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Bovine serum albumin triggered waste-free aerobic oxidative coupling of thiols into disulphides on water: An extended synthesis of bioactive dithiobis(phenylene)bis(benzylideneimine) via sequential oxidative coupling–condensation reactions in one pot from aminothiophenol and benzaldehyde

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ABSTRACT

Bovine serum albumin (BSA) has been explored for aerobic oxidative coupling of thiols (aromatic, heterocyclic as well as aliphatic) "on water" towards formation of disulphides (S—S) without using any metal/non-metal complexes, bases and additives, which renders the process environmentally benign and economically attractive with good recyclability (up to four cycles). The developed green protocol was further extended for synthesis of diallyldisulphide (DADS), an important constituent of natural occurring allicin. Among various synthesized disulphides, bis(2-aminophenyl)disulphide, obtained by oxidative coupling of 2-aminothiophenol in BSA, was further utilized for condensation with benzaldehyde in the same pot thus enabling easy access to bioactive dithiobis(phenylene)bis(benzyldeneimine). This is the first example of BSA catalysed sequential (oxidation/condensation) reaction where one S—S and two C—N bonds are formed solely "on water."

1. Introduction

The organic synthesis with minimal environmental impact has become the focus of chemists and the use of natural catalysts [1–6] (viz., proteins, enzymes, whole cell, etc.) has steadily ascended owing to inherited environmental and ecological benefits. In the same vein, the use of water to facilitate eco-sustainable chemical reactions is also gaining momentum because either its use as a solvent or its release as a by-product, will clearly have the least impact on the environment [7–9]. Furthermore, there is representative "on water" [10–16] reactions termed by Sharpless and co-workers [10] where conducting the reaction "on water" can be substantially beneficial because of its high heat capacity, increase in reaction rate, selectivity and an improved safety profile with ease of operation due to the insolubility of both reactants and products in aqueous conditions. In this context, numerous organic transformations including oxidation of aldehyde into carboxylic acid "on water" using molecular oxygen as an environmentally benign and sustainable oxidant have surfaced [11]. Nevertheless, aerobic oxidation reactions promoted by biocatalysts under neutral reaction conditions are rare and lack generality "on water."

Among various oxidation reactions, the selective oxidative coupling of thiols (—SH) to corresponding disulphides (S—S bond) under mild reaction conditions is critical from biological and chemical viewpoints [17–26]. The formation of disulphide bond is also a matter of interest for the industrial production of some agrochemicals and pharmaceuticals [27–37] like pyritinol [33], DADS (a major decomposition product of allicin found in *Allium sativa*) [36] and dithiobis(phenylene)bis(benzyldeneimine), an antimicrobial agent against human pathogens [34,35] (Fig. 1).

Conventionally, a large number of oxidative coupling protocols [38–55] including ball-milling [38], Fe(BTC) [40], diaryltelluride [43], gold nanoparticles [46] and hypervalent iodine(III) [47] have been documented for the synthesis of disulphides [52–55]. However, most of these approaches suffer from inadequacies such as low selectivity due to over oxidation [42] of final product into

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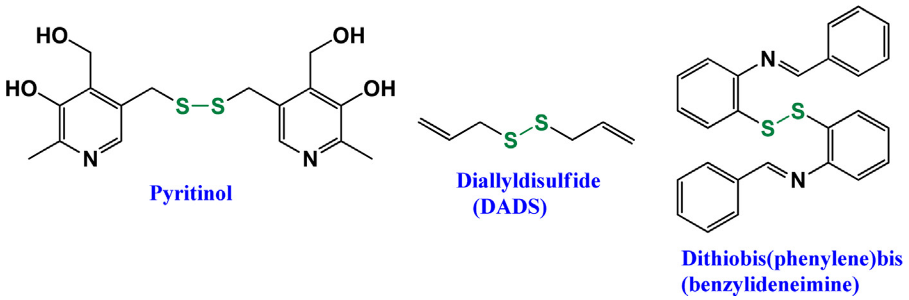

Fig. 1. Biological active scaffolds containing S—S bond.

sulphoxides/sulphones, expensive and toxic nature of catalysts with poor recovery and finally laborious work up procedures with generation of a lot of waste materials. Recently, Wu and co-workers [51] have reported an effective and recyclable photocatalytic method for selective conversion of thiols into disulphides with high turnover number (TON) but visible-light irradiation of quantum dots is necessary. Against this milieu, it is a surprise that only few biocatalysts [56–58] including horseradish peroxidase or mushroom tyrosinase [56], baker's yeast [57] and enzyme laccases [58] have been known for aerobic oxidative coupling of thiols into disulphides but these reactions occurs in aqueous-organic medium along with maintenance of pH conditions [56] and use of ABTS as radical initiator [58]. So there is a strong need to develop such a biocatalytic system for oxidation of thiols to disulphides which comprises all, i.e. inexpensive biocatalyst, aerobic oxygen and water as a sole reaction medium besides recyclability of the biocatalyst (Fig. 2).

In this context, BSA [59–68] (also known as "Fraction V") a ubiquitous and inexpensive, non-enzymatic transport protein derived from cows, occupies a unique position due to its versatility to catalyse an array of chemical reactions [59–71] including the asymmetric thia-Michael [72] reaction. It is one of the most studied proteins that have a strong affinity to bind organic molecules by reversible non-covalent complexation in its hydrophobic pockets thus providing an environment for a number of organic transformations including reduction [60], Knoevenagel condensation [61] and Gewald reaction [62]. Based upon our ongoing interest on BSA catalysed Aldol/Knoevenagel–Doebner condensation [69], multicomponent Biginelli reaction [70] besides oxidation of tertiary amine to N-oxide at pH 9 by Colonna et al. [59], we ventured to explore BSA as a biocatalyst for waste-free aerobic oxidation of thiols to disulphides "on water" which received considerable interest for various chemical transformations [10–16] as water is a cheap, nontoxic solvent as well as it increases the reactivity or selectivity of the reaction, often difficult to attain in organic solvents.

Among various disulphides (Fig. 1), bis(2-aminophenyl) disulphide [73–80] is particularly known to participate towards formation of bis(2-aminophenyl)disulphidediimines, a Schiff bases ligand [73] (Fig. 3) which possess sound antibacterial activity [74] and are also used as basic scaffold in various chemical transformations [75–78]. Despite promising biological profiles, synthesis of these Schiff bases requires two steps involving metal/base [38,39,42,47] catalysed oxidation of 2-aminothiophenol into corresponding bis(2-aminophenyl)disulphide which upon isolation and purification followed by condensation with benzaldehyde in anhydrous [73] ethanol affords the desired product bis(2-aminophenyl)disulphidediimines (Fig. 3) having one S—S and two C—N bonds. Against this drawback, creation of multiple bonds [81–83] in one pot without changing the reaction condition and isolating the intermediate helps in minimizing waste, time and energy which are most important aspects of green chemistry and generally accomplished by tandem [84–87] (consecutive/sequential) reactions. It is worth mentioning that 2-aminothiophenol which is a versatile synthon [73–80], on one side undergoes self-oxidative coupling into product bis(2-aminophenyl)disulphide [47] while on the other side it undergoes condensation–cyclization with benzaldehyde leading to benzothiazole [88–90]. Hence it would be very challenging if aerobic oxidative coupling–condensation between 2-aminothiophenol and benzaldehyde undergoes in a tandem manner in one pot towards formation of bis(2-aminophenyl)disulphidediimines (Schiff base) instead of benzothiazole on water (Fig. 3). Further, formation of these Schiff bases [73] on water under neutral conditions would be an interesting preposition as generally condensation

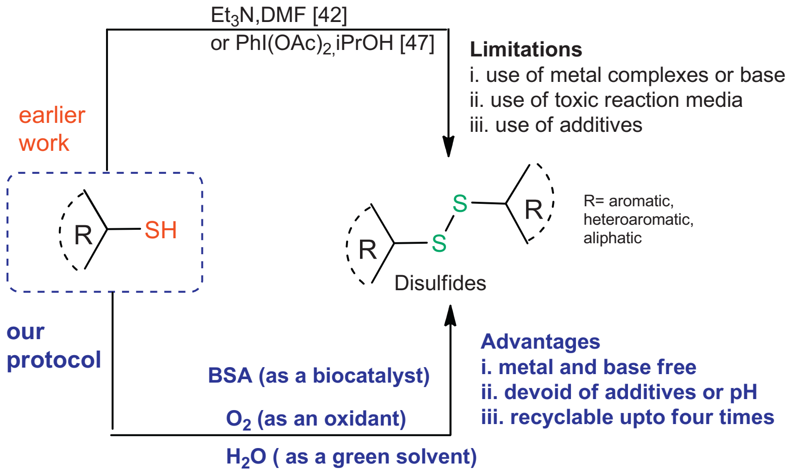

Fig. 2. BSA catalysed first oxidative coupling of thiols into disulphides (S—S bond) under neutral condition.