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Synthesis of Phenylthio Substituted 4*H*-Pyrans and 2-Pyridinones by Conjugate Addition-Cyclization of CH-Acids to α,β-Unsaturated Ketones

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Summary. The conjugate addition of malononitrile to α,β-unsaturated ketones catalyzed by piperidine yielded 2-amino-4-aryl-6-methyl-5-(phenylthio)-4*H*-pyran-3-carbonitriles. The reaction of α,β-unsaturated ketones with cyanoacetamide led to 2-pyridone derivatives. The reaction of malononitrile and ethyl cyanoacetate with an enaminone occurred under elimination of dimethylamine to yield 2-pyridone.

Keywords. α,β-Unsaturated ketones; *Michael* addition; 2*H*-Pyrans; 2-Pyridones.

Synthese phenylthiosubstituierter 4*H*-Pyrane und 2-Pyridinone durch konjugierte Addition-Cyclisierung von CH-Säuren an α,β-ungesättigte Ketone

Zusammenfassung. Die konjugierte Addition von Malonitril an α,β-ungesättigte Ketone, die durch Piperidin katalysiert wird, ergibt 2-Amino-4-aryl-6-methyl-5-(phenylthio)-4*H*-pyran-3-carbonitrile. Die Reaktion α,β-ungesättigter Ketone mit Cyanacetamid führt zu Pyridonderivaten. Die Umsetzung von Malonitril und Ethylcyanoacetat mit einem Enaminon erfolgt unter Eliminierung von Dimethylamin und liefert 2-Pyridonderivate.

Introduction

Polyfunctionalized dihydropyrans are a common structural unit in a number of natural products such as secoiridoid monoterpenes and biogenetically related indole alkaloids [1, 2]. Some 2-pyridone derivatives are also of considerable biological importance, both as cardiotonic agents, such as milrinone [3] (Fig. 1, **A**), and as potential HIV-1 specific reverse transcriptase inhibitors (Fig. 1, **B**) [2, 3].

During the last few years we have developed a synthetic pathway to some functionalized 4-amino-3,4-dihydro-2*H*-pyrans by *hetero-Diels-Alder* reaction of 1-oxa-1,3-butadienes with enol ethers [5–7]. Electron withdrawing substituents, at C-3 of the heterodiene systems such as cyano and phenylthio groups, facilitate the reactions.

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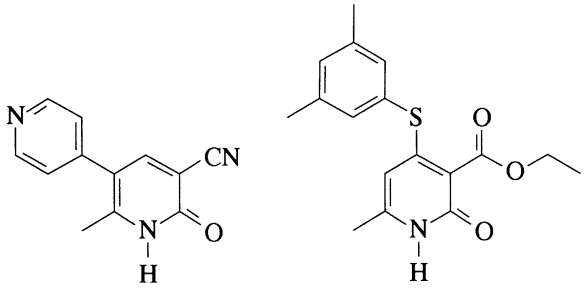


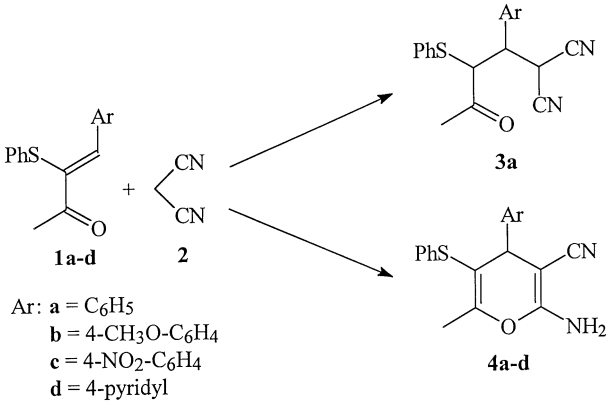
Fig. 1

In continuation of our program, we focused on the synthesis of substituted 2-amino-4*H*-pyrans. This type of compounds can be prepared by conjugate addition-cyclization of malononitrile to α,β-unsaturated ketones [8–12]. It was found that cyano, alkoxycarbonyl, acyl, or aryl substituents in the enone system play an important role stabilizing the enolic tautomer and thus enabling sequential O-cyclization to the pyran ring [10]. Unsubstituted α,β-unsaturated carbonyl compounds did not undergo cyclization upon addition of malononitrile.

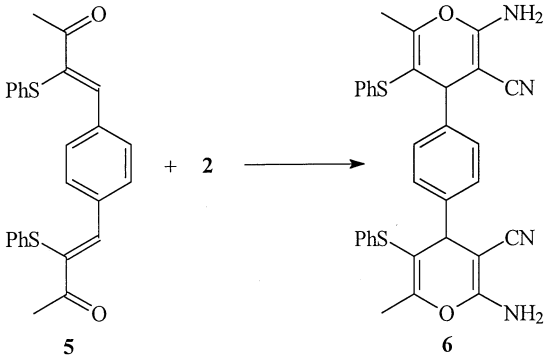
Results and Discussion

In this paper, we report on the *Michael* addition of malononitrile (**2**), cyanoacetamide (**7**), and ethyl cyanoacetate (**17**) with α,β-unsaturated ketones containing a phenylthio group at the α-position and phenyl (**1a**), 4-methoxyphenyl (**1b**), 4-nitrophenyl (**1c**), 4-pyridyl (**1d**), and N,N-dimethylamino (**1e**) groups at the β-carbon. The aim of this work was to determine the influence of the phenylthio group as well as that of the aryl, pyridyl, and dimethylamino substituents on course, rate, and yield of the reactions.

Since the *Michael* acceptor **1** seemed to be unstable at higher temperatures, we tried to carry out the reaction with **2** under mild conditions. Heating of **1a** with **2** in the presence of piperidine in acetonitrile resulted in a complex mixture from which the noncyclic *Michael* adduct **3a** was isolated in low yield (10%, Scheme 1). Its



Scheme 1

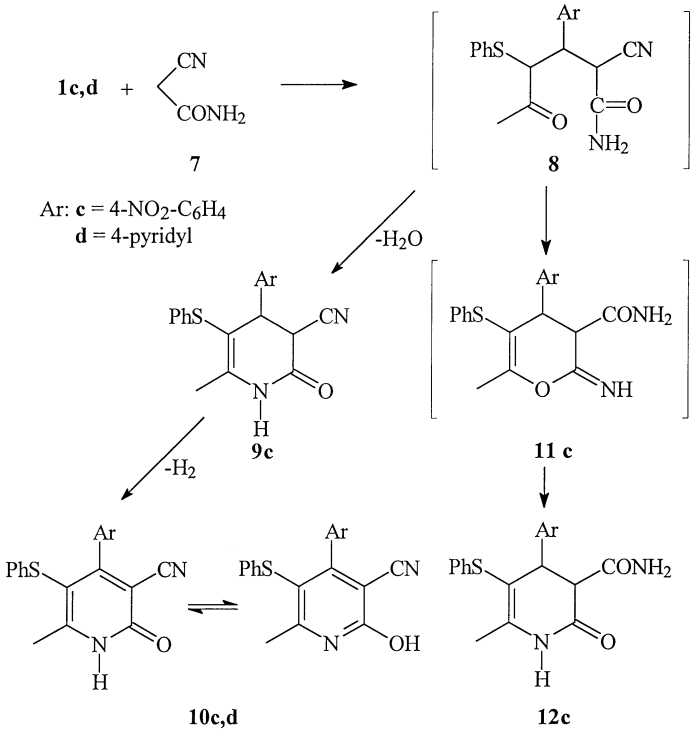


Scheme 2

structure was established by analytical and spectroscopic data. In an attempt to improve the yield and to complete the reaction to the pyran stage, **1a** was treated with **2** in the presence of piperidine in boiling ethanol. The desired pyran derivative **4a** was obtained in good yield. The spectroscopic features of **4a** corresponded to the 2-amino-4*H*-pyran structure. The reactions of **1b–d** with **2** proceeded similar to that of **1a** and yielded **4b–d** (Scheme 1). It is worth mentioning that **1c** and **1d**, possessing 4-nitrophenyl or 4-pyridyl substituents in β-position, reacted easier with **2** than **1a**, **b**. The time needed to complete the reactions with **1c**, **d** was shorter and the yields of products **4c**, **d** were considerable higher than those of **4a**, **b**.

The efficiency of the above reactions prompted us to extend this procedure to the synthesis of compounds containing two pyran units attached to a benzene ring. The aim of the experiment was to perform a double *Michael* addition of **2** to a substrate containing two α,β-unsaturated carbonyl groups attached to the benzene ring in positions 1 and 4. The synthesis of the appropriate substrate **5** was achieved by condensation of terephthalaldehyde with phenylthioacetone in boiling toluene in the presence of piperidine. The reaction of **5** with **2** in a molar ratio of 1:2 carried out in absolute ethanol and catalyzed by piperidine afforded the desired 1,4-*bis*(pyranyl)-benzene **6** (Scheme 2) in moderate yield. Its structure was confirmed by analytical and spectroscopic data which are similar to those of **4a**.

We then tried to use **7** as the CH-acid. Since the reaction of **1a** with **7** in boiling ethanol or toluene in the presence of piperidine or ammonium acetate and acetic acid failed, **1c** and **1d** were chosen as more reactive substrate. Compound **1c**, treated with **7** in boiling ethanol in the presence of piperidine, afforded three products: **9c**, **10c**, and **12c** (Scheme 3). Their structure was established on the basis of analytical and spectroscopic data. The presence of two pairs of doublets in the ^{1}H NMR spectrum of **9c** indicated that it was a mixture of two diastereoisomers with *cis* and *trans* stereochemistry at C-3 and C-4 (ratio of diastereoisomers: 10:4.4). The larger value of the coupling constant ($J = 7.2$ Hz) was assigned to the *trans* diastereoisomer which was the major product. Compound **10c** was obtained by dehydrogenation of **9c**. Formation of **9c** and **10c** can be rationalized as depicted in Scheme 3. The reaction of **1c** with **7** involves in the first step the formation of *Michael* adduct **8** which then undergoes cyclization to 2-pyridone **9** by elimination of water. The structure of the third product **12c** was established on the basis of MS

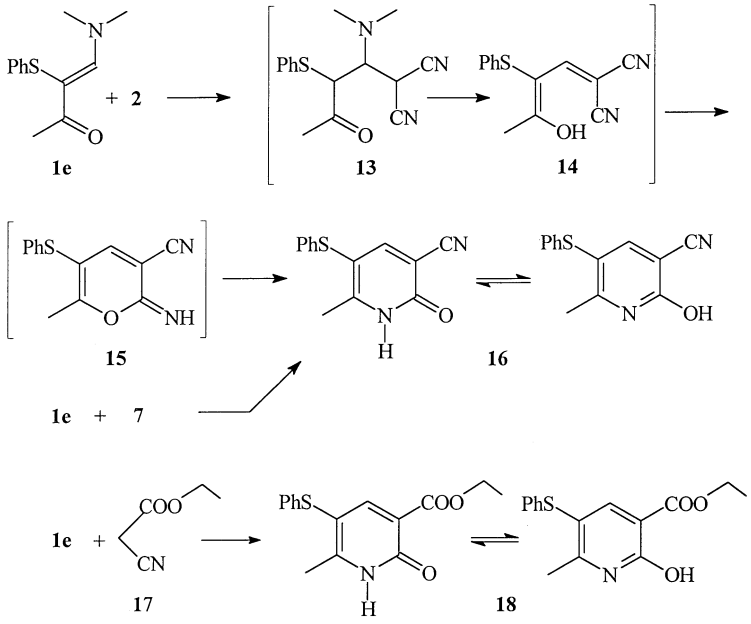


Scheme 3

IR, ^{1}H, and ^{13}C NMR data. From this evidence we assume that the preliminary formed *Michael* adduct **8** is transformed into a pyridine ring with participation of the cyano group. The suggested mechanism of this reaction is outlined in Scheme 3. In the case of reaction of **1d** with **7** we isolated the pyridone **10d** as the sole product. Its spectroscopic features are similar to those of **10c**.

Reaction of compound **1e**, containing a dimethylamino group in β-position, with **2** and **17** at ambient temperature in ethanolic solution in the presence of piperidine led to the formation of the pyridine derivatives **16** and **18** in moderate yields (Scheme 4). The formation of **16** may be rationalized by assuming the mechanism given in Scheme 4. Addition of **2** to **1e** gives rise to the *Michael* adduct **13** which subsequently eliminates dimethylamine and undergoes cyclization to the imino-pyran **15** as an intermediate. The presence of piperidine and dimethylamine in the reaction mixture promotes the ring transformation of **15** to the 2-pyridone **16**. The initial elimination of dimethylamine from the *Michael* adduct **13** is the key step in this process that precludes the cyclization of **13** to a 2-aminopyran derivative. The structure of **16** was confirmed by analytical and spectroscopic data. The formation of **18** occurs in a similar way.

When this work was in progress, a similar reaction of **2** with 1-aryl-3-dimethylamino-2-propen-1-one (an enaminone) was published [15]. According to this investigation, the initial step of reaction of this enaminone with **2** is a *Knoevenagel* reaction, followed by hydrolysis of one cyano group to amide, subsequent cyclization, and elimination of dimethylamine, resulting in 4-aryl-



Scheme 4

pyridin-2-one-3-carbonitrile. In contrast to this reaction, cyanoacetamide reacted with the above enaminone according to the *Michael* reaction mechanism, yielding isomeric 6-aryl-pyridin-2-one-3-carbonitrile.

If we assume the mechanism suggested in Ref. [15] for the reaction of **2** with enaminone **1e**, we should obtain the isomeric 4-methyl-5-(phenylthio)-pyridin-2-one-3-carbonitrile instead of **16**. Therefore, this mechanism can be excluded in the case of **16** whose constitution followed from a detailed analysis of its spectroscopic properties [16]. The unequivocal proof the structure of **16** came from its HMBC spectrum [17]. The methyl group singlet correlates with two carbon resonances at 159.3 and 106.1 ppm. For the signal of the heteroaromatic proton there are correlations with signals of all four pyridine carbon atoms and the CN carbon ($\delta = 115.9$ ppm).

In order to ascertain whether the reactions of **1e** with **2** and **7** proceed according to two different mechanisms, as has been suggested in Ref. [15], we performed the reaction of **1e** with **7** under the same conditions as described for **2**. When the reaction was carried out at ambient temperature, we observed only traces of a new product (TLC). After two weeks at room temperature we managed to isolated a small amount of compound **16**. Prolonged heating of **1e** and **7** in toluene in the presence of piperidine also led to formation of compound **16** in very low yield. The identity of the samples **16** obtained in reactions of **1e** with **2** and **1e** with **7** was confirmed in all respects. Thus, the key step of the reaction of **1e** with both **2** and **7** is a *Michael* addition followed by elimination of dimethylamine.

It is interesting to note that compounds **10c**, **16**, and **18** show strong fluorescence, most pronounced with **16** (blue).

Experimental

Melting points were determined on a Boetius hot stage apparatus and are corrected. IR spectra were recorded on a Bruker IFS 48 instruments as KBr pellets and in HCB, nujol ^{1}H NMR spectra were taken at 500 MHz (Bruker AMX 500) in $CDCl_3$ or *DMSO*-d_6 solutions (*TMS* as internal standard). ^{13}C signal assignments were confirmed by DEPT experiments. For HMBC spectra (*DMSO*-d_6), standard software supplied by the manufacturer was used. The absorption spectra were recorded on a UV/VIS diode array spectrophotometer HP 8452A in acetonitrile. The emission spectra were taken in acetonitrile solutions on a spectrometer constructed in the Department of Physical Chemistry and Electrochemistry of the Jagiellonian University. Mass spectra were obtained with a Finnigan Mat 95 (70 eV). Microanalyses were performed on a Perkin Elmer Analyser 240 in the Regional Laboratory of Physicochemical Analyses in Kraków; their results were in satisfactory agreement with the calculated values.

Phenylthioacetone [5], 4-N,N-dimethyl)-3-phenylthio-3-buten-2-one [14], and 4-aryl-3-phenylthio-3-buten-2-one [13] were synthesized according to procedures described in the literature.

3-Phenylthio-4-(4-pyridyl)-3-buten-2-one (**1d**; $C_{15}H_{13}NOS$)

1d was obtained similarly to the procedure described for **1a** [13]. Yellow oil; b.p.: 195°C/5 torr; IR (KBr): $\nu = 3147$–3115 (CH), 1688 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.30 (s, 3H, CH_3), 7.23–7.32 (m, 5H, CH arom), 7.60 (d, 2H, CH arom), 7.66 (s, 1H, CH vinyl), 8.66–8.67 (d, 2H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 27.7 (CH_3), 124.0, 127.2, 128.7, 129.6, 134.0, 138.2, 139.0, 141.7, 150.0, 198.4 (C=O) ppm.

2-Cyano-5-oxo-3-phenyl-4-(phenylthio)-hexanenitrile (**3a**; $C_{19}H_{16}N_2OS$)

A mixture of 2.54 g **1a** (10 mmol), 0.8 g of **2** (12 mmol), and a few drops of piperidine in 40 cm^3 of acetonitrile was heated in a water bath at 50°C for 4 h. The solvent was removed under vacuum, and the oily product was purified by column chromatography on silica gel using $CHCl_3$ as eluent. After removing the solvent, the yellow oil was treated with *t*-butyl-methyl ether and cooled in a refrigerator. The precipitated solid was recrystallized from *t*-butyl-methyl ether.

Colourless prisms; m.p.: 115–116°C; yield: 10%; IR (HCB, nujol): $\nu = 3066$ (C–H arom), 2885 (C–H), 2253 (C≡N), 1708 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.13 (s, 3H, CH_3), 3.54–3.58 (dd, $J = 4$ Hz, $J = 12$ Hz, 1H, HC-3), 4.24–4.27 (d, $J = 12$ Hz, 1H, CH), 5.09 (d, $J = 4$ Hz, 1H, CH), 7.34–7.50 (m, 10 H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 28.0 (C-2), 28.9 (CH_3), 45.7 (C-3), 58.5 (C-4), 111.2, 111.5 (CN), 128.2, 129.4, 129.6, 129.9, 134.0, 134.1 (C arom), 199.5 (C=O) ppm; MS: *m*/*z* (%) = 320.2 (25) $[M]^{+\cdot}$, 277.1 (8) $[M\text{-}CH_3CO]^+$, 212.1 (100) $[M\text{-}CH_3CO, CH(CN)_2]^+$, 165.1 (7) $[C_6H_5SCHCOCH_3]^+$, 109 (11) $[C_6H_5S]^+$, 77 (7) $[C_6H_5]^+$, 43 (31) $[CH_3CO]^+$.

2-Amino-4-aryl-6-methyl-5-(phenylthio)-4H-pyran-3-carbonitriles (**4**); *general procedure*

To a solution of 10 mmol of **1a**–**d** and 11 mmol (0.73 g) of **2** in *ca.* 40 cm^3 absolute ethanol, a few drops of piperidine were added. The reaction mixture was refluxed for 3 h, concentrated to a one third of the initial volume, and cooled. The solid product was collected by filtration, washed with ethanol, and purified by recrystallization from ethanol.

2-Amino-6-methyl-4-phenyl-5-(phenylthio)-4H-pyran-3-carbonitrile (**4a**; $C_{19}H_{16}N_2OS$)

Colourless prisms; m.p.: 135°C; yield: 64%; IR (HCB, nujol): $\nu = 3466$, 3319–3193 (N–H), 3062–3021 (C–H arom), 2925, 2849 (C–H), 2195 (C≡N), 1680 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ,

500 MHz): 2.23 (s, 3H, CH_3), 3.95 (s, 1H, HC-4), 4.53 (s, 2H, NH_2), 7.11–7.12 (d, 2H, CH arom), 7.16–7.30 (m, 8H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 17.5 (CH_3), 42.4 (C-4), 61.4 (C-3), 108.0 (C-5), 119.1 (CN), 126.3, 127.4 (CH arom), 127.9–128.1 (C arom), 128.5, 129.2 (C arom.), 134.1 (*i*-SPh), 142.7 (*i*-Ph), 151.6 (C-6), 158.4 (C-2) ppm; MS: *m/z* (%) = 320.1 (8) $[M]^{+\cdot}$, 243.1 (18) $[M\text{-}C_6H_5]^+$, 211.1 (9) $[M\text{-}C_6H_5S]^+$, 45.1 (100), 43.1 (23).

2-Amino-4-(4-methoxyphenyl)-6-methyl-5-(phenylthio)-4H-pyran-3-carbonitrile (**4b**; $C_{20}H_{18}N_2O_2S$)

Colourless crystals; m.p.: 148°C; yield: 49%; IR (HCB, nujol): ν = 3431–3193 (N–H), 3067 (C–H arom), 2954, 2841 (C–H), 2201 (C≡N), 1680 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.23 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.92 (s, 1H, CH), 4.47 (s, 2H, NH_2), 6.81–6.84 (d, 2H, CH arom), 7.03–7.05 (d, 2H, CH arom), 7.17–7.22 (m, 3H, C arom), 7.27–7.30 (t, 2H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 17.5 (CH_3), 41.6 (C-4), 55.2 (OCH_3), 61.8 (C-3), 108.3 (C-5), 113.9 (C-3′), 119.1 (CN), 126.3, 128.1, 129.0, 129.2 (C arom), 134.2 (*i*-SPh), 134.9 (C-1′), 151.3 (C-6), 158.2, 158.9 (C-2, C-4′) ppm; MS: *m/z* (%) = 350.2 (54) $[M]^{+\cdot}$, 243.1 (49), $[M\text{-}C_6H_4OCH_3]^+$, 241.1 (100), $[M\text{-}C_6H_5S]^+$, 225.1 (11), 148.1 (16), 109 (8), $[C_6H_5S]^+$, 43.1 (11).

2-Amino-6-methyl-4-(4-nitrophenyl)-5-(phenylthio)-4H-pyran-3-carbonitrile (**4c**; $C_{19}H_{15}N_3O_3S$)

Pale yellow prisms; m.p.: 163°C; yield: 66%; IR (HCB, nujol): ν = 3656–3212 (N–H), 3066 (C–H arom), 2920 (C–H), 2188 (C≡N), 1681 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.28 (s, 3H, CH_3), 4.11 (s, 1H, CH), 4.66 (s, 2H, NH_2), 7.13–7.15 (d, 2H, CH arom), 7.20–7.24 (t, 1H, CH arom), 7.26–7.30 (m, 4H, CH arom), 8.13–8.15 (d, 2H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 17.5 (CH_3), 42.4 (C-4), 60.0 (C-3), 106.9 (C-5), 118.5 (CN), 123.8 (C-3′), 126.9 (C-2′), 128.5, 129.0, 129.3 (C, SPh), 133.1 (*i*-SPh), 147.2, 149.2, 149.8 (C-1′, C-4′), 152.1 (C-6), 158.6 (C-2) ppm; MS: *m/z* (%) = 365.1 (59) $[M]^{+\cdot}$, 256.1 (70) $[M\text{-}C_6H_5S]^+$, 243.1 (100) $[M\text{-}C_6H_4NO_2]^+$, 210.1 (17), 109 (13), $[C_6H_5S]^+$, 45.1 (15).

2-Amino-6-methyl-5-(phenylthio)-4-(4-pyridyl)-4H-pyran-3-carbonitrile (**4d**; $C_{18}H_{15}N_3OS$)

Colourless needles; m.p.: 182°C; yield: 87%; IR (HCB, nujol): ν = 3370–3259 (N–H), 3072–3031 (C–H arom), 2976 (C–H), 2190 (C≡N), 1676 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.27 (s, 3H, CH_3), 3.96 (s, 1H, CH), 4.78 (s, 2H, NH_2), 7.05–7.06 (d, 2H, CH arom), 7.15–7.17 (d, 2H, CH arom), 7.21–7.24 (t, 1H, CH arom), 7.27–7.30 (t, H, CH arom), 8.51–8.52 (d, 2H, CH arom) ppm; ^{13}C NMR ($CDCl_3$, δ 125 MHz): 17.5 (CH_3), 41.9 (C-4), 59.7 (C-3), 106.7 (C-5), 118.6 (CN), 123.1 (C-3′), 126.8, 128.5, 129.3 (C, SPh), 133.3 (*i*-SPh), 149.9 (C-2′), 152.2, 151.24 (C-6, C-4′), 158.9 (C-2) ppm; MS: *m/z* (%) = 321.2 (23) $[M]^{+\cdot}$ 243.1 (100) $[M\text{-}C_5H_4N]^+$, 212.1 (31) $[M\text{-}C_6H_5S]^+$, 134.1 (9), 109.0 (34) $[C_6H_5S]^+$, 78.0 (14), $[C_5H_4N]^+$, 77 (17), $[C_6H_5]^+$, 65 (19), 51 (30), 43.1 (42).

1,4-Bis(3-(phenylthio)-3-butene-2-on-4-yl)-benzene (**5**; $C_{26}H_{22}O_2S_2$)

A solution of 6.7 g terephthalaldehyde (50 mmol) and 16.77 g phenylthioacetone (101 mmol) in toluene was refluxed until the theoretical amount of H_2O was collected. The solvent was removed under vaccum, and the resulting solid was purified by recrystallization from ethanol.

Yellow solid; m.p.: 137°C; yield: 51%; IR (KBr): ν = 3431, 3343, 3055–2923 (C–H), 1676 (C=O), 1581 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.33 (s, 6H, CH_3), 7.18–7.20 (t, 2H, CH arom), 7.22–7.24 (d, 4H, CH arom), 7.26–7.29 (t, 4H, CH arom), 7.88 (m, 6H, CH arom, H vinyl) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 27.6 (CH_3), 126.6, 127.9, 129.4, 130.8, 133.7, 134.9, 135.7, 142.6,

198.8 (C=O) ppm; MS: *m/z* (%) = 430.0 (48) $[M]^+$, 321.1 (26) $[M\text{-}C_6H_5S]^+$, 282.1 (100), 253.1 (25), 239.1 (18), 234.1 (11), 218 (23), 211.1 (54), 178.1 (41), 149.1 (16), 109 (38), $[C_6H_5S]^+$, 77 (19) $[C_6H_5]^+$, 65.1 (18), 51.0 (14), 43 (60) $[CH_3CO]^+$.

1,4,Bis-(2-amino-3-cyano-6-methyl-5-(phenylthio)-4H-pyran-4-yl)-benzene (**6** $C_{32}H_{26}N_4O_2S_2$)

To a solution of 2.15 g **5** (5 mmol) and 0.79 g **2** (12 mmol) in 80 cm^3 of absolute ethanol a few drops of piperidine were added. The reaction mixture was refluxed for 4 h. The solvent was removed under vacuum, and the residue was submitted to column chromatography using $CHCl_3/CH_3OH$ as eluent. Further purification was accomplished by crystallization from CH_3OH_3/CH_3COCH_3 to give 27% of **6**.

Colourless solid; m.p.: 234–237°C; IR (KBr): $\nu = 3475$–3166 (N–H), 3073–3011 (C–H arom), 2892 (C–H), 2188 (C≡N), 1674 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500 MHz): 2.16 (s, 6H, CH_3), 3.77 (s, 2H, HC-4), 6.92 (s, 4H, NH_2), 7.02 (d, 4H, CH arom), 7.18–7.23 (m, 6H, CH arom), 7.32–7.36 (m, 4H, CH arom) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125 MHz): 17.5 (CH_3), 42.9 (C-4), 57.0 (C-3), 106.6 (C-5), 120.3 (CN), 126.4, 127.5, 127.9, 129.7, 134.6, 142.9 (C arom), 153.1 (C-6), 159.8 (C-2) ppm; MS: *m/z* (%) = 562.0 (5) $[M]^+$, 496.0 (22), 430 (20), 396 (14), 387.1 (23), 287.1 (27), 243.1 (100) $[C_{13}H_{11}N_2OS]^+$, 218.0 (22), 166.1 (38), 123.0 (57), 109.0 (51) $[C_6H_5S]^+$, 77.1 (19) $[C_6H_5]^+$, 66 (46), 43 (42) $[CH_3CO]^+$.

Reactions of **7** *with* **1c** *and* **1d**

A solution of 2.99 g **1c** (10 mmol) and 0.93 g **7** (11 mmol) in 70 cm^3 of absolute ethanol containing a few drops of piperidine was refluxed for 3 h. Then the reaction mixture was left for 3 days and concentrated to one half of its initial volume. The precipitated solid was collected by filtration, and the filtrate was concentrated again. After a few days, new crops of the solid were obtained. The crude product was separated and purified by column chromatography on silica gel using $CHCl_3$ as eluent. From the reaction mixture of **1c** with **7**, three product (**9c**, **10c**, and **12c**) were isolated. Further purification was accomplished by crystallization from ethanol. Reaction of **1d** with **7** afforded **10d**.

2-Hydroxy-6-methyl-5-(phenylthio)-4-(4-nitrophenyl)-3,4-dihydropyridine-3-carbonitrile (**9c**; $C_{19}H_{15}N_3O_3S$)

Colourless prisms; m.p.: 176–177°C; yield: 26%; IR (HCB, nujol): $\nu = 3223$–2885 (O–H), 2258 (C≡N), 1708 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): *trans*: 2.30 (s, 3H, CH_3), 3.90–3.92 (d, 1H, $J = 7.2$ Hz), 4.22–4.23 (d, 1H, $J = 7.2$ Hz); *cis*: 2.35 (s, 3H, CH_3), 3.73–3.74 (d, 1H, $J = 4.2$ Hz), 4.01–4.02 (d, 1H, $J = 4.2$ Hz), 7.20–7.35 (m, 7H, CH arom), 8.15–8.19 (d, 2H, CH arom), 8.50 (1H, OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 18.1, 18.3, 40.7, 41.5, 46.1, 46.7, 106.5, 108.3, 113.6, 115.0, 124.2, 124.3, 127.3, 127.5, 128.6, 129.2, 129.4, 129.5, 129.6, 133.6, 133.9, 139.1, 139.4, 142.8, 144.2, 147.9, 148.1, 160.7, 161.6 ppm; MS: *m/z* (%) = 365.1 (100) $[M]^{+\cdot}$, 297.1 (27), 281.1 (11), 256.1 (23) $[M\text{-}C_6H_5S]^+$, 251.1 (25), 118.1 (10), 85 (29), 83 (45), 44 (22).

2-Hydroxy-6-methyl-5-(phenylthio)-4-(4-nitrophenyl)-pyridine-3-carbonitrile (**10c**; $C_{19}H_{13}N_3O_3S$)

Pale yellow prisms; m.p.: 254–257°C; yield: 5%; IR (HCB, nujol): $\nu = 3046$ (C–H arom), 2996 (C–H), 2910–2758 (O–H), 2227 (C≡N), 1656 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.75 (s, 3H, CH_3), 6.80–6.82 (d, 2H, CH arom), 7.15–7.21 (m, 3H, CH arom), 7.31–7.33 (d, 2H, CH arom), 8.20–8.22 (d, 2H, CH arom), 13.8 (bs, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 20.3 (CH_3), 110.2, 123.5, 126.6, 126.7, 129.0, 129.5, 135.4, 141.4, 148.4, 164.8 ppm; UV: $\lambda_{max} = 358$ nm ($\log\varepsilon = 6.72$); emission: $\lambda_{max} = 501$ nm; MS: *m/z* (%) = 363.1 (100) $[M]^{+\cdot}$, 256.1 (9), 129.1 (10), 114.1 (12), 74.1 (27), 73 (14), 69.1 (12), 57.1 (18), 55.1 (16), 43.1 (19), 41 (15).

2-Hydroxy-6-methyl-5-(phenylthio)-4-(4-nitrophenyl)-3,4-dihydropyridine-3-carboxamide (**12c**; $C_{19}H_{17}N_3O_4S$)

Amide **12c** was isolated by column chromatography on silica gel in $CHCl_3$ as the third product from the reaction mixture of **1c** and **7**.

Pale yellow prisms; m.p.: 203–204°C; yield: 6%; IR (HCB, nujol): $\nu = 3457$ (N–H), 3300–3072 (O–H), 2951–2924 (C–H), 1680, 1647, 1597 (C=O and C=C) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 500 MHz): 2.24 (s, 3H, CH_3), 3.51 (d, $J = 3.5$ Hz, 1H, CH), 4.09 (d, $J = 3.5$ Hz, 1H, CH), 7.26–7.30 (m, 3H), 7.37–7.40 (m, 3H), 7.56–7.58 (d, 2H, CH arom), 7.79 (s, 1H, NH), 8.28–8.30 (d, 2H, CH arom), 10.30 (s, 1H, OH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125 MHz): 17.5 (CH_3), 47.4, 55.5, 100.4, 123.7, 125.4, 126.3, 129.1, 136.2, 143.4, 146.6, 149.0, 166.1, 169.4 ppm; MS: *m*/*z* (%) = 383.1 (6) $[M]^{+\cdot}$, 339.1 (24), 200.2 (13), 157.1 (9), 129.1 (19), 114.1 (21), 111.1 (15), 103.1 (18), 97.1 (27), 85.1 (36), 83.1 (32), 81.1 (22), 74.1 (71), 73.0 (48), 71.1 (54), 69.1 (57), 60 (53), 57.1 (100), 55.1 (76).

2-Hydroxy-6-methyl-5-(phenylthio)-4-(4-pyridyl)-pyridine-3-carbonitrile (**10d**; $C_{18}H_{13}N_3OS$)

The synthesis of **10d** was carried out in a similar way to that of **10c**. Fractional crystallization from ethanol afforded 21% of the product.

Yellow solid; m.p.>360°C; IR (HCB, nujol): $\nu = 3042$ (C–H arom), 2801–2571 (O–H), 2220 (C≡N), 1676 (C=C) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 500 MHz): 2.70 (s, 3H, CH_3), 6.99–7.01 (d, 2H, CH arom), 7.14–7.17 (t, 1H, CH arom), 7.24–7.27 (m, 4H, CH arom), 8.60–8.61 (d, 2H, HC-2′), 13.33 (s, 1H, OH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125 MHz): 19.3 (CH_3), 101.6 (C-3), 105.0 (C-5), 115.0 (CN), 122.0 (C-3′), 125.4, 125.5 (*p*-SPh, *o*-SPh), 129.2 (*m*-SPh), 136.2 (*i*-SPh), 143.7 (C-4′), 149.3 (C-2′), 159.8, 159.9 (C-2 and C-4), 162.9 (C-6) ppm; MS: *m*/*z* (%) = 319.1 (100) $[M]^{+\cdot}$, 242.1 (15), $[M\text{-}C_6H_5]^+$, 109 (8) $[C_6H_5S]^+$, 77 (21) $[C_6H_5]^+$, 51 (15), 42.1 (29).

2-Hydroxy-6-methyl-5-(phenylthio)-pyridine-3-carbonitrile (**16**; $C_{13}H_{10}N_2OS$)

To a solution of 4.42 g **1e** (20 mmol) in 50 cm^3 of absolute ethanol, 1.45 g **2** (22 mmol) and a few drops of piperidine were added. The reaction mixture was kept at room temperature for 2–5 days until a precipitate solidified. The solid was collected by filtration and washed with ethanol. Evaporation of the mother liquor afforded additional material.

Colourless needles (ethanol); m.p.: 260–262°C; yield: 52%.

Compound **16** was also obtained when equimolar amounts of **1e** and **7** were refluxed in toluene for 12 h: colourless needles from ethanol, yield: 7%. The identity of the samples obtained in the reactions of **1e** with **2** and **7** was confirmed by m.p., mixed m.p., and by comparison of their ^1H NMR spectra.

IR (HCB nujol): $\nu = 3304$ (NH), 2925–2773 (O–H), 2227 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 2.60 (s, 3H, CH_3), 7.12–7.14 (d, 2H, CH arom), 7.22–7.25 (t, 1H, CH arom), 7.29–7.32 (t, 2H, CH arom), 7.99 (s, 1H, CH-4), 13.56 (s, 1H, OH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125 MHz): 18.9 (CH_3), 102.0 (C-3), 106.1 (C-5), 115.9 (CN), 126.2, 126.8 (*o*-SPh, *p*-SPh), 129.6 (*m*-SPh), 136.5 (*i*-SPh), 155.0 (C-4), 159.3 (C-6), 160.3 (C-2) ppm; UV: $\lambda_{max} = 340$ nm ($\log\varepsilon = 6.72$); emission: $\lambda_{max} = 461$ nm; MS: *m*/*z* (%) = 242.1 (100) $[M]^{+\cdot}$, 77.0 (10) $[C_6H_5]^+$, 51.0, (10), 42.1 (15) $[CH_3]^+$.

3-Ethoxycarbonyl-2-hydroxy-6-methyl-5-(phenylthio)-pyridine (**18**; $C_{15}H_{15}NO_3S$)

A toluene solution of 1.1 g **1e** (5 mmol) and 0.6 g **17** (5.3 mmol) with a few drops of piperidine was refluxed for 4 h. The solvent was removed under vacuum; the resulting oil solidified after cooling and was purified by column chromatography on silica gel using $CHCl_3$ as eluent. Recrystallization from chloroform/petrol ether gave colourless prisms.

M.p.: 168–170°C; yield: 35.3%; IR (HCB, nujol): $\nu = 2980$–2672 (O–H), 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.33–1.36 (t, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.31–4.36 (q, 2H, CH_2), 7.07–7.08 (d, 2H, CH arom), 7.15–7.18 (t, 1H, CH arom), 7.25–7.28 (t, 2H, CH arom), 8.36 (s, 1H, CH-4), 13.72 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 14.2 (ω-CH_3), 61.4 (CH_2), 126.1 (*p*-SPh), 127.0 (*o*-SPh), 129.3 (*m*-SPh), 136.5 (*i*-SPh) ppm; UV: $\lambda_{max} = 340$ nm ($\log\varepsilon = 6.73$); emission: $\lambda_{max} = 457$ nm; MS: *m/z* (%) = 289.1 (100) $[M]^{+\cdot}$, 243.0 (46), 217.0 (16), 146.0 (20), 121.0 (7).

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