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Benzylation of alcohols by using bis[acetylacetonato]copper as catalyst

Okan Sirkecioglu,* Bekir Karliga and Naciye Talinli

Istanbul Technical University, Faculty of Science and Letters, Chemistry Department, Maslak 34469 Istanbul, Turkey

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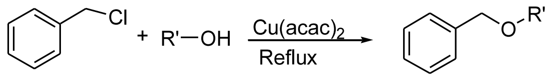
Abstract—Selective *O*-benzylation of primary hydroxy compounds has been achieved in the presence of bis[acetylacetonato]copper with benzyl chloride. We showed that bis[acetylacetonato]copper was very efficient in promoting the benzylation of primary aliphatic alcohols versus secondary aliphatic alcohols and phenolic hydroxy groups selectively.

There have been many reports on the formation of the ether linkage, but only a few are known from hydroxy compounds and halides.[1] Numerous methods are available for protecting an alcohol moiety. Conversion into corresponding ethers has been recognized as a common and useful method for the protection of hydroxyl groups. Most commonly used by protecting groups are the tetrahydropyranyl (THP), *t*-butyldimethylsilyl (TBDMS) and benzyl (Bn) groups. Benzyl ethers are widely utilized as alcohol protecting groups. They are easily installed but with poor selectivity between primary and secondary alcohol groups,[2] e.g. in carbohydrates, are stable to a wide range of reagents and readily removed in the presence of many common functionalities via catalytic hydrogenolysis, dissolving metals or Lewis/Brönsted acids.[3] On the other hand, selectivity of reaction pathways is extremely important in organic reactions such as etherification.[4,5]



Scheme 1.

Table 1. Benzylation of various alcohols using Cu(acac)$_2$

Entry	Alcohol (R′-OH)	Reaction time (h)	Yield[a] (%)	Yield[b] (%)
1	*n*-Octyl alcohol	3	92	12
2	Cyclohexanol	3	90	10
3	Cholesterol	4	85	10
4	Benzyl alcohol	5	60	8
5	4-Hydroxybenzyl alcohol	3	94	15
6	4-Methoxybenzyl alcohol	4	85	10
7	3-Butyn-2-ol	5	–[c]	–[c]
8	*Iso*-propyl alcohol	5	–[c]	–[c]
9	Ethylene glycol	3	90	10
10	Propylene glycol	2	70	8
11	Glycerol	4	70	8
12	2-Ethyl-1,3-hexane diol	5	65	10

[a] Reaction performed without solvent.
[b] Reaction performed in THF.
[c] No benzylic ether derivative formed.

We report here an effective, inexpensive and selective benzylation reaction of hydroxyl groups using

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Keywords: selective etherification; benzylic ether; bis[acetylacetonato]copper.

* Corresponding author. E-mail: sirkeci@itu.edu.tr

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bis[acetylacetonato]copper which was found to be an efficient and cheaper catalyst than the nickel complex.[6] Benzyl alcohol, 4-(hydroxymethyl)phenol, ethylene glycol, propylene glycol, glycerol, 2-ethylhexane-1,3-diol, cholesterol, 4-(hydroxymethyl)anisole, *n*-octyl alcohol, *iso*-propyl alcohol, 3-butyn-2-ol and cyclohexanol reacted with benzyl chloride. When a mixture of the alcohol and the halide are heated under reflux in the presence of catalytic amount of the copper complex, evolution of hydrogen halide occurred immediately and a high yield of the corresponding ether was obtained. This reaction can be conducted in an open vessel; the materials and catalyst can be used as obtained from commercial sources without any purification. The high yields of the products and simple reaction procedure make this method attractive for the syntheses of benzylic ethers. The reaction is described in Scheme 1 and representative results are summarized in Tables 1 and 2.

The data reported in Tables 1 and 2 lead to the following remarks:

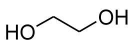
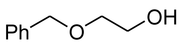
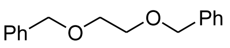
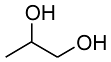
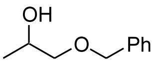
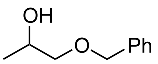
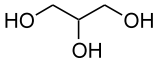
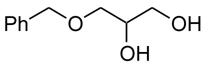
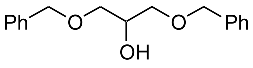
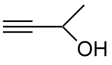
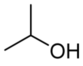
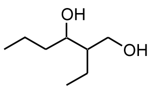
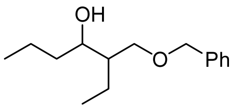
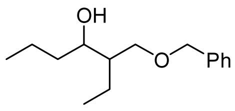
(i) Most of the alcohols studied here were converted into their corresponding benzylic ethers in good yields using a catalyst cheaper than those reported in the literature.[1,2,6]

(ii) Etherification was completed within 2–5 h.[7,8]

(iii) In the presence of our catalyst system, phenolic hydroxy groups did not give the corresponding benzylic ethers.

(iv) When cyclic secondary alcohols such as cyclohexanol and cholesterol were reacted with benzyl chloride the expected benzylic ethers were formed.

Table 2. Selective benzylation using $Cu(acac)_2$[7,8]

Entry	Alcohol	Benzyl chloride	Product	Yield (%)
1	 1 eq.	1 eq.		90
	1 eq.	2 eq.		85
2	 1 eq.	1 eq.		70
	1 eq.	excess		70
3	 1 eq.	1 eq.		70
	1 eq.	3 eq.		74
4	 1 eq.	excess	No ether product	-
5	 1 eq.	excess	No ether product	-
6	 1 eq.	1 eq.		65
	1 eq.	excess		62

However, *iso*-propyl alcohol and 3-butyn-2-ol did not yield corresponding ethers as in the case of cyclic alcohols. This result can be attributed to the low boiling point of the alcohols used, since, the reaction yields decreased when benzylations reactions were performed using THF as solvent,[9] as seen in Table 1.

(v) Benzylic ethers on primary alcohol groups were selectively formed from di or tri hydroxy alcohols. It is noteworthy that, when the benzylation reactions were carried out with an excess of benzyl chloride, the same ether products which were synthesized before were isolated.

(vi) Benzylation of cholesterol was carried out in $PhCH_2Cl$ as reactant and solvent on a large scale. The driving force for this reaction was the higher boiling point of benzyl chloride which was higher than the melting point of cholesterol. A similar result has been reported by Yamashita[6] using a nickel catalyst.

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7. Preparation of benzyl ethers with bis[acetylacetonato]copper. General procedure:
   Method 1: Benzyl chloride (1 mmol), alcohol (1 mmol) and bis[acetylacetonato]copper (0.025 mmol) were heated under reflux for 2–5 h. The reaction mixture was cooled then passed through a short column of neutral aluminum oxide to remove the catalyst. The crude product was distilled under vacuum to give the benzyl ether in high yield.
8. Selective benzylation: Method 2: Excess benzyl chloride, alcohol (1 mmol) and bis[acetylacetonato]copper (0.075 mmol) were heated under reflux for 2–5 h. The reaction mixture was cooled then passed through a short column of neutral aluminum oxide to remove the catalyst. The crude product was distilled under vacuum to give the benzyl ether in high yield.
9. Preparation of benzyl ethers with bis[acetylacetonato]copper in THF. General procedure:
   Method 3: A solution of benzyl chloride (1 mmol), alcohol (1 mmol) and bis[acetylacetonato]copper (0.025 mmol) in dry THF (30 ml) was heated under reflux for 2–10 h. The reaction mixture was cooled then passed through a short column of neutral aluminum oxide to remove the catalyst. The crude product was distilled under vacuum and to give the benzyl ether in high yield.