Chemistry of Heterocyclic Compounds, Vol. 29, No. 10, 1993

REACTION OF 2-CHLOROACETYL-1,3-CYCLOHEXANEDIONES WITH CYCLIC SCHIFF'S BASES. A NEW APPROACH TO 8-AZA-D-HOMOGONE-1,3,5(10),9(11),13-PENTAENE-12,17A-DIONE

O. V. Gulyakevich, A. L. Mikhal'chuk, and A. A. Akrem

We have studied the reaction of 3,4-dihydroisoquinolines and their hydrochlorides with 2-chloroacetyl-1,3-cyclohexanediones. We have shown that the reaction in alcoholic solutions of HCl leads to annelation of the cyclic Schiff's bases by β-triketones with formation of ABCD-tetracyclic 8-aza-D-homogonanium chlorides, treatment of which with bases gives 9,11-dehydro derivatives of 8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-diones.

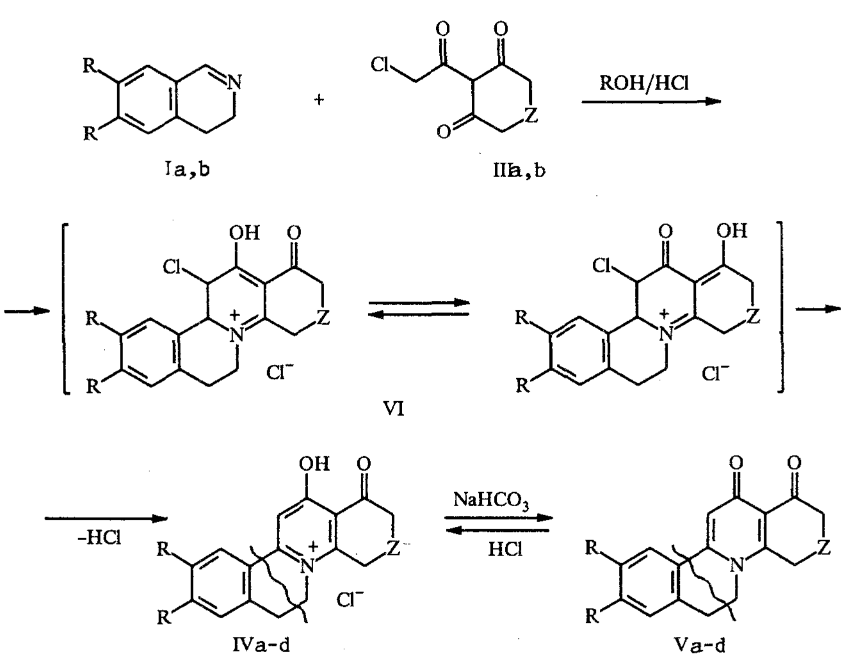
Annelation of cyclic Schiff's bases (3,4-dihydroisoquinolines, 3,4-dihydropyrrolo[1,2-a]pyrazines) by β-triketones (2-acyl-1,3-cycloalkanediones) and their derivatives is a convenient one-step approach by the scheme AB + D → ABCD to condensed nitrogen-containing heterocyclic compounds related to steroids [1-7]. It was of interest to study the possibility of accomplishing this reaction with β-triketones substituted in the acyl moiety, in particular the 2-chloroacetyl derivatives of 1,3-cycloalkanediones we obtained previously in [8, 9]. We know that cyclic Schiff's bases react with methylene-active compounds [10, 11], with enols and enol derivatives of β-dicarbonyl compounds [4, 5, 11-14]. Considering this, 2-chloroacetyl-1,3-cyclohexanediones are convenient substrates for the reaction of annelation with cyclic Schiff's bases, leading either to 11-chloro-substituted 8-aza-D-homogonanes, or to their 9,11-dehydro derivatives. Study of the properties of chloroacetyl-substituted 1,3-cyclohexanediones has shown that in the presence of basic reagents they undergo intramolecular cyclization to cycloalkano[b]-furanones [8, 9]. On the other hand, it has been hypothesized that 11-halo-8-aza-D-homogonanes are unstable [15] and convert spontaneously to 9,11-dehydro derivatives, obtained previously either by dehydrogenation of the corresponding 9,11-hydro analogs (using chloranil [16, 17], copper bromide [15], platinum group catalysts [17], or photochemically [18]) or as a result of condensation of N-oxides of 3,4-dihydroisoquinolines (nitrones) with β-triketones [16, 17]. The 11-substituted 9,11-dehydro derivatives of 8-aza-D-homogonanes have also been obtained by condensation of 8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-diones with aromatic and heteroaromatic aldehydes [19]. We know that 9,11-dehydro derivatives of 8-aza-D-homogonanes, like their hydrogenated precursors, display immunotropic action [20] and therefore are of interest as a basis for development of new low-molecular immunomodulators. Considering this, it was expedient to study in more detail the reaction of 2-chloroacetyl-1,3-cyclohexanediones with 3,4-dihydroisoquinolines.

According to current ideas and experimental data [21-23], 2-acyl-1,3-cycloalkanesdions exist in completely enolized form with strong intramolecular hydrogen bonding. In the presence of bases, which essentially are cyclic Schiff's bases, they are deprotonated, forming anions. On the other hand, in the presence of acids in β-triketones, the dienol forms are also realized along with the enol form with the chelated proton [21-23], which has been confirmed by isotope exchange [24]. At the same time, protonation of 3,4-dihydroisoquinolines leads to quaternization of the nitrogen atom and facilitates reaction with enols. Thus, it seemed valid to assume that accomplishment of the reaction of 2-chloroacetyl-1,3-cyclohexanediones with 3,4-dihydroisoquinolines or their hydrochlorides in the presence of acids allows us on the one hand to eliminate deprotonation of the β-triketone and the intramolecular S_N2 reaction [8, 9], simultaneously promoting its further enolization [24]; and on the other hand, ensures protonation of the imine, facilitating its reaction with the enol of the β-triketone.

Institute of Bioorganic Chemistry, Academy of Sciences of Belarus, Minsk 220141. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1368-1373, October, 1993. Original article submitted August 6, 1993.

0009-3122/93/2910-1172$12.50

Scheme 1

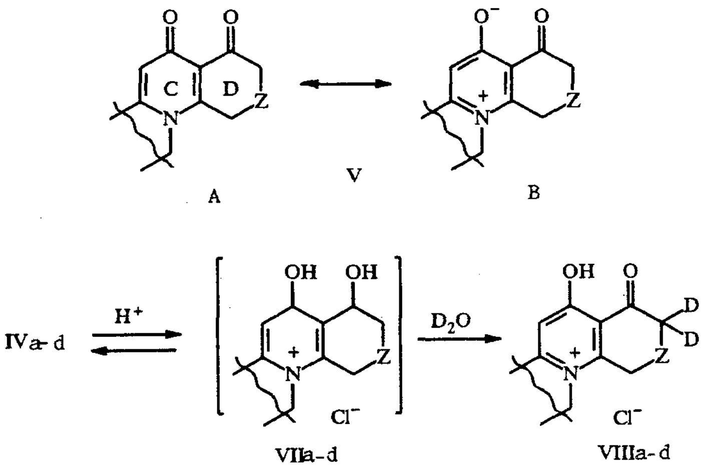


Ia, IVa,b, Va,b R = H; Ib, IVc,d V, R = OMe; IIa, IVa,b Z = CH_2; IIIb, IVb,d Z = CMe_2

The reaction of 3,4-dihydroisoquinolines (Ia, b) and also their hydrochlorides (IIa, b) with 2-chloroacetyl-1,3-cyclohexanediones (IIIa, b) in alcohol solutions of HCl (see Experimental Section, techniques A, B) supported the hypothesis made and, through the 8-aza-D-homogonanium chlorides (IVa-d) obtained for the first time, led to 9,11-dehydro derivatives of 8-aza-D-homogonanes (Va-d). At elevated pressure and temperature (technique B), the yields of target products (IVa-d) on the average were 5-6% higher than for conventional boiling of an equimolar mixture of the reagents in alcoholic solutions of HCl (technique A). However, we should note that in the absence of an excess of acid, we could not obtain the desired tetracyclic condensation products IV from hydrochlorides IIa, b and β-triketones IIIa, b. This is probably explained by the impossibility of forming dienol forms in the absence of excess acid [21-24]. The dehydro derivatives Va-d, in contrast to their hydrogenated precursors [25], form hydrochlorides IVa-d. The latter did not only exist in solutions but also were quite stable compounds, which were separated and proved to be stable in the crystalline state. This result probably is a consequence of the significant polarization of the γ-pyridone ring C, due to the important contribution of the limiting structure (VB, Scheme 2). Treatment of the intermediate 8-aza-D-homogonanium chlorides IVa-d with bases leads to 9,11-dehydro derivatives Va, b, d, obtained earlier by other methods [15-18], and also to the derivative (Vc) described here for the first time. Treatment of the 9,11-dehydro derivatives Va, b, d obtained by alternate methods [15-17] with alcoholic solutions of HCl (technique C) leads to 8-aza-D-homogonanium chlorides IVa, b, d in yields approaching quantitative. The chlorides IVa-d, in contrast to the derivatives Va-d, are quite soluble in water and alcohols. They are not very stable at elevated temperatures and begin to intensely darken even 50-70°C before melting. In this case, it is interesting to note the lack of differences between the melting points of the chlorides IVa, b and the corresponding derivatives Va, b.

The structure of the 8-aza-D-homogonanes Va-d obtained was confirmed by the set of physicochemical data and comparison with known samples obtained by alternate methods [15, 18], and also with literature data [16-18]. According to the PMR spectral data, the 8-aza-D-homogonanium chlorides IVa-d are characterized by a significant downfield shift of practically all the resonance signals of the protons relative to the corresponding signals observed for the free bases Va-d. This indicates a distribution of positive charge over the entire conjugation system. Nevertheless, analysis of the $\Delta\delta_{IV-V}$ values for the individual groups of protons (~0.2 for 1-H, 4-H; 0.3-0.5 for 6-H; 0.5-0.6 for 7-H; 0.5-0.7 for 15-H; and ~0.5 for 17-H) suggests significant localization of the positive charge on the γ-pyridone ring C and preferentially on the nitrogen atom. The resonance signals for the bases Va, c and chlorides IVa-d were assigned according to the data in [15], where the assignments were made on the basis of a study of the homonuclear Overhauser effect. We should note the substantial difference between the nature of the PMR spectra for compounds Va, c and IVa-d compared with their hydrogenated analogs [6-8], which may be explained by

Scheme 2



the significant flattening of the ABCD-tetracycle due to conjugation between rings A and C. In a PMR study of derivatives IVa-d, we observed that in deutero-donor solvents (D_2O, CD_3OD) in the presence of excess acid, deutero exchange occurs, involving the methylene group $C_{(17)}H_2$ with formation of deutero derivatives (VIIIa-d), probably the result of keto-enol tautomerism (IV ⇄ VII, Scheme 2). It is noteworthy that isotope exchange of the hydrogen at the carbon atom $C_{(7)}$ directly bonded to the quaternized nitrogen atom is not observed.

According to IR spectroscopy data, 8-aza-D-homogonanium chlorides IVa-d have a characteristic set of absorption bands in the 1700-1300 cm^{-1} region. In this case, in contrast to the derivatives Va, c, the highest frequency band in this region is shifted toward higher frequencies and is observed at 1711-1684 cm^{-1}, which is probably connected with a change in the charge and flattening of the D ring. The electronic absorption spectra of the chlorides IVa-d are complex due to superposition of a number of absorption bands, on the background of which we observe intense bands at 261-264, 289-315, and 371-373 nm. Differentiation of the spectra showed that they also are complex and are due to contributions from two or more absorption bands.

TABLE 1. Characteristics of Compounds IVa-d and Vc

Compound	Empirical formula	T_{mp}, °C* (solvent for crystallization)	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm	Yield, % method
IVa	$C_{17}H_{16}ClNO_2$	240 (methanol: ether)	3450...3380,3200...2400, 1710, 1670, 1625, 1610, 1590, 1575, 1438, 1252, 791	211(4,28); 264(4,22); 312(4,28)	82,2(A) 84,8(B) 95(C)
IVb	$C_{19}H_{20}ClNO_4$	246...254 (ethanol: ether)	3440, 3200...2400, 1700, 1660, 1600, 1570, 1435, 1335, 1248, 785	198(4,33); 217(4,28); 265(4,39); 315(4,14)	72,7(A) 84,8(B) 97,6(C)
IVc	$C_{19}H_{20}ClNO_2$	208...215 (methanol: ether)	3440, 3200...2400, 1684, 1600, 1569, 1527, 1495, 1448, 1368, 1267, 1220, 1144, 856, 808	209(4,35); 251(4,16); 290(3,89); 371(4,17)	79(A) 81,8(B) 91,7(C)
IVd	$C_{21}H_{24}ClNO_4$	246...250 (chloroform)	3430, 3200...2400, 1700, 1660, 1600, 1564, 1525, 1494, 1470...1435, 1356, 1335, 1289, 1268, 1218, 1147, 798	208(4,30); 228(4,36); 253(4,20); 263(4,15); 289(3,97); 330(3,97); 373(4,09)	75,9(A) 80,1(B) 89,7(C)
Vc	$C_{19}H_{19}NO_4$	222...224 (chloroform: ether)	1680, 1627, 1605, 1586, 1570, 1522, 1490, 1460...1440, 1337, 1258	210(4,33); 265(4,59)	90,7

---

*Compounds IVa-d melt with decomposition; resinification of the material begins 50-70°C before the melting point.

TABLE 2. PMR Spectra of Compounds IVa-d and Va, c

Compound	Chemical shift, δ, ppm, spin-spin coupling constant (J), Hz									
	~1-H (1H)	~2-H 2-OCH$_3$)	~3-H 3-OCH$_3$)	~4-H (1H)	~6-H (2H) t**	~7-H (2H) t**	11-H (1H) s	15-H (2H)	~16-H 16-CH$_3$)	17-H (2H)
IVa	7,44d*	7,46 (1H)t*	7,64 (1H) t*	7,84d*	3,41	4,73	7,55	378t**	2,40 (2H) m	2,96t**
IVb	7,47d*	7,53 (1H)t*	7,69 (1H) t*	7,89d*	3,37	4,64	7,64	3,53 s	1,26 (6H) s	2,83s
IVc	7,24s	4,00 (3H)s	4,02 (3H) s	7,43s	3,30	4,63	6,93	3,67t**	2,38 (2H) m	2,95t**
IVd	7,19s	3,99 (3H)s	4,00 (3H) s	7,46s	3,35	4,69	6,96	3,62s	1,20 (6H) s	2,72s
Va	7,29d*	7,35 (1H) t*	7,44 (1H) t*	7,60d*	3,16	4,12	6,84	3,01t**	2,14 (2H) m	2,51t**
Vc	6,82s	3,93 (3H)s	3,96 (3H) s	7,16 s	3,08	4,13	6,76	3,04t**	2,17 (2H) m	2,34t**

*J = 8.0.

**J = 6.0.

Thus, we have established that reaction of 2-chloroacetyl-1,3-cyclohexanediones IIIa, b with 3,4-dihydroisoquinolines Ia, b and their hydrochlorides IIa, b in alcoholic solutions of HCl leads to formation of 8-aza-D-homogonanium chlorides IVa-d, from which as a result of treatment with bases we obtained the previously undescribed 9,11-dehydro derivative Vc and also the known derivatives Va, b, d. The reaction probably is accomplished through intermediate formation of the 11-chloro derivative (VI, Scheme 1), which is unstable and under the reaction conditions is converted to the end products IVa-d.

EXPERIMENTAL

The course of the reaction and the purity of the compounds obtained were monitored using TLC on Silufol UV-254 plates, eluting agent 9:1 chloroform–methanol, visualization in UV light and also by iodine vapors with subsequent roasting of the chromatograms at 300-350°C. The melting points were determined on a Boetius heating stage. The IR spectra were recorded by L. P. Solova on the UR-20 in KBr disks. The electronic spectra were taken by S. N. Kiseleva on the Specord M-400 in ethanol solutions ($2.5\text{-}5.0 \cdot 10^{-4}$ moles/liter). The PMR spectra were obtained by I. Yu. Skorynin on the Bruker AC-200 (200 MHz) in $CDCl_3$, internal standard TMS. The mass spectra were measured on the Varian MAT-311 spectrometer, direct sample injection, ionization radiation energy 70 eV.

The results of elemental analysis (performed by V. A. Nekrashevich) of compounds IVa-d, Vc for C, H, Hal, and N correspond to the calculated values. The characteristics of the hydrochlorides IVa-d and base Vc are presented in Tables 1 and 2. The 3,4-dihydroisoquinolines Ia, b, their hydrochlorides IIa, b, and the 2-chloroacetyl-1,3-cyclohexanediones IIIa, b were obtained according to the methods described in [8, 9, 26, 27] and their physicochemical characteristics corresponded to data given in the literature. Alcoholic solutions of HCl were obtained according to the familiar technique in [28] by addition of acetylchloride to absolute alcohol.

12-Hydroxy-1,3,5(10),8,11,13-hexaen-17a-one-8-aza-D-homogonanium Chloride (VIa). A. 1.89 g (10 mmoles) β-triketone IIIa was added to a solution of 1.68 g (10 mmoles) hydrochloride IIa in 20 ml 5% HCl in ethanol. The reaction mixture was boiled for 24 h, then cooled. The precipitate was filtered and recrystallized from a 2:1 ethanol–ether mixture. Obtained: 2.5 g hydrochloride IVa, as colorless crystals.

B. 1.28 g hydrochloride IVa was obtained from 0.66 g (5 mmoles) 3,4-dihydroisoquinoline Ia in 30 ml 5% HCl in ethanol and 0.94 g (5 mmoles) β-triketone IIIA by holding in a sealed ampul at 110°C for 5 h.

C. 0.57 g hydrochloride IVa was obtained from 0.53 g (2 mmoles) 8-aza-D-homogonane Va [15] and 5 ml 3% HCl in methanol.

Using techniques A, B, and C, we similarly synthesized 12-hydroxy-16,16-dimethyl-1,3,5(10),8,11,13-hexaen-17a-one-8-aza-D-homogonanium chloride (IVb), 12-hydroxy-2,3-dimethoxy-1,3,5(10),8,11,13-hexaen-17a-one-8-aza-D-homogonanium chloride (IVc), and 12-hydroxy-16,16-dimethyl-2,3-dimethoxy-1,3,5(10),8,11,13-hexaen-17a-one-8-aza-D-homogonanium chloride (IVd).

8-Aza-D-homogonane (Va). 5 ml of a saturated solution of sodium hydrocarbonate was added to a solution of 1.5 g (5 mmoles) hydrochloride IVa in 10 ml H_2O. This was extracted with chloroform (3 × 20 ml). The combined extract was dried over magnesium sulfate, filtered, and evaporated. The residue was crystallized from a 2:5 methanol–ether mixture. Obtained: 1.23 g (92.7%) product Va. T_{mp} 237-240°C (cf. lit. data in [15-17, 29]).

8-Aza-D-homogonane (Vb). We obtained 0.83 g (94.3%) product Vb similarly from 0.91 g (3 mmoles) hydrochloride Vb. T_{mp} 247-250°C (cf. lit. data [15-17, 29]).

2,3-Dimethoxy-8-aza-D-homogona-1,3,5(10),9(11),13-pentaene-12,17a-dione (Vc). From 1.45 g (4 mmoles) hydrochloride IVc, we obtained 1.18 g (93.6%) product Vc in the form of cream-colored crystals (cf. lit. data [15-17, 29]).

8-Aza-D-homogonane (Vd). From 1.95 g (5 mmoles) hydrochloride IVd, we obtained 1.6 g (97.1%) product Vd. T_{mp} 286°C (cf. lit. data in [15, 30]).

REFERENCES

1. A. A. Akhrem and Yu. A. Titov, Total Steroid Synthesis, Plenum, New York (1970).
2. F. A. Lakhvich, L. G. Lis, and A. A. Akhrem, Usp. Khim., **53**, No. 6, 1014 (1984).
3. A. L. Mikhal'chuk, O. V. Gulyakevich, V. N. Peresada, A. M. Likhosherstov, and A. A. Akhrem, Zh. Obshch. Khim., **63**, No. 3, 701 (1993).
4. V. N. Pshenichnyk, O. V. Gulyakevich, and V. A. Khripach, Vestsi Akad. Nauk BSSR, Ser. Khim. Navuk, No. 5, 114 (1986).
5. O. V. Gulyakevich, A. L. Mikhal'chuk, and V. A. Khripach, Zh. Org. Khim., **27**, No. 1, 213 (1991).
6. A. L. Mikhal'chuk, O. V. Gulyakevich, A. A. Zenyuk, A. V. Korchik, L. G. Lis, V. A. Khripach, L. I. Ukhova, and A. A. Akhrem, Dokl. Akad. Nauk, **317**, No. 6, 1397 (1991).
7. A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov, and A. A. Akhrem, Khim. Geterotsikl. Soedin., No. 3, 374 (1993).
8. A. A. Akhrem, V. N. Pshenichnyi, O. V. Gulyakevich, and V. A. Khripach, Khim. Geterotsikl. Soedin., No. 8, 1130 (1985).
9. V. N. Pshenichnyk, O. V. Gulyakevich, and V. A. Khripach, Zh. Org. Khim., **25**, No. 9, 1882 (1989).
10. S. Patai (ed.), The Chemistry of the Carbon–Nitrogen Double Bond, Interscience, London (1970), p. 797.
11. A. A. Akhrem and Yu. G. Chernov, Dokl. Akad. Nauk, **298**, No. 3, 616 (1988).
12. S. V. Mikhalevskaya, L. F. Gladchenko, V. A. Serzhanina, and N. S. Kozlov, Khim. Geterotsikl. Soedin., No. 10, 1409 (1989).
13. A. A. Akhrem and Yu. G. Chernov, Dokl. Akad. Nauk, **255**, No. 4, 865 (1980).
14. A. A. Akhrem, E. V. Borisov, and Yu. G. Chernov, Zh. Org. Khim., **26**, No. 5, 1114 (1990).
15. V. N. Pshenichnyi, O. V. Gulyakevich, E. V. Borisov, and V. A. Khripach, Zh. Org. Khim., **23**, No. 8, 1765 (1987).
16. A. A. Akhrem, A. M. Moiseenkov, and A. I. Poselenov, Dokl. Akad. Nauk, **210**, No. 4, 841 (1973).
17. A. A. Akhrem, A. M. Moiseenkov, A. I. Poselenov, and V. A. Krivoruchko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1853 (1973).
18. A. A. Akhrem, V. Z. Kurbako, O. V. Gulyakevich, V. N. Pshenichnyi, V. A. Kripach, and N. I. Garbuz, Khim. Geterotsikl. Soedin., No. 8, 1135 (1985).
19. V. N. Pshenichnyki, O. V. Gulyakevich, E. V. Borisov, and V. A. Khripach, Zh. Org. Khim., **255**, No. 1, 115 (1989).
20. B. B. Kuz'mitskii, I. G. Dad'kov, Yu. L. Zhuravkov, N. A. Konoplya, G. S. Lyubin, A. E. Mashkovich, V. M. Nasek, O. V. Gulyakevich, V. N. Pshenichnyki, and V. A. Khripach, Vestsi Akad. Nauk BSSR, Ser. Khim. Navuk., No. 1, 64 (1989).
21. E. V. Borisov and T. S. Khlebnikova, Dokl. Akad. Nauk BSSR, **31**, No. 6, 539 (1987).
22. E. V. Borisov, T. S. Khlebnikova, and F. A. Lakhvich, Zh. Org. Khim., **26**, No. 6, 2445 (1990).
23. E. V. Borisov, T. S. Khlebnikova, D. B. Rubinov, and F. A. Lakhvich, Zh. Org. Khim., **28**, No. 6, 1306 (1992).

24. A. L. Mikhal'chuk and O. V. Gulyakevich, Physiologically Active Compounds Labeled with Radioactive and Stable Isotopes [in Russian], IAE, Moscow (1991), p. 89.
25. A. A. Akhrem, A. M. Moiseenkov, and V. A. Krivoruchko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1302 (1973).
26. W. M. Welly and G. R. Govindachari, Organic Reactions [Russian translation], Inostr. Lit., Moscow (1953), Bk. 6, p. 98.
27. F. L. Pyman, J. Chem. Soc., No. 23, 1610 (1909).
28. L. Fieser and M. Fieser, Reagents for Organic Synthesis [Russian translation], Mir, Moscow (1971), Vol. 4, p. 134.
29. A. A. Akhrem, A. M. Moiseenkov, V. A. Krivoruchko, and A. I. Poselenov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 3, 710 (1973).
30. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, S. U. Sagaidak, N. I. Garbuz, and V. Z. Kurbako, Zh. Org. Khim., **17**, No. 12, 1527 (1981).