Pergamon

Tetrahedron Letters 39 (1998) 5631–5634

TETRAHEDRON LETTERS

An efficient and highly selective cleavage of *N-tert*-butoxycarbonyl group under microwave irradiation

D. Subhas Bose* and V. Lakshminarayana

Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad, 500 007, India.

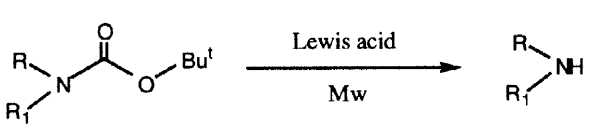
Received 9 March 1998; revised 22 May 1998; accepted 26 May 1998

Abstract:

A simple and high yielding method for the cleavage of *t*-Boc carbamates is described which occurs under mild and solvent-free conditions using microwave irradiation.

Keywords: Microwave irradiation, *tert*-butylcarbamate, Lewis acid catalyst, Chemoselectivity.

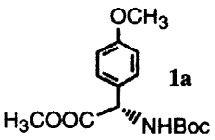
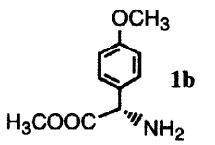
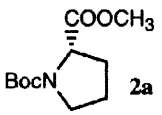
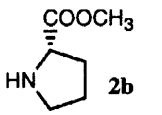
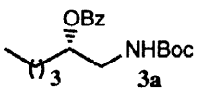
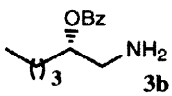
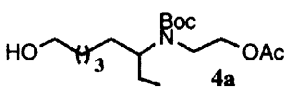
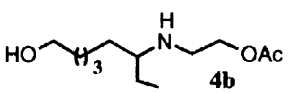
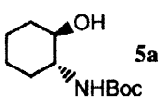
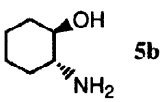
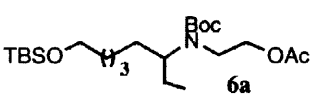
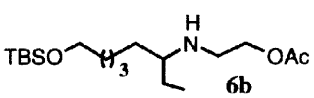
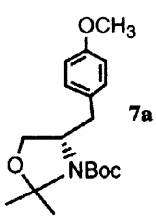
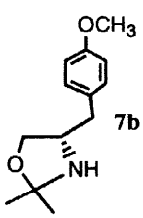
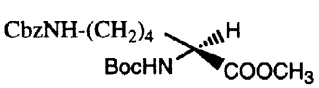
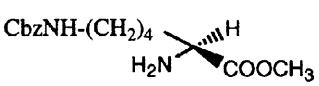
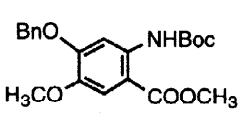
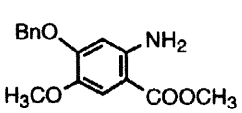
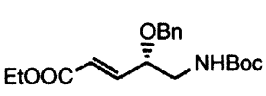
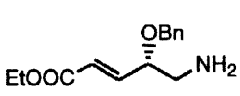
Carbamates are extensively used as protective groups during the synthesis of amino acids, peptides and other natural products [1]. Among the various amine-protecting groups, the *tert*-butoxycarbonyl group (*t*-Boc) is frequently used due to its chemical stability towards catalytic hydrogenolysis, basic and nucleophilic reagents. However, the co-existence with acid-sensitive groups cannot be employed since removal requires relatively strong acidic conditions. As organic chemists challenge themselves to synthesize more complex natural products, the need of developing new and more effective reagents, especially those which deprotect with high selectivity in the presence of other groups, is still one of the most important manipulations in modern organic synthesis. Several methods have been documented in the literature for *t*-Boc cleavage such as $BF_3.OEt_2$ [2], CF_3COOH [3] and bromocatechol borane [4]. After surveying new reagent systems, we found that the use of the Lewis acid aluminium chloride ($AlCl_3$) under microwave irradiation was highly favourable for our purpose. The reaction proceeds efficiently in high yields at ambient pressure within a few minutes [5]. Herein, we wish to report an effective and selective reagent for the cleavage of *t*-Boc carbamates to their corresponding amines.



In recent years, organic reactions on solid supports [6,7] and those that are assisted by microwaves [8], especially under solvent-free conditions [9], have attracted special attention because of their enhanced selectivity, milder reaction conditions and

0040-4039/98/$19.00
PII: S0040-4039(98)01094-6

Table 1. Microwave-assisted cleavage of *t*-Boc carbamates

entry	substrate	time, min.	product[a]	Yield (%)[b]
1	 **1a**	1.5	 **1b**	85
2	 **2a**	1.0	 **2b**	88
3	 **3a**	1.2	 **3b**	80
4	 **4a**	1.8	 **4b**	86
5	 **5a**	2.0	 **5b**	89
6	 **6a**	1.6	 **6b**	83
7	 **7a**	2.5	 **7b**	90
8	 **8a**	1.4	 **8b**	95
9	 **9a**	0.8	 **9b**	93
10	 **10a**	1.7	 **10b**	76

[a] All products gave satisfactory analytical and ^{1}H NMR spectroscopic data [11].

[b] Unoptimized yields of pure isolated products.

associated ease of manipulation. The Lewis acid catalyst, $AlCl_3$ is widely used [10] for the Friedel-Crafts alkylation and acylation of aromatic systems, Fries rearrangement and other reactions. To our surprise, however, its generality and use in the cleavage of *t*-Boc under microwave irradiation is not known, to the best of our knowledge.

The results summarized in Table 1 indicate that the reaction is successful for a variety of *t*-Boc protected primary and secondary amines. It is noteworthy that acid-sensitive as well as base-sensitive protecting groups and ester† and ether linkages could survive under the reaction conditions. Of particular interest is the selective cleavage of *t*-Boc in the presence of benzyl carbamate (entry **8**), a system known to be difficult to achieve selectively. It should be emphasized that results obtained with substrate **6a** reflect the excellent chemoselectivity of this method even in the presence of TBS and acetate protecting groups. In addition to that, stereochemical integrity at the amine-bearing carbon was retained.

General procedure : The deprotection of *t*-Boc proline ester (**2a**) is representative of the general procedure employed$^{\Phi}$. *tert*-Butyl carbamate (0.217 g, 1.0 mmol) and aluminium chloride (0.134 g, 1.0 mmol) doped on a neutral alumina (1.0 g) were mixed thoroughly on a vortex mixer. The reaction mixture was placed in an alumina bath inside an unmodified household microwave oven (operating at frequency 2450 MHz) and irradiated for a period of 1 min. After completion of the reaction (monitored by TLC, EtOAc :hexane, 9:1 v/v), it was neutralised with aqueous sodium bicarbonate solution and the product was extracted into ethyl acetate (2 x 15 ml).The ethyl acetate layer was separated, dried over magnesium sulfate, filtered, and the crude product thus obtained was purified by column chromatography to afford pure methyl ester (**2b**) in 88% yield.

In conclusion, we have developed a facile solid state method for the cleavage of *t*-Boc groups under fairly mild conditions#. We believe that the reagent system described here has potential application in solid-phase synthesis due to its high chemoselectivity, efficiency and simplicity. The salient features of this new method are reduced reaction times, minimisation of side products and excellent yields.

Acknowledgement : V.L.N, thanks CSIR, New Delhi for award of a research fellowship.

Footnotes:

*E-Mail : root@csiict.ren.nic.in

†During the studies on β-lactam antibiotics concurrent deprotection of the carboxyl ester (benzyl) and amino protecting group (*t*-Boc) was observed by using aluminium chloride (3.0 eq.) and anisole (3.0 eq.) in CH_2Cl_2-CH_3NO_2 at r.t. in 3 h. Ref: Tsuji T,

Kataoka T, Yoshioka M, Sendo Y, Nishitani Y, Hirai S, Maeda T, Nagata W. Tetrahedron Lett. 1979; 2793- 2796.

Φ*CAUTION*: In view of the hazardous associated with the reagent and evolution of gases during the reaction due caution is recommended for its use at elevated temperatures. We suggest that the microwave oven be operated carefully and for a shorter duration of time because of the possible higher localized temperatures attained.

Work on the similar line has been reported independently by Siro JG, Martin J, Garcia-Navio JL, Remuinan MJ, Vaquero J. Synlett, 1998; 147-148 (as suggested by the Editor, this reference has been incorporated).

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[11] Compounds **2b,5b,8b** isolated as aminehydrochloride salt.
Data for **2b:** $[\alpha]_D$ = -28.9° (c 0.5, H_2O), lit. $[\alpha]_D$ = -33 ± 2° (c 0.5, H_2O). **5b:** ^1H NMR (DMSO d_6): δ 1.18-1.42 (m, 4 H), 1.63-1.66 (m, 2 H), 1.87-2.05 (m, 2 H), 2.65 (m, 1 H), 3.40 (m, 1 H), 4.53 (br s, 1 H), 7.75 (br s, 3 H, NH_2HCl). $[\alpha]_D$ = -34.2° (c 1.0, H_2O), lit. $[\alpha]_D$ = -36.8° (c 0.4, H_2O), Takada H, Takagi S, Kawakubo H, Bull. Chem. Soc. Jpn, 1994; 67: 1196-1197. (±) **6a:** ^1H NMR ($CDCl_3$): δ 0.08 (s, 6 H), 0.81-0.96 (m, 12 H), 1.21-1.65 (m, 19 H), 2.05 (s, 3 H), 3.13-3.32 (m, 2 H), 3.55-3.65 (m, 2 H), 3.85-3.96 (m, 1 H), 4.12-4.22 (m, 2 H). **7b:** ^1H NMR ($CDCl_3$): δ 1.41 (s, 6 H), 2.05 (br s, 1 H), 2.75 (d, 2 H, J = 6.8 Hz), 3.44-3.68 (m, 2 H), 3.65 (s, 3 H), 4.63 (d, 1 H, J = 6.8 Hz), 6.78 (d, 2 H, J = 9.0 Hz), 7.08 (d, 2 H, J = 9.0 Hz). $[\alpha]_D$ = -20.0° (c 0.68, $CHCl_3$). **8a:** $[\alpha]_D$ = 9.0° (c 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$): δ 1.45 (s, 9 H), 1.50-1.82 (m, 6 H), 3.12-3.28 (m, 2 H), 3.75 (s, 3 H), 4.18-4.32 (m, 1 H), 4.80 (bs, 1 H, exchangeable with D_2O), 5.03 (bs, 1 H), 5.08 (s, 2 H), 7.23 (s, 5 H). **8b:** $[\alpha]_D$ = +14.0° (c 1.0, H_2O), lit. $[\alpha]_D$ = +15.5° (c 2.0, H_2O).

IICT Communication No. 3985