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N-Chlorosuccinimide: A simple and efficient reagent for the preparation of symmetrical disulfides

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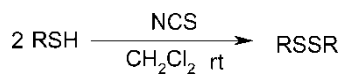
The efficient oxidative coupling of thiols to disulfides with N-chlorosuccinimide (NCS) at room temperature is described. Simple workup, economical method, high yields of products are some advantages of this method.

Keywords: Thiols; Disulfides; N-Chlorosuccinimide (NCS); Oxidation

1. Introduction

Disulfide bond formation is important in many biological and chemical processes [1]. Among several methods of preparing disulfides most involve oxidation of thiols [2, 3]. Several reagents for the synthesis of disulfides have been reported such as cerium (IV) salts [4], transition metal oxides [5], bromine [6], bromine on silica gel hydrate [7], trichloronitromethane [8], trichloro isocyanuric acid [1,3,5-tri-chloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione] [9], SO₂Cl₂ [10], manganese dioxide [11], pyridinium chlorochromate (PCC) [12], KMnO₄/CuSO₄ [13], nitric oxide [14], sodium perborate [15], calcium hypochlorite and silica gel [16], H₂O₂ [17], hydrogen peroxide in fluoro alcohols [18], solvent free permanganate [19], O₂ catalyzed by Co(II) phthalocyanines in ionic liquids [20], 2,6-dicarboxypyridinium chlorochromate [21], cetyltrimethylammonium dichromate [22] and potassium ferricyanide [23]. These methods have some disadvantages, including use of often expensive, toxic reagents and metal oxides, low yields, long reaction times and high temperature or over oxidation of disulfides to sulfoxides.

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SCHEME 1

2. Results and discussions

As part of our research on oxidation of organic compounds especially thiols with different oxidizing agent [24–26], we developed a simple, efficient, practical and green procedure with improved yields and short reaction time, using NCS as an environmentally benign, neutral and commercially available cheap reagent for the synthesis of disulfides from thiols under neutral conditions (scheme 1).

The reactions were carried out in the simplest manner, by mixing thiols and the NCS in CH_2Cl_2 at room temperature. The best result was obtained by using 0.5 equivalent of NCS. Oxidation of thiols with NCS proceeded smoothly at room temperature to afford the corresponding disulfides in high yields in a very short time. The results are summarized in table 1, which clearly indicates the scope of the reaction with respect to various thiols.

The reactions were carried out in other solvents such as acetone, petroleum ether, diethyl ether, and ethyl acetate which gave the corresponding disulfides in high yields. In the case of a protic solvent such as methanol further oxidation of thiols has been observed.

The comparison of the present method with respect to the amount of the thiols, reaction time and yields with those of the literature reports dealing with oxidation of thiols to disulfides, reveals that this newly developed method is superior to many reported procedures. In order to show the advantages and drawbacks of this reagent over some other oxidants, we have compared some of our results with those reported in the literature in table 2.

Table 1. Synthesis of symmetrical disulfide using NCS.

Entry	R	Yield (%)
1	C_6H_5	96
2	<i>p</i> -Br C_6H_4	92
3	<i>p</i> -Cl C_6H_4	94
4	2-Naphthyl	93
5	$\text{C}_6\text{H}_5\text{CH}_2$	92
6	CH_3CH_2	90
7	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$	91
8	$\text{CH}_3\text{CH}_2\text{CHCH}_3$	89
9	$(\text{CH}_3)_3\text{C}$	80
10	$\text{CH}_3(\text{CH}_2)_6\text{CH}_2$	90

Table 2. Comparison of NCS with some of the other reagents for oxidation of thiols.

Substance	Condition	Time (min)/Yield (%)	Reagent	Reference
PhSH	$\text{CH}_2\text{Cl}_2/\text{rt}$	3/96	NCS	–
PhSH	$\text{CH}_3\text{CN}/\text{rt}$	8/93	2,6-DCPCC	21
PhSH	$\text{CH}_3\text{CN}/\text{rt}$	120/99	$\text{Bu}_3\text{SnOMe}/\text{FeCl}_3$	27
PhSH	$\text{CH}_2\text{Cl}_2/20^\circ\text{C}$	114/94	PCC	12
PhSH	Solid state	10/79	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	28
PhSH	$\text{CH}_3\text{CN}/\text{rt}$	270/93	Carols acid/ SiO_2	29

3. Experimental

All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. IR and $^1\text{H-NMR}$ spectra were recorded on Perkin Elmer 781 and Bruker DPX500 instruments. The progress of the reaction was monitored by TLC.

3.1 General procedure

To the stirred solution of thiols (1 mmol) in dichloromethane (5 ml), NBS (0.5 mmol) was added. The mixture was then stirred for 3 min. The progress of the reaction was monitored by TLC. After completion of the reaction, CH_2Cl_2 (10 ml) was added and the mixture was washed successively with water ($2 \times 20 \text{ mL}$). The organic layer was separated and dried by adding anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure gave almost pure product. Further purification was achieved by column chromatography on silica gel (ethylacetate:hexane (1:4)) to give pure product in good to excellent yield (table 1). The products were characterized by IR and $^1\text{H NMR}$ and by comparison of the spectral data with those of authenticated samples.

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