Oxidation of *N*-acyl-2-(cycloalk-1-enyl)anilines with ozone and hydrogen peroxide

R. R. Gataullin,[a]★ M. F. Nasyrov,[c] D. I. D´yachenko,[b] A. A. Fatykhov,[a] O. V. Shitikova,[a] L. V. Spirikhin,[a] and I. B. Abdrakhmanov[a]

[a]Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 69 prosp. Oktyabrya, 450054 Ufa, Russian Federation. Fax: +7 (347 2) 35 6066. E-mail: chemorg@anrb.ru
[b]Bashkir State Agricultural University, 34 ul. 50-letiya Oktyabrya, 450003 Ufa, Russian Federation
[c]Ufa State University of Petroleum Technology, 1 ul. Kosmonavtov, 450062 Ufa, Russian Federation

Treatment of the ozonization products from *N*-acetyl- or 2-methyl-*N*-trifluoroacetyl-6-(cyclopent-1-enyl)anilines with $NaBH_4$ gives 6-methyl-2-tetrahydropyranylaniline. When treated with Me_2S, the ozonization products yield the corresponding oxoaldehyde dimethyl acetals. The oxidation of *N*-acetyl-2-(cyclopent-1-enyl)- or -(cyclohex-1-enyl)anilines with H_2O_2 in HCOOH affords ω-(2-acetamidophenyl)-5-oxopentanoic or -6-oxohexanoic acid, respectively. The reaction of *N*-acetyl-2-(cyclopent-1-enyl)aniline with H_2O_2 in the presence of Na_2WO_4 and H_3PO_4 gives 3,1-benzooxazine in high yield.

Key words: 2-(cycloalk-1-enyl)anilines, ozonization, oxidation with hydrogen peroxide, dimethyl acetals, 6-methyl-2-(tetrahydropyranyl)aniline, oxo acids, 3,1-benzooxazines.

2-Acyl- or 2-(1-alkoxyalkyl)anilines find use in the synthesis of heterocyclic compounds. For example, benzooxazines[1] or indoles[2] are obtained from 2-acyl-, 2-(1-hydroxyalkyl)-, and 2-(1-methoxyalkyl)anilides. There is a great number of methods for the acylation of aromatic compounds; however, each method has its inherent limitations. Thus, the Friedel—Crafts acylation mostly occurs at the *para*-positions of anilines[3] and is not acceptable for the synthesis of *ortho*-substituted derivatives. In the present work, a method for the synthesis of anilines with functionalized alkyl substituents in the *ortho*-position from 2-(cycloalk-1-enyl)anilines under mild conditions is proposed.

Results and Discussion

Ozonization of anilides **1** [4] or **2** in MeOH followed by treatment with $NaBH_4$ gave tetrahydropyranylaniline **3** in good yield (Scheme 1). Obviously, an intermediate diol undergoes cyclodehydration into pyran.[5]

Treatment of the ozonization products from cyclopentenes **1** or **2** with Me_2S yields dimethyl acetals **4** and **5**, respectively. The reactions of anilides **1** or **6** [6] with hydrogen peroxide in HCOOH at 40 °C gives oxo acids **7** and **8** in good yields. The oxidation of anilide **9** with H_2O_2 in H_3PO_4 in the presence of Na_2WO_4 affords 3,1-benzooxazine **10** in high yield, while its isomer **11** changes, under the same conditions, to epoxide **12** (Scheme 2).

The reaction mixture also contains its C(1´)-epimer (~10%); unfortunately, it was not isolated in the individual state.

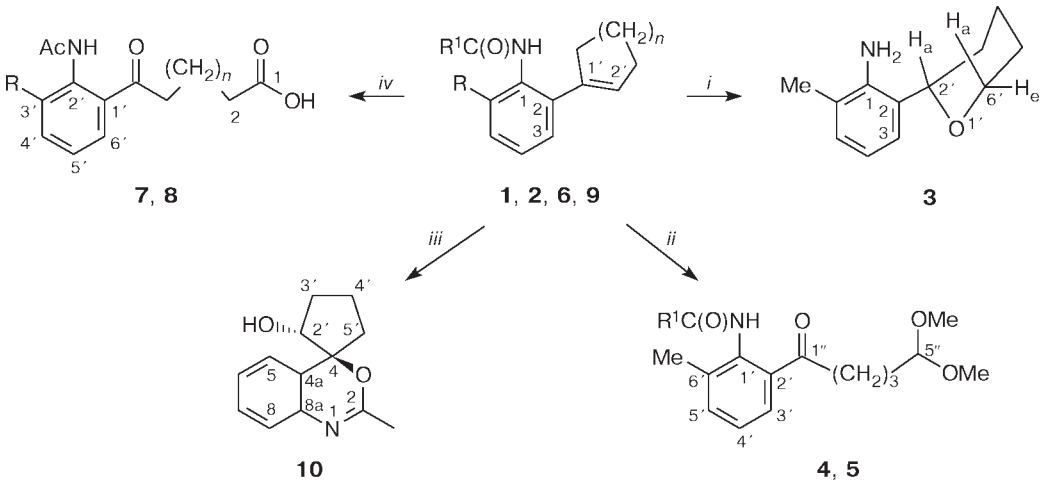
The structures of the compounds obtained were unambiguously determined from IR and ^1H and ^{13}C NMR spectra and elemental analysis data. Thus, the IR spectrum of aniline **3** shows absorption bands of the NH_2 stretching vibrations at 3368 and 3456 cm^{-1}. The mass spectrum of tetrahydropyranylaniline **3** contains a peak of a molecular ion with *m/z* 191. The ^1H NMR spectrum of compound **3** contains a signal at δ 4.4 (dd, J = 2.0 and 11.1 Hz) of the H(2´) proton, which suggests its axial position (the assignment was done using selective homodecoupling). A signal of the equatorial H_e(6´) proton appears at δ 4.1 (dd, J = 3.2 and 11.4 Hz), whereas a signal of the axial H_a(6´) proton is shifted upfield (δ 3.6, ddd, J = 2.7, 11.1, and −11.4 Hz).

The mass spectra of benzooxazine **10** and epoxide **12** contain a molecular ion peak with *m/z* 217. The ^{13}C NMR (JMOD) spectrum of benzooxazine **10** shows a signal of the C(4) atom at δ 90, which agrees with our previous data.[7] The configuration of the substituent in compound **10** is indicated on the assumption that an intermediate epoxide is formed.[8] In the ^1H NMR spectrum of epoxide **12**, the coupling constants of the H(2´) proton are zero.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 118—121, January, 2002.

1066-5285/02/5101-124 $27.00

Scheme 1

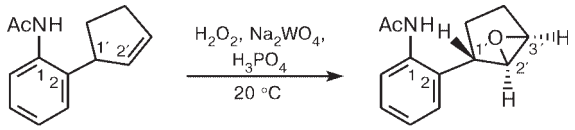


	n	R	R^1		*n*	R	R^1		*n*	R	R^1		*n*	R	R^1
1	1	Me	Me	**4**	—	—	Me	**6**	2	H	Me	**8**	2	H	—
2	1	Me	CF_3	**5**	—	—	CF_3	**7**	1	Me	—	**9**	1	H	Me

Reagents and conditions: *i*. O_3 (1), $NaBH_4$ (2), MeOH, 0 °C; *ii*. O_3 (1), Me_2S (2), MeOH, 0 °C; *iii*. H_2O_2, Na_2WO_4, H_3PO_4, 20 °C; *iv*. H_2O_2, HCOOH, 40 °C.

Comparison with the literature data[9] allowed us to conclude that the H(1′) and H(2′) atoms are *trans* to each other in this compound.

Scheme 2



Thus, the oxidation of *ortho*-(cycloalk-1-enyl)anilines can be used to obtain anilines with various oxygen-containing substituents.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300.13 and 75.47 MHz) in $CDCl_3$ with Me_4Si as the internal standard. IR spectra were recorded on a UR-20 spectrometer. The purity of the reaction products was checked on Silufol UV-254 plates. Mass spectra were recorded on a MX 1320 spectrometer (EI, 70 eV).

The products were purified using silica gel (Chemapol Co.) and $NaBH_4$ and Na_2WO_4 (both high-purity grade). High-purity solvents (CH_2Cl_2 and EtOAc) were distilled over P_2O_5. Commercial hydrogen peroxide was concentrated by removing water. Commercial methanol was distilled over Mg metal. Commercial formic acid was distilled.

2-(Cyclopent-1-en-1-yl)-6-methyl-*N*-trifluoroacetylaniline (2) was prepared by the reaction of 2-(cyclopent-1-en-1-yl)-6-methylaniline with trifluoroacetic anhydride.[4]

6-Methyl-2-(tetrahydropyran-2-yl)aniline (3). Ozone (10 mmol) was passed through a solution of compound **1** or **2** (10 mmol) in 10 mL of MeOH at 0—5 °C. The reaction mixture was kept at this temperature for 5 min, and $NaBH_4$ (0.6 g, 15.8 mmol) was added with stirring; the temperature was no higher than 10—15 °C. The reaction mixture was kept at ~20 °C for 18 h and diluted with a water—AcOH mixture (10 : 1). Then the reaction product was extracted with CH_2Cl_2, and the extracts were washed with 5% $NaHCO_3$ and with a saturated solution of NH_4Cl, and dried over Na_2SO_4. Evaporation of the solvent gave tetrahydropyran **3**; its physicochemical parameters are presented in Tables 1—3.

***N*-[2-(5,5-dimethoxypentanoyl)-6-methylphenyl]acetamide (4) and *N*-[2-(5,5-dimethoxypentanoyl)-6-methylphenyl]-2,2,2-trifluoroacetamide (5).** Ozone (6 mmol) was passed through a solution of compound **1** or **2** (6 mmol) in 10 mL of MeOH at 0—5 °C. The reaction mixture was kept at this temperature for 5 min, and Me_2S (0.5 g, 8 mmol) was added with stirring. The reaction mixture was kept for 48 h, and the solvent was evaporated to give the corresponding acetals **4** or **5** (see Table 1). The product was purified by column chromatography (short column, silica gel (3 g), CH_2Cl_2 as an eluent).

5-(2-Acetamido-3-methylphenyl)-5-oxopentanoic (7) and 6-(2-acetamidophenyl)-6-oxohexanoic (8) acids.[12] Hydrogen peroxide (8.82 mmol) as a 50% solution (0.6 g) was added at 40 °C to solutions of the corresponding amides **1** or **6** (2.32 mmol) in 0.6 mL of 90% HCOOH. The reaction mixture was kept at ~20 °C for 24 h. Product **8** precipitated in the form of crystals. In the case of compound **7**, AcOEt (30 mL) was added, and the resulting solution was washed twice with water and dried with $MgSO_4$. The solvent was evaporated, and the product was recrystallized from acetone.

***N*-Acetyl-2-(cyclopent-1-en-1-yl)aniline (9) and *N*-acetyl-2-(cyclopent-2-en-1-yl)aniline (11)** were obtained according to the known procedures[4,6] by the reaction of *ortho*-(cyclopent-1-en-

Table 1. Yields and physicochemical and spectral parameters of compounds **2**—**5** and **7**—**12**

Compound	Yield (%)	Found / Calculated (%)				Molecular formula	M.p.*/°C	IR, ν/cm^{-1}
		C	H	F	N			
2	87	62.44 62.23	5.25 4.80	21.16 20.71	5.20 4.83	$C_{14}H_{14}F_3NO$	102—104	3200 (NH)
3**	67	75.04 75.39	8.67 8.90	— 	7.02 7.33	$C_{12}H_{17}NO$	—	3368, 3456 (NH_2)
4**	59	65.00 65.51	7.98 7.90	— 	4.63 4.77	$C_{16}H_{23}NO_4$	—	1740, 1665, 1640 (C=O)
5**	66	54.89 55.33	5.60 5.80	16.02 16.41	4.09 4.03	$C_{16}H_{20}F_3NO_4$	—	1750, 1660, 1630 (C=O)
7	62	62.98 63.87	6.33 6.51	— 	5.44 5.32	$C_{14}H_{17}NO_4$	145 (acetone)	1712, 1660, 1645 (C=O)
8	59	63.53 63.87	6.42 6.51	— 	5.21 5.32	$C_{14}H_{17}NO_4$	155 (HCO_2H)	1716, 1664, 1640 (C=O)
9	95	78.02 77.58	7.44 7.51	— 	6.80 6.96	$C_{13}H_{15}NO$	120 (C_6H_6)	3220 (NH)
10	83	71.03 71.87	6.82 6.96	— 	6.76 6.45	$C_{13}H_{15}NO_2$	143 (CH_2Cl_2)	3600 (OH)
11	94	77.23 77.58	7.35 7.51	— 	6.72 6.96	$C_{13}H_{15}NO$	132 (C_6H_6)	3280 (NH)
12	45	72.02 71.87	6.79 6.96	— 	6.65 6.45	$C_{13}H_{15}NO_2$	134—138 (Et_2O)	3280 (NH)

* Solvents used for recrystallization are given in parentheses.
** R_f 0.30 (CH_2Cl_2—MeOH, 95 : 5) for **3**, 0.50 ($CHCl_3$) for **4**, and 0.50 ($CHCl_3$) for **5**.

Table 2. ^{1}H NMR spectra of compounds **2**—**5** and **9**—**12** ($CDCl_3$) and **7** and **8** (DMSO-d_6)

Compound	δ (*J*/Hz)
2	1.83 (m, 2 H, CH_2); 2.02 (s, 3 H, Me); 2.31—2.42 (m, 4 H, 2 CH_2); 5.57 (m, 1 H, CH); 6.93 (t, 1 H, H(4), J = 7.8); 7.02 and 7.12 (both d, 1 H each, H(3), H(5), J = 7.8); 7.63 (br.s, 1 H, NH)
3	1.62—2.28 (m, 6 H, 3 CH_2); 2.21 (s, 3 H, Me); 3.57 (ddd, 1 H, H_a(6′), J_1 = 2.7, J_2 = 11.1, J_3 = –11.4); 4.12 (dd, 1 H, H_e(6′), J_1 = 3.2, J_2 = 11.4); 4.29 (br.s, 2 H, NH_2); 4.35 (dd, 1 H, H(2′), J_1 = 2.0, J_2 = 11.1); 6.66 (t, 1 H, H(4), J = 7.5); 6.91 (d, 1 H, H(3), J = 7.5); 7.02 (d, 1 H, H(5), J = 7.5)
4	1.63 (m, 2 H, CH_2); 1.68 (m, 2 H, CH_2); 2.14 (c, 3 H, Me); 2.20 (s, 3 H, Me); 2.98 (t, 2 H, CH_2, J = 7.0); 3.30 (s, 6 H, 2 Me); 4.39 (t, 1 H, $CH(OMe)_2$, J = 5.5); 6.71—7.65 (m, 3 H, Ar); 8.19 (s, 1 H, NH)
5	1.58—1.72 (m, 4 H, 2 CH_2); 2.34 (s, 3 H, Me); 3.00 (t, 2 H, CH_2, J = 7.0); 3.34 (s, 6 H, 2 Me); 4.37 (t, 1 H, $CH(OMe)_2$, J = 5.5); 7.25 (t, 1 H, H(4′), J = 7.6); 7.42 (d, 1 H, H(3′), J = 7.8); 7.70 (d, 1 H, H(5′), J = 8.0); 10.51 (s, 1 H, NH)
7	2.50—2.58 (m, 2 H, CH_2); 2.74 (s, 3 H, Me); 2.88 (s, 3 H, Me); 3.02 (t, 2 H, CH_2, J = 7.4); 3.60 (t, 2 H, CH_2, J = 7.1); 7.91 (t, 1 H, H(5′), J = 7.6); 8.01 (d, 2 H, H(4′), H(6′), J = 7.6); 10.20 (s, 1 H, COOH)
8	1.10—1.21 (m, 4 H, 2 CH_2); 1.57 (s, 3 H, Me); 1.80 (t, 2 H, CH_2, J = 6.6); 2.64 (t, 2 H, CH_2, J = 6.6); 6.71 (t, 1 H, H(4′), J = 7.8); 7.10 (t, 1 H, H(5′), J = 7.8); 7.45 (d, 1 H, H(6′), J = 8.4); 7.80 (d, 1 H, H(3′), J = 8.4); 10.65 (s, 1 H, COOH)
9	1.89—2.01 (m, 2 H, CH_2); 2.04 (s, 3 H, Me); 2.40—2.53 (m, 2 H, CH_2); 2.51—2.64 (m, 2 H, CH_2); 5.80 (br.s, 1 H, C=CH); 6.97 (t, 1 H, H(5), J = 7.7); 7.10 (m, 2 H, H(4), H(6)); 7.55 (d, 1 H, H(3), J = 8.0); 8.03 (br.s, 1 H, NH)
10	1.70—2.01 (m, 2 H, CH_2); 2.03 (s, 3 H, Me); 2.08—2.21 (m, 2 H, CH_2); 2.35—2.50 (m, 2 H, CH_2); 2.73 (br.s, 1 H, OH); 4.11 (d, 1 H, CH, J = 4.6); 6.96 (d, 1 H, Ar, J = 7.6); 7.10—7.33 (m, 3 H, Ar)
11	1.70 (m, 2 H, CH_2); 2.05 (s, 3 H, Me); 2.42—2.53 (m, 2 H, CH_2); 3.71 (m, 1 H, CH); 4.02 (s, 1 H, NH); 5.83—6.01 (m, 2 H, HC=CH); 7.04—7.44 (m, 4 H, Ar)
12	1.41—1.83 (m, 4 H, 2 CH_2); 2.11 (s, 3 H, Me); 3.20 (m, 1 H, H(1′)); 3.52 and 3.59 (both s, 1 H each, H(3′), H(2′)); 6.90—7.20 (m, 4 H, Ar); 8.13 (s, 1 H, NH)

Table 3. ^{13}C NMR spectra of compounds **2**—**5**, **9**, **10**, and **12** ($CDCl_3$) and **7** and **8** (DMSO-d_6) and mass spectra of compounds **3**, **7**, **8**, **10**, and **12**

Compound	δ (*J*/Hz)	$[M]^+$, *m/z*
2	18.2 (Me); 23.5, 33.9, 35.4 (3 CH_2); 117.6 (CF_3); 124.5 (C(4)); 128.6 (C(2)); 130.5 (C(6)); 131.2 (C(3)); 132.6 (C(5)); 132.7 (C(2′)); 139.1 (C(1′)); 141.9 (C(1)); 154.7 (C=O)	—
3	17.1 (Me); 23.4, 25.6, 29.3 (C(5′)), (C(4′)), (C(3′)); 68.5 (C(6′)); 79.8 (C(2′)); 117.2 (C(5)); 122.5 (C(3)); 124.7 (C(4)); 125.3 (C(2)); 129.4 (C(6)); 143.1 (C(1))	191
4	18.8, 20.9 (2 Me); 19.9, 31.6, 40.5 (3 CH_2); 52.8 $(OMe)_2$; 104.1 ($CH(OMe)_2$); 125.3 (C(5′)); 126.4 (C(6′)); 131.7 (C(3′)); 134.7 (C(1′)); 134.9 (C(4′)); 135.9 (C(2′)); 169.7 (NHC=O); 204.3 (PhC=O)	—
5	18.7 (Me); 19.2, 31.6, 39.8 (3 CH_2); 52.7 $(OMe)_2$; 104.1 ($CH(OMe)_2$); 116.0 (q, CF_3, J = 280); 126.8 (C(5′)); 127.3 (C(6′)); 130.8 (C(3′)); 132.4 (C(1′)); 135.7 (C(4′)); 135.9 (C(2′)); 155.0 (q, C=O, J = 37); 203.8 (PhC=O)	—
7	17.7, 22.7 (2 Me), 19.0, 39.5, 32.7 (3 CH_2); 124.8 (C(5′)), 125.6 (C(6′)), 132.5 (C(3′)), 132.8 (C(1′)), 134.7 (C(4′)), 137.4 (C(2′)); 168.3 (NHC=O); 174.0 (COOH); 202.7 (PhC=O)	263
8	24.6 (Me); 23.4, 24.0, 33.5, 39.2 (4 CH_2); 120.8 (C(3′)); 122.9 (C(5′)); 124.5 (C(1′)); 130.5 (C(6′)); 133.7 (C(4′)); 138.9 (C(2′)); 168.7 (NC=O); 174.4 (COOH); 204.3 (PhC=O)	263
9	24.4 (Me); 23.2, 33.7, 36.4 (3 CH_2); 121.7 (C(6)); 124.0 (C(4)); 127.3 (C(2′)); 127.6 (C(3)); 128.7 (C(1′)); 130.1 (C(5)); 134.4 (C(2)); 140.6 (C(1)); 168.2 (C=O)	—
10	21.5 (Me); 20.5, 31.6, 34.7 (3 CH_2); 75.9 (CHOH); 90.0 (C(4)); 123.5 (C(4a)); 123.6 (C(6)); 125.1 (C(7)); 125.8 (C(8)); 129.1 (C(5)); 139.1 (C(8a)); 160.3 (C(2))	217
12	24.5 (Me); 24.0, 27.3 (2 CH_2); 46.4 (C(1′)); 58.5, 60.0 (C(2′), C((3′)); 122.8 (C(6)); 124.4 (C(4)); 127.8 (C(5)); 130.0 (C(2)); 130.9 (C(3)); 136.7 (C(1)); 169.1 (C=O)	217

1-yl)aniline[10] or *ortho*-(cyclopent-2-en-1-yl)aniline[11] (1.6 g, 10 mmol) with Ac_2O (1.3 g, 13 mmol). The products were recrystallized from benzene.

2-Methylspiro[4*H*-benzo[d][1,3]oxazine-4,1′-cyclopentan]-2′-ol (10) and *N*-acetyl-2-(2,3-epoxycyclopent-1-yl)aniline (12). The known procedure[8] was modified. A 50% solution of H_2O_2 (0.34 g, 4.98 mmol) was added to a mixture of amide **9** (or **11**) (0.5 g, 2.48 mmol), a solution of Na_2WO_4 (50 mg, 0.17 mmol) in 0.2 mL of water, and a drop of conc. H_3PO_4 in 5 mL of MeOH. The reaction mixture was kept at 30 °C for 24 h, dissolved in 50 mL of CH_2Cl_2, washed with saturated solutions of Na_2CO_3 and $Na_2S_2O_3$ and with water, and dried with $MgSO_4$. After CH_2Cl_2 was evaporated, benzooxazine **10** began to crystallize on the flask walls. The crystals were recrystallized from Et_2O. Compound **12** was isolated by chromatography on silica gel in benzene.

References

1. *Comprehensive Organic Chemistry*, Ed. D. Barton and W. D. Ollis, Pergamon Press, Oxford—New York—Toronto—Sydney—Paris—Frankfurt, 1979, **9**.
2. M. Kazuyuki, K. Katsunori, T. Katsutoshi, M. Hideto, and I. Takeshi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1261.
3. G. Florence, *Bull. Sci. Pharmacol.*, 1933, **40**, 325.
4. R. R. Gataullin, I. S. Afon´kin, I. V. Pavlova, I. B. Abdrakhmanov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 398 [*Russ. Chem. Bull.*, 1999, **49**, 396 (Engl. Transl.)].
5. V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, 1964, **29**, 123.
6. R. R. Gataullin, I. S. Afon´kin, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 118 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 122].
7. R. R. Gataullin, I. S. Afon´kin, A. A. Fatykhov, L. V. Spirikhin, E. V. Tal´vinskii, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 633 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 659].
8. C. Venturello, E. Alneri, and M. Ricci, *J. Org. Chem.*, 1983, **48**, 3831.
9. B. M. Trost and D. L. Van Vranken, *J. Am. Chem. Soc.*, 1990, **112**, 1261.
10. R. R. Gataullin, T. V. Kazhanova, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 171 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 174].
11. I. B. Abdrakhmanov, V. M. Sharafutdinov, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 2160 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
12. A. F. Plate, A. A. Mel´nikov, T. A. Italinskaya, and R. A. Zelenko, *Zh. Org. Khim.*, 1960, **30**, 1250 [*J. Org. Chem. USSR*, 1960, **30** (Engl. Transl.)].

Received February 15, 2001;
in revised form September 10, 2001