Minor Research Project

(F. No. 47-2074/11/WRO dated 23rd February 2012)

Report on

OXIDATIVE COUPLING OF THIOLS TO DISULFIDES USING OXONE-POTASSIUM BROMIDE IN ACETONITRILE-WATER MEDIUM

Submitted to

University Grants Commission (WRO) Pune

By

Dr. B. V. Tamhankar

Principal Investigator

and

Dr. Sandip R. Sabale

Co-Principal Investigator

P.G. Department of Chemistry,

Jaysingpur College,

Jaysingpur-416101, Maharashtra, India

OXIDATIVE COUPLING OF THIOLS TO DISULFIDES USING OXONE-POTASSIUM BROMIDE IN ACETONITRILE-WATER MEDIUM

ABSTRACT :

Oxone-potassium bromide in acetonitrile-water medium was found to be an efficient reagent system for oxidative coupling of thiols to disulfides at room temperature. The reagent system avoids the over oxidation of sulfides to sulfoxides/sulfones.

INTRODUCTION :

Oxidation of thiols to disulfides is one of the most exploited method for disulfide synthesis mainly because a large number of thiols are commercially available or can be synthesized easily. Disulfide bond formation is important in peptides,[1] in bio-active molecules as well as in oil-sweetening processes.[2] Disulfides are used in sulfenylation of enolates[3] and other anions while some disulfides have been found to be useful as vulcanizing agents[4] for rubber and elastomers imparting them suitable tensile strength. Furthermore, as compared to thiols, disulfides being more stable to organic reactions like alkylation, acylation, etc. thiol groups are many-a-times protected as disulfides and after targeted transformation desired sulfide is regenerated by reduction or by other S-S bond cleavage reagents.[5] Due to such a wide spread applicability of disulfides, the oxidation of sulfides to disulfides (**1.1** → **1.2**) has been the subject of several investigations.[6]

METHODS OF SYNTHESIS OF DISULFIDES : A BRIEF ACCOUNT.

The literature survey revealed that till date more than sixty reagents are

available for oxidation of sulfides to disulfides. Some of the earlier reported methods are summarized in Table-I (CHART-2) and some recent significant methodologies are discussed in the following paragraphs.

The oxidative protocols can be divided into two broad categories –

I) Aerobic oxidation, in presence of catalyst.

II) Non-aerobic oxidations.

I) Aerobic Oxidation Methods :

Most of the air-mediated protocols for oxidative coupling of thiols involve the use of transition metal (Fe^{+3}, Co^{+2}, etc.) catalyst or basic catalyst.

a) Using transition metal catalysts :

Sain et al.[7] have reported the use of Fe(III) – EDTA complex for the oxidation of thiols to disulfides (**3.1** → **3.2**). The method worked well with a variety of thiols but with *tert*.BuSH and long-chain alkyl thiols (C_8 and above) the reactions needed longer time and the rates were found to be pH dependent. However, Fe(III) – EDTA complex is less stable at higher pH (>11). In fact, iron gets precipitated as $Fe(OH)_3$ and the reaction fails to yield corresponding disulfide. To overcome this problem, Sainet al.[8] have reported the use of cobalt-phthalocyaninetetrasulfonamide (**3.3a**) and cobalt tetrasulfophthalo-cyanine tetrasodium salt (**3.3b**) as catalyst. Using these catalysts in alkaline medium a variety of thiols were air-oxidised to corresponding disulfides. An efficient, aerobic oxidation of thiols to disulfides using another transition-metal phthalocyanine in aqueous, water-in-oil and oil-in-water medium has also been reported.[9] The main drawback of transition-metal phthalocyanine catalysts is its poor solubility in organic solvents. To circumvent this problem, quite recentlyChavan et al[10] have reported cobalt-phthalocyanine (**3.3c,d**) in $[bmim]^+[BF_4]^-$ (**3.4**) as catalyst-reaction medium for oxidative coupling of thiols to disulfides. The reusability of the catalyst as well as reaction medium

(solvent) are the main advantages of this protocol.

Iranpoor et al[11] have reported the oxidative coupling of thiols using sodium iodide in presence of Fe(III) species such as $FeCl_3$, $Fe(NO_3)_3.9\ H_2O$, $FeCl_3.6H_2O$ as catalysts amongst which $FeCl_3.6H_2O$ was proved to be the best. It was claimed that air (O_2) present in the flask as well as solvent can effect this oxidation because in argon atmosphere the yield of expected disulfides was only 5%.

b) Using basic catalyst :

The philosophy of using basic catalysts for the aerobic oxidation of thiols to disulfides is based upon the observation that, pKa value of most of the thiols range between 7-11. Thus, treatment with base would deprotonate the thiols in a preliminary step which will then undergo aerobic oxidation to yield disulfides. In light of this, the use of basic alumina was suggested by Liu et al[12] while that of hydrotalcite clay was recommended by Hirano et al[13] in aerobic oxidation of thiols.

CsF-Celite is a well-known solid base. It is a non-hygroscopic reagent generating fluoride ions which has an effect on coupling reactions because of its high capacity of hydrogen bond formation. Voelter et al.[14] have reported the use of CsF-Celiteas a reusable base in aerobic oxidation of a variety of thiols to corresponding disulfides (**4.1** → **4.2**). The notable advantage of this reagent is its capacity to oxidize dithiols, without formation of polymeric products (**4.3** → **4.4**).

Very recently Joshi et al[15] have reported the use of potassium phosphate as a strong, reusable and inexpensive base catalyst in aerobic oxidation of thiols (Scheme-I, Chart-4).

II) Non-aerobic methods :

The non-aerobic methods for oxidative coupling of thiols to disulfides can be divided into following categories :

a) Nitronium ion based methods
b) DMSO based methods
c) Use of halogens and variants
d) Use of peroxy compounds
e) Use of dichromates, permanganates, chlorites, etc.
f) Enzyme catalyzed and electrochemical methods
g) Miscellaneous methods.

a) Nitronium ion based methods :

The attack of NO^+ion on thiol generates thionitrite. Most of the work based upon the strategy of generation of thionitrites has been done between 1998-2002. In fact, scientists aimed at synthesizing pharmacologically important thionitrites. However, thionitrites being highly unstable yielded corresponding disulfides (Scheme-II, CHART-4) via formation of thiyl radicals followed by dimerization.

Based upon this philosophy, the use of $Cu(NO_3)_2$ – nitrogen oxide combination was reported by Iranpoor et al.[16] Subsequently, Zolfigol et al[17] reported two methods for the generation of NO^+ using $Mg(HSO_4)_2$ as well as silica sulfuric acid (Schemes-I and II, CHART-5). All these methods involve an *in situ* generation of NO^+ ion which will convert thiols to disulfides via formation of thionitrites intermediate. Recently Firouzabadiet al[18] have reported the use of gaseous N_2O_4 immobilized on polyvinyl pyrrolidone as a storable source of NO^+ ion. PVP-N_2O_4 is a greenish powder, stable for months together at 0^oC. The use of PVP-N_2O_4 can be directed to prepare either disulfides or sulfones (Scheme-III, CHART-5). Demiret al[19] have reported the use of trichloronitromethane as a source of NO^+. Using this reagent, they have successfully oxidized a variety ofheteroaromaticthiols as well as biological thiols like cysteine (**6.1**) and glutathione (**6.2**) to corresponding disulfides. In all these methods attempts have been directed for the generation of NO^+ ion. Very recently, Misraet al[20] have used

directly 65% HNO_3 as a source of NO^+ ion and successfully oxidized a variety of thiols to disulfides

(Scheme-I, CHART-6).

b) DMSO mediated methods :

The applications of DMSO as a solvent as well as reagent in a variety of oxidative transformations are well documented in the literature.[21] However, the major drawback of DMSO is its low oxidizing power which could be increased by treatment with a variety of oxophilic co-reagents like oxalyl chloride, cyanuric chloride etc. Karimi et al[22] have reported a DMSO mediated oxidation of thiols in the presence of trimethylsilyl chloride and cyanuric chloride (**7.1**) for oxidation of sulfides to disulfides. The plausible mechanism of oxidation has also been given. Karimi et al.[23] have also reported the usefulness of hexamethyldisilazene (HMDS) to increase oxidizing power of DMSO to effect the same oxidation (Schemes I and II, CHART-7).

c) Use of halogens and variants :

Riekeet al[24] have reported the use of liquid bromine for oxidation of liquid thiols to disulfides under solvent free conditions. In this method, bromine acts as an oxidant as well as an indicator. This scalable process suffers from a serious drawback that out of two bromine atoms one is lost in the form of HBr making the protocol non-atom economical. Ali et al[25] have reported a slight modification to this protocol. They have reported the use of bromine on hydrated silica gel for the same reaction, wherein hydrated silica-gel works as a heat as well as HBr scavenger (**8.1** → **8.2**).

Trichloroisocyanuric acid (**8.3**) is an easily handled and colorless solid compound useful as a source of chlorine. Like bromine the use of chlorine, generated using trichloroisocyanuric acid, for oxidation of sulfides to disulfides was quite logical and this concept was executed by Zhong et al [26]. However, the method suffered from the

drawback of the use of toxic pyridine as a scavenger of liberated HCl. Also, the time needed for the reaction was slightly longer than that, when Br_2 was used.

Handling of liquid bromine is quite difficult hence the idea of using bromo compounds in place of molecular bromine was considered as a right alternative. In view of this NBS-triphenylphospine,[27] NCS-dimethyl sulfide[28a] as well as iodine-morpholine[28b] complex were successfully used to effect oxidative coupling of thiols to disulfides. Recently, the use of dibromoderivative of 5,5-dimethylhydation (**8.4**) was reported by two different groups[29,30], while the use of monochloropolystyrenehydantoin beads (**8.5**) in aqueous medium has also been reported.[31] In both the cases, the reaction proceeds through transfer of halogen from amide to thiol.

d) Use of peroxides :

The use of peroxy compounds in oxidative organic transformations is quite routine in organic synthesis. The use of H_2O_2 for oxidation of thiols was reported to take a very long time.[32] However, the use of fluorous solvents like trifluoroethanol or hexafluoroisopropanol have been reported to increase the rate of this oxidation.[33]McKillop et al[34] have reported the use of sodium per borate tetrahydrate as a very cheap, safe and easily handled oxidant for oxidative coupling of thiols as well as selenides (**9.1** → **9.2**). The important advantage of the use of sodium perborate is, no over oxidation product results even with the use of excess oxidant. Surprisingly, there are no reports on the use of Oxone for this transformation. Hajipour et al[35] have reported the use of benzyltriphenylphosphoniumperoxymonosulfate (BTPP) (**9.5**) as a useful reagent to effect oxidation of sulfides (**9.1**) to disulfides (**9.2**) as well as sulfoxides (**9.3**) The reagent BTPP was prepared by reaction between benzyltriphenylphosphonium chloride and Oxone (**9.3** → **9.5**). Similarly, tetrabutylammonium peroxidisulfate[36] (**9.8**) has also been reported in oxidative coupling of thiols.

e) Use of permanganates, dichromates, chlorites, etc.

Pyridiniumchlorochromate (PCC) is a well known oxidant useful in the oxidation of alcohols to carbonyls. Salehiet al[37] have reported the use of PCC

whileTajkaksh et al[38] have reported the use of 2,6-dicarboxypyridinium chlorochromate (2,6-DCPCC) for the oxidation of thiols to disulfides. The use of potassium dichromate was introduced by Lopez et al [39] while the use of polymer supported dichromate form viz. Dowex 1-X8-Cr_2O_7 was reported by Shirini et al[40] as a safer and easy to handle reagent. Very recently, dichromate ion attached to a carrier viz. cetyltrimethylammonium ion was reported by Patel et al[41] (**10.1** → **10.3**). CeTMA-Cr_2O_7 is soluble in organic solvents such as CH_2Cl_2 and is much easier to use than $K_2Cr_2O_7$.

Kageyama et al[42] have observed the oxidation of sulfides to sulfoxides using sodium bromite while claiming that sodium chlorite is less reactive for the same oxidation. Taking clue from these observations, Ramdas et al[4] exemplified the usefulness of sodium chlorite for oxidation of thiolsto disulfides as well as for oxidation of dialkyldithiocarbamic acids (**10.4**) to tetraalkylthiuram disulfides (**10.5**) in high yields.

Shabaniet al[43] have reported a solvent-free method for oxidation of thiols using $KMnO_4$ – $CuSO_4$. The protocol was extended towards oxidation of amines, thioethers, etc.

f) Enzyme catalyzed and electrochemical methods :

There has been considerable interest in the development of the methodologies using enzymes as catalysts. Peroxidase enzymes are responsible for oxidation of thiols to disulfides in biological systems (e.g. cysteine, glutathione, etc.) Taking clue from that Sreedhar et al[44] have reported this oxidation using Horseradish peroxidase as well as Mushroom tyrosinase at room temperature. The important advantage of this protocol is the ability of these enzymes to oxidize the thiols having electron-withdrawing groups. Literature survey revealed that except enzymes, diethylazodicarboxylate[45] (DEAD) is the only reagent capable to oxidize p-nitrothiophenol (**10.6** → **10.7**). Rao et al[46] have

reported the use of Baker's yeast for the oxidation of thiols to disulfides while Leite et al[47] have reported an electrochemical method for the similar conversion.

PRESENT WORK :

The detailed survey of the literature on the oxidative coupling of thiols to disulfides revealed that, the use of halogens (especially Br_2) is one of the oxidant of choice for this transformation. So also, use of peroxy compounds is also the method of choice of many workers. Surprisingly, direct use of Oxone for this oxidation has not been attempted earlier. In view of our earlier experiences with the use of Oxone in oxidation of hydrazides,[48] in bromination of activated arenes[49] as well as in the synthesis of azo-bis-nitriles[50] we planned to explore the possibility of using either Oxone or bromonium ion (derived from Oxone and potassium bromide) for this transformation. However, the idea suffered from two serious drawbacks

i) Use of Oxone may effect oxidation of thiols to disulfides which may further undergo oxidation to yield sulfonate (**11.1** → **11.2** → **11.3**).

ii) In case of thiols containing ring activating groups ring bromination will be the probable side reaction (**11.4** → **11.5**&**11.6**).

The literature survey also revealed that Oxone as well as bromine, both are capable to oxidize thioethers to sulfoxides. Thus, the study of oxidation of thiols to disulfides if is to be undertaken the care should be taken that at any moment neither Oxone nor bromine should remain in the reaction mixture in excess. With our earlier experiences with Oxoneand potassium bromide we decided to use *in situ* generated bromonium ion for this transformation. To avoid the presence of excess of bromonium ion in the reaction mixture, we planned the drop wise addition of solution of Oxone to the solution of potassium bromide and thiol. This will lead to the slow generation of

Br^+which will bring about oxidation of thiols to sulfides (**11.7** → **11.8** → **11.9**) but will not effectbromination of activated arene and oxidize disulfide to sulfonate.

To check the feasibility of this modification, we decided to undertake

the oxidation of an aromatic acid hydrazide, deliberately. This is because, oxidation of a hydrazide with Oxone has been reported by us to give N,N-diacyl hydrazine.[48] So also, the oxidation of hydrazides with halogens[51] (TCICA) is reported to yield corresponding acid (and not N,N-diacyl hydrazine) (Scheme-I, CHART-12). Thus, it would be interesting to check the feasibility of changing the path of the reaction by taking recourse to the slow generation of bromonium ion, by dropwise addition of Oxone to the solution of potassium bromide.

To begin with, to a mixture of benzoic acid hydrazide**12.1** (5 mmol) and potassium bromide (5 mmol) in water (20 ml) was added dropwise the aqueous solution of Oxone (5 mmol). The reaction was very fast and subsided within 30 minutes. The work-up of the reaction mixture yielded two products viz., N,N'-dibenzoyl hydrazine (minor) **(12.2a)** and benzoic acid (major) **(12.3a)**. Work-up of the reaction mixture was very simple because the resultant acid was soluble in ether while corresponding N,N'-diacylhydrazine was insoluble in ether. This result clearly revealed that it is possible to change the path of oxidation by adopting an operationally simple modification of the reaction procedure. The result of this study was confirmed by repeating the studies with *p*-toluic acid hydrazide (**12.1b**), as another substrate, which yielded *p*-toluic acid as the major (~80%) product. Both these results prompted us to undertake the oxidation of thiols.

Thiophenol (**12.4**) was selected as a model compound for this study. To a well stirred solution of thiophenol (3 mmol) and potassium bromide (3mmol) in acetonitrile-water (7 ml) was added dropwise the solution of Oxone (3 mmol in 5 ml H_2O). The rate

of addition of Oxone was so controlled that each next drop of Oxone will get added after the initial yellow colour of the reaction mixture vanishes. The addition needed ~5 min. The reaction mixture was stirred till the completion of the reaction (TLC, as indicated by disappearance of hollow, white spot due to thiol). The routine work-up of the reaction

mixture yielded a sticky liquid which was purified by simple filtration through a short column of silica gel to afford thick liquid, which solidified upon standing. It was characterized by spectral methods. ^{1}H NMR spectrum (**Fig. 2**) showed two multiplets i) between δ 7.15 – 7.28 for six aromatic protons *meta* and *para* to sulfur and ii) between δ 7.40 – 7.50 for four aromatic protons ortho to sulfur. However, the signal due to –SH proton near δ 1.2 – 1.4 was absent. The spectrum indicated the formation of the desired product but could not confirm it, as the ^{1}H NMR spectrum of starting thiophenol was expected to exhibit the similar pattern. The formation of disulfide was confirmed from mass spectrum of the compound (**Fig. 3**). It showed the M^{+} ion peak at 218 amu. as well as the peak at 109 amu. ($m^{+}/2$). These two peaks suggested the formation of the disulfide which is symmetric in nature viz., diphenyl disulfide. The other peaks in the MS were at 185 and 154amu. The probable path for the genesis of these ions is depicted in CHART-12. This result encouraged us to extend our studies on the oxidative coupling of sulfides to disulfides. The important point to note was, the non-formation of either an over oxidation product or a ring brominated product.

The oxidation of *p*-chlorothiophenol, *p*-methylthiophenol and *p*-methoxythiophenol were performed exactly under the same reaction conditions as were used for the oxidation of thiophenol. The reactions furnished corresponding disulfides in excellent yields and purity. The structures of all these disulfides were confirmed from their ^{1}H NMR as well as MS studies.

The disulfide derived from *p*-chlorothiophenol in it's ^{1}H NMR spectrum (**Fig.5**) showed two clear doublets with coupling constant of 8 Hz, (each) at δ 7.23 and 7.38, while the mass spectrum (**Fig.6**) of the same exhibited the peaks at 286 (M^+), 288 (M^++2) and 290 (M^++4) indicating the presence of two chlorine atoms in the product. The spectrum also showed the peaks at 143 and 145 (M^+/2), at 108 and at 99 amu.

The disulfide derived from *p*-methylthiophenol in it's ^{1}H NMR spectrum (**Fig.7**) exhibited a singlet at δ 2.23 for aromatic methyl group protons and two doublets for aromatic protons at δ 7.02 and 7.36 (J=8Hz, each) characteristic of AA'BB' pattern. The peaks in the MS (**Fig.8**) at 246 (M^+), 123 (M^+/2) and at 91 (tropyliumcation) assisted in confirming the structure.

^{1}H NMR spectrum (**Fig. 9**) of disulfide derived from *p*-methoxythiophenol exhibited a singlet at δ 3.75 due to methoxyl group protons and two doublets at δ 6.78 and 7.36 characteristic of AA'XX' pattern for aromatic ring protons. These doublets clearly indicated that bromination has not taken place at all even after the presence of ring activating methoxyl group. Thus, this modified protocol brings about selective oxidation of thiols to disulfides in preference to ring bromination in activated arenes.

The protocol was extended towards the oxidation studies with *p*-methoxybenzylmercaptan. In this case also, corresponding disulfide was obtained in excellent yield and no formation of ring brominated product was observed as indicated from the ^{1}H NMR spectrum (**Fig.10**). It showed two singlets at δ 3.58 and at 3.80 for the benzylic methylene and for methoxyl group protons and two doublets at δ 6.82 and 7.18 due to the aromatic protons *ortho* to and *meta* to the methoxyl group.

The attention was then turned towards oxidation of heterocyclic thiol viz. pyridine-2-thiol. The oxidation of this thiol also yielded corresponding disulfide as indicated from it's ^{1}H NMR spectrum (**Fig.11**).

The oxidation studies with aliphatic thiols (n-BuSH, n-hexyl-SH, dodecanethiol) and with cyclohexylthiol were also successful and yielded corresponding disulfides. The results of these studies are summarized in Table-II (CHART- 13) .

CONCLUSION :

In conclusion, we have developed a mild, efficient and chemoselective method for the oxidation of thiols to corresponding disulfides using Oxone-potassium bromide in aqueous acetonitrile medium. The key to the success of this protocol is controlled generation of bromonium ion to effect oxidation of sulfides to disulfides avoiding ring bromination as well as over oxidation products.

EXPERIMENTAL

Thiophenol (Sd fine chemicals), *p*-chlorothiophenol, *p*-methyl thiophenol, *p*-methoxythiophenol, benzylmercaptan, hexanethiol, n-butanethiol, *p*-methoxybenzylmercaptan, cyclohexanethiol, dodecanethiol (Lancaster) were used as received. Oxone (Alfa), potassium bromide (Qualigens) were used. IR spectra were recorded on Perkin-Elmer FT-IR-783 instrument. NMR spectra were recorded on Bruker AC-200 or MSL-800 (200 MHz or 300 MHz, respectively) using $CDCl_3$ as a solvent and TMS as an internal standard. δ values are expressed in ppm. Mass spectra were recorded on Varian- instrument.

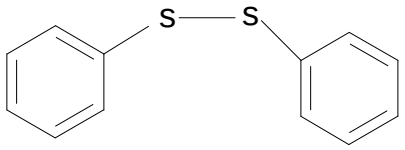
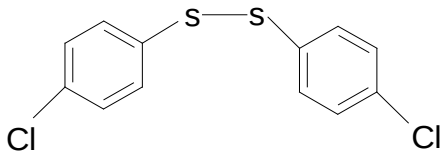
GENERAL PROCEDURE :

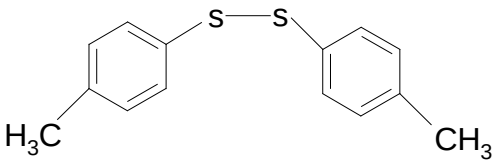
To a well stirred solution of thiol (10 mmol) in acetonitrile (5 ml) and potassium bromide (10 mmol) in water (2 ml) was added dropwisethe solution of oxone (10 mmol) in water (10 ml). Each next drop of solution of Oxone was added after the disappearance of the yellow colour formed to the reaction mixture. After addition, the reaction mixture was stirred till the completion of reaction (TLC, as indicated by the disappearance of the hollow spot of thiol). The reaction mixture was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate and ether was removed to get a residue which was filtered through a short column of silica gel to get pure disulfide.

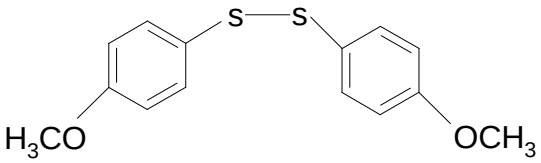
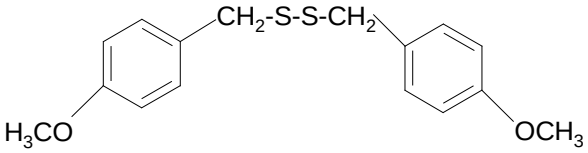
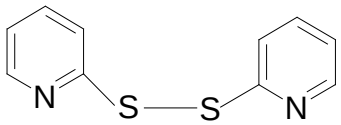
All the disulfides were characterized by comparison of their physical constants with those reported in the literature as well as by spectral methods.

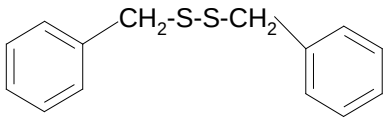
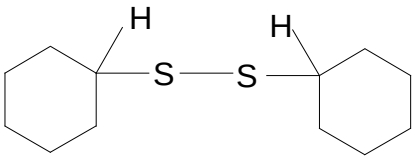
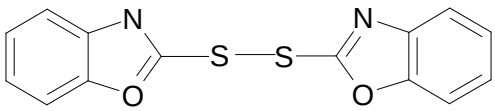
Spectral data of the disulfides is summarized below :

Spectroscopic data :

Diphenyldisulfide	
	mp 59-60°C; (Lit.[20] 60°C), IR (KBr, **fig.1**): 2924, 1599, 1493, 1452, 1408, 1261, 1069, 757, 695 cm^{-1}; 'H NMR ($CDCl_3$, **fig.2**): δ 7.15-7.28 (6H,m,Ar-Hs *meta* and *para* to-s), 7.40-7.50 (4H,m,Ar-Hs *ortho* to –s). MS (**fig.3**): m/z (%) 218 (m^+,90), 185(20), 154(30), 109 (100), 65(45).
4,4'-Dichloro diphenyl disulfide	
	mp 69°C; (Lit.[29] 70-71°C), IR (KBr, **fig.4**): 3077, 2924, 1643, 1472, 1385, 1093, 1009, 815, 740 cm^{-1}; 'H NMR ($CDCl_3$, **fig.5**); δ 7.23 (4H,d, J=8Hz, Ar-H*ortho* to –Cl), 7.38 (4H,d, J=8Hz, Ar-H*meta* to –Cl); MS (**fig.6**): m/z (%) 286, 288, 290 (M^+, $M+2^+$, $M+4^+$, 48, 30, 12), 143, 145 (100, 33), 108, 99, 63.
4,4'-Dimethyl diphenyl disulfide	
	mp 43°C; (Lit.[20] 45-46°C), ^1H NMR ($CDCl_3$, **fig.7**); δ 2.23 (6H, s, 2Ar-CH_3), 7.02 (4H,d, J=8Hz, Ar-

	Hs*ortho* to $-CH_3$), 7.36 (4H, d, J=8Hz, Ar-Hs*meta* to $-CH_3$); MS (**fig.8**): m/z (%) 246 (M^+, 78), 123 (100), 91, 79.

4,4'-Dimethoxy diphenyl disulfide	
	mp 41°C; (Lit.[24] 44-45°C), ^{1}H NMR ($CDCl_3$, **fig.9**) : δ 3.75 [6H,s,Ar-$(OCH_3)_2$], 6.78 (4H, d, J=8 Hz, Ar-Hs*ortho* to $-OCH_3$), 7.36 (4H,d, J=8 Hz, Ar-Hs*meta* to $-OCH_3$).
4,4'-Dimethoxy benzyl disulfide	
	mp 96-97°C; (Lit.[20] 99°C), ^{1}H NMR ($CDCl_3$**fig.10**): δ3.58 (4H,s, 2 Ar-CH_2), 3.80 (6H,s,2xAr-OCH_3), 6.82 (4H,d, J=8Hz, Ar-Hs*ortho* to $-OCH_3$), 7.18 (4H,d, J=8 Hz, Ar-Hs*meta* to $-OCH_3$).
Pyridyl disulfide	
	mp 52°C; (Lit.[20] 54-57°C), ^{1}H NMR ($CDCl_3$, **fig.11**): δ 7.07 (2H, m, 2xH_6 from pyridine ring), 7.56 (4H,m, 2xH_4& H_5 from pyridine ring), 8.41 (2H, d, 2xH_3 from pyridine ring).
Benzyl disulfide	

	mp 70°C; (Lit.[20] 72°C), IR (KBr, **fig. 12**): 3019, 2959, 1519, 1467, 1422, 1365, 1215, 1154, 669 cm^{-1}; ^1H NMR ($CDCl_3$, **fig.10**) : δ 3.5 (4H,s, 2Ar-CH_2), 7.1–7.25 (10H,m, Ar-Hs); MS (**fig.14**): m/z (%) 214 (20), 123 (20), 91 (100), 77,65.
Cyclohexyl disulfide	
	Oil; ^1H NMR ($CDCl_3$, **fig.15**): δ 1.25-1.36 (6H,m), 1.79 (2H,bs), 2.04 (2H,bs), 2.72 (1H,m). Spectrum is poorly resolved.
n-Hexyl disulfide	
$(CH_3 - (CH_2)_4 - CH_2-S-)_2$	Oil; ^1H NMR ($CDCl_3$, **fig.16**) : δ 0.96 (6H, t, 2xCH_3), 1.39 (4H,m, 2xCH_3-CH_2-), 1.67 (4H,m, 2xCH_2-CH_2-S), 2.72 (4H,m,2x s-CH_2).
2,2'-Dibenzothiazole disulfide	
	mp 182°C; (Lit.[4] 184°C), ^1H NMR ($CDCl_3$**fig.17**) : 7.27 – 7.50 (4H, m, ArHs*para* and *meta* to –N), 7.62 (2H,m, Ar-Hs*ortho* to S), 7.8 (2H, m, Ar-Hs*ortho* to N); MS (**fig.18**) : m/z (%) : 154 (10), 121 (100), 91 (8), 77 (18).

REFERENCES :

1) Bodanszky, M.
Principles of Peptide Synthesis; Springer, Berlin, **1984**, Chapter 4.

2) Jocelyn, P.C.
in*Biochemistry of the Thiol Groups*, Academic Press,
New York, **1992**.

3) Bischoff, L.; David, C.; Martin, L.; Meudal, H.; Roquers, B.-P.; Fournie-Zaluski, M.-C.
J. Org. Chem. 62, **1997**, 4848.

4) Ramdas, K.; Srinivasan, N.
*Synth.Commun.*25, **1995**, 227.

5) Malti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.
*Synth.Commun.*18, **1988**, 575.

6) a) Page, P. Ed.
Organosulfur Chemistry Synthetic Aspects; Academic Press,
San Diego, **1995**.

b) Oae, S. Ed.
OrganosulfurChemistry : Structure and Mechanism;
CRC, Boca Raton, FL **1991**.

c) Capozzi, G.; Modena, G. in Patai, S.
The Chemistry of Thio' Groups, Part-II, Wiley : New York,

1974, 785.

7) Sain, B.; Rao, T.V.; Murthy, P.S.; Joshi, G.C. PrasadaRao, T.S.R.; Jain, A.K. *J. Chem. Res*. (S) **1998**, 300.

8) N. Rao, K.; Rao, T.V.; Jain, S.L.; Sain, B. *Synth.Commun*.32, **2002**, 1151.

9) Chauhan, S.M.S.; Gulati, A.; Sahay, A.; Nizar, P.N.H. *J. Mol. Catal. A : Chem.*105, **1996**, 159.

10) Chauhan, S.M.S.; Kumar A.; Srinivas, K.A. *Chem. Commun.***2003**, 2348.

11) Iranpoor, N.; Zeynizadeh, B. *Synthesis***1999**, 49.

12) Liu, K. – T.; Tong, Y. – C. *Synthesis***1978**, 669.

13) Hirano, M.; Monobe, H.; Yakabe, S.; Marimoto, T. *J. Chem. Res*. (S) **1999**, 374.

14) Tasadaque, S.; Shah, A.; Khan, K.M.; Fecker, M.; Voelter, W. *Tetrahedron Lett*., 44, **2003**, 6789.

15) Joshi, A.V.; Bhusare, S.; Baidossi, M.; Qufisheh, N.; Sasoon, Y. *Tetrahedron Lett*., 46, **2005**, 3583.

16) Iranpoor, N.; Firouzabadi, H.; Zolfigol, M.A. *Synth.Commun*., 28, **1998**, 1179.

17) a) Zolfigol, M.A. *Synth.Commun.,* 30, **2000**, 1593.

b) Zolfigol, M.A.
Tetrahedron, 57, **2001**, 9509

18) Iranpoor, N.; Flrougabadi, H.; Pourali, A.
Tetrahedron, 58, **2002**, 5179.

19) Demir, A.S.; Igdir, A.C.; Mahasneh, A.S.
Tetrahedron, 55, **1999**, 12399.

20) Misra, A.K.; Agnihotri, G.
Synth.Commun., 34, **2004**, 1079.

21) Mancuso, A.J.; Swern, W.
*Synthesis,***1981**, 865.

22) Karimi, B.; Zareyee, D.
Synlett.,**2002**, 346.

23) Karimi, B.; Zareyee, D.; Hajarkhani, H.
*Synthesis,***2002**, 2513.

24) Rieke, R.O.; Wu, X.; Zhu, L.
Synth.Commun., 26, **1996**, 191.

25) Ali, M.H.; McDermott, M.
Tetrahedron Lett., 43, **2002**, 6271.

26) Zhong, P.; Guo, M. –P.
Synth.Commun., 31, **2001**, 1825.

27) Fryen, P.

Synth.Commun., 25, **1995**, 959.

28) a) Corey, E.J.; Kim, C.U.

J. Am. Chem. Soc, .94, **1972**, 7586.

b) Ramdas, K.; Srinivasan, N.

Synth.Commun., 26, **1996**, 4179.

29) Khazaei, A.; Zolfigol, M.A.; Rostami, A.

Synthesis, 18, **2004**, 2959.

30) Alam, A.; Takaguchi, Y.; Tsuboi, S.

Synth.Commun. , 35, **2005**, 1329.

31) Akdag, A.; Webb, T.; Worley, S.D.

Tetrahedron Lett., 47, **2006**, 3509.

32) McMillan, F.H.; King, J.A.

J. Am. Chem. Soc., 70, **1948**, 4143.

33) Kesavan, V.; Daniele, B.D.; Begne, J.P.

Synthesis, **2000**, 223.

34) McKillop, A.; Koyuncu, W.

Tetrahedron Lett., 31, **1990**, 5007.

35) Hajipour, A.R.; Mallakapour, S.E.; Adibi, H.

J. Org. Chem., 67, **2002**, 8666.

36) Chen, F-E.; Lu, Y. –W.; He, Y. –P.; Luo, Y. –F.; Yan, M.-G.

Synth.Commun., 82, **2002**, 3487.

37) Salehi, P.; Farrokhi, A.; Gholizateh, M.

Synth. Common., 31, **2001**, 2777.

38) Tajabaksh, M.; Hosseinzadeh, R.; Shakoori, A.
Tetrahedron Lett., 45, **2004**, 4889.

39) Lopez, C.; Conzalez, A.; Cossio, F.P.; Palomo, C.
Synth.Commun., 15, **1985**, 1197.

40) Shirini, F.; Lakouraj, M.M.; Baltrok, I.M.; Asadi,D.
Synth.Commun., 33, **2003**, 1833.

41) Patel, S.; Misra, B.K.
Tetrahedron Lett., 45, **2004**, 1371.

42) Kageyama, T.; Ueno, Y.; Okawara, M.
Synthesis, **1983**, 815.

43) Shabani, A.; Lee, D.G.
Tetrahedron Lett.42, **2001**, 5833.

44) Sreedhar, M.; Vadivel, S.K.; Bhalerao, O.T.
Synth.Commun., 28, **1998**, 1499.

45) Yoneda, F.; Suzuki, K.; Nitla, Y.
J. Org. Chem., 32, **1967**, 727.

46) Rao, K.R.; Kumar, H.M.S.
Bio. Org. Med. Chem. Lett., 1, **1991**, 507.

47) Leite, S.L.S.; Pardini, V.L.; Viertier, H.
Synth.Commun., 20, **1990**, 393.

48) Desai, U.V.; Kulkarni, P.P.; Kadam, A.J.; Mane, R.B.;

Wadgaonkar, P.P.

J. Chem. Res.(S), 4, **2000**, 184.

49) Desai, U.V.; Tamhankar, B.V.; Mane, R.B.; Wadgaonkar, P.P.;

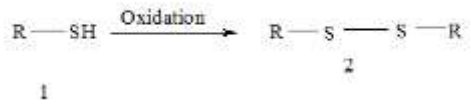
Bedekar, A.V.

Synth.Commun., 31, **2001**, 2021.

50) Desai, U.V.; Tamhankar, B.V.; Mane, R.B.; Kulkarni, P.P.; Wadgaonkar, P.P.
Synth.Commun., 32, **2002**, 3643.

51) Mohite, S.A.; Desai, U. V. Unpublished results.

CHART-1



1 2

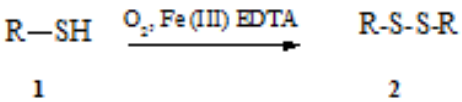
R= alkyl, aryl, heteroaryl,etc.

CHART - 2

Table-I : Oxidation of Sulfides to Disulfides

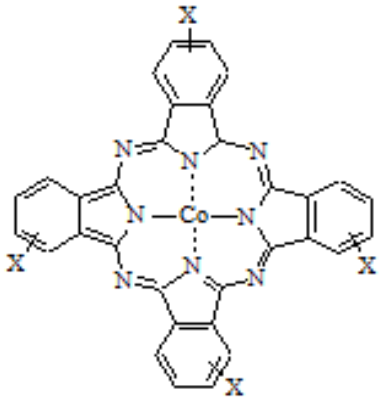
Entry	Reagent	Ref
1	Ce (IV) Salts	48
2	$Bu_3SnOMe/FeCl_3$	49
3	Borohydride Exchange Resin (BER)-Transition metal Salts	50
4	MnO_2	51
5	Halosilane CrO_3	52
6	Nickel peroxide	53
7	Chromium peroxide	54
8	Diaryl telluroxide	55
9	Ag-trifluoromethane sulfonate	56
10	NCS-Me_2S	28
11	NBS-TPP	27
12	Thallium acetate	57
13	$BaMnO_4$	58
14	Ethyl dichlorophosphate	59
15	Na Tellurite	60
16	Zinc bismuthate	61
17	$SmCl_3/BiCl_3$	62
18	DABCO-IO_4	63

CHART-3



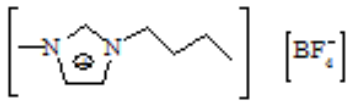
1 **2**

R = alkyl, aryl, heteroaryl, etc.



3

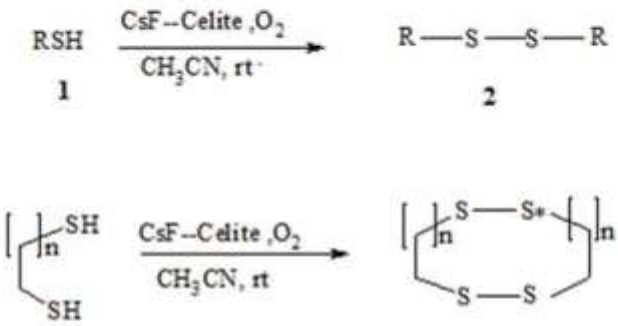
a; X = SO_2NH_2
b; X = SO_2Na
c; X = H
d; X = NO_2

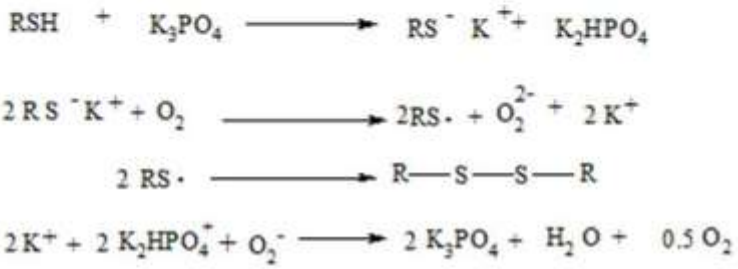


4

CHART - 4

Scheme-I





Scheme-I I

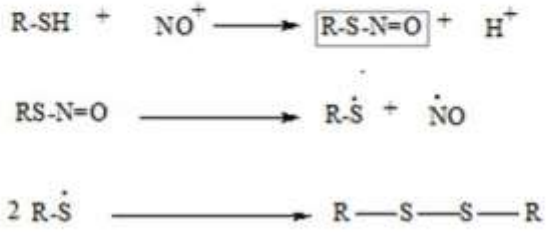
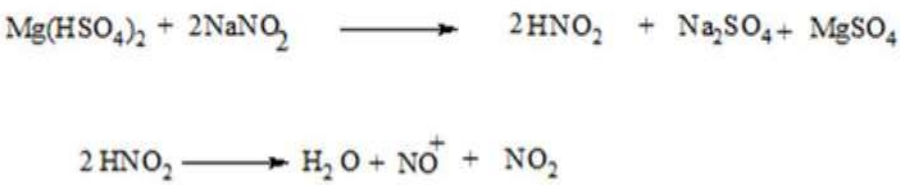
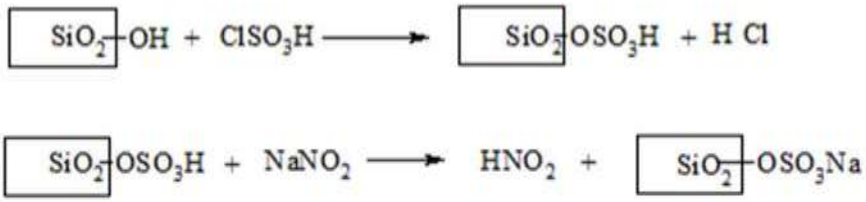


CHART- 5

Scheme- I



Scheme-II



Scheme-III

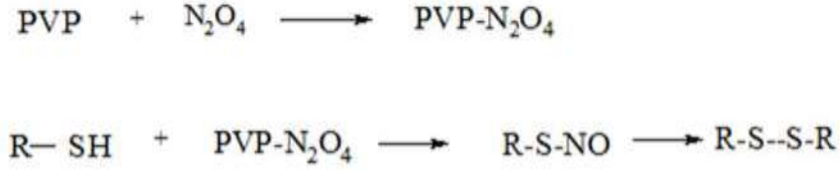
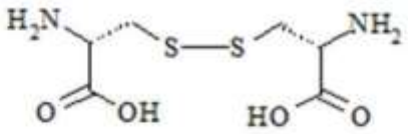
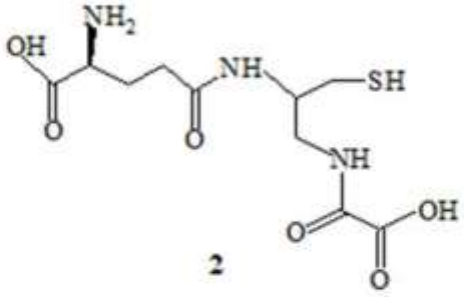


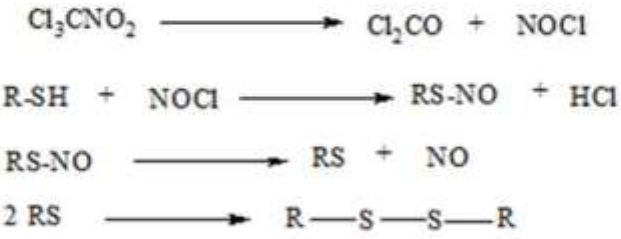
CHART - 6



1



2



Scheme-I

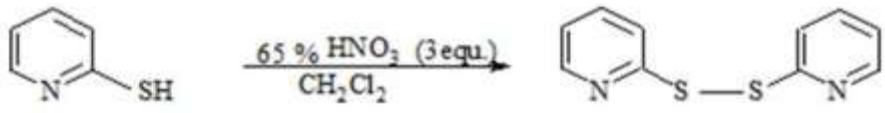
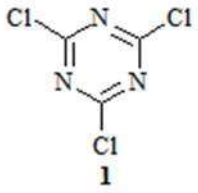
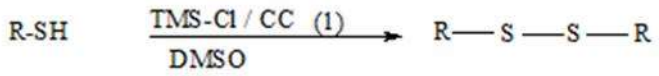


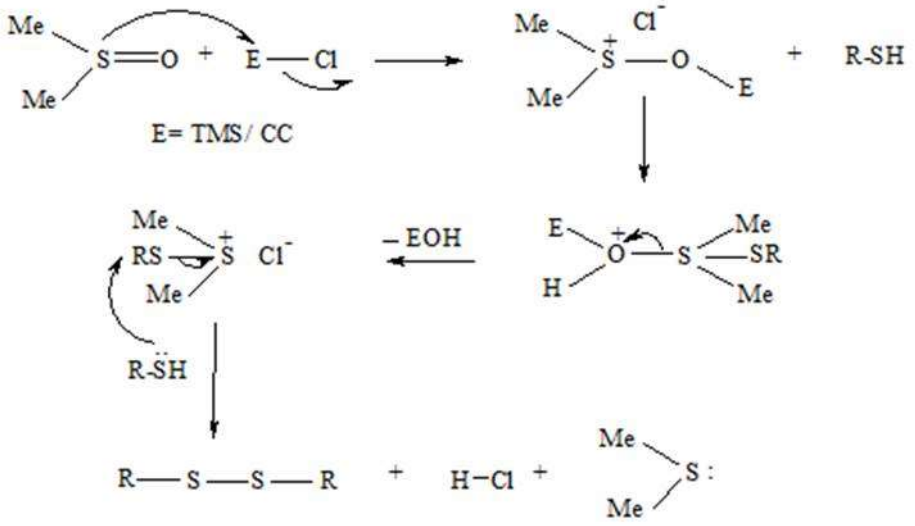
CHART - 7



1



Scheme-I



Scheme-II

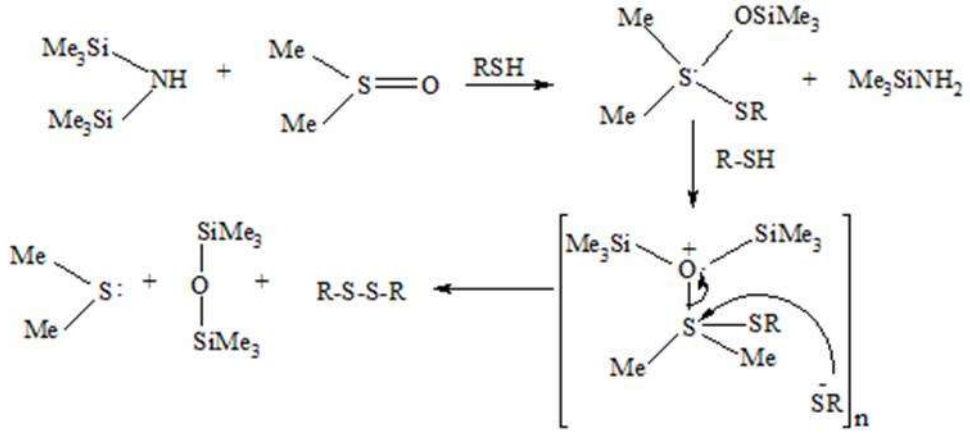
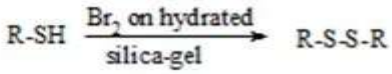
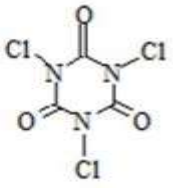


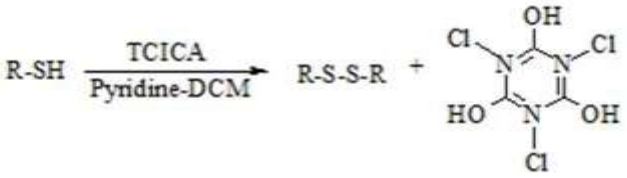
CHART - 8

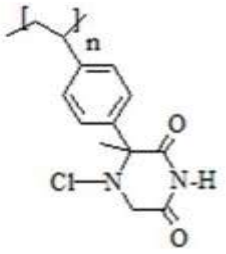


1 2



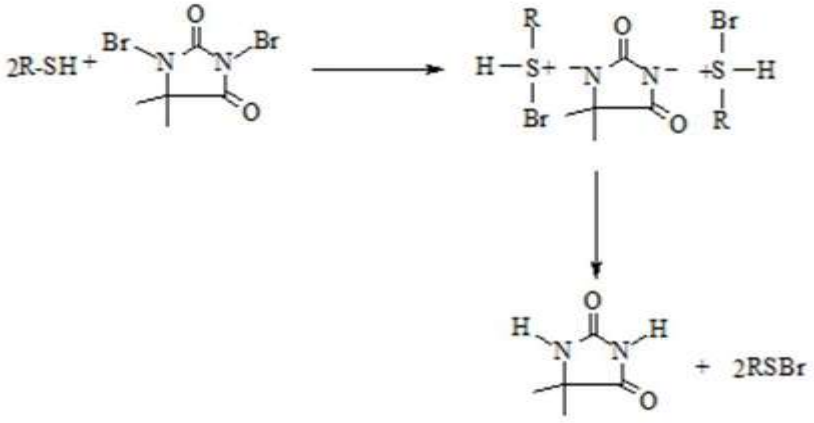
3 TCICA





4

Scheme-I



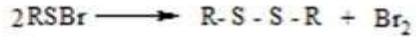
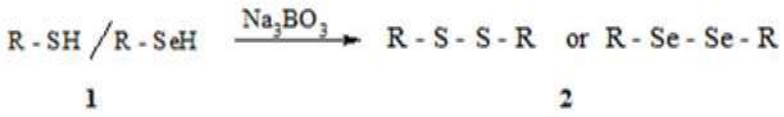
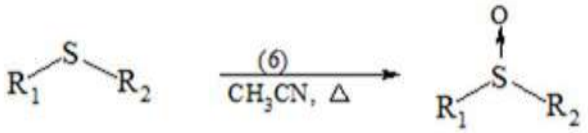


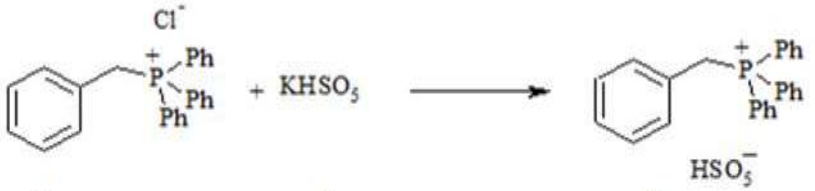
CHART- 9



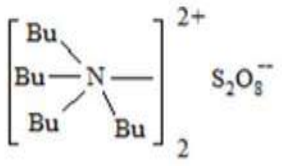
1 2



R_1 = H or alkyl 3

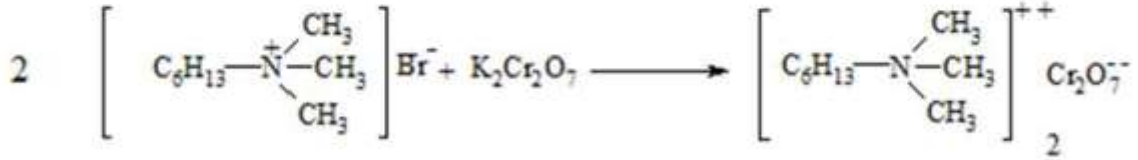


4 5 6

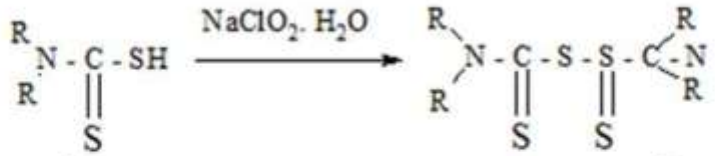


7

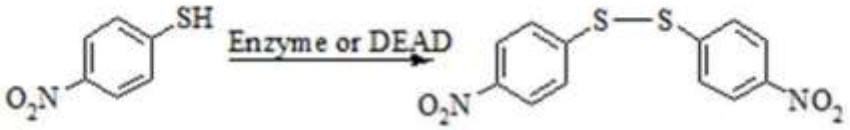
CHART-10



1 2 3

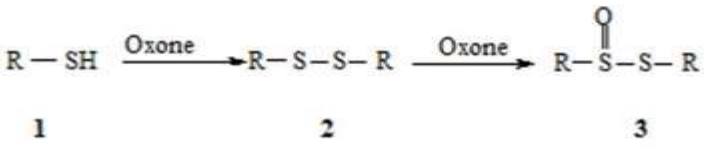


4 5

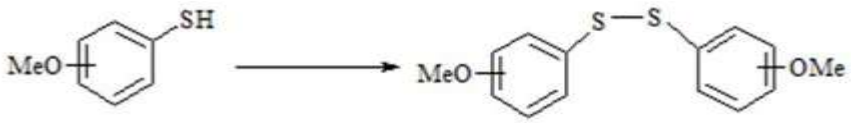


6 7

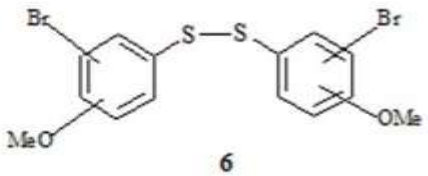
CHART-11



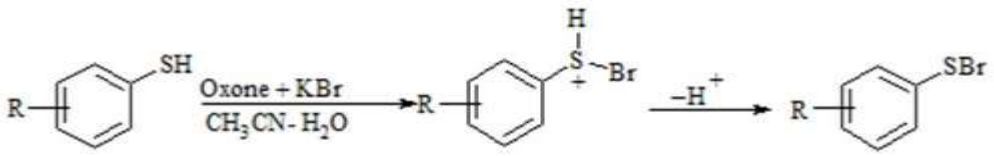
1 2 3



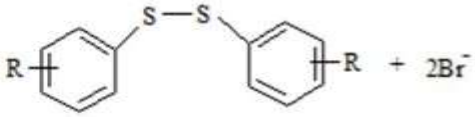
4 5



6

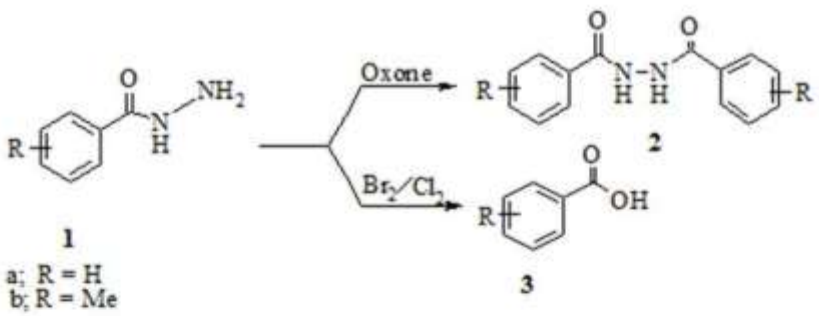


7 8



9

CHART-12

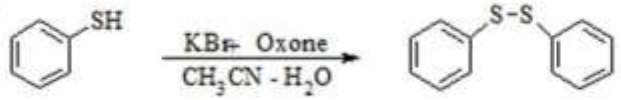


1

a; R = H
b; R = Me

2

3



4

5

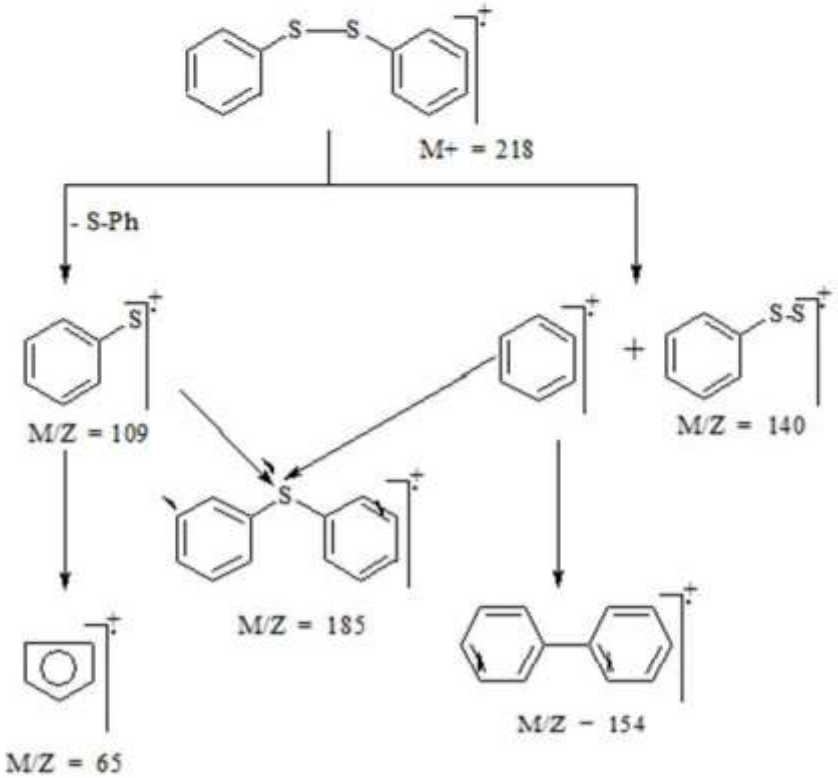


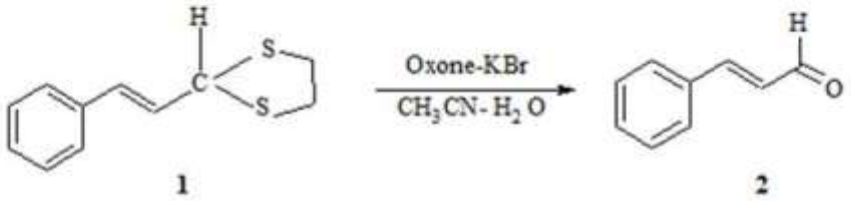
CHART – 13

Table-2 : Oxidative Coupling of Thiols to Disulfides using Oxone-potassium bromide in Acetonitrile –Water medium

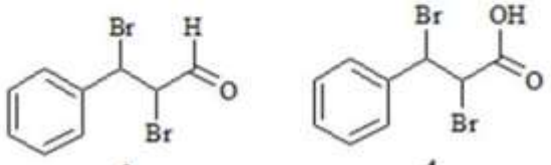
Entry	R	Time (h)	Yield (%)	M.P.^{0}C (Lit)
1	Ph	2	85	56 (60) [20]
2	4-Cl-Ph	2	87	69 (70-71) [29]
3	4- CH_3-Ph	2	89	43 (45-46) [20]
4	4- CH_3O-Ph	2	91	41 (44-45) [24]
5	4- CH_3O-Ph-CH_2	2	89	96-97 (99) [20]
6	Pyridyl	2	93	52 (54-57) [20]
7	Ph-CH_2	2	94	70 (72) [20]
8	Cyclohexyl	2	88	Oil
9	n-C_6H_{13}	3	90	Oil
10	2-Mercapto-Benzothiazole	2	89	182 (184) [4]
11	n-$C_{12}H_{25}$	3	92	30 (32) [4]
12	n-C_4H_9	3	86	Oil

- Yield refers to pure and isolated products
- All products were characterized by IR ^{1}H NMR and MS spectra

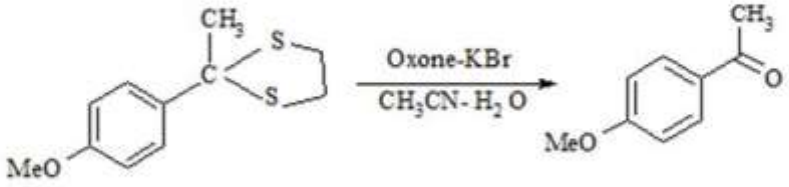
CHART- 14



1 2

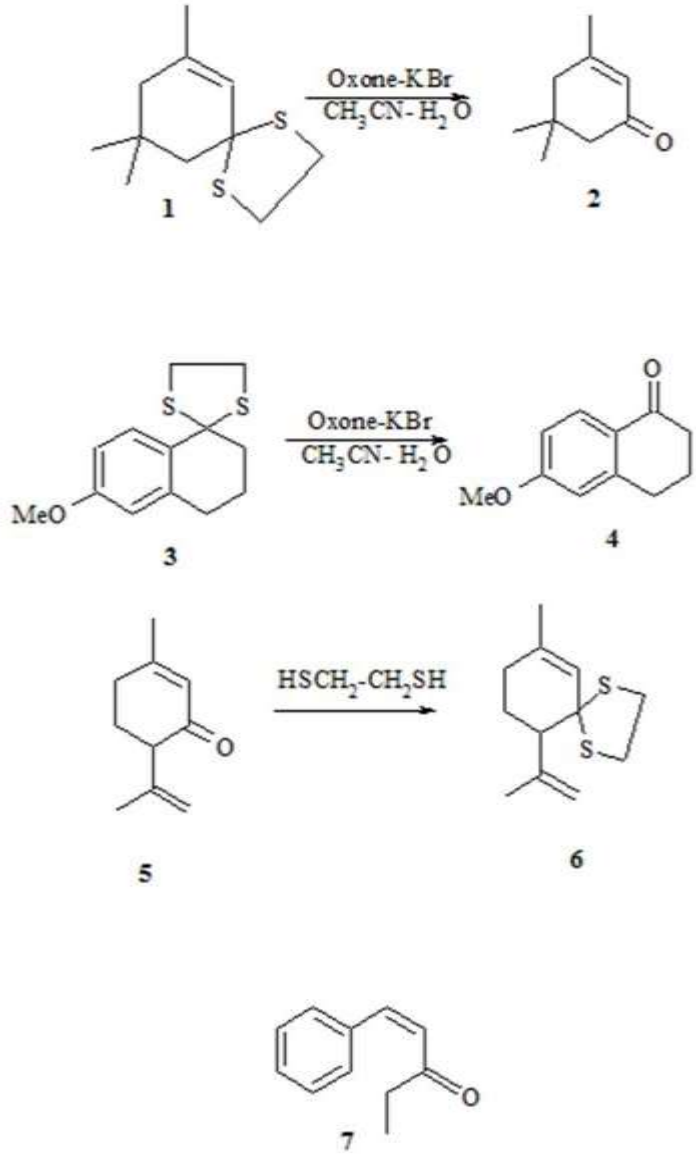


3 4



5 6

CHART- 15



Acknowledgement: Dr. B.V. Tamhnakar is thankful to UGC (WRO) Pune for sanctioning UGC Minor Research Project (F. No. 47-2074/11/WRO dated 23rd February 2012).