

A Simple and Efficient Protocol for the Deprenylation of Ethers and Esters Catalysed by Zirconium(IV) Chloride-Sodium Iodide¹

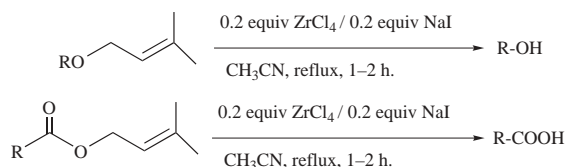
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Received 9 July 2003

Abstract: An efficient protocol for the deprotection of prenyl ethers and esters is developed using 20 mol% ZrCl₄-NaI (1:1) in CH₃CN as a reagent system. A variety of substrates as well as functional groups well tolerate the present reaction conditions.

Key words: deprenylation, protecting groups, esters, catalytic, zirconium(IV) chloride



Scheme 1

Development of new protecting groups and efficient protocols for selective protection/deprotection is a challenging problem and plays a prominent role in organic synthesis, especially in the case where sensitive structural features limit reagent choice. The chemistry of protecting groups continues to be an active area of research, while protection and deprotection of both hydroxyl and acid groups have been given considerable attention in the recent years.² The increase in the complexity of the target molecule increases the demand for mild and selective methods for the masking and unmasking of the protecting groups. The allyl group³ has been frequently used because of its stability towards acid, alkali and a number of other reagents. Among the related allylic groups such as prenyl,⁴ crotyl,⁵ meth-allyl,⁶ currently much attention has been given to prenyl group for protection of alcohols and acids. Several methods have been developed for the deprotection of prenyl ethers that include, bases,⁷ TiCl₄-*n*-Bu₄NI,⁸ ZrCl₄-NaBH₄,⁹ and oxidative methods,¹⁰ while other reagents such as Pd(OAc)₂,¹¹ CeCl₃·7H₂O-NaI,¹² TMSOTf¹³ are also reported for the cleavage of prenyl esters. However, many of these methods use the reagents in stoichiometric quantities, require longer reaction times besides the lack of selectivity. In continuation of our earlier work on protection and deprotection¹⁴⁻¹⁶ by catalytic use of Lewis acids, herein, we report an efficient deprenylation method using 20 mol% ZrCl₄ and NaI (1:1) in CH₃CN at reflux as an efficient reagent system to cleave both prenyl ethers and esters in the presence of a variety of acid/base sensitive groups and substrates such as carbohydrates, terpenes and amino acids (Scheme 1).

Initially, when **1** was treated with 20 mol% ZrCl₄ in CH₃CN at room temperature, the reaction was very sluggish (40–50 h) and gave **1a** in 80% yield, while the same at reflux was complete in 20 hours to give **1a** in 78% yield.

However, in a further study, treatment of **1** with 20 mol% ZrCl₄ in the presence of 20 mol% NaI (1:1) in CH₃CN at reflux, indeed, was very efficient and deprenylation was complete in 1.5 hours and gave **1a** in 91% yield.

After establishing the reaction conditions, prenyl ethers were prepared from a variety of aliphatic, aromatic, sugar and terpenoidal substrates and subjected to deprenylation to provide the corresponding alcohols (Table 1).¹⁷ The deprotection proceeds in high yields with high chemoselectivity, wherein other allylic groups such as allyl (entry 6) and crotyl (entry 7) are unaffected. Similarly, in addition to acid sensitive THP (entry 3) and acetonide (entries 8 and 9) groups and base sensitive acetate and benzoate (entries 4 and 5), benzyl group (entries 1 and 9), also remain intact. Carbohydrates and terpenoids are also found to be unaffected under the present reaction conditions. The results are summarized in Table 1.

In a further study to evaluate the efficiency of 20 mol% ZrCl₄-NaI (1:1) for the deprotection of prenyl esters, a variety of esters were prepared from substrates of different nature and subjected to hydrolysis. Accordingly, treatment of ester **11** with ZrCl₄-NaI (1:1) in CH₃CN at reflux gave the acid **11a** (Table 2) in 1.5 hours in 88% yield. Similarly, ester **13** with a hetero atom in the ring, also underwent a facile hydrolysis to give the acid **13a**, while deprenylation of the esters **14** and **16**, derived from acid sensitive Boc protected amino acids, and **15** with Cbz group, gave **14a–16a**, consolidates the utility of the present reagent system in peptide chemistry.

The plausible mechanism for the deprenylation of prenyl ethers and esters is depicted in Scheme 2.

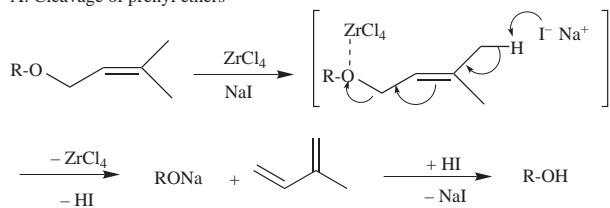
In conclusion, 20 mol% ZrCl₄ and NaI (1:1) in CH₃CN at reflux was found to be an effective reagent system for the deprenylation. The salient features of the present protocol are a) the reagent is catalytic (20 mol%), b) the reaction time is short, c) ethers and esters are cleaved, d) a variety of substrates and functional groups are resistant

Table 1 20 Mol% ZrCl₄-NaI (1:1) Catalyzed Deprotection of Prenyl Ethers

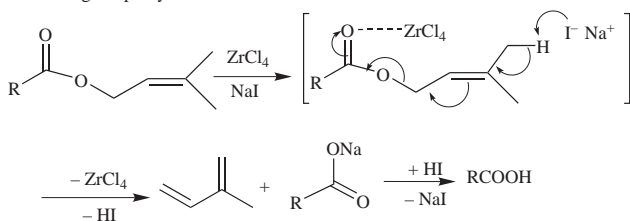
Entry	Starting material	Product ^a	Time (h)	Yield (%)
1			1.5	91
2			2	94
3			1.25	78
4			1.5	84
5			1.5	92
6			1	86
7			1	79
8			1.5	87
9			1.5	82
10			1.5	86

^a All the products were identified by IR, ¹H NMR, mass and TLC analysis with authentic samples.

A: Cleavage of prenyl ethers



B: Cleavage of prenyl esters

**Scheme 2**

and e) usefulness in peptide chemistry. Thus, the present method would find wide applications in organic synthesis for the selective deprotection of both prenyl ethers and esters.

Acknowledgment

Ch. G. Reddy acknowledges the financial support in the form of a fellowship from UGC, New Delhi.

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Table 2 20 Mol% ZrCl₄-NaI (1:1) Catalyzed Deprotection of Prenyl Esters

Entry	Starting material	Product ^a	Time (h)	Yield (%)
1			1.5	88
2			1	85
3			1.5	90
4			2	88
5			2	91
6			2	88

^a All the products were identified by IR, ¹H NMR, mass and TLC analysis with authentic samples.

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 (17) **General Experimental Procedure:** A stirred solution of the prenyl ether/ester (1 mmol) in CH₃CN (5 mL) was treated with ZrCl₄ (0.046 g, 0.2 mmol), NaI (0.03 g, 0.2 mmol) and heated at reflux until complete consumption of the starting material (TLC analysis). The solvent was removed under reduced pressure, the residue dissolved in EtOAc (2 × 10 mL) and washed with H₂O (2 × 10 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure to afford a crude product which on purification by column chromatography (silica gel, 60–120, EtOAc–hexane, 5:95) furnished alcohol/acid. Spectral data for selected compounds: Compound **4**: IR (neat): 1510, 1745, 2362, 2858, 2936 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.36–1.43 (m, 8 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.10 (s, 3 H), 3.57 (t, *J* = 6.5 Hz, 2 H), 3.88 (d, *J* = 4.7 Hz, 2 H), 4.05 (t, *J* = 6.4 Hz, 2 H), 5.29–5.32 (t, *J* = 6.5 Hz, 1 H). MS (EI): *m/z* (%) = 228 [M⁺]. Compound **8**: IR (neat): 1376, 1510, 1620, 2932, 2986 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.38 (s, 6 H), 1.42 (s, 3 H), 1.52 (s, 3 H), 1.68 (s, 3 H), 1.73 (s, 3 H), 3.87 (d, *J* = 4.6 Hz, 2 H), 4.03 (ddd, *J* = 4.0, 6.6 Hz, 1 H), 4.25 (ddd, *J* = 4.0, 4.5 Hz, 2 H), 4.32 (dd, *J* = 2.5, 5.1 Hz, 1 H), 4.39 (dd, *J* = 1.5, 8.0 Hz, 1 H), 4.61 (dd, *J* = 2.5, 8.0 Hz, 1 H), 5.28–5.31 (t, *J* = 6.5 Hz, 1 H) 5.52 (d, *J* = 5.1 Hz, 1 H). MS (EI): *m/z* (%) = 328 [M⁺]. Compound **6a**: IR (neat): 1260, 1510, 1590, 2920, 3515 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.36–1.64 (m, 8 H), 3.39–3.42 (t, *J* = 5.6 Hz, 2 H), 3.59–3.63 (t, *J* = 5.4 Hz, 2 H), 3.92 (d, *J* = 6.2 Hz, 2 H), 5.18–5.25 (m, 2 H) 5.84–5.86 (m, 1 H). MS (EI): *m/z* (%) = 158 [M⁺]. Compound **7a**: IR (neat): 1226, 1523, 2862, 2958, 3506 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.36–1.61 (m, 8 H), 1.72 (d, *J* = 6.4 Hz, 3 H), 3.37 (t, *J* = 6.5 Hz, 2 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 3.96 (d, *J* = 4.8 Hz, 2 H), 5.61 (m, 2 H). MS (EI): *m/z* (%) = 172 [M⁺]. Compound **15**: IR (neat): 1220, 1345, 1565, 1745, 2885, 2930 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 0.94–1.20 (m, 6 H), 1.77 (s, 3 H), 1.82 (s, 3 H), 2.18 (m, 1 H), 4.31 (m, 1 H), 4.61 (d, *J* = 6.6 Hz, 2 H), 5.14 (s, 2 H), 5.32 (t, *J* = 6.4 Hz, 1 H) 7.39 (m, 5 H). MS (EI): *m/z* (%) = 319 [M⁺], 252 [M⁺ – 69]. Compound **16**: IR (neat): 1225, 1350, 1545, 1750, 2865, 2935 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.22 (s, 9 H), 1.77 (s, 3 H), 1.81 (s, 3 H), 2.47 (t, *J* = 4.8 Hz, 2 H), 3.38 (t, *J* = 4.6 Hz, 2 H), 4.56 (d, *J* = 6.4 Hz, 2 H), 5.10 (br s, 1 H) 5.31 (t, *J* = 6.4 Hz, 1 H). MS (EI): *m/z* (%) = 258 [M⁺ + 1].