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USE OF AMIDE COUPLING REAGENTS IN THE SYNTHESIS OF "POLYMERIZABLE".DIACRYLAMIDE DERIVATIVES OF DIBENZO CROWN ETHERS

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Abstract: 4',4"(5")-Diacrylamidodibenzo-18-crown-6 (**4**), 4',4"(5")-Diacrylamido-5',5"(4")-di-tert-butyldibenzo-18-crown-6 (**8**) and 4',4"(5")-diacrylamidodibenzo-21-crown-7 (**12**) were synthesized through amide coupling reaction. The dibenzo crown ethers were nitrated using conc.HNO_3 and glacial acetic acid to give dinitro derivatives, which followed by reduction using Pd/C with hydrazine hydrate to obtain diamine derivative and finally formation diacrylamide using acrylic acid via amide coupling reaction. This method has great potential for synthesis of diacrylamide derivatives of dibenzo crown ethers. The targeted compounds were obtained in good yields.

Key words: Dibenzo-18-crown-6, Dibenzo-21-crown-7, 4',4"(5")-Di-tert-butyldibenzo-18-crown-6, 4',4"(5")-Diacrylamidodibenzo-18-crown-6 and 4',4"(5")-Diacrylamido-5',5"(4")-di-tert-butyldibenzo-18-crown-6.

Introduction:

Crown ethers[I], due to their selective cationic binding affinities and their adjustable hydrophobicities, are readily used as phase transfer catalyst [II-IV], toxic metal separation and supramolecular self-assemblies in the field of molecular electronics[V]. Crown ethers were incorporated into polymers[VI] 30 years ago and many such polymers have been synthesised from macrocyclic monomers[VII-XII]. The polymer inclusion membranes containing crown ethers are also known[XIII, XIV]. The polymerization can be achieved using addition polymerisation or condensation polymerisation through a suitable polymerizable group introduced on crown ether moiety. The functional group like tetrafluoro vinyl[XV], acryl amide[XVI], p-phenyl vinylene[XVII] were introduced for this purpose. The acrylamide functionality was found to be important to produce polymeric materials of crown ethers.

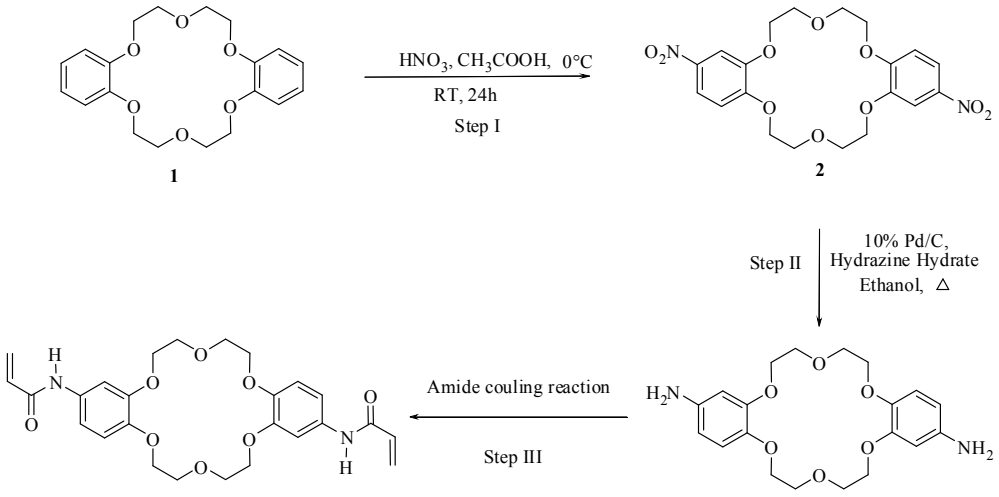
The synthesis of acrylamide derivatives of dibenzo-18-crown-6 ether and monobenzo-crown ether and their co-polymerization was reported earlier[XVIII] which was prepared by acylation reaction of the corresponding amino crown ether with acryloyl chloride in N, N-dimethylformamide. However the method uses toxic acryloyl chloride. In order to avoid hazardous acryloyl chloride, we have reported the amide formation by using amide coupling reagents and acrylic acid.

In this paper we also reported the preparation of diacrylamide derivatives of di-tert-butyldibenzo-18-crown-6 ether and dibenzo-21-crown-7 ether. Therefore the aim of the study was to synthesis the diacrylamido derivatives using amide coupling reagent with acrylic acid and also to synthesize the other

acrylamido derivatives such as 4',4"(5")-di-tert-butyldibenzo-18-crown-6 ether and dibenzo-21-crown-7 using this amide coupling reaction strategy.

Results and Discussion:

The synthesis of diacrylamido derivatives of dibenzo-crown ethers was outlined in scheme 1, 2, 3. The synthesis of 4',4"(5")-diacrylamidodibenzo-18-crown-6 (**4**) was carried out by nitration of dibenzo-18-crown-6 (**1**) using conc.HNO_3 and glacial acetic acid at 0°C in 95% yield, followed by reduction using Pd/C with Hydrazine hydrate at 90°C in 82% yield (Scheme 1).The amide coupling reaction was carried out with acrylic acid and the corresponding diaminodibenzo crown ethers through different amide coupling reagents. (Table 1) The best combination was found to be hydroxybenzotriazole (HOBt) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), which gave high yields of product.



1 2 3 4

Scheme 1

Table 1. Amide coupling reaction of Diamino crown ethers.

Entry	Diamino compound	Product	HOBt (eq.)	CouplingReagent (eq.)	Yield[a] %
1	3	4	2.0	DCC(2.2)	20
2	3	4	2.0	DIC(2.2)	60
3	**3**	**4**	**2.0**	**EDCI(2.2)**	**65**
4	**7**	**8**	**2.0**	**EDCI(2.2)**	**61**
5	**11**	**12**	**2.0**	**EDCI(2.2)**	**58**

[a] isolated yield.
[b] Reaction conditions: Diamino compound (2.56 mmol), temp. 25°C, reaction time = 24h.

The synthesis of 4',4"(5')-di-tert-butyldibenzo-18-crown-6 (**5**) was carried out using t-BuOH in DCM in presence of different acids (Scheme 2). The best results were obtained in presence of conc. H_2SO_4. In order to optimize the conditions the reaction was carried out using different quantities of t-BuOH and conc. H_2SO_4 at room temperature.

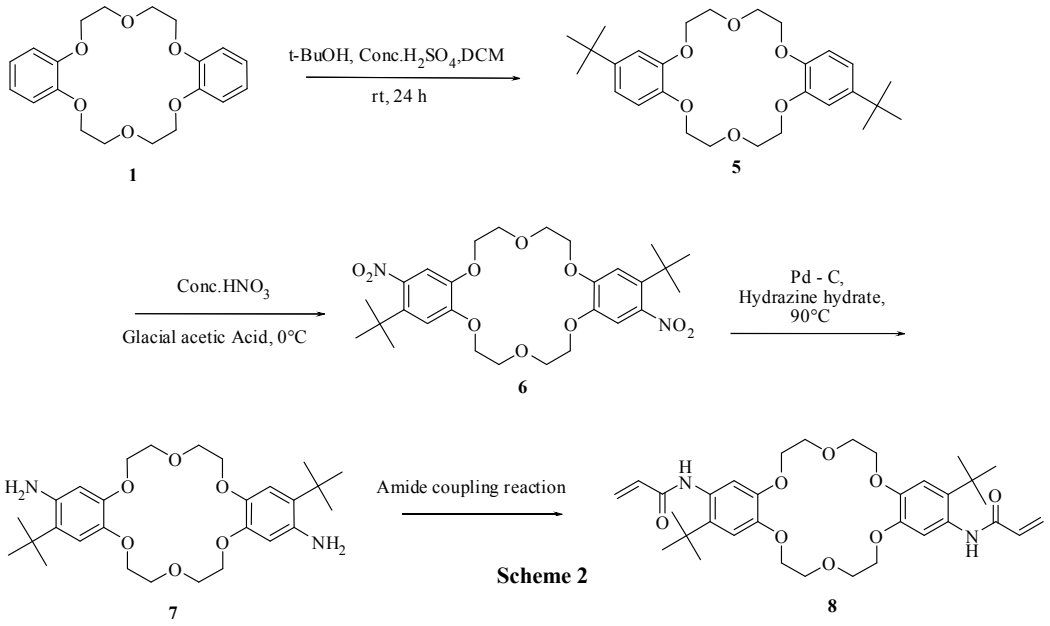
Table 2. Synthesis of **5** using t-BuOH

Entry	t-BuOH (eq.)	Acid (eq.)	Temp (°C)	Yield[a] of 5 g (%)
1	2.2	Conc.H_2SO_4 (2.5)	25	0.32(24)
2	2.2	Conc.H_2SO_4 (5)	25	0.61(46)
3	**4.0**	Conc.H_2SO_4 (**10**)	**25**	**0.95(72)**
4	4.0	O-Phosphoric acid (10)	25	No reaction
5	4.0	PPA(10)	25	0.4(30)
6	4.0	PPA(10)	60	0.65(49)

[a] isolated yield.
[b] Reaction conditions: Dibenzo-18-crown-6 (2.77 mmol), DCM (20mL), reaction time = 2h.

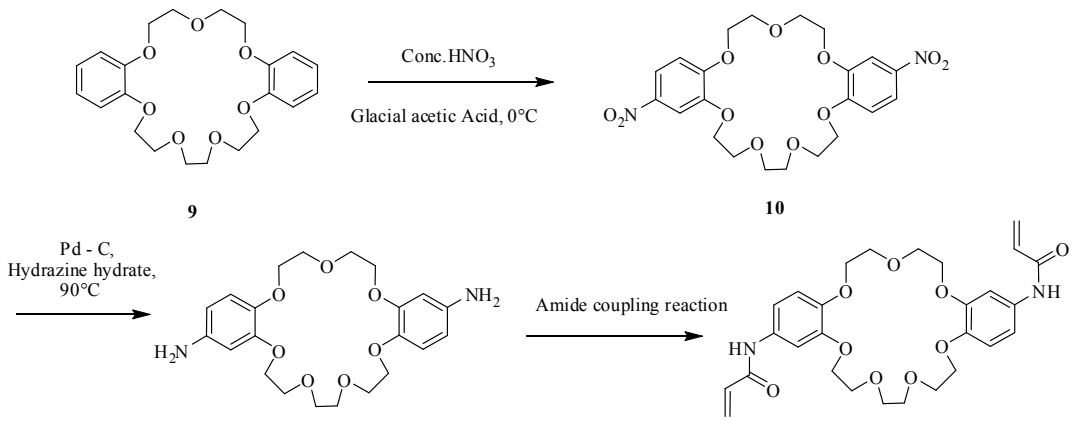
Thus, the alkylation was effectively carried out using only 4.0 equivalents of t-BuOH and 10 mL of conc. H_2SO_4 at 25°C.

The nitration of (**5**) was carried out using carried out using conc.HNO_3 and glacial acetic acid in 85% yield, followed by reduction using Pd/C with hydrazine hydrate to obtain 4',4"(5")-diamino-5',5"(4")-di-t-butyldibenzo-18-crown-6 (**7**) in 75% yield, which was further reacted with acrylic acid through amide coupling reaction using EDCI and HOBt to give (**8**) in 61% yield.



Scheme 2

Similarly 4',4"(5")-diacrylamidodibenzo-21-crown-7 (**12**) was synthesised using dibenzo-21-crown-7 (**9**) by nitration followed by reduction of nitro compound and finally amide formation in 58% yield (Scheme 3).



9 **10** **11** **12**

Scheme 3

Experimental

All reagents were obtained from commercial sources and used as received. All solvents were reagent grade. 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 300MHz 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.

General method for preparation of 5

To the stirred solution of **1** (1g, 2.77mmol) in DCM (20 mL), was added dropwise a mixture of t-BuOH (0.52g, 11.08mmol) in conc. H_2SO_4 (10 mL) under cooling. The reaction mixture was stirred for 2h at 25°C. After completion of the reaction, 50mL of water was added. The product was extracted in DCM (2 X 20 mL) and the combined extract was dried over Na_2SO_4. The solvent was evaporated and solid product was purified by column chromatography on silica gel using ethyl acetate: pet ether (1: 3 v/v) to obtain **5**, white solid. Yield 72%; mp 94-96°C [lit. 94°C]; IR (KBr) cm^{-1} :3070 (Ar-H), 2873 [-C$(CH_3)_3$], 1588, 1519 (C=C), 1266, 1147 (Ar-O-C), 1065 (C-O-C); ^{1}H NMR 300 MHz ($CDCl_3$/TMS): δ 1.27 (s, 18H, 2-C$(CH_3)_3$), 4.00-4.06 (m, 8H, 4CH_2O), 4.13-4.21 (m, 8H, 4CH_2OAr), 6.78-6.93 (m, 6H, Ar-H).

General method for preparation of 2,6,10

Dibenzo crown ethers **1,5,9** (2.77 mmol) were suspended in 15mL of glacial acetic acid and allowed to cool at 0°-5°C. To this a mixture of conc. HNO_3 (3mL, 25 eq., 70%) and glacial acetic acid (4mL) was added drop wise under cooling conditions. Then the reaction mixture was stirred for 24h at 25°C. After completion of reaction the reaction mixture was poured into ice cold water (100mL) to obtain pale yellow precipitate, which was allowed to settle down and was filtered and dried to obtain **2,6,10** as yellow solid products. The product further purified by recrystallization using chloroform.

*4',4"(5")-Dinitrodibenzo-18-crown-6 (**2**):* Pale yellow solid, Yield 95%; mp 207-212°C [lit. 208-213°C]; IR (KBr) cm^{-1}:3098 (Ar-H), 2926 (C-H), 1588 (C=C), 1513, 1341 (NO_2), 1278, 1139 (Ar-O-C), 1058 (C-O-C); ^{1}H NMR 300 MHz ($CDCl_3$/TMS): δ, ppm 3.98-4.10 (m, 8H, 4CH_2O), 4.10-4.19 (m, 8H, 4CH_2OAr), 6.78-7.00 (m, 2H, Ar-H), 7.71 (dd, *J*=1.1, 2.6 Hz, 2H, Ar-H), 8.04-7.80 (m, 2H, Ar-H).

*4',4"(5")-Dinitro-5',5"(4")-di-tert-butyldibenzo-18-crown-6 (**6**):* Yellow Solid, Yield 85%; mp 95-98°C; IR (KBr) cm^{-1}:3093 (Ar-H), 2950 (C-H), 1588 (C=C), 1524, 1355 (NO_2), 1267, 1139 (Ar-O-C), 1064 (C-O-C); ^1H NMR 300 MHz ($CDCl_3$/TMS): δ, ppm 1.36 (s, 18H, 2-$C(CH_3)_3$), 3.93-3.99 (m, 8H, 4CH_2O), 4.00-4.22 (m, 8H, 4CH_2OAr), 6.87 (s, 2H, Ar-H), 6.93 (s, 2H, Ar-H).

*4',4"(5")-Dinitrodibenzo-21-crown-7 (**10**):* Pale yellow solid, Yield 87%; mp 142-145°C ; IR (KBr) cm^{-1}: 3098 (Ar-H), 2926 (C-H), 1588 (C=C), 1513, 1341 (NO_2), 1278, 1139 (Ar-O-C), 1058 (C-O-C); ^1H NMR 300 MHz ($CDCl_3$/TMS): δ, ppm 3.86-3.88 (t, 4H, 2 CH_2O), 3.93-4.07 (m, 8H, 4CH_2O), 4.19-4.28 (m, 8H, 4CH_2OAr), 6.87- 6.93 (m, 2H, Ar-H), 7.73-7.78 (m, 2H, Ar-H), 7.86-7.91 (m, 2H, Ar-H).

General method for preparation of 3,7,11

Dinitro crown ethers 2,6,10 (2.19 mmol) were suspended in 20 mL ethanol. To this mixture 5% wt/wt Pd on carbon and hydrazine monohydrate (6mL, 60eq.) was added. The reaction mixture was refluxed for 5h at 90°C. The hot reaction mixture was filtered through celite bed and on cooling the white crystals of diaminodibenzo-18-crown-6 (**3**) were separated out, whereas compounds **7** and **11** were obtained by evaporating the solvent as black liquids. The diaminodibenzo-18-crown-6 was further purified by recrystallization using ethanol.

*4',4"(5")-Diaminodibenzo-18-crown-6 (**3**):* White solid, Yield 82%, mp 183-184°C [lit. 180-184°C]; IR (KBr) cm^{-1} : 3417, 3346, 3225 (-NH_2), 3088 (Ar-H), 2917 (C-H), 1591, 1517 (C=C), 1275, 1127 (Ar-O-C), 1048 (C-O-C); ^1H NMR 300 MHz ($CDCl_3$/TMS): δ, ppm 1.80 (br. s, 2H, -NH_2), 3.94-4.05 (m, 8H, 4CH_2O), 4.05-4.35 (m, 8H, 4CH_2OAr), 6.17- 6.25 (m, 2H, Ar-H), 6.28 (dd, *J*=1.3, 2.5 Hz, 2H), 6.52-6.78 (m, 2H, Ar-H).

*4',4"(5")-Diamino-5',5"(4")-di-tert-butyldibenzo-18-crown-6 (**7**):* Black liquid, Yield 75%, IR (KBr) cm^{-1}: 3467, 3351, 3214 (-NH_2), 2951 (C-H), 1591, 1516 (C=C), 1267, 1174 (Ar-O-C), 1077 (C-O-C); Unstable compound further utilized directly.

*4',4"(5")-Diaminodibenzo-21-crown-7 (**11**):* Black liquid, Yield 70%; IR (KBr) cm^{-1}: 3428, 3351, 3218 (-NH_2), 3050 (Ar-H), 2923 (C-H), 1591, 1515 (C=C), 1276, 1130 (Ar-O-C), 1057 (C-O-C). Unstable compound further utilized directly.

General procedure for preparation of 4,8,12

Diamino crown ethers 4,8,12 (2.56 mmol) were dissolved in 20mL of DCM. To this a mixture of 2.2 equiv. of acrylic acid, 2.0 equiv. of HOBt and 2.2 equiv. EDCI was added under stirring. The reaction mixture was stirred at 25°C for 24h. After completion reaction, 20 mL of water was added to the reaction mixture. The product was extracted twice in DCM (2 x 20mL) and the combined extracts were dried in Na_2SO_4. After evaporating the solvent solid product was obtained. The product was further purified using column chromatography using 1:1 Ethyl acetate: Pet ether.

*4',4"(5")-Diacrylamidodibenzo-18-crown-6 (**4**):* White solid, Yield 65%, mp 166-168°C; IR (KBr) cm^{-1}: 3267 (-NH), 3076 (Ar-H), 2933,2879 (C-H), 1660 (C=O), 1629 (C=C acryl group), 1606, 1517 (C=C), 1259, 1136 (Ar-O-C), 1059 (C-O-C); ^1H NMR 300 MHz (($CD_3)_2SO$/TMS):

δ, ppm 3.82 (m, 8H, $4CH_2O$), 4.02 (m, 8H, $4CH_2OAr$), 5.70 (m, 2H, =CH, acryl group), 6.17-6.23 (m, 2H, $=CH_2$ acryl group), 6.35-6.38 (m, 2H, $=CH_2$ acryl group), 6.87 (m, 2H, Ar-H), 7.14 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H).

*4',4"(5")-Diacrylamido-5',5"(4")-di-t-butyldibenzo-18-crown-6 (**8**):* Yellow solid, Yield 61%, mp 78-82°C; IR (KBr) cm^{-1}: 3255 (-NH), 3050 (Ar-H), 2945 (C-H), 1661 (C=O), 1624 (C=C acryl group), 1520 (C=C), 1215, 1134 (Ar-O-C), 1079 (C-O-C); ^1H NMR 300 MHz ($CDCl_3$/TMS): δ, ppm 1.27-1.56 (m, 18H, 2-$C(CH_3)_3$), 1.97 (br s, 2H, -NH), 3.74-4.04 (m, 8H, $4CH_2O$), 4.14-4.30 (m, 8H, $4CH_2OAr$), 5.64-5.83 (m, 2H, =CH, acryl group), 6.23-6.32 (m, 2H, $=CH_2$ acryl group), 6.38-6.54 (m, 2H, $=CH_2$ acryl group), 6.92-6.97 (s, 2H, Ar-H), 7.19-7.22 (s, 2H, Ar-H).

*4',4"(5")-Diacrylamidodibenzo-21-crown-7 (**12**):* Yellow solid, Yield 58%, mp 130-132°C; IR (KBr) cm^{-1} : δ, ppm 3278 (-NH), 2917,2866 (C-H), 1660 (C=O), 1604 (C=C acryl group), 1515 (C=C), 1232, 1132 (Ar-O-C), 1059 (C-O-C); ^1H NMR 300 MHz ($CDCl_3$/TMS): 1.74 (br s, 2H, -NH), 3.76-3.87 (t, 4H, 2 CH_2O), 3.91-3.98 (m, 8H, $4CH_2O$), 4.08-4.21 (m, 8H, $4CH_2OAr$), 5.70-5.74 (m, 2H, =CH, acryl group), 6.27- 6.43 (m, 4H, $=CH_2$ acryl group), 6.74-6.81 (m, 2H, Ar-H), 7.40-7.43 (m, 2H, Ar-H), 7.73 (m, 2H, Ar-H).

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