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A facile route to a novel aza-crown ether incorporating three thiophene moieties

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Abstract

The preparation of the first of a novel type of large thiophene-containing aza-crown ether is reported. The macrocycle is synthesised by linking a 3,4-dialkoxythiophene moiety with two 3-hydroxythiophene units and ring closure is effected by reaction with piperazine via the Mannich reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aza-crown; thiophene; macrocycle; Mannich reaction.

The syntheses of non-aromatic and benzene-containing aza-crown ethers have been widely reported.[1] However, thiophene analogues are poorly represented in the literature.[2] Aza-crown ethers have complexing properties which are intermediate between those of crown ethers and those of nitrogen donor macrocycles. They exhibit enhanced coordinating ability towards ammonium salts and transition metals over crown ethers[3,4] as well as having important applications as synthetic receptors in molecular recognition processes.[5] We report in this paper a new route to the first of a novel type of large aza-crown ether incorporating three thiophene rings. The method of ring closure employed utilises the Mannich reaction, which gives selective substitution of the 3-alkoxythiophene units over the 3,4-dialkoxythiophene unit. The synthetic route is shown in Scheme 1.

To diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, **1**, (1 equiv.) and anhydrous potassium carbonate (1.2 equiv.) in DMF (1.0 cm^3 $mmol^{-1}$), heated at 100°C, was added 5-tosyloxy-3-oxa-pentan-1-ol (1.2 equiv.) in DMF (0.5 cm^3 $mmol^{-1}$) by means of a syringe pump. After the addition, heating was continued for 12 h. The solvent was removed in vacuo and the crude mixture was partitioned between water and EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. Diethyl 3,4-bis(5′-hydroxy-3′-oxapentyloxy)thiophene-2,5-dicarboxylate, **2**, was obtained in 56% yield[6] as an oil after column chromatography (silica: EtOAc). To crude **2** (5.10 g, 0.012 mol), in dry DCM (45 cm^3) and triethylamine (10 cm^3), was added methanesulfonyl chloride (8.04 g, 0.07

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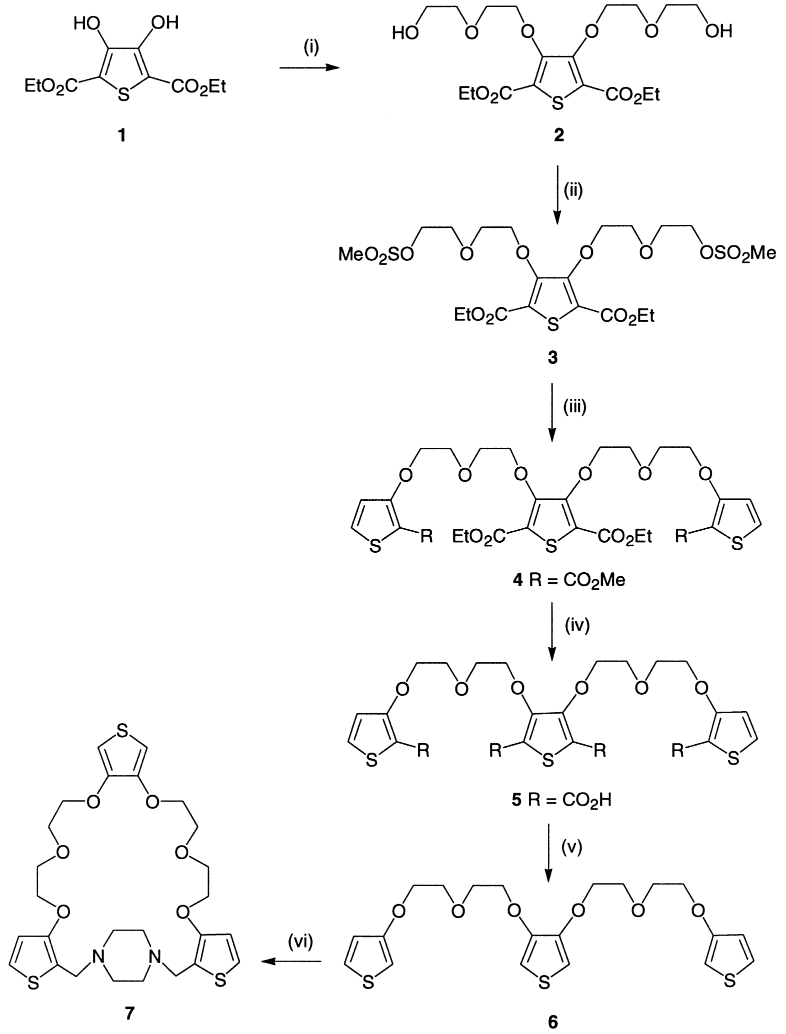

Scheme 1. (i) K_2CO_3, 5-tosyloxy-3-oxapentan-1-ol, DMF, Δ 100°C. (ii) methanesulfonyl chloride, DCM/triethylamine, 0°C. (iii) methyl 3-hydroxythiophene-2-carboxylate, K_2CO_3, DMF, Δ 100°C. (iv) 2 M $NaOH_{(aq)}$, EtOH, Δ 60°C, 4 M HCl. (v) Cu_2O, quinoline, Δ 180°C, under N_2. (vi) 37% $CH_2O_{(aq)}$, piperazine, g.AcOH.

mol) with ice cooling. The mixture was stirred at room temperature for 10 min, and then poured into water (100 cm^3). The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated. The resulting oil was purified by column chromatography, (silica: EtOAc–light petroleum, 2:1), to give diethyl 3,4-bis(5′-methanesulfonyloxy-3′-oxapentyloxy)thiophene-2,5-dicarboxylate, **3**, as an oil (3.22 g, 47% yield).[7] To add the end thiophene units, **3** (2.14 g, 3.64 mmol) was added to a suspension of methyl 3-hydroxythiophene-2-carboxylate (1.25 g, 8.23 mmol) and potassium carbonate (1.50 g, 10.87 mmol) in DMF (50 cm^3) and stirred and heated (100°C) for 12 h. Upon cooling, the inorganic material was filtered off and the filtrate was evaporated to dryness in vacuo. The resulting oil was dissolved in EtOAc (75 cm^3) and washed with water. The organic layer was dried ($MgSO_4$), and evaporated to give an oil, which was subjected to column chromatography, (silica: EtOAc–light petroleum, 3:1), to give diethyl 3,4-bis[5′-(2″-methoxycarbonyl-3″-thienyloxy)-3′-oxapentyloxy]-thiophene-2,5-dicarboxylate, **4**, (1.93 g, 75%).[8] Having successfully coupled the three thiophene moieties, the tetraester, **4**, was stirred with a 30% excess of sodium hydroxide solution (2 M) and an equal volume of ethanol at 60°C for 1 hour. The cooled solution was acidified with hydrochloric acid (4 M), and the subsequent slurry was stirred for a further hour. The ethanol was removed in vacuo and the precipitate filtered off and recrystallised from water to afford 3,4-bis[5′-(2″-carboxy-3″-thienyloxy)-3′-oxapentyloxy]thiophene-2,5-dicarboxylic acid, **5**, as a white solid, (92%).[9] In order to decarboxylate the tetraacid, compound **5**, quinoline (3 cm^3 g^{-1}) and copper(I) oxide (0.25 mol per mol of CO_2 expected) were heated (180°C) for 45 min under nitrogen. Upon cooling, the mixture was filtered and the residue was washed with diethyl ether. The combined filtrate and ethereal washings were extracted with hydrochloric acid (4 M), water and sodium carbonate solution (10%). The diethyl ether layer was dried (Na_2SO_4) and evaporated. The crude compound was purified by centrifugal chromatography, (silica: light petroleum-EtOAc, 1:1), to give 3,4-bis[5′-(3″-thienyloxy)-3′-oxapentyloxy]thiophene, **6**, as a white solid (81%).[10] In the final step, **6** (0.67 g, 1.47 mmol) was added to glacial acetic acid (50 cm^3), piperazine (0.13 g, 1.51 mmol) and aqueous formaldehyde (37%, 0.24 cm^3, 2.96 mmol) and stirred overnight. The solvent was removed in vacuo and the residue was basified (4 M NaOH) and extracted with dichloromethane, (3×20 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to give the crude product which was purified by column chromatography, (alumina: light petroleum–EtOAc, 5:1), to give 2,5,8,14,17,20-hexaoxa-27,30-diaza-11,24,33-trithia-27,30-ethylenpentacyclo[30.3.^{1,32}2.^{27,30}0.^{21,25}0.^{9,13}]-pentatriaconta-1(32),9,12,21,(25),22,34-hexene, **7**, as a white crystalline solid (0.41 g, 49%).[11]

The macrocycle **7** was obtained as the sole product of the reaction. This was somewhat surprising as cyclisation should also be possible between the 2-position of the 3,4-dioxy substituted thiophene ring and the 2-position of one of the 3-oxy substituted thiophene rings. However, this latter reaction clearly does not occur as no asymmetrically substituted product was isolated from the column chromatography fractions.

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6. ν_{max} (film) 3426, 2937, 2872 and 1717 cm^{-1}; δ_H ($CDCl_3$) 1.37 (6H, t, *J* 7.3 Hz, CH_3), 3.63–3.65 (4H, m, OCH_2), 3.80–3.84 (8H, m, OCH_2), 4.35 (4H, q, CO_2CH_2), 4.39–4.41 (4H, m, $ArOCH_2$); δ_C ($CDCl_3$) 14.2 (CH_3), 61.5 (CO_2CH_2), 61.7 (CH_2OH), 70.2, 72.9 and 74.1 (OCH_2), 119.7 (C2/C5), 153.2 (C3/C4), 160.5 (C=O); (Found: C, 49.71; H, 6.72. $C_{18}H_{28}O_{10}S$ requires C, 49.53; H, 6.47%).
7. ν_{max} (film) 2960, 2910 and 1710 cm^{-1}; δ_H ($CDCl_3$) 1.37 (6H, t, *J* 7.3 Hz, $O_2CH_2\mathit{CH_3}$), 3.06 (6H, s, SO_2CH_3), 3.80–3.87 (8H, m, OCH_2), 4.34 (4H, q, *J* 7.3 Hz, CO_2CH_2), 4.36–4.39 (8H, m, OCH_2); δ_C ($CDCl_3$) 14.2 ($CH_2\mathit{CH_3}$), 37.5 (SO_2CH_3), 61.4 ($CO_2\mathit{C}H_2$), 68.9, 69.3, 70.5 and 73.7 (OCH_2), 119.6 (C2/C5), 153.0 (C3/C4), 160.4 (C=O); (Found: C, 40.62; H, 5.49. $C_{20}H_{32}O_{14}S_3$ requires C, 40.53; H, 5.44%).
8. ν_{max} (film) 3110, 2980, 2950 and 1710 cm^{-1}; δ_H ($CDCl_3$) 1.36 (6H, t, *J* 7.3 Hz, $O_2CH_2\mathit{CH_3}$), 3.81 (6H, s, CO_2CH_3), 3.87–3.92 (8H, m, OCH_2), 4.24–4.39 (12H, m, CO_2CH_2 and OCH_2), 6.85 (2H, d, *J* 5.6 Hz, ArH on C4), 7.37 (2H,

d, J 5.6 Hz, ArH on C5); δ_C ($CDCl_3$) 14.2 ($O_2CH_2\mathit{CH_3}$), 51.6 ($CO_2\mathit{CH_3}$), 61.4 ($CO_2\mathit{CH_2}$), 69.6, 70.8, 71.7 and 73.8 (OCH_2), 110.0 (C2′), 117.5 (C4′), 119.5 (C2/C5), 130.5 (C5′), 153.2 (C3/C4), 160.6 ($\mathit{C}O_2Et$), 161.1 ($\mathit{C}O_2Me$), 162.0 (C3′); (Found: C, 50.62; H, 4.91. $C_{30}H_{36}O_{14}S_3$ requires C, 50.27; H, 5.06%).

9. M.p. 150–152°C. ν_{max} (KBr) 3100, 2920, 2600, 1710 and 1690 cm^{-1}; δ_H ($CDCl_3$/DMSO-d_6) 3.84–3.88 (8H, m, CH_2OCH_2), 4.26–4.30 (4H, m, $ArOCH_2$), 4.36–4.40 (4H, m, $ArOCH_2$), 6.90 (2H, d, J 5.6 Hz, ArH on C4′), 7.45 (2H, d, J 5.6 Hz, ArH on C5′), (no signal observed for CO_2H); δ_C ($CDCl_3$/DMSO-d_6) 69.3, 70.3, 71.4 and 73.5 (OCH_2), 111.0 (C2′), 117.6 (C4′), 120.6 (C2/C5), 130.7 (C5′), 152.3 (C3/C4), 160.4 (C3′), 162.1 and 163.2 (C=O); (Found: C, 43.25; H, 4.09. $C_{24}H_{24}O_{14}S_3$ requires C, 45.57; H, 3.82%, $C_{24}H_{24}O_{14}S_3.2H_2O$ requires C, 43.11; H, 4.22%).
10. M.p. 98.5–100°C. ν_{max} (KBr) 3100, 3090, 2920, 2895, 2850 and 1575 cm^{-1}; δ_H ($CDCl_3$) 3.87–3.92 (8H, m, CH_2OCH_2), 4.09–4.18 (8H, m, $ArOCH_2$), 6.23–6.25 (4H, m, ArH on C2/C5 and C2′), 6.75–6.78 (2H, m, ArH on C4′), 7.14–7.17 (2H, m, ArH on C5′); δ_C ($CDCl_3$) 69.6, 69.7, 69.9 and 70.0 (OCH_2), 97.6 (C2′), 98.1 (C2/C5), 119.6 (C4′), 124.7 (C5′), 147.1 (C3/C4), 157.5 (C3′); (Found: C, 52.33; H, 5.35. $C_{20}H_{24}O_6S_3$ requires C, 52.61; H, 5.30%).
11. M.p. 94–96°C. ν_{max} (KBr) 3110, 2930, 2890, 1570 and 1555 cm^{-1}; δ_H ($CDCl_3$-DMSO-d_6) 2.49 (8H, s, NCH_2), 3.61 (4H, s, $ArCH_2N$), 3.81–3.90 (8H, m, CH_2OCH_2), 4.09–4.15 (8H, m, $ArOCH_2$), 6.25 (2H, s, ArH), 6.79 (2H, d, J 5.3Hz, ArH on C4′), 7.08 (2H, d, J 5.6Hz, ArH on C5′); δ_C ($CDCl_3$−DMSO-d_6) 51.8 ($ArCH_2N$), 52.0 (NCH_2), 69.6, 70.0, 70.1 and 71.6 (OCH_2), 98.2 (C2/C5), 117.7 (C4′), 118.0 (C2′), 122.4 (C5′), 147.0 (C3/C4), 154.1 (C3′); (Found: C, 55.27; H, 6.16; N, 4.74. $C_{26}H_{34}N_2O_6S_3$ requires C, 55. 10; H, 6.05; N, 4.94%); *mle* 566 (M^+, 100%).