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THERMOLYTIC REMOVAL OF *t*-BUTYLOXYCARBONYL (BOC) PROTECTING GROUP ON INDOLES AND PYRROLES

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Summary: The *t*-Butyloxycarbonyl (BOC) group on indoles and pyrroles can be removed cleanly and in high yield by simple thermolysis: no acid, no base, no solvent is required.

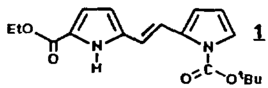
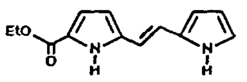
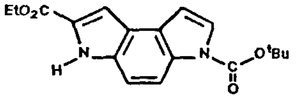
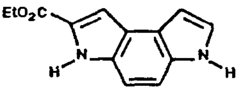
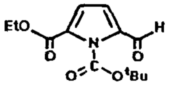
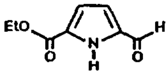
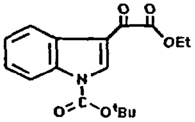
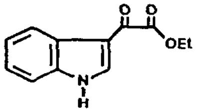
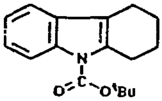
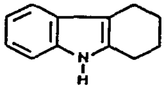
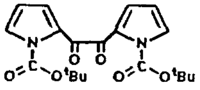
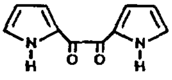
In recent years considerable attention has been given to the problem of finding suitable protecting groups for indoles and pyrroles.[2] The *t*-butyloxycarbonyl (BOC) group, though not resistant to strong acids or bases, has, nevertheless, proven to be extremely useful since it directs lithiation α to the indole and pyrrole nitrogens at low temperature (-78°C).[3] Our work on the synthesis of the antitumor agent CC-1065 offered us the opportunity to explore the reactivity of this group, and we report here a procedure for removing it in excellent yield.

To introduce the BOC group we used the remarkably mild conditions of Grehn and Ragnarsson.[4] We found, however, that yields were improved appreciably (10-20%) by using a simplified workup procedure. Thus, after all starting material had been consumed (TLC), the solvent was removed and the residue was purified directly by silica gel flash chromatography (typically, CH_2Cl_2:hexanes, 1:1 to 10:1), to afford pure BOC protected substrates in high yields (> 95%).

Removal of the BOC group is usually effected with 1:1 trifluoroacetic acid (TFA) and CH_2Cl_2.[4,5] These conditions, however, were deleterious to our electron-rich substrates. Specifically, for the deprotection of ester **1**, we examined a variety of acidic conditions [TFA concentration (%) in CH_2Cl_2, 1% to 100%; temperature, -78°C to room temperature], but were unable to effect this transformation in a satisfactory, reproducible yield (typically, 20-40%). Although we were able to remove the BOC group under basic conditions (excess NaOEt , EtOH, rt, overnight, 80-85% yield), [3,5a] we discovered serendipitously, while taking a melting point of **1**, that the protecting group starts to fall off just above 150°C (TLC check). Indeed this proved to be a good way to make certain that a particular substrate would survive the thermolysis.

In a typical procedure, when a sample of **1**, in a round bottom flask maintained under an argon atmosphere, was heated in an oil bath (180-185°C, bath temperature), the deprotection was complete after 20-30 minutes, as evidenced by cessation of bubbling. The resulting product was homogeneous by both TLC and NMR, and sufficiently pure for use in a subsequent step. Purification by flash chromatography afforded in good yield (92%), the light and acid sensitive olefin, **2**. A number of substrates were similarly deprotected in high yield (Table). The thermolytic conditions may appear to be extremely harsh, but in our experience they are preferrable to strongly acidic or basic condition.[7] The melting points of some of the reaction products (entries 2, 4, 6) are actually as high as or higher than the temperature required to remove the BOC group.

TABLE: Thermal Removal of BOC Groups

Entry	Substrate	Product	mp °C (lit. mp °C, ref)	Yield%
1	 1	 2	157-159	92
2			184-186	97
3			72-74 (75,6a)	94
4			184-184.5 (185-186.5,6b)	99
5			116 (118-120,6c)	96
6			200-202 (203-204,6b)	93

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References and Notes

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5. a) Franzen, H.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc. Chem. Commun.* **1984**, 1699.
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   b) Behr, D.; Brandange, S.; Lindstrom, B. *Acta Chem. Scand.* **1973**, *27*, 2411.
   c) Aldrich Chemical Co. catalog.
7. A referee has pointed out a recent report of thermolytic removal of BOC groups on secondary aliphatic amines in refluxing diphenyl ether: a) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459. b) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465. This indicates that the thermolytic removal of the BOC group has greater scope, and it may prove useful in amino acid chemistry.[4,5]

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