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Caesium carbonate as a highly efficient catalyst for the synthesis of macrocyclicdiamides

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Abstract

In this research work, we report the synthesis of macrocyclicdiamides from the reaction of diesters and aliphatic diamines in the presence of caesium carbonate. It has been demonstrated that among the carbonate of alkali metals (Li_2CO_3, Na_2CO_3, K_2CO_3 and CS_2CO_3), CS_2CO_3 appears to be the best catalyst for macrocyclization. Diesters with different substitution patterns on the aromatic ring reacted smoothly with diamines under optimal conditions, affording the corresponding macrocycles in high yields. Introducing a rigid group (e.g., sulfone) on the substrate led to somewhat decreased yield. Various substrates proved to be suitable for this macrocyclization reaction, especially, the flexible ones.

Keywords: Macrocyclicdiamide; azaoxathia crown; synthesis; macrocycle and caesium carbonate (CS_2CO_3).

Introduction

The pioneering work of Pedersen [1] on the syntheses and the study of the complexation properties of macrocyclic host systems such as crown ethers, aza crown ethers, cryptands, macrocyclicdiamides and tetraamides has generated significant interest in host–guest and supramolecular chemistry [2,3]. These macrocycles have been shown in order to exhibit important applications including

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selective ion complexation, molecular recognition, biological applications, nanostructures preparation as well as many other applications in diverse fields of supramolecular chemistry [4]. Crown ethers are of particular interest incorporating amide groups such as macrocyclicdiamides and tetraamides. It was shown that such groups improve the binding properties of the crown compounds towards metal ions [5]. Furthermore, macrocyclic amides are precursors in the preparation of aza crown ethers and similar compounds [4]. Some diamide-containing macrocycles have been utilized as new catalysts [6]. Moreover, special interest has been directedtoward the synthesis of multi-site macrocycles which are capable of binding simultaneously to two or more metal ions and molecules [7,8].

During the past years, much more information has been available on the synthesis of macrocyclic amides. Two successful approaches include the reaction of diester or diacid dichloride with diamine [10]. Structures of monomers and the cavity sizes have been identified as major contributing factors for the synthesis of macrocycles. Recent developments in macrocyclic chemistry and the related area have heightened the need for the improved and new synthetic procedures. The published synthetic procedures have some disadvantages such as, long reaction times, the use of toxic and large volumes of solvents, harsh reaction conditions and low yields. Thus, despite advances, the further developments of efficient and practical procedures for the synthesis of macrocycles are still highly desirable.

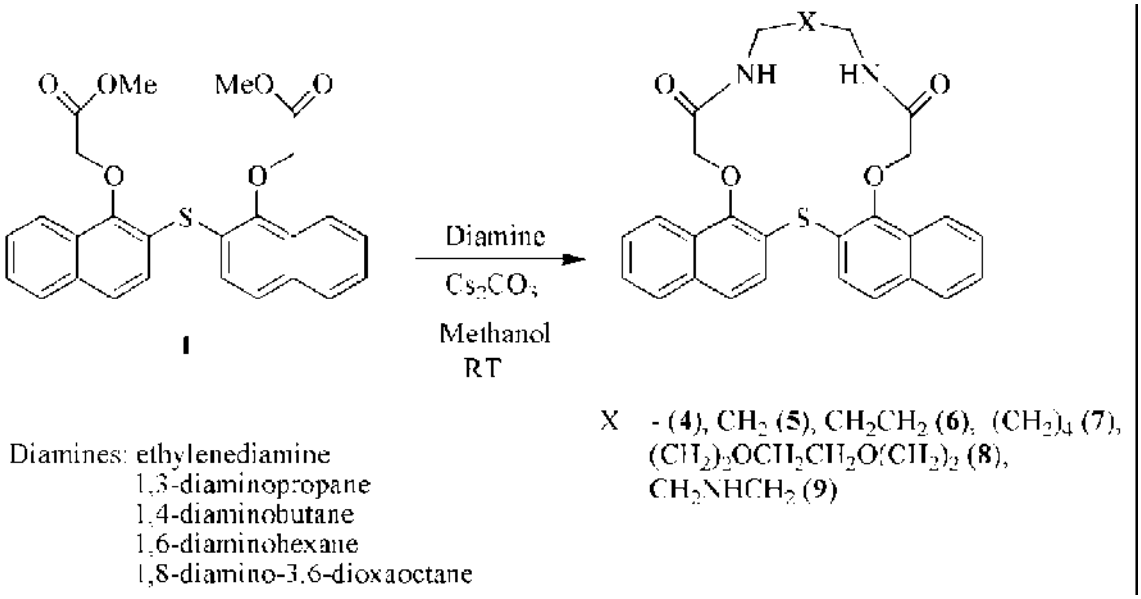
In continuation of our studies on the synthesis of novel macrocycles [11-17], herein, we successfully developed a simple, efficient and practical method for the synthesis of macrocyclicdiamidesby the use of caesium carbonate as the catalyst.

Experimental

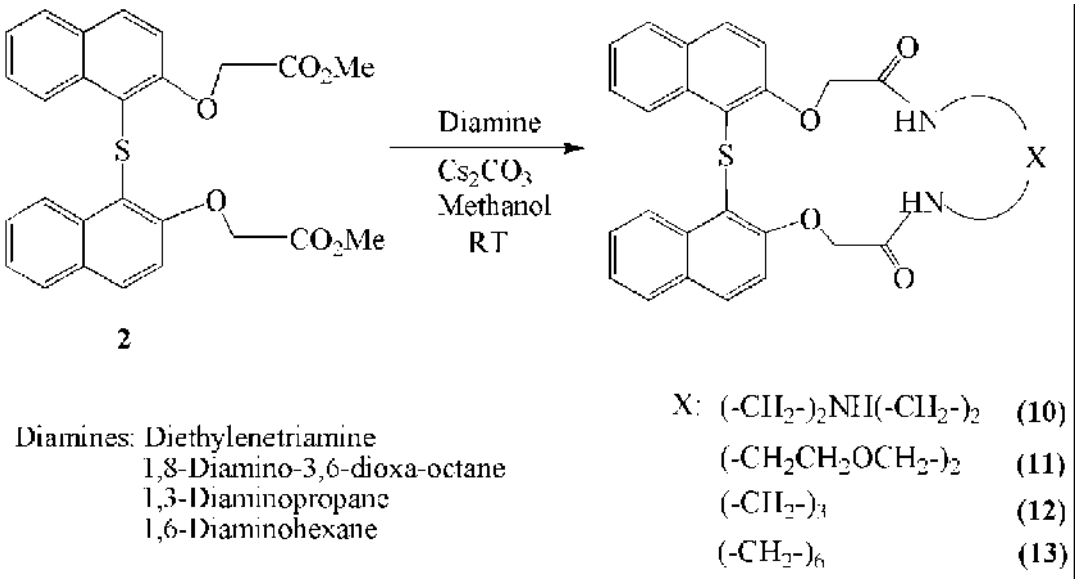
General

The reactions were carried out in an efficient hood. All the materials were purchased from Merck, Fluka and Aldrich chemical companies. Methanol was distilled over Lind 4Å molecular sieves and stored over them tightly. The melting points (uncorrected) were measured by an Electrothermal engineering LTD 9100 apparatus. Elemental analysis was performed by a CHN-O- Rapid Heraeus elemental analyzer. FTIR spectra were recorded by a Perkin-Elmer model 543 and BRUKER spectrometer. All ^{1}H NMR and ^{13}C NMR experiments were acquired on a Bruker Avance DPX 300 and 250 MHz spectrometer, and Mass spectra were

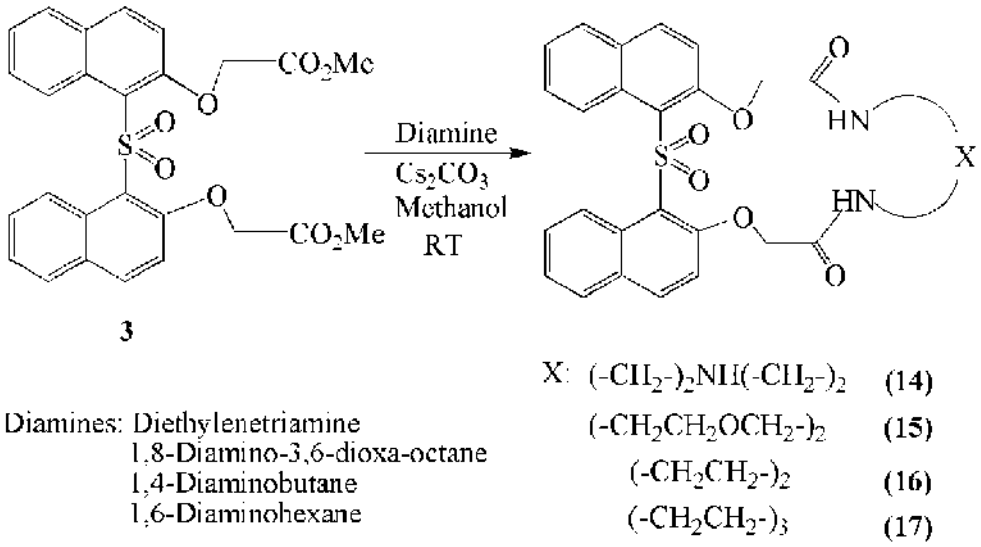
obtained by Shimadzu GC-MS-QP 1100 EX model.



Scheme 1. Synthesis of macrocyclicdiamides bearing 1-hydroxy naphthalene subunit (**4**-**9**)



Scheme 2. Synthesis of 2-hydroxy naphthalene containing macrocyclicdiamides (**10**-**13**)



Scheme 3. Synthesis of macrocyclicdiamides bearing 2-hydroxy naphthalene subunit (**14-17**)

General procedure for the synthesis of macrocyclicdiamides

Diamine (1mmol) and caesium carbonate (0.25eq, 0.5 mmol, 0.16 g) were added to diester (1mmol) in dry methanol. The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), water was added to the reaction mixture and extracted with chloroform (3×50 mL). The combined chloroform layers were dried (Na_2SO_4), and evaporated under reduced pressure to afford crude product, which was purified by column chromatography (silica gel) using chloroform/methanol (4:1) as eluent to obtain macrocycles ingood to excellent yields.

7,16-Diaza-1-4,10,13,19-tetraoxa 6,17-dioxo-2,3;20,21-dinaphtho-cyclouneicosane (8)

The synthesis of this macrocycle was carried out according to the general procedure in 87% yield in the reaction of 1 (1mmol, 0.462 g) and 1,8-diamino-3,6-dioxaoctane (1mmol, 0.15 mL). mp 195-196 °C; IR (KBr): 3385 (NH amide), 3357 (NH amide), 2935, 1682 (carbonyl), 1594, 1556, 1468, 1267, 1246,1152, 1032, 811, 765 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 3.42-3.45 (8H, m), 3.48-3.50 (4H, t), 4.48 (4H, s), 7.29-7.31 (b, 2H, NH amide), 7.37 (d, J= 10 Hz, 2H, Ar), 7.42-7.43 (m, 2H, Ar), 7.79-7.87 (m, 4H, Ar), 7.91 (t, J= 10 Hz, 2H, Ar), 8.42 (d, J= 10 Hz, 2H, Ar) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.2 (carbonyl), 169.5, 157.2, 136.7, 131.5, 131.4, 129.5, 129.3, 128.9, 127.4, 126.8, 125.6, 124.2, 124.5, 117.8, 115.2, 114.5, 70.78, 69.91, 69.84, 39.43 ppm; MS EI (electron impact) m/z (relative

intensity %): (M^+, molecular ion) 546 (19), 358 (9), 300 (41), 287 (27), 216 (59), 187 (100), 147 (37), 128 (49), 115 (67), 85 (61), 57 (26), 44 (53); Anal. calcd. for $C_{30}H_{30}N_2O_6S$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.90; H, 5.54; N, 5.14.

7,10,13-Triaza-1-thia-4,16-dioxa-6,14-dioxo-2,3;17,18-dinaphtho-cyclooctadecane (9).

According to the general procedure, **9** has been successfully synthesized by the reaction of **1** (1mmol, 0.462 g) and diethylenetriamine (1mmol, 0.11 mL) in high yield (92%), as a white solid.mp 231-232°C; IR (KBr): 3391, 3256, 2985, 1681, 1665, 1610, 1506, 1412, 1262, 1067, 745cm-1; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.47-2.50 (b, 4H, CH_2), 3.12 (s, 4H, CH_2), 4.58 (s, 4H, CH_2), 7.31-7.42 (m, 8H), 7.85-7.93 (m, 4H), 8.34-8.36 (b, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.1 (carbonyl), 169.7, 158.8, 136.9, 131.7, 130.5, 128.3, 128.8, 126.3, 125.5, 119.3, 115.2, 68.7, 39.5, 38.7, 28.3, 25.3ppm; ms: m/z (relative intensity %**)**: 501 $[M]^+$ (molecular ion,12**)**, 483 (15**)**, 300 (42**)**, 287 (23**)**, 187 (35**)**, 144 (100), 128 (25**)**, 115 (56**)**, 56 (31**)**, 44 (14**);** Anal. calcd. for $C_{28}H_{27}N_3O_4S$: C, 67.05; H, 5.43; N, 8.38. Found: C, 67.04; H, 5.44; N, 8.41.

7,14-Diaza-1-thia-4,17-dioxa-6,15-dioxo 2,3;18,19-dinaphtho-cyclononadecane (13).

The reaction was run according to the general procedure, by the reaction of 2 (1mmol, 0.462 g) and 1,6-diaminohexane (1mmol, 0.12 g) for the preparation of 13 in 91% yield. mp 173-174°C; IR (KBr): 3367, 3061, 2975, 2940, 2885, 1683, 1626, 1593, 1532, 1504, 1462, 1445, 1353, 1296, 1273, 1214, 1158, 1041, 882 Cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ : 2.41 (s, 2H, CH_2), 3.44 (s, 2H, CH_2), 3.49 (t, J= 15 Hz, 4H, CH_2), 3.91 (t, J= 3.5 Hz, 4H, CH_2), 4.56 (s, 4H, CH_2), 7.03-7.08 (2H, d, J=9 Hz), 7.46-7.51 (2H, ddd, J= 7.5, 7.5, 0.9 Hz), 7.69-7.74 (2H, ddd, J= 7.8, 7.8, 1.2 Hz), 7.79-7.86 (4H, t, J= 9.3 Hz), 9.17-9.19 (2H, d, J= 8.7 Hz) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ: 168.05, 155.31, 135.90, 130.54, 129.09, 127.82, 127.63, 126.34, 124.93, 117.85, 112.06, 69.26, 67.51, 67.2, 60.29, 34.11 ppm; MS EI (electron impact) m/z (relative intensity %): 514 [M]+ (11), 434 (35), 316 (9), 300 (74), 271 (16), 215 (28), 202 (25), 187 (78), 176 (27), 144 (34), 115 (100), 114 (22), 102 (29), 88 (17), 69 (12), 44 (56); Anal. calcd. for $C_{30}H_{30}N_2O_4S$: C, 70.01; H, 5.88; N, 5.44. Found: C, 69.97; H, 5.89; N, 5.47.

7,14-Diaza-1-sulfoxo-4,17-dioxa-6,15-dioxo-2,3;18,19-dinaphtho-cyclononadecane (17).

Following the general procedure, 17 was afforded by the reaction of 3 (1 mmol, 0.494

g) and 1,6-diaminohexane (1 mmol, 0.12 g); as a white powder in 84% yield. mp 186-187 °C; IR (KBr): 3362, 3075, 2928, 2893, 1699, 1672, 1634, 1593, 1557, 1512, 1477, 1439, 1341, 1287, 1163, 1127, 1121, 1078, 1025, 979, 882, 757 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.42 (s, 2H, CH_2), 3.47 (s, 2H, CH_2), 3.49 (t, J= 15 Hz, 4H, CH_2), 3.98 (t, J= 3.5 Hz, 4H, CH_2), 4.55 (s, 4H, CH_2), 7.07 (d, J = 9Hz, 2H), 7.42 (ddd, J = 0.9, 7.2, 7.4 Hz, 2H), 7.68 (ddd, J = 1.2, 7.8, 7.9 Hz, 2H), 7.83 (t, J = 9.3 Hz, 4H,), 9.17 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 168.12, 155.37, 135.94, 130.57, 129.08, 127.82, 127.63, 126.49, 125.04, 117.91, 112.17, 68.97, 67.73, 66.78, 61.25, 33.96 ppm; MS EI (electron impact) m/z (relative intensity %): 546 $[M]^+$ (14), 483 (8), 318 (5), 297 (24), 271 (29), 145 (11), 58 (15), 56 (35), 55 (57), 43 (100); Anal. Calcd. for $C_{30}H_{30}N_2O_6S$: C, 65.92; H, 5.53; N, 5.12; Found: C, 65.89; H, 5.52; N, 5.15.

Results and discussion

Initially, we carried out a set of experiments using **1** [13] as model substrate and diethylenetriamine for the optimization of macrocycle synthesis; the results are summarized in Table 1. We investigated the possible macrocyclization reaction between the above substrates with carbonate salts of alkali metals (Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3), $CaCO_3$ and $NaHCO_3$ as catalysts.

Initial catalyst screening indicated that caesium carbonate displayseed the highest catalytic activity in terms of reaction efficiency (93% isolated yield) (Table 1). The isolated yields of aza crowns and literature references of reported macrocycles were reported in Table 2.

The 2,2'-thiobis(1-hydroxy naphthalene) containing macrocycles (**4-9**) have been successfully synthesized by the reaction of corresponding diester (**1**) [13]and diamine in methanol using caesium carbonate as an excellent catalyst at room temperature (Scheme 1).

Also, a variety of macrocyclicdiamides containing 1,1'-thiobis(2-hydroxy naphthalene) subunit (**10-13**) has been readily synthesized by the reaction ofcorresponding diester (**2**) [14] and appropriate diamine in methanol in the presence of caesium carbonate at room temperature (Scheme 2).

Finally, caesium carbonatehas been successfully used in the synthesis of 1,1'-sulfoxobis (2-hydroxy naphthalene) containing macrocycles (**14-17**) by the reaction of corresponding diester (**3**) and appropriate diamine (Scheme 3). Compound **3** was prepared by the reaction of **2** and

hydrogen peroxide as reported previously [16].

The synthesis of sulfide containing macrocycles by the procedure described here is much more convenient than the sulfones (Table 2). The structure of diarylsulfones is tetrahedral and rigid [18]. The syn-structure of dibenzosulfide and anti-structure of dibenzosulfoxide derivatives can help to explain this result [17]. The syn-structure of dibenzosulfide and anti-structure of dibenzosulfoxides were determined by X-ray crystallography [17] and, as a result, structurally different dinaphthosulfide and dinaphthosulfoneprecuesors explain differences between the yields of macrocycles (Table 2).

The method has many advantages over previously published procedures [12,15,19], for instance, simple reaction conditions and work up, the use of small volume of solvents and high yields.

As summarized in Table 1, $Li_2(CO_3)$ proved to be a suitable catalyst for this macrocyclization reaction.

Table 1. Condition optimization for macrocyclization between diester **(9)** and diethylenetriamine

Entry[a]	**catalyst**	**3/catalyst**[b]	**Yields(%)**[c]
1	Cs_2CO_3	1:1	93
2	Cs_2CO_3	1:0.50	93
3	Cs_2CO_3	1:0.25	92
4	Cs_2CO_3	1:0.10	68
5	Na_2CO_3	1:1	74
6	$NaHCO_3$	1:1	12
7	K_2CO_3	1:1	79
8	Li_2CO_3	1:1	86
9	$CaCO_3$	1:1	56

[a]Room temperature,24 h, [b]Moles of ester and catalyst,[c]Isolated yields

Table 2. The synthesis of macrocyclicdiamides by Cs_2CO_3

Aza crown	Yield (%)[a]	Ref.[b]	Aza crown	Yield (%)[a]	Ref.[b]
4	88	13	**11**	88	14
5	87	13	**12**	86	14
6	84	13	**13**	79	-
7	78	13	**14**	63	64
8	75	-	**15**	61	61
9	92	13	**16**	59	58
10	91	14	**17**	71	-

[a]Isolated yield
[b]Reference

Conclusion

We have developed a catalytic system for the synthesis of macrocyclicdiamides using caesium carbonate. This catalyst can efficiently promote the desired reactions, giving the corresponding macrocycles in high yields. Also, diesters can be readily transformed into macrocyclicdiamides by $Li_2(CO_3)$.

Acknowledgments

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