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Ceric Ammonium Nitrate in the Deprotection of *tert*-Butoxycarbonyl Group

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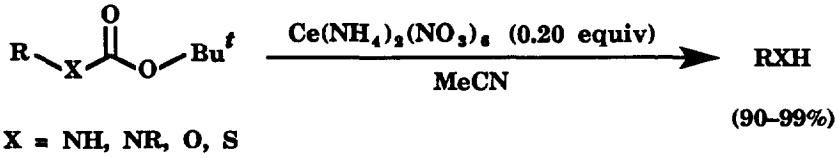
Abstract: The *tert*-butoxycarbonyl protecting group for amines, alcohols, and thiols was removed efficiently (90–99% yields) by use of 0.20 equivalent of $Ce(NH_4)_2(NO_3)_6$ in acetonitrile.

The *tert*-butoxycarbonyl (*t*-BOC) group is often used for protection of amino acids in peptide synthesis.[1,2] Reagents applied for removal of the *t*-BOC group include hydrochloric acid in ethyl acetate,[3] sulfuric acid in dioxane,[4] anhydrous hydrogen fluoride,[5] boron trifluoride diethyl etherate in acetic acid,[6] trimethylsilyl triflate,[7,8] trimethylsilyl perchlorate,[9] and trifluoroacetic acid.[1] Deprotection of the *t*-BOC group under neutral conditions was not hitherto described, yet it is highly desirable. Herein we report our new findings that CAN acted as a catalyst for removal of the *t*-BOC group from organic compounds under neutral conditions (Scheme 1).

Scheme 1



X = NH, NR, O, S

Ceric ammonium nitrate (CAN) can function as a one-electron transfer catalyst in various organic reactions.[10–12] Very recently we have found an efficient way to detritylate protected nucleosides and nucleotides by using CAN as the catalyst. Under these reaction conditions, several acid sensitive groups survive including isopropylidene, (dimethylamino)methylidene, *tert*-butyldimethylsilyl, and acyl functionalities.[13] Feasibility

of deprotection of the trityl group involving CAN depends upon stability of the resultant carbocations. Removal of mono(*p*-methoxy)trityl group from 5'-*O*-mono(*p*-methoxy)trityl adenosine proceeds about 10 times faster than that of the trityl group from 5'-*O*-trityl adenosine.[13]

We considered that the electron-withdrawing groups directly connected to *tert*-butyl functionality (e.g., $RXCOOBu^t$) would increase the potential for it to become a carbocationic species. Thus we intended to investigate the possibility of using CAN as a catalyst for efficient removal of the *t*-BOC group from amino acids and the related compounds.

A *t*-BOC containing compound (i.e., **1–6**) in acetonitrile was treated with 0.20 equiv of CAN. After the solution was heated at reflux, the solvent was removed and the residue was purified by chromatography to give the deprotected products (i.e., **7–12**) in 90–99% yields. This deprotection procedure was applicable to compounds bearing a *t*-BOC group attached to a nitrogen atom (i.e., **1–3**), an oxygen atom (i.e., **4**), or a sulfur atom (i.e., **5**), as shown in Table. By use of the same method, debutylation also occurred in ester **6** to afford the corresponding acid **12** in 98% yield. Furthermore, we found that the same deprotection proceeded at 25 °C, yet a longer reaction time (38–48 h) was required.

Our results shown in Table indicate that some functionalities remained intact under the conditions involving CAN. They include benzyl esters as well as indole, pyrimidine, and phthalimide nuclei. Moreover, we did not observe any undesired racemization in amino esters (i.e., **7–9**). The pH value of the mixtures also remained the same in the course of the reaction.

We propose a mechanism in Scheme 2 for removal of the *t*-BOC group from organic molecules. An essential step involves oxidation of carbonyl group in **13** to the corresponding radical cations **14** while reduction of Ce(IV) to Ce(III) takes place.[13] Radical cations **14** then undergo fragmentation to give *tert*-butyl cation **15** and carboxylate radicals **16**. Regeneration

Scheme 2

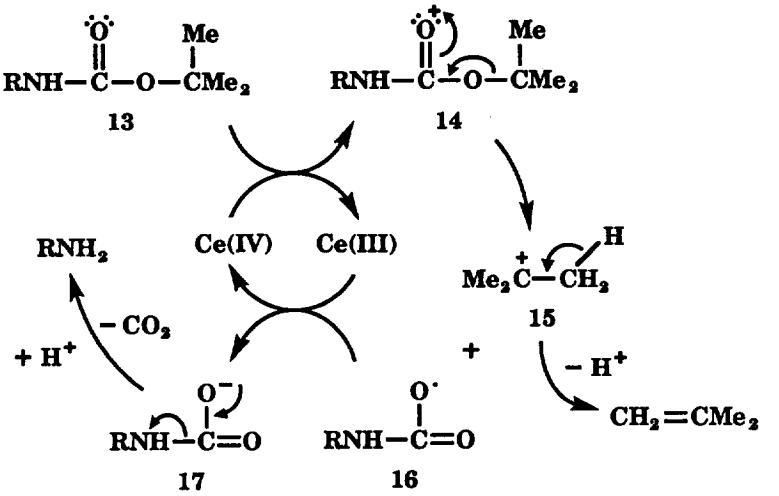
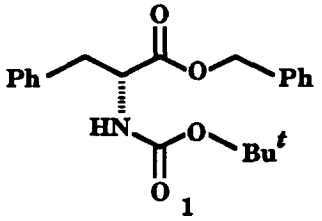
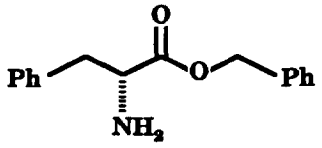
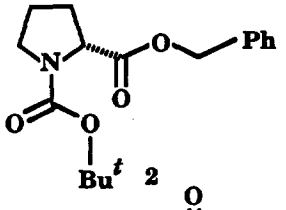
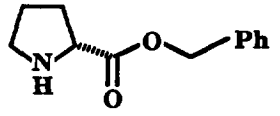
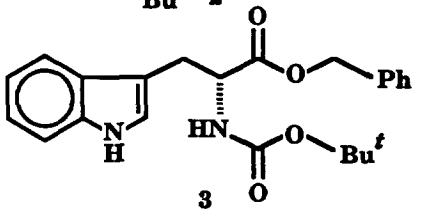
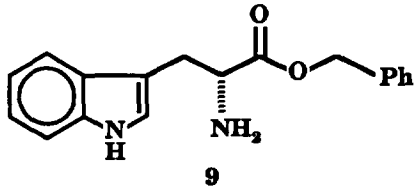
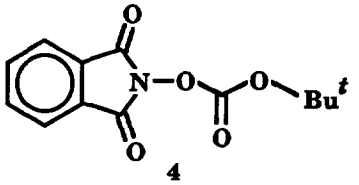
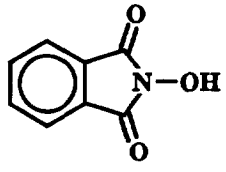
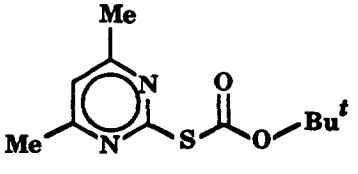
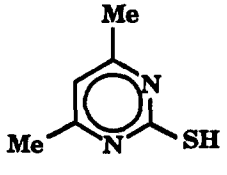
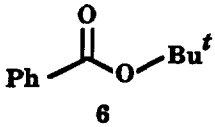
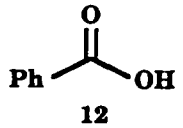


Table. Removal of the *t*-BOC or the *tert*-Butyl Group from Organic Compounds by Use of CAN (0.20 equiv) in CH_3CN at Reflux .

starting material	time (h)	product[a]	yield (%)
 1	10	 7	95[b]
 2	2	 8	93
 3	8	 9	90
 4	1	 10	99
 5	0.2	 11	96
 6	5	 12	98

[a]The spectra data of the isolated products were identical to those of the authentic samples.

[b]A mixture of CH_3CN and MeOH (1:1) was used as the solvent.

of Ce(IV) from Ce(III) during reduction of carboxylate radicals **16** to carboxylate ions **17** allows use of CAN in a catalytic amount for the entire deprotection process. Finally, extrusion of CO_2 from **17** followed by protonation gave the free amines.

In conclusion, CAN was found to act as an efficient catalyst for removal of the *t*-BOC group from an amino, hydroxyl, or mercapto functionality in organic compounds. Advantages associated with this newly developed method include mild and neutral reaction conditions, a short reaction time, and only a catalytic amount of reagent required (i.e., CAN).

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