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Application of Bayer-Villiger Reaction to the Synthesis of Dibenzo-18-crown-6, Dibenzo-21-crown-7 and Dihydroxydibenzo-18-crown-6

Druman R. Utekar and Shriniwas D. Samant*
*Department of Chemistry, Institute of Chemical Technology, N. M. Parekh Road, Matunga, Mumbai 400019, India. *E-mail:samantsd@yahoo.com*
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ABSTRACT. Dibenzo-18-crown-6, dibenzo-21-crown-7 and dihydroxy dibenzo-18-crown-6 were synthesized by Bayer-Villiger oxidation strategy. Dibenzo-18-crown-6 and dibenzo-21-crown-7 could be synthesized through a three-step protocol starting from salicylaldehyde. Salicylaldehyde was reacted with *bis*-(2-chloroethyl)ether using K_2CO_3 in acetonitrile to link the two phenolic groups with the oxyethylene bridge followed by conversion of the formyl group to the hydroxy group via a Baeyer-Villiger reaction and finally linking the two phenolic group with appropriate oxyethylene bridge. The two target crown ethers were obtained in overall yield, 24% and 30%, respectively. This method has a great potential for synthesis of symmetrical as well as unsymmetrical dibenzo crowns with varying oxyethylene bridges. Baeyer-Villiger oxidation could be used to prepare dihydroxy derivative of dibenzo-18-crown-6 through acetylation of dibenzo-18-crown-6 followed by Baeyer-Villiger oxidation. The Baeyer-Villiger oxidation could be substantially accelerated using trifluoroacetic acid.

Key words: Crown ether, Dibenzo-18-crown-6, Diacetyldibenzo-18-crown-6, Dihydroxydibenzo-18-crown-6, *m*-Chloroperbenzoic acid

INTRODUCTION

Dibenzocrown ethers and their derivatives are important due to their use in the extraction of various metal ions.[1,2] Dibenzo crown ethers finds application in preparation of molecular chalice,[3] light fluorous phase transfer catalysts,[4] fluorescent sensors,[5] liquid crystals,[6] etc. Substitution on the benzene rings in these crown play important role in their binding ability. The desired substitution can be had through aromatic electrophilic substitution on the crown[7,8] or through synthesis involving cyclization of substituted catechol derivatives.[9,10] The substitution can be further used for the introducing other desired functions[11] or for building bis crown ethers.[12,13] For example, dibenzo-18-crown-6 containing phenolic –OH group on two benzene rings is used for the preparation of *bis*-crown ethers.[12,13]

The synthesis of dibenzo[3n]crown-n with various oxyethylene bridges has been reported. In this area, synthesis of symmetrical crowns, having both the oxyethylene bridges identical, is comparatively easy; as has been seen with a well-known procedure of preparation of dibenzo-18-crown-6 in overall 39–48% yield.[14] However, preparation of unsymmetrical crowns,[15] having different oxyethylene bridges, is difficult.

Pedersen first reported the preparation of symmetrical and unsymmetrical dibenzo crowns by the condensation of tosylate of polyethylene glycols with catechol.[1] He also described another method involving the condensation of tosylates of polyethylene glycols and catechol, having one hydroxy group protected by tetrahydropyranyl group, followed by deprotection of the hydroxy group, and finally condensation with a suitable dihalide of polyglycol.[1] In another process, catechol is monobenzylated prior to linking the two catechol molecules.[16–18] The monobenzyl ether of catechol is reacted with tosylate of polyethylene glycol followed by catalytic hydrogenolysis to remove the benzyl group. The resulting α,ω-*bis*(*o*-hydroxyphenoxy) polyethylene ether is reacted with dichloro derivative of appropriate polyethylene glycol to obtain the desired crown.[16–18] Though this method is suitable for unsymmetrical crowns, selective preparation of monobenzylated catechol is the main problem, as always a mixture of mono- and di-protected catechols is formed.

The above methods of preparation of dibenzo crowns are lengthy and, particularly in the case of unsymmetrical crowns, give low yields. In order to induce more selectivity, and to avoid the problems faced using catechol, synthesis from salicylaldehyde has been reported, where the formyl group serves as a latent functionality for hydroxyl group.[19,20] Salicylaldehyde is reacted with *bis*-(2-chloroethyl)ether to link the two phenolic groups with oxyethylene bridge (35% yield) followed by conversion of the formyl group to the hydroxy group (24% yield) by Baeyer-Villiger reaction using H_2O_2 in acetic acid. This method apprears to be

promising for the preparation of symmetrical as well as unsymmetrical dibenzo crowns. However, the reaction requires 24–48 h, proceeds in very poor yield, and the isolation of the product is difficult.

On the background of the importance of symmetrical and unsymmetrical dibenzo crowns we were interested in the synthesis of these crowns and their derivatives, particularly hydroxyl derivatives, where the hydroxyl group would be an additional legend. For this we found Baeyer-Villiger oxidation route to be very promising. Thus, we are presenting the synthesis of dibenzo-18-crown-6, dibenzo-21-crown-7 and dihydroxydibenzo-18-crown-6 in high yield employing Baeyer-Villiger oxidation as an efficient intermediate step.

RESULTS AND DISCUSSION

Synthesis of Dibenzo-18-crown-6 and Dibenzo-21-crown-7

Condensation of salicylaldehyde (**1**) with *bis*-(2-chloroethyl) ether (**2**) was carried out in different solvents and in the presence of different bases (*Table* 1).

The best combination was found to be of solvent acetonitrile and base K_2CO_3. The yield of *bis*[2-(*o*-formylphenoxy)]ethyl ether (**3**) obtained using this combination was much higher (65%) than that reported earlier (35%) using Na_2CO_3-DMF.[20]

In the reported procedure for the preparation of *bis*[2-(*o*-hydroxyphenoxy)]ethyl ether, hydrogen peroxide in acetic acid has been used for the conversion of formyl group to hydroxyl group; probably the oxidizing species could be peracetic acid. However, we found that the yield of the product was less and isolation of the product from acetic acid was difficult. In order to circumvent these problems, we tried *m*-CPBA for the Baeyer-Villiger oxidation of **3** in dichloromethane (DCM). *m*-CPBA is soluble in DCM and is environmentally safe. Using this combination 68% yield of **4** was obtained.

***Table* 1.** Reaction of **1** and **2**

Entry	Base	Solvent	Temp., °C	Yield of **3**[a,b], %
1	Na_2CO_3	DMF	95	41
2	Na_2CO_3	Acetonitrile	85	46
3	K_2CO_3	DMF	95	45
4	K_2CO_3	Acetonitrile	85	65
5	$CsCO_3$	DMF	95	35
6	$CsCO_3$	Acetonitrile	85	42

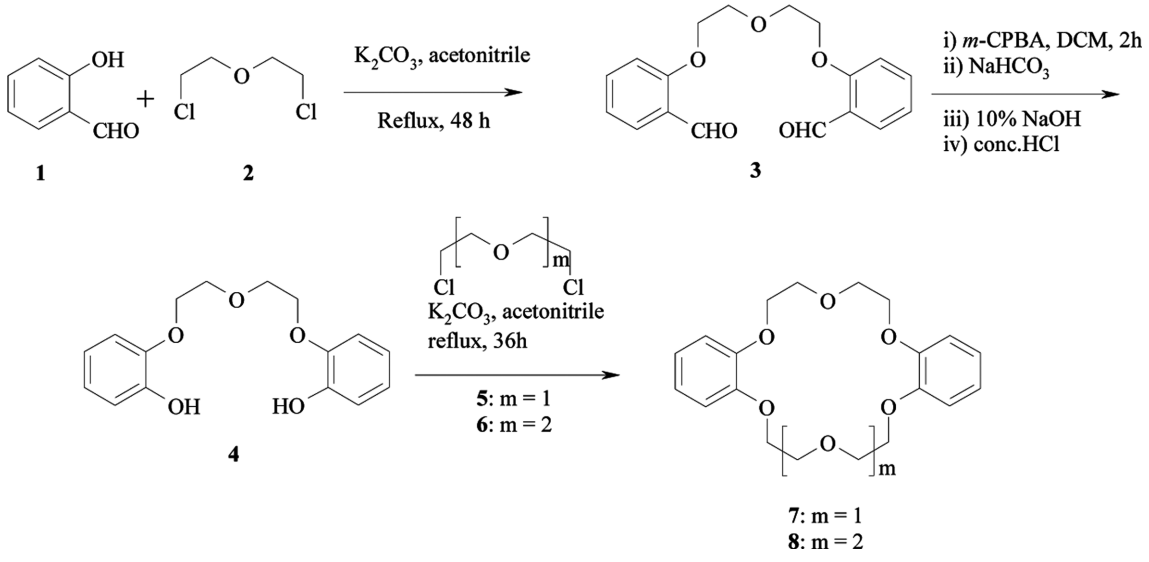
[a]isolated yield.
[b]Reaction conditions: Salicylaldehyde (8.19 mmol), base (8.19 mmol), **2** (4.09 mmol), solvent (2 mL), reaction time = 48 h.

Reaction of *bis*[2-(*o*-hydroxyphenoxy)]ethyl ether (**4**) with appropriate polyethyleneglycol dihalides (**5** and **6**) in acetonitrile in the presence of K_2CO_3 gave improved yield of **7** and **8**, respectively (*Scheme* 1).

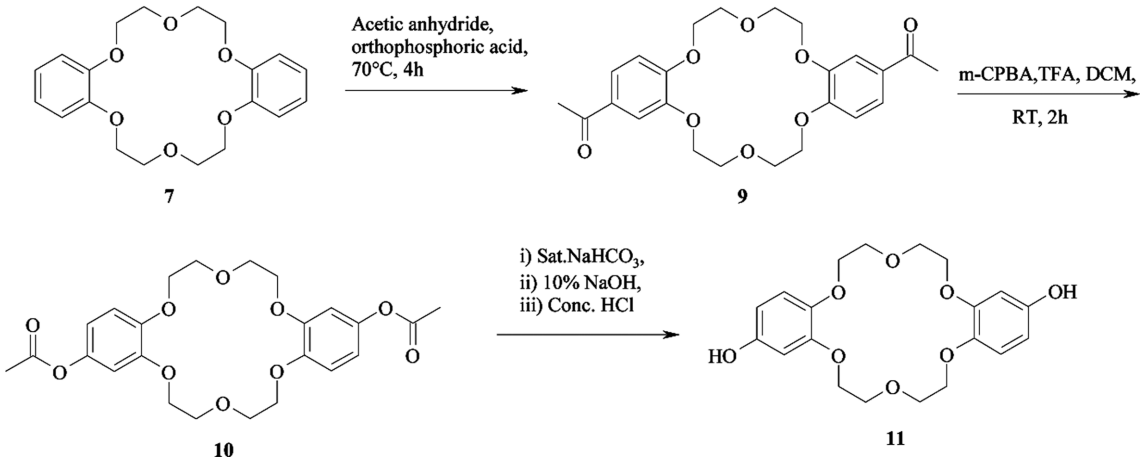
The method has great potential for the synthesis of unsymmetrical dibenzo crown ethers. We obtained **8** in the highest yield reported so far.

Synthesis of Dihydroxydibenzo-18-crown-6

The preparation of hydroxyl derivatives of monobenzo-15-crown-5 and monobenzo-18-crown-6 is known through acylation of the monobenzocrown followed by Baeyer-Villiger oxidation and hydrolysis.[21,22] However, prepara-



***Scheme* 1.**



***Scheme* 2.**

tion of dihydroxydibenzo-18-crown-6 ether is not reported by this method. Rieckemann prepared dihydroxydibenzo-18-crown-6 ether by nitration of dibenzo-18-crown-6, followed by reduction of nitro, diazotization of amino, and replacement of diazo group by hydroxyl group.[23] However this method is lengthy and gives low overall yield of the product.

In order to avoid these problems, the preparation of **11** was planned through acylation followed by Baeyer-Villiger oxidation.

Acetylation of dibenzo-18-crown-6 to its diacetyl derivative using acetic anhydride and phosphoric acid is known.[24] In this reference a large amount of phosphoric acid and acetic anhydride are used and the reaction is carried out at 70 °C. We found that at 70 °C the mass tarnishes possibly due to decomposition of the crown. In order to optimize the conditions the reaction was carried out using different quantities of acetic anhydride and phosphoric acid and the reaction was carried out at 70 °C and 60 °C; the reaction was very slow at 50 °C (*Table* 2).

Thus, the acetylation could be effectively carried out using only 25 equivalents of acetic anhydride in 3 mL of phosphoric acid at 60 °C.

Bayer-Villiger oxidation of **9** could not be effected using hydrogen peroxide. The oxidation took place with *m*-CPBA; however, the yield was low. It is known that when *m*-CPBA is used in combination with trifluoroacetic acid (TFA) the Bayer-Villiger oxidation is accelerated and the yield of the product is high.[25] In this reaction TFA is believed to form trifluoroperacetic acid which is a better oxidizing agent. Hence the reaction was carried out with *m*-CPBA in the presence of different amount of TFA (*Table* 3). Addition of 2.2 equivalents of TFA along with 4.5 eq. of *m*-CPBA gave excellent results. The diacetoxy derivative was hydrolyzed using 10% NaOH to obtain the desired dihydroxy derivative **11**.

***Table* 3.** Bayer-Villiger oxidation of **9** in the presence of *m*-CPBA and TFA

Entry	*m*-CPBA, equiv.	TFA, equiv.	Time, h	Yield of **10**[a], %
1	4.5	–	8	20
2	4.5	0.5	8	48
3	4.5	2.2	2	80
4	**4.5**	**2.2**	**3**	**82**
5	H_2O_2 (10)	Acetic acid (5mL)	24	No product

Reaction conditions: 9 (2.25 mmol), TFA (4.5 mmol, 2.2 equiv.), *m*-CPBA (10.12 mmol, 4.5 equiv.) Dichloromethane (10 mL).
[a]isolated yield.

***Table* 2.** Acetylation of Dibenzo-18-crown-6 (**7**) using acetic anhydride and orthophosphoric acid

Entry	**7**, mmol	$(CH_3CO)_2O$ eq.	H_3PO_4 mL	Temp. °C	Time h	Yield of **9**[a], %
1	2.78	50	1	70	4	52
2	2.78	50	2	70	4	60
3	2.78	25	2	70	4	40
4	2.78	25	3	70	4	85
5	**2.78**	**25**	**3**	**60**	**4**	**95**

[a]isolated yield.

CONCLUSION

Dibenzo-18-crown-6 and dibenzo-21-crown-6 could be synthesized through a three-step protocol starting from salicyladehyde and involving conversion of the formyl group of salicyladehyde to hydroxyl group by Bayer-Villiger reaction. This method has a great potential for synthesis of symmetrical as well as unsymmetrical dibenzo crowns with varying oxyethylene bridges. The two target crown ethers were obtained in the highest overall yields, 24% and 30% respectively. Baeyer-Villiger oxidation could be used to prepare dihydroxy derivative of dibenzo-18-crown-6 through acetylation followed by the oxidation. The Baeyer-Villiger oxidation could be substantially accelerated using trifluoroacetic acid. Through this protocol hydroxyl groups can be easily introduced in crown ethers.

EXPERIMENTAL

All reagents were obtained from commercial sources and used as received. *m*-CPBA was stated to be of 55–75% purity; molar equivalents were calculated based on a nominal 50% purity. Melting points were determined in open capillary tubes on a μ-ThermoCal-10 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. IR spectra were carried out on a Perkin Elmer Spectrum 100 FTIR spectrophotometer.

***bis*[2-(*o*-Formylphenoxy)ethyl]ether (3):** In a round bottom flask (50 mL), K_2CO_3 (1.13 g, 8.19 mmol), acetonitrile (20 mL) and salicylaldehyde, (1.0 g, 8.19 mmol) were mixed and heated to 85 °C with stirring. *bis*(2-Chloroethyl)ether (0.58 g, 4.09 mmol) in acetonitrile (2.0 mL) was added over 3 h at 85 °C in small portions and the mixture was heated at 85 °C for 48 h. The solution was cooled and acetonitrile was removed under vacuum. The oily residue was acidified with dil. HCl (0.45 M, 200 mL). The solution was extracted with chloroform (2 × 20 mL), the chloroform layer dried over Na_2SO_4, and evaporated to give an oily compound. It was purified using column chromatography on silica gel (ethyl acetate: pet ether –3:7 v/v) to afford **3**; white solid, Yield 65%, mp 73–75 °C [mp 75–76 °C lit.[19]]. IR spectrum, ν, cm^{-1}: 3075 (Ar–H), 2945 (C–H), 2766 (CHO), 1681 (C=O), 1592, 1482 (C=C), 1234 (Ar–O–C), 1042 (C–O–C) cm^{-1}; ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.98 (4H, t, $2CH_2O$), 4.26 (4H, t, $2CH_2OAr$), 6.99 (4H, m, ArH), 7.51(2H, m, ArH), 7.81(2H, m, ArH), 10.44 (2H, s, CHO).

***bis*[2-(*o*-hydroxyphenoxy)]ethyl ether (4):** To a stirred suspension of **3** (1.0 g, 3.18 mmol) in DCM (10 mL), was added dropwise a solution of *m*-CPBA in DCM (2.46 g, 14.33 mmol, DCM 10 mL). The reaction mixture was stirred for 2 h at 25 °C. After completion of the reaction, saturated $NaHCO_3$ (50 mL) was added. The product was extracted in DCM (2×20 mL) and the combined extract was dried over Na_2SO_4. The solvent was evaporated and the solid product was purified by column chromatography on silica gel using ethyl acetate: pet ether (1:1 v/v). Alternatively the product could be purified by dissolving the crude product in 10% NaOH and precipitating it with conc. HCl as a white solid (**4**), Yield 68%, mp 98–101 °C [mp 96–99 °C (19)]. IR spectrum, ν, cm^{-1}: 3222 (broad, OH), 2934 (CH), 1608, 1515, 1452 (C=C), 1357, 1284 (Ar–O–C), 1222 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.58 (s, 2H, Ar–OH), 6.32–6.82 (m, 8H, ArH), 3.85–4.25 (m, 8H, OCH_2CH_2O).

Dibenzo-18-crown-6 (7): A suspension of **4** (1.0g, 3.45 mmol) and K_2CO_3 (0.47g, 3.45 mmol) in acetonitrile (20 mL) was heated to 85 °C. *bis*(2-Chloroethyl) ether (0.49 g, 3.45 mmol) in acetonitrile (2.0 mL) was added dropwise over 3 h. The mixture was heated at 85 °C for 36 h, cooled, and acetonitrile was removed in vacuum. The residue was acidified with dil. HCl (0.45 M, 200 mL). The aqueous layer was extracted with chloroform (2×20 mL). The chloroform layer was dried over Na_2SO_4 and the solvent evaporated in vacuum to give an oily compound which was purified by column chromatography on silica gel using ethyl acetate: pet ether (2:8 v/v) (**7**), white solid, Yield 69%, mp 161–163 °C [mp 163–164 °C lit.[2]]. IR spectrum, ν, cm^{-1}: 3031 (Ar–H), 2932 (C–H), 1596, 1514, 1453 (C=C), 1258 (Ar–O–C), 1132 (C–O–C), 933 (C–C), 778 (Ar–H) cm^{-1}; ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.86 (4H, s, $2CH_2O$), 3.89 (2H, t, CH_2O), 4.02 (2H, m, CH_2 O), 4.14 (4H, t, $2CH_2OAr$), 4.19 (4H, t, $2CH_2OAr$), 6.95 (8H, m, ArH).

Dibenzo-21-crown-7 (8): 8 was prepared by following the procedure given for **7** and using *bis*(2-chloroethoxy) ethane (0.64 g, 3.45 mmol) in acetonitrile (2.0 mL). It was obtained as a white solid (**8**), Yield 54%, mp 105–108 °C [mp 104–107 °C lit.[2]]. IR spectrum, ν, cm^{-1}: 3076 (Ar–H), 2935 (C–H), 1593, 1506, 1453 (C=C), 1259 (Ar–O–C), 1117 (C–O–C) cm^{-1}; ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.88 (4H, s, $2CH_2O$), 3.92 (4H, t, $2CH_2O$), 4.03 (4H, m, $2CH_2O$), 4.16 (4H, t, $2CH_2OAr$), 4.20 (4H, t, $4CH_2OAr$), 6.93 (8H, m, ArH).

Diacetyldibenzo-18-crown-6 (9): In a round bottom flask (100 mL), dibenzo-18-crown-6 (1.0 g, 2.78 mmol), acetic anhydride (69.5 mmol, 25 equiv., 7.09 mL) and 3 mL of orthophosphoric acid were mixed and heated to 60 °C

while stirring using a magnetic stir bar in water bath for 4 h. After completion of reaction, the reaction mixture was cooled to room temperature and 50 mL of ice cold water was added to obtain white solid product, which was filtered and dried. It was purified using flash column chromatography on silica gel (ethyl acetate 100%) to afford (**9**); white solid, Yield 95%, mp 170–171 °C [mp 171–173 °C lit.[23]]. IR spectrum, ν, cm^{-1}: 3072 (Ar–H), 2948, 2881 (C–H), 1675 (C=O), 1588, 1515 (C=C), 1273, 1220 (Ar–O–C), 1078 (C–O–C) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.54 (6H, $2COCH_3$), 3.99 (8H, t, $4CH_2O$), 4.20 (8H, t, $4CH_2OAr$), 6.81 (2H, m, ArH), 7.48 (2H, m, ArH), 7.53 (2H, m, ArH).

Diacetoxydibenzo-18-crown-6 (10): To a stirred suspension of **9** (1.0 g, 2.25 mmol) and *m*-CPBA (1.75 g, 10.12 mmol) in DCM (10 mL), was added dropwise TFA (1.53 mL, 4.5 mmol). The reaction mixture was stirred for 2 h at 25 °C. After completion of the reaction as monitored by TLC, saturated $NaHCO_3$ (50 mL) was added. The product was extracted in methylene chloride (2×20 mL) and the combined extract was dried over Na_2SO_4. The solvent was evaporated and the solid product was purified by column chromatography on silica gel using ethyl acetate: pet ether (3:7 v/v). (**10**), white solid, Yield 82%, mp 164–166 °C. IR spectrum, ν, cm^{-1}: 3070 (Ar–H), 2923, 2891 (CH), 1759 (C=O), 1602, 1514, 1429 (C=C), 1371, 1213 (Ar–O–C), 1057 (C–O–C) cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.26 (6H, $2CH_3$), 3.98 (8H, t, $4CH_2O$), 4.13 (8H, t, $4CH_2OAr$), 6.60 (4H, m, ArH), 6.82 (2H, m, ArH).

Dihydroxydibezo-18-crown-6 (11): To a stirred suspension of **10** (1.0 g, 2.10 mmol) in water (10 mL) was added 10% NaOH (5 mL). The reaction mixture was stirred for 3 h at 25 °C. After completion of the reaction as monitored by TLC, conc. HCl was added drop wise until the solution becomes just acidic to litmus to obtain a white precipitate, which was filtered and dried. The product was purified by dissolving the white solid in 10% NaOH and reprecipitating using conc.HCl to afford (**11**), white solid, Yield 90%, mp 189–191 °C [mp 190–194 °C lit.[22]]. IR spectrum, ν, cm^{-1}: 3222 (broad, OH), 2934 (CH), 1608, 1515, 1452 (C=C), 1357, 1284 (Ar–O–C), 1222 cm^{-1}. ^1H NMR spectrum (300 MHz, MeOD), δ, ppm (*J*, Hz): 4.07 (8H, t, $4CH_2O$), 4.12 (8H, t, $4CH_2OAr$), 6.32 (2H, dd, ArH), 6.45 (2H, d, ArH), 6.76 (2H, d, ArH).

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