Tetrahedron Letters, Vol.33, No.2, pp. 265-268, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

THE SYNTHESIS OF 2-BORONO-1,3-XYLYL CROWN ETHERS[1]

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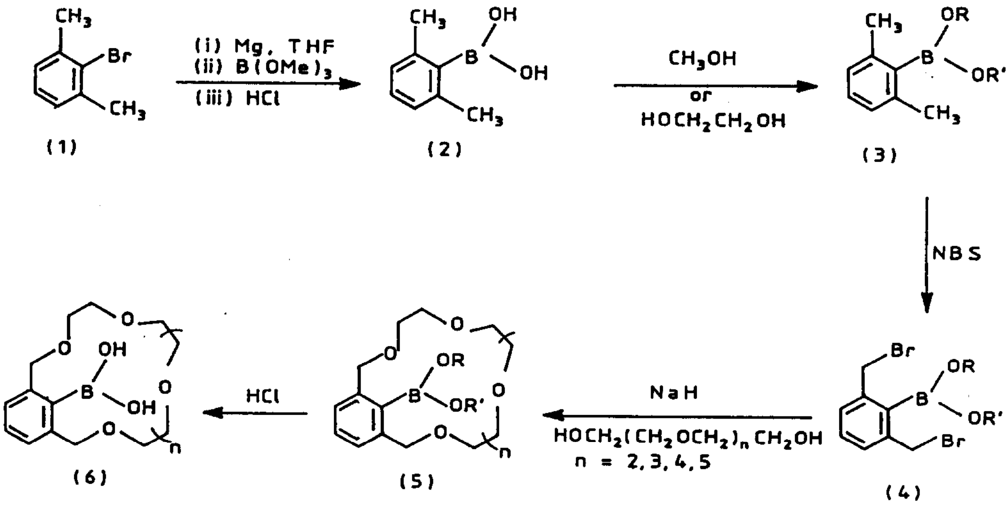
Abstract: *A synthetic route to 2-borono-1,3-xylyl crown ethers is described using a previously inaccessible 1,3-bis(bromomethyl) benzene boronate synthon.*

The design and synthesis of macrocyclic polyethers in which a quest metal ion is complexed in close proximity to a redox centre has been the subject of numerous publications[2-7]. A significant number of these types of compounds utilise ferrocene as the redox centre[4-7] or are conjugated to this centre via a π electron system[5,6]. However due to the cationic nature of the ferrocene / ferrocenium redox couple these compounds cannot exhibit electrochemically enhanced cation binding[7] as do macrocyclic compounds[3] containing centres reduceable to radical anions. In an attempt to produce an electrochemically active macrocycle reduceable to a radical anion[8] we have incorporated a boronic acid residue within a 1,3-xylyl crown ether. This residue is unusual in that it is capable of functioning both as a complexation agent for metal ions and saccharides[9].

The synthesis of 2-borono-1,3-xylyl crown ethers (6, n = 1, 2, 3, 4) was effected as shown in Scheme 1. 1,3-Xylyl-2-boronic acid (2) was synthesised according to literature procedures[10] from 2-bromo-1,3-xylene (1). The boronic acid group of compound (2) was protected either as the methyl boronate ester (3, R=R'= CH_3) or as the cyclic boronate ester (3, R-R'=CH_2-CH_2) in quantitative yields using methyl alcohol or ethylene glycol in refluxing dry benzene with 3Å molecular sieves (Soxhlet or Dean-Stark apparatus). Bromination of (3) with N-bromosuccinimide in the presence of azoisobutyronitrile (AIBN) in refluxing carbon tetrachloride afforded the previously[10] inaccessible 1,3-bis(bromomethyl)benzene boronate synthons (4, R=R'=CH_3 or R-R'= CH_2-CH_2) in quantitative yields. Spectroscopic analysis



R = R' = CH_3 ; R — R' = CH_2 — CH_2
n = 1 , 2 , 3 , 4

Scheme 1 .

confirm the structures: (**4, R=R'=CH$_3$**) 250 MHz ^{1}H n.m.r. ($CDCl_3$): δ 3.70 (6H, s, OCH_3), 4.52 (4H, s, $ArCH_2$), 7.34-7.38 (3H, m, ArH); i.r. ν_{max} 610 (C-Br), 1060, 1470 (C-B), 1340 (B-O) cm^{-1}; (**4, R-R'=CH$_2$-CH$_2$**) 250 MHz ^{1}H n.m.r. ($CDCl_3$): δ 4.47 (4H, s, OCH_2-CH_2O), 4.82 (4H, s, $ArCH_2$), 7.28-7.36 (3H, m, ArH); i.r. ν_{max} 600 (C-Br), 1060, 1470 (C-B), 1320 (B-O) cm^{-1}.

Macrocyclisation of compound (**4**) with polyethylene glycols ($HOCH_2(CH_2OCH_2)_nCH_2OH$, n = 2, 3, 4, 5) in benzene/ sodium hydride (reflux, 20 h) under conditions of high dilution gave the 1,3-xylyl crown ether derivatives of boronate ester (**5, R=R'= CH$_3$** or **R-R'= CH$_2$-CH$_2$**, n = 1, 2, 3, 4). Acid hydrolysis (4M HCl, RT, 18 h) of the methyl boronate ester of (**5, R=R'= CH$_3$**, n= 1, 2, 3, 4) afforded the desired 2-borono-1,3-xylyl crown ethers (**6**, n = 1, 2, 3, 4) (40-50 % yield) after acid-base extractive work up. The corresponding cyclic boronate ester of (**5, R-R'= CH$_2$-CH$_2$**, n = 1, 2) failed to undergo hydrolysis under these or more drastic conditions to afford compound (**6**). Compound (**6**) was purified by flash chromatography (silica gel, $CHCl_3$ / MeOH 98 : 2 eluant) and was obtained as a colourless oil whose spectral properties were in agreement with its structure. The ^{1}H n.m.r spectra of 2-borono-1,3-xylyl crown ethers show absorptions due to OCH_2 groups between δ 3.53 and 3.85, two singlets for magnetic non-equivalent benzylic protons at δ 4.78 and 5.08, due to intramolecular hydrogen bonding of boronic acid and the oxygen atoms of the macrocyclic ring, and a multiplet for the aromatic protons between δ7.10 and 7.42. The i.r. spectrum of these compounds showed characteristic peaks at 1420 cm^{-1} (B-C) and 1370 cm^{-1} (B-O)[11]. The small absorption peak at 3460 cm^{-1} for the OH of boronic acid also supports the presence of intramolecular hydrogen bonding with the oxygen atoms of the crown. In the accurate FAB mass spectra of 2-borono-1,3-xylyl crown ethers (**6**, n=1 to 4), molecular ion (M^++1) peaks were not observed due to elimination of H_2O from $-B(OH)_2$ group. However for crown ethers (**6**, n=1, 2) distinct peaks were observed at 279 and 323 respectively for [(M^++1) -H_2O]. For the two larger crown ethers (**6**, n=3, 4), the [(M^++1) -H_2O] peaks were not prominent probably due to ring elimination. However the characteristic peaks at 149 for $Ph(CH_2\text{-})_2\text{-}B(OH)_2$ and at 131 for $Ph(CH_2\text{-})_2\text{-}B{=}O$ were observed in the FAB mass spectra of all crown ethers (**6**, n=1 to 4).

Compound (**6**) was mentioned in the literature[12] without characterisation as an intermediate in the preparation of 2-hydroxy-1,3-xylyl crown ethers. Attempts to use this route in our hands, resulted in the isolation of a mixture of crown ethers which included debrominated 1,3-xylyl crown ether, 2-hydroxy-1,3-xylyl crown ether and some of the desired product. The new synthetic route reported here can be exploited in the preparation of nitrogen and sulphur containing 2-borono crown ethers and this work is currently in progress. Complexation studies on 2-borono crown ethers[13] with metal ions show a pattern of selectivity comparable to that observed for 1,3-xylyl crown ethers[14].

Acknowledgments: The author thanks the GEC / SERC Fellowship of Engineering (FEng) for the award of a Senior Fellowship in Molecular and Biomolecular Electronics and the SERC for support under Grant GR/F 16424. The award to C D'S by the FEng / GEC of two Buchi evaporators and an FT / IR instrument, to facilitate this and other programmes of research is also acknowledged. We finally thank Dr. Ballantine of the SERC Mass Spectrometry service centre, Swansea, for the accurate FAB mass spectrometry measurements.

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(Received in UK 5 November 1991)