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Synthesis of Novel Oxa-Isosteres of Spermidine and Spermine

Paul Kong Thoo Lin*, Nuala M. Maguire and Daniel M. Brown+

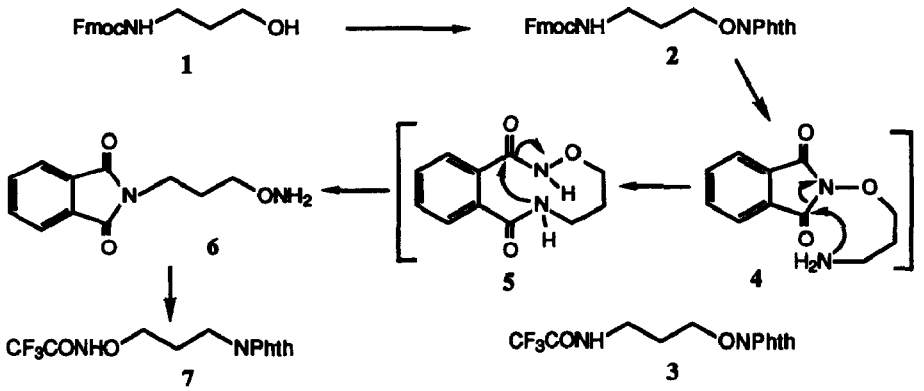
The Robert Gordon University, School of Applied Sciences, St. Andrew Street, Aberdeen AB1 1HG, UK.

+MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.

Abstract: 3-Bromopropylamine hydrobromide reacts with *N*-hydroxyphthalimide in the presence of DBU to give, not the expected *N*-(3-aminopropyloxy)phthalimide, but *N*-(3-aminooxypropyl)-phthalimide, **6**, formed by an unusual intramolecular rearrangement. Coupling of the pentamethyl-chroman-6-sulphonyl (Pmc) derivatives of **9** and **13** with *N*-Bpoc-aminopropanol affords a differentially protected 6-oxaspermidine **10** and 6,9-dioxaspermine **14** respectively from which the protecting groups are removed independently.

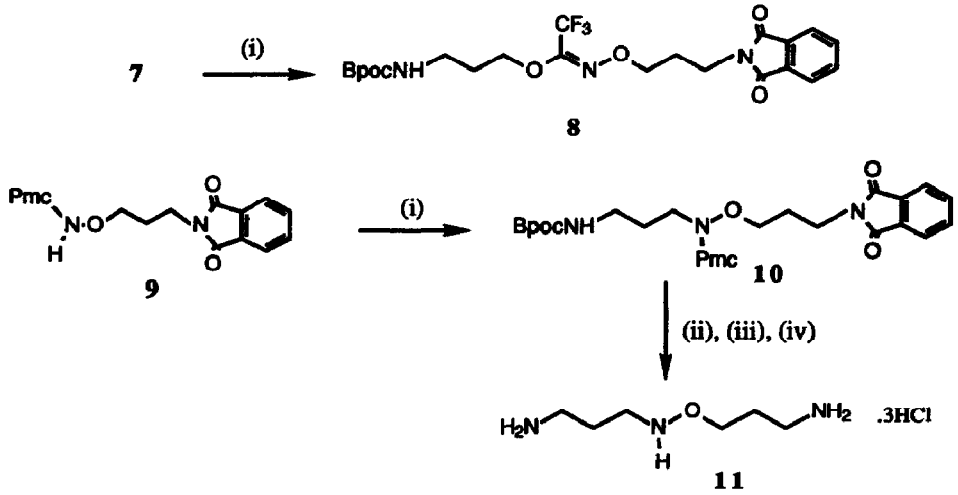
Polyamines are essential for the normal growth processes of mammalian cells. Their biosynthesis is accelerated during cell division, in cancerous tissues and in infected cells during viral replication.[1,2,3] Polyamine analogues are of considerable interest as anticancer and, recently, as antimalarial agents.[4,5] In looking for analogues with antiviral activity we investigated the synthesis of some oxyamine derivatives,[6] particularly with the intention of introducing differentially removable protecting groups for further synthetic elaboration. During this work we encountered chemistry that revealed a facile rearrangement to give an oxyamine as an intermediate. Activating the oxyamine with an arenesulphonyl group followed by Mitsunobu coupling with an *N*-protected amino alcohol gave novel oxa-analogues of spermidine and spermine.

Fmoc-Aminopropan-3-ol **1** was coupled under Mitsunobu conditions with *N*-hydroxyphthalimide to form **2**. On deprotection with DBU followed by trifluoroacetylation the product was found to be identical to that formed from 3-aminopropyl bromide and *N*-hydroxyphthalimide/DBU then ethyl trifluoroacetate. However it differed from **3** formed by treating trifluoroacetamidopropanol with tosyl chloride followed by nucleophilic displacement with *N*-hydroxyphthalimide.[7] The structure of **3** has recently been confirmed crystallographically.[8]



It became clear that deprotecting the Fmoc-derivative **2** gave, not the expected *N*-(3-aminopropyloxy)-phthalimide, **4**, but the isomeric *N*-(3-aminooxypropyl)phthalimide **6**.[9] We account for this by two sequential acyl transfer reactions, the first giving rise to the presumed large ring intermediate, **5**. Each step in the rearrangement leads to the replacement of an hydroxamic by an amidic residue. It is known[10] that phthalimidooxyalkyl derivatives undergo very much more facile aminolysis than the corresponding phthalimides and this must correlate with the direction that the potentially reversible reaction takes. The aminolysis is evidently rate-determining since neither **4** nor **5** is observed. Conversion of **6** to the TFA derivative gives **7** as the sole product (95%). The C_2 homologue of **4** formed from bromoethylamine hydrobromide and *N*-hydroxyphthalimide and the C_4, C_5 and C_6 homologues released from their Fmoc-derivatives by DBU all undergo rearrangement to give only the corresponding *N*-(aminooxyalkyl)-phthalimide.[11]

The rearrangement is being investigated further, particularly with a view to halting the process at the large ring intermediate. We note that it bears formal analogy to other ester-amide and amide-amide transfer reactions, the latter however requiring very strong base catalysis.[12,13] An acetyl transfer in an acetamido-oxyalkylamine has also been reported.[14]

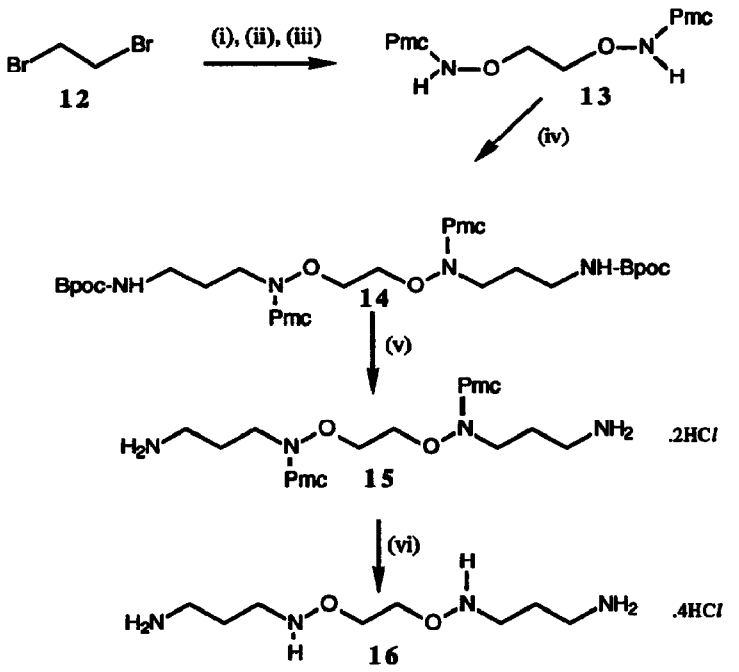


(i) $BpocNH(CH_2)_3OH/Ph_3P/DEAD/THF$, (ii) $H_2NNH_2.H_2O/C_2H_5OH$ refluxing o/n
(iii) dry HCl/CH_3OH, (iv) dry HCl/glacial CH_3COOH o/n at 70°C

To extend the polyamine chain further *N*-Bpoc-aminopropanol (*N*-[2-(biphenylyl)-prop-2-yloxy-carbonyl]aminopropanol) was coupled with the TFA derivative, **7**, using the Mitsunobu reaction. The single product was not the result of *N*-alkylation that might have been expected from reported equivalent syntheses of *N*-trifluoroacetyl secondary amines,[15,16] but instead the isomeric imidate **8**; treatment of the latter with NH_3-MeOH gave an amidine and the original alcohol. The formation of an imidate was confirmed crystallographically on the product derived from 4-nitrobenzyl alcohol and *N*-(4-nitrobenzyloxy)-trifluoroacetamide.[17] However, arenesulphonyl activating groups for the aminooxy-functionality were satisfactory, undergoing coupling, rapid compared with the corresponding sulphonamides.[18] The pentamethylchroman-6-sulphonyl (Pmc) derivative **9**, not heretofore used in this connection, was preferred

because of its considerably greater acid lability during deprotection.[19] Thus, **9** was coupled to *N*-Bpoc-aminopropanol in quantitative yield to give the fully protected target, **10**. Removal of the phthaloyl group (80%) then the Bpoc residue (86%) gave the N_5-Pmc derivative, which with HCl-AcOH afforded 6-oxa-spermidine **11** as its trihydrochloride as sole product (76%).[20] Removal of the Bpoc and phthaloyl residues could also be effected in the reverse order.

Further elaboration of the Mitsunobu reaction allowed us to synthesise a 6,9-dioxa-analogue[21] **16** of spermine by coupling the 1,2-bis-(Pmc-aminooxy)ethane[22] **13** with *N*-Bpoc-aminopropanol followed by sequential deprotection as shown in scheme below. The synthesis of other spermine analogues based on the double Mitsunobu reaction are presently being investigated in our laboratory.



(i) N-hydroxyphthalimide/DBU in DMF at 85°C for 2 hrs, (ii) reflux in conc.HCl/glacial AcOH
(iii) Pmc-Cl/pyridine (iv) *N*-Bpoc-aminopropanol/Ph_3P/DEAD in THF (v) MeOH/HCl (vi) HCl/glacial AcOH

We have been able to report the synthesis of novel analogues of spermidine and spermine, the former *via* an interesting rearrangement and, as far as we are aware, involving the first use of an arenesulphonyl activated oxyamine in a Mitsunobu coupling reaction. We are currently using the above strategy to synthesise other polyamine oxa-analogues. Biological evaluation of the above compounds is being carried out at the Rowett Research Institute, Aberdeen, in collaboration with Dr. Susan Bardocz and the results will be reported elsewhere.

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21. δ_H in d_6-DMSO: 16, 1.80–2.22 (4H, m, 2x -$CH_2CH_2CH_2$), 2.70-3.10 (4H, 2x -CH_2NH_2), 3.10-3.45 (4H, m, 2x-ONHCH_2-), 4.35 (4H, s, 2x -CH_2ONH-), 7.90-8.50 (6H, broad s, 2x -NH_3^+).
22. δ_H in d_6 DMSO: 15, 1.30 (12H, s, Pmc 2x CH_3), 1.70-2.10 (14H, m, Pmc CH_2, $H_2NCH_2CH_2$- and Pmc CH_3), 2.35 (12H, s, Pmc 2x CH_3), 2.50-2.65 (4H, m, Pmc CH_2), 2.75-2.95 (4H, m, H_2NCH_2), 3.10-3.40 (8H, m, -CH_2NHOCH_2-).

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