Mendeleev Commun., 2004, 14(1), 34–35

Oxidative coupling of thiols in solution and under solvent-free conditions

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DOI: 10.1070/MC2004v014n01ABEH001831

A mild and efficient method for the oxidative coupling of thiols by ammonium dichromate in the presence of silica chloride and wet SiO_2 in solution and under solvent free conditions is reported.

The selective oxidation of thiols to disulfides is of biological and synthetic interest.[1] Thiols can be readily overoxidised so that many studies have been carried out for their controlled oxidation.[2] Thus, a number of oxidising agents such as oxygen,[3] barium permanganate,[4] iodine–hydrogen iodide,[5] aqueous HIO_3,[6] $(NO_3)_3CeBrO_3$,[7] sodium perborate,[8] pyridinium chlorochromate,[9] MnO_2–HCl,[10] Caro's acid supported on silica gel[11] and $CuNO_3 \cdot 3H_2O$[12] have been used to oxidise thiols to disulfides. However, a milder and more selective reagent is still in demand.

In continuation of our studies on silica chloride,[13–15] we were interested in using this reagent in combination with $(NH_4)_2Cr_2O_7$ and wet SiO_2 for the oxidation of thiols to disulfides.

Here we report a mild, efficient and convenient method for the oxidative coupling of thiols to disulfides in solution and under solvent-free conditions. The oxidation of different thiols by ammonium dichromate in the presence of silica chloride and wet SiO_2 was investigated in the absence of solvent (Scheme 1, Table 1). In an easy procedure, a mixture of reactants was stirred at 80 °C for an appropriate time (Table 1). The resulting disulfides were isolated in good to high yields. The over-oxidation of products was not observed with the use of this method.[†]

$$2\mathrm{RSH} \xrightarrow{\text{i or ii}} \mathrm{RSSR}$$

Scheme 1 *Reagents and conditions:* i, $(NH_4)_2Cr_2O_7$/silica chloride/wet SiO_2, solvent free, 80 °C; ii, $(NH_4)_2Cr_2O_7$/silica chloride/wet SiO_2, CH_2Cl_2, reflux.

In order to compare the results with those obtained in solution, we tried to study the coupling reaction in dichloromethane. Table 1 exhibits no appreciable difference between the results obtained in solution and under neat condition.

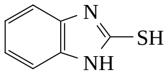
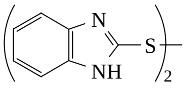
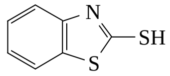
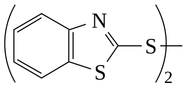
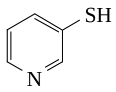
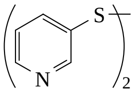
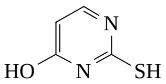
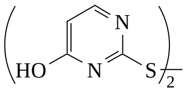
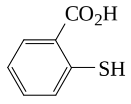
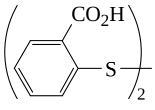
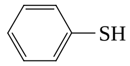
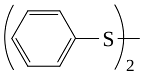
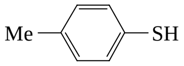
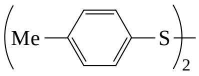
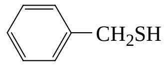
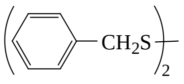
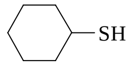
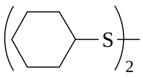
Note that oxidation did not proceed with ammonium dichromate, silica chloride or wet SiO_2 alone. These results could be attributed to the probable *in situ* generation of H_2CrO_4 in a low concentration at the surface of wet SiO_2 by silica chloride and ammonium dichromate.

To illustrate the efficiency of the proposed method, Table 2 compares our results with reported data on the relevant reagents.[8,9]

The method proposed can be used for the preparative synthesis of disulfides from corresponding thiols.

This work was supported in part by the Guilan University Research Council.

Table 1 Oxidative coupling of thiols by ammonium dichromate in the presence of silica chloride and wet SiO_2.

Entry	Substrate	Product	Solvent-free oxidation		Oxidation in solution		mp/°C or bp/°C found (reported)
			Time/min	Yield (%)[a]	Time/min	Yield (%)[a]	
1			3	97	5	92	—
2			3	95	8	90	183–184 (182.5–183.5)[16]
3			5	95	8	95	—
4			15	90	20	85	—
5			2	90	7	90	286–287 (289–290)[16]
6			1	90	5	92	59–60 (60)[17]
7			1	92	7	90	45–46 (45–46)[18]
8			1	90	5	86	71–72 (72)[19]
9			1	92	5	90	127–129 (125–130)[20]

[a]Isolated yield.

Table 2 Oxidation of thiophenol and benzylmercaptane with our method (*1*), sodium perborate (*2*) and pyridinium chlorochromate (*3*).

Substrate	Yield (%) (*t*/min)		
	1	*2*	*3*
PhSH	90 (1)	92 (120)	94 (114)
$PhCH_2SH$	90 (1)	93 (120)	91 (108)

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Received: 14th July 2003; Com. 03/2157

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† *General procedure for the oxidation of thiols in dichloromethane*. A suspension of a substrate (1 mmol), $(NH_4)_2Cr_2O_7$ (0.252 g, 1 mmol), silica chloride (0.3 g) and wet SiO_2 (50 wt%, 0.2 g) in dichloromethane (3 ml) was heated for a specified time (Table 1) under reflux. The progress of the reaction was monitored by TLC, and the mixture was filtered upon completion. The residue was washed with CH_2Cl_2 (10 ml). Then, anhydrous $MgSO_4$ was added to the filtrate and filtered off after 10 min. Solvent evaporation followed by column chromatography on silica gel gave corresponding disulfides in good to high yields.

General procedure for the oxidative coupling of thiols under solvent-free conditions. A mixture of a substrate (1 mmol), $(NH_4)_2Cr_2O_7$ (0.252 g, 1 mmol), wet SiO_2 (50 wt%, 0.2 g) and silica chloride (0.3 g) was heated at 80 °C for a specified time (Table 1). The progress of the reaction was monitored by TLC. The reaction mixture was triturated with CH_2Cl_2 (10 ml) and then filtered. Anhydrous $MgSO_4$ was added to the filtrate and filtered off after 10 min. Solvent evaporation followed by column chromatography on silica gel gave the corresponding disulfides in good to high yields.

Spectroscopic data for the products are as follows.

Table 1, entry 1: ^{1}H NMR (60 MHz, DMSO) δ: 8.01 (br., 2H), 7.70 (d, 4H), 7.26 (d, 4H). Found (%): C, 56.30; H, 3.36; N, 18.80, S, 21.51. Calc. for $C_{14}H_{10}N_4S_2$ (%): C, 56.35; H, 3.38; N, 18.78; S, 21.49.

Table 1, entry 3: ^{1}H NMR (60 MHz, DMSO) δ: 8.50 (s, 2H), 8.30 (d, 2H), 7.70 (d, 2H), 7.00 (q, 4H). Found (%): C, 54.48; H, 3.67; N, 12.75; S, 29.15. Calc. for $C_{10}H_8N_2S_2$ (%): C, 54.51; H, 3.66; N, 12.72; S, 29.11.

Table 1, entry 4: ^{1}H NMR (60 MHz, DMSO) δ: 8.20 (d, 2H), 9.00 (br., 2H), 6.00 (d, 2H). Found (%): C, 42.80; H, 1.83; N, 12.51; S, 28.56. Calc. for $C_8H_4N_2S_2O_2$ (%): C, 42.85; H, 1.80; N, 12.49; S, 28.59.