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Note

Synthesis of dibenzo-18-crown-6 ether containing pyrimidine derivatives

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The strategy employed for the synthesis of new macro-molecules containing pyrimidine moiety involved acetylation of dibenzo-18-crown-6 (**1**) to yield 4,4'-diacetyl derivative of dibenzo-18-crown-6 (**2**) which was further reacted with different aldehydes to give corresponding chalcone **3**. Reaction of chalcones 4 with guanidine hydrochloride gives target molecule. The structures of synthesized compounds have been characterized on the basis of spectroscopic data.

Keywords: Dibenzo-18-crown-6, acetylation, chalcones, guanidine hydrochloride, dibenzo-18-crown-6 containing pyrimidine

Pyrimidine and thienopyrimidine derivatives have attracted a great deal of interest owing to their medicinal activities[1–3]. Pyrimidine derivatives and heterocyclic annelated pyrimidines continue to attract great interest due to the wide variety of interesting biological activities such as anticancer[4], antiviral[5], antitumor[6], anti-inflammatory[7,9] and antimicrobial activities. Some of them have been successfully used as calcium channel blockers, antihypertensive agents, and antagonists[10]. Moreover, several marine alkaloids whose molecular structures contain the dihydro-pyrimidinones core also exhibit interesting biological activities[11]. The earliest method for the synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones reported by Biginelli in 1893 involved the one-pot condensation of an aldehyde, β-ketoester, and urea under strong acidic conditions with low yield (often 20%–50%)[12]. Herein a new derivative of dibenzo-18-crown-6 containing pyrimidine (**Scheme I**) is reported.

Results and Discussion

In the experimental procedure, the reaction was generally run at a molar ratio i.e. in first step acetylation of dibenzo-18-crown-6 by using acetic anhydride in presence of orthophosphoric acid as a catalyst. The second step involves the reaction between diacetyl derivative of dibenzo-18-crown-6 **2** and different substituted aldehydes give corresponding chalcones **3**. In the next step the reaction between chalcone and guanidine hydro-chloride has been carried out to get 2-amino-pyrimidine derivatives of dibenzo 18-crown-6. The structures of synthesized compounds were established on the basis of IR, ^{1}H and ^{13}C NMR and elemental analysis.

Experimental Section

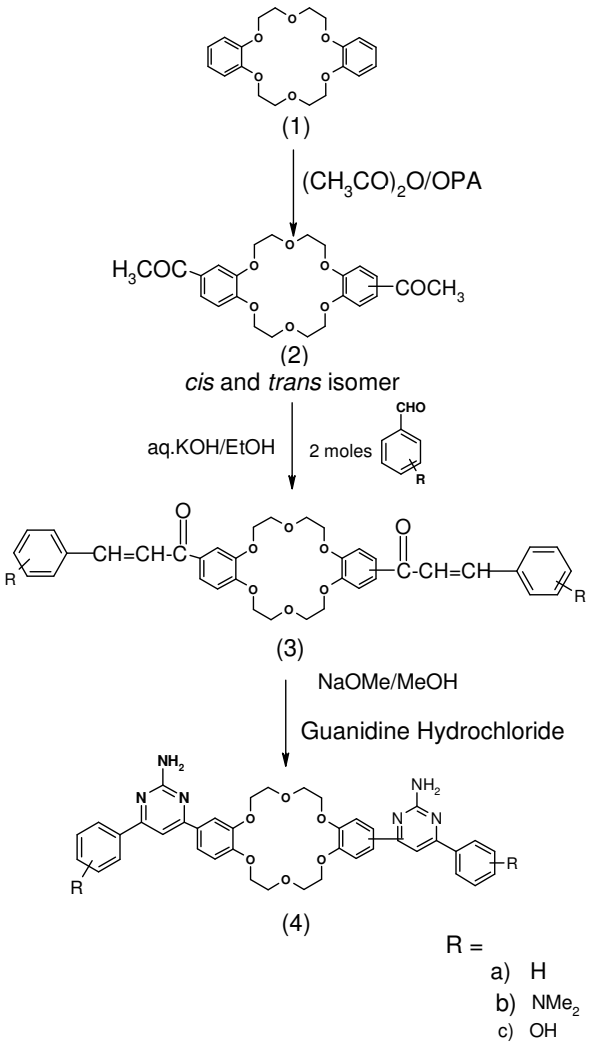
The melting points were determined in open capillary tube and are uncorrected. Infrared spectra were recorded using KBr pellets on a Perkin-Elmer Spectrum on FTIR spectrometer. The ^{1}H NMR and ^{13}CMR spectra were recorded in DMSO/$CDCl_3$ on a Jeol-JMSD-300 spectrophotometer.

4, 4'-Di acetyl dibenzo-18-crown-6 (2)

Dibenzo-18-crown-6 (1 mmole), acetic anhydride (5 mL) and 1-2 mL of orthophosphoric acid was taken in round bottomed flask and the reaction-mixture heated at 70°C on water bath for 3-4 hr. After completion of the reaction, reaction-mixture was cooled to room temp, and then poured onto the crushed ice white solid, which was filtered and recrystallized from ethyl alcohol. Purity of compound was checked by using TLC. m.p. 170°C (lit: 171-73°C); Yield: 78% IR(KBr): 2926 (CH), 1671(C=O), 1595, 1508, 14531428, 1359, 1271, 1217, 1133, 1057 cm^{-1};^{1}H NMR (DMSO-d_6): δ 2.6 (s, 6H) 4.1-4.2 (m, 8H), 4.2-4.43 (m, 8H), 6.99-7.5 (m, 6H);^{13}C NMR (DMSO-d_6, 125MHz): δ 196.74, 152.82, 148.36, 130.50, 123.37, 121.19, 113.07, 111.61, 111.31, 111.16, 110.96, 77.31, 77.00, 76.68, 70.72, 69.84, 69.43, 68.61, 68.28, 30.83, 26.

4,4'Di (acrylophenonyl) dibenzo-18-crown-6 (3a)

To 0.3 g of KOH in 10 mL ethanol taken in a round bottomed flask 4,4'-diacetyl dibenzo-18-crown-6 (**2**) (0.5 mmole) was added and the reaction-mixture was stirred at room temp. Then benzaldehyde (1 mmole) was added and the reaction-mixture stirred for 4-5 hr.



Scheme I

The reaction was monitored by using TLC. After completion of reaction the reaction mixture was poured into ice water and neutralized with dil. HCl. The separated solid was filtered, dried and recrystallized by using ethanol. m.p. 210°C; Yield: 60%; IR (KBr): 2930 (CH), 1670 (C=O), 1575, 1466, 1371, 1328, 1284, 1198 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.2 (dd, 2H), 2.3 (dd, 2H), 3.4-4.6 (m, 16H), 6.3-8 (m, 16H). ^{13}C NMR (DMSO-d_6, 125MHz): δ 194, 153, 146, 141, 139, 128, 122, 118, 117, 113, 78, 67, 65, 64, 62, 42, 38, 25. Anal. Calcd. for $C_{38}H_{36}O_8$ C, 73.52; H, 5.85; O, 20.63. Found: C, 73.60; H, 5.90; O, 20.60%.

4,4'Di(acrylophenonyl) dibenzo 18 Crown- 6 3b: (4-*N*, *N*'-dimethyl benzaldehyde)

m.p. 230ºC; yield: 70%; IR(KBr): 2926, 1678, 1586, 1532, 1427, 1278, 1238, 1120, 957 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.8 (dd, 2H), 2.8 (dd, 2H), 3.1(s, 12H) 3.8-4 (m, 8H), 4.1-4.3(m, 8H)6.8-8(m, 14H); ^{13}C NMR (DMSO-d_6, 125MHz): δ 214.66, 190.35, 132.03, 121.29, 112.84, 112.47, 111.93, 111.06, 77.37, 77.05, 76.73, 69.42, 68.32, 40.68, 40.09, 33.71, 26.19, 24.37.Anal. Calcd. for $C_{42}H_{46}N_2O_8$: C, 71.35; H, 6.56; O, 18.12; N, 3.97. Found: C, 71.40; H, 6.60; O, 18.20;N, 3.95%.

4, 4'Di (acrylophenonyl) dibenzo 18 Crown- 6 3c: (4-hydroxy benzaldehyde). m.p. 260ºC; yield: 80%; IR (KBr): 3429, 2924, 1675, 1596, 1512, 1428, 1268, 1130, 957 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.1 (dd, 2H), 2.5 (dd, 2H), 3.8-4 (m, 8H), 4.1-4.3 (m, 8H) 6.8-8 (m, 14H), 10 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 196.30, 151.80, 147.34, 131.61, 129.89, 129.65, 123.09, 120.72, 111.86, 110.31, 79.13, 68.53, 67.53, 67.73, 67.37, 67.09, 40.11, 39.91, 26.26. Anal. Calcd. for $C_{38}H_{36}O_{10}$: C, 69.91; H, 5.56; O, 24.52. Found: C, 69.85; H, 5.60; O, 24.50%.

4, 4'-Di (2-amino-4-phenyl) pyrimidyl) dibenzo-18 -crown-6 (4a)

A mixture of chalcone **3** (1 mmole), guanidine hydrochloride (2.5 mmole), sodium methoxide (4 mmole) in 20 mL methanol was refluxed on water-bath for 6-8 hr. After completion of reaction the reaction-mixture was poured into ice water and the separated solid was filtered, dried and recrystallized from ethanol; m.p. 265ºC; Yield: 67 %.

4, 4'Di (2amino 4-*N, N*'dimethylphenyl) pyrimidyl) dibenzo 18 -crown- 6 (4b). m.p. 260°C; yield: 80%; IR (KBr): 3314, 3299 (NH_2), 2930 (CH), 1630 (C=N), 1565, 1476, 1361, 1338, 1274, 1178 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.5 (s, 2H, NH_2), 3.0 (s, 2H, NH_2), 3.2-3.4 (s, 12H) 3.9-4 (m, 8H), 4.1-4.3 (m, 8H) 6.8-8 (m, 14H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 138.91, 128.52, 128.06, 125.91, 125.35, 122.33, 115.14, 40.11, 39.91, 39.71, 39.50, 39.29, 39.09, 38.88. Anal. Calcd. for $C_{44}H_{50}O_6N_8$: C, 67.14; H, 6.41; O, 14.25; N, 12.20. Found: C, 67.10; H, 6.35; O, 14.22; N, 12.15%.

4,4'-Di (2-amino-4-hydroxy)pyrimidyl) dibenzo 18-Crown-6 4c. m.p. >300°C; Yield: 72%.

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References

1 1 D J Brown, *Comprehensive Heterocyclic Chemistry* edited by A R Katritzky & C W Rees (Pergamon Press, Oxford), 3, **1984**, p. 443.

2 B Roth & C Cheng, *Progress in Medicinal Chemistry* edited by G B Ellisand G E West, (Elsevier Biomedical Press, New York), 19, **1982**, p. 267.

3 M S A E–A El-Gaby, S G Abdel-Hamide, M M Ghorab & S M El-Sayed, *Acta Pharm*, 49**, 1999,** 149.

4 C R Petrie, H B Cottam, P A Mckernan, R K Robins & G R Revankar, *J Med Chem*, 8 ,**1985**, 1010.

5 M N Nasr & M M Gineinah, *Arch Pharm*, 335**, 2002**, 289; DOI:10.1002/1521-4184(200208)335:6289.

6 P G Baraldi, M G Pavani, M Nunez, P Brigidi, B Vitali, R Gambari & R, Romagnoli, *Bioorg Med Chem*, 10, **2002,** 449; DOI: 10.1016/S0968-0896 (01)00294-2.

7 S M Sondhi, M Johar, S Rajvanshi, S G Dastidar, R Shukla, R Raghubir & J W Lown, *Australian J Chem*, 54**, 2001,** 69; DOI: 10.1071/CH00141.

8 A Z M S Chowdhury, M M Matin & M N Anwar, Chittagong Univ Stud Part II 21 (1997) 79; *Chem Abstr*, 130**, 1999**, 237530p

9 (a) Kappe, C O, *Tetrahedron*, 49**, 1993**, 6937;
(b) Rovnyak G C, Kimball S D, *Synthesis*, 3171; Beyer, B, Cucinotta, G, Dimarco J D, Gougoutas J, Hedberg A Malley, M McCarthy J P, Zhang R Moreland, S, *J Med Chem*, 38, **1995**, 119;
(c) Atwal, K S , Rovnyak G C , Kimball S D , Floyd D M. Moreland S, Swanson B N, Gougoutas J Z, Schwartz J, Smillie K M, Malley M F, *J Med Chem*, 33, **1990**, 2629.

10 (a) Kappe C O, Fabian W M F, *Tetrahedron*, 53, **1997**, 2803.
(b) Kappe C O, *Eur J Med Chem*, 35, **2000**, 1043.

11 (a) Ranu B C, Hajra U , Jana, *J Org Chem*, 65, **2000**, 6270.
(b) Overman L E , Rabinowitz M H, Renhowe, *J Am Chem. Soc*,117, **1995,** 2657.

12 Biginelli P, *Gazz Chim Ital*, 23, **1893**, 360.