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Novel Synthesis of 1,4-Diazacrown Ethers by Reductive Coupling of Aromatic Diimines

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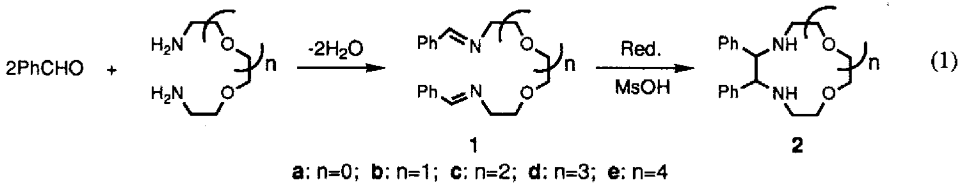
Abstract: The electroreduction or chemical reduction with zinc powder has been found to be effective to intramolecular coupling of aromatic diimines yielding 1,4-diazacrown ethers. The latter reduction was particularly effective to formation of 1,4-diaza-12-crown-4 derivatives due to the template effect of Zn^{2+}.

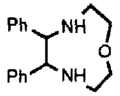
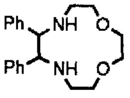
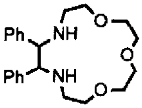
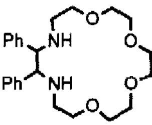
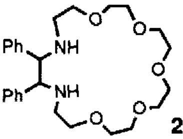
The synthesis of diazacrown ethers[1,2] has usually been achieved by acylation of diamines with diacid chlorides followed by reduction of the resultant diamides or by alkylation of diamines with dihalides though both methods require the conditions of high dilution.[3] On the other hand, in our continuing studies on the electroreductive coupling of unsaturated systems, we have found that 1,4-diazacrown ethers **2** are effectively synthesized by intramolecular coupling of aromatic diimines **1** promoted by electroreduction (Method A)[4] or chemical reduction with zinc powder (Method B)[6] (eq. 1).



(1)

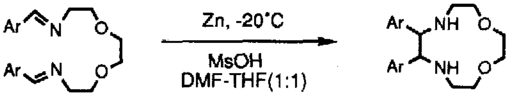
Diimines **1a-e** (n=0~4) were prepared quantitatively by reflux of benzaldehyde with the corresponding diamines for 1 hour in benzene. The reductive coupling of **1** was carried out in the presence of methanesulfonic acid (MsOH). A variety of 1,4-diazacrown ethers could be synthesized by this reductive coupling as shown in Table 1. Although both methods showed similar results in the synthesis of **2a**, **2d** and **2e**, Method B gave better yields and *trans*-diastereoselectivities than did Method A in the synthesis of **2b** and **2c**. The best result was obtained when the reduction of **1b** was carried out with Method B at -50°C in DMF-THF (1:1). The reduction with Method B was also found to be highly effective for the reductive coupling of aromatic diimines prepared from aromatic aldehydes other than benzaldehyde as the results are shown in Table 2.

Table 1. Reductive Intramolecular Coupling of Aromatic Diimines **1**

1	method	temp.	solvent	2	% yield[a]	*trans:cis* [b]
1a	A	25°C	DMF	 **2a**	40	~100: 0
	A	25°C	DMF-THF(1:1)		49	~100: 0
	B	25°C	DMF		49	~100: 0
	B	-50°C	DMF-THF(1:1)		43	~100: 0
1b	A	25°C	DMF	 **2b**	57	55:45
	A	25°C	DMF-THF(1:1)		75	65:35
	A	-20°C	DMF-THF(1:1)		68	60:40
	B	25°C	DMF		78	80:20
	B	-50°C	DMF		85	85:15
	B	25°C	DMF-THF(1:1)		85	80:20
	B	-50°C	DMF-THF(1:1)		90	90:10
1c	A	25°C	DMF	 **2c**	60	50:50
	A	25°C	DMF-THF(1:1)		72	60:40
	B	25°C	DMF		74	65:35
	B	-50°C	DMF-THF(1:1)		85	75:25
1d	A	25°C	DMF	 **2d**	67	50:50
	A	25°C	DMF-THF(1:1)		73	50:50
	B	25°C	DMF		72	65:35
	B	-50°C	DMF-THF(1:1)		77	65:35
1d	A	25°C	DMF	 **2e**	56	40:60
	A	25°C	DMF-THF(1:1)		62	45:55
	B	25°C	DMF		55	60:40
	B	-50°C	DMF-THF(1:1)		65	60:40

a. Isolated yields. b. See ref. 7.

Table 2. Synthesis of 1,4-Diaza-12-crown-4 Derivatives

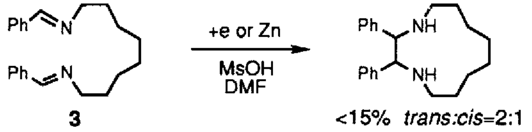


1f-l **2f-l**

Ar	2	% yield[a]	*trans:cis*[b]
p-$MeOC_6H_4$	**2f**	86	90:10
p-ClC_6H_4	**2g**	86	85:15
p-$MeO_2CC_6H_4$	**2h**	52	50:50
1-Furyl	**2l**	70	95: 5

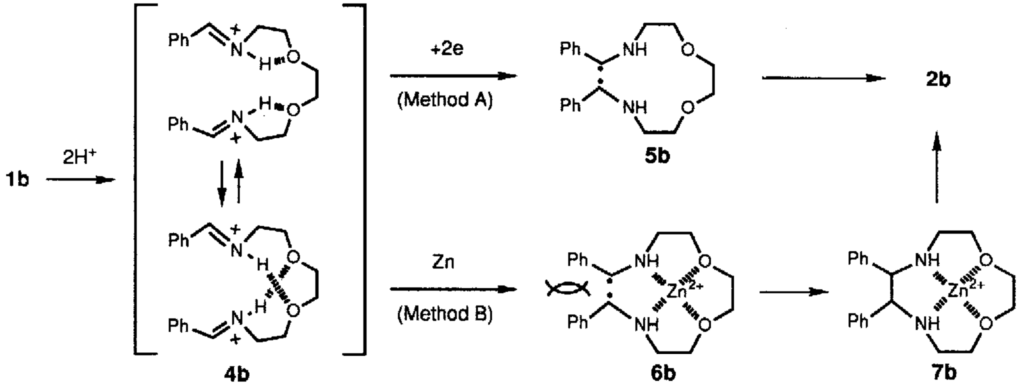
a. Isolated yields. b. Determined by ^1H NMR. See ref. 9.

Although a ring closing reaction leading to formation of a macrocyclic compound has been known to be not always easily achievable, macrocyclic products **2** were formed in reasonable yields by the reductive intramolecular coupling of **1** as shown above. This result is explainable by contribution of the oxygen atoms in the ether linkage of **1**, since the reduction of the carbon chain analog (**3**) corresponding to **1a** gave poor results under the same reduction conditions (eq. 2).



(2)

Thus it seems reasonable that the interaction between hydrogen and oxygen atoms in the diprotonated **1** (**4**) makes the two iminium moieties close and hence, assists the intramolecular coupling of the biradical species **5** or **6** which is generated by donation of two electrons to **4** (Scheme 1). The fact that Method B gave better results in the formation of **2b** (n=1) than did Method A is explained by the template effect[10] of Zn^{2+}. Thus, a complex **6b** is formed almost concertedly with the transfer of two electrons to **4b** from Zn and the formation of **6b** makes the intramolecular coupling of two radical centers easier than the coupling in **5b** and also the product (**7b**) is more stable than **2b**. High *trans*-diastereoselectivity in the formation of **2b** is due to the repulsion between two phenyl groups in **6b**. Since the diameter of hole in 12-crown-4 is close to the ionic diameter of Zn^{2+} (1.48 Å),[11] the template effect of Zn^{2+} is the most conspicuous in the formation of 1,4-diaza-12-crown-4 derivative (**2b**) and decreases with increasing the ring size of **2** (n=1~3). As expected, the template effect of Zn^{2+} was negligible in the formation of 1,4-diaza-9-crown-3 derivative (**2a**, n=0).



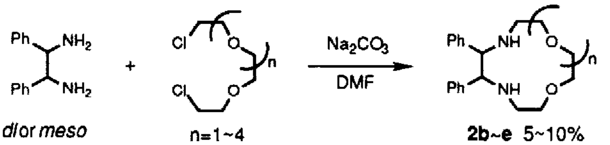
Scheme 1

References and Notes

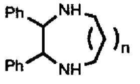
1. For a review: Sutherland, I. O. *Chem. Soc. Rev.*, **1986**, *15*, 63-91.
2. For recent reports of modified azacrown ethers: (a) Nakatsuji, Y.; Wakita, R.; Harada, Y.; Okahara, M. *J. Org. Chem.*, **1989**, *54*, 2988-2990. (b) Bradshow, J. S.; Krakowiak, K. E.; An, H.; Izatt, R. M. *Tetrahedron*, **1990**, *46*, 1163-1170. (c) Zinic, M.; Frkanec, L.; Skaric, V.; Trafton, J.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.*, **1990**, 1726-1728. (d) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *J. Org. Chem.*, **1991**, *56*, 268-272. Other references cited therein.
3. For a review: Krakowiak, K. E.; Bradshow, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.*, **1989**, *89*, 929-971.
4. The electroreduction was carried out according to our previously reported method:[5] A solution of Et_4NOTs (4 g) in DMF (40 mL) was put into a divided cell (50 mL beaker) equipped with a lead cathode (5 X 10 cm^2), a carbon rod anode, and a ceramic diaphragm. To the catholyte were added a diimine **1** (5 mmol) and methanesulfonic acid (25 mmol). After electricity was passed at a constant current of 0.5 A

(2.2 *F*/mol), the catholyte was poured into sat. $NaHCO_3$ aq (200 mL) and extracted with CH_2Cl_2. The product **2** was isolated by column chromatography on basic Al_2O_3 (activity III, hexane-AcOEt).

5. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.*, **1991**, *56*, 3063-3067.
6. Typical procedure is as follows: To a solution of **1** (2 mmol) in THF (10 mL) and DMF (10 mL) was added MsOH (0.96 g, 10 mmol) and zinc powder (0.65 g, 10 mmol) at -50 °C and the suspension was stirred for 12 h at this temperature. After addition of 50 mL of sat. $NaHCO_3$ aq, the mixture was extracted with CH_2Cl_2. The product **2** was isolated by column chromatography on basic Al_2O_3 (activity III, hexane-AcOEt).
7. Each diastereomers of **2b**, **2c** and **2e** could be separated by column chromatography on basic Al_2O_3. The diastereomeric ratio of **2d** was determined by its ^{13}C NMR spectrum, since diastereomers of **2d** could not be separated. The stereoconfigurations of each isomers of **2b~e** were confirmed by their comparison with the authentic samples prepared from *dl*- or *meso*-1,2-diphenylethylenediamine by the usual alkylation.[8] The product **2a** was obtained as a single stereoisomer and assigned to be trans by the correlation of its ^1H NMR spectrum with **8**.[5] The chemical shifts (σ values) of methyn protons (singlet) adjacent to nitrogen atom in **2a** and **8** were as follows: *trans*-**2a** 4.34; *trans*-**8a** 4.22; *cis*-**8a** 3.71; *trans*-**8b** 4.08; *cis*-**8b** 3.84.



dl or *meso* n=1~4 **2b~e** 5~10%



8a n=1
8b n=2

^{13}C NMR spectra of **2a-e** (50MHz, $CDCl_3$, σ values) were as follows. *trans*-**2a**: 48.82 (2 C, t), 66.30 (2 C, d), 76.16 (2 C, t), 126.60 (2 C, d), 127.40 (4 C, d), 127.91 (4 C, d), 141.42 (2 C, s). *trans*-**2b**: 48.06 (2 C, t), 69.68 (2 C, d), 69.89 (4 C, t), 127.18 (2 C, d), 128.42 (8 C, d), 142.94 (2 C, s). *cis*-**2b**: 46.73 (2 C, t), 66.14 (2 C, d), 69.67 (2 C, t), 70.84 (2 C, t), 127.08 (2 C, d), 127.97 (4 C, d), 128.64 (4 C, d), 141.20 (2 C, s). *trans*-**2c**: 46.45 (2 C, t), 69.38 (2 C, d), 69.82 (2 C, t), 69.95 (2 C, t), 70.55 (2 C, t), 127.14 (2 C, d), 128.20 (4 C, d), 128.56 (4 C, d), 142.03 (2 C, s). *cis*-**2c**: 46.44 (2 C, t), 67.05 (2 C, d), 69.15 (2 C, t), 70.18 (2 C, t), 70.39 (2 C, t), 127.19 (2 C, d), 127.84 (4 C, d), 129.13 (4 C, d), 140.14 (2 C, s). *trans*-**2d**: 46.98 (2 C, t), 69.50 (2 C, d), 70.53 (2 c, t), 70.60 (2 C, t), 70.86 (2 C, t), 71.01 (2 C, t), 127.28 (2 C, d), 128.33 (4 C, d), 128.59 (4 C, d), 142.01 (2 C, s). *cis*-**2d**: 46.87 (2 C, t), 67.90 (2 C, d), 70.57 (2 C, t), 70.79 (2 C, t), 71.07 (2 C, t), 71.20 (2 C, t), 127.21 (2 C, d), 127.94 (4 C, d), 129.10 (4 C, d), 140.51 (2 C, s). *trans*-**2e**: 47.44 (2 C, t), 69.86 (2 C, d), 71.17 (2 C, t), 71.20 (2 C, t), 71.32 (4 C, t), 71.42 (2 C, t), 71.54 (2 C, t), 127.73 (2 C, d), 128.38 (4 C, d), 128.65 (4 C, d), 142.17 (2 C, s). *cis*-**2e**: 47.25 (2 C, t), 68.00 (2 C, d), 71.02 (2 C, t), 71.20 (2 C, t), 71.32 (4 C, t), 71.49 (2 C, t), 127.36 (2 C, d), 128.14 (4 C, d), 129.05 (4 C, d), 140.90 (2 C, s).

8. Maeda, H.; Furuyoshi, S.; Nakatsuji, Y.; Okahara, M. *Bull. Chem. Soc. Jpn.*, **1983**, 3073-3077.
9. The stereoconfigurations of **2f-i** were determined by comparison of their ^1H NMR spectra (200MHz, $CDCl_3$) with **2b**. The chemical shifts (σ values) of methylene protons (triplet) adjacent to nitrogen atom in **2b,f-i** were as follows: *trans*-**2b** 2.75; *cis*-**2b** 2.87; *trans*-**2f** 2.73; *cis*-**2f** 2.84; *trans*-**2g** 2.72; *cis*-**2g** 2.82; *trans*-**2h** 2.72; *cis*-**2h** 2.82; *trans*-**2i** 2.75; *cis*-**2i** 2.91.
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11. (a) Pedersen, C. J. *J. Am. Chem. Soc.*, **1967**, *89*, 7017-7036. (b) Pedersen, C. J. *J. Am. Chem. Soc.*, **1970**, *92*, 386-394.

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