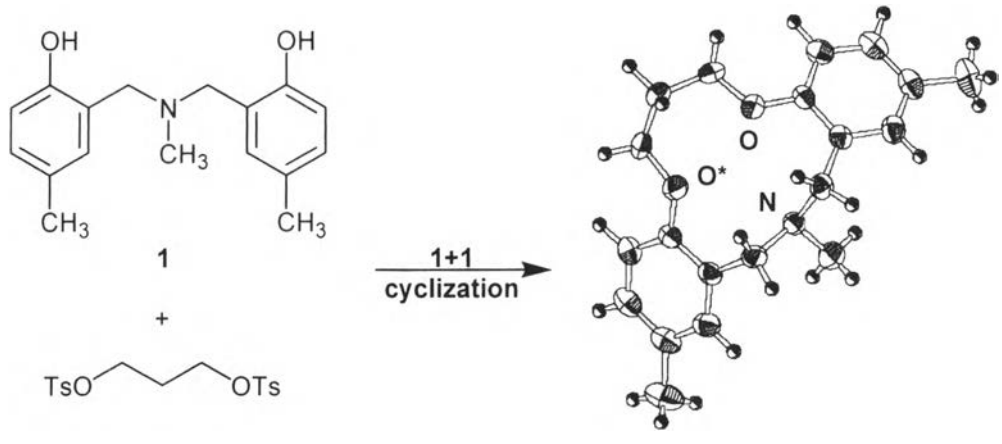
CHAPTER VI

EFFECTIVE AND SELECTIVE ONE-POT SYNTHESIS FOR DIBENZO-MONOAZA-12-CROWN-3 BASED ON *N,N*-BIS(2-HYDROXYBENZYL)ALKYLAMINE DERIVATIVES

Graphical Abstract



Abstract

N,N-Bis(2-hydroxybenzyl)alkylamine offers a selective and effective one-pot synthesis for dibenzo-monoaza-12-crown-3 via the reaction with 1,3-bis(tosyloxy)propane.

Key words: Macrocycle, Cyclization, Phenol, Dibenzo-monoaza-12-crown-3, *N,N*-Bis(2-hydroxybenzyl)alkylamine

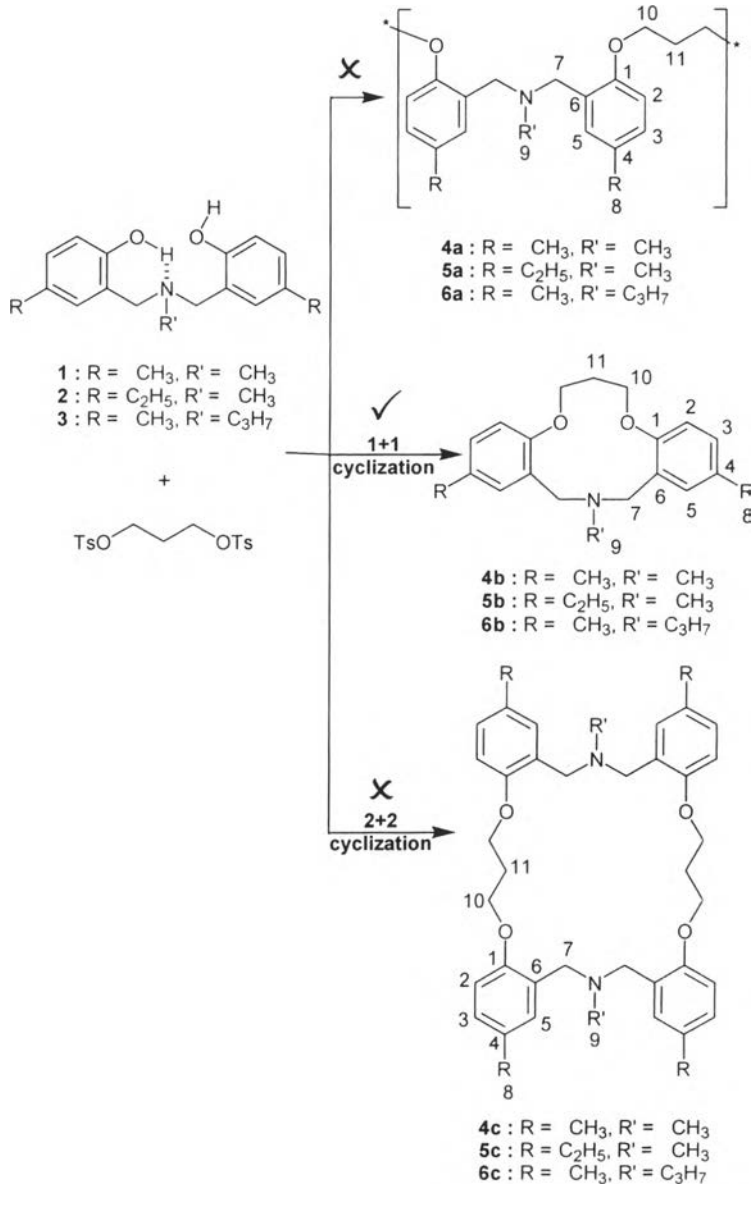
Chemistry of supramolecules is a challenging theme to develop the recognition at molecular level.[1] In principle, supramolecular phenomena are achieved from either self-assemblies or macrocyclic compounds. In the case of self-assemblies, the key points involve the molecular design with a significant non-covalent bond and the condition to initiate host-guest interaction.[2] For macrocycles, the selective cyclization is needed for synthesizing the specific ring with inclusion properties as seen in the cases of crown ethers[3-4] and calixarenes.[5] It should be noted that the syntheses to deliver cyclic compounds require the dilute condition[6] and/or the metal template for controlling the type of the reaction, such as [1+1] and [2+2] cyclization.[7] The difficulties in producing macrocycle are, thus, the selection of effective metal template, selective cyclization, purification, and separation (i.e., chromatography, recrystallization, etc.).

Crown ethers are macrocycles obtained from the reaction among the reactive ethylene glycol.[3] In most cases, crown ethers are produced under template effect to achieve the macrocyclic size as desired. For example, potassium ion is known as a template for 18-crown-6 whereas sodium ion is used for 15-crown-5. It should be noted that only a certain condition, the macrocycles are achieved in high yield to follow with separation steps.[3]

Recently, Agai *et al.* proposed the synthesis of dibenzo-monoazacrown ethers based on phenol-aza-phenol derivatives.[8] In that case, monoaza-12-crown-4 was the smallest crown ethers obtained from [1+1] cyclization of tosylated derivatives using potassium iodide under the basic condition. Although the synthesis gave the novel dibenzo-monoaza crown ethers, the yield was about 30%.

For the past few years, our group has focused on benzoxazine and its dimerized derivatives, i.e., *N,N*-bis(2-hydroxybenzyl)alkylamines (Scheme 1, compounds **1**-**3**).[9-13] These dimerized compounds have unique structures with inter- and intramolecular hydrogen bonds to perform asymmetric reaction[9] and selective cyclization via esterification and etherification.[10-11] Considering the unit of *N,N*-bis(2-hydroxybenzyl)-alkylamines, it should be noted that the unit gives us a diphenol linked with aza-methylene group to produce dibenzo-azacrown derivatives. Considering the reaction of *N,N*-bis(2-hydroxybenzyl)alkylamines with 1,3-

bis(tosyloxy)propane, one may recognize the feasible reactions of linear polymerization and macrocyclization ([1+1] and/or [2+2] pathways) as shown in Scheme 1. To our surprise, we found that the reaction gives [1+1] macrocycle in high yield without by-products. In this article, we report the selective and effective synthesis pathway of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives to provide inevitably a [1+1] dibenzo-monoaza-12-crown-3 derivative.



Scheme 1 Feasible reaction of *N,N*-bis(2-hydroxybenzyl)alkylamine and 1,3-bis(tosyloxy)propane

The reaction of *N,N*-bis(2-hydroxy-5-methylbenzyl)methylamine[13], **1**, and 1,3-bis(tosyloxy)propane was carried out as follows. A white powder of **1** (0.27 g, 1 mmol) was refluxed in acetonitrile (150 mL) with potassium hydroxide (0.11 g, 2 mmol) for an hour. A solution of 1,3-bis(tosyloxy)propane (0.38 g, 1 mmol) in acetonitrile (70 mL) was added dropwisely and refluxed continuously for 3 days before removing solvent. The crude product was dissolved in dichloromethane, washed several times with water, before drying over anhydrous sodium sulfate. The solvent was removed to obtain the white product.

To answer the question about which compound in Scheme 1 is obtained, we carried out the structural characterizations as follows. Compound **1** gave the peaks at 3240 cm^{-1} (intermolecular H-bond), 3200-2600 cm^{-1} (intramolecular H-bond), 1612 cm^{-1} (trisubstituted benzene), 1350 cm^{-1} (C-N-C stretching), and 1242 cm^{-1} (C-N stretching). After the reaction with 1,3-bis(tosyloxy)propane, a new peak at 1065 cm^{-1} due to Ar-O-CH_2 stretching was clarified while the broad OH peak was disappeared implying the successful etherification.[14] The peak shifts (1350 to 1327 and 1242 to 1250 cm^{-1}) refering to the changes in vibrational mode of C-N-C and C-N stretching suggested the change in structure. The compound **4** obtained may either be any of those shown in Scheme 1. The ^1H NMR of **4** (Table 1) declares the protons of *N,N*-bis(2-hydroxybenzyl)alkylamine (positions of 2, 3, 5, 7, 8, and 9, as shown in **4a**, **4b**, and **4c** in Scheme 1) and of propyl chain (positions of 10 and 11) whereas the ^1H-^{13}C HMBC shows nearby interaction between C1 and H10. These confirm the successful reaction of *N,N*-bis(2-hydroxybenzyl)alkylamines and 1,3-bis(tosyloxy)propane. It is important to note that ^1H-^1H NOESY demonstrates the strong interaction of H7 with H10 and H11 implying the possibility of cyclic formation either [1+1] or [2+2].

The matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) shows a single peak at m/z = 312.6 which precisely equals to the [1+1] formation from a propyl chain and an *N,N*-bis(2-hydroxybenzyl)alkylamine.[15]

It is important to note that the macrocyclization depends on the nucleophilic reaction between phenoxide species of *N,N*-bis(2-hydroxybenzyl)alkylamines and

1,3-bis(tosyloxy)propane. When the reaction was carried out with sodium hydroxide, we found that the product was rarely obtained. However, the system with potassium hydroxide produced **4** in high yield (75%). In other words, the selective reaction might relate to the role of potassium hydroxide in inducing the phenoxide species to result an effective reaction. It may come from the intramolecular cyclization taking place faster than intermolecular cyclization. Other conditions, such as using the high concentration (> 5 mM) and/or applying toluene as the solvent, hardly gave any macrocycles.

Table 1 NMR data for **4** in $CDCl_3$

position	^1H δ_H, number of protons, multiplicity [J (Hz)]	^{13}C δ_c	^1H-^{13}C HMBC	^1H-^1H NOESY
1	-	155.586	-	-
2	6.736, 2H, d (7.90)	111.638	C1, C3, C4, C5, C6	H3, H10
3	6.984, 2H, d (8.56)	128.379	C1, C2, C4, C5, C6	H2, H8
4	-	128.802	-	-
5	6.977, 2H, s	131.901	C1, C2, C3, C4, C6	H7, H8, H9
6	-	128.125	-	-
7	3.614, 4H, s	58.224	C1, C5, C6, C9	H5, H9, H10
8	2.259, 6H, s	20.495	C1, C2, C3, C4, C5, C6	H3, H5
9	2.137, 3H, s	40.959	C7	H5, H7
10	4.204, 4H, t (5.02)	67.789	C1, C11	H2, H7, H11
11	2.217, 2H, qu (4.86)	28.524	C10	H10

Compound **4** was recrystallized in methanol to obtain the colorless cubic crystals. Single crystal analysis by Rigaku RAXIS-RAPID imaging plate with a software TEXSAN was carried out to clarify the structure.[16] The result demonstrates

the orthorhombic space group *Pnma* of asymmetric unit belonging to macrocyclic compound. The $R1$ value (4.7%) suggests the accuracy of [1+1] symmetrical macrocyclic compound. The TEXSAN gives an ORTEP view (Figure 1) declaring a 12-membered ring macrocyclic compound. It is natural to expect the mixture of [1+1] and [2+2] macrocycles as products. We, then, repeated our single crystal X-ray analysis using different crystals. All of the crystals showed the structure of **4b** suggesting the selective reaction without the side reaction for **4c**. We suspected that the reaction might be controlled by [1+1] template stabilized under the rigidity of benzene ring and the inter- and intramolecular hydrogen bonds of *N,N*-bis(2-hydroxybenzyl)alkylamine.

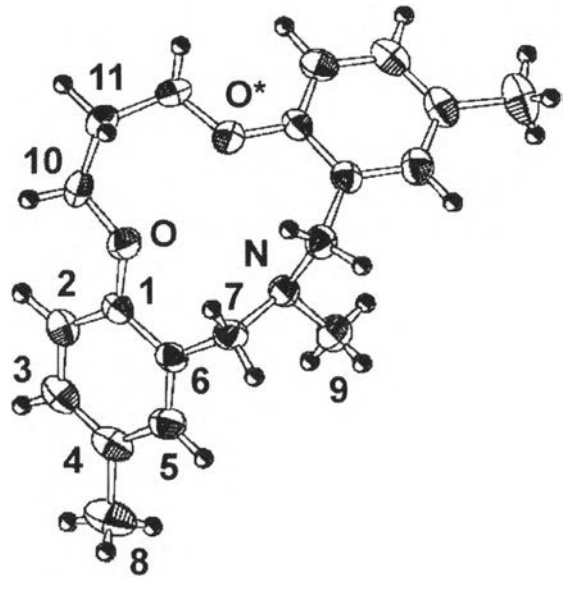


Figure 1. ORTEP view of **4b** with the atomic numbering scheme.

To confirm that *N,N*-bis(2-hydroxybenzyl)alkylamine leads to the selective and effective cyclization, we further clarified by using different derivatives, i.e., *N,N*-bis(2-hydroxy-5-ethylbenzyl)methylamine, **2**, and *N,N*-bis(2-hydroxy-5-methylbenzyl)propylamine, **3.** We found that the compound obtained are **5b**[17] and **6b**[18] as confirmed by FTIR, NMR, and MALDI-TOF MS. Considering **4b**, **5b**, and

6b, we emphasized that the structure is symmetrical with propylene unit linked by nitrogen and oxygen atoms as monoaza-12-crown-3 derivatives.

The present work declares an effective and selective macrocyclization based on *N,N*-bis(2-hydroxybenzyl)alkylamines to achieve dibenzo-monoazacrown ethers derivatives linked with propylene unit for over 75% yield. The advantages of this synthesis strategy are (i) the ease of obtaining *N,N*-bis(2-hydroxybenzyl)alkylamines (as it is quantitatively obtained from the ring opening of benzoxazines with phenols)[14], (ii) the effective and selective reaction which might be due to the unique inter- and intramolecular hydrogen bonds of *N,N*-bis(2-hydroxybenzyl)alkylamines and the rigidity of the benzene ring, and (iii) the role of potassium hydroxide to inititate phenoxide species for nucleophilic reaction with tosyl derivatives and [1+1] template. At present, we are studying inclusion phenomena of these macrocyclic compounds.

Acknowledgement

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(15) The characterization for **4b**: $C_{20}H_{25}NO_2$: mp = 203°C; FTIR (KBr, cm^{-1}): 1504 (vs, trisubstituted benzene), 1327 (vs, C-N-C stretching), 1250 (vs, C-N stretching), 1065 (s, Ar-O-CH_2); ^1H NMR (600 MHz, $CDCl_3$): δ 2.137 (s, 3H, N-CH_3), 2.217 (qu, 2H, C-CH_2-C, J_1 = 4.86 Hz), 2.259 (s, 6H, Ar-CH_3), 3.614 (s, 4H, N-CH_2-Ar), 4.204 (t, 4H, CH_2-O, J_2 = 5.02 Hz), 6.736 (d, 2H, Ar-H, J_3 = 7.90 Hz), 6.977 (s, 2H, Ar-H), 6.984 (d, 2H, Ar-H, J_4 = 8.56 Hz); ^{13}C NMR (600 MHz, $CDCl_3$): δ 20.495, 28.524, 40.959, 58.224, 67.789, 111.638, 128.125, 128.379, 128.802, 131.901, 155.586; MALDI-TOF MS: *m/z* 312.6 ($M+H^+$); Anal. Calc. for $C_{20}H_{25}O_2N$: C: 77.14, H: 8.09, N: 4.50, O: 10.28. Found: C: 76.38, H: 7.69, N: 4.46.

(16) Crystal data for **4b**: $C_{10}H_{12.5}ON_{0.5}$, M = 155.71, orthorhombic, a = 9.3556(7), b = 15.341(1), c = 11.8139(8) Å, V = 1695.6(4) $Å^3$, T = 296 K, space group *Pnma*

(no.62), Z = 8, μ(Mo-Kα) = 0.78 cm^{-1}, 12579 reflections measured, 1616 unique (*R*int = 0.032) which were used in all calculations. The final *R*1 = 0.047 and *R*w = 0.121. X-ray data for compound **4b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258583. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033. e-mail: deposit@ccdc.cam.ac.uk).

(17) The characterization for **5b**: $C_{22}H_{29}NO_2$: FTIR (KBr, cm^{-1}): 1503 (vs, trisubstituted benzene), 1248 (vs, C-N stretching), 1057 (s, Ar-O-CH_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.106 (6H, t, Ar-C-CH_3, J_1 = 7.622 Hz), 2.069 (3H, s, N-CH_3), 2.170 (2H, qu, C-CH_2-C, J_2 = 4.837 Hz), 2.484 (4H, q, Ar-CH_2-C, J_3 = 7.622 Hz), 3.571 (s, 4H, N-CH_2-Ar), 4.141 (t, 4H, CH_2-O, J_4 = 4.984 Hz), 6.679 (d, 2H, Ar-H, J_5 = 8.209 Hz), 6.911 (s, 2H, Ar-H), 6.936 (d, 2H, Ar-H, J_6 = 8.208 Hz); MALDI-TOF MS: *m/z* 338.85.

(18) The characterization for **6b**: $C_{22}H_{29}NO_2$: FTIR (KBr, cm^{-1}): 1505 (vs, trisubstituted benzene), 1253 (vs, C-N stretching), 1054 (s, Ar-O-CH_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.804 (3H, t, CH_3-C-C-N, J_1 = 7.329 Hz), 1.440 (2H, m, C-CH_2-C-N, J_2 = 7.622 Hz), 2.028 (qu, 2H, C-CH_2-C, J_3 = 4.984 Hz), 2.220 (6H, s, Ar-CH_3), 2.345 (2H, t, C-C-CH_2-N, J_4 = 7.327 Hz), 3.557 (s, 4H, N-CH_2-Ar), 4.166 (t, 4H, CH_2-O, J_5 = 4.984 Hz), 6.718 (d, 2H, Ar-H, J_6 = 8.209 Hz), 6.926 (d, 2H, Ar-H, J_7 = 8.208 Hz), 7.076 (s, 2H, Ar-H); MALDI-TOF MS: *m/z* 340.75.