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Synthesis of new 4-(pyrimidin-4-yl)pyrazol-3-one derivatives

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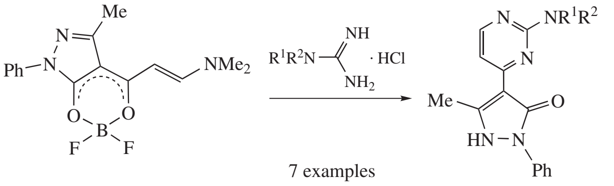
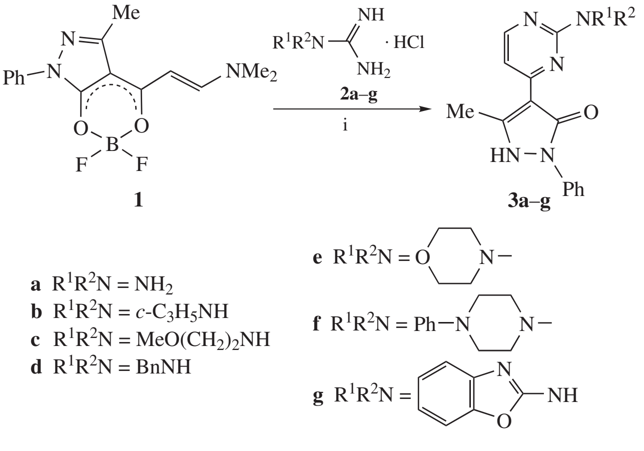
New 4-(2-R-pyrimidin-4-yl)-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones were obtained by reaction of difluoroboron chelate of 4-acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole with guanidine and its derivatives.



The construction of molecules involving two or more various N-, O-heterocyclic fragments bonded directly or *via* different spacers with the purpose to study both their properties and biological activities emerged to be a trend of modern organic chemistry.[1–4] Among compounds of such a type one may consider pyrazolylpyrimidines, which contain N-heterocycles found in living objects. For instance, 4-pyrazolyl-*N*-arylpyrimidin-2-amines modulate kinase activities and can be used to treat various diseases, including those associated with immune system disorders and skin diseases.[5] Some 3,5-diaryl-1-(pyrimidin-2-yl)-4,5-dihydro-1*H*-pyrazoles possess antioxidant, antiphlogistic, analgesic,[6] and antiproliferative[7] properties. Pyrazolylpyrimidines are successfully employed as ligands in coordination chemistry. Complexes of Pt, Pd with mepirizole were found to exhibit anticancer activity being less toxic than cisplatin.[8] Pyrazolylpyrimidine complexes with Zn and Cu reveal luminescence properties[9–11] due to the presence of fluorophore pyrimidine core.

Here we suggest the convenient synthesis of new 4-(pyrimidin-4-yl)pyrazol-3-one derivatives based on the approach that we previously[12] employed for obtaining new ligands containing two pyrazole rings, *viz*., 1-aryl-2-(pyrazol-3-yl)ethanone azines. This approach comprised the reaction of aroylacetone difluoroboron chelates with hydrazines. Analogously we prepared recently new bipyrazole derivatives from difluoroboron chelate of 4-acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole.[13]



Scheme 1 *Reagents and conditions*: i, AcONa, BuOH, Δ, 3 h.

In this study, chelate complex **1** (the condensation product of 4-acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole difluoroboron chelate and *N*,*N*-dimethylformamide dimethyl acetal[12,13]) was reacted with guanidine and its derivatives **2a**–**g** as dinucleophiles. Refluxing these reactants in *n*-butanol in the presence of sodium acetate afforded the corresponding pyrimidinylpyrazolones **3a**–**g** (Scheme 1).†

Compounds **3a**–**g** are yellow crystalline substances well soluble in chloroform, THF and DMSO, poorly soluble in diethyl

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† ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C NMR spectra were measured on a Bruker Avance 600 spectrometer (150 MHz for ^{13}C). Residual signals of the deuterated solvent (δ 2.50 for DMSO-d_6) were used as a reference in the ^{1}H NMR spectra. Multiplet signals of the deuterated solvent (δ 39.50 for DMSO-d_6) were the reference in the ^{13}C NMR spectra. IR spectra were recorded on a Bruker Alpha spectrometer. High resolution mass spectra were recorded on a Bruker micrOTOF II instrument (ESI). Measurements were carried out in the positive ranges (capillary voltage was 4500 V). The masses were scanned in the range *m*/*z* 50–3000 Da using an external and an internal calibration (Electrospray Calibrant Solution, Fluka). An acetonitrile solution of a compound was syringed, the flow rate was 3 μl min^{-1}, nitrogen was a sprayer gas (4 dm^3 min^{-1}), the interface temperature was 180 °C. Commercially available guanidines **2a**–**g** hydrochlorides were purchased from Matrix Scientific.

Difluoroboron chelate of (*E*)-3-dimethylamino-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one **1** was prepared as reported.[12,13]

Compounds **3a**–**g** *(general procedure)*. Sodium acetate (1.2 mmol) and the corresponding guanidine hydrochloride **2a**–**g** (1 mmol) were added to the suspension of chelate **1** (1 mmol) in butanol (5 ml). The mixture was refluxed for 3 h. The solvent was removed, the residue was crystallized from acetonitrile, washed with diethyl ether and dried *in vacuo*.

*4-(2-Aminopyrimidin-4-yl)-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3a**. Yield 60%, mp 235–236 °C. IR (KBr, ν/cm^{-1}): 3423 (NH$_2$, NH), 1654 (C=O), 1592. ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 3H, Me), 6.51 (d, 1H, CH=, *J* 2 Hz), 7.10 (t, 1H, *p*-H$_{\text{Ph}}$, *J* 7 Hz), 7.35 (t, 2H, *m*-H$_{\text{Ph}}$, *J* 7 Hz), 8.10 (m, 5H, *o*-H$_{\text{Ph}}$ + CH= + NH$_2$), 14.20 (br.s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 16.47 (Me), 91.21 (C$^{4'}$), 100.55 (C^5), 118.14 (Ph), 123.32 (C$^{5'}$), 129.42 (Ph), 139.56 (Ph), 147.21, 154.14, 159.35 and 164.90 (C^2, C^4, C^6 and C$^{3'}$). HRMS (ESI), *m*/*z*: 268.1196 [M+H]$^+$ (calc. for $C_{14}H_{14}N_5O$, *m*/*z*: 268.1193).

ether and benzene. Their mass spectra show peaks of the ions [M+H]$^+$. The ^{1}H NMR spectra of compounds **3a–g** in DMSO-d_6 are characterized by the singlets for the pyrazolone methyl group at δ 2.32–2.39 ppm. Pyrimidine protons resonate as doublets at 6.51–6.98 (H-5) and 8.03–8.10 ppm.

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*4-[2-(Cyclopropylamino)pyrimidin-4-yl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3b**. Yield 52%, mp 253–254 °C. IR (KBr, ν/cm^{-1}): 3398 (NH), 1615 (C=O), 1592. ^{1}H NMR (DMSO-d_6) δ: 0.69 (br. s, 2H, CH$_2$), 0.95 (br. s, 2H, CH$_2$), 2.32 (s, 3H, Me), 2.80 (br. s, 1H, CH), 6.72 (d, 1H, CH=, *J* 2 Hz), 7.11 (t, 1H, *p*-H$_{\text{Ph}}$, *J* 7 Hz), 7.38 (t, 2H, *m*-H$_{\text{Ph}}$, *J* 7 Hz), 8.09 (m, 3H, *o*-H$_{\text{Ph}}$ + CH=), 8.55 (br. s, 1H, NH), 14.75 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 8.13 (CH$_2$), 17.60 (Me), 23.93 (NCH), 92.10 (C$^{4'}$), 101.80 (C^5), 119.25 (Ph), 124.60 (C$^{5'}$), 129.86 (Ph), 140.74 (Ph), 147.59, 156.04, 159.25 and 166.34 (C^2, C^4, C^6 and C$^{3'}$). HRMS (ESI), *m*/*z*: 308.1508 [M+H]$^+$ (calc. for $C_{17}H_{18}N_5O$, *m*/*z*: 308.1506).

*4-[2-(2-Methoxyethylamino)pyrimidin-4-yl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3c**. Yield 50%, mp 161–162 °C. IR (KBr, ν/cm^{-1}): 3423 (NH), 1637 (C=O), 1499. ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 3H, Me), 3.40 (m, 4H, 2CH$_2$), 3.70 (s, 3H, OMe), 6.48 (d, 1H, CH=, *J* 2 Hz), 7.10 (t, 1H, *p*-H$_{\text{Ph}}$, *J* 7 Hz), 7.35 (t, 2H, *m*-H$_{\text{Ph}}$, *J* 7 Hz), 8.03 (m, 3H, *o*-H$_{\text{Ph}}$ + CH=), 8.81 (br. s, 1H, NH), 14.21 (br. s, 1H, NH). HRMS (ESI), *m*/*z*: 326.1605 [M+H]$^+$ (calc. for $C_{17}H_{20}N_5O_2$, *m*/*z*: 326.1612).

*4-[2-(Benzylamino)pyrimidin-4-yl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3d**. Yield 56%, mp 213–214 °C. IR (KBr, ν/cm^{-1}): 3424 (NH), 1638 (C=O), 1593, 1491. ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, Me), 4.59 (br. s, 2H, CH$_2$), 6.54 (d, 1H, CH=, *J* 2 Hz), 7.10 (t, 1H, *p*-H$_{\text{Ph}}$, *J* 7 Hz), 7.16–7.51 (m, 7H, Ph), 8.07 (m, 3H, *o*-H$_{\text{Ph}}$ + CH=), 9.21 (br. s, 1H, NH), 14.34 (br. s, 1H, NH). HRMS (ESI), *m*/*z*: 358.1658 [M+H]$^+$ (calc. for $C_{21}H_{20}N_5O$, *m*/*z*: 358.1662).

*5-Methyl-4-(2-morpholinopyrimidin-4-yl)-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3e**. Yield 48%, mp 211–212 °C. IR (KBr, ν/cm^{-1}): 3434 (NH), 1628 (C=O), 1593, 1499. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, Me), 3.75 (m, 8H, 4CH$_2$), 6.71 (d, 1H, CH=, *J* 2 Hz), 7.12 (t, 1H, *p*-H$_{\text{Ph}}$, *J* 7 Hz), 7.40 (t, 2H, *m*-H$_{\text{Ph}}$, *J* 7 Hz), 8.03 (m, 3H, *o*-H$_{\text{Ph}}$ + CH=), 15.25 (br. s, 1H, NH). HRMS (ESI), *m*/*z*: 338.1614 [M+H]$^+$ (calc. for $C_{18}H_{20}N_5O_2$, *m*/*z*: 338.1612).

*5-Methyl-2-phenyl-4-[2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl]-1,2-dihydro-3*H*-pyrazol-3-one* **3f**. Yield 53%, mp 179–180 °C. IR (KBr, ν/cm^{-1}): 3434 (NH), 2858, 1617 (C=O), 1594, 1497. ^{1}H NMR (DMSO-d_6): 2.32 (s, 3H, Me), 3.24 (br. s, 4H, 2CH$_2$), 3.38 (br. s, 4H, 2CH$_2$), 6.69–7.44 (m, 7H, *m*-H$_{\text{Ph}}$ + *p*-H$_{\text{Ph}}$ + CH=), 8.08 (m, 5H, *o*-Ph + CH=), 15.32 (br. s, 1H, NH). HRMS (ESI), *m*/*z*: 413.2083 [M+H]$^+$ (calc. for $C_{24}H_{25}N_6O$, *m*/*z*: 413.2084).

*4-[2-(Benz[*d*]oxazol-2-ylamino)pyrimidin-4-yl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **3g**. Yield 47%, mp 296 °C (decomp.). IR (KBr, ν/cm^{-1}): 3385 (NH), 2796, 1639 (C=O), 1578, 1548. ^{1}H NMR (DMSO-d_6): 2.39 (s, 3H, Me), 6.91 (br. s, 1H, CH=), 7.03–7.69 (m, 8H, *m*-H$_{\text{Ph}}$ + *p*-H$_{\text{Ph}}$ + Ar + CH=), 8.07 (d, 2H, *o*-H$_{\text{Ph}}$, *J* 7 Hz), 8.17 (br. s, 1H, NH), 12.68 (br. s, 1H, NH). HRMS (ESI), *m*/*z*: 385.1397 [M+H]$^+$ (calc. for $C_{21}H_{17}N_6O_2$, *m*/*z*: 385.1408).

In conclusion, the presented synthesis of pyrimidinyl pyrazolone derivatives is yet another example of an efficient application of the available difluoroboron chelates as key compounds in the design of heterocycles for possible promising applications.

The synthesis of the starting 4-acetyl-5-hydroxy-1-phenyl-1*H*-pyrazole was carried out within the framework of the State task for 2018 (no. 0090-2017-0023).

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