Discrimination of Spermidine Amino Functions by a New Protecting Group Strategy; Application to the Synthesis of Guanidinylated Polyamines, Including Hirudonine

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Agmatine and hirudonine, guanidine derivatives of putrescine and spermidine, respectively, are synthesised by the application of a new protecting group strategy for polyamines, which uses *N*-nitroguanidinyl as a precursor of guanidine functions and selectively blocks spermidine at *N*-1 and *N*-8 with trifluoroacetyl and at *N*-4 by 4-azidobenzyloxycarbonyl.

The participation of polyamines (*e.g.* putrescine, **1** and spermidine, **2**) in cellular growth and proliferation[1] has created much interest in the development of chemotherapeutic agents to modulate these functions.[2] Most mammalian cells possess a polyamine biosynthetic pathway, but many also exhibit a specific polyamine uptake system.[3,4] Such systems are potential vehicles for delivering cytotoxic agents into cells, and attempts have already been made to exploit this in cancer chemotherapy.[5–7] The substrate-binding sites of polyamine transporters are thought to contain carboxylate groups, which interact with protonated polyamines.[8] Strong guanidinium–carboxylate interactions have been observed in enzyme–substrate complexes,[9] suggesting that guanidinylated polyamine derivatives will be readily accepted by polyamine uptake mechanisms. Indeed, the anti-tumour agent methylglyoxal-bis(guanylhydrazone) (MGBG) and analogues are known to be taken up by polyamine transporters, and inhibit polyamine biosynthesis.[10]

We report the synthesis of polyamine derivatives, where one or more of the primary amino groups of **1** and **2** have been replaced by a guanidine function.[11] These derivatives are agmatine **3**, an arginine metabolite, and hirudonine **4**, which is located in the central nervous system of the leech *Hirudo medicinalis* L.[12] We illustrate new protecting group strategies that will be of general use for the synthesis of polyamines selectively modified at particular amino functions.

The presence of a guanidine group in a synthetic intermediate can be problematic because the basicity of guanidines often makes further synthetic transformations difficult. Primary amines can be converted into *N*-nitroguanidines by reaction with 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboximidamide (DMNPC, **5**).[13] We have found that this reaction proceeds faster and more cleanly in methanol, than reported in dioxan.[14] Nitroguanidines exhibit low basicity, and so are easily carried through several stages of a synthesis before their final reduction to guanidines.[14] The use of the nitroguanidine group as a masked guanidine was initially applied to the synthesis of **3** from **1** (see Scheme 1). The monoprotected putrescine **6**[15] was converted into **7** by treatment with DMNPC in methanol. In preference to electrochemical reduction[14] we found catalytic transfer hydrogenation enabled simultaneous deprotection of the primary amine and reduction of the nitroguanidine to yield **3**, isolated as its sulfate salt.

Treatment of **2** with CF_3CO_2Et in MeCN containing traces of water gave **8** in 89% yield (Scheme 2). Compound **8** is isolated directly as its trifluoroacetate salt, with the trifluoroacetic acid produced by partial hydrolysis of CF_3CO_2Et. Similar selectivity has been reported for the ruthenium-catalysed condensation of nitriles with **2**, yielding 1,8-*N*-bis-substituted diamides,[16] and for acylations of spermidine using 3-acylthiazolidine-2-thiones[17] or acyl cyanides.[18] The free *N*-4-position of **8** was protected with 4-azidobenzyloxycarbonyl (ACBZ) using 4-azidobenzyl-4-nitrophenyl carbonate (ABNPC, **9**)[19] in THF to yield the fully protected spermidine derivative **10**. Deprotection of the terminal amino groups was achieved by treatment of **10** with conc. NH_3 in MeOH to give **11**. This was treated with DMNPC (2 equiv.) in MeOH to afford **12**. Removal of the *N*-4-protecting group was effected by treating **12** with excess of dithiothreitol (DTT) and Et_3N.[20] DTT reduces the azido group to an amine, triggering a fragmentation of the carbamate, which leads to liberation of **13**. This method of deprotection is chemoselective, and suggests great potential for the 4-azidobenzyloxycarbonyl group in polyamine syntheses, where 'orthogonal' protecting groups are often required. Finally, reduction of the nitroguanidines in **13** by catalytic transfer hydrogenation as before generated **4**, isolated as its crystalline sulfate salt. This compound has previously been obtained by direct reaction of spermidine with *S*-methylisothiourea, but no yield was given.[21]

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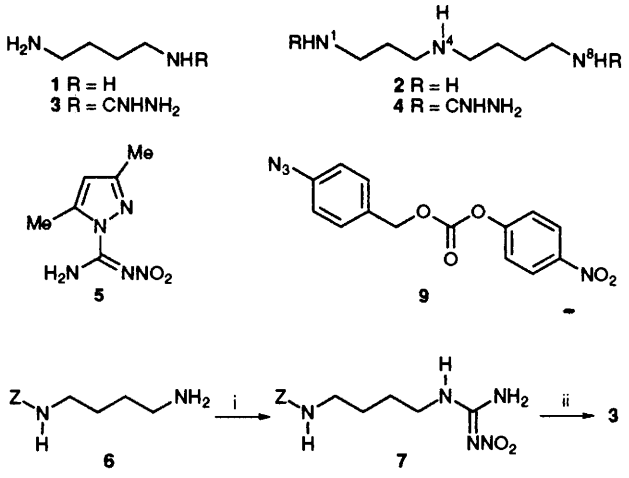
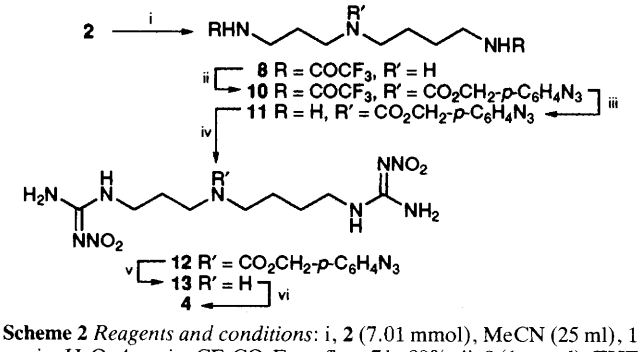


Scheme 1 *Reagents and conditions*: i, **6** (2.69 mmol), MeOH (10 ml), DMNPC (1 equiv.), room temp., 3 days, 85%; ii, 7 (0.81 mmol), 5% w/v HCO_2H–MeOH; 20 ml, 10% Pd/C (1 mass equiv.), room temp., 2 h, 52% **3** (Z = $PhCH_2OCO$)



Scheme 2 *Reagents and conditions*: i, **2** (7.01 mmol), MeCN (25 ml), 1 equiv. H_2O, 4 equiv. CF_3CO_2Et, reflux, 7 h, 89%; ii, **8** (1 mmol), THF (9 ml), ABNPC (1.1 equiv.), dark, room temp., 24 h, 92%; iii, **10** (0.22 mmol), MeOH (8 ml), conc. NH_3 (2 ml), dark, room temp., 6 days, 82%; iv, **11** (1.7 mmol), MeOH (10 ml), DMNPC (2 equiv.), dark, room temp., 3 days, 81%; v, **12** (0.64 mmol), MeOH–H_2O (9 : 1 v/v; 5 ml), DTT (4 equiv.), Et_3N (4 equiv.), room temp., 4 h, 50%; vi, **13** (0.31 mmol), HCO_2H–H_2O (5% w/v; 7.5 ml), 10% Pd/C (0.5 mass equiv.), room temp., 3 h, 89%

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