Trimethylchlorosilane (TMSCl) and Cyanuric Chloride (CC) Catalyzed Efficient Oxidative Coupling of Thiols with Dimethylsulfoxide

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Abstract: Different types of thiols were rapidly and efficiently converted to disulfides using DMSO in the presence of catalytic amounts of either trimethylchlorosilane (TMSCI) or cyanuric chloride (CC).

Key words: thiols, disulfides, oxidative coupling

Oxidative conversion of thiols to disulfides is of importance from both the biological¹ and synthetic point of view,² as shown by a plethora of procedures and methods that have been devised for this transformation.^{2,3} The reported reagents suffer from one or more of the following disadvantages such as availability of reagent, toxicity, high cost, or laborious work-up procedures. Very recently the catalytic coupling of thiols were the subject of some investigations.⁴ Among these, it was shown that DMSO in combination with a variety of co-reagents can be used for this purpose.⁵ However, many of these protocols suffer from drawbacks such as long reaction times, use of excess of DMSO (usually as solvent) and, in certain cases, moderate to low yield of the desired disulfides. Thus, the development of new improved protocol for a high yielding oxidative coupling of thiols to disulfides using inexpensive reagents such as DMSO is still required. Application of DMSO in organic transformations is of interest because of its stability, ease of handling, non-corrosiveness, its safe nature and inexpensiveness. However, the major limitation of the use of DMSO is its low oxidizing power. This problem can be circumvented by prior treatment of DMSO with a variety of oxophilic co-reagents as shown by the pioneering work of Swern et. al.⁶ Along this line, herein, we wish to disclose that DMSO in the presence of 10 mol% of trimethylchlorosilane (TMSCl), oxidizes thiols to corresponding disulfides (Scheme 1, Table 1).

We first examined the oxidation of thiophenol as a model substrate in the presence of a fivefold excess of DMSO and a stoichiometric amount of TMSCl in CH_2Cl_2 as solvent (10 mL). The reaction was completed within 10 minutes at room temperature and the corresponding diphenyldisulfide was isolated in excellent yield (95%). However, in continuation of this study, we found that the reaction also proceeded well in the presence of a catalytic amount of TMSCl and a lower excess of DMSO (3 equiv).

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Scheme 1

Table 1 collects the results attained in the oxidation of typical aromatic (Method A, entries 1, 4, 6, 8, 13), aliphatic (Method A, entries 10, 16, 19, 21) and alicyclic thiols (Method A, entry 23) together with the optimized reaction conditions. Inspection of these data clearly shows the efficiency of the presented method for oxidative coupling of thiols to their disulfide in substantially good to excellent yields. The reactions are clean and the work-up of the reaction products is easy.

On the other hand it was known from the pioneering work of Senier that cyanuric chloride could function as a highly oxophilic reagent for the conversion of carboxylic acids into their acid chlorides.⁷ Subsequent to this observation, the use of CC as a chemical reagent has been previously reported for converting carboxylic acids into chlorides, esters, amides, peptides, macrolactones,^{8,9} mild and selective reduction of carboxylic acids, 10 synthesis of $\alpha\mbox{-diazo}$ ketones,¹¹ deoxygenation of sulfoxides,¹² synthesis of β lactams,¹³ converting alcohols into alkyl chlorides,¹⁴ and DMSO-mediated Swern oxidation of alcohols.¹⁵ These observations encouraged us to test the ability of cyanuric chloride for catalyzing the oxidative coupling of thiols to the corresponding disulfides in presence of DMSO. A variety of structurally diverse thiols undergo facile coupling to the corresponding disulfides when treated with CC (0.1-0.4 equiv) and DMSO (1.5 equiv) at room temperature (Table 1, Method B and C). It is worth mentioning that shorter reaction times were achieved when the reaction was carried out in the presence of stoichiometric amounts of CC (Table 1, Method B, entries 2, 11, 14, 17, 25). The efficiency of the method in comparison with the TMSCI/DMSO protocol can be clearly understood in the term of quantitative coupling of sodium dimethyl- and diethyldithio carbamate (Table 1, entries 27-30).

Entry	R	Method ^a	Time (min)	Yield ^{b,c} (%)	Bp/torr or mp	Lit. bp/torr or mp
1	C ₆ H ₅	А	30	90	57–58	59-60 ^{4d}
2	C ₆ H ₅	В	30	95	_	-
3	C_6H_5	С	120	94	_	-
4	$4-FC_6H_4$	А	20	91	179–180/13	178/1316
5	$4-FC_6H_4$	С	180	92	_	-
6	$2-MeC_6H_4$	А	30	75	36–38	36–38
7	$2-MeC_6H_4$	С	120	95	_	-
8	$3-\text{MeC}_6\text{H}_4$	А	45	92	43–45	44-45 ^{4d}
9	$3-\text{MeC}_6\text{H}_4$	С	120	95	-	-
10	$4-MeOC_6H_4CH_2$	А	60	95	98–99	99 ¹⁷
11	$4-MeOC_6H_4CH_2$	В	40	98	-	-
12	$4-MeOC_6H_4CH_2$	С	130	93	-	-
13		А	50	88	180–182	177-180 ^{4d}
14		В	60	99	_	_
15		С	180	98	_	_
16	C_4H_9	А	55	83	88–91/3	116-118 ^{4d}
17	C ₈ H ₁₇	В	40	92	_	-
18	C ₈ H ₁₇	С	170	92	_	-
19	2-Furyl	А	50	92	121-122/0.5	$119 - 121/1^{4d}$
20	2-Furyl	С	120	95	_	_
21	C ₆ H ₅ CH ₂	А	30	91	69–72	$71 - 72^{4d}$
22	$C_6H_5CH_2$	С	200	93	-	-
23	$c - C_6 H_{11}$	А	45	95	138-140/1	138-141/118
24	$c - C_6 H_{11}$	С	190	92	-	_
25	HOCH ₂ CH ₂	В	60	89	-	-
26	HOCH ₂ CH ₂	С	150	82	-	-
27	S II Me ₂ N—C—SNa	А	300	NR	_	_
28	S Me ₂ NCSNa	В	20	95	149–151	150 ¹⁹
29	S II Me ₂ N—C—SNa	С	180	95	_	_
30	S II Et _a N—C—SNa	С	120	96	68–69	68–70 ¹⁹

^a Method A = thiol:DMSO:TMSCl, 1:3:0.1; Method B = thiol:DMSO:CC, 1:1.5:0.4; Method C = thiol:DMSO:CC, 1:3:0.1, respectively.

^b Yields refer to isolated pure products.

^c All reactions were performed in CH₂Cl₂ (3 mL per mmol of substrate) as solvent.

^d Bp at atmospheric pressure.



Scheme 2

The exact mechanism of this reaction is not known. One hypothesis is that the thiol coupling might be performed by atmospheric oxygen. In order to investigate this hypothesis, we first examined the oxidation of thiophenol using DMSO (3 equivalents) in the presence of 10 mol% TMSCl under a nitrogen atmosphere. Interestingly, this reaction was also completed within 30 minutes. This observation certainly suggests that the *thiol oxidation is not* done by atmospheric oxygen. On the other hand, when the same oxidation process was conducted in the presence of two equivalents of pyridine, the reaction was not completed even after 4 hours. Therefore, a pausible explanation for this observation is that at the first step of the reaction TMSCl or CC (as E-Cl) reacts with DMSO to produce activated species 1, which in turn reacts with thiol to give intermediate 2 and concomitant release of HCl and hexamethyldisiloxane (Method A) or 4,6-dichloro-1,3,5-triazin-2-ol (Method B, C). A rapid reaction of 2 with the second molecule of thiol leads to disulfide and evolution of dimethyl sulfide. The HCl, then re-enters the reaction cycle and acts as TMSCl or CC (Scheme 2).

In summary, we have demonstrated new mild and efficient methods for the oxidation of thiols to disulfides using TMSCl and CC as catalyst. The reactions are clean and the work-up of the reaction products is easy. Moreover, both TMSCl and CC are cheap and easily available reagents.

All of the products are known; the isolated products gave satisfactory mp, bp and mass spectra. The mps are not corrected. Petroleum ether with a bp 40–60 $^{\circ}$ C was used.

Oxidation of Thiols to Disulfides; Typical Procedure

To a soln of thiol (5 mmol) and DMSO (Method A, 15 mmol) in CH_2Cl_2 (15 mL) TMSCl (0.5 mmol) was added at r.t. and the mixture was stirred for the time indicated in Table 1. Progress of the reaction was monitored by TLC (petroleum ether). After completion,

the reaction was quenched with an aq soln of NaOH (10%, 25 mL), and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was separated, washed with 10% NaOH (10 mL) and H_2O (2 × 25 mL), and dried over anhyd Na₂SO₄. Evaporation of the solvent under reduced pressure gave the almost pure disulfide. Further purification of the product was achieved by recrystallization using appropriate solvents or column chromatography through a silica-gel column using petroleum ether as eluent.

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