Synthesis of 3-nitropyrid-2(1*H*)-ones from *C*-nitroacetamide and 1,3-dicarbonyl compounds

V. P. Kislyi, A. M. Shestopalov, N. D. Kagramanov, and V. V. Semenov*

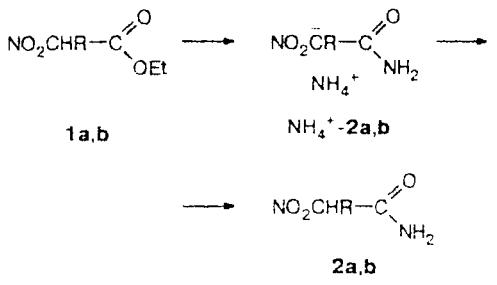
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: 007 (095) 135 5328.

The reaction of nitroacetamide with 1,3-dicarbonyl compounds afforded 3-nitropyrid-2(1*H*)-ones. The chemical reactivities of nitroacetamide and nitroacetohydrazide were compared.

Key words: nitroacetamide, nitroacetohydrazide, 3-nitropyrid-2(1*H*)-ones.

3-Aminopyridones belong to a class of compounds that are of certain interest in terms of biological activity. One of them has been patented as a highly effective cardiotonic,[1] and others were obtained as semi-products in syntheses of preparations that exhibit a high activity against the immunodeficiency virus.[2–5] One of the methods for the synthesis of these compounds is hydrogenation of 3-nitropyridones; therefore, it was interesting to study the reactions of nitroacetamide with 1,3-dicarbonyl compounds.

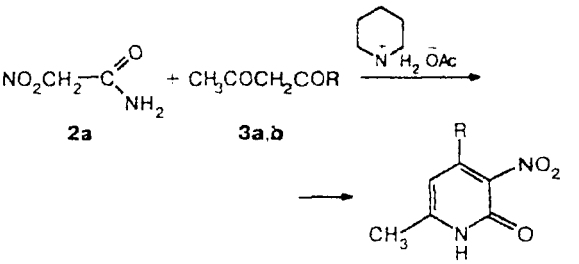
We simplified the procedure[6] for the preparation of nitroacetamide: instead of heating a mixture of ethyl nitroacetate (**1a**) and an ethanolic solution of ammonia in a sealed tube, we developed a method that did not require elevated pressure and temperature. Dissolution of ester **1a** in aqueous ammonia gave the ammonium salt of nitroacetamide (NH_4^+-**2a**), which was then neutralized with HCl; the solution was concentrated and nitroacetamide (**2a**) was extracted with acetone. 2-Nitropropionamide (**2b**) was prepared by a similar procedure from 2-nitropropionate (**1b**).



1a,b NH_4^+-**2a,b** **2a,b**

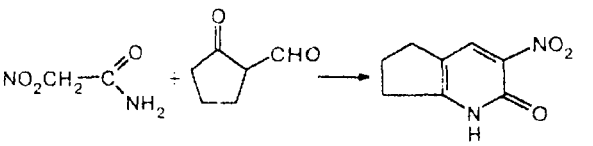
R = H (**a**); CH_3 (**b**)

The reaction of nitroacetamide **2a** with acetylacetone (**3a**) afforded pyridone (**4a**) in 43 % yield. Two isomeric pyridones can be formed in the reaction of amide **2a** with 1,1,1-trifluoroacetylacetone (**3b**) and 2-formylcyclopentanone (**3c**), but only one of the isomers (**4b** or **4c**) was found in the reaction products.



2a **3a,b** **4a,b**, 43%

R = CH_3 (**3a**, **4a**); R = CF_3 (**3b**, **4b**)



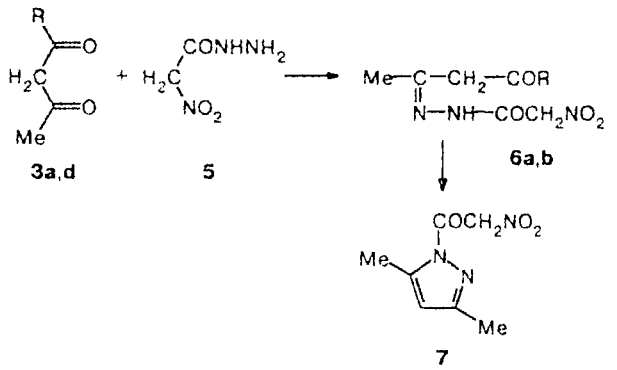
2a **3c** **4c**, 54%

It should be noted that such dicarbonyl compounds as benzoylacetone, tenoyltrifluoroacetone, ethyl acetoacetate, and ethyl-3-aminobut-2-enoate did not react with nitroacetamide under the conditions studied, which may result from a decreased activity of the nitromethylene unit. At the same time, it is known that the above dicarbonyl compounds react with other compounds of similar structure (cyanoacetamide, cyanothioacetamide, malonamide). The decreased activity of the nitromethylene moiety is quite noticeable when one compares the reactions of nitroacetohydrazide (**5**) and cyanoacetohydrazide. The latter is known to react with diketones to form 1-amino-3-cyanopyridones.[7] We have found that the reaction of hydrazide **5** with ethyl acetoacetate (**3d**) only affords the corresponding hydrazones (**6b**), while the intermediate hydrazone (**6a**), which is formed in the reaction with acetylacetone, undergoes

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 559—562, March, 1997.

1066-5285/97/4603-0539 $18.00

cyclization to afford 3,5-dimethyl-1-nitroacetylpyrazole (**7**). Thus, the nucleophilicity of the cyanomethylene anion in cyanoacetohydrazide is stronger than that of the "free" (terminal) amino group, and the nucleophilicity of the nitromethylene anion in nitroacetohydrazide is weaker than that of the "free" amino group.



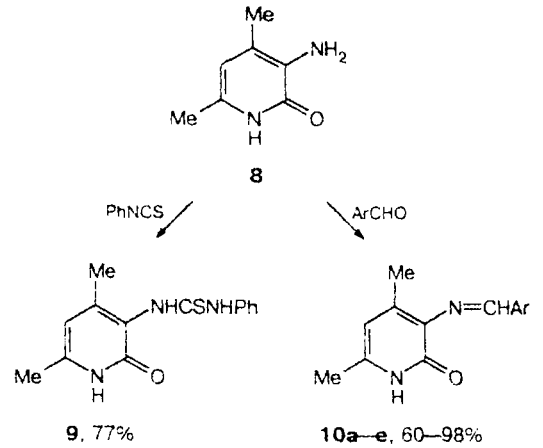
3a,d **5** **6a,b** **7**

R = Me (**3a**, **6a**); OEt (**3d**, **6b**)

The catalytic reduction of nitropyridone **4a** afforded the corresponding aminopyridone (**8**) in 95 % yield.

4a **8**

The study of the properties of the amino group in this compound showed that it is rather reactive: the reaction with phenylisothiocyanate gave the corresponding thiourea, and the Schiff's bases (**10**) were formed in high yields in the reaction with aromatic aldehydes.



9, 77% **10a—e**, 60—98%

Ar = Ph (**10a**); 3,4-$(MeO)_2$Ph (**10b**); 2,4-Cl_2Ph (**10c**); 4-NO_2Ph (**10d**); pyrid-3-yl (**10e**).

Hydrogenation of the latter compounds to give the corresponding (arylmethyl)amines, which are rather close structural analogs of the anti-AIDS preparations described above, are to be published later.

Experimental

^1H and ^{19}F NMR spectra were obtained on an WM-250 instrument at working frequencies of 250.13 MHz and 235.34 MHz, respectively. ^{13}C and ^{14}N spectra were obtained on an AM-300 instrument at working frequencies of 75.47 MHz and 21.69 MHz, using the following internal standards: $SiMe_4$ for ^1H and ^{13}C NMR, CF_3COOH for ^{19}F NMR, and nitromethane for ^{14}N NMR. Unless specified otherwise, NMR spectra were recorded in DMSO-d_6. IR spectra were obtained on a UR-20 instrument (in KBr pellets). Mass spectra were recorded on a Finnigan-Mat instrument (EI, ionizing voltage 70 eV). Ethyl nitroacetate was prepared by the procedure in Ref. 8. The characteristics of products **4a—c** and **8** are given in Table 1, and those of products **10a—e**, in Table 2.

Nitroacetamide (2a). 1. Ethyl nitroacetate (13.3 g, 0.1 mol) was added to concentrated aqueous ammonia (67 mL), and the solution was stirred and kept at 20 °C for 3 days. The aqueous solution was then concentrated, and the solid was filtered off to afford 10.8 g (89 %) of the ammonium salt (NH_4^+-**2a**), ^1H NMR, δ: 4.00—4.50 (s, 4 H, NH_4^+), 5.96 (s, 1 H, CH), 6.65 (s, 1 H, NH), 8.77 (s, 1 H, NH); ^{14}N: −32.8 (NO_2), −359.4 (NH_4^+). IR (cm^{-1}): 1480 (ν(C=N)), 1340 ($\nu_{as}NO_2$), 1170 (ν_sNO_2).

2. The ammonium salt of nitroacetamide was dissolved with light heating in water (50 mL) and neutralized with 10% HCl until acidic reaction. The resulting solution was evaporated, and nitroacetamide was extracted with hot acetone (3×20 mL) from the mixture with ammonium chloride. The acetone was removed on a rotary evaporator, and the residue was crystallized from alcohol to afford 8.36 g (90%) of the product, m.p. 98—99 °C (*cf.* 99—100 °C)[6]. ^1H NMR (Me_2CO-d_6), δ: 5.30 (s, 2 H, CH_2); 7.60 (s, 1 H, NH); 7.82 (s, 1 H, NH). IR (cm^{-1}): 1650 (νCONH), 1570 ($\nu_{as}NO_2$), 1380 (ν_sNO_2). MS, *m/z* (I_{rel} (%)): 104 [M^+] (5), 61 [M^+−CONH+H] (12), 58 [M^+-NO_2] (100), 44 [$M^+-NO_2-CH_2$] (49), 42 [$M^+-NO_2-NH_2$] (20).

2-Nitropropioamide (2b). 1. Ethyl 2-nitropropionate (1.47 g, 0.01 mol) was added to concentrated aqueous ammonia (7 mL), and the solution was stirred and kept for 4 days. The aqueous solution was then concentrated and filtered to afford 1.36 g (91 %) of the ammonium salt of 2-nitropropioamide (NH_4^+-**2b**).

2. The salt NH_4^+-**2b** was treated as described above for amide **2a**. Nitropropioamide **2b** was extracted from the mixture with ammonium chloride with hot acetone (3×15 mL). The acetone was evaporated, and the residue was crystallized from ethanol to afford 1.15 g (90%) of the product, m.p. 85—87 °C. Found (%): C, 30.8; H, 5.2; N, 23.5. $C_3H_6N_2O_3$. Calculated (%): C, 30.5; H, 5.1; N, 23.7. ^1H NMR, δ: 1.70 (d, 3 H, CH_3); 5.42 (q, 1 H, CH); 7.00 (s, 1 H, NH); 7.50 (s, 1 H, NH).

2,6-Dimethyl-3-nitropyrid-2(1*H*)-one (4a). The ammonium salt of nitroacetamide (48 g, 0.397 mol) was dissolved in water (350 mL), and acetylacetone (50 mL, 0.5 mol) and piperidine acetate (20 g, 0.134 mol) were added to the solution. Orange crystals of product **4a** began to form after 3 days. The solution was allowed to stand for two weeks, and the product was then filtered off and washed with water and a small amount of ethanol to yield 24.6 g of **4a**.

Table 1. Characteristics of nitropyridones **4a—c** and aminopyridone **8**

Compound	M.p./°C (solvent)	Molecular formula	Found / Calculated (%) C	H	N	^{1}H NMR, δ (*J*/Hz)	IR, ν/cm^{-1}	MS, [M$^+$]	Yield (%)
4a	262—263	$C_7H_8N_2O_3$	50.1 50.0	4.7 4.8	16.6 16.8	2.18 (d, 3 H, ^4J = 0.4), 2.28 (d, 3 H, ^4J = 0.8), 6.10 (m, 1 H), 12.40 (s, 1 H)	1650 (νCONH), 1520 ($\nu_{as}NO_2$), 1370 (ν_sNO_2)	168	47
4b	227—228 (EtOH)	$C_7H_5F_3N_2O_3$	37.5 37.9	2.1 2.3	12.4 12.6	2.55 (d, 3 H, ^4J = 0.8), 6.45 (q, 1 H, ^4J = 0.8)	1670, 1630 (νCONH), 1540 ($\nu_{as}NO_2$), 1350 (ν_sNO_2)	222	34
4c	210—212 (DMF)	$C_8H_8N_2O_3$	53.0 53.3	4.5 4.5	15.2 15.6	2.10 (m, 2 H), 2.70 (m, 2 H), 2.90 (m, 2 H), ($CH_2CH_2CH_2$), 8.24 (s, 1 H, CH), 12.7 (s, 1 H, NH)	1672 (νCONH), 1592 (νCONH), 1576 ($\nu_{as}NO_2$)	180	54
8	207—208 (DMF)	$C_7H_{10}N_2O$	61.0 60.9	7.4 7.3	20.4 20.3	1.93 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 4.40 (s, 2 H, NH_2), 5.70 (s, 1 H, CH), 11.26 (s, 1 H, NH)	2900—3440 (νNH), 1630, 1600 (νCONH)	138	88

Table 2. Characteristics of Schiff's bases **10a—e**

Compound	M.p. /°C	Molecular formula	Found / Calculated (%) C	H	N	^{1}H NMR (δ)	IR, ν/cm^{-1}	MS, [M$^+$]	Yield (%)
10a	165—167	$C_{14}H_{14}N_2O$	74.5 74.3	6.4 6.2	12.1 12.4	2.17 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 6.00 (s, 1 H, CH), 7.50—8.00 (m, 5 H, arom.), 9.70 (s, 1 H, CH=N), 11.50 (s, 1 H, NH)	2800 (NH), 1650 (CONH), 1620 (CONH)	226	75
10b	225—227 (decomp.)	$C_{16}H_{18}N_2O_3$	67.0 67.1	6.2 6.3	9.9 9.8	2.18 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.00 (s, 3 H, CH), 7.00—7.60 (m, 3 H, arom.), 9.90 (s, 1 H, CH=N), 11.50 (s, 1 H, NH)	2800 (NH), 1640 (CONH), 1630 (CONH)	286	60
10c	300 (subl.)	$C_{14}H_{12}Cl_2N_2O$	56.6 56.9	4.3 4.1	9.4 9.5	2.19 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 6.10 (s, 1 H, CH), 7.50—8.20 (m, 3 H, arom.), 10.10 (s, 1 H, CH=N), 11.80 (s, 1 H, NH)	2800 (NH), 1645 (CONH), 1625 (CONH)	294	95
10d	320—323 (decomp.)	$C_{14}H_{13}N_3O_3$	61.6 62.0	4.7 4.8	15.3 15.5	2.20 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 6.10 (s, 1 H, CH), 8.00—8.40 (m, 4 H, arom.), 9.80 (s, 1 H, CH=N), 11.80 (s, 1 H, NH)	2800 (NH), 1650 (CONH) 1620 (CONH), 1530 ($\nu_{as}NO_2$), 1350 (ν_sNO_2)	271	98
10e	230 (decomp.)	$C_{13}H_{13}N_3O$	68.2 68.7	5.5 5.8	18.2 18.5	2.20 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 6.05 (s, 1 H, CH), 7.50—9.70 (m, 5 H, arom.), 11.80 (s, 1 H, NH)	2800 (NH), 1620 (CONH)	227	71

6-Methyl-3-nitro-4-trifluoromethylpyrid-2(1*H*)-one (4b). Piperidine acetate (5 g, 33 mmol) was added to a solution of 1,1,1-trifluoroacetylacetone (1.12 g, 0.01 mol) and nitroacetamide (1.22 g, 0.011 mol) in water (12 mL), and the mixture was kept for 3 days at 20 °C. The solution was then evaporated, and the residue was crystallized from ethanol to yield 0.61 g of the product.

3-Nitro-5,6-trimethylpyrid-2(1*H*)-one (4c). Piperidine acetate (5 g, 33 mmol) was added to a solution of 2-formylcyclopentanone (3.08 g, 0.02 mol) and nitroacetamide (2.43 g, 0.02 mol) in ethanol (15 mL), and the mixture was kept for 1 day. The reaction mixture was then concentrated and poured into water. The residue was dissolved in ethanol, the solution was passed through silica gel, the ethanol was evaporated, and the product was crystallized from DMF to yield 2.4 g of **4c**.

Potassium salt of 2-nitroacetohydrazide (K-5). A solution of ethyl nitroacetate (3.3 g, 0.025 mol) and hydrazine hydrate (3.7 g, 0.074 mol) in water (20 mL) was kept for 1 day. After that, KOH (1.4 g, 0.025 mol) was added to the solution, and the solution was concentrated to 1/5 of the initial volume. The precipitate that formed was filtered off to yield 3.1 g (96 %) of the product, ^{1}H NMR, δ: 4.00—4.50 (br.s, 2 H, NH_2), 5.96 (s, 1 H, CH), 10.06 (s, 1 H, NH).

Ethyl 3-(nitroacetylhydrazono)butanoate (6b). AcOH (0.12 mL, 2 mmol) was added to a solution of the potassium salt of nitroacetohydrazide (0.31 g, 2 mmol) and ethyl acetoacetate (0.26 mL, 2 mmol) in water (3 mL). After ~1 min, the precipitate that formed was filtered off to yield 393 mg (85 %) of **6b**, m.p. 93—94 °C. Found (%): C, 41.4; H, 5.5; N, 18.2. $C_8H_{13}N_3O_5$. Calculated (%): C, 41.6; H, 5.7; N, 18.2. A mixture of *Z*- and *E*-isomers (in a 2.2 : 1 ratio) was observed in the ^{1}H NMR spectrum. The signals for CH_3(Et), CH_3(C=N), CH_2(C=N), CH_2(Et), CH_2NO_2, and NHCO, respectively, are given (δ). The main isomer (*Z*): 1.20 (t, 3 H), 1.90 (s, 3 H), 3.30 (s, 2 H), 4.15 (q, 2 H), 5.70 (s, 2 H), 11.00 (s, 1 H); the minor isomer (*E*): 1.20 (t, 3 H), 1.95 (s, 3 H), 3.40 (s, 2 H), 4.15 (q, 2 H), 5.45 (s, 2 H), 10.80 (s, 1 H). IR (cm^{-1}): 3200, 3060 (ν_{val}NH), 1725 (νCOO), 1680 (νCONH), 1560 ($\nu_{as}NO_2$), 1350 (ν_sNO_2). MS, *m/z* (I_{rel} (%)): 231 [M^+] (3), 185 [M^+-NO_2] (33), 158 [$M^+-COOEt$] (9), 144 [$M^+-COCH_2NO_2+H$] (8), 111 [$M^+-NO_2-COOEt-H$] (41), 98 [$M^+-CH_2NO_2-COOEt$] (51).

3,5-Dimethyl-1-nitroacetylpyrazole (7). AcOH (0.12 mL, 2 mmol) was added to a solution of potassium salt of nitroacetohydrazide **K-5** (0.31 g, 2 mmol) and acetylacetone ((0.2 mL, 2 mmol) in water (2.5 mL). After 1 day, white crystals were filtered off to yield 50 mg (13.6 %) of **7**. Found (%): C, 45.9; H, 4.8; N, 22.9. $C_7H_9N_3O_3$. Calculated (%): C, 45.9; H, 5.0; N, 22.9. ^{1}H NMR (Me_2CO-d_6), δ: 2.05 (s, 3 H, CH_3); 2.20 (s, 3 H, CH_3); 5.05 (s, 2 H, CH_2NO_2); 5.80 (s, 1 H, CH). MS, *m/z* (I_{rel} (%)): 183 [M^+] (14), 109 [M^+-NO_2-CO] (17), 95 [$M^+-COCH_2NO_2$] (100), 81 [$M^+-COCH_2NO_2-CH_2$] (8).

3-Amino-4,6-dimethylpyrid-2(1*H*)-one (8). A solution of pyridone (**4a**) (5.8 g, 34.5 mmol) and 2% Pd/C (0.75 g) in DMF (25 mL) was placed into an autoclave. The hydrogenation was carried out at 60 °C and 40 atm. of H_2 for 3 h. The solution was then cooled, and the product was filtered off and crystallized from DMF to yield 4.2 g of compound **8**.

***N*-(4,6-Dimethyl-2-oxo(1*H*)-pyrid-3-yl)-*N'*-phenylthiourea (9).** Phenylisothiocyanate (946 mg, 5 mmol) was added to a solution of aminopyridone **8** (690.8 mg, 5 mmol) in acetonitrile (10 mL). After one day, the acetonitrile was evaporated, and the residue was crystallized from ethanol to yield 1.05 g (77 %) of **9**, m.p. 160 °C. Found (%): C, 61.8; H, 5.3; N, 15.5. $C_{14}H_{15}N_3OS$. Calculated (%): C, 61.5; H, 5.5; N, 15.4. MS, *m/z* (I_{rel} (%)): 273 [M^+] (5). ^{1}H NMR (Me_2CO-d_6), δ: 2.00 (s, 3 H, CH_3); 2.15 (s, 3 H, CH_3); 5.80 (s, 1 H, CH); 7.00—8.50 (m, 5 H, arom); 8.50 (s, 1 H, NH); 11.70 (s, 1 H, NH).

Preparation of Schiff's bases from aminopyridone (8). General procedure. An aldehyde (5.5 mmol) was added to a solution of amine **8** (5.0 mmol) in DMF (3 mL), and then 3 or 4 drops of acetic acid were added to the solution. After some time, the product was filtered off.

3-(Benzylidenamino)-4,6-dimethylpyrid-2(1*H*)-one (10a) was synthesized from **8** (704 mg, 5.1 mmol) and benzaldehyde (811 mg, 7.65 mmol). The yield was 865 mg.

3-(3,4-Dimethoxybenzylidenamino)-4,6-dimethylpyrid-2(1*H*)-one (10b) was synthesized from **8** (683.9 mg, 4.95 mmol) and 3,4-dimethoxybenzaldehyde (1.64 g, 9.9 mmol). The yield was 850.4 mg.

3-(2,4-Dichlorobenzylidenamino)-4,6-dimethylpyrid-2(1*H*)-one (10c) was synthesized from **8** (690.8 mg, 5 mmol) and 2,4-dichlorobenzaldehyde (1.14 g, 6.5 mmol). The yield was 1.4 g.

4,6-Dimethyl-3-(4-nitrobenzylidenamino)pyrid-2(1*H*)-one (10d) was synthesized from **8** (690.7 mg, 5 mmol) and 4-nitrobenzaldehyde (831 mg, 5.5 mmol). The yield was 1.33 g.

4,6-Dimethyl-3-(pyrid-4-ylmethylenamino)pyrid-2(1*H*)-one (10e) was synthesized from **8** (680.1 mg, 4.95 mmol) and pyridine-3-carboxaldehyde (769 mg, 7.43 mmol). The yield was 799 mg.

References

1. P. S. Moline, Span. ES 512599; *Chem. Abstrs.*, 1984, **100**, 174671.
2. J. M. Hoffman, J. S. Wai, C. M. Thomas, R. B. Levin, J. A. O'Brien, and M. E. Goldman, *J. Med. Chem.*, 1992, **35**, 3784.
3. W. S. Saari, J. S. Wai, T. E. Fisher, C. M. Thomas, J. M. Hoffman, C. Rooney, A. M. Smith, J. H. Jones, D. L. Bamberger, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, and P. S. Anderson, *J. Med. Chem.*, 1992, **35**, 3792.
4. J. S. Wai, T. Williams, D. L. Bamberger, T. E. Fisher, J. M. Hoffman, R. J. Hudkosky, S. C. MacTough, C. S. Rooney, W. S. Saari, C. M. Thomas, M. E. Goldman, J. A. O'Brien, E. A. Emini, J. H. Nunberg, J. C. Quintero, W. A. Schleif, and P. S. Anderson, *J. Med. Chem.*, 1993, **36**, 249.
5. J. M. Hoffman, A. M. Smith, C. S. Rooney, T. E. Fisher, J. S. Wai, C. M. Thomas, D. L. Bamberger, J. L. Barnes, T. M. Wiliams, J. H. Jones, B. D. Olson, J. A. O'Brien, M. E. Goldman, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, and P. S. Anderson, *J. Med. Chem.*, 1993, **36**, 953.
6. S. K. Brownstein, *J. Org. Chem.*, 1958, **23**, 113.
7. P. C. Phadke and D. W. Rangnekar, *Synthesis.*, 1986, 860.
8. V. P. Kislyi, A. L. Laikhter, B. I. Ugrak, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 76 [*Russ. Chem. Bull.*, 1994, **43**, 70 (Engl. Transl.)].

Received July 19, 1996;
in revised form November 1, 1996