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

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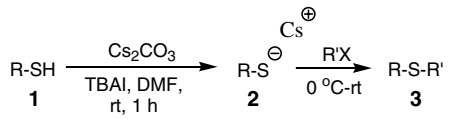
Abstract—A mild and improved method for the synthesis of thioethers has been developed. In the presence of cesium carbonate, tetrabutylammonium iodide, and DMF, various alkyl and aryl thiols underwent S-alkylation to afford structurally diverse sulfides in high yield. Unprotected mercaptoalcohols and 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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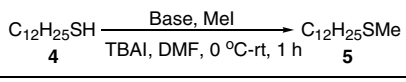
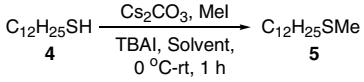
Table 1. Synthesis of Dod-S-Me (**5**) using various bases



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

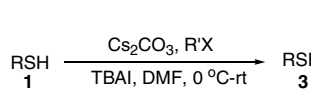
1 h (entry 5). In addition, the simultaneous formation of disulfide products stemming from aerial oxidation and overalkylation was completely mitigated. We attribute the high yield and excellent chemoselectivity as further evidence of the 'cesium effect'.[15]

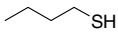
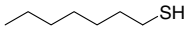
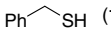
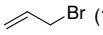
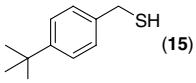
Next, various solvents were then subjected to our S-alkylation procedures to evaluate the scope and limitations of the reaction. We found that anhydrous DMF was the solvent of choice, whereas other polar aprotic solvents were less suitable (Table 2, entries 2–6). With the optimized conditions in hand,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



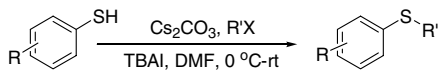
Entry	Thiol (**1**)	Halide (R′X)	Time (h)	Yield of **3** (%)[a]
1	 (**6**)	*n*-BuBr (**7**)	2	93
2	 (**8**)	(**9**)	1	Quant
3	$C_{11}H_{23}SH$ (**10**)	MeI (**11**)	1	Quant
4	 (**12**)	*n*-PrI (**13**)	2	Quant
5	**12**	 (**14**)	1	81
6	 (**15**)	 (**16**)	18	Quant

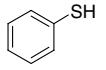
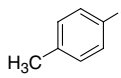
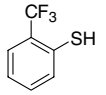
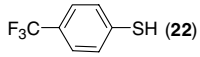
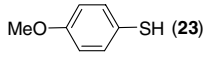
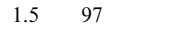
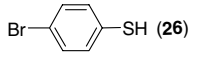
[a] Yields refer to isolated pare products characterized by IR, MS, ^1H and ^{13}C NMR spectroscopic data, and elemental analysis.

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**)

Table 4. Cs_2CO_3-promoted S-alkylation of aromatic thiols with halides



Entry	Thiol (ArSH)	Halide (R′X)	Time (h)	Yield (%)[a]
1	 (**17**)	$C_{12}H_{25}Br$ (**18**)	1	Quant
2	 (**19**)	**11**	1	93
3	 (**20**)	BnBr (**21**)	1	85
4	 (**22**)	**21**	1	99
5	 (**23**)	 (**24**)	1.5	97
6	**23**	 (**25**)	1	93
7	**23**	**7**	2	80
8	 (**26**)	BnCl (**27**)	2	88
9	**17**	 (**28**)	3	75

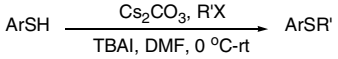
[a] Yields refer to isolated pure products characterized by IR, MS, ^1H and ^{13}C NMR spectroscopic data, and elemental analysis.

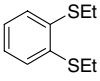
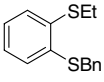
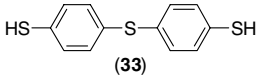
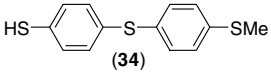
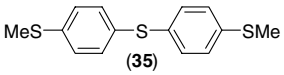
reacted quickly with BnCl (**27**) giving rise to the *S*-benzyl thioether **37**. It is important to highlight, that no ether formation was observed. Furthermore, 2-thioethylamine hydrochloride (**38**) underwent efficient coupling with 2-bromoethylamine·HBr (**39**) generating the symmetrical nitrogen–sulfur–nitrogen (NSN) ligand precursor **40** cleanly in moderate yield. Notably, in both examples, protection of the alcohol or the primary amine proved unnecessary, confirming the high chemoselectivity of this protocol.

At this stage, it was gratifying to note that the chemoselective S-alkylation of biologically important molecules such as ribosides and amino acid derivatives followed a similar course. As represented in Scheme 3, the coupling of the commercially available 6-mercaptopurine riboside (**41**) using benzyl chloride (**27**) yielded the S-benzylated-6-purinethiol riboside (**42**) in 62% yield. Again, O-alkylation of the primary or secondary alcohols was not detected. Recently, an improved method using NaOMe in MeOH at reflux temperature for the synthesis of various S-alkylated cysteine derivatives, which are important pharmacophores in anti-leukemia drug discovery research.[17] In this study, various *N*-acetyl cysteine analogs underwent efficient S-alkylation under the strongly basic conditions and no racemization was reported. However, cysteine methyl ester itself was found to epimerize. Owing to our mild conditions, we decided to investigate S-alkylation of this substrate as a direct comparison. Under the disclosed conditions, L-cysteine methyl ester·HCl (**43**) underwent coupling exclusively at the sulfur moiety to afford *S*-benzyl cysteine methyl ester (**44**) in moderate yield with accompaniment of starting material **43**. After purification, a direct comparison of the optical rotations of the synthesized product with the authentic sample revealed no racemization or ester hydrolysis had occurred during the alkylation making our protocol highly attractive.

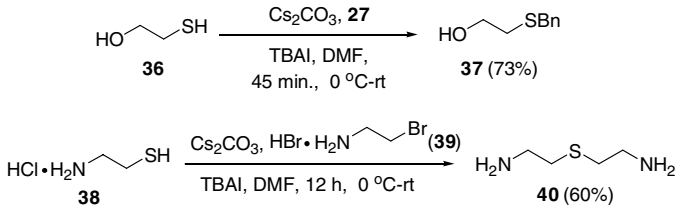
Having fully established the scope and limitations of this methodology in solution, we next directed our attention toward a solid-phase synthesis, since this technique is becoming a standard tool in combinatorial chemistry and the drug discovery process.[18] As illustrated in

Table 5. Alkylation of bis-thiols

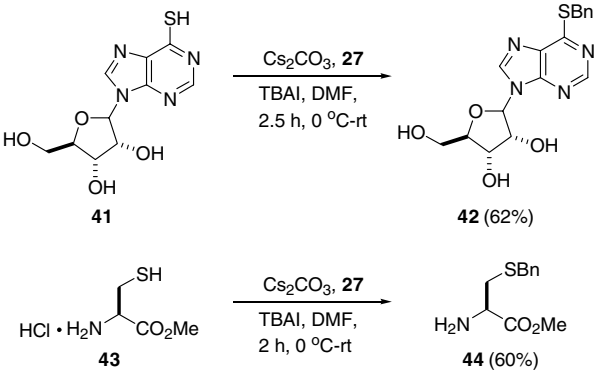


Entry	Dithiol (ArSH)	Conditions	Product (ArSR′)	Time (h)	Yield (%)[e]
1	 (**29**)	 (**30**)[a]	 (**31**)	2	90
2	**29**	**30** then **21**[b]	 (**32**)	4.5	90
3	 (**33**)	**11**[c]	 (**34**)	1	85
4	**33**	**11**[d]	 (**35**)	1.5	Quant

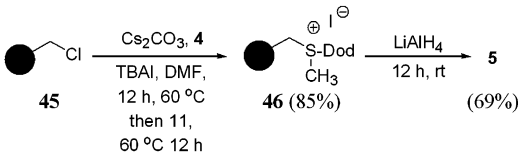
[a] 2.2 equiv Cs_2CO_3, 2.2 equiv TBAI, 2.2 equiv EtBr, 0 °C to rt.
[b] 1 equiv Cs_2CO_3, 1 equiv TBAI, 1.1 equiv EtBr, Stir 2 h, then add 1 equiv Cs_2CO_3, 1 equiv TBAI, 1.1 equiv BnBr, Stir 2.5 h, 0 °C to rt.
[c] 1 equiv Cs_2CO_3, 1 equiv TBAI, 1.1 equiv MeI, 0 °C to rt.
[d] 2.2 equiv Cs_2CO_3, 2.2 equiv TBAI, 2.2 equiv MeI, 0 °C to rt.
[e] Yields refer to isolated pure products characterized by IR, ^1H and ^{13}C NMR spectroscopic data, and elemental analysis.



Scheme 2.



Scheme 3.



Scheme 4.

Scheme 4, using Merrifield's resin (**45**) as the solid support, 1-dodecanethiol (**11**) was efficiently tethered to the resin by stirring overnight for 12 h at 60 °C. This temperature was found to be optimal from our previous experiments reported for the incorporation of selenides on solid support.[11] After stirring for the time period mentioned, MeI (**11**) was injected into the milky white suspension containing the resin-bound sulfide linkage and allowed to react for an additional 12 h to generate methyl dodecyl sulfonium salt (**46**) in high yield. Subsequent detachment of sulfide **5** from the resin was smoothly accomplished using LAH at room temperature to afford the requisite crude Dod-S-Me (**5**) in good yield and high purity. This product proved to be identical with that prepared via solution phase synthesis (Table 1, entry 5). Further examples and applications of this solid-phase technique will be reported in due course.

In conclusion, we have developed an efficient synthetic method for the synthesis of various thioethers via an efficient coupling of a thiol and an alkyl halide in the presence of Cs_2CO_3, TBAI, and DMF. Our convenient reaction conditions are compatible with numerous substrates and generally result in higher product yields when compared to conventional protocols. In addition, the common drawbacks seen using existing procedures were circumvented. Exclusive chemoselective S-alkylation using unprotected mercaptoalcohols and aminothiols is a particularly noteworthy feature of this approach. Finally, the successfully preparation of a sulfide on solid support in moderate yield and purity is also disclosed. Application of this methodology toward the synthesis of sulfur heterocycles is currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.062.

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