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Sodium Dodecyl Sulfate-assisted Synthesis of 1-(Benzothiazolylamino)methyl-2-naphthols in Water

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An efficient synthesis of 1-(benzothiazolylamino)methyl-2-naphthols has been developed in water by one-pot condensation of 2-naphthol, aldehydes and 2-aminobenzothiazole catalyzed by sodium dodecyl sulfate. Advantages of the methodology include a very short reaction time, excellent yields and catalytic use of the sodium dodecyl sulfate.

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o-Quinone methides (o-QMs) are highly reactive, transient species that have been applied as intermediates in the synthesis of several natural products including flavonoids, isoflavans, chromenes and benzopyrans.^[1-4] Because of their synthetic utility and biological importance, various methods have been reported for generating these extremely reactive intermediates that rely on the use of catalysts, acidic or basic conditions, high temperatures or long reaction times.^[5–8] The *ortho* aldolization of phenols with aldehydes followed by Lewis acid-assisted water elimination is probably the most convenient path available up to now. The o-OM thus generated then participates in a regiospecific, [4+2] cycloaddition reaction with olefins, enol ethers or enamines, along with formation of side products.^[1a,9] In recent years, trapping of o-QM by suitable nucleophiles has been used to provide a rapid access to novel Michael addition products.^[10–11]

With growing concern over the environmental impact of chemicals and tight legislation, development of greener chemical processes in synthetic chemistry has been advocated. At the heart of green chemistry are alternative reaction media. They are the basis of many of the cleaner chemical technologies that have reached commercial development. Water is among the most environmentally friendly and least expensive solvents, and thus reactions in aqueous medium have gained considerable momentum.^[12-14] In many of these reactions, water not only acts as a greener solvent but also accelerates reaction rates and enhances reaction selectivity.^[15] However, most organic substances are

insoluble in water and this hampers the complete exploitation of water as a solvent in organic synthesis.

Sodium dodecyl sulfate (SDS) is a surfactant, and the surfactant used in water can make organic materials soluble, so it can solve the drawback of the reactions in water. The use of SDS as a catalyst in aqueous medium for promoting various transformations is well documented in the literature.^[16] Therefore, development of a new method that is efficient and leads to better yields under environmental friendly conditions is well appreciated.

Benzothiazole is an important heterocyclic unit that has been widely used as a key building block for pharmaceutical agents. Its derivatives are endowed with many pharmacological properties such as antitubercular, antiallergic, anti-inflammatory and fungicidal activity.^[17] Recently, two reports appeared for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols using LiCl and heteropolyacid (HPA).^[18] In continuation of our interest in green synthesis and the use of o-QM as an intermediate in the synthesis of organic molecules with interesting biological properties,^[19] herein we report a green. one-pot, efficient synthesis of 1-(benzothiazolylamino)methyl-2-naphthols catalyzed by sodium dodecyl sulfate (SDS) in water (Scheme 1).

Initially, the efficacy of various catalysts was tested for the model reaction of 4-chlorobenzaldehyde, 2-nathphol and 2-aminobenzothiazole to give 1-((benzo[d]thiazol-2-ylamino) (4-chloro-phenyl)-methyl)naphthalen-2-ol (4g) under different



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Table 1. Comparison of different reaction conditions for the synthesis of 4g

Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) and water (3.0 mL). SDS, sodium dodecyl sulfate; *p*TSA, *p*-toluenesulfonic acid

| Sr. no. | Catalyst | Catalyst [mol-%] | Time [h] | Yield [%] ^A |
|---------|----------------------|------------------|----------|------------------------|
| 1 | SDS | 20 | 1 | 88 |
| 2 | SDS | 10 | 1 | 81 |
| 3 | SDS | 5 | 1 | 76 |
| 4 | SDS | 30 | 1 | 71 |
| 5 | SDS | 50 | 1 | 57 |
| 6 | _ | _ | 6 | 50 |
| 7 | pTSA | 20 | 3 | 69 |
| 8 | YbCl ₃ | 20 | 6 | 40 |
| 9 | Yb(OTf) ₃ | 20 | 1 | 75 |
| 10 | $Sc(OTf)_3$ | 20 | 1 | 55 |

^AIsolated yield.

Table 2. The comparison of different solvents for synthesis of 4g using SDS as catalyst

Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol), 2-aminobenzothiazole (1.0 mmol), catalyst (20 mol-%) and solvent (3.0 mL)

| Sr. no. | Solvent | Time [h] | Yield [%] ^A | |
|---------|-------------------|----------|------------------------|--|
| 1 | H ₂ O | 1 | 88 | |
| 2 | DMF | 6 | B | |
| 3 | DMSO | 6 | _B | |
| 4 | Acetonitrile | 6 | 12 | |
| 5 | Toluene | 6 | 45 | |
| 6 | Ethanol | 6 | 15 | |
| 7 | Methanol | 6 | _B | |
| 8 | CHCl ₃ | 6 | 10 | |
| 9 | Acetone | 6 | B | |
| 10 | THF | 6 | 10 | |

^AIsolated yield.

^BNo product formation was observed.

reaction conditions. The results, indicated in Table 1, showed that among the screened catalysts such as *p*-toluenesulfonic acid (pTSA), YbCl₃, Yb(OTf)₃, Sc(OTf)₃ and SDS, SDS was superior, with better yields isolated in comparable or shorter times. In other cases, formation of xanthenes was observed as a by-product along with the desired product. Recently, Kumar et al. reported the synthesis of Betti base in water catalyzed by Triton X-100.^[20] They showed that among different surfactants used, Triton X-100 was the most effective for this reaction.

Next, we optimized the catalyst loading for the model reaction by varying the catalyst amount from 5 to 50 mol-%. It was observed that increasing the catalyst loading up to 20 mol-% increased the yield of 4g, but beyond 20 mol-%, it did not improve; rather, it decreased (Table 1). Thus, we took 20 mol-% of SDS as the optimum amount for further studies. It should also be pointed out here that the reaction gave only 50% of 4g in the absence of SDS after 6 h (Table 1, entry 6), confirming the effectiveness of the catalyst.

We also examined the influence of solvents on the reaction yields. It was found that a very low yield of the desired product **4g** was obtained in organic solvents, except toluene in which **4g** was obtained in 45% yield (Table 2). Yield of **4g** was 88% in Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol), 2-aminobenzothiazole (1.0 mmol), SDS (20 mol-%) and water (3.0 mL)

| Sr. no. | R | \mathbb{R}^1 | Product ^A | Time [h] | Yield [%] ^B |
|---------|--------------------|--------------------------------------|----------------------|----------|------------------------|
| 1 | Н | Н | 4a | 2 | 80 |
| 2 | Н | 4-CH ₃ O | 4b | 2 | 84 |
| 3 | Н | 3-CH ₃ O | 4c | 2 | 89 |
| 4 | Н | 2-CH ₃ O | 4d | 2 | 86 |
| 5 | Н | 2,4-(CH ₃ O) ₂ | 4e | 2 | 92 |
| 6 | Н | 4-CH ₃ | 4f | 2 | 93 |
| 7 | Н | 4-C1 | 4g | 1 | 88 |
| 8 | Н | 3-C1 | 4h | 1 | 84 |
| 9 | Н | 4-N | 4i | 2 | 80 |
| 10 | Н | 4 - F | 4j | 2 | 82 |
| 11 | Н | 3-Br | 4k | 2 | 78 |
| 12 | Н | 2-F | 41 | 2 | 92 |
| 13 | Н | 3-NO ₂ | 4m | 3 | 75 |
| 14 | Н | 4-NO ₂ | 4n | 3 | 76 |
| 15 | 7-OCH ₃ | 4-C1 | 40 | 1 | 71 |
| 16 | 5-Aza | 4-C1 | 4p | 5 | 74 |

^AStructure of all the products was well characterized by ¹H and ¹³C NMR and mass spectroscopy.

^BIsolated yield after purification by column chromatography.

water using SDS as catalyst. It shows that water not only acts as a reaction medium but also assists the reaction rate. The role of SDS is not clear but it is expected that it provides a micellar environment and acts as mild Brønsted acid in aqueous medium.

To explore the scope of this reaction, various substituted aromatic aldehydes were reacted with 2-naphthol and 2-aminobenzothiazole under optimized reaction conditions, and the results are shown in Table 3. The reaction proceeded efficiently with both aldehydes containing electron-withdrawing and electron-releasing substituents. However, the yield of product was lower with aldehydes containing electron-withdrawing substituents compared with aldehydes with electron-donating groups (Table 3, entries 9, 13, 14). The reaction of 4-chlorobenzaldehyde with other activated phenols such as 7-methoxy-2-naphthol, 6-hydroxyquinoline and 2-aminobenzothiazole gave corresponding products in 71 and 74% yield respectively (Table 3, entries 15, 16) but with 2-methoxyphenol, reaction did not proceed.

All the synthesized compounds were characterized by ¹H NMR and mass spectroscopy (see Accessory Publication). Presumably the reaction proceeds through the formation of an o-QM intermediate followed by Michael addition by 2-aminobenzothiazole to give the desired product, as shown in Scheme 2. Formation of the imine as an intermediate was ruled out by examining the reaction of the corresponding imine generated in situ with 2-naphthol, which did not result in the formation of product. It is interesting to mention that under these conditions, formation of xanthenes was not observed as a by-product. Further studies for in situ trapping of o-QM generated in aqueous media for the synthesis of different heterocylic compounds are under progress in our laboratory.

In conclusion, we have developed an efficient method for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols by trapping the *o*-QM generated by the reaction of a reactive phenol with aldehyde in the presence of SDS in situ with 2-aminobenzothiazole as nucleophile in aqueous medium.



Scheme 2.

Simplicity, good yields and purity of the products, efficiency of the catalyst and a clean reaction are the salient features of this method. The method can be applied for the generation of new molecules by trapping the *o*-QM.

General Procedure for the Synthesis of 1-(Benzothiazolylamino)methyl-2-naphthols

To a mixture of 2-naphthol (0.2 g, 1.0 mmol), 4-chlorobenzaldehyde (0.214 g, 1.0 mmol) and 2-aminobenzothiazole (0.21 g, 1.0 mmol) in H₂O (3.0 mL) was added SDS (0.2 equiv.). The reaction mixture was heated at100°C for an appropriate time (see Table 3). The reaction progress was followed by TLC (hexane/ethyl acetate 8:2). On completion of the reaction, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2×20 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure, and the residue was percolated through a band of silica gel (60–120 mesh) using hexane/ethyl acetate (9:1 v/v) as an eluent to give pure compound **4g** in 88% yield. All the compounds were characterized by ¹H NMR, ¹³C NMR, IR spectroscopy and mass spectrometry.

Accessory Publication

Spectral data (¹H NMR, ¹³C NMR and electrospray ionization mass spectrometry (ESI-MS)) for 4a-p are available on the Journal's website.

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