

## A Facile and Highly Chemoselective Protection of Primary Hydroxyl Groups with 2-Methyl-1-Butene.

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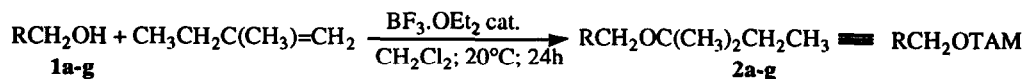
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*Key words: chemoselective protection; primary alcohols; tert-amyl ether*

**Abstract:** *The chemoselective formation of tert-amyl ether (tam-ether) of primary hydroxyl groups in the presence of secondary hydroxyl groups is described.*

In this paper we describe a new chemoselective protection of primary hydroxyl groups. Many protective groups have been developed for this purpose<sup>1</sup> (eg. *tert*-butyl ether, triphenylmethyl ether and derivatives, *tert*-butyldimethylsilyl ether, pivaloate ester etc...)<sup>1</sup>. However most of these methods suffer either of low yielding or drastic conditions for the preparation and/or the removal step, or availability of the reagents (eg. price, low boiling point, etc..), or difficulty in the purification of the products. Since few protective groups cannot satisfy all these criteria, elaboration of new protective groups is still needed. Among known procedures for the selective protection of primary hydroxyl groups, the *tert*-butyl group presents several advantages: price, good yields. However, formation of *tert*-butyl ethers require large excess of isobutene and particular reaction conditions (bubbling of isobutene in a solution of CH<sub>2</sub>Cl<sub>2</sub> containing the alcohol)<sup>2</sup>. We found that isobutene can be advantageously replaced by a nearly *stoichiometric amount* of 2-methyl-1-butene (1 or 2 equivalents) for the highly selective protection of primary hydroxyl groups of several substrates<sup>3</sup> (Scheme 1 and Table 1) in almost neat conditions (20 mol/L in CH<sub>2</sub>Cl<sub>2</sub>) and in the presence of 10% molar of BF<sub>3</sub>.OEt<sub>2</sub><sup>4,5</sup>.

Scheme 1



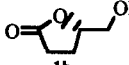

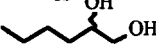
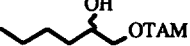


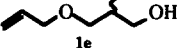
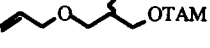
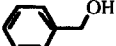
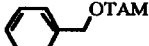
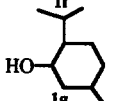
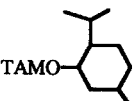


It is noteworthy that in the presence of secondary hydroxyl groups, we observed the sole formation of mono-*tert*-amyl ethers (mono-*tam*-ether), at the primary position, with less than 2-4% of the bis-*tert*-amyl ethers (entries 3-5). Furthermore, this protection can be performed with benzylic hydroxyl groups (entry 6) and in the presence of other functional groups as alkyl halide (entry 1), lactone (entry 2), allyl ether (entry 5). The high selectivity in favour of primary hydroxyl groups is demonstrated by the very low reactivity of menthol with 2-methyl-1-butene under the same reaction conditions (less than 3% of the formation of the corresponding *tam*-ether **2g** after 72 h at 20°C, entry 7).

The typical procedure for the *tam*-ether (*tert*-amyl ether) formation of a primary hydroxyl group is as follow : alcohol **1c** (0.507 mg, 4.3 mmol) with 2-methyl-1-butene (0.47 mL, 4.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.2 mL) was stirred at room temperature and  $\text{BF}_3 \cdot \text{OEt}_2$  (0.053 mL, 0.43 mmol) added<sup>6</sup>. After the reaction solution was stirred for 24 hours at room temperature, the volatiles were distilled off at reduced pressure and the crude residue was purified by flash chromatography (100%  $\text{CH}_2\text{Cl}_2$ , then 1:1 *c*- $\text{C}_6\text{H}_{12}$ /EtOAc) to afford 0.628 g (78%) of pure *tam*-ether **2c** and 40mg of bis-*tert*-amyl ether (3%).

Removal of the protective group has been realized under mild conditions as described for *tert*-butyl ethers<sup>2</sup>, to afford the corresponding acetates in typical yields of 90-95% .

Table 1

Entry	Substrate	<i>tam</i> -ether (yield %) <sup>f</sup>
1		 <b>2a</b> (98)
2		 <b>2b</b> (80)
3		 <b>2c</b> (78) <sup>b</sup>
4		 <b>2d</b> (83) <sup>c</sup>
5		 <b>2e</b> (85) <sup>d</sup>
6		 <b>2f</b> (85)
7		 <b>2g</b> (3) <sup>e</sup>

a) 2 eq. of 2-methyl-1-butene were used except for entry 3 where 1eq. was used; yield in isolated product; b) <3% of bis-*tert*-amyl ether; c) <6% of bis-*tert*-amyl ether; d) <2% of bis-*tert*-amyl ether; e) 72 h at RT.

This new procedure for the selective protection of primary hydroxyl groups is of great interest because of the excellent chemoselectivity observed, ease and mild conditions employed (catalytic amount of  $\text{BF}_3 \cdot \text{OEt}_2$ )<sup>7</sup>, excellent stability in acidic or alcalin medium, mild removal step.

#### References and notes :

- Greene T.W., *Protective Groups in Organic Synthesis*, ed. John Wiley & Sons, New-York, 1981.
- Alexakis A., Gardette M., Colin S., *Tetrahedron Lett.*, 1988, 29, 2951-2954.
- Compounds **1a-g** are commercially available.
- tert*-amyl ethyl ether has been previously prepared in the presence of  $\text{Hg}(\text{OAc})_2$  by: Brown H.C., Rei M.H., *J. Am. Chem. Soc.*, 1969, 91, 5646-5647.
- All new *tert*-amyl ether gave satisfactory spectroscopic data.
- Use of either  $\text{AlCl}_3$ ,  $\text{LiClO}_4$ ,  $\text{SnCl}_4$ , *p*-TSA did not allow us to obtain the desired *tert*-amyl ethers, whereas  $\text{H}_2\text{SO}_4$  conc. and Amberlyst H-15 gave rise to the expected *tam*-ethers.
- When one equivalent of  $\text{BF}_3 \cdot \text{OEt}_2$  is used, the reaction does not occur and starting material is recovered unchanged.

(Received in France 16 July 1993; accepted 19 July 1993)