Selective Deprotection of N-Boc-Protected *tert*-Butyl Ester Amino Acids by the $CeCl_3 \cdot 7H_2O$−NaI System in Acetonitrile

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Introduction

The utilization of natural and unnatural α-amino acids in the chemical, physical, and biological sciences continues to grow.[1a] In addition to their key biological roles as components of peptides, proteins, and other natural products, α-amino acids are utilized in the pharmaceutical, agrochemical, and related industries. Recently, multifunctional α-amino acids have also been utilized in organic synthesis as chiral auxiliaries, reagents, and catalysts for asymmetric synthesis.[1b] For these reasons, the task of differentiating the carboxyl and amino groups becomes particularly important in the synthetic use of α-amino acids. Since the amino group is commonly protected[2] by Boc (*tert*-butoxycarbonyl), while the acid group is frequently protected as an ester,[3] such as *tert*-butyl ester,[4] selective deprotection of both groups has imposed a challenge. Several methods have been reported for the selective deprotection of Boc groups in the presence of *tert*-butyl esters.[5] In contrast, to the best of our knowledge, only one previous example for the selective deprotection of the *tert*-butyl esters in the presence of N-Boc groups under nonaqueous conditions has been reported to date.[6] In this regard, the realization of such an idea would broaden the synthetic usefulness of these two protecting groups. We now report that the *tert*-butyl ester can be cleaved in preference to the N-Boc protecting group by the $CeCl_3 \cdot 7H_2O$−NaI system in acetonitrile, representing a reversal of the usual selectivity under acidic conditions.

Fukuzawa has demonstrated that the $CeCl_3 \cdot 7H_2O$−NaI system promotes the carbon−carbon bond formation between α-halogeno ketones and carbonyl compounds under anhydrous conditions.[7] We have extended this work and have reported a variety of useful selective deprotections in high yield utilizing $CeCl_3$ in the presence of NaI, without the necessity of anhydrous conditions.[8,9] The efficiency of the $CeCl_3 \cdot 7H_2O$−NaI system in deprotection reactions of carbonyl and hydroxyl groups[10] prompted us to study as to whether this combination would be effective in promoting other useful organic transformations.[11]

Results and Discussion

We began an investigation in which a series of simple *tert*-butyl esters were treated with a suspension of $CeCl_3 \cdot 7H_2O$ and NaI in refluxing acetonitrile.[12] Usual workup furnished the pure carboxylic acid. We believe that *tert*-butyl ester cleavage was effected by $CeCl_3 \cdot 7H_2O$−NaI (Scheme 1) through the selective coordination of cerium with *tert*-butyl ester oxygen atoms to form a complex (**2**) which then undergoes water hydrolysis to carboxylic acid (**3**), liberating the *tert*-butyl carbocation. The latter is trapped by nucleophilic attack of iodide ion to afford *tert*-butyl iodide **4** as identified by GC-MS. In general, 1.5 equiv of $CeCl_3 \cdot 7H_2O$ and 1.3 equiv of NaI were found to give the best results (Table 1).

Unfortunately attempts to extend this procedure to the selective deprotection of *tert*-butyl esters in the presence of N-Boc protecting groups met with failure. In fact, the treatment of N-Boc-(S)-α-alanine *tert*-butyl ester derivative **5a** with $CeCl_3 \cdot 7H_2O$ in the presence of NaI in

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(6) Wu, Y. Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847−2849.

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Scheme 1

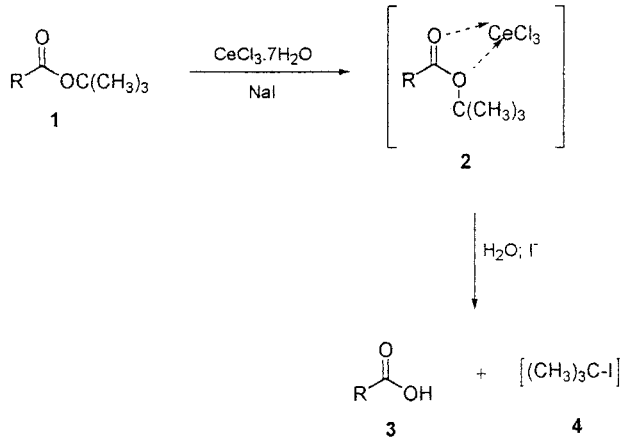
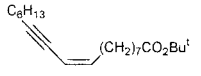
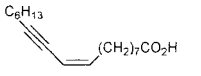
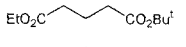
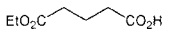
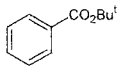
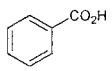
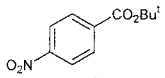
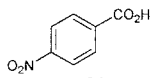
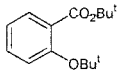
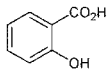
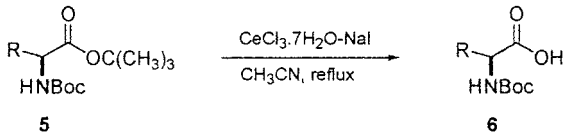


Table 1. Deprotection of *tert*-Butyl Esters by $CeCl_3.7H_2O$ in Refluxing Acetonitrile

Entry	Starting Material[a]	Time	Product	Yield (%)[b]
1	 1a	4.5 h	 3a	86
2	 1b	5 h	 3b	88
3	 1c	5 h	 3c	90
4	 1e	7 h	 3d	91
5	 1f	3,5 h	 3f	91[c]

[a] All starting materials were prepared from commercially acids and using *tert*-butyl 2,2,2-trichloroacetimidate (Armostrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483−2486). [b] The yields are of isolated, purified products. [c] No selectivity was obtained, and the *tert*-butyl ether is also removed.

Scheme 2

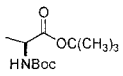
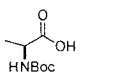
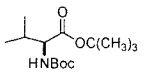
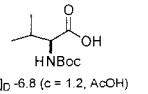
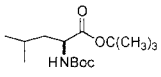
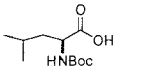
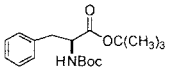
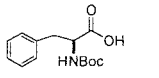
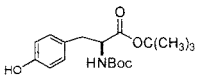
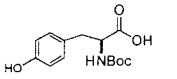
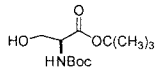
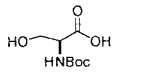
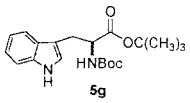
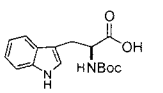
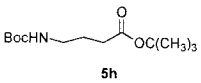
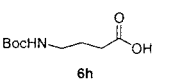
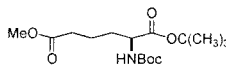
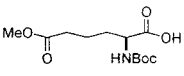
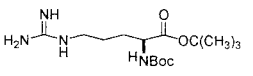
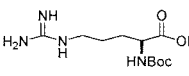
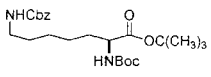
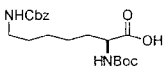


refluxing acetonitrile gave free amino acid with the removal of both protecting groups. On the basis of the unexpected difficulty of the selective deprotection of *tert*-butyl esters in the presence of N-Boc groups, we studied the lability of *tert*-butyl ester and N-*tert*-butoxycarbonyl groups toward the $CeCl_3{\cdot}7H_2O$−NaI reagent system.

From the literature[13] it is known that N-Boc protecting groups of amino acids can be removed in refluxing aqueous acetone in the presence of NaI. The proposed mechanism is based on the fact that heating NaI with

(13) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339−2358.

Table 2. N-Boc-Protected Amino Acids from *tert*-butyl Esters Substrates

Entry	Substrate[a]	Time	Product[b]	Yield (%)[c]
1	 5a	4 h	 $[\alpha]_D$ +23.3 (c = 1.0, MeOH) 6a	75
2	 5b	6 h	 $[\alpha]_D$ -6.8 (c = 1.2, AcOH) 6b	99
3	 5c	5 h	 $[\alpha]_D$ -24.0 (c = 0.9, AcOH) 6c	87
4	 5d	6 h	 $[\alpha]_D$ +24.5 (c = 1.0, EtOH) 6d	78
5	 5e	2 h	 $[\alpha]_D$ +4.3 (c = 1.5, MeOH) 6e	80
6	 5f	2 h	 $[\alpha]_D$ +8.7 (c = 2.8, MeOH) 6f	89
7	 5g	1 h	 $[\alpha]_D$ -21.1 (c = 1.0, AcOH) 6g	80
8	 5h	4 h	 6h	75
9	 5i	2 h	 $[\alpha]_D$ -8.6 (c = 1.1, MeOH) 6i	87
10	 5j	2 h	 $[\alpha]_D$ -8.7 (c = 2.1, H_2O) 6j	79
11	 5k	1 h	 $[\alpha]_D$ -12.1 (c = 1.3, MeOH) 6k	85

[a] In all substrates, N-Boc protecting groups were introduced by the method of Fiat (Ponnusanny, E.; Fotadar, U.; Spisni, A.; Fiat, D. *Synthesis* **1986**, 48−49), and all *tert*-butyl esters were prepared using *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (Mathias, L. *Synthesis* **1979**, 561−576). [b] All products were identified by their IR, NMR, GC/MS, and $[\alpha]_D$ values in comparison with their authentic samples. [c] Isolated yields.

the free carboxylic acid group of amino acid generates hydrogen iodide (HI) in situ.[14] This result suggested to us that under our conditions the desired N-Boc protected amino acid, as a result of *tert*-butyl ester removal, is

necessary in liberating hydrogen iodide, which is also responsible for the hydrolysis of N-Boc group. Indeed, the N-Boc group was not cleaved when the carboalkoxy group of amino acid is a methyl ester, inasmuch this carboxylic acid group is stable under our reaction conditions. We noticed, moreover, that in the absence of NaI the treatment of amino acid **5a** with $CeCl_3 \cdot 7H_2O$ alone furnishes the desired product **6a** in only 5% yield after extended reaction times. These observation led us to believe that selective removal of a *tert*-butyl ester group in the presence of the N-Boc group depended on a more efficient generation of complex **2** (Scheme 1). In an effort to increase the solubility of $CeCl_3 \cdot 7H_2O$ in acetonitrile (ca. 3 g/100 mL), the $CeCl_3 \cdot 7H_2O-NaI$ mixture was refluxed in acetonitrile for 24 h to promote the selective deprotection (Scheme 2). When this mixture was then added to substrate **5d**, we obtained a 78% yield of the desired N-Boc-protected amino acid **6d**, (Table 2, entry 4). Since the exact nature of the intermediate obtained by the reaction of the *tert*-butyl ester derivative with cerium salt is not yet known, we can only speculate about the mechanistic role of NaI, it is probable that a halide-exchange reaction between $CeCl_3$ and NaI occurs during the treatment in refluxing acetonitrile, which is responsible for the enhancement of activity and/or solubility of cerium salt. Thus, the characterization of all components generated during the tratment of the $CeCl_3 \cdot 7H_2O$ an NaI in refluxing acetonitrile is being carried out in our laboratories.

It is worthwhile to note as soon as TLC and/or GC analyses show the disappearance of the starting materials, hydrolysis, evaporation of the solvent, and column chromatography on silica gel gave the desired selective deprotection. Our results are reported in Table 2. The yields were calculated after purification of the products by liquid chromatography on silica gel. The structure of the products were determined by comparison with authentic samples and confirmed from their spectral data. All *tert*-butyl ester N-Boc (S)-amino acid derivatives were selectively deprotected without racemization as confirmed by the optical rotation of the products in Table 2. As shown in the table, *tert*-butyl esters can be selectively cleaved in the presence of other functional groups, such as the hydroxy group of the serine (entry 6); no dehydration[11a] was observed. It is also noteworthy that a *tert*-butyl ester can be selectively cleaved in the presence of a methyl ester (Table 2, entry 9). Further, the removal of the *tert*-butyl ester from the N^{α}-Boc-N^{ϵ}-Cbz-Lys substrate **5k**[15] demostrates that our conditions are compatible with other commonly used amino protecting groups, e.g., the basis of the carbobenzyloxy (Cbz) group.

In summary, we have shown an interesting example of selective deprotection of the *tert*-butyl esters in the presence of N-Boc protecting groups of several amino acids. It is clear that the simplicity of this approach, the low cost of the reagents, and the mild nature of cerium(III) chloride in comparison to other Lewis acids enhance the attractiveness of the reagent system described here. Additional studies to improve this methodology, particularly with regard to examining other soft nucleophiles in combination with $CeCl_3$, are underway. We hope that under optimized conditions most side reactions will be eliminated.

Experimental Section[16]

General Methods. For general experimental details, see ref 10a.

Representative Procedure for the $CeCl_3 \cdot 7H_2O$/NaI Cleavage of *tert*-Butyl Esters (Table 1, entry 3). To a stirred suspension of *tert*-butyl benzoate (**1c**; 0.178 g, 1 mmol) and NaI (0.195 g, 1.3 mmol) in acetonitrile (10 mL) was added $CeCl_3 \cdot 7H_2O$ (0.56 g, 1.5 mmol), and the resulting mixture was stirred for 5 h at reflux. The reaction progress was monitored by withdrawing aliquots which were analyzed by GLC, and the products were identified by GC-MS. The reaction mixture was diluted with ether and treated with 0.5 N HCl (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (4 × 25 mL). The combined organic layers were washed twice with aqueous saturated NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The obtained acid was purified by column chromatography to give 0.11 g (90% yield) of benzoic acid as a white solid, which was identical to the commercial product.

General Procedure for the Selective Removal of a *tert*-Butyl Ester Group. A suspension of $CeCl_3 \cdot 7H_2O$ (1.5 mmol) and NaI (1.3 mmol) in acetonitrile (10 mL) was stirred for 24 h at refluxing temperature. After being cooled to room temperature, this mixture was treated with the *tert*-butyl ester N-Boc α-amino acid derivative (1 mmol), and the mixture was stirred at reflux temperature until TLC indicates complete removal of *tert*-butyl ester group. The reaction was quenched by adding 0.5 N HCl, and the solvent was removed in vacuo at room temperature. The crude material was dissolved in a suitable organic solvent and washed with water and and brine. After drying (Na_2SO_4) and solvent removal, the obtained N-Boc protected α-amino acids were purified by column chromatography; yields are reported in Table 2.

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