A New, Practical and Efficient Method for Protecting Alcohols as *tert*-Butyl Ethers

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Abstract: A new method for protecting alcohols as *tert*-butyl ethers is reported. The reaction is performed in *tert*-butyl acetate in the presence of a catalytic amount of $HClO_4$. The process is extremely efficient and primary and secondary alcohols as well as diols are protected under very mild conditions. Remarkably, *tert*-butyl acetate can be easily recovered after the workup of the reaction and recycled.

Key words: protecting groups, *tert*-butyl ethers, alcohols, *tert*-butyl acetate

The *tert*-butyl ether is reported to be 'one of the most underused alcohol protecting groups'.[1] Traditionally, alcohols can be protected as their *tert*-butyl ethers through either of two commonly used procedures; in both cases, a *tert*-butyl carbocation intermediate is generated either from isobutylene or *tert*-butyltrichloroacetimidate, in the presence of a strong mineral or Lewis acid catalyst. Although the use of isobutylene generally leads to the formation of clean products in high yields, the requirement for gas to be bubbled through substrate solutions for long periods of time is often an unattractive option. The use of *tert*-butyltrichloroacetimidate as an alternative is, instead, costly and, although the reagent can be easily prepared in a work day,[2] its use for large amounts of substrate is not appealing because of the atom waste in the form of trichloroacetamide. Moreover, chromatographic purification from residual trichloroacetamide is often difficult. In both cases, the presence of a strong mineral or Lewis acid catalyst is mandatory for successful conversions and this can hamper the application of these methodologies to the protection of tertiary alcohols and phenols; furthermore, in some cases, even the protection of secondary alcohols is unsatisfactory. Recently, Bartoli et al.[3] reported an interesting alternative to the procedures mentioned above: in their approach, Boc_2O was used as a *tert*-butyl source and anhydrous $Mg(ClO_4)_2$ as a catalyst – these mild conditions were found to be compatible with many functional groups.

The *tert*-butyl ether moiety has somewhat unusual features as a protecting group: it is one of the few types of ether that is stable under strong basic conditions, it can be easily removed, and its bulkiness could play a crucial role in stereoselective syntheses.[4]

In the course of a project aimed at the stereoselective synthesis of *cis* and *trans* 4-hydroxypipecolic acid,[4c] we came across unexpected difficulties in the protection of 4-cyano-3-hydroxybutyric acid ethyl ester (Table 1, entry 6) as its *O*-*tert*-butyl ether in the early stages of the synthesis. Both traditional methodologies gave low conversions, whereas the procedure proposed by Bartoli et al.[3c] required the use of a large excess of Boc_2O due to its decomposition through a competing reaction – conditions that we preferred to avoid in view of future large-scale applications. Furthermore, the latter procedure is not appropriate for substrates containing a free amino group which, in principle, can be converted into a *N*-Boc derivative. Therefore, for the generation of the *tert*-butyl cation, we decided to apply experimental conditions known to lead to the esterification of carboxylic acids.[5] We thus added a catalytic amount (0.1 equiv) of $HClO_4$ to a solution of our secondary alcohol in *tert*-butyl acetate at 25 °C, and were delighted to observe the complete conversion of the substrate into the corresponding *tert*-butyl ether after three days. To our knowledge, no examples of the protection of alcohols as their *tert*-butyl ethers under such conditions have been reported. This result gave us the opportunity to complete our planned synthesis and, in addition, prompted us to explore and expand the scope of the reaction as a general alternative and inexpensive route to the generation of *tert*-butyl ethers. To this end, primary, secondary, and propargylic alcohols, as well as diols were considered. The best results obtained by applying the proposed methodology are reported in Table 1. Aliphatic primary alcohols (entries 1–3) gave complete conversion into the corresponding *O*-*tert*-butyl ethers after reasonably short times at room temperature in the presence of 0.2 equivalents of catalyst at a 0.04–0.05 M concentration of substrate. Both *N*-Cbz and *N*-Fmoc protecting groups were compatible with the reaction conditions, although, unexpectedly, with the *N*-Fmoc-protected 3-amino-1-propanol (entry 2), 23 hours were necessary to reach complete conversion.[6] The conversion rate with acyclic aliphatic secondary alcohols was more difficult to predict based on the substrate structure. Whereas (*S*)-diethyl 2-hydroxysuccinate (entry 4) was quantitatively converted into the corre-

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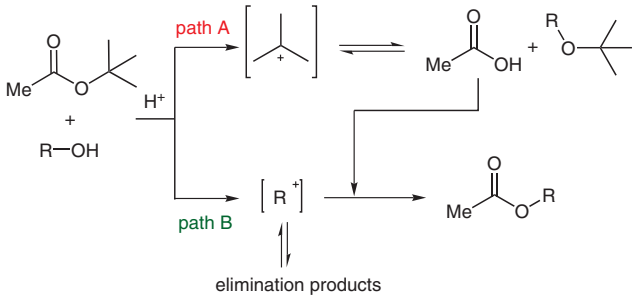
sponding *tert*-butyl ether[7] in one hour at a 0.05 M substrate concentration, a larger excess of *tert*-butyl acetate (substrate concentration equal to 0.025 M) and three days of stirring were necessary to generate 75% conversion in the case of 2-octanol (entry 5). Cyclic secondary alcohols such as cyclohexanol (entry 7), (*R*)-menthol (entry 8), cyclododecanol (entry 9), cholesterol and desmosterol (cholesta-5,24-dien-3β-ol, entries 10 and 11, respectively), could all be successfully converted into the corresponding *tert*-butyl ether with yields ranging from 66 to 100%. In general, shorter reaction times and lower amounts of catalyst are required for unhindered cyclic secondary alcohols (entries 7, 9, 10, and 11) compared to open chain ones, whereas for menthol an increase in both dilution (0.025 M) and reaction time was required.



Scheme 1 Different pathways occurring in the reaction medium

This data may be explained by the high conformational mobility of the open chain alcohols that could hamper the attack of the *tert*-butyl cation. As for 1,2-diols (entries 12–14), cyclohexandiol (entry 12) gave a mixture of mono (**12a**) and disubstituted (**12b**) *tert*-butyl ethers in a 2:1 ratio using 0.2 equiv of catalyst after four days. We obtained practically the same results with (*R*,*R*)-tartaric acid dimethyl ester (entries 13 and 14) at a 0.05 M concentration and 0.2 equiv of $HClO_4$, we measured a 2:1 ratio of mono- (**13a**) and diprotected (**13b**) compounds after 23 hours. As in the case of cyclohexanediol, longer reaction times did not increase the conversion into **13b**, meaning that equilibrium was reached. By changing the reaction conditions, we managed to obtain a 1:1 ratio between the two products (entry 14) by extremely diluting the solution to 0.0025 M. After 44 hours, we stopped the reaction as it no longer proceeded, and the two products were separated by chromatography (EtOAc–*n*-Hexane, 1:4) to give **13b** (R_f = 0.35; 43%) and **13a** (R_f = 0.11; 41%). When the monoprotected derivative **13a** was again subjected to the same conditions, a 1:1 ratio was again established, the reaction was worked-up and the two products separated. In this way we managed to obtain the desired diprotected compound **13b** in an acceptable 63% yield. This is a good result because, as far as we know, the protection of tartaric acid as the synthetically useful di-*tert*-butyl ether[8] is notoriously difficult and generally leads to low yields. Although the use of large volumes of *tert*-butyl acetate in this case (and, in general, where a 0.025 M substrate concentration was necessary) appears economically unfavorable, we found that the *tert*-butyl acetate can be easily recovered almost quantitatively by distillation after work-up of the reaction mixture.

Unfortunately, elimination is the main pathway followed by tertiary and tertiary allylic alcohols (entries 15 and 17 respectively), whereas the tetrahydropyridin-4-ol shown in entry 18 gave exclusively the corresponding acetate derivative.

Table 1 Protection of Alcohols as their Corresponding *tert*-Butyl Ethers

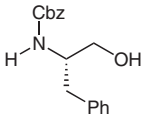
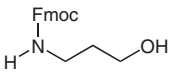
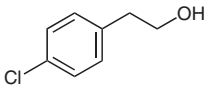
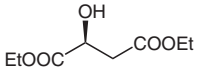
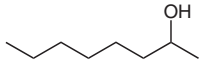
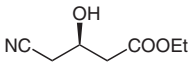
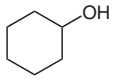
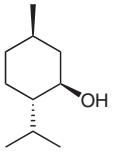
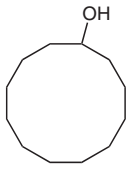
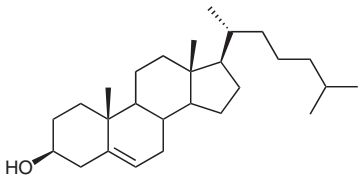
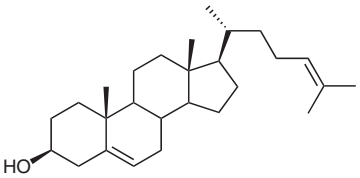
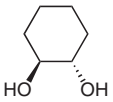
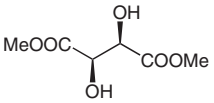
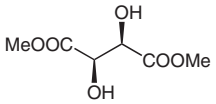
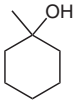
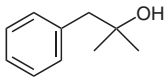
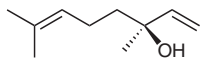
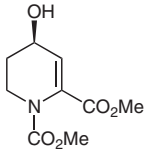
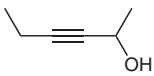
Entry	ROH	[ROH] (M)	Cat.[a]	Product	Time (h)	Conv.[b] (yield)[c] (%)
1		0.05	0.2	**1**	4.5	100
2		0.04	0.2	**2**	23	100
3		0.05	0.2	**3**	4.5	100
4		0.05	0.2	**4**	1	100
5		0.025	0.2	**5**	3 d	75
6		0.8	0.1	**6**	3 d	100
7		0.1	0.1	**7**	3 d	100

Table 1 Protection of Alcohols as their Corresponding *tert*-Butyl Ethers (continued)

Entry	ROH	[ROH] (M)	Cat.[a]	Product	Time (h)	Conv.[b] (yield)[c] (%)
8		0.025	0.2	**8**	5 d	70 (60)
9		0.01	0.2	**9**	20	94 (70)
10		0.05	0.1	**10**	5	100 (91)
11		0.05	0.3	**11**	23	87 (66)
12		0.1	0.2	**12**	4 d	100[d]
13		0.05	0.2	**13**	23	100[d]
14		0.0025	0.2	**13**	44	100[e]
15		0.025	0.2	**14**	3 d	–
16		0.05	0.1	**15**	24	15
17		0.05	0.2	**16**	7	–
18		0.04	0.2	**17**	4	100[f]
19		0.05	0.2	**18**	1	100 (78)
20		0.025	0.2	**19**	1	100 (75)

[a] Equivalents of $HClO_4$.
[b] Conversions determined by GC and or H^1NMR analysis.
[c] Isolated products.
[d] 2:1 ratio between mono and deprotected.
[e] 1:1 ratio between mono and deprotected.
[f] The O-acetylated product was recovered.

As depicted in Scheme 1, besides the formation of the *tert*-butyl cation according to path A, the protonation of the hydroxy group (path B) induces the competitive formation of a stable carbocation through loss of water. As a result, the attack of acetic acid on this stable carbocation leads to the corresponding acetylated derivative. Predictably, the more stable the alkyl carbocation, the more path B is the favored process. In these cases, a large excess of the *tert*-butylating agent could disadvantage the competing elimination pathway, however, with 2-methyl-1-phenylpropan-2-ol (entry 16) we were able to obtain the *tert*-butyl ether in only 15% yield. Nevertheless, propargylic alcohols such as 2-hexyn-1-ol and 3-hexyn-2-ol (entries 19 and 20) were easily converted into the correspondent protected ethers in one hour.[10]

In conclusion, the $HClO_4$/*tert*-butyl acetate procedure represents a practical tool to synthesize protected *tert*-butyl ethers. It can be considered as a good compromise between efficiency and low cost of the reagents. Good results have been obtained with primary, secondary and cyclic alcohols, with the mild reaction conditions being compatible with the presence of many other functional and protecting groups. The products can be easily recovered from the crude reaction mixture and easily purified; moreover, for large-scale preparations, the excess of *tert*-butyl acetate can be easily recovered by simple distillation of the crude material and used in further experiments.

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References and Notes

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis.*; Wiley: New York, **1999**, 65–67.

(2) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

(3) (a) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Palazzi, P.; Sambri, L. *Synlett* **2006**, 2104. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Sambri, L. *J. Org. Chem.* **2006**, *71*, 9580. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2006**, *348*, 905. (d) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427.

(4) (a) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1. (b) Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243. (c) Occhiato, E. G.; Scarpi, D.; Guarna, A.; Tabasso, S.; Deagostino, A.; Prandi, C. *Synthesis* **2009**, 3611.

(5) (a) Anelli, P. L.; Fedeli, F.; Gazzotti, O.; Lattuada, L.; Lux, G.; Rebasti, F. *Bioconjugate Chem.* **1999**, *10*, 137. (b) Chen, H.; Feng, Y.; Xu, Z.; Ye, T. *Tetrahedron* **2005**, *61*, 11132; This procedure is commonly used to convert N-unprotected amino acids into *tert*-butyl esters.

(6) The conversion of unprotected 5-aminopentan-1-ol into the corresponding 5-*tert*-butoxypentan-1-amine has been successfully performed in the presence of 0.5 equiv of $HClO_4$.

(7) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743.

(8) (a) Polonski, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 629. (b) Uray, G.; Lindner, W. *Tetrahedron* **1988**, *44*, 4357.

(9) Several phenols have also been considered. Unfortunately most of them mainly gave FC alkylation products. Only mono- and di-nitro phenols were converted into the correspondent *tert*-butyl ethers although in low yields.

(10) General Procedure for the Synthesis of *tert*-Butyl Ethers: To a solution of the alcohol in *t*-BuOAc, was added $HClO_4$ and the mixture was stirred at 25 °C until the reaction was complete (reaction monitored by TLC or GC). Na_2CO_3 (2 equiv) was added and the mixture was stirred for 40 min. After filtration, the solvent was removed under vacuum (for the re-use of *t*-BuOAc, this was washed with a saturated solution of $NaHCO_3$, then with H_2O and finally dried over Na_2SO_4). The *tert*-butyl ether was separated from the residual alcohol by flash chromatography on silica gel (petroleum ether–Et_2O or *n*-hexane–EtOAc). Compounds **4**,[7] **5**,[3d] **6**,[4c] **7**,[14] **8**,[3d] **10**,[3d] **12a**,[12,13] **12b**,[11,13] **13a**,[8] and **13b**[8] are known, and their spectroscopic data correspond to those reported. **1**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.40–7.31 (m, 5 H), 7.30–7.15 (m, 5 H), 5.26–5.12 (br s, 1 H), 5.09 (s, 2 H), 4.03–3.86 (s, 1 H), 3.34–3.20 (m, 2 H), 2.94–2.83 (m, 2 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 155.8 (s), 138.3 (s), 136.5 (s), 129.4 (d, 2 C), 128.4 (d, 2 C), 128.2 (d, 2 C and 1 C), 128.0 (d, 2 C), 126.2 (d), 72.8 (s), 66.5 (t), 61.1 (t), 52.5 (d), 37.8 (t), 27.5 (q, 3 C). MS (ESI): *m*/*z* (%) = 364 (100)[M$^+$ + Na], 341 (14) [M]$^+$, 286 (19). **2**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.76 (d, *J* = 7.3 Hz, 2 H), 7.60 (d, *J* = 7.3 Hz, 2 H), 7.43–7.29 (m, 4 H), 5.68–5.52 (br s, 1 H), 4.41–4.36 (m, 2 H), 4.28–4.18 (m, 1 H), 3.46 (t, *J* = 5.5 Hz, 2 H), 3.40–3.20 (m, 2 H), 1.82–1.66 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 156 (s), 143.8 (s, 2 C), 141.1 (s, 2 C), 127.4 (d, 2 C), 126.8 (d, 2 C), 124.9 (d, 2 C), 119.7 (d, 2 C), 73.0 (s), 66.4 (t), 60.6 (t), 47.3 (d), 40.1 (t), 29.8 (t), 27.5 (q, 3 C). MS (ESI): *m*/*z* (%) = 376 (100)[M$^+$ + Na], 353 (19) [M]$^+$, 298 (6). MS (EI, 70 eV): *m*/*z* (%) = 353 (0.1) [M]$^+$, 178 (100). **3**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.27–7.14 (m, 4 H), 3.52 (t, *J* = 7.3 Hz, 2 H), 2.79 (t, *J* = 7.3 Hz, 2 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 137.9 (s), 131.7 (s), 130.2 (d, 2 C), 128.1 (d, 2 C), 72.9 (s), 62.7 (t), 36.8 (t), 27.6 (s, 3 C). MS (EI, 70 eV): *m*/*z* (%) = 212 (2)[M]$^+$, 182 (3), 57 (100). **9**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.58–3.65 (m, 1 H), 1.61–1.50 (m, 2 H), 1.34 (br, 20 H), 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 73.1 (s), 68.6 (d), 31.9 (t, 2 C), 28.7 (q, 3 C), 24.6 (t, 2 C), 24.0 (t), 23.2 (t, 4 C), 21.1 (t, 2 C). MS (EI, 70 eV): *m*/*z* (%) = 240 (3)[M]$^+$, 183 (18), 166 (3), 57 (100). **11**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.31–5.29 (m, 1 H), 5.10–5.06 (m, 1 H), 3.34–3.26 (m, 1 H), 2.32–2.23 (m, 2 H), 2.12 (ddd, *J* = 13.4, 4.9, 2.1 Hz, 1 H), 2.06–1.93 (m, 2 H), 1.87–1.79 (m, 4 H), 1.70–1.35 (m, 11 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.34–1.00 (m, 7 H), 1.18 (s, 9 H), 0.99 (s, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.670 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 142, 131, 125, 120, 73.3, 71.4, 56.8, 56.1, 50.3, 42.3, 42.1, 39.8, 37.8, 36.6, 36.1, 35.6, 32.0, 31.9, 31.3, 28.5 (3 C), 28.2, 25.7, 24.7, 24.3, 21.0, 19.3, 18.6, 17.6, 11.8. MS (EI, 70 eV): *m*/*z* (%) = 440 (2) [M]$^+$, 57 (100). **17**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (d, *J* = 4.4 Hz, 1 H), 5.28 (pseudo q, *J* = 4.3 Hz, 1 H), 4.09 (dt, *J* = 13.3, 4.4 Hz, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.28 (ddd, *J* = 13.3, 9.2, 5.5 Hz, 1 H), 2.04 (s, 3 H), 1.98–1.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 170.0 (s), 164.7 (s), 153.9 (s), 135.3 (s), 116.3 (d), 63.5 (d), 53.4 (q), 52.4 (q), 40.5 (t), 29.2 (t), 21.0 (q); MS: *m*/*z* (%) = 257 (14)[M]$^+$, 225 (40), 198 (49), 183 (60), 152 (77), 94 (100). **18**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.00 (s, 2 H),

2.11 (t, *J* = 4.3 Hz, 2 H), 1.45 (m, 2 H), 1.17 (s, 9 H), 0.86 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 85.1 (s), 81.2 (s), 73.8 (s), 50.6 (t), 27.3 (q), 21.8 (t), 20.7 (t), 13.3 (q). MS (EI, 70 eV): *m*/*z* (%) = 139 (88), 81 (100), 79 (96), 59 (74), 57 (63). **19**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.19 (q, *J* = 6.6 Hz, 1 H), 2.10 (q, *J* = 7.5 Hz, 2 H), 1.31 (d, *J* = 6.6 Hz, 3 H), 1.17 (s, 9 H), 1.10 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 84.8 (s), 82.3 (s), 73.9 (s), 57.0 (d), 27.9 (q), 23.8 (q), 13.6 (q), 12.3 (t). MS (EI, 70 eV): 139 (70), 81 (100), 79 (80), 59 (88), 57 (94).

(11) Schauble, J. H.; Trauffer, E. A.; Deshpande, P. P.; Evans, R. D. *Synthesis* **2005**, 1333.
(12) Kim, B. K.; Piao, F.; Lee, E. J.; Kim, J. S.; Jun, M. J.; Lee, B. M. *Bull. Korean Chem. Soc.* **2004**, *25*, 881.
(13) Iranpoor, N.; Baltork, I.; Mohammadpour, I. *Tetrahedron Lett.* **1990**, *31*, 735.
(14) Brown, H. C.; Kurek, J. T.; Rei, M.-H.; Thomson, K. L. *J. Org. Chem.* **1985**, *50*, 1171.