Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

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To cite this article: Bahador Karami , Mahnaz Farahi , Morteza Montazerozohori & Masoud Nasr-Esfahani (2011): Silica-supported ICl as a novel heterogeneous system for the rapid and selective oxidation of thiols to symmetrical disulfides, Journal of Sulfur Chemistry, 32:5, 483-488

To link to this article: http://dx.doi.org/10.1080/17415993.2011.606625

Journal of Sulfur Chemistry
Vol. 32, No. 5, October 2011, 483–488

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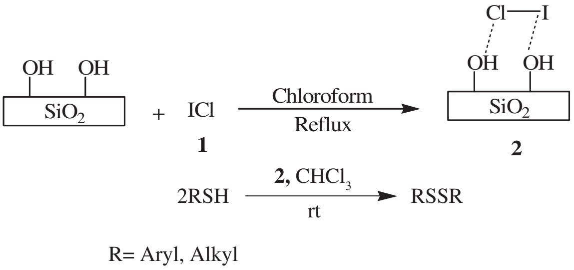
(*Received 17 December 2010; final version received 16 July 2011*)

ICl–SiO_2 as a new reactive system was prepared by treatment of iodine monochloride with activated silica gel in chloroform. ICl–SiO_2 in a heterogeneous system efficiently converted thiols to the corresponding disulfides under mild conditions in high yields at room temperature.



Keywords: iodine monochloride; iodination; thiols; disulfides; heterogeneous conditions

1. Introduction

In recent years, iodine monochloride (**1**) has been widely used for various organic transformations such as iodination of activated aromatic substrates (*1*), synthesis of 6-iodo quinazoline-4(3H)-one derivatives (*2*), iodination of nucleic acids in organic solvents (*3*), generation of electrophilic iodine from reactions with CF_3COOAg, CH_3COONa or $(CH_3COO)_2Pb$ (*4*), stereoselectivity in iodo-deboronation and chloro-deboronation of hindered alkenyl boronate esters using either ICl–NaOMe or ICl–pyridine (*5*), addition to branched E-alkenes (*6*), synthesis of α-iodo β-ketosulfones from the corresponding β-ketosulfones (*7*) and application as a volumetric reagent (*8*). Iodine monochloride (**1**) has also been used as an iodinating agent without involving a catalyst. It has two crystalline forms α and β that contain non-planar chains of ICl (**1**) molecules arranged in a zig-zag manner (*9*). This compound (**1**) has high vapor pressure and, similar to I_2 molecules, evaporates easily. While it has been used frequently, there is some hazard while using it.

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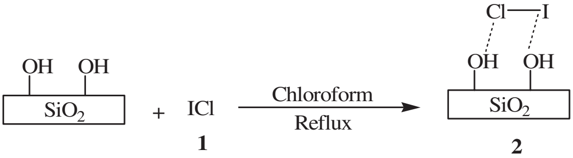
ISSN 1741-5993 print/ISSN 1741-6000 online

http://dx.doi.org/10.1080/17415993.2011.606625
http://www.tandfonline.com

Recently, silica-supported reagents have been gaining considerable attention because of their higher activity due to the larger surface area, high mechanical and thermal stabilities, ease of handling, low toxicity, non-corrosivity, and ease of separation and work-up (*10*). On the other hand, heterogeneous processes have been well studied recently for their prospective applications in organic synthesis. The high efficiency of these processes is traditionally thought to be due to the above advantages. In continuation of our studies on heterogeneous systems and solid acids (*11*), herein we report a novel solid-supported reagent (**2**) based on iodine monochloride (**1**) supported on silica gel as an efficient and mild reagent for iodination and oxidation of thiols to the corresponding disulfides. We now report that we have supported ICl (**1**) on activated silica gel (Scheme 1) to stabilize it and make it easier to use and handle.



Scheme 1. Supported ICl (**1**) on activated silica gel.

Conversion of thiols into the related disulfides is of interest from both biological and chemical points of view (*12*). Disulfides, especially diaryl disulfides, are very commonly used as electrophiles in the sulfenylation of enolates and other anions (*13*). Oxidative S–S coupling of thiols can be done under biological conditions in the presence of oxidants such as flavins and cytochromes (*14*). In the laboratory, thiols can be oxidized to the corresponding disulfides by several oxidants such as redox dyes (*14*), nitro compounds (*15*), diazocompounds (*16*), sulfoxides (*17*), halogens (*18*), 2-polyvinyl-pyridine/bromine complex (*19*), H_2O_2 (*20*), $KMnO_4/CuSO_4$ (*21*), DMSO/I_2 (*12a*, *22*) and sodium perborate (*23*) and by electrochemical methods (*24*). Due to the synthetic importance of disulfides, interest in new chemical and biotic methods has been increasing (*25*). Some of the methods mentioned above suffer from disadvantages such as long reaction times, unavailability and toxicity of reagents and isolation of products. Therefore, the introduction of readily available, safe and stable reagents for the oxidation of thiols to disulfides is still a necessity. In continuation of our studies on the oxidation of thiols to disulfides (*11c*, *26*), we introduce the novel heterogeneous reagent (**2**) for this organic transformation.

2. Results and discussion

Silica gel-supported iodine monochloride (**2**) is stable as a light pink solid and can be successfully used even after 5 months of storage. It can be prepared from the reaction of ICl (**1**) with activated silica gel in refluxing chloroform for 12 h (Scheme 1).There are some reports about charge-transfer complexes between a wide range of carbonyl compounds and ICl (**1**) (*27*) and a π-type complex formed between ethyne and ICl (**1**) (*28*). In these charge-transfer complexes, I_2 or ICl (**1**) molecules use an anti-bonding σ*-orbital to accept π-electrons from aromatic molecules or a lone pair of electrons from an *n*-donor molecule according to Mulliken's theory (*29*). Based on these results, we believe that iodine monochloride (**1**) binds to the surface of silica gel via an interaction between the hydroxyl group of silica gel and positive iodine in ICl (**1**) (Scheme 1). Unreacted ICl (**1**) on reacting with water produces HCl and HOI, which can be measured via titration of the two acids with sodium hydroxide (Scheme 2) (*1c*, *30*). Therefore, the amount of the supported ICl (**1**) on silica gel can be determined.

$$ICl + H_2O \longrightarrow HCl + HOI$$

$$HCl + HOI + 2NaOH \longrightarrow NaOI + NaCl + 2H_2O$$

Scheme 2. Reaction of unreacted ICl (**1**) with water yielding HCl and HOI.

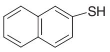
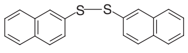
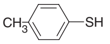
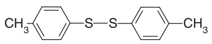
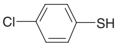
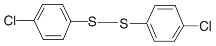
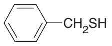
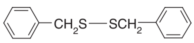
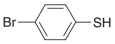
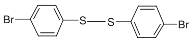
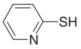
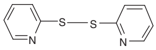
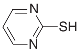
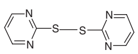
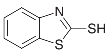
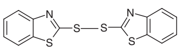
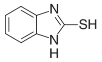
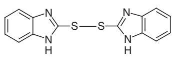
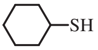
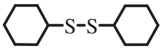
Oxidation of thiols is a common procedure for the preparation of disulfides. Therefore, after preparation of ICl–SiO_2 (**2**), we were interested in using it with organic solvents for *in situ* generation of ICl (**1**) to oxidize aliphatic and aromatic thiols under mild and heterogeneous conditions (Scheme 3). Initially, different types of thiols were treated with ICl–SiO_2 (**2**) in chloroform. The oxidation reaction was performed under mild and heterogeneous conditions at room temperature in good to excellent yields for a relatively short period of time (Table 1).

$$2RSH \xrightarrow[\text{rt}]{\mathbf{2},\ CHCl_3} RSSR$$

R=Aryl, Alkyl

Scheme 3. Oxidation of the thiols to the corresponding disulfides.

Table 1. Oxidative coupling of thiols using silica gel-supported iodine monochloride (**2**) system in chloroform at room temperature.

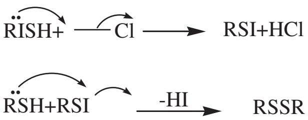
Run	Thiols	Disulfides	Reaction time (min)	Yield[a,b] (%)	m.p. (°C)	
					Found	Literature
1			40	95	144–146	142–145 (*25a*)
2			40	92	43–44	44–45 (*25a*)
3			50	95	72–73	70–7 (*25a*)
4			45	92	69–71	69–70 (*25a*)
5			40	95	90–92	91–93 (*25a*)
6			60	90	55–56	55–57 (*25a*)
7			70	90	133–135	134–136 (*26b*)
8			50	85	177–179	177–180 (*26b*)
9			70	88	202–204	202–204 (*26b*)
10	$CH_3(CH_2)_3CH_2SH$	$(CH_3(CH_2)_3CH_2S)_2$	45	90	Oil (*26b*)	
11	$CH_3(CH_2)_6CH_2SH$	$(CH_3(CH_2)_6CH_2S)_2$	45	90	Oil (*26b*)	
12	$CH_3(CH_2)_3SH$	$(CH_3(CH_2)_3S)_2$	45	92	Oil (*25a*)	
13			45	92	Oil (*25a*)	

Notes: [a] Refers to isolated yields.
[b] Identified by MS and ^1H- and ^{13}C-NMR spectroscopy.

As shown in Table 1, compounds in Entries 1, 2 and 4 have two positions for iodination because of the presence of an active aromatic ring, but the results showed that only S–S coupling occurred (Scheme 3). These results highlight the chemoselectivity of our method (or this reagent) in oxidation of thiols.

To examine the effect of the solvents, the oxidation of 4-methylthiophenol was performed in different solvents. The observations showed that oxidations in nucleophilic solvents such as methanol, ethanol, acetonitrile and ether were not complete. We suggest that these solvents competitively react with the ICl (**1**) reagent and that large amounts of reagent are needed. Both chloroform and dichloromethane were good solvents under the reaction conditions, but chloroform was better because of the good solubility of starting materials and products.

The oxidation reactions are heterogeneous because thiols are soluble in chloroform, whereas reagent (**2**) is not soluble in it. Hence, oxidation presumably occurs at the surface of the heterogeneous reagent (**2**) via a slow controlled *in situ* release of a small amount of ICl (**1**). Consequently, this new supported system effectively acts as an ICl source. Therefore, we proposed the following mechanisms based on previously reported results about the applications of ICl (**1**) (Scheme 4) (*1–9*, *31*).



Scheme 4. Suggested mechanism of the oxidation of thiols.

3. Conclusion

In conclusion, in this work, we have prepared a reactive and heterogeneous reagent for the oxidation of thiols to disulfides. This new system is equivalent to iodine monochloride but more stable and easier to use and handle. In addition, we suggest that this reagent could be used for the iodination of a wide variety of organic compounds. Therefore, its other applications are currently under study in our laboratory.

4. Experimental

4.1. *General*

Chemicals were purchased from Aldrich, Fluka and Merck chemical companies and were freshly used after purification by standard procedures. The products were isolated and identified by comparison of their physical and spectral data with those given in the literature (*25*, *26*). IR spectra were recorded on FT-IR JASCO-680 using KBr disks and the ^{1}H-NMR spectra were obtained on a Brucker instrument 300 MHz model as $CDCl_3$ solutions, and the chemical shifts are expressed in δ with Me_4Si (TMS) as the internal standard.

4.2. *Activation of silica gel*

Chromatography-grade silica gel (10 g, 70–230 mesh) was heated in an electric furnace at 400°C for 4 h. Then, it was cooled to room temperature to obtain activated silica gel (9.12 g).

4.3. *Preparation of silica-supported ICl (2)*

To a stirred solution of iodine monochloride (**1**) (0.487 g, 3 mmol) in 10 ml of chloroform, activated silica gel (9.12 g) was added and the mixture was refluxed for 12 h. Then, it was cooled to room temperature and the mixture was filtered and washed three times with 10 ml of chloroform to remove unreacted ICl (**1**). Then, the filtrate was dried to yield silica-supported ICl (**2**) (9.485 g), which contained 0.365 g (2.247 mmol) of supported ICl (**1**). This amount was in agreement with that obtained from the titration of unreacted ICl (**1**) with 0.1 M NaOH solution (*1c*, *30*).

4.4. *General procedure for oxidation of thiols to the corresponding disulfides*

To a solution of 1 mmol thiols in 10 ml of chloroform at room temperature, 4.2 g (1 mmol) of silica gel-supported iodine monochloride (**2**) was added. The reaction mixture was stirred for 40–70 min. Completion of the oxidation reaction was followed by TLC (*n*-hexane: ethyl acetate). After completion of the reaction, the reaction mixture was filtered and then the residue was washed with chloroform (10 ml). Chloroform was removed under water bath and simple distillation and disulfides were obtained as pure products.

4.5. *Typical procedure for oxidation of 4-methylthiophenol (Entry 2, Table 1)*

To a solution of 1 mmol (0.1242 g) 4-methylthiophenol in 10 ml of chloroform at room temperature, 2 mmol (4.2 g) silica gel-supported iodine monochloride (**2**) was added. The reaction mixture was stirred for 40 min. Completion of oxidation reaction was followed by TLC (*n*-hexane: ethyl acetate, 9:1). After completion of the reaction, the reaction mixture was filtered and then the residue was washed with chloroform (10 ml). Chloroform was removed under water bath and simple distillation and 4,4-dimethyl diphenyl disulfide was obtained as white crystals, 0.2266 g (92%); m.p. 45–47°C [Lit (*25a*, *26b*). 44–45°C]. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.50 (d, 4H, $J = 8$ Hz), 7.20 (d, 4H, $J = 8$ Hz), 2.46 (S, 6H, $2CH_3$). MS (*m*/*z*): (70 eV): 246 (M^+).

Acknowledgements

The authors acknowledge the Yasouj University, Yasouj, Iran, for the partial support provided for this work.

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