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Boron-chelate assisted synthesis of new bipyrazole derivatives

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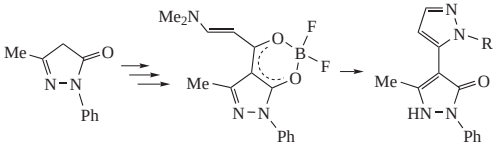
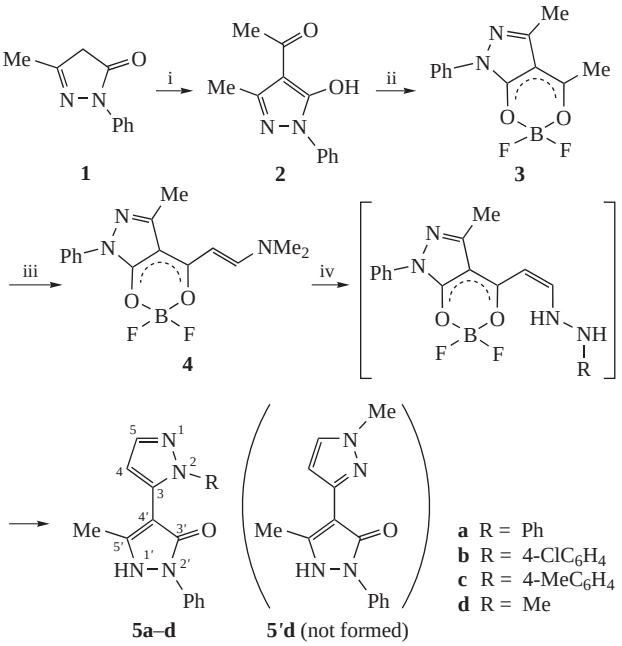
New 2*H*,3′*H*-3,4′-bipyrazol-3′-ones were obtained by reaction of hydrazines with difluoroboron chelate of 4-acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole. Relative isoxazolyl pyrazolone derivative was synthesized from this chelate and hydroxylamine.



In the last years, the interest to the chemistry of pyrazoles has significantly risen due to their numerous applications. Pyrazole derivatives exhibit agricultural and pharmaceutical activities.[1–6] Nucleosides that contain pyrazole substituent as a base were created.[7] Pyrazoles are used in supramolecular and polymer chemistry, in the food industry, and as cosmetic colorings and UV stabilizers, while some possess liquid crystal properties[8,9] and find application as ligands in coordination chemistry.[10] Over the last two-three decades, compounds containing two or more pyrazole fragments have acquired special popularity, since they served as the basis for various metal complexes including multinuclear ones. Among them, poly(pyrazol-1-yl)alkanes,[11,12] bis(pyrazol-4-yl)methane,[13] poly(pyrazol-1-yl)borates,[14] bis- and tris(pyrazol-1-ylmethyl)amines,[15] poly(pyrazol-1-ylmethyl)benzenes,[16] 2,6-di(pyrazol-1-yl)pyridine,[17] 4,6-di(pyrazol-1-yl)pyrimidine[17] can be mentioned.



Scheme 1 *Reagents and conditions:* i, $MeC(OEt)_3$, then $AcOH–H_2O$, Δ; ii, $B(OBu)_3$, $BF_3·OEt_2$; iii, $Me_2NCH(OMe)_2$; iv, $RNHNH_2$.

Earlier,[18] we have described new ligands containing two pyrazole rings, *viz.*, 1-aryl-2-(pyrazol-3-yl)ethanone azines. Synthesis of these compounds involves the condensation of amide acetals with the methyl group of aroylacetones difluoroboron chelates followed by heterocyclization with hydrazine.

In continuation of our design of new pyrazole-containing ligands, we employed this methodology using difluoroboron chelate of 4-acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole as the key compound.

Pyrazolone **1** was prepared according to the known procedure[19] from phenyl hydrazine and ethyl acetoacetate. Then by reported reaction[20] of compound **1** with triethyl orthoacetate and further acidosis, 4-acetyl-5-hydroxy-pyrazole **2**[21] was obtained (Scheme 1).

Difluoroboron chelate **3** was prepared from compound **2** according to the described method[22] under mild conditions (~20 °C) by the action of butoxydifluoroboron generated *in situ* from boron trifluoride etherate and tributyl borate. The condensation of DMF dimethyl acetal [$Me_2NCH(OMe)_2$] with difluoroboron chelate **3** in THF proceeded at room temperature (see Scheme 1).† The methyl group at the chelate ring was the reaction site, and chelate complex **4** containing dimethylaminovinyl fragment was formed. Note that the reaction between $Me_2NCH(OMe)_2$ and pyrazole **2**

† ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C NMR, ^{1}H NOE, 2D ^{1}H–^{13}C HMBC, and ^{1}H–^{1}H gNOESY spectra were recorded on a Bruker Avance 600 spectrometer (600 and 150 MHz for ^{1}H and ^{13}C, respectively). Residual signals of the deuterated solvent (δ 7.27 for $CDCl_3$ and 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 and δ 77.00 for $CDCl_3$) were the reference in the ^{13}C NMR spectra. ^{11}B NMR spectra were recorded on a Bruker AC-200P instrument (64.21 MHz) with $BF_3·OEt_2$ as the external standard. Positive chemical shifts in ^{11}B NMR spectra are located downfield in respect to the signal of $BF_3·Et_2O$. IR spectra were recorded on a Bruker Alpha spectrometer. High resolution mass spectra were measured 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 injected by a syringe, the flow rate was 3 μm min^{-1}, nitrogen was a sprayer gas (4 dm^3 min^{-1}), the interface temperature was 180 °C.

under drastic refluxing in xylene caused resinification and none of product could be identified.

Chelates **3** and **4** were isolated in 80 and 65% yields, respectively. They are white (**3**) and orange (**4**) crystalline compounds stable in air, soluble in DMF, DMSO, pyridine, chloroform, acetone, poorly soluble in THF, acetonitrile, ethanol, and insoluble in Et_2O and hexane. The ^{11}B NMR spectra of complexes **3** and **4** show signals in the field of four-coordinate B atom, and the mass spectra contain peaks of the ions $[M–BF_2]^+$ for chelate **3** and $[M+H]^+$ for compound **4**. In the ^1H NMR spectrum of complex **3** (in $CDCl_3$), two singlets for the methyl groups protons at δ 2.52 and 2.67 ppm, as well as signals from protons of phenyl substituent are observed. The ^1H NMR spectrum of chelate **4** (in DMSO-d_6) is characterized by one set of signals with singlets for the protons of the NMe_2 group at δ 3.21 ppm and Me group at δ 3.3 ppm. The coupling constant of the doublets for the protons at the double bond of dimethylaminovinyl group of compound **4** (δ 5.53 and 8.38 ppm) has a value of ~9 Hz, which is characteristic of *E*-configuration of such enamines.

Chelate complex **4** containing dimethylaminovinyl substituent reacts with one equivalent of arylhydrazines in refluxing EtOH to afford the corresponding 2-aryl-5′-methyl-2′-phenyl-1′,2′-dihydro-2*H*,3′*H*-3,4′-bipyrazol-3′-ones **5a**–**c** in 53–75% yields (see Scheme 1). Compounds **5a**–**c** are white or light-yellow crystalline substances well soluble in DMSO, acetonitrile, ethanol and acetone, poorly soluble in ethyl acetate, chloroform and diethyl ether, and insoluble in hexane. Their mass spectra show peaks of the ions $[M+H]^+$. The ^1H NMR spectra of compounds **5a**–**c** in DMSO-d_6 contain singlet for the protons of methyl group at δ ~1.8 ppm and signals for the protons of the pyrazole rings at δ ~6.5 and ~7.7 ppm.

The initial step of the process is replacement of the Me_2N group by the NH_2 group of aryl hydrazines. Subsequent step involves cyclization with opening of the chelate ring and deboration. The exclusive formation of pyrazolones **5a**–**c** was confirmed by 2D NMR spectroscopy (*i.e.*, boron chelate **4** undergoes regioselective transformation according to Scheme 1). The NOESY spectrum of compound **5b** reveals cross peaks due to interaction between the methyl protons and *ortho*-protons of the aryl group. It means that the aryl substituent is located at N^2 atom of pyrazole ring formed. Previously,[18] it was shown that reaction of phenylhydrazine with difluoroboron chelate of benzoylacetone resulting in the pyrazol ring formation occurs similarly to the process outlined in Scheme 1.

Methylhydrazine reacts with nonsymmetric β-dicarbonyl compounds to give two regioisomers of the corresponding pyrazole derivatives.[23] Therefore, one could expect the formation of two isomers from chelate **4**, namely, **5d** (see Scheme 1) and **5′d**, when the cyclization could involve an initial replacement of the Me_2N group by the MeNH one of methylhydrazine. In fact, this reaction afforded exclusively (1-methylpyrazol-5-yl)-substituted pyrazolone **5d** with no traces of isomer **5′d**. Bipyrazole **5d** appears as a is light green crystalline substance well soluble in DMSO, acetonitrile, ethanol and acetone, poorly soluble in ethyl acetate, diethyl ether, and insoluble in chloroform and hexane. Position of the NMe group in compound **5d** was confirmed by 2D NMR spectra. Its 2D ^1H–^{13}C HMBC spectrum in DMSO-d_6 demonstrates the correlation between protons of NMe and carbon atom C^3, whereas no correlations is observed between the NMe protons and carbon atom C^5.

Reactions of chelate **4** with both hydrazine hydrate and hydroxylamine proceed smoothly in boiling ethanol resulting in

*4-Acetyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole difluoroboron chelate* **3**. Tributyl borate (0.45 ml, 1.7 mmol) was added to a solution of compound **2** (1.0 g, 4.6 mmol) in THF (5 ml). The mixture was stirred for 15 min, then $BF_3{\cdot}OEt_2$ (0.43 ml, 3.4 mmol) was added dropwise, and this was stirred at 20 °C for 2 h. The precipitate formed was filtered off and recrystallized from MeCN. Yield 0.97 g (80%), mp 215–216 °C. ^1H NMR ($CDCl_3$) δ: 2.52 (s, 3H, Me), 2.67 (s, 3H, Me), 7.40 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.52 (t, 2H, *m*-H_{Ph}, *J* 8 Hz), 7.88 (d, 2H, *o*-H_{Ph}, *J* 8 Hz). ^{11}B NMR ($CDCl_3$) δ: 1.27. HRMS (ESI), *m*/*z*: 217.0954 $[M-BF_2]^+$ (calc. for $C_{12}H_{14}N_2O_2$, *m*/*z*: 217.0953).

*(*E*)-3-Dimethylamino-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one difluoroboron chelate* **4**. $Me_2NCH(OMe)_2$ (0.28 ml, 2.1 mmol) was added to a suspension of chelate **3** (0.5 g, 1.8 mmol) in THF (5 ml). The mixture was stirred at 20 °C for 2 h, the precipitate formed was filtered off and recrystallized from MeCN. Yield 0.38 g (65%), mp 269–270 °C. ^1H NMR (DMSO-d_6,) δ: ^1H NMR ($CDCl_3$) δ: 3.21 (s, 6H, 2Me), 2.67 (s, 3H, Me), 5.53 (d, 1H, CH=, *J* 9 Hz), 7.35 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.52 (t, 2H, *m*-H_{Ph}, *J* 8 Hz), 7.79 (d, 2H, *o*-Ph, *J* 8 Hz), 8.38 (d, 1H, CH=, *J* 9 Hz). ^{11}B NMR ($CDCl_3$) δ: 1.29. HRMS (ESI), *m*/*z*: 320.1382 $[M+H]^+$ (calc. for $C_{15}H_{17}BF_2N_3O_2$, *m*/*z*: 320.1379).

Bipyrazoles **5a**,**d** *and* **6** (*general procedure*). The corresponding hydrazine (1.1 mmol) was added to the suspension of chelate **4** (1 mmol) in ethanol (5 ml). The mixture was refluxed for 3 h. The solvent was removed, the residue was crystallized from MeCN, washed with diethtl ether and dried *in vacuo*.

*5′-Methyl-2,2′-diphenyl-1′,2′-dihydro-2*H,*3′*H*-3,4′-bipyrazol-3′-one* **5a**. Yield 53%, mp 202–203 °C. IR (KBr, ν/cm^{-1}): 3045–2608 (CH=), 1627 (C=O), 1594, 1500. ^1H NMR (DMSO-d_6) δ: 1.82 (s, 3H, Me), 6.51 (s, 1H, CH=), 7.28 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.32 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.43 (m, 4H, *m*-H_{Ph}), 7.65 (m, 4H, *o*-H_{Ph}), 7.78 (s, 1H, CH=). HRMS (ESI), *m*/*z*: 317.1396 $[M+H]^+$ (calc. for $C_{19}H_{17}N_4O$, *m*/*z*: 317.1397).

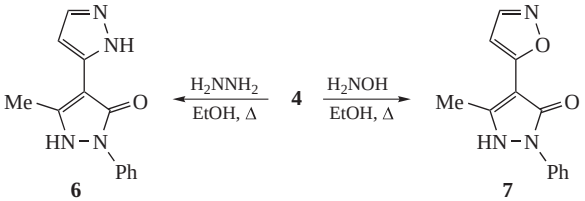
*2,5′-Dimethyl-2′-phenyl-1′,2′-dihydro-2*H,*3′*H*-3,4′-bipyrazol-3′-one* **5d**. Yield 45%, mp 88–89 °C. IR (KBr, ν/cm^{-1}): 2923–2666 (CH=), 1610 (C=O), 1589, 1499. ^1H NMR (DMSO-d_6) δ: 2.11 (s, 3H, Me), 3.74 (s, 3H, NMe), 6.25 (s, 1H, CH=), 7.25 (t, 1H, *p*-H_{Ph}), 7.44 (t, 2H, *m*-H_{Ph}, *J* 8 Hz), 7.49 (s, 1H, N=CH), 7.74 (d, 2H, *o*-H_{Ph}, *J* 8 Hz). ^{13}C NMR (DMSO-d_6) δ: 12.20 (Me), 36.73 (MeN), 106.57 (C^4), 120.40 (*o*-C_{Ph}), 125.23 (*p*-C_{Ph}), 128.76 (*m*-C_{Ph}), 133.60 (C^3), 137.60 (C^5), signals $C^{5'}$, $C^{4'}$ and $C^{3'}$ are not observed. HRMS (ESI), *m*/*z*: 255.1251 $[M+H]^+$ (calc. for $C_{14}H_{15}N_4O$, *m*/*z*: 255.1240).

*5′-Methyl-2′-phenyl-1′,2′-dihydro-2*H,*3′*H*-3,4′-bipyrazol-3′-one* **6**. Yield 60%, mp 205–206 °C. IR (KBr, ν/cm^{-1}): 3248 (NH), 2922–2588 (CH=), 1640 (C=O), 1596, 1500. ^1H NMR (DMSO-d_6) δ: 2.41 (s, 3H, Me), 5.40 (br. s, 2H, NH), 6.50 (s, 1H, CH=), 7.19 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.45 (t, 2H, *m*-H_{Ph}, *J* 8 Hz), 7.61 (s, 1H, N=CH), 7.80 (d, 2H, *o*-H_{Ph}, *J* 8 Hz). HRMS (ESI), *m*/*z*: 241.1092 $[M+H]^+$ (calc. for $C_{20}H_{19}N_4O$, *m*/*z*: 241.1084).

Compounds **5b**,**c** (*general procedure*). The corresponding hydrazine hydrochloride (1.1 mmol) and AcONa (1.1 mmol) were added to a suspension of chelate **4** (1 mmol) in ethanol (5 ml),. The mixture was refluxed for 6 h, cooled to 20 °C, and 10 ml of water was added. The solution was extracted with ethyl acetate (3×10 ml), the organic extracts were combined and dried over sodium sulfate, the solvent was removed, the residue was washed with diethyl ether and dried *in vacuo*.

*2-(4-Chlorophenyl)-5′-methyl-2′-phenyl-1′,2′-dihydro-2*H,*3′*H*-3,4′-bipyrazol-3′-one* **5b**. Yield 70%, mp 261–262 °C. IR (KBr, ν/cm^{-1}): 3099–2605 (CH=), 1619 (C=O), 1593, 1497. ^1H NMR (DMSO-d_6) δ: 1.89 (s, 3H, Me), 6.51 (s, 1H, CH=), 7.24 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.47 (m, 6H, *m*-H_{Ph} + C_6H_4Cl), 7.67 (m, 2H, *o*-H_{Ph}), 7.78 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6) δ: 12.44 (Me), 93.74 (C^4), 109.73 (C^4), 120.37 (*o*-C_{Ph}), 125.18 (*o*-C_6H_4), 125.42 (*p*-C_{Ph}), 128.85 and 128.90 (*m*-C_{Ph} and *m*-$C_{C_6H_4}$), 131.29 (C–Cl), 133.87 (C^3), 137.89 (*ipso*-C_{Ph}), 139.20 (*ipso*-$C_{C_6H_4}$), 140.36 (C^5), 147.07 ($C^{5'}$), signal $C^{4'}$ was not observed. HRMS (ESI), *m*/*z*: 351.0996 $[M+H]^+$ (calc. for $C_{19}H_{16}ClN_4O$, *m*/*z*: 351.1007).

*5′-Methyl-2′-phenyl-2-(*p*-tolyl)-1′,2′-dihydro-2*H,*3′*H*-(3,4′-bipyrazol)-3′-one* **5c**. Yield 55%, mp 214–215 °C. IR (KBr, ν/cm^{-1}): 3037–2786 (CH=), 1625 (C=O), 1593, 1501. ^1H NMR (DMSO-d_6) δ: 1.82 (s, 3H, Me), 2.35 (s, 3H, 4-*Me*C_6H_4), 6.51 (s, 1H, CH=), 7.21 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.35 (m, 6H, *m*-H_{Ph} + 4-MeC_6H_4), 7.68 (m, 2H, *o*-Ph), 7.73 (s, 1H, N=CH). HRMS (ESI), *m*/*z*: 331.1543 $[M+H]^+$ (calc. for $C_{20}H_{19}N_4O$, *m*/*z*: 331.1553).



6 **7**

Scheme 2

bipyrazole **6** and isoxazolyl pyrazolone **7**, respectively (Scheme 2).‡ These compound are light-green crystalline substances well soluble in DMSO, acetonitrile, ethanol and acetone, poorly soluble in ethyl acetate, chloroform and diethyl ether, and insoluble in hexane. Their mass spectra contain peaks of $[M+H]^+$. The ^{1}H NMR spectrum of compound **6** in DMSO-d_6 reveals signals for the pyrazole protons (δ ~6.5 and ~7.6 ppm). In the ^{1}H NMR spectrum of derivative **7** ($CDCl_3$), the signals for the isoxazol protons are observed at δ ~6.5 and ~8.1 ppm. Both spectra contain the signals for the methyl group and phenyl substituent protons.

In conclusion, the synthesis of bipyrazole and isoxazolylpyrazole derivatives is yet another example of an efficient application of the boron-chelate assisted synthesis methodology for the design of heterocycles.

The synthesis of the starting 4-acetyl-5-hydroxy-1-phenyl-1*H*-pyrazole **3** was carried out within the framework of the State task for 2018 (no. 0090-2017-0023).

‡ *4-(Isoxazol-5-yl)-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one* **7**. Hydroxyl amine (1.1 mmol) was added to a suspension of chelate **4** (1 mmol) in ethanol (5 ml) . The mixture was refluxed for 6 h, during which the solid completely dissolved. The solution was cooled to 20 °C, and water (10 ml) was added. The mixture was extracted with EtOAc (3 × 10 ml), the combined extracts were dried over sodium sulfate, the solvent was removed, the residue was washed with diethyl ether and dried *in vacuo*. Yield 76%, mp 170–171 °C. IR (KBr, ν/cm^{-1}): 3206 (NH), 2902–2590 (CH=), 1637 (C=O), 1598, 1505. ^{1}H NMR ($CDCl_3$) δ: 2.41 (s, 3H, Me), 6.45 (s, 1H, CH=), 7.10 (t, 1H, *p*-H_{Ph}, *J* 8 Hz), 7.22 (t, 2H, *m*-H_{Ph}), 7.40 (d, 2H, *o*-H_{Ph}, *J* 8 Hz), 8.15 (s, 1H, N=CH). HRMS (ESI), *m*/*z*: 242.0933 $[M+H]^+$ (calc. for $C_{13}H_{12}N_3O_2$, *m*/*z*: 242.0924).

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