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Unsymmetrical Disulfides Synthesis via Sulfenium Ion

Amarchand Parida,^[a] Khokan Choudhuri^[a] and Prasenjit Mal*^[a]

Abstract: An umpolung approach towards unsymmetrical disulfides synthesis *via* sulfenium ion is reported. *In situ* generated electrophilic sulfenium ion from electron rich thiols reacted with second thiols to yield unsymmetrical disulfides. Using iodine catalyst and DMAP (4-dimethylaminopyridine)-water as promoter, the target syntheses were achieved in one pot under aerobic condition.

Organic disulfides are important functional moieties found in various marine natural products,^[1] pharmaceuticals,^[2] materials^[3] and polymers.^[4] Disulfides are also known for their odors especially in kitchen items like in onions and garlics.^[5] Pharmaceutically active disulfides are known to have antiinflammatory,^[6] antitumour,^[7] antioxidants^[8] and antiulcer^[9] activities. Chemically, organo-disulfides are being used in catalyst,^[10] in ligand designing,^[11] towards producing fine chemicals and in functional group protections.^[12] In addition, the concept of Constitutional Dynamic Chemistry (CDC)^[13] and Dynamic Combinatorial Chemistry (DCC)^[14] is documented using the chemistry of disulfides. Due to the reversibility nature of the disulfide bond, formation of many products could be possible when more than one thiol building blocks present in equilibrium.^[15] Therefore, it's always challenging to synthesize selectively any unsymmetrical disulfides from mixture of thiols in one pot.^[16]

In Figure 1a, few examples of either pharmaceutically important or naturally occurring molecules containing disulfides functionalities are shown.^[16b] The known approaches for the synthesis of disulfides are mainly based on using molecular oxygen,^[17] transition metals,^[18] phosphine-free cationic rhodium(I) complex catalyst,^[19] Cu(I)-phenanthroline catalyst,^[20] base catalyzed,^[21] non-transition metals,^[22] oxidants,^[23] sodium perborate,^[24] metal organic frame works (MOFs),^[25] microwave assisted,^[26] electrochemical methods,^[27] etc. Recently Dethe and co-workers developed synthesis of unsymmetrical disulfides using fac-Ir(ppy)3 as photocatalyst and visible light from white LED (Figure 1b).^[28] Similarly, unsymmetrical disulfide synthesis is oxidant also O₂ as the reported using and cobalt(II)phthalocyanine-tetra-sodium sulfonate as the catalyst (Figure 1b).^[29] Herein, we report one pot synthesis of unsymmetrical organo-disulfides (Figure 1c) via umpolung approach in ethanol solvent, using molecular iodine as catalyst (20 mol %) and 4-dimethylaminopyridine (DMAP)-water as promoter of the reaction.

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Figure 1. a) Unsymmetrical disulfides in natural products and a symmetrical disulfide as Ellman's reagent. b) Synthesis of unsymmetrical disulfides using catalysts like cobalt-phthalocyanine^[29] and photoredox catalysis.^[28] c) Our current approach.

Controlling of chemical reactions by non-covalent or weak interactions are gaining significant interests. To make newer or functional materials on demand appropriate interactions like halogen bonding,^[30] charge-transfer,^[31] hydrophobic effect,^[32] cation- π ,^[33] anion- π ,^[34] etc. are generally used routinely. The concept of S-H···π hydrogen bonding interaction has been newly introduced in literature.^[35] Due to the S-H··· π interaction, hydrogens of thiols prefer to form a stable complex with the π electrons of arenes (Scheme 1a). Contrastingly, we have shown here that via umpolung reactivity of sulfur or S-H bond, direct C-S coupling could be possible through an intermediate sulfenium ion (Scheme 1b).[36] In ethanol solvent, sulfenium ions were generated in situ using molecular iodine as catalyst and DMAPwater as a promoter of the reaction (vide infra).[37] From the mixture of electron rich and electron deficient thiols, electron rich thiols tend to make more stable sulfenium ions. Following. electrophile sulfenium ions expected to react with the second thiols and followed by oxidation led to thermodynamically stable^[38] unsymmetrical disulfides (Scheme 1c)





Scheme 1. Unsymmetrical disulfides synthesis. a) S–H···π hydrogen bonding by the arenes. b) Electron rich thiols led to electrophile sulfenium ion to react with the electron deficient thiols for c) unsymmetrical disulfide synthesis.

Table 1. Condition Optimization

		MeO 2ab		s 2bb
MeO 1a 1b	SH I ₂ , Base, Air solvent, 70 °C, 3 h	s.s.	OMe	

			MeO	zaa		
Entry	Catalyst (20 mol %)	Solvent	Base (1.0 equiv)	Yield 2ab (%) ^b	Yield 2aa (%)	Yield 2bb (%)
1	l2	H ₂ O	КОН	69	12	7
2	l2	H ₂ O	Cs ₂ CO ₃	55	15	7
3	l2	H ₂ O	КОН	65 ^c	15	7
4	l ₂	H₂O	2,6- lutidine	58	27	11
5	l ₂	DMF	NaH	67	12	10
6	l2	H ₂ O/DMF	DMAP	31	20	10
7	l2	H ₂ O/EtOH	DMAP	79	8	5
8	l2	H ₂ O	K ₂ CO ₃	53	21	8
9	l2	H₂O	[#] BuOK	31	12	7
10	PIFA	HFIP	-	67 ^d	7	5
11	PIDA	HFIP	-	75 ^d	14	7
12	l ₂	CH ₃ CN	-	38 ^d	30	10
13	Nal	CH₃CN	-	33 ^d	10	5
14	NIS	EtOH/H ₂ O	-	62 ^d	15	10
15	l ₂	H ₂ O/EtOH	DMAP	48 ^e		
16	l ₂	EtOH/H ₂ O	КОН	45	49	5

17	l ₂	H ₂ O	DMAP	15	45	30	
18	l ₂	EtOH/H ₂ O	DMAP	10	10	5 ^f	

^eReaction condition: **1a** (0.36 mmol, 38 µL), **1b** (0.36 mmol, 44 µL) and I₂ (0.072 mmol, 18 mg), 2 mL solvent (2:1 ratio of EtOH-H₂O). ^bIsolated yields. ^cCuI as additive. ^dAt room temperature. ^eReaction was carried out in absence of oxygen/air. ^f Catalytic (20 mol%) DMAP.



Scheme 2. Unsymmetrical disulfides synthesis.

Towards optimization of the condition (Table 1), reactions were carried out at ambient temperature, under aerobic condition and continued for 3 to 5 h. Two thiol partners in equal amounts were taken in various solvents by screening different catalysts. The best condition was found to be using 20 mol % of molecular iodine in EtOH-H₂O (2:1) and in presence of 1.0 equiv DMAP. However, using of stoichiometric amount of iodine did not help further towards improvement of the yield of unsymmetrical disulfides. Similarly, the reaction also failed to give any better results in any other organic solvents. When either EtOH or water was used as the only solvent, a sluggish reaction was observed. In water, the organic thiols were found to be immiscible. The reaction proceeded as non-competitive manner in absence of DMAP and symmetrical disulfides were formed faster than the unsymmetrical ones. Among the bases (entries 1-10) like 2,6-dilutidine, NaH,

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BuOK, K_2CO_3 and DMAP, DMAP resulted in the best result (entry 7). Similarly, results from oxidant other than iodine (entries 10-11, 13-14) and organic solvents (10-13) were also not encouraging. In addition, stoichiometric amount of KOH was used as base in EtOH/H₂O but the yield of unsymmetrical disulfide was poor (entry 16). However, only DMAP in H₂O did not provide any better results (entry 17). Similarly, use of catalytic amount of DMAP did not result in the improvement of the product formation (entry 18).

Under optimized condition, various unsymmetrical disulfides were synthesized in good to excellent yields (Scheme 2). Aryl thiols like para-nitro thiophenol, 2-mercapto pyridine, 4-trifluoromethyl thiophenol, 2-pyridyl thiol, etc. also responded well to our methodology. The best yield (ca. 90%) of the unsymmetrical disulfide was obtained when 4-nitro thiophenol **1g** and 4-methoxy thiophenol **1a** were used as the coupling partners. However, the formation of symmetrical disulfides could not be avoided and those were isolated as minor products (**2aa – 2mm**, Scheme 2). Maximum 15% symmetrical disulfide could be detected as **2ee** during the synthesis of **2ae**.



Scheme 3. Unsymmetrical disulfides from aliphatic thiols.

The methodology was further extended for the synthesis of unsymmetrical disulfides with aliphatic thiols as the coupling partners (Scheme 3). Ethyl mercaptan with 4-nitrothiophenol led to 68% of unsymmetrical disulfide **4gm**. Similarly, Ethyl mercaptan with dodecane thiol resulted in 84% of **4im**. However, 63% of 1-dodecyl-2-(4-methoxyphenyl) disulfane **4ai** was isolated when reacted 4-methoxy thiophenol reacted with dodecane thiol.

Control experiments shown in Scheme 4 helped to establish the mechanism (Scheme 5) of the reaction. When 1e and 1b reacted under standard condition with 1.5 equiv of 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl radical (TEMPO), no TEMPO-thiol adduct was detected. However, formation of the disulfides 2eb, 2ee and 2bb, respectively, in 50%, 22% and 10% yields (Scheme 4a) could rule out any radical pathway. TEMPO is an oxidant, so it is expected to oxidize the thiophenol to the respective homo coupled product. Either no TEMPO adduct was identified or formation of unsymmetrical disulfides in relatively higher percentage, supported for the sulfenium ion intermediate formation. When the same reaction was conducted in presence of butylated hydroxytoluene (BHT), adduct 10a was isolated with 18% yield in addition to all possible symmetrical and unsymmetrical disulfides (Scheme 4b). Possibly, the sulfenium ion generated from 1a reacted with the phenolate anion generated from BHT. The experiments shown in Scheme 4c and 4d, could also support for the formation of sulfenium ion. Under standard reaction condition the disulfide exchange reactions of **2bb** with **1a** led to the formation of thermodynamically stable product **2ab** with 64% yield. However, when unsymmetrical disulfide **2ag** was treated with **1k**, no disulfide exchange product formation was observed (Scheme 4d). This observation establishes that the reaction was thermodynamically controlled and more stable unsymmetrical disulfide was formed.



Scheme 5. a) Plausible mechanism of the reaction. b) Use of DMAP-water as a promoter^[37] for the reaction and followed by catalyst regeneration by molecular oxygen.

For synthetic utility of the methodology, reactions were performed in large scale. When thiophenol (1b) and 4-chloro thiophenol (1c) in were reacted in 2 g scale,

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2cb was isolated in 70% yield (Scheme 6a). Similarly, dodecane thiol (1i) and ethyl mercaptan 1m led to 4im in 79% vield (Scheme 6b). The reaction proceeded via a stable sulfenium ion from the more electron rich thiol. Therefore, the selectivity for the unsymmetrical disulfide formation was also observed for the aliphatic thiols.

a) 2 g scale (aromatic disulfide)



rt - 70 °C, 3h 4im 1i, 3.8 mL 1m. 1.2 mL (16.09 mmol) (3.3 g, 79%) (16.09 mmol)

c) simultaneous two unsymmetrical disulfides synthesis



Scheme 6. a) and b) Large scale synthesis of unsymmetrical disulfides. c) Simultaneous synthesis of two unsymmetrical disulfides.

In a single step two different type of diaryl sulfides (9a and 9b) could also be accessible easily by the treatment of mesitylene with diary sulfide 2ag in presence of iodine(III) reagent PhI(OAc)2 in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent (Scheme 6c). Upon oxidation by PIDA, 2ag possibly generated two stable sulfenium ion which reacted further with the nucleophile mesitylene for aromatic electrophilic substitution (EArS) to access the diaryl sulfides.[39]

In summary, an umpolung based protocol for the synthesis of unsymmetrical disulfides is demonstrated by the control of collective weak interactions. Within a reaction system due to normal polarity preferences, thiophenol and arenes form a stable complex via to S-H···π hydrogen bonding interaction. However, the umpolung reactivity was dominated by in situ generation of thermodynamically stable sulfenium ions towards synthesis of unsymmetrical disulfides. As a metal free synthetic methodology, using iodine catalyst and DMAP (4-dimethylaminopyridine)-water as promoter of the reaction, the unsymmetrical disulfides syntheses were achieved. We anticipate that this work might find appropriate applications in the area of supramolecular catalysis in organic chemistry.

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