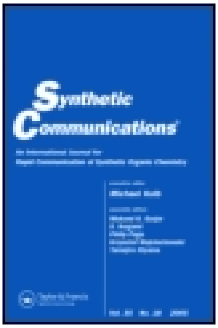

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Efficient and Convenient Oxidation of Thiols to Symmetrical Disulfide with Silica-PCl_5/$NaNO_2$ in Water

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Efficient and Convenient Oxidation of Thiols to Symmetrical Disulfide with Silica–PCl_5/$NaNO_2$ in Water

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Abstract: A very simple, environmentally benign, cost-effective, and efficient synthesis of disulfides from thiols using silica–PCl_5/$NaNO_2$ in aqueous medium has been described. The reaction was found to occur rapidly under mild conditions, and disulfides were obtained easily through a simple workup.

Keywords: Aqueous medium, disulfide, oxidation, silica-PCl_5, thiols

Disulfides are important from synthetic and biological points of view.[1] Oxidative coupling of thiols to disulfide through thionitrite formation is a potential method.[2] This is usually performed by a reagent combination of inorganic acid–sodium nitrite in appropriate solvent. Generally, chlorinated solvents such as dichloromethane or water–alcohol are used as solvent. Use of strong acid and chlorinated solvents often limits the utility of this protocol. Hence, there is a scope for further improvement by avoiding the use of strong/hazardous acids and chlorinated solvents. Recently, we have developed a novel heterogenized solid acid, silica–PCl_5.[3] Silica–PCl_5 can be prepared conveniently from silica and PCl_5, which is inexpensive and available commercially. Ease in handling, low cost, simple preparation, and formation of non toxic phosphate

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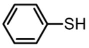
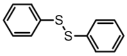
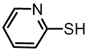
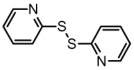
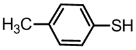
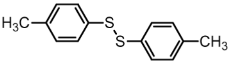
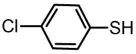
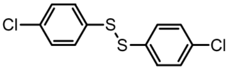
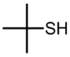
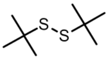
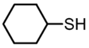
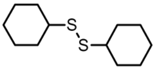
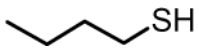
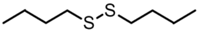
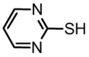
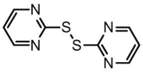
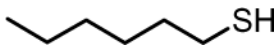
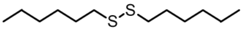
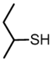
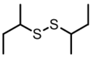
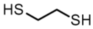
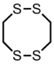
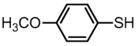
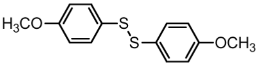
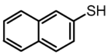
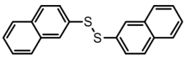
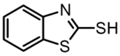
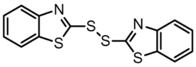
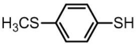
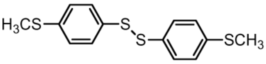
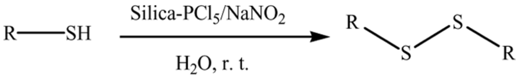
Table 1. Synthesis of disulfides

Entry	Substrate	Product[a]	Time (min)	Yield[c] (%)
1			3	95
2			5	92
3			5	95
4			6	92
5			4	89
6			3[b]	82
7			2[b]	81
8			4	90
9			2[b]	78
10			3[b]	81
11			5	92
12			4	91
13			5	93
14			4	90
15			4	89

[a] All products were identified by comparison of their physical and spectral data with those reported in literature.

[b] After extraction, the contents were stirred until decolorization of the solution.

[c] Isolated yield.



Scheme 1. Oxidation of thiols.

by-products allows this reagent to perform simple, safe, and environmentally benign oxidative coupling of thiols to disulfides.

To investigate the potential of this reagent for performing oxidative coupling of thiols to disulfides, we selected thiophenol as model substrate. Initially, the reaction was carried out by stirring a reaction mixture of silica–PCl_5, $NaNO_2$, and thiophenol in dichloromethane (DCM) containing a catalytic amount of water at room temperature. Immediate green coloration was observed, which disappeared after a few minutes. On analysis by gas chromatography–mass spectrometry (GC-MS), clean and complete conversion of thiophenol into disulfide was found. Next, we were interested to know whether this reaction can be done in aqueous medium. We reasoned that even though some of the P–Cl bonds get hydrolyzed, the resulting P–OH moiety may still show activity. To illustrate this, the same reaction was carried out in water in place of organic solvent at room temperature.

Indeed, the reaction occurred in a similar manner without any difference. After having studied the feasibility of oxidative coupling of thiols to disulfides in aqueous medium, different kinds of thiols were then examined (Scheme 1). Reaction was investigated with a variety of thiols as shown in Table 1. Aromatic and heterocyclic thiols underwent excellent disulfide formation. With primary and secondary aliphatic thiols, some side products were also formed. With tertiary mercaptans, which are otherwise difficult substrates, conversion took place easily with no side product formation. In all cases, isolation of disulfide was extremely facile because the phosphate by-product remained bound to the silica and disulfide, being water insoluble, was easily separated. In those instances when disulfides are liquid, isolation can be done by simple phase separation.

In conclusion, we have demonstrated a simple, cost-effective, and practical method for oxidative coupling of thiols to disulfides. Reaction in aqueous medium, easy isolation, and generation of nontoxic phosphate by-products makes this reaction environmentally benign and convenient.

EXPERIMENTAL

Preparation of Silica–PCl_5

Dry silica (15 g) was mixed with 10 g of PCl_5. To this, 50 ml of dry DCM were added dropwise, and the mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the contents were heated at 70°C for 3 h with stirring. HCl was removed with a slow stream of nitrogen. Contents were then washed with 100 ml of DCM, filtered under vacuum, and dried at 100°C for 3 h. The free-flowing, white silica–PCl_5 thus obtained was stored in a tightly caped bottle. Infrared spectra of both silica and silica–PCl_5 were similar, and both showed strong adsorption at 1098 cm^{-1} and 800 cm^{-1}. Acid–base titration of the reagent gave a total acid content of 54 mg KOH/g of silica-PCl_5.

General Procedure

Silica–PCl_5 (2.1 g, 2 mmol) and $NaNO_2$ (0.14 g, 2 mmol) were taken in a round-bottom flask. To this, 2 mL of water were added immediately, followed by addition of the thiol. A green or red color was produced. The reaction mixture was stirred vigorously. The color disappears within 2–6 min, indicating completion of the reaction. As soon as the color disappears, reaction contents were neutralized with $NaHCO_3$, extracted with appropriate solvent, and dried over anhyd. Na_2SO_4. Removal of the solvent in vacuo gave the pure product. In the case of aliphatic primary and secondary thiols, the moment color starts disappearing, the reaction was neutralized with sodium bicarbonate and extracted with an appropriate solvent. The extract was further stirred untill the color completely disappears and then eluted through a short column of silica.

Spectral Data for Selected Compounds

4,4′-Dimethyl Phenyl Disulfide (**3**)

White solid; mp 44–45°C (lit., 43–46°C). ^1H NMR ($CDCl_3$/TMS 400 MHz): δ 2.25 (s, 6H), 7.03 (d, $J = 8$ Hz, 4H), 7.30–7.35 (m, 4H). EIMS m/z: 246 (M^+), 213, 198, 182, 123, 108, 79, 77, 45.

2,2′-Dipyrimidyl Disulfide (**8**)

Light yellow solid; mp 134–136°C, ^1H NMR (DMSO-d_6/TMS 400 MHz): δ 7.21 (t, 2H), 8.65 (m, 4H). EIMS m/z: 222 (M^+), 158, 80, 79, 53.

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