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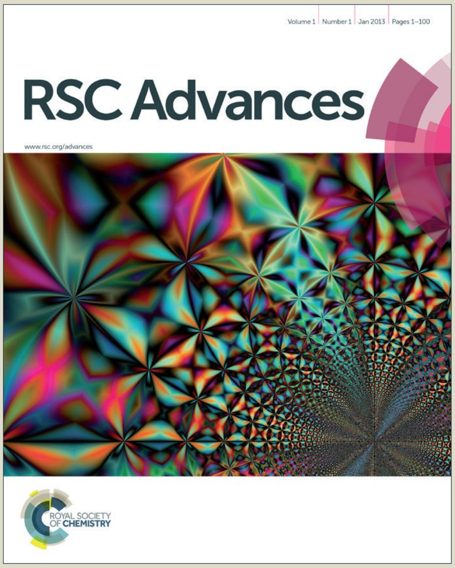

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Vis/NIR Light Driven Mild and Clean Synthesis of Disulfides in the presence of $Cu_2(OH)PO_4$ under Aerobic Condition

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A highly efficient one-pot strategy has been developed for the synthesis of disulfide in the presence of air under the irradiation of Vis/NIR light. Copper hydroxyphosphate (CHP) $Cu_2(OH)PO_4$, has been used as a Vis/NIR active photocatalyst. Disulfide forms on the surface of the catalyst by a radical mechanism. The protocol is useful for solvent free disulfide synthesis from variety of thiols.

Organic molecules hardly interact with the visible light, which is strongly emitted by the sun. Recently, researchers have used a variety of visible light-absorbing transition metal complexes to catalyze a broad range of reactions,[1] amongst them ruthenium bipyridyl complexes are well explored in visible light activated reactions. MacMillan's group has carried out trifluoromethylation, C-H functionalization, coupling of α-carboxyl sp^3 carbons with aryl halides and several other reactions using $Ru(bpy)_3^{2+}$ complexes as photocatalyst.[2-5] [2+2] photocycloadditions has been carried out by Yoon's group using visible light photocatalyst.[6] Stephenson has shown photoredox catalysis in flow reactors under the irradiation of visible light.[7]

Considering above mentioned points; here we report a copper based photocatalyst that is used for the coupling of thiols to their corresponding disulfides. Disulfide bonds play a major role in determining the structure and stability of protein.[8] Interstrand disulfide bond between Cys residues can stabilize the parallel β-sheet secondary structure.[9] Cyclic disulfide-rich peptides have exceptional stability and are promising frameworks for drug design.[10] Wang et al. showed hydrophobic drugs can self-assemble into nanomedicines by inserting disulfide bond.[11] Disulfide bonds are useful to introduce a self-healing ability in a covalently cross-linked rubber and polymeric materials.[12,13] 6,6′-dithiodinicotinic acid reacts with cell –SH groups to form mixed disulfide bonds that help to reduce the dissemination of the tumour from the brain to the lungs.[14] Disulfide bonds are also useful in drug delivery systems and organic synthesis.[15-17]

In general peroxides, molecular oxygen, metal complexes, halogens, and organic oxidants are used to synthesize disulfides from their corresponding thiols.[18-23] Dhakshinamoorthy et al. used Fe(BTC) to perform aerobic oxidation of thiols to disulfides.[24] Copper salts can be used as a catalyst for oxidative coupling of thiols to disulfides.[25,26] However, most of the procedures require, oxidants, heat, base, solvent or very expensive reagents. Among the photocatalytic methods, Oba et al. used diaryltellurides under photosensitized condition to make disulfides.[27] Recently, Li and co-workers applied CdSe QDs in the photocatalytic oxidation of thiols to disulfides.[28] These methods uses UV light or very toxic materials.

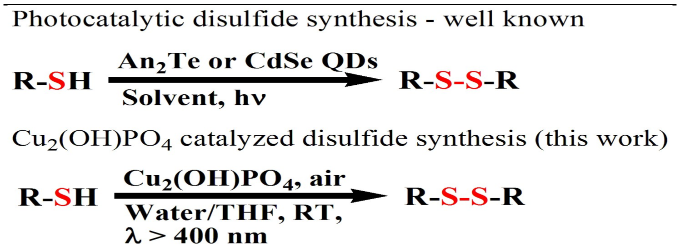

Figure 1. Conventional and $Cu_2(OH)PO_4$ photocatalyzed approaches for disulfide synthesis.

In this research, we have developed a clean method for disulfide synthesis by using copper hydroxyphosphate (CHP) $Cu_2(OH)PO_4$ photocatalyst as shown in figure-1. This protocol does not require any sacrificial agents or oxidants.

Recently, hydroxyphosphate (CHP) has gained much attention mainly because of its magnetic, [29] and catalytic properties.[30,31] Xiao et al. used $Cu_2(OH)PO_4$ as a catalyst for hydroxylation of

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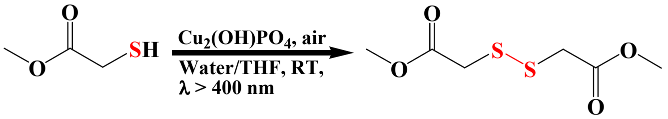
phenol, benzene and naphthol in presence of H_2O_2.[32] Recently, Wang et al. showed $Cu_2(OH)PO_4$, as a NIR active photocatalyst for decomposition of 2,4-dichlorophenol.[33] Two Cu atom in CHP has a two different environments, the axially elongated $CuO_4(OH)_2$ octahedra share their corners with axially compressed $CuO_4(OH)$ trigonal bipyramids. The photogenerated electron–hole pairs at the $CuO_4(OH)$ trigonal bipyramids are separated by transferring the electrons to the neighboring $CuO_4(OH)_2$ octahedra.[34] Thus, the well separated electron–hole pairs are capable of doing the photochemical reactions. Most of the photocatalysts are active in UV-Visible region and they are quite inactive in NIR region, which constitutes about 43% of sunlight, so we looked for a photocatalyst that is active both in visible as well as NIR region of the solar spectrum and able to work under aerobic condition. Thus, $Cu_2(OH)PO_4$ meets our both the criteria which are useful to convert thiols to their corresponding disulfide under aerobic condition in the presence of light without addition of any oxidants.

The synthesized catalyst was characterized by scanning electron microscopy (SEM), UV/Vis/NIR absorption and XRD. The SEM image of $Cu_2(OH)PO_4$ shows well-shaped crystals, which are 5-6 μm in length and 2-2.5 μm in width, with a deep valley on the surface. The UV/Vis/NIR absorption spectrum of the $Cu_2(OH)PO_4$ sample obtained from its diffuse reflectance spectrum shows a high absorption in the NIR region. All the diffraction peaks can be indexed to the orthorhombic phase of $Cu_2(OH)PO_4$ (JCPDS No. 720592) with the lattice constants a=8.08Å , b=8.430Å , and c=5.90Å (Fig. S1, ESI†).

The proposed disulfide formation was first evaluated and optimized with methyl thioglycolate (model compound). Typically, the copper catalyst was dispersed in THF/water and to it methyl thioglycolate was added. The reaction mixture was allowed to stir for an hour in the dark and then irradiated (λ > 400 nm or λ = 828 nm) for a specified time period in the presence of air at room temperature (Table 1). Only the desired disulfide was detected. In the absence of light and copper catalyst (table 1, entry 2, 7), the reaction fails to produce disulfide.

Table 1. Various reaction conditions for the coupling of methyl thioglycolate to form methyl glycolate disulfide.[a]



Entry	conditions	time[h]	yield [%][b]	[TON][c]
1	THF/H_2O	2	93	35
2	dark	28	0	0
3	Water	2	92	35
4	DCM	3	70	27
5	Isopropanol	3	78	30
6	$Isopropanol/H_2O$	3	83	32
7	no catalyst	48	0	0
8	THF/H_2O	2	92, 90	35,[d] 34[e]

[a] Methyl thioglycolate (1.6 mmol) and the catalyst (0.042mmol) were added in 10 ml of THF/H_2O mixture irradiated by a 125 W medium pressure mercury lamp with wavelength λ >400 nm in presence of air. [b] Based on the isolated pure product. [c] TON: mmol of substrate converted/ mmol of catalyst. [d] First reuse. [e] Second reuse.

The high selectivity of disulfides was formed in the presence of water. In case of insolubility in water, THF/water mixture is the suitable solvent (Table 1, entry 1). Organic solvents provide the moderate yield of disulfide when compared to water (Table 1, entry 4, 5). Then we extended our studies towards reusability of $Cu_2(OH)PO_4$ for this disulfide formation. It was reused for two consecutive runs without much loss in its activity (Table 1, entry 8). The XRD pattern of the fresh and two times used $Cu_2(OH)PO_4$ shows clearly that the crystalline nature is preserved during the photocatalysis (Fig. S2, ESI†).With the optimized conditions at hand, we explored the disulfide formation by using different thiols. The yields as well as TON of different thiols presented in table 2 were based on isolated products of disulfides.

Table 2. Substrate scope for the conversion of thiols to corresponding disulfides.[a]

$$\text{R-SH} \xrightarrow[\text{Water/THF, RT, } \lambda > 400\text{ nm}]{Cu_2(OH)PO_4\text{, air}} \text{R-S-S-R}$$

Entry	Substrate	Yield [%][b]	TON[c]
1	$HOCH_2CH_2SH$	95	36
2	CH_3OCOCH_2SH	98	37
3	$HOOCCH_2CH_2SH$	98	37
4	$HSCH_2CH_2CH_2SH$	56	21
5	C_6H_5SH	92	35
6	$4\text{-}MeOC_6H_4SH$	93	35
7	$4\text{-}MeC_6H_4SH$	85	32
8	$4\text{- }ClC_6H_4SH$	90	34
9	$4\text{- }F_3CC_6H_4SH$	76	29

[a] Conditions : thiols (1.6mmol) and catalyst (0.042mmol) in 10 ml of water {in case of insolubility in water, THF/H_2O mixture was used (entry 2, 4, 5-9)}, exposed to light for 2 hours (λ > 400 nm). [b] Based on isolated pure product. [c] TON calculated from isolated product.

Aliphatic thiols were converted in excellent yields (table 2, entry 1-4) and the catalyst was quite tolerant to various functional groups (table 2, entry 6-9). Thiophenol and its substituted derivatives are quite tolerant to the photocatalyst as well as they were coupled

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oxidatively to their corresponding disulfides in good to excellent yield (table 2, entry 5-9). Encouraged by these results, we extended our investigations towards the NIR photocatalysis. Recently, upconversion nanoparticles are quite useful for working in NIR region.[35] But upconversion nanoparticles are quite expensive and required toxic metals. On the other hand, our photocatalyst $Cu_2(OH)PO_4$ exhibited wide absorbance from 650 nm to 1600 nm and easy to synthesize. Hence we thought to explore the coupling reactions of thiols to disulfides using NIR light in the presence of photocatalyst, $Cu_2(OH)PO_4$. The coupling reaction of different thiols under the irradiation of NIR light in the presence of $Cu_2(OH)PO_4$ is shown in table-3. In presence of NIR light, disulfides were formed smoothly. Aliphatic as well as aromatic thiols were converted to their corresponding disulfides in good yields.

Table 3. Substrate scope for the conversion of thiols to their corresponding disulfides in the presence of NIR light.[a]

Entry	Substrate	Yield[%][b]	TON[c]
1	$HOCH_2CH_2SH$	80	30
2	CH_3OCOCH_2SH	83	32
3	$HOOCCH_2CH_2SH$	92	35
4	4- ClC_6H_4SH	70	27
5	4-$MeOC_6H_4SH$	80	30
6	4-MeC_6H_4SH	65	25

[a] Conditions: thiols (1.6 mmol) and catalyst (0.042mmol) in 10 ml of water {in case of insolubility in water, THF/H_2O mixture was used (entry 2, 4-6) }, exposed to NIR light for 12 hours (λ = 828 nm) [for NIR light source we used an 828 nm diode laser]. [b] Based on isolated pure product. [c]TON calculated from isolated product.

One of the most famous ancient philosophers in Greece, Aristotle, said “No Coopora nisi Fluida”, which means “No reaction occurs in the absence of solvent.”[36] During the course of our investigations, we were interested in solvent-free formation of disulfide, as solvent-free system has many advantages: reduced pollution, low costs, and simplicity in process and handling. The oxidative coupling of thiols were carried out by mixing properly the desired thiols with the catalyst in a vial and exposed to visible light under constant stirring (λ > 400 nm). The results are presented in table 4. Solvent-free disulfide conversion gives a good yield of disulfides, but the yields are less in comparison to solvent rich systems, this may be due to the uneven exposure of light on the catalyst. However, grinding of thiols with the catalyst does not improve the yield. Initially, we thought that the solid thiols may not react as effectively as their liquid partners in solvent-free condition but the solid thiols were converted as well with a good yield. Aliphatic and aromatic thiols were also converted to their corresponding disulfides at a good yield.

Table 4. Substrate scope for the solvent-free conversion of thiols to their corresponding disulfides in the presence of visible light.[a]

Entry	Substrate	Yield[b]	TON[c]
1	$HOCH_2CH_2SH$	53	20
2	CH_3OCOCH_2SH	56	21
3	4- ClC_6H_4SH	52	20
4	4-$MeOC_6H_4SH$	53	20
5	$SHCH_2CH_2CH_2SH$	45	17
6	4-MeC_6H_4SH	51	19

[a] Conditions : thiols (1.6 mmol) and catalyst (0.042mmol) are mixed properly and exposed to light for 4 hours (λ > 400 nm). [b] Based on isolated pure product. [c] TON calculated from isolated product.

The interaction between the catalyst and the thiols were studied to understand the reaction mechanism. $Cu_2(OH)PO_4$ catalyst solution was stirred for half an hour in the dark in two different vials. In one vial we added methyl thioglycolate and another we added 2-mercaptoethanol, the reaction mixtures were stirred for another half an hour in the dark to allow maximal complexation between the catalyst and the thiol, then we added both the reaction mixtures to a single vial and irradiated with visible light in the presence of air for about 2 hours, methyl glycolate disulfide and bis(2-hydroxyethyl) disulfide were formed exclusively. We have not observed any heterocoupling during the course of the reactions (Fig. S3, ESI†). Above experiments indicates that, the disulfides have been formed on the surface of the catalyst before diffuse to the solution.

The involvement of oxygen suggests that free radical species take part in the reaction. To confirm the presence of radicals in the catalysis, we have used TEMPO, (2,2,6,6 tetramethylpiperidin-1-yl)oxyl, to establish the presence of S-centered radicals.[37] In our experiments we have not detected the reactions between TEMPO with the thiol, the addition of TEMPO to the catalytic mixture decrease the disulfide yields. On the basis of our experiments with the radical scavengers, we conclude that free radicals play an important role in the catalytic process. By looking into literature[29] as well as our reaction conditions we proposed the mechanism for disulfide formation, which is shown in scheme-1.

The photogenerated electron-hole pairs in $Cu_2(OH)PO_4$ are separated by transferring electrons from $CuO_4(OH)$ trigonal bipyramids (TBP) to the neighboring $CuO_4(OH)_2$ octahedra (OCT), which creates Cu^{III} sites at the $CuO_4(OH)$ trigonal bipyramids (TBP) and Cu^{I} sites at the $CuO_4(OH)_2$ octahedra(OCT). The surface bound deprotonated thiols were oxidized at TBP Cu^{III} sites to generate sulfur centered radicals, which coupled to form corresponding disulfide on the surface of the catalyst before being diffuse to the solvent and subsequently Cu^{III} reduces to Cu^{II}. On the other hand Cu^{I} reacts

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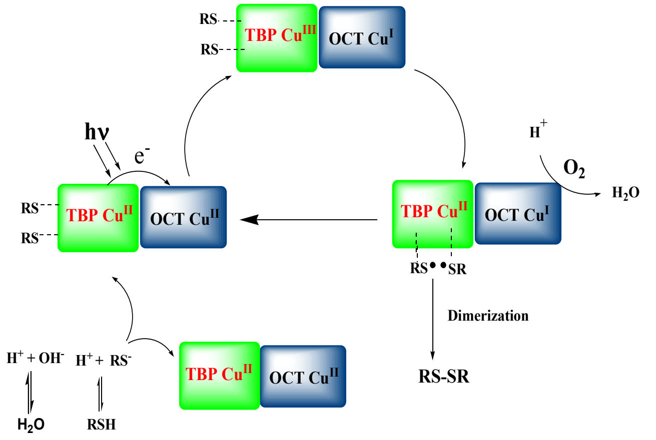
with H^+ and O_2 in the solution to generate Cu^{II} and completes the full photocatalytic cycle.



Scheme 1. Proposed mechanism for disulfide formation.

Conclusions

In conclusion, we have developed an attractive and clean catalytic procedure for the selective oxidative coupling of thiols to their corresponding disulfides. This method does not require any sacrificial agents, oxidants or solvent and, proceeds efficiently under the irradiation of visible as well as NIR light at room temperature. The disulfides have been formed on the surface of the catalyst by coupling of thiyl radicals before being diffuse to solvent. As this method has many advantages, so this method can be an attractive alternative to existing procedures for synthesizing disulfides from thiols.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of material, general procedure for disulfide synthesis and spectroscopic data.]. See DOI: 10.1039/c000000x/

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