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Microwave-assisted synthesis of bipyrazolyls and pyrazolyl-substituted pyrimidines

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Dedicated to Charles W. Rees, in memoriam

Abstract—We describe the preparation of 1,4′-bipyrazolyls and 4-pyrazolylpyrimidines by the reaction of 2-pyrazolyl-3-dimethylamino acrylate and acrylonitrile with double nucleophilic reagents such as hydrazines, urea and guanidine. Reactions were performed under microwave irradiation in 5–60 min. This is a useful procedure for the preparation of valuable compounds with applications in medicinal and coordination chemistry.

1. Introduction

Pyrimidine derivatives form the basis of a large number of pharmacological products, for example, as inhibitors of HIV-1 integrase,[1] anticancer drugs[2] and protein kinase inhibitors.[3] The pharmacological properties of pyrazole derivatives have also been reviewed recently.[4,5] Pyrazolyl-substituted pyrimidines show analgesic activity[6] and have been used in coordination chemistry as bitopic ligands.[7]

Bipyrazolyls show interesting properties in coordination chemistry; for example, 4,4′-bipyrazolyl compounds have been used in the construction of coordination networks and in self-assembly.[8] Consequently, the preparation of 1,4′-bipyrazolyl systems could form the basis for a new kind of multi-site ligand and even for the synthesis of chains of polypyrazoles.

3-(Dimethylamino)propenoates are starting materials for a wide variety of heterocyclic compounds, particularly for the construction of the pyrimidine ring.[9] These compounds are analogues of 1,3-dicarbonyl compounds and are more stable than α-formyl acetates. They have been used for the preparation of heterocyclic compounds by reaction with double nucleophiles and with electrophiles. We therefore chose these substrates for the preparation of our target compounds. In this regard, 2-pyrazolyl-3-dimethylamino acrylate and acrylonitrile were our starting materials.

Microwave irradiation is a useful heating technique that is able to improve many kinds of reactions[10] and it has been applied successfully in the preparation of heterocyclic compounds.[11–16]

We have applied microwaves to heterocyclic chemistry,[17,18] to cycloaddition reactions,[19,20] in the study of the so-called microwave effect[21] and also for the preparation of heterocyclic compounds with applications in coordination and supramolecular chemistry.[22]

In the work described here, we applied this methodology for the preparation of 1,4′-bipyrazolyls and 4-pyrazolyl-substituted pyrimidines. Although many 4,4′-bipyrazolyls and pyrazolylpyrimidines have been described, those joined through pyrazole position 4 are not common.

2. Results

2.1. Synthesis of precursors

We planned the synthesis of bipyrazolyls and pyrazolyl-substituted pyrimidine bases by the reaction of 2-pyrazolyl-3-dimethylamino acrylate and acrylonitrile with double nucleophiles.

The starting materials were prepared from pyrazolyl acrylate and acrylonitrile by reaction with the Vilsmeier reagent[23] ($POCl_3$/DMF) at 80 °C for 16 h. However, under these conditions a complex mixture was obtained, with formylation in

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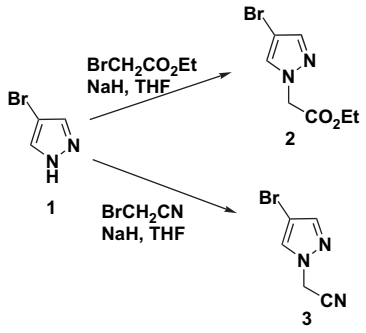
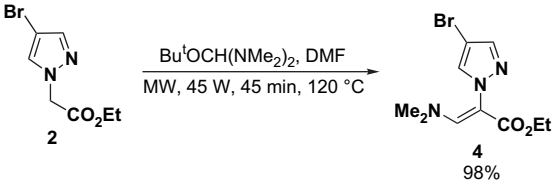
the activated 4-position of the pyrazole ring being the main reaction. Also, decarboxylation has been previously observed in the reaction of pyridinium acetic acid with electrophiles,[24] and in the Vielsmeir–Haack formylation of 4-nitropyrazoles.[25] In order to protect position 4, we used 4-bromopyrazole as the starting material. Thus, ethyl 4-bromopyrazolyl acetate (**2**) and acetonitrile **3** were prepared by alkylation of 4-bromopyrazole with ethyl bromoacetate and bromoacetonitrile in anhydrous THF using sodium hydride as a base (Scheme 1). Reaction at room temperature for 4 h afforded compounds **2** and **3** in 73% and 94% yield, respectively.

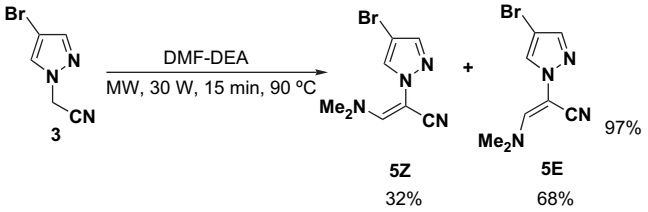


Scheme 1.

Formylation of **2** and **3** was performed under microwave irradiation. Use of the Vilsmeier reagent gave a complex mixture and, as a consequence, we used dimethyl formamide-diethyl acetal (DMF-DEA). Formylation of **2** was performed by irradiation at 30 W for 15 min (temp 90 °C) using a 2-fold excess of DMF-DEA without addition of any solvent. These conditions gave only a modest 10% yield of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylic acid ethyl ester (**4**) (Scheme 2). The use of prolonged reaction times led to a decrease in the yield due to decomposition of the final product. However, in the case of compound **3**, irradiation at 30 W for 15 min (temp 90 °C) afforded an excellent yield (97%) of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile (**5**) as a 32:68 mixture of *Z* and *E* isomers, respectively (Scheme 3).



Scheme 2.



Scheme 3.

The preparation of **4** was improved using Bredereck's reagent (*tert*-butoxy-bis-dimethylaminomethane).[26] Irradiation at 45 W (temp 120 °C) for 45 min gave an excellent yield (98%) of compound **4** as a single isomer (*Z*-isomer). In this reaction, 1 mL/mmol of DMF was used to homogenize the reaction mixture and to improve the absorption of microwave irradiation. It is remarkable that conventional heating for 6 h at 120 °C is necessary to obtain similar results.

The configuration of the double bond in **4** and **5** was determined by NOE experiments (Fig. 1). In compound **5**, isomer **5E** shows a 1% NOE on H_5 (7.54) on irradiation at 7.04 (olefin hydrogen) and a 4% NOE with the dimethylamino group (3.18); isomer **5Z** shows only a 4% NOE with the dimethylamino group (2.70) on irradiation at 6.71 (olefin hydrogen). In compound **4**, a single isomer was obtained in which the double bond has the *Z*-configuration. Irradiation at 7.52 again showed a 3% NOE with the dimethylamino group (2.33 and 3.07).

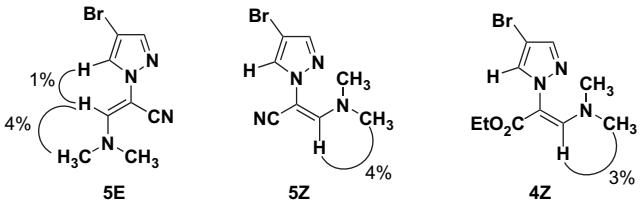


Figure 1.

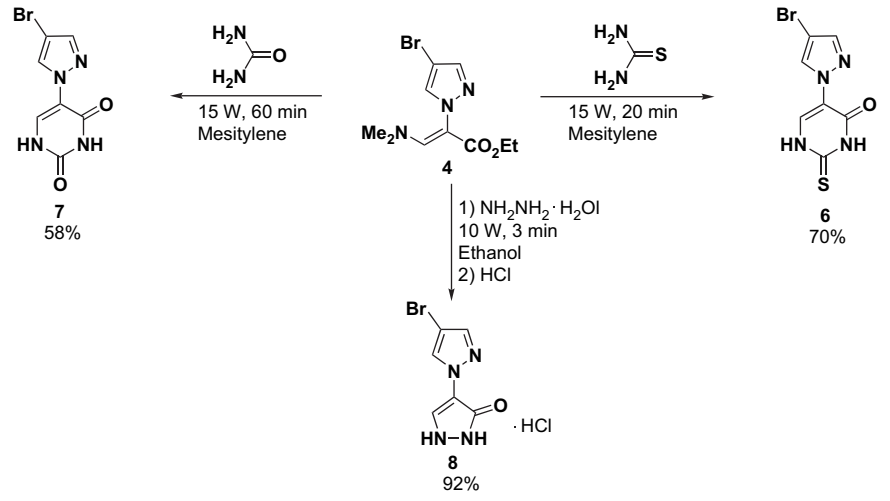
2.2. Cyclization reactions

Reaction of the precursors described above with double nucleophiles gave the desired compounds (Schemes 4 and 5). Urea, thiourea and guanidine were used to obtain a wide variety of pyrazolyl-substituted pyrimidines. For example, uracil and thiouracil derivatives **7** and **6** were prepared by reaction of **4** with urea and thiourea, respectively, and aminopyrimidines **9** and **10** were made by reaction of **5** with thiourea and guanidine, respectively. Finally, the use of hydrazine and phenylhydrazine gave bipyrazolyl derivatives **8**, **11** and **12**.

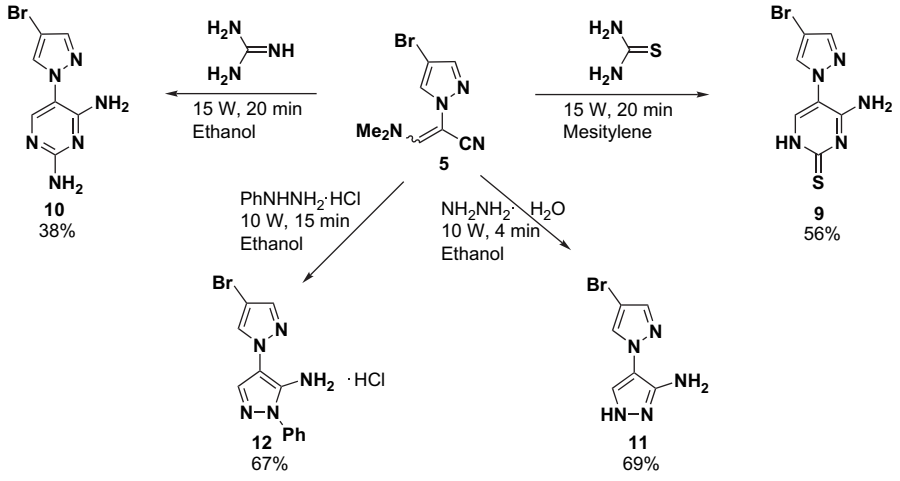
All reactions were performed under microwave irradiation using a small quantity of solvent (1 mL/mmol) to homogenize the reaction mixture (in most cases both reactants are solids). When possible we used an apolar solvent like mesitylene to ensure that the reagents and not the solvent absorbed microwave radiation. However, with very polar compounds the use of a polar solvent (ethanol) was necessary to dissolve the reagents. Reaction times were in the range of 20–60 min with mesitylene and 4–15 min with the more polar ethanol.

These conditions gave good yields of bipyrazolyls and pyrazolylpyrimidines and represents a general procedure for the preparation of these heterocyclic systems.

In conclusion, we have described a new procedure for the preparation of 4-pyrazolyl-substituted pyrimidines and 1,4′-bipyrazolyls starting from 2-pyrazolyl-3-dimethylamino acrylate and acrylonitrile under microwave irradiation



Scheme 4.



Scheme 5.

conditions. This result opens a new way to prepare valuable compounds in medicinal chemistry, such as 4-pyrazolyl-substituted pyrimidine bases, as well as systems of relevance in coordination chemistry.

3. Experimental

3.1. General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Unity 500 spectrometer with TMS as the internal standard. IR spectra were obtained with Nicolet-550 FTIR and ThermoNicolet-IR-100 spectrophotometers. The mass spectra were recorded on a VG AutoSpec apparatus using electron impact at 70 eV and atmospheric pressure chemical ionization (ApCI). Flash column chromatography was performed on silica gel 60 (Merck, 230–400 mesh).

Reactions under microwave irradiation were performed in a CEM Discover or a modified PROLABO MAXIDIGEST MX35. Temperature was measured with an IR pyrometer and, in the latter oven, controlled using a computer with PACAM MPX-2 software.

3.1.1. 2-(4-Bromopyrazol-1-yl)acetic acid ethyl ester 2. Sodium hydride (11 mmol, 0.27 g) was added to a suspension of 4-bromopyrazole **1** (10 mmol, 1.47 g) in dry THF (20 mL) under argon. The mixture was stirred until the evolution of hydrogen had finished. The mixture was cooled to 0 °C and a solution of bromoethyl acetate (10 mmol, 1.14 mL) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 14 h. The solvent was evaporated in vacuo and the residue extracted with dichloromethane (3×10 mL), filtered and concentrated to give an orange oil (1.71 g, 73%). The oil was distilled under reduced pressure using Kugelrohr apparatus to afford pure **2** as a colourless oil (0.804 g, 47%). Bp 183 °C (oven temperature)/10 mmHg. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.29 (t, J=7.32 Hz, 3H, CH_3), 4.23 (q, J=7.32 Hz, 2H, –CH_2–O), 4.87 (s, 2H, N–CH_2–), 7.51 (s, 2H, H_3 and $H_{5\text{-pyrazole}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 14.03 (CH_3), 53.46 (CH_2), 62.03 (N–CH_2), 94.05 (C–Br), 130.68 ($C_{5\text{-pyrazole}}$), 140.62 ($C_{3\text{-pyrazole}}$), 167.25 (C=O). IR (KBr) ν (cm^{-1}): 3132, 2984, 1751, 1217. MS (APcI) m/z: 232.0 (M^+).

3.1.2. 2-(4-Bromopyrazol-1-yl)acetonitrile 3. Sodium hydride (11 mmol, 0.27 g) was added to a suspension of 4-bromopyrazole **1** (10 mmol, 1.47 g) in dry THF (20 mL) under argon. The mixture was stirred until the evolution of hydrogen had finished. The mixture was cooled to 0 °C and a solution of bromoacetonitrile (10 mmol, 0.7 mL) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 14 h. The solvent was evaporated in vacuo and the residue was extracted with dichloromethane (3×10 mL). The organic extract was dried with magnesium sulfate and the solvent evaporated in vacuo to afford pure **3** as a white solid (1.76 g, 94%). Mp (hexane) 66.0–67.6 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 5.06 (s, 2H, CH_2), 7.56 (s, 1H, $H_{5\text{-pyrazole}}$), 7.59 (s, 1H, $H_{3\text{-pyrazole}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 39.97 (CH_2), 95.47 (C–Br), 113.22 (CN), 129.7 ($C_{5\text{-pyrazole}}$), 141.95 ($C_{3\text{-pyrazole}}$). IR (KBr) ν (cm^{-1}): 3127, 2939, 1439, 1415. MS (APcI): *m/z* 185.0 (M^+).

3.1.3. 2-(4-Bromopyrazol-1-yl)-3-dimethylaminoacrylic acid ethyl ester 4. A mixture of (4-bromopyrazol-1-yl)acetic acid ethyl ester **2** (2.57 mmol, 0.60 g), *tert*-butyloxy-bis-dimethylaminomethane (2.81 mmol, 0.58 mL) and DMF (1 mL) was introduced into a Pyrex flask and irradiated at 45 W for 30 min. The crude product was distilled under reduced pressure using Kugelrohr apparatus to give pure **4**. Yield: 0.728 g, 98%; bp 154 °C (oven temperature)/ 1.5 mbar. ^{1}H NMR ($CDCl_3$, ppm) δ: 1.20 (t, J=7.0 Hz, 3H, CH_3–), 2.33 (br s, 3H, N–CH_3), 3.07 (br s, 3H, N–CH_3), 4.13 (q, J=7.0 Hz, 2H, O–CH_2–), 7.44 (s, 1H, H_3), 7.51 (s, 1H, $H_{5\text{-pyrazole}}$), 7.57 (s, 1H, $H_{3\text{-pyrazole}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 14.48 (–CH_3), 36.35 (br s, N–CH_3), 47.28 (br s, N–CH_3), 60.13 (O–CH_2), 93.48 (C–Br), 100.25 (C_2), 134.69 (C_3), 140.44 ($C_{3\text{-pyrazole}}$), 146.83 ($C_{5\text{-pyrazole}}$), 166.62 (C═O). IR (KBr) ν (cm^{-1}): 3140, 3102, 1686, 1626. EIMS: *m/z* 287.0 (M^+).

3.1.4. (*Z*)- and (*E*)-2-(4-Bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile 5Z and 5E. A mixture of (4-bromopyrazol-1-yl)acetonitrile **3** (2.5 mmol, 0.47 g) and DMF-DEA (5 mmol, 0.85 mL) was introduced into a Pyrex flask and irradiated at 30 W for 15 min. The crude mixture was filtered through silica gel (7 cm×2 cm) using ethyl acetate. The solvent was evaporated and the product distilled under reduced pressure using Kugelrohr apparatus to afford a 32:68 mixture of **5Z** and **5E**, as determined by ^{1}H NMR. Yield: 0.585 g, 97%; bp 170 °C (oven temperature)/4 mbar. IR (neat) ν (cm^{-1}): 3124, 2924, 2189,1642. EIMS: *m/z* 240.0 (M^+).

Compound **5E**: ^{1}H NMR ($CDCl_3$, ppm) δ: 3.19 [s, 6H, N–$(CH_3)_2$], 7.04 (s, 1H, N–CH═C), 7.5 (s, 1H, $H_{3\text{-pyrazole}}$), 7.54 (s, 1H, $H_{5\text{-pyrazole}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 42.50 (N–CH_3), 82.59 (C_2), 94.11 (C–Br), 117.6 (CN), 130.67 ($C_{5\text{-pyrazole}}$), 140.79 ($C_{3\text{-pyrazole}}$), 149.83 (C_3).

Compound **5Z**: ^{1}H NMR ($CDCl_3$, ppm) δ: 2.71 (s, 6H, N–$(CH_3)_2$), 6.72 (s, 1H, N–CH═C), 7.54 (s, 1H, $H_{5\text{-pyrazole}}$), 7.58 (s, 1H, $H_{3\text{-pyrazole}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 81.17 (C_2), 94.84 (C–Br), 119.58 (CN), 133.96 ($C_{5\text{-pyrazole}}$), 141.58 ($C_{3\text{-pyrazole}}$), 147.99 (C_3).

3.1.5. 5-(4-Bromopyrazol-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one 6. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylic acid ethyl ester **4** (1.0 mmol, 0.288 g), thiourea (10 mmol, 0.76 g) and anhydrous mesitylene (1 mL) was introduced into a Pyrex flask and irradiated at 15 W for 20 min. The product was purified by column chromatography on silica gel (hexane/ethyl acetate 8:2) to give a yellow solid. Yield: 0.192 g, 70%; mp 191–193 °C (decomposition). ^{1}H NMR (DMSO-d_6, ppm) δ: 7.82 (s, 1H, $H_{3\text{-pyrazole}}$), 7.86 (s, 1H, $H_{5\text{-pyrazole}}$), 8.36 (s, 1H, $H_{6\text{-pyrimidine}}$), 12.8 (br s, 1H, NH), 13.1 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm) δ: 93.46 (C–Br), 119.36 ($C_{5\text{-pyrimidine}}$), 131.01 ($C_{6\text{-pyrimidine}}$), 134.8 ($C_{5\text{-pyrazole}}$), 140.63 ($C_{3\text{-pyrazole}}$), 156.56 (C═O), 174.28 (C═S). IR (KBr) ν (cm^{-1}): 3071, 1697, 1632, 1354. EIMS: *m/z* 271.9366 (M^+).

3.1.6. 5-(4-Bromopyrazol-1-yl)-1*H*-pyrimidin-2,4-dione 7. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylic acid ethyl ester **4** (1.0 mmol, 0.288 g), urea (10 mmol, 0.6 g) and anhydrous mesitylene (1 mL) was introduced into a Pyrex flask and irradiated at 15 W for 60 min. The product was purified by column chromatography on silica gel using ethyl acetate. A pale yellow solid was obtained. Yield: 0.158 g, 58%; mp T>250 °C (decomposition). ^{1}H NMR (DMSO-d_6, ppm) δ: 7.74 (s, 1H, $H_{5\text{-pyrazole}}$), 7.91 (s, 1H, $H_{6\text{-pyrimidine}}$), 8.21 (s, 1H, $H_{3\text{-pyrazole}}$), 11.15 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm) δ: 92.85 (C–Br), 115.18 ($C_{5\text{-pyrimidine}}$), 131.58 ($C_{5\text{-pyrazole}}$), 140.08 ($C_{3\text{-pyrazole}}$), 149.93 ($C_{6\text{-pyrimidine}}$), 150.41 (C_2═O), 159.75 (C_4═O). IR (KBr) ν (cm^{-1}): 3213, 3084, 1707. EIMS: *m/z* 255.9599 (M^+).

3.1.7. 4-Bromo-1′,2′-dihydro-[1,4′]bipyrazolyl-3′-one hydrochloride 8. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylic acid ethyl ester **4** (1.0 mmol, 0.288 g), hydrazine monohydrate (2 mmol, 0.1 mL) and ethanol (1 mL) was introduced into a Pyrex flask and was cooled to −10 °C. Hydrochloric acid (37%, 11 drops) was added. The solution was allowed to warm up to room temperature and the mixture was irradiated at 10 W for 3 min. The solvent was evaporated in vacuo and dichloromethane (15 mL) was added. The resulting precipitate was identified as the pure product (0.145 g, 92%). Mp 233.7–235.0 °C. ^{1}H NMR (DMSO-d_6, ppm) δ: 7.69 (s, 1H, $H_{3\text{-pyrazole}}$), 7.84 (s, 1H, $H_{5'\text{-pyrazolone}}$), 8.09 (s, 1H, $H_{5\text{-pyrazole}}$), 12.01 (s_{broad}, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm) δ: 92.47 (C–Br), 108.95 ($C_{4'\text{-pyrazolone}}$), 123.45 ($C_{5'\text{-pyrazolone}}$), 129.89 ($C_{5\text{-pyrazole}}$), 139.55 ($C_{3\text{-pyrazole}}$), 152.65 (C═O). IR (KBr) ν (cm^{-1}): 3146, 2966, 1569, 1494. EIMS: 226.9810 (M^+).

3.1.8. 4-Bromo-1′-phenyl-1′*H*-[1,4′]bipyrazolyl-5′-ylamine hydrochloride 12. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile **5** (1.0 mmol, 0.241 g), phenylhydrazine hydrochloride (2 mmol, 0.29 g) and ethanol (1 mL) was introduced into a Pyrex flask and irradiated at 10 W for 15 min. The product was purified by column chromatography on silica gel (hexane/ethyl acetate 7:3). A red solid was obtained. Yield: 0.230 g, 67%; mp 135.5–136.1 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 4.71 (s, 2H, NH_2), 7.41 (t, J=7.3 Hz, 1H, $H_{p\text{-Ph}}$), 7.52 (t, J=7.8 Hz, 2H, $H_{m\text{-Ph}}$), 7.58–7.62 (m, 4H, $H_{o\text{-Ph}}$, $H_{5'}$, H_3), 7.71 (s, 1H, H_5). ^{13}C NMR ($CDCl_3$, ppm) δ: 93.98 (C–Br), 108.51 ($C_{4'}$), 123.85 ($C_{o\text{-Ph}}$), 127.99 (C_5), 128.04 ($C_{p\text{-Ph}}$), 129.69 ($C_{m\text{-Ph}}$), 131.51 ($C_{5'}$), 137.99 ($C_{3'}$), 138.17 ($C_{ipso\text{-Ph}}$),

140.12 (C_3). IR (KBr) ν (cm^{-1}): 3406, 3322, 1625, 1595. EIMS: *m/z* 303.0117 (M^+).

3.1.9. 5-(4-Bromopyrazol-1-yl)pyrimidine-2,4-diamine 10. Guanidine hydrochloride (2 mmol, 0.19 g) was dissolved in ethanol (3 mL) and a solution of sodium hydroxide (2 mmol, 0.08 g) in ethanol (2 mL) was added dropwise to give a basic pH. The resulting solution was filtered to remove sodium chloride. The filtrate was mixed with 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile **5** (1.0 mmol, 0.241 g) and basic alumina (1 g). The mixture was irradiated at 15 W for 20 min. The crude product was extracted with chloroform and alumina was removed by filtration. The filtrate was purified by column chromatography on silica gel using ethyl acetate. A pale yellow solid was obtained. Yield: 0.098 g, 38%; mp 127 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 4.88 (br s, 2H, NH_2), 5.68 (br s, 2H, NH_2), 7.66 (s, 1H, $H_{3\text{-pyrazole}}$), 7.68 (s, 1H, $H_{5\text{-pyrazole}}$), 7.93 (s, 1H, $H_{6\text{-pyrimidine}}$). ^{13}C NMR ($CDCl_3$, ppm) δ: 94.77 (C–Br), 109.76 ($C_{5\text{-pyrimidine}}$), 129.57 ($C_{5\text{-pyrazole}}$), 141.59 ($C_{3\text{-pyrazole}}$), 150.20 ($C_{6\text{-pyrimidine}}$), 157.86 ($C_{4\text{-pyrimidine}}$), 161.64 ($C_{2\text{-pyrimidine}}$). IR (KBr) ν (cm^{-1}): 2923, 2853, 1464. EIMS: *m/z* 253.9911 (M^+).

3.1.10. 5-(4-Bromopyrazol-1-yl)-2-thioxo-2,3-dihydro-1*H*-pyrimidine-4-amine 9. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile **5** (1.0 mmol, 0.241 g), thiourea (10 mmol, 0.76 g) and anhydrous mesitylene (1 mL) was introduced into a Pyrex flask and irradiated at 15 W for 20 min. Water (3 mL) was added and the resulting solid was filtered off. The solid was washed with hot methanol (2×1 mL) to afford the pure product. Yield: 0.142 g, 56%; mp 256 °C (decomposition). ^{1}H NMR (DMSO-d_6, ppm) δ: 7.19 (s, 1H, NH), 7.82 (s, 1H, $H_{6\text{-pyrimidine}}$), 7.86 (s, 1H, $H_{3\text{-pyrazole}}$), 8.23 (br s, 1H, NH), 8.30 (s, 1H, $H_{5\text{-pyrazole}}$), 12.51 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm) δ: 93.83 (C–Br), 111.92 ($C_{5\text{-pyrimidine}}$), 132.01 ($C_{5\text{-pyrazole}}$), 138.83 ($C_{6\text{-pyrimidine}}$), 141.67 ($C_{3\text{-pyrazole}}$), 157.10 ($C_{4\text{-pyrimidine}}$), 178.84 (C=S). IR (KBr) ν (cm^{-1}): 3368, 3232, 3127, 1650. EIMS: 270.9523 (M^+).

3.1.11. 4-Bromo-1′*H*-[1,4′]bipyrazolyl-3′-ylamine 11. A mixture of 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylonitrile **5** (1.0 mmol, 0.241 g), hydrazine monohydrate (2 mmol, 0.1 g, 0.11 mL) and ethanol (1 mL) was introduced into a Pyrex flask and was cooled to −10 °C. Hydrochloric acid (37%, 11 drops) was added. The mixture was allowed to warm up to room temperature and was irradiated at 10 W for 4 min. The solvent was evaporated in vacuo and the addition of dichloromethane (3 mL) gave the hydrochloride as a precipitate. The solid was filtered off and dissolved in water (15 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (4×5 mL). The organic extract was dried over magnesium sulfate and the solvent was evaporated under vacuum to afford a solid (0.158 g, 69%). Mp 152.4–154.9 °C. ^{1}H NMR (DMSO-d_6, ppm) δ: 4.5–6.5 (br s, 2H, NH_2), 7.79 (s, 1H, H_3), 8.00 (s, 1H, $H_{5'}$), 8.34 (s, 1H, H_5). ^{13}C NMR (DMSO-d_6, ppm) δ: 93.11 (C–Br), 111.44 ($C_{4'}$), 125.27 ($C_{5'}$), 129.96 (C_5), 139.98 (C_3), 141.02 ($C_{3'}$). IR (KBr) ν (cm^{-1}): 3476, 3346, 1598, 1537. EIMS: 227.9640 (M+1).

Acknowledgements

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