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Synthesis of Some Novel Pendant-Armed Cyclen Derivatives

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A new easy-to-run route to some novel pendant-armed benzene-containing cyclen derivatives is proposed. In this route, the use of potassium carbonate instead of (N,N)-diisopropylethylamine as proton trapper caused a remarkable increase of yields.

Keywords: Tetra-azamacrocycle, Cyclen, Cyclen derivatives.

INTRODUCTION

Cyclen derivatives are of considerable interest because of their versatile complexing properties and important applications in biochemistry and medicine [1-4]. They are widely developed as extractants, cation (transition metal ions and lanthanide ions) and anion sensors, DNA recognition and cleavage agents and particularly as Magnetic Resonance Imaging contrast agents [5-8]. The successful application of several cyclen derivatives complexes for biomedical applications has stimulated interest for new cyclen-based ligands with different types of pendant arms in an attempt to find new ligands having different chemical, biological or catalytic properties. The new developments include synthesis of functionalized cyclen with same or mixed pendant arms [9], conversion of one functionality into another [10], selective N,N'-dialkylation of cyclen with mixed pendant arms and tetra-N-alkylation of cyclen by direct N-alkylation [11,12].

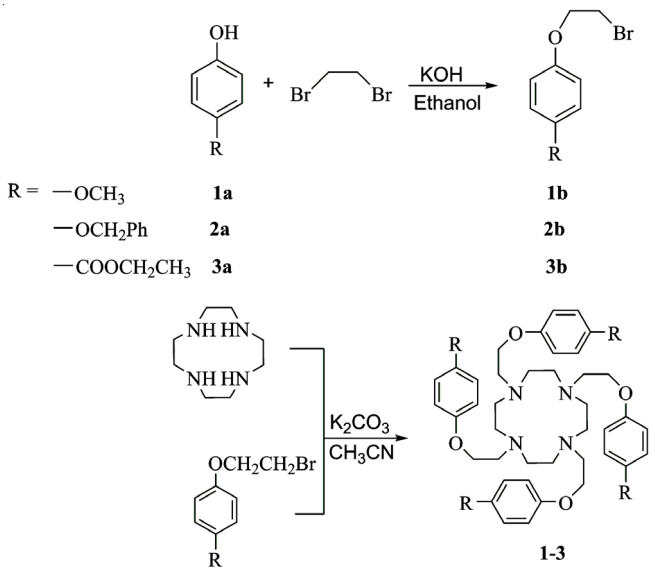
Smith *et al*. [13] reported the synthesis of pendant donor macrocyclic ligand 1,4,7,10-*tetrakis*((S)-2-hydroxyl-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane((S)-thphpc12) in quantitative yield from cyclen and (2S)-(+)-3-phenoxy-1,2-epoxypropane. They found pendant donor macrocycles derived from cyclen almost invariably coordinate to a metal ion in such a way that all four pendant arms project in the same direction. If, in addition to carrying a donor atom, the pendant arms also have an aromatic moiety attached to them, the possibility arises of using the coordination of the ligand to a metal ion as a way of assembling a molecular receptor with a substantial cavity that arises from the juxtaposition of the four aromatic groups. Encouraged by these considerations, we report herein the synthesis of some novel pendant-armed benzene-containing cyclen derivatives **1-3**, with potassium carbonate as proton trapper instead of (N,N)-diisopropylethylamine (**Scheme-I**). Moreover, other two cyclen derivatives **4** and **5** were also prepared based on compounds **2** and **3**, respectively.

EXPERIMENTAL

Cyclen was synthesized by the method of Athey and Kiefer [14-16]. All solvents and reagents were purchased from commercial sources and used as received. All aqueous solutions were prepared from deionized or distilled water. MS (ESI) mass spectral data were recorded on a Finnigan LCQDECA mass spectrometer. NMR spectra were acquired on a Bruker AC 300 spectrometer (^{1}H NMR: 300 MHz, 500 MHz, ^{13}C NMR: 75.47 MHz, 500 MHz). The chemical shifts are in δ values relative to the internal standard TMS. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Melting points were measured on a hot-plated microscope apparatus and are not corrected. TLC was performed on alumina sheets (Merck KgaA, 20 × 20 cm, Silica gel 60 F254).

General procedure

1-(2-Bromoethoxy)-4-methoxybenzene (1b): To a solution of dibromoethane (56.4 g, 0.3 mol), KOH (14 g, 0.25 mol) in 150 mL ethanol was added **1a** (24.8 g, 0.2 mol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (acetone/petroleum ether 1:3 silica gel). After disappearance of the starting material (about



Scheme-I: Synthesis of **1b**, **2b**, **3b** and cyclen derivatives **1**, **2**, **3**

18 h), the remaining solids were removed by filtration and filtrate was cooled to give white solids. The solids were recrystallized in ethanol to yield **1b**, white solid, yields: 68.5 %. m.p.: 50-51 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.88-6.82 (m, 4H, $C_6\underline{H}_4$), 4.25-4.23 (t, 2H, $BrCH_2C\underline{H}_2O$), 3.77 (s, 3H, $C\underline{H}_3O$), 3.62-3.60 (t, 2H, $BrC\underline{H}_2CH_2O$).

1-(2-Bromoethoxy)-4-benzyloxybenzene (2b): To a solution of dibromoethane (56.4 g, 0.3 mol), KOH (10 g, 0.18 mol) in 150 mL EtOH was added to **2a** (30 g, 0.15 mol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (acetone/petroleum ether 1:2 silica gel). After disappearance of the starting material (about 24 h), the remaining solids were removed by filtration and filtrate was cooled to give white solids. The solids were recrystallized in ethanol to yield **2b**, white solid, yields: 71.1 %. m.p.: 79-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43-7.32 (m, 5H, $C_6\underline{H}_5$), 6.93-6.84 (m, 4H, $C_6\underline{H}_4$), 5.02 (s, 2H, $PhC\underline{H}_2O$), 4.26-4.22 (t, 2H, $OC\underline{H}_2CH_2Br$), 3.63-3.59 (t, 2H, $BrC\underline{H}_2CH_2O$).

Ethyl 4-(2-bromoethoxy) benzoate (3b): To a solution of dibromoethane (37.6 g, 0.2 mol), K_2CO_3 (27.6 g, 0.2 mol) in 100 mL CH_3CN was added **3a** (10 g, 0.06 mol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (ethyl acetate/petroleum ether 1:5 silica gel). After disappearance of the starting material (about 22 h), the remaining solids were removed by filtration and the precipitate was washed several times with CH_3CN. The mother liquor and washings were combined and evaporated to dryness in a rotavapor. The pale yellow residue was purified by silica column chromatography using 15:1, petroleum ether/ ethyl acetate, to yield compound **3b**, white solid, yields: 76.4 %. m.p.: 72-73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.02-7.99 (d, 2H, $C_6H_2\underline{H}_2^{ortho}$-COOEt), 6.94-6.91 (m, 2H, $C_6H_2\underline{H}_2^{meta}$-COOEt), 4.38-4.36 (t, 2H, $BrCH_2C\underline{H}_2O$), 4.34-4.32 (q, 2H, $CH_3C\underline{H}_2O$), 3.69-3.63 (t, 2H, $BrC\underline{H}_2CH_2O$), 1.40-1.35 (t, 3H, $C\underline{H}_3CH_2O$).

1,4,7,10-*Tetrakis*[2-((4-methoxy)phenoxy)ethyl]-1,4,7,10-tetraazacyclododecane (1): To a solution of cyclen (0.2 g, 1.16 mmol), **1b** (1.34 g, 5.8 mmol) in 30 mL CH_3CN was added K_2CO_3 (0.83 g, 6.0 mmol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (CH_2Cl_2/CH_3OH 7:1 silica gel). After disappearance of the starting material (about 8 h), the remaining solids were removed by filtration and filtrate was cooled to give compound **1**, white solid, yields: 89.5 %. m.p.: 101-102 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 6.79-6.69 (16H, dd, $C_6\underline{H}_4$), 4.02 (8H, s, cyclen-$CH_2C\underline{H}_2O$), 3.75 (12H, s, $OC\underline{H}_3$), 3.27 (8H, s, cyclen-$C\underline{H}_2CH_2O$), 3.13 (16H, s, $NC\underline{H}_2C\underline{H}_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$), δ (ppm): 153.78, 153.09, 115.45, 114.73 ($\underline{C}_6H_4$), 67.22 (cyclen-$CH_2\underline{C}H_2O$), 55.74 ($O\underline{C}H_3$), 54.82 (cyclen-$\underline{C}H_2CH_2O$), 53.66 ($N\underline{C}H_2\underline{C}H_2N$). MS (ESI, CH_2Cl_2/MeOH + 1 % AcOH) *m/z* (%): 773.5 [M^+] (100), 795.50 [M+Na]$^+$ (37). IR (KBr, ν_{max}, cm^{-1}): 3444.2, 2931.5, 2832.9, 1509.8, 1233.7, 1034.9, 827.6.

1,4,7,10-*Tetrakis*[2-((4-benzyloxy)phenoxy)ethyl]-1,4,7,10-tetraazacyclododecane (2): To a solution of cyclen (0.2 g, 1.16 mmol), **2b** (1.78 g, 5.8 mmol) in 30 mL CH_3CN was added K_2CO_3 (0.83 g, 6.0 mmol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (CH_2Cl_2/CH_3OH 7:1 silica gel). After disappearance of the starting material (about 6 h), the remaining solids were filtered off and washed several times with deionized water and CH_3OH to yield compound **2**, white solid, yields: 90.8 %. m.p.: 139-140 °C. ^{1}H NMR (300MHz, $CDCl_3$), δ (ppm): 7.38-7.30 (20H, m, $C_6\underline{H}_5$), 6.87-6.77 (16H, dd, $C_6\underline{H}_4$), 4.95 (8H, s, $PhC\underline{H}_2$), 3.96 (8H, s, cyclen-$CH_2C\underline{H}_2O$), 2.82 (8H, s, cyclen-$C\underline{H}_2CH_2O$), 2.75 (16H, s, $NC\underline{H}_2C\underline{H}_2N$). ^{13}C NMR (75.47MHz, $CDCl_3$), δ (ppm): 153.33, 151.86, 115.46 ($\underline{C}_6H_4$), 137.39, 128.60, 127.93 ($\underline{C}_6H_5$), 70.74 ($C_6H_5\underline{C}H_2O$), 67.24 (cyclen-$CH_2\underline{C}H_2O$), 54.83 (cyclen-$\underline{C}H_2CH_2O$), 53.70 ($N\underline{C}H_2\underline{C}H_2N$). MS (ESI, CH_2Cl_2/MeOH + 1 % AcOH) *m/z* (%): 1078.8 [M^+] (6). IR (KBr, ν_{max}, cm^{-1}): 3444.1, 2925.4, 2825.3, 2798.1, 1508.8, 1233.7, 1041.6, 826.0, 760.3, 734.7.

1,4,7,10-*Tetrakis*[2-((4-ethoxyacyl)phenoxy)ethyl]-1,4,7,10-tetraazacyclododecae (3): To a solution of cyclen (0.2 g, 1.16 mmol), **3b** (1.58 g, 5.8 mmol) in 30 mL CH_3CN was added K_2CO_3 (0.83 g, 6.0 mmol). The resulting solution was heated under reflux and the progress of the reaction monitored by TLC (CH_2Cl_2/CH_3OH 7:1 silica gel). After disappearance of the starting material (about 8 h), the remaining solids were filtered off and washed several times with deionized water and CH_3OH to yield compound **3**, white solid, yields: 83.2 %. m.p.: 130-131 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.95-7.92, (8H, d, $C_6H_2\underline{H}_2^{ortho}$-COOEt), 6.85-6.82 (8H, d, $C_6H_2\underline{H}_2^{meta}$-COOEt), 4.37-4.30 (8H, q, $CH_3C\underline{H}_2O$), 4.05-4.02 (8H, t, cyclen-$CH_2C\underline{H}_2O$), 2.86-2.84 (8H, t, cyclen-$C\underline{H}_2CH_2O$), 2.74 (16H, s, $NC\underline{H}_2C\underline{H}_2N$), 1.62-1.35(12H, t, $C\underline{H}_3CH_2O$). ^{13}C NMR (500 MHz, $CDCl_3$), δ (ppm): 166.40 ($\underline{C}OCH_2CH_3$), 162.61, 131.61, 123.08, 114.11 ($\underline{C}_6H_4$), 66.99 (cyclen-$CH_2\underline{C}H_2O$), 60.69 ($CH_3\underline{C}H_2O$), 54.61 (cyclen-$\underline{C}H_2CH_2O$), 53.93 ($N\underline{C}H_2\underline{C}H_2N$), 14.47 ($\underline{C}H_3CH_2O$). MS (ESI, CH_2Cl_2/MeOH + 1 % AcOH) *m/z* (%): 940.7 [M^+] (72), 963.7 [M+ Na]$^+$ (100), 979.9 [M+ K]$^+$ (5). IR (KBr, ν_{max}, cm^{-1}): 3444.3, 2975.8, 2810.6, 2810.3, 1712.4, 1607.2, 1510.6, 1279.3, 1256.9, 1102.9, 1021.4, 842.3.

1,4,7,10-*Tetrakis*[2-((4-hydroxy)phenoxy)ethyl]-1,4,7,10-tetraazacyclododecane (4): Compound **2** (0.2 g, 0.19 mmol) dissolved in a mixture of CH_2Cl_2 (50 mL) and glacial CH_3OH (10 mL) was hydrogenated under 1 atm of H_2 in the

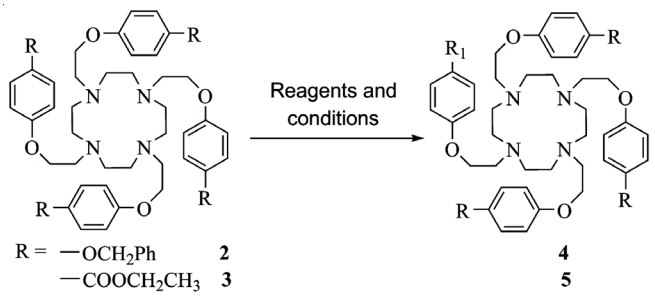
presence of 5 % Pd/C (0.04 g). After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of Celite^{R} and the precipitate was washed several times with CH_2Cl_2 and CH_3OH. The mother liquor and washings were combined and concentrated under diminished pressure to yield an off-white solid. The solid was recrystallized in ethanol to yield a white solid compound **4**, yields: 90.4 %. m.p.: 223-224 °C. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 6.68,-6.67 (8H, d, $C_6H_2\underline{H}_2^{ortho}$-OH), 6.60-6.58 (8H, d, $C_6H_2H_2^{meta}$-OH), 4.00 (8H, s, cyclen-$CH_2C\underline{H}_2O$), 3.53 (8H, s, cyclen-$C\underline{H}_2CH_2O$), 3.46 (16H, s, $NC\underline{H}_2C\underline{H}_2N$). ^{13}C NMR (500 MHz, CD_3OD), δ (ppm): 154.31, 152.97, 118.01, 117.53 ($\underline{C}_6H_4$), 66.99 (cyclen-$CH_2\underline{C}H_2O$), 54.76 (cyclen-$\underline{C}H_2CH_2O$), 51.82 ($N\underline{C}H_2\underline{C}H_2N$). MS (ESI, CH_2Cl_2/MeOH + 1 % AcOH) *m/z* (%): 717.40 [M$^+$] (100), 718.40 [M+H] $^+$ (36), 739.40 [M+Na] $^+$ (72), 755.60 [M+K] $^+$ (3). IR (KBr, ν_{max}, cm^{-1}): 3383.9, 3175.3, 2923.7, 2857.4, 1510.7, 1450.4, 1372.5, 1216.6, 1053.0, 853.7.

1,4,7,10-*Tetrakis*[2-((4-carboxyl)phenoxy)ethyl]-1,4,7,10-tetraazacyclododecane (5): A stirred sample of **3** (0.1 g, 0.11 mmol) in methanol (10 mL) was treated with aqueous NaOH (2 M, 10 mL). Stirring was continued at 60-65 °C for 12 h. The pH of the solution was adjusted to 7.0 with dilute HCl (2 M). The sample was concentrated. The residue was suspended in a mixture of CH_2Cl_2 and CH_3OH (9:1). Filtration and concentration of the resulting solution afforded a white solid compound **5**, yields, 97.2 %. m.p.: 240-241 °C. ^{1}H NMR (300MHz, CD_3OD), δ (ppm): 7.93-7.91 (8H, d, $C_6H_2\underline{H}_2^{ortho}$-COOH), 6.91- 6.89 (8H, d, $C_6H_2\underline{H}_2^{meta}$-COOH), 4.25 (8H, s, cyclen-$CH_2C\underline{H}_2O$), 3.45-3.30 (8H, s, cyclen-$C\underline{H}_2CH_2O$), 3.15 (16H, s, $NC\underline{H}_2C\underline{H}_2N$). ^{13}C NMR (500 MHz, DMSO-d_6), δ (ppm): 166.78 (C_6H_4-$\underline{C}OOH$), 161.25, 131.25, 123.48, 114.29 ($\underline{C}_6H_4$), 63.39 (cyclen-$CH_2\underline{C}H_2O$), 55.94 (cyclen-$\underline{C}H_2CH_2O$), 51.69 ($N\underline{C}H_2\underline{C}H_2N$). MS (ESI, CH_2Cl_2/MeOH + 1 % AcOH) *m/z* (%): 829.50 [M$^+$] (100), 851.50 [M+Na]$^+$ (7). IR (KBr, ν_{max}, cm^{-1}): 3616.6, 3471.1, 2932.7, 2852.2, 2602.7, 2508.6, 1694.3, 1607.2, 1260.7, 848.3.

RESULTS AND DISCUSSION

We investigated the effect of solvent, time or temperature on the yields of tetra-N-alkylation of cyclen. Choice of an appropriate solvent is essential for avoiding other alkylation. Acetonitrile proved to be a suitable solvent for quadruple alkylation due to the improvement of proton transfer. Under other protonic solvents, the tetra-N-alkylation cannot fully proceed, not even with high excesses of alkylating reagents at prolonged times (2 weeks). The reaction carried out at 82 °C was found to give purer products than the room temperature within 8 h. In addition, with (N,N)-diisopropylethylamine as proton trapper, we found the reaction generated a significant outgrowth and gave a lower overall yield (57-58 %), unsatisfactory slightly with regard to a synthetic demand. These very moderate yields of cyclen derivatives prompted us to look for more favourable conditions for the reaction. We also tried to use an alternative base. Replacement of (N,N)-diisopropylethylamine by triethylamine also kept yields at the same level. However, the use of potassium carbonate instead of (N,N)-diisopropylethylamine caused a remarkable increase of yields (83-91 %). It appears that the nature of the proton trapper in the nucleophilic substitution process is of crucial importance. It could be assumed that this effect is mainly due to the close carbonate-potassium ion pair. On the one hand, the potassium ion acts as a Lewis catalyst toward the leaving group, while on the other hand, the carbonate ion activates the nucleophilicity of the neighboring nitrogen atom through hydrogen bonding. This situation is very similar to the classical one invoked rationalized *syn* elimination in the E_2 reaction of neutral substances [17].

Based on the cyclen derivatives **2** and **3**, we also synthesized other two compounds (**Scheme-II**). One-pot catalytic debenzylation and hydrogenation of the resulting 1,4,7,10-*tetrakis*(2-*p*-phenzoxyl-phenoxyl-ethyl)-1,4,7,10-tetraazacyclododecane (**2**) with 5 % Pd/C in mixed solvents of CH_2Cl_2/CH_3OH (1:5) at room temperature led to the corresponding off-white solid **4** in 90 % isolated yield [18]. Hydrolysis of 1,4,7,10-*tetrakis*(2-(4-ethylformat-phenoxyl)-ethyl)-1,4,7,10-tetraazacyclododecane (**3**) with 1 M sodium hydroxide in CH_3OH/water (1:1), followed by recrystallization from methanol, afforded the compound **5** in excellent yield as a white solid [19].



Scheme-II: Synthesis of cyclen derivatives **4** and **5**. Reagents and conditions: (1) For compound **4**, CH_2Cl_2/CH_3OH, Pd/C, room temperature; (2) For compound **5**, CH_3OH/NaOH, reflux

Conclusion

In summary, we have synthesized some novel pendant-armed benzene-containing cyclen derivatives and compared to previous methods proposed for the synthesis of cyclen derivatives, the association of potassium carbonate undoubtedly constitutes an improvement: lower the time of response, simply dispose and enhance the yield. This procedure could certainly be successfully applied to synthesize more complicated structures containing a functionalized pendant arm. Further work of these new cyclen derivatives concerning the interaction with cations, anions and neutral molecules is currently in progress.

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