Synthesis and reactions of 2-hydroxy-5,5-dimethyl- and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranones with *N*-nucleophiles

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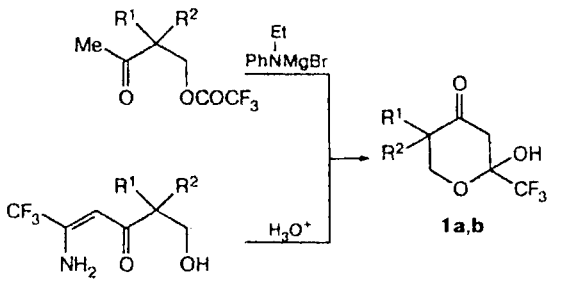
Condensation of 4-hydroxy-3,3-dimethyl- and 4-hydroxy-3,3-pentamethylenebutan-2-ones with ethyl trifluoroacetate in the presence of LiH in hexane afforded 2-hydroxy-5,5-dimethyl- and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranones, whose behavior in reactions with *N*-nucleophiles is analogous to that of unsymmetrical polyfluorinated β-diketones.

Key words: condensation, β-hydroxyketones, ethyl trifluoroacetate, tetrahydro-4-pyranones; aminoenones, CF_3-containing pyrazoles and Δ^2-isoxazolines.

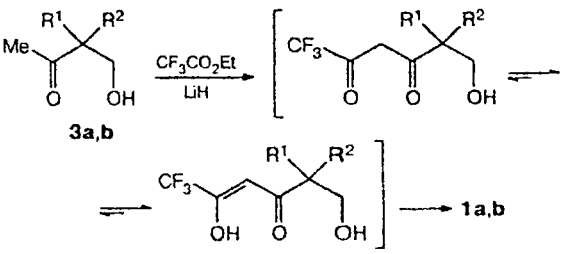
Recently,[1] we have demonstrated that intramolecular cyclization of 2,2-dimethyl- и 2,2-pentamethylene-3-hydroxobutyl trifluoroacetates under the action of *N*-phenyl-*N*-ethylammonium magnesium bromide afforded 2-hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyranone (**1a**) and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranone (**1b**), respectively. These compounds were also obtained by acid hydrolysis of the corresponding 2-amino-6-hydroxy-5,5-dialkyl-1,1,1-trifluorohex-2-en-4-ones (**2a,b**), which were the products of condensation of trifluoroacetonitrile with 4-hydroxy-3,3-dialkylbutan-2-ones (**3a,b**).[2]



2a,b **1a,b**

a: $R^1 = R^2 = CH_3$; **b**: $R^1 + R^2 = (CH_2)_5$

However, when we came up against the problem of the use of tetrahydropyranones **1a,b** in rather large amounts, we found that both these approaches are not satisfactory from the preparative standpoint because cyclization gave products in low yields and aminoenones **2a,b** are difficultly accessible. Condensation of ethyl trifluoroacetate with β-hydroxyketones **3a,b** in the presence of LiH in hexane appeared to be the most suitable procedure for the synthesis of compounds **1a,b**, which allowed us to use more readily available ethyl trifluoroacetate instead of gaseous trifluoroacetonitrile and to increase the yield of the reaction products to 50%.



3a,b

a: $R^1 = R^2 = CH_3$; **b**: $R^1 + R^2 = (CH_2)_5$

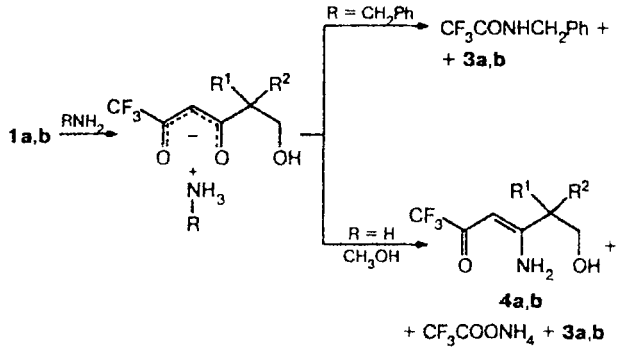
Because tetrahydropyranones **1a,b** are cyclic hemiketals of the corresponding β-hydroxy-1,3-diketones, it is reasonable to suggest that in the reactions with *N*-nucleophiles these compounds will behave analogously to the previously described unsymmetrical fluorine-containing 1,3-diketones, which react with ammonia and amines at the carbonyl group of the nonfluorinated substituent[3] and give pyrazoles[4] and Δ^2-isoxazolines[5] in the reactions with hydrazine and hydroxylamine, respectively. We studied the reactions of tetrahydropyranones **1a,b** with ammonia, benzylamine, hydrazine, and hydroxylamine and found that the reactions of the compounds under consideration with *N*-nucleophiles are accompanied by cleavage of the tetrahydropyranone ring and occur at the β-diketone fragment to form analogous products containing hydroxylalkyl groups.

When tetrahydropyranones **1a,b** were treated with a methanol solution of ammonia at room temperature,

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 6, pp. 1201—1205, June, 1998.

1066-5285/98/4706-1170 $20.00 © 1998 Plenum Publishing Corporation

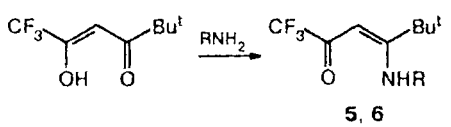
hydroxyaminoenones **4a,b** were isolated in yields of no more than 70% due to partial decomposition of compounds **1a,b** to corresponding β-hydroxyketones **3a,b** and CF_3COONH_4. In an aqueous medium, this direction of the reaction predominated and the yields of compounds **4a,b** decreased to 20—25%. The reaction of tetrahydropyranones **1a,b** with benzylamine afforded *N*-benzyltrifluoroacetamide and β-hydroxyketones **3a,b** regardless of the nature of the solvent (methanol or benzene).



a: $R^1 = R^2 = Me$; **b**: $R^1 + R^2 = (CH_2)_5$

Evidently, at the first stage of the reaction, ammonia and benzylamine act as bases and convert tetrahydropyranones **1a,b** into the corresponding acyclic salts of β-hydroxyhexane-2,6-diones,[6] which then react with excess amine at both electrophilic centers. It should be noted that in a methanol solution ammonia attacks predominantly the carbon atom of the carbonyl group, which is not bonded to the CF_3 group, to give compounds **4a,b**, while benzylamine reacts at the trifluoroacetyl fragment to form *N*-benzyltrifluoroacetamide.

It should be noted that pivaloyltrifluoroacetone, which is related to compounds **1a,b**, is prone to decomposition under the action of amines to a lesser extent. Thus, boiling of pivaloyltrifluoroacetone in aqueous ammonia gave 4-amino-5,5-dimethyl-1,1,1-trifluoro-3-hexen-2-one (**5**) in 66% yield, and boiling with benzylamine afforded 4-benzylamino-5,5-dimethyl-1,1,1-trifluoro-3-hexen-2-one (**6**) in 63% yield.



5, **6**

R = H (**5**), R = CH_2Ph (**6**)

In these cases, even the bulky *tert*-butyl group does not change the direction of the nucleophilic attack, and the reactions with amines occur at the sterically hindered carbonyl group. However, taking into account the yields of products **5** and **6**, in these cases the alternative attack on the carbonyl carbon atom of the CF_3CO group must not be ruled out.

Hydroxyaminoenones **4a,b** are isomeric to compounds **2a,b**, which have been prepared previously from trifluoroacetonitrile and β-hydroxyketones **3a,b**,[2] and differ substantially from **2a,b** in the spectral characteristics. At the same time, the ^1H NMR spectra of compounds **4a,b** and **5** have much in common. Thus, the ^1H NMR spectrum of compound **4a** has singlets of the *gem*-dimethyl and methylene groups at δ 1.23 and 3.66, respectively, a broadened singlet of the hydroxyl group at δ 3.06, and a doublet of the vinyl proton (J = 1.6 Hz) at δ 5.46. In aminoenone **5**, this proton is observed in the form of a doublet (J = 2.1 Hz) at δ 5.52, and in aminoenone **6**, in which one hydrogen atom of the NH_2 group is replaced by the benzyl fragment, this proton occurs as a singlet at δ 5.75. These data suggest that in compounds **4a,b** and **5**, the splitting of the signal of the vinyl proton into a doublet is associated with long-range spin-spin interaction with the proton of the NH group, which is not involved in intramolecular hydrogen bonding with the carbonyl oxygen atom. The signals of the protons of the amino group of compound **4a** occur as two significantly broadened singlets at δ 7.5 (the hydrogen atom involved in intramolecular hydrogen bonding with the oxygen atom of the OH group) and 10.5 (the hydrogen atom involved in intramolecular hydrogen bonding with the oxygen atom of the C=O group) (Table 1), which suggests that the double bond has the *Z* configuration. The presence of two signals of the nonequivalent protons of the amino group is indicative of a stronger intramolecular hydrogen bond in the aminoenone fragment of compound **4a** compared to that in compound **2a**, in which the hydrogen atoms of the NH_2 group are observed in the form of a broadened two-proton singlet at δ 7.3.[2]

Treatment of tetrahydropyranone **1a** with an excess of hydrazine hydrate at room temperature or upon heating afforded a mixture of 5-hydroxy-Δ^2-pyrazoline **7** and pyrazole **8a** in a ratio of 2 : 1, which was determined based on the ^1H NMR spectral data. Boiling of this mixture in alcohol in the presence of concentrated HCl gave pyrazole **8a** without an admixture of pyrazoline **7**, which indicates that the latter compound readily undergoes dehydration. The reaction of tetrahydropyranone **1b** with hydrazine hydrate yielded only pyrazole **8b**. Most probably, conversion of compounds **1a,b** into pyrazoles **8a,b** proceeds through initial formation of hydrazones at the carbonyl group that is not bonded to the trifluoromethyl substituent followed by cyclization at the carbonyl carbon atom of the CF_3CO group to form the corresponding pyrazolines, which then undergo dehydration to give pyrazoles **8a,b**.

The ^1H NMR spectrum of pyrazole **8a** has three singlets at δ 1.32, 3.64, and 6.32, which correspond to the *gem*-dimethyl group, the methylene group, and the hydrogen atom of the pyrazole ring, respectively. The signals of the labile protons of the OH and NH groups are not observed in the ^1H NMR spectrum. In the IR spectrum, these protons are observed at 3075, 3130,

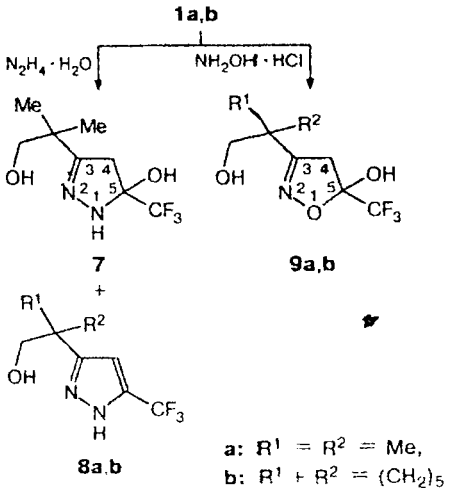
Table 1. Major characteristics of compounds **4a,b**, **5**, **6**, **8a,b**, **9a,b**, **10**, and **11**

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%) C	H	N	^{1}H NMR, δ, *J*/Hz	IR, ν/cm^{-1}
4a	70	75—76	$C_8H_{12}F_3NO_2$	45.68 45.50	5.73 5.73	6.62 6.63	1.23 (s, 6 H, 2 CH_3); 3.06 (br.s, 1 H, OH); 3.66 (s, 2 H, CH_2—O); 5.46 (d, 1 H, =CH, *J* = 1.6); 7.5 (br.s, 1 H, NH); 10.5 (br.s, 1 H, NH)	1545, 1605, 1650, 3210, 3340
4b	59	119—120	$C_{11}H_{16}F_3NO_2$	52.43 52.59	6.69 6.42	5.35 5.57	1.3—2.0 (m, 10 H, $(CH_2)_5$); 1.83 (br.s, 1 H, OH); 3.63 (s, 2 H, CH_2—O); 5.53 (d, 1 H, =CH, *J* = 2.0); 6.6 (br.s, 1 H, NH); 10.7 (br.s, 1 H, NH)	1545, 1600, 1645, 3170, 3350
5	66	93—94	$C_8H_{12}F_3NO$	49.38 49.23	6.05 6.20	7.30 7.18	1.26 (s, 9 H, Bu^t); 5.52 (d, 1 H, =CH, *J* = 2.1); 6.2 (br.s, 1 H, NH); 10.4 (br.s, 1 H, NH)	1545, 1610, 1650, 3170, 3330
6	63	65—66	$C_{15}H_{18}F_3NO$	63.32 63.15	6.20 6.36	4.84 4.91	1.04 (s, 9 H, Bu^t); 3.85 (s, 2 H, CH_2); 5.75 (s, 1 H, =CH); 7.2—7.4 (m, 5 H, C_6H_5)	1505, 1550, 1590, 1630, 3300, 3500
8a	66	125—126	$C_8H_{11}F_3N_2O$	46.37 46.16	5.27 5.33	13.48 13.46	1.32 (s, 6 H, $2CH_3$); 3.64 (s, 2 H, CH_2—O); 6.32 (s, 1 H, =CH)	1510, 1580, 3075, 3130, 3195, 3380
8b	60	104—105	$C_{11}H_{15}F_3N_2O$	52.18[a] 52.27	6.27[a] 6.18	10.29[a] 11.08	1.2—2.1 (m, 10 H, $(CH_2)_5$); 3.54 (s, 2 H, CH_2—O); 6.33 (s, 1 H, =CH)	1505, 1570, 3075, 3130, 3200
9a	65	105—106	$C_8H_{12}F_3NO_3$	42.33 42.30	5.36 5.32	6.11 6.17	1.20 (s, 3 H, CH_3); 1.21 (s, 3 H, CH_3); 3.25 (AB system, Δδ = 0.21, 2 H, CH_2, J_{AB} = 18.5); 3.62 (s, 2 H, CH_2—O)	1620, 3130, 3530, 3610
9b	68	75—76	$C_{11}H_{16}F_3NO_3$	48.90 48.62	6.45 6.12	5.15 5.24	1.2—2.1 (m, 10 H, $(CH_2)_5$); 3.24 (AB system, Δδ = 0.21, 2 H, CH_2, J_{AB} = 18.5); 3.61 (s, 2 H, CH_2—O)	1635, 3270, 3420, 3515
10	77	121—122	$C_8H_{11}F_3N_2$	50.18 50.00	5.93 5.77	14.38 14.58	1.34 (s, 9 H, Bu^t); 5.5 (br.s, 1 H, NH); 6.32 (s, 1 H, =CH)	1505, 1570, 3065, 3120, 3185
11	72	84—85	$C_8H_{12}F_3NO_2$	45.35 45.50	5.86 5.73	6.78 6.63	1.24 (s, 9 H, Bu^t); 3.22 (AB system, Δδ =0.19, 2 H, CH_2, J_{AB} = 18.1); 3.65 (br.s, 1 H, OH)	1630, 3130

[a] The averaged result of four combustion runs.

3195, and 3380 cm^{-1}. Pyrazole **8b** has analogous spectral characteristics. However, we failed to obtain reliable data of elemental analysis for **8b**. In spite of the fact that two samples, which have been twice recrystallized from aqueous alcohol and were obtained in different runs, were analyzed, the averaged results of four combustion runs gave underestimated (by 1%) contents of carbon and nitrogen (Table 1). Apparently, pyrazole **8b** strongly holds water, which is masked by signals of the protons of the cyclohexane ring in the ^{1}H NMR spectrum.

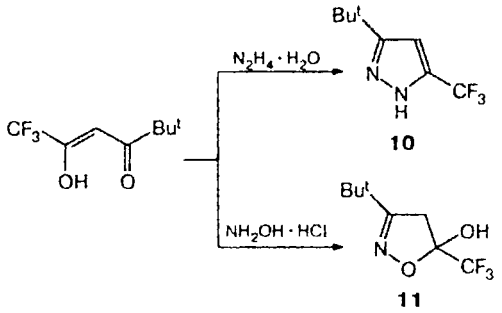
The reaction of tetrahydropyranones **1a,b** with $NH_2OH \cdot HCl$ regioselectively afforded Δ^2-isoxazolines (**9a,b**) in good yield. The formation of these compounds is also evidence in favor of the conclusion that the attack of the *N*-nucleophile occurred preferentially on the carbonyl carbon atom of the nonfluorinated substituent. High stability of compounds **9a,b** to dehydration is



attributable to the strong electron-withdrawing effect of the CF_3 group on the hemiketal hydroxyl group. In pyrazoline **7**, which contains the hemiaminal hydroxyl group, this effect is less pronounced due to which the reactions of hydrazine with fluorine-containing 1,3-diketones yielded predominantly pyrazoles.[4]

The ^{1}H NMR spectrum of isoxazoline **9a** is characterized by the presence of an AB system of the protons of the CH_2 group of the isoxazoline ring with the maximum at δ 3.25 and J_{AB} = 18.2 Hz, a singlet of the protons of the CH_2 group of the alkyl substituent at δ 3.62, and two singlets of the methyl groups at δ 1.20 and 1.21, which are nonequivalent due to the presence of the chiral center in the molecule. The signals of the protons of the hydroxyl groups are not observed in the ^{1}H NMR spectrum. The presence of the hydroxyl groups in molecule **9a** can be judged from the IR spectrum, which shows the absorption bands at 3130, 3530, and 3610 cm^{-1}. Isoxazoline **9b**, which, according to the data of elemental analysis (underestimated C content and overestimated H content) (Table 1), contains some amount of water, has similar spectral characteristics.

With the aim of comparing and making reliable assignment of the signals in the IR and ^{1}H NMR spectra, we prepared 3(5)-*tert*-butyl-5(3)-trifluoromethylpyrazole (**10**) and 3-*tert*-butyl-5-hydroxy-5-trifluoromethyl-Δ^2-isoxazoline (**11**), which are the closest analogs of pyrazoles **8a,b** and isoxazolines **9a,b**, respectively, from pivaloylthrifluoroacetone, hydrazine hydrate, and hydroxylamine hydrochloride. The spectral characteristics of the synthesized compounds agree well with the data reported for compounds **8a,b** and **9a,b** (Table 1).



To summarize, the results of this work allow conclusions that tetrahydropyranones **1a,b** react with *N*-nucleophiles analogously to unsymmetrical fluorine-containing β-diketones and can be used for preparing various heterocyclic compounds containing trifluoromethyl and hydroxylalkyl substituents owing to which these heterocycles, in turn, can be used for constructing more complex systems.

Experimental

The IR spectra were recorded on an IKS-29 instrument as Nujol mulls. The ^{1}H NMR spectra were measured on a Tesla BS-567A spectrometer operating at 100 MHZ in $CDCl_3$ with Me_4Si as the internal standard.

The yields, melting points, data of elemental analysis, and ^{1}H NMR and IR spectra of the synthesized compounds are given in Table 1.

2-Hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyranone (1a) and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranone (1b). Ethyl trifluoroacetate (7.2 mL, 8.5 g, 0.06 mol) was added dropwise to a suspension of LiH (1.2 g, 0.15 mol) in hexane (50 mL). Then β-hydroxyketone **3a** (7.0 g, 0.06 mol) was added dropwise upon heating during 15 min. The reaction mixture was refluxed with stirring for 3 h and then was decomposed with dilute (1 : 3) hydrochloric acid upon cooling. After the usual workup of the organic layer and evaporation of the solvent, the residue was crystallized out. The yield was 6.4 g (50%), m.p. 104—105 °C (hexane). Tetrahydropyranone **1b** was prepared in a similar manner. The yield was 44%, m.p. 84—85 °C. The spectral data for compounds **1a,b** were reported previously.[2]

4-Amino-1,1,1-trifluoro-6-hydroxy-5,5-dimethylhex-3*Z*-en-2-one (4a) and 4-amino-1,1,1-trifluoro-6-hydroxy-5,5-pentamethylenehex-3*Z*-en-1-one (4b). A saturated ammonia solution in methanol (5 mL) was added to tetrahydropyranone **1a** (0.5 g, 2.4 mmol). The reaction mixture was kept at ~20 °C for 1 day. Methanol was evaporated, and the crystalline precipitate was dissolved in ether. Undissolved CF_3COONH_4 was filtered off, and ether was distilled off. The crystals of compound **4a** were recrystallized from aqueous alcohol. The yield was 0.35 g. Hydroxyaminoenone **4b** was prepared from tetrahydropyranone **1b** in a similar manner.

Treatment of tetrahydropyranones **1a,b** with benzylamine in methanol or benzene afforded *N*-benzyltrifluoroacetamide. The yield was 62%, m.p. 74—75 °C (hexane) (Ref. 7: m.p. 74.5—75.5 °C). IR, ν/cm^{-1}: 1500, 1560, 1610, 1700, 3120, 3320. ^{1}H NMR, δ: 4.50 (d, 2 H, CH_2, J = 5.9 Hz); 6.70 (br.s, 1 H, NH); 7.33 (m, 5 H, C_6H_5).

4-Amino-1,1,1-trifluoro-5,5-dimethylhex-3*Z*-en-2-one (5). A 25% aqueous solution of ammonia (10 mL) was added to pivaloyltrifluoroacetone (1.0 mL, 1.12 g, 5.7 mol). The reaction mixture was refluxed for 2 h. The crystals that precipitated upon cooling were recrystallized from aqueous alcohol. The yield was 0.73 g.

4-Benzylamino-1,1,1-trifluoro-5,5-dimethylhex-3*Z*-en-2-one (6). Benzylamine (0.3 mL, 0.29 g, 2.8 mmol) was added to a solution of pivaloyltrifluoroacetone (0.5 mL, 0.56 g, 2.8 mmol) in methanol (5 mL). The reaction mixture was kept at ~20 °C for 1 day. After evaporation of the solvent, the residue was recrystallized from aqueous alcohol. The yield was 0.48 g.

3(5)-(2-Hydroxy-1,1-dimethylethyl)-5(3)-trifluoromethylpyrazole (8a), 3(5)-(2-hydroxy-1,1-pentamethyleneethyl)-5(3)-trifluoromethylpyrazole (8b), and 3(5)-*tert*-butyl-5(3)-trifluoromethylpyrazole (10). A solution of hydrazine hydrate (0.3 mL, 0.31 g, 3.9 mmol) in ethanol (5 mL) and one drop of concentrated HCl were added to a solution of tetrahydropyranone **1a** (0.5 g, 2.4 mmol) in ethanol (5 mL). The reaction mixture was refluxed for 1 h. After evaporation of the solvent, a mixture (2 : 1) of pyrazoline **7** and pyrazole **8a** was obtained in a yield of 0.35 g. ^{1}H NMR of pyrazoline **7**, δ: 1.11 (s, 3 H, CH_3); 1.14 (s, 3 H, CH_3); 2.97 (AB system, Δδ = 0.29, 2 H, CH_2, J_{AB} = 17.9 Hz); 3.58 (s, 2 H, CH_2—O); 4.8 (br.s, 2 H, 2 OH); 6.0 (br.s, 1 H, NH). Boiling of a solution (0.3 g) of the mixture of compounds **7** and **8a** obtained in ethanol (3 mL) with five drops of concentrated HCl during 5 h afforded (after recrystallization from water) pyrazole **8a**. Pyrazoles **8b** and **10** were prepared in a similar manner without additional boiling in the presence of HCl.

5-Hydroxy-3-(2-hydroxy-1,1-dimethylethyl)-5-trifluoromethyl-Δ^2-isoxazoline (9a), 5-hydroxy-3-(2-hydroxy-1,1-pentamethyleneethyl)-5-trifluoromethyl-Δ^2-isoxazoline (9b), and 3-*tert*-butyl-5-hydroxy-5-trifluoromethyl-Δ^2-isoxazoline (11). A 0.5 *N* solution of hydrochloric acid (5 mL), a solution of hydroxylamine hydrochloride (0.35 g, 5.0 mmol) in water (4 mL), and ethanol (4 mL) were added to tetrahydropyranone **1a** (0.5 g, 2.4 mmol) until the homogeneous solution was formed. The reaction mixture was refluxed for 1 h and concentrated. Then water (10 mL) was added, and the mixture was extracted with ether. The ethereal solution was dried with anhydrous Na_2SO_4. Ether was evaporated, and the residue was washed with hexane. The yield was 0.35 g. Isoxazolines **9b** and **11** were prepared in a similar manner.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-33373).

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Received November 11, 1997;
in revised form January 8, 1998