The Mannich reaction in the synthesis of N,S-containing heterocycles
5.* Synthesis and structures of new pyrimido[2,1-*b*][1,3,5]thiadiazine derivatives

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Reactions of 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines with formaldehyde and primary amines gave earlier unknown 3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3,5]thiadiazine derivatives in 58—94% yields. In boiling AcOH, these pyrimidothiadiazines underwent the retro-Mannich reaction leading to the starting pyrimidine-2-thiones. The structure of 3-(4-ethoxyphenyl)-6-oxo-8-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile was studied by X-ray diffraction analysis.

Key words: the Mannich reaction, 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines, formaldehyde, primary amines, pyrimido[2,1-*b*][1,3,5]thiadiazines, the retro-Mannich reaction, X-ray diffraction analysis.

The chemistry of 1,3,5-thiadiazine derivatives is a promising and developing research area.[1] In the last few years, fused 1,3,5-thiadiazines have become of considerable interest because of, on the one hand, the accessibility of the starting 2-mercaptoazoles and -azines and, on the other hand, a wide palette of practical applications of compounds of this group. In particular, *symm*-triazolo[3,4-*b*][1,3,5]thiadiazine derivatives[2—5] and substituted thiazolo[3´,4´:1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines[6] have antibacterial and fungicidal effects, respectively, and [1,3,5]thiadiazino[3,2-*a*]benzimidazole derivatives exhibit herbicidal and insecticidal activities.[7] According to patented data,[8] some imidazo- and pyrimido[2,1-*b*]-[1,3,5]thiadiazines are broad-spectrum pesticides. Thus, the synthesis of novel compounds of this type is of current interest.

Among the most popular and preparatively accessible methods for construction of the 1,3,5-thiadiazine system is the multicomponent "double" Mannich cyclocondensation of various 2-mercaptoazoles and -azines with primary amines and formaldehyde. For instance, this method has been used earlier to obtain thiadiazines fused with 1,2,4-triazole,[2—6,9—12] imidazole, 1,2,4-triazine,[13] and benzimidazole rings.[14] In this way, we have recently synthesized for the first time pyrido[2,1-*b*][1,3,5]thiadiazine[15] and imidazo[2,1-*b*][1,3,5]thiadiazine derivatives.[16] Since this approach is simple and highly efficient and involves accessible starting reagents, it seems to be promising for combinatorial chemistry. Proceeding further in these investigations, we studied the behavior of accessible[17] 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines **1a,b** under the conditions of the "double" Mannich condensation.

We found that reactions of thioxopyrimidines **1** with primary aromatic amines and an excess of formaldehyde in EtOH give new pyrimido[2,1-*b*][1,3,5]thiadiazines **2a—f** in high yields (Scheme 1). The process is regioselective: the cyclization involves the S—C(2)—N(3)H fragment, while isomeric products (like structure **3**) arising from double aminomethylation at the S—C(2)—N(1)H fragment were not detected. The order of addition of the reagents did not affect the yield of the final product. For instance, the yield of thiadiazine **2f** was 60%, regardless of whether we added formalin first to a suspension of thioxopyrimidine **1b** and then *p*-toluidine or *vice versa*. An assumed reaction mechanism involves the formation

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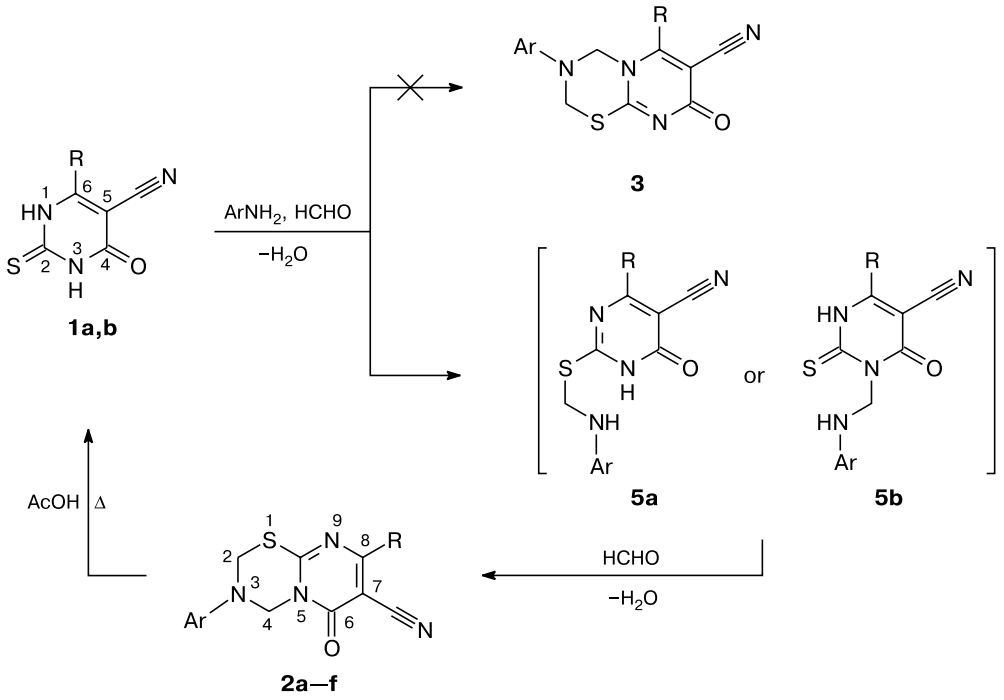
Scheme 1



1: R = Ph (**a**), 4-MeC_6H_4 (**b**);
2: R = Ph, Ar = 4-$EtOC_6H_4$ (**a**); R = 4-MeC_6H_4, Ar = 4-$EtOC_6H_4$ (**b**); R = 4-MeC_6H_4, Ar = 4-FC_6H_4 (**c**); R = 4-MeC_6H_4, Ar = 4-ClC_6H_4 (**d**); R = 4-MeC_6H_4, Ar = 4-BrC_6H_4 (**e**); R = Ar = 4-MeC_6H_4 (**f**)

at the first step of the corresponding *N*-(hydroxymethyl)amines **4**, which react with thiones **1a,b** to give intermediate **5a** or **5b** (the formation of these intermediates is consistent with the regioselectivity of the process). The initial *N*(3)-aminomethylation of pyrimidinethiones **1a,b** is supported by numerous data[18] on aminomethylation of structurally similar cyclic thioamides (5-substituted thiohydantoins and rhodanines). At the same time, under the conditions of the Mannich reaction, analogous substrates (2-thiouracil[18] and 6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one[13]) undergo only *S*-aminoalkylation, which suggests possible heterocyclization through intermediate **5a**. It should be noted that 6-methyl-2-thiouracil, a structural analog of thioxopyrimidines **1**, does not react under these conditions and its crystals are recovered unchanged from the reaction mixture.

However, the scope of this synthesis of pyrimido[2,1-*b*][1,3,5]thiadiazines is restricted to sterically unhindered reactive amines. For instance, we failed to use in this reaction amines with bulky substituents (*tert*-butylamine, 2-ethyl-6-methylaniline, and 2,6-xylidine). In an attempt to obtain analytically pure pyrimidothiadiazines **2a** and **2f** by recrystallization from glacial AcOH, we found that the acid causes partial decomposition of the 1,3,5-thiadiazine ring. According to TLC data, the retro-Mannich reaction leading to pyrimidine derivatives **1a,b** was completed in 10 min when refluxing a solution of compound **2a** or **2f** in AcOH.

IR spectra of pyrimidothiadiazines **2a—f** show no absorption bands due to the N—H stretching vibrations. The absorption bands due to the stretching vibrations of the cyano and carbonyl groups appear at 2223—2210 and 1657—1640 cm^{-1}, respectively. The absorption bands due to the C=N stretching vibrations in the pyrimidine ring appear at 1615—1605 cm^{-1}. Apart from the characteristic signals for the aromatic substituents, the ^1H NMR spectra of compounds **2a—f** exhibit two broadened peaks at δ 5.40—5.47 and 5.65—5.74. These are unresolved (at 200 MHz) multiplets relating to the $C(2)H_2$ and $C(4)H_2$ protons.

To elucidate the regiodirectivity of the reaction and unambiguously choose between alternative structures **2** and **3**, we examined structure **2a** by X-ray diffraction analysis. The general view of the molecule is shown in Fig. 1. The central bicyclic system C(1)—C(7)N(1)—N(3)S(1) in structure **2a** is nonplanar. The pyrimidinone ring is slightly twisted: the maximum deviation of the atoms from the root-mean-square plane is 0.043(1) Å; the bond length distribution in this ring is characteristic of conjugated systems. The heterocycle N(1)N(3)C(5)C(6)S(1) is nonplanar because of its

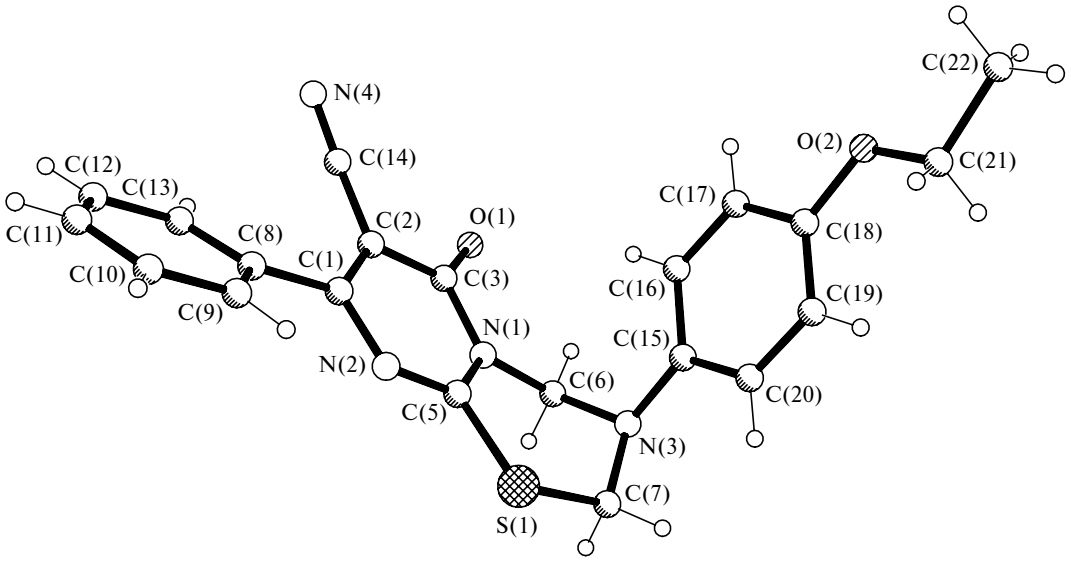


Fig. 1. General view of structure **2a**.

unsaturation and exists in the envelope conformation: the C(5)—C(7)N(1)S(1) atoms form a plane (the root-mean-square deviations of the atoms from this plane do not exceed 0.036(1) Å) with which the plane formed by the C(6), C(7), and N(3) atoms makes an angle of 57.9°. It is characteristic that the conjugation of the lone electron pairs of the S atom with the conjugated system of the pyrimidine ring results in a large difference between the S(1)—C(5) and S(1)—C(7) bond lengths (1.744(4) and 1.839(4) Å, respectively). The N(3) atom has a pyramidal configuration; the sum of the bond angles at this atom is 345.5(3)° and the bond lengths are 1.431—1.434(3) Å.

In conclusion, the three-component Mannich reaction of 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines with formaldehyde and primary amines is an efficient and simple regioselective route to novel 3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine derivatives.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (in Nujol). Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyser instrument. The purity of the compounds obtained was checked by TLC on Silufol UV 254 plates in acetone—heptane (1 : 1). Spots were visualized in the iodine vapor or under UV light. Melting points were determined on a Kofler hot stage and are given uncorrected. The starting 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines **1a,b** were prepared according to a known procedure[17] and recrystallized from AcOH.

3,8-Diaryl-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3,5]thiadiazine-7-carbonitriles 2a—f (general procedure). An excess of aqueous 37% HCHO (5—6 mL) was added to a suspension of an appropriate pyrimidine-2-thione **1a,b** (2 mmol) in EtOH (15 mL). The mixture was heated with stirring to complete dissolution and then an appropriate primary amine (2.2 mmol) was added in one portion. The resulting mixture was refluxed with vigorous stirring for 3 min and then stirred at ~20 °C for 4 h. The precipitate of pyrimidothiadiazine **2a—f** was filtered off and washed three times with EtOH.

3-(4-Ethoxyphenyl)-6-oxo-8-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2a). Yield 94%, yellow crystals, m.p. 197—199 °C (Me_2CO—Pr^iOH (2 : 1)). Found (%): C, 64.50; H, 4.62; N, 14.40. $C_{21}H_{18}N_4O_2S$. Calculated (%): C, 64.60; H, 4.65; N, 14.35. IR, ν/cm^{-1}: 2210 (CN); 1640 (C=O); 1615 (C=N). ^{1}H NMR, δ: 1.33 (t, 3 H, C$\underline{H}_3$CH$_2$O, ^3J = 7.0 Hz); 3.94 (q, 2 H, CH$_3$C$\underline{H}_2$O, ^3J = 7.0 Hz); 5.40, 5.66 (both m, 2 H each, C(2)H$_2$ and C(4)H$_2$); 6.90 (q, 4 H, 4-EtOC$_6\underline{H}_4$, ^3J = 9.0 Hz); 7.49 (m, 3 H, Ph, C(3)H—C(5)H); 7.90 (br.d, 2 H, Ph, C(2)H and C(6)H, ^3J = 7.6 Hz).

3-(4-Ethoxyphenyl)-8-(4-methylphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2b). Yield 63%, light yellow needles, m.p. 207—209 °C. Found (%): C, 64.99; H, 4.93; N, 13.95. $C_{22}H_{20}N_4O_2S$. Calculated (%): C, 65.33; H, 4.98; N, 13.85. IR, ν/cm^{-1}: 2218 (CN); 1646 (C=O); 1610 (C=N). ^{1}H NMR, δ: 1.33 (t, 3 H, C$\underline{H}_3$CH$_2$O, ^3J = 7.1 Hz); 2.41 (s, 3 H, Me); 3.93 (q, 2 H, CH$_3$C$\underline{H}_2$O, ^3J = 7.1 Hz); 5.40, 5.65 (both m, 2 H each, C(2)H$_2$ and C(4)H$_2$); 6.93 (q, 4 H, 4-EtOC$_6\underline{H}_4$, ^3J = 9.1 Hz); 7.28 (d, 2 H, 4-MeC$_6$H$_4$, H(3) and H(5), ^3J = 8.3 Hz); 7.83 (d, 2 H, 4-MeC$_6$H$_4$, H(2) and H(6), ^3J = 8.3 Hz).

3-(4-Fluorophenyl)-8-(4-methylphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2c). Yield 58%, colorless crystals, m.p. 235—237 °C (Me_2CO). Found (%): C, 63.59; H, 3.99; N, 14.85. $C_{20}H_{15}FN_4OS$. Calculated (%): C, 63.48; H, 4.00; N, 14.81. IR, ν/cm^{-1}: 2223 (CN); 1657 (C=O); 1608 (C=N). ^{1}H NMR, δ: 2.42 (s, 3 H, Me); 5.43, 5.70 (both m, 2 H each, C(2)H$_2$ and C(4)H$_2$); 7.00—7.19 (m, 4 H, 4-FC$_6$H$_4$); 7.27 (d, 2 H, 4-MeC$_6$H$_4$, H(3) and H(5), ^3J = 8.3 Hz); 7.84 (d, 2 H, 4-MeC$_6$H$_4$, H(2) and H(6), ^3J = 8.3 Hz).

3-(4-Chlorophenyl)-8-(4-methylphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2d).

Yield 59%, colorless crystals, m.p. 251—253 °C. Found (%): C, 60.93; H, 3.80; N, 14.29. $C_{20}H_{15}ClN_4OS$. Calculated (%): C, 60.83; H, 3.83; N, 14.19. IR, ν/cm^{-1}: 2222 (CN); 1655 (C=O); 1605 (C=N). ^{1}H NMR, δ: 2.42 (s, 3 H, Me); 5.45, 5.73 (both m, 2 H each, C(2)H_2 and C(4)H_2); 7.20 (q, 4 H, 4-ClC_6H_4, ^3J = 8.0 Hz); 7.29 (d, 2 H, 4-MeC_6H_4, H(3) and H(5), ^3J = 8.2 Hz); 7.84 (d, 2 H, 4-MeC_6H_4, H(2) and H(6), ^3J = 8.2 Hz).

3-(4-Bromophenyl)-8-(4-methylphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2e). Yield 59%, colorless crystals, m.p. 262—264 °C. Found (%): C, 54.50; H, 3.42; N, 12.85. $C_{20}H_{15}BrN_4OS$. Calculated (%): C, 54.68; H, 3.44; N, 12.75. IR, ν/cm^{-1}: 2219 (CN); 1645 (C=O); 1610 (C=N). ^{1}H NMR, δ: 2.42 (s, 3 H, Me); 5.47, 5.74 (both m, 2 H each, C(2)H_2 and C(4)H_2); 7.12, 7.43 (both d, 2 H each, 4-BrC_6H_4, ^3J = 8.9 Hz); 7.28 (d, 2 H, 4-MeC_6H_4, H(3) and H(5), ^3J = 8.2 Hz); 7.83 (d, 2 H, 4-MeC_6H_4, H(2) and H(6), ^3J = 8.2 Hz).

3,8-Bis(4-methylphenyl)-6-oxo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazine-7-carbonitrile (2f). Yield 60%, light yellow needles, m.p. 241—242 °C (Me_2CO). Found (%): C, 66.93; H, 4.83; N, 15.00. $C_{21}H_{18}N_4OS$. Calculated (%): C, 67.36; H, 4.85; N, 14.96. IR, ν/cm^{-1}: 2218 (CN); 1650 (C=O); 1615 (C=N). ^{1}H NMR, δ: 2.26, 2.41 (both s, 3 H each, 2 Me); 5.44, 5.70 (both m, 2 H each, C(2)H_2 and C(4)H_2); 7.06 (q, 4 H, 4-Me$C_6\underline{H}_4$—N, ^3J = 8.4 Hz); 7.28 (d, 2 H, 4-MeC_6H_4, H(3) and H(5), ^3J = 8.1 Hz); 7.82 (d, 2 H, 4-MeC_6H_4, H(2) and H(6), ^3J = 8.1 Hz).

Synthesis of 6-aryl-5-cyano-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines 1a,b from pyrimido[2,1-*b*][1,3,5]thiadiazines 2a,f. A solution of pyrimidothiadiazine **2a** or **2f** (1.5 mmol) in AcOH (10—15 mL) was refluxed for 10 min and then kept at ~20 °C for 5 days. The precipitate was filtered off and washed with EtOH. The yield of tetrahydropyrimidine **1a** was 56%, m.p. 305—310 °C (decomp.) (*cf.* Ref. 17: m.p. 300—302 °C). The yield of tetrahydropyrimidine **1b** was 53%, m.p. 295—300 °C (decomp.) (see Ref. 17: m.p. 290—291 °C). Both products were identical with samples described earlier.

X-ray diffraction analysis of compound **2a** was carried out at ~20 °C for a single crystal (0.45×0.40×0.15 mm) on an Enraf—Nonius CAD-4 automatic four-circle diffractometer (λ-CuK_α radiation, graphite monochromator, ω/2θ scan mode, θ_{max} = 64.9°, sphere segment $-1 \le h \le 10$, $-1 \le k \le 33$, $-1 \le l \le 16$). The total number of reflections was 3969. Crystals of compound **2a** are orthorhombic: a = 9.349(2) Å, b = 28.684(7) Å, c = 14.212(4) Å, V = 3811.3(16) Å^3, Z = 8, d_{calc} = 1.361 g cm^{-3}, μ = 1.715 cm^{-1}, F(000) 1632, space group *Pnca*. The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation with the SHELXS97 and SHELXL97 programs.[19,20] In refinement, 3130 reflections were used (2079 reflections with $I > 2\sigma(I)$); the number of parameters refined was 254; the number of reflections per parameter was 8.18; the weighting scheme was $\omega = 1/[\sigma^2(F_0^2) + (0.1127P)^2 + 1.4562P]$, where $P = (F_0^2 + 2F_c^2)/3$; max. (mean) shift/esd in the final cycle was 0.0011 (0.001). Calculations were corrected for anomalous scattering; PSI scan semiempirical absorption correction was applied (T_{min} = 0.4677, T_{max} = 0.7001). All hydrogen atoms were objectively located from the electron density difference map and refined isotropically. Final residuals were $R_1(F^2)$ = 0.0964 and $R_w(F^2)$ = 0.2018, GOF = 1.055 for all reflections and $R_1(F)$ = 0.0601 and $R_w(F^2)$ = 0.1739, GOF = 1.055 for reflections with $I > 2\sigma(I)$. The residual electron densities in the final refinement cycle were 0.50 and −0.25 e Å^{-3}. Comprehensive X-ray diffraction data for compound **2a** have been deposited with the Cambridge Crystallographic Data Center (CCDC 610045; CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

References

1. R. K. Smalley, in *Comprehensive Heterocyclic Chemistry II, Vol. 6, Six-Membered Rings With Two Or More Heteroatoms and Fused Carbocyclic Derivatives*, Ed. A. J. Boulton, Elsevier, Oxford, UK, 1996, p. 783.
2. Z. Wang, Haoxin Shi, and Haijian Shi, *Synth. Commun.*, 2001, **31**, 2841.
3. Z. Wang, T. You, Haijian Shi, and Haoxin Shi, *Molecules*, 1996, **1**, 89; Avail. URLs: http://www.mdpi.net/molecules/list96.htm; http://www.springerlink.com.
4. Z. Wang, T. You, Hai-Jian Shi, and Hao-Xin Shi, *Gaodeng Xuexiao Huaxue Xuebao*, 1997, **18**, 550; *Chem. Abstrs*, 1997, **127**, 95265t.
5. Hao-Xin Shi, Hai-Jian Shi, and Z. Wang, *Youji Huaxue*, 2000, **20**, 344; *Chem. Abstrs*, 2000, **133**, 120280c.
6. S. Yadav Lal Dhar, A. Vaish, and S. Sharma, *J. Agric. Food Chem.*, 1994, **42**, 811; *Ref. Zh., Khim.* [*Russian Journal of Abstracts, Chemistry*], 1994, 24Zh334.
7. S. Liu, X. Qian, J. Chen, and G. Song, *Monatsh. Chem.*, 2000, **131**, 953.
8. S. Farooq and H.-P. Streibert, US Pat. 4 443 445 (1984).
9. Z. A. Hozein, A. A. O. Sarhan, H. A. H. El-Sherief, and A. M. Mahmoud, *Z. Naturforsch., Teil B*, 1997, **52**, 1401; *Chem. Abstrs*, 1998, **128**, 88906v.
10. Haijian Shi, Haoxin Shi, and Z. Wang, *J. Heterocycl. Chem.*, 2001, **38**, 929.
11. Haijian Shi, Z. Wang, and Haoxin Shi, *Chimia*, 1997, **51**, 529; *Ref. Zh., Khim.* [*Russian Journal of Abstracts, Chemistry*], 1998, 13Zh272.
12. Haijian Shi, Z. Wang, and Haoxin Shi, *Synth. Commun.*, 1999, **29**, 2027.
13. Z. A. Hozein, *J. Chem. Res. (S)*, 2000, 3, 99.
14. A. A. O. Sarhan, S. H. Abdel-Hafez, H. El-Sherief, and T. Aboel-Fadl, *Synth. Commun.*, 2006, **36**, 987.
15. V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Dokl. Akad. Nauk*, 2003, **389**, 763 [*Dokl. Chem.*, 2003, **389**, No. 4—6, 92 (Engl. Transl.)].
16. K. A. Frolov, V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 2158 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 2226.
17. S. Kambe, K. Saito, H. Kishi, A. Sakurai, and H. Midorikawa, *Synthesis*, 1979, 287.
18. M. Tramontini, *Synthesis*, 1973, 703.
19. G. M. Sheldrick, *SHELXS97, Program for the Solution of Crystal Structure,* University of Göttingen, Göttingen (Germany), 1997.
20. G. M. Sheldrick, *SHELXL97, Program for the Refinement of Crystal Structures,* University of Göttingen, Göttingen (Germany), 1997.

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