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# $BiBr_3$, an efficient catalyst for the benzylation of alcohols: 2-phenyl-2-propyl, a new benzyl-type protecting group

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## Abstract

The benzylation of aliphatic alcohols with various benzylic alcohols has been achieved in the presence of $BiBr_3$ under mild conditions. 2-Phenylpropan-2-ol proved to be the most efficient and can be considered as a novel protecting group. © 2000 Elsevier Science Ltd. All rights reserved.

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Numerous methods are available for protecting an alcohol moiety.[1] Conversion into the corresponding ethers has been recognized as a common and useful method for the protection of hydroxyl groups. Most commonly used are the tetrahydropyranyl (THP), 1-ethoxyethyl (EE), *t*-butyldimethylsilyl (TBDMS), benzyl (Bn) derivatives, etc. The experimental conditions used for benzylation being rather drastic (BnBr, DMSO, KOH), the need for a milder method is very important.

In the course of our ongoing research using bismuth(III) halides[2,3] as reagents for halogenation reactions, we recently reported a new, simple and efficient $BiBr_3$-promoted etherification that allows the synthesis of symmetrical benzylic ethers from benzylic alcohols.[2] This reaction is specific to benzylic alcohols. Several attempts with aliphatic alcohols proved unsuccessful. This difference of reactivity prompted us to examine the possibility of using this method to protect aliphatic alcohols as benzylic ethers.

The potential of this approach was demonstrated by the synthesis of a series of alkyl–benzyl ethers from various benzylic alcohols (benzyl alcohol (Bn-OH), 1-phenylethanol (Pe-OH) and 2-phenylpropan-2-ol (Pp-OH)) in the presence of $BiBr_3$ as catalyst.

Bismuth(III) salts as catalysts are attracting the attention of an increasing number of chemists in various domains.[4] To the best of our knowledge, the results reported here are the first examples of the use of $BiBr_3$ to promote the formation of benzylic ethers. The reaction is described in Scheme 1 and the results are summarized in Table 1.

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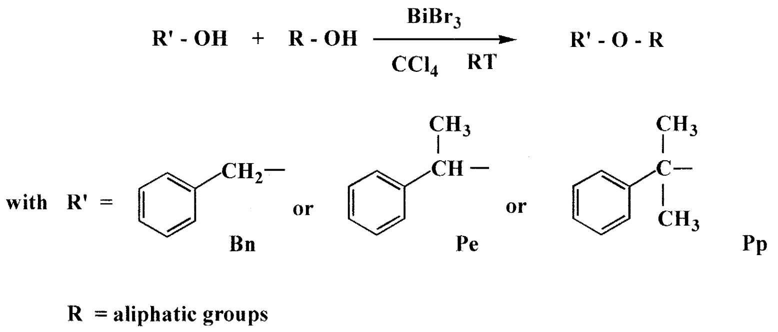

Scheme 1.

Table 1
Protection of alcohols as benzyl-type ethers using $BiBr_3$ as catalyst in $CCl_4$ at 25°C[a]

| | | 2-Phenylpropan-2-ol | | 1-Phenylethanol | | Benzyl alcohol | |
|---|---|---|---|---|---|---|---|
| **Entry** | **R-OH** | **Reaction time (min)** | **ROR'[b] % ( )[c]** | **Reaction time (min)** | **ROR'[b] % ( )[c]** | **Reaction time (h)** | **ROR'[b] % ( )[c]** |
| 1 | **methanol** | 5 | 100 (95) | 30 | 89 (81) | 8 | 100 (92) |
| 2 | **1-butanol** | 5 | 100 (95) | 20 | 100 (92) | 90 | 100 (95) |
| 3 | **1-octanol** | 5 | 100 (95) | 30 | 92 (88) | 72 | 90 (87) |
| 4 | **2-methylbutanol** | 5 | 100 (96) | 15 | 99 (95) | 24 | 92 (89) |
| 5 | **2-butanol** | 5 | 100 (94) | 5 | 73 (67) | 96 | 82 (77) |
| 6 | **cyclohexanol** | 60 | 98 (92) | 120 | 82 (78) | 96 | 70 (65) |
| 7 | **tertiobutanol** | 30 | 98 (90) | 120 | 100 (95) | 2 | 82 (76) |

[a] ROH (1 equiv.); R'OH (1 equiv.); $BiBr_3$ (1 equiv.). For the experimental conditions, see note 5.

[b] G.C. monitoring; the by-products were symmetrical ethers (R'OR'). The yield of the unsymmetrical ether, ROR', can be optimized by using a slight excess of benzylic alcohols ( 1.2 mol. equiv.). The excess is converted to the symmetrical ether R'OR' whereas all the aliphatic alcohol is converted to the unsymmetrical ether (ROR'). For example, if cyclohexanol (1 mol. equiv. ) is reacted with 1-phenylethanol (1.2 mol. equiv.), a 100% yield of the unsymmetrical ROR' ether is obtained within 2 h. In most cases, the two ethers are easily separated by column chromatography.

[c] Isolated yield of pure product displaying $^1$H NMR data consistent with its assigned structure.

As shown in Table 1, various aliphatic alcohols were reacted with either benzyl, 1-phenylethyl and 2-phenyl-2-propyl alcohols in the presence of $BiBr_3$ in $CCl_4$ at room temperature to provide the expected ethers (ROBn, ROPe or ROPp). According to the experimental conditions used,[5] it was expected that a complex would first form between ROH and $BiBr_3$ due to the weak Lewis acid character of the latter.[6]

The data reported in Table 1 call for the following remarks:

(i) all the alcohols studied were converted in good yields into their corresponding benzylic ethers under conditions milder (room temperature, neutral medium) and cheaper than those usually described in the literature;[1]

(ii) etherifications were completed within 5–60 min, 5–120 min and 2–96 h for, respectively, 2-phenylpropan-2-ol, 1-phenylethanol and benzyl alcohol;

(iii) whatever the aliphatic alcohol, the reactivity of Pp-OH was significantly higher than Pe-OH and especially higher than Bn-OH. For example (Table 1, entry 2), under identical conditions, Pp-OH gave a 95% yield of ether after 5 min, while Pe-OH afforded nearly the same yield after 20 min. In contrast, benzyl alcohol displayed a substantially lower reactivity. Completion of the reaction required much longer reaction times, i.e. up to 90 h.

It appears that the formation of benzylic ethers by the method reported here is more convenient than the usual *O*-benzylation. However, for the 2-phenyl-2-propyl and 1-phenylethyl protecting groups to find wide applications in organic synthesis, they must be easily cleaved under mild conditions.

In this respect, ethers **1**–**10** were submitted to hydrogenolysis in the presence of ammonium formate and 10% Pd/C in ethanol at 50°C. The results are given in Table 2.

Table 2
Deprotection of benzylic ethers (ROBn and ROPe) using ammonium formate and 10% Pd/C

| Ethers | Reaction time | Ethers | Reaction time |
|---|---|---|---|
| Pe-O-1-butyl **(1)** | 2 h 30 | Bn-O-tertiobutyl **(6)** | 2 h 30 |
| Pe-O-tertiobutyl **(2)** | 2 h 30 | Pp-O-1-butyl **(7)** | 2 h 30 |
| Pe-O-cyclohexyl **(3)** | 2 h 45 | Pp-O-2-butyl **(8)** | 2 h |
| Pe-O-2-butyl **(4)** | 2 h 30 | Pp-O-cyclohexyl **(9)** | 2 h |
| Bn-O-1-butyl **(5)** | 2 h 15 | Pp-O-tertiobutyl **(10)** | 2 h |

It can be seen that ethers deriving from 1-phenylethanol (**1**–**4**) and 2-phenylpropan-2-ol (**7**–**10**) were as easy to cleave as those derived from benzyl alcohol. All the reactions mentioned above were completed in a short time (2–2 h 45 min). However, owing to the tertiary nature of the 2-phenyl-2-propyl group, we anticipated that this group could also be easily cleaved under acidic conditions, in contrast to conventional benzyl ethers.

Compounds **1**–**10** were, therefore, submitted to acidolysis on treatment with 50% trifluoroacetic acid (5 mol. equiv.) in $CH_2Cl_2$ at room temperature.

As expected, benzyl and 1-phenylethyl ethers proved much more stable under these conditions than those derived from 2-phenylpropan-2-ol. For instance, no cleavage of ethers **1**–**6** was detected within

48 h. In contrast, ethers **7**–**10** derived from 2-phenylpropan-2-ol were cleaved under the same acidic conditions within 4 h.

Consequently, the 2-phenyl-2-propyl group provides a novel useful method for the protection of hydroxyl groups. It can be removed in experimental conditions affecting neither benzyl nor phenylethyl ethers. In addition, it is usable with substrate-possessing unsaturated functions that would have been affected by hydrogenolysis.

In summary, our procedure, based on the utilization of $BiBr_3$, provides a new simple, efficient and useful alternative for the preparation of benzylic ethers; in particular, those derived from 1-phenylethanol and 2-phenylpropan-2-ol. The advantages of this procedure are mainly: (i) the mild conditions; (ii) easy work-up; (iii) very good yields; and (iv) fast reaction times.

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5. Benzylation of alcohols. General procedure: A mixture of ROH (1.25 mmol), $BiBr_3$ (1.25 mmol) in $CCl_4$ (3 ml) at room temperature was stirred vigorously for 15 min (1 to 2 min for tertiary alcohols). To this stirred suspension, a solution of R′OH (1.25 mmol) in $CCl_4$ (2 ml) was slowly added and the stirring continued. On completion (GC and TLC monitoring), the reaction mixture was filtered and the solvent was removed under reduced pressure to provide the product, which was purified on a silica gel chromatography with dichloromethane.
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