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Efficient Synthesis of *tert*-Butyl Ethers under Solvent-Free Conditions

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Abstract: A simple and efficient synthesis of *tert*-butyl ethers from various alcohols and substituted phenols using *tert*-butyl bromide in the presence of basic lead carbonate as a catalyst. The catalyst is easily recovered via filtration and can be reused up to three times without appreciable loss of activity.

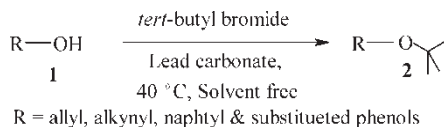
Keywords: *tert*-butyl bromide, *tert*-butyl ethers, lead carbonate, reusable catalyst, solvent free

INTRODUCTION

The protection of alcohols as *tert*-butyl ethers has become a widely utilized procedure in organic synthesis.^[1] The *tert*-butyl ether is one of the most underused alcohol protecting groups, although it is stable under strongly basic condition and can be cleaved with a relative ease under acidic conditions.^[2] The chemical syntheses of *tert*-butyl ethers are well documented in the literature.^[1,2] Some of the common practices involve the exposure of the alcoholic or phenolic species to excess of isobutylene in the presence of acid catalysts such as borontrifluoride–phosphoric acid complex or sulfuric acid at 0–25°C^[3] or trifluoromethane sulfonic acid in dichloromethane at –50°C.^[4] In some examples, nonacidic conditions such as reaction of *tert*-butanol and alkanol using anhydrous magnesium sulfate are reported to synthesize *t*-butyl alkyl ethers. This method is useful for the synthesis of *tert*-butyl esters as well.^[5] Other methods include Pd/P(*t*-Bu)₃-catalyzed

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**Scheme 1.**

reactions of aryl halides with sodium *tert*-butoxide for the synthesis of aryl *tert*-butyl ethers^[6] and magnesium perchlorate-catalyzed reaction of alcohol with *tert*-butyldicarbonate (Boc₂O) to get alkyl and aryl *tert*-butyl ethers.^[7] Most of these protocols require either longer reaction time or critical reaction conditions such as reaction of low boiling isobutylene under autoclave conditions. Also in these protocols, they normally require chromatographic separations for obtaining pure products. Herein, we report a method that works within a couple of hours under mild reaction conditions as shown in Scheme 1. The products are normally obtained in the pure form by solvent trituration and filtration Table 1.

RESULT AND DISCUSSION

In this articles, we report a simple and efficient etherification of allyl, alkynyl alcohols, and substituted phenols, which easily reacted with *tert*-butyl

Table 1. Reaction of phenol with *tert*-butyl bromide under various conditions^a in the presence of 2PbCO₃Pb(OH)₂

Entry	Amount of <i>t</i> -BuBr (mmol)	2PbCO ₃ Pb(OH) ₂ (mmol)	Time (h)	Temp. (°C)	Yield ^b (%)
1	20	1	1.5	40	>90
2	10	1	2	50	55 (45) ^c
3	20	2	1.5	40	90
4	10	2	1.5	40	<50
5	15	2	1.5	50	65
6	20	1(3) ^d	1.5	40	90 (85) ^d
7	40	—	4	50	<25

^aReaction condition: phenol (10 mmol), *t*-BuBr, 2PbCO₃Pb(OH)₂, temperature and time as shown.

^bIsolated product.

^cRecovered phenol.

^dRun with recycled lead carbonate obtained by washing with ethyl acetate and drying.

bromide in the presence of lead carbonate at 35–45°C under solvent-free conditions with good to excellent yields of respective tert-butyl ethers within 1–2.25 h. The results are summarized in Table 2. The same process was successfully extended to get other tert-butyl ether derivatives; for example (entry 10, Table 2), 3-hydroxy-benzyl alcohol (10 mmol) reacted with tert-butyl bromide (40 mmol) in the presence of lead carbonate (2 mmol) at 40°C over 2.25 h to give the corresponding product of 1-tert-butyl-3-(tert-butoxy methyl) benzene in 88% yield. Similarly allyl, alkynyl, 1-pentanol, and 1-octanol (entries 1–4, Table 2) reacted smoothly with tert-butyl bromide in the presence of lead carbonate to afford 85, 86, 80, and 82% of 3-tert-butoxy prop-1-ene, tert-butyl prop-2-ynyl ether, tert-butyl pentyl ether, and tert-butyl octyl ether, respectively.

Recovery of the catalyst was accomplished by simple filtration or by centrifugation followed by washing with ethyl acetate. Notably, the reactions gave excellent results with various substituted phenols (entries 5–8); α - and β -naphthol (entries 11 and 12) can be converted into the corresponding tert-butyl ethers in high yields, without any detectable side products arising from an electrophilic addition to the aromatic ring. The reaction is highly chemoselective. In fact, other functionalities present in the phenols such as methoxy, chloro, and fluoro groups survived under the adopted reaction conditions.

EXPERIMENTAL


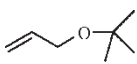
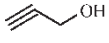
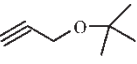

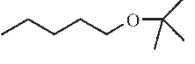
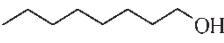
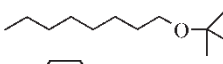
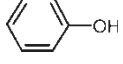
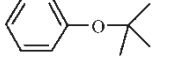
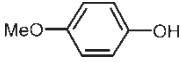
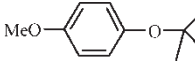
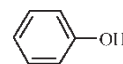
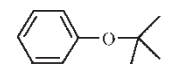
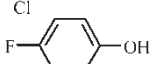
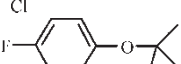
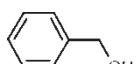
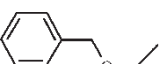
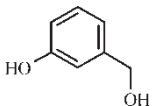
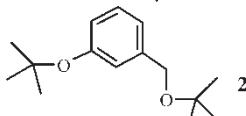
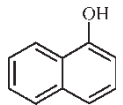
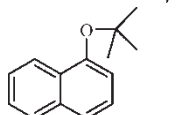
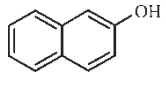
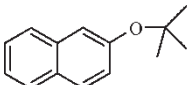
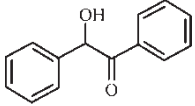
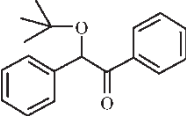

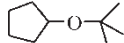
NMR spectrum was recorded on 300-MHz and 400-MHz Bruker spectrometers. All chemicals were commercially available and used without further purification except 3-hydroxy benzylalcohol, which was synthesized in house from 3-hydroxy benzaldehyde according to the procedure mentioned in the literature.^[8]

General Procedure for tert-Butyl Ethers

To a mixture of phenol (10 mmol) and lead carbonate (1 mmol) taken in a two-necked, 50-mL, round-bottomed flask cooled to 0°C, tert-butyl bromide (20 mmol) was added dropwise. The mixture was stirred and heated in an oil bath at 40°C for the given period of time (Table 2). After completion of the reaction, EtOAc (2 × 10 mL) was added to the reaction mixture, stirred for a while, and filtered. The filtrate was washed with 10% NaOH followed by saturated brine solution, dried over anhydrous Na₂SO₄, and concentrated on a rotavap to afford pure tert-butoxybenzene (entry 4, Table 2, **2e**) in 90% yield. All products were characterized by NMR spectral analysis.

In conclusion, we have developed a new general and convenient method for the synthesis of tert-butyl ethers under mild conditions.

Table 2. Synthesis of *tert*-butyl ether under mild conditions

Entry	Substrate	Time (h)	Product ^a	Temp. (°C)	Yield (%) ^b
1		1.25	 2a	35	85
2		1.25	 2b	35	86
3		1	 2c	40	80
4		1	 2d	40	82
5		1.5	 2e	40	90
6		1.5	 2f	40	92
7		1.5	 2g	40	88
8		1.25	 2h	40	82
9		1.8	 2i	40	96
10		2.25	 2j	40	88
11		2	 2k	45	75
12		1.5	 2l	45	86
13		2		45	82
14		2		40	84

^aAll products are known except **2a**, **2b**, **2c**, and **2j**, which are novel and characterized by NMR spectral analysis.

^bIsolated yields.

Data

3-Tert-butyl prop-1-ene 2a: ^1H NMR: δ (ppm) = 1.2 (s, 9H), 3.90–3.92 (d, 2H), 5.10–5.11 (d, 1H), 5.13–5.14 (d, 1H), 5.8–5.9 (m, 1H); ^{13}C NMR: δ (ppm) = 27.5 (CH₃), 63.05 (OCH₂), 73.6 (C), 115.6 (C), 136.2 (C).

t-Butyl prop-2-ynyl ether 2b: ^1H NMR: δ (ppm) = 1.25 (s, 9H), 2.4 (s, 1H), 4.1 (s, 2H); ^{13}C NMR: δ (ppm) = 27.3 (CH₃), 31.0 (CH), 36.3 (C), 53.24 (C), 72.82 (C).

t-Butyl pentyl ether 2c: ^1H NMR: δ (ppm) = 0.76 (t, 3H), 1.2 (s, 9H), 1.25 (m, 2H), 1.36 (m, 2H), 1.57 (m, 2H), 3.56 (m, 2H); ^{13}C NMR: δ (ppm) = 14.0 (CH₃), 22.7 (CH₃), 28.3 (CH₂), 29.2 (CH₂), 32.0 (CH₂), 62.0 (OCH₂), 71.9 (C).

1-t-Butoxyoctane 2d:^[7] ^1H NMR: δ (ppm) = 0.88 (t, J = 6.8, 3H), 1.19 (s, 9H), 1.20–1.40 (m, 10H), 1.45–1.55 (m, 2H), 3.32 (t, J = 6.6, 2H); ^{13}C NMR: δ (ppm) = 14.0 (CH₃), 22.6 (CH₂), 26.2 (CH₂), 27.5 (CH₃), 29.3 (CH₂), 29.5 (CH₂), 30.7 (CH₂), 31.8 (CH₂), 61.6 (CH₂), 72.3 (C).

1-t-Butoxybenzene 2e:^[7] ^1H NMR: δ (ppm) = 1.35 (s, 9H), 6.95–7.00 (m, 2H), 7.05–7.10 (m, 1H), 7.25–7.30 (m, 2H); ^{13}C NMR: δ (ppm) = 29.4 (CH₃), 78.3 (C), 123.3 (CH), 124.2 (CH), 128.8 (CH), 131.9 (C).

1-t-Butoxy-4-methoxybenzene 2f:^[7] ^1H NMR: δ (ppm) = 1.33 (s, 9H), 3.72 (s, 3H), 6.76 (m, 4H); ^{13}C NMR: δ (ppm) = 28.0 (CH₃), 56 (C), 71.7, 78.0 (C), 113.8 (CH), 123.5 (C), 154.3 (C).

1-t-Butoxy-3-chlorobenzene 2g:^[7] ^1H NMR: δ (ppm) = 1.35 (s, 9H), 6.88 (dd, 1H), 7.00 (t, 1H), 7.05 (dd, 1H), 7.18 (t, 1H); ^{13}C NMR: δ (ppm) = 28.8 (CH₃), 79.2 (C), 122.2 (CH), 123.4 (CH), 124.3 (CH), 129.6 (CH), 134.0 (C), 156.4 (C).

1-t-Butoxy-4-fluorobenzene 2h:^[7] ^1H NMR: δ (ppm) = 1.31 (s, 9H), 6.93 (s, 2H), 6.94 (s, 2H); ^{13}C NMR: δ (ppm) = 28.7 (CH₃), 78.5 (C), 115.2 (d, CH), 125.5 (d, CH), 151.1 (C), 159.1 (d, C).

1-(t-Butoxymethyl)benzene 2i:^[7] ^1H NMR: δ (ppm) = 1.31 (s, 9H), 4.47 (s, 2H), 7.25–7.40 (m, 5H); ^{13}C NMR: δ (ppm) = 27.7 (CH₃), 64.1 (CH₂), 73.4 (C), 127.1 (CH), 127.4 (CH), 128.3 (CH), 139.9 (C).

1-t-Butoxy-3-(tert-butoxymethyl)benzene 2j: ^1H NMR: δ (ppm) = 1.29 (s, 9H), 1.35 (s, 9H), 4.42 (s, 2H), 6.8 (d, 1H), 6.9 (s, 1H), 7.0 (d, 1H), 7.3 (m, 1H); ^{13}C NMR: δ (ppm) = 27.6 (CH₃), 28.8 (CH), 63.8 (OCH₂), 73.3 (C), 77.9 (C), 113.7 (C), 116.7 (C), 119.8 (C), 128.5 (CH), 141.0 (CH), 158.8 (CH).

1-t-Butoxynaphthalene 2 k:^[7] ¹H NMR: δ (ppm) = 1.46 (s, 9H), 7.10 (dd, 1H), 7.33 (t, 1H), 7.40–7.45 (m, 2H), 7.50 (d, 1H), 7.75–7.80 (m, 1H), 8.20–8.25 (m, 1H). ¹³C NMR: δ (ppm) = 29.1 (CH₃), 79.7 (C), 116.3 (CH), 122.3 (CH), 123.4 (CH), 125.1 (CH), 125.4 (CH), 125.9 (CH), 127.5 (CH), 130.0 (C), 134.8 (C), 152.1 (C).

2-t-Butoxynaphthalene 2l:^[7] ¹H NMR: δ (ppm) = 1.41 (s, 9H), 7.18 (dd, 1H), 7.35–7.45 (m, 3H), 7.65–7.80 (m, 3H). ¹³C NMR: δ (ppm) = 28.9 (CH₃), 78.9 (C), 119.7 (CH), 124.4 (CH), 125.0 (CH), 125.9 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 130.3 (C), 134.1 (C), 152.1 (C).

2-t-Butoxy-1,2-diphenylethanone 2 m:^[7] ¹H NMR: δ (ppm) = 1.25 (s, 9H), 5.62 (s, 1H), 7.20–7.55 (m, 8H), 8.05–8.10 (m, 2H). ¹³C NMR: δ (ppm) = 28.0 (CH₃), 76.0 (C), 79.7 (CH), 126.1 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 130.0 (CH), 132.7 (CH), 135.2 (C), 138.6 (C), 200.1 (C).

t-Butoxycyclopentane 2n:^[7] ¹H NMR: δ (ppm) = 1.18 (s, 9H), 1.40–1.50 (m, 4H), 1.60–1.85 (m, 4H), 3.95–4.05 (m, 1H). ¹³C NMR: δ (ppm) = 23.7 (CH₂), 28.6 (CH₃), 34.9 (CH₂), 72.8 (CH), 73.5 (C).

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