; H, 3.16; N, 19.00.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-ethylthio-1,3,4-thiadiazole (9b). (yield = 40%), mp 142–146°C; IR (KBr): 1326 and 1142 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6): δ 1.42 (t, 3H, CH_3), 3.42 (q, 2H, CH_2), 4.19 (s, 3H, CH_3N), 7.78 (s, 1H, H-C_4 imidazole); ms: *m/z* 304 (M^+, 100), 271 (43), 217 (20), 203 (28), 171 (50), 126 (79), 84 (43). Anal. Calcd. For $C_9H_{12}N_4O_2S_3$: C, 35.51; H, 3.97; N, 18.40. Found: C, 35.53; H, 3.98; N, 18.38.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(n-propylthio)-1,3,4-thiadiazole (9c). (yield = 81%), mp 130–132°C; IR (KBr):1367 and 1132 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, CH_3), 1.6–2.3 (m, 2H, CH_2), 3.28–3.44 (m, 5H, CH_3SO_2, CH_2S), 4.34 (s, 3H, CH_3N), 7.41 (s. 1H, H-C_4 imidazole); ms: *m/z* 318 (M^+, 72), 277 (100), 204 (26), 201 (16), 173 (57), 139 (43), 974 (43), 80 (64), 70 (85). Anal. Calcd. For $C_{10}H_{14}N_4O_2S_3$: C, 37.72; H, 4.43; N, 17.59. Found: C, 38.02; H, 4.64; N, 17.60.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(benzylthio)-1,3,4-thiadiazole (9d). (yield = 70%), mp 159–161°C; IR (KBr): 1362 and 1142 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): δ 3.44 (s, 3H, CH_3SO_2), 4.32 (s, 3H, CH_3N), 4.62 (s, 2H, CH_2), 7.30–7.60 (m, 6H, H-C_4 imidazole, 5H, aromatic); ms: *m/z* 366 (M^+, 72), 344 (15), 204 (15), 1481 (11), 90 (100), 64 (79). Anal. Calcd. For $C_{14}H_{14}N_4O_2S_3$: C, 45.88; H, 3.85; N, 15.29. Found: C, 45.88; H, 4.22; N, 14.97.

General procedure for the synthesis of 2-(1-methyl-2-methylsulfonyl-1*H*-imidazol-5-yl)-5-alkylsulfonyl-1,3,4-thiadiazole (10). To a stirred solution of compound **9** (0.35 mmol) in glacial acetic acid (1 mL), excess amount of hydrogen peroxide 37% (1 mL) was added and refluxed for 2 h. Evaporating of the solvent under reduced pressure gave compound **10**, which was crystallized from ethanol.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(methylsulfonyl)-1,3,4-thiadiazole (10a). (yield = 46%), mp 240–242°C; IR (KBr): 1326 and 1142 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6):δ 3.49 (s, 3H, CH_3SO_2), 3.62 (s, 3H, CH_3SO_2), 4.29 (s, 3H, CH_3N), 7.78 (s, 1H, H-C_4 imidazole); ms: *m/z* 322 (M^+, 21), 217 (21), 123 (21), 93 (29), 85 (50), 79 (59), 66 (100). Anal. Calcd. For $C_8H_{10}N_4O_4S_3$: C, 29.80; H, 3.13; N, 17.38. Found: C, 29.62; H, 3.00; N, 17.60.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(ethylsulfonyl)-1,3,4-thiadiazole (10b). (yield = 55%), mp 203–206°C; IR (KBr): 1337 and 1133 cm^{-1} (SO_2); ^1H NMR (DMSO-d_6):δ 1.56 (t, 3H, CH_3), 3.52 (s, 3H, CH_3SO_2), 3.68 (q, 2H, CH_2SO_2), 4.45 (s, 3H, CH_3N), 7.66 (s, 1H, H-C_4 imidazole); ms: *m*/*z* 336 (M^+, 100), 218 (60), 173 (73), 139 (58), 123 (66), 98 (60), 80 (80), 58 (15). Anal. Calcd. For $C_9H_{12}N_4O_4S_3$: C, 32.13; H, 3.60; N, 16.65. Found: C, 32.45; H, 3.39; N, 16.46.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(n-propylsulfonyl)-1,3,4-thiadiazole (10c). (yield = 60%), mp 189–192°C; IR (KBr): 1326 and 1142 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ 1.12 (t, 3H, CH_3), 1.75–2.36 (m, 2H, CH_2), 3.44 (s, 3H, CH_3SO_2), 3.71 (t. 2H, CH_2SO_2), 4.35 (s, 3H, CH_3N), 7.40 (s, 1H, H-C_4 imidazole); ms: *m*/*z* 350 (M^+, 100), 336 (27), 145 (61), 91 (10), 62 (70). Anal. Calcd. For $C_{10}H_{14}N_4O_4S_3$: C, 34.27; H, 4.03; N, 15.99. Found: C, 34.24; H, 4.04; N, 16.00.

2-(1-Methyl-2-methylsulfonyl-1H-imidazol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole (10d). (yield = 50%), mp 197–199°C; IR (KBr): 1337, 1147 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ 3.45 (s, 3H, CH_3SO_2), 4.36 (s, 3H, CH_3N), 4.83 (s, 2H, CH_2), 7.3–7.53 (m, 6H, H-C_4 imidazole, 5H benzyl); ms: *m*/*z* 398 (M^+, 10), 334 (26), 137 (16), 91 (100), 63 (99).). Anal. Calcd. For $C_{14}H_{14}N_4O_4S_3$: C, 42.20; H, 3.54; N, 14.06. Found: C, 42.42; H, 3.54; N, 14.27.

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S_NAr Reaction of 2,5-Dinitrofuran: A Mild and Efficient Method for the Preparation of 2-Aryloxy-5-nitrofuran

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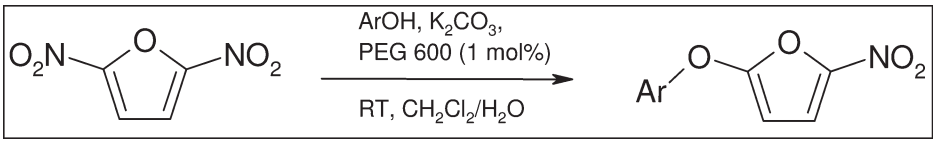

2,5-Dinitrofuran which can be easily prepared by nitration of 2-nitrofuran, on phase transfer catalysed S_NAr reaction with phenol gave good yield of 2-aryloxy-5-nitrofuran.

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INTRODUCTION

Oxygen-containing heterocycle namely furans are important constituents of a variety of important classes of pharmacologically active compounds. These compounds are known to exhibit different activities, such as lipogenes inhibitors [1], antiarrhythmics [2], potassium channel blockers [3], antimicrobials such as antimalarials [4], EGFR (HER-1, erbB 1) inhibitors [5], cyclogenes-2 inhibitors [6], protein tyrosin kinase inhibitors [7], anaesthetics [8], 5-HT1D receptor antagonists [9], and nonsteroidal antiinflammatory drugs [10].

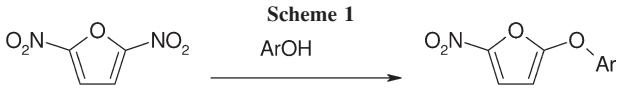
Initial attempt to react phenol with 2-chloro-5-nitrofuran under different neutral, basic, and phase transfer catalyst condition were unsuccessful. Starting material could not be isolated, which indicates 2-chloro-5-nitrofuran is unstable. In this communication, we report the mild and efficient phase transfer catalyzed S_NAr reaction of 2,5-dinitrofuran with phenols. The nucleophilic substitution of nitro group in furan derivatives like 5-nitro-2-furancarbaldehyde, with different nucleophiles like phenoxide [11], alkoxide [12], hydrogen halide [13], azide, arylmercaptides, benzenesulfinate [14], have been reported. The similar reactions with other furan derivatives like 5-nitro-2-furancarboxylate [15–17], 5-nitro furfurylnitrate [18], and 5-nitro-2-furfurylidenemalononitrile [19], since the 2-nitrofuran derivative is available easily than corresponding 2-halofuran analogs, the former becomes the synthetic equivalent of choice 2-furyl synthon. To overcome this problem we have used 2,5-dinitrofuran as comparatively more stable alternative to 2-chloro-5-nitrofuran. Only a few examples have been reported literature for nucleoplilic substitution of 2,5-dinitrofuran [20–22], The nulceophiles used in majority of these reports are soft carbon nucleophiles like anions derived from ethyl acetate or diethyl malonate, benzenesulphonates, thiophenolates, and amines [23]. However, there is no report of reaction of 2,5-dinitrofuran with phenol.

RESULTS AND DISCUSSION

2,5-Dinitrofuran can be readily prepared from 2-nitrofuran by treatment of conc. HNO_3 [23]. 2,5-Dinitrofuran can under go S_NAr substitution reaction to yield 2-substituted-5-nitrofuran. The S_NAr substitution in case of 5-nitro-2-furancarbaldehyde [11] and 5-nitro-2-furancarboxylate [16,17] is reported to give good yield with NaH in DMSO. The same method when used for the preparation of 2-substituted-5-nitrofuran from 2,5-dinitrofuran, it gave a very poor yield of desired product. We have carried out a series of reactions with different base and solvent combinations to optimize the reaction conditions (Scheme 1). The results are shown in Table 1. It was found that high temperature or strong base resulted in poor yield of desired product. Instability of dinitrofuran could possibly be the reason for poor yield as the unreacted nitro compound could not be isolated from the reaction mixture. This reaction thus demands a mild condition. It was observed that reaction goes smoothly in biphasic system (entry 9; Table1), and the rate of reaction accelerates by addition of Phase transfer Catalyst 18Crown6 (entry 10; Table 1).

Effect of type of catalyst on condensation of 3-hydroxyquinoline and 2,5-dinitrofuran was then studied using different phase transfer catalysts and conditions. The results are shown in Table 2. It reveals that poly ethylene glycol 600 (PEG 600), which is the most economic, is also equally efficient to catalyze the reaction. Kinetics of this reaction was studied by ^1H NMR of the reaction aliquots with 0, 0.1, 1, 2, and 5 mol % of PEG

Scheme 1



600. The results are shown in Figure 1. It appears from the study that 1 mol % is the minimum requirement of catalyst that gives 90% conversion in about 3 h.

The optimized condition of 1.0 mol % of PEG 600 was used for the reactions with different phenols. (Scheme 2); the results are displayed in Table 3. Electron withdrawing substituents such as F, NO_2, and Ph groups facilitates the reaction allowing shorter reaction times and yield was high (entry 3,4,5, and 11, Table 3). Electron donating substituents OMe and Me groups require comparatively longer time and low yield (entry 2,6, and 12, Table 3).

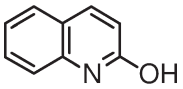
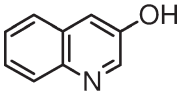
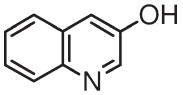
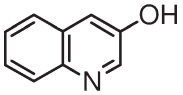
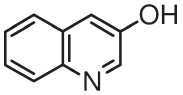
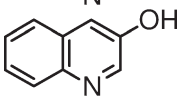
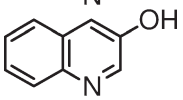
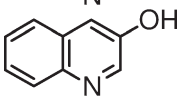
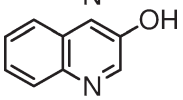
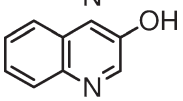
In Conclusion, A mild and efficient method for the preparation of 2-aryloxy-5-nitrofuran is developed. It provides the first example of phase transfer catalyzed S_NAr reaction of 2,5-dinitrofuran.

EXPERIMENTAL

2-Nitrofuran and 18crown6 were purchased from Aldrich. Commercial solvents and reagents were used as received. Flash column chromatography was performed over silica gel H (100–200 or 200–300 mesh) using hexane/ethyl acetate. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either 300 MHz spectrometer. NMR chemical shifts were reported in δ (ppm) using the δ 2.54 signal of DMSO (^1H NMR) and the δ 39.94 signal of DMSO (^{13}C NMR) as internal standards. Mass spectra were recorded using either chemical

Table 1

Screening of reaction condition for the substitution of nitro from 2,5-dinitrofuran by Ar—OH.

Sr. No.	Ar—OH	Base	Solvent	Temp. °C	Catalyst	Yield[a] (%)
1		Cs_2CO_3	DMF	RT	–	5
2		Cs_2CO_3	DMF	60	–	6
3		K_2CO_3	DMF	RT	–	3
4		TEA	CH_3CN	RT	DMAP[b]	0
5		–	DMF	RT	KF[c]	0
6		–	DMF	60	–	0
7		–	CH_2Cl_2	RT	–	0
8		–	CH_2Cl_2/H_2O	RT	–	0
9		K_2CO_3	CH_2Cl_2/H_2O	RT	–	33
10		K_2CO_3	CH_2Cl_2/H_2O	RT	18Crown6[b]	89

[a] The yields reported are after isolation and purification by the column chromatography.
[b] 0.1 mol %.
[c] 1.0 mmol.

Table 2

Optimization of type and quantity of phase transfer catalyst for S_NAr reaction of 2,5-dinitrofuran with phenol in CH_2Cl_2:Water (1:1) at room temperature.

Sr. No.	PTC	Mol % of PTC	Yield[a] (%)
1	18 Crown 6	1	90
2	PEG 600	5	98
3	PEG 600	2	99
4	PEG 600	1	98
5	PEG 600	0.1	89
6	PEG 600	0.01	83

[a] The yields reported are after isolation and purification by the column chromatography.

ionization or electron impact ionization. Thin layer chromatography was used to monitor reaction progress.

Typical procedure for the synthesis of 2,5-dinitrofuran. A mixture of 5.8 g (50 mmol) of 2-nitrofuran and 100 mL of conc. HNO_3(70%) was heated to 60°C for 4 h. Mixture was then cool to room temperature diluted with 100 mL of cold water and neutralized with Na_2CO_3 solution. Extracted with CH_2Cl_2. Combined organic layer washed with brine and dried over anhydrous Na_2SO_4. Recrystallisation from ethanol gave 4.0 g of 2,5-dinitrofuran as a yellow solid, mp 100°C.

Typical procedure for the synthesis of compounds 1–14 using PEG 600. Mixture of 2,5-dinitrofuran (1.0 mmol), phenol (1.0 mmol), and K_2CO_3 (1.0 mmol) was taken in 3.0 mL mix of 1:1 dichloromethane (CH_2Cl_2) and water. PEG 600 (0.01 mmol) was then added and mixture was stirred at room temperature till the good conversion was observed on TLC. Organic layer separated. Aqueous layer washed with CH_2Cl_2. Combined organic layer washed with water and then with brine. Organic layer dried over anhydrous Na_2SO_4, evaporated and purified by column chromatography.

3-[(5-Nitro-2-furyl)oxy]quinoline: (Table 1, entry 10). Yellow solid, yield 89%; mp 167–170°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.30(1H, d, J = 3.8 Hz, F H-4), 7.69(1H, m,), 7.81(1H, td, J = 7.7, 1.5 Hz,), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.02(1H, d, J = 6.8 Hz,), 8.10(1H, d, J = 8.7 Hz,), 8.41(1H, d, J = 2.6 Hz,), 9.01(1H, d, J = 2.6 Hz,); ^{13}C NMR (DMSO, 75 MHz) : δ = 157.8, 147.8, 145.9, 144, 129.9, 129.3, 128.5, 128.3, 123.2, 117.7, 93.6. HRMS (EI, *m*/*e*) calcd for $C_{13}H_8N_2O_4$ (M^+) 256.22, found 256.02.

2-Nitro-5-phenoxyfuran: (Table 2, entry 1). Brown solid, yield 79%; mp 53–55°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.04(1H, d, J = 3.8 Hz, F H-4), 7.35(3H, m, P H), 7.50(2H, m, P H), 7.79(1H, d, J = 3.8 Hz, F H-3). HRMS (EI, *m*/*e*) calcd for $C_{10}H_7NO_4$ (M^+) 205.17, found 204.96.

2-(4-Methoxyphenoxy)-5-nitrofuran: (Table 2, entry 2). Brown solid, yield 82%; mp 69–71°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 3.77(3H, s, CH_3), 5.86(1H, d, J = 3.8 Hz, F H-4), 7.05(2H, m, P H), 7.30(2H, m, P H), 7.76(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz) : δ = 159.8, 177.7, 147.1, 120.8, 118,115.7, 91.3. HRMS (EI, m/e) calcd for $C_{11}H_9NO_5$ (M^+) 235.19, found 235.02.

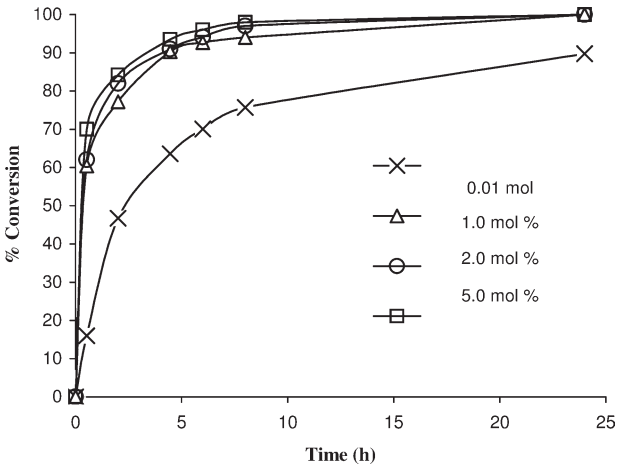


Figure 1. Effect of PTC concentration on kinetics of S_NAr reaction of 2,5-dinitrofuran with phenol in CH_2Cl_2: water (1:1) at room temperature.

2-(4-Fluorophenoxy)-5-nitrofuran: (Table 2, entry 3). Yellow solid, yield 96%; mp 73–75°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.00(1H, d, J = 3.8 Hz, F H-4), 7.35(2H, m, P H), 7.44(2H, m, P H), 7.78(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz): δ = 161.3, 158.4, 158.1, 149.6, 149.5, 144.0, 121.1, 120.9, 117.5, 117.2, 116.9, 91.8. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6FNO_4$ (M^+) 223.16, found 223.02.

2-Nitro-5-(4-nitrophenoxy)furan: (Table 2, entry 4). Yellow solid, yield 98%; mp 87–90°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.40(1H, d, J = 4.2 Hz, F H-4), 7.59(2H, m, P H), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.35(2H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 163.9, 158.6, 155.3, 144.8, 144.7, 126.3, 126.1, 118.8, 116.7, 115.7, 95.2. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6N_2O_6$ (M^+) 250.16, found 249.95.

2-(Biphenyl-4-yloxy)-5-nitrofuran: (Table 2, entry 5). Yellow solid, yield 97%; mp 153–156°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.13(1H, d, J = 4.2 Hz, F H-4), 7.45(5H, m, P H), 7.71(2H, m, P H), 7.78(3H, m, P H); ^{13}C NMR (DMSO, 75 MHz) : δ = 158.3, 153.6, 139.3, 138.6, 129.4, 129.1, 128.1, 127.1, 119.5, 117.9, 93.1. HRMS (EI, *m*/*e*) calcd for $C_{16}H_{11}NO_4$ (M^+) 281.27, found 281.05.

2-Methyl-5-[(5-nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 6). Yellow solid, yield 83%; mp 122–124°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.50(3H, s, CH_3), 6.09(1H, d, J = 4.2 Hz, F H-4), 7.40(1H, d, J = 8.7 Hz, P H), 7.76(1H, dd, J = 8.7, 3.0 Hz, P H), 7.79(1H, d, J = 4.2 Hz, F H-3), 8.53(1H, d, J = 3.0 Hz, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 157.9, 156.1, 148.5, 144.1, 139.9, 127.1, 124.3, 117.4, 92.0. HRMS (EI, *m*/*e*) calcd for $C_{10}H_8N_2O_4$ (M^+) 220.18, found 220.02.

Scheme 2

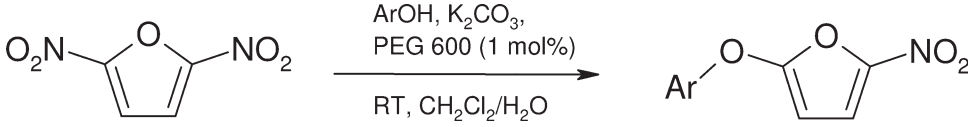
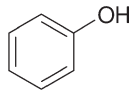
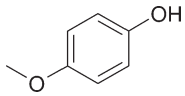
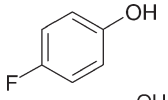
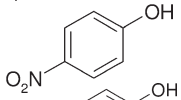
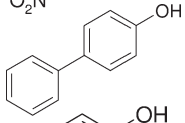
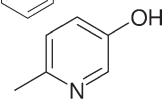
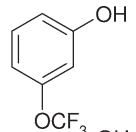
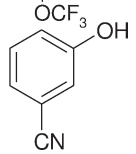
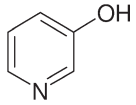
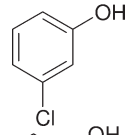
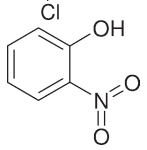
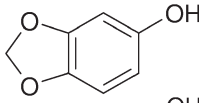
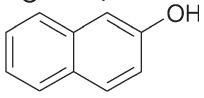
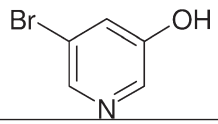


Table 3

PTC catalyzed S_NAr reaction of 2,5-dinitrofuran with different phenols (Scheme 2).

S. No.	Ar	Time (h)	Isolated yield[a] (%)
1		4	79
2		4	82
3		3	96
4		2	98
5		2	97
6		3	83
7		4	77
8		4	85
9		3	98
10		1	79
11		2	97
12		1	84
13		1	87
14		4	85

[a] The yields reported are after isolation and purification by the column chromatography.

2-Nitro-5-[3-(trifluoromethoxy)phenoxy]furan: (Table 2, entry 7). Yellow liquid, yield 77%. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.21(1H, d, J = 5.3 Hz, F H-4), 7.40(2H, m, P H), 7.49(1H, s, P H), 7.64(1H, m, P H), 7.81(1H, d, J = 5.3 Hz, P H); HRMS (EI, *m*/*e*) calcd for $C_{11}H_6F_3NO_5$ (M^+) 289.16, found 289.01.

3-[(5-Nitrofuran-2-yl)oxy]benzonitrile: (Table 2, entry 8). White solid, yield 85%; mp 112–116°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.25(1H, d, J = 4.2 Hz, F H-4), 7.70(2H, m, P H), 7.81(2H, m, P H), 7.95(1H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 156.5, 153.9, 131.8, 130.0, 123.7, 122.0, 117.6, 117.0, 113.1, 93.8. HRMS (EI, *m*/*e*) calcd for $C_{11}H_6N_2O_4$ (M^+) 230.18, found 230.02.

3-[(5-Nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 9). White solid, yield 98%; mp 88–91°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.18(1H, d, J = 3.8 Hz, F H-4), 7.56(1H, dd, J = 7.7, 4.7 Hz, P H), 7.81(1H, d, J = 3.8 Hz, F H-3), 7.87(1H, ddd, J = 8.5, 2.8, 1.1 Hz, P H), 8.56(1H, dd, J = 4.5, 1.1 Hz, P H), 8.68(1H, d, J = 3.0 Hz, P H); HRMS (EI, *m*/*e*) calcd for $C_9H_6N_2O_4$ (M^+) 206.16, found 206.09.

2-(3-Chlorophenoxy)-5-nitrofuran: (Table 2, entry 10). Yellow liquid, yield 79%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.18(1H, d, J = 4.2 Hz, F H-4), 7.34(1H, m, P H), 7.41(1H, m, P H), 7.53(2H, m, P H), 7.80(1H, d, P H); HRMS (EI, *m*/*e*) calcd for $C_{10}H_6ClNO_4$ (M^+) 239.61, found 239.02.

2-Nitro-5-(2-nitrophenoxy)furan: (Table 2, entry 11). Yellow solid, yield 97%; mp 97–99°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.20(1H, d, J = 4.2 Hz, F H-4), 7.59(2H, m, P H), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.35(2H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 157.0, 145.8, 144.8, 140.7, 136.4, 127.9, 126.7, 122.4, 117.6, 93.3. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6N_2O_6$ (M^+) 250.16, found 249.95.

5-[(5-Nitrofuran-2-yl)oxy]-1,3-benzodioxole: (Table 2, entry 12). Yellow solid, yield 84%; mp 96–98°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.92(1H, d, J = 4.2 Hz, F H-4), 6.10(2H, s, CH_2), 6.83(1H, m, P H), 6.99(1H, d, J = 8.7 Hz, P H), 7.09(1H, d, J = 2.6 Hz, P H), 7.76(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz): δ = 159.5, 148.2, 147.6, 145.5, 143.8, 117.7, 11.9, 108.5, 102.1, 101.6, 91.2. HRMS (EI, *m*/*e*) calcd for $C_{11}H_7NO_6$ (M^+) 249.18, found 249.15.

2-(Naphthalen-2-yloxy)-5-nitrofuran: (Table 2, entry 13). Brown solid, yield 87%; mp 73–76°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.15(1H, d, J = 4.2 Hz, F H-4), 7.55(3H, m, P H), 7.82(1H, d, J = 3.8 Hz, F H-3), 7.87(1H, d, J = 2.6 Hz, P H), 7.97(2H, dt, J = 9.3, 7.3 Hz, P H), 8.08(1H, d, J = 9.1 Hz, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 158.5, 151.5, 144.7, 133.9, 131.4, 131.1, 128.2, 128.0, 127.6, 126.5, 118.8, 117.9, 115.5, 93.2 ppm. HRMS (EI, *m*/*e*) calcd for $C_{14}H_9NO_4$ (M^+) 255.23, found 255.08.

3-Bromo-5-[(5-nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 14). White solid, yield 85%; mp 106–109°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.30(1H, d, J = 4.2 Hz, F H-4), 7.81(1H, d, P H), 8.28(1H, m, P H), 8.70(2H, t, J = 1.9 Hz, P H); ^{13}C NMR (DMSO, 75 MHz) : δ = 156.4, 150.7, 147.9, 144.5, 139.4, 129.2, 120.2, 117.0, 93.7. HRMS (EI, *m*/*e*) calcd for $C_9H_5BrN_2O_4$ (M^+) 285.05, found 284.01.

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$NaBH_4$-I_2 Mediated Chemoselective Reduction of γ-Lactam and Thio-γ-lactam in Presence of Gem-dicarboxylates: An Easy Access to 1,3-Diaryl Pyrrolidines

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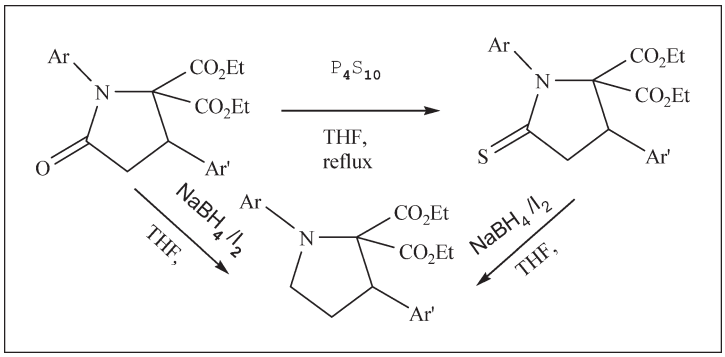

Substituted pyrrolidine derivatives were synthesized in high yield by $NaBH_4/I_2$ mediated chemoselective reduction of *N*-aryl-γ-lactam and *N*-aryl-thio-γ-lactam-2,2-dicarboxylate. With excess $NaBH_4/I_2$, carbonyl functionality of the ester groups remained unchanged.

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INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds. Among them, substituted pyrrolidines are found in numerous natural products and biologically active compounds as structural motifs [1]. Depending on the substitution pattern and functionalization, different substituted pyrrolidines have been shown to be effective antibacterials or fungicides agents and glycosidase inhibitors. A potent class of cis- and trans-di-aryl pyrrolidines that inhibit biosynthetic pathways, specially the synthesis of leukotriene-B4, can be useful for treatment of asthma, arthritis, inflammatory bowel disease, and psoriasis [2]. A series of alkaloids broussonetines A–L and broussonetinines A and B extracted from the branches of Broussonetia kazinoki (Oriental tree, termed ''himekouzo'' in Japan) have a common functionalized pyrrolidine ring system. All these compounds are strong inhibitors of α- and β-glucosidase, β-galactosidase, and α- and β-mannosidase enzymes. These compounds display different selectivity toward different enzymes [3]. Medicinal chemistry program investigated that pyrrolidines bearing an aromatic or heteroaromatic substituent at the C-3 position acts as central nervous system (CNS) stabilizers [1b].

RESULTS AND DISCUSSION

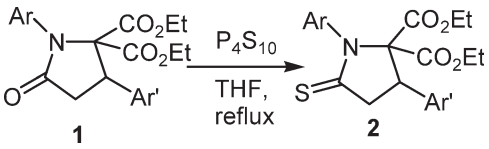
Several strategies have also been developed for the synthesis of pyrrolidines. To utilize the synthetic γ-lactams (prepared in our laboratory), we are eager to develop a chemoselective methodology to reduce the lactam carbonyl group in presence of gem-dicarboxylates for the synthesis of a pyrrolidine moiety. Chemoselective methods for the reduction of lactams to amines have also been achieved using diisobutyl aluminium hydride, diborane, sodium borohydride, and rhodium catalyzed hydrosilation [4].

As part of our on going interest in selective reduction [5] on γ-lactam derivatives, we choose $NaBH_4/I_2$ reagent system to investigate its application [6] on *N*-aryl-thio-γ-lactam derivatives [7] which are prepared from *N*-aryl-γ-lactam derivatives.

The starting material *N*-aryl-γ-lactam diesters **1a–f** was prepared following the general method [5,8,9]. The thio-γ-lactam diesters **2a–f** are prepared by refluxing the lactam with P_4S_{10} [10] in dry THF for 6 h (Scheme 1 and Table 1).

Some thio-lactams have also been found to be CNS active. These compounds cause clonic and tonic convulsions in mice a few seconds after ip (intraperitoneal) injection. The five-membered thio-lactam can cause mild sedation at lower doses (500 mg/kg) and convulsions at higher doses (1000 mg/kg) [11].

Scheme 1



Formation of BH_3: THF *in situ* by the reaction of $NaBH_4$ with I_2 in dry THF has already been reported [12] and when we treated the resulting lactams with $NaBH_4/I_2$ in dry THF which furnished substituted pyrrolidines **3a–f** in good yields (Scheme 2 and Table 2).

In presence of excess $NaBH_4/I_2$ in dry THF, carbonyl functionality of the ester groups remain unchanged.

As the mechanism of the reaction is uncertain and as we are unable to isolate the intermediate, the plausible mechanism may be written as depicted in Scheme 3 [12].

All the compounds were characterized by interpretation of the usual spectroscopic and analytical data.

CONCLUSION

Thus 1,3-diaryl pyrrolidine can be prepared by chemoselective reduction of carbonyl and thio carbonyl group of *N*-aryl-γ-lactam and *N*-aryl-thio γ-lactam by $NaBH_4$-I_2 in dry THF. Here we successfully disclose the applicability of $NaBH_4$-I_2 reagent system on lactam-carbonyl group as well as thio-lactam carbonyl group in dry THF. As pyrrolidine is the precursor of pyrrole this methodology has been successfully applied to the synthesis of a range of *N*-aryl-pyrroles.[5]

EXPERIMENTAL

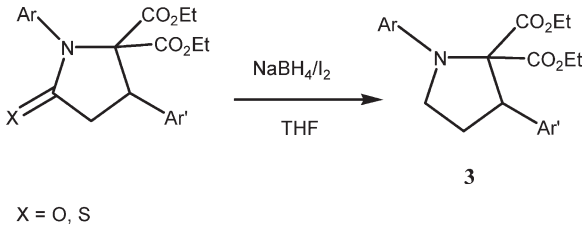
^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a BRUKER-AC 200 MHz and 400 MHz spectrometer. Chemical shifts are reported in ppm. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz). ^{13}C NMR (50 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a BRUKER-AC 200 MHz and 400 MHz Spectrometer with complete proton decoupling. IR spectra were recorded on a Perkin-Elmer 883 and Shimadzu FTIR-8300 infrared spectrometers. EIMS (70 eV) spectra were taken using a VG Auto spec M mass spectrometer, and ESI-MS spectra were taken using Waters LCT mass spectrometer. All reagents and solvents are obtained from commercial suppliers.

Table 1

Synthesis of 1,3-diaryl-5-thioxopyrrolidine-2,2-dicarboxylates **2(a–f)** from 1,3-diaryl-2,2-dicarbethoxy-5-oxo-pyrrolidine **1(a–f).**

Substrate 5-oxo-pyrolidine	Ar	Ar′	5-thiooxo-pyrolidine	Yield (%)
1a	4-F-C_6H_4	Phenyl	**2a**	85
1b	4-Cl-C_6H_4	Phenyl	**2b**	83
1c	4-CH_3-C_6H_4	Phenyl	**2c**	77
1d	3,4-F,F-C_6H_3	Phenyl	**2d**	90
1e	4-F-C_6H_4	2-Thienyl	**2e**	78
1f	4-F-C_6H_4	2-Furyl	**2f**	80

Scheme 2



Chromatographic purification was done with either 60–120 or 100–200 mesh silica gels (SRL). Petroleum ether refers to the fraction boiling in the range 60–80°C. Tetrahydrofuran was freshly distilled over sodium-benzophenone.

General procedure for synthesis of diethyl *N*-aryl-5-thioxo-3-aryl/heteroaryl-pyrrolidine-2,2-dicarboxylates 2a–f. To a stirred solution of γ-lactam diester (1 mmol) in dry THF (30 mL), P_4S_{10} (3 mmol) was added under argon atmosphere, and the reaction mixture was refluxed for 5 h. Solvent was evaporated under vacuum, and the residue basified with ammonia solution. The aqueous layer then extracted with $CHCl_3$ and the combined organic layer was washed with brine and followed by water several times, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Light yellow solid appeared. The product was purified by column chromatography.

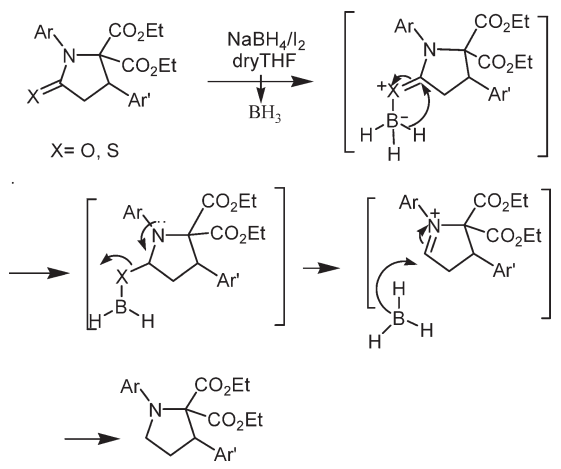
Diethyl 1-(4-fluorophenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2a. White solid; yield 85%; mp 105–106°C (from ethyl acetate-petroleum ether); (Found: C, 63.94; H, 5.43; N, 3.21. Calculated for $C_{22}H_{22}FNO_4S$: C, 63.61; H, 5.30; N. 3.37%); ν_{max} (liquid film)/cm 1729.70, 1508.41; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.78 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.96 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 3.48–3.6 (m, 3H, $NCSCH_2$, $OC(H)HCH_3$), 3.85–3.95 (m, 2H, OCH_2CH_3), 4.08–4.17 (m, 1H, $OC(H)HCH_3$), 4.74 (t, 1H, J = 9.3 Hz,

Table 2

Synthesis of 1,3-diaryl-pyrrolidine-2,2-dicarboxylates **3(a-f).**

Substrate 5-oxo-/5-thio-oxo pyrolidine	Ar	Ar′	Product	Yield (%)
1a	4-F-C_6H_4	Phenyl	**3a**	84
2a	4-F-C_6H_4	Phenyl	**3a**	82
1b	4-Cl-C_6H_4	Phenyl	**3b**	83
2b	4-Cl-C_6H_4	Phenyl	**3b**	80
1c	4-CH_3-C_6H_4	Phenyl	**3c**	77
2c	4-CH_3-C_6H_4	Phenyl	**3c**	65
1d	3,4-F,F-C_6H_3	Phenyl	**3d**	83
2d	3,4-F,F-C_6H_3	Phenyl	**3d**	81
1e	4-F-C_6H_4	2-Thienyl	**3e**	78
2e	4-F-C_6H_4	2-Thienyl	**3e**	62
1f	4-F-C_6H_4	2-Furyl	**3f**	82
2f	4-F-C_6H_4	2-Furyl	**3f**	86

Scheme 3



C(3)*H*Ph), 7.07–7.17 (m, 2H, Ar-*H*), 7.22–7.37 (m, 7H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.26, 13.42 (2× OCH_2CH_3), 47.70 (NCSCH_2), 47.87 (C(3)Ph), 62.14, 62.63 (2× OCH_2CH_3), 85.42 (*C*(2)), 115.92, 116.38, 128.29, 128.36, 128.56, 130.65, 130.83, 135.36, 135.61, 160.01 (Ar*C*), 165.71, 166.06 (2× *C*OOCH_2CH_3), 207.29 (N*C*S).

Diethyl 1-(4-chlorophenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylates 2b. Light yellow crystalline solid; yield 83%; mp 135–136°C (from ethylacetate-petroleum ether); (Found: C, 61.04; H, 4.97; N, 3.16. Calculated for $C_{22}H_{22}ClNO_4S$: C, 61.18; H, 5.09; N, 3.24%) ν_{max} (liquid film)/cm 1733.14, 1490.68; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.77 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.96 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.47–3.59 (m, 3H, NCSCH_2, OC(*H*)HCH_3), 3.84–3.96 (m, 2H, OCH_2CH_3), 4.09–4.14 (m, 1H, OC(*H*)HCH_3), 4.72 (t, 1H, J = 9.3 Hz, C(3)*H*Ph), 7.19–7.42 (m, 9H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.25, 13.40 (2× OCH_2CH_3), 47.73 (NCSCH_2), 47.97 (*C*(3)Ph), 62.17, 62.68 (2× OCH_2CH_3), 85.34 (*C*(2)), 128.34, 128.55, 129.40, 130.28, 134.91,135.59, 138.00 (Ar*C*), 165.65, 166.00 (2× *C*OOCH_2CH_3), 207.15 (N*C*S). ESI-MS for $C_{22}H_{22}NO_4SCl$ [M],[M + H+]: 432.10 (^{35}Cl); 434.10 (^{37}Cl).

Diethyl 1-(*p*-tolyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2c. White crystalline solid; yield 77%; mp 118–120°C (from ethyl acetate-petroleum ether); (Found: C, 67.52; H, 6.05; N, 3.44. Calculated for $C_{23}H_{25}NO_4S$: C, 67.15; H, 6.08; N, 3.40); ν_{max} (liquid film)/cm 1729.83, 1511.40; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.78 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 0.92 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.36 (3H, s, ArCH_3), 3.49–3.60 (m, 3H, NCSCH_2, OC(*H*)HCH_3), 3.61–3.94 (m, 2H, OCH_2CH_3), 3.98–4.14 (m, 1H, OCH_2CH_3), 4.74 (t, 1H, J = 9.3 Hz, C(3)*H*Ph)), 7.1–7.25 (m, 5H, Ar-*H*), 7.28–7.42 (m, 4H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.27, 13.30 (2× OCH_2CH_3), 21.22 (ArCH_3), 47.69 (NCSCH_2), 47.89 (*C*(3)Ph), 61.98, 62.51 (2× OCH_2CH_3), 85.47 (*C*(2)), 128.18, 128.28, 128.34, 128.49, 129.80, 135.73, 136.86, 138.90 (Ar*C*), 165.78, 166.04 (2× *C*OOCH_2CH_3), 206.83 (N*C*S). ESI-MS for $C_{23}H_{25}NO_4S$ [M],[M + H^+]: 412.13.

Diethyl 1-(3,4-difluoro phenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2d. Light yellow crystalline solid; yield 90%; mp 78–83°C (from ethyl acetate-petroleum ether); ν_{max} (liquid film)/cm 1736.14, 1509.61; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.77 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.00 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.48–3.56 (dd, 2H, J = 8.8, 22.4 Hz, NCSCH_2), 3.84–3.91 (m, 1H, OCH_2CH_3), 3.92–4.00 (1H, m, OCH_2CH_3)), 4.11–4.21 (1H, m, OCH_2CH_3), 4.24–4.29 (1H, m, OCH_2CH_3)), 4.72 (t, 1H, J = 9.2 Hz, C(3)*H*Ph), 6.94–7.04 (m, 1H, Ar-*H*)), 7.17–7.21 (m, 2H, Ar-*H*), 7.24–7.31 (m, 5H, Ar-*H*). δC (100 MHz; $CDCl_3$; Me_4Si) 13.29, 13.55 (2× OCH_2CH_3), 47.76 (NCSCH_2), 47.92 (*C*(3)Ph), 62.41, 62.85 (2× OCH_2CH_3), 85.37 (*C*(2)), 117.44, 117.62, 17.81, 118.83, 119.01, 125.78, 125.81, 128.41, 128.45, 128.67, 135.52, 135.58, 165.60 (Ar*C*), 166.06, 167.31 (2× *C*OOCH_2CH_3), 207.51 (N*C*S). $C_{22}H_{21}NO_4F_2S$ [M],[M + H+]:434.19.

Diethyl 1-(4-fluoro phenyl)-5-thioxo-3-(2-thienyl)-pyrrolidine-2,2-dicarboxylate 2e. Light yellow crystalline solid; yield 78%; mp 112–1116°C (from ethyl acetate-petroleum ether); (Found: C, 57.03; H, 4.87; N. 3.29. Calculated for $C_{20}H_{20}NO_4FS_2$: C, 57.04; H, 4.78; N. 3.32%); ν_{max} (liquid film)/cm 1733.14, 1498.88; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 0.92 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.98 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.55–3.78 (m, 2H, NCSCH_2), 3.91–3.97 (m, 1H, OCH_2CH_3), 4.00–4.04 (m, 2H, OCH_2CH_3), 4.05–4.16 (m, 1H, OCH_2CH_3), 4.96–5.01 (dd, 1H, J = 8.4, 11.2 Hz, C(3)*H*), 6.99–7.04 (m, 2H, Ar-*H*), 7.08–7.15 (m, 2H, Ar-*H*), 7.24–7.29 (m, 3H, Ar-*H*). ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ 13.40 (2× OCH_2CH_3), 43.38 (NCSCH_2), 48.46 (C(3)), 62.42, 62.61 (2× OCH_2CH_3), 84.89 (*C*(2)), 116.13, 116.36, 125.55, 126.56, 126.90, 130.40, 130.48, 135.30, 135.33, 137.42, 161.22, 163.70 (Ar*C*), 165.17, 165.90 (2× *C*OOCH_2CH_3), 206.12 (N*C*S). $C_{20}H_{20}NO_4FS_2$ [M],[M + H^+]: 422.16.

Diethyl 1-(4-fluorophenyl)-5-thioxo-3-(2-furyl)-pyrrolidine-2,2-dicarboxylate 2f. Light yellow crystalline solid; yield 80%; mp 133–134°C (from ethyl acetate-petroleum ether); (Found: C, 57.62; H, 4.85; N, 3.31. Calculated for $C_{20}H_{20}NO_5FS$: C, 56.99; H, 4.78; N. 3.32%); ν_{max} (liquid film)/cm 1735.85, 1508.40; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 0.92 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.00 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.43–3.74 (m, 2H, NCSCH_2), 3.76–3.81 (m, 1H, OCH_2CH_3), 3.85–4.05 (m, 1H, OCH_2CH_3), 4.06–4.12 (m, 2H, OCH_2CH_3), 4.76–4.81 (dd, 1H, J = 8.8, 11.6 Hz, C(3)*H*), 6.28–6.33 (dd, 2H, J = 2.8, 19.2 Hz, Ar-*H*), 6.96–7.09 (m, 2H, Ar-*H*), 7.11–727 (m, 2H, Ar-*H*), 7.37 (s, 1H, Ar-*H*). ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ 13.46, 13.52 (2× OCH_2CH_3), 42.26 (NCSCH_2), 45.84 (*C*(3)), 62.74, 62.78 (2× OCH_2CH_3), 83.68 (*C*(2)), 109.08, 110.60, 115.95, 116.09, 130.50, 130.58, 135.03, 135.06, 142.69, 148.68, 161.20, 163.28 (Ar*C*), 164.98, 165.89 (2× *C*OOCH_2CH_3), 205.91 (N*C*S). $C_{20}H_{20}NO_5FS$ [M],[M + H^+]: 406.17.

General procedure for the synthesis of 1-aryl-2,2-dicarbethoxy-3-aryl/heteroarylpyrrolidine 3(a–f) from diethyl 1,3-diaryl-5-oxo-pyrrolidine-2,2-dicarboxylates 1(a–f). To a stirred solution of $NaBH_4$ (4 mmol) in dry THF (20 mL), a solution of iodine (3 mmol) in dry THF (5 mL) was added drop wise under an argon atmosphere at 0°C over 45 min. Next γ-lactam diester (1 mmol) in dry THF (5 mL) was added to the reagent mixture, which was stirred at 25–30°C for 2 h. Then the mixture was refluxed for 20 min, cooled to 0°C, and the excess hydride was carefully destroyed with dilute HCl solution and then neutralized with dilute NaOH solution. The organic layer was separated, and the aqueous layer was extracted

with ether. The combined organic extracts were washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude products were purified by column chromatography. Colorless viscous oily materials were identified by spectroscopic methods.

General procedure for the synthesis of 1-aryl-2,2-dicarbethoxy-3-aryl/heteroarylpyrrolidine 3(a–f) from diethyl *N*-aryl-5-thioxo-3-aryl/heteroaryl-pyrrolidine-2,2-dicarboxylates (2a–f). To a stirred solution of $NaBH_4$ (3 mmol) in dry THF (20 mL), solution of iodine (2 mmol) in dry THF (5 mL) was added drop by drop, under an argon atmosphere at 0°C. The thio-γ-lactam diester (1 mmol) in dry THF (5 mL) was added to the mixture and next the resulting reaction mixture was stirred for 3–5 h at room temperature (25–30°C). After completion, the reaction (checking by TLC), the reaction mixture was cooled to 0°C, and excess hydride was carefully destroyed by adding dilute HCl solution. Then it was neutralized with dilute NaOH solution. The organic layer was evaporated out under reduced pressure and the aqueous layer was extracted with ether. The combined organic layer was washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude products were purified by column chromatography. Colorless viscous oily materials were identified by spectroscopic methods.

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3a. Yellow viscous oily material; yield (84% from 1a; 82% from 2a); (Found: C, 68.66; H, 6.25; N, 3.61. Calculated for $C_{22}H_{24}FNO_4$: C, 68.56; H, 6.28; N, 3.63%); ν_{max} (liquid film)/cm 1726.24; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.85 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.12 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.42–2.51 (m, 2H, C(4)H_2), 3.63–3.86 (m, 4H, OCH_2CH_3), 4.09–4.25 (m, 3H, C(5)H_2, C(3)*H*), 6.58–6.65 (m, 2H, Ar-*H*), 6.84–6.93 (m, 2H, Ar-*H*), 7.20–7.35 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.869, 14.117 (2× OCH_2CH_3), 29.61 (*C*(4)), 50.31(*C*(5)), 54.85 (*C*(3)), 61.20, 61.62 (2× OCH_2CH_3), 114.58 (*C*(2)), 115.020, 115.59, 115.74, 153.79, 158.48 (Ar*C*), 168.18, 169.43 (2× $COOCH_2CH_3$).

1-(4-Chlorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3b. Yellow viscous oily material; yield (83% from 1b; 80% from 2b); (Found: C, 65.68; H, 5.99; N, 3.51. Calculated for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49%); ν_{max} (liquid film)/cm 1729.25; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.87 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.16 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.38–2.57 (m, 2H, C(4)H_2), 3.64–3.91(m, 4H, OCH_2CH_3), 4.14–4.24 (3H, m, C(5)H_2, C(3)H), 6.54–6.62 (m, 2H, Ar-*H*), 7.09–7.17 (m, 2H, Ar-*H*), 7.21–7.34 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.49, 13.97 (2× OCH_2CH_3), 28.94 (*C*(4)), 50.07 (C(5)), 55.06 (*C*(3)), 61.37, 61.84 (2× OCH_2CH_3), 115.47 (*C*(2)), 122.78, 128.22, 128.30, 128.46, 137.88, 144.31 (Ar*C*), 167.87, 169.40 (2× $COOCH_2CH_3$).

1-(*p*-Tolyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3c. Yellow viscous oily material; yield (77% from 1c; 65% from 2c); (Found: C, 72.51; H, 7.10; N, 3.65. Calculated for $C_{23}H_{27}NO_4$: C,72.42; H, 7.13; N, 3.67%); ν_{max} (liquid film)/cm 1735.17; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.90 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.17 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.27 (s, 3H, Ar-CH_3), 2.41–2.57 (m, 2H, C(4)H_2), 3.66–3.95 (m, 4H, OCH_2CH_3), 4.20 (q, 3H, J = 7.4 Hz, C(5)H_2, C(3)*H*), 6.63 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.01–7.05 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.27–7.32 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.35, 13.78 (2× OCH_2CH_3), 20.15 (ArCH_3), 28.81 (*C*(4)), 49.74 (*C*(5)), 54.80 (*C*(3)), 60.94, 61.38 (2× OCH_2CH_3), 114.25 (*C*(2)), 126.69, 127.35, 127.97, 128.29, 128.82, 138.02, 143.21 (Ar*C*), 168.11, 169.60 (2× $COOCH_2CH_3$).

1-(3,4-Difluorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3d. Yellow viscous oily material; yield (83% from 1d; 81% from 2d); (Found: C, 65.62; H, 5.73; N, 3.50. Calculated for $C_{22}H_{23}F_2NO_4$: C, 65.50; H, 5.75; N, 3.47 %.); ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.85 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.16 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.38–2.47 (m, 2H, C(4)H_2), 3.61–3.91 (m, 4H, OCH_2CH_3), 4.14–4.25 (m, 3H, C(5)H_2, C(3)*H*), 6.26–6.33 (m, 1H, Ar-*H*), 6.43–6.55 (m, 1H, Ar-*H*), 6.87–7.02 (m, 1H, Ar-*H*), 7.19–7.33 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.45, 13.93 (2× OCH_2CH_3), 28.87 (*C*(4)), 50.35 (*C*(5)), 54.97 (*C*(3)), 61.47, 61.92 (2× OCH_2CH_3), 103.35, 103.78, 109.49, 109.55 (Ar*C*), 116.40 (*C*(2)), 116.74, 127.70, 128.24, 128.39, 137.75, 140.80, 141.06, 142.52, 142.72, 145.52, 145.78, 147.51, 147.78, 152.36, 152.63 (Ar*C*), 167.79, 169.22 (2× $COOCH_2CH_3$).

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-(2-thienyl) pyrrolidine 3e. Yellow viscous oily material; yield (78% from 1e; 62% from 2e); (Found: C, 61.48; H, 5.63; N, 3.56. Calculated for $C_{20}H_{22}FNO_4S$: C, 61.37; H, 5.66; N, 3.58%); ν_{max} (liquid film)/cm 1726.40; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.97 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 1.17 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 2.46–2.54 (m, 2H, C(4)H_2), 3.69–3.82 (m, 2H, OCH_2CH_3), 3.86–3.99 (m, 2H, OCH_2CH_3), 4.14–4.25 (m, 2H, C(5)H_2), 4.45 (dd, 1H, J = 7.5, 9.8 Hz, C(3)*H*), 6.57–6.64 (m, 2H, Ar-*H*), 6.83–6.96 (m, 4H, Ar-*H*), 7.19–7.22 (m, 1H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.64, 13.95 (2× OCH_2CH_3), 30.64 (*C*(4)), 50.10 (*C*(5)), 50.23 (*C*(3)), 61.55, 61.84 (2× OCH_2CH_3), 114.64 (*C*(2)), 115.08, 115.39, 115.54, 124.73, 126.38, 126.57, 140.45, 142.13, 142.16, 153.73, 158.43 (Ar*C*), 168.15, 169.15 (2× $COOCH_2CH_3$).

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-(2-furyl) pyrrolidine 3f. Yellow viscous oily material; yield (82% from 1f; 86% from 2f); (Found: C, 64.07; H, 5.88; N, 3.75. Calculated for $C_{20}H_{22}FNO_5$: C, 63.99; H, 5.91; N, 3.73%); ν_{max} (liquid film)/cm 1736.16; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 1.02 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.14 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.34–2.52 (m, 2H, C(4)H_2), 3.67–3.74 (m, 2H, OCH_2CH_3), 3.80–4.01 (m, 2H, OCH_2CH_3), 4.12–4.34 (m, 3H, C(5)H_2, C(3)*H*), 6.18 (d, 1H, J = 3 Hz, Ar-*H*), 6.30 (t, 1H, J = 1.9 Hz, Ar-*H*), 6.55–6.62 (m, 2H, Ar-*H*), 6.83–6.91 (2H, m, Ar-*H*), 7.34 (d, 1H, J = 1.8 Hz, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.69, 13.86 (2× OCH_2CH_3), 27.59 (*C*(4)), 48.75 (*C*(5)), 49.89 (*C*(3)), 61.59, 61.82 (2× OCH_2CH_3), 107.62, 110.24, 114.61 (*C*(2)), 115.05, 115.12,115.27, 141.92, 151.63, 153.67, 158.37 (Ar*C*), 168.22, 169.07 (2× $COOCH_2CH_3$).

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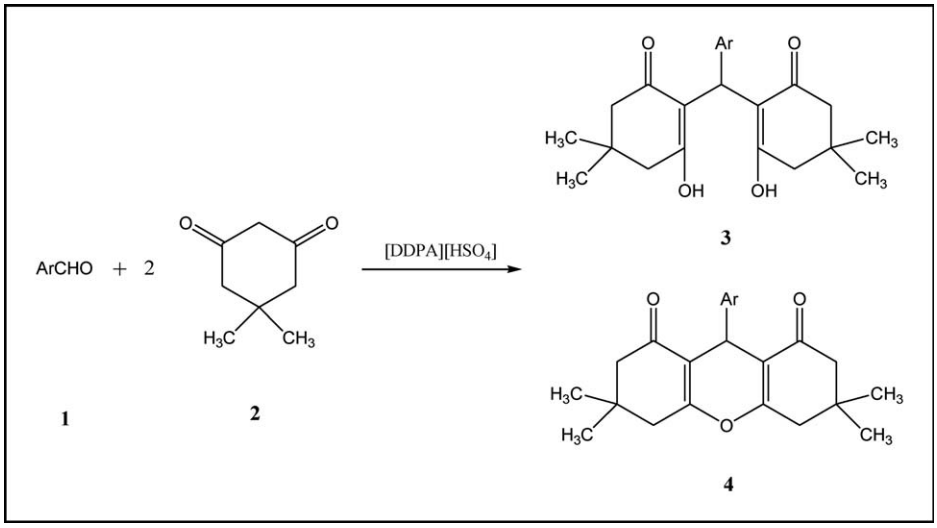

A biodegradable functionalized ionic liquid 3-(*N*,*N*-dimethyldodecylammonium)propanesulfonic acid hydrogen sulfate ([DDPA][HSO_4]) was prepared and used as a Brønsted acid–surfactant-combined catalyst for the eco-friendly one-pot synthesis of 1,8-dioxo-octahydroxanthenes at 100°C in water. Under these conditions, the reaction of various aromatic aldehydes with dimedone generated 1,8-dioxo-octahydroxanthenes in good yields with a simple postreaction procedure. The products could simply be separated from the catalyst/water system, and the catalyst could be reused at least six times without noticeably decreasing the catalytic activity.

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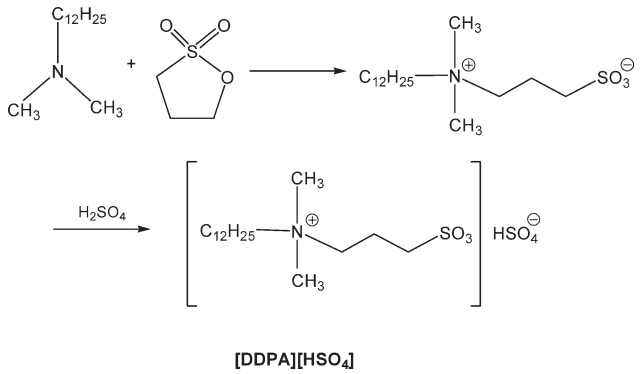
INTRODUCTION

1,8-Dioxo-octahydroxanthenes are an important class of heterocyclic compounds which have been found as a substructure in a large number of naturally occurring molecules. Because of their biological activity, 1,8-dioxo-octahydroxanthenes and their derivatives occupy a prominent position in medicinal chemistry [1]. These heterocyclic compounds have also been investigated for agricultural bactericide activity, anti-inflammatory effect, and antiviral activity. Additionally, 1,8-dioxo-octahydroxanthenes have been used as versatile synthons because of their inherent reactivity of the inbuilt pyran ring [2]. Various methods have been reported for the synthesis of these compounds catalyzed mainly by organic and mineral acids; however, these methods often suffer from the disadvantages such as long reaction times, harsh reaction conditions, toxicity, and difficulty in postprocedure of product separation. Because of these drawbacks, the synthetic approaches have been improved by the condensation of aromatic aldehydes and active methylene carbonyl compounds in the presence of the catalysts, such as *p*-dodecylbenzenesulphonic acid [3], *p*-toluenesolfonic acid [4], Fe^{3+}-montmorilonite [5], $NaHSO_4$-SiO_2 or silica chloride [6], Amberlyst-15 [7], silica sulfuric acid [8], trichloroisocyanuric acid [9], $(NH_4)_2HPO_4$ [10], Dowex-50W [11], $SbCl_3/SiO_2$, cyanuric chloride and $BiCl_3$ [12], $ZrOCl_2 \cdot 8H_2O$ [13], and HPWA/MCM-41[14]. Additionally, these compounds could also be obtained with the assistance of microwave [15] or ultrasound irradiation [16]. However, the search for the new readily available and green catalysts is still being actively pursued.

Scheme 1



[DDPA][HSO$_4$]

Nowadays ionic liquids (ILs) have attracted much interest as excellent alternatives to organic solvents due to their favorable properties. Functionalized ionic liquids (FILs), which possess the advantageous characteristics of solid acids and mineral acids, are designed to be used as novel catalysts in organic synthesis. The use of ILs as reaction medium/catalysts may offer a convenient solution to both the solvent emission and catalytic recycling problem. Some researchers have already used ILs as solvents/catalyst for condensation reactions [17]. Fan *et al*. [17a] used $InCl_3{\cdot}4H_2O$ and Wang and coworkers [17b] used $NaHSO_4$ in IL 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) for the synthesis of 1,8-dioxo-octahydroxanthenes via condensation of aromatic aldehydes with 1,3-cyclohexanedione. Dabiri *et al*. [17c] used acidic IL 1-methlyimidazolium triflouroacetate ([Hmim]TFA) as an efficient reusable catalyst for the synthesis of these compounds. Srinivasan and coworkers [16b] reported an efficient method promoted by acidic IL [Hbim]BF_4 under ultrasound irradiation. In fact, the use of task specific ionic liquids (TSILs) as catalysts is an area of ongoing activity; however, the development and exploration of Brønsted-acidic TSILs are currently in the preliminary stage. To date, research of some ''greener'' halogen-free ILs with phosphate or octyl sulfate anions and the effects of the anion and toxicology have appeared in literature [18]. Thus, it is necessary to synthesize less expensive and halogen-free TSILs, which can also be used straightforwardly with the simple procedure.

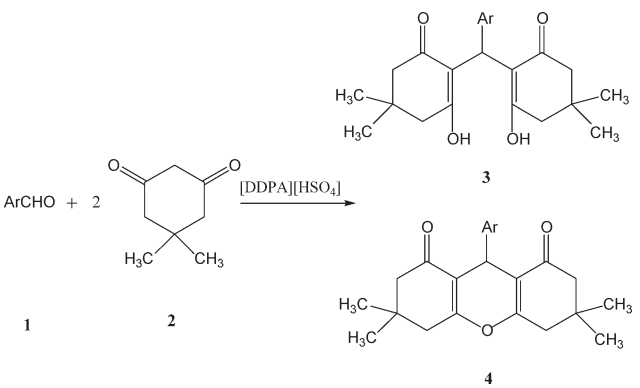
In our previous work, some novel and efficient functionalized halogen-free acidic ILs have been designed and synthesized for eco-friendly synthesis in aqueous media [19]. In continuation of our work in studying acid-catalyzed reactions in IL-water system, we report here the synthesis of 1,8-dioxo-octahydroxanthenes via one-pot condensation of aldehydes and dimedone in the halogen-free acidic IL 3-(*N*,*N*-dimethyldodecylammonium)propanesulfonic acid hydrogen sulfate ([DDPA][HSO_4]).

RESULTS AND DISCUSSION

The biodegradable surfactant zwitterionic-type precursor (*N*,*N*-dimethyl-*N*-dodecylammonium propane sulfonate) was prepared through a one-step direct sulfonation reaction of *N*,*N*-dimethyl-*N*-dodecyl amine and 1,3-propanesulfone. The zwitterions acidification was accomplished by mixing of zwitterions with sulfuric acid (98%, aq.) to convert the pendant sulfonate group into [DDPA][HSO_4] (Scheme 1). The chemical yields for both the biodegradable zwitterions formation and acidification steps were essentially quantitative as neither reaction produced byproducts, the [DDPA][HSO_4] synthesis was 100% atom efficient. The fresh new IL with HSO_4^- anion is somewhat viscous colorless liquid at room temperature and entirely miscible with water and soluble or partly soluble in organic solvents.

In the initial catalytic activity experiments (Scheme 2), 4-hydroxybenzaldehyde and dimedone were used as the model reactants at reflux in different solvents as reaction media (Table 1). As shown that the reaction could proceed effectively in water and organic solvents, including C_2H_5OH, CH_3CN, $CHCl_3$, CH_2Cl_2, C_6H_{12}, C_6H_6 (entries 3–9), and [DDPA][HSO_4]/H_2O, was found to be the most effective catalyst system and gave the highest yield of 94% (entry 2) among the solvents selected. However, in case of [DDPA][HSO_4]/solvent-free catalyst system, only the noncyclodehydrated intermediate 9-(4-hydroxyphenyl)-3,3,6,6-tetramethy-3,4,5,6,7,9-hexahydro-*H*-xanthene-1,8(2*H*)-dione **3a** was obtained with a high yield of 95% (entry 1), furthermore, **4a** could be obtained when water or organic solvents were added to **3a** and stirred for 1 h at reflux conditions. It indicated that the solubility of reactants and catalyst in the solvent could effect the cyclodehydration step of the intermediate **3a** to afford 1,8-dioxo-octahydroxanthenes. The [DDPA][HSO_4] could not disperse and contact efficiently with the reactant under solvent-free condition, which hinders the conversion of **3a** to **4a** in the cyclodehydration reaction.

Scheme 2



1 **2** **3** **4**

Table 1

Influence of the catalytic system of [DDPA][HSO_4]/solvent on 1,8-dioxo-octahydroxanthenes.[a]

Entry	Catalyst/Solvent	Isolated yield (%)	
		4	**3**
1	[DDPA][HSO_4]/solvent free	/	95[b]
2	[DDPA][HSO_4]/H_2O	94	/
3	[DDPA][HSO_4]/C_2H_5OH	76	/
4	[DDPA][HSO_4]/CH_3CN	85	/
5	[DDPA][HSO_4]/$CHCl_3$	87	/
6	[DDPA][HSO_4]/CH_2Cl_2	83	/
7	[DDPA][HSO_4]/C_6H_{12}	80	/
8	[DDPA][HSO_4]/C_6H_6	78	/
9	[DDPA][HSO_4]/$C_6H_5CH_3$	82	/

[a] 5 mmol 4-hydroxybenzaldehyde, 10 mmol dimedone, 0.5 mmol [DDPA][HSO_4], reflux, 1 h.
[b] The reaction was carried out at 100°C.

The chemical industry is under extensive pressure to replace many of the volatile organic compounds that are currently used as solvents in organic synthesis. For overcoming these problems, one approach is to use the water as the green medium, another approach is to develop new processes involving the solvent-free conditions. For the environmental and economic reasons, the [DDPA][HSO_4]/H_2O was then used as catalytic system with the above same model reaction to optimize the reaction condition. As shown in Table 2, no desirable product could be detected when a mixture of 4-hydroxybenzaldehyde and dimedone was heated at 100°C for 6 h in the absence of [DDPA][HSO_4] (entry 1), which indicated that the catalysts should be absolutely necessary for this condensation. Varying the percentage of the catalyst showed that 10 mol % of [DDPA][HSO_4] was optimum (entry 5), the use of larger amounts of catalyst did not improve yields, whereas decreasing the amounts of [DDPA][HSO_4] decreased yields. Furthermore, the effect of reaction temperature on the condensation was also investigated and the optimum temperature was 100°C. It is noteworthy that the reaction did not go to completion and only noncyclodehydrated **3a** was obtained at room temperature for 6 h (entry 8).

Table 2

Synthesis of 1,8-dioxo-octahydroxanthenes under different conditions.[a]

Entry	Catalyst	TSILs (mol %)[b]	*T* (°C)	Time (h)	Yields (%)[c]
1	–	–	100	6.0	–
2	[DDPA][HSO_4]	4	100	6.0	90
3	[DDPA][HSO_4]	6	100	4.5	92
4	[DDPA][HSO_4]	8	100	1.5	92
5	[DDPA][HSO_4]	10	100	1.0	94
6	[DDPA][HSO_4]	12	100	1.0	94
7	[DDPA][HSO_4]	15	100	1.0	94
8	[DDPA][HSO_4]	10	r.t.	6.0	72[d]
9	[DDPA][HSO_4]	10	50	4.0	79
10	[DDPA][HSO_4]	10	80	1.0	84

[a] 5 mmol 4-hydroxybenzaldehyde, 10 mmol dimedone, water is used as a solvent.
[b] Molar ration of [DDPA][HSO_4] to benzaldehyde.
[c] Isolated yields of **4a**.
[d] Isolated yields of **3a**.

Table 3

Reusing of the ionic liquid [DDPA][HSO_4].[a]

Entry	Run	Isolated yield of **4a** (%)
1	Fresh	94
2	1	93
3	2	93
4	3	92
5	4	91
6	5	91
7	6	90

[a] 5 mmol 4-hydroxybenzaldehyde, 10 mmol dimedone, 0.5 mmol [DDPA][HSO_4], 100°C, 1.0 h.

When optimizing the reaction condition, the recycling performance of [DDPA][HSO_4] was investigated using the above same model reaction. After the separation of the produced **4a**, the catalyst-containing filtrate was reused in the next run without further purification. The data listed in Table 3 showed that the [DDPA][HSO_4] could be reused at least six times without obviously decreasing the catalytic activity. Compared with the traditional solvents and catalysts, the easy recycling performance is also an attractive property of this IL for the environmental protection and economic reasons.

Then, the condensation reaction of structurally varied aldehydes with dimedone in the presence of [DDPA][HSO_4] as an environment catalyst was explored under the optimized reaction conditions described above and the results are presented in Table 4.

It can easily be seen that in all cases, the reactions gave the products not only in good yields ranged from 87 to 95%m but also in excellent selectivity of **4a–l**. Aromatic aldehydes carrying either electron-donation or electron-withdrawing substituents afforded good yields of 1,8-dioxo-octahydroxanthenes in high purity, additionally, and ortho-, meta- and para-substituted substrates reacted almost equally well, although orthogroup (entry 3) has steric hindrance.

The results obtained with benzaldehyde and dimedone under the optimized conditions were compared with the results of other catalysts reported in the literatures, the data listed in Table 5 showed that the [DDPA][HSO_4]

Table 4

Synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [DDPA][HSO_4].[a]

Entry	Ar	Product	Time (h)	mp (°C) [Lit]	Yields (%)[b]
1	p-HOC_6H_4	**4a**	1.0	245–247 [5]	94
2	p-FC_6H_4	**4b**	1.0	223–225 [15]	95
3	o-ClC_6H_4	**4c**	1.0	226–228 [5]	94
4	p-ClC_6H_4	**4d**	1.0	230–232 [5]	96
5	p-BrC_6H_4	**4e**	1.5	231–233 [15]	87
6	m-$NO_2C_6H_4$	**4f**	1.0	146–117 [15]	97
7	p-$NO_2C_6H_4$	**4g**	1.0	221–223 [5]	95
8	p-$CH_3C_6H_4$	**4h**	1.5	212–214 [5]	94
9	p-$CH_3OC_6H_4$	**4i**	2.0	235–237 [5]	95
10	C_6H_5	**4j**	1.0	198–200 [5]	93
11	Thiophene-2-carbaldehyde	**4k**	1.0	159–161 [12b]	88
12	Pyridine-2-carbaldehyde	**4l**	1.0	200–202 [12b]	87

[a] 5 mmol benzaldehyde, 10 mmol dimedone, 0.5 mmol [DDPA][HSO_4], 100°C.

was relatively a good catalyst for this reaction, additionally, this catalyst was biodegradable.

In conclusion, a Brønsted acid–surfactant-combined IL DDPA][HSO_4] was synthesized in an atom-economic procedure. The [DDPA][HSO_4] was found to be an efficient catalyst for one-pot synthesis of 1,8-dioxo-octahydroxanthenes in aqueous media, offering the practical convenience in the product separation from the catalytic system. The merit of this methodology is that it is simple, mild, and efficient and has potential application in green chemistry.

EXPERIMENTAL

Melting points were determined on an X-6 microscope melting apparatus and reported uncorrected. The IR spectra were run on a Nicolete spectrometer and expressed in cm^{-1} (KBr). ^{1}H-NMR spectra were recorded on a Bruker DRX300 (300 MHz) and ^{13}C-NMR spectra on a Bruker DRX300 (75.5 MHz) spectrometer. Elemental analyses were recorded on Perkin-Elmer C apparatus. Mass spectra were obtained with an automated Finnigan Trace Ultra-Trace DSQ LC-MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

Synthesis of acidic halogen-free acidic ionic liquid ([DDPA][HSO_4]). The FIL [DDPA][HSO_4] was prepared according to our previous work with some changes [16]. The structure of [DDPA][HSO_4] was analyzed by ^{1}H-NMR, elemental analyses, and MS spectral data (Scheme 1).

To a solution of 13.3 g N, *N*-dimethyl-*N*-dodecyl amine (0.10 mol) in 30 mL 1,2-dichloroethane was added 12.2 g 1,3-propanesultone (0.10 mol) in portion within 15 min, and then the mixture was stirred under nitrogen for 2 h at 55–60°C. When cooled to room temperature, a white precipitate thus formed was then filtered and washed with petroleum ether. The product was refined from a mixture of water, ethanol, and ether, 98% yield of white solid product was obtained, mp 320–322°C (decomposing) with darkening at 300°C.

The mixture of 13.3 g N, *N*-dimethyl-*N*-dodecylammonium propane sulfonate (0.10 mol) and 10.0 g sulfuric acid solutions (98%; 0.10 mol) was stirred for 2 h at 80°C. Then, the combined solution was dried in a vacuum at 100°C. The produced [DDPA][HSO_4] was washed repeatedly with diethyl ether to remove unreacted material and dried in a vacuum again, and then the [DDPA][HSO_4] was obtained quantitatively and in high purity as colorless oil.

The selected spectral data for SO_3H-functionalized halogen-free [DDPA][HSO_4]: [DDPA][HSO_4] ^{1}H-NMR (300 MHz, D_2O): δ 0.53 (t, 3H, J = 6.62 Hz, —CH_3), 0.95–1.02 (m, 18H, —$(CH_2)_9$—), 1.42 (m, 2H, —C—CH_2—C—N), 1.83–1.87 (m, 2H, —C—CH_2—C—SO_3), 2.60 (t, 2H, J = 6.91 Hz, —CH_2—SO_3), 2.77 (s, 6H, N—CH_3), 2.98 (t, J = 7.95 Hz, 2H, —C—CH_2—N), 3.14 (t, J = 8.25 Hz, 2H, —CH_2—C—C—SO_3). Anal. Calcd. For CHNOS: C, 47.09; H, 9.07; N, 3.23; Found: C, 46.82; H, 9.08; N, 3.09. MS (*m*/*z*): 432.18 ($M^+ - 1$).

Table 5

Condensation reaction with different catalystic system.

Entry	Catalyst/Solvent	T (°C)	Time (h)	Yields (%)	Ref.
1	[DDPA][HSO_4]/H_2O	100	1.0	93	This work[a]
2	Fe^{3+}-montmorillonite	100	6.0	94	[5]
3	Cyanuric chloride	120	50 min	92	[12b]
4	$BiCl_3$	80	3.0	90	[12c]
5	$InCl_3{\cdot}4H_2O$/[bmim]BF_4	80	4.0	87	[17a]
6	[Hmim]TFA	80	3.0	85	[17c]

[a] 5 mmol benzaldehyde, 10 mmol dimedone, 0.5 mmol [DDPA][HSO_4], 100°C, 1.0 h.

General procedure for 1,8-dioxo-octahydroxanthenes catalyzed by [DDPA][HSO_4]. To a round-bottomed flask charged with aldehyde (5 mmol) **1**, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **2** in 5 mL of water was added [DDPA][HSO_4] (0.5 mmol) under stirring. The mixture was then stirred for a certain time at 100°C. On completion (monitored by thin layer chromatography), the precipitated crude product was collected by filtration and recrystallized form ethanol (95%) to afford pure 1,8-dioxo-octahydroxanthenes **4**. The filtrate containing the catalyst could be reused directly in the next run without further purification. The products were identified by IR, ^{1}H-NMR, and physical data (mp) with those reported in the literatures (Table 4).

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Efficient Preparation of 3-Substituted Quinazolinediones Directly from Anthranilic Acids and Isocyanates

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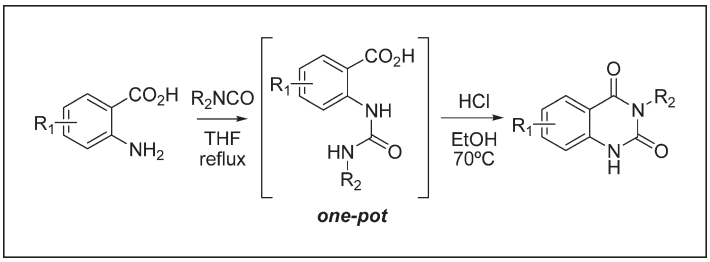
Dedicated in memory of Keith Fagnou, 1971–2009.



An efficient and practical synthesis of 3-substituted quinazolinediones is described. The protocol uses readily available isocyanates and anthranilic acids as precursors in a one-pot operation and has been demonstrated on >50 g scale. Isolation of the products via filtration directly from the reaction media is facile, affording high-purity material. This procedure was then applied to the synthesis of Zenarestat.

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INTRODUCTION

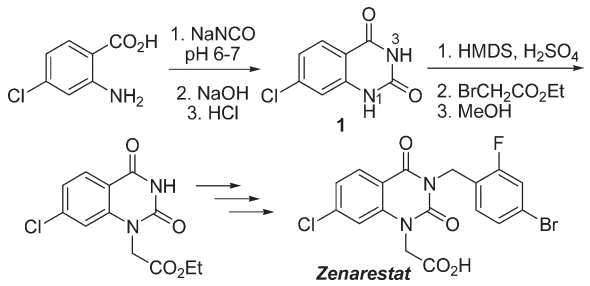
Quinazolinedione heterocycles are important structural motifs in a variety of natural products as well as active pharmaceutical ingredients [1]. They can also serve as building blocks for other classes of compounds such as substituted quinazolinones and quinazolines. As a result, the preparation of this privileged motif has been extensively studied [1]. Of the many reports that discuss the preparation of the 1*H*,3*H*-quinazolinediones, the most direct approach results from the reaction of anthranilic acids with urea or with sodium or potassium cyanate as exemplified by the preparation of **1**, in the synthesis of Zenarestat, a novel aldose reductase inhibitor for the treatment of diabetic complications (Scheme 1) [2].

Zenarestat, as with many other medicinally interesting examples of quinazolinediones, have unsymmetrical substitution patterns across the two nitrogen atoms [3]. The completion of its synthesis from **1** relies on the selective reaction of an alkylating agent with the parent heterocycle. However, the dependence on selective alkylation in the use of 1*H*,3*H*-quinazolinediones as building blocks for their substituted derivatives often proves difficult leading to mixtures of regioisomers [2,4].

Therefore, methods which allow for selective substitution on one of the nitrogen atoms are of great value in the preparation of these important molecules [5]. Selective alkylation reactions have been shown to be possible at the 1-position using bis(trimethylsilyloxy)quinazolines as activated precursors (see Scheme 1) [2]. However, reports of regioselective reactions at the 3-position are very scarce and typically require separation of a mixture of compounds [4]. Instead, chemists have turned to the use of prefunctionalized building blocks for the selective introduction of substituents. Anthranilate esters [6], *o*-amino benzonitriles [7], and 2-nitro benzoates [8] have all been used in the preparation of the 3-substituted quinazolinediones. Transition metal-catalyzed processes have also been developed using *o*-halo benzoates [9] and *o*-iodoanilides [10].

In the context of developing a scale-up route of an active pharmaceutical ingredient, we were faced with the preparation of a 3-alkyl quinazolinedione. It occurred to us that the most direct route to such a motif would be from the commercially available anthranilic acid and isocyanate coupling partner. If anthranilic acids would be capable of directly forming the urea without protection of the acid moiety, a simple cyclization reaction could then occur to furnish the 3-alkyl quinazolinedione in a single pot. This approach was seldomly described in the literature [11] but has been observed as a side reaction [7a,b]. Nonetheless, we were pleased to see that high yields and purities could be obtained and that simple isolation of the desired compounds via filtration was possible. Herein, we disclose convenient and scaleable procedures (mutligram scale) for the one-pot synthesis of 3-substituted quinazolinediones, which is general for a wide variety of anthranilic acids as well as aliphatic, benzylic, and aromatic isocyanates.

Scheme 1. Preparation of 7-chloroquinazoline-(1*H*,3*H*)dione in the synthesis of Zenarestat.



RESULTS AND DISCUSSION

As a probe for the scope of anthranilic acids that participate in this reaction, we chose allyl isocyanate as the coupling partner. All anthranilic acids that we tested in this protocol reacted well with excess (1.1–1.5 equiv.) allyl isocyanate at reflux in tetrahydrofuran (THF). Reaction times were moderate (3–6 h), but no detrimental effects on conversion or purity was observed if the reaction was left overnight for convenience. We also did not observe any advantages to the use of additives such as base (Et_3N) or nucleophilic catalysts (DMAP and NMI). Once the addition reactions had reached high conversion [12], the solvent was switched from THF to EtOH [13] and ~10 equiv. (2.5 mL/g) of concentrated HCl was added to the mixture, which was then heated to 70°C. The cyclization step was generally fast 1–3 h but was variable depending on the substitution pattern [14]. We were pleased to find that the high crystallinity of the substituted quinazolinediones allowed for direct crystallization from the reaction. Once the reaction was cooled in an ice bath (internal temperature ~5°C), water (20 mL/g) was added to the mixture. This slurry was stirred for 30 min, filtered, washed with water, and then heptanes before drying under a stream of nitrogen. Table 1 outlines the scope of anthranilic acids used in this procedure. All reactions were performed on multigram scale (~2 g) and were scaled to 55 g for 5-methoxy anthranilic acid (Entry 4). We found that substitution at all positions of the ring was tolerated. Moreover, we did not observe any significant electronic effects with the exception of strong electron withdrawing substituents at the 6-position, such as nitro, which did not allow for the initial addition reaction to occur efficiently. In most cases, we observed very high purities [15] and compounds were suitable for full characterization without further purification.

In some cases, we did observe formation of an ethyl ester of the urea adduct as an impurity. In general, this was rejected under the current isolation protocol; however, in some cases, as with 5-bromo anthranilic acid, it was impossible to completely reject this impurity. We were pleased to see that simple treatment of the solid under standard ester hydrolysis conditions, followed by reisolation of the product effectively destroyed and rejected this impurity (Scheme 2).

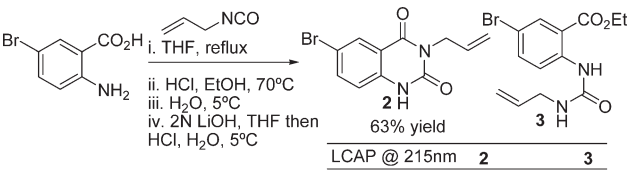
While the current protocol was optimized for allyl isocyanate, we briefly investigated the use of other isocyanates in this transformation. We were particularly interested in verifying the applicability of the protocol over a diverse class of isocyanates. We therefore turned our attention to aryl, benzyl, and branched aliphatic substrates. Anthranilic acid was reacted under the same conditions as before with a variety of isocyanates as outlined in Table 2. In general, we were pleased to observe that the reaction was very effective in affording good yields of the quinazolinedione products. In the case of branched aliphatics, we found that cyclic isocyanates (Entry 6) were tolerated but that others reacted sluggishly as illustrated by sec-butylisocyanate (Entry 7). However, as the procedure was not optimized for each different isocyanate, initial purities were generally slightly lower. When compounds obtained were not pure enough for analytical characterization, an isopropanol trituration improved the purity to an acceptable level (Entry 3). For benzyl isocyanates, we found that higher purities were obtained when the isocyanate was used as the limiting reagent (entries 4 and 5) [16].

While column chromatography can be used to upgrade purity, the high insolubility of these crystalline compounds complicates chromatography and is not recommended on gram scale. We found that the purities obtained using this protocol were more than sufficient to perform subsequent steps on these very useful building blocks. This is exemplified by the formal synthesis of Zenarestat (Scheme 3).

Known isocyanate **4** [17] was reacted with commercially available 4-chloro anthranilic acid under our standard protocol on. The quinazolinedione **5** [18] was obtained (1 g) as a white solid in 68% yield. This material was then directly used in the subsequent alkylation with ethyl bromoacetate to afford ethyl ester **6** in 90% yield. Hydrolysis of this ester was already described on kilo scale to afford Zenarestat [2,18].

In conclusion, we have developed a very efficient and facile one-pot procedure for the preparation of 3-substituted quinazolinediones, which allows for the direct use

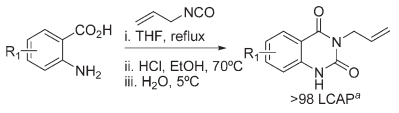
Scheme 2. Purity upgrade with 3-allyl-6-bromo quinazoline-dione.

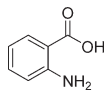
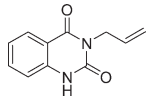
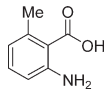
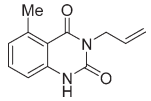
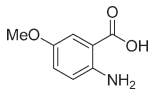
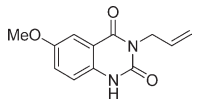
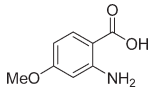
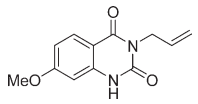
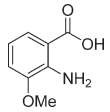
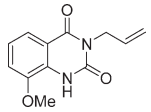
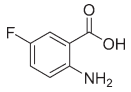
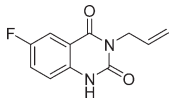
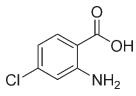
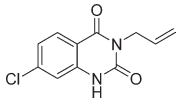
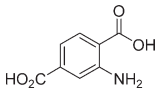
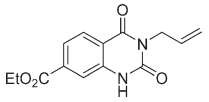


LCAP @ 215nm	2	3
initial purity	88	12
after hydrolysis (2N LiOH, THF then HCl, 5ºC)	>99	<1

Table 1

Scope of anthranilic acid with allyl isocyanate.



Entry	Anthranilic acid	3-Allyl quinazolinedione	Yield (%)[b]
1			71
2			66
3			84
4			79
5			64
6			69
7			63
8			72[c]

[a]LCAP, liquid chromatography area percent at 215 nm.
[b]Isolated yield.
[c]Product treated with H_2SO_4 in EtOH to complete esterification.

of anthranilic acids and isocyanates. As many of these reagents are commercially available or readily prepared, we anticipate this procedure should find significant use in the preparation of this important pharmacophore.

EXPERIMENTAL SECTION

All reagents and solvents were used as received from their commercial supplier [15]. See Supporting Information available for 1H and 13C NMR spectra for all new compounds.

General procedure A (2 g scale). In round-bottomed flask with a magnetic stir bar, the anthranilic acid derivative is dissolved in THF (10 mL/g) and 1.1 equiv. of isocyanate is added to the mixture, which is stirred in an oil bath at 70°C. Once complete (or a minimum of 80%) conversion to addition adduct is achieved, the reaction is cooled and the solvent is rotary evaporated and replaced with EtOH (10 mL/g). Then, 2 mL/g of concentrated HCl (12.1*M*) is added and the mixture is reheated to 70°C until complete conversion to the 3-substituted quinazolinedione is determined by high pressure liquid chromatography (HPLC). The reaction mixture is cooled in an ice bath (internal temperature ~5°C) and water (20 mL/g) is added, which causes a precipitate to form. This slurry is stirred for 30 min, filtered, washed with water (10 mL/g), and then heptanes (3 × 10 mL/g) before drying the solids under a stream of nitrogen. Products are generally obtained as white or off-white solids.

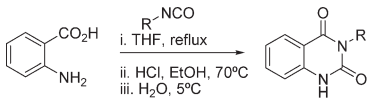
General procedure B (used for a reaction on 55 g scale; Table 1, Entry 4). In a three-neck round-bottomed flask equipped with a mechanical stirrer, internal temperature probe, and a condenser, anthranilic acid is charged to THF (10 mL/g). To this stirring mixture is added 1.1 equiv. of isocyanate and the mixture is stirred at reflux. Once complete (or a minimum of 80%) conversion to addition adduct is achieved, the solvent was switched to EtOH (10 mL/g). Then, 2 mL/g of concentrated HCl (12.1*M*) is added and the mixture is reheated to an internal temperature of 70°C until complete conversion to the 3-substituted quinazolinedione is determined by HPLC. The reaction mixture is cooled in an ice bath (internal temperature ~5°C) and water (20 mL/g) is added over 15 min, which causes a precipitate to form. This slurry is stirred for 30 min, filtered, washed with water (10 mL/g), and then heptanes (3 × 10 mL/g) before drying the solids under a stream of nitrogen. Products are generally obtained as white or off-white solids.

3-Allylquinazoline-2,4(1H,3H)-dione (Table 1, Entry 1). Prepared according to general procedure A. Melting point (°C): 181.4–184.5 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 752, 958, 1652, 1709, 3071; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 4.73 (d, J = 5.71 Hz, 2 H); 5.23 (d, J = 10.25 Hz, 1 H); 5.33 (d, J = 17.18 Hz, 1 H); 5.91–6.04 (m, 1 H); 7.15 (d, J = 8.14 Hz, 1 H); 7.25 (m, 1 H); 7.63 (t, J = 7.71 Hz, 1 H); 8.14 (d, J = 7.95 Hz, 1 H); 10.62 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 42.9, 114.6, 115.2, 117.9, 123.4, 128.4, 131.7, 135.1, 138.6, 152.1, 162.1. HRMS calculated for $C_{11}H_{10}N_2O_2$ $[M + H]^+$ 203.0815; Found: 203.0815.

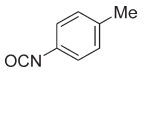
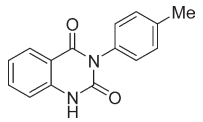
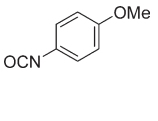
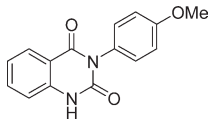
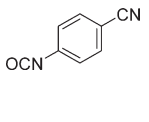
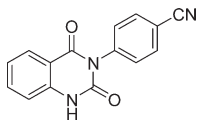
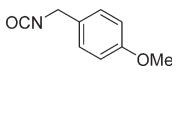
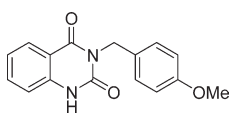
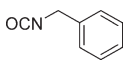
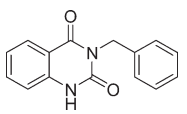
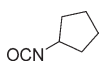
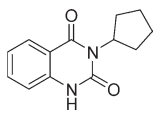
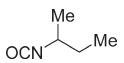
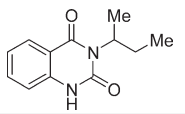
3-Allyl-5-methylquinazoline-2,4(1H,3H)-dione (Table 1, Entry 2). Prepared according to general procedure A. Melting point (°C): 211.6–214.8 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 729, 940, 1448, 1648, 1702, 2901; ^{1}H-NMR δ

Table 2

Scope of isocyanate with anthranilic acid.



92-99 LCAP[a]

Entry	Isocyanate	Quinazolinedione	Yield (%)[b]
1			67
2			82
3			72[c]
4			89[d]
5			84[d]
6			80
7			<10

[a]LCAP, liquid chromatography area percent at 215 nm.
[b]Isolated yields.
[c]Product triturated in iPrOH.
[d]Isocyanate used as the limiting reagent.

(ppm) ($CHCl_3$-d): 2.79 (s, 3 H,), 4.69 (d, J = 5.54 Hz, 2 H), 5.22 (d, J = 10.23 Hz, 1 H), 5.32 (d, J = 17.20 Hz, 1 H), 5.91–6.04 (m, 1 H), 6.99 (d, J = 7.58 Hz, 2 H), 7.44 (t, J = 7.75 Hz, 1 H), 10.67 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 22.7, 42.8, 113.0, 113.3, 117.5, 126.5, 132.1, 133.9, 139.8, 142.7, 151.8, 162.5. HRMS calculated for $C_{12}H_{12}N_2O_2$ $[M + H]^+$ 217.0972; Found: 217.0992.

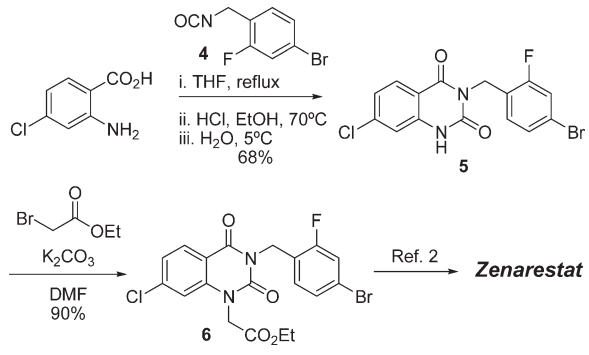
3-Allyl-6-methoxyquinazoline-2,4(1H,3H)-dione (Table 1, Entry 3). Prepared according to general procedure A. Melting point (°C): 198.7–202.9 ($EtOH/H_2O$). IR (ν_{max}/cm^{-1}): 815, 1335, 1642, 1702, 2889; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 3.87 (s, 3 H); 4.72 (d, J = 5.66 Hz, 2 H); 5.23 (d, J = 10.24 Hz, 1 H); 5.32 (d, J = 17.17 Hz, 1 H); 5.92–6.04 (m, 1 H); 7.06 (d, J = 8.82 Hz, 1 H); 7.24 (dd, J = 2.85, 8.77 Hz, 1 H); 7.56 (d, J = 2.88 Hz, 1 H); 10.11 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 43.0, 55.8, 108.8, 115.1, 116.6, 117.8, 124.7, 131.8, 132.7, 151.5, 155.8, 162.0. HRMS calculated for $C_{12}H_{12}N_2O_3$ $[M + H]^+$ 233.0921; Found: 233.0911.

3-Allyl-7-methoxyquinazoline-2,4(1H,3H)-dione (Table 1, Entry 4). Prepared according to general procedure B. Melting point (°C): 220 ($EtOH/H_2O$). IR (ν_{max}/cm^{-1}): 761, 1432, 1618, 1711, 3198; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 3.89 (s, 3 H); 4.67 (d, J = 5.66 Hz, 2 H); 5.21 (d, J = 10.20 Hz, 1 H); 5.29 (d, J = 17.11 Hz, 1 H); 5.91–5.97 (m, 1 H); 6.44 (s, 1 H); 6.79 (d, J = 8.91 Hz, 1 H); 8.05 (d, J = 8.82 Hz, 1 H); 8.88 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 42.8, 55.8, 98.1, 111.5, 117.6, 130.4, 132.0, 140.3, 151.7, 165.1. HRMS calculated for $C_{16}H_{14}N_2O_3$ $[M + Na]^+$ 255.0740; Found: 255.0733.

3-Allyl-8-methoxyquinazoline-2,4(1H,3H)-dione (Table 1, Entry 5). Prepared according to general procedure A. Melting point (°C): 210.2 ($EtOH/H_2O$). IR (ν_{max}/cm^{-1}): 744, 1076, 1264, 1642, 3069; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 3.96 (s, 3 H); 4.67 (d, J = 5.65 Hz, 2 H); 5.21 (d, J = 10.26 Hz, 1 H); 5.29 (d, J = 17.20 Hz, 1 H); 5.88–6.01 (m, 1 H); 7.09 (d, J = 7.96 Hz, 1 H); 7.16 (t, J = 7.96 Hz, 1 H); 7.70 (d, J = 7.91 Hz, 1 H); 8.18 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 42.9, 56.2, 114.3, 114.9, 117.7, 119.4, 122.8, 129.0, 131.7, 145.4, 149.9, 162.0. HRMS calculated for $C_{12}H_{12}N_2O_3$ $[M + Na]^+$ 255.0740; Found: 255.0736.

3-Allyl-6-fluoroquinazoline-2,4(1H,3H)-dione (Table 1, Entry 6). Prepared according to general procedure A. Melting point (°C): 202.0–204.8 ($EtOH/H_2O$). IR (ν_{max}/cm^{-1}): 768, 1280, 1440, 1616, 1659; ^{1}H-NMR (400 MHz, $CHCl_3$-d): 4.71 (d, J = 5.63 Hz, 2 H); 5.25 (d, J = 10.22 Hz, 1 H); 5.33 (d, J = 17.19 Hz, 1 H); 5.90–6.03 (m, 1 H); 6.84 (d, J = 8.82 Hz, 1 H); 6.96 (t, J =

Scheme 3. Formal synthesis of Zenarestat.



8.54 Hz, 1 H); 8.16 (t, J = 7.16 Hz, 1 H); 10.76 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 43.0; 101.8 (d, J = 26.1 Hz); 111.2 (d, J = 1.65 Hz); 111.9 (d, J = 22.7 Hz); 118.1, 131.4, 131.5 (d, J = 3.6 Hz); 140.5 (d, J = 12 Hz); 152.2, 161.2, 166.8 (d, J = 255.8 Hz). HRMS calculated for $C_{11}H_{10}FN_2O_2$ $[M + H]^+$ 221.0721; Found: 221.0721.

3-Allyl-7-chloroquinazoline-2,4(1H,3H)-dione (Table 1, Entry 7). Prepared according to general procedure A. Melting point (°C): 205.6–209.5 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 767, 1077, 1434, 1609, 2862; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 4.71 (d, J = 5.67 Hz, 2 H); 5.19–5.38 (m, 2 H); 5.90–6.03 (m, 1 H); 7.13 (s, 1 H); 7.15–7.30 (m, 2 H); 8.08 (d, J = 8.50 Hz, 1 H); 10.30 (s, 1 H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 42.5, 113.2, 115.0, 116.9, 123.2, 130.0, 133.0, 139.8, 141.0, 150.2, 161.4. HRMS calculated for $C_{11}H_{10}ClN_2O_2$ $[M + H]^+$ 237.0425; Found: 237.0424.

Ethyl 3-allyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (Table 1, Entry 8). Prepared according to general procedure A. The solid obtained from this procedure was then resuspended in EtOH (10 mL/g) and 2 mol equiv. of H_2SO_4 was added. The reaction was then heated in an oil bath at 70°C. On complete conversion of the mixture to the ethyl ester product, the reaction was cooled to ~5°C and water (20 mL/g) was added, which causes a precipitation to form. This slurry was then filtered and washed with water (10 mL/g) and then heptanes (3 × 10 mL/g) before drying the solids under a stream of nitrogen.

Melting point (°C): 202.6–209.0 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 742, 1222,1277, 1637, 1719, 3184; ^{1}H-NMR δ (ppm) (DMSO-d_6): 1.32 (3 H, t, J = 7.02 Hz), 4.33 (2 H, q, J = 7.06 Hz), 4.47 (2 H, s), 5.06–5.16 (2 H, m), 5.81–5.91 (1 H, m), 7.65 (1 H, d, J = 8.17 Hz), 7.72 (1 H, s), 7.99 (1 H, d, J = 8.15 Hz), 11.58 (1 H, s). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 14.5, 42.7, 62.0, 116.6 (s), 117.0 (s), 117.3 (s), 122.7 (s), 128.5 (s), 133.0 (s), 135.7 (s), 139.9 (s), 150.2 (s), 161.6 (s), 165.1 (s). HRMS calculated for $C_{14}H_{15}N_2O_4$ $[M + H]^+$ 275.1026; Found: 275.1025.

3-Allyl-6-bromoquinazoline-2,4(1H,3H)-dione (Scheme 2). Prepared according to general procedure A. The solid obtained from this procedure was then dissolved in THF (10 mL/g) and 2*N* LiOH (5 mol equiv.) is added to the stirring mixture at room temperature. On consumption of the ester by-product, the reaction was cooled to ~5°C and concentrated HCl was added dropwise until the pH was <2. This caused a precipitate to form, which was filtered, washed with water (10 mL/g), and then heptanes (3 × 10 mL/g) before drying the solids under a stream of nitrogen.

Melting point (°C): 232.0–234.3 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 673, 818, 1440, 1644, 2920; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 4.69 (d, J = 5.70 Hz, 2 H); 5.19–5.36 (m, 2 H); 5.89–6.00 (m, 1 H); 7.01 (d, J = 8.59 Hz, 1 H); 7.71 (d, J = 8.62 Hz, 1 H); 8.27 (s, 1 H); 10.01 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): 43.1, 116.1, 116.2, 118.2, 131.0, 131.4, 137.3, 138.0, 151.4, 160.8. HRMS calculated for $C_{11}H_9BrN_2O_2$ $[M + H]^+$ 280.9920; Found: 280.9921.

3-(4-Methylphenyl)quinazoline-2,4(1H,3H)-dione (Table 2 Entry 1). Prepared according to general procedure A. Melting point (°C): 265.3–267.1 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 753, 1397, 1648, 1723, 3194; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 2.44 (s, 3 H); 6.89 (d, J = 8.15 Hz, 1 H); 7.16–7.25 (m, 3 H); 7.34 (d, J = 7.82 Hz, 2 H); 7.48–7.56 (m, 1 H); 8.14 (d, J = 7.92 Hz, 1 H); 9.84 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 21.3, 114.8, 115.3, 123.4, 128.2, 128.6, 130.1, 132.1, 135.2, 138.8, 138.8, 151.8, 162.7. HRMS calculated for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0972; Found: 253.0966.

3-(4-Cyanophenyl)quinazoline-2,4(1H,3H)-dione (Table 2 Entry 3). Prepared according to general procedure A. The solid obtained from this procedure was suspended in isopropyl alcohol and stirred for 3 h. The slurry was then filtered and washed with water (10 mL/g) and then heptanes (3 × 10 mL/g) before drying the solids under a stream of nitrogen.

Melting point (°C): 262.4 (IPA). IR (ν_{max}/cm^{-1}): 749, 1490, 1667, 2216, 2932; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.22–7.27 (m, 2 H); 7.61 (d, J = 8.08 Hz, 2 H); 7.72 (t, J = 7.77 Hz, 1 H); 7.94 (d, J = 8.06 Hz, 1 H); 7.98 (d, J = 8.11 Hz, 2 H); 11.65 (s, 1 H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ 40.4, 40.6, 111.6, 114.8, 115.8, 119.0, 123.1, 128.1, 131.1, 133.4, 135.9, 140.3, 140.7, 150.3, 162.5. HRMS calculated for $C_{15}H_9N_3O_2$ $[M + H]^+$ 264.0768; Found: 264.0775.

3-(4-Methoxybenzyl)quinazoline-2,4(1H,3H)-dione (Table 2 Entry 4). Prepared according to general procedure A. The material obtained from this procedure was 94 LCAP. A small sample was purified via silica gel chromatography to obtain an analytically pure sample using EtOAc/DCM gradient 0–50% DCM.

Melting point (°C): 213.8 (EtOAc/DCM). IR (ν_{max}/cm^{-1}): 751, 1242, 1653, 1710, 2901; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 3.77 (s, 3 H); 5.20 (s, 2 H); 6.83 (d, J = 8.27 Hz, 2 H); 7.01 (d, J = 8.17 Hz, 1 H); 7.17–7.28 (m, 5 H); 7.50 (d, J = 8.27 Hz, 2 H); 7.60 (t, J = 7.75 Hz, 1 H); 8.14 (d, J = 7.95 Hz, 1 H); 8.99 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 43.6, 55.2, 113.7, 114.7, 115.0, 123.4, 128.5, 129.1, 130.6, 135.0, 138.5, 152.2, 159.1, 162.3. HRMS calculated for $C_{16}H_{14}N_2O_3$ $[M + Na]^+$ 305.0897; Found: 305.0890.

3-Benzylquinazoline-2,4(1H,3H)-dione (Table 2 Entry 5). Prepared according to general procedure A. Melting point (°C): 225.4–227.4 (EtOH/H_2O). IR (ν_{max}/cm^{-1}): 691, 752, 1448, 1652, 2901; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 5.28 (s, 2 H); 7.06 (d, J = 8.12 Hz, 1 H);

7.19–7.35 (m, 4 H); 7.51–7.65 (m, 3 H); 8.14 (d, J = 7.94 Hz, 1 H); 10.20 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 44.2, 114.6, 115.0, 123.5, 127.7, 128.4, 128.5, 128.9, 135.1, 136.8, 138.5, 152.0, 162.3. HRMS calculated for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0972; Found: 233.0966.

3-Cyclopentylquinazoline-2,4(1H,3H)-dione (Table 2 Entry 6). Prepared according to general procedure A. The material obtained from this procedure was 92 LCAP. A small sample was purified via silica gel chromatography to obtain an analytically pure sample using EtOAc/DCM gradient 0–50% DCM.

Melting point (°C): 235.8 (EtOAc/DCM). IR (ν_{max}/cm^{-1}): 757, 1400, 1649, 1171, 2901; ^{1}H-NMR (400 MHz, $CHCl_3$-d): δ 1.89–1.97 (m, 2 H); 2.05 (s, 2 H); 2.16–2.26 (m, 2 H); 5.42–5.54 (m, 1 H); 7.08 (d, J = 8.12 Hz, 1 H); 7.17–7.29 (m, 1 H); 7.60 (t, J = 7.69 Hz, 1 H); 8.13 (d, J = 7.95 Hz, 1 H); 10.35 (s, 1 H). ^{13}C-NMR (101 MHz, $CHCl_3$-d): δ 26.0, 28.6, 53.2, 114.6, 115.1, 123.2, 128.4, 134.8, 138.5, 152.2, 162.7. HRMS calculated for $C_{13}H_{14}N_2O_2$ $[M + H]^+$ 231.1128; Found: 231.1121.

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[12] All reactions had a minimum of 80% conv. before they were taken forward.

[13] Other solvents were screened but EtOH or iPrOH were optimal.

[14] While 2-amino-3-nicotinic acid reacted with the isocyanate, its cyclization was very slow (>7 days). The cause of this observation is currently under investigation.

[15] HPLC analysis was performed using the following conditions: Zorbax SB C18, RRHT, 1.8 μm (50 × 4.6) 0.1% H_3PO_4 in water/MeCN start 90:10, ramp to 50:50 over 8 min, ramp to 5:95 over 4 min. Total: 12 min, 2 mL/min, 35°C, 215 nm, 5 μL.

[16] Dibenzylureas formed from excess isocyanate were difficult to reject under our current protocol.

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A Green and Selective Synthesis of 2-Aryloxazines and 2-Aryltetrahydropyrimidines

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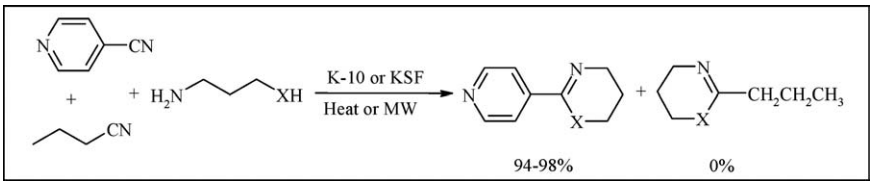

An efficient method for the selective synthesis of 2-substituted oxazines and tetrahydropyrimidines by the reaction of arylnitriles with 3-amino-1-propanol and 1,3-diaminopropane in the presence of montmorillonite K-10 and KSF as inexpensive, environmentally benign, and reusable catalysts under classical heating conditions and microwave irradiation is reported.

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INTRODUCTION

5,6-Dihydro-4*H*-1,3-oxazines and 1,4,5,6-tetrahydropyrimidines are important heterocyclic compounds, which are found in both various biologically active natural compounds and designed medicinal agents [1]. These heterocycles exhibit a wide variety of biological activities and pharmacological properties such as muscarinic agonist [2], antiviral and inflammatory activities [3], and also acting as anthelmintics [4], antidepressants [5], and fungicides [6]. Due to the significant interest in these heterocyclic compounds, a number of methods have been reported for their synthesis from different precursors [7–16].

Montmorillonite clays (K-10 and KSF) are environmentally friendly and economically feasible solid acids that offer several advantages such as noncorrosiveness, low cost, ease of handling, and reusability [17]. The reactions catalyzed by montmorillonite clays are usually carried out under mild conditions with high yields and high selectivities, and the work-up of these reactions is very simple. The combination of these solid acid catalysts with microwave irradiation provides even more benign processes.

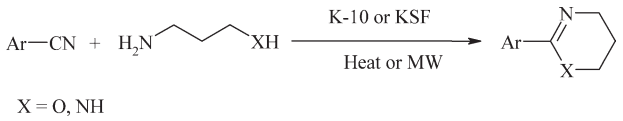
In continuation of our research on the development of new synthetic methodologies [18], herein we report a selective method for synthesis of 2-aryloxazines and tetrahydropyrimidines by the reaction of arylnitriles with 3-amino-1-propanol and 1,3-diaminopropane in the presence of montmorillonite K-10 and KSF under thermal conditions and microwave irradiation (Scheme 1).

RESULTS AND DISCUSSION

At first, to determine the optimized reaction conditions, 4-cyanopyridine was allowed to react with 3-amino-1-propanol in the presence of montmorillonite K-10 and KSF clays under various reaction conditions to obtain respective 1,3-oxazine. The results are summarized in Table 1. As shown, the best result was obtained with 4-cyanopyridine (1 mmol), 3-amino-1-propanol (4 mmol), and montmorillonite K-10 (0.09 g) or KSF (0.12 g) at 125°C (Table 1, entry 3). While the yields were reduced by decreasing the amount of 3-amino-1-propanol (Table 1, entries 1, 2), K-10 or KSF (Table 1, entries 4–6), and temperature (Table 1, entries 7, 8). To examine the effect of montmorillonite clay catalysts, the same reaction was performed in the absence of the catalysts. Under these conditions, the corresponding 1,3-oxazine was obtained in only 15% yield (Table 1, entry 9). In the reaction of 4-cyanopyridine with 1,3-diaminopropane, the best yield of the corresponding tetrahydropyrimidine was also obtained under the same reaction conditions. The reaction of 4-cyanopyridine with 3-amino-1-propanol and 1,3-diaminopropane was also investigated under microwave irradiation. The experimental results showed that the highest yields of the corresponding 1,3-oxazine and tetrahydropyrimidine were obtained with irradiation power of 800 W at 90°C and of 1000 W at 120°C, respectively.

Under the optimized reaction conditions, various aromatic nitriles reacted with 3-amino-1-propanol and 1,3-diaminopropane in the presence of catalytic amounts of montmorillonite K-10 and KSF to provide the corresponding 2-substituted oxazines (Table 2, entries 1–6) and tetrahydropyrimidines (Table 3, entries 1–5) in high yields and purity, respectively. Heteroaromatic nitriles such as 3-cyano and 4-cyanopyridines and thiophene-2-carbaldehyde underwent smooth conversion into the

Scheme 1



corresponding 2-substituted oxazines (Table 2, entries 7–9) and tetrahydropyrimidines (Table 3, entries 6–8) in excellent yields. The results showed that the yields of the products are comparable under thermal conditions and microwave irradiations, but the reaction times are considerably shorter under microwave irradiation.

To show the general applicability of this method, the reaction of 4-cyanopyridine was performed on a 20 mmol scale. The result was comparable with that obtained by the small scale experiment.

The structures of the products were established by ^{1}H NMR, ^{13}C NMR, IR, and mass spectra and elemental analysis.

Dinitriles such as 1,3- and 1,4-dicyanobenzenes were converted to the respect mono-oxazines (Table 2, entries 10, 11) and mono-tetrahydropyrimidines (Table 3, entries 9, 10) under the same reaction conditions with excellent chemoselectivity even in the presence of large excess of 3-amino-1-propanol or 1,3-diaminopropane. Transformation of dinitriles to their mono-oxazines and mono-tetrahydropyrimidines is of practical importance because the remaining nitrile group can be converted to other important functional groups.

It is also noteworthy that alkylnitriles did not react under the same reaction conditions and remained intact in the reaction mixture. Therefore, the present method was found to be convenient and chemoselective for the conversion of arylnitriles to their 1,3-oxazines and tetrahydropyrimidines in the presence of alkylnitriles (Scheme 2).

Table 1

Optimization of conditions in the reaction of 4-cyanopyridine (1 mmol) with 3-amino-1-propanol in the presence of K-10 and KSF.

Entry	3-Amino-1-propanol (mmol)	K-10 (g)	KSF (g)	T (°C)	Yield (%)[a] K-10	Yield (%)[a] KSF
1	2	0.09	0.12	125	71	69
2	3	0.09	0.12	125	83	85
3	4	0.09	0.12	125	95	98
4	4	–	0.09	125	–	86
5	4	0.06	0.06	125	80	73
6	4	0.03	0.03	125	65	63
7	4	0.09	0.12	70	60	60
8	4	0.09	0.12	100	70	75
9	4	–	–	125	15	15

[a] Isolated yield.

Finally, the possibility of recovering and reusing of the catalysts, which is very important from practical and economical point of views was examined. In this respect, the reaction of 4-cyanopyridine with 3-amino-1-propanol (Table 2, entry 7) was investigated in the presence of montmorillonite K-10 and KSF. After completion of the reaction, EtOH was added, and the catalyst were separated by filtration and reused in the next cycle. The results shown in Table 4 illustrate that the catalysts can be used at least eight times without significant loss of their activities.

In conclusion, we have developed an efficient and chemoselective protocol for the conversion of arylnitriles to their corresponding 2-substituted oxazines and tetrahydropyrimidines under thermal conditions and

Table 2

Synthesis of 2-aryloxazines.[a]

Entry	Ar	K-10 Thermal Yield%[b] (Time, h)	K-10 MW Yield%[b] (Time, min)	KSF Thermal Yield%[b] (Time, h)	KSF MW Yield%[b] (Time, min)
1	C_6H_5	94 (2.3)	92 (5)	90 (2.5)	90 (5)
2	4-ClC_6H_4	92 (1.5)	92 (7.5)	90 (1.5)	94 (7)
3	3-ClC_6H_4	90 (1.25)	98 (7)	94 (1.4)	90 (6)
4	4-BrC_6H_4	95 (3.4)	90 (6.5)	89 (2.25)	90 (6)
5	3-BrC_6H_4	90 (1)	85 (8)	95 (1.25)	89 (9)
6	3-$O_2NC_6H_4$	90 (1.25)	85 (3)	85 (1.1)	80 (2)
7	4-pyridyl	95 (1.1)	94 (3)	98 (1)	94 (3)
8	3-pyridyl	96 (1.3)	95 (3)	90 (1)	91 (6.5)
9	2-furyl	90 (2.5)	91 (4)	94 (1.5)	91 (4)
10	4-NCC_6H_4	97 (1.1)	93 (2)	99 (1)	95 (2)
11	3-NCC_6H_4	95 (1)	95 (3)	98 9 (1.1)	98 (2)

[a] Isolated yield.
[b] The products were identified by their physical and spectral data [9,12,13,19].

Table 3

Synthesis of tetrahydropyrimidines.[a]

Entry	Ar	K-10 Thermal Yield%[b] (Time, h)	K-10 MW Yield%[b] (Time, min)	KSF Thermal Yield%[b] (Time, h)	KSF MW Yield%[b] (Time, min)
1	C_6H_5	93 (6.25)	90 (6.5)	90 (6)	91 (7)
2	4-ClC_6H	90 (4.5)	91 (7.5)	85 (4)	90 (8)
3	3-ClC_6H_4	90 (5)	95 (8)	96 (4.5)	90 (10)
4	4-BrC_6H_4	95 (3.5)	95 (8)	90 (2.8)	90 (10)
5	3-BrC_6H_4	92 (4.25)	90 (9)	95 (3.5)	95 (8)
6	4-pyridyl	94 (2.5)	95 (4)	94 (2.5)	95 (4)
7	3-pyridyl	85 (10)	95 (4.5)	85 (10)	95 (4.5)
8	2-furyl	95 (5)	95 (8)	95 (5)	95 (8)
9	4-NCC_6H_4	90 (6.5)	98 (7)	90 (6.5)	98 (7)
10	3-NCC_6H_4	95 (5.8)	95 (8)	95 (5.8)	95 (8)

[a] Isolated yield.
[b] The products were identified by their physical and spectral data [9,15,19].

microwave irradiation. The use of cheap, commercially available, reusable, and environmentally friendly catalysts make this method eco-friendly and economically acceptable. Other advantages of the present method are easy work-up, short reaction times, and high yields of the products.

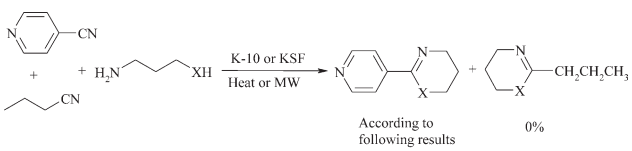
EXPERIMENTAL

Melting points were obtained by Stuart Scientific apparatus and are uncorrected. Yields refer to isolated products. ^1H and ^{13}C NMR (500 and 125 MHz) spectra were recorded on a Bruker-Avance AQS 500 spectrometer in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on Shimadzu IR-435 spectrophotometer. Mass spectra were obtained on platform II spectrometer from Micromass; E1 mode at 70 eV. The microwave system used in these experiments includes the following items: Micro-SYNTH labstation, complete with glass door, dual magnetron system with pyramid-shaped diffuser, 1000 W delivered power, exhaust system, magnetic stirrer, ''quality pressure'' sensor for flammable organic solvents, ATCFO fiber optic system for automatic temperature control.

General procedure for the synthesis of 1,3-oxazines and tetrahydropyrimidines under thermal conditions. A mixture of nitrile (1 mmol), 3-amino-1-propanol or 1,3-diaminopropane (4 mmol), and montmorillonite K-10 (0.09 g) or KSF (0.12 g) was stirred at 125°C for the appropriate time according to Tables 2 and 3. The progress of the reaction was monitored by TLC (eluent: ethyl acetate/*n*-hexane, 4:1). After completion of the reaction, EtOH (15 mL) was added, and the catalyst was removed by filtration. The solvent was evaporated, and the crude product was purified by column chromatography on neutral alumina to afford the pure product.

General procedure for the synthesis of 1,3-oxazines and tetrahydropyrimidines under microwave irradiation. A mixture of nitrile (1 mmol), 3-amino-1-propanol or 1,3-diaminopropane (4 mmol), and montmorillonite K-10 (0.09 g) or

Scheme 2



Catalyst/conditions	X = O Yield (%)[a]	X = O Time	X = NH Yield (%)[a]	X = NH Time
K-10 (0.09 g)/Heat	95	1.1 h	94	2.5 h
KSF (0.12 g)/Heat	98	1 h	94	2.5 h
K-10 (0.09 g)/MW	94	3 min	95	4 min
KSF (0.12 g)/MW	94	3 min	95	4 min

[a] Isolated yield.

Table 4

Reusability of the catalysts in the reaction of 4-cyanopyridine with 3-amino-1-propanol.[a]

Run	K-10 Time (h)	K-10 Yield (%)[b]	KSF Time (h)	KSF Yield (%)[b]
1	1.1	95	1	98
2	1.1	95	1	98
3	1.1	95	1	98
4	1.1	95	1	98
5	1.1	95	1	98
6	1.1	95	1	98
7	1.1	95	1	98
8	1.1	92	1	95

[a] Reaction conditions: 4-cyanopyridine (1 mmol), 3-amino-1-propanol(4 mmol), K-10 (0.09 g) or KSF (0.12 g) at 125°C.
[b] Isolated yield.

KSF (0.12 g) was subjected to microwave irradiation at the required power level according to the optimized conditions for the appropriate time (Tables 2 and 3). After completion of the reaction as indicated by TLC, EtOH (15 mL) was added, and the catalyst was separated by filtration. Evaporation of the solvent and purification of the crude product by column chromatography on neutral alumina gave the pure product.

2-(4-Cyanophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 10). mp 162–163°C; ir (KBr) 3045, 2920, 2210, 1644, 1503, 1420, 1343, 1260, 1133, 1090, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 4.38 (t, J = 5.4 Hz, 2H), 3.63 (t, J = 5.8 Hz, 2H), 2.00 (qn, J = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 138.3, 131.8, 127.5, 118.6, 113.7, 65.4, 42.8, 21.8; ms: m/z 186 (M^+), 160, 130, 102, 76, 52. Anal. Calcd. For $C_{11}H_{10}N_2O$: C, 70.96; H, 5.41; N, 15.04. Found: C, 70.83; H, 5.37; N, 15.15.

2-(3-Cyanophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 11). mp 153–155°C; ir (KBr) 3062, 2920, 2222, 1660, 1580, 1478, 1375, 1170, 1090, 800, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.13 (d, J = 9 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 4.37 (t, J = 5.3 Hz, 2H), 3.61 (t, J = 5.8 Hz, 2H), 1.99 (qn, J = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 135.4, 133.4, 131.1, 130.8, 128.9, 118.5, 112.4, 65.5, 42.7, 21.8; ms: m/z 186 (M^+), 185 ($[M - 1]^+$), 149, 130, 102, 76. Anal. Calcd. For $C_{11}H_{10}N_2O$: C, 70.96; H, 5.41; N, 15.04. Found: C, 70.85; H, 5.35; N, 15.13.

2-(3-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 3). mp 131–132°C; ir (KBr) 3300, 2922, 2800, 1620, 1571, 1550, 1373, 1330, 1220, 1110, 840, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.56 (d, J = 10.2 Hz, 1H), 7.37 (d, J = 10.9 Hz, 1H), 7.26–7.30 (m, 1H), 4.9 (br s, 1H), 3.48 (t, J = 5.7 Hz, 4H), 1.87 (qn, J = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 138.7, 134.4, 129.8, 129.6, 126.6, 124.2, 42.2, 20.6. Anal. Calcd. For $C_{10}H_{11}ClN_2$: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.54; H, 5.75; N, 14.32.

2-(3-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 5). mp 138–139°C; ir (KBr) 3192, 3059, 2933, 1607, 1547, 1512, 1362, 1302, 1194, 862, 798, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.57 (d, J = 10.2 Hz, 1H), 7.51 (d, J = 10.8 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 5.2 (br s, 1H), 3.51 (t, J = 5.7 Hz, 4H), 1.86 (qn, J = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 138.5, 132.9, 129.9, 129.5, 124.8, 122.5, 42.0, 22.7; ms: m/z 240 ($[M + 2]^+$), 238 (M^+), 237 ($[M - 1]^+$), 182, 159, 102, 76. Anal. Calcd. For $C_{10}H_{11}BrN_2$: C, 50.23; H, 4.64; N, 11.72. Found: C, 50.37; H, 4.69; N, 11.64.

2-(4-Pyridyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 6). mp 97–99°C; ir (KBr) 3200, 2921, 2854, 1622, 1596, 1533, 1362, 1305, 1280, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 6.1 Hz, 2H), 7.54 (d, J = 6.1 Hz, 2H), 3.53 (t, J = 5.8 Hz, 4H), 2.8 (br s, 1H), 1.87 (qn, J = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 150.1, 144.3, 120.4, 42.2, 20.4; ms: m/z 161 (M^+), 160 ($[M - 1]^+$), 131, 105, 78. Anal. Calcd. For $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 66.89; H, 6.93; N, 25.

2-(3-Pyridyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 7). Yellow oil; ir (neat) 3300, 2805, 1617, 1593, 1421, 1394, 1200, 1019, 817, 770, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.26–7.32 (m, 1H), 3.54 (t, J = 5.7 Hz, 4H), 2.6 (br s, 1H), 1.90 (qn, J = 5.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 150.8, 147.2, 134.1, 132.7, 123.2, 42.3, 22.7. Anal. Calcd. For $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.19; H, 6.81; N, 26.13.

2-(4-Cyanophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 9). mp 69–71°C; ir (KBr) 3213, 3020, 2922, 2240, 1626, 1537, 1492, 1367, 1308, 1186, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3, Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 4.1 (br s, 1H), 3.49 (t, J = 6.3 Hz, 4H), 1.84 (qn, J = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 140.1, 131.3, 126.7, 117.9, 112.5, 41.4, 19.7. Anal. Calcd. For $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.18; H, 5.90; N, 22.77.

2-(3-Cyanophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 10). mp 136–139°C; ir (KBr) 3177, 3025, 2959, 2220, 1622, 1541, 1475, 1367, 1194, 806 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (d, J = 5.3 Hz, 1H), 7.66 (d, J = 5.1 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 4.2 (br s, 1H), 3.51 (t, J = 5.8 Hz, 4H), 1.87 (qn, J = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 138.5, 132.9, 130.4, 129.9, 129.2, 118.4, 112.5, 42.4, 20.6; ms: m/z 185 (M^+), 184 ($[M - 1]^+$), 129, 102, 75. Anal. Calcd. For $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.21; H, 5.94; N, 22.75.

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One-Pot Synthesis of Pyrano- and Furanoquinolines Catalyzed by Molten Tetra-*n*-butylphosphonium Bromide Under Solvent-Free Conditions

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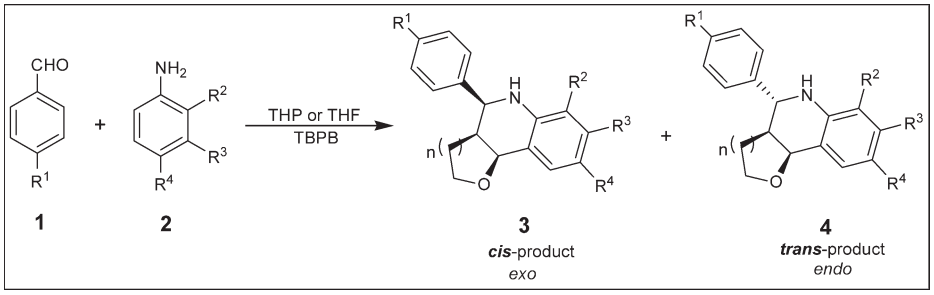

Molten tetra-*n*-butylphosphonium bromide is found to be a practical and inexpensive catalytic media for stereoselective one-pot synthesis of pyranoquinoline and furanoquinoline derivatives in good to excellent yields. Products of undesirable reactions resulting from polymerization are not observed. The use of this catalyst media avoids the use of any cocatalysts or toxic organic solvents.

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INTRODUCTION

Pyranoquinoline and furanoquinoline derivatives are found abundantly in a variety of natural and synthetic products, which exhibit various physiological properties and are potentially bioactive compounds [1]. These skeletons exist in many alkaloids such as veprisine, oricine, and flindersine [2], which possess a wide rang of biological activity such as antiallergenic [3], antibacterial [4], psychotropic [5], anti-inflammatory [6], and estrogenic activity [7]. Hence, for the preparation of these complex molecules, there has been interest in organic synthesis. One of the most straightforward routs to their synthesis involves imino-Diels–Alder reaction with various dienophiles in the presence of Lewis acids [4,8]. However, the application of these methods suffers from some disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction times, unsatisfactory yields, low selectivity, or the use of toxic solvents. On the other hand, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. Therefore, despite a number of precedents, an efficient, practical, and facile method for these transformations is desired.

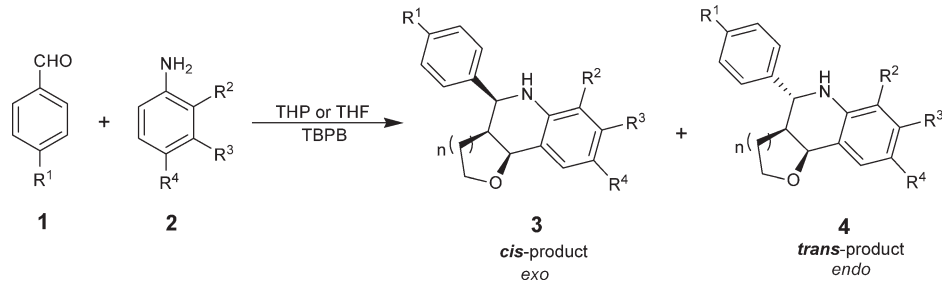
Due to the environmental concerns the use of benign solvents as an alternative to volatile organic solvents are much interest to organic chemists [9]. The use of ionic liquids as reaction media and catalyst can offer a solution to solvent emission and catalyst recycle problems [10]. Ionic liquids possess a number of interesting properties, especially their lack of vapor pressure, a widely accessible temperature range with lack of flammability, and ease of product recovery that reduce environmental emissions [11].

Recently, ionic liquids have been successfully used as solvents with catalytic activity for a variety of reactions but their use as catalyst under solvent-free conditions need to be more attention [12]. However, the high cost of most conventional ionic liquids and apprehension about their toxicity [13] especially imidazolium systems with PF_4 and BF_4 anions are as toxic as benzene to certain aquatic ecosystems, and also liberate hazardous HF during recycling have led us to explore the use of more benign salts in the molten state as practical alternatives. During our endeavors to explore the utility of ionic liquid in organic transformations, we have recently reported a practical and efficient protocol for thiolysis of epoxides in the presence of tetra-*n*-butylphosphonium bromide (TBPB) as an inexpensive and commercially available ionic liquid [14].

RESULTS AND DISCUSSION

In further extension of our work in the context of economical chemistry [14], herein, we would like to report

Scheme 1



the use of molten tetra-*n*-butylphosphonium bromide (m-TBPB) as an inexpensive ionic liquid for efficient one-pot synthesis of pyrano- and furanoquinoline derivatives under solvent-free conditions (Scheme 1).

Several aldimines (formed *in situ* from aromatic aldehydes and anilines in ionic liquid) and 3,4-dihydro-2*H*-pyran (DHP) or 2,3-dihydrofuran (DHF) were heated in the presence of m-TBPB medium to afford the corresponding pyrano- and furanoquinolines in 72–86% yield. The high-yield transformation did not form any significant amounts of undesirable side products. Among the various ionic liquids such as tetra-*n*-butylammonium bromide, tetra-*n*-butylammonium chloride, tetra-*n*-butylammonium fluoride, and *n*-butylpyridinium tetrachloroferrate ([bpy]$FeCl_4$) which were studied for this reaction, m-TBPB used here gave better yields (also better selectivity) with short reaction times. However, in the absence of ionic liquid, the reaction did not yield any product even after a long reaction time (15–20 h). In all cases, the products were obtained as a mixture of **3** exo- and **4** endo-isomers favoring the endo-diastereomer **4**.

On the other hand, this procedure is highly diastereoselective. The products were formed as a mixture of s-cis and s-trans isomers, which could be separated by column chromatography over silica gel and whose ratio was determined by ^{1}H-NMR spectra of the crude products. The results shown in Table 1 clearly indicate the scope and generality of diasteroselective condensation with respect to various aryl aldehydes and anilines with DHP or DHF.

The reaction is fairly general, clear, rapid, and efficient. The experimental procedure for this transformation is remarkably straightforward and unlike previously reported methods, the presence procedure does not require the use of toxic organic solvents or inert atmospheres. The proposed mechanism of formation of quinoline is shown in Scheme 2, being similar to that previously suggested [10c].

CONCLUSIONS

In conclusion, we have demonstrated a new, straightforward, efficient, and stereoselective method for the one-pot synthesis of pyrano- and furanoquinolines, using m-TBPB as a commercially available ionic liquid. The significant feature of this method include (a) operational simplicity, (b) inexpensive reagent, (c) high yields of product, (d) high diastereoselectivity, and (e) the use of relatively nontoxic catalytic media.

EXPERIMENTAL

General procedure for one-pot synthesis of pyrano- and furanoquinoline derivatives in the presence of m-TBPB under solvent-free conditions. A mixture of aryl aldehyde (1 mmol), aniline derivative (1 mmol), and DHP or DHF (2 mmol) in m-TBPB (1 mmol) was heated at 50°C under stirring for the appropriate time according to Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC) (4:1, hexane/acetone) and after completion, it was poured into cooled mixture of (1:1) water/ethanol and stirred for 5 min. The solid was suction filtered, washed with cold ethanol (2 × 10 mL), and filtered. The resulting product was directly charged on small silica gel column and eluted with a mixture of acetone/*n*-hexane (1:4) to afford pure products.

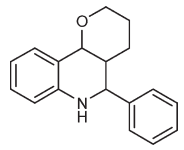
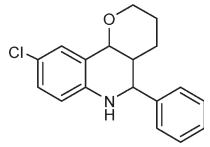
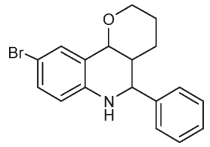
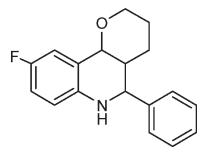
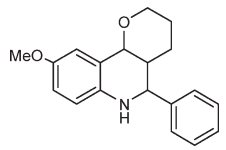
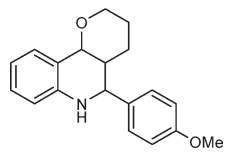
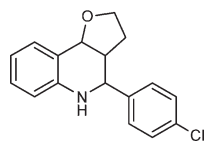
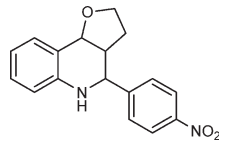
Analytical data for selected compounds. ***Product 1.*** Trans: mp: 123–124°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.25–7.45 (6H, m), 7.05 (1H, t, J = 7.8 Hz), 6.75 (1H, t, J = 7.8 Hz), 6.55 (1H, d, J = 7.8 Hz), 5.34 (1H, d, J = 5.6 Hz), 4.70 (1H, d, J = 2.8 Hz), 3.35–3.65 (3H, m), 2.15 (1H, m), 1.25–1.55 (4H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 145.2, 141.1, 128.3, 128.0, 127.6, 127.5, 126.8, 119.8, 118.3, 114.4, 72.8, 60.6, 59.3, 38.9, 25.4, 18.0; ir (KBr), ν (cm^{-1}): 3378, 2936, 1605, 1485, 1071, 750.

Cis: colorless solid, mp: 94–95°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.35–7.45 (5H, m), 7.25 (1H, d, J =7.8 Hz), 7.05 (1H, t, J = 7.8 Hz), 6.80 (1H, t, J = 7.8 Hz), 6.50 (1H, d, J = 7.8 Hz,), 4.75 (1H, d, J = 10.5 Hz), 4.40 (1H, d, J = 2.8 Hz), 3.95 (2H, m), 3.75 (1H, t, J = 11.7 Hz), 2.15 (1H, m), 1.85(1H, m), 1.65 (1H, m), 1.50 (1H, m), 1.25 (1H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 144.1, 141.7, 130.2, 128.7, 128.0, 127.2, 127.1, 120.0, 116.8, 113.5, 73.9, 68.0, 54.1, 38.2, 23.5, 21.4; ir (KBr), ν (cm^{-1}): 3374, 2928, 1610, 1489, 1077, 750.

Product 2. Trans: colorless solid, mp: 154–155°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.37–7.28 (6H, m), 7.03 (1H, d, J = 8.2 Hz), 6.53 (1H, d, J = 8.3 Hz), 5.24 (1H, brs), 4.64 (1H, brs), 3.89 (1H, brs), 3.61 (1H, d, J = 11.2 Hz), 3.43–3.31 (1H, m), 2.13–2.07 (1H, m), 1.78–1.31 (4H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 145.6, 141.3, 128.1, 128.0, 127.3, 127.1, 126.8, 119.3, 118.0, 114.4, 72.7, 60.5, 59.0, 38.2, 25.4, 18.2; ir (KBr), ν

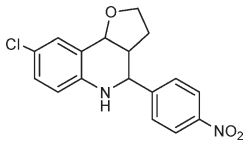
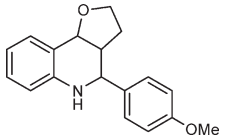
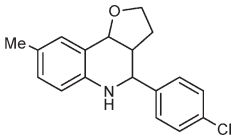
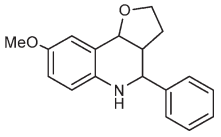
Table 1

One-pot synthesis of pyrano- and furanoquinoline in the presence of m-TBPB under solvent-free conditions.

Entry	Product[a]	Time (h)	Yield (%)[b]	trans/cis[c]	de%
1		1.25	79	95/5	90
2		1.30	81	93/7	86
3		1.30	72	92/8	84
4		1.30	78	93/7	86
5		1.15	85	88/12	76
6		1.30	73	85/15	70
7		1.15	83	90/10	80
8		1	82	96/4	92

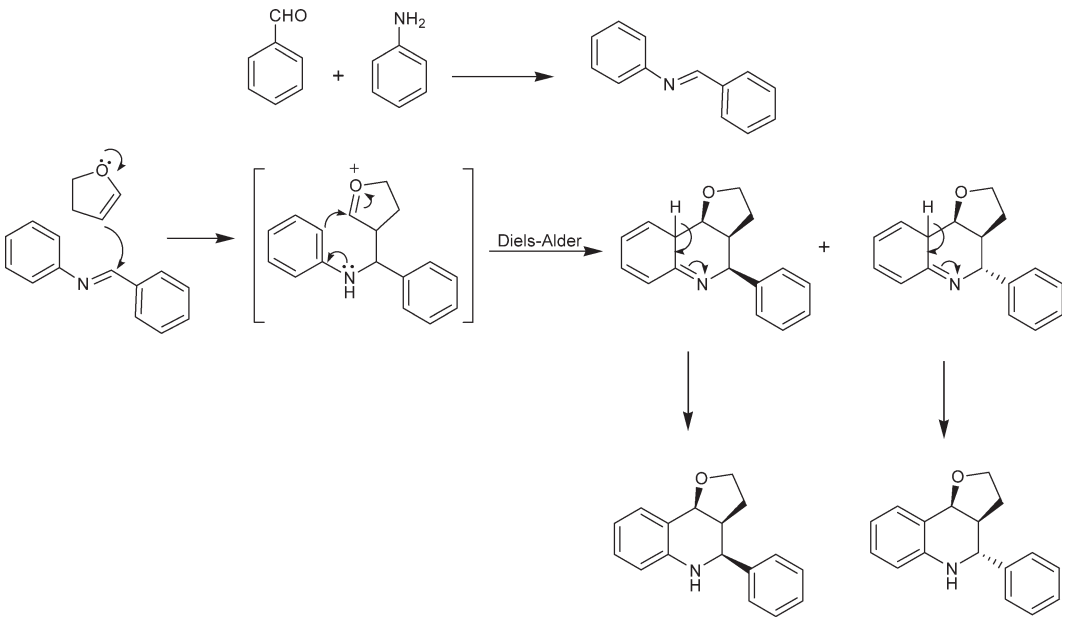
(*Continued*)

Table 1
(*Continued*)

Entry	Product[a]	Time (h)	Yield (%)[b]	trans/cis[c]	de%
9		1.10	86	90/10	80
10		1.40	80	88/12	75
11		1	85	90/10	90
12		1.15	85	92/8	80

[a] All products were characterized with ^{1}H-NMR, ^{13}C-NMR, IR, and comparison of their physical and spectral data with those samples in the literatures.8
[b] Isolated yields.
[c] The isomeric ratio is based on isolation by column chromatography.

Scheme 2



(cm^{-1}): 3362, 3326, 2937, 1615, 1487, 1071, 920, 820, 800, 750, 700.

Cis: colorless solid, mp 122–123°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.37 (5H, m), 7.19 (1H, s), 7.03 (1H, d, J = 8.3 Hz), 6.45 (1H, d, J = 8.3 Hz), 4.67 (1H, d, J = 10.5 Hz), 4.33 (1H, s), 4.08 (2H, m), 3.73 (1H, m), 2.05 (1H, m), 1.83–1.31 (4H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 143.2, 141.8, 130.3, 129.1, 128.6, 127.6, 126.1, 121.8, 121.7, 115.2, 73.8, 68.4, 54.8, 38.6, 23.9, 22.0; ir (KBr), ν (cm^{-1}): 3348, 2934, 1494, 1265, 920, 825, 810, 750, 700.

Product 5. Trans: colorless solid, mp: 146–147°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.40–7.29 (5H, m), 7.03 (1H, s), 6.73 (1H, d, J = 8.2 Hz), 6.57 (1H, d, J = 8.2 Hz), 5.31 (1H, d, J = 5.4 Hz), 4.61 (1H, s), 3.73 (3H, s), 3.67 (1H, brs), 3.61–3.36 (2H, m), 2.15 (1H, m), 1.54–1.26 (4H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 152.8, 141.3, 139.1, 128.3, 127.4, 126.8, 121.1, 115.7, 115.0, 111.8, 72.9, 60.8, 59.5, 55.8, 39.1, 25.3, 17.9; ir (KBr), ν (cm^{-1}): 3295, 2942, 1502, 1262, 1065, 921, 825, 810, 735, 710.

Cis: dense liquid, ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.43–7.27 (5H, m), 6.82 (1H, s), 6.75 (1H, d, J = 9.1 Hz), 6.49 (1H, d, J = 8.5 Hz), 4.62 (1H, d, J = 10.5 Hz), 4.38 (1H, s), 4.10 (1H, m), 3.75 (5H, m), 2.10 (1H, m), 1.84–1.30 (4H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 151.9, 142.2, 138.7, 128.1, 127.7, 126.0, 121.3, 116.7, 115.5, 114.7, 74.5, 68.3, 55.7, 55.1, 38.8, 24.0, 21.9; ir (neat), ν (cm^{-1}): 3361, 2938, 1504, 1255, 1032, 920, 825, 810, 735, 710.

Product 6. Trans: solid, mp: 146–147°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.32 (2H, d, J = 8.0 Hz), 7.18 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 6.84 (2H, d, J = 8.0 Hz), 6.64 (1H, t, J = 8.0 Hz), 6.45 (1H, d, J = 8.0 Hz), 4.64 (1H, d, J = 10 Hz), 4.36 (1H, d, J = 2.5 Hz), 4.06 (1H, m), 3.97 (1H, d, J = 3.0 Hz), 3.82 (3H, s), 3.63 (1H, t, J = 10.0 Hz), 2.02 (1H, m), 1.82 (1H, m), 1.64 (1H, m), 1.44 (1H, m), 1.28 (1H, m).

Cis: solid, mp: 154–155°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.38 (1H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.00 (1H, m), 6.82 (2H, d, J = 8.0 Hz), 6.77 (1H, t, J = 8.0 Hz), 6.50 (1H, d, J = 8.0 Hz), 5.26 (1H, d, J = 3.0 Hz), 4.60 (1H, d, J = 3.0 Hz), 3.84 (1H, m), 3.82 (3H, s), 3.58 (1H, m), 3.22 (1H, m), 2.04 (1H, m), 1.58–1.30 (4H, m).

Product 7. Trans: solid, mp: 147–148°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.35 (4H, s), 7.14 (1H, d, J = 7.8 Hz), 7.05 (1H, t, J = 7.8 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.42 (1H, d, J = 8.0 Hz), 4.58 (1H, d, J = 5.0 Hz), 4.08 (1H, m), 3.85 (3H, m), 2.45 (1H, m), 2.0 (1H, m), 1.72 (1H, m); ir (KBr), ν (cm^{-1}): 3379, 2940, 1495, 1261, 810, 750.

Cis: solid, mp: 152–153°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.4 (1H, d, J = 7.8 Hz), 7.36 (4H, s), 7.05 (1H, t, J = 7.8 Hz), 6.68 (1H, t, J = 7.8 Hz), 6.56 (1H, d, J = 7.8 Hz), 5.25 (1H, d, J = 8.0 Hz), 4.65 (1H, d, J = 3 Hz), 3.78 (1H, brs), 3.40–3.62 (2H, m), 2.18 (1H, m), 1.56 (2H, m); ir (KBr), ν (cm^{-1}): 3345, 2931, 1492, 1265, 815, 750.

Product 8. Trans: solid, mp: 155–156°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.31 (2H, d), 7.81 (2H, d), 7.4 (1H, d), 7.2 (1H, t), 6.91 (1H, t), 6.7 (1H, d), 5.4 (1H, d), 4.9 (1H, m), 3.81–3.89 (3H, m), 2.81–2.92 (1H, m), 2.1–2.3 (1H, m), 1.65 (1H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 147.0, 144, 131.0, 129.2, 127.3, 125.4, 124, 122, 120.1, 115, 68, 58, 54, 47, 25; ir (KBr), ν (cm^{-1}): 3296, 2940, 1480, 1072, 750, 800.

Product 9. Trans: solide, mp: 160–161°C; ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.29 (2H, d), 7.78 (2H, d), 7.41 (1H, d), 7.1 (1H, d), 6.6 (1H, s), 4.65 (1H, d, J = 5.0 Hz), 4.28 (1H, m), 3.75–3.32 (3H, m), 2.25 (1H, m), 2.2 (1H, m), 1.65 (1H, m); ^{13}C-NMR ($CDCl_3$), δ (ppm): 148, 145, 132.2, 129.3, 128.3, 125.1, 124, 122.3, 117, 115, 63.2, 54, 40.1, 27.3, 21.2; ir (KBr), ν (cm^{-1}): 3360,2931,1495,1261, 900, 800,750,700.

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An Efficient and Clean Michael Addition of Indoles to Electron-Deficient Olefins Under Solvent- and Catalyst-Free Condition

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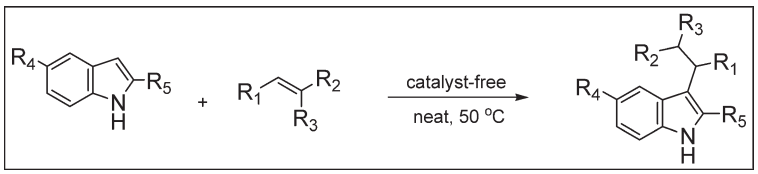

An efficient Michael addition of indoles to electron-deficient olefins under solvent- and catalyst-free condition afforded biologically important 3-substituted indole derivatives in good to excellent yields was reported. The acidic N—H proton of indole plays a key role in Michael addition of indoles to electron-deficient olefins. This very simple procedure provides an efficient and clean process for the synthesis of indole derivatives.

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INTRODUCTION

The development of new environmentally friendly reaction is a challenging goal for organic chemist [1–3]. Due to its low cost, reduced pollution, simplicity in process, and handling, the reaction under the solvent-free conditions has been extensively explored recently [4,5]. Indole and many of its derivatives are present in many compounds with pharmacological and biological activities [6,7]. Therefore, the development of green strategies to synthesize indole derivatives has attracted much attention in recent years. Michael addition is one of the most important tools for the synthesis of 3-substituted indole derivatives [8–10]. Electron-deficient olefins are strong Michael acceptors, and Michael adducts of electron-deficient olefins can be readily transformed into different functionalities [8–10].

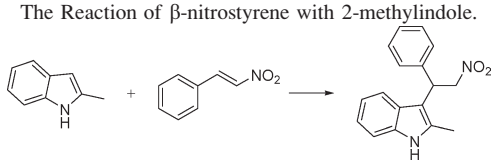
Owing to the importance of this transformation, several procedures have been reported in literature. A wide variety of acid catalysts [11,12], Lewis acids [13–19], or other catalysts [20–30] were used for this reaction. However, these catalysts still appeared to have several shortcomings, for example, toxicity of metal salts. Recently, catalyst-free Michael addition of nitrostyrene with indole was developed [31,32]. However, the reaction required higher temperature and use benzene or water as the solvent [31,32]. The development of more efficient and environmentally accessible method is still required. Here, we would like to report for the first time a clean Michael addition of indoles to electron-deficient olefins under solvent- and catalyst-free condition. The reaction avoids both an organic solvent and the need for a catalyst. Considering that the indole has an acidic N—H proton and hydrogen bonding can play a key role in organcatalysts, we supposed indole itself as catalyst in Michael addition of indoles to electron-deficient olefins. This very simple procedure provides an efficient and clean process for the synthesis of indole derivatives.

RESULTS AND DISCUSSION

In our initial study, we observed the reaction of β-nitrostyrene with 2-methylindole at 50°C without any catalyst in different solvents. Conducting the reaction in CH_2ClCH_2Cl or toluene did not get the desired product after 12 h. Only 6% of adduct was obtained after 12 h when CH_3CN was used as solvent (Table 1, entry 3). During the period, an interesting phenomenon attract our attention, after mixing the two starting materials together, a thick yellow oil was formed quickly without the addition of solvent. Considering that indole has an acidic N—H proton, we hypothesize indole itself can act as catalyst in Michael addition of indoles to electron-deficient olefins. When the oil was heated at 50°C without any solvent, the desired product was obtained in excellent yield within 1.5 h (Table 1, entry 4). When the reaction was carried out under argon with identical experimental conditions, the desired Michael addition product was obtained with the excellent yield (95%) (Table 1, entry 5), which showed the procedure did not require any inert atmospheric condition. The addition also occurs at room temperature but extensive reaction time (4 h) is required and isolated yield of product is lower (81%; Table 1, entry 6).

Table 1

The Reaction of β-nitrostyrene with 2-methylindole.



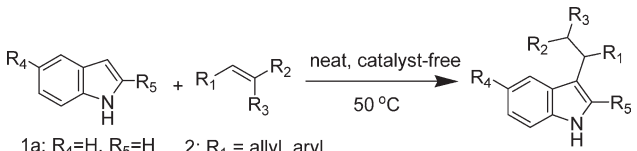
Entry[a]	*T* (°C)	Solvent	Time (h)	Yield[b] (%)
1	50	CH_2ClCH_2Cl	12	Trace
2	50	Toluene	12	Trace
3	50	CH_3CN	12	6
4	50	Neat	1.5	95
5[c]	50	Neat	1.5	95
6	r.t.	Neat	4	81

[a] Unless noted, reactions were carried out with 0.5 mmol of 2-methylindoles, 0.4 mmol of β-nitrostyrene.
[b] Isolated yield after flash chromatography.
[c] The reaction was carried out in Ar.

With the best reaction conditions in hand, we next turned our interest to the reaction scope, and the results are summarized in Table 2. It clearly indicates that β-nitrostyrenes, vinyl ethyl cyanoacetates, and vinyl malononitriles (Scheme 1) could react with indoles under the best reaction conditions to give the corresponding 3-substituted indole derivatives in good to excellent yields. First, indole **1a** was used as a standard substrate to study the reactivity of different nitroalkenes in this reaction. A wide range of nitroalkenes bearing electron-donating (**3d**–**3g**), electron- withdrawing (**3b**, **3c**) group substituted at aromatic ring, and heteroaromatic (**3h**) groups could react with indole **1a** and the Michael addition products **3** were obtained with excellent yields (Table 2, entries 1–8). The results suggest that nitroalkenes with an electron-withdrawing group substituted at aromatic ring react much faster than nitroalkenes with an electron-donating substituent (Table 2, entries 1–7). The generality of the reaction was further demonstrated by using substituted indoles such as 5-methylindole, 5-methoxyindole, and 2-methylindole; good to excellent yields were obtained. As seen in Table 2, the indole bearing Br group resulted in a lower yield and required a longer reaction time (Table 2, entry 9). When we introduced a 5-methoxy group or methyl group to

Table 2

The Michael addition of indoles to electron-deficient olefins under solvent-free and catalyst-free condition.



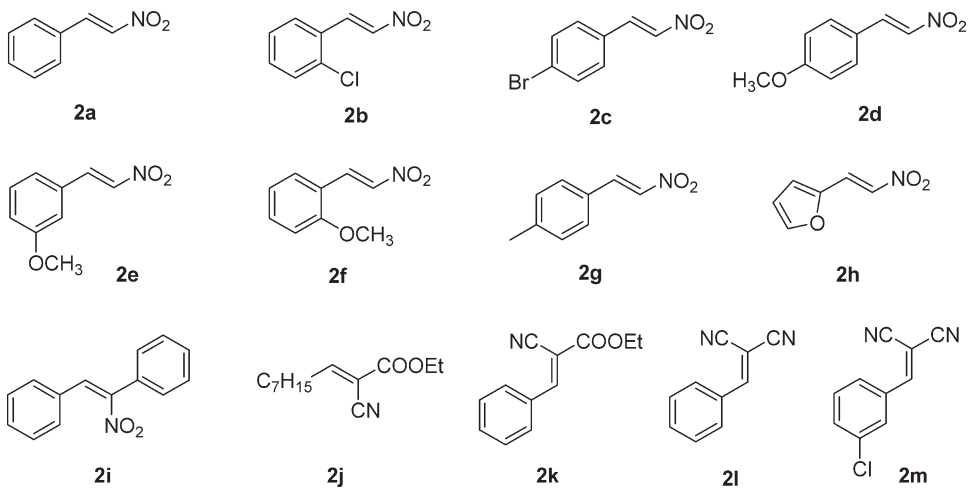
1a: R_4=H, R_5=H
1b: R_4=H, R_5=Me
1c: R_4=Br, R_5=H
1d: R_4=MeO, R_5=H

2: R_1 = allyl, aryl
R_2, R_3 = CN, NO_2, COOEt, aryl

Entry[a]	Indoles	Olefins	Product	Time (h)	Yield[b] (%)
1	**1a**	**2a**	**3a**	20	95 (85)[f]
2	**1a**	**2b**	**3b**	10	99
3	**1a**	**2c**	**3c**	10	98
4	**1a**	**2d**	**3d**	24	94 (76)[f]
5	**1a**	**2e**	**3e**	24	95
6	**1a**	**2f**	**3f**	24	96
7	**1a**	**2g**	**3g**	20	95 (81)[f]
8	**1a**	**2h**	**3h**	20	90 (68)[f]
9	**1c**	**2a**	**3i**	50	76 (73)[f]
10	**1d**	**2a**	**3j**	5	93 (83)[f]
11	**1b**	**2a**	**3k**	1.5	94 (80)[f]
12	**1b**	**2d**	**3l**	3	96
13	**1b**	**2g**	**3m**	2	98
14	**1b**	**2i**	**3n**	24	90[c]
15	**1b**	**2j**	**3o**	24	61[d]
16	**1b**	**2k**	**3p**	20	85[e]
17	**1b**	**2l**	**3q**	28	70
18	**1b**	**2m**	**3r**	20	96

[a] Unless noted, reactions were carried out with 0.4 mmol of electron-deficient olefins, 0.5 mmol of indoles.
[b] Isolated yield after flash chromatography.
[c] dr = 3.8:1.
[d] dr = 1.3:1.
[e] dr = 1.1:1.
[f] Data of H_2O as catalyst in parentheses refers to the results in literature [32].

Scheme 1. The structure of olefins.



5-position of indole or 2-position of indole, to our delight, the reaction proceeded very well, giving the corresponding products in excellent yield even with shorter reaction time (Table 2, entries 10–13). A possible explanation may be due to the presence of 5-methoxy group in 5-position of indole or the methyl group in 2-position of indole, which increased the electron density of the aromatic ring to accelerate the reaction. Moreover, with α,β-disubstituted nitroalkene, we observed low diastereoselectivity, the ^{1}H-NMR spectra of **3n** revealed the presence of diastereomer in the ratio of 3.8:1 for **3n** (Table 2, entry 14). Furthermore, to the best of our knowledge, few reports about conjugate addition of indoles with vinyl ethyl cyanoacetates and vinyl malononitriles have been reported in the literature. The results (Table 2, entries 15–18) showed that our present synthetic methodology can get these conjugate addition products with high yields. The ^{1}H-NMR spectra of **3o**, **3p** revealed the presence of diastereomers in the ratio of 1.3:1 for **3o** and 1.1:1 for **3p**.

To demonstrate the synthetic utility of the present system, we carried out the reaction in large scale. The mixture of 40 mmol of (*E*)-1-(2-nitrovinyl)benzene and 60 mmol of 2-methylindole was stirred at 50°C without solvent and catalyst for 1.5 h. The corresponding adduct **3k** was obtained in 96% yield (Scheme 2).

To gain insight into the reaction mechanism, we examined *N*-methylindole as a substrate under solvent- and catalyst-free condition at 50°C (Scheme 3). As expected, it was found that the target Michael adducts was obtained only in a trace amount even with prolonged reaction time (10 h). In any event, the presence of the acidic N—H proton seems mandatory as every attempt to use *N*-methylindole for these reactions failed to get the product. Therefore, we assume that an acidic N—H proton of indole activates the nitro moiety, a drastic enhancement of the rates and the yields of the products are observed (Scheme 4). Further application of the catalytic activity of acidic N—H proton of indole and a detailed study of the catalytic mechanism are in progress.

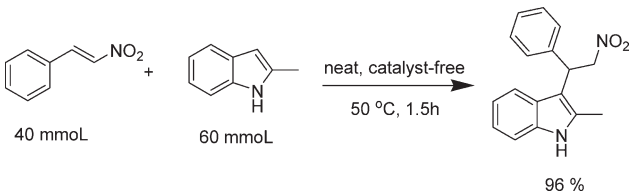
CONCLUSIONS

In summary, we have developed a rare example of an efficient Michael addition of indoles to electron-deficient olefins that avoids both an organic solvent and the need for a catalyst. The reaction is a green method for the synthesis of important 3-substituted indole derivatives with the advantages such as mild condition and high yields. Furthermore, this reaction is the first example of electron-deficient olefins activation catalyzed by an acidic N—H proton of indoles and its application to other addition reactions are underway.

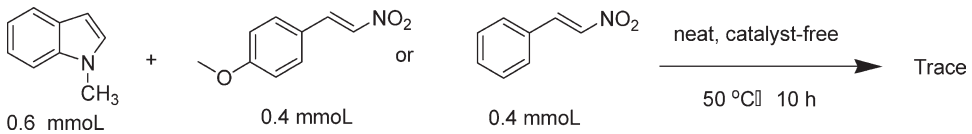
EXPERIMENTAL

Indoles were purchased from Alfa Aesar Company. Electron-deficient olefins were prepared according to the literature procedures and spectral data were consistent with the literature report. All solvent were purchased from commercial sources and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254} plates. Column chromatography was performed on silica

Scheme 2. Large-scale reaction of (*E*)-1-(2-nitrovinyl) benzene with 2-methylindole.



Scheme 3. The reaction of β-nitrostyrenes with *N*-methylindole.



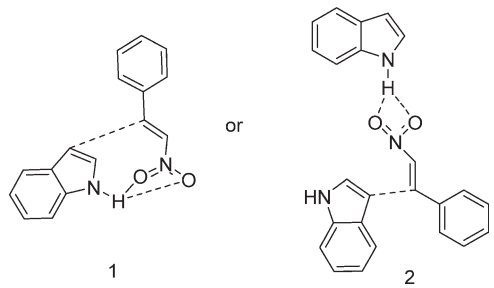
gel (300–400 mesh). NMR spectra were recorded on a 300-MHz instrument. ^{1}H-NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance used as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C-NMR chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). IR data were obtained from FT spectrometer and recorded as cm^{-1}.

The optimization of reaction conditions of β-nitrostyrene with 2-methylindole. In a tube equipped with a magnetic stirring bar, 0.5 mmol of 2-methylindoles, 0.4 mmol of β-nitrostyrene was added. Thick yellow oil was formed quickly, and then the mixture was stirred with the time and temperature shown in Table 1. After the completion of the reaction, the raw product was purified by silica gel column chromatography (EtOAc/petroleum ether) to give light yellow oil with the yield shown in Table 1.

General experimental procedure for the synthesis of 3a–3u. In a tube equipped with a magnetic stirring bar, electron-deficient olefin (0.4 mmol) and indole (0.6 mmol) was added. Then the tube was closed with a rubber stopper, the reaction mixture was stirred for the appropriate time at 50°C. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography to yield the desired product. The compounds **3a–3l** and **3r** are known compounds; their identities were proven by means of melting points, ^{1}H-NMR, ^{13}C-NMR, and IR. All the analytical data were in accord with the spectra reported in the literature. The compounds **3m–3q** are new compounds; their identities were proven by means of HRMS, ^{1}H-NMR, ^{13}C–NMR, and IR.

3-(2-Nitro-1-phenylethyl)-1H-indole [33] (3a). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3411, 2898, 1547, 1453, 1420, 1374, 1336, 742, 700. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.89 (dd, J = 8.7, 8.4, 12.5 Hz, 1H), 5.01 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.15 (t, J = 7.8 Hz, 1H), 6.93 (s, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.14–7.30 (m, 7H), 7.42 (d, J = 7.8 Hz, 1H), 7.99 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.8, 136.0, 128.4, 127.3, 127.2, 127.1, 125.6, 122.2, 121.1, 119.4, 118.4, 113.9, 110.9, 79.09, 41.1.

Scheme 4. The two proposed reaction mechanism.



3-(1-(2-Chlorophenyl)-2-nitroethyl)-1H-indole [33] (3b). White solid. yield: 99%. mp 144.1–145.3°C. IR (KBr), ν (cm^{-1}): 3438, 2958, 2913, 1547, 1436, 1411, 1379, 1334, 1096, 742. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.91–5.01 (m, 2H), 5.72 (t, J = 7.8 Hz, 1H), 7.03–7.21 (m, 6H), 7.30 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 5.7 Hz, 2H), 8.05 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.5, 133.8, 130.1, 129.0, 128.8, 127.33, 126.2, 122.8, 122.0, 120.0, 118.9, 113.2, 111.4, 77.7, 38.0.

3-(1-(4-Bromophenyl)-2-nitroethyl)-1H-indole [34] (3c). Pale pink solid. yield: 98%. mp 122.7–123.9°C. IR (KBr), ν (cm^{-1}): 3396, 2946, 2915, 1535, 1484, 1427, 1380, 1337, 744. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.84 (dd, J = 8.7, 8.4, 12.5 Hz, 1H), 4.98 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.10 (t, J = 7.8 Hz, 1H), 6.92 (s, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.14–7.21 (m, 3H), 7.30 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.5 Hz, 3H), 8.04 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.3, 136.5, 132.0, 129.5, 125.9, 122.9, 121.6, 121.5, 120.1, 118.8, 113.8, 111.5, 79.2, 41.0.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1H-indole [32] (3d). White solid. yield: 94%. mp 152.5–153.6°C. IR (KBr), ν (cm^{-1}): 3379, 2986, 1547, 1509, 1243, 746. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.77 (s, 3H), 4.89 (dd, J = 8.4, 8.4, 12.1 Hz, 1H), 5.04 (dd, J = 7.6, 7.4, 12.0 Hz, 1H), 5.13 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 7.01–7.09 (m, 2H), 7.16–7.25 (m, 3H), 7.35 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 8.07 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 158.9, 136.5, 131.2, 128.8, 126.1, 122.6, 121.4, 119.9, 119.0, 114.8, 114.3, 111.3, 79.7, 55.2, 40.8.

3-(1-(3-Methoxyphenyl)-2-nitroethyl)-1H-indole [35] (3e). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3414, 2910, 2834, 1548, 1487, 1456, 1376, 1261, 743. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.69 (s, 3H), 4.86 (dd, J = 8.4, 8.4, 12.6 Hz, 1H), 4.97 (dd, J = 7.8, 7.5, 12.5 Hz, 1H), 5.11 (t, J = 15.9 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.87 (t, J = 17.4 Hz, 3H), 7.04 (t, J = 14.7 Hz, 1H), 7.12–7.26 (m, 3H), 7.43 (d, J = 7.8 Hz, 1H), 8.01 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 159.9, 141.0, 136.5, 129.9, 126.1, 122.6, 121.7, 120.1, 119.9, 118.9, 114.1, 114.1, 112.5, 111.5, 79.5, 55.2, 41.5.

3-(1-(2-Methoxyphenyl)-2-nitroethyl)-1H-indole [33] (3f). Pale yellow viscous oil. yield: 96%. IR (KBr), ν (cm^{-1}): 3415, 2898, 2836, 1548, 1489, 1457, 1373, 1244, 745. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.85 (s, 3H), 4.89–5.03 (m, 2H), 5.58 (t, J = 7.8 Hz, 1H), 6.80 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.01–7.27 (m, 6H), 7.45 (d, J = 7.8 Hz, 1H), 7.97 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 156.9, 136.4, 128.9, 128.7, 127.3, 126.5, 122.4, 122.0, 120.8, 119.7, 119.1, 113.9, 111.3, 110.9, 78.2, 55.5, 35.5.

3-(2-Nitro-1-p-tolylethyl)-1H-indole [32] (3g). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3415, 2916, 1548, 1512, 1455, 1422, 1376, 743. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 4.88 (dd, J = 8.4, 8.7, 12.2 Hz, 1H), 5.01 (dd, J = 7.8, 7.5, 12.2 Hz, 1H), 5.12 (t, J = 7.8 Hz, 1H), 6.94 (s, 1H), 7.02–7.20 (m, 6H), 7.29 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 8.00 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$),

δ 136.7, 136.0, 135.7, 129.1, 127.1, 125.6, 122.1, 121.1, 119.4, 118.5, 114.1, 110.9, 79.1, 40.7, 20.5.

3-(1-(Furan-2-yl)-2-nitroethyl)-1H-indole [33] (3h). Pale yellow viscous oil. yield: 90%. IR (KBr), ν (cm^{-1}) 3403, 2915, 1543, 1505, 1455, 1421, 1371, 1340, 734. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.87 (dd, J = 7.5, 7.5, 12.6 Hz, 1H), 5.01 (dd, J = 8.1, 8.1, 12.3 Hz, 1H), 5.22 (t, J = 7.7 Hz, 1H), 6.13 (d, J = 3 Hz, 1H), 6.28 (s, 1H), 7.02 (s, 1H), 7.08–7.21 (m, 2H), 7.32 (t, J = 18.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 8.05 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 152.3, 142.2, 136.3, 125.7, 122.8, 122.6, 120.1, 118.7, 111.6, 110.5, 107.4, 77.9, 35.7.

5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole [32] (3i). Pale pink solid. yield: 76%. mp 116.6–117.5°C. IR (KBr), ν (cm^{-1}): 3427, 2907, 1548, 1456, 1373, 1104, 799. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.89 (dd, J = 8.1, 8.1, 12.3 Hz, 1H), 4.99 (dd, J = 8.4, 8.1, 12.2 Hz, 1H), 5.10 (t, J = 7.8 Hz, 1H), 7.02 (s, 1H), 7.15–7.29 (m, 7H), 7.53 (s, 1H), 8.13 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.7, 135.1, 129.0, 127.9, 127.7, 127.6, 125.6, 122.7, 121.4, 114.0, 113.2, 112.8, 79.4, 41.3.

5-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole [33] (3j). Pale yellow viscous oil. yield: 93%. IR (KBr), ν (cm^{-1}): 3415, 2951, 1549, 1484, 1453, 1375, 798, 701. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.74 (s, 3H), 4.89 (dd, J = 8.4, 8.4, 12.3 Hz, 1H), 5.00 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.10 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 5.4 Hz, 2H), 6.92 (s, 1H), 7.15–7.30 (m, 6H), 7.98 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 153.7, 138.7, 131.1, 128.4, 127.2, 127.0, 126.1, 121.8, 113.5, 112.2, 111.6, 100.4, 79.0, 55.4, 41.0.

2-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole [33] (3k). Pale pink solid. yield: 94%. mp 94.5–95.7°C. IR (KBr), ν (cm^{-1}): 3413, 2919, 1545, 1457, 1431, 1384, 1299, 741, 704. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.31 (s, 3H), 5.08–5.23 (m, 3H), 6.98–7.11 (m, 2H), 7.20–7.36 (m, 7H), 7.82 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.1, 134.9, 132.4, 128.3, 126.8, 126.6, 126.4, 120.8, 119.2, 118.1, 110.2, 108.3, 78.1, 40.0, 11.4.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-2-methyl-1H-indole [12] (3l). Pale pink solid. yield: 96%. mp 155.5–156.4°C. IR (KBr), ν (cm^{-1}): 3425, 2921, 1612, 1546, 1510, 1460, 1381, 1244, 1183, 1031, 745. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 3.71 (s, 3H), 5.01–5.17 (m, 3H), 6.79 (d, J = 8.7 Hz, 2H), 6.98–7.10 (m, 2H), 7.19 (d, J = 8.4 Hz, 3H), 7.35 (d, J = 7.8 Hz, 1H), 7.83 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 158.0, 135.0, 132.3, 131.13, 127.9, 126.4, 120.8, 119.2, 118.1, 113.7, 110.2, 108.5, 78.4, 54.7, 39.4, 11.4.

2-Methyl-3-(2-nitro-1-p-tolylethyl)-1H-indole [36] (3m). Pale pink solid. yield: 98%. mp 152.7–153.9°C. IR (KBr), ν (cm^{-1}): 3413, 2917, 1619, 1544, 1456, 1429, 1384, 1204, 739. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 2.34 (s, 3H), 5.04–5.22 (m, 3H), 6.99–7.09 (m, 4H), 7.17–7.24 (m, 3H), 7.36 (d, J = 7.8 Hz, 1H), 7.82 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.2, 135.9, 134.9, 132.2, 128.9, 126.7, 126.6, 126.4, 120.8, 119.2, 118.1, 110.1, 108.5, 78.2, 39.6, 20.4, 11.4.

2-Methyl-3-(2-nitro-1,2-diphenylethyl)-1H-indole (3n). Pale pink solid. yield: 90%. dr = 3.8:1. mp 158.5–161.4°C. IR (KBr), ν (cm^{-1}): 3420, 2921, 1549, 1490, 1454, 1358, 1303, 739. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.17 (s, 0.6 H), 2.40 (s, 2.4H), 5.36 (d, J = 12.0 Hz, 1H), 6.68 (d, J = 12.3 Hz, 1H), 6.97–7.39 (m, 11H), 7.49–7.77 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.0, 135.4, 133.6, 132.6, 129.8, 129.5, 128.9, 128.8, 128.5, 128.4, 128.3, 127.6, 127.3, 127.1, 126.5, 121.1, 121.0, 119.7, 119.6, 118.7, 110.8, 110.6, 93.7, 93.2, 46.92, 46.5, 12.1. HRMS (ESI-TOF) ($M + H^+$):357.1603, found: 320.1601.

Ethyl 2-cyano-3-(2-methyl-1H-indol-3-yl)decanoate (3o). Pale yellow viscous oil. yield: 61%. dr = 1.3:1. IR (KBr), ν (cm^{-1}): 3394, 2931, 2855, 2360, 2336, 1741, 1459, 1369, 1302, 1245, 1024, 741. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 0.80–0.90 (m, 5H), 1.20 (t, J = 14.7 Hz, 13H), 2.37 (s, 1.7H), 2.43 (s, 1.3H), 3.52–3.60 (m, 1H), 3.93 (t, J = 17.1 Hz, 2H), 4.19 (t, J = 11.1 Hz, 1H), 7.03–7.13 (m, 2H), 7.25 (s, 1H), 7.51 (d, J = 7.2 Hz, 0.5H), 7.59 (d, J = 7.5 Hz, 0.5H), 7.88 (br, 0.5H), 7.95 (br, 0.5H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 166.1, 165.8, 135.5, 135.4, 133.5, 132.9, 126.8, 121.2, 121.1, 119.5, 119.4, 118.7, 118.5, 116.9, 116.6, 110.5, 108.4, 108.3, 62.5, 62.1, 43.7, 43.4, 39.0, 38.9, 31.8, 31.7, 29.2, 29.1, 29.0, 29.0, 27.5, 27.4, 22.55, 14.0, 13.8, 13.4, 12.3, 12.1. HRMS (ESI-TOF) ($M + H^+$):355.2386, found: 355.2388.

Ethyl 2-cyano-3-(2-methyl-1H-indol-3-yl)-3-phenylpropanoate (3p). Pale yellow viscous oil. yield: 85%. dr = 1.1:1. IR (KBr), ν (cm^{-1}): 3401, 2981, 2922, 2245, 1740, 1457, 1305, 1244, 1030, 742, 694. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 0.88 (t, J = 14.4 Hz, 1.5H), 1.06 (t, J = 14.4 Hz, 1.5H), 2.24 (s, 1.5H), 2.34 (s, 1.5H), 3.91–3.99 (m, 1H), 4.05–4.12 (m, 1H), 4.46 (d, J = 9.9 Hz, 0.5H), 4.60 (d, J = 9.9 Hz, 0.5H), 5.01 (t, J = 17.7 Hz, 1H), 7.00–7.08 (m, 2H), 7.17–7.36 (m, 5H), 7.48 (t, J = 18.0 Hz, 2H), 7.91 (br, 0.5H), 7.97 (br, 0.5H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 165.7, 165.4, 139.6, 139.2, 135.4, 135.1, 133.2, 133.0, 128.8, 128.7, 128.6, 127.7, 127.6, 127.4, 127.3, 127.2, 127.0, 121.4, 121.3, 119.8, 119.7, 118.7, 118.4, 116.6, 116.4, 110.7, 110.6, 109.5, 109.4, 62.8, 62.5, 43.4, 43.2, 42.4, 42.0, 13.6, 13.4, 12.4, 12.2. HRMS (ESI-TOF) ($M + H^+$): 333.1603, found: 320.1604.

2-((2-Methyl-1H-indol-3-yl)(phenyl)methyl)malononitrile (3q). White solid. yield: 70%. mp 164.4–166.1°C. IR (KBr), ν (cm^{-1}): 3405, 2895, 2712, 2650, 2252, 1952, 1458, 1419, 1348, 1307, 1245, 1040, 762, 728. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.39 (s, 3H), 4.66 (d, J = 9.4 Hz, 1H), 4.94 (d, J = 9.4 Hz, 1H), 7.03–7.15 (m, 2H), 7.25–7.43 (m, 7H), 8.02 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.7, 134.9, 133.4, 128.5, 127.5, 126.9, 125.7, 121.3, 119.6, 117.7, 112.2, 112.0, 110.5, 107.4, 43.7, 27.2, 11.8. HRMS (ESI-TOF) ($M + H^+$):286.1344, found: 286.1338.

2-((3-Chlorophenyl)(2-methyl-1H-indol-3-yl)methyl)malononitrile (3r). White solid. yield: 96%. mp 190.4–192.1°C. IR (KBr), ν (cm^{-1}): 3376, 2920, 2255, 1592, 1569, 1456, 1427, 1307, 1244, 1193, 746. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.43 (s, 3H), 4.63 (d, J = 9.6 Hz, 1H), 4.90 (d, J = 9.6 Hz, 1H), 7.02–7.17 (m, 2H), 7.25–7.37 (m, 6H), 8.08 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.1, 135.4, 135.0, 134.0, 130.2, 128.3, 127.9, 125.2, 122.0, 120.3, 118.0, 112.4, 112.1, 111.1, 111.0, 107.2, 43.9, 27.6, 12.4. HRMS (ESI-TOF) ($M + H^+$): 320.0955, found: 320.0949.

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