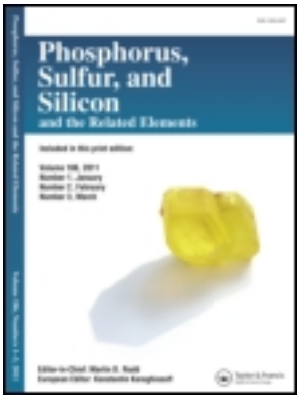

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Rapid and Convenient Method for the Synthesis of Symmetrical Disulfides

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RAPID AND CONVENIENT METHOD FOR THE SYNTHESIS OF SYMMETRICAL DISULFIDES

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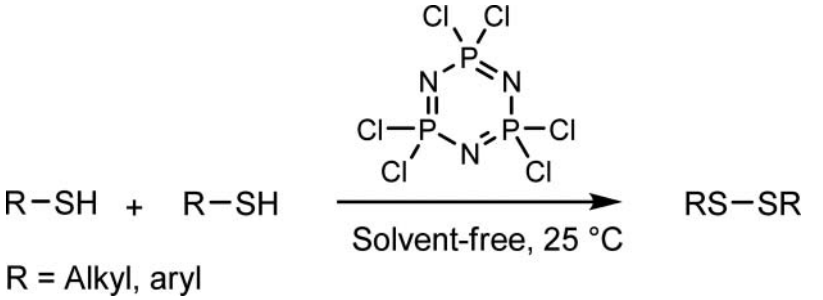
GRAPHICAL ABSTRACT



Abstract *We present here the results on the use of 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride as an efficient promoter in the conversion of thiols to the corresponding symmetrical disulfides under solvent-free conditions. Aromatic thiols bearing electron donating and electron withdrawing groups, heteroaromatic, and alkyl thiols reacted efficiently to afford excellent yields of disulfides in short reaction times after easy work-up. Different functional groups including carboxyl, methoxy, methylthio, and halogen are tolerated.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files*: Additional figures and tables.

Keywords Thiols; disulfides; solvent-free conditions; oxidative conversion; 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAPC)

INTRODUCTION

One of the main aims of green chemistry is the reduction of the use of organic solvents because of the economical and environmental concerns associated with them, and therefore, the development of solvent-free synthetic methods[1] is of the utmost importance.

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Compounds containing a disulfide linkage have been used for the preparation of dynamic combinatorial libraries,[2] catenanes,[3] macrocycles,[4] rotaxanes, and micelles.[5] These examples demonstrate the wide applications of disulfides and show that the synthesis of disulfide bonds is a pivotal transformation in modern research.[6]

Oxidative conversion of thiols is the most typical method of preparation disulfides because there are a large number of commercially available thiols and the interconversion between thiols and disulfides is easy.[7] On the other hand, disulfides are relatively more stable toward organic reactions, such as oxidation, alkylation, and acylation, compared to the corresponding free thiols; the thiol group can conveniently be protected as a disulfide.[6b] These aspects are responsible for the continuous interest in the development of new, selective, and efficient protocols for the preparation of disulfides. Reagents such as silica-PCl_5/$NaNO_2$,[8a] metal ions,[8b] molecular oxygen,[8c] halogens,[8d–g] sodium perborate,[8h] H_2O_2,[8i] tripropylammonium fluorochromate,[8j] 1,3-dibromo-5,5-dimethylhydantoin,[8k] and DMSO[8l] among others have been utilized for the preparation of symmetrical disulfides.[9–12]

However, some of these protocols suffers from drawbacks such as long reaction times,[11d] toxicity,[8j] high cost of the required reagent(s),[11e] unpleasant work-up,[11g] heavy metal contamination,[8b] in certain cases, moderate to low yields,[12a] the production of foul-smelling dimethyl sulfide as a waste product,[8l] and organic solvents are always used. Owing to the wide range of chemical and biological activity of disulfides, the development of an alternative synthetic methodology is of paramount importance.

Due to our interest in new applications for 1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAPC),[13] we decide to study the use of it as the reagent in the conversion of thiols to symmetrical disulfides (Scheme 1).

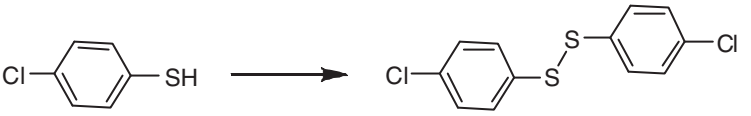
Scheme 1

Chlorocyclophosphazenes, as a type of phosphazene compound, have many special characteristics. They have various applications ranging from elastomers to anticancer drug delivery systems.[14] TAPC, a member of the class of cyclophosphazenes, has been widely used in organic reactions.[15] According to the reference method,[16] TAPC has been prepared by reacting ammonium chloride with phosphorus pentachloride. These starting materials are cheaper and more readily available.

To the best of our knowledge, there have been no reports employing TAPC as a promoter for the conversion of thiols to disulfides. Initially, we chose 4-chlorothiophenol as a substrate to establish the best condition for the preparation of the corresponding disulfide in the presence of different amount of TAPC at 25 °C under solvent-free conditions.

After careful examinations, the use of 50 mol% of TAPC under solvent-free conditions for 2 min at 25 °C was found to be the optimal condition for the disulfide synthesis (Table 1, entry 5). In the absence of TAPC, the reaction did not occur at all. An increase in the amount of TAPC did not improve the yields significantly. Subsequently, the scope of the reaction substrate was extended. Under the optimized conditions a variety of aromatic, heterocyclic, and aliphatic thiols were converted smoothly to produce disulfides. Excellent yields and high purity in most cases indicated by both the NMR and TLC analyses. Aromatic thiols having

Table 1 Effect of increasing amount of TAPC on the preparation of symmetrical disulfide[a]



Entry	TAPC (mmol)	Yield%[b]
1	0	0
2	0.1	53
3	0.2	74
4	0.4	85
5	0.5	93

[a]Reaction conditions: The reactions were performed with 4-chlorothiophenol (1 mmol) for 2 min, at 25 °C.
[b]Isolated yield.

either electron donating or withdrawing substituents reacted efficiently to afford excellent yields of disulfides despite electronic effects. The utility of this promoter in the conversion of heteroaromatic thiols was also tested. Thus, 2-mercaptobenzothiazole (Table 2, entry 8) was quantitatively transformed to the desired disulfide. Moreover, the scope of this methodology was found not to be limited to aromatic thiols, as aliphatic thiols underwent conversion to the corresponding disulfides in excellent yields (Table 2, entries 11–12). Furthermore, 2-mercaptoacetic acid (Table 2, entry 10) was utilized to obtain the corresponding disulfide in 90% yield without interference from the carboxyl functional group.

As can be seen from the results in Table 2, the selectivity of the present method is fairly wide, as carboxyl, methoxy, methylthio, and halogen functionalities do not interfere during the formation of the product disulfides. Unfortunately, furan-2-methanethiol (Table 2, entry 9) failed to produce acceptable yield of the disulfide product. This thiol produced a mixture of products, which were difficult to separate; after laborious separation, we obtained an unacceptable yield of the desired disulfide.

In order to compare the results with those obtained in solution, we tried to study the coupling reaction in CH_2Cl_2. The results showed no appreciable difference between the results obtained in solution and under solvent-free conditions. But reaction in CH_2Cl_2 is likely to raise environmental problems, and hence the challenge for a sustainable environment calls for the use of alternative procedures avoiding the use of harmful solvents. Thus, solvent-free conditions were selected for the synthesis of disulfide compounds.

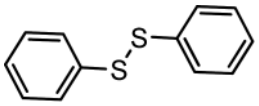
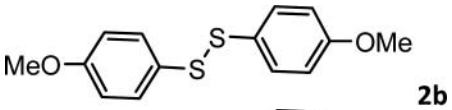
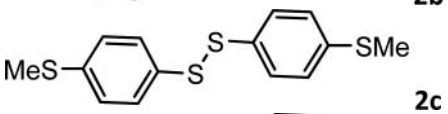
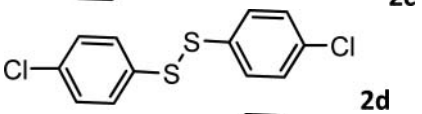
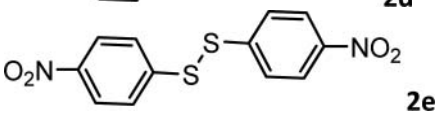
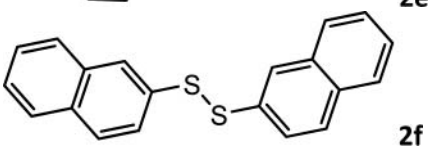
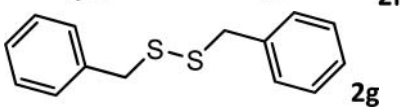
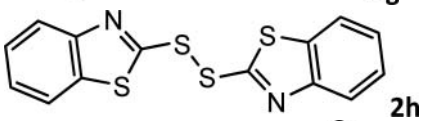
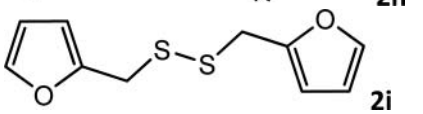
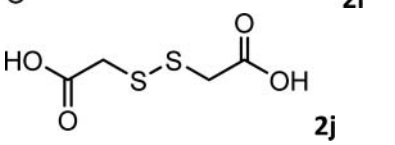
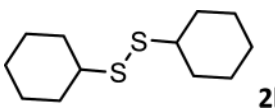
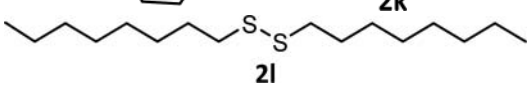
To illustrate the efficiency of this method, Table 3 compares our results with reported data on the relevant methods. As can be seen, TAPC is superior to these reagents in terms of yields and reaction times under these conditions.

To demonstrate the validity and regioselectivity of this reagent system, we studied this transformation in the presence of alkene, nitrile, aldehyde hydroxyl, and sulfide, and the results are summarized in Scheme 2. These studies obviously show that this reagent system can be applied for the chemoselective the conversion of thiols to symmetrical disulfides in the presence of the above-mentioned functional groups in multifunctional compounds.

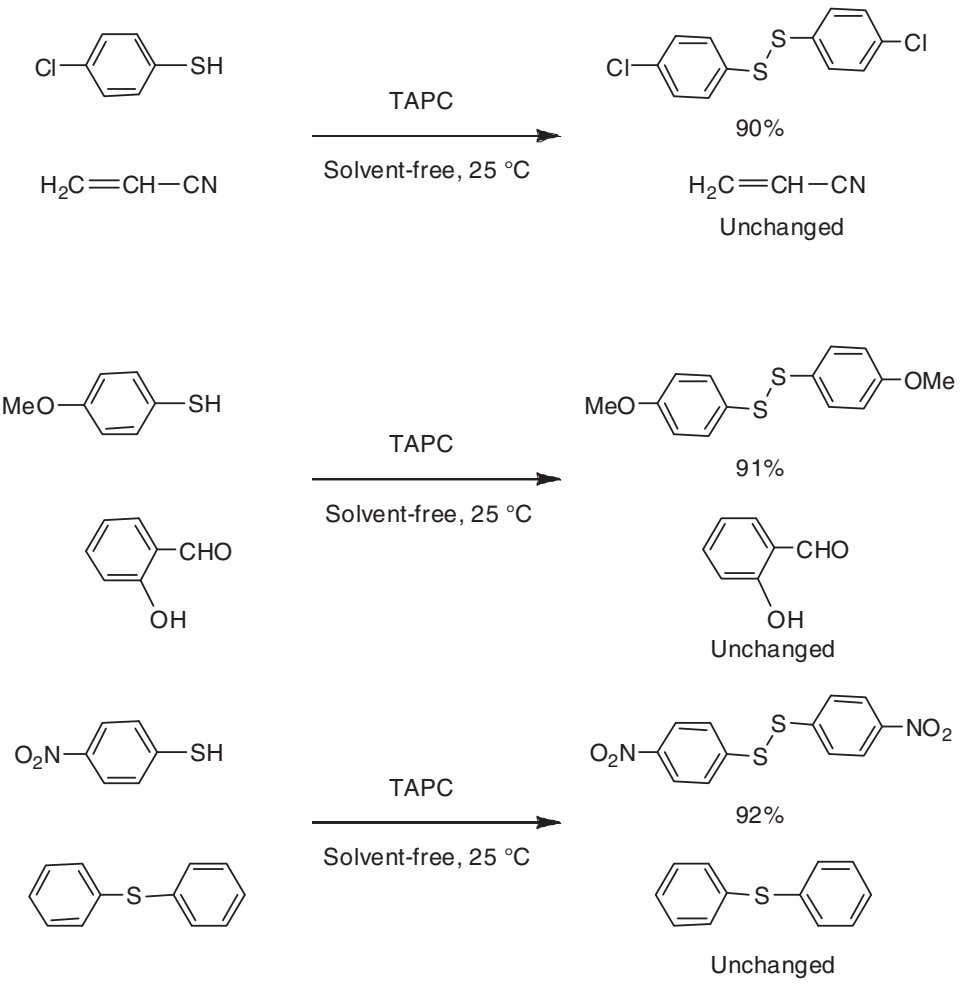
The actual mechanism of the present protocol and the precise role of TAPC are not clear at this stage. However, it is plausible that at the first stage TAPC reacts with two molecules of thiol (**1**) to produce a reactive species[19] (**3**) and by-product hydrochloric acid, and then the former is promoted by the latter to undergo phosphorus–sulfur bond cleavage.

Table 2 TAPC-promoted conversion of thiols to symmetrical disulfides[a]

R–SH ⟶ RS–SR

Entry	Disulfide 2	Yield (%)[b]/time (min)	Mp/°C (Lit Mp)	Reference
1	 **2a**	92 (2)	58 (60)	11d
2	 **2b**	90 (2)	38–40 (41–43)	10i
3	 **2c**	94 (2)	80 (80–82)	11e
4	 **2d**	93 (2)	70 (71–72)	11d
5	 **2e**	95 (2)	176–177 (175–177)	10i
6	 **2f**	90 (2)	141–143 (140)	17a
7	 **2g**	90 (2)	66 (69–72)	11f
8	 **2h**	92 (2)	178–179 (179–180)	11f
9	 **2i**	Trace	—	—
10	 **2j**	90 (2)	Oil (Oil)	11f
11	 **2k**	93 (2)	Oil (Oil)	11e
12	 **2l**	95 (2)	Oil (Oil)	17b

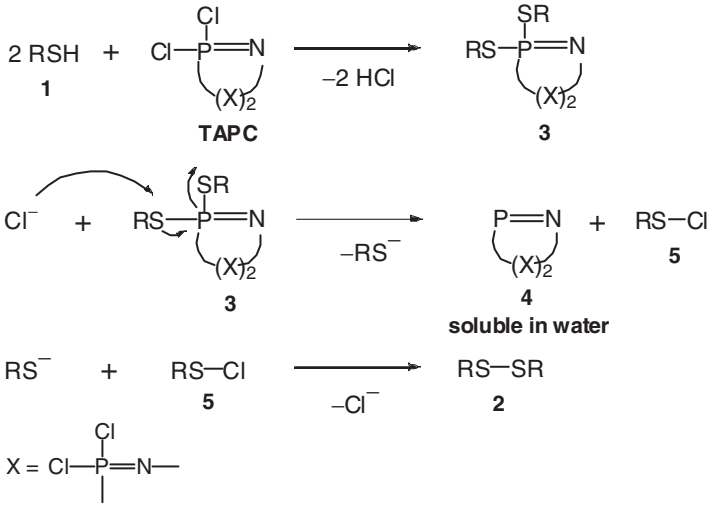
[a]The purified products were characterized by mp and ^{1}H NMR and compared with the original spectra.
[b]Yields refer to pure isolated products.



Scheme 2

The resulting sulfenyl chloride (**5**) acts as a sulfur electrophile to couple with the thiolate anion to yield the corresponding disulfide (**2**) and chloride anion (see Scheme 3). It is significant that the by-product (**4**), is soluble in water and as a result, does not contaminate the product. Simple extraction afforded pure product. Future work will include additional studies of the scope and mechanism of this transformation, and the utilization of this transformation to a variety of organosulfur chemistry processes.

In conclusion, we have successfully demonstrated a novel application of TAPC for the efficient synthesis of disulfide derivatives. This simple procedure can be applied to a wide variety of aromatic and aliphatic thiols. The ambient reaction conditions, easy availability of starting materials, shorter reaction times, simple manipulation, and excellent product yields make this catalytic system an alternative method for the synthesis of disulfide derivatives. Moreover, because the reaction can be performed without solvent, any tedious work-up is avoided. Further extensions of the reaction substrates and the investigation of the reaction mechanism are in progress in our laboratory.



Scheme 3

EXPERIMENTAL

Materials and Methods

The thiols, phosphorus pentachloride, and ammonium chloride were commercially available. Melting points were determined in a capillary tube and are not corrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-200 NMR spectrometer using TMS as an internal standard.

Table 3 Comparison of some of the results obtained with TAPC and some reported methods

Entry	Substrate	Conditions[Ref.]	Yield%	Time
1	**2d**	**This work**	**93**	**2 min**
		KO_2/toluene/N_2/25 °C[11d]	72	12 h
		PCC/solvent-free[12a]	92	1.2 h
		$PhCH_2Ph_3PHSO_5$/CH_3CN/80 °C[11i]	97	1 h
2	**2j**	**This work**	**90**	**2 min**
		PCC/solvent-free[12a]	47	1.7 h
		$Al(NO_3)_3{\cdot}9H_2O/SiO_2$-$SO_3H/CH_2Cl_2$/25 °C[11h]	99	2.6 h
		This work	**93**	**2 min**
3	**2k**	K_3PO_4/CH_3CN/25 °C[10a]	89	1 h
		PCC/solvent-free[12a]	86	3 h
		$PhCH_2Ph_3PHSO_5$/CH_3CN/80 °C[11i]	90	2.5 h
4	**2l**	**This work**	**95**	**2 min**
		MoO_2Cl_2/DMSO/70 °C[18]	87	24 h
		PCC/solvent-free[12a]	87	4 h
		$[Rh(cod)_2]BF_4$/8 PPh_3/CH_2Cl_2/4 °C[12h]	86	1 h

General Procedure for the Preparation of Disulfides

A mixture of thiol (1 mmol) and TAPC (0.5 mmol, 0.174 g) was prepared. The mixture was stirred at room temperature for 2 min (Table 2). The progress of the reaction was monitored by TLC. After the completion of the reaction, H_2O (10 mL) was added to the reaction mixture and filtered to afford pure product. In the case of liquid disulfides, the residue was then extracted with EtOAc (4 × 5 mL), and the combined extracts were dried over $MgSO_4$. The filtrate was evaporated, and the corresponding disulfide was obtained as the only product.

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