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An efficient synthesis of *tert*-butyl ethers/esters of alcohols/amino acids using methyl *tert*-butyl ether

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ABSTRACT

A facile synthesis of a wide variety of *tert*-butyl ethers and *tert*-butyl ester derivatives under mild conditions is described. Alcohols etherified with *tert*-butyl methyl ether as *tert*-butyl source and solvent, in the presence of sulfuric acid. Many amino acid *tert*-butyl esters have been synthesized by this procedure. The reaction is simple, inexpensive, easily scaled up, and proceeds without observable racemization. A green method was developed for the deprotection of this group using Amberlite resin IR 120-H as catalyst.

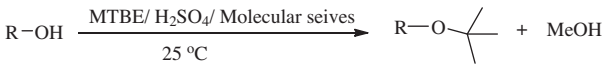
tert-Butyl group is a very important protecting group for acids, alcohols, and phenols in organic chemistry and peptide synthesis,[1] because of their stability toward strong basic conditions like organolithium and organomagnesium compounds. *tert*-Butyl groups are one of the underused protecting groups, since they are sensitive toward strong acids and harsh formation conditions.[2]

Alcohols are protected as *tert*-butyl ethers by two general methods; by generating *tert*-butyl carbocation intermediate from isobutylene in the presence of BF_3 ether–phosphoric acid,[3] sulfuric acid[4] at −25 °C or with trifluoromethane sulfonic acid[5] at −50 °C. Although use of isobutylene leads to a clean reaction with good conversion, but it calls for an expensive autoclave and long gas purging time under very cold reaction conditions.[6] Additionally, the gas used in large excess needs to be purged out of the reaction mass. Thus problem gets compounded by the highly flammable nature of the gas which also has very unpleasant smell. *tert*-Butyl trichloroacetimidate[7] is sometimes used as an alternative to gaseous isobutylene. Here the problem lies with the usage of costly reagents and high chromatographic purification of residual trichloroacetimidate. In both the methods, Lewis or mineral acids are used to enhance the yield.

On the other hand Bartoli et al.[8] reported an unusual and interesting method for *tert*-butyl ethers preparation by using Boc anhydride as *tert*-butyl source and metal perchlorate as catalyst and found that this method is compatible with many functional groups. But this method is inappropriate to alcohol containing amine functionalities, where in principle it may form *N*-Boc derivative. Recently Alessandro et al.[9] have found an efficient method of preparing *tert*-butyl ethers by using *tert*-butyl acetate as *tert*-butyl source and metal perchlorate as catalyst at ambient condition. This method leads to the formation of acetylated derivative as the byproduct.

Methyl *tert*-butyl ether (MTBE) is the safest ether among the ether solvents used in the laboratory and in industrial processes. MTBE alone decomposes to give isobutylene and methanol in the presence of acid catalyst.[10] Many methyl esters are prepared using MTBE under reflux temperature.[11] In this connection and to the best of our knowledge, we here report for the first time the synthesis of *tert*-butyl ethers using MTBE as a source of *tert*-butyl group as well as the solvent. We have utilized molecular sieves (4A × 1.5 mm) as methanol trapping agent, which is produced in the reaction[12] (Scheme 1).

In order to establish a suitable reaction condition for the above discussed conversion, choice of acids, solvent, and temperature is critical. In this perspective compound 9-fluorenylmethanol (**1a**) was chosen as a model substrate to optimize the reaction conditions (Scheme 2). Initially several acids were screened (Table 1 entries 1–9), sulfuric acid and methanesulfonic acid were found to be excellent (entries 5 and 6) among the acids used. Thionyl chloride did not give satisfactory result. On the other hand solvent effect has also been investigated (Table1, entries10–13) and found that the solvents used were ineffective to get desired product in a good yield.



Scheme 1. Preparation of *tert*-butyl ethers using MTBE and sulfuric acid.

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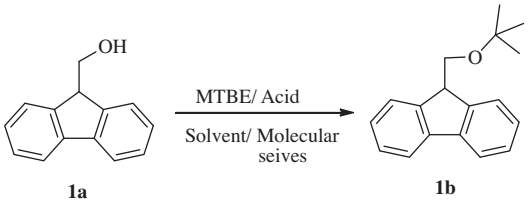


Scheme 2. Protection of 9-fluorenylmethanol (**1a**) with different acids/solvents/concentrations/temperatures.

Table 1
Effect of acid and solvent on the conversion of **1a**–**1b** at 25 °C[a]

Entry	Acid (1 mmol)	Solvent	Yield[b] (%)
1	Acetic acid	—	0
2	Formic acid	—	0
3	Conc. HCl	—	0
4	Sulfamic acid	—	Trace
5	Sulfuric acid	—	81
6	Methanesulfonic acid	—	75
7	Phosphoric acid	—	0
8	Trifluroacetic acid	—	31
9	Thionyl chloride	—	67
10	Sulfuric acid	Methanol	0
11	Sulfuric acid	MDC	31
12	Sulfuric acid	THF	29
13	Sulfuric acid	DMF	0

[a] Compound **1a** (10 mmol), acid (10 mmol), MTBE (10 mL), and solvent (10 mL), 6 h.
[b] Isolated yield.

Influence of the amount of acid on the yield of the product was also evaluated and found that 2 mol % sulfuric acid results in maximum yield of the product (Table 2, entry 4), whereas increasing the concentration of sulfuric acid resulted in the gradual loss of yield (Table 2, entries 5 and 6).

In continuation of the above, effect of temperature was also monitored and found that carrying out the reaction at 10 °C (Table 3, entry 3) results in moderate yield, whereas at 25 °C (entry 5) good yield was observed. By gradually increasing the temperature above 25 °C yields were decreased.

After the optimization of reaction conditions, several examples such as alcohols and phenols were subjected to explore the scope and limitation of this developed protocol (Scheme 1).[13] Under the standard reaction conditions different alcohols were converted into corresponding *tert*-butyl ethers and the results are presented in Table 4.

Simple primary alcohols such as hexanol (entry 1), heptanol, (entry 2) and octanol (entry 3) underwent smooth etherification with good conversion in short time, whereas aromatic alcohols like benzyl alcohol (entry 4) and 9-fluorenylmethanol (entry 5) have formed respective *tert*-butyl ethers under this condition without any ring alkylated product. Cyclic secondary alcohols such as cyclohexanol (entry 6), menthol, (entry 7) and cyclododecanol

Table 2
Screening of acid concentration[a]

Entry	H_2SO_4 (mol %)	Yield[b] (%)
1	0.5	61
2	1.0	70
3	1.5	83
4	2.0	94
5	2.5	81
6	3.0	73

[a] 9-Fluorenylmethanol **1a** (1 mmol), MTBE (10 mL), at 25 °C for 4 h.
[b] Isolated yield.

Table 3
Reaction of **1a** with MTBE at various temperatures[a]

Entry	Temperature (°C)	Yield[b] (%)
1	−10	15
2	0	24
3	10	69
4	20	85
5	25	94
6	30	76
7	40	61
8	50	11

[a] Compound **1a** (10 mmol), acid (2.0 mol %) and MTBE (10 mL), reaction time 6 h.
[b] Isolated yield.

(entry 8) were also easily etherified under this reaction condition. Other alcohols like octane-2-ol (entry 9) and methyl mandelate (entry 10) gave 70–74% yield in 7 h. Diols such as tartaric acid methyl ester (entry 11) and ethylene glycol (entry 12) gave 65–68% of di *tert*-butyl ethers after 10 h reaction. With glycerol (entry 13), we were able to get 45% of tri *tert*-butyl ether. Alkyne diol and alkene diol were etherified using this method without any addition or substitution product. Butyne-1,4-diol (entry 14) gave a 61% yield whereas butene-1,4-diol (entry 15) gave 63% of di *tert*-butylated product. Yields were very low in the case of diol and triol because of their conformational mobility in the solution. We were able to achieve maximum conversion by using excess of MTBE in both diols and triol.

To test the chemo selectivity, threo-norpseudophedrine (entry 16) and 2-aminoethanol (entry 17) were subjected to reaction condition. Here alcohol was converted into the corresponding *tert*-butyl ethers in short time, leaving amino group intact, whereas ring alkylation was observed in case of phenol (entry 18) and 1-napthol (entry 19).

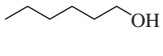
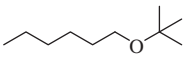
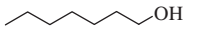
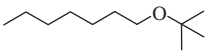
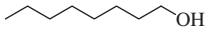
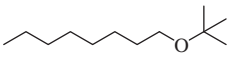
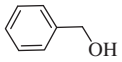
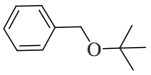
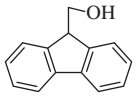
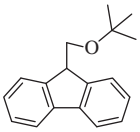
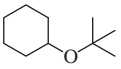
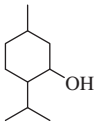
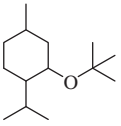
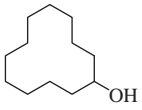
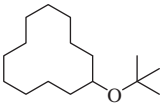
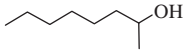
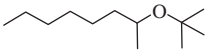
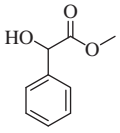
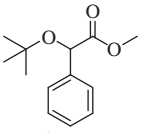
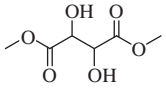
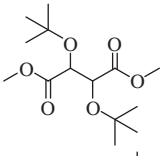
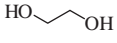
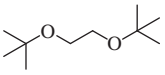
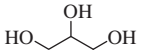
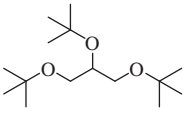
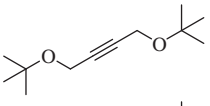
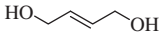
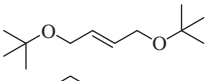
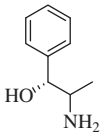
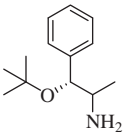
In the light of the above, this method was further extended to one pot preparation of *tert*-butyl ether and *tert*-butyl ester of amino acids.[14] Amino acids were subjected to the reaction conditions as discussed above and found that di *tert*-butyl product was formed and the obtained results are tabulated in Table 5. Here, with respect to amino acids satisfactory results were not obtained. However employing this protocol, configuration of the products was unchanged which is a remarkable feature of this system. When the reaction was carried out using magnetic stirrer recovery of molecular sieves was very less and hence we used vortex shaker to achieve good yield of products with significant recovery of molecular sieves which can be further used.

Preliminary experiments were carried out to understand the mechanism of the reaction for the formation of *tert*-butyl ethers. We assumed that MTBE decomposes to *tert*-butyl carbocation and methoxide ion under acidic condition. This carbocation reacts with the alcohol to give *tert*-butyl ether (path A of Scheme 3). Our hypothesis is well supported by the reaction of MTBE with triphenylmethanol (entry 20 in Table 4). This results in the formation of (methoxymethanetriyl)tribenzene with an excellent yield (as path B of Scheme 3) along with the formation of *tert*-butanol. The stability of the carbocation plays an important role in this reaction.

Cleavage of *tert*-butyl ether: A simple and green methodology was developed for the deprotection of *tert*-butyl ethers to the corresponding alcohol with a good yield. Amberlite resin IR120-H was used as a catalyst and methanol was found to be the best solvent for the reaction. As a model reaction we have selected 9-fluorenylmethanol *tert*-butyl ether **1b** (Scheme 4).[15] Various solvents were employed to achieve good conversion, methanol served the purpose, where the other solvents were not up to the satisfactory level (Table 6).

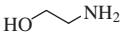
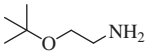
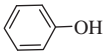
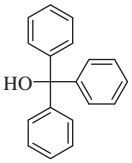
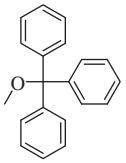
In conclusion, we report a very simple, efficient, and practical method to prepare *tert*-butyl ethers using MTBE and H_2SO_4 under

Table 4
Conversion of alcohol to *tert*-butyl ethers

Entry	Substrate	Product	Reaction time (h)	Yield[a] (%)
1			4	91
2			4	90
3			4	90
4			5	78
5			4	94
6			7	79
7			7	75
8			8	70
9			7	70
10			7	74
11			10	65[b]
12			10	68[b]
13			12	45[b]
14			8	61[b]
15			8	63[b]
16			4	81

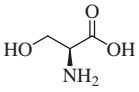
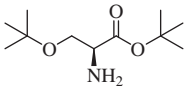
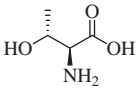
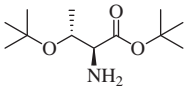
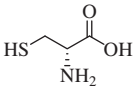
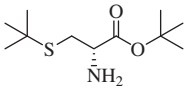
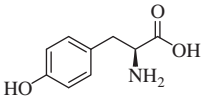
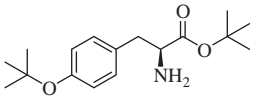
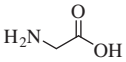
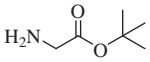
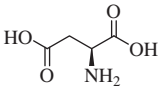
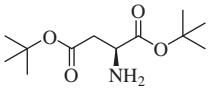
(*continued on next page*)

Table 4 (*continued*)

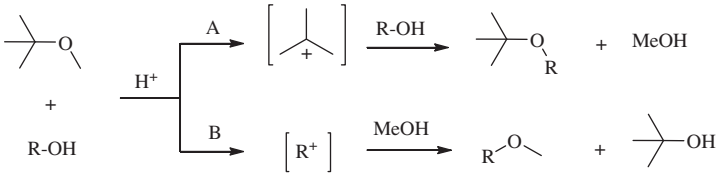
Entry	Substrate	Product	Reaction time (h)	Yield[a] (%)
17			4	76
18		–	12	0[c]
19		–	12	0[c]
20			6	95[d]

[a] Isolated yield.
[b] Excess of MTBE used (20 volume w.r.t. weight of the starting material).
[c] Ring alkylated product observed as prominent.
[d] Product formed according to path B.

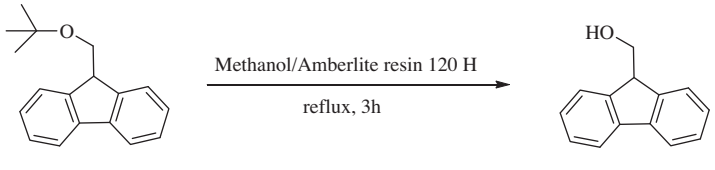
Table 5
tert-Butyl ethers and esters of amino acids

Entry	Starting material	Product	Reaction time (h)	Yield[a] (%)
1			2	35
2			2	30
3			2	32
4			2	27
5			2	51
6			2	39

[a] Isolated yield.



Scheme 3. Proposed mechanism of the reaction path way.



1b **1a**

Scheme 4. Conversion of **1b**–**1a** using solid support resin.

Table 6
Conversion of **1b**–**1a** with different solvents

Entry	Solvent	Time (h)	Yield (%)
1	Acetonitrile	3	70
2	MDC	3	65
3	Methanol	3	91
4	Ethyl acetate	3	50
5	THF	3	78

ambient condition. This method is useful for the preparation of *tert*-butyl ethers and laboratory scale preparation of *tert*-butyl protection of amino acids under normal laboratory condition and also we have developed a green protocol for the deprotection of *tert*-butyl ether.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.108.

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13. Procedure for the preparation of *tert*-butyl ethers: 10 mmol of substrate, 2 g of molecular sieves and 10 mL of MTBE were taken in a 50 mL round bottom flask fitted with septum and cooled to 25 °C. To this solution 20 mmol of sulfuric acid was added very slowly using syringe. Reaction was carried out at 25 °C for given reaction time as shown in Table 4. Reaction mass was slowly quenched in to 20 mL of saturated aqueous solution of sodium bicarbonate. Organic layer was separated and washed with water (2 × 20 mL), dried over anhydrous sodium sulphate. Unreacted MTBE was recovered and reused. Obtained residue was purified by eluting through flash column using hexane and MTBE (10:1).
14. Procedure for the preparation of *tert*-butyl ether and esters of amino acids: 10 mmol of amino acid, 4 g of molecular sieves and 20 mL of MTBE was taken in a 50 mL round bottom flask fitted with a septum and cooled to 25 °C. To this solution 30 mmol of sulfuric acid was added very slowly using syringe. Reaction was carried out at 25 °C for given reaction time as shown in Table 5. Reaction was slowly quenched in to 25 mL of saturated aqueous solution of sodium bicarbonate. Organic layer was separated, and aqueous layer was extracted twice with hexane. Combined organic layer was washed with water, dried over sodium sulphate and the solvent was removed by distillation.
15. Procedure for the deprotection of *tert*-butyl ether: Compound **1b** (1 g) was taken in 5 mL of methanol in a 50 mL round bottom flask and 1 g of amberlite resin 120-H was added. Reaction mass was refluxed for 5 h, filtered and washed with methanol. Methanol was removed under vacuum to yield pure compound **1a**.