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Synthesis of New Lariat Ethers Containing Polycyclic Phenols and Heterocyclic Aromatic Compound on Graphite Surface *via* Mannich Reaction

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Synthesis of novel lariat ethers containing polycyclic phenols and heterocyclic aromatic compound using graphite *via* Mannich reaction are herein described. For this purpose *N*-(methoxymethyl) azacrown ether **4** was synthesized in nearly quantitative yield. The reaction of *N*-(methoxymethyl) azacrown ether **4** with polycyclic phenols and heterocyclic aromatic compound was performed in 10-20 min in the presence of graphite. The graphite powder can be reused up to five times after simple washing with acetone.

Keywords: Azacrown ether, Mannich reaction, Graphite, Solvent less

INTRODUCTION

The Mannich reaction is one of the most useful synthetic methods for functionalizing azacrown ethers with proton-ionizable phenol groups [1].

Phenolic sidearms have been extensively used to enhance the stability of the macrocyclic ligand for selected metal ions. The sidearms are often composed of UV-active or fluorophoric proton-ionizable materials that allow an analytical determination of certain cations by spectrophotometric methods [2].

The present study is a continuation of our efforts to develop simple and general methods for the preparation of new lariat ethers. A key element of this research is the incorporation of additional proton-ionizable ligating units with chromophoric and fluorophoric abilities onto ion-selective macrocycles to provide changes in properties of the azacrown ether upon metal ion binding while maintaining or improving the ion selectivities of the macrocycle [3,4].

We have previously shown that new lariat ethers can be prepared by the reaction of azacrown ether **3**, phenols and paraformaldehyde on solid supported (CaO and graphite) [5,6]. In continuation of our interest in Mannich base synthesis, in peculiar on solid supports, we now described new method to the aminoalkylation of polycyclic and heterocyclic aromatic compounds.

EXPERIMENTAL

Instrumentation, Analyses and Starting Materials

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrometer in pure deuterated solvents with tetramethylsilane as an internal standard. IR spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 ev. Melting points were determined in open capillary tubes in a Büchi-535 circulating oil melting point apparatus. The purity

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determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. Column chromatography was carried out on columns of silica gel 60 (70-230 mesh) in glass columns (2-3 cm diameter) using 15-30 gram of silica gel per one gram of crude mixture. Chemicals Material were either prepared in our laboratories or were purchased from Fluka, Aldrich and Merck Chemical Companies

Synthesis of 1,2-Phenylenedioxy Diacetic Acid (1)

To the mixture of catechol (11 g, 0.1 mol), and chloroacetic acid (28.4 g, 0.3 mol) at 90 °C on a water-bath, a solution of NaOH 33% (W/V) (48 g, in 97.5 ml water) was added dropwise. The mixture was stirred at 90 °C for 2 h, and after cooling to room temperature, the solution was kept in ice bath. Then concentrated HCl was added dropwise to the solution with stirring. The mixture was allowed to warm to room temperature and the solution was filtered and the white precipitates were washed with cold water. Crystallization of the residue from hot water afforded white solid of **1**, (20.5 g, 91% yield). m.p.: 178-179 °C, (Lit. [19]: 177-178 ºC). IR (KBr): 662(w), 753(m), 781(w), 822(w), 858(w), 1062(m), 1193(s), 1209(s), 1232(s), 1402(w), 1433(m), 1508(s), 1598(w), 740(s), 2535(w), 2631(w), 2850(m) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 4.68 (s, 4H), 6.88-6.90 (m, 4H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 65.5, 114.4, 121.8, 147.7, 170.7. Mass m/z (%): 228 (M^+ +2, 1.7), 227(M^++1, 10.1), 226(M^+, 87.0), 181(8.9), 168(14.3), 151(27.9), 135(15.2), 123(100), 107(38.7), 81(52.7), 64(43.4), 43(25.7).

[2-(2-Chloro-2-oxoethoxy)phenoxy]acetyl chloride (2a). [2-(Carboxymethoxy)phenoxy]acetic acid (5.65 g, 0.025 mol) was heated in thionyl chloride (50 ml) for 4 h at 50-60 °C. The thionyl chloride was evaporated at low temperature and residue was recrystallized from petroleum ether to give **2a** as a white cream solid in 85% (5.4 g) yield. m.p.: 48-49 °C, (Lit. [19]: 48-49 ºC). ^1H NMR ($CDCl_3$): δ = 4.99 (s, 4H), 6.78-6.95 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 73.6, 116.3, 123.5, 146.8, 170.6. Anal. Calcd. for $C_{10}H_8Cl_2O_4$ (263.074): C, 45.66; H, 3.07. Found: C, 45.75; H, 2.95.

Ethyl 2[2-(2-ethoxy-2-oxoethoxy) phenoxy] acetate (2b). 1,2-Phenylenedioxy diacetic acid (2.26 g, 0.01 mol), ethanol (75 ml) and concentrated sulfuric acid (0.1 ml) were refluxed with stirring for 12 h. The ethanol was removed in vaccum and the residue was dissolved in $CHCl_3$ (100 ml). The organic layer was washed with saturated sodium bicarbonate solution (2 × 100 ml), and water (2 × 100 ml), dried (anhydrous calcium chloride) and $CHCl_3$ was removed under reduced pressure to give **2** as a yellow oil (90% yield). IR (CH_2Cl_2): 750.3(m), 1068.5(m), 1186.1(s), 1595(s), 1759(s), 2981.7(w), 3066.6(m) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.28 (t, 6H), 4.27 (q, 4H), 4.72 (s, 4H), 6.92 (s, 4H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.5, 61.6, 67.1, 115.4, 122.9, 148.4, 169.4.

5,6,7,8,9,10-Hexahydro-2*H*-1,13,4,7,10-benzodioxatriaza cyclo pentadecine-3,11 (4*H*,12*H*)-dione (3). A solution of 1,2-phenylenedioxy dicarboxylicacid diester **2** (2 g, 7.1 mmol) and diethylentriamine (0.73 g, 7.1 mmol) in ethanol (100 ml) was left at room temperature for overnight. Then white needles precipitate which were filtered as aza-crown ether **3** in 80% yield. Decomposed in 233 °C. IR (KBr): 750(s), 1040(s), 1120(s), 1210(s), 1250(vs), 1320(s), 1420(s), 1450(s), 1500(s), 1540(s), 1590(w), 1640(vs), 2850(s), 2950(s), 3030(w), 3380(s), 3430(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.75 (s, 1H), 2.94 (t, 4H), 3.50 (t, 4H), 4.48 (s, 4H), 6.84-7.00 (m, 4H), 7.81 (s, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 38.5, 47.8, 67.2, 112.6, 122.4, 146.4, 167.6. Mass m/z (%): 295(M^++2, 0.9), 294 (M^++1, 2.9), 293 (M^+, 5.4), 225(50.6), 180(10.5), 167(17.3), 150(14.9), 121(17.7), 85(33.6), 69(78.7), 56(78.4), 43(100).

7-(Methoxymethyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7, 10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (4). Azacrown ether **3** (5 mmol) was added to solution of paraformaldehyde (6 mmol) in 75 ml of dry CH_3OH. The mixture was stirred at room temperature for 24 h. CH_3OH was evaporated under vacuum at 40 °C. *N*-(Methoxymethyl) azacrown ether **4** was obtained in quantitive yield. m.p.: 161-162 °C. IR (KBr): 575(m), 756(s), 822(m), 1053(s), 1130(s), 1223(m), 1265(s), 1427(w), 1512(s), 1543(m), 1593(w), 1686(vs), 2843(m), 3414(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.96 (t, 4H, J = 5.3 Hz), 3.30 (s, 2H), 3.56 (t, 4H, J = 5.3 Hz), 4.11 (s, 2H), 6.83-7.03 (m, 4H), 7.42 (s, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.2, 49.9, 56.0, 67.0, 81.5, 112.7, 121.9, 146.2, 167.4. Mass m/z (%): 307(-OMe, 0.3), 306(16.8), 305(7.0), 194(12.0), 293(2.6), 225(18.1), 155(11.7), 139(39.2), 121(18.3), 85(34.8), 65(8.1), 42(100). Anal. Calcd. for $C_{16}H_{23}N_3O_6$ (337.371): C, 56.96; H, 6.87. Found: C, 56.82; H, 6.65.

General Procedure for Synthesis of Compounds 5-21

N-(Methoxymethyl) azacrown ether **4** (1 mmol), polycyclic phenol or heterocyclic aromatic compound (1.2 mmol), and graphite (1 g) were thoroughly mixed. The resulting fine powder was transferred to a round-bottom flask and stirred in an oil bath at 100 ºC for the 10-20 min. After cooling, acetone was added to the mixture and graphite was removed by filtration. Evaporation of the solvent under reduced pressure gave the crude products, which were purified by flash column chromathography (eluent:*n*-hexane/EtOAc 1/1) or recrystallized from EtOAc.

7-[(1-Hydroxy-2-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (5). Rrecrystallization from EtOAc gave compound **5** as white powder in 81% yield. m.p.: 177 °C. IR (KBr): 752(m), 810(m), 1045(s), 1126(s), 1261(s), 1439(m), 1504(s), 1543(s), 1666(vs), 2851(w), 2924(w), 3290(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.76 (t, 4H, J = 5.3 Hz), 3.52 (t, 4H, J = 5.3 Hz), 3.91 (s, 2H), 4.50 (s, 4H), 6.93-7.10 (m, 5H), 7.24-7.41 (m, 3H), 7.45 (s, 2H), 7.70 (d, 1H, J = 8.1 Hz), 7.79 (d, 1H, J = 8.3 Hz), 10.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.7, 52.7, 58.1, 68.7, 114.2, 115.2, 119.2, 121.4, 123.0, 125.0, 126.1, 126.5, 127.4, 134.1, 147.5, 152.2, 168.3. Mass m/z (%): 450(M^++1, 0.5), 435(0.5), 381(0.4), 367(1.0), 311(0.9), 294(3.4), 293(5.2), 292(3.9), 225(41.0), 162(1.8), 156(63.7), 128(100), 102(26.5), 85(37.5), 69(82.6), 56(63.1). Anal. Calcd. for $C_{24}H_{26}N_4O_5$ (449.499): C, 66.80; H, 6.05. Found: C, 66.95; H, 6.23.

7-[(2-Hydroxy-1-naphthyl)methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (6). Rrecrystallization from EtOAc gave compound **6** as white powder in 83% yield. m.p.: 185-186 °C. IR (KBr): 748(s), 810(w), 1045(s), 1122(m), 1207(w), 1257(s), 1315(m), 1439(s), 1500(s), 1543(m), 1593(m), 1678(vs), 2847(w), 2916(w), 3406(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.80 (t, 4H, J = 5.3 Hz), 3.49 (t, 4H, J = 5.3 Hz), 4.17 (s, 2H), 4.44 (s, 4H), 6.80-7.06 (m, 5H), 7.18-7.35 (m, 2H), 7.49 (s, 2H), 7.59 (d, 1H, J = 8.9 Hz), 7.70 (d, 1H, J = 7.2 Hz), 7.87 (d, 1H, J = 8.5 Hz), 9.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.9, 51.3, 53.1, 68.3, 112.5, 114.7, 118.3, 121.4, 122.8, 126.5, 128.7, 129.7, 133.0, 147.2, 154.7, 168.1. Anal. Calcd. for $C_{24}H_{26}N_4O_5$ (449.499): C, 66.80; H, 6.05. Found: C, 66.67; H, 5.86.

7-[(8-Hydroxy-7-quinolinyl)methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (7). Rrecrystallization from EtOAc gave compound **7** as white powder in 89% yield. m.p.: 222 °C. IR (KBr): 752(s), 818(m), 1053(s), 1130(s), 1215(s), 1257(s), 1439(m), 1504(s), 1682(vs), 2851(w), 3302(m), 3410(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.78(t, 4H, J = 5.3 Hz), 3.54 (t, 4H, J = 5.3 Hz), 3.89 (s, 2H), 4.32 (s, 4H), 6.82-7.04 (m, 4H), 7.22 (d, 1H, J = 8.4 Hz), 7.35-7.40 (m, 2H), 7.89 (s, 2H), 8.09 (dd, 1H, J_1 = 8.3, J_2 = 1.4 Hz), 8.62 (dd, 1H, J_1 = 4.2, J_2 = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.6, 51.1, 52.7, 67.5, 113.2, 117.4, 118.9, 121.7, 122.2, 127.7, 129.8, 135.9, 137.9, 146.8, 148.0, 150.3, 167.3. Anal. Calcd. for $C_{24}H_{26}N_4O_5$ (450.487): C, 63.99; H, 5.82. Found: C, 64.14; H, 5.95.

7-[(5-Chloro-8-hydroxy-7-quinolinyl)methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (8). Rrecrystallization from EtOAc gave compound **8** as white powder in 92% yield. m.p.: 238 °C. IR (KBr): 751(w), 818(w), 1049(m), 1261(m), 1439(m), 1527(m), 1682(s), 2808(m), 3321(m), 3418(m). ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.79 (t, 4H, J = 5.3 Hz), 3.54 (q, 4H J = 5.3 Hz), 3.87 (s, 2H), 4.40 (s, 4H), 6.80-7.05 (m, 4H), 7.51 (dd, 1H, J_1 = 9.1, J_2 = 8.5 Hz), 7.52 (s, 1H), 7.82 (s, 2H), 8.42 (dd, 1H, J_1 = 8.5, J_2 = 1.5 Hz), 8.71 (dd, 1H, J_1 = 4.3, J_2 = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.4, 50.4, 52.6, 67.4, 113.1, 119.5, 122.2, 122.5, 125.5, 128.9, 132.8, 146.7, 148.6, 149.3, 167.4. Mass m/z (%): 484(M^+, 0.3), 412(0.2), 372(0.8), 370(1.4), 306(0.5), 305(0.2), 294(10.7), 293(8.2), 292(25.8), 274(0.9), 249(4.1), 225(44.6), 192(47.1), 163(26.7), 128(48.5), 85(58.9), 69(84.7), 56(100). Anal. Calcd. for $C_{24}H_{25}ClN_4O_5$ (484.932): C, 55.44; H, 5.20. Found: C, 55.29; H, 5.02.

7-[(1-Chloro-4-hydroxy-9-oxo-9*H*-thioxanthen-3-yl) methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (9). Rrecrystallization from EtOAc gave compound **9** as white powder in 71% yield. Decomposed = 220 °C. IR (KBr): 748(s), 806(m), 1045(s), 1122(m), 1261(s), 1299(s), 1435(s), 1500(s), 1543(s), 1593(m), 1678(vs), 2847(w), 3306(br) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 2.46 (t, 4H, J = 5.3 Hz), 3.37 (t, 4H, J = 5.3 Hz), 3.74 (s, 2H), 4.43 (s, 4H), 7.00-7.12 (m, 4H), 7.31 (s, 1H), 7.42 (d, 2H, J = 7.2 Hz), 7.58 (t, 2H, J = 7.1 Hz), 8.14 (s, 2H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ =

34.5, 50.7, 53.3, 69.1, 115.8, 122.4, 124.1, 126.2, 126.7, 128.0, 128.7, 129.2, 129.8, 132.4, 134.8, 147.8, 150.2, 167.7, 178.9. Anal. Calcd. for $C_{28}H_{26}ClN_3O_6S$ (568.041): C, 59.20; H, 4.61. Found: C, 59.35; H, 4.43.

7-[(4-Hydroxy-1-methyl-9-oxo-9*H*-thioxanthen-3-yl) methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (10). Rrecrystallization from EtOAc gave compound **10** as white powder in 75% yield. Decomposed = 226 °C. IR (KBr): 748(s), 810(w), 1045(s), 1122(m), 1211(m), 1257(s), 1304(m), 1439(s), 1500(s), 1543(s), 1593(m), 1678(vs), 2847(w), 2924(w), 3306(br) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 2.54(s, 3H), 2.66 (t, 4H, J = 5.3 Hz), 3.41 (t, 4H, J = 5.3 Hz), 3.74 (s, 2H), 4.47 (s, 4H), 7.04-7.16 (m, 6H), 7.47 (d, 1H, J = 7.7 Hz), 7.63 (t, 1H, J = 7.7 Hz), 8.15 (s, 2H), 8.25 (d, 2H, J = 8.1 Hz), 11.08 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 32.4, 34.5, 50.8, 53.7, 69.1, 115.7, 121.5, 122.4, 125.5, 126.1, 128.7, 129.7, 130.1, 132.0, 132.5, 135.5, 147.7, 149.1, 167.6, 181.5, 183.4. Anal. Calcd. for $C_{29}H_{29}N_3O_6S$ (547.623): C, 63.60; H, 5.34. Found: C, 63.49; H, 5.45.

7-[(1-Fluoro-4-hydroxy-9-oxo-9*H*-thioxanthen-3-yl) methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (11). Rrecrystallization from EtOAc gave compound **11** as white powder in 73% yield. Decomposed = 227 °C. IR (KBr): 748(s), 810(w), 1045(s), 1122(m), 1207(w), 1257(s), 1315(m), 1439(s), 1500(s), 1543(m), 1593(m), 1678(vs), 2847(w), 2916(w), 3406(br) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 2.63 (t, 4H, J = 5.3 Hz), 3.37 (t, 4H, J = 5.3 Hz), 3.72 (s, 2H), 4.42 (s, 4H), 6.98-7.14 (m, 4H), 7.43-7.61, 8.11 (s, 2H), 7.21 (d, 1H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 34.6, 50.9, 53.1, 68.9, 113.1, 113.5, 115.5, 116.5, 122.3, 126.6, 128.5, 129.3, 132.6, 135.4, 146.8, 147.6, 153.8, 157.9, 167.5, 178.0. Anal. Calcd. for $C_{28}H_{26}FN_3O_6S$ (551.587): C, 60.97; H, 4.75. Found: C, 61.14; H, 4.58.

3-[(3,11-Dioxo-3,4,5,6,9,10,11,12-octahydro-2*H*-1,13,4,7, 10-benzodioxatriazacyclopentadecin-7(8*H*)-yl)methyl]-4-hydroxybenzaldehyde (12). Rrecrystallization from EtOH gave compound **12** as white powder in 81% yield. m.p.: 221-222 °C. IR (KBr): 760(s), 838(m), 1053(s), 1126(s), 1219(s), 1257(s), 1439(m), 1504(s), 1597(s), 1659(vs), 1686(vs), 3086(m), 3398(s) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 2.43 (t, 4H, J = 5.3 Hz), 3.31 (t, 4H, J = 5.3 Hz), 3.57 (s, 2H), 4.33 (s, 4H), 6.82 (d, 1H, J = 8.3 Hz), 6.88-7.05 (m, 4H), 7.52 (dd, 1H, J_1 = 8.4, J_2 = 1.9 Hz), 7.68 (d, 1H, J = 1.9 Hz), 7.71 (s, 2H), 9.46 (s, 1H), 10.73 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 35.1, 49.9, 51.9, 67.3, 114.1, 115.6, 121.9, 124.7, 128.1, 129.6, 133.2, 146.7, 161.7, 166.8, 190.7. Mass m/z (%): 429(M^++2, 0.3), 428(M^++1, 3.0), 427(M^+, 5.8), 425(0.4), 356(3.0), 306(1.4), 294(2.0), 293(5.8), 292(12.0), 247(14.7), 225(23.0), 176(12.2), 139(24.9), 121(33.9), 85(62.6), 56(100.0). Anal. Calcd. for $C_{22}H_{25}N_3O_6$ (427.451): C, 61.88; H, 5.90. Found: C, 62.01; H, 6.06.

***N*-[(3,11-Dioxo-3,4,5,6,9,10,11,12-octahydro-2*H*-1,13,4, 7,10-benzodioxatriazacyclopentadecin-7(8*H*)-yl)methyl]-2-hydroxybenzamide (13).** Rrecrystallization from EtOAc gave compound **13** as white powder in 77% yield. m.p.: 187-188 °C. IR (KBr): 748(s), 818(w), 1057(s), 1126(m), 1223(s), 1257(s), 1443(m), 1508(s), 1539(s), 1678(vs), 2854(m), 3286(s), 3418(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.67 (t, 4H, J = 5.3 Hz), 3.40 (t, 4H, J = 5.3 Hz), 4.23 (d, 2H, J = 5.4 Hz), 4.38 (s, 4H), 6.80-6.99 (m, 6H), 7.34 (t, 1H, J = 7.4 Hz), 7.54 (s, 2H), 7.81 (d, 1H, J = 7.4 Hz), 8.95 (t, 1H, J = 5.2 Hz), 12.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.0, 49.6, 51.5, 67.2, 113.3, 115.1, 117.3, 118.5, 121.7, 127.9, 133.8, 146.2, 159.9, 166.8, 170.3. Anal. Calcd. for $C_{22}H_{26}N_4O_6$ (442.465): C, 59.72; H, 5.92. Found: C, 59.90; H, 6.10.

7-(3-Ethyl-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*, 12*H*)-dione (14). Rrecrystallization from EtOAc gave compound **14** as white powder in 83% yield. m.p.: 160 °C. IR (KBr): 748(s), 814(m), 1045(s), 1122(s), 1211(s), 1257(s), 1439(m), 1458(s), 1504(s), 1659(vs), 2827(m), 3329(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.89 (t, 3H, J = 7.5 Hz), 2.27 (q, 2H, J = 7.5 Hz), 2.65 (t, 4H, J = 5.3 Hz), 3.45 (t, 4H, J = 5.3 Hz), 3.67 (s, 2H), 4.40 (s, 4H), 6.62 (t, 1H, J = 7.4 Hz), 6.75 (d, 1H, J = 6.5 Hz), 6.81-6.96 (m, 5H), 7.38 (s, 2H), 9.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.3, 22.1, 35.1, 52.1, 57.1, 68.0, 114.4, 119.0, 120.6, 122.4, 126.3, 128.2, 130.2, 146.8, 153.6, 167.6. Mass m/z (%): 429(M^++2, 0.1), 428(M^++1, 2.2), 427(M^+, 3.0), 425(0.7), 355(3.8), 305(5.2), 294(0.7), 293(3.0), 292(12.0), 247(1.7), 225(16.4), 155(10.5), 139(39.9), 121(40.3), 85(71.1), 56(100.0). Anal. Calcd. for $C_{23}H_{29}N_3O_5$ (427.494): C, 64.62; H, 6.84. Found: C, 64.48; H, 6.98.

7-(2-Hydroxy-3-isopropyl-6-methylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (15). Rrecrystallization from EtOAc gave compound **15** as white powder in 85% yield. m.p.: 202-203 °C. IR (KBr): 752(s), 814(m), 1049(s), 1122(s), 1211(s), 1261(s), 1439(m), 1458(s), 1504(s), 1547(s), 1666(vs), 2820(m), 2947(m), 3340(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.88(s, 3H), 0.91(s, 3H), 2.13(s, 3H), 2.78 (t, 4H, J = 5.3 Hz), 2.83-290 (m, 1H), 3.48 (t, 4H, J = 5.3 Hz), 3.72 (s, 2H), 4.41 (s, 4H), 6.52 (d, 2H, J = 7.6 Hz), 6.82-6.96 (m, 5H), 7.34 (s, 2H), 9.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 19.7, 22.2, 26.6, 35.5, 53.7, 54.4, 68.5, 113.2, 114.9, 119.1, 121.5, 122.9, 125.2, 133.6, 147.3, 154.2, 168.2. Mass m/z (%): 457(M^++2, 0.3), 456(M^++1, 1.8), 455(M^+, 2.3), 382(2.0), 294(1.3), 293(7.1), 292(8.6), 249(0.5), 225(33.8), 204(12.1), 167(15.4), 147(28.8), 119(39.1), 85(59.8), 69(100.0). Anal. Calcd. for $C_{22}H_{26}N_4O_6$ (442.465): C, 65.91; H, 7.30. Found: C, 65.79; H, 7.43.

7-(2-Hydroxy-5-methylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (16). Purification by flash column chromatography, eluted with n-hexane/ ethyl acetate (1/1), gave compound **16** as white powder in 87% yield. m.p.: 206 °C. IR (KBr): 3400(s), 3200(br), 2900(m), 2860(m), 2680(vs), 1662(vs), 1598(m), 1540(s), 1506(s), 1438(m), 1259(s), 1215(s), 1128(s), 1047(s), 815(s), 740(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.22 (s, 3H), 2.75 (t, 4H, J = 5.3 Hz), 3.54 (t, 4H, J = 5.3 Hz), 3.73 (s, 2H), 4.51 (s, 4H), 6.64 (d, 1H, J = 8.0 Hz), 6.87-7.07 (m, 6H), 7.56 (s, 2H), 8.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 20.8, 36.2, 53.3, 56.0, 68.7, 114.9, 116.1, 122.4, 123.2, 129.5, 130.0, 131.0, 147.6, 154.0, 168.3. MS m/z (%): 415(M^++2, 1.2), 414(M^++1, 4.2), 413(M^+, 10.0), 396(2.4), 341(16.5), 292(37.7), 225(41.9), 206(15.5), 180(12.3), 176(23.2), 162(27.5), 121(93.3), 91(85.4), 85(60.8), 69(60.0), 56(86.6), 43(100.0). Anal. Calcd. for $C_{22}H_{27}N_3O_5$ (413.467): C, 63.91; H, 6.58; N, 10.16. Found: C, 63.75; H, 6.43; N, 9.87.

7-(2-Hydroxy-5-nitrobenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11 (4*H*,12*H*)-dione (17). Rrecrystallization from EtOH gave compound **17** as yellow powder in 50% yield. Decomposed = 239.5 °C (decomp.). IR (KBr): 3390(s), 3200(br), 2850(m), 1667(vs), 1600(s), 1550(vs), 1530(vs), 1500(s), 1440(s), 1335(vs), 1295(s), 1257(s), 1218(s), 1128(s), 1085(m), 1056(s), 830(m), 817(m), 750(s) cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz): δ = 2.51 (t, 4H, J = 5.3 Hz), 3.37 (t, 4H, J = 5.3 Hz), 3.65 (s, 2H), 4.40 (s, 4H), 6.89 (d, 1H, J = 8.9 Hz), 6.96-7.11 (m, 4H), 7.80 (s, 2H), 7.95 (dd, 1H, J = 8.9, 2.3 Hz), 8.11 (d, 1H, J = 2.2 Hz). ^{13}C NMR (DMSO-d_6): δ = 35.5, 50.6, 52.4, 68.3, 114.7, 115.6, 122.4, 124.7, 126.0, 126.3, 126.6, 139.7, 147.4, 162.6, 167.4. MS m/z (%): 445(M^++1, 0.3), 444(M^+, 1.3), 427(14.3), 414(0.5), 356(0.4), 340(0.4), 292(4.9), 225(39.2), 207(10.6), 193(5.3), 180(9.7), 167(20.5), 150(19.3), 121(22.3), 113(18.0), 85(48.7), 69(80.7), 56(92.4), 43(100.0). Anal. Calcd. for $C_{21}H_{24}N_4O_7$ (444.438): C, 56.75; H, 5.44; N, 12.61. Found: C, 56.68; H, 5.39; N, 12.43.

7-(1*H*-Indol-3-ylmethyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (18). Rrecrystallization from EtOAc gave compound **18** as white powder in 70% yield. m.p.: 190-191 °C. IR (KBr): 748(s), 818(m), 1049(s), 1126(s), 1219(s), 1257(s), 1439(m), 1504(s), 1535(s), 1597(m), 1686(vs), 2804(w), 2928(w), 3271(m), 3414(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.75 (t, 4H, J = 5.3 Hz), 3.54 (t, 4H, J = 5.3 Hz), 3.85 (s, 2H), 4.41 (s, 4H), 6.70 (t, 2H, J = 7.4 Hz), 6.85-7.04 (m, 4H), 7.08 (s, 2H), 7.30 (d, 1H, J = 8.1 Hz), 7.61 (s, 2H), 7.63 (d, 1H, J = 7.3 Hz), 8.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.6, 46.6, 51.9, 67.6, 110.7, 111.3, 118.9, 119.5, 122.2, 122.5, 124.1, 127.3, 136.4, 146.5, 167.5. Mass m/z (%): 423(M^++1, 0.2), 422(M^+, 0.5), 421(0.1), 420(0.3), 349(0.8), 306(0.4), 293(0.6), 292(1.5), 280(1.5), 245(1.1), 225(20.2), 167(10.3), 130(100.0), 102(27.7), 85(48.4), 69(82.9). Anal. Calcd. for $C_{23}H_{26}N_4O_4$ (422.477): C, 65.39; H, 6.20. Found: C, 65.54; H, 6.36.

7-[(2-Methyl-1*H*-indol-3-yl)methyl]-5,6,7,8,9,10-hexa-hydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (19). Rrecrystallization from EtOAc gave compound **19** as white powder in 73% yield. m.p.: 192-193 °C. IR (KBr): 741(s), 818(m), 1049(s), 1122(s), 1223(s), 1257(s), 1439(m), 1508(s), 1535(s), 1597(m), 1678(vs), 2804(w), 2893(w), 3329(m), 3406(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.37 (s, 3H), 2.74 (t, 4H, J = 5.3 Hz), 3.48 (t, 4H, J = 5.3 Hz), 3.73 (s, 2H), 4.35 (s, 4H), 6.50 (t, 1H, J = 7.5 Hz), 6.83-7.06 (m, 5H), 7.18 (d, 1H, J = 8.1 Hz), 7.52 (d, 1H, J = 7.5 Hz), 7.54 (s, 2H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 11.7, 35.7, 47.5, 52.3, 67.2, 107.3, 110.3, 113.0,

117.9, 119.3, 121.2, 122.2, 128.5, 133.3, 135.1, 146.6, 167.5. Mass m/z (%): 436(M^+, 0.7), 364(1.3), 363(0.5), 294(1.5), 293(1.6), 292(1.8), 280(2.5), 249(0.8), 225(11.9), 157(28.4), 144(100.0), 102(10.2), 85(19.1), 69(34.3). Anal. Calcd. for $C_{24}H_{28}N_4O_4$ (436.504): C, 66.04; H, 6.47. Found: C, 66.18; H, 6.33.

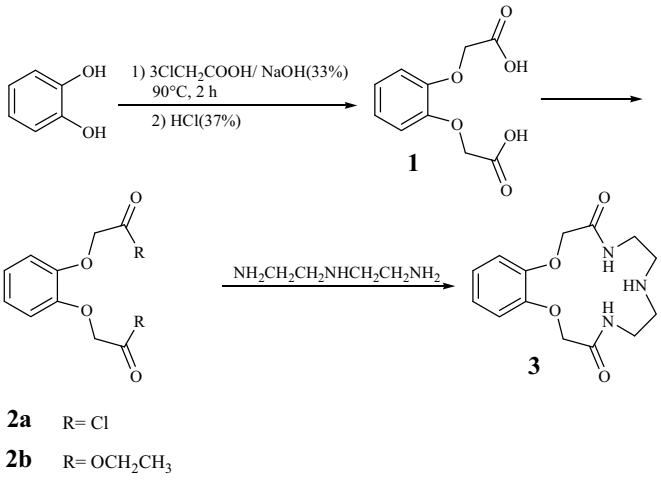
7-(1*H*-Imidazol-1-ylmethyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*, 12*H*)-dione (20). Rrecrystallization from EtOAc gave compound **20** as white powder in 82% yield. m.p.: 172-173 °C. IR (KBr): 756(s), 814(m), 1061(s), 1126(s), 1215(s), 1261(s), 1439(m), 1504(s), 1539(s), 1593(w), 1678(vs), 2851(w), 3402(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.79 (t, 4H, J = 5.3 Hz), 3.62 (t, 4H, J = 5.3 Hz), 4.49 (s, 4H), 4.90 (s, 2H), 6.86-7.03 (m, 5H), 7.08 (s, 1H), 7.43(s, 2H), 7.53(s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 34.8, 49.5, 60.4, 67.3, 113.2, 119.7, 122.4, 129.6, 137.7, 146.3, 167.5. Anal. Calcd. for $C_{18}H_{23}N_5O_4$ (373.406): C, 57.90; H, 6.21. Found: C, 57.78; H, 6.08.

7-(1*H*-Benzimidazol-1-ylmethyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopenta-decine-3,11(4*H*,12*H*)-dione (21). Rrecrystallization from EtOAc gave compound **21** as white powder in 84% yield. m.p.: 180 °C. IR (KBr): 741(s), 818(m), 1049(s), 1126(s), 1215(m), 1261(s), 1450(m), 1504(s), 1535(s), 1597(w), 1678(vs), 2858(w), 3421(s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.84 (t, 4H, J = 5.1 Hz), 3.61 (t, 4H, J = 5.3 Hz), 4.46 (s, 4H), 5.07 (s, 2H), 6.86-7.05 (m, 4H), 7.13-7.26 (m, 2H), 7.37 (s, 2H), 7.46 (d, 1H, J = 7.9 Hz), 7.77 (d, 1H, J = 7.7 Hz), 7.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.2, 50.3, 60.3, 67.5, 109.6, 113.5, 120.5, 122.6, 123.6, 134.3, 143.3, 146.5, 167.6. Anal. Calcd. for $C_{22}H_{25}N_5O_4$ (423.465): C, 62.40; H, 5.95. Found: C, 62.26; H, 6.13.

RESULTS AND DISCUSSION

Aza-crown ethers have been prepared by template effect, [7] high dilution technique, [8] reaction of diester with diamine or polyamine [9] or fast addition technique [10].

The reaction sequence leading to the formation of the aza-crown ether **3** is shown in Scheme 1. Each of the starting materials for the three step processes is readily available. Catecol was allowed to react with chloroacetic acid in the



Scheme 1

presence of 33% (w/v) sodium hydroxide solution at 90 °C, for 2 h to give sodium 1,2-phenylenedioxydiacetate, which was acidified with concentrated HCl to yield 1,2-phenylene dioxydiacetic acid **1** in 91% yield. Treatment of diacid **1** with thionyl chloride give 85% yield of white cream solid of 1,2-phenylene dioxydiacetyl dichloride **2a**. The cyclization reaction between dicarboxylic acid dichloride **2a** and diethylenetriamine was performed by the preceding procedure without high dilution technique. This step was carried out with fast addition of diethylenetriamine in dry ethyl acetate into a solution of dicarboxylic acid dichloride in dry ethyl acetate over a few seconds with vigorously stirring at room temperature. The mixture was stirred for further 20 min to give compound **3** in 45% yield. We also decided to use a different pathway to prepare compound **3**, as follows. Treatment of diacid **1** with ethanol in the presence of sulfuric acid as catalyst under reflux condition for 12 h, gave 90% yield of dicarboxylic acid diester **2b** as a yellow oil. The cyclization reaction was then performed by mixing of dicarboxylic acid diester **2b** and diethylenetriamine in ethanol at room temperature and keeping over night without stirring. After that, azacrown ether **3** was precipitated out as white needle crystals and filtered in 80% yield. The successful cyclization at the terminal amine position seems to be due to the difference in the reactivities between the terminal (primary) and the secondary amine nitrogens in the starting diethylenetriamine materials and it appeared to be dependent on the macrocycle's ring size.

For synthesis of new lariat ethers, the reaction of the azacrown ether **3** with *α*-naphtol and paraformaldehyde *via* Mannich reaction was chosen as a model and its behavior was studied under a variety of conditions *via* TLC and NMR spectroscopy (Table 1).

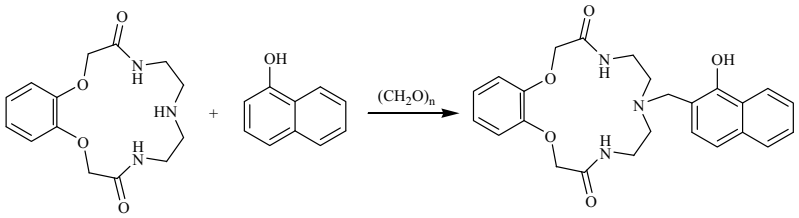
Mannich reaction of azacrown ether **3** and *α*-naphtol with appropriate solvent was carried out under reflux conditions (entries 1, 4, 7). We next screened CaO and graphite for Mannich reaction of azacrown ether **3** under similar conditions. We found the yields were further improved to 12-25% and graphite is better than CaO (entries 2, 3, 5, 6, 8, 9). In another study to increase the yield, experiments were done under solven-free condition in the presence of CaO and graphite. But with these methods yield was very low (27-37 %) (Table 1 entries 13 and 14). Increases of time and temperature have no effect on the yield (Table 1, entries 15 and 16).

Bogatsky and co-worker reported that secondary amines can be converted to methoxymethyl amines, which are active electrophilic reagents in the Mannich reaction and react

Table 1. Mannich Reaction of Azacrown Ether **3** (1 mmol) with *α*-Naphtol (1 mmol) and Paraformaldehyde (1.1 mmol) under Various Conditions

Entry	Conditions	T (ºC)	t (min)	Yield (%)[a]	Ref.
1	Benzene	Reflux	120	12	[11]
2	Benzene/CaO	Reflux	120	16	
3	Benzene/graphite	Reflux	120	21	
4	CCl_4	Reflux	120	10	[12]
5	CCl_4/CaO	Reflux	120	12	
6	CCl_4/graphite	Reflux	120	16	
7	Toluene	Reflux	120	19	[11]
8	Toluene/CaO	Reflux	120	22	
9	Toluene/graphite	Reflux	120	25	
10	Al_2O_3/MW		1.5	N.R.	[13]
11	(GMA)[b]	100	120	N.R.	[14]
12	(AMA)[c]	100	120	N.R.	[15]
13	CaO	100	20	27	[5]
14	Graphite	100	20	32	[6]
15	Graphite	100	60	35	
16	Graphite	130	10	37	

[a] Isolated yield. [b]Graphite/CH_3SO_3H. [c]Al_2O_3/CH_3SO_3H.



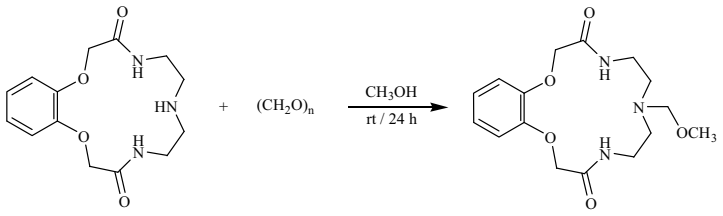
Scheme 2

readily with electron rich aromatics such as phenols [12].

In view of this subject, the reaction of azacrown ether **3** with paraformaldehyde and methanol at room temperature for 24 h afforded *N*-(methoxymethyl) azacrown ether **4** in nearly quantitative yield. *N*-(Methoxymethyl) azacrown ether **4** was used in the next step without any purification (Scheme 3).

To exploit a method for preparation of new lariat ethers **5-21**, the reaction of the *N*-(methoxymethyl) azacrown ether **4** (1 mmol) with α-naphtol (1 mmol) *via* Mannich reaction was chosen as a model and its behavior was studied under a variety of conditions *via* TLC and NMR spectroscopy (Table 2).

Condensation of the *N*-(methoxymethyl) azacrown ether **4** and *α*-naphtol with appropriate solvent was carried out under reflux conditions (entries 1, 3, 5) [11,12]. The final product **5** was obtained in 2 h of heating with low yields (10-19%). We next screened graphite for Mannich reaction of *N*-(methoxymethyl) azacrown ether **4** under similar conditions. We found the yields were further improved to 16-25% (entries 2, 4, 6). In another study, the effect of microwave was investigated and it was found that compound **5** was not prepared under this condition (entry 7) [13]. In an attempt to "greenfiy" the synthetic procedure and increase its rate and yield experiments were done under solven-free condition [14]. During the course of our studies aimed at developing solvent-free procedures, [15-17] we have now discovered that graphite alone promotes a very efficient Mannich reaction of activated



3 **4**

Scheme 3

Table 2. Mannich reaction of *N*-(methoxymethyl) Azacrown Ether **4** (1 mmol) with *α*-Naphtol (1 mmol) under Various Conditions

Entry	Conditions	T (ºC)	t (min)	Yield (%)[a]	Ref.
1	Benzene	Reflux	120	12	[11]
2	Benzene/graphite	Reflux	120	21	
3	CCl_4	Reflux	120	10	[12]
4	CCl_4/graphite	Reflux	120	16	
5	Toluene	Reflux	120	19	[11]
6	Toluene/graphite	Reflux	120	25	
7	Al_2O_3/MW		1.5	N.R.	[13]
8	(GMA)[b]	100	120	N.R.	[14]
9	(AMA)[c]	100	120	N.R.	[15]
10	CaO	100	20	70	
11	Graphite	70	3600	75	
12	Graphite	100	10	81	
13	Graphite	130	6	82	

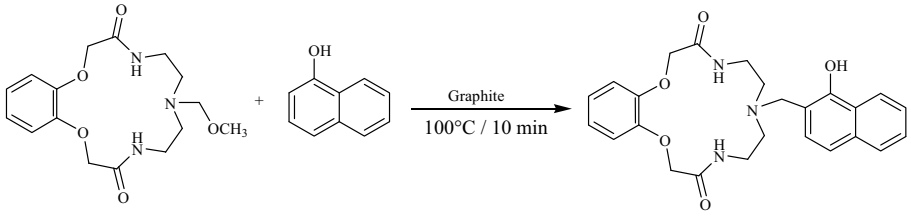
[a] Isolated yield. [b]Graphite/CH_3SO_3H. [c]Al_2O_3/CH_3SO_3H.

and unactivated phenol compounds with *N*-(methoxymethyl) azacrown ether **4** at 100 °C in high yield, without any of the environmental disadvantages of using toxic solvents. Moreover the effect of different amount of graphite on the model compound was studied in another experiment. The result showed that the best yield was obtained when 1 g of graphite was used. The increase in amount of graphite had negligible effects on the efficiency of the reaction. Furthermore the use of smaller amounts of graphite led to a pasty reaction mixture which makes the stirring difficult and so had not good effects on the efficiency of the model reaction.

In a typical experiment, graphite, *N*-(methoxymethyl) azacrown ether **4** (1 mmol) and α-naphtol (1 mmol) were mixed thoroughly. The mixture was heated in an oil bath at 100 °C with stirring for 10 min until the reaction was completed (Scheme 4). The product was isolated by simple extraction of the solid mass by acetone followed by the usual workup.

A variety of structurally divergent proton-ionizable ligating units possessing a wide range of functional groups was chosen to investigate the scope and the generality of the graphite promoted Mannich reaction (Table 3).

In a similar manner to the reaction of α-naphtol, β-naphtol, was reacted with *N*-(methoxymethyl) azacrown ether **4** in the presence of graphite to produce the corresponding product **2** in



4 **5**

Scheme 4

Table 3. Mannich Reaction of *N*-(Methoxymethyl) Azacrown Ether **4** (1 mmol) with Polycyclic Phenols and Heterocyclic Aromatic Compound (1 mmol)

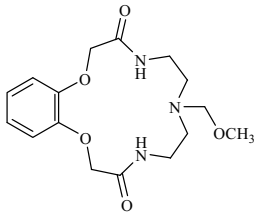
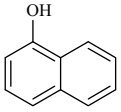
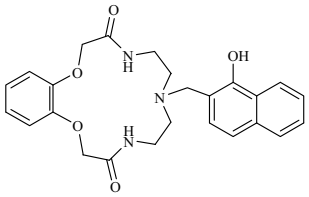
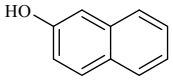
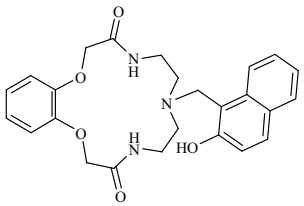
Entry	Amine	Poly nuclear phenols or heterocycles aromatic	Product	Time (min)	Yield (%)[a]
1	 **4**		 **5**	10	81
2	**4**		 **6**	10	83

Table 3. Continued

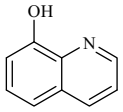
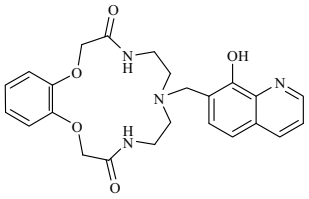
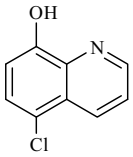
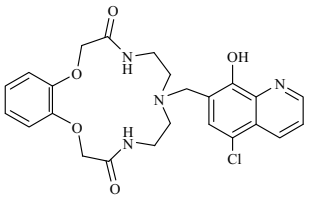
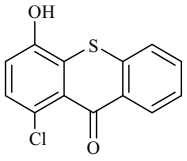
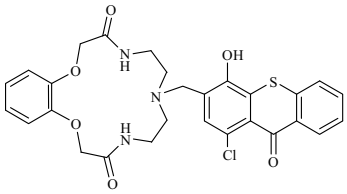
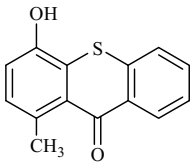
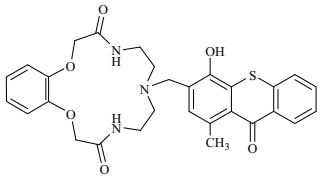
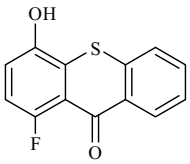
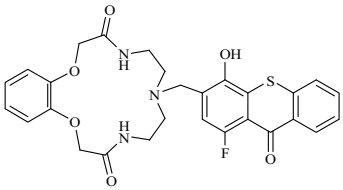
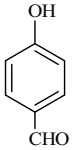
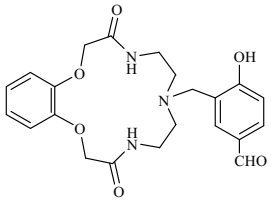
3	**4**		 **7**	12	89
4	**4**		 **8**	12	92
5	**4**		 **9**	15	71
6	**4**		 **10**	14	75
7	**4**		 **11**	16	73
8	**4**		 **12**	16	81

Table 3. Continued

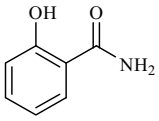
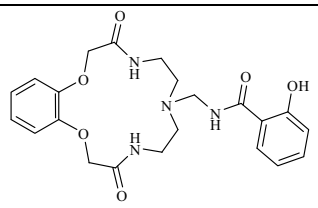
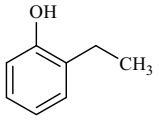
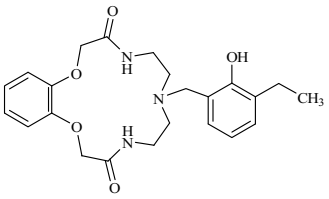
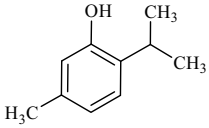
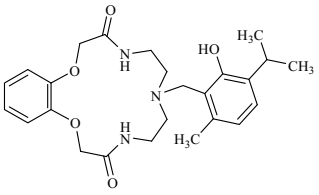
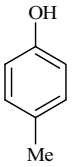
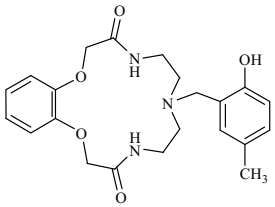
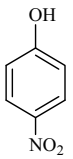
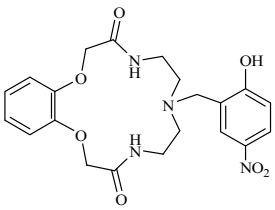
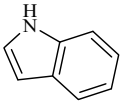
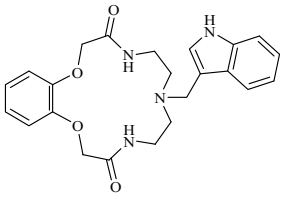
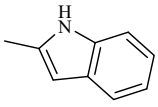
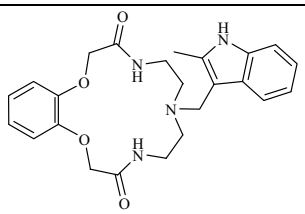
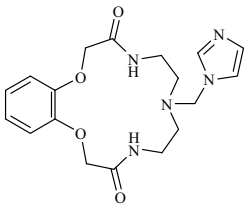
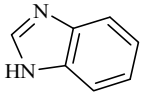
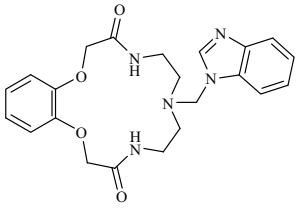
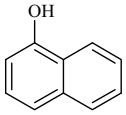
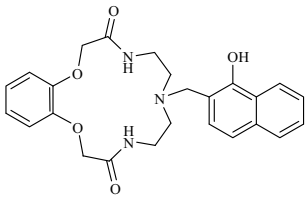
9	**4**		 **13**	12	77
10	**4**		 **14**	10	83
11	**4**		 **15**	10	85
12	**4**		 **16**	10	87
13	**4**		 **17**	20	50
14	**4**		 **18**	12	70

Table 3. Continued

15	**4**		 **19**	11	73
16	**4**		 **20**	10	82
17	**4**		 **21**	10	84
18[b]	**4**		 **5**	14	75

[a]Isolated yields. [b]Isolated yields is after 5 time reused graphite.

83% yields (Table 3, entry 2).

As expected, various polycyclic phenols were found to react with *N*-(methoxymethyl) azacrown ether **4** in the presence of graphite to give the corresponding lariat ethers in good to excellent yields. As shown in Table 3, the presented method is suitable for aminoalkylation of 5-chloro-8-hydroxyquinoline and 8-hydroxyquinoline.

We decided herein to synthesis some of new lariat ethers containing thioxanthone derivatives as side arms. The Mannich reaction between *N*-(methoxymethyl) azacrown ether **4** and thioxantone building blocks allowed the preparation of three-dimensional new lariat ethers **9-11** (Table 3, entries 5-7).

In the next step, we tried to attach the *p*-hydroxy benzaldehyde side arm to the azacrown ether ring by derivatization of *N*-(methoxymethyl) azacrown ether **4**. The carbonyl group at *para* position on the benzo unit of the final lariat ether is attractive site for functionalization such as imines that lead to synthesis of new chromogenic lariat ethers.

N-H acids (amides) are appropriate for the functionalization

of azacrown ethers using Mannich reaction. Heating *N*-(methoxymethyl) azacrown ether **4** with salicylamide at 100 °C for 12 min gave products of aminomethylation in good yield.

Aminomethylation of phenols with *N*-(methoxymethyl) azacrown ether **4** usually occurs in the positon *ortho* to the phenolic OH group even if the *para* position is unsubstituted. Possibly preferential attack on the *ortho* positions is caused by formation of a six membered transition state where the phenolic proton activates the aminomethylating reagent [18]. Formation of benzylamine bonds occurred very rapidly within 10-20 min when the phenols had either electron-donating or electron-withdrawing substituents.

In another study, we used thymol as a phenolic fragment for the prepration of new lariat ether. For comparison we also investigated reaction of the *N*-(methoxymethyl) azacrown ether **4** with *p*-cresol in the presence of graphite under modified reaction conditions (100 °C and 10 min) to afford the lariat ether **16** in high yield. A similar product and yield distribution as those with previous method were obtained whereas the rate of reaction was enhanced.

In the presence of graphite, *N*-(methoxymethyl) azacrown ether **4** and *p*-nitro phenol was heated at 100 °C for 20 min to give **17** in a 50% yield. *N*-(Methoxymethyl) azacrown ether **4** is effective aminomethylation reagent for various functional groups besides phenols and amides such as indoles and imidazoles. The synthesis of new lariat ether containing indoles and imidazoles was also an object of our study.

The Mannich reaction of *N*-(methoxymethyl) azacrown ether **4** with α-naphtol on a 30 mmol scale proceeded as well as 1 mmol scale. It is important to stress that the catalyst was recycled and reused for five runs (Table 3, entry 18) with only a slight drop in activity.

In conclusion, we have described a novel and highly efficient solvent-free protocol for Mannich reaction of polycyclic phenols and heterocyclic aromatic compounds using nontoxic and inexpensive graphite powder. The advantages of this environmentally benign and safe protocol, mild reaction conditions, high product yields, short reaction times, reusability of graphite, and the elimination of solvents.

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REFERENCES

[1] a) A.V. Bordunov, J.S. Bradshaw, V.N. Pastushok, R.M. Izatt, Synlett (1996) 993; b) Y. Habata, S. Akabori, J.S. Bradshaw, R.M. Izatt, Ind. Eng. Chem. Res. 39 (2000) 3465.

[2] a) M. Nakamura, H. Sakka, M. Takagi, K. Ueno, Chem. Lett. 9 (1981) 1305; b) H. Nishida, Y. Katayama, H. Katsuki, H. Nakamura, M. Takagi, K. Ueno, Chem. Lett. (1982) 1853; c) Y. Katayama, R. Fukuda, T. Iwasaki, K. Nita, M. Takagi, Anal. Chim. Acta 204 (1988) 113; d) M. Shamsipur, M. Sadeghi, K. Alizadeh, H. Sharghi, R. Khalifeh, Anal. Chim. Acta 630 (2008) 57.

[3] a) A.W. Czarnik, Acc. Chem. Res. 27 (1990) 302; b) A.P. De Silva, H.Q.N. Gunaratne, T. Gunnlaugsson, A.J.M. Huxley, C.P. McCoy, J.T. Rademacher, T.E. Rice, Chem. Rev. 97 (1997) 1515; c) D. Marquis, J.-P. Desvergne, H. Bouas-Laurent, J. Org. Chem. 60 (1995) 7984; d) D.M. Rudkevich, W. Verboom, E. Van Der Tol, C.J. Van Staveren, F.M. Kaspersen, J.W. Verhoeven, D.N. Reinhoudt, J. Chem. Soc., Perkin Trans. 2 (1995) 131; e) L. Fabbrizzi, M. Licchell, P. Pallavicini, A. Perotti, D. Sacchi, Angew. Chem., Int. Ed. Engl. 33 (1994) 1975.

[4] a) T.W. Brockmann, J.M. Tour, J. Am. Chem. Soc. 117 (1995) 4437; b) R.A. Bartsch, E. Chapoteau, B. P. Czech, J. Krzykawski, A. Kumar, T.W. Robinson, J. Org. Chem. 59 (1994) 616; c) W. Zazulak, E. Chapoteau, B.P. Czech, A. Kumar, J. Org. Chem. 57 (1992) 6720; d) N. Su, J.S. Bradshaw, X.-X. Zhang, H. Song, P.B. Savage, G. Xue, K.E. Krakowiak, R.M. Izatt, J. Org. Chem. 64 (1999) 8855.

[5] H. Sharghi, R. Khalifeh, Heterocycles 71 (2007) 1601.

[6] H. Sharghi, R. Khalifeh, Can. J. Chem. 86 (2008) 426.

[7] H.K. Frensdorff, J. Am. Chem. Soc. 93 (1971) 600.

[8] H. Stetter, J. Marx, Liebigs Ann. Chem. 607 (1957) 59.

[9] a) I. Tabushi, Y. Taniguchi, H. Kato, Tetrahedron Lett. 18 (1977) 1049; b) I. Tabushi, H. Okino, Y. Kuroda, Tetrahedron Lett. 17 (1976) 4339.

[10] a) H. Sharghi, H. Eshghi, Tetrahedron 51 (1995) 913;

b) H. Sharghi, Z. Paziraee, Synthesis (2004) 600; c) H. Sharghi, A. Zare, Synthesis (2006) 999.

[11] a) K.-W. Chi, H.-C. Wei, T. Kottke, R.J. Lagow, J. Org. Chem. 61 (1996) 5684; b) N. Su, J.S. Bradshaw, P.B. Savage, K.E. Krakowiak, R.M. Izatt, S.L. De Wall, G.W. Gokel, Tetrahedron 55 (1999) 9737.

[12] N.G. Lukyanenko, V.N. Pastushok, A.V. Bordunov, Synthesis (1991) 241.

[13] M.M. Mojtahedi, A. Sharifi, F. Mohsenzadeh, M.R. Saidi, Synth. Commun. 30 (2000) 69.

[14] a) S. Besoluk, M. Kucukislamoglu, M. Nebioglu, M. Zengin, M. Arslan J. Iran. Chem. Soc. 5 (2008) 62; b) F. Shirini, M.A. Zolfigol, A.-R. Abri, J. Iran. Chem. Soc. 5 (2008) 96; c) A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. Parhami, A.R. Moosavi Zare, J. Iran. Chem. Soc. 5 (2008) 100; d) M. Hosseini-Sarvari, H. Sharghi J. Iran. Chem. Soc. 5 (2008) 384; e) A. Khalafi-Nezhad, A. Parhami, A. Zare, A.R. Moosavi Zare, J. Iran. Chem. Soc. 5 (2008) 413; f) F. Shirini, M.A. Zolfigol, A. Shahriari J. Iran. Chem. Soc. 5 (2008) 420; g) A. Sharifi, M.S. Abaee, A. Tavakkoli, M. Mirzaei J. Iran. Chem. Soc. 5 (2008) S113; h) M. Hosseini-Sarvari, J. Iran. Chem. Soc. 5 (2008) S118.

[15] a) H. Sharghi, M. Hosseini Sarvari, Synthesis (2003) 243; b) H. Sharghi, M. Hosseini Sarvari, Synthesis (2004) 2165; c) H. Sharghi, Z. Shahsavari-Fard, Helv. Chim. Acta 88 (2005) 42; d) H. Sharghi, M. Hosseini Sarvari, Helv. Chim. Acta 88 (2005) 2282; e) H. Sharghi, M. Hosseini Sarvari, R. Eskandari, Synthesis (2006) 2047.

[16] a) H. Sharghi, B. Kaboudin, J. Chem. Res. (S) (1998) 628; b) H. Sharghi, K. Niknam, Iran. J. Chem. & Chem. Eng. 18 (1999) 36 (Chem. Abstr. 132 (2000) 122357m); c) H. Sharghi, M. Hosseini Sarvari, J. Chem. Res. (S) (2001) 446; d) H. Sharghi, M. Hosseini Sarvari, J. Org. Chem. 68 (2003) 4096; e) H. Sharghi, M. Hosseini Sarvari, Synth. Commun. 33 (2003) 205; f) H. Sharghi, M. Hosseini Sarvari, Teterahedron 59 (2003) 3627; g) H. Sharghi, M. Hosseini Sarvari, Synthesis (2003) 879; h) H. Sharghi, Z. Shahsavari-Fard, J. Iran. Chem. Soc. 2 (2005) 47; i) H. Sharghi, Z. Shahsavari-Fard, Phosphorus, Sulfur and Silicon 180 (2005) 1.

[17] a) H. Sharghi, K. Niknam, A.R. Massah, J. Heterocyc. Chem. 36 (1999) 601; b) H. Sharghi, M. Hosseini Sarvari, Synlett (2001) 99; c) H. Sharghi, M. Hosseini Sarvari, Synthesis (2002) 1057; d) H. Sharghi, M. Hosseini Sarvari, Tetrahedron 58 (2002) 10323; e) H. Sharghi, M. Hosseini Sarvari, J. Chem. Res. (S) (2001) 446; f) H. Sharghi, M. Hosseini Sarvari, J. Chem. Res. (S) (2003) 176; g) F. Kazemi, H. Sharghi, M.A. Nasseri, Synthesis (2004) 205; h) H. Sharghi, M. Hosseini Sarvari, J. Iran. Chem. Soc. 1 (2004) 28; i) H. Sharghi, M. Hosseini Sarvari, J. Org. Chem. 69 (2004) 6953; j) H. Sharghi, M. Hosseini Sarvari, R. Eskandari, J. Chem. Res. (S) (2005) 482; k) H. Sharghi, M. Hosseini Sarvari, Tetrahedron 61 (2005) 10903; l) H. Sharghi, M. Hosseini Sarvari, J. Chem. Res. (S) (2006) 205.

[18] J. Wang, Yingyong Huaxue 13 (1996) 69 (Chem. Abstr. 126: 144263).

[19] X. Wang, T. Wei, J. Chen, J. Li, Synth. Commun. 26 (1996) 2765.