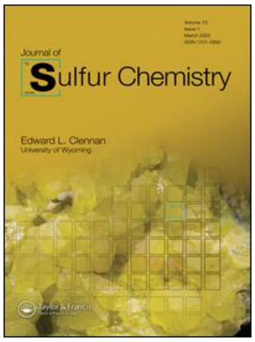

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Practical and efficient recyclable oxidative system for the preparation of symmetrical disulfides under aerobic conditions

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ABSTRACT
An efficient and practical oxidative coupling of thiols to symmetrical disulfides is developed at room temperature under aerobic conditions. The commercially available sodium methoxide solution 30 wt. % in methanol together with the air was used as a retrievable promoter system and green oxidant, respectively, for the preparation of symmetrical disulfides. The desired products were obtained in good to high yields by an economical procedure. No overoxidation of the symmetrical disulfides was observed, and various functional groups were well tolerated in the current protocol. Moreover, the new reagent reduces the generation of hazardous waste due to its high reusability. The reaction proceeded in the absence of light, and it was not inhibited by TEMPO. Also, the low yield of TEMPO-benzyl thiol adduct was detected under these conditions. Based on our experiments, a possible mechanism was proposed in the absence and presence of TEMPO.

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Thiol; oxidative coupling; symmetric disulfide; reaction mechanisms; sustainable chemistry

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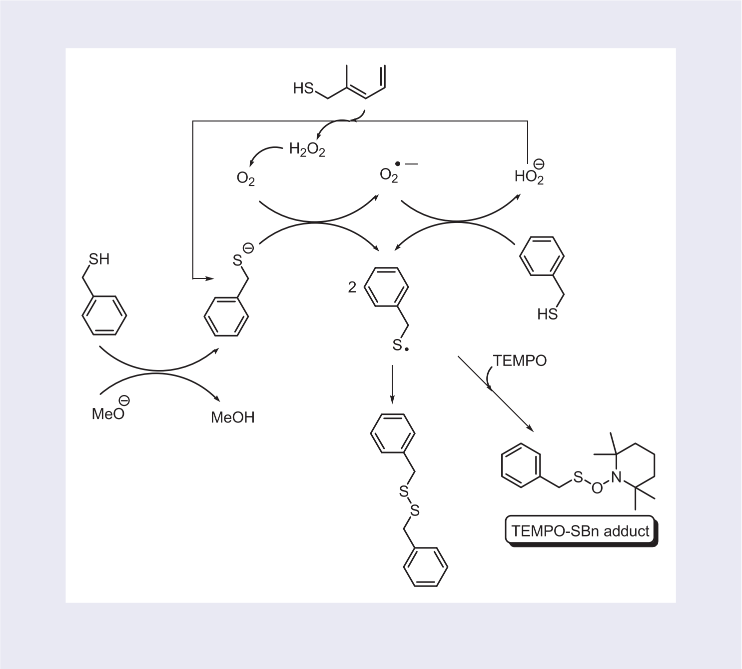


1. Introduction

Organosulfur compounds have been attracted much attention in different fields, such as biology, chemical protection, sulfenylation of enolates, and the preparation of bioactive organosulfur compounds [1–4]. The S–S bond formation is an essential step in the vulcanization, peptide stabilization, and DNA-cleavage [5]. The 'Merox process' is employed in the petroleum refinery industry for the thiol removal through the oxidative coupling of thiols to disulfides using NaOH or ammonia [6]. Organic disulfides or disulfanes (R–S–S–R) conventionally prepared by oxidative coupling of thiols or sulfur-containing compounds [5,7], which occasionally leads to the formation of side products such as trimers and polymers [8]. The thiosulfinates, thiosulfonates, and sulfonic acids often may be formed during the oxidation of thiols due to the over-oxidization of products [9]. Thus, the oxidative homocoupling of thiols to disulfides under mild and eco-friendly conditions without over-oxidation is a significant process in organic chemistry and biochemistry [5,10].

A variety of synthetic methods have been reported for the synthesis of symmetrical disulfides from the thiols, including enzymatic and electrochemical methods [10–12]. The oxidative formation of S–S bond was reported by using a variety of catalysts, such as sulfonyl chloride/$NaHCO_3$ [13], nanocatalysts [14], phase transfer catalysts [15], nitric oxide [16], haloacid/dimethyl sulfoxide [17], hydrogen peroxide in fluoro alcohols [18], and manganese (III) Schiff-base complex [19]. Also, the oxidation of the thiols to the symmetrical disulfides was carried out using base catalysts such as anhydrous potassium phosphate [20] and trimethylamine under ultrasonic irradiation [21].

Unfortunately, some of these protocols typically have drawbacks; for example, (a) fabrication of the scarce and transition metal-containing catalysts through the multi-step processes at high temperatures within long times along with separation and purification in each step, (b) generation of hazardous wastes, (c) high reaction temperature for long reaction times, (d) tedious workup procedure, (e) limited substrate-scope and low selectivity, and (f) overoxidation of the products to the sulfoxide and sulfone, or oxidation of other functional groups within the molecule or formation of the inactive metal-thiolate complex [22]. Although hydrogen peroxide was considered to be a green oxidant, its industrial synthesis via the so-called anthraquinone auto-oxidation process is not sustainable [23]. Furthermore, the overoxidation of products into sulfonic acids was reported for the base-catalyzed oxidation of thiols in various heterogeneous catalyst systems [24]. Therefore, as a sustainable alternative for the hazardous and toxic oxidants, it is preferred to carry out the oxidative coupling thiols by molecular oxygen or air as green and cheap oxidants.

Herein, the commercially available sodium methoxide solution 30 wt. % in methanol was used as a recyclable promoter system to conduct the aerobic oxidative coupling of thiols into the symmetrical disulfides. Our experimental results demonstrated that the simultaneous presence of molecular oxygen and thiolate in methanol, but neither reagent individually, promotes the oxidation of thiols to the symmetrical disulfides.

2. Experimental

2.1. General

Unless specified, all chemicals were analytical grade and purchased from Merck, Sigma Aldrich, and Fluka Chemical Companies and used without further purification. Products were characterized by their physical constant and FT-IR, NMR, and Mass spectral analysis. The purity determination of the substrates and reaction monitoring was accompanied by TLC using silica gel SIL G/UV 254 plates. The purity determination and MS (EI) data of the products was accomplished by GC-MS on an Agilent 6890N GC system with a 5973N mass selective detector under 70 eV conditions. The FT-IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer used in the range of 4000–400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance III 600 and 400 MHz instruments. All chemical shifts are quoted in parts per million (ppm) relative to TMS using a deuterated solvent.

2.2. A typical procedure for the preparation of symmetrical disulfides

A variety of thiols (10 mmol) were added into sodium methoxide 30 wt. % in methanol (1.85 mL, 10 mmol) (NaOMe/MeOH-30), and the solution was stirred at room temperature under air atmosphere. After completion of the reaction, the desired products were extracted with ethyl acetate or n-hexane (3 × 2 mL). The collected extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The pure symmetrical disulfides were obtained as liquids or solids. The known and new products were characterized and identified by melting point, FT-IR, ^{1}H NMR and ^{13}C NMR, and mass analysis.

2.3. The synthesis of 4,4′-dithiobisbenzoic acid

4-Mercaptobenzoic acid (1.54 g, 10.0 mmol) was added into sodium methoxide 30 wt. % in methanol (3.7 mL, 20 mmol), and the mixture was stirred at room temperature under air atmosphere for eight hours. The solution was concentrated by rotary evaporator under vacuum and adjusted to pH = 2 by adding hydrochloric acid (0.02 M). The white precipitate was collected and dried under reduced pressure.

3. Results and discussion

3.1. Aerobic oxidation of various thiols promoted by using sodium methoxide solution 30 wt. % in methanol

The benzyl mercaptan was selected as a model substrate, and initial experiments were conducted to find the optimal conditions. Different mole ratios of the model substrate and NaOMe/MeOH-30% were stirred at room temperature under air atmosphere for one hour. The GC-MS showed a 100% conversion when one equivalent of NaOMe/MeOH-30% was employed, and the corresponding disulfide was isolated in 97% yield by a simple extraction workup. Although a significant drop in the yield (58%) was observed by reducing the amount of NaOMe/MeOH ∼ 30% (0.5 equiv.) during one hour, the reaction showed a 100% conversion, and the desired disulfide was obtained in 93% isolated yield after 12 hours.

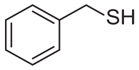
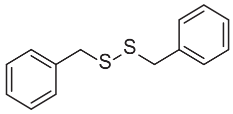
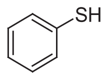
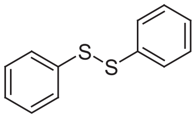
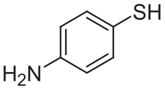
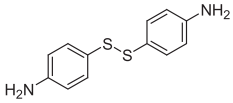
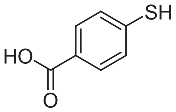
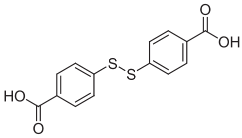
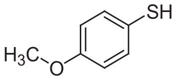
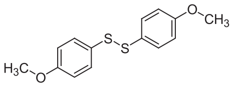
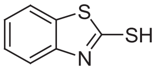
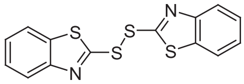
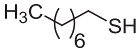
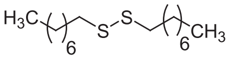
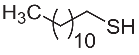
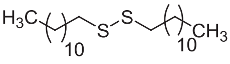
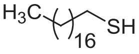
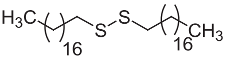
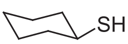
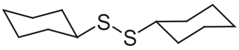
Two blank experiments, one in methanol and the other in ethanol, were carried out at room temperature under air atmosphere. In contrast to a previous report [25], the corresponding disulfide was not detected even after 24 hours (monitored by TLC and GC-MS), and benzyl mercaptan was recovered. Also, the stirring of benzyl mercaptan into a solution of triethylamine (1.0 equiv.) in methanol at room temperature under air atmosphere gave no disulfide after one hour (monitored by TLC and GC-MS). A low yield of dibenzyl disulfide (12%) was detected after one hour when the model reactant was added into one equivalent of NaOH in methanol at room temperature under air atmosphere. This low yield was probably due to the limited solubility of NaOH in methanol, as switching to a mixture of methanol/water solvent (80/20 v/v%) partially improved the yield (42%).

The sodium benzyl thiolate (BnS^-Na^+) was obtained in 97% yield as a white solid after evaporation of methanol when the model reaction was carried out at room temperature under N_2 atmosphere (See Supplementary Information, Figure S1). Dibenzyl disulfide was detected, the presence of one multiplet at 7.30–7.22 ppm and one singlet at 3.59 ppm, in ∼ 3% yield by ^1H NMR analysis.

The model reaction was completed within 20 min when pure oxygen at 0.3 MPa pressure was injected in the reaction vessel at room temperature. The air was chosen instead of pure oxygen as an oxidant due to the cost-efficiency of the strategy, including the cost of purchase, logistics supply, maintenance, storage, etc. Therefore, the treatment of various thiols with one equivalent of NaOMe/MeOH-30% at room temperature under air atmosphere was chosen as the optimized conditions for the aerobic oxidative coupling of thiols into symmetrical disulfides.

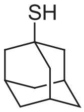
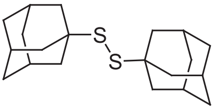
As one can see in Table 1, a broad scope of thiols including primary, secondary, tertiary, aromatic, and heteroaromatic thiols were smoothly transformed to the corresponding disulfides within 32 min to 10 h stirring at room temperature under air atmosphere. The substituents such as methoxy, amine, and carboxylic acid were well tolerated (Table 1, entries 3–5). The short, medium, and long-chain linear aliphatic symmetrical disulfides were also obtained in 95–97% yields (Table 1, entries 7–9). It is worth mentioning that the

Table 1. Aerobic oxidative coupling of various thiols in the presence of NaOMe/MeOH ~ 30% (1.0 equiv.) at room temperature under air atmosphere.

Entry	Substrate 1	Product 2	Time/h	Isolated yield/%	Melting point/°C	
					Found	Reported
1	 1a	 2a	55 min	97	Oil	58–59 [26]
2	 1b	 2b	4.2	94	60–61	57 [27]
3	 1c	 2c	1.8	95	77–79	75–77 [28]
4	 1d	 2d	8	85	319–321	> 300 [28]
5	 1e	 2e	7	96	33–34	33–34 [29]
6	 1f	 2f	8	97	176–177	181–183 [29]
7	 g	 2g	35 min	97	Oil	Oil [30]
8	 1h	 2h	9	95	Oil	20–31 [26]
9	 1i	 2i	9	95	63–64	62.8 [31]
10	 1j	 2j	32 min	95	Oil	Oil [26]

(*continued*).

Table 1. Continued.

11	 1k	 2k	10	90	89–90	–

linear aliphatic thiols having longer hydrocarbon chain required a longer reaction time in comparison with octane thiol (Table 1, entries 8 and 9 vs. 7). The sterically hindered thiols such as cyclohexane thiol and 1-adamantane thiol gave the corresponding disulfides in 95% and 90% yields, respectively (Table 1, entries 10 and 11).

Our results showed that the reaction time was influenced by the nature of the substituents on the aromatic ring, for example, the aerobic oxidative homocoupling of 4-amino thiophenol is more favorable than 4-mercaptobenzoic acid (Table 1, entry 3 and 4). The shorter reaction time in the oxidative coupling of 4-amino thiophenol and 4-methoxythiophenol could be attributed to the effect of amine and methoxy groups (Table 1, entries 3 and 5).

The corresponding symmetrical disulfides were obtained in good to high yields without trimer or polymer by-products, over oxidation into sulfones, or β-H abstraction from the disulfide to produce olefin and RSS^- or RS^-, which indicates a clean transformation. The selectivity of the current oxidative system was demonstrated when substrate such as 4-mercaptobenzoic acid was treated under optimal conditions, which afforded the respective product in 85% yield (Table 1, entry 4). Many reported methods in the literature failed to oxidize the tertiary thiol, possibly due to steric hindrance, whereas 1-adamantanethiol gave the desired product in 90% yield at room temperature after 10 hours (Table 1, entry 11). 4-Nitrothiophenol was not oxidized even after 12 h, probably due to the most stable of the 4-nitrothiophenolate anion.

3.2. *Study of the reaction mechanism*

Many studies have been reported on the mechanism of oxidative coupling of thiols [10,11]. It was indicated that only the anionic thiolates could be oxidized into symmetrical disulfides [32]. Also, the redox potential of the thiol-disulfide system is usually pH-dependent, and the oxidation of thiolate can be modulated by the inductive effect of substituents next to sulfur atom [33].

Several experiments were performed to gain insight into the oxidative coupling mechanism in the presence of NaOMe/MeOH-30%.

3.3. *Influence of water and methanol*

It was found that a small amount of water (0.2 mL per 2.0 mmol benzyl thiol) had no notable effect on the yield and the reaction time of the model reaction (see Supplementary Information, Figure S2). However, the benzyl thiol (BnSH) remains unchanged when an aqueous solution of sodium benzyl thiolate was left for 12 hours without stirring at room temperature under the air atmosphere, and the dibenzyl disulfide was not detected (see Supplementary Information, Figure S3). Thus, it is indicated that the water can inhibit the aerobic oxidation of the benzyl thiol and benzyl thiolate. A mixture of benzyl thiol and dibenzyl disulfide was detected in a ratio of about 1:1 when methanol was added to sodium benzyl thiolate under the above conditions, at room temperature under air atmosphere for 12 hours without stirring, in the absence of any reagents or other additives (see Supplementary Information, Figure S4). This fact reveals that thiolate can be intermediate in the current protocol.

3.4. Influence of air and light

As mentioned, the dibenzyl disulfide (Bn_2S_2) was detected only in $<3\%$ yield as well as sodium benzyl thiolate (BnS^-Na^+) in 97% yield (see Supplementary Information, Figure S1) when an equimolar mixture of benzyl thiol and NaOMe/MeOH-30% was stirred at room temperature for one hour under N_2 atmosphere. This experiment demonstrated that the oxygen in the air plays a vital role as the oxidant.

To the investigation of the light effect, an equimolar mixture of MeONa/MeOH-30% and benzyl thiol was stirred at room temperature in a round-bottom flask, which was covered with aluminum foil. The result was almost the same as the reaction at ambient light; hence, the current strategy is not light-induced.

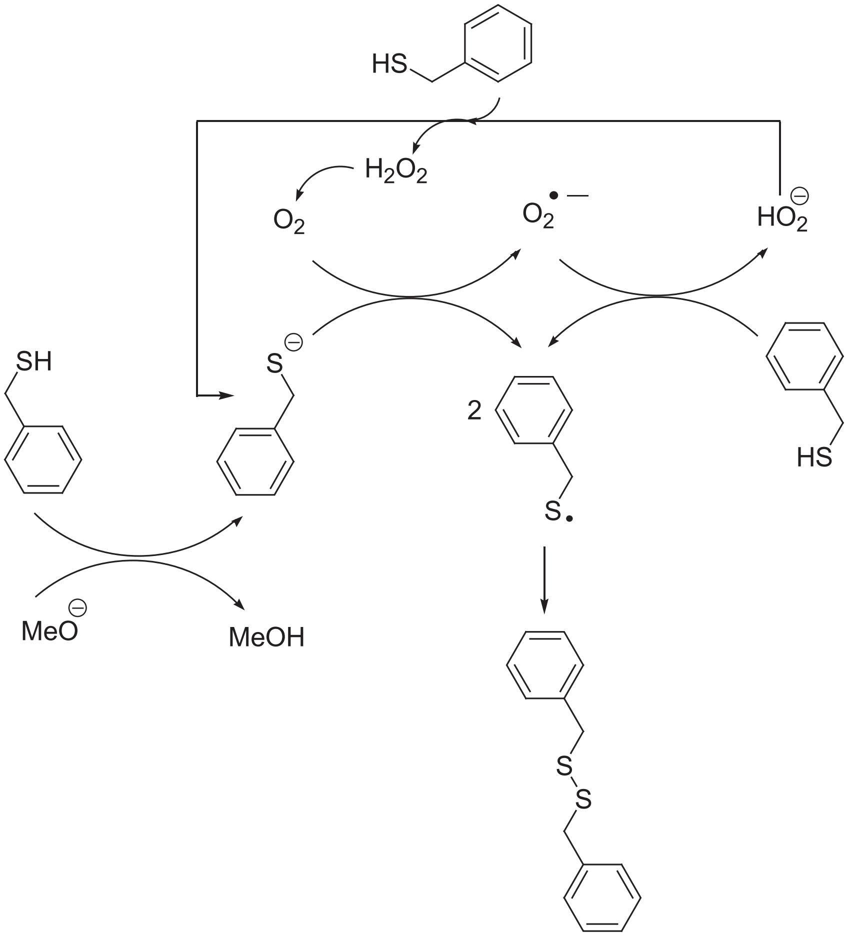
3.5. Mechanism aerobic oxidative homocoupling of thiol in the basic medium

The possible mechanism for this oxidative coupling of thiols in NaOMe-MeOH-30% (Conc. 6.27 mmol/mL) is proposed in Scheme 1. It is well-known that organic thiol (RSH) transformed to its anion in the presence of a strong base [34].

The thiolate anion can react with oxygen in the air to generate a thiyl radical (RS•) and superoxide ion (O_2•—) through a reversible single electron transfer (SET) [35,36]. NaOMe-MeOH-30% can also promote this molecular oxygen electro-reduction. Then, two thiyl radicals dimerize to give the symmetrical disulfide. The peroxide anion can also oxidize another molecule of thiol through a hydrogen atom transfer mechanism [37], which leads to generating the thiyl radical and hydrogen peroxide anion (HO_2^-). Moreover, the reaction between HO_2^- and benzyl mercaptan can give the benzylthiolate anion and hydrogen peroxide, whereas H_2O_2 can generate molecular oxygen for beginning a new oxidative chain reaction. This fact is in agreement with our experimental results.

In consideration of the mechanism of the aerobic oxidative coupling of thiols, NaOMe-MeOH-30% system acts as a homogeneous recyclable promoter system that abstracts hydrogen from thiol and also activates the molecular oxygen in the air to give the thiyl radical.

As previously indicated, the thiophenolate anions can be stabilized through a resonance of the electron pair on the sulfur atom with the π system of the benzene ring [38]. Therefore, based on the reactivity sequence of thiophenols *viz. p*-aminothiophenole > thiophenol > 4-methoxythiophenol ~ 4-mercaptobenzoic acid > > *p*-nitrothiophenol (Table 1, entries 2–5), it was proposed that reaction of the anion with oxygen is rate-limiting as Russell *et al.* reported a similar reactivity sequence for the oxidation of carbanions [39]. If ionization of the thiol was rate-limiting, the reverse order of reactivity was expected.



Scheme 1. A possible route of aerobic oxidative homocoupling of benzyl thiol using high recyclable NaOMe/MeOH-30% at room temperature under the air atmosphere.

3.6. Influence of TEMPO

In continuation of the mechanism study, the model reaction was carried out in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (5.0 mol %) as a thiyl radical (RS•) scavenger. In contrast to a previous report [40], two products *viz.* dibenzyl disulfide (Bn_2S_2) and TEMPO-benzyl sulfide adduct (TEMPO-SBn) were detected by the GC-MS analysis in a ratio of 93.5% and 6.5%, respectively (Table 2, entry 1) (see Supplementary Information, Figure S5–S8). The ratio of TEMPO-SBn adduct to Bn_2S_2 remained practically unchanged when the molar ratio of TEMPO/BnSH was raised to one or three equivalents (Table 2, entries 2 and 3).

The Bn_2S_2 showed fragment ions at m/z 91, 181, 214, and 246 with a base peak m/z 91, which was characteristic of the fragment $[C_6H_5CH_2]^{+\bullet}$ (see Supplementary Information, Figure S5). The symmetrical dibenzyl sulfide ion $[C_6H_5{-}CH_2{-}S{-}CH_2{-}C_6H_5]^{+\bullet}$ was characterized at m/z 214, which was formed through the loss of one sulfur atom from the parent molecular ion of Bn_2S_2 $[C_6H_5{-}CH_2{-}S{-}S{-}CH_2{-}C_6H_5]^{+\bullet}$ at m/z 246.

Table 2. Mechanistic studies on the model reaction in the presence of TEMPO[a].

Entry	The molar ratio of Benzyl thiol to TEMPO	The ratio of products/%[b]	
		Bn_2S_2	TEMPO-SBn
1	1.0:0.05	93.5	6.5
2	1.0:1.0	89.8	10.2
3	1.0:3.0	89.3	10.8

[a] Reaction conditions: benzyl thiol (1.0 mmol), solution of NaOMe/MeOH ~ 30% (1.0 mmol), air atmosphere, room temperature, reaction time (55 min).

[b] Monitored by GC-MS.

TEMPO-SBn fragment ions were observed at m/z 91, 160, 216, and 280 with a base peak m/z 91 (see Supplementary Information, Figure S6). The peaks at m/z 280 and 188 were assigned to the parent molecular ion of TEMPO-SBn ion and $[\text{TEMPO–S}]^{+\bullet}$, respectively. The base peak at m/z 91 was also assigned to the fragment $[C_6H_5CH_2]^{+\bullet}$, and the peak at m/z 109 was probably due to a radical cation with a formula of $[C_7H_{11}N]^{\bullet+}$.

These experiments demonstrated that the oxidation of thiols by NaOMe/MeOH-30% is independent of TEMPO concentration.

Other control experiments were performed in the presence of TEMPO. Although the reaction of TEMPO and benzyl thiol did not proceed under the nitrogen atmosphere, the adduct TEMPO-SBn and Bn_2S_2 were detected in the presence of molecular oxygen (see Supplementary Information, Figure S9–S13). This result suggests that the oxidation of thiols by TEMPO is also molecular oxygen dependent. Therefore, it was concluded that TEMPO promoted the oxidation of thiols by superoxide through either electron transfer or covalent reaction.

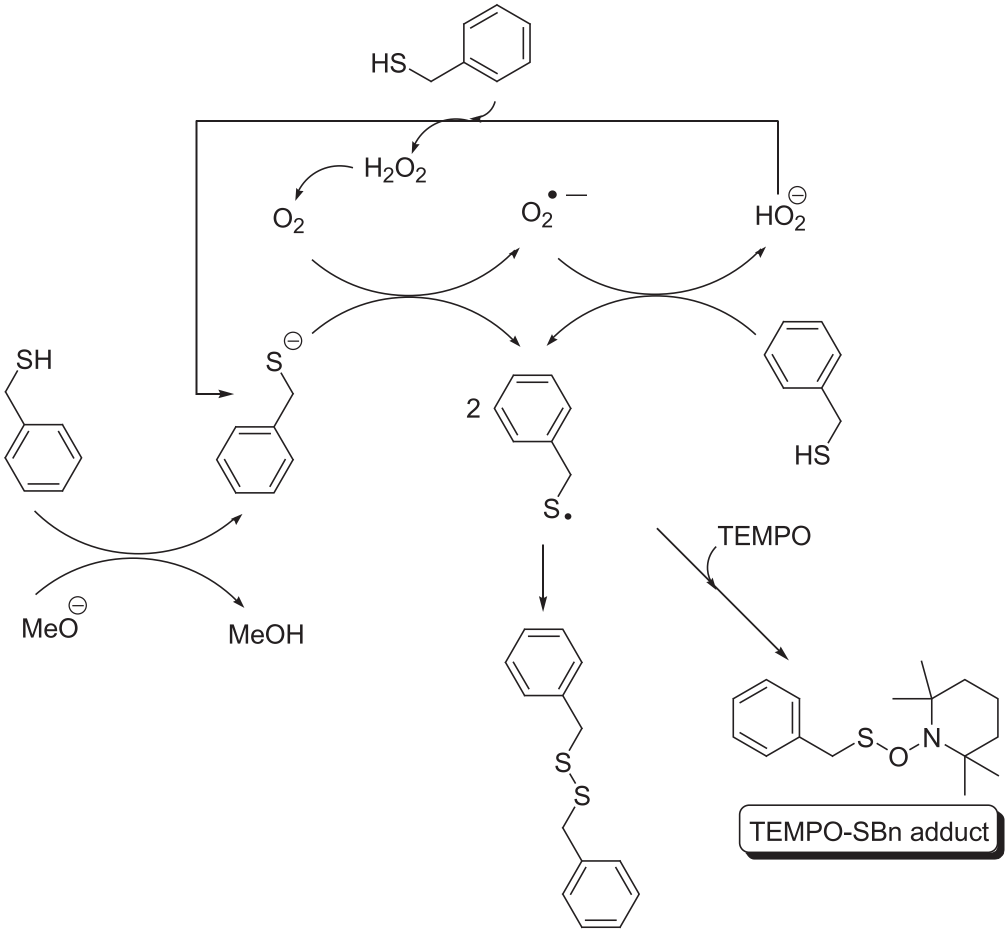
These results encourage us to present an alternative reaction mechanism of aerobic oxidative coupling of benzyl thiol in the presence of TEMPO under an air atmosphere in a base medium (Scheme 2). Regarding the acidity of TEMPO ($pK_{a(\text{TEMPO})} = 5.5$), the protonation of TEMPO is excluded in the current protocol. The reaction of TEMPO with thiyl radicals of benzyl mercaptan gives TEMPO-SBn adduct.

3.7. Reusability of the current catalytic system for the aerobic oxidative coupling of thiols

Finally, the reusability of NaOMe/MeOH-30% was monitored using sequential oxidation of benzyl thiol under optimized reaction conditions. After completion reaction (monitored by TLC), the product was extracted with *n*-hexane (4 × 5 mL). The solvent was evaporated from the collected extractions by a rotary evaporator, which gave a pure desired product. The fresh thiol was added to the residue NaOMe/MeOH-30%, and the reaction was conducted for the next run. The pure 2a was obtained in 97–95% yields as well as 100% conversion for ten subsequence runs. These results showed that the current oxidative system is highly recyclable.

3.8. Investigation of a large scale application

2,2′-dithiobisbenzothiazole (MBTS) is a well-known accelerator in the rubber and plastic industry. To illustrate the potential industrial application of the protocol, a



Scheme 2. Alternative reaction mechanism of aerobic oxidative coupling benzyl thiol in the presence of MeONa/MeOH ~ 30% and TEMPO under an air atmosphere at room temperature.

gram scale aerobic oxidative coupling of 2-mercaptobenzothiazole was performed. 2-Mercaptobenzothiazole (16.7 g, 100 mmol) was stirred in NaOMe/MeOH-30% (18.5 mL, 100 mmol) at room temperature under air atmosphere overnight. The 2,2′-dithiobisbenzothiazole was obtained in a high purity 92% isolated yield (30.6 g) by using a simple *n*-hexane extraction without using a high-cost column chromatography technique.

3.9. Merits and superiority of the current aerobic oxidative coupling of thiols

Our oxidative coupling system was superior in comparison with the most reported method and reagents in the literature, for example, Soleiman-Beigi and Arzehgar reported the synthesis of diphenyl disulfide in 90% yield from thiophenol using 1.5 equivalents morpholin-4-ium morpholine-4-carbo-dithioate and CuCl together with 18 equivalent KOH at 110°C after 20 h [41]. Also, diphenyl disulfide was obtained in 72–94% yield using a solution of dithioates of Meldrum's acid, dimedone, or barbituric acid in DMF or DMSO as sulfur transfer reagents in the presence of Cs_2CO_3 and Et_3N at 60–100°C within four hours in the N_2 atmosphere [26]. The same product was afforded in 98% yield at room temperature after 4.2 hours in the presence of NaOMe/MeOH-30%.

Only 39% and 44% yield of dihexyl disulfide and dicyclohexyl disulfide were obtained using 15 mol% of $MnCO_3$ and gallic acid in water at 80°C in pH $=$ 9, adjusted by Na_2CO_3 solution, under 0.3 MPa pressure of molecular oxygen [42]. Furthermore, the reagents were not recyclable, and the products were required to purify by the column chromatography. The dioctyl disulfide and dicyclohexyl disulfide were isolated in 97% and 95% yield by a simple separation process using one equivalent highly recyclable of NaOMe/MeOH-30% system at room temperature under air atmosphere after 35 and 32 min, respectively.

Iodine together with a stoichiometric amount of DMSO was used for the preparation of the symmetric disulfides in good to high yield under conventional and microwave heating conditions; however, this method failed for aliphatic thiols [43].

Tert-butyl nitrite (TBN) with oxygen was also used to preparation of symmetrical disulfides [44]. The use of pure oxygen, generation of NO_X as by-products, higher temperature, and lower yields within longer reaction times are the disadvantages of this methodology in comparison with the current protocol.

Although the oxidative coupling of 1-adamantane thiol to the corresponding disulfide was reported using $RhH(PPh_3)4$/1,4-bis(diphenylphosphino)butane (dppb) and pure oxygen at 40 °C after two hours, this transition metal-containing catalyst is expensive, and it can generate a metal waste through leaching [45]. Moreover, the $RhH(PPh_3)_4$/dppb was not recovered or recycled. Bis-adamantyl disulfide was obtained in 95% yield and selectivity 100% after ten hours in the air atmosphere at room temperature by our highly recyclable MeONa/MeOH-30% system. Bis-adamantyl disulfide was characterized by FTIR, ^1H NMR, ^{13}C NMR, and mass spectra (see Supplementary Information, Figures S14–S16).

4. Conclusion

In conclusion, we have demonstrated efficient and simple oxidation of thiols to symmetrical disulfides in good to high yields and 100% conversions using sodium methoxide solution 30 wt.% in methanol under ambient conditions. The current protocol is practical convenience and highly recyclable. This method can be highly attractive for industrial applications owing to its merits, such as high to the excellent yield of desired products, broad substrate scope, cost-effectiveness, and simple purification in the scale-up procedures. Moreover, the current oxidative system could be sustainability recycled into the next runs, and no by-products and over oxidation were observed. The reaction mechanism of the oxidative coupling of thiols was investigated in the presence of NaOMe/MeOH $\sim$ 30% and TEMPO, and an intermediate adduct of TEMPO-benzyl sulfide was detected by GC-MS. We are working to develop the continuous-flow procedure of this batch oxidative coupling thiols to disulfides.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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