ORGANIC LETTERS

2005
Vol. 7, No. 3
427−430

Unusual and Unexpected Reactivity of *t*-Butyl Dicarbonate (Boc_2O) with Alcohols in the Presence of Magnesium Perchlorate. A New and General Route to *t*-Butyl Ethers

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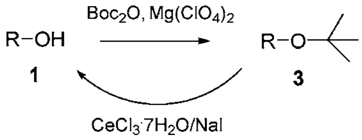
Received November 8, 2004

ABSTRACT

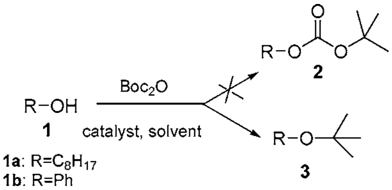


A new mild method for protecting alcohols as *t*-butyl ethers is reported. The reaction proceeds with $Mg(ClO_4)_2$ and Boc_2O and shows general applicability. The deprotection of *t*-butyl ethers has also been revisited. Preliminary results indicate the $CeCl_3{\cdot}7H_2O/NaI$ system is a very suitable catalyst for their removal.

In the past few years, metal perchlorates have been widely exploited as Lewis acid promoters in various organic transformations. In particular, perchlorate salts have shown a high ability to activate 1,3-dicarbonyl systems and have found considerable application in various acylation[1] and esterification[2] procedures, in the synthesis of β-enamino esters,[3] and in the protection of amines as *N*-Boc derivatives.[4]

We now report that, surprisingly, the reaction of 1-octanol **1a** (Scheme 1) with *tert*-butyl dicarbonate (Boc_2O, 1.5 equiv) in the presence of anhydrous $Mg(ClO_4)_2$ does not give the corresponding Boc-derivative **2a**, as expected, but rather a mixture of *t*-butyl octyl ether **3a** (66%) and unreacted alcohol (30%) after 18 h at room temperature.

Scheme 1



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(1) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *34*, 6331. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett* **2003**, 39. (c) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, 4611. (d) Chakraborti, A. K.; Gulhane, R.; Shivani *Synlett* **2003**, 1805. (e) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani *Tetrahedron* **2003**, *59*, 7661. (f) Lu, K.-C.; Hsieh, S.-Y.; Patkar, L. N.; Chen, C.-T.; Lin, C.-C. *Tetrahedron* **2004**, *60*, 8967.

(2) (a) Gooβen, L.; Döhring, A. *Adv. Synth. Catal.* **2003**, *345*, 943. (b) Bartoli, G.; Boeglin, J.; Bosco, M.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2005**, in press.

(3) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 239.

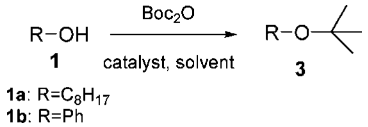
(4) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 1794.

10.1021/ol047704o CCC: $30.25

Similar behavior was observed with an aromatic substrate such as phenol (**1b**), which can be easily converted in the corresponding *t*-butyl ether **3b** in 84% yield. These preliminary results seemed extremely interesting, as they represented a potential solution to a longstanding problem in organic synthesis, namely, *t*-butyl ether formation. The *t*-butyl ether in fact is "one of the most underused alcohol protecting groups",[5] although it is one of the few ethers stable under strongly basic conditions.[6] Its scarce employment in organic synthesis is probably due to the conditions required for its formation. Most of the known methodologies[5,6] in fact require harsh conditions based on the reaction of an alcohol with isobutylene in the presence of a strong acidic catalyst. Moreover, the reaction involves the formation of a *t*-butyl carbocationic intermediate, thus avoiding the application of these methodologies to the protection of aromatic alcohols,[7] which predominantly undergo a Friedel−Crafts alkylation.

Thus, the peculiar observed reactivity prompted us to optimize the reaction conditions to develop a new route to *t*-butyl ethers. A series of experiments carried out on **1a** and **1b** (Table 1) indicated that the best yields were obtained in the presence of 10 mol % anhydrous Mg(ClO$_4$)$_2$ and 2.3 equiv of Boc$_2$O at 40 °C in CH$_2$Cl$_2$ or under neat conditions. Although Zn(ClO$_4$)$_2$•6H$_2$O is usually more active than Mg(ClO$_4$)$_2$,[1c] in this particular reaction, lower yields were obtained in the presence of hydrated zinc perchlorate, probably due to the presence of water (Table 1, entry 6). In the absence of the perchlorate salt, both alkyl and aromatic substrates reacted with Boc$_2$O, giving only the *t*-butyl carbonate **2** after prolonged reaction times (Table 1, entries 5 and 10).

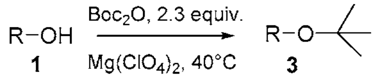
Table 1. Reaction of 1-Octanol (**1a**) and Phenol (**1b**) with Boc$_2$O, under Various Conditions, in the Presence of 10 mol % Mg(ClO$_4$)$_2$, unless Otherwise Mentioned

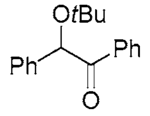
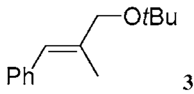
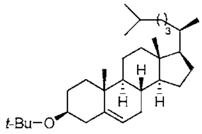
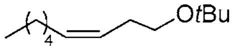
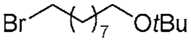
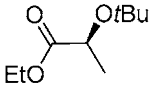
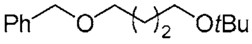
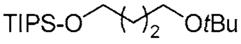
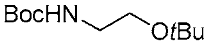


entry	ROH	Boc$_2$O	solvent	time (h)	*T* (°C)	yield % of **3**
1	**1a**	1.5	/	18	rt	66
2	**1a**	1.5	CH$_2$Cl$_2$	7	40	65
3	**1a**	1.5	/	7	40	79
4	**1a**	2.3	/	7	40	82
5	**1a**	1.5	/	144	rt	0 (13)[a]
6	**1a**	2.3	/	18	40	72[b]
7	**1b**	1.5	/	21	40	84
8	**1b**	2.3	/	21	40	93
9	**1b**	2.3	CH$_2$Cl$_2$	13	40	90
10	**1b**	1.5	/	125	40	0 (95)[a]

[a] Reaction carried out without catalyst; the yield in parentheses refers to the recovered carbonate **2**. [b] Reaction carried out with 10% mol Zn(ClO$_4$)$_2$•6H$_2$O as the catalyst.

Table 2. Protection of Alcohols as *t*Bu-Ethers by Reaction with Boc$_2$O (2.3 equiv) in the Presence of 10 mol % Mg(ClO$_4$)$_2$ at 40 °C



Entry	Product	solvent	t (h)	Yields (%)
1	2-octyl-O*t*Bu **3c**	/	30	84
2	c-C$_5$H$_9$-O*t*Bu **3d**	CH$_2$Cl$_2$	30	83
3	(R)-menthyl-O*t*Bu **3e**	CH$_2$Cl$_2$	28	70
4	PhCH$_2$-O*t*Bu **3f**	/	43	93
5	 **3g**	CH$_2$Cl$_2$	20	79
6	*p*-OMe-C$_6$H$_4$-O*t*Bu **3h**	/	24	84
7	*m*-Cl-C$_6$H$_4$-O*t*Bu **3i**	/	32	82
8	*p*-F-C$_6$H$_4$-O*t*Bu **3j**	CH$_2$Cl$_2$	15	71
9	1-naphtyl-O*t*Bu **3k**	CH$_2$Cl$_2$	24	65
10	2-naphtyl-O*t*Bu **3l**	CH$_2$Cl$_2$	15	82
11	 **3m**	/	29	84
12	 **3n**	CH$_2$Cl$_2$	30	89
13	 **3o**	/	15	88
14	NO$_2$-CH$_2$CH$_2$-O*t*Bu **3p**	CH$_2$Cl$_2$	8	95
15	 **3q**	CH$_2$Cl$_2$	31	81
16	 **3r**	/	32	80
17	 **3s**	CH$_2$Cl$_2$	28	86
18	 **3t**	CH$_2$Cl$_2$	22	76
19	 **3u**	CH$_2$Cl$_2$	15	88

The procedure succeeded in the synthesis of a large variety of *t*-butyl ethers. The best obtained results are reported in Table 2. The etherification process worked well with primary, secondary, benzylic, allylic, and homoallylic alcohols, and

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(5) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 65−67.

(6) Kocienski, P. J. In *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2004; pp 59−61.

(7) (a) Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345. (b) Holcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 111.

neither isomerization of the substrate (entries 11 and 13) nor racemization (entries 3, 12, and 16) were observed. Unfortunately, tertiary alcohols failed to give the desired ether, only the starting material being recovered after prolonged reaction times.

Notably, the reaction gave excellent results with a large variety of aromatic alcohols. Various substituted phenols (entries 6−8) and 1- and 2-naphthol (entries 9 and 10) can be converted into the corresponding *t*-butyl ethers in high yields, and no product derived from an eletrophilic addition to the aromatic ring was ever detected.

The reaction is highly chemoselective. In fact, other functionalities present in the alcohol such as a carbonyl, an ester, and a nitro group, a carbon−carbon double bond or a fluoride, a chloride, and a bromide survived under the adopted reaction conditions.

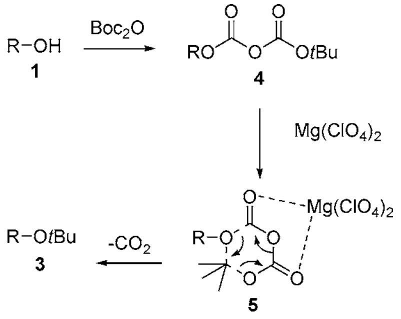
The compatibility of some typical protecting groups with the reaction conditions was also evaluated. Benzyl and (i-Pr)$_3$Si (TIPS) ether derivatives were almost completely unaffected (entries 17 and 18). Concerning the amine function, the *N*-Boc-derivative is compatible with the reaction conditions; in fact, the expected protected amino-ether was obtained in high yield (entry 19).

Some preliminary experiments were carried out in order to understand the reaction mechanism for the formation of *t*-butyl ethers. We found that Boc$_2$O alone decomposes in the presence of Mg(ClO$_4$)$_2$ to give CO$_2$, *t*-BuOH, and isobutylene. The formation of a *t*-butyl carbocation intermediate can be therefore assumed. This carbocation could be in some way captured by the alcohol present in the reaction mixture to give the *t*-butyl ether. But this hypothesis must be excluded since it is well-known that phenols undergo electrophilic substitution at the aromatic ring in the presence of a *t*-butyl carbocation,[7] and we never observed any addition product, even with highly activated *p*-methoxy phenol[8] (Table 2, entry 6). However, the fact that Boc$_2$O decomposes in the presence of Mg(ClO$_4$)$_2$ can explain why an excess of Boc$_2$O is required to obtain good yields in *t*-butyl ethers, since its decomposition is a competitive reaction.

On the other hand, the formation of the carbonate **2** as a reaction intermediate can be excluded. In fact, *t*-butyl octyl carbonate **2a**, prepared according to a known procedure,[9] and the commercially available *t*-butyl phenyl carbonate **2b** react in the presence of Mg(ClO$_4$)$_2$ to give 1-octanol **1a** and phenol **1b**, respectively, without any trace of *t*-butyl ethers **3a** and **3b**.

It has been reported[10] that in the synthesis of RO−Boc from R−OH and Boc$_2$O catalyzed by DMAP, a mixed dicarbonate intermediate like **4** is formed (Scheme 2). On this basis, a reasonable mechanistic hypothesis could invoke the initial formation of the mixed dicarbonate **4**, which, coordinated by the catalyst, decomposes to the *tert*-butyl ether **2** and CO$_2$ through a concerted cyclic mechanism.

Scheme 2. Possible Mechanistic Explanation for the Formation of *t*-Butyl Ethers



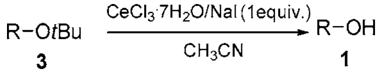
According to the previously reported procedure,[10] we synthesized the *t*-butyl cyclopentyl dicarbonate **4d** as a mixture with the corresponding carbonate. Upon treating this inseparable mixture with Mg(ClO$_4$)$_2$, formation of the corresponding *t*-butyl ether **3d** was detected. Studies are in progress to produce further evidence of this hypothesis.

The cleavage of *t*-butyl ethers to deprotected alcohols requires strongly acidic conditions[5,6] that are generally “not mild enough to accommodate acid-sensitive functional groups”.[6]

Recently, we reported[11] that the CeCl$_3$•7H$_2$O/NaI system is able to cleave the carbon−oxygen bond of ethers (R′O−R) provided that the substrates feature particular structural properties, i.e., when the R framework bonded to oxygen is able to stabilize a positive charge.[12] Since the *t*-butyl group[13] can generate a stable tertiary carbocation, we successfully tested the CeCl$_3$•7H$_2$O/NaI procedure using the *t*-butyl ethers we just obtained.

Preliminary experiments gave very satisfactory results (Table 3). Both alkyl and aromatic *t*-butyl ethers can be reconverted into the corresponding alcohols simply by heating in CH$_3$CN in the presence of 1 equiv of CeCl$_3$•7H$_2$O/NaI. Studies are in progress to extend this procedure to

Table 3. Deprotection of *t*-Bu-Ethers in the Presence of CeCl$_3$•7H$_2$O (1 equiv) and NaI (1 equiv) in CH$_3$CN



entry	reagent	*t* (h)	*T* (°C)	yield of **1** (%)
1	1-octyl-O*t*Bu **3a**	8	70	94
2	Ph-O*t*Bu **3b**	8	40	93
3	(*R*)-menthyl-O*t*Bu **3e**	17	70	>98

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[8] In addition, we carried out a decomposition test of Boc$_2$O with Mg(ClO$_4$)$_2$ also in the presence of anisole as the carbocation scavenger. We did not observe the formation of any *tert*-butyl anisole, not even in trace amounts.

[9] Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798.

[10] Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368.

[11] Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101

[12] (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209. (b) Bartoli, G.; Bellucci, M. C.; Cappa, A.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696. (c) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897. (d) Yadav, J. S.; Reddy, B. V. S. *Synlett* **2000**, 1275. (e) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149.

functionalized substrates and to check its consistency with other protecting groups.

In conclusion, the $Mg(ClO_4)_2$-promoted procedure we have presented here provides a very good method for obtaining *t*-butyl ethers from alcohols, since it works under mildly acidic conditions and many functional groups survive the protection process.

Moreover, all side products of the reaction are volatile compounds, so that the purification of the products is very simple and convenient. Typically, *t*-butyl ethers have to be separated only from the residual starting materials.

Finally, a simple and mild method for deprotecting *t*-butyl ethers based on the $CeCl_3{\cdot}7H_2O$/NaI system gives very satisfactory preliminary results. The value of the protection procedure here proposed will increase if combined with a general and simple deprotection step.

Acknowledgment. Work was carried out in the framework of the National Project “Stereoselezione in Sintesi Organica. Metodologie e Applicazioni” supported by MIUR, Rome, by the University of Bologna, and in the framework of “Progetto di Finanziamento Pluriennale, Ateneo di Bologna” and supported by National project FIRB “Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci”.

Supporting Information Available: Experimental procedures, full characterization, and copies of both proton and carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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