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LETTERS

A mild deprotection procedure for *tert*-butyl esters and *tert*-butyl ethers using $ZnBr_2$ in methylene chloride

Yong-qian Wu,* David C. Limburg, Douglas E. Wilkinson, Mark J. Vaal and Gregory S. Hamilton

Department of Research, Guilford Pharmaceuticals, Inc., 6611 Tributary Street, Baltimore, MD 21224, USA

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Abstract

$ZnBr_2$ in methylene chloride is a mild reagent for deprotecting *tert*-butyl esters and ethers. © 2000 Elsevier Science Ltd. All rights reserved.

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One of the most commonly used protection groups for carboxyl and hydroxyl groups has been the *tert*-butyl (*t*-Bu) group. The *t*-butyl esters and ethers are relatively hindered protection groups and can be easily prepared from a variety of carboxylic acids and alcohols, respectively.[1] Stable to most mild basic conditions, they lend themselves as useful tools in organic synthesis. Trifluoroacetic acid (TFA) is reported most often in literature as the preferred deprotecting reagent.[1] $ZnBr_2$ or its complex with other reagents has been previously reported as a deprotecting reagent for protection groups such as Boc from

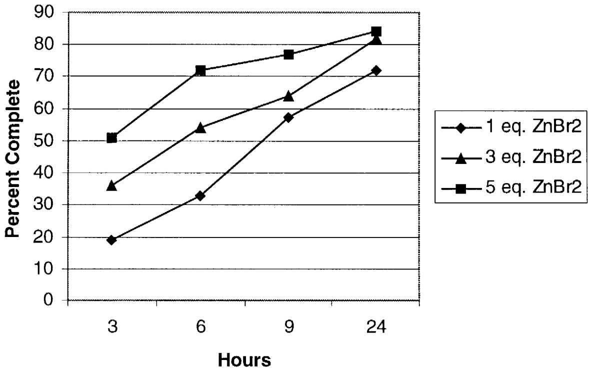

Fig. 1.

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[*] Corresponding author.

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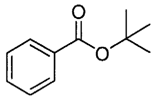
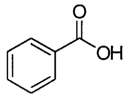
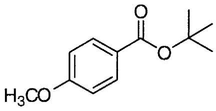
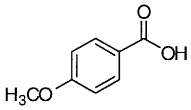
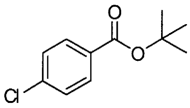
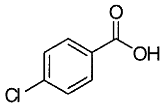
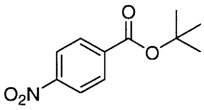
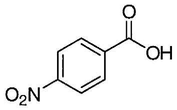
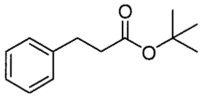
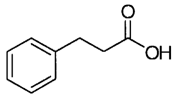
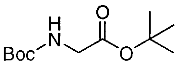
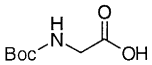
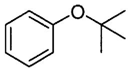
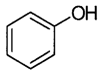
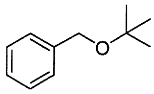
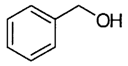
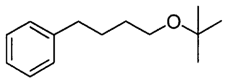
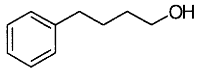
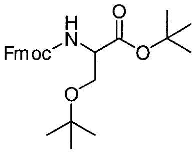
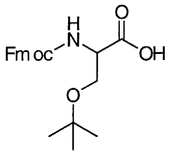
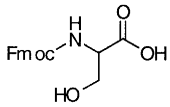
Table 1
Deprotection of *tert*-butyl esters and ethers

Entry	Substrate	Time (h)	Product	Yield(%)[a, b]
1		24		86
2		6		93
3		24		85
4		48		62
5		12		91
6		12		86
7		12		79
8		12		82
9		24		78
10		2		47
		12		88

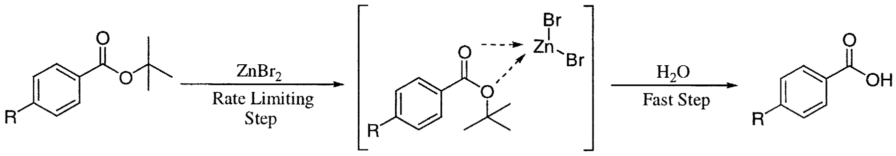
[a] All products were identified by comparison with authentic samples.

[b] Isolated yield.

secondary amines,[2] MEM,[3] and TMSEC.[4,5] We herein report its usage as a mild deprotecting reagent for *t*-butyl esters and ethers.

To explore optimal reaction conditions, we first examined the rate of cleavage and the effects of excess reagent. We performed the deprotection of *t*-butyl benzoate (entry 1) using increasing amounts of $ZnBr_2$, assessing product formation at set intervals. As shown in Fig. 1, the initial rate is accelerated with increasing amounts of $ZnBr_2$. The cleavage rate quickly plateaued at a 5:1 ratio of $ZnBr_2$ to the substrate and the reaction was >75% complete in the first 6 h.

Next we examined how differing substitution on the phenyl ring affected the rate of deprotection. Interestingly, compounds bearing electron donating groups are more efficiently cleaved than those bearing electron withdrawing groups as shown in Table 1 (entries 2–4). This may suggest that formation of the complex between $ZnBr_2$ and substrate, not the subsequent water hydrolysis is the rate limiting step in the deprotection (Scheme 1).



Scheme 1.

Similar to aromatic esters, aliphatic esters are deprotected as well (entry 5). As previously reported,[2] Boc protecting groups on primary amines were unaffected in this mild reaction condition. We found entry 6 was selectively cleaved at the *t*-butyl ester, while the Boc group on the nitrogen remained intact. This may be important for chemical transformation of various amino acids.

We have also demonstrated the deprotection of *t*-butyl ethers. Reactions were completed within 12–24 h. Phenyl and benzyl ethers were shown to be cleaved faster than the aliphatic ethers (entries 7–9). An attempt was made to selectively cleave the *t*-butyl ester over the *t*-butyl ether, however it was not very successful (entry 10). After 2 h, the ratio of starting material, mono-cleavage at the ester site and cleavage at both sites was 1:2:1. No mono-cleavage at the *t*-butyl ether site was observed. Prolonged exposure to $ZnBr_2$ resulted in complete cleavage at both sites. This suggests that the cleavage rate for *t*-butyl esters is faster than *t*-butyl ethers, but it was not selective.

In summary, we have developed a mild deprotection method for the cleavage of *t*-butyl esters and ethers. We have also demonstrated the selective deprotection of *t*-butyl esters in the presence of primary *N*-Boc groups.

Procedure: to a solution of *tert*-butyl benzoate (0.356 g, 0.002 mol) in 4 mL dichloromethane was added zinc bromide (2.25 g, 0.01 mol) and the solution stirred for 24 h. At this time, 40 mL of water was added and the mixture was stirred for 2 h. The layers were separated and the aqueous layer was extracted with 3×40 mL of dichloromethane. The combined organic portions were dried over magnesium sulfate, filtered and the solvent removed by evaporation to yield pure product. Yield: 0.21g (86%) of benzoic acid as a white solid, which was identical to the commercial product.

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