Selective Protection of Mixed Primary–Secondary Amines. Simple Preparation of N^1,N^8-Bis(t-butoxycarbonyl)spermidine

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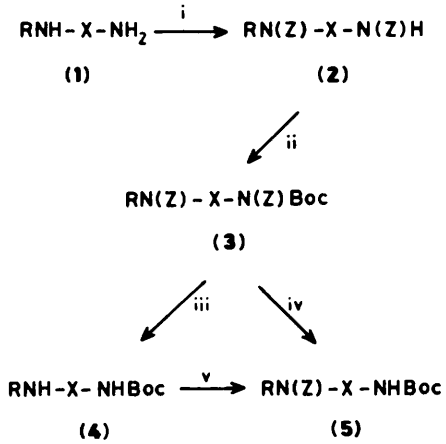
A new, simple, and efficient preparative procedure of a potentially wide scope for the selective protection of mixed primary–secondary amines, based on acylation followed by exhaustive t-butoxycarbonylation is presented.

A large number of protecting groups for amino functions are available nowadays for synthetic manipulation.[1] However, there seems to exist no satisfactory method of general applicability for the specific blocking of primary and secondary amine moieties present in the same molecule. To this end we have developed a novel, simple, and efficient procedure for the selective protection of mixed primary–secondary amines, using an aliphatic (**1a**) and an aromatic (**1b**) model compound.

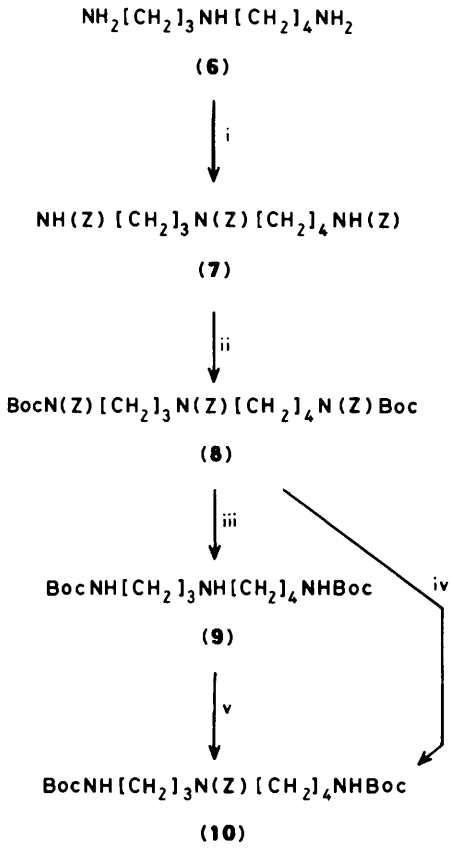
The new strategy is outlined in Scheme 1. Introduction of two benzyloxycarbonyl (Z) groups onto (**1a,b**) with conventional methods affords (**2a**) and (**2b**), which are then smoothly converted into (**3a**) and (**3b**) in high yields (92 and 90%, respectively) using a slight excess of di-t-butyl dicarbonate (Boc_2O) in acetonitrile in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP).[2]

The removal of the auxiliary Z groups offered two possibilities. First, the catalytic hydrogenolysis of both Z functions furnished the selectively protected amines (**4a**) and (**4b**) in excellent yields (94 and 98%, respectively, after a simple work-up). The fact that a Boc and a Z group were bonded to the same nitrogen atom did not seem to affect the lability of the latter in this context. On the other hand, treatment of (**3a,b**) with 1.5 equiv. of 1,1,3,3-tetramethylguanidine (TMG) in methanol cleaved off only the Z group residing on the originally primary amino function, thus giving the protected (**5a**) and (**5b**) in 93 and 99% yields, respectively.[3] These compounds were identical in all respects with those obtained by conventional benzyloxycarbonylation of (**4a**) and (**4b**). This TMG-induced methanolysis proceeded with a remarkable selectivity since only traces (<2%) of the anomalous cleavage products (**2a**) and (**2b**) could be detected in the crude mixtures (^{1}H n.m.r., t.l.c.). Exhaustive t-butoxycarbonylation of benzyl urethanes followed by methanolysis in the presence of TMG thus offers a new alternative for cleavage of such compounds to give the corresponding t-butyl analogues.

This novel protection strategy is also applicable with only minor modifications to spermidine [(**6**), Scheme 2], a polyamine of considerable biological interest.[4] By analogy with the above model substrates, the readily accessible tri-Z derivative (**7**) is exhaustively t-butoxycarbonylated with Boc_2O–DMAP in acetonitrile to give (**8**) in 92% yield. The complete removal of the auxiliary Z groups is conveniently accomplished by catalytic transfer hydrogenation, thus giving the pure N^1,N^8-Boc_2-spermidine (**9**) in 74% isolated yield.[5] Recent experiments have also revealed that the TMG-mediated methanolysis of (**8**) furnished essentially pure (**10**) in acceptable yield and, as in the case of the previously discussed model



Scheme 1. Z = $PhCH_2OCO$, Boc = Bu^tOCO, **a**: R = Et, X = CH_2CH_2, **b**: R = Me, X = *p*-C_6H_4. *Reagents*: i, Z–Cl (pyridine or aq. Na_2CO_3); ii, Boc_2O, DMAP (MeCN, room temp., 15 h); iii, (**3a**), HCO_2NH_4, Pd/C (80% aq. HOAc, room temp., 2 h); (**3b**), H_2, Pd/C (MeOH); iv, TMG (MeOH, room temp., 15 h); v, (**4a**), Z_2O (CH_2Cl_2); (**4b**), Z–Cl (pyridine).



Scheme 2. *Reagents*: i, Z–Cl (aq. Na_2CO_3); ii, Boc_2O, DMAP (MeCN, room temp., 15 h); iii, HCO_2NH_4, Pd/C (MeOH, room temp., 1 h); iv, TMG (MeOH, room temp., 19 h); v, Z_2O (CH_2Cl_2).

substrates, the structure of (**10**) was confirmed by an independent synthesis from (**9**).

Preliminary attempts to achieve this selective protection of mixed primary–secondary amines by a direct approach were largely unsuccessful. Thus, when (**1a**) was treated with 1 equiv. of Boc_2O in dry dichloromethane mainly the di-Boc derivative was isolated in moderate yield. Only traces of a mixture of (**4a**) and the other mono-Boc isomer could be detected as judged from the ^1H n.m.r. spectrum of the acid-wash fraction. Similarly, earlier investigations have indicated that a complex mixture of miscellaneous Boc-derivatives were obtained when a spermidine homologue was treated with Boc-N_3 in dimethyl sulphoxide.[6] In comparison with our novel approach, the selectively protected (**4a**), (**4b**), and (**9**) could be obtained from the corresponding free amines (**1a**), (**1b**), and (**6**) in 78, 80, and 59% overall yields respectively using this convenient three-step procedure. In conclusion, our novel strategy represents a useful complement for the optional modification of mixed primary–secondary amines but the full scope of this approach remains to be explored.

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