A Mild and Highly Selective Deprotective Method of Prenyl Ethers Using Ytterbium Triflate†

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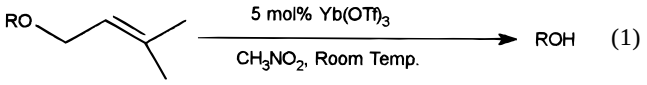
The correct choice of protecting groups[1] is often decisive for the realization of the overall operation of the total synthesis of complex natural products. Hence, a wide range of such groups are currently available for the different functional groups. The proposed use of an allylic protective group by Gigg[2] has paved the way for the related allyl groups[3] such as crotyl,[4] prenyl,[5] methallyl,[6] etc. The crotyl and prenyl groups are readily removed by base (t-BuOK, DMSO)[7] with concomitant isomerization of allylic protecting groups; hence, the difference in rates does not appear to be sufficient to allow good selectivities.[4] Herein, we describe a highly selective deprotection method for the prenyl protecting group in preference over the allyl and crotyl groups, by using $Yb(OTf)_3$ as Lewis acid catalyst.

Rare earth triflates[8] are versatile Lewis acids that have been employed in a number of reactions both in organic and aqueous media in catalytic quantities. Since the first utilization of $Yb(OTf)_3$ by Forsberg et al.,[9] it has found a wide utility in organic synthesis. In connection with our studies on the synthesis of calanolides (anti HIV active coumarins), we have observed a facile prenyl group deprotection, under the influence of a catalytic amount of $Yb(OTf)_3$ as a Lewis acid catalyst (eq 1). This acid-catalyzed deprenylation reaction has prompted us to undertake a study of the deprotection of prenyl and other relevant allyl groups.



(1)

R = Alkyl, aryl, carbohydrate units

Table 1

compd	time (h)	temp[a] (°C)	yield (%)
1	0.5	rt	79
2	2	rt	85
3	1	rt	90
4	12	rt	72
5	1	rt	74
6	24	rt	55
7	10	100	70
8	9	rt	85
9	2	rt	80
10	12	rt	55
11	2	rt	60
12	12	100	60

[a] rt = room temperature.

To start a general study, *p*-methoxyphenol was converted into prenyl, allyl, and crotyl ethers and these ethers were subjected to deprotection reaction using a catalytic (5 mol %) amount of $Yb(OTf)_3$ in CH_3NO_2 as solvent at room temperature. It was observed that only prenyl ether underwent a facile deprotection in 30 min, while both the allyl and crotyl ethers were unaffected even after 24 h. This observation is of immense importance due to (a) mild reaction conditions, (b) use of catalytic quantities (5 mol %) of acid reagent, and (c) unlike the base (t-BuOK) catalyzed reaction the present method using the acid, $Yb(OTf)_3$, is highly selective toward deprenylation.

Having established its high selectivity toward deprenylation, we prepared several prenyl ethers and subjected them to deprenylation (Figure 1). $Yb(OTf)_3$ smoothly cleaved both the aromatic as well as aliphatic prenyl ethers (**1**−**6**) in excellent yields. Similarly, the esters (**7** and **8**) also underwent smooth cleavage under the standard reaction conditions. These mild and general conditions were extended to carbohydrate-derived prenyl ethers (**9**−**11**) having acid sensitive acetonide groups, which gave the expected products. However, the exception for the generality was observed for the two substrates (**7** and **12**), where the reaction had to be performed at 100 °C instead of room temperature. All the results are summarized in Table 1.

Thus this reagent can be considered as a general deprenylating agent for aliphatic and aromatic as well as carbohydrate prenyl ethers. The added advantage of $Yb(OTf)_3$ is that it is highly selective for the prenyl ethers, while the other allylic groups such as crotyl and allyl are untouched. On the basis of this observation we propose that the coordination of Yb with ethereal oxygen (Figure 2), double bond migration, coordination of −OTf with the carbocation, and finally loss of H^+ from the methyl group to −OR would lead to smooth deprotection. This model also helps us in explaining the high selectivity observed for the prenyl group over the allyl and crotyl groups by the stability of the initially formed carbocation.

In conclusion, a mild, efficient, and highly selective prenyl deprotection method has been developed using Yb-

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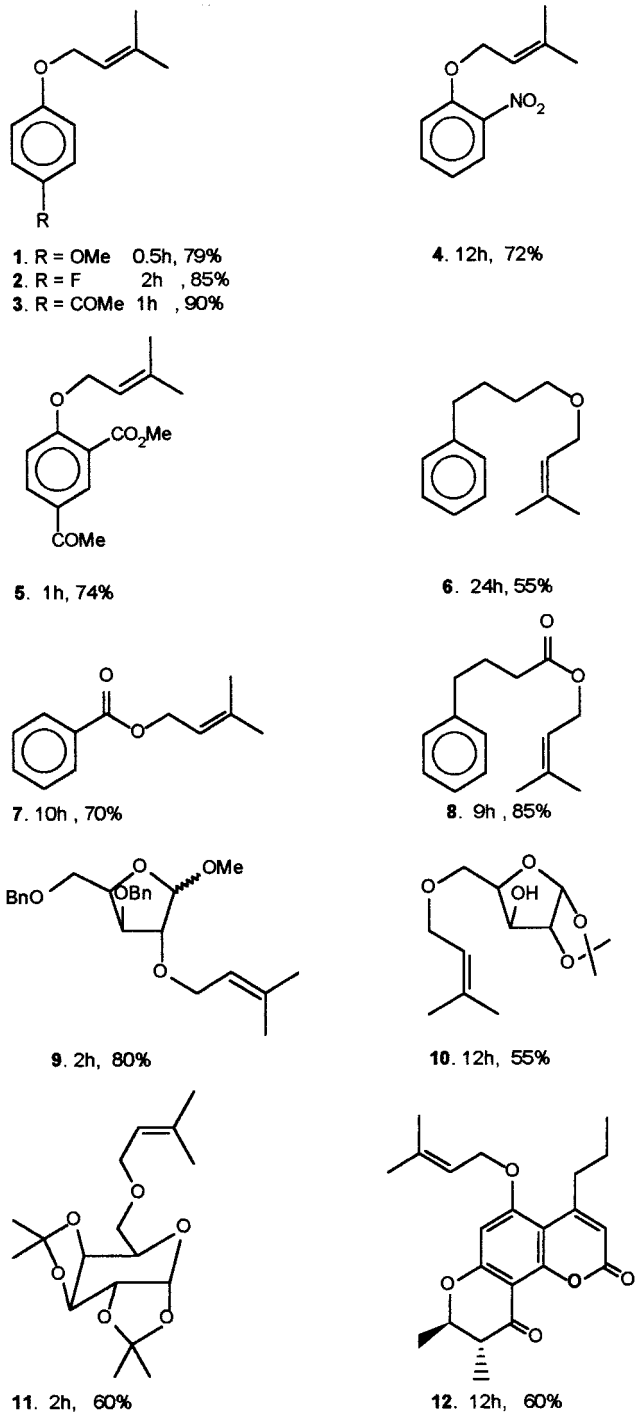

Figure 1. (a) All the compounds were characterized by ^{1}H NMR and IR data. (b) Reactions were carried out at room temperature except for **7** and **12** (100 °C). (c) Isolated yields are reported. (d) The prenyl ethers **1-8**, **10**, and **11** were prepared from the corresponding commercially available starting materials; **9** and **12** were prepared from the known alcohols.[10,11]

$(OTf)_3$ under catalytic conditions. The advantages of this method are easy accessibility, reusability of reagent, and high chemoselectivity as well as mild reaction conditions. This protocol should find widespread use in organic synthesis with a special reference to selective deprotection among the various allylic groups.

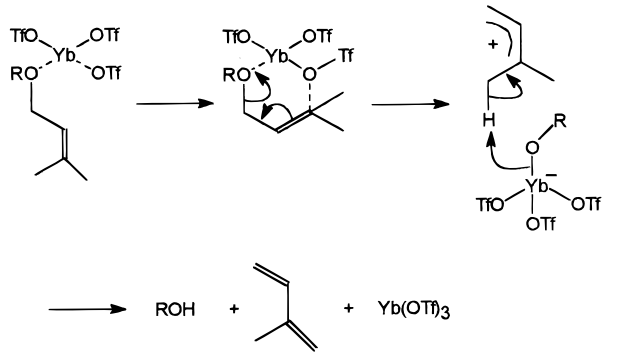

Figure 2.

Experimental Section

Typical Experimental Procedure for the Deprenylation with Yb(OTf)$_3$: A solution of substrate **3** (204 mg, 1.0 mmol) in nitromethane (2 mL) was treated with $Yb(OTf)_3$ (31 mg, 0.05 mmol) and stirred at room temperature. At the completion of reaction (TLC analysis), the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). Combined organic layers were washed with water (2 × 5 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the crude residue by column chromatography (silica gel, 7:3 hexane−ethyl acetate) gave p-acetyl phenol 90% yield.

^{1}H NMR spectral data for selected compounds (200 MHz, $CDCl_3$, TMS, δ in ppm): **3**, 1.75, 1.83 (2s, 6H), 2.54 (s,3H), 4.55 (d, 2H, *J* 7.3 Hz), 5.47 (t, 1H, *J* 6.0 Hz), 6.90 (d, 2H, *J* 7.3 Hz), 7.90 (d, 2H, *J* 7.3 Hz); **5** (mp 51−52 °C), 1.75, 1.85 (2s, 6H), 2.58 (s, 3H), 3.90 (s, 3H), 4.70 (d, 2H, *J* 6.0 Hz), 5.50 (t, 1H, *J* 5.3 Hz), 6.98 (d, 2H, *J* 7.3 Hz), 8.07 (dd, 1H, $J_{1,3}$ 8.0 Hz, $J_{1,2}$ 2.0 Hz), 8.30 (d, 1H, *J* 2.6 Hz); **8**, 1.68, 1.75 (2s, 6H), 1.85−2.03 (m, 2H), 2.30 (t, 2H, *J* 6.7 Hz), 2.63 (t, 2H, *J* 6.7 Hz), 4.55 (d, 2H, *J* 7.3 Hz), 5.30 (t, 1H, *J* 4.8 Hz), 7.10−7.30 (m, 5H); **10** ($[\alpha]_D$ −41.5° (*c* 1.0, $CHCl_3$)), 1.30, 1.45, 1.69, 1.78 (4s, 12H), 3.75−3.93 (m, 3H), 3.95−4.15 (m, 1H), 4.17−4.25 (m, 2H), 4.56 (d, 1H, *J* 3.3 Hz), 5.28 (t, 1H, *J* 5.5 Hz), 5.90 (d, 1H, *J* 2.8 Hz); **12** (mp 152−153 °C), 0.97 (t, 3H, *J* 6.1 Hz), 1.22 (d, 3H, *J* 5.6 Hz), 1.53 (d, 3H, *J* 5.6 Hz), 1.79, 1.85 (2s, 6H), 2.5 (m, 1H), 2.80 (t, 2H, *J* 6.7 Hz), 4.25 (m, 1H), 4.59 (d, 1H, *J* 6.1 Hz), 5.50 (t, 1H, *J* 5.6 Hz), 6.0 (s, 1H), 6.25 (s, 1H).

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Supporting Information Available: NMR spectra (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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