Monatsh Chem (2014) 145:1151–1154
DOI 10.1007/s00706-014-1178-9

ORIGINAL PAPER

Simple and efficient oxidative transformation of thiols to disulfides using $Cu(NO_3)_2{\cdot}3H_2O$ in H_2O/AcOEt

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Received: 10 November 2013 / Accepted: 11 February 2014 / Published online: 11 March 2014

Abstract A simple and efficient methodology is described for the preparation of symmetric disulfides from corresponding thiols in the presence of $Cu(NO_3)_2$ and in H_2O/AcOEt (1:2). This process is environmentally friendly and economical because it does not use toxic or expensive reagents.

Keywords Disulfide · Oxidative transformation · Copper nitrate · Aqueous media

Introduction

Disulfides are beneficial building blocks for the synthesis of organosulfur compounds [1–3], which have important roles in biological and chemical processes [4–6]. A relatively broad range of methods for their preparation are reported in the literature [7–14]. However, the most commonly exploited method is oxidative conversion of thiols to the corresponding disulfides [15–33]. This approach benefits from the wide range of thiols that are commercially available.

Additionally, numerous reagents and catalysts have been applied to oxidize thiols to disulfides under a range of experimental conditions [17–36]. However, these reagents suffer from disadvantages, such as long reaction times, low yields, low selectivity, toxicity, difficulty of preparation, generate undesirable waste materials, overoxidation, tedious work-up of products, and a need for a large excess of the reagents and catalysts. Therefore, there is still interest in developing green, economical, and mild methods to produce the desirable disulfides in high yields and short reaction times. In accordance with these aims and in continuation of our previous reports on the synthesis of disulfides [22, 27, 34, 35], we searched for a novel methodology for the preparation of disulfides for use as intermediates in organic synthesis with a view to minimizing one or more of the aforementioned drawbacks by using $Cu(NO_3)_2{\cdot}3H_2O$ under aqueous conditions.

Results and discussions

Initially, to investigate the oxidative conversion of thiols to disulfides in homogenous aqueous conditions, various catalysts were examined with 4-bromothiophenol as the model substrate at room temperature (Scheme 1; Tables 1 and 2). $Cu(NO_3)_2{\cdot}3H_2O$, $Al(NO_2)_3$, $Fe(NO_2)_3{\cdot}9H_2O$, $(NH_4)_2Ce(NO_3)_6$, and $Bi(NO_2)_3$ facilitated this transformations successfully with good to excellent yields (75–98 % yield; Table 1, entries 1–5), whereas the reaction was not successful with $K_3Fe(CN)_6{\cdot}3H_2O$, $Ce(SO_4)_4{\cdot}4H_2O$, $CuCl_2$, CuCl, $NaNO_3$, and NH_4NO_3 (Table 1, entries 6–11). Reaction in the presence of other salts of iron and copper was also ineffective. We concluded that cations as well as the nitrate anion (NO_3^-) are important for the reactions.

A series of different solvents were examined, among which AcOEt/H_2O (2:1) was the most effective (Table 2, entry 3). Gratifyingly, the use of AcOEt/H_2O (2:1), an inexpensive and environmentally benign solvent, resulted in disulfide in nearly quantitative yields (98 %). In the absence of ethyl acetate no reaction was

Electronic supplementary material The online version of this article (doi:10.1007/s00706-014-1178-9) contains supplementary material, which is available to authorized users.

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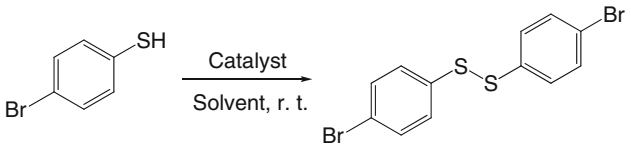
Scheme 1



Scheme 2

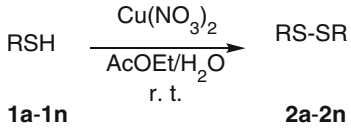


Table 1 Optimization study: catalyst screening

Entry	Catalyst	Time/min	Yield/%[a]
1	$Cu(NO_3)_2{\cdot}3H_2O$	18	98
2	$Al(NO_2)_3$	40	80
3	$Fe(NO_2)_3{\cdot}9H_2O$	100	75
4	$(NH_4)_2Ce(NO_3)_6$	50	92
5	$Bi(NO_2)_3$	35	87
6	$K_3Fe(CN)_6{\cdot}3H_2O$	50	NR
7	$Ce(SO_4)_4{\cdot}4H_2O$	50	NR
8	$CuCl_2$	50	NR
9	CuCl	50	NR
10	$NaNO_3$	60	NR
11	NH_4NO_3	60	NR

Model reaction conditions: 1 mmol 4-bromothiophenol and 1 mmol catalyst in 3 cm^3 $AcOEt/H_2O$ (2:1) at room temperature

NR no reaction observed

[a] Yield refers to isolated product

Table 2 Optimization study: screening of solvent of reactions

Entry	Solvent (v/v)	Time/min	Yield/%[a]
1	AcOEt	50	55
2	$AcOEt/H_2O$ (1:1)	50	80
3	$AcOEt/H_2O$ (2:1)	18	98
4	H_2O	50	NR
5	$EtOH/H_2O$ (1:1)	50	NR
6	$EtOH/H_2O$ (2:1)	50	NR
7	CH_3CN	50	NR
8	CH_3CN/H_2O (2:1)	50	NR
9	CH_2Cl_2/H_2O (2:1)	50	NR

Model reaction conditions: 1.0 mmol 4-bromothiophenol and 1.0 mmol $Cu(NO_3)_2{\cdot}3H_2O$ in 3 cm^3 solvent under air and at room temperature

NR no reaction observed

[a] Yield refers to isolated product

observed (Table 2, entry 4). Importantly, product work-up could be carried out without using additional organic solvents, but simply separating the organic layer and evaporating it after drying. We believe that this feature renders the process practical, economical, and environmentally friendly.

Investigation of the optimization of reaction conditions mentioned in Tables 1 and 2 clearly indicated that $Cu(NO_3)_2{\cdot}3H_2O$ in H_2O/AcOEt is a versatile reagent for the synthesis of disulfides from the corresponding thiols. A broad range of symmetric disulfides were synthesized cleanly and smoothly under optimized reactions conditions (Scheme 2; Table 3).

The reaction was tolerant of various substituents, such as CO_2H, Br, NH_2, and CH_3. As shown in Table 3, the position of the substituent on the aromatic ring does not play a vital role in the yield of the product. However, excellent yields of disulfides were obtained with thiols containing electron-withdrawing groups (Table 3, entries 8–10). 2-Amino-, 4-aminobenzenethiols, and 2-mercaptopyridine were also converted into the corresponding disulfides more rapidly than other thiols (6–10 min; Table 3, entries 6, 7, and 9). As can be seen, these functionalities remain intact during the formation of the product disulfides. This protocol was also satisfactory with some heteroaryl thiols furnishing the desired products with somewhat longer reaction times and lower yields in comparison with aliphatic and aromatic thiols (Table 3, entries 11–14).

Conclusions

We developed a simple and efficient methodology for the preparation of symmetric disulfides from the corresponding thiols in the presence of $Cu(NO_3)_2{\cdot}3H_2O$ as an inexpensive and commercially available catalyst. The present method is of general applicability to aromatic, aliphatic, and heteroaryl thiols. This method is characterized by simple work-up, short reaction times, mild reaction conditions, high chemoselectivity, and excellent yields. In addition, this process is environmentally friendly and economical because it uses $AcOEt/H_2O$ as the solvent and $Cu(NO_3)_2{\cdot}3H_2O$ as the reagent, low consumption of solvent, and does not use toxic or expensive reagents.

Experimental

Chemicals were purchased from commercial suppliers and were used without further purification. Yields refer

Table 3 Oxidation of thiols to disulfides with copper(II) nitrate at room temperature in AcOEt/H_2O

Entry	Thiol	Product	Time/min	Yield/%[a]	M.p. (lit. m.p.)/°C	References
1	PhSH	**2a**	20	88	60–61(59–61)	[17, 37]
2	$PhCH_2SH$	**2b**	60	85	66–67 (66–68)	[17, 37]
3	Naphthyl-2-SH	**2c**	30	80	142–145 (143–145)	[31]
4	4-Me-PhSH	**2d**	23	80	43–45 (43–44)	[22]
5	4-Br-PhSH	**2e**	18	98	89–92 (90–92)	[37]
6	4-NH_2-PhSH	**2f**	10	87	75–78 (76–78)	[31]
7	2-NH_2-PhSH	**2g**	2	82	88–89 (89–91)	[37]
8	2-CO_2H-PhSH	**2h**	45	95	277–280 (278–280)	[27]
9	2-Pyridyl-SH	**2i**	4	92	54–55 (55–56)	[17, 36]
10	4,6-Me_2-pyrimidyl-2-SH	**2j**	25	92	166–169 (167–169)	[24]
11	Benzoxazolyl-2-SH	**2k**	100	75	90–94 (92–94)	[37]
12	Benzthiazolyl-2-SH	**2l**	120	71	177–179 (178–179)	[37]
13	5-(4-Me-Ph)-1,3, 4-oxadiazolyl-2-SH	**2m**	120	70	69–72	–
14	$CH_3(CH_2)_3$-SH	**2n**	65	83	Oil	[26]

[a] Isolated yield

to isolated products. Melting points were determined on an Electrothermal 9,100 apparatus. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. Mass spectra were recorded on an Agilent Technology (HP) 5,973 instrument (ionizing voltage 70 eV). Elemental analyses were done on a Carlo-Erba EA1110 CHNO-S analyzer. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates.

*General experimental procedure for the preparation of symmetrical disulfides **2a–2n***

To a solution of 1.0 mmol thiol in 2 cm^3 ethyl acetate was added at once a solution of 1.0 mmol $Cu(NO_3)_2{\cdot}3H_2O$ in 1 cm^3 water. Then the reaction mixture was stirred vigorously at room temperature under an air atmosphere until completion of the reaction (Table 3). The reaction progress was controlled by TLC (*n*-hexane/EtOAc 30:1 for **2a–2e**, **2n**; *n*-hexane/EtOAc 6:1 for **2f–2m**). The reaction mixture was then separated and washed with a solution of 10 % NaOH (2 × 15 cm^3). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain the desired product **2a–2n** with high purity. Known compounds were characterized by comparison of NMR spectral data and melting points with those reported in the literature.

*1,2-Bis[5-(p-methylphenyl)-1,3,4-oxadiazole-2-yl] disulfide (**2m**, $C_{18}H_{14}N_4O_2S_2$)*

White solid; $R_f = 0.5$ (*n*-hexane/AcOEt 6:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (s, 6H, $(CH_3)_2$), 7.35 (d, $J = 8.4$ Hz, 4H, Ar–H), 7.99 (d, $J = 8.4$ Hz, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.68$ (CH_3), 120.72, 127.07, 129.84, 142.62, 152.44 (OC=N), 164.93 (OC=N) ppm; MS (EI, 70 eV): *m/z* (%) = 57.2 (72), 64.0 (100), 69.2 (28), 85.2 (32), 85.2 (31), 96.1 (37), 97.2 (38), 128.0 (64), 160.0 (37), 192.0 (12), 255.9 (26), 258.0 (17), 280.5 (10), 337.6 (5), 382.0 (3).

Acknowledgment We gratefully acknowledge the financial support from the Ilam University Research Council.

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