Synthesis of pyrazolo[1,5-*c*]pyrimidines from difluoroboron chelates of aroylacetones

V. A. Dorokhov, I. V. Kravtsov, P. A. Belyakov, and S. V. Baranin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 135 5328. E-mail: vador@ioc.ac.ru

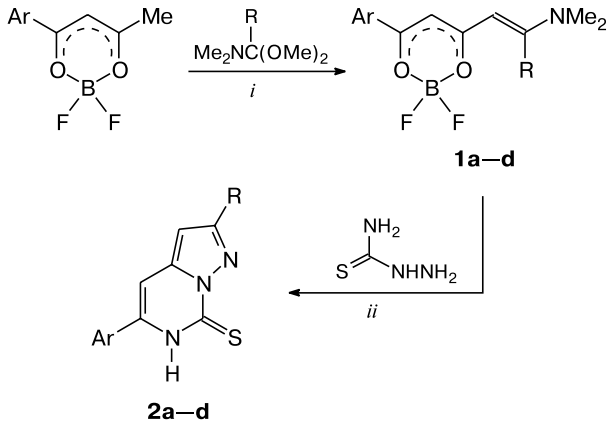
A convenient method was developed for the synthesis of derivatives of 6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione and 7-aminopyrazolo[1,5-*c*]pyrimidine from difluoroboron chelate complexes of aroylacetones, amide acetals, and thiosemicarbazide or aminoguanidine.

Key words: aroylacetones, difluoroboron chelates, amide acetals, thiosemicarbazide, aminoguanidine, 6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thiones, 7-aminopyrazolo[1,5-*c*]pyrimidines.

Recently,[1] we have developed a convenient method for the synthesis of 5-aroylmethylpyrazoles and their hydrazones from difluoroboron chelate complexes of aroylacetones, amide acetals, and hydrazines. This method is based on the ability of amide acetals to react with boron β-diketonates at the exocyclic methyl group. The resulting condensation products are difluoroboron chelates of 1-aryl-5-dimethylaminopent(hex)-4-ene-1,3-diones **1a**—**e**. Proceeding further in this area, we investigated reactions of chelates **1a**—**e** with reagents containing more than two nucleophilic centers: thiosemicarbazide and aminoguanidine.

It turned out that chelate complexes **1a**—**d** react with thiosemicarbazide on prolonged reflux in butanol to give the corresponding 6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione derivatives **2a**—**d** (Scheme 1).

Scheme 1



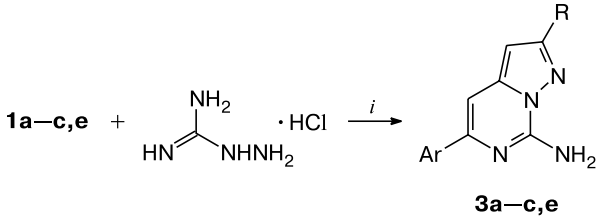
i. THF, 20 °C; *ii*. BuOH, Δ, 40 h

R = H; Ar = Ph (**a**), 2-$C_{10}H_7$ (**b**);
R = Me; Ar = 2,4-$Me_2C_6H_3$ (**c**), 2-$C_{10}H_7$ (**d**)

Compounds **2** are white crystalline solids that are soluble in chloroform and benzene and negligibly soluble in ethanol, ethyl acetate, and hexane. Their mass spectra contain molecular ion peaks [M^+]. The ^{1}H NMR spectra of compounds **2** in $CDCl_3$ show broadened singlets for the protons of the endocyclic NH group at δ ~10.27—10.14, signals for the H(4) protons of the pyrimidine ring at δ ~7.38—6.64, and signals for the H(3) protons of the pyrazole ring at δ ~6.64—6.36. It should be noted that compound **2d** is insoluble in hexane, benzene, ethyl acetate, ethanol, and acetonitrile and poorly soluble in chloroform.

Chelates **1a**—**c,e** reacted with aminoguanidine hydrochloride in boiling butanol for ~30 h in the presence of an equimolar amount of sodium acetate (for *in situ* transformation of the aminoguanidine salt into a free base). The reaction products were 7-aminopyrazolo[1,5-*c*]pyrimidines **3a**—**c,e** (Scheme 2).

Scheme 2

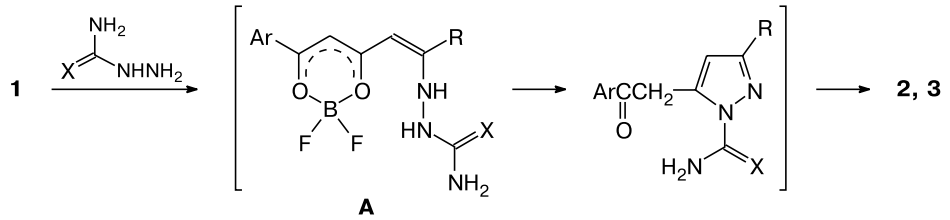


i. BuOH, AcONa, Δ, 30 h

R = H, Ar = Ph (**a**); R = H, Ar = 2-$C_{10}H_7$ (**b**);
R = Me, Ar = 2,4-$Me_2C_6H_3$ (**c**); R = H, Ar = 2,4-$Me_2C_6H_3$ (**e**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 992—994, May, 2007.

Scheme 3



X = S, NH

Compounds **3** are white crystalline solids that are soluble in chloroform and benzene but are poorly soluble in ethanol, ethyl acetate, and hexane. Their mass spectra contain molecular ion peaks [M^+]. The ^{1}H NMR spectra of compounds **3** show broadened singlets for the protons of the amino group at δ ~6.17—6.40, singlets for the H(4) protons of the pyrimidine ring at δ ~6.75—7.31, and singlets for the H(3) proton of the pyrazole ring at δ ~6.19—6.51. The mechanism of the reactions of boron complexes **1** with thiosemicarbazide and aminoguanidine, as well as with hydrazines,[1] involves initial replacement of the NMe_2 group by thiosemicarbazide or aminoguanidine resulting in intermediate **A**, which undergoes cyclization (with breaking of the chelate ring) into bicyclic compounds **2** or **3** (Scheme 3).

2D NMR studies revealed that the reaction is regioselective and yields pyrazolo[1,5-*c*]pyrimidines **2** or **3** as the sole products. For instance, the COSY spectrum of compound **3c** in $CDCl_3$ shows a cross peak due to a spin-spin coupling of the methyl protons (δ 2.49) at the C(2) atom of the bicyclic compound with the H(3) proton of the pyrazole ring (δ 6.19).

It should be noted that pyrazolo[1,5-*c*]pyrimidines are least studied among various types of these bicyclic derivatives.[2] In the known syntheses of thiones of the type **2** and amines of the type **3**, thiosemicarbazide and aminoguanidine have been mainly used as well. A reaction of thiosemicarbazide with heptane-2,4,6-trione gives 2,5-dimethyl-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione and that with aminoguanidine hydrochloride yields 7-amino-2,5-dimethylpyrazolo[1,5-*c*]pyrimidine.[3] In the patent,[4] it is stated that the range of the starting triones in these transformations can be extended. The corresponding bicyclic 2,5-diphenyl thione has been synthesized from 2,6-diphenylpyrylium perchlorate in two steps.[5] Reactions of thiosemicarbazide with 1-aryl-5-phenylpent-1-yne-3,5-diones produce 2-aryl-5-phenyl-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thiones.[6] Some pyrazolo[1,5-*c*]pyrimidines have been reported to exhibit biological (*e.g.*, hypnotic, sedative, and antimicrobial) activities.[4,7]

We proposed a new strategy of construction of the pyrazolo[1,5-*c*]pyrimidine system from easily accessible carbonyl compounds. In contrast to the previous approach, our method affords 2-unsubstituted thiones **2** and amines **3**.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument (250 and 63 MHz, respectively) at 25 °C. ^{11}B NMR spectra were recorded on a Bruker AC-200 instrument (64 MHz) with $BF_3 \cdot Et_2O$ as the internal standard.

IR spectra were recorded on a Specord M-82 instrument (KBr pellets).

Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV).

A difluoroboron complex of benzoylacetone was prepared according to a modified procedure:[8] BF_3 etherate was used instead of gaseous BF_3.

Difluoroboron complexes of 2,4-dimethylbenzoylacetone and 2-naphthoylacetone were synthesized analogously, isolated, and used without additional purification in reactions with amide acetals.

A difluoroboron chelate complex of 5-dimethylamino-1-phenylpent-4-ene-1,3-dione (**1a**) was prepared as described earlier.[1] Difluoroboron chelates of 1-aryl-5-dimethylaminopent(hex)-4-ene-1,3-diones **1b—e** were synthesized analogously from difluoroboron complexes of appropriate aroylacetones.

Difluoroboron chelate complex of 5-dimethylamino-1-(2-naphthyl)pent-4-ene-1,3-dione (1b) was obtained from a difluoroboron chelate of 2-naphthoylacetone and dimethylformamide dimethyl acetal. The yield was 95%, m.p. 274—275 °C. Found (%): C, 64.80; H, 5.12; N, 4.44. $C_{15}H_{18}BF_2NO_2$. Calculated (%): C, 64.97; H, 5.02; N, 4.59. MS, *m/z* (I_{rel} (%)): 315 $[M]^+$ (100), 271 $[M - NMe_2]^+$ (79). ^{1}H NMR (DMSO-d_6), δ: 3.07, 3.35 (both s, 6 H, NMe_2); 5.41 (d, 1 H, CH=, J = 12.3 Hz); 6.63 (s, 1 H, CH=); 7.59, 8.00 (both m, 6 H, Ar); 8.22 (d, 1 H, CH=, J = 12.3 Hz); 8.51 (s, 1 H, Ar). ^{11}B NMR (CH_3CN), δ: 1.37. IR, ν/cm^{-1}: 2908, 1640, 1600, 1544.

Difluoroboron chelate complex of 5-dimethylamino-1-(2,4-dimethylphenyl)hex-4-ene-1,3-dione (1c) was obtained from a difluoroboron chelate of 2,4-dimethylbenzoylacetone and dimethylacetamide dimethyl acetal. The yield was 84%, m.p. 216—217 °C. Found (%): C, 62.43; H, 6.72; N, 4.85. $C_{16}H_{20}BF_2NO_2$. Calculated (%): C, 62.57; H, 6.56; N, 4.56. MS, *m/z* (I_{rel} (%)): 307 $[M]^+$ (87), 263 $[M - NMe_2]^+$ (94). ^{1}H NMR (DMSO-d_6), δ: 2.28 (s, 3 H, Me); 2.36, 2.57 (both s, 6 H, 2,4-$\underline{Me}_2C_6H_3$); 3.17, 3.24 (both s, 6 H, NMe_2); 5.26 (s, 1 H, CH=); 5.88 (s, 1 H, CH=); 7.07 (m, 2 H, Ar); 7.34 (d, 1 H,

Ar, J = 7.9 Hz). ^{11}B NMR (CH_3CN), δ: 1.19. IR, ν/cm^{-1}: 3012, 2932, 1572, 1560 (br).

Difluoroboron chelate complex of 5-dimethylamino-1-(2-naphthyl)hex-4-ene-1,3-dione (1d) was obtained from a difluoroboron chelate of 2-naphthoylacetone and dimethylacetamide dimethyl acetal. The yield was 88%, m.p. 248—249 °C. Found (%): C, 65.50; H, 5.72; N, 4.55. $C_{18}H_{18}BF_2NO_2$. Calculated (%): C, 65.68; H, 5.51; N, 4.26. MS, m/z (I_{rel} (%)): 329 $[M]^+$ (50), 285 $[M - NMe_2]^+$ (75). ^{1}H NMR (DMSO-d_6), δ: 2.61 (s, 3 H, Me); 3.22, 3.27 (both s, 6 H, NMe_2); 5.37 (s, 1 H, CH=); 6.62 (s, 1 H, CH=); 7.58, 8.00 (both m, 6 H, Ar); 8.46 (s, 1 H, Ar). ^{11}B NMR (CH_3CN), δ: 1.37. IR, ν/cm^{-1}: 3060, 1600, 1552 (br).

Difluoroboron chelate complex of 5-dimethylamino-1-(2,4-dimethylphenyl)pent-4-ene-1,3-dione (1e) was obtained from a difluoroboron chelate of 2,4-dimethylbenzoylacetone and dimethylformamide dimethyl acetal. The yield was 93%, m.p. 195—196 °C. Found (%): C, 61.42; H, 6.22; N, 4.82. $C_{15}H_{18}BF_2NO_2$. Calculated (%): C, 61.46; H, 6.19; N, 4.78. MS, m/z (I_{rel} (%)): 293 $[M]^+$ (100), 249 $[M - NMe_2]^+$ (38), 228 (46). ^{1}H NMR ($CDCl_3$), δ: 2.34, 2.51 (both s, 6 H, 2,4-$\underline{Me}_2C_6H_3$); 3.01, 3.26 (both s, 6 H, NMe_2); 4.98 (d, 1 H, CH=, J = 12.3 Hz); 5.78 (s, 1 H, CH=); 7.02 (d, 1 H, Ar, J = 7.9 Hz); 7.04 (s, 1 H, Ar); 7.43 (d, 1 H, Ar, J = 7.9 Hz); 8.08 (d, 1 H, CH=, J = 12.3 Hz). ^{11}B NMR (CH_3CN), δ: 1.20. IR, ν/cm^{-1}: 2912, 1640, 1580, 1560.

2-Substituted 5-aryl-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thiones 2a—d (general procedure). A mixture of difluoroboron complex **1a—d** (1 mol) and thiosemicarbazide (1.5 mol) was refluxed in *n*-butanol (15 mL) for 30 h. After the reaction was completed (TLC data), the solvent was removed and the dry residue was dissolved in chloroform and filtered through a short column with SiO_2. The solvent was removed and the residue was recrystallized from a suitable solvent and dried *in vacuo*.

5-Phenyl-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione (2a). The yield was 54%, m.p. 205—206 °C (from benzene). Found (%): C, 63.18; H, 4.08; N, 18.22. $C_{12}H_9N_3S$. Calculated (%): C, 63.41; H, 3.99; N, 18.49. MS, m/z (I_{rel} (%)): 226 $[M]^+$ (100), 195 (10), 169 (27), 139 (20), 115 (21). ^{1}H NMR ($CDCl_3$), δ: 6.60 (d, 1 H, H(3), J = 2.0 Hz); 7.02 (s, 1 H, H(4)); 7.50—7.70 (m, 5 H, Ph); 8.17 (d, 1 H, H(2), J = 2.0 Hz); 10.27 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 99.7, 101.7, 126.3, 129.4, 130.5, 131.4, 138.2, 138.7, 147.0, 168.8. IR, ν/cm^{-1}: 3164, 3108, 2988, 2844, 1640, 1524, 1328, 1256.

5-(2-Naphthyl)-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione (2b). The yield was 43%, m.p. 240—241 °C (from benzene). Found (%): C, 69.14; H, 4.13; N, 15.04. $C_{16}H_{11}N_3S$. Calculated (%): C, 69.29; H, 4.00; N, 15.15. MS, m/z (I_{rel} (%)): 277 $[M]^+$ (69), 245 (13), 219 (23). ^{1}H NMR ($CDCl_3$), δ: 6.64 (d, 1 H, H(3), J = 2.0 Hz); 7.15 (s, 1 H, H(4)); 7.60—8.10 (m, 7 H, Ar); 8.20 (d, 1 H, H(2), J = 2.0 Hz); 10.16 (s, 1 H, NH). IR, ν/cm^{-1}: 3160, 3044, 2984, 2848, 1632, 1524, 1332, 1256.

5-(2,4-Dimethylphenyl)-2-methyl-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione (2c). The yield was 47%, m.p. 217—218 °C (from benzene—hexane). Found (%): C, 66.73; H, 5.76; N, 15.53. $C_{15}H_{15}N_3S$. Calculated (%): C, 66.88; H, 5.61; N, 15.60. MS, m/z (I_{rel} (%)): 269 $[M]^+$ (100), 254 (79), 236 (13), 211 (13). ^{1}H NMR ($CDCl_3$), δ: 2.35, 2.39, 2.54 (all s, 9 H, 3 Me); 6.36 (s, 1 H, H(3)); 6.64 (s, 1 H, H(4)); 7.10—7.30 (m, 3 H, Ar); 10.14 (s, 1 H, NH). IR, ν/cm^{-1}: 3380, 3164, 3108, 3076, 2956, 2844, 1640, 1596, 1528.

2-Methyl-5-(2-naphthyl)-6*H*-pyrazolo[1,5-*c*]pyrimidine-7-thione (2d). The yield was 41%, m.p. 279—280 °C. Found (%): C, 69.95; H, 4.61; N, 14.28. $C_{17}H_{13}N_3S$. Calculated (%): C, 70.08; H, 4.50; N, 14.42. MS, m/z (I_{rel} (%)): 291 $[M]^+$ (100), 276 (18). ^{1}H NMR (DMSO-d_6), δ: 2.40 (s, 3 H, Me); 6.56 (s, 1 H, H(3)); 7.38 (s, 1 H, H(4) pyrim.); 7.60—8.00 (m, 6 H, Ar); 8.39 (s, 1 H, o-H_{napht}); 13.19 (s, 1 H, NH). IR, ν/cm^{-1}: 3168, 3128, 3060, 3008, 1636, 1600, 1520.

7-Amino-5-aryl-2-R-pyrazolo[1,5-*c*]pyrimidines 3a—c,e (general procedure). A mixture of difluoroboron complex **1a—c,e** (1 mol), aminoguanidine (1.2 mol), and anhydrous sodium acetate (1.2 mol) was refluxed in *n*-butanol (15 mL) for 15 h. After the reaction was completed (TLC data), the solvent was removed and the dry residue was dissolved in chloroform and filtered through a short column with SiO_2. The filtrate was concentrated and the residue was recrystallized from a suitable solvent and dried *in vacuo*. The resulting white crystals were poorly soluble in hexane, ethyl acetate, and ethanol, yet being soluble in diethyl ether and chloroform.

7-Amino-5-phenylpyrazolo[1,5-*c*]pyrimidine (3a). The yield was 60%, m.p. 156—157 °C (from hexane). Found (%): C, 68.44; H, 4.82; N, 26.57. $C_{12}H_{10}N_4$. Calculated (%): C, 68.56; H, 4.79; N, 26.65. MS, m/z (I_{rel} (%)): 210 $[M]^+$ (100), 182 (28), 168 (36), 154 (27), 140 (35). ^{1}H NMR ($CDCl_3$), δ: 6.17 (s, 2 H, NH_2); 6.46 (d, 1 H, H(3), J = 2.0 Hz); 7.31 (s, 1 H, H(4)); 7.35—7.55 (m, 3 H, Ph); 8.05 (m, 3 H, Ph, H(2)). IR, ν/cm^{-1} (KBr): 3460, 3284, 3192, 3060, 1652, 1608, 1544. IR, ν/cm^{-1} ($CHCl_3$): 3520, 3460, 3404, 3300, 3060, 3012, 1648, 1632, 1604, 1540.

7-Amino-5-(2-naphthyl)pyrazolo[1,5-*c*]pyrimidine (3b). The yield was 42%, m.p. 199—200 °C (from benzene). Found (%): C, 73.73; H, 4.74; N, 21.45. $C_{16}H_{12}N_4$. Calculated (%): C, 73.83; H, 4.65; N, 21.52. MS, m/z (I_{rel} (%)): 260 $[M]^+$ (100). ^{1}H NMR ($CDCl_3$), δ: 6.00 (s, 2 H, NH_2); 6.51 (d, 1 H, H(3), J = 2.0 Hz); 7.27 (s, 1 H, H(4)); 7.48 (s, 1 H, H(2)); 7.50, 8.00 (both m, 6 H, Ar); 8.54 (s, 1 H, o-H_{napht}). IR, ν/cm^{-1}: 3300, 3132, 3048, 1664, 1608, 1560.

7-Amino-5-(2,4-dimethylphenyl)-2-methylpyrazolo[1,5-*c*]pyrimidine (3c). The yield was 45%, m.p. 202—203 °C (from benzene). Found (%): C, 71.18; H, 6.54; N, 22.07. $C_{15}H_{16}N_4$. Calculated (%): C, 71.40; H, 6.39; N, 22.20. MS, m/z (I_{rel} (%)): 252 $[M]^+$ (87), 251 $[M - H]^+$ (100), 237 (10), 211 (10). ^{1}H NMR ($CDCl_3$), δ: 2.37, 2.38, 2.49 (all s, 9 H, 3 Me); 6.19 (s, 1 H, H(3)); 6.22 (s, 2 H, NH_2); 6.78 (s, 1 H, H(4)); 7.08—7.30 (m, 3 H, Ar). IR, ν/cm^{-1}: 3312, 3220, 3096, 2912, 1664, 1608, 1560.

7-Amino-5-(2,4-dimethylphenyl)pyrazolo[1,5-*c*]pyrimidine (3e). The yield was 48%, m.p. 166—167 °C (from benzene—hexane). Found (%): C, 70.42; H, 6.04; N, 23.42. $C_{14}H_{14}N_4$. Calculated (%): C, 70.57; H, 5.92; N, 23.51. MS, m/z (I_{rel} (%)): 238 $[M]^+$ (100), 237 $[M]^+$ (88). ^{1}H NMR ($CDCl_3$), δ: 2.38, 2.39 (both s, 6 H, 2 Me); 6.40 (s, 2 H, NH_2); 6.42 (d, 1 H, H(3), J = 2.0 Hz); 6.90 (s, 1 H, H(4)); 7.10 (s, 1 H, H(2)); 7.35 (m, 2 H, Ar); 7.98 (s, 1 H, o-H_{arom}). ^{13}C NMR ($CDCl_3$), δ: 20.3, 21.3, 97.4, 101.9, 126.6, 129.3, 131.6, 135.7, 136.5, 138.2, 142.1, 143.7, 146.8, 149.6. IR, ν/cm^{-1}: 3448, 3284, 3188, 3052, 2956, 1652, 1608, 1548, 1508.

This work was financially supported by the Russian Academy of Sciences (Basic Research Program of the Presidium of the Russian Academy of Sciences "Develop-

ment of the Methodology of Organic Synthesis and Creation of Compounds with Valuable Practical Properties").

References

1. V. A. Dorokhov, I. V. Kravtsov, P. A. Belyakov, and S. V. Baranin, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 867 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 898].
2. M. H. Elnagdi, M. R. H. Elmoghayar, and G. H. Elgemeie, *Adv. Heterocycl. Chem.*, 1987, **41**, 319.
3. E. Kranz, J. Kurz, and W. Donner, *Chem. Ber.*, 1972, **105**, 388.
4. Ger. Pat. DE 2 058 501; *Chem. Abstr.*, 1972, **77**, 88530.
5. E. A. Zvezdina, M. P. Zhdanova, I. I. Nechayuk, I. A. Barchan, Yu. N. Simkina, and T. A. Buchnaya, *Khim.-Farm. Zh.*, 1986, **20**, 1328 [*Pharm. Chem. J.*, 1986, **20** (Engl. Transl.)].
6. M. G. Marey, D. M. Aly, and M. M. Mishrikey, *Bull. Chem. Soc. Jpn*, 1992, **65**, 3419.
7. Ger. Pat. DE 2 131 790; *Chem. Abstr.*, 1973, **78**, 97694.
8. G. T. Morgan and R. B. Tunstall, *J. Chem. Soc.*, 1924, **54**, 1963.

Received January 30, 2007;
in revised form February 21, 2007