Chemistry of Heterocyclic Compounds, Vol. 43, No. 1, 2007

SYNTHESIS OF 3-SUBSTITUTED PYRROLIDINES

A. V. Kurkin, E. A. Sumtsova, and M. A. Yurovskaya

A method was developed for the synthesis of derivatives of 3-substituted pyrrolidines from activated alkenes by 1,3-dipolar cycloaddition of unstable 2-benzylazomethylide, generated in situ from N-benzyl-N-(methoxymethyl)-N-(trimethylsilyl)amine. A method was developed for the reduction of 4-(3-pyrrolidyl)pyridine, prepared by the above-mentioned method, to the corresponding derivatives of (3-pyrrolidyl)piperidine with high yields under mild conditions.

Keywords: N-benzyl-N-(methoxymethyl)-N-(trimethylsilylmethyl)amine, piperidines, reduction of pyridines, 1,3-dipolar cycloaddition to alkenes.

The enormous interest in the various derivatives of pyrrolidine is due to the wide range of biological activity exhibited by these heterocyclic compounds. The development of a universal method for the synthesis of the pyrrolidine ring under mild conditions is the most important problem in the synthesis of alkaloids and their derivatives. In spite of the fact that a large number of the most varied compounds containing a pyrrolidine ring have been synthesized, no methods have been published for the synthesis of 4-pyrrolidylpiperidine derivatives that would provide interesting models for various synthetic transformations both at the nitrogen atom of the piperidine ring and at the nitrogen atom of the pyrrolidine ring. Our investigation concerned the synthesis of compounds that are interesting from the standpoint both of combinatorial chemistry and of possible use in laboratory synthesis.

We produced the 3-substituted pyrrolidines by 1,3-dipolar cycloaddition of the little-known unstable azomethine ylide to various olefins containing electron-withdrawing groups as substituents at the double bond [1, 2]. The reagent was generated *in situ* from N-benzyl-N-(methoxymethyl)-N-(trimethylsilylmethyl)amine (**1**) in polar solvents in the presence of a catalyst. Apart from the main olefin (4-vinylpyridine) that we needed for the production of the required pyrrolidylpyridine, we used styrene and benzyl acrylate as model compounds. The use of such olefins in the this reaction with various types of catalyst (F^-, protic acids, Lewis acids) has been described. However, no systematic investigations into the effect of the nature of the catalyst and the reaction conditions on the course of the process have been described in the literature [2, 3].

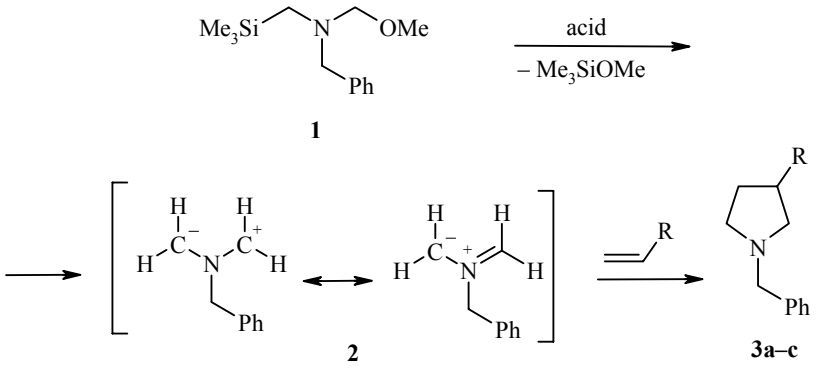
In addition, the use of the costly and unstable N-benzyl-N-(methoxymethyl)-N-(trimethylsilyl-methyl)amine (**1**) as starting compound prevented the widespread application of such a method for the construction of the pyrrolidine ring. For this reason we decided, first of all, to optimize the method for the preparation of the amine **1**. A method for the synthesis of the amine **1** by the successive alkylation of benzylamine with chloromethyltrimethylsilylmethane followed by transformation into the corresponding tertiary amine by the action of a 37% aqueous solution of formaldehyde in methanol at low temperature was described

* Dedicated to E. J. Lukevics on his 70th birthday

M. V. Lomonosov Moscow State University, Moscow, Russia; e-mail: kurkin@direction.chem.msu.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 41-48, January, 2007. Original article submitted October 2, 2006.

in [1, 4]. We synthesized the amine **1** with an 84% yield after optimizing the reaction conditions by increasing the reaction time and changing the method of isolation of the product. (Instead of distilling under high vacuum we used the amine straight from the reaction without further purification.)

The amine, which is essentially the precursor of the simplest iminium ylide, is converted by the action of acid into the ylide **2**, which presumably enters into 1,3-dipolar cycloaddition to the corresponding dipolarophiles.



3 **a** R = CO_2Bn, **b** R = Ph, **c** R = 4-Py

We conducted the 1,3-dipolar cycloaddition in polar solvents by mixing equivalent amounts of the amine (**1**) and the dipolarophile. The acid was added to the reaction mixture at -5-0°C. The mixture was then kept at room temperature, while the reaction was monitored by TLC. It should be noted that such olefins as styrene and 4-vinylpyridine partly isomerized under the reaction conditions.

In order to optimize the reaction conditions we investigated the effect of various acids and solvents on the product yields. Their effectiveness is presented in Table 1.

TABLE 1. The Effectiveness of the Employed Catalysts and Solvents

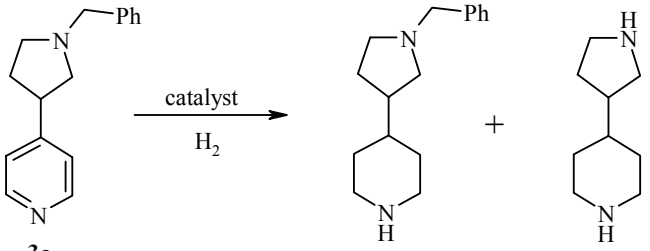
R	Acid	Solvent	Time, h	Yield, %
CO_2Bn	CF_3CO_2H	CH_2Cl_2	2	92
	CF_3CO_2H	Benzene	5	70
	$MeCO_2H$	CH_2Cl_2	3	52
	LiF *	MeCN	7	76
Ph	CF_3CO_2H	CH_2Cl_2	3	68
	$MeCO_2H$	CH_2Cl_2	5	17
	LiF*	MeCN	9	40
4-Py	CF_3CO_2H	CH_2Cl_2	3	82
	$MeCO_2H$	CH_2Cl_2	5	30
	LiF*	MeCN	8	58

*Reaction conditions: Room temperature, amine **1**–alkene–acid molar ratios 1:1:1.25.

The best results for all the olefins were obtained with trifluoroacetic acid in methylene chloride at room temperature. Increase in the reaction time and increase in temperature did not lead to an increase in the yield of the cyclic adduct, and this is probably explained by polymerization of the olefins. It should also be noted that the yield of the 1,3-cycloaddition product depends on the electronegativity of the substituent at the double bond in so far as increase in the electronegativity of the substituent leads to a decrease of the energy in the LUMO of the dipolarophile and facilitates its entry into cycloaddition. In fact, when olefins activated by electron-withdrawing substituents (acrylic ester and 4-vinylpyridine) were used it was possible to obtain yields of 92 and 82% respectively for the cyclic adducts **3a** and **3c**. A lower yield of the cyclic adduct **3b** is obtained when styrene, which does not contain an electron-withdrawing substituent, is used as dipolarophile. However, in this case too our chosen reaction conditions make it possible to increase the yield of the cyclic adduct **3b** substantially compared with the yield obtained in earlier work (20%) [2].

It should be noted that not only pyrrolidinopyridine but also all the other models that we synthesized show great promise for further use in synthesis and other practical applications. Thus, compound **3a** is a cyclic amino acid that can be used as the starting compound for the creation of a large combinatorial library of compounds in the search for new biologically active substances. The reduction of N-benzyl-3-phenylpyrrolidine **3b** can be used for the production of previously unknown derivatives of 3-cyclohexylpyrrolidine.

As stated before, the principal aim of the present work was to synthesize derivatives of pyrrolidylpiperidines. In this connection the next stage of our investigations was to develop methods for the reduction of N-benzyl-4-(3-pyrrolidyl)pyridine (**3c**) to the corresponding derivative of 4-pyrrolidylpiperidine **4** with hydrogen in the presence of heterogeneous catalysts.



3c **4** **5**

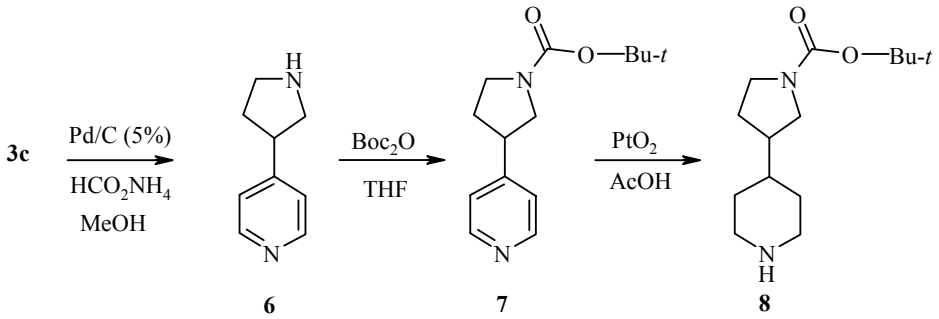
As a result of reduction of the cyclic adduct **3c** at 70°C at 60 atm hydrogen pressure in the presence of heterogeneous Pd/C (10%) or Rh/C (5%) in ethyl acetate we obtained a 1:1 mixture of compounds **4** and **5**. The NH derivative **5** is evidently formed as a result either of debenzylation of the product from reduction of the pyridine ring or of initial debenzylation of the cyclic adduct **3c** followed by hydrogenation of the pyridine ring. In any case the structure of compound **5** restricts the use of the molcule in further chemical transformations since the nitrogen atom of the piperidine ring and the nitrogen atom of the pyrrolidine ring have similar pK_a values of 11.2 and 11.3 respectively.

We tried changing the conditions for the hydrogenation of the pyridine ring by varying the temperature and pressure, increasing the hydrogenation time and the amount of catalyst, and using different solvents, but in all cases the yield of the N-benzyl derivative did not exceed 62%.

By using Adams' catalyst [platinum(II) oxide monohydrate] in trifluoroacetic acid at 60°C and 60 atm we were able to increase the yield of **4** to 89%.

In order to extend the synthesis possibilities of the method performed the reductive debenzylation of the cyclic adduct **3c** without affecting the pyridine ring. We used the Pd/C (5%)–ammonium formate–methanol reduction system [4] for the synthesis of the debenzylation product **6** and obtained compound **6** with a yield of 91%.

Since the benzyl group is, as we demonstrated, often removed in the hydrogenation process, we decided to use a different protecting group to block one of the reaction centers. In our opinion, it is more convenient to use Boc protection for these purposes. The N-Boc derivative **7** was prepared with a high yield by reaction of the cyclic adduct **6** and an equivalent amount of Boc_2O in THF. By using Adams' catalyst under mild conditions in acetic acid at 40°C and 60 atm it was possible to hydrogenate the pyridine ring, while retaining the protecting group, and to obtain compound **8** with a yield of 86%. Hydrogenation in the presence of the less costly catalyst Pd/C (10%) in ethyl acetate at 80°C and 90 atm reduces the yield of 4-(N-*tert*-butoxy-carbonylpyrrolidin-3-yl)piperidine (**8)** to 71% (Table 2).



Thus, the nitrogen atom of the piperidine ring in compound **8** becomes the only reaction center for attack by various reagents, and this opens up unlimited possibilities for further synthetic modifications to the molcules that we obtained. When necessary, the *tert*-butoxycarbonyl protecting group can be easily removed under mild conditions.

The compounds that we obtained are suitable synthons for use in the production of libraries of small molcules and in the search for physiologically compounds among 3-substituted pyrrolidine derivatives.

TABLE 2. The Results from Reduction of the Cyclic Adducts

Substrate	Catalyst	Temperature, °C	Pressure, atm	Yield, %		
				4	**5**	**8**
3c	Pd/C (10%)	70	60	54	46	—
	Rh/C (5%)	50	70	62	38	—
	PtO_2	60	60	89	11	—
7	PtO_2	40	60	—	14*	86
	Pd/C (10%)	80	90	—	—	71

*Detected in the NMR spectra.

EXPERIMENTAL

The IR spectra were recorded for suspensions in vaseline oil or for the pure liquid compounds on a UR-20 instrument. The chromato-mass spectrometric investigations of the reaction mixtures and the isolated compounds were conducted on a Carlo Erba/Kratos Fractovap Series 4200 gas-liquid chromatograph: Ultra-1 column, Hewlett Packard, 25 m×0.2 mm, layer thickness 0.33 μ, carrier gas helium (1 ml/min), stream splitter 1:10, evaporator temperature 280°C, temperature gradient from 150 to 280°C (5 deg/min), mass-spectral detector ITD-700 (Finnigan MAT), electron-impact ionization, 70 eV, range of masses *m*/*z* 45-400. The ^1H

and ^{13}C NMR spectra were obtained on a Bruker AMX-400 spectrometer (400 and 100 MHz respectively) in deuterochloroform with TMS as internal standard. The melting points were determined in open capillaries, and the presented values were not corrected. The reactions and the purity of the isolated compounds were monitored by TLC on Silufol UV-254 plates and by gas chromatography–mass spectrometry.

N-Benzyl-N-(methoxymethyl)trimethylsilylmethylamine (1). To a solution of chloromethyltrimethylsilane (61.13 g, 0.5 mol) in absolute acetonitrile (800 ml) we added benzylamine (107.16 g, 1 mol). The reaction mixture was stirred at 90-100°C for 12 h and cooled to room temperature. The precipitated benzylamine hydrochloride was filtered off, and the filtrate was concentrated under vacuum. Water was added to the residue, the solution was extracted with hexane (2×100 ml), and the organic layer was washed with saturated solution of sodium chloride (200 ml) and dried with anhydrous sodium sulfate. After removal of the volatile components under vacuum and holding over P_2O_5 in a desiccator the residue was added with stirring and cooling to 0°C to a 37% aqueous solution formaldehyde (43.85 g, 0.54 mol) and methanol (31.93 g, 0.54 mol). The mixture was stirred at this temperature for 1 h and then at 10-15°C for 3 h. Then we added dry potassium carbonate (50 g) to the reaction mixture and stirred the mixture for 2 h. The obtained light-brown organic layer was decanted, dry potassium carbonate was added to it (5 g), and the organic layer was decanted again. The solid inorganic residue was washed with ether (2×20 ml), and the organic phases were mixed together and concentrated under vacuum. The residue was used in subsequent experiments without further purification. ^1H NMR spectrum, δ, ppm: 0.1 (9H, s, $(CH_3)_3Si$); 2.13 (2H, s, $CH_2Si(CH_3)_3$); 3.20 (3H, s, OCH_3); 3.72 (2H, s CH_2O); 3.95 (2H, s, $CH_2C_6H_5$); 7.19-7.22 (5H, m, C_6H_5).

1,3-Dipolar Cycloaddition (General Procedure). To a solution of methylene chloride (600 ml), containing of the olefin (0.21 mol), we added dropwise with stirring of compound **1** (0.21 mol). The reaction mixture was stirred for 30 min, cooled to -5°C, and kept for 30 min. A solution of trifluoroacetic acid in methylene chloride (21.12 ml) was added dropwise with vigorous stirring so that the temperature of the reaction mixture did not exceed 10°C. The reaction mixture was stirred for 6 h, and the reaction was monitored by TLC. At the end of the reaction a concentrated aqueous solution of $NaHCO_3$ (0.5 liter) was added to the reaction mixture to pH 8. The organic layer was separated, washed with water and a saturated aqueous solution of sodium chloride, and dried with anhydrous sodium sulfate. The aqueous layer was extracted with methylene chloride (3×300 ml), and the combined organic phases were washed with water, combined with the first fraction, and dried with anhydrous sodium sulfate. The organic solvent was removed under vacuum, and the residue in the form of a dark-brown oil was distilled under vacuum.

Benzyl N-Benzylpyrrolidine-3-carboxylate (3a) [3]. The yield was 92%; bp 201°C (2 mm Hg). IR spectrum, ν, cm^{-1}: 1730 (C=O). ^1H NMR spectrum, δ, ppm: 1.82-1.94 (1H, m); 2.32-2.43 (1H, m); 2.56-2.65 (1H, m); 2.74-2.83 (2H, m); 2.94-3.02 (1H, m); 3.31-3.37 (1H, m); 3.71 (2H, s, $NCH_2C_6H_5$); 5.23 (2H, s, $OCH_2C_6H_5$); 7.35-7.45 (10H, m, C_6H_5).

N-Benzyl-3-phenylpyrrolidine (3b) [2]. The yield was 68%; bp 167°C (2 mm Hg). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.80-1.92 (1H, m); 2.34-2.43 (1H, m); 2.61-2.69 (1H, m); 2.79-2.85 (2H, m); 2.89-2.97 (1H, m); 3.19-3.24 (1H, m); 3.73 (2H, s, $NCH_2C_6H_5$); 7.27-7.64 (10H, m, C_6H_5).

4-(N-Benzylpyrrolidin-3-yl)pyridine (3c) [2]. The yield was 82%; bp 176°C (2 mm Hg). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.81-1.89 (1H, m); 2.37-2.45 (1H, m); 2.64-2.70 (1H, m); 2.81-2.85 (2H, m); 2.90-2.97 (1H, m); 3.37-3.41 (1H, m); 3.75 (2H, s, $NCH_2C_6H_5$); 7.22 (2H, d, J = 6.1, H-3,5 Py); 7.26-7.40 (5H, m, C_6H_5); 8.51 (2H, d, J = 6.1, H-2,6 Py).

N-(N-Benzylpyrrolidin-3-yl)piperidine (4). To a mixture of absolute ethanol (125 ml), of compound **3c** (23.81 g, 0.1 mol), and of trifluoroacetic acid (37.5 ml) in an autoclave we added of $PtO_2 \cdot H_2O$ (1 g). Hydrogen was passed through the reaction mixture at 60°C and 60 atm until it was no longer absorbed. The reaction was monitored by TLC. The catalyst was filtered off, and the organic solvent was removed under vacuum. The residue was treated with 300 ml of a concentrated solution of sodium hydroxide with cooling and extracted with methylene chloride (3×200 ml). The organic layer was washed with water and saturated sodium

chloride solution and dried with anhydrous sodium sulfate. The organic solvent was removed under vacuum, and the residue was chromatographed on a column of silica gel in the 1:5 ethyl acetate–petroleum ether solvent system. The yield was 89%, and the product formed a light-yellow liquid that crystallized on standing; mp 63°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41-1.52 (5H, m); 1.75-1.84 (1H, m); 1.87-2.15 (3H, m); 2.31 (1H, t, *J* = 9); 2.55-2.66 (1H, m); 2.72-2.89 (4H, m); 3.46 (1H, t, *J* = 9); 3.70 (2H, s, $NCH_2C_6H_5$); 7.25-7.46 (5H, m, C_6H_5). Found, %: C 79.97; H 7.82; N 11.81. $C_{16}H_{18}N_2$. Calculated, %: C 80.63; H 7.61; N 11.75.

4-(Pyrrolidin-3-yl)piperidine (5). To a solution of compound **4** (23.83 g, 0.1 mol) in ethyl acetate (200 ml) in an autoclave we added 25 g of 5% Pd/C. Hydrogen was passed through the reaction mixture for 30 h at 70°C and 60 atm until it was no longer absorbed. The reaction was monitored by TLC. The catalyst was filtered off, the organic solvent was removed under vacuum, and the residue was chromatographed on a column of silica gel in the 1:5 ethyl acetate-petroleum ether system. The yield was 76%. The product formed a viscous yellow liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38-1.54 (5H, m); 1.72-1.88 (2H, m); 1.87-2.15 (3H, m); 2.31 (1H, t, *J* = 9); 2.55-2.70 (2H, m); 2.72-2.89 (4H, m); 3.42-3.54 (1H, m). Found, %: C 69.92; H 11.68; N 18.28. $C_9H_{18}N_2$. Calculated, %: C 70.08; H 11.68; N 18.16.

4-(Pyrrolidin-3-yl)pyridine (6). A solution of compound **3c** (23.75 g, 0.1 mol) and ammonium formate (23.8 g, 0.38 mol) in methanol (700 ml) was stirred at room temperature for 30 min, and 5% Pd/C (5 g) was added in an atmosphere of argon. The reaction mixture was stirred at 80-90°C for 8 h and cooled to room temperature. The catalyst was filtered off, and the solvent was removed under vacuum. The residue was treated with a concentrated solution of sodium hydroxide (200 ml) with cooling and extracted with methylene chloride (3×400 ml). The organic phase was washed with water, saturated sodium carbonate solution, and saturated sodium chloride solution and dried with anhydrous sodium sulfate. The organic solvent was evaporated under vacuum, and the residue in the form of a light-brown oil was distilled under vacuum; bp 112°C (2 mm Hg). The yield was 13.47 g (91%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80-1.88 (1H, m); 2.35-2.44 (1H, m); 2.61-2.72 (2H, m); 2.82-2.86 (2H, m); 2.92-2.99 (1H, m); 3.33-3.46 (1H, m); 7.26 (2H, d, *J* = 6.1); 8.49 (2H, d, *J* = 6.1). Found, %: C 72.41; H 8.18; N 18.95. $C_9H_{12}N_2$. Calculated, %: C 72.94; H 8.16; N 18.90.

4-(N-*tert*-Butoxycarbonylpyrrolidin-3-yl)pyridine (7). A solution of compound **6** (12.1 g, 0.08 mol) and triethylamine (16.5 ml, 0.08 mol) in THF (250 ml) was stirred with cooling on an ice bath. After 20 min a solution of Boc_2O (17.85 g, 0.08 mol) in THF was added. The temperature of the reaction mixture was then raised to 30°C, and the mixture was stirred until the release of CO_2 had ceased. The reaction was monitored by TLC. The solvent was removed under vacuum, the residue was treated with water, and 500 ml of methylene chloride was added. The organic layer was washed with a dilute solution of acetic acid and dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was recrystallized from hexane; mp 72°C (from hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 [9H, s, $(CH_3)_3C$]; 1.84 (1H, d, *J* = 13); 2.35-2.44 (1H, m); 2.61-2.72 (2H, m); 2.92-3.03 (2H, m); 3.36 (1H, d, *J* = 13); 7.26 (2H, d, *J* = 6.1); 8.49 (2H, d, *J* = 6.1). Found, %: C 67.57; H 8.08; N 11.34. $C_{14}H_{20}N_2O_2$. Calculated, %: C 67.72; H 8.12; N 11.28.

4-(N-*tert*-Butoxycarbonylpyrrolidin-3-yl)piperidine (8). A. To a mixture of compound **7** (24.83 g, 0.1 mol) and acetic acid (50 ml) in absolute ethanol (125 ml) in an autoclave we added $PtO_2 \cdot H_2O$ (1 g). Hydrogen was passed through the reaction mixture at 40°C and 60 atm for 24 h until it was no longer absorbed. The reaction was monitored by TLC. The catalyst was filtered off, and the solvent was removed under vacuum. The residue was treated with 300 ml of a concentrated solution of sodium hydroxide with cooling and extracted with methylene chloride (3×200 ml). The organic layer was washed with water that had been saturated with sodium chloride and dried with anhydrous sodium sulfate. The solvent was evaporated under vacuum, and the residue was chromatographed on a column of silica gel in the 1:5 ethyl acetate–petroleum ether system. The yield was 86%. The product was a light-yellow oil that crystallized on standing; mp 124°C.

B. To a solution of compound **7** (24.83 g, 0.1 mol) in ethyl acetate (200 ml) in an autoclave we added 10% Pd/C (20 g). Hydrogen was passed through the reaction mixture at 80°C and 90 atm for 10 h until it was no longer absorbed. The reaction was monitored by TLC. The catalyst was filtered off, and the solvent was

removed under vacuum. The residue was chromatographed on a column of silica gel in the 1:5 ethyl acetate–petroleum ether system. The yield was 71%, and the product was a light-yellow oil, which crystallized on standing; mp 124°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27-1.40 (2H, m); 1.44 (9H, s, $(CH_3)_3C$); 1.49-1.64 (3H, m); 1.70-1.82 (2H, m); 1.93-2.15 (3H, m); 2.37 (1H, t, *J* = 11); 2.55-2.70 (2H, m); 2.72-2.89 (2H, m); 3.42-3.54 (1H, m); 3.40 (1H, d, *J* = 11). Found, %: C 65.95; H 10.38; N 11.46. $C_{14}H_{26}N_2O_2$. Calculated, %: C 66.11; H 10.30; N 11.01.

REFERENCES

1. A. Padwa and W. Dent, *J. Org. Chem.*, **52**, 235 (1987).
2. E. Laborde, *Tetrahedron Lett.*, **33**, 6607 (1992).
3. Y. Terao, H. Kotaki, N. Imai, and K. Achiwa, *Chem. Pharm. Bull.*, **33**, 2762 (1985).
4. P. L. Kotian, T. H. Lin, Y. El-Kattan, and P. Chand, *Organic Process Research Development*, **9**, 193 (2005).
5. S. Ram and L. D. Spicer, *Tetrahedron Lett.*, **28**, 515 (1987).