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Catalytic role of sodium dodecyl sulfate: Selective synthesis of 1, 2-disubstituted benzimidazoles in water

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ABSTRACT

A simple and efficient procedure for the synthesis of 1, 2-disubstituted benzimidazoles has been developed by a one-pot reaction of *o*-phenylenediamine with both aromatic and aliphatic aldehydes in the presence of sodium dodecyl sulfate in aqueous medium at room temperature in open air without any organic solvent. The surfactant is recycled. A plausible mechanistic approach has also been suggested.

1. Introduction

Functionalized benzimidazoles represent an important class of *N*-containing heterocyclic compounds and have received considerable attention in recent times because of their applications as antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistamines among others [1–5]. They are important intermediates in many organic reactions [6,7] and act as ligands to transition metals for modelling biological systems [8,9]. In addition, the treatment potency of benzimidazoles in diseases such as ischemia–reperfusion injury [10], hypertension [11], obesity [12] *etc.* have been recently reported. Owing to the potential biological and other technical interest of the benzimidazole family of compounds, a number of synthetic strategies have been developed for the preparation of substituted benzimidazoles.

There are currently a number of synthetic methodologies available for the synthesis of benzimidazoles. Generally, the condensation of *o*-phenylenediamines and carboxylic acids (or their derivatives such as nitriles, imidates, and orthoesters) had been widely used for the benzimidazole synthesis, but harsh dehydrating conditions (170–180 °C) are usually required [13–15]. Alternative approaches such as palladium catalyzed tandem carbonylation–cyclization reaction of *o*-phenylenediamine [16], palladium catalyzed tandem dehydration coupling reaction of 2-bromoaniline [17], rhodium catalyzed hydroformylation reaction of *N*-alkenyl phenylenediamines [18], reductive cyclization reaction of *o*-nitroaniline with aldehydes [19], solid-phase supported synthesis [20] *etc.* have also been developed to prepare functionalized benzimidazoles. However, directly employing the condensation–aromatisation reaction of *o*-phenylenediamines and aldehydes under oxidative condition turned out to be the most facile and effective method to synthesize 2-substituted benzimidazole **4** [21–27] and 1, 2-disubstituted benzimidazole **3** from readily available cheap starting materials [28–32].

Among the reactions of *o*-phenylenediamine with aldehyde, the selectivity in forming 1, 2-disubstituted benzimidazole **3** and 2-substituted benzimidazole **4** is an issue of high interest. As a large body of protocols have been established for synthesizing benzimidazoles of type **4** [21–27], relatively rare methods have been reported to directly prepare 1, 2-disubstituted benzimidazole 3 with ideal selectivity [28–32]. Recently, several elegant catalyst systems have been developed to prepare **3** in excellent chemoselectivity by employing some organic solvents and water as the medium in the presence of costly organometallic catalysts [27,29,31,32]. The use of large volumes of volatile hazardous organic solvents and toxic rare earth metal catalysts in industrial processes posed a serious threat to the environment. Thus, procedures involving alternative benign solvents in reaction, isolation and purification are of high priority in industry. Given the desire for developing more economical and facile methods of less environmental impact in organic synthesis, we wish to report herein the sodium dodecyl sulfate (SDS) catalyzed selective synthesis of 1, 2-substituted bezimidazole derivatives in water at room temperature.

2. Results and discussion

We initially employed *o*-phenylenediamine and benzaldehyde (1:1 mmol) for the reaction in water, but could not get the expected 1, 2-disubstituted benzimidazole, along with a mixture of the three

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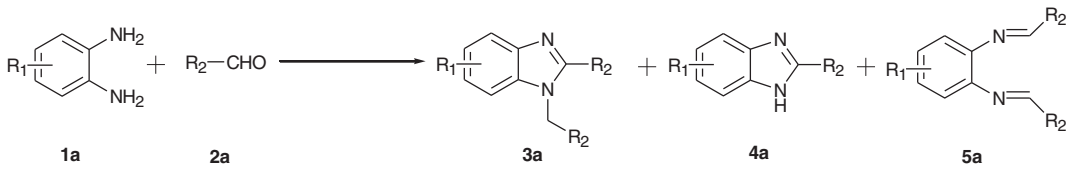


Scheme 1. Plausible transformations.

Table 1
Optimisation of benzimidazole synthesis using benzaldehyde and o-phenylenediamine with varying surfactants.

Entry	Ratio of aldehyde and diamine	Surfactant	Amount of surfactant (mg)	Temp (°C)	Time (h)	% Yield[a] of 3	% Yield[a] of 4	% Yield of 5[a]
1	1:2	SDS	100	RT	0.5	96	4	Nil
2	1:2	SDS	50	RT	0.5	94	6	Nil
3	1:2	SDS	20	RT	0.5	96	4	Nil
4	1:2	SDS	15	RT	0.5	94	6	Nil
5	1:2	SDS	10	RT	0.5	95	5	Nil
6	1:2	SDS	7	RT	0.5	80	15	5
7	1:2	SDS	5	RT	0.5	64	30	6
8	1:2	SDS	5	50	8	68	25	7
9	1:2	TBAB	100	RT	10	78	15	7
10	1:2	TBAB	100	50	10	76	15	9
11	1:2	TBAB	200	100	10	80	16	4
12	1:2	CTAB	100	RT	10	66	15	19
13	1:2	CTAB	200	100	10	68	17	15
14	1:2	CPC	100	RT	10	78	18	4
15	1:2	CPC	200	100	10	80	20	2
16	1:2	TBAH	100	RT	10	76	16	8
17	1:2	TBAH	200	100	10	78	18	4
18	1:2	TBAI	100	RT	10	68	28	4
19	1:2	TBAI	200	100	10	74	22	4

[a] % Yield refers to the isolated yield of all the compounds.

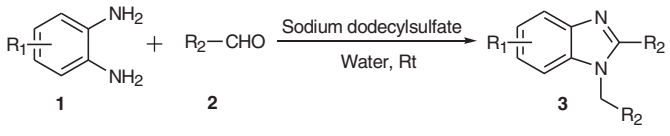
other products at room temperature under open atmosphere (Scheme 1). An increase in the reaction time, reaction temperature and by changing the molar proportion of the reactants does not make any influence on the ratio of the product distribution. As it is reported that surfactants can also catalyse many reactions [33,34] we attempted the above study using 1 mmol of anhydrous SDS in the above reaction mixture of *o*-phenylenediamine and benzaldehyde (1:2 mmol) using the same reaction condition at room temperature. This revised protocol gave only a single product by a very simple workup procedure which was identified as 1, 2-disubstituted benzimidazole (3a).

This excellent chemoselectivity induced by sodium dodecyl sulfate (SDS) inspired us to investigate this transformation in details. In order to establish an optimised reaction protocol, varied reaction conditions were applied (Table 1) on the above model study using 1 equiv mmol of *o*-phenylenediamine and 2 equiv mmol of benzaldehyde including the use of different types of surfactants *viz*. SDS, Tetra-n-butylammonium bromide (TBAB), Cetyl trimethyl ammonium bromide (CTAB), Cetyl pyridinium chloride (CPC) and Tetra-n-butylammonium iodide (TBAI) in different proportions (Table 1). It is interesting to note that, although all the surfactants used gave 3, as the major product but SDS showed excellent selectivity in forming the desired product 3. Based on the above study as depicted in Table 1, we finally optimised the reaction condition as follows: 10 mg SDS in water is to be used for a 1:2 mmol ratio of \o-phenylenediamines and aldehydes at room temperature.

After getting established the optimised reaction condition, we attempted to generalize the designed protocol using a wide variety of 1, 2 diamines and aldehydes. Except few aliphatic aldehydes the developed process found to be excellent both in terms of yield, selectivity and time (Table 2). The synthesis of such kind of benzimidazole derivatives from aliphatic aldehydes were not addressed by many of the existing methods. The aldehydes with electron donating (Entries 6, 7 and 12 Table 2) as well as with electron withdrawing groups (Entries 2–5, 8, 11, 20 and 21 Table 2) participated in the reaction uniformly. Apparently, the nature and position of substitution on the aryl ring did not make any much different in reactivity. Sensitive molecules like furan-2-aldehyde, 5-bromo thiophene-2-aldehyde, pyridine-4-carboxaldehyde (Entry 13, 14, & 23 Table 2) produced the corresponding benzimidazoles without any difficulty. In significance, when the reaction of naphthalene-1-carboxaldehyde and *o*-phenylenediamine was carried out following our method, gave excellent yield of the corresponding benzimidazole (Entry 16, Table 2). The study also indicated that unsubstituted aromatic aldehydes gave better yields of the product compared to the substituted systems and that the response of aliphatic aldehydes towards the conversion is not encouraging. As shown in Table 2 (Entry 15, Table 2), cinnamaldehyde furnished corresponding product **3o** in modest yield whereas valeraldehyde gave only traces amount of target product. The scope of this reaction has been explored by subjecting the protocol on different diamines and aldehydes following Scheme 2.

This fascinating applicability of the method towards diversified 1, 2-diamines and aldehydes prompted us to design some large benzimidazole derivatives that can serve as lead compound in pharmaceutical research and to our delight we have able to synthesize a large benzimidazole derivative (**A**) from a reaction between 3,3′-diamino benzidine (B) and benzaldehyde (C) in excellent yield (Scheme 3).

A plausible mechanism (Scheme 4) of the reaction has been proposed on the basis of formation of a Schiff base as intermediate which has been isolated and characterized by NMR spectroscopy. Further, it is also observed that the prepared Schiff base (5) when subjected to undergo the same reaction under identical condition i.e.

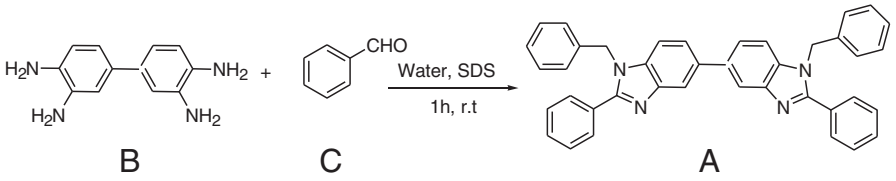


Scheme 2. Preperation of 1, 2-disubstituted benzimidazole.

Table 2
Preperation of diversified benzimidazole derivatives in aqueous SDS.

Entry	R_1	R_2	Time	Temperature	Product	% Yield
1	H	Ph	0.5 h	Rt	3a	96
2	H	4-$CH_3OC_6H_4$	2 h	Rt	3b	88
3	H	4-FC_6H_4	1.5 h	Rt	3c	87
4	H	4-ClC_6H_4	1.5 h	Rt	3d	85
5	H	4-$NO_2C_6H_4$	8 h	Rt	3e	79
6	H	4-$NMe_2C_6H_4$	2 h	Rt	3f	85
7	H	4-Isopopyl C_6H_4	1.5 h	Rt	3g	83
8	H	3-$NO_2C_6H_4$	24 h	Rt	3h	82
9	H	3-OHC_6H_4	5 h	Rt	3i	85
10	H	3-$OPhC_6H_4$	3 h	Rt	3j	82
11	H	2-ClC_6H_4	1.5 h	Rt	3k	79
12	H	2-OHC_6H_4	15 h	90 °C	3l	82
13	H	Furan-2-yl	4 h	Rt	3m	85
14	H	5-Bromo-thiophene-2-yl	6 h	R t	3n	75
15	H	PhCH=CH2	5 h	Rt	3o	78
16	H	1-Napthyl	6 h	Rt	3p	69
17	3-CH_3	4-Isopopyl C_6H_4	2 h	Rt	3q	82
18	3-CH_3	3-$OPhC_6H_4$	7 h	Rt	3r	76
19	3-CH_3	5-Bromo-thiophene-2-yl	8 h	Rt	3s	74
20	3-CH_3	2-ClC_6H_4	5 h	Rt	3t	72
21	3-benzoyl	4-ClC_6H_4	12 h	Rt	3u	75
22	3-benzoyl	Ph	14 h	Rt	3v	84
23	H	Pyridine 4-carboxaldehyde	14 h	90 °C	3w	82
24	H	H	8 h	Rt	3x	68
25	H	Valeraldehyde	12 h	Rt	3y	Trace
26	H	Cyclohexayl	4 h	Rt	3z	84

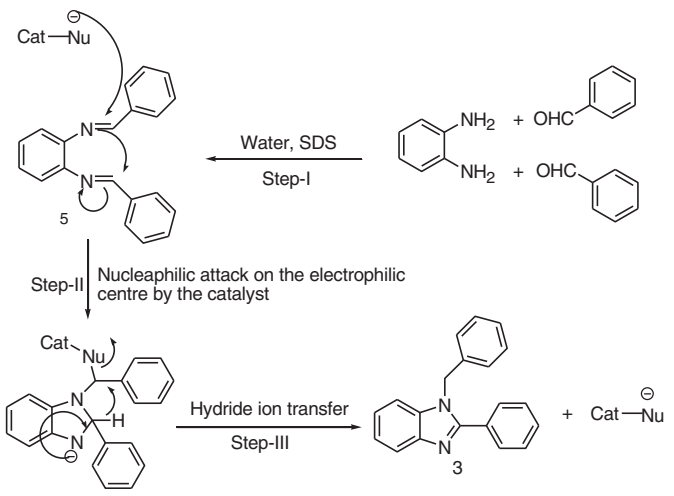
% Yield refers to the isolated yield of all the compounds after chromatographic separation.



Scheme 3. Preperation of a bis benzimidazole.

at room temperature in presence of SDS in water also yielded the same product in excellent yield. It is then followed by the nucleophilic attack of the catalyst on one of the eletrophilic imino carbon. Subsequent cyclisation and 1, 3-hydride shift leads to the formation of benzimidazoles (3).

As was mentioned earlier, a easy work up procedure of the reaction and reuse of the catalyst, SDS directly from the aqueous extract of the reaction mixture for a fresh run is a great advantage of the developed process. Gratifyingly, it was tested that the recovered water layer can be reused for six consecutive runs (Table 3).



Scheme 4. Plausible mechanism of benzimidazole formation in water-SDS.

3. Conclusion

Based on the above discussions, we can conclude that commercially available sodium dodecyl sulfate can be used as a cheap source to synthesize 1, 2-disubstituted benzimidazole derivatives in an expeditious and selective way in water at ambient temperature. Several functional groups such as –Cl, –Br, –NO_2, –OMe and sensitive molecules like 5-bromo thiophene-2-carboxaldehyde, furan-2-carboxaldehyde are compatible with the reaction conditions. The reaction procedures are operationally straightforward, mild, and environmentally protecting, and moreover the amount of water and SDS used, is reusable. Since benzimidazole derivatives are often used in the synthetic, medicinal and biological chemistry, the reaction procedure, being endowed with so many attractive features, could find applications as alternative green reaction methodology. Explorations of further applications of surfactants like sodium dodecyl sulfate are underway in our laboratory.

4. Experimental

4.1. General procedure for 1, 2-disubstituted benzimidazole

In a typical experimental procedure, *o*-phenylelenediamine and benzaldehyde in 1:2 molar ratios was taken in a 100 ml round bottom flask. To this water and 10 mg sodium dodecyl sulfate was admixed.

Table 3
Recycling experiment using SDS.

Entry	No. of cycles	% Yield
1	0	92
2	1	87
3	2	82
4	3	78
5	4	72
6	5	68

% Yield refers to the isolated yield of the compound after chromatography.

The reaction mixture was then allowed to stir at room temperature with magnetic spinning bar. A foamy mass appeared immediately and get settled like a precipitate. After the completion of the reaction, the solid reaction mixture was washed with dichloromethane (5×4`) and the washings were collected and evaporated under vacuum. The crude product was then crystallized from ethanol. The desired purified product was characterized by spectral (IR, ^{1}H and ^{13}C NMR) data and compared to those reported in literature.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.01.005.

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