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Convenient Preparations of t-Butyl Esters and Ethers from t-Butanol

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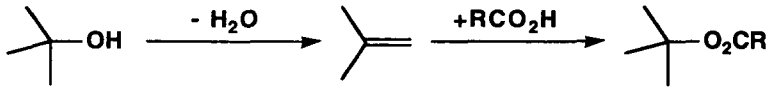
Abstract: *A one-pot preparation of t-butyl esters and ethers is described that proceeds from the carboxylic acid or alcohol and t-butanol using only anhydrous magnesium sulfate and catalytic sulfuric acid as additional reagents. The method affords t-butyl esters and ethers in good yields and is applicable to a variety of substrates.* © 1997 Elsevier Science Ltd.

The t-butyl ester enjoys a unique place among protecting groups for carboxylic acids due to its relative resistance to nucleophilic attack and its ready removal by acidolysis. Thus the protection of carboxylic acids as their t-butyl esters continues to be an important synthetic procedure. However, the properties that make t-butyl esters popular as a protecting group simultaneously render their preparation more difficult than other esters. Many methods have been reported for the preparation of t-butyl esters. Some of the more popular methods include the reaction of a carboxylic acid chloride and t-butanol in pyridine,[1a] the reaction of a carboxylic acid chloride and an alkali metal t-butoxide, the reaction of a carboxylic acid and a t-butyl halide,[1c] the reaction of a carboxylic acid and BOC anhydride,[1d] the reaction of a carboxylic acid S-2-pyridinyl ester with t-butanol,[1e] the oxidation of aldehyde in t-butanol,[1f] the reaction of a carboxylic acid and DMF di-t-butyl acetal[1g] or with a t-butyl isourea,[1h] as well as the direct reaction of a carboxylic acid and t-butanol mediated by 1,1'-carbonyldiimidazole,[1i] a carbodiimide,[1j] and by ultrasound.[1k] The most versatile and simple method, however, continues to be the reaction of a carboxylic acid and isobutylene in the presence of an acid catalyst.[2] The principal difficulties with the isobutylene procedure lie in the need to use pressure - resistant equipment when using this gas in the condensed state, as is usually done, as well as the expense and frequent lack of an immediately available laboratory source of isobutylene. We sought to devise a more convenient procedure for the preparation of t-butyl esters by the isobutylene method, using commonly available and easily handled t-butanol as an in situ source of isobutylene.[3] We expected that the acid catalyst necessary for the esterification reaction could simultaneously serve as a catalyst for the dehydration of t-butanol to isobutylene, if the reaction could be driven by the removal of water with a dehydrating agent:



After screening a variety of acid catalyst - dehydrating agent mixtures, we found that a simple dispersion of concentrated sulfuric acid on powdered anhydrous magnesium sulfate gave good yields of t-butyl esters. This procedure combines the convenience of using reagents available in every organic laboratory with a simple, one -

pot reaction at room temperature. The sulfuric acid - magnesium sulfate dehydrating agent/catalyst is prepared in the reaction flask by adding concentrated sulfuric acid to a stirred suspension of magnesium sulfate. The sulfuric acid is adsorbed onto the magnesium sulfate and the pH of the reaction solvent remains neutral.[4] No internal pressure is developed, thus obviating the need to use the pressure vessels required with isobutylene gas.

In a typical small scale experiment, concentrated sulfuric acid (0.55 mL, 10 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (4.81 g, 40 mmol) in 40 mL of solvent. The mixture was stirred for 15 minutes, after which the carboxylic acid (10 mmol) was added. Tertiary butanol (4.78 mL, 50 mmol) was added last. The mixture was stoppered tightly and stirred for 18 h at 25 °C, or until the reaction was complete by tlc analysis. The reaction mixture was then quenched with 75 mL of saturated sodium bicarbonate solution and stirred until all magnesium sulfate had dissolved. The solvent phase was separated, washed with brine, dried ($MgSO_4$), and concentrated to afford the crude t-butyl ester which was purified by chromatography, distillation, or recrystallization as appropriate. Results with a variety of carboxylic acids are summarized in Table 1.

Table 1

Entry	Carboxylic Acid	3° Alcohol	Solvent	Yield[a]	mp, °C
1.	Benzoic acid	t-BuOH	CH_2Cl_2	93%	oil
2.	Benzoic acid	t-Amyl	CH_2Cl_2	54%	oil
3.	4-Methylbenzoic acid	t-BuOH	$ClCH_2CH_2Cl$	85%	oil
4.	3-Fluorobenzoic acid	t-BuOH	$C_6H_5CH_3$	91%	oil
5.	4-Nitrobenzoic acid	t-BuOH	CH_2Cl_2	80%	114 - 116[b]
6.	4-Methoxybenzoic acid	t-BuOH	$CHCl_3$	87%[c]	oil
7.	Salicyclic acid	t-BuOH	CH_2Cl_2	84%	oil
8.	Cinnamic acid	t-BuOH	CH_2Cl_2	82%	oil
9.	Oleic acid	t-BuOH	CH_2Cl_2	88%	oil
10.	3-Phenylpropionic acid	t-BuOH	C_6H_6	88%	oil
11.	2-Furoic acid	t-BuOH	CH_2Cl_2	60%	oil
12.	5-Bromo-2-thiophenecarboxylic acid	t-BuOH	CH_2Cl_2	83%	oil
13.	N-CBZ-Alanine	t-BuOH	CH_2Cl_2	87%	oil
14.	N-CBZ-β-Alanine	t-BuOH	CH_2Cl_2	75%	oil

(a) All yields refer to purified products. All products gave satisfactory ^1H NMR and mass spec data and were homogeneous by tlc. (b) lit mp 115 - 117 °C (Reference 1k). (c) The reaction was carried out for 60 h.

The reaction was successful for various of aromatic, aliphatic, olefinic, heteroaromatic, and protected amino acids. Other acid catalysts, such as powdered potassium bisulfate, Nafion® acidic resin, Dowex-50® acidic resin, phosphorus pentoxide,[5] and methanesulfonic acid all failed to afford the product ester when substituted for concentrated sulfuric acid under these conditions. No reaction was observed by the use of

anhydrous magnesium sulfate in the absence of sulfuric acid. The use of sulfuric acid in the absence of anhydrous magnesium sulfate also failed to afford the product ester, affording only the recovered acid and isobutylene polymers. Anhydrous calcium sulfate and anhydrous sodium sulfate were ineffective. Aliphatic and aromatic hydrocarbons such as cyclohexane and toluene, and chlorinated alkanes such as dichloromethane, chloroform, and 1,2-dichloroethane were all suitable solvents for this reaction. However, the use of ethereal solvents, in which the sulfuric acid is soluble, such as dioxane,[6] THF and DME afforded only recovered starting carboxylic acids. Tertiary amyl alcohol afforded a lower yield of ester (Entry 2). 3-Ethyl-3-pentanol failed to afford any ester with benzoic acid. Methanol, ethanol, and 2-propanol also failed to afford any significant amounts of ester when substituted for t-butanol under these conditions. Only starting carboxylic acid was recovered when profoundly insoluble carboxylic acids, such as N-benzoylglycine and 4-hydroxybenzoic acid, were used.

An examination of the compatibility of various functional groups with this procedure revealed that alcohols were converted to their t-butyl ethers under these conditions. Thus, various primary and secondary alcohols were converted to their t-butyl ethers. Results are summarized in Table 2.

Table 2

Entry	Alcohol	3° Alcohol	Solvent	Yield[a]	mp, °C
1.	1-Decanol	t-BuOH	CH_2Cl_2	93%	oil
2.	Benzyl alcohol	t-BuOH	CH_2Cl_2	93%	oil
3.	4-Nitrobenzyl alcohol	t-BuOH	CH_2Cl_2	95%	oil
4.	4-Methoxybenzyl alcohol	t-BuOH	CH_2Cl_2	---[b]	---
5.	2-Phenyl-1-ethanol	t-BuOH	Cyclohexane	92%	oil
6.	1-Phenyl-1-ethanol	t-BuOH	Cyclohexane	---[b]	---
7.	3-Phenyl-1-propanol	t-BuOH	CH_2Cl_2	78%	oil
8.	1-Phenyl-2-propanol	t-BuOH	Cyclohexane	67%	oil
9.	Cinnamyl alcohol	t-BuOH	CH_2Cl_2	---[b]	---
10.	4-Phenyl-1-butanol	t-BuOH	CH_2Cl_2	88%	oil
11.	4-Phenyl-2-butanol	t-BuOH	Cyclohexane	68%	oil
12.	CBZ-Serine methyl ester	t-BuOH	CH_2Cl_2	87%	oil
13.	CBZ-Ethanolamine	t-BuOH	CH_2Cl_2	85%	oil

(a) All yields refer to purified products. All products gave satisfactory ^1H NMR and mass spec data and were homogeneous by tlc. (b) Starting material was decomposed.

The reaction was successful for a variety of aliphatic, aromatic, benzylic, and protected amino alcohols. Alcohols that are particularly prone to carbonium ion formation, such as 4-methoxybenzyl alcohol (Entry 4), 1-phenyl-1-ethanol (Entry 6) and cinnamyl alcohol (Entry 9) were poor substrates for these conditions, affording polymers and/or symmetrical ethers as the major product(s). Secondary alcohols afforded lower yields than primary alcohols. Yields of secondary alcohol t-butyl ethers were improved by 10% - 20% by the use of

cyclohexane as solvent instead of dichloromethane. Optimum results for t-butyl ether formation required some modification of the conditions used to prepare t-butyl esters. Thus, concentrated sulfuric acid (0.55 mL, 10 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (4.81 g, 40 mmol) in 30 mL of solvent. The mixture was stirred for 15 minutes. A mixture of t-butanol (4.78 mL, 50 mmol) and the alcohol (10 mmol) dissolved in 10 mL of solvent was then added. The mixture was stoppered tightly and stirred for 18 h at 25 °C, or until the reaction was complete by tlc analysis. The reaction mixture was then quenched with 75 mL of 5% sodium bicarbonate solution and stirred until all magnesium sulfate had dissolved. The solvent phase was separated, washed with brine, dried ($MgSO_4$), and concentrated to afford the crude t-butyl ether which was purified by chromatography or distillation.

The extension of this methodology to phenols was also examined. Treatment of phenol under these conditions resulted in the formation of a mixture of all possible ring alkylation products, as determined by GC and chromatographic analysis and comparison to authentic materials. No phenol t-butyl ether was detected.

In summary, an extremely simple method for the preparation of t-butyl esters and ethers has been developed that uses reagents available in every organic laboratory. The method generally affords good yields of the t-butyl ester and ether products using a heterogeneous acid catalyst - dehydrating system as a means of generating isobutylene in situ.

References and Notes

1. See, for example: (a) Altschul, R. *J. Am. Chem. Soc.*; **1948**, *70*, 2569 - 2572; (b) Al-Awadi, N. A.; Al-Bashir, R. F.; ElDusouqui, O. M. E. *Tetrahedron*, **1990**, *46*, 2903 - 2910; (c) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.*, **1977**, *42*, 1286 - 1290; (d) Pozdnev, V. F. *J. Gen. Chem. USSR (Engl. Transl.)*, **1988**, *58*, 592 - 597; (e) Kim, S.; Lee, J. I. *J. Org. Chem.*,**1984**, *49*, 1712 - 1716; (f) Yamazaki, S. *Chemistry Letters*, **1995**, 127 - 128; (g) Widmer, U. *Synthesis*, **1983**, 135 - 136; (h) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.*, **1994**, *59*; 3216 - 3218; (i) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.*, **1984**, *32*, 5044 - 5047; (j) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.*, **1982**, *47*, 1962 - 1965; (k) Khurana, J. M.; Sahoo, P. K.; Maikap, G. C. *Synth. Commun.*, **1990**, *20*, 2267 - 2271.

2. See, for example, reference 1a.

3. By contrast, the use of methyl tert-butyl ether under similar conditions has been reported to afford the carboxylic acid methyl ester; see Derevitskaya, V. A.; Klimov, E. M.; Kochetkov, N. K. *Tetrahedron Letters*, **1970**, *11*, 4269 - 4270.

4. As determined by filtration of the reaction mixture, washing with water, and determination of the pH of the aqueous phase.

5. The use of phosphorus pentoxide (1 equivalent to carboxylic acid) and t-butanol (5 equivalents to carboxylic acid) in chloroform, in the absence of anhydrous magnesium sulfate, afforded the desired t-butyl esters in yields comparable to those reported in the Table.

6. Altschul, R. *J. Am. Chem. Soc.*, **1946**, *68*, 2605 - 2609.

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