ChemComm

A novel solid-phase reductive alkylation route to acridine and dansyl polyamine conjugates

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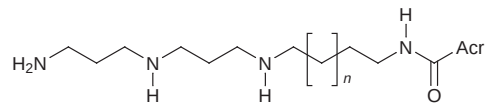
Received (in Cambridge, UK) 19th May 1999, Accepted 11th June 1999

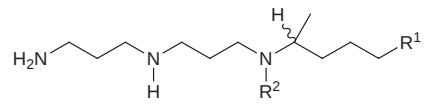
Solid-phase organic synthesis (SPOS) routes to target unsymmetrical polyamines and their acridinyl and dansyl conjugates have been developed based upon borane–pyridine complex (BAP) mediated reductive alkylation, azide reduction with triphenylphosphine, and the use of pent-4-enoyl (Pnt) as an orthogonal amine protecting group.

Polyamines and especially their unsymmetrical conjugates display a wide range of important biological activities making them useful as lead compounds for a wide range of potential therapies.[1] These medicinal chemical applications include potential anti-parasitic drugs as potent inhibitors of the enzyme trypanothione reductase[2] and cytotoxic compounds such as acridine–spermine conjugates that display significant sequence selectivity on binding to an oligonucleotide.[3] It has recently been shown that dansylated polyamines are novel glutamate (NMDA) receptor antagonists.[4] (−)-15-Deoxyspergualin, a potent immunosupressor, is a spermidine–guanidine conjugate for the treatment of corticoresistant acute renal graft rejection.[5] The regiocontrolled synthesis of unsymmetrical polyamine conjugates continues to attract the attention of bioorganic and synthetic chemists,[5–8] but these approaches often, of necessity, include a number of steps for orthogonal protecting group introduction and removal that makes the overall multistep syntheses certainly time consuming and sometimes low yielding. Furthermore, such solution-phase syntheses are simply not amenable to the rapid preparation of a wide range of conjugates for biological evaluation, and therefore attention has been turned recently to the use of solid-phase organic synthesis (SPOS) for the preparation of polyamine conjugates with the potential for compound-library design.[9–13] At the forefront of these studies are Bradley and co-workers who have addressed the synthesis of trypanothione (spermidine containing) libraries in their elegant studies of SPOS for polyamine amides and lactams.[9] Independently, Houghten and co-workers have recently used SPOS reductive alkylation to prepare diazepine derivatives and parallel SPOS borane reduction of triamides afforded large numbers of unsymmetrically substituted diethylenetriamines.[10]

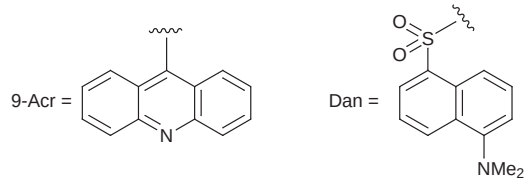
We have designed a series of unsymmetrical polyamine conjugates **1**–**5** as targets to illustrate our proof of concept that reductive alkylation is a practical approach to such substituted compounds using SPOS methodologies. The potential of this reductive alkylation route is in the ability to prepare a range of linear unsymmetrical polyamines. By design, the amine distribution along the polymethylene chain can be varied, in a controlled manner, using the sequence elaborated below. Acridin-9-ylcarbonyl thermine **1** and thermospermine **2** require reductive alkylation of an aldehyde with an amine bound to the resin. The corresponding conjugate **3**, with a regiospecific methyl substituent, requires alkylation of this resin using a methyl ketone. Azide dansyl conjugate **4** and didansylated **5** will be prepared from the same resin-bound intermediate.[13] Azide aldehyde **9** was prepared from 4-bromobutyl acetate **6**, by azide nucleophilic displacement of the halide affording **7**



1 $n = 0$
2 $n = 1$

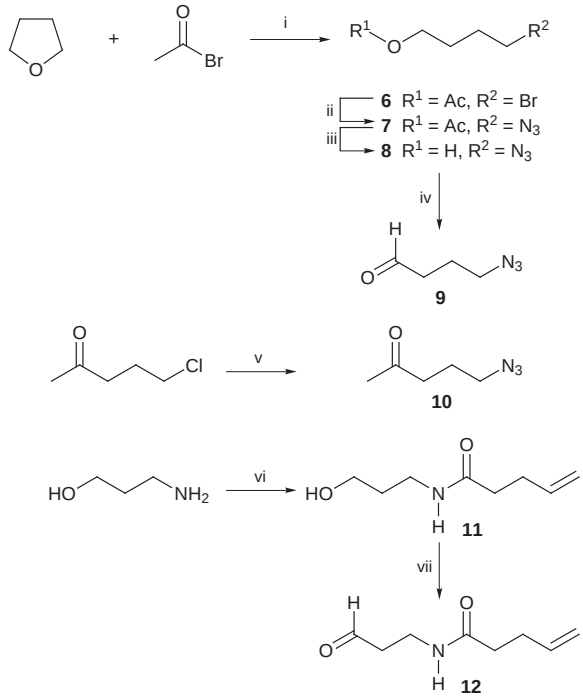


3 R^1 = NHCO-9-Acr, R^2 = H
4 $R^1 = N_3$, R^2 = Dan
5 R^1 = NHDan, R^2 = Dan

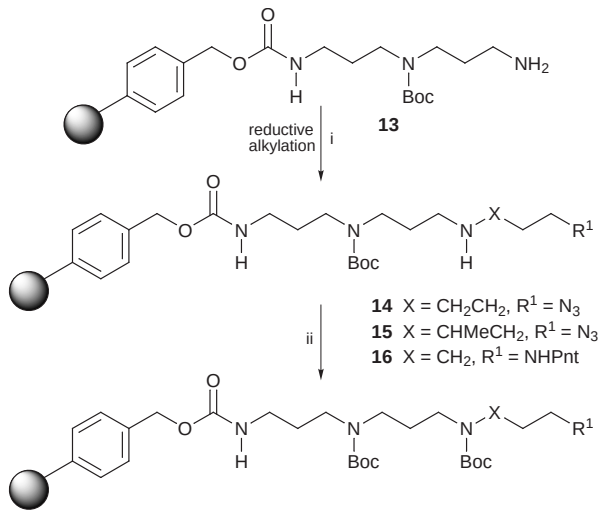


(NaN$_3$, DMSO, 25 °C, 16 h, 95%), ester saponification to azide primary alcohol **8** (2 M aq. NaOH, MeOH, 25 °C, 3 h, 85%), and then Swern oxidation of this alcohol to the desired aldehyde **9** (50%) (Scheme 1). Azide ketone **10** was prepared from the readily available 5-chloropentan-2-one (NaN$_3$, cat. NaI, DMSO, 50 °C, 18 h, 90%).[14] 3-Pent-4-enoylaminopropanal **12** was prepared from the corresponding 3-aminopropan-1-ol by *N*-acylation with the symmetrical anhydride Pnt$_2$O [15] affording amide primary alcohol **11** (CH_2Cl_2, 0 °C, 1 h, 72%) which was oxidised to the desired amide aldehyde **12** (PDC, CH_2Cl_2, 25 °C, 3 h, 76%).

Wang resin was activated under rigorously anhydrous conditions with 4-nitrophenyl chloroformate (*N*-methylmorpholine, CH_2Cl_2, 25 °C, 19 h) and then reacted with N^1-*tert*-butoxycarbonyl-N^1-(3-aminopropyl)-1,3-diaminopropane[2,6] (CH_2Cl_2, 16 h)[16] affording resin **13**. That this reaction went to completion was verified by the use of gel-phase ^{13}C NMR spectroscopy.[17] Reductive alkylation of portions of resin **13** with aldehyde **9**, ketone **10** and aldehyde **12** afforded resins **14**–**16** respectively (BAP, 3:1 DMF–EtOH, 48 h) (Scheme 2).[18] Washed and dried samples of resins **14** and **15** displayed characteristically strong IR bands (by diffuse reflectance) for the resin-bound azide functional group at 2090 cm^{-1}. Portions of these resins **14**–**16** were Boc protected (excess of Boc$_2$O, CH_2Cl_2, 2 × 12 h) on the newly formed secondary amines affording resins **17**–**19** respectively. A further portion of resin **15** was *N*-dansylated (2 equiv. dansyl chloride, 2 equiv. *N*-methylmorpholine, CH_2Cl_2, 2 × 18 h) and half of this product was cleaved from the resin (1:1 TFA–CH_2Cl_2, 25 °C, 2 h) to afford azide dansyl polyamine **4** as a white solid. The remaining half was reacted with PPh$_3$ and water (1 equiv. H$_2$O, THF, 2 ×



Scheme 1 *Reagents and conditions*: i, ZnBr, reflux; ii, NaN_3, DMSO; iii, 2 M aq. NaOH, MeOH; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (Swern); v, NaN_3, cat. NaI, DMSO, 50 °C; vi, Pnt_2O, CH_2Cl_2; vii, PDC, CH_2Cl_2.



Scheme 2 *Reagents and conditions*: i, aldehyde or ketone, BAP, 3:1 DMF-EtOH; ii, Boc_2O, CH_2Cl_2; iii, PPh_3, H_2O, THF; iv, I_2, 1:1 H_2O–THF.

18 h) to convert the azide into a primary amine, which has previously been reported only for solution-phase synthesis,[5,19] and this newly formed amine was then *N*-dansylated. Cleavage from the resin yielded didansylated polyamine **5** as a white solid in 35% yield over the six steps (resin loading, reductive alkylation, dansylation, azide reduction, dansylation and resin cleavage). Resins **17** and **18** were similarly reacted with PPh_3 to afford resin-bound primary amines **20** and **21** respectively.

The Pnt group has been used to protect a variety of substituted amines including amino sugars[15] in solution phase, and nucleotides in SPOS.[20] The primary amine protected by a Pnt group in resin **19** was unmasked by treatment with I_2 and water (1:1 H_2O–THF, 25 ºC, 18 h) affording resin **22**.[15,20] Resin-bound amines **20**–**22** were acylated using acridine-9-carboxylic acid activated with N^1-hydroxybenzotriazole (DMF, 2 × 15 h). The resulting acylated resins were cleaved affording targets **1**–**3** as their free bases after final purification by flash column chromatography over silica gel (eluant 8:5:1 CH_2Cl_2–MeOH-conc. aq. NH_3)† in order to remove traces of triamine starting material which had been crosslinked.

Here we report a novel reductive alkylation SPOS route to unsymmetrical polyamines and their conjugates. The feasibility of preparing unsymmetrical polyamines anchored on Wang resin as a solid support, and then selective unmasking of amines to reveal sites for conjugation, will find ready applications. Furthermore, our SPOS uses of Pnt as an amine protecting group orthogonal to Boc, and of azide reduction with PPh_3 should have wide applicability in combinatorial chemistry where libraries of amines are constructed.

We thank the Atlantic Arc for Medicinal Chemistry (GP2A), the ARC (Association pour la Recherche sur le Cancer) and the Ligue Nationale contre le Cancer for financial support of this project. We acknowledge S. Sinbandhit and M. Le Roch (Université de Rennes 1) and A. J. Geall (University of Bath) for useful discussions and their input into these studies.

Notes and references

†Each acridine conjugate **1**–**3** was homogeneous by TLC (silica gel, eluant CH_2Cl_2–MeOH–conc. aq. NH_3 (8:5:1) and reverse-phase HPLC using a 5 μm Supelcosil ABZ + plus column eluting with 70:30 0.1% aq. TFA–MeCN, UV detection at 256 nm. Unoptimised yields were typically 5% over 6 steps.

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Communication 9/04023D