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A mild and efficient procedure for the synthesis of ethers from various alkyl halides

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Abstract

A simple, mild and practical procedure has been developed for the synthesis of symmetrical and unsymmetrical ethers by using DMSO, TBAI in the presence of K_2CO_3. We extended the utility of Potassium carbonate as an efficient base for the preparation of ethers. A wide range of alkyl aryl and dialkyl ethers are synthezied from treatment of aliphatic alcohols and phenols with various alkyl halides in the prescence of efficient base Potassium carbonate. Secondary alkyl halides were easily converted to corresponding ethers in releatively good yields . This is a mild, simple and practical procedure for the preparation of ethers in high yields and suitable times under mild condition.

Keywords: Phenols, ethers, tetrabutylammonium iodide, alkyl halides, synthesis.

Introduction

The ethers are important classes of organic compounds which are used widely in the field of active pharmaceutical materials such as teicoplanin, vancomycin and biological processes [1]. One of the most common methods for the preparation of ethers is synthesis Williamson [2]. In this synthesis, from treatment of an alcohol with an organo halide in which we used a strong base alkoxide ion is obtained. Then, alkoxide ion displaces a halogen ion via an SN_2 reaction. This is a very valuable and useful reaction in the history of organic chemistry because the productions obtained by this method are considered of great use in the fields of economy, industry and medicine. In industry, this method is most

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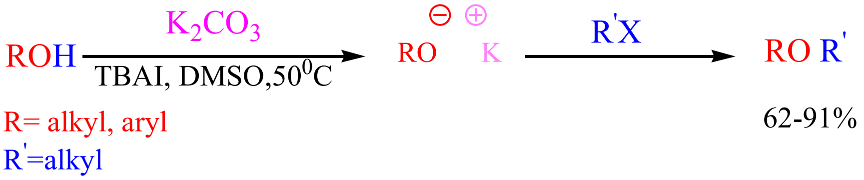
often accomplished with the use of organic solvents or by phase-transfer catalysts under reflux condition and in the presence of a strong base. But, this synthesis is effective when it is used from primary alkyl halide, because in the use of secondary and tertiary alkyl halides, competing elimination reaction is observed [3-6]. Alkylation of alcohols is a very convenient and common method and usually is suitable for synthesis of symmetrical and asymmetrical ethers [7].

An authentic research shows that there are many ways to produce ethers such as use of ullmann coupling [8], magnesium reagent [9] and clay catalyst [10], ionic liquids [11], mitsunbu reaction [12], CsF–Celite [13] and reduction of carbonyl compounds [14]. However, most of these methods have some limitations such as: use of very strong basic catalyst, low yields, high temperature and longer reaction time [9,11]. But, it is important to find useful procedures with use of base catalysts for the preparation of ethers.

Now, we wish to report an efficient, simple and practical method for preparation of ethers with the use of K_2CO_3 , DMSO and TBAI as phase-transfer catalysts at 50 ºC in which it can overcome such types of limitations. (Scheme 1).



Scheme 1.

Experimental

General

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electro thermal 9100 apparatus and are not corrected. The IR spectra were obtained on a FT-IR Hartman- Bomen spectrophotometer such as KBr disks, or neat. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a BrukerAvance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC. All products are known and were characterized by comparing their physical and spectral data with those of the authentic samples.

Typical procedure for benzyl ethyl ether synthesis (Table 3, entry1)

The mixture of benzyl alcohol (1.5 mmol) TBAI (1 mmol) and DMSO were stirred under reflux conditions at 50 ^{0}C for 100 min in the presence of K_2CO_3 (1 mmol). Ethyl iodide (1 mmol) was, then, added to the mixture reaction and synthesized the corresponding ether (Table 1, Entry 1). The progress of reaction was monitored by TLC. After completion of the reaction, solvent was evaporated *in vacuo* to give benzyl ethyl ether which was purified by preparative TLC (silica gel, eluent *n*-hexane: EtOAc = 4:1) and pure benzyl ethyl ether was obtained (91%).

Dibenzyl Ether ($C_{12}H_{14}O$) (Table 3, Entry 2): Yield: 90%; colorless liquid^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (s, 4H), 7.29-7.55 (m, 10H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.3, 127.8, 127.9, 128.6, 138.5 ppm.

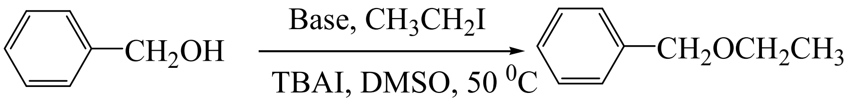
1-Ethoxybenzene ($C_8H_{10}O$) (Table 3, entry 11): Yield: 82%; yellow liquid ^{1}H NMR (400 MHz, CDCl3): δ= 1-29-1.33 (t, 3H, CH_3), 4.11-4.20 (q, 2H, CH_2), 7.24-7.36 (m, 3H, Ar-H), 7.53-7.54 (d, 2H, Ar-H), ^{13}C NMR (100 MHz, CDCl3): δ= 14.1, 40.1, 126.9, 131.5, 132.9, 158.4.

1-Butoxybenzene ($C_{10}H_{14}O$) (Table 3, entry 14): Yield: 81%; colorless liquid ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.93 (t, J=7.2 Hz, 3H), 1.36-1.46 (sext, J= 7.2 Hz, 2H), 1.54-162(quint, J= 7.6 Hz, 2H), 3.86-3.90(t, 2H), 7.24-7.54 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.0, 31.1, 31.3, 36.3, 126.9, 128.5, 128.7, 138.7 ppm.

Results and discussion

In order to optimize the reaction condition, we study the effect of various bases and solvents on system. In the first stage, the selection base was tested. We studied the treatment of benzyl alcohol (1.5 mmol) at 50ºC and in the presence of base (1 mmol), TBAI (1 mmol) and DMSO with ethyl iodide (1.2 mmol) (scheme 2). The results have been presented in Table1.

Several bases were studied for the synthesis of benzyl ethyl ether by using TBAI (1mmol) and DMSO as solvent. When Na_2CO_3, K_2CO_3 and $(NH_4)_2CO_3$ were used as bases, they produced 68%, 91% and 64% of the product, (Table 1, entries 2, 5 and 8). The use of Li_2CO_3, Rb_2CO_3, Ag_2CO_3, and $BaCO_3$ as base produced relatively good yields of product (81%, 79%, 77% and 72%) (Table 1, entry 10, 7,6 and 3). Bases such as K_3PO_4, which are widely used in Cu-catalyzed protocols for the C–O, and C–S bonds, afforded the desired ether only in moderate yield (69%, Table 1, entry 1). The use of t-BuOK as a base furnished only=56% of the product (Table 1, entry 8). Also, the use of triethylamine as base produced very low yield 41% (Table1, entry 4). Therefore, the best result was obtained with petasium carbonate (K_2CO_3) as a base (Table 1, Entry 5).



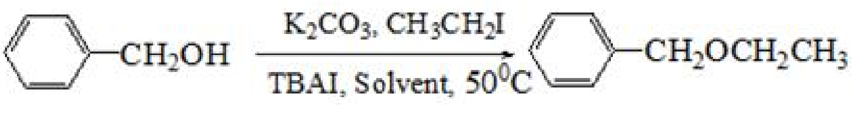
Scheme 2.

Table 1. Synthesis of benzyl ethyl ether with using various bases

Entry	Base	Yield (%)
1	K_3PO_4	69
2	Na_2CO_3	68
3	Li_2CO_3	81
4	Triethylamine	41
5	K_2CO_3	91*
6	Rb_2CO_3	79
7	Ag_2CO_3	77
8	t-BuOK	56
9	$(NH_4)_2CO_3$	64
10	$BaCO_3$	72

Then, to find and evaluate the limitations of the reaction (Scheme 3), several solvents were examined for O-alkylation method. Based on results of table 2, we found that DMSO (Table 2, Entry 6) was the best solvent to perform the reaction. Reactions were carried out at 50 ºC for all solvents. The use of less polar solvent like toluene yielded 62% of the benzyl ethyl ether (Table 2, Entry 3). The use of polar and high boiling solvents like DMF, NMP and DMSO furnished 81%, 74%, and 90% product (Table 2, Entries 1,7 and 6).

The use of isopropanol, acetonitrile and 1,4-dioxane as solvents produced only 55%, 64%, 41% product (Table 2, Entry 4, 2 and 5).

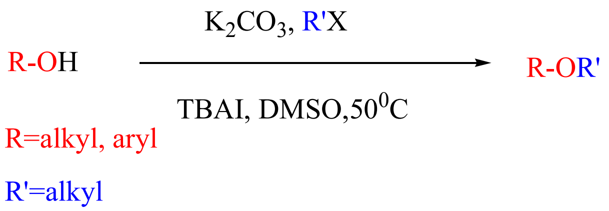


Scheme 3.

Entry	Solvent	Yield (%)
1	DMF	81
2	CH_3CN	64
3	Toluene	60
4	Isopropanol	55
5	1,4-Dioxane	41
6	DMSO	91
7	NMP	74

Therefore, we decided to use alcohols (1.5 mmol), TBAI (1 mmol), K_2CO_3 (1 mmol) and alkyl halides (1 mmol) at 50ºC in the presence of DMSO as solvent for the preparation of corresponding ethers (Scheme 4).

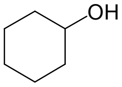
The method is very general and a wide range of aliphatic and aromatics alcohols react easily with various alkyl halides in order to synthesize symmetrical and unsymmetrical ethers (Table 3). As revealed in Table 3, allyl and benzyl ethers produced excellent yields. Benzyl ethers produced from treatment of benzyl alcohols with various alkyl halides (Table 3, Entries 1-6) generally give high yields. Ethers produced from reaction of alkyl alcohols with benzyl halides (Table 3, Entries 7-8) give relatively high yields. Also, asymmetrical ethers from treatment of phenols with benzyl halides (Table 3, Entries 9-10) generally give higher yields than their treatment with various alkyl halides (Table 3, Entries 11-16). Also, we study the effect of substituent in the para-position phenol and benzyl alcohols that their results are found in (Table 3, Entries 6 and 9). As demonstrated in Table 1, primary alkyl halides treated quickly providing the corresponding ethers within 100-150 min in good yields. However, secondary alkyl halides (Table 3, Entries 5,13 and 15) converted to corresponding ethers in more long times.



Scheme 4.

Table 3. Synthesis ethers from various alkyl halides [a]

Entry	ROH	R'X	Time(min)	Yield [b](%)
1	$PhCH_2OH$	CH_3CH_2I	100	91
2	$PhCH_2OH$	$PhCH_2Br$	115	90
3	$PhCH_2OH$	$CH_3(CH_2)_2CH_2Br$	135	88
4	$PhCH_2OH$	$CH_2{=}CHCH_2Br$	120	87
5	$PhCH_2OH$	$(CH_3)_2CHBr$	700	81
6	4- $OCH_3C_6H_5CH_2OH$	CH_3CH_2I	110	89

7		$PhCH_2Br$	140	82
8	$CH_3CH_2CH_2OH$	$PhCH_2Br$	125	82
9	4- $NO_2C_6H_5OH$	$PhCH_2Br$	150	87
10	C_6H_5OH	$PhCH_2Br$	140	84 [39-40]
11	C_6H_5OH	CH_3CH_2I	130	82
12	C_6H_5OH	$CH_2=CHCH_2Br$	135	80
13	C_6H_5OH	$(CH_3)_2CHBr$	870	62
14	C_6H_5OH	$CH_3CH_2CH_2CH_2Br$	145	81
15	C_6H_5OH	$CH_3CH_2CH(CH_3)Br$	980	68
16	C_6H_5OH	$CH_3CH_2CH_2Br$	140	79

[a] All the products are known compounds and were characterized by comparison of their NMR spectral data and physical properties with those reported in the literature [2,3,7,10,13].

[b] Melting point for known compounds.

Conclusion

In conclusion, herein, we reported a novel and highly efficient method for the synthesis of symmetrical and unymmetrical ethers by using K_2CO_3. We extended the utility of Potassium carbonate as an efficient base for the preparation of ethers. In this way, we described a convenient, mild and simple method for the synthesis of ethers in good yields with suitable times.

Acknowledgments

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