2-ARYL-3,5-DINITRO-1,2-DIHYDROPYRIDINES

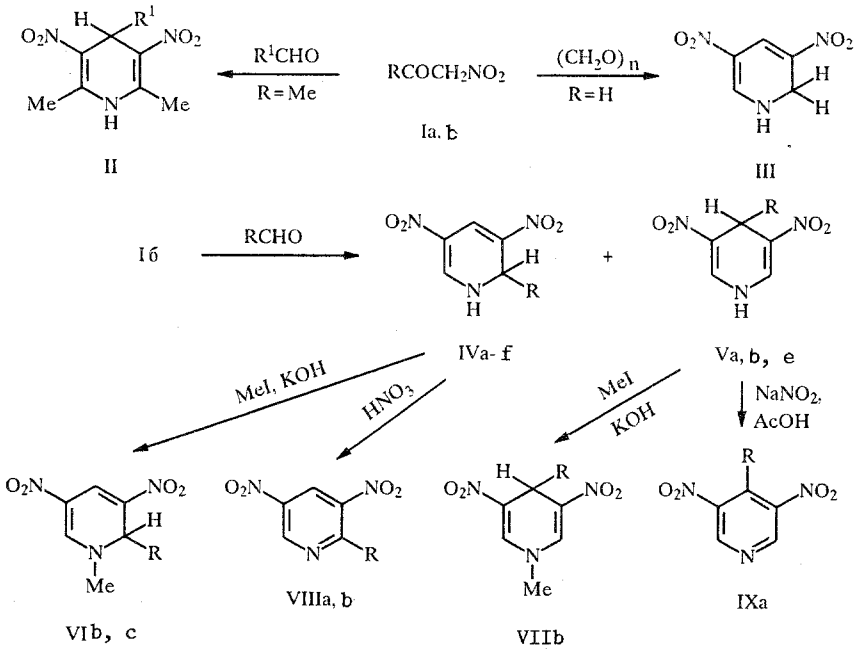
B. Vigante, Ya. Ozols, and G. Dubur

The reaction of α-nitroacetaldehyde with paraformaldehyde or aromatic aldehydes and ammonium acetate in acetic acid yielded 2-aryl-3,5-dinitro-1,2-dihydropyridines. Aromatic aldehydes, in an ethanol and acetic acid mixture, gave isomeric 3,5-dinitro-1,4-dihydropyridines in addition to 1,2-dihydropyridines. Physicochemical properties and reactivities of the compounds have been studied.

A search was made for methods of obtaining 3,5-dinitro-1,4-dihydropyridines, in which the 2 and 6 positions are unsubstituted. These compounds are of interest because they are potential agonists of potassium ions [1, 2] and also because they can be used as model compounds for studying the acid–base properties of 1,4-dihydropyridines as NH-acids.

Both 2,6-dimethyl-3-nitro- and 3,5-dinitro-1,4-dihydropyridine containing aryl or heterocyclic substituents at position 4 are known [1, 2] and were obtained from α-nitroacetone Ia and the corresponding aldehyde by modification of the Hantzsch synthesis.

As a starting compound we chose α-nitroacetaldehyde Ib [3]; this is closely related to nitroacetone, which under the conditions of the Hantzsch synthesis gives 2,6-unsubstituted 1,4-dihydropyridine, a compound which is difficult to obtain by other methods. Instead of free α-nitroacetaldehyde, we used its potassium salt because of the tendency to polymerization and the explosive nature of the free compound.



Ia R = Me, b R = H; IV—IX a R = Ph; b R = C_6H_4Br-4; c R = C_6H_4OMe-4; d R = $C_6H_4NO_2$-4; e R = $C_6H_4NO_2$-3, f R = $C_6H_4OCHF_2$-2 R^1 = H; Ph; C_6H_4Br-4

We found that α-nitroacetaldehyde Ib underwent an unusual reaction in condensing with paraformaldehyde and ammonium acetate in acetic acid to give 3,5-dinitro-1,2-dihydropyridine III, whereas the α-nitroacetone Ia under these conditions cyclized by the usual route to 1,4-dihydropyridine [4].

Institute of Organic Synthesis, Latvian Academy of Sciences, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 64-70, January, 1993. Original article submitted October 16, 1991.

0009-3122/93/2901-0055$12.50

TABLE 1. ^{13}C NMR Spectra of 3,5-Dinitro-1,2-dihydropyridines IVa and b and 3,5-Dinitro-1,4-dihydropyridines Va and b (chemical shifts ^{13}C, δ, ppm)

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	Aromatic carbons			
						C_o	C_M	C_p	C_i
IVa	55,60	130,24	148,17	126,69	125,79	128,96	129,0	127,12	139,36
IV b	55,90	129,90	148,35	122,40	126,11	129,46	131,96	119,27	138,73
Va	133,62	132,09	39,79	132,09	133,62	128,16	128,20	127,41	141,43
V b	134,02	131,76	39,60	131,76	134,02	130,22	131,22	120,76	140,91

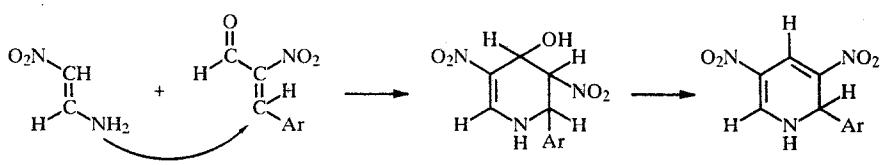
Using aromatic aldehydes in place of paraformaldehyde gave the previously inaccessible 2-aryl-3,5-dinitro-1,2-dihydropyridines IVa-f in good yield. The increase in the yield of 1,2-dihydropyridine was limited by the partial polymerization of the starting nitroacetaldehyde in the course of the reaction.

Until now, the principal method of obtaining 1,2-dihydropyridine was a three-stage synthesis involving the reduction of a pyridine salt obtained from 1,4-dihydropyridine [5, 6]. Recently it was shown [7, 8] that by varying reaction conditions (medium and temperature) acetoacetic ester with aromatic aldehydes under conditions of the Hantzsch synthesis gave isomeric 1,2-dihydropyridines.

In our case, using Ib as the methylene component in the Hantzsch synthesis we obtained 3,5-dinitro-1,4-dihydropyridine. Thus, the reaction of Ib with several aromatic aldehydes in a mixture of ethanol and acetic acid in the presence of ammonium acetate, gave small amounts of 1,4-dihydroisomers Va and b (TLC) in addition to the 1,2-dihydropyridines IVa and b. The α-nitroacetone Ia under these conditions gave only 1,4-dihydropyridine II. It was not possible to separate preparative amounts of the mixture of IVa and b and Va and b by column or thin-layer chromatography, because their R_f values are very similar in all the solvent systems we tried. Experimental separation of the isomers IVa and b and Va and b will be discussed below.

The mechanism generally accepted for the Hantzsch synthesis [9, 10] involves the initial formation of an enamine and an α,β-unsaturated ketone, followed by a Michael addition and subsequent cyclization and loss of a water molecule. Another possible reaction path for the Hantzsch synthesis has been suggested [7, 11]: under certain conditions the enamine acting as N-nucleophile added to the double bond of the unsaturated ketone, which then forms the 1,2-dihydroisomer. Apparently the nitroenamine formed during the course of the reaction preferentially reacts with α-arylideneacetoacetaldehyde with attack by the nitrogen atom at the double-bond β-carbon atom of the α,β-unsaturated aldehyde (scheme 1), leading to the formation of the 1,2-dihydropyridine IVa-f.

Scheme 1



The classical mechanism of the Hantzsch synthesis is involved to a minor extent — the Michael addition of the nitroenamine gives 1,4-dihydropyridine Va,b, and e (scheme 2). One of the factors affecting the enamine addition shown in schemes 1 and 2 is the steric effect of the methyl group, which when present in the enamine (nitroacetone Ia) gives exclusively the 1,4-dihydroisomer.

In this condensation, aromatic aldehydes containing both electron-donor and electron-acceptor substituents were used, but the nature of the substituents had little effect on the yield of 1,2-dihydropyridine or on the ratio of 1,2- and 1,4-dihydroisomers. In all the experiments the 1,2-dihydropyridines IVa-f and a mixture of isomers were separated by column or thin-layer preparative chromatography, since α-nitroacetaldehyde, because of its great reactivity, undergoes partial polymerization.

The reaction of Ib with benzaldehyde and p-bromobenzaldehyde in a mixture of ethanol and acetic acid gave a mixture of isomers IVa and b, and Va and b as orange crystals. The difference in the ease of oxidation of the isomers IVa and b and Va and b was used to separate them; when the mixture of isomers was heated for a short time in 6N nitric acid,

TABLE 2. Properties of 2-Aryl-3,5-dinitro-1,2-dihydropyridines III, IVa-f, and VIb and c

Compound	Empirical formula	mp, °C	UV spectrum, λ_{max}, nm (lg ε)	UV spect. of anion	IR spect., ν, cm^{-1}	PMR spectrum, DMSO-D_6, δ, ppm					Yield, %
						4-CH, c, 1H	arom. proton*	2-CH, d 1H	6-CH, d 1H	N—H, 1H (N—CH_3, s 3H)	
III	$C_5H_5N_3O_4$	180	208 (3,70); 228 (4,20); 380 (4,31); 460 (3,85)	520	1660, 3300	4,67	—	8,00	8,60	10,22	38
IVa	$C_{11}H_9N_3O_4$	181	205 (4,11); 237 (3,92); 375 (4,15); 450 (3,83)	518	1[illegible] 3400	6,13	7,38	8,31	8,62	10,82	73
IVb	$C_{11}H_8BrN_3O_4$	227	205 (4,15); 223 (4,26); 370 (4,18); 457 (3,86)	500	1[illegible] 1650, 3 3240	6,13	7,29...7,60	8,29	8,62	10,78	41
IVc	$C_{12}H_{11}N_3O_5$	167...170	205 (4,20); 223 (4,31); 370 (4,16); 457 (3,80)	500	1610, 1640, 3160, 3220	6,04	6,69...7,33; 3,71	8,27	8,58	10,76	70
IVd	$C_{11}H_8N_4O_6$	189...192	205 (4,34); 263 (4,27); 370 (4,26); 460 (3,94)	518	1600, 1645, 3260, 3320	6,29	7,62...8,24	8,29	8,64	10,65	68
IVe	$C_{11}H_8N_4O_6$	244...246	205 (4,10); 230 (4,25); 370 (4,15); 455 (3,75)	510	1620, 1660, 3180, 3220	6,15	7,00...7,55	8,29	8,60	10,70	34
IVf	$C_{12}H_9F_2N_3O_5$	165	205 (4,20); 237 (4,08); 370 (4,23); 450 (3,90)	515	1620, 1660, 3180, 3220	6,38	7,18....7,56**	8,27	8,56	10,73	39
VIb	$C_{12}H_{10}BrN_3O_4$	167...170	207 (4,18); 226 (4,13); 375 (4,13), 460 (3,77)	—	—	6,09	7,36...7,64	8,24	8,82	(3,22)	50
VIc	$C_{13}H_{13}N_3O_5$	110...115	206 (4,34); 233 (4,05); 380 (4,11); 4,68 (4,00)	—	—	6,00	6,89...7,44; 3,73	8,27	8,82	(3,24)	53

*For compound IVa — singlet; remaining compounds — multiplet.

**The $OCHF_2$-group proton gives a triplet at 7.11 ppm with J = 74 Hz.

TABLE 3. Data for 4-Aryl-3,5-dinitro-1,4-dihydropyridines Va,b, and e and VIIb

Compound	Empirical formula	mp, °C	UV spectrum, λ_{max}, nm (log ε)	UV spect. of anion	IR spectrum, ν, cm^{-1}	PMR spectrum, DMS-D_6, δ, ppm				Yield, %
						4-CH, s 1H	arom. proton*	2,6-CH, d 2H	N—H, 1H (N—CH_3, s 3H)	
Va	$C_{11}H_9N_3O_4$	268	207 (4,18); 237 (4,00); 304 (3,91); 440 (3,90)	580	1630, 1670, 3360	5,47	8,22	8,09	10,42	20
Vb*	$C_{11}H_8BrN_3O_4$	263	205 (4,23); 227 (4,12); 304 (3,75); 440 (3,85)	580	1610, 1670, 3140, 3360	5,53	7,24...7,60	8,18	10,56	28
Ve	$C_{11}H_8N_4O_6$	280	207 (4,34); 252 (4,16); 307 (3,86); 440 (3,83)	580	1600, 1660, 3260, 3340	5,75	7,53...7,87	8,09	10,29	72
VIIb	$C_{12}H_{10}BrN_3O_4$	95...98	205 (4,20); 225 (4,19); 314 (3,75); 456 (3,87)	—	—	5,49	7,27...7,58	8,29	(3,56)	41

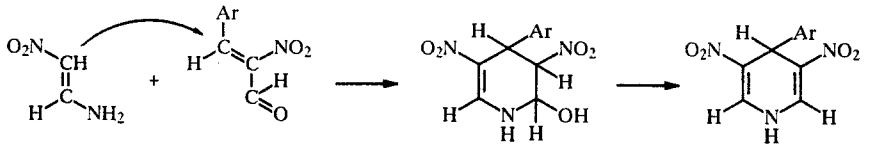
*For compound Va — singlet; others — multiplet.

TABLE 4. Data for 3,5-Dinitropyridines VIIIa and b and IXa

Compound	Empirical formula	mp, °C	PMR spectrum (DMS-D_6), δ, ppm				Yield, %
			4-CH, d, 1H	arom. prot.*	2-CH, s, 1H	6-CH, d, 1H	
VIIIa	$C_{11}H_7N_3O_4$	83...85	9,60	7,51	—	9,16	79
VIIIb	$C_{11}H_6BrN_3O_4$	126	9,64	7,51...7,80	—	9,20	89
IXa	$C_{11}H_7N_3O_4$	75...80	—	7,35	9,30	9,30	51

*For compounds VIIIa and IXa — singlet; for VIIIb — multiplet.

Scheme 2



only the 1,2-dihydropyridines IVa and b were oxidized, while the 1,4-isomers Va and b remained insoluble and were filtered off. 2-Aryl-3,5-dinitropyridines VIIIa and b were obtained by TLC as white crystals. The 1,2-dihydropyridines IVa - f were stable to oxidation by quinone derivatives. Thus, when IVa and chloranil were refluxed in benzene for 30 h no oxidation of the dihydropyridine ring was seen. The 3,5-dinitro-1,4-dihydropyridines Va and b were essentially resistant to oxidation even when heated in 6N nitric acid at 80°C. Keeping Va in acetic acid saturated with nitrogen oxides for 8 h at 80°C led to the oxidation of the dihydropyridine ring to 3,5-dinitropyridine IXa, which differed from the pyridine VIIIa; this was confirmed by finding the aryl group at position 4 in the 1,4-dihydropyridine Va.

The structure of the synthesized compounds was confirmed by spectral methods. To establish the structure of compounds of the type IV and V, the ^{13}C and ^1H NMR spectra were studied. The chemical shifts of the carbon atoms in the ^{13}C spectra of compounds Va and b confirmed the structure of the 3,5-dinitro-1,4-dihydropyridines (Table 1). In contrast to Va and b, in compounds IVa and b, atoms $C_{(3)}$ and $C_{(5)}$, and also $C_{(2)}$ and $C_{(6)}$, are nonequivalent, indicating that the molecule is not symmetric, and confirming the 1,2-dihydropyridine structure.

In the PMR spectra of the dihydroisomers Va, b, and e, the signal from the 4-CH proton occurs as a singlet at ~5.5 ppm (Table 2), but the protons at positions 2 and 6 gave rise to a doublet with J = 3 Hz. In the PMR spectrum of 3,5-DINITRO-1,2-dihydropyridine IVa-f, the signal from the proton at position 4 (singlet) was displaced in the down-field direction (see Table 2) to ~6.50 ppm, while the proton at positions 2 and 6 gave rise to two doublets, reflecting spin–spin interaction (J = 3 Hz) with the N-H protons.

A low-intensity peak from the molecular ion (M^+, 6% of maximum) in the mass spectrum of Va corresponded to $C_{11}H_9N_3O_4$. In the mass-spectrometric process, the 1,2-dihydropyridines IVa and b and III were dehydrogenated and in the spectra were found low-intensity peaks $M^+ - 2$, from the molecular ion of 3,5-dihydropyridines VIIIa and b.

The UV spectra of 3,5-dinitro-1,2-dihydropyridines IVa-f and 1,4-dihydropyridine Va, b, and e had the expected absorptions for 1,4- and 1,2-dihydropyridine systems. The maximum absorption of the long-wave band for 1,4-dihydropyridine Va, b, and e was at 440 nm, while the 3,5-dinitro-1,2-dihydropyridine IVa-f underwent a bathochromic shift of about 15 nm. Compared with 2,6-dimethyl-3,5-dinitro-1,4-dihydropyridine [12], the absorption maximum for Va,b, and e showed a bathochromic shift of 15 nm. The N-methyl derivatives of 1,2- and 1,4-dihydropyridine had weak bathochromic absorptions compared with the corresponding N-unsubstituted dihydropyridines.

Owing to the presence of two nitrogroups, the dihydroisomers IVa and Va are stronger NH-acids than other known 1,4-dihydropyridines [4]. Compounds III, IVa-f and Va, b, and e dissociated slightly in aqueous sodium bicarbonate and completely in alcoholic alkaline solution. The anions of the 1,2-dihydropyridine IVa-f and III were red, λ_{max} 500 nm, while the anions of 3,5-dinitro-1,4-dihydropyridine Va,b, and e were dark violet with λ_{max} 580 nm. In dimethoxyethane, the 1,2-dihydropyridines IVb and c formed anions with equimolar quantities of potassium hydroxide, and were methylated with

methyl iodide to give N-methyl-1,2-dihydropyridine VIb and c. N-Methyl-3,5-dinitro-1,4-dihydropyridine VIIb was obtained in the same way.

EXPERIMENTAL

IR spectra were obtained on a UR-20 (in Nujol), UV spectra on a Specord UV-vis spectrometer (in ethanol), and PMR spectra on a Bruker WH-90 (in DMSO-d_6, internal standard TMS). ^{13}C NMR were recorded on a Bruker WM-360 (90.5 MHz) in DMSO-d_6, internal standard cyclohexane (δ 27.44 ppm). Mass spectra were obtained using an AEI MS-50. The purity of the compounds was checked by TLC using Silufol UV-254 plates in chloroform–hexane–acetone–ethanol (9:7:2:1). Preparative TLC was carried out on free silica gel L100/160 microns; eluent chloroform–hexane–acetone–ethanol (9:7:2:1). Physical constants are presented in Tables 1-4.

Elemental analysis data (C, H, and N) for III, IVa-f, Va, b, and e, VIb and c, VIIb, VIIIa and b, and IXa were in agreement with calculated values. The potassium salt of α-nitroacetaldehyde was obtained by the method described in [3, 13, 14].

3,5-Dinitro-1,2-dihydropyridine III. A mixture of the potassium salt of nitroacetaldehyde (1.27 g, 10 mmole), paraform (0.4 g), and ammonium acetate (1.6 g) in glacial acetic acid (20 ml) was refluxed for 5 min. The reaction mixture was then poured into water (100 ml), neutralized to pH 6 with sodium carbonate, and extracted with ethyl acetate (3 × 30 ml). The extract was dried over anhydrous sodium sulfate, the solvent removed at reduced pressure, the residue dissolved in acetone (10 ml), and chromatographed on preparative plates (220 × 260 mm) of silica gel 2-3 mm. The bright orange band (R_f = 0.16) of 1,2-dihydropyridine III was eluted from the silica gel with acetone, the solvent evaporated under vacuum, and the residue recrystallized from methanol.

2-Substituted 3,5-Dinitro-1,2-dihydropyridines IVa-f. A mixture of the potassium salt of nitroacetaldehyde Ib (1.27g, 10 mmole), the aromatic aldehyde (5 mmole), and ammonium acetate (3.4 g) in glacial acetic acid (40 ml) was refluxed for 5 h. It was then poured into water (100 ml), and neutralized to pH 6 with solid sodium carbonate. The dihydropyridine was extracted with ethyl acetate (3 × 50), washed with water (2 × 50), and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum, the residue dissolved in acetone (20 ml) and chromatographed in three stages, as described above. The bright orange band was collected, eluted with acetone, the solvent evaporated under vacuum and the residue recrystallized from methanol.

4-Substituted 3,5-Dinitro-1,2-dihydropyridines Va, b, and e. To the aromatic aldehyde (5 mmole) dissolved in ethanol (50 ml) was added ammonium acetate (2.5 g), the potassium salt of nitroacetaldehyde (1.27 g, 10 mmole) and glacial acetic acid (5 ml). After heating on a water bath for 5 h, the excess ethanol was evaporated at reduced pressure, and the residue poured into water (100 ml). Extraction with ethyl acetate and chromatography as described above gave a mixture of IVa, b, and e and Va, b, and e as orange crystals. This mixture was suspended in nitric acid (20 ml, 6N) and heated on a water bath at 70°C for 15 min. Yellow crystals of Va, b, and e formed on cooling, and were recrystallized from dilute (80%) methanol.

The filtrate was poured into water (100 ml), neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate (3 × 20 ml). The extract was washed with water (2 × 20 ml) and dried over anhydrous sodium sulfate. The ethyl acetate was removed under reduced pressure, and the residue chromatographed, as described earlier (solvent system chloroform–hexane–acetone, 9:7:1). Plates were visualized in UV light, and the colorless band containing VIIIa, b, and e collected. After elution with acetone and evaporation of the solvent under vacuum, the residue was recrystallized from dilute (80%) methanol. The bright orange band was separated and worked up as described above to give an additional quantity of 1,4-dihydropyridine Va, b, and e.

2-Aryl-3,5-dinitropyridines VIIIa and b. A suspension of 3,5-dinitro-1,2-dihydropyridines IVa and b (3 mmole) in nitric acid (30 ml, 6H) was heated at 80°C until the solution did not lose color (about 10 min). The solution was cooled, diluted with water (30 ml), and neutralized to pH 6 with saturated sodium bicarbonate. The pyridines VIIIa and b were extracted with ether, the extract washed with water (2 × 40 ml), and dried over anhydrous sodium sulfate. The solvent was distilled under vacuum and the residue recrystallized from dilute (80%) methanol.

N-Methyl-2-aryl-3,5-dinitro-1,2-dihydropyridines VIb and c. The 3,5-dinitro-1,2-dihydropyridines IVb and c were dissolved in dry dimethoxyethane (30 ml) and powdered potassium hydroxide (1.68 g, 30 mmole) added. Methyl iodide (0.57

g, 9 mmole) was added to the bright-red anionic material which formed and the mixture heated on the water bath for 5 min. The solvent was evaporated under vacuum, and the residue triturated with water (50 ml) to give the orange N-methyl-1,2-dihydropyridines VIb and c which were recrystallized from methanol (80%).

N-Methyl-4-(p-bromophenyl)-3,5-dinitro-1,2-dihydropyridine VIIb. 3,5-Dinitro-1,4-dihydropyridine Vb (0.98 g, 3 mmole) was dissolved in dry dimethoxyethane (50 ml) and powdered potassium hydroxide (1.68 g, 30 mmole) added. To the violet anionic product obtained was added methyl iodide (0.63 ml, 10 mmole), and the mixture heated on the water bathml for 10 min. The solvent was removed under reduced pressure, the residue dissolved in acetone (10 ml), and the inorganic material filtered off. The filtrate was chromatographed on preparative plates, as described earlier using chloroform–hexane–acetone (9:7:1). The bright yellow band (R_f = 0.32) was collected, the solvent removed under reduced pressure, and the residue recrystallized from methanol.

4-Phenyl-3,5-dinitropyridine IXa. 1,4-dihydropyridine Va (0.74 g, 3 mmole) was dissolved in glacial acetic acid (20 ml). The solution was heated at 80°C, and sodium nitrite (2.5 g, 30 mmole) added portionwise over a period of 8 h. After standing for 24 h at 20°C, water (50 ml) was added and the solution neutralized with sodium bicarbonate. The product was extracted with ether (3 × 30 ml), the extract washed with water (2 × 50 ml), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give an oil, which was crystallized from dilute (80%) methanol.

REFERENCES

1. Offenleg. 3206671, BRD/G. Franckowiak, H. Böshagen, F. Bossert, S. Goldman, H. Meyer, E. Weninger, J. Stoltefus, M. Schram, G. Thomas, and R. Towart, Chem. Abs., **98**, 215488 (1983).
2. Offenleg. 3447169, BRD/G. Franckowiak, Chem. Abs., **105**, 172304 (1986).
3. K. K. Babievskii, V. M. Belikov, and N. A. Tikhonov, Izv. Akad. Nauk SSSR, No. 5, 1161 (1970).
4. B. A. Vigante, M. I. Terekhova, Ya. Ya. Ozols, and É. S. Petrov, and G. Ya. Dubur, Khim. Geterosikl. Soedinen., No. 9, 1228 (1989).
5. V. K. Lusis, A. E. Zandersons, D. Kh. Mutsenietse, and G. Ya. Dubur, Khim. Geterosikl. Soedinen., No. 4, 508 (1983).
6. A. Z. Zandersons, V. K. Lusis, D. Kh. Mutsenietse, and G. Ya. Dubur, Khim Geterotsikl. Soedinen., No. 1, 81 (1987).
7. C. N. O'Callaghan, J. Chem. Res. (M.), No. 9, 2901 (1986).
8. C. N. O'Callaghan and T. B. H. McMurry, J. Chem. Res. (M.), No. 6, 1546 (1988).
9. U. Eisner and J. Kuthan, J. Chem. Rev., **72**, 1 (1972).
10. A. Katritzky, D. L. Ostercamp, and T. G. Yousaf, Tetrahedron, **42**, 5729 (1986).
11. J. A. Berson and E. Brown, J. Am. Chem. Soc., **77**, 444 (1955).
12. É. É. Lietin'sh, R. M. Zolotoyabko, B. S. Chekavichus, A. É. Sausin', V. K. Lusis, and G. Ya. Dubur, Khim. Geterotsikl. Soedinen., No. 9, 1232 (1989).
13. T. Severin and B. Brück, Chem. Ber., **98**, 3847 (1965).
14. H. Bredereck, F. Effenberger, and G. Simchen, Angew. Chem., **73**, 493 (1961).