



NOTE

Phosphorus Oxychloride Promoted Hydrogen Peroxide for Selective Oxidation of Thiols to Disulfides

M.M. LAKOURAJ* and V. HASANTABAR

Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, Babolsar 47416, Iran

*Corresponding author: Fax: +98 1125342350; Tel: +98 1125342350; E-mail: lakouraj@umz.ac.ir

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Oxidation of aliphatic and aromatic thiols to the corresponding symmetric disulfides was achieved by using $\text{POCl}_3/\text{H}_2\text{O}_2$. A new procedure for the oxidation of thiols to disulfides without any over oxidation has been reported. It is noteworthy that the reaction is clean and tolerates oxidatively sensitive functional groups.

Key Words: Disulfides, Oxidation, Thiols, Hydrogen peroxide, Phosphorus oxychloride.

Modern methods for the formation of disulfide bonds are required for the synthesis of many biologically active compounds involved in chemical and biological processes¹. There are many biologically active peptides and peptide mimetics that possess unsymmetrical disulfide bonds².

Disulfides are used for the preparation of self-assembled monolayers³ and monolayer-protected clusters with versatile properties⁴. Several methods based on oxidative S-S coupling have been reported for the synthesis of disulfides from thiols and protected thiols including coupling with redox dyes⁵, diazo compounds⁶, sulfoxides⁷, halogens⁸, H_2O_2 ⁹, $\text{KMnO}_4/\text{CuSO}_4$ ¹⁰, DMSO/I_2 ¹¹, sodium perborate¹², bismuth(III) nitrate pentahydrate¹³, 1,3-dibromo 5,5-dimethylhydantoin¹⁴ and electrochemical methods¹⁵. Some of the methods mentioned suffer from a variety of disadvantages such as long reaction times, unavailability of the reagents and difficult isolation of products¹⁶. In continuation of our studies on applications H_2O_2 as a green oxidant¹⁷, we are now interested in using the $\text{POCl}_3/\text{H}_2\text{O}_2$ system for the conversion of thiols to disulfides.

Chemicals were purchased from Merk, Fluka and Aldrich chemical companies. Some disulfides were separated and purified by chromatographic techniques and also identified by comparison of their m.p., IR, NMR with those reported in literature¹⁸⁻²⁰.

General procedure for oxidation of thiol by $\text{POCl}_3/\text{H}_2\text{O}_2$:

The appropriate thiol (0.01 mol), Et_2O (8 mL) and (25 %) H_2O_2 (0.6 mL) were mixed in a round-bottomed flask. Then POCl_3 (0.5 mL) was added dropwise and the mixture stirred with a magnetic bar on an ice bath. After appropriate time (Table-1),

the solid disulfides that precipitated in the flask were filtered and washed. But about liquid disulfides the mixture was quenched by adding (10 %) Na_2CO_3 . The product was extracted with EtOAc (4×5 mL) and the combined extracts were dried (Na_2SO_4). The filtrate was evaporated and the corresponding disulfides were obtained. The crude disulfides were purified by chromatography on silica gel plate to afford the corresponding pure disulfides.

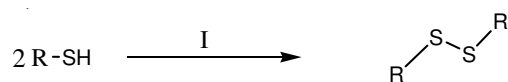
TABLE-1
OXIDATION OF THIOL BY $\text{POCl}_3/\text{H}_2\text{O}_2$

Entry	Thiol	Time (min)	Yield (%)	m.p. (found) lit.
1	PhSH	20	98	(59-61) 61 ¹⁹
2	$\text{CH}_3\text{-PhSH}$	10	96	(42-44) 44-45 ¹⁸
3	<i>p</i> -Br-PhSH	5	95	(93-94) 91-93 ¹⁸
4	2-Thionaphthol	15	93	(144-146) 142-145 ¹⁸
5	Ph- CH_2SH	30	95	(69-71) 69-70 ¹⁸
6	$\text{CH}_3\text{-(CH}_2)_3\text{SH}$	35	89	Oil ¹⁸
7	$\text{CH}_3\text{-(CH}_2)_7\text{SH}$	35	91	Oil ¹⁸
8	$\text{C}_6\text{H}_{11}\text{SH}$	45	90	Oil ¹⁸
9	HO- $\text{CH}_2\text{-CH}_2\text{SH}$	40	92	Oil ²⁰
10	2-Mercapto benzothiazole	8	97	(176-178) 177-180 ¹⁸

The $\text{H}_2\text{O}_2/\text{POCl}_3$ system can be used for the gentle, efficient and selective oxidation of a wide range of thiols. The route for the synthesis of disulfides is shown in **Scheme-I**.

In order to determine which organic solvent would be most suitable, we oxidized thiophenol in the presence of common organic solvents such as THF, acetone, Et_2O , 1,4-dioxane,

CH₃CN and MeOH. The results showed that Et₂O is generally the best solvent in term of yield and reaction period. To explore the role of POCl₃ we performed a set of preliminary experiments on thiophenol as a model substrate using 35 % aqueous hydrogen peroxide in presence of different amount of phosphorus oxychloride (POCl₃) in Et₂O at 0 °C. The results are presented in Table-2.



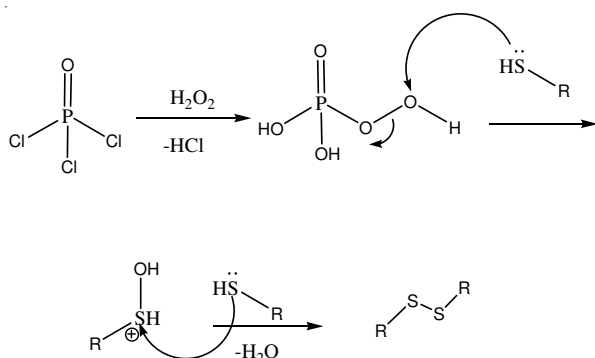
Scheme-I

Entry	POCl ₃	H ₂ O ₂	Yield (%) ^b
1	1.0	0.5	75
2	1.0	1.0	68
3	0.5	1.0	70
4	0.5	0.5	98

a: Reactions were performed with thiophenol (0.01 mol), within 20 min at 0 °C. b: Isolated yields.

It shows that to achieve a quantitative yield of corresponding disulfides, a ratio 1.0:0.5:0.5 of thiol/H₂O₂/POCl₃ was required.

It is proposed that treatment of H₂O₂ with POCl₃ produces monoperphosphoric acid. The electrophilicity of monoperphosphoric acid is higher than H₂O₂ which can easily transfer active oxygen to the thiol (Scheme-II).



Scheme-II

To extend the scope of the reaction and to generalize the procedure, we investigated the thiol coupling of a variety of organic thiol under these optimized reaction condition (Table-1).

All the reactions occurred with complete selectivity for disulfide formation, no overoxidation products were detected in the reaction mixtures.

The inherent advantages cost, smoothness and high yields of pure product, justify the use of *in situ* generated monoperphosphoric acid as an efficient reagent for oxidation of thiols.

On comparison of the available reagent for such oxidation, the *in situ* generated monoperphosphoric acid system possesses certain features that over oxidation can be avoided and mild reaction condition is used.

Conclusion

Summing up, it is found that POCl₃/H₂O₂ is an efficient and convenient oxidizing reagent for the mild and selective oxidation of thiols to disulfides.

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