A Facile and Selective Cleavage of Prenyl Esters Catalyzed by $CeCl_3 \cdot 7\ H_2O$-NaI

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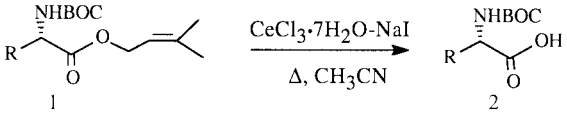
Abstract: A highly selective cleavage of prenyl esters has been achieved in high yields using $CeCl_3 \cdot 7\ H_2O$-NaI in refluxing acetonitrile under neutral conditions. This method is mild and compatible with a wide variety of functional groups such as BOC, Cbz, acetate, allyl, benzyl, tetrahydropyranyl, PMB ethers, allyl, methyl, and benzyl esters present in the molecule.

Key words: cerium reagents, 3-methylbut-2-enoate, α-amino acids



Scheme 1

Protection of acids with appropriate protecting groups plays an important role in the multi-step synthesis of many natural products.[1] Carboxylic acids can be protected as anhydrides, amides or esters.[2] However, the final stage of chemical process frequently requires their cleavage so as to regenerate the parent carboxylic acid. Unsaturated esters are particularly versatile acid-protecting groups because of their stability toward a variety of reaction conditions, ease of formation and /or removal under specific conditions. As a result, several procedures have been developed to facilitate the cleavage of prenyl esters under various reaction conditions. These include the use of expensive reagents such as $Pd(OAc)_2$,[3a] $PdCl_2(Ph_3P)_2$,[3b] $(Ph_3P)_3RhCl$,[4a] $Pd(Ph_3P)_4$[4b] and Me_2CuLi[5] as well as strong acids.[6] However, many of these procedures are of limited synthetic scope due to the lack of selectivity,[6a] the use of expensive,[3,4] corrosive[6a] and/or hazardous reagents,[6c] the requirement of high temperature or long reaction time[6b] and the necessity of anhydrous conditions.[5] Therefore, there is a need to develop a simple and efficient procedure for the cleavage of prenyl esters under mild conditions. Lanthanide salts are unique Lewis acids[7] that are currently of great research interest. Cerium halides are relatively non-toxic, readily available at low cost and are fairly stable to water.[8]

We wish to report that $CeCl_3 \cdot 7\ H_2O$-NaI is an efficient reagent for the selective cleavage of prenyl esters over a wide range of functional groups. The prenyl esters can be selectively deprotected to the corresponding acids using cerium(III) chloride heptahydrate-sodium iodide under mild conditions (Scheme 1).

The cleavage was effected by $CeCl_3 \cdot 7\ H_2O$-NaI in refluxing acetonitrile under neutral conditions. The deprotection proceeded efficiently in high yields with high chemoselectivity. The combination of cerium(III) chloride with NaI selectively cleaved prenyl esters leaving benzyl, methyl and allyl esters intact. Such selectivity can be applied in synthetic sequences in which two ester groups must be unmasked at different stages of the synthesis. It should be noted that the prenyl esters bearing α-stereogenic centres gave the parent acids with complete retention of the original configuration.[9,10] This method is highly chemoselective to deprotect prenyl esters without affecting the other functional groups. We have examined the possibility of $CeCl_3 \cdot 7\ H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. But best results were obtained with an equimolar ratio of $CeCl_3 \cdot 7\ H_2O$ and NaI. However, in the absence of NaI the deprotection was slow by $CeCl_3$ alone in refluxing acetonitrile and took a longer reaction time to achieve complete conversion. This clearly indicates that the addition of 1 equivalent of NaI is crucial in the deprotection to obtain high yields of acids. The reactions are clean and complete with in 1.5–3.5 hours. Due to the short reaction times required for this cleavage, a number of functional groups, which are capable of reacting with $CeCl_3 \cdot 7\ H_2O$, remain intact. The major advantage of this cleavage is in the selective removal of prenyl esters in the presence of highly acid sensitive THP ethers, which is lacking in the existing methods. Prenyl esters were more rapidly deprotected than allyl and PMB ethers by these conditions. Further, the compatibility of this procedure is illustrated by the selective removal of prenyl group without affecting olefins, carbamates, ethers and halides. There are many advantages in the use of cerium(III) chloride for this cleavage, which avoids the use of strongly acidic or basic conditions. The method does not require the use of expensive reagents or anhydrous solvents and no precautions need to be taken to exclude moisture from the reaction medium. Thus, the present method is mild and tolerates a wide range of functional groups. As evident from the Table, acid sensitive protecting groups such as Ac, BOC, CBz, PMB and THP ethers survive under the reaction conditions. Other carboxylic acid protecting groups such as amides, alkyl and benzyl esters are stable

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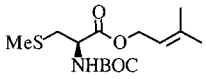
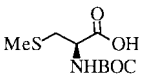
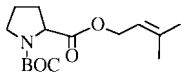
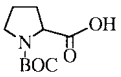
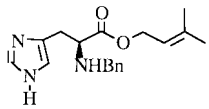
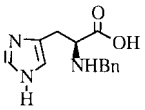
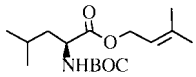
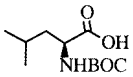
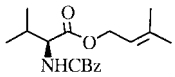
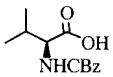
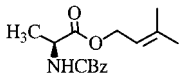
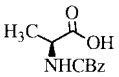
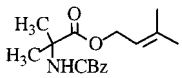
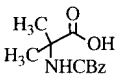
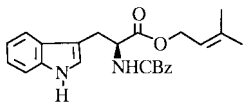
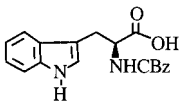
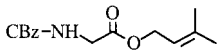
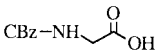
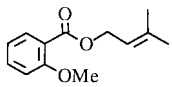
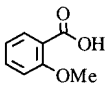
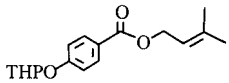
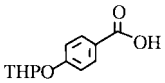
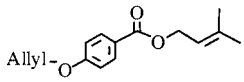
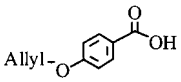
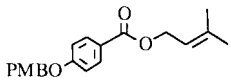
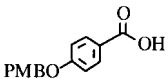
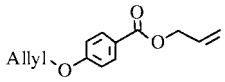
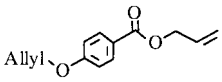
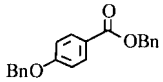
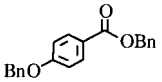
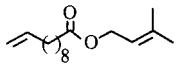
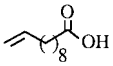
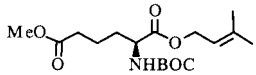
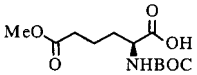
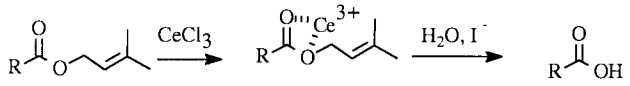
Table Selective Cleavage of Prenyl Esters by $CeCl_3 \cdot 7\ H_2O$-NaI

Entry	Substrate **1**	Product[a] **2**	Time (h)	Yield[b] (%)
a			1.5	93
b			2.0	92
c			2.0	88
d			1.5	91
e			2.0	92
f			2.5	90
g			2.0	92
h			3.0	88
i			2.5	91
j			2.0	85
k			2.5	92
l			2.0	87
m			2.0	85
n			10.0	–
o			10.0	–
p			3.5	88
q			3.5	90

[a] All products were characterized by ^1H NMR, IR and mass spectra.
[b] Isolated and unoptimized yields.

to $CeCl_3 \cdot 7\ H_2O$-NaI. The cleavage may be effected through the activation of carbonyl group by cerium(III) resulting in the formation of oxonium ion which is attacked by I^- nucleopile to afford the corresponding carboxylic acid (Scheme 2).



Scheme 2

In summary, this paper describes a mild and efficient method for the selective deprotection of prenyl esters to their parent carboxylic acids using $CeCl_3 \cdot 7\ H_2O$-NaI under neutral conditions thereby leaving acid- and base-labile protecting groups intact. The high levels chemoselectivity in this process combined with a simple operation, high yields and ready availability of reagents at low cost will find a wider use of the prenyl ester in organic synthesis.

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(9) **Experimental Procedure**: A mixture of 3-methylbut-2-enoate (5 mmol) $CeCl_3 \cdot 7\ H_2O$ (5 mmol) and NaI (5 mmol) in acetonitrile (15 mL) was stirred at reflux temperature for a specified time as required to complete the reaction (Table). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 2:8) to afford pure acid. Spectral data for the compounds **1e**: Liquid, ^{1}H NMR ($CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.8 Hz), 0.98 (d, 3 H, *J* = 6.8 Hz), 1.73 (s, 3 H), 1.78 (s, 3 H), 2.10–2.21 (m, 1 H), 4.28 (dd, 1 H, *J* = 5.5, 10.3 Hz), 4.60 (d, 2 H, *J* = 7.0 Hz), 5.10 (s, 2 H), 5.20 (brs, NH), 5.35 (m, 1 H), 7.28–7.40 (m, 5 H). MS (EI): *m/z* = 319 [M^+]. IR (KBr): ν 3347, 2965, 1723, 1511, 1220, 988, 722 cm^{-1}. **2e**: Solid, $[\alpha]_D^{20}$ +6.3 (*c* 4, $CHCl_3$), Aldrich: $[\alpha]_D^{20}$ (*c* 4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, 3 H, *J* = 7.0 Hz), 0.99 (d, 3 H, *J* = 7.0 Hz), 2.10–2.23 (m, 1 H), 4.20 (m, 1 H), 5.08 (s, 2 H), 5.80 (brs, NH), 7.25–7.40 (m, 5 H). MS (EI): *m/z* = 251 [M^+]. IR (KBr): ν 3339, 3037, 1695, 1531, 1229, 978, 729 cm^{-1}. **1f**: Liquid, ^{1}H NMR ($CDCl_3$): δ = 1.40 (d, 3 H, *J* = 6.8 Hz), 1.78 (s, 3 H), 1.80 (s, 3 H), 4.38 (m, 1 H), 4.60 (d, 2 H, *J* = 7.0 Hz), 5.10 (s, 2 H), 5.37 (m, 1 H), 5.45 (brs, NH), 7.37–7.40 (m, 5 H). MS (EI): *m/z* = 291 [M^+]. IR (KBr): ν 3342, 3035, 2965, 1724, 1525, 1453, 1209, 1065, 917, 735 cm^{-1}. **2f**: Solid, $[\alpha]_D^{20}$ –13.9 (*c* 2, HOAc), Aldrich: $[\alpha]_D^{23}$ –14.2 (*c* 2, HOAc). ^{1}H NMR (DMSO-d_6): δ = 1.48 (d, 3 H, *J* = 7.0 Hz), 4.40 (m, 1 H), 5.18 (s, 2 H), 5.27 (brs, NH), 7.28–7.40 (m, 5 H), 8.15 (brs, OH). MS (EI): *m/z* = 223 [M^+]. IR (KBr): ν 3333, 3036, 1695, 1536, 1458, 1252, 1075, 1027, 914, 739 cm^{-1}.

(10) IICT Commun. No: 01/x/09