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Chemoselective hydrolysis of *tert*-butyl esters in acetonitrile using molecular iodine as a mild and efficient catalyst

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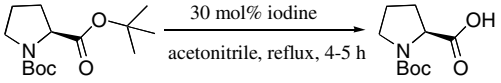
Abstract—A simple, mild and efficient method for the hydrolysis of *tert*-butyl esters using molecular iodine as a catalyst is described. Acid labile protecting groups, such as *N*-Boc, OBn, OAc and double bonds, are compatible under the reaction conditions.

The *tert*-butyl ester group is a versatile protecting group for carboxylic acids. Since this group is stable at most mild basic conditions, it is a useful tool in the synthesis of amino acids, peptides and natural products.[1] Further, the *tert*-butoxycarbonyl (Boc) group is mainly used for the protection of amines. Hydrolysis of a *tert*-butyl ester group in the presence of Boc and vice versa are frequently encountered requirements in peptide and amino acid synthesis. Although several methods have been reported for the selective deprotection of *N*-Boc in the presence of *tert*-butyl esters,[2] chemoselective deprotection of a *tert*-butyl ester group in the presence of *N*-Boc is still a challenging task. Strong protic acids,[1] such as HCl, TFA, H_2SO_4[3a] and HNO_3,[3b] are reported for *tert*-butyl ester hydrolysis in aqueous and organic solvents with varying chemoselectivity. In aqueous conditions, these reagents cleave all acid labile protecting groups, whereas in organic solvents the *N*-Boc group can be selectively removed, for example, by using H_2SO_4 in *tert*-butyl acetate[2a] and 1 M HCl in ethyl acetate.[2c] In contrast, H_2SO_4 in CH_2Cl_2[3b] and HNO_3 in CH_2Cl_2[3c] have also been recently reported for the hydrolysis of *t*-butyl esters as well as *N*-Boc groups. Apart from these protic acid reagents, various other Lewis acids, such as $TiCl_4$,[4] silyl triflates,[5] silica gel in toluene,[6] $ZnBr_2$ in CH_2Cl_2[7,8] and $CeCl_3{\cdot}7H_2O$–NaI in acetonitrile,[9] have been reported for this hydrolysis. To the best of our knowledge, $ZnBr_2$ in CH_2Cl_2[7] and $CeCl_3{\cdot}7H_2O$–NaI in acetonitrile are the only reported methods for the selective hydrolysis of *tert*-butyl esters in the presence of *N*-Boc protection. However, many of the above mentioned methods suffer from disadvantages, such as strong acidic conditions, long reaction times and unsatisfactory yields. Therefore, there is still a need for a general method for *tert*-butyl ester hydrolysis in the presence of Boc protection.

Elemental iodine has been found to catalyse a number of organic transformations and there have been many reports in the literature using iodine as a Lewis acid.[10] Previously we reported an efficient clay[11] catalysed hydrolysis of *tert*-butyl esters. In continuation of our efforts to develop new methods using iodine as a catalyst for different organic conversions,[12] herein we report a mild and convenient method for the chemoselective hydrolysis of *tert*-butyl esters.

In a typical experimental procedure, the *tert*-butyl esters derived from different aromatic carboxylic acids and *N*-Boc-protected amino acids were taken in acetonitrile to which 30 mol % iodine and 40 μL water were added and the resulting mixture refluxed. Hydrolysis of the *tert*-butyl esters took place within 4–5 h (Scheme 1). A variety of substrates were amenable to the reaction conditions, and good to high yields of the corresponding carboxylic acids were obtained. No reaction was



Scheme 1.

Keywords: *tert*-Butyl esters; *tert*-Butoxycarbonyl; Molecular iodine; Chemoselective hydrolysis.
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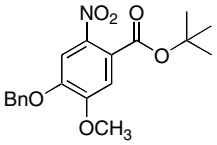
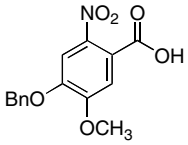
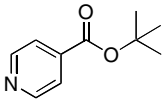
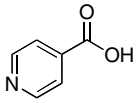
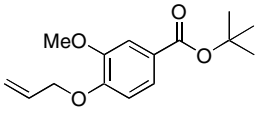
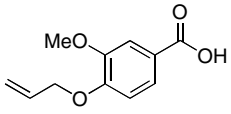
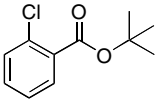
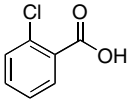
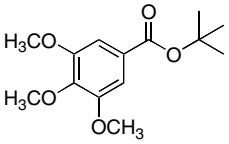
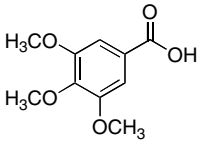
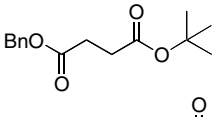
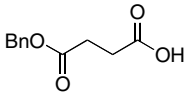
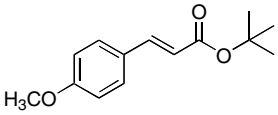
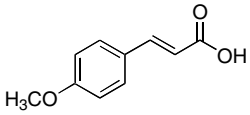
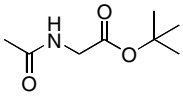
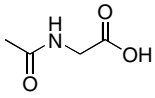
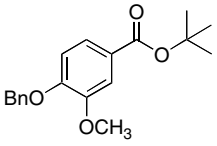
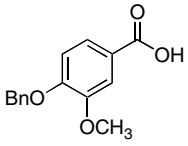
Table 1. Iodine catalysed *tert*-butyl ester hydrolysis

Entry	Substrate (**1**)	Product[a] (**2**)	Time (h)	Yield[b] (%)
a			3	89
b			4	92
c			4	87
d			4	85
e			3	82
f			3	89
g			4	86
h			3	90
i			3	85

[a] All products were characterised by ^{1}H NMR and mass spectroscopy.
[b] Yield of isolated product.

observed in the absence of either iodine or water. To check the generality of this reagent system, we reacted a number of *tert*-butyl esters with different steric properties and potentially reactive functionalities (Tables 1 and 2). Acid labile groups, such as OBn, OMe, OAc, double bonds, and chloro and nitro substituents, were unaffected under the reaction conditions.

The chemoselectivity of this reaction was also explored with Boc-protected amino acid *tert*-butyl esters. The hydrolysis of esters occurred smoothly without affecting the *N*-Boc protection. It is evident from Table 2, that the Boc-protected amino acids were obtained in high yields after hydrolysis, supporting the mild nature of this reagent.

The possible reason for the ester hydrolysis is the release of hydrogen iodide (HI) in the presence of water in the reaction medium. It is known that *tert*-butoxycarbonyl (Boc) groups can be removed in refluxing acetone in the presence of NaI.[13] Cleavage of Boc groups was proposed to occur due to the liberation of HI in situ.[14] In comparison, iodine in refluxing acetonitrile is very mild such that it does not lead to *N*-Boc deprotection.

In conclusion, we have shown[15] that the use of molecular iodine is a novel alternative for *tert*-butyl ester hydrolysis, especially in the presence of *N*-Boc protection. The operational simplicity, good availability, high yields and mild nature of the reagent makes this procedure a useful addition to the existing methods.

Table 2. Iodine catalysed hydrolysis of *tert*-butyl ester in the presence of Boc

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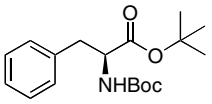
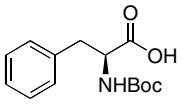
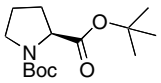
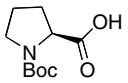
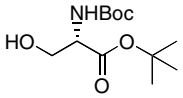
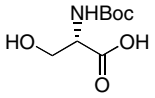
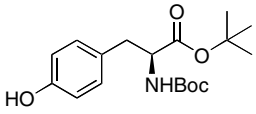
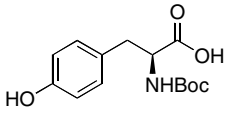
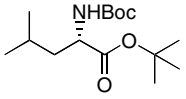
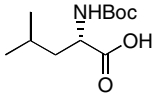
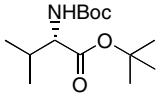
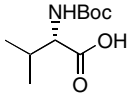
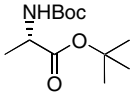
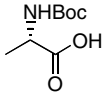
a			5	89
b			5	92
c			4	87
d			5	85
e			6	82
f			5	89
g			5	86

[a] All products were characterised by ^{1}H NMR and mass spectroscopy.
[b] Yield of isolated product.

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15. Experimental procedure: Iodine (30 mol %) was added to a solution of *N*-Boc proline *tert*-butyl ester (**3b**, 0.5 mmol) in acetonitrile (2 mL) and after adding water (40 μL) the reaction was stirred at reflux for 5 h. After complete conversion as indicated by TLC, the reaction mixture was diluted with aqueous $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through silica gel (Merck, 100–200 mesh) using hexane–ethyl acetate (2:8) to afford pure *N*-Boc proline (**4b**) in 92% yield. *Spectral data*: (**4b** Table 2): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.40 (d, $J = 8.85$ Hz, 9H), 1.78–2.04 (m, 3H), 2.10–2.30 (m, 1H), 3.28–3.54 (m, 2H), 4.04–4.18 (td, $J = 3.68$ Hz, 1H); Compound (**4c**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.45 (s, 9H), 3.70 (dd, $J = 3.68$ Hz, $J = 11.06$ Hz, 1H), 3.85 (dd, $J = 3.68$ Hz, $J = 11.06$ Hz, 1H), 4.03–4.13 (m, 1H), 6.04 (d, $J = 7.37$ Hz, 1H).