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Selective Mono-Boc-Protection of Bispidine

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Abstract: Mono-Boc-protection of bispidine was achieved using equimolar amounts of TFA and Boc_2O with iodine as catalyst.

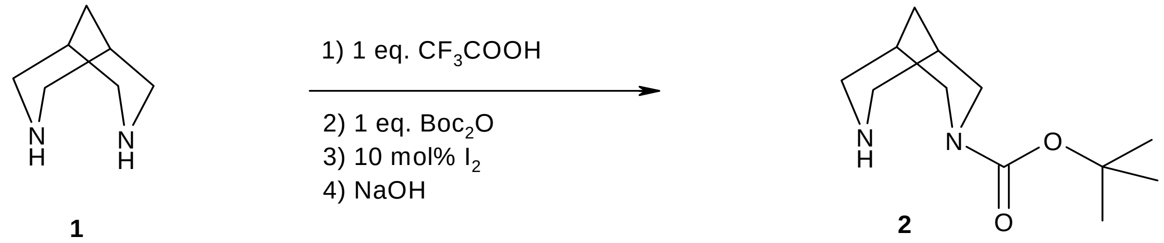
Introduction

Prompted by the recent publication of the mono-Boc protection of diamines (1), we here report some of our efforts to mono-protect valuable diamines. While the problem of monoprotection of diamines, *e.g.* piperazine, in most cases is solved by using a large excess of the diamine, this strategy is not practical in case of valuable diamines. Wille and Kaiser (1) report the use of flow chemistry to mono-protect diamines and achieve a typical yield of about 45% using 0.8 equivalents of Boc_2O and methanol as solvent. Lee *et al*. (2) used one equivalent of HCl to block one of the two nitrogens of diamines as the hydrochloride salt and achieved a yield of 87% using an equimolar amount of Boc_2O in the case of ethylenediamine. Varala *et al*. (3) have introduced the use of iodine to catalyse Boc-protection of amines. Other variations of this reaction protocol include the use of sulfonic acid functionalized silica gel (4) and ionic liquids (5).

Results and discussion:

In our work we tried to combine the use of one equivalent of acid to block one nitrogen with the use of iodine as catalyst for the protection of valuable diamines with one equivalent of Boc_2O.

In a model reaction using piperazine and HCl we achieved an isolated yield 70-80% of the mono-Boc piperazine. The first attempts to mono-protect bispidine under these conditions gave a yield of about 20-30%. This yield could be improved substantially by substituting TFA for HCl.



With the method detailed below, we thus achieved an isolated yield of 55% of mono-Boc bispidine.

Currently we are working on the scope and limitations of this mono-Boc protection protocol.

Procedure:

3,7-Diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (N-Boc-bispidine (2))

To the stirred solution of bispidine (1 mmol) in methanol (2 ml) a solution of trifluoroacetic acid (1 mmol) in methanol (5 ml) was added drop-wise at 0-5° C. The mixture was stirred for 15 min and after addition of water (2 ml) stirring was continued for 30 min at room temperature to achieve equilibrium of the various triflate salts. Then, a solution of Boc_2O (1 mmol) and iodine (10 mol %) in methanol (4 ml) was added drop wise over 10 min. Reaction progress was checked by TLC. After 3 hrs volatiles were removed *in vacuo* and 5% sodiumthiosulphate solution (5 ml) was added to the residue followed by extraction with diethyl ether (2×10 ml) to remove the neutral di-Boc product. The aqueous phase was adjusted to pH 10 using 20% NaOH and extracted with chloroform (3×20 ml).The combined organic phases were dried over sodium sulphate and the solvent was removed under vacuum to obtain the crude product that was purified by column chromatography on 50 g of aluminum oxide 90 (basic, Merck) and a 0-10% gradient of methanol and methylene chloride. The product **2** was isolated as an oil (55%) with 97% HPLC purity.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.3 (m, 4H), 2.97 (m, 4H), 2.10 (s, 1H), 1.79 (m, 2H), 1.67(m, 2H), 1.46 (s, 9H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 155.09, 79.19, 48.96, 47.75, 30.28, 28.40, 27.36

Reference List

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