

A Green and Highly Efficient Alkylation of Thiols in Water

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An environmentally benign and efficient process for the preparation of thioethers was developed by simple and practical reactions of alkyl halides and thiols in water in the presence of K_2CO_3 or Et_3N in very high yields. The reaction of aryl, alkyl, aliphatic and hindered thiols with various alkyl halides gave the corresponding products with significant advantages such as high conversions, short reaction time, mild reaction conditions, and low cost, simple workup with good to quantitative yields.

Keywords: Green chemistry, Thiols, Thioether, Water

INTRODUCTION

Development of benign and efficient processes with simple work-up with high purity of the products with high yields is currently receiving considerable attention. In this context, water played an important role in the process of achieving elegant solutions with the ultimate goal of hazard-free, waste-free, energy-efficient synthesis of biologically active compounds with potential application in the pharmaceutical or agrochemical industries [1].

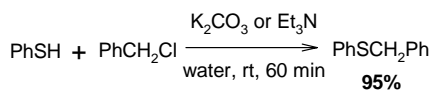
Thioethers are very useful building blocks in the synthesis of various organosulfur compounds; they have useful applications in organic synthesis, in bioorganic, medicinal and heterocyclic chemistry [2]. Thioethers can also act as safety-catch linker in peptides chemistry [3] and as useful heteroatomic functional groups in organic synthesis such as chiral sulphoxides that can be used as auxiliaries in asymmetric syntheses [4]. Moreover, thioethers have been employed as sulfur-based ligands in transition metal complexes in industrial metal sulfide catalysts [5]. In this respect, a number of synthetic methods for preparation of

thioethers derivatives have been reported in the literature by the reaction of thiols with organic halides [6] or alkenes [7] in the presence of catalyst in organic solvent. However, there exist various limitations with the reported methodologies such as long reaction times, use of halogenated solvents, difficulty in recovery of high boiling solvents, high temperatures, requirement of special efforts for preparation of catalysts, use of costly catalysts, and relatively moderate yields. These problems were overcome to some extent by recently reported green methods using Micheal addition [8] under solvent free condition or in water and ring opening reaction of epoxides [9] with thiols and alkylation of thiols with alkyl halides or alcohols under solvent-free conditions, ionic liquids and water as reaction medium [10].

RESULTS AND DISCUSSION

At one of the aims of our research was developing green chemistry by using water as reaction medium or by performing organic transformations under solvent-free conditions [11,12]. In this regard, we would like to describe a highly efficient, simple, and eco-friendly method for the synthesis thioethers from thiols and alkyl halides in water at

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Scheme 1. Optimization of reaction conditions

room temperature with high yields.

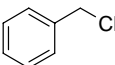
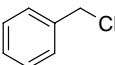
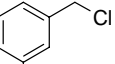
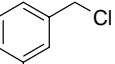
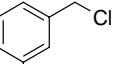
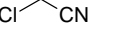
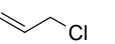
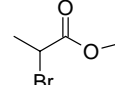
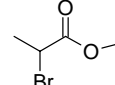
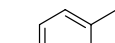
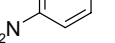
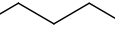
In order to find the best reaction conditions, we first studied the reaction of thiophenol and benzylchloride with different loading of starting materials in the presence of triethylamine and K_2CO_3 in water. It was found that by simple mixing of thiophenol (3 mmol), benzyl chloride (3 mmol) and triethylamine (3.2 mmol) or K_2CO_3 (3.5 mmol) in water, (2 ml), corresponding thioethers was afforded in excellent yield at room temperature in 60 min (Scheme 1). Furthermore, the base plays a crucial role in the success of the reaction in terms of the rate and the yields. In pure water in the absence of base, very poor yield resulted in 6 h at room temperature. On the contrary, Et_3N showed higher yields compared with K_2CO_3 in water.

With optimized reaction conditions in hand, the scope of the reaction was explored and systematic variations on the two components were examined (Table 1). The results proved to be quite general, reasonably fast and clean, so that a wide range of different thiols underwent alkylation in water with several alkyl halides affording the corresponding products in excellent yields. With respect to the scope of thiols, we observed that a range of structurally diverse thiols undergo efficient transformation, including aliphatic, aromatic, substituted aromatic thiols bearing electron-withdrawing or electron-donating group as do heterocyclic thiols with alkyl halides in excellent yields. The range of suitable alkyl halides explored included the commercially available alkyl chlorides, bromides and iodides. In general, no marked difference was observed in terms of yields and reaction time, and functional groups such as $-\text{CO}_2\text{R}$ and $-\text{CN}$ remained intact in this method. We also explored the chemoselectivity of the reaction conditions. Scheme 2 clearly shows that in the presence of an alcohol or a phenol the reaction with a thiol is completely selective and the corresponding thioether is the sole product. In the case of aniline, mixtures of thioether and alkylated aniline were formed.

Finally, the simple procedure described here appears to be efficient and competitive with other methods reported recently in the literature (Table 2).

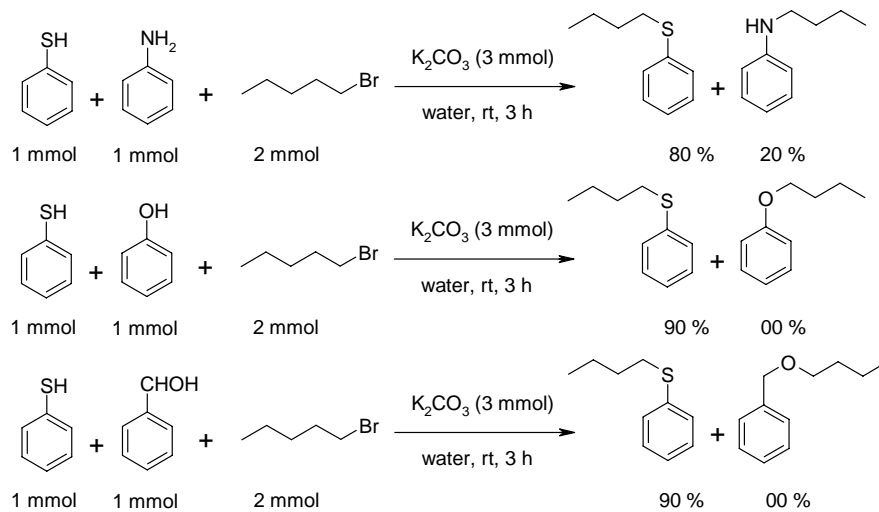
In conclusion, a simple and practical method for C-S bond

Table 1. S-Alkylation of Thiols with Alkyl Halides in Water

Entry	Alkyl halide	Thiols	Yields (%) ^(a)
1		2a	95(90)
2		2b	95(90)
3		2c	92(92)
4		2d	86(72)
5		2e	92(80)
6		2f	80(74)
7		2g	76(68)
8		2h	80(80)
9		2i	82(70)
10		2a	95(92)
11		2b	95(90)
12		2c	92(88)
13		2e	82(84)
14		2h	78(70)
15		2a	90(80)
16		2b	90(76)
17		2h	92(78)
18		2a	95(92)
19		2b	95(88)
20		2h	80(72)
21		2a	92(90)
22		2b	90(92)
23		2e	90(84)
24		2h	82(70)
25	$\text{CH}_3(\text{CH}_2)_6\text{Br}$	2a	80(70)
26		2b	85(72)
27		2c	84(72)
28		2a	90(80)
29		2b	92(86)
30		2c	88(80)
31		2a	92(94)
32		2b	86(82)
33		2c	82(74)
34		2a	95(90)
35	CH_3I	2b	92(88)
36		2c	80(74)

^aThe number in parentheses show the yield obtained by using K_2CO_3 in place of Et_3N .

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Scheme 2. Selectivity of reaction conditions

Table 2. Comparison of the Reaction Conditions for the Alkylation of Thiols with the Recently Reported Catalyst in the Literature

Entry	Catalyst	Solvent	Temperature	Yields	Ref.
1	ZrCl ₄	SFC	50 °C	90	[10d]
2	CS ₂ CO ₃ /TBAI	DMF	rt	98	[6a]
3	ZnCl ₂	THF	Reflux	80	[10a]
4	IL	IL	rt	92	[10c]
5	ZrCl ₄ /NaI	SFC	rt	90	[10e]
6	-	H ₂ O	rt	85	[10b]
7	AIPW ₁₂ O ₄₀	CH ₂ Cl ₂	rt	92	[10f]
8	Et ₃ N	H ₂ O	rt	95	This work

formation in water has been explored. The advantages of the method which are worth mentioning are mild reaction conditions, high yields of the products, usually short reaction times and easy isolation of the solid thioethers which is easily achieved by a simple filtration.

EXPERIMENTAL

General Procedure for the S-Alkylation of Thiols by Alkyl Halides

To a mixture of alkyl halides (3 mmol) and thiols (3 mmol) in water, Et₃N (3.2 mmol) or K₂CO₃ (3.5 mmol) were added and stirred at room temperature for the time reported in Table

1. In the case of solid thioethers, pure products were isolated by filtration, and oily thioethers were extracted by ethyl acetate and dried over anhydrous Na₂SO₄. Evaporation of the ethyl acetate afforded the desired pure product in most cases. In a few cases, the crude product was further purified by flash column chromatography to provide the corresponding product. All compounds were characterized based on their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

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