



Tetrabutyl ammonium bromide-mediated benzylation of phenols in water under mild condition



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ABSTRACT

Benzylation of phenol was successfully achieved in water under room temperature mediated by tetrabutylammonium bromide (TBAB) for only 2 h affording the corresponding benzyl phenyl ether with good to excellent yields. This protocol is very efficient, simple, avoiding catalysts, easy to work-up after reaction, and especially 'green'.

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1. Introduction

Benzylation of phenol is a very important organic reaction and was first reported by McKillop using dichloromethane as a solvent in 1974.¹ Since then, a wide variety of procedures have been developed to reach this goal, including the use of crown ethers,² phase-transfer catalysis (PTC),³ ionic liquids,⁴ microwave method, and so on.⁵ However, most of protocols suffer rigorous conditions, such as the strong base and high temperature. Furthermore, many of the above-mentioned methods carried out in toxic, volatile, and flammable organic solvent, examples of dichloromethane, acetonitrile, and 2-methyltetrahydrofuran or in high boiling point polar solvent, such as *N,N*-dimethylformamide. Thus, the development of an efficient, safe, and environmentally friendly method of benzylation of phenol is very attractive.

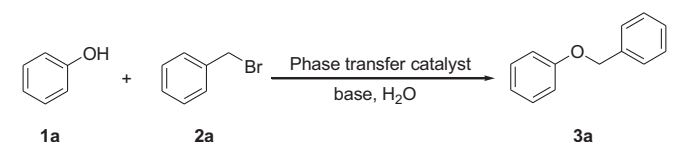
Organic reactions in water have recently attracted great interests. The substitution of organic solvent as reaction media by water minimizes the environmental impact, besides lowering the cost and decreasing operational danger. In addition to economic and human aspects, water presents many physico-chemical properties that can be useful in the reactions, such as high polarity, ion solvating capacity, and the ability to form hydrogen bonds to form a structured liquid, and to aggregate apolar molecules dissolved in

the water. Therefore, performing organic reactions in water may profit by these beneficial aspects. So, the concept of water mediated nucleophilic displacement reactions, as a green protocol, needs more attention. In recent years, a variety of PTCs involving the application of tetrabutyl ammonium bromide (TBAB) has been successfully conducted using water or co-solvent for reaction medium.⁶ Interested in this area, in this paper we reported the use of tetrabutyl ammonium bromide (TBAB) as the phase transfer catalyst for the preparation of benzyl phenyl ether in aqueous media under mild conditions.

2. Results and discussion

To extend applicability of water as a green reaction media and for the search of facile benzylation method, we initially investigated on the model reaction of benzyl bromide and phenol in pure water to optimize the reaction conditions. To our delight, an 86% isolated yield of desired product was obtained with 1 equiv of tetrabutyl ammonium chloride (TBAC) as the phase transfer catalyst, K_3PO_4 as the base at room temperature for 2 h (Table 1, entry 1). Phenol underwent O-alkylation instead of extensive C-alkylation in water under our weak base conditions, which was sharp in contrast to the existed report.^{5m,n} Surprisingly, the yield was dramatically improved up to 98% when TBAB instead of TBAC was used as a phase transfer catalyst (Table 1, entry 2). Other inorganic bases, such as $K_2HPO_4 \cdot 3H_2O$, NaOH, KOH, and K_2CO_3 can also be used in this reaction instead of K_3PO_4 (Table 1, entries 3–6). Among all the

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Table 1
Optimization of reaction conditions^a


Entry	Phase transfer catalyst	Base	t (h)	Yield ^b (%)
1	TBAC	K ₃ PO ₄	2	83
2	TBAB	K ₃ PO ₄	2	98
3	TBAB	K ₂ HPO ₄ ·3H ₂ O	2	73
4	TBAB	NaOH	2	39
5	TBAB	KOH	2	64
6	TBAB	K ₂ CO ₃	2	90
7	TBAB	K ₃ PO ₄ (1.5 equiv)	2	97 ^c
8	TBAB	K ₃ PO ₄ (1.2 equiv)	2	90 ^c
9	TBAB	K ₃ PO ₄ (1.5 equiv)	1	89 ^c
10	—	K ₃ PO ₄ (1.5 equiv)	2	—

^a Unless otherwise noted, the reaction conditions were as follows: phenol (0.5 mmol), benzyl bromide (1.2 equiv), phase transfer catalyst (1.0 equiv), base (2.0 equiv), and water (2 mL), room temperature, air, in a sealed tube.

^b Isolated yields.

^c TBAB (0.5 equiv).

bases, the K₃PO₄ gave the highest yield (Table 1, entry 2). An isolated yield of 97% was obtained even when the quantities of TBAB and the base were decreased to 0.5 and 1.5 equiv, respectively (Table 1, entries 7, 8). However, the yield of the reaction was decreased when shorten the time to 1 h (Table 1, entry 9). No benzylation of phenol to benzyl phenyl ether was observed under the reaction conditions in the absence of phase transfer catalyst (Table 1, entry 10).

With the optimized conditions in hand, the substrate scope of commercially available phenols was investigated and the results were summarized in Table 2. Generally speaking, the reaction proceeded smoothly in the presence of a variety of functional groups including electron-donating, electron-neutral, and electron-withdrawing, such as methyl, methoxyl, chloro, bromo, tertiary butyl, formacyl, and cyano groups. It was noteworthy that the sterically hindered substrates also delivered the desired product in high yields (Table 2, entries 7–10). Especially, even for the 1,2-benzenediol that bearing two hydroxyl in ortho-position could also give the corresponding product in high yield of 90% (Table 2,

Table 2
Benzylation of benzyl bromide with different phenols^a

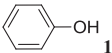
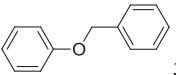
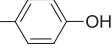
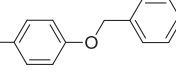
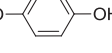
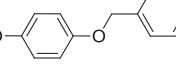
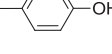
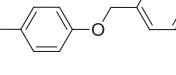
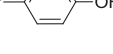
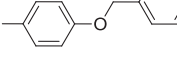
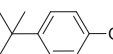
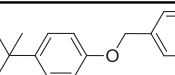
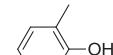
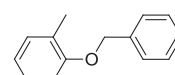
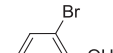
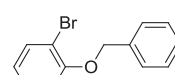
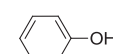
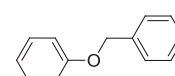
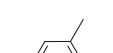
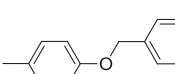
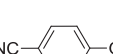
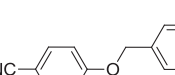
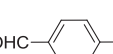
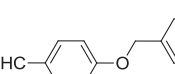
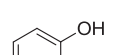
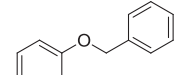

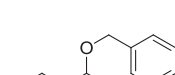
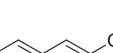
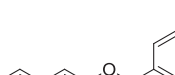

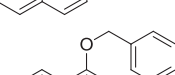
Entry	Phenol	Product	Yield ^b (%)
1			97
2			74
3			99
4			99
5			99

Table 2 (continued)

Entry	Phenol	Product	Yield ^b (%)
6			79
7			93
8			98
9			82
10			99
11			98
12			88
13			90
14			86
15			66
16			76

^a Reaction conditions: phenol (0.5 mmol), benzyl bromide (1.2 equiv), TBAB (0.5 equiv), base (1.5 equiv), and water (2 mL), room temperature, 2 h, air, in a sealed tube.

^b Isolated yields.

entry 13). It would be specially mentioned that naphthol **1o** and heterocycle phenol **1p** were both tolerated and afforded the etherification products in moderate yields (Table 2, entries 14–16).

In order to make a more systematic study, different kinds of groups on the phenyl ring in the benzyl bromide were also examined. As shown in Table 3, the reaction was not significantly affected by the steric effect of the phenols (Table 3, entries 6, 7, 11). For example, the benzylation of **1a** with *ortho*-benzyl bromide proceeded smoothly, affording the corresponding products **3ah** in almost quantitative yield. Also the electronic properties of the groups at the aryl moiety of benzyl bromides had some effect on the reaction. Generally, the benzyl bromides bearing electron-

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