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Detritylation with ytterbium triflate

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Abstract

Ytterbium triflate catalyzes the hydrolysis of tritylamines and trityloxy compounds to the corresponding amines and alcohols under mild conditions in high yields. The reactions are conducted in tetrahydrofuran in the presence of 1 equivalent of water. © 2000 Elsevier Science Ltd. All rights reserved.

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Trityl and related groups have been used extensively for *N*- and *O*-protection, where detritylation is accomplished either with a protonic acid (e.g. HCl, CF₃CO₂H, CCl₃CO₂H) or a Lewis acid (e.g. ZnBr₂, diisopropylaluminum chloride).^{1–11}

As part of our work on the synthesis of new electrophoric reagents, we observed that *N*-trityl-β-{*p*-[3',5'-bis(trifluoromethyl)benzyloxy]phenyl}ethylamine **1** resisted detritylation under various conditions ordinarily effective for this purpose, such as 1N HCl in ethanol, as summarized in Table 1. However, compounds **2–5** underwent facile detritylation under this latter condition. We speculated that the nonpolar environment around the nitrogen in **1** might explain the aberrant behavior of this compound, since this might make it resist *N*-protonation.

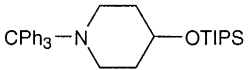
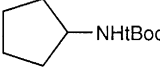
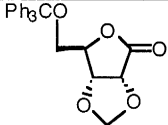
Accordingly, we tested compounds **6** and **7**, where we considered that the major difference between them might be that **6**, possessing an *o*-methoxy substituent, would provide a more polar environment around the *N*-trityl group. While not confirming our hypothesis (e.g. H-bond and inductive differences may exist), the compounds did behave as anticipated, with **6** and **7** undergoing 95 and 0% detritylation, respectively, in ethanolic 1N HCl. Compound **7** also resisted detritylation under some other conditions known to accomplish this kind of reaction, as summarized in Table 1.

Returning to our goal of detritylating **1**, we tested ytterbium triflate as a Lewis acid for this purpose, motivated by the following three considerations: (1) the reagent is known to be a Lewis acid catalyst;¹² (2) the reagent might bring in a polar environment; and (3) Yb has a relatively small radius in the lanthanide series.¹³ Indeed, when we reacted **1** at room temperature with a catalytic amount (0.15 mol equivalent) of

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Table 1
 Detritylation reactions^a

Compound	Structure	Reagent	Solvent	Yield ^b (%)
1	$\text{Ph}_3\text{CNHCH}_2\text{CH}_2$ -  - $\text{OCH}_2\text{C}_6\text{H}_3(\text{CF}_3)_2$	1NHCl $\text{CF}_3\text{CO}_2\text{H}$ $\text{Yb}(\text{OTf})_3$ $\text{Eu}(\text{OTf})_3$	EtOH EtOH THF THF	0 0 89 78
2	$\text{Ph}_3\text{CNHCH}_2\text{CON}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_3-3',5'-(\text{CF}_3)_2$	1NHCl $\text{Yb}(\text{OTf})_3$	EtOH THF	98 94
3	$\text{Ph}_3\text{CNHCH}_2\text{CONHCH}_2\text{C}_6\text{H}_3-3',5'-(\text{CF}_3)_2$	1NHCl $\text{Yb}(\text{OTf})_3$	EtOH THF	97 93
4	$\text{Ph}_3\text{CNHCH}_2\text{COOCH}_2\text{C}_6\text{H}_3-3',5'-(\text{CF}_3)_2$	1NHCl $\text{Yb}(\text{OTf})_3$	EtOH THF	95 95
5	$\text{Ph}_3\text{CNHCH}_2\text{COOCH}_2\text{C}_6\text{F}_5$	1NHCl $\text{Yb}(\text{OTf})_3$	EtOH THF	96 94
6	<i>o</i> - $\text{Ph}_3\text{CNHCH}_2\text{C}_6\text{H}_4\text{OCH}_3$	1NHCl	EtOH	95
7	$\text{Ph}_3\text{CNHCH}_2\text{C}_6\text{H}_5$	1NHCl $\text{CF}_3\text{CO}_2\text{H}$ $\text{CCl}_3\text{CO}_2\text{H}$ ZnCl_2 $\text{Yb}(\text{OTf})_3$ $\text{Eu}(\text{OTf})_3$ $\text{CF}_3\text{SO}_3\text{H}$ $\text{Ti}(\text{OPr-}i)_4$	EtOH EtOH EtOH THF THF THF THF THF	0 0 0 0 93 89 30 21
8	<i>p</i> - $\text{CH}_3\text{COC}_6\text{H}_4\text{CH}_2\text{OCPh}_3$	$\text{Yb}(\text{OTf})_3$	THF	90
9	$\text{C}_6\text{H}_5\text{CH}_2\text{OCPh}_3$	$\text{Yb}(\text{OTf})_3$	THF	92
10		$\text{Yb}(\text{OTf})_3$	THF	89 ^c
11		$\text{Yb}(\text{OTf})_3$	THF	0 ^d
12		$\text{Yb}(\text{OTf})_3$	THF	94 ^e

a: 15% Catalytic amount of trityl compound with 1 equivalent of water; b: Isolated yields; c: with TIPS intact; d: with N-t-Boc intact; e: with acetal intact.

$\text{Yb}(\text{OTf})_3$ in tetrahydrofuran containing 1 equivalent of water, the yield of detritylated product was 89%. Since the yield dropped to 78% when europium triflate was used instead, the smaller size of ytterbium might have helped. Also shown in Table 1 is the success of these reagents in detritylating **7**, as well as three *O*-trityl compounds (**8**, **9**, **12**). We also detritylated **2–5** with $\text{Yb}(\text{OTf})_3$ in high yields as seen.

It has been reported that ytterbium triflate is stable to water,¹² which argues against a mechanism in which the added water reacts with this reagent to produce trifluoromethanesulfonic acid as the true catalyst. Consistent with this, there was no hydrolysis of the formylidene acetal, an acid-sensitive group, in **12**. 4-(Triisopropylsiloxy)-*N*-tritylpiperidine **10** was detritylated (89%) without TIPS loss, and the

N-*t*-Boc compound **11** was stable. Nevertheless, we observed that **1** underwent 30% detritylation when treated with triflic acid.

In summary, we have developed a mild and efficient detritylation reaction that is effective both in general and also when applied to nonpolar compounds resistant to conventional detritylation conditions.¹⁴

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- The deprotection of compound **1** is representative of our method. To *N*-trityl- β -{*p*-[3',5'-bis(trifluoromethyl)benzyl-oxy]phenyl}ethylamine (605 mg, 1 mmol) in 5 ml THF was added 93 mg (0.15 mmol) of ytterbium triflate. After stirring at rt for 10 min under N₂, the mixture was treated with 20 μ L H₂O and stirred for a further 4 h. Saturated, ice-cold NaHCO₃ (15 ml) was added and the combined (3 $\times$ 25 ml) ethyl acetate extracts were washed with brine (3 $\times$ 10 ml) and dried over Na₂SO₄. Purification by flash chromatography with ethyl acetate:hexanes:triethyl amine (1:1:0.1) gave 323 mg (89%) of a white solid. ¹H NMR (CDCl₃), δ 2.15–2.17 (2H, t, CH₂), 2.74–2.78 (2H, m, CH₂), 2.92 (2H, b, NH₂), 5.13 (2H, s, OCH₂), 6.91–7.17 (4H, q, Ar) 7.83–7.90 (3H, q, Ar).