Highly selective deprotection of tert-butyl esters using ytterbium triflate as a catalyst under mild conditions

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Ytterbium triflate catalyses the deprotection of tert-butyl esters selectively in the presence of other esters under mild conditions in almost quantitative yields. The reactions are carried out in nitromethane (45°C - 50°C) using 5 mole percent of the catalyst.

The tert-butyl group is one of the most commonly used protecting groups for carboxylic acids in organic synthesis. Due to its steric hindrance, this group is stable under normal alkaline conditions. Trifluoroacetic acid is used very often as the deprotecting reagent. Recently there is a report on the use of ZnBr₂ for the deprotection of tert-butyl esters. But in most of the cases a large excess of the reagent has been used for the deprotection and there are hardly a few methods known for selective deprotection of tert-butyl esters.

Ytterbium triflate has been found to be a mild and useful Lewis acid catalyst for a number of reactions in the literature. We have developed a simple procedure for the selective deprotection of tert-butyl group of carboxylic esters using ytterbium triflate, 1 as a catalyst and the results are presented in Table I.

The tert-butyl esters of carboxylic acids were prepared either by using isobutylene gas or isourea method. When tert-butyl benzoate was treated with a catalytic amount (5 mole %) of ytterbium triflate 1 in nitromethane (45°C-50°C), a clean deprotection occurred within 6 hr in excellent yield. In the case of meta-methoxy-tert-butylbenzoate a facile deprotection was observed under similar reaction conditions and the free acid was obtained in 98% yield (entry 2).

Next we examined the rate of the reaction on the substitution pattern of the phenyl ring. Interestingly compounds bearing electron donating group are less reactive than the compounds bearing electron withdrawing groups (entries 3 and 4).

Our methodology worked well for the selective cleavage of tert-butyl ester in the presence of benzyl, allyl, methyl and propargyl esters. In all these cases the mono esters were obtained in excellent yields (entries 5-8). When tert-butylmandelate derivative was treated with the catalyst 1 under similar conditions, the deprotected acid was obtained in excellent yield with no loss of optical purity (based on optical rotation) (entry 9). The deprotection of the tert-butyl esters could also be carried out successfully using recovered catalyst. Recently there was a report on N-detritylation with ytterbium triflate in THF-H₂O mixture. Therefore an attempt was made for the deprotection of trityl ester in nitromethane in presence of 1 but surprisingly there was no reaction and the starting material was recovered completely (entry 10).

Next we tried our methodology for the deprotection of tert-BOC group in amino acids. The results are summarised in Table II. The reaction of Boc-phenylalanine with 1 was very slow but the amino acid could be obtained in excellent yield (entry 1). However, in the case of Boc-proline derivative the reaction did not occur even after a long period of time (24 hr) with 10 mole % of catalyst (entry 2). Even when the reaction was carried out with 1 under conditions which effects N-detritylation no appreciable deprotection of this substrate could be observed. The possible reason for this may be the generation of free NH₂ which inactivates the catalyst. Keeping this in mind, this methodology was then extended to the study of deprotection of tert-butyl esters of amino acid derivatives.

The tert-butyl esters of amino acids in which amino terminal was protected with benzoxycarbonyl (Z) (entries 3-5) and fluorenylmethoxycarbonyl (Fmoc) (entries 6-7) were treated with the 1 and the corresponding carboxylic acids were isolated in almost quantitative yields. Not even a trace of N-deprotected compounds could be detected under the reaction conditions.

We also made an attempt for the selective deprotection of tert-butyl ester in presence of tert-butyl ether. 4-(tert-Butoxy)-tertiarybutylbenzoate was treated with 1 at 50°C. Unfortunately no selectivity was observed and both the protective groups were cleaved within 6 hours.
Table I—Yterbium triflate catalysed deprotection of tert-butyl esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (hr)</th>
<th>Product</th>
<th>Yield (&lt;sup&gt;b&lt;/sup&gt;)</th>
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<tr>
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<td>6</td>
<td>OOH</td>
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<tr>
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<tr>
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<tr>
<td>10</td>
<td>ORR₁</td>
<td>24</td>
<td>no reaction</td>
<td>—</td>
</tr>
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</table>

<sup>a</sup> R=tert-butyl, R₁=trityl.  
<sup>b</sup> Yield refers to pure, isolated products.
In summary, we have developed a mild and efficient methodology for the selective cleavage of tert-butyl esters using ytterbium triflate which is environmentally friendly and is reusable. Moreover under the reaction conditions other types of ester protective groups are unaffected.

**Typical experimental procedure:** A mixture of tert-butyl benzoate (0.200 g, 1.12 mmole) and ytterbium triflate (5 mole%, 35 mg) was taken in nitromethane (3 mL) and the reaction mixture was heated at 45-50°C for 6 hr. The solvent was removed under vacuum and ether (5 mL) was added to the mixture. It was then filtered through a pad of Celite and removal of solvent and recrystallisation of the residue yielded benzoic acid as a white solid m.p 121°C (0.136 g, 99%).

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**References**