World Academy of Science, Engineering and Technology
International Journal of Environmental and Ecological Engineering
Vol:8, No:10, 2014

S-S Coupling of Thiols to Disulfides Using Ionic Liquid in the Presence of Free Nano-Fe_2O_3 Catalyst

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Abstract**—**An efficient and green method for oxidation of thiols to the corresponding disulfides is reported using ionic liquid $[HSO_3N(C_2H_4OSO_3H)_3]$ in the presence of free nano-Fe_2O_3 at 60°C. Ionic liquid is selective oxidant for S-S Coupling variety aliphatic and aromatic of thiols to corresponding disulfide in the presence of free nano-Fe_2O_3 as recoverable catalyst. Reaction has been performed in methanol as an inexpensive solvent. This reaction is clean and easy work-up with no side reaction.

Keywords**—**Thiol, Disulfide, Ionic liquid, Free Nano-Fe_2O_3, Oxidation, Coupling.

I. Introduction

OXIDATIVE coupling of thiols to disulfides is of interest from biological, synthetic and oil-sweetening point of view [1]-[5]. Since thiol can be over oxidized, extensive research has been carried out in recent years to control their oxidation [6]-[10]. The oxidation coupling of thiols to disulfides is an essential reaction in the synthesis of natural products, and further oxidation to disulfide S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acids is possible. Weak S-S bonds in these compounds impart high reactivity [6] and in natural products, these moieties and related cyclic analogues areassociated with interesting biological activity [11]. Reagents such as molecular oxygen [12], metal ions [13], $Bu_3SnOMe/FeCl_3$ [14], nitric oxide [15], halogens [16]-[19], sodium perborate [20], borohydride exchange resin (BER)-transition metal salt system [21], a morpholine iodine complex [22], picolinium chlorochromate (PCC) [23], ammonium persulfate [24], $KMnO_4/CuSO_4$ [25], H_2O_2 [26], solvent free permanganate [27], PVP–N_2O_4 [28] and cesium fluoride–celite, –O_2 [29] have been used for oxidation of thiols to disulfides, but some of these procedures are not satisfactory because of several reasons such as overoxidation to sulfoxides and other by-products, tedious work-up of products, low yields, long reaction time, heavy metal contamination, toxicity, and cost effective reagents or catalysts. Ionic liquids (ILs) belong to the molten salts group and are generally composed of bulky and asymmetric organic cations and organic or inorganic anions. Most ionic liquids exhibit desirable attributes, namely a negligible vapor pressure, a wide temperature range where they are liquid, high thermal and chemical stabilities, and a good solvating capacity for both organic and inorganic compounds, among others [30], [31]. Therefore, ionic liquids appear as more attractive and competitive solvents compared to the conventional volatile organic solvents, especially due to their negligible vapor pressure and high thermal stability.

Additionally, the huge number of possible ionic liquids that can be synthesized by a proper selection of the cation/anion combinations allows the tuning of their solvation ability for a variety of solutes. This tailoring feature makes possible to choose an ionic liquid that presents reduced solubility in the feed liquid phase and a high affinity for the target solute to be removed. In recent years, there has been growing interest in the catalytic properties of transition metal nanoparticles [31], [32]. Noble metal nanomaterials have attracted attention because of their potential applications in catalysis, energy, electronics, and biotechnology [32]. There are several methods have been reported for thiol coupling including LaFe0.9Co0.1O3 nanoparticles [33], PVP-Capped Silver Nanoparticles [34], Fe@SBA-15/H_2O_2 [35], Ni-nanoparticles [36]. Among the various NPs in recent years, iron oxide NPs catalyst emerged as the green catalyst, due to their low toxicity, abundance and interesting activities which allow the utilization of mild reaction condition [37]. We report a simple, green and efficient methodology for chemo selective oxidation of thiols to disulfides with Ionic Liquid oxidant with using free nano-Fe_2O_3 catalyst in methanol at 60°C.

II. Experimental Section

A. General Information

Chemicals and solvents were purchased from merck, Fluka and Aldrich Companies. Reaction progress was monitored by Potentiometer with DMi-141-SC special intelligent electrode for sulfur. HNMR and 13C NMR spectra were respectively recorded on 500 MHz by using a Bruker Avance 500 spectrometer. IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer.

B. Ionic Liquid Preparation

A 50 ml suction flask was used. It was equipped with a constant-pressure dropping funnel containing 0.558 g triethanolamine in 20 ml of CH_2Cl_2 is dissolved and gas inlet tube for conducting HCl gas over an adsorbing solution i.e. water. Into it were charged 1 ml chlorosulfonic acid in 20 ml CH_2Cl_2 is dissolved. Triethanolamine was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Fig. 2). After the addition was complete the upper solution was decant and then

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the lower viscous solution (1.5 ml) were transferred into a vial.

C. Fe-Nanoparticle Preparation

We prepared free nano-Fe_2O_3 as a catalyst with High catalytic activity and ease of recovery from the reaction mixture using an external magnet based on our previously reported paper [38].

D. Typical Procedure for Oxidation of Thiol to Disulfide

Ionic Liquid (0.22 g) and nano-Fe_2O_3 (0.08 g) were completely dissolved in 5 ml Methanol. 1 mmol Thiophenol was added to solution. The mixture was stirred at 60^0C on Steam water bath for 20 min, after cooling of mix solution, the reaction progress was monitored by potentiometer. At the end of reaction, solution was centrifuged for 10 min with rpm 2000 and nano-Fe_2O_3 was separated for again usage, solution was extracted in 5 ml n-Hexane and then n-hexane was removed by heating. Solid was obtained in yield 99.1%. White solid; mp 60-62°C; 1H NMR (500 MHz, CDCl3): δ 7.23-7.98 (m); IR (KBr): V 3020, 1585, 1497, 1342, 1215, 757, 669 cm^{-1}.

III. Result and Discussion

The oxidative coupling of thiols to their corresponding products occurred in the presence of the nano-Fe_2O_3 as a catalyst and ionic liquid as oxidant. Products were obtained in high yields. Thiophenol was chosen as a model substrate for optimization of thiol oxidation. Among the solvents used, methanol was the most effective for the oxidation reaction because ionic liquid as the best solubility in comparison of other solvents (Table I, Entries 10, 11). The reaction was also studied at different temperatures, and the results showed that the best efficiency is at 60°C (Table I, Entry 1). The effect of reaction time showed that the thiophenol conversion and the selectivity for Diphenyl Disulfide increases with increasing reaction time and passed through a maximum at 20 min (Table I, Entries 2, 4).The oxidative coupling reaction of Thiophenol was also achieved using different amounts of catalyst. The conversion rate of the oxidative coupling reaction increased with a high amount of catalyst and Ionic Liquid (Table I, Entries 1-3). Low conversion was detected in the absence of catalyst (Table I, Entry 6). In the absence of Ionic Liquid reaction has Low efficiency with different amounts of nano-Fe_2O_3 (Table I, Entries 7-9). Therefore, the optimum reaction conditions were that of Entry 1, 0.08 g NPs, 0.22 g ionic liquid reaction temperature of 60°C, and reaction time of 20 min. As can be seen from Table II, a variety of aromatic thiols (Table II, Entries 1–5) were easily converted to the corresponding disulfides in short times and in excellent yields and aliphatic (Table II, Entries 6–8) thiols have long reaction time and low efficiency. As a result of Table II reactivity comparison showed that 2-naphtalen thiol > 4-Br thiophenol > 4-Me thiophenol > thiophenol > thiosalicylic acid. Potentiometic graph shows Thiophenol has converted to Diphenyl disulfide. 1.14 g Thiophenol was added to the potentiometer cell with 2-propanol solvent and stirred for 2 min and then titer with $AgNO_3$ 0.01 N as titrant. Thiophenol as a blank was titrated with $AgNO_3$, potential is started from -700 mv, after 5 ml incrementing of titrant, potential was reached to -200 mv, and for coupling reaction, after addition of 5 ml titrant, potential from -500 mv was reached to -200 mv (Fig. 4).

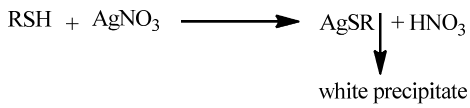


Fig. 1 Potentiometric reaction

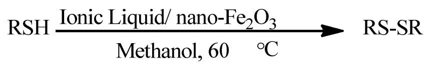


Fig. 2 Oxidative coupling of thiols by Ionic Liquid in the presence of nano-Fe_2O_3

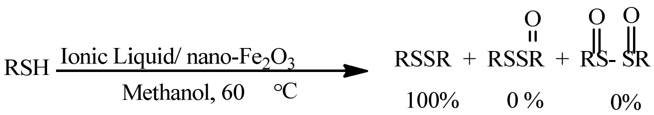


Fig. 3 Chemoselectivity in the oxidative coupling of thiols

TABLE I
Reaction Conditions Optimization for Oxidation of Thiophenol

Entry	NPs(g)	Ionic liquid(g)	Solvent	Temp(°C)	Time (min)	Conversion
1	0.08	0.22	CH_3OH	60	20	99.1
2	0.04	0.11	CH_3OH	60	20	95.5
3	0.015	0.04	CH_3OH	60	20	87
4	0.04	0.11	CH_3OH	60	10	83.7
5	0.04	0.11	CH_3OH	rt	20	76
6	-	0.11	CH_3OH	60	20	55.6
7	0.05	-	CH_3OH	60	30	53
8	0.04	-	CH_3OH	60	40	52
9	0.02	-	CH_3OH	60	50	48
10	0.04	0.11	CH_2Cl_2	60	120	NR
11	0.04	0.11	CH_3CN	60	120	NR

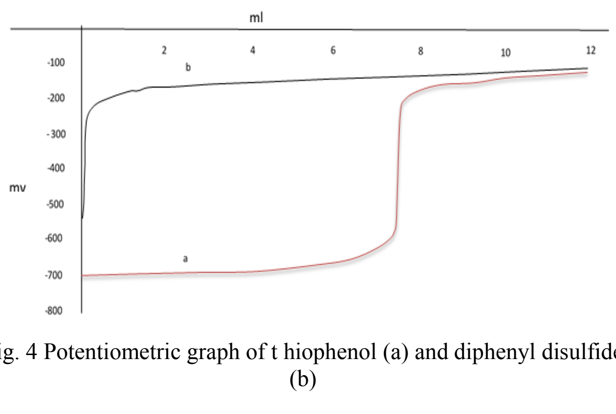
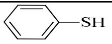
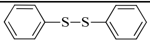
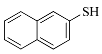
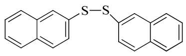
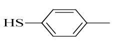
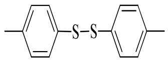
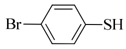
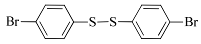
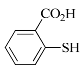
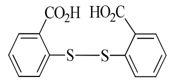
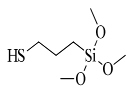
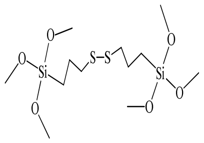


Fig. 4 Potentiometric graph of t hiophenol (a) and diphenyl disulfide (b)

TABLE II
COUPLING OF THIOL TO THE CORRESPONDING DISULFIDE USING COMBINATION IONIC LIQUID AND NPS

Entry	Substrate	Product	Time (min)	Tem (^0C)	Yield %
1			20	60	95.5
2			10	60	99.1
3			10	60	97.5
4			10	60	97.8
5			20	60	94.9
6			75	60	98.5
7	CH_3CH_2SH	CH_3CH_2S—SCH_2CH_3	60	60	45
8	$CH_3CH_2CH_2SH$	$CH_3CH_2CH_2S$—$SCH_2CH_2CH_3$	60	60	51

IV. CONCLUSION

In conclusion, this is an oxidative method for symmetric synthesis of thiols to disulfides. The simple procedure, the easy and clean work-up, green chemicals, the inexpensive recyclable catalyst and highly efficient of reaction is noticeable.

ACKNOWLEDGMENT

Financial Support is done by research and Development of 4th Gas refinery of Busher South Pars Gas Complex.

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