

Benylation of Alcoholic Hydroxyl Groups with Benzyl Mesylate by Using a Catalytic Amount of Lithium Tetrakis(pentafluorophenyl)borate in the Coexistence of Lithium Triflate and Magnesium Oxide

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Several alcohols possessing alkali-labile substituents such as halogen, ester and ketone were effectively benzylationed with benzyl mesylate by using a catalytic amount of lithium tetrakis(pentafluorophenyl)borate [$\text{LiB}(\text{C}_6\text{F}_5)_4$] in the coexistence of lithium triflate (LiOTf) and magnesium oxide (MgO) to afford the corresponding benzyl ethers in good to excellent yields.

Benzylation of alcohols is often conducted for the protection of hydroxyl group of alcohols since thus formed benzyl ether can survive under various reaction conditions and may easily be deprotected by catalytic hydrogenation under mild conditions. Therefore, a benzyl ether group is often employed as a protected hydroxyl group in the synthesis of complex molecules such as natural products. Most benzylation of alcohols [benzyl bromide (BnBr), sodium hydride (NaH) in DMF] is typically carried out under strongly alkaline conditions, and alkali-labile functional groups cannot survive through the reaction. There have been developed some useful procedures for benzylation of alcohols under milder conditions:¹ for example, the use of benzyl trichloroacetimidate affected benzylation under mild acidic conditions, which was compatible with ester and acetal protecting groups.² Also, treatment of optically pure ethyl lactate with silver(I) oxide (Ag_2O) and BnBr gave benzyl ether without racemization while benzylation of the above ethyl lactate under the typical benzylation conditions gave benzyl ether in 50–75% ee.³ Further, treatment of carbohydrates with benzyl triflate, generated in situ from benzyl alcohol and triflic anhydride in 2,6-di-*t*-butylpyridine at -70°C , gave the corresponding benzylationed derivatives.⁴ Considering the reported procedures described above, a development of a new method which can realize more efficient benzylation of hydroxyl groups under even milder conditions is still desired for the preparation of benzyl ethers from alcohols possessing alkali-sensitive functional groups in the same molecule.

Recently, it was reported from our laboratory that $\text{LiB}(\text{C}_6\text{F}_5)_4$ showed a unique catalytic activity in Friedel–Crafts benzylation of aromatic compounds when benzyl chlorides or mesylates was used in the coexistence of MgO .⁵ In the above reaction, $\text{LiB}(\text{C}_6\text{F}_5)_4$ effectively activated benzyl mesylates, and its benzyl group was smoothly introduced to aromatic rings. It was then supposed that the activated benzyl mesylates would react with other nucleophiles such as alcohols. In this communication, we would like to report a practical method for the benzylation of alcohols possessing alkali-labile substituents such as halogen, ester and ketone with benzyl mesylate to give the corresponding benzyl ethers in good to excellent yields under almost neutral conditions.

In order to optimize the benzylation conditions, benzylation of 1-octanol was first tried. When 1-octanol was benzylationed with benzyl mesylate in the presence of MgO (1.6 equiv) by using 10

mol% of $\text{LiB}(\text{C}_6\text{F}_5)_4$ at 40°C in dichloromethane, the corresponding benzyl ether was obtained in 54% yield (Table 1, entry 1).⁶ No benzylation reaction did proceed when $\text{LiB}(\text{C}_6\text{F}_5)_4$ was not added (entry 2). When the reaction was carried in the absence of MgO , the yield turned out to be low (entry 1). At higher temperatures, further Friedel–Crafts reaction of the formed benzyl ether with benzyl mesylate took place and the yield decreased (entry 3). In order to avoid the above polybenzylation reaction, the benzylation was carried out therefore by using *p*-chlorobenzyl mesylate which afforded *p*-chlorobenzyl ether, a less reactive ether, to the Friedel–Crafts reaction. Then, the yield improved and *p*-chlorobenzyl ether was obtained in 75% yield (entry 4).⁷ In order to further improve the yield of the above benzylation reaction, a stoichiometric amount of LiOTf ⁸ was added on the assumption that the catalyst, $\text{LiB}(\text{C}_6\text{F}_5)_4$, would be regenerated by trapping the formed benzyl ether with LiOTf . As a result, the benzylation reaction proceeded more efficiently and gave the benzyl ether in higher yields. It was also found that using a mixed solvent of cyclohexane–dichloromethane (2:1) helped the reaction to proceed more smoothly than using dichloromethane (entry 5). When the reaction was carried out by using *p*-chlorobenzyl mesylate, *p*-chlorobenzyl ether was also obtained in good yield (entry 6). When LiOTf alone was used as an activator, the yield of the benzylation reaction decreased to 54% (entry 7).

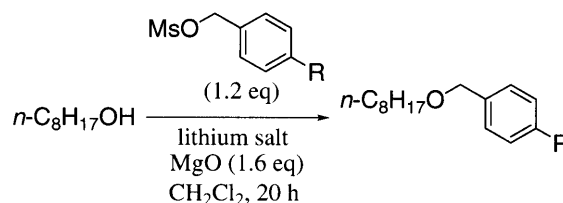


Table 1. Effects of lithium salts on benzylation reaction of 1-octanol

Entry	R	$\text{LiB}(\text{C}_6\text{F}_5)_4$ /mol%	LiOTf /eq	Temp/ $^\circ\text{C}$	Yield/% ^h
1	H	10	—	40	54 (31 ^a)
2	H	—	—	40	N.R.
3	H	5	—	70	45 ^{b,c}
4	Cl	5	—	70	75 ^{b,d}
5	H	10	1.0	40	79 (91 ^{e,f})
6	Cl	10	1.0	r.t.	86 ^{e,g}
7	H	—	1.0	40	54

^aThe reaction was carried out in the absence of MgO . ^bThe reactions

were carried out in 1,2-dichloroethane. ^cThe reaction time was 9 h.

^dThe reaction time was 15 h. ^eThe reactions were carried out in

cyclohexane–dichloromethane (2:1). ^fThe reaction conditions; r.t., 24

h. ^gThe reaction time was 45 h. ^hIsolated yield.

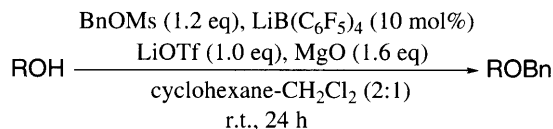
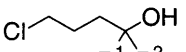
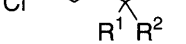
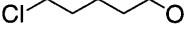
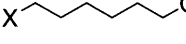
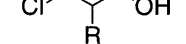
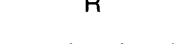
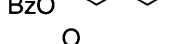
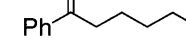


Table 2. Benzylation reactions of alcohols with benzyl mesylates by using lithium salts and MgO

Entry	Alcohols	Yield/% ^d
1		96
2		86 (91 ^a)
3		71
4		90
5		quant.
6		quant.
7		97
8		62
9		97 ^b
10		72 ^{b,c}

^aThe reaction was carried out by using *p*-chlorobenzyl mesylate and the reaction time was 48 h. ^bThe reactions were carried out by using benzyl mesylate (1.4 eq), LiOTf (3.0 eq) and MgO (2.0 eq). ^cThe reaction time was 48 h. ^dIsolated yield.

Next, benzylation of several alcohols was further examined (Table 2). Generally, it is difficult to prepare the corresponding benzyl ethers from halohydrins under strongly alkaline conditions because the conditions cause some side reactions such as intermolecular or intramolecular etherification of halohydrins or olefin formation by elimination of hydrogen halide. Our preliminary experiments on benzylation of 4-chloro-1-butanol under several conditions of using NaH and BnBr in DMF, benzyl trichloroacetimidate and triflic acid, or Ag₂O and BnBr in DMF had led to the corresponding benzylated products in rather low yields. On the other hand, treatment of 4-chloro-1-butanol with benzyl mesylate using the catalyst system described above (Table 1, entry 5) afforded a benzylated product in 96% yield (entry 1). Benzylation of secondary and tertiary halohydrins gave the benzylated products in good yields. In these cases, benzylation proceeded more slowly than that of primary alcohol (entries 2 and 3).⁸ Several other halohydrins also gave satisfactory results under the present conditions (entries 4–8). Further, the benzylation of alcohols possessing ester or ketone groups were examined. It is known that alcoholysis or aldol condensation of esters and also aldol condensation of ketones often take place under strongly alkaline conditions. According to the present procedure, however, benzylation of alcohols possessing ester or ketone groups gave the benzylated products in good to high yields (entries 9 and 10).⁹

A typical experimental procedure⁶ is described for the reaction of 4-chloro-1-butanol with benzyl mesylate (Table 2, entry 1): to a mixture of LiB(C₆F₅)₄ (0.05 mmol), LiOTf (0.50 mmol) and MgO (0.80 mmol) was added a solution of 4-chloro-1-butanol (0.50 mmol) and benzyl mesylate (0.60 mmol) in a mixture of cyclohexane (1.30 mL) and dichloromethane (0.70 mL)

under an argon atmosphere. The mixture was stirred for 24 h at room temperature and then filtered through silica gel. The eluent was concentrated in vacuo, and the crude product was purified by preparative TLC to afford benzyl 4-chlorobutyl ether (0.48 mmol, 96%).

Thus, it is noted that a new and convenient method for the benzylation of alcohols with benzyl mesylate was developed by using a catalytic amount of LiB(C₆F₅)₄ in the coexistence of LiOTf and MgO. Advantageously the present benzylation reaction proceeded under almost neutral conditions to give the corresponding benzyl ethers in good to excellent yields.

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- Monobenzoyl 1,6-hexanediol was obtained by treating 1,6-hexanediol with benzoyl chloride in pyridine and 5-hydroxypentyl phenyl ketone was obtained by treating ε-caprolactone with phenyl magnesium bromide in ether.