Cis-Selective Iodinative Etherification of *N*-Alkenyl-*N*-(2-hydroxyalkyl)anilines

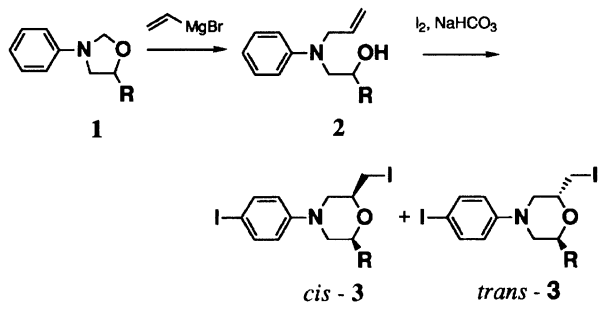
Tomihiro NISHIYAMA,* Kouji KITANO, Hiroshi KISHI, and Fukiko YAMADA
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Senriyama, Suita, Osaka 564
(Received May 6, 1993)

Synopsis. Several 6-alkyl- or 6-aryl-2-(iodomethyl)-morpholines were prepared in good yields with regio- and cis-selectivity from *N*-alkenyl-*N*-(2-hydroxyalkyl)anilines by electrophilic iodinative etherification.

The formation of cyclic compounds from double bond-containing nucleophiles promoted by an electrophile has been widely investigated. For example, iodo derivatives of lactone,[1] tetrahydrofuran,[2] or ribose[3] were prepared by treatment of 4-hexenoic acid or 4-penten-1-ol derivatives. In addition to well investigated iodinative etherification, a number of interesting applications to the preparation of pyrrolidines[4] and other heterocycles[5,6] have been reported. This approach has received growing interest, and an excellent review on the regio- and stereoselective aspects of this important reaction has been written by Cardillo and Orena.[7] However, the analogous iodinative etherification of aniline derivatives with iodine, which would be expected to lead to morpholine derivatives, has not been reported. Here, we report the regio- and cis-selective syntheses of 6-alkyl- or 6-aryl-2-(iodomethyl)morpholines by the iodinative etherification of *N*-alkenyl-*N*-(2-hydroxyalkyl)anilines, as outlined in Scheme 1.

The required *N*-alkenyl-*N*-(2-hydroxyalkyl)anilines **2** are readily prepared by the following method: oxazolidines **1**[8] were easily synthesized by the reaction of the corresponding *β*-anilino alcohols[9] with paraformaldehyde in quantitative yields. The Grignard reactions of **1** with alkenylmagnesium bromide proceeded smoothly at room temperature to give **2** in 80—95% yields.

Iodinative etherification was examined under two different reaction conditions: *N*-iodosuccinimide (NIS) in CH_2Cl_2 and iodine/$NaHCO_3$ in Et_2O–H_2O. Iodinative etherification of **2a** with 4 equiv of NIS in CH_2Cl_2 at room temperature for 4 h afforded a small amount of 2-iodomethyl-4-(*p*-iodophenyl)-6-methylmorpholine (**3a**), along with *N*-allyl-*N*-(2-hydroxypropyl)-*p*-iodoaniline, the main product. However, treatment of **2a** with iodine in the presence of $NaHCO_3$ in ether–H_2O at room temperature gave only **3a** in a 60% yield, as would be expected from the greater stability of six- over seven-membered rings and a general preference for *exo* cyclization over *endo* cyclization.[10] Similarly, in the cyclization of **2e** without Markovnikov preference, the *exo* cyclization product **3e** was obtained (Run 8). The obtained morpholine **3a** consisted of two isomers with cis preference (cis/trans=88/12, Run1). In addition, no isomerization of *cis*-**3a** to *trans*-**3a** was observed under these conditions. On exposure of **2a** to a large excess of iodine, the reaction was completed within 2 h at room temperature (Run 2). When the para-position was blocked with a methyl group, iodinative etherification led to 2-iodomethyl-6-methyl-4-(*p*-tolyl)morpholine (**3b**) in a 63% yield with cis preference (cis/trans=73/27, Run 3). Other examples are listed in Table 1 along with reaction conditions, the combined isolated yields of *cis*- and *trans*-**3**, and their ratios. Previously, Barluenga and co-workers reported the intermolecular cyclization reaction of diallyl ether with anilines in the presence of Hg(II), followed by reductive removal of mercury with $NaBH_4$, to give 3,5-dimethyl-4-phenylmorpholines as a mixture of two isomers in the range of 41 : 59—9 : 91.[11] However, identification of the two stereoisomers was not determined.

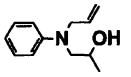
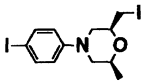
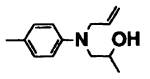
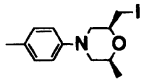
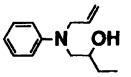
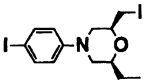
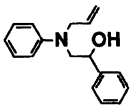
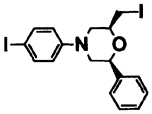
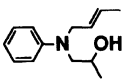
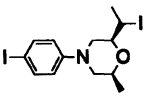


Scheme 1.

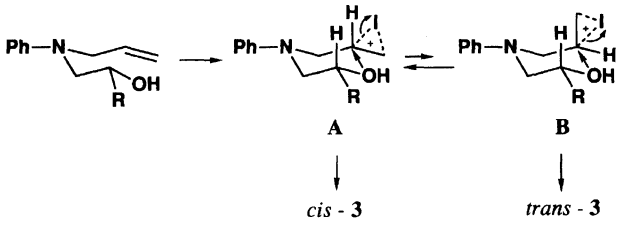
The currently accepted mechanism for this cyclization assumes the formation of a cyclic three-membered iodonium ion by electrophilic attack of a positive iodine species upon the double bond. Although there is no concrete evidence for the three-membered iodonium ring, the formation of *cis*-**3** may be rationalized in terms of an intermediate chair conformation such as **A**, with substituent R and the iodonium ion in the equatorial positions, as shown in Scheme 2.

Cis/trans stereochemical assignments for **3** were made in analogy with known 2,6-dialkylmorpholines[12—15] on the basis of ^{13}C NMR data for the corresponding deiodinated derivatives. The iodine attached to the iodomethyl carbon can be removed with $NaBH_4$ reduction in DMSO, giving the corresponding 2,6-dialkylmorpholine derivatives.[16] Furthermore, the iodomethyl carbons of the cis isomers appeared at a higher field relative to those of the corresponding trans isomers in their ^{13}C NMR spectra.[17] For example, the iodomethyl carbons of *cis*- and *trans*-**3a** appeared at δ=4.6 and 5.4, respectively.

Table 1. Cis-Selective Iodinative Etherification of *N*-Alkenyl-*N*-(2-hydroxyalkyl)anilines

Run	*N*-Alkenyl-*N*-(2-hydroxyalkyl)anilines		Reaction conditions: Temp °C	Time h	Ratio I_2/**2**	Main product		Yield %	Cis : Trans[a)]
1		**2a**	20	11	6		**3a**	60	88 : 12
2			20	2	10			93	88 : 12
3		**2b**	20	28	2.3		**3b**	63	73 : 27
4		**2c**	20	12	6		**3c**	88	82 : 18
5			20	2	10			86	83 : 17
6		**2d**	20	14	10		**3d**	69	84 : 16
7			0	2.5	15			65	86 : 14
8		**2e**	20	2	10		**3e**	91	85 : 15

a) The ratio was determined by capillary GC analysis.



Scheme 2.

We attempted to extend this approach to the syntheses of 1,4-oxazepines and 1,4-oxazocines, but were unable to isolate any of the desired seven- and eight-membered ring compounds.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL GSX-400 spectrometer in $CDCl_3$ solution using $(CH_3)_4Si$ as an internal standard. Gas chromatography was performed on a Hewlett–Packard 5890A instrument fitted with an OV101 capillary column. Mass spectra were recorded with a Perkin–Elmer Model 910 gas chromatographic mass spectrometer at 70 eV.

General Method for the Iodinative Etherification of 2. To a stirred solution of 96 mg of **2c** (0.47 mmol) and 700 mg of $NaHCO_3$ in 25 mL of Et_2O–H_2O (4 : 1) was added 1.19 g of iodine (4.7 mmol) in one portion at room temperature. After being stirred for 2 h, the mixture was washed with aqueous $Na_2S_2O_3$ to remove the excess iodine. After the usual work-up, the obtained reaction mixture was chromatographed on silica gel with 50% ether in hexane to give a mixture of *cis*- and *trans*-2-ethyl-6-iodomethyl-4-(*p*-iodophenyl)morpholine (**3c**) in an 86% yield.

***cis*-2-Iodomethyl-4-(*p*-iodophenyl)-6-methylmorpholine (3a):** ^{13}C NMR δ=4.6, 18.7, 52.8, 54.5, 72.1, 74.8, 82.0, 118.4, 137.9, and 150.2; ^{1}H NMR δ=1.27 (d, J=6.2 Hz, 3H), 2.42 (dd, J=10.6 and 4.4 Hz, 1H), 2.44 (dd, J=10.6 and 4.4 Hz, 1H), 3.18 (dd, J=10.4 and 6.4 Hz, 1H), 3.25 (dd, J=10.4 and 5.3 Hz, 1H), 3.37 (d, J=11.7 Hz, 1H), 3.68—3.75 (m, 1H), 3.73 (d, J=11.7 Hz, 1H), 3.80—3.85 (m, 1H), 6.67 (d, J=9.2 Hz, 2H), and 7.53 (d, J=9.2 Hz, 2H); MS m/z (rel intensity)=443 (M^+, 11), 317 (8), 316 (100), 274 (17), 272 (15), 232 (7), 231 (12), 230 (15), 203 (8), 145 (5), 144 (7), and 127 (6). Found: C, 32.32; H, 3.36; N, 3.11%. Calcd for $C_{12}H_{15}NOI_2$: C, 32.53; H, 3.41; N, 3.16%.

***cis*-2-Iodomethyl-6-methyl-4-(*p*-tolyl)morpholine (3b):** ^{13}C NMR δ=4.9, 18.7, 20.4, 53.9, 55.6, 72.3, 75.1, 97.1, 116.5, 116.8, 129.7, and 148.6; ^{1}H NMR δ=1.26 (d, J=6.6 Hz, 3H), 2.27 (s, 3H), 2.38 (dd, J=10.3 and 3.3 Hz, 1H), 2.42 (dd, J=10.3 and 2.2 Hz, 1H), 3.18 (dd, J=10.3 and 6.6 Hz, 1H), 3.25 (dd, J=10.3 and 5.5 Hz, 1H), 3.34 (d, J=11.7 Hz, 1H), 3.69—3.76 (m, 2H), 3.82—3.87 (m, 1H), 6.83 (d, J=8.4 Hz, 2H), and 7.08 (d, J=8.4 Hz, 2H); MS m/z (rel intensity)=332 (M^+, 6), 331 (59), 205 (11), 204 (100), 162 (31), 160 (48), 132 (6), 120 (17), 119 (30), 118 (35), 117 (7), and 91 (32). Found: C, 47.07; H, 5.51; N, 4.20%. Calcd for $C_{13}H_{18}NOI$: C, 47.15; H, 5.48; N, 4.23%.

***cis*-2-Ethyl-6-iodomethyl-4-(*p*-iodophenyl)morpholine (3c):** ^{13}C NMR δ=4.7, 9.9, 26.3, 52.9, 53.1, 74.9, 81.9, 118.1, 137.9, and 150.3; ^{1}H NMR δ=1.03 (t, J=7.3 Hz, 3H), 1.54—1.65 (m, 2H), 2.42 (dd, J=11.6 and 2.4 Hz, 1H), 2.50 (dd, J=11.6 and 2.8 Hz, 1H), 3.18 (dd, J=10.3 and 6.6 Hz, 1H), 3.25 (dd, J=10.3 and 5.9 Hz, 1H), 3.38 (d, J=10.2 Hz, 1H), 3.53—3.62 (m, 1H), 3.65—3.72 (m, 1H), 3.72 (d, J=10.2 Hz, 1H), 6.67 (d, J=8.8 Hz, 2H), and 7.52 (d, J=8.8 Hz, 2H); MS m/z (rel intensity)=457 (M^+, 12), 331 (8), 330 (100), 288 (14), 286 (16), 246 (17), 232 (6), 231 (13), 230 (15), and 203 (10). Found: C, 34.32; H, 3.71; N, 3.11%. Calcd for $C_{13}H_{17}NOI_2$: C, 34.16; H, 3.75; N, 3.06%.

***cis*-2-Iodomethyl-4-(*p*-iodophenyl)-6-phenylmorpholine (3d):** ^{13}C NMR δ=4.9, 53.8, 55.0, 74.5, 78.0,

82.3, 118.3, 126.2, 128.2, 128.5, 137.9, 139.1, and 150.1; ^{1}H NMR δ=2.62—2.72 (m, 1H), 3.31—3.35 (m, 2H), 3.54 (d, J=10.3 Hz, 1H), 3.79—3.86 (m, 2H), 4.76 (d, J=10.3 Hz, 1H), 6.69 (d, J=8.8 Hz, 2H), 7.33—7.42 (m, 5H), and 7.53 (d, J=8.8 Hz, 2H); MS m/z (rel intensity)=505 (M^+, 5), 378 (23), 334 (24), 272 (32), 251 (17), 231 (44), 230 (36), 208 (46), 203 (15), 195 (12), 146 (16), 145 (52), 144 (29), 130 (16), 128 (26), 127 (45), 118 (14), 117 (58), 116 (8), 115 (9), 105 (78), 104 (53), 103 (47), 91 (45), 79 (20), 78 (66), 77 (100), and 76 (38). Found: C, 40.30; H, 3.42; N, 2.80%. Calcd for $C_{17}H_{17}NOI_2$: C, 40.42; H, 3.39; N, 2.77%.

***cis*-2-(1-Iodoethyl)-4-(*p*-iodophenyl)-6-methylmorpholine (3e):** ^{13}C NMR δ=18.8, 24.2, 26.8, 51.4, 54.6, 71.9, 78.8, 81.8, 118.1, 137.9, and 150.4; ^{1}H NMR δ=1.27 (d, J=6.2 Hz, 3H), 1.96 (d, J=6.9 Hz, 3H), 2.45 (dd, J=10.3 and 11.7 Hz, 1H), 2.60 (dd, J=10.3 and 11.7 Hz, 1H), 3.34—3.38 (m, 2H), 3.63 (d, J=11.3 Hz, 2H), 3.79—3.84 (m, 1H), 4.15—4.22 (m, 1H), 6.67 (d, J=9.2 Hz, 2H), and 7.52 (d, J=9.2 Hz, 2H); MS m/z (rel intensity)=457 (M^+, 5), 331 (13), 330 (100), 274 (22), 272 (8), 232 (9), 231 (16), 230 (20), 203 (9), 146 (6), 128 (6), 127 (8), 104 (5), 77 (6), and 76 (6). Found: C, 34.09; H, 3.80; N, 3.09%. Calcd for $C_{13}H_{17}NOI_2$: C, 34.16; H, 3.75; N, 3.06%.

Reductive Deiodination of 3 with $NaBH_4$. To a solution of $NaBH_4$ (0.05 g, 1.3 mmol) in dry DMSO (10 mL) was added 0.12 g of **3a** (0.27 mmol, cis/trans=88/12) in DMSO (5 mL). The mixture was stirred for 4 h at 80 °C. The mixture was then poured into water and extracted with dichloromethane. The combined organic layers were washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel with 30% CH_2Cl_2 in hexane to give a quantitative yield of 4-(*p*-iodophenyl)2,6-dimethylmorpholine (cis/trans=86/14).

References

1) B. B. Snider and M. I. Johnston, *Tetrahedron Lett.*, **26**, 5497 (1985); Y. Ohfune, K. Hori, and M. Sakaitani, *Tetrahedron Lett.*, **27**, 6079 (1986); P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).

2) Y. Tamaru, S. Kawamura, and Z. Yoshida, *Tetrahedron Lett.*, **26**, 2885 (1985).

3) F. Freeman and K. D. Robarge, *J. Org. Chem.*, **54**, 346 (1989).

4) R. Kinsman, D. Lathbury, P. Vernon, and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, **1987**, 243.

5) T. Hosokawa, M. Hirata, S. Murahashi, and A. Sonoda, *Tetrahedron Lett.*, **21**, 1821 (1976).

6) M. Hirama, M. Iwashita, Y. Yamazaki, and S. Ito, *J. Am. Chem. Soc.*, **107**, 1797 (1985).

7) G. Cardillo and M. Orena, *Tetrahedron*, **46**, 3321 (1990).

8) T. Nishiyama, T. Nishikawa, and F. Yamada, *J. Heterocycl. Chem.*, **26**, 1687 (1989).

9) *N*-(2-Hydroxypropyl)anilines were prepared by the regio-selective ring opening reaction of propylene oxide with anilines in the presence of a metal salt. *N*-(2-Hydroxy-2-phenylethyl)aniline was isolated by column chromatography: M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett.*, **31**, 4661 (1990). *N*-(2-Hydroxybutyl)aniline was prepared by the reaction of 2-hydroxybutyric acid with aniline, followed by reduction with $LiAlH_4$.

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

11) J. Barluenga, C. Najera, and M. Yus, *Synthesis*, **1978**, 911.

12) A. J. Jones, C. P. Beeman, M. U. Hasan, A. F. Casy, and M. M. A. Hassan, *Can. J. Chem.*, **54**, 126 (1976).

13) A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Can. J. Chem.*, **51**, 1782 (1973).

14) H. Boothe and G. C. Gidley, *Tetrahedron*, **21**, 3429 (1965).

15) B. Nilsson and S. Hernestam, *Org. Magn. Reson.*, **11**, 116 (1978).

16) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969).

17) G. C. Levy, R. L. Lichter, and G. L. Nelson, "Carbon-13 NMR Spectroscopy," 2nd ed, Wiley, New York (1980).