ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 5, pp. 996–1000. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © A.P. Kozachenko, O.V. Shablykin, E.B. Rusanov, A.N. Vasilenko, V.S. Brovarets, 2009, published in Zhurnal Obshchei Khimii, 2009, Vol. 79, No. 5, pp. 824–828.

Transformation of the Condensation Products of 2-Acylamino-3,3-dichloroacrylonitriles with Imidazole into Pyrazolo[1,5-*a*]pyrimidine Derivatives

A. P. Kozachenko[a], O. V. Shablykin[a], E. B. Rusanov[b], A. N. Vasilenko[a], and V. S. Brovarets[a]

[a] *Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02660 Ukraine*
e-mail: brovarets@bpci.kiev.ua

[b] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 5, Kiev, 02660 Ukraine*

Received July 1, 2008

Abstract—Successive treatment of accessible 2-acylamino-3,3-dichloroacrylonitriles with imidazole and hydrazine hydrate led to the formation of 4-acylamino-3(5)-amino-5(3)-(1*H*-imidazol-1-yl)pyrazoles, and condensation of the latter with acetylacetone afforded 3-acylamino-2-(1*H*-imidazol-1-yl)-5,7-dimethylpyrazolo [1,5-*a*]pyrimidines whose structure was reliably determined by X-ray analysis.

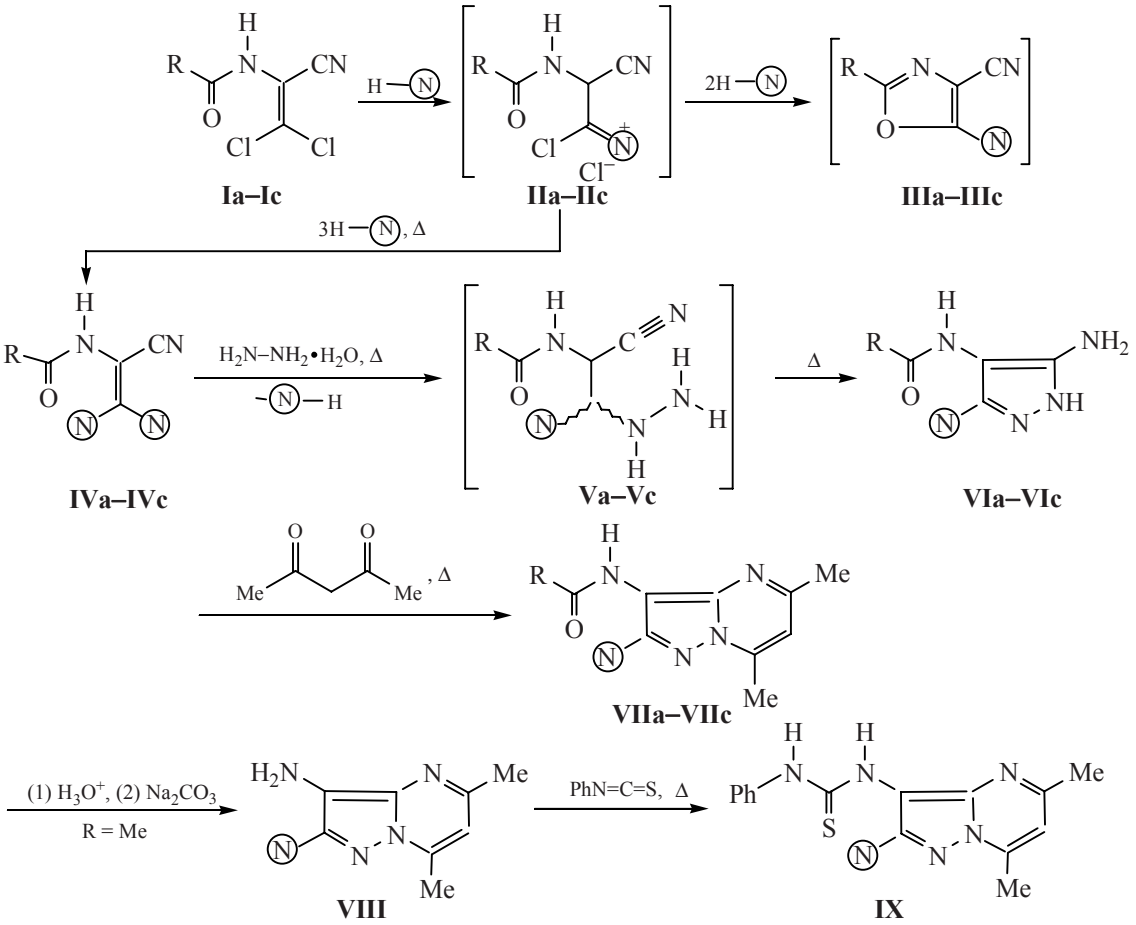
DOI: 10.1134/S1070363209050223

More than 30 years ago it was reported that accessible multicenter electrophiles, 2-acylamino-3,3-dichloroacrylonitriles **I**, react in a specific mode with primary and secondary amines, as well as with pyrrolidine, piperidine, and morpholine, to give the corresponding 5-amino-1,3-oxazole-4-carbonitrile derivatives [1, 2]. In the present work we found that reactions of compounds **I** with imidazole take a different pathway. Instead of the expected transformation sequence **I** → **II** → **III**, the process follows alternative scheme **I** → **II** → **IV** (see below). Presumably, the reaction of strongly basic imidazole with intermediates **II** via nucleophilic replacement of the labile chlorine atom by imidazole residue with formation of compounds **IV** is faster than cyclization of **II** to oxazoles **III**. The elemental compositions of compounds **IV** were consistent with the assumed structure (Table 1), and the presence of acylamino group in their molecules was confirmed by the IR data (Table 2). The structure of **IV** was also proved by COSY, NOESY, HMQC, and HMBC heteronuclear correlation spectra (Fig. 1, Table 3), which allowed us to assign all ^{1}H and ^{13}C signals in their NMR spectra.

It should be noted that assignment of signals from the imidazole fragment was complicated by overlap of the 5-H_a and 4-H_b signals (δ 7.23 ppm); nevertheless, using two-dimensional HMQC and HMBC techniques, we succeeded in not only assigning signals from carbon atoms in both imidazole rings but also determining the positions of poorly resolved signals from 5-H_a and 4-H_b. The presence in the NOESY spectrum of cross peaks at δ 9.54 (CONH)/7.86 ppm (2-H_c, 6-H_c) and at δ 7.23 (5-H_a)/7.86 ppm (2-H_c, 6-H_c) also supported the structure of **IVb** shown in Fig. 1.

Thus identification of compounds **IV** is beyond doubt. 2-Acylamino-3,3-bis(1*H*-imidazol-1-yl)acrylonitriles reacted with hydrazine hydrate on heating via replacement of one imidazole residue by hydrazino group and subsequent cyclization involving the cyano group (transformation sequence **IV** → **V** → **VI**). The IR spectra of the products lacked absorption band typical of cyano group (Table 2), and the presence of an amidine fragment in compounds **VI** was confirmed by their cyclocondensation with acetylacetone, which gave previously unknown 3-acylamino-2-(1*H*-imidazol-1-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines **VII**. The structure of one of these compounds was reliably determined by X-ray analysis (Fig. 2).

Distribution of bond lengths and bond angles over the $N^{1-3}C^{1-6}$ central bicyclic fragment of molecule **VIIb** is typical of such fused heterocyclic systems; nevertheless, we found only two analogous structures



R = Me (**a**), Ph (**b**), 4-MeC_6H_4 (**c**), Ⓝ = 1*H*-imidazol-1-yl.

Table 1. Yields, melting points, and elemental analyses of compounds **IV** and **VI–IX**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IVa	76	258–260 (THF)	54.22	4.02	34.32	$C_{11}H_{10}N_6O$	54.54	4.16	34.69
IVb	84	202–204 (dioxane)	62.93	3.91	27.31	$C_{16}H_{12}N_6O$	63.15	3.97	27.62
IVc	87	195–197 (dioxane)	64.38	4.52	26.13	$C_{17}H_{14}N_6O$	64.14	4.43	26.40
VIb	75	243–245 (THF)	58.51	4.29	31.09	$C_{13}H_{12}N_6O$	58.20	4.51	31.33
VIc	77	235–237 (THF)	59.23	4.95	30.02	$C_{14}H_{14}N_6O$	59.56	5.00	29.77
VIIa	72	255–257 (EtOH)	57.85	5.00	31.44	$C_{13}H_{14}N_6O$	57.77	5.22	31.09
VIIb	76	136–138 (EtOH)	64.82	5.04	25.08	$C_{18}H_{16}N_6O$	65.05	4.85	25.29
VIIc	78	200–202 (EtOH)	66.12	5.42	24.61	$C_{19}H_{18}N_6O$	65.88	5.24	24.26
VIII	66	220–222 (C_6H_6)	57.64	4.96	37.01	$C_{11}H_{12}N_6$	57.88	5.30	36.82
IX	65	>280 (EtOH)	59.22	5.01	26.56	$C_{18}H_{17}N_7S$[a]	59.49	4.71	26.98

[a] Found, %: S 8.63. Calculated, %: S 8.82.

Table 2. IR and ^{1}H NMR spectra of compounds **IV** and **VI–IX**

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
IVa	1690 (NC=O), 2237 (C=N), 3030–3170 (NH_{assoc})	1.98 s (3H, CH_3), 7.06–8.07 m (6H, H_{arom}), 10.14 s (1H, NH)
IVb	1660 (NC=O), 2255 (C=N), 3030–3200 (NH_{assoc})	7.03–8.15 m (11H, H_{arom}), 10.58 s (1H, NH)
IVc	1670 (NC=O), 2240 (C=N), 3120–3260 (NH_{assoc})	2.39 s (3H, CH_3), 7.02–8.14 m (10H, H_{arom})
VIb	1645[a] (NC=O, δ NH_2), 2800–3260 (NH_{assoc}), 3340, 3425 (NH_2)	5.10 br.s (2H, NH_2), 6.96–7.96 m (8H, H_{arom}), 9.40 s (1H, NH), 11.69 br.s (1H, NH)
VIc	1645[a] (NC=O, δ NH_2), 2800–3240 (NH_{assoc}), 3300, 3400 (NH_2)	2.39 s (3H, CH_3), 5.09 br.s (2H, NH_2), 6.94–7.86 m (7H, H_{arom}), 9.32 s (1H, NH), 11.66 br.s (1H, NH)
VIIa	1660 (NC=O), 3060–3290 (NH_{assoc})	2.10 s (3H, CH_3), 2.53 s (3H, CH_3), 2.69 s (3H, CH_3), 6.94–8.08 m (4H, H_{arom}), 9.52 s (1H, NH)
VIIb	1655 (NC=O), 2900–3450 (NH_{assoc})	2.54 s (3H, CH_3), 2.74 s (3H, CH_3), 7.00–8.11 m (9H, H_{arom}), 10.06 s (1H, NH)
VIIc	1675 (NC=O), 3000–3275 (NH_{assoc})	2.41 s (3H, CH_3), 2.52 s (3H, CH_3), 2.72 s (3H, CH_3), 6.98–8.13 m (8H, H_{arom}), 9.98 s (1H, NH)
VIII	3270, 3370 (NH_2)	2.49 s (3H, CH_3), 2.61 s (3H, CH_3), 4.00 br.s (2H, NH_2), 6.72–8.29 m (4H, H_{arom})
IX	2900–3300 (NH_{assoc})	2.57 s (3H, CH_3), 2.71 s (3H, CH_3), 6.98–8.19 m (9H, H_{arom}), 9.15 br.s (1H, NH), 10.22 br.s (1H, NH)

[a] Band with a shoulder.

in the Cambridge Structural Database [3, 4]. The $N^{1–3}C^{1–6}$ central bicyclic fragment is almost planar: the mean-square deviation of atoms from the plane is 0.014 Å (the maximal deviation does not exceed 0.027 Å). The $N^4C^9N^5C^{10}C^{11}$ imidazole ring is turned through a dihedral angle of 24.2° with respect to the above plane. The $C^{12}–N^6$ bond [1.363(3) Å] is shorter than standard single C–N bond (1.45 Å), and the sum of bond angles

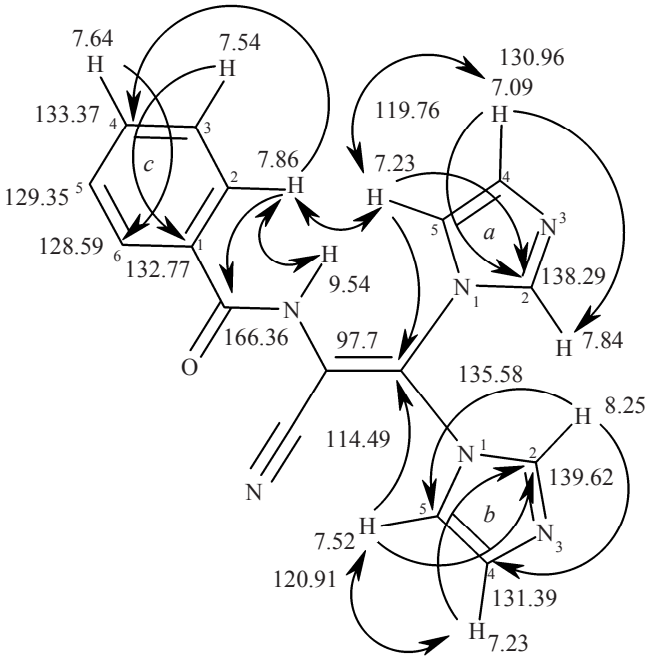


Fig. 1. Principal correlations (shown with arrows) and chemical shifts of protons and carbon nuclei (δ_H, δ_C, ppm) in the ^{1}H and ^{13}C NMR spectra of compound **IVb**.

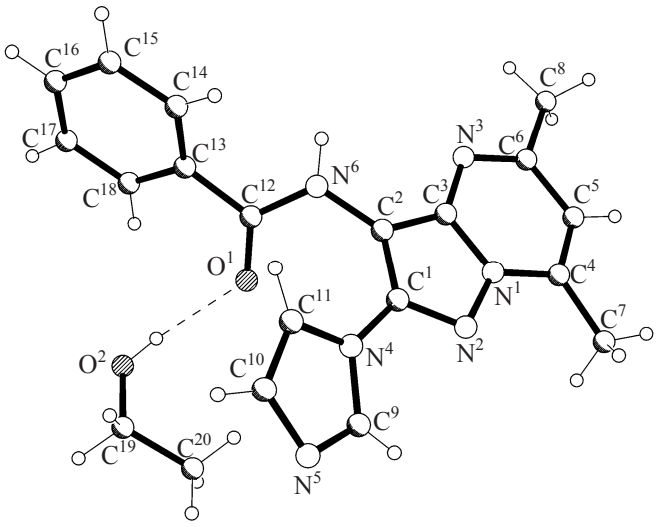


Fig. 2. Structure of the molecule of compound **VIIb** (solvate with ethanol) according to the X-ray diffraction data. Principal bond lengths: $C^1–N^2$ 1.334(3), $C^1–C^2$ 1.404(3), $C^2–C^3$ 1.384(3), $C^3–N^1$ 1.381(3), $N^1–N^2$ 1.361(2), $C^1–N^4$ 1.409(3), $C^4–C^5$ 1.352(3), $C^5–C^6$ 1.412(3), $C^3–N^3$ 1.356(3), $C^6–N^3$ 1.319(3), $C^2–N^6$ 1.411(3), $C^{12}–N^6$ 1.363(3), $C^{12}–O^1$ 1.227(3), $C^4–N^1$ 1.377(3), $C^9–N^4$ 1.366(3), $C^9–N^5$ 1.303(3), $C^{10}–N^5$ 1.373(3), $C^{10}–C^{11}$ 1.340(3), $C^{11}–N^4$ 1.372(3) Å.

Table 3. Correlations in the COSY, NOESY, HMQC, and HMBC spectra of compound **IVb**[a]

^{1}H, δ, ppm	^{1}H, δ, ppm		^{13}C, δ_C, ppm	
	COSY	NOESY	HMQC	HMBC
7.64 ($C^{4c}H$)	7.54	7.54	133.37	128.59 (C^{2c}, C^{6c})
7.54 ($C^{3c}H$, $C^{5c}H$)	7.86, 7.14	7.86, 7.64	129.35	129.35 (C^{3c}, C^{5c}), 132.77 (C^{1c})
7.86 ($C^{2c}H$, $C^{6c}H$)	7.54	7.23, 9.54, 7.54	128.59	128.59 (C^{2c}, C^{6c}), 133.37 (C^{4c}), 166.36 (CO)
9.54 (CONH)	–	7.86	–	–
7.23 ($C^{5a}H$)	7.09, 7.84	7.86, 7.09	119.76	130.96 (C^{4a}), 138.29 (C^{2a}), 135.58 (*C*=CCN)
7.09 ($C^{4a}H$)	7.23, 7.84	7.23	130.96	138.29 (C^{2a})
7.84 ($C^{2a}H$)	7.09, 7.23	–	138.29	119.76 (C^{5a}), 130.96 (C^{4a})
7.52 ($C^{5b}H$)	7.23, 8.25	7.23	120.91	131.39 (C^{4b}), 139.62 (C^{2b}), 135.58 (*C*=CCN)
7.23 ($C^{4b}H$)	7.52, 8.25	7.52	131.39	139.62 (C^{2b})
8.25 ($C^{2b}H$)	7.52, 7.23	–	139.62	131.39 (C^{4b}), 120.91 (C^{5b})

[a] For numbering of carbon atoms in structure **IVb**, see Fig. 1.

at the N^6 atom is 357.5(18)°; these data indicate conjugation of lone electron pair on the N^6 atom with the carbonyl π-bond. Compound **VIIb** crystallizes as solvate with ethanol. The solvate ethanol molecule is linked to the carbonyl group through hydrogen bond O^2–$H^2\cdots O^1$ [$O^1\cdots O^1$ 2.830(2), O^2–H^2 0.82(2), $N^2\cdots O^1$ 2.012 Å, ∠ONO 174(2)°]. No shortened intermolecular contacts were found in the crystalline structure of **VIIb**.

Unambiguous determination of the structure of compound **VIIb** confirmed the structure of not only its analogs **VIIa** and **VIIc** but also their precursors **VIa**–**VIc**.

To conclude, it should be noted that the acetyl protection can be removed from compound **VIIa** by acid hydrolysis. New heterocyclic base **VIII** thus obtained can be modified by treatment with phenyl isothiocyanate (as shown in scheme), as well as by other reagents, which may be important from the viewpoint of search for bioregulators among pyrazolo [1,5-*a*]pyrimidine derivatives.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^{1}H NMR spectra were measured on a Varian VXR-300 instrument, and the ^{1}H and ^{13}C NMR spectra of compound **IVb** were obtained on a Varian Mercury-400 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as internal reference.

The X-ray diffraction data for a single crystal of **VIIb**·EtOH, 0.06×0.26×0.29 mm, were acquired at room temperature on a Bruker Smart Apex II diffractometer (λMoK_α irradiation, graphite monochromator, θ_{max} = 26.29°, spherical segment $15 \le h \le 21$, $-8 \le k \le 9$, $-16 \le l \le 16$). Total of 11734 reflections were measured, 3651 of which were independent (R_{int} = 0.0412). Monoclinic crystal system, $C_{20}H_{22}N_6O_2$, *M* 378.44, space group $P2_1/c$ (no. 14); unit cell parameters: *a* = 17.0575(9), *b* = 8.2334(4), *c* = 13.6631(7) Å; β = 102.861(3)°; *V* = 1870.72(16) Å^3; *Z* = 4; d_{calc} = 1.344 g cm^{-3}; μ = 0.091 mm^{-1}; *F*(000) = 800. The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using SHELXS97 and SHELXL97 software packages [4, 5]; 2333 reflections with $I > 2\sigma(I)$ were included in the refinement procedure (314 refined parameters, 7.4 reflections per parameter); weight scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0712R)^2 + 0.4247R]$, $R = (Fo^2 + 2Fc^2)/3$; the ratio of the maximal (average) shift to the error in the last iteration was 0.001 (0.000). A correction for absorption was introduced using SADABS program (T_{min}/T_{max} = 0.607417). All hydrogen atoms were localized from the Fourier difference series, and their positions were

refined in isotropic approximation. Only hydrogen atoms on C^{20}, O^2, and C^8 were localized on the basis of geometry considerations. Protons in the methyl group (C^8H_3) are disordered by two positions with equal populations. The final divergence factors were $R^1(F^2) = 0.0902$, $R_W(F^2) = 0.1429$, goodness of fit 0.983 (all reflections) and $R^1(F) = 0.0513$, $R_W(F^2) = 0.1230$, *GOF* 0.983 [reflections with $I > 2\sigma(I)$]. The residual electron density from the Fourier difference series after the last iteration was 0.52 and –0.20 *e* Å^{-3}. The complete set of crystallographic data for compound **VIIb** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 690549).

2-Acylamino-3,3-bis(1*H*-imidazol-1-yl)acrylonitriles IVa–IVc *(general procedure).* Imidazole, 0.6 mol, was added to a solution of 0.1 mol of dichloroacrylonitrile **Ia**–**Ic** in 200 ml of tetrahydrofuran, and the mixture was heated for 8 h under reflux. The mixture was cooled, the precipitate was filtered off, the solvent was removed under reduced pressure, the residue was treated with water, and the precipitate was filtered off and purified by recrystallization.

5-Amino-4-acylamino-3-(1*H*-imidazol-1-yl)-1*H*-pyrazoles VIa–VIc *(general procedure).* Hydrazine hydrate, 0.01 mol, was added to a solution of 0.005 mol of compound **IVa**–**IVc** in 40 ml of tetrahydrofuran, and the mixture was heated for 6 h under reflux and left to stand for 12 h at 20–25°C. The precipitate was filtered off, and the product was brought into further syntheses without additional purification. Analytical samples of compounds **VIb** and **VIc** were obtained by recrystallization from tetrahydrofuran.

3-Acylamino-2-(1*H*-imidazol-1-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines VIIa–VIIc *(general procedure).* Acetylacetone, 5 ml, was added to a solution of 0.004 mol of compound **VIa**–**VIc** in 5 ml of toluene, and the mixture was heated for 5 h under reflux. Volatile substances were removed under reduced pressure, and the residue was purified by recrystallization from ethanol.

2-(1*H*-Imidazol-1-yl)-5,7-dimethylpyrazolo[1,5-*a*]-pyrimidin-3-amine (VIII). A solution of 0.001 mol of compound **VIIa** in 5 ml of concentrated hydrochloric acid was heated for 6 h under reflux. The mixture was evaporated under reduced pressure, the residue was dissolved in 10 ml of water, 5 ml of a 10% aqueous solution of sodium hydrogen carbonate was added, the mixture was extracted with chloroform (2×10 ml), the extract was dried over magnesium sulfate, the solvent was removed under reduced pressure, and the residue was purified by recrystallization from benzene.

***N*-[2-(1*H*-Imidazol-1-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl]-*N*′-phenylthiourea (IX).** Phenyl isothiocyanate, 0.0055 mol, was added to a solution of 0.005 mol of compound **VIII** in 10 ml of acetonitrile. The mixture was heated for 3 h under reflux, the solvent was removed under reduced pressure, and the residue was recrystallized from ethanol.

REFERENCES

1. Drach, B.S., Sviridov, E.P., Kisilenko, A.A., and Kirsanov, A.V., *Zh. Org. Khim.*, 1973, vol. 9, no. 9, p. 1818.
2. Drach, B.S., Sviridov, E.P., and Lavrenyuk, T.Ya., *Zh. Org. Khim.*, 1974, vol. 10, no. 6, p. 1271.
3. Schweizer, E.E., Hayes, J.E., Rheingold, A., and Wei Xu, *J. Org. Chem.*, 1987, vol. 52, p. 1810.
4. Tian Li and Wang Da-Xiang, *Acta Crystallogr., Sect. E*, 2005, vol. 61, no. 7, p. 1286.
5. Sheldrick, G.M., *SHELX97. Program for the Solution of Crystal Structure*, Gottingen: Univ. of Gottingen, 1997.
6. Sheldrick, G.M., *SHELX97. Program for the Refinement of Crystal Structure*, Gottingen: Univ. of Gottingen, 1997.