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A mild and highly convenient chemoselective alkylation of thiols using Cs_2CO_3–TBAI

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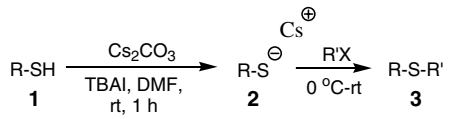
Abstract—A mild and improved method for the synthesis of thioethers has been developed. In the presence of cesium carbonate, tetrabutylammonium iodide, and DMF, various alkyl and aryl thiols underwent S-alkylation to afford structurally diverse sulfides in high yield. Unprotected mercaptoalcohols and thioamines reacted chemoselectively at the sulfur moiety exclusively. An example of a one-pot, solid-phase synthesis of a thioether is also described.

Thioethers have emerged as preeminent classes of organic compounds, which hold useful applications as key reagents in organic synthesis, bio-organic, medicinal, and heterocyclic chemistry.[1] Numerous synthetic methods exist for the preparation of sulfides,[2–7] however, the classical method of choice is the condensation of a metal alkyl or aryl thiolate with an alkyl halide in the presence of a strong base.[8] The synthetic scope of this aforementioned reaction condition is often hampered by prolonged reaction times, high temperatures, the use of cumbersome bases and result in low product yields. In addition, these procedures are often not applicable to the synthesis of sulfides, which contain epimerizable stereocenters. Moreover, side products including sulfonium salts and disulfides may accompany the corresponding thioether products. During the course of our synthetic studies toward sulfur heterocycles[9] and bioactive compounds such as nelfinavir,[10] a potent HIV protease inhibitor containing the sulfide moiety, the need for a mild approach for the construction of the C–S bond that circumvent the common impediments is clearly warranted.

Over the past several years, we have reported numerous chemoselective cesium base-promoted alkylation procedures for the formation of a plethora of functional groups.[11] Recently, we disclosed a mild and efficient synthesis of unsymmetrical organoselenides using cesium bases.[12] Building on these successful results, we now report herein the facile synthesis of thioether **3** by the chemoselective alkylation of in situ generated thiolate anion **2** easily prepared from thiol **1** using cesium carbonate (Cs_2CO_3), tetrabutylammonium iodide (TBAI), and anhydrous DMF in the presence of various alkyl halides (Scheme 1).

Initially, the choice of base was examined (Table 1, entries 1–8). As a representative procedure employed, 1-dodecanethiol (1 mmol) (**4**) was stirred under nitrogen atmosphere at room temperature for 1 h in the presence of a base (1 mmol), TBAI (1 mmol),[13] and DMF. The reaction mixture was subsequently cooled to 0 °C, methyl iodide (1.1 mmol) was added, and the reaction mixture was allowed to slowly warm to room temperature. Of the bases examined, cesium carbonate was far superior to deliver the odorless dodecyl methyl sulfide (Dod-S-Me) (**5**)[14] exclusively, in quantitative yield after



(R = alkyl, aryl, or alkyl aryl; R' = alkyl)

Scheme 1.

Keywords: Thioethers; Thiols; Alkyl halides; Cesium carbonate; Tetrabutylammonium iodide.
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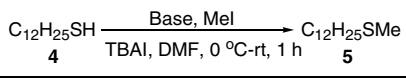
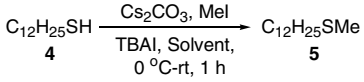
Table 1. Synthesis of Dod-S-Me (**5**) using various bases



Entry	Base (1 equiv)	Yield (**5**) (%)
1	Li_2CO_3	79
2	Na_2CO_3	69
3	K_2CO_3	82
4	Rb_2CO_3	79
5	**Cs_2CO_3**	**Quant**
6	$BaCO_3$	72
7	$(NH_4)_2CO_3$	73
8	Ag_2CO_3	65

Table 2. Synthesis of Dod-S-Me (**5**) using various solvents



Entry	Solvent	Yield (**5**) (%)
1	DMF	Quant
2	DMAC	83
3	DMSO	83
4	NMP	74
5	CH_3CN	68
6	HMPA	69

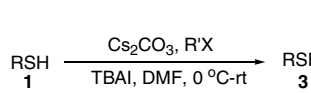
1 h (entry 5). In addition, the simultaneous formation of disulfide products stemming from aerial oxidation and overalkylation was completely mitigated. We attribute the high yield and excellent chemoselectivity as further evidence of the 'cesium effect'.[15]

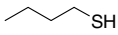
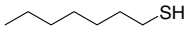
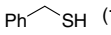
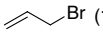
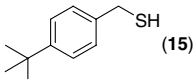
Next, various solvents were then subjected to our S-alkylation procedures to evaluate the scope and limitations of the reaction. We found that anhydrous DMF was the solvent of choice, whereas other polar aprotic solvents were less suitable (Table 2, entries 2–6). With the optimized conditions in hand, numerous halides and structurally diverse thiols were examined and found to be generally applicable to the developed techniques.

As demonstrated in Table 3, various primary aliphatic bromides and alkyl thiols reacted quickly providing the unsymmetrical thioethers **3** within 2 h in remarkable yields (entries 1–5). In turn, a sterically more demanding secondary halide such as 2-iodopropane (**16**) offered similar results, however, longer reaction times were required for the desired transformation (entry 6). As expected, tertiary halides were resistant to alkylations under these conditions.

In addition, our method was highly useful for the preparation of numerous alkyl aryl thioethers in excellent yields. For example, thiophenol (**17**) reacts with 1-bromododecane (**18**) producing the requisite thioether in quantitative yield using our mild Cs_2CO_3–TBAI method (Table 4, entry 1). Substituted aromatic thiols bearing an electron-withdrawing or electron-donating group also reacted efficiently with a wide array of halides in outstanding yields (entries 2–8). Furthermore, alkylation of thiophenol (**17**) with crotyl bromide (**29**) gave rise to the S_N2 product, where the S_N2' product was not detected (entry 9).

Table 3. Alkylation of alkyl thiols and aryl alkyl thiols using various halides



Entry	Thiol (**1**)	Halide (R′X)	Time (h)	Yield of **3** (%)[a]
1	 (**6**)	*n*-BuBr (**7**)	2	93
2	 (**8**)	(**9**)	1	Quant
3	$C_{11}H_{23}SH$ (**10**)	MeI (**11**)	1	Quant
4	 (**12**)	*n*-PrI (**13**)	2	Quant
5	**12**	 (**14**)	1	81
6	 (**15**)	 (**16**)	18	Quant

[a] Yields refer to isolated pare products characterized by IR, MS, ^1H and ^{13}C NMR spectroscopic data, and elemental analysis.

After substantiating the generality of the approach, we then directed our efforts toward the alkylation of aryl bis-thiols. Dithiols are commonly used as precursors toward organo-polysulfides, spirans, macrocycles and serve as efficacious analogs in asenical therapy.[16] In addition, the coordination chemistry of dithiolate ligands has also been extensively studied. Keeping this in mind, we extended the above preliminary results using various alkyl bromides (2.2 equiv) in the presence of 1 equiv of an arene dithiol (Table 5). As shown in entry 1, benzene-1,2-dithiol (**29**), underwent S-alkylation using ethyl bromide (**30**) as the halide of choice to afford the corresponding dialkylated 1,2-benzenedithiol compound **31** in excellent yield (90%) after 2 h. Subsequently, we developed a slightly modified procedure for a one-pot, sequential S-alkylation, using two different alkyl halides that resulted in the synthesis of functionalized 1,2-benzenedithiol derivatives. For example, dithiol **29**, reacted with 1.1 equiv of EtBr to give the mono-S-alkylated product with complete consumption of the starting dithiol (TLC) after 2 h. After stirring for this time period, additional Cs_2CO_3 was added (1 equiv) and allowed to react for another hour. At this point, a different activated halide, benzyl bromide (**21**) was added to generate the unsymmetrical functionalized-1,2-benzenedithiol adduct **32** in high yield (entry 2). Following the aforementioned protocol, 4,4′-thiobisbenzenethiol (**33**) underwent mono-S-methylation quickly giving rise to **34** (entry 3). However, when MeI (2.2 equiv) was employed, the symmetrical dimethyl dithioether **35** product was produced as an off-white solid in quantitative yield (entry 4).

The chemoselective S-alkylation in the presence of unprotected reactive functional groups such as mercaptoalcohols and thioamines also proved successful. As demonstrated in Scheme 2, 2-mercaptoethanol (**36**)