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A novel practical cleavage of *tert*-butyl esters and carbonates using fluorinated alcohols

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ABSTRACT

Thermolytic cleavage of *t*-butyl esters and *t*-butyl carbonates was accomplished using TFE (2,2,2-trifluoroethanol) or HFIP (hexafluoroisopropanol) as solvent. Thus, a practical method to cleanly convert *t*-butyl esters and carbonates into the corresponding carboxylic acids, decarboxylated products, or alcohols in nearly quantitative yields was developed. The product is recovered by a simple solvent evaporation. The practicality of this methodology was demonstrated on alkyl, aryl, and heteroaromatic esters.

Among various protecting groups for carboxylic acids, the *tert*-butyl (*t*-Bu) group is perhaps the most widely used due to its exceptional stability toward a variety of reagents and reaction conditions.[1] As a result, cleavage of the *t*-butyl group on esters remains to be of prime importance in organic synthesis. Deprotection of *t*-butyl esters is generally achieved by employing strong protic acids such as trifluoroacetic and hydrochloric acids[1,2], or Lewis acid-catalyzed conditions using $ZnBr_2$[3a], $CeCl_3$[3b], and SiO_2.[3c] In certain circumstances, highly activated *t*-butyl esters can be cleaved under basic conditions using LiOH.[3d] Methods involving the thermolytic neat-cleavage (>200 °C) of *t*-butyl esters have also been reported[4], but these are very harsh conditions for many substrates.

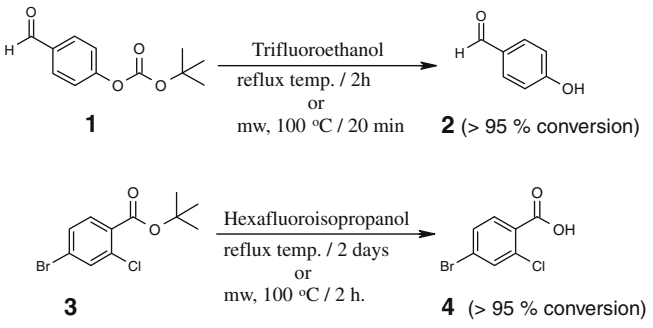
Similarly, *t*-butyl carbonates, which are more reactive than *t*-butyl esters, can be deprotected using trifluoroacetic acid[3g] or hydrochloric acid.[1b] On the other hand, basic conditions using KOH[1b] or Na_2CO_3[3e,3f] to give the corresponding alcohols have been also reported. Additionally, the cleavage of both the *t*-butyl carbonates and *t*-butyl esters has been achieved with the use of relatively mild TMSOTf-lutidine conditions.[5]

Because each of these methods requires the use of specific reagents and/or suffers drawbacks due to substrate sensitivity to acids, attempts to find alternative practical conditions are still desirable. Herein, we report a practical method to cleanly convert *t*-butyl esters and carbonates into the corresponding carboxylic acids, decarboxylated products, or alcohols in high yields.

We reported recently a new method to deprotect N-Boc-amines using 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) as a solvent in quantitative yields.[6] We now wish to report the expansion of this methodology to the cleavage of *t*-butyl esters and carbonates. The reaction conditions are neutral and do not require additional reagents apart from the solvent. Thus, the product is recovered by simple solvent evaporation without any work up and, in some cases, no further purification is needed.

Compared to other solvents, TFE (bp = 73 °C) and HFIP (bp = 58 °C) are unique due to their high ionizing powers, strong hydrogen bond donor abilities, mild acidic characters (pK_a = 12.4 and pK_a = 9.3, respectively)[7], and low nucleophilicity for transesterification. These outstanding features encouraged us to explore their use in the cleavage of *t*-butyl esters and carbonates. Initially, the cleavages were conducted at the solvent reflux temperature. Although the deprotection process was successful under these conditions, long reaction times were often required (Scheme 1). In order to shorten the reaction times, the cleavages were also examined under microwave-assisted conditions[8] and the results are shown in Scheme 1. These results suggest that although microwave heating is not essential in this process, the reactions are significantly accelerated with this protocol.

In an effort to explore the role of the solvent in this deprotection process, *tert*-butyl ester **3** was subjected to experiments in different solvents. Thus, TFE and HFIP were replaced with solvents such



Scheme 1.

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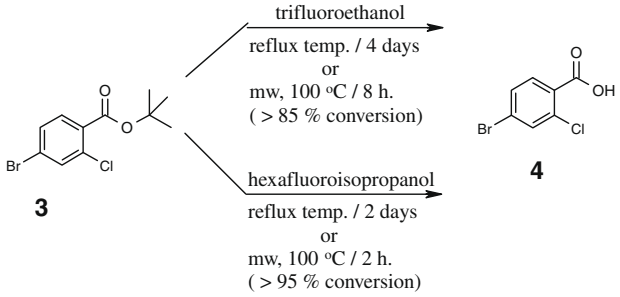
as chloroform, acetone, acetonitrile, and tetrahydrofuran under the same conditions as those indicated in Scheme 1 (microwave, 100 °C/2 h). Using these solvents or neat conditions, unreacted *tert*-butyl ester **3** was cleanly recovered in most cases, and the formation of product **4** was not detected by NMR. When non-fluorinated alcohols such as MeOH and EtOH were used as solvents, the unreacted *tert*-butyl ester **3** was again the main component in the resulting crude mixture with some of the deprotected product (<10% by NMR). Furthermore, in these cases the corresponding methyl or ethyl esters were also observed as side products.

In order to study the generality and scope of this methodology, the deprotection of a series of alkyl, aryl, and heteroaromatic *t*-butyl esters and carbonates was initiated. First, the deprotection of a series of *t*-butyl carbonates was performed, varying the nature of the substituents on the Boc-hydroxy moiety. In all cases, the product was obtained in essentially quantitative yields; the results are summarized in Table 1. It was confirmed that these reaction conditions are compatible with silicon-protecting groups such as –OTBDMS (Table 1, entry 5). More importantly, compounds that are sensitive to typical acidic conditions, such as compounds **5** and **7** gave the corresponding deprotected product in excellent yields (Table 1, entry 2 and 3). It is reported in the literature[9] that the use of trifluoroacetic acid (TFA) on substrate **5** gives a 6:4 mixture of the desired product **6** and 4-*t*-butyl-2,6-dimethylphenol as a side product. These results suggest that our conditions suppress the side reactions produced by *tert*-butyl cation formation.

For the cleavage of *tert*-butyl esters it was found that HFIP is a better solvent than TFE. Thus, the use of HFIP over TFE as a solvent on the same substrate under similar conditions consistently reduced the reaction times (Scheme 2).

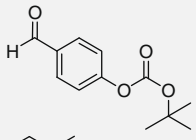
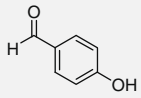
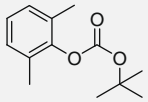
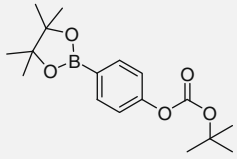
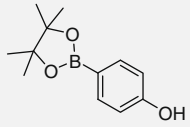
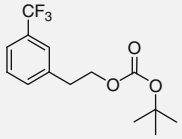
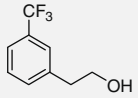
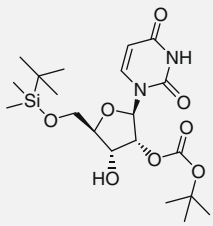
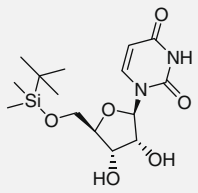


Scheme 2.

In general, the cleavage of *t*-butyl esters using HFIP under microwave-assisted conditions proceeds cleanly; the results are shown in Table 2. In all cases, the corresponding carboxylic acids[10] were obtained in excellent yields. In appropriately functionalized substrates such as entries 4 and 5 (Table 2), subsequent decarboxylation of the acid intermediate occurred readily under the reaction conditions.

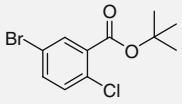
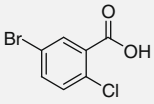
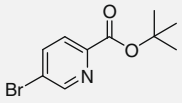
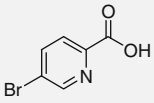
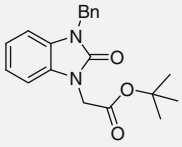
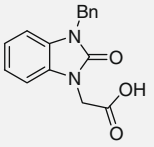
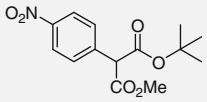
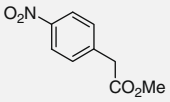
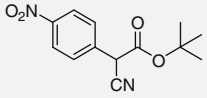
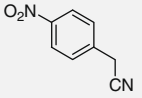
In summary, a practical and high-yielding method for the cleavage of *t*-butyl esters and *t*-butyl carbonates using TFE or HFIP has been discovered. Under this protocol, the product is isolated by simple solvent evaporation and minimal work up conditions. These conditions are compatible with other protecting groups such as –OTBDMS, –OBn, and with other functional groups such as boronic esters and aldehydes. This methodology can be also utilized on substrates that are sensitive to deprotection under typical acidic conditions (TFA or HCl).

Table 1
Deprotection of various *t*-butylcarbonates using TFE as a solvent under microwave-assisted conditions at 100 °C[11]

Entry	*t*-Butylcarbonate		Time (h)	Product		Yield[a] (%)
1		**1**	0.5		**2**	98
2		**5**	1		**6**	96[b]
3		**7**	1		**8**	96
4		**9**	1		**10**	95[b]
5		**11**	1		**12**	97

[a] Isolated yield.
[b] Calculated by NMR of the crude (product has low boiling point).

Table 2
Cleavage of various *t*-butyl esters using HFIP as a solvent under microwave-assisted conditions[12]

Entry	*t*-Butylester		Temp/Time (h)	Product		Yield[a] (%)
1		**3**	100 °C/2		**4**	96[a]
2		**13**	100 °C/3		**14**	95
3		**15**	100 °C/2		**16**	85[b]
4		**17**	100 °C/4 or 150 °C/1		**18**	82 71
5		**19**	100 °C/1		**20**	96

[a] Isolated yield.
[b] Estimated yield by NMR.

Acknowledgments

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11. *Typical experimental procedure for the cleavage of t-butyl-carbonates*: A solution of the *t*-butylcarbonate **1** (0.222 g, 1 mmol) in TFE (2,2,2-trifluoroethanol) (5 mL) was placed in a sealed microwave vial. The reaction mixture was heated at 100 °C in a Biotage—Initiator™ Sixty microwave until the complete disappearance of the starting material. After cooling to room temperature, the mixture was evaporated to dryness under reduced pressure to provide the pure product **2**; mp 115–117 °C (lit.[10c] 113–117 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (br s, 1H), 6.99 (d, J = 8.59 Hz, 2H), 7.83 (d, J = 8.59 Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.24, 161.59, 132.53, 129.90, 116.03; MS-ESI: m/z (%) 123 ($M+H^+$, 100); Anal. Calcd for $C_7H_6O_2$: C, 68.85; H, 4.95. Found: C, 68.84; H, 4.87.
12. *Typical experimental procedure for the cleavage of t-butyl-esters*: A solution of the *t*-butyl ester **3** (0.291 g, 1 mmol) in HFIP (hexafluoroisopropanol) (5 mL) was placed in a sealed microwave vial. The reaction mixture was heated to 100 °C (see Table 2) in a Biotage—Initiator™ Sixty microwave instrument until the complete disappearance of the starting material. After cooling to room temperature, the mixture was evaporated to dryness under reduced pressure to provide the pure product **4**; mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (dd, J = 8.69, 1.89 Hz, 1H), 7.74 (d, J = 8.31 Hz, 1H), 7.85 (d, J = 1.89 Hz, 1H), 13.59 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 165.93, 132.99, 132.86, 132.41, 130.55, 130.39, 125.02; MS-ESI: m/z, 233 ($M-H)^-$; Anal. Calcd for $C_7H_4BrClO_2$: C, 35.71; H, 1.71. Found: C, 35.83; H, 1.42.