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Selective Removal of the *N*-BOC Protective Group using Silica Gel at Low Pressure

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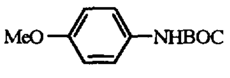
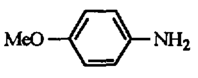
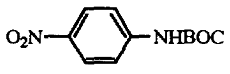
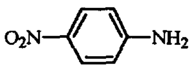
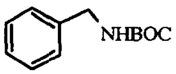
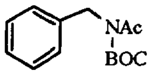
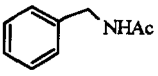
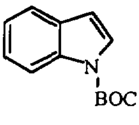
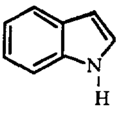
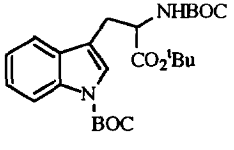
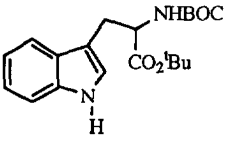
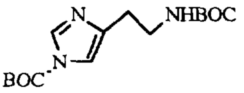
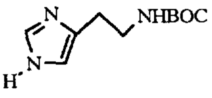
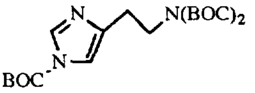
Abstract: Selective removal of BOC groups from nitrogen atoms in conjugation with an aromatic or carbonyl group, employing silica gel, is described.

The BOC (*tert*-butoxycarbonyl) protective group has found extensive use in organic synthesis.[1] New, selective methods for its removal are therefore of importance. Stafford *et. al.* recently reported a method for the selective removal of one BOC group from *t*-butylimidodicarbonates, and *N*-BOC substituted amides, employing magnesium perchlorate as a Lewis acid.[2] We recently found that *N*-BOC protected indoles and heterocondensed pyrroles could be deprotected simply by adsorbing the substrate onto silica gel, followed by gentle heating under reduced pressure.[3] This modification of the original procedure[4] - to heat the substrate to about 180°C - was found better suited for highly acid- and thermally-sensitive heterocondensed pyrroles. In order to investigate the generality of this method, other BOC substituted amines were treated under similar conditions (Table).

Table. Removal of BOC From Different *N*-BOC Substituted Amines.[a]

substrate	product	reaction time / h	yield / %[b]
		144	83
		48	92
	no reaction	>144	—
		15	92
		8	93
		7	80

		10	94
		15	93

a: The substrate dissolved in methylene chloride, was evaporated onto 10 times its weight of silica gel (35-70 Mesh). After treatment at 50°C / 0.2 mmHg for the time indicated the product was purified by flash chromatography. b: Isolated yield.

A useful selectivity in removal was noted. BOC groups attached to nitrogen atoms part of an aromatic system or in conjugation with an aromatic or carbonyl group, were removed in high yields. BOC substituents at alifatic amines were left unaffected. The results with the tryptophan- and histamine derivatives might be of special interest. Notably, a *tert*-butyl ester, present in the molecule, was found to be resistant under the conditions employed. [5]

The following observations were made when *N*-BOC substituted indole was used as the substrate: a/ Reduced pressure is necessary for the reaction to proceed at a reasonable rate. When pre-treated[6] silica gel was used at atmospheric pressure under nitrogen at 50°C, only 15 % conversion was observed after 8 h. In a parallell experiment conducted at 0.2 mmHg, total conversion was observed after the same time period. b/ No reaction ocurred on hydrophobated silica gel[7] where the acidic silanol hydrogens were substituted by TMS (trimethylsilyl) groups, indicating that the reaction is mediated by the free silanol groups of the gel. c/ The by-product 3-*tert*-butyl indole was detected in the crude product (indole:3-*tert*-butyl indole, 95:5, GLC). For comparison, TFA / methylene chloride (3:7), without any carbocation scavenger added[8], was used for removal of the BOC substituent of indole. The same by-product was again formed, but in a higher ratio (indole:3-*tert*-butyl indole, 82:18, GLC).

In summary, silica gel at reduced pressure is a useful reagent for selective removal of BOC groups at nitrogen atoms in further conjugation with an aromatic or a carbonyl group.

REFERENCES AND NOTES

1. Greene, T.W.; Wuts, P.G.M. In *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1991.
2. Stafford, J.A.; Brackeen, M.F.; Karanewsky, D.S.; Valvano N.L. *Tetrahedron Lett.* **1993**, *34*, 7873-7876.
3. Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron* **1995**, *51*, 10323-10342.
4. Rawal, V.; Cava, M. *Tetrahedron Lett.* **1985**, *26*, 6141-6142. See citations in ref. 3 for the use of this procedure in the deprotection of indoles and other nitrogen protected compounds.
5. For a recent report on removal of *N*-BOC groups in amino acid *tert*-butyl esters see: Gibson, F.S.; Bergmeier, S.C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216-3218.
6. The silica gel was kept at 50°C / 0.2 mmHg for 24 h before use.
7. Prepared by refluxing 20g of silica gel (35-70 Mesh) in a mixture of 50ml of HMDS, 1ml of TMSCl and 0.5g of ammonium sulphate for 96h, followed by evaporation of the solvent and drying at 0.2 mmHg.
8. Mehta, A.; Jaouhari, R.; Benson, T.J.; Douglas K.T. *Tetrahedron Lett.* **1992**, *33*, 5441-5444 and references cited therein.

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