A Novel Synthesis of Unsymmetric 1,2-Diamines from N-Substituted 2-Methylaziridines

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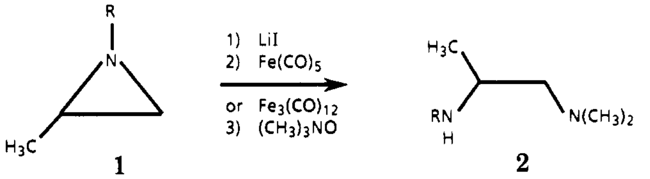
Received September 20, 1989

This paper reports a one-pot synthesis of unsymmetric 1,2-diamines from aziridines and amine oxides, using lithium iodide and triiron dodecacarbonyl in THF.

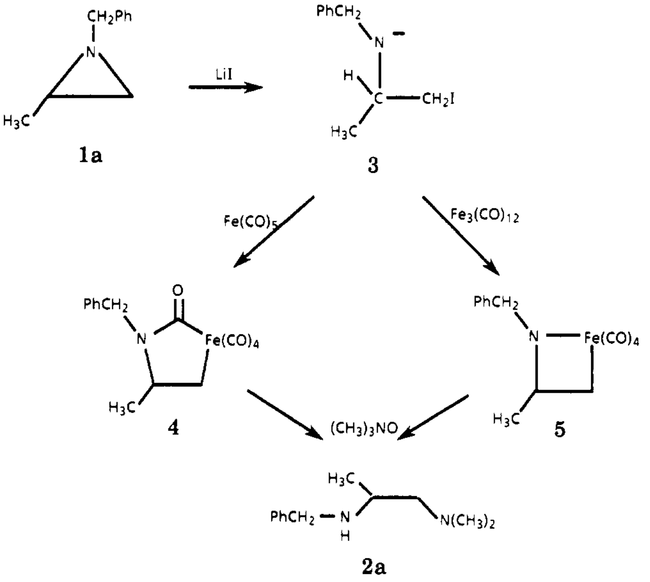
1,2-Diamines are important due to their value as reagents and naturally occurring compounds for organic chemistry[1] and due to their ability to serve as ligands for both transition-metal and main group metal complexes.[2] Thus, a synthesis which makes an unsymmetric 1,2-diamine readily available from inexpensive starting materials is valuable.[3,4] In this paper, we report a novel synthesis of an unsymmetric 1,2-diamine starting with an aziridine and an amine oxide and allowing them to react with lithium iodide and an iron carbonyl in tetrahydrofuran.



The steps of this transformation include: the ring opening of the aziridine by lithium iodide; the formation of an iron complex by $Fe(CO)_5$ or $Fe_3(CO)_{12}$; and finally, the conversion of this complex to the diamine by dehydrated trimethylamine oxide. Control experiments show that the lithium iodide, an iron carbonyl complex, and the amine oxide are definitely needed for the conversion of aziridine **1a** to diamine **2a** (R = $PhCH_2$). When either the LiI or an iron carbonyl complex was not included, or when trimethylamine oxide was replaced by trimethylamine, only a mixture of the starting aziridine and a dimer of the aziridine is formed.

To determine the exact nature of the intermediate metal complex(es) involved in this sequence, after the ring-opening reaction of aziridine **1a** by lithium iodide, the reaction with an iron carbonyl source was monitored by infrared spectroscopy. For the reaction with $Fe(CO)_5$, the carbonyl stretching region of the IR spectrum has absorptions at 1990, 1970, 1910, and 1730 cm^{-1} and for the reaction with $Fe_3(CO)_{12}$ at 2040, 2010, and 1930 cm^{-1}. These absorptions are consistent with the generation of neutral acyl(alkyl)iron complexes such as **4** and **5**. As stated above, upon addition of trimethylamine oxide, both reactions generate diamine **2a**.

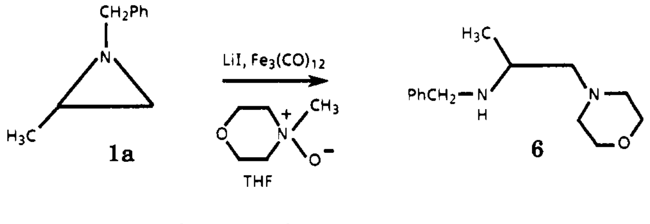
Conversion of the organometallic intermediate to the diamine only occurs with trimethylamine oxide. Using diethylmethylamine oxide, in place of trimethylamine oxide, gives only the starting material **1a** and the dimer of **1a**, i.e., no diamine is formed.



This total transformation is more easily accomplished (and in somewhat higher yield) by simply mixing together the aziridine, hydrated trimethylamine oxide, lithium iodide, and $Fe_3(CO)_{12}$ in THF and allowing the mixture to stir for at least 20 h at room temperature (Table I). For the conversion of **1a** to **2a**, the yield is the same whether the reaction is run under an argon atmosphere or *in a loosely stoppered Erlenmeyer flask*.

Three points about this one-pot transformation are surprising. First, the reaction displays no air or moisture sensitivity, i.e., it works equally well in the open air with the hydrated amine oxide as it does under an argon atmosphere with the dehydrated amine oxide. Second, although the yields for these reactions are moderate, the products are very clean and require little purification. Finally, the reactions which form the metallacyclic intermediate and the reaction of the metallacycle with trimethylamine oxide must occur faster than the reaction between the amine oxide and $Fe_3(CO)_{12}$.

Though a variety of electron-donating groups on the aziridine nitrogen are compatible with this chemistry, the amine oxide is restricted to trimethylamine oxide (Table I). A sterically unhindered amine oxide such as *N*-methylmorpholine oxide gives a very low yield, and diethylmethylamine oxide gives no diamine product. These results imply that the loss of the methyl group is an S_N2 reaction.



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(1) (a) Kohn, H.; Jung, S.-H. *J. Am. Chem. Soc.* **1983**, *105*, 4106. (b) Jung, S.-H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399.

(2) See for example: Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Interscience Publishers: New York, 1972; Chapter 21.

(3) For some conversions of olefins to 1,2-diamines, see: (a) Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511. (b) Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787. (c) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (d) Michejda, C. J.; Campbell, D. H. *Ibid.* **1979**, *101*, 7687. (e) Backvall, J.-E. *Tetrahedron Lett.* **1978**, 163. (f) Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1979**, 962.

(4) For the conversion of electron-deficient aziridines to 1,2-diamines, see: Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969; pp 262-273.

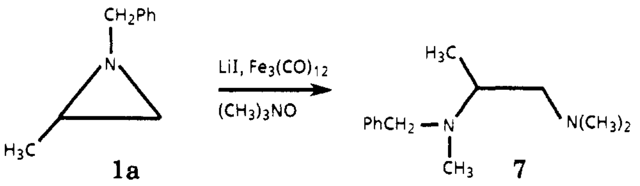
0022-3263/90/1955-2531$02.50/0

Table I. Aziridines and Amine Oxides Used for the Preparation of 1,2-Diamines

aziridine 1	R	amine oxide	product diamine (yield, %)
a	$PhCH_2$	Me_3NO	**2a** (40)
b	*p*-OMe-$C_6H_4CH_2$	Me_3NO	**2b** (40)
c	C_6H_{13}	Me_3NO	**2c** (40)
d	$PhCH_2$	*N*-methylmorpholine oxide	**6** (10)

In an attempt to determine the relative stereochemistry of the product diamine, 7-benzyl-7-azabicyclo[4.1.0]heptane was allowed to react with lithium iodide, $Fe_3(CO)_{12}$, and trimethylamine oxide. This aziridine also was subjected to the conditions for the sequential transformation. Unfortunately, in both cases, the starting 1,2,3-trisubstituted aziridine was recovered unchanged.

When the reaction for the one-pot conversion of **1a** to **2a** is attempted at a higher concentration (0.5 M as compared to 0.03 M), **2a** is not the product, rather the methylated compound **7** is formed. Unlike the synthesis of **2a**, which gives the free organic compound, this reaction is contaminated by a diamine–iron complex. However, this complex is readily decomposed to give the pure organic material simply by stirring the crude product in chloroform with added HCl.



1a **7**

Though the exact mechanism of the transformation of an aziridine to a 1,2-diamine is not known, the formation of **7** at higher concentration suggests that the methyl transfer is an intermolecular reaction and not an intramolecular one. The intramolecular methyl transfer reaction most likely does not take place because it would be a 5-endo-tet reaction, which according to Baldwin's rules is disfavored.[5]

Experimental Section

General. Except where noted, all reactions were carried out using oven-dried glassware that was cooled under an argon atmosphere or in a desiccator, and all reactions were conducted under an argon atmosphere.

Tetrahydrofuran was freshly distilled from potassium benzophenone ketyl. Iron pentacarbonyl was filtered prior to use.

Instrumentation. A Varian Model 3300 gas chromatograph was used for GC analyses with a flash vaporization injector, 225 °C; flame ionization detector, 325 °C; and a 12 ft × $^1/_8$ in. 5% SP-2100 on 100/200 supelcoport column. Temperature programming was used: initial temperature of 50 °C for 2 min; increased by 10 °C per min to 250 °C; increased by 20 °C per min to 300 °C; hold at 300 °C for 4 min.

All infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR with KBr cells. All NMR spectra were recorded on a Nicolet NT-300 or a Bruker 250 MHz NMR spectrometer with chemical shifts referenced to tetramethylsilane at 0.00 ppm. All GC/mass spectra were recorded on a Hewlett-Packard Model 9133 spectrometer using a 0.25 mm × 15 m fused silica capillary SPB-1 column and temperature programming. High-resolution mass spectra were recorded on a Kratos model mass spectrometer.

1-(Dimethylamino)-2-(benzylamino)propane (2a). A mixture of 0.55 g (1.0 mmol) of $Fe_3(CO)_{12}$ in 15 mL of THF was stirred at room temperature for 1 h in flask A. This reaction was then monitored by IR spectroscopy until it showed only a single terminal CO stretch at 2050 cm^{-1} and no bridging CO stretches. In flask B, a mixture of 0.15 g (1.0 mmol) of 1-benzyl-2-methylaziridine and 0.20 g (1.5 mmol) of lithium iodide in 15 mL of THF was allowed to refluxed for 15 min. After this reaction cooled to room temperature, the solution from flask A was transferred into flask B using a 10-mL syringe, and the combined solution was allowed to stir at room temperature for 4 h. After the reaction had stirred at room temperature for 2 h, it was monitored by IR spectroscopy which shows peaks in the carbonyl stretching region at 2040, 2010, and 1930 cm^{-1}. The solution was evaporated to eliminate any $Fe(CO)_5$, and then 30 mL of freshly distilled THF and 0.55 g (5.0 mmol) of trimethylamine oxide were added. (This is the weight of dihydrated amine oxide used. The water was removed by adding benzene and distilling off the benzene/water azeotrope before the amine oxide was added to the reaction flask.) This solution was allowed to stir for at least 20 h. The reaction mixture was added to 50 mL of ether, extracted with 100 mL of water, in three portions, and dried with K_2CO_3, and the solvent was evaporated. The remaining oil was easily purified by using a short alumina column in a disposable pipet (10% CH_2Cl_2 in hexane as eluent) to give 0.06 g (30% yield) of **2a**: ^1H NMR ($CDCl_3$) δ 1.03 (d, *J* = 6.0 Hz, 3 H), 2.01 (dd, *J* = 4.1, 12.2 Hz, 1 H), 2.12 (s, 6 H), 2.27 (br s, 1 H), 2.34 (dd, *J* = 10.2, 12.0, Hz, 1 H), 2.69–2.76 (m, 1 H), 3.68 (d, *J* = 13.5 Hz, 1 H), 3.94 (d, *J* = 13.2 Hz, 1 H), 7.22–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.32 (q), 45.68 (q), 49.06 (d), 51.45 (t), 66.21 (t), 125.7–129.4, 140.71 (s); IR ($CDCl_3$) 3000 (m), 2840 (m), 1460 (m), 1380 (w), 1270 (w), 1040 (w), 910 (s), 740 (s) cm^{-1}; MS m/e 192 (2.1), 135 (7.6), 134 (85.9), 92 (7.7), 91 (100), 65 (8.3), 59 (9.4), 58 (30.9); high-resolution MS found 192.1642, calculated for $C_{12}H_{20}N_2$ 192.1634.

Replacing $Fe_3(CO)_{12}$ by $Fe(CO)_5$ To Give 2a. A mixture of 0.15 g (1.0 mmol) of 1-benzyl-2-methylaziridine and 0.20 g (1.5 mmol) of lithium iodide in 30 mL of THF was allowed to reflux for 15 min. This reaction was cooled to room temperature. Then 0.15 mL (1.2 mmol) of $Fe(CO)_5$ was added, and the solution was again heated to reflux for 3 h. When this reaction was monitored by IR spectroscopy, peaks in the carbonyl stretching region are observed at 1990, 1970, 1910, and 1730 cm^{-1}. The solution was then evaporated to eliminate any excess $Fe(CO)_5$, and 30 mL of freshly distilled THF and 0.55 g (5.0 mmol) of trimethylamine oxide were added. This solution was allowed to stir for at least 20 h. The reaction mixture was added to 50 mL of ether, extracted with 100 mL of water, in three portions, and dried with K_2CO_3. Evaporation of the solvent gave only one major compound, as determined by gas chromatography, which could be easily isolated by using a short alumina column in a disposable pipet (10% CH_2Cl_2 in hexane as eluent) to give 0.06 g (30% yield) of **2a**.

Control Experiment: No Lithium Iodide. A mixture of 0.55 g (1.0 mmol) of $Fe_3(CO)_{12}$ in 30 mL of THF was stirred at room temperature for 1 h, 0.15 g (1.0 mmol) of **1a** was added, and the reaction mixture was allowed to stir at room temperature for 96 h. When the reaction had stirred for 44 h and for 70 h, it was monitored by IR spectroscopy, which showed peaks at 2040 and 2020 cm^{-1}. Trimethylamine oxide (0.55 g, 5.0 mmol) was added, and the reaction mixture was allowed to stir at room temperature for an additional 20 h. The solution was then extracted with 100 mL of water, dried with K_2CO_3, and evaporated to dryness. The crude product (0.14 g) was a 9:1 ratio of of the starting aziridine **1a** and a dimer of **1a**, as determined by GC.

Control Experiment: No $Fe_3(CO)_{12}$. A mixture of 0.15 g (1.0 mmol) of **1a** and 0.20 g (1.5 mmol) of LiI in 30 mL of THF was allowed to reflux for 15 min and then was cooled to room temperature. Trimethylamine oxide (0.55 g, 5.0 mmol) was added, and the reaction mixture was allowed to stir at room temperature overnight. The solution was then extracted with 100 mL of water, dried with K_2CO_3, and evaporated to dryness. The crude product contained a nearly quantitative recovery (0.14 g) of the starting aziridine **1a**.

Control Experiment: Using Trimethylamine Instead of Trimethylamine Oxide. This reaction was performed in the same manner as reaction for the conversion of **1a** to **2a**, with $Fe_3(CO)_{12}$, except that after the solution in flask A and solution flask B were mixed and allowed to stir for 4 h, 1 mL (10 mmol)

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(5) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

of trimethylamine was added instead of trimethylamine oxide. This reaction was allowed to stir for at least 20 h. The crude product (0.14 g) consisted of 93% starting aziridine **1a** and 5% dimer of **1a**, as determined by gas chromatography.

The reaction was also performed in the same manner as in the conversion of **1a** to **2a** with $Fe(CO)_5$, except 4 mL (40 mmol) of trimethylamine was added. This reaction gave (0.15 g crude weight) almost exclusively aziridine **1a**, as determined by gas chromatography.

Using Diethylmethylamine Oxide Instead of Trimethylamine Oxide. This reaction was performed in the same manner as the reaction for the conversion of **1a** to **2a**, with $Fe_3(CO)_{12}$, except that 0.70 g (5.0 mmol) of diethylmethylamine oxide[6] was added and the solution was allowed to stir at room temperature for 2 days. The crude product (0.14 g) showed a 2:1 mixture of starting aziridine **1a** and the dimer of **1a**, as determined by GC.

One-Pot Synthesis of 2a. A mixture of 0.55 g (1.0 mmol) of $Fe_3(CO)_{12}$, 0.15 g (1.0 mmol) of 1-benzyl-2-methylaziridine, **1a**, 0.20 g (1.5 mmol) of lithium iodide, and 0.55 g (5.0 mmol) of trimethylamine oxide dihydrate (this material was NOT dehydrated) in 30 mL of THF was allowed to stir at room temperature under argon for at least 20 h. The reaction mixture was added to 30 mL of ether, then extracted with 100 mL of water in three portions, and finally dried with K_2CO_3. Evaporation of the solvent gave only one major compound, as determined by gas chromatography, which could be easily isolated using a short alumina column in a disposable pipet (10% CH_2Cl_2 in hexane as eluent) to give 0.08 g (40% yield) of **2a**.

This reaction was repeated in a loosely stoppered Erlenmeyer flask. After purification, this reaction also gave 0.08 g (40% yield) of **2a**.

1-(Dimethylamino)-2-((*p*-methoxybenzyl)amino)propane (2b). This reaction was run in the same manner as the analogous one-pot conversion of **1a** to **2a**, except that 0.18 g (1.0 mmol) of 1-(*p*-methoxybenzyl)-2-methylaziridine, **1b**, was used. The crude product showed one major compound, by gas chromatography, which could be purified in the same manner as **2a** to give 0.08 g (40% yield) of **2b**: ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 6.3 Hz, 3 H), 1.99 (dd, J = 3.9, 12.0 Hz, 1 H), 2.12 (s, 6 H), 2.10–2.22 (m, 1 H), 2.31 (dd, J = 10.2, 11.7 Hz, 1 H), 2.67–2.74 (m, 1 H), 3.61 (d, J = 12.9 Hz, 1 H), 3.79 (s, 3 H), 3.86 (d, J = 12.9 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.31 (q), 45.63 (q), 48.98 (d), 50.80 (t), 55.20 (q), 66.20 (t), 113.70 (d), 129.30 (d) 132.91 (s), 158.48 (s); IR (neat) 3301 (w), 3061 (w) 3029 (w), 2965 (s), 2853 (s), 2818 (s), 2768 (s), 1756 (w), 1673 (w), 1611 (s), 1585 (m), 1511 (s), 1457 (s), 1372 (m), 1301 (m), 1248 (s), 1176 (m), 1143 (m), 1037 (s), 840 (s), 824 (s), 733 (m) cm^{-1}; MS *m/e* 222 (1.3), 165 (2.9), 164 (23.3), 122 (8.2), 121 (100), 91 (3.3), 89 (1.3), 78 (5.0), 77 (4.4), 59 (2.6), 58 (16.3); high-resolution MS found 222.1714, calculated for $C_{13}H_{22}N_2O$ 222.1723.

1-(Dimethylamino)-2-(hexylamino)propane (2c). This reaction was run in the same manner as the analogous one-pot conversion of **1a** to **2a**, except that 0.14 g (1.0 mmol) of 1-hexyl-2-methylaziridine, **1c**, was used. The crude product showed one major compound, by gas chromatography, which could be purified in the same manner as **2a** to give 0.07 g (40% yield) of **2c**: ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.3 Hz, 3 H), 1.20–1.40 (m, 6 H), 1.45–1.50 (m, 2 H), 2.01 (dd, J = 3.9, 12.0 Hz, 1 H), 2.19 (s, 6 H), 2.23 (dd, J = 9.9 Hz, the other coupling constant is obscured by a peak at 2.19 ppm, 1 H), 2.15–2.35 (m, 1 H), 2.46–2.51 (m, 1 H), 2.69–2.74 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.08 (q), 18.66 (d), 22.65 (t), 27.18 (t), 30.28 (t), 31.84 (t), 45.82 (q), 47.82 (t), 50.61 (d), 63.39 (t); IR (neat) 3300 (w), 3034 (w), 2958 (s), 2927 (s), 2855 (s), 2819 (s), 2771 (s), 1458 (s), 1377 (m), 1341 (m), 1265 (s), 1142 (m), 1037 (s) cm^{-1}; MS *m/e* 186 (0.8), 129 (8.8), 128 (100), 126 (0.8), 112 (1.1), 86 (3.3), 85 (1.4), 84 (3.1), 72 (2.3), 71 (3.5), 70 (5.3), 69 (0.9), 68 (1.2), 60 (1.4), 59 (16.3), 58 (70.3); high-resolution MS found 186.2108, calculated for $C_{11}H_{26}N_2$ 186.2102.

1-Morpholino-2-(benzylamino)propane (6). This reaction was run in the same manner as the analogous one-pot conversion of **1a** to **2a**, except that 0.60 g (1.0 mmol) of 4-methylmorpholine *N*-oxide was used. As determined by gas chromatography, the crude product consisted of about 20% of **2d**, 50% of a dimer of **1a**, and 30% of a high molecular weight compound which could not be identified. After purification by column chromatography using a short column in a disposable pipet, 0.02 g (10%) of **2d** was obtained: ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 6.1 Hz, 3 H), 2.10–2.38 (m, 8 H), 3.50–3.75 (m, 4 H), 3.65 (d, J = 13.2 Hz, 1 H), 3.95 (d, J = 13.5 Hz, 1 H), 7.27–7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.23, 47.26, 51.18, 53.71, 65.06, 67.09, 126.8–128.3, 140.79; IR ($CDCl_3$) 3028 (w), 2967 (s), 2934 (m), 2859 (m), 2816 (s), 1744 (w), 1670 (w), 1494 (w), 1455 (s), 1376 (w), 1297 (w), 1116 (s), 1069 (m), 1014 (w) cm^{-1}; MS *m/e* 234 (0.3), 135 (10.5), 134 (100), 101 (31.5), 100 (28.3), 91 (99.7); high-resolution MS found 234.1742, calculated for $C_{14}H_{22}N_2O$ 234.1737.

Attempted Reaction of 7-Benzyl-7-azabicyclo[4.1.0]heptane. This reaction was performed in the same manner as the reaction for the conversion of **1a** to **2a** with $Fe_3(CO)_{12}$, and also in the same manner as the one-pot conversion of **1a** to **2a**, except 0.19 g (1.0 mmol) of 7-benzyl-7-azabicyclo[4.1.0]heptane was used. In each case a nearly quantitative yield (0.18 g) of starting material was recovered.

Control Experiment: The Effect of Concentration. This reaction was run in the same manner as the analogous one-pot conversion of **1a** to **2a**, except that 0.74 g (5.0 mmoles) of **1a**, 2.75 g (5.00 mmol) of $Fe_3(CO)_{12}$, 1.0 g (7.5 mmol) of lithium iodide, 2.75 g (25 mmol) of $Me_3NO{\cdot}2H_2O$, and 10 mL of THF were used. After workup, the crude product (0.43 g) showed 1-(dimethylamino)-2-((benzylmethyl)amino)propane, **7**, as the major component. However, other indications, especially the maroon color, are that this is mainly an iron complex. The crude product was dissolved in 10 mL of $CHCl_3$, and 1 mL of concentrated HCl was added. This was allowed to stir at room temperature overnight. Then 20 mL of CH_2Cl_2 was added, and the solution was washed with a saturated $NaHCO_3$ solution until the water layer was basic. The organic layer was then extracted with 2 × 20 mL of water, dried with K_2CO_3, and evaporated. This gave 0.33 g (32% yield) of compound **7**: ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3 H), (2.19 (s), 2.22 (s), 2.09–2.31 (m), 10 H), 2.44 (dd, J = 6.6, 12.3 Hz, 1 H), 2.87 (q, J = 6.8 Hz, 1 H), 3.52 (d, J = 13.2 Hz, 1 H), 3.62 (d, J = 13.5 Hz, 1 H), 7.23–7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.98 (q), 36.58 (q), 46.07 (q), 54.74 (d), 58.34 (t), 63.55 (t), 126.8–128.8, 140.03 (s). IR ($CDCl_3$) 3029 (w), 2973 (s), 2859 (m), 2823 (s), 2794 (s), 2777 (s), 1665 (w), 1494 (w), 1454 (s), 1368 (w), 1264 (w), 1127 (w), 1028 (m) cm^{-1}; MS *m/e* 206 (1.0), 149 (11.7), 148 (100), 92 (6.2), 91 (85.5), 58 (11.7); high-resolution MS found 206.1785, calculated for $C_{13}H_{22}N_2$ 206.1787.

Acknowledgment. We wish to thank the National Science Foundation (Grant CHE-8603898) for financial support of this work and Elaine Cudmore for the typing and drawings in this manuscript. The 300-MHz NMR spectrometer used in this study was purchased with the aid of an NSF instrumentation grant (CHE-8102974). The Kratos mass spectrometer was purchased with the aid of an NSF instrumentation grant (PCM-8219912). The 250-MHz NMR spectrometer was purchased with the aid of an Academic Challenge Award from the Ohio Board of Regents.

Registry No. **1a**, 24417-03-6; **1a** (dimer), 125641-47-6; **1b**, 56338-34-2; **1c**, 27159-39-3; **2a**, 125641-44-3; **2b**, 125641-45-4; **2c**, 125641-46-5; **6**, 106476-34-0; **7**, 125641-48-7; Me_3NO, 1184-78-7; $Et_2N(O)Me$, 115206-20-7; 4-methylmorpholine *N*-oxide, 7529-22-8; 7-benzyl-7-azabicyclo[4.1.0]heptane, 24417-01-4.

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[6] Hickinbottom, W. J. *Reactions of Organic Compounds*; Longmans, Green and Co.: London, 1948; p 309, method 1.