

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 synthesized from treatment of aliphatic alcohols and phenols with various alkyl halides in the presence of efficient base Potassium carbonate. Secondary alkyl halides were easily converted to corresponding ethers in relatively 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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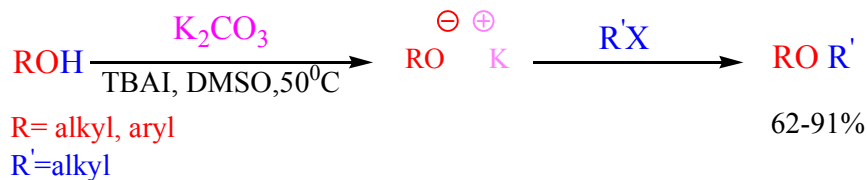
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often accomplished with the use of organic solvents or by phase-transfer catalysts under reflux condition and in the presence of a strong base. But, this synthesis is effective when it is used from primary alkyl halide, because in the use of secondary 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 °C 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 °C for 100 min in the presence of K₂CO₃ (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 (C₁₂H₁₄O) (Table 3, Entry 2): Yield: 90%; colorless liquid ¹H NMR (400 MHz, CDCl₃): δ = 4.71 (s, 4H), 7.29-7.55 (m, 10H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 72.3, 127.8, 127.9, 128.6, 138.5 ppm.

1-Ethoxybenzene (C₈H₁₀O) (Table 3, entry 11): Yield: 82%; yellow liquid ¹H NMR (400 MHz, CDCl₃): δ= 1.29-1.33 (t, 3H, CH₃), 4.11-4.20 (q, 2H, CH₂), 7.24-7.36 (m, 3H, Ar-H), 7.53-7.54 (d, 2H, Ar-H), ¹³C NMR (100

MHz, CDCl₃): δ= 14.1, 40.1, 126.9, 131.5, 132.9, 158.4.

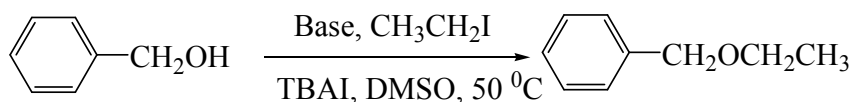
1-Butoxybenzene (C₁₀H₁₄O) (Table 3, entry 14): Yield: 81%; colorless liquid ¹H NMR (400 MHz, CDCl₃): δ= 0.93 (t, J=7.2 Hz, 3H), 1.36-1.46 (sext, J= 7.2 Hz, 2H), 1.54-1.62 (quint, J= 7.6 Hz, 2H), 3.86-3.90 (t, 2H), 7.24-7.54 (m, 5H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ= 13.7, 22.0, 31.1, 31.3, 36.3, 126.9, 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 50°C 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 Table 1.

Several bases were studied for the synthesis of benzyl ethyl ether by using TBAI (1mmol) and DMSO as solvent. When Na₂CO₃, K₂CO₃ and (NH₄)₂CO₃ were used as bases, they produced 68%, 91% and 64% of the product, (Table 1, entries 2, 5 and 8). The use of Li₂CO₃, Rb₂CO₃, Ag₂CO₃, and BaCO₃ 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,



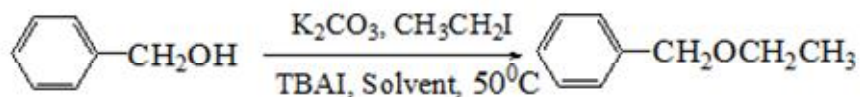
Scheme 2.

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 °C for all solvents. The use of polar solvent like toluene yielded 62% of 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 64%, 41% product (Table 2, Entry 4, 2 and 5). 1,4-dioxane as solvents produced only 55%,



Scheme 3.

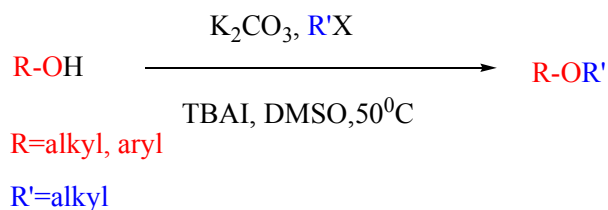
| Entry | Solvent | Yield (%) |
|-------|--------------------|-----------|
| 1 | DMF | 81 |
| 2 | CH ₃ CN | 64 |
| 3 | Toluene | 60 |
| 4 | Isopropanol | 55 |
| 5 | 1,4-Dioxane | 41 |
| 6 | DMSO | 91 |
| 7 | NMP | 74 |

Therefore, we decided to use alcohols (1.5 mmol), TBAI (1 mmol), K₂CO₃ (1 mmol) and alkyl halides (1 mmol) at 50°C 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

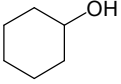
substituent in the para-position phenol and 150 min in good yields. However, secondary benzyl alcohols that their results are found in alkyl halides (Table 3, Entries 5,13 and 15) (Table 3, Entries 6 and 9). As demonstrated in converted to corresponding ethers in more long Table 1, primary alkyl halides treated quickly times. providing the corresponding ethers within 100-



Scheme 4.

Table 3. Synthesis ethers from various alkyl halides ^a

| Entry | ROH | R'X | Time(min) | Yield ^b (%) |
|-------|--|--|-----------|------------------------|
| 1 | PhCH ₂ OH | CH ₃ CH ₂ I | 100 | 91 |
| 2 | PhCH ₂ OH | PhCH ₂ Br | 115 | 90 |
| 3 | PhCH ₂ OH | CH ₃ (CH ₂) ₂ CH ₂ Br | 135 | 88 |
| 4 | PhCH ₂ OH | CH ₂ =CHCH ₂ Br | 120 | 87 |
| 5 | PhCH ₂ OH | (CH ₃) ₂ CHBr | 700 | 81 |
| 6 | 4- OCH ₃ C ₆ H ₅ CH ₂ OH | CH ₃ CH ₂ I | 110 | 89 |

| | | | | |
|----|---|--|-----|---------------------|
| 7 |  | PhCH ₂ Br | 140 | 82 |
| 8 | CH ₃ CH ₂ CH ₂ OH | PhCH ₂ Br | 125 | 82 |
| 9 | 4- NO ₂ C ₆ H ₅ OH | PhCH ₂ Br | 150 | 87 |
| 10 | C ₆ H ₅ OH | PhCH ₂ Br | 140 | 84 ³⁹⁻⁴⁰ |
| 11 | C ₆ H ₅ OH | CH ₃ CH ₂ I | 130 | 82 |
| 12 | C ₆ H ₅ OH | CH ₂ =CHCH ₂ Br | 135 | 80 |
| 13 | C ₆ H ₅ OH | (CH ₃) ₂ CHBr | 870 | 62 |
| 14 | C ₆ H ₅ OH | CH ₃ CH ₂ CH ₂ CH ₂ Br | 145 | 81 |
| 15 | C ₆ H ₅ OH | CH ₃ CH ₂ CH(CH ₃) Br | 980 | 68 |
| 16 | C ₆ H ₅ OH | CH ₃ CH ₂ CH ₂ Br | 140 | 79 |

^aAll 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].

^bMelting 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 K₂CO₃. 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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