Original Article

Surfactant-Assisted Syntheses of Benzimidazole Derivatives in Aqueous Media

Hoda Banary [a,*]| Eskandar Kolvari[a,*] | Parvin Hajiabbasi Tabar Amiri[b]

[a] *Department of Chemistry, Faculty of Science, Semnan University, Semnan, Iran*
[b] *Department of chemistry, Damghan University, Damghan, Semnan, Iran*

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ABSTRACT

A simple and efficient method for synthesis of 1,2-disubstituted benzimidazoles has been developed by a one-pot reaction of *o*-phenylenediamine with aryl aldehydes in the presence of sodium lauryl ether sulfate (SLES) in aqueous medium at ambient temperature without any organic solvent. The optimum SLES loading was observed at 15 mol%. The procedure is simple and the expected benzimidazole compounds were isolated in good yields. The present method provides the advantages of convenience, energy-saving eco-friendliness, mild reaction conditions, and no use of hazardous solvents.

Introduction

Functionalized benzimidazoles represent a significant class of *N*-containing heterocyclic compounds and have received remarkable attention in recent times because of their applications as antihypertensive, antivirale, antiulcer, antifungals, antihistamines, anticancer, and among others [1-7]. Benzimidazole ring is a significant pharmacophore in new drug discovery [8, 9] and exhibit a significant activity against several viruses such as HIV [10, 11], influenza [12], herpes (HSV-1) [13], RNA [14], and human cytomegalovirus (HCMV) [11].

Traditionally, synthesis of benzimidazoles involves the condensation of *o*-phenylene diamin with aldehydes [15-17], and carboxylic acids, or their derivatives (nitriles, amidate, and ortho ester) under harsh dehydrating conditions [18-24]. The reported methods have advantages; some of which suffer from shortcomings, for example, the need for heating, using microwave heating using ultrasound procedures. This method can also

***Corresponding Authors: Eskandar Kolvari** (Kolvari@semnan.ac.ir))**& Hoda Banary** (hoda_banary@yahoo.com)

avoid reflux conditions avoids usage of additional energy sources. No need for the catalyst synthesis. In our continued interest in and heterocyclic compounds of biological importance, we report the first instance of the synthesis of 1, 2-disubstituted benzimidazoles from the condensation of different benzaldehydes and diamines in H_2O, at ambient temperature in the presence of surfactant and absent of any catalyst. The use of SLES in these reactions is included notable features such as clean reaction profiles, minimization of waste, operational simplicity, non-toxicity, shorter reaction times, easy experimental work-up procedure, high yields of the products, and avoids usage of organic solvents [25-27]. The catalytic effect of micellar sodium lauryl ether sulfate (SLES) in this reaction is displayed in **Figure 1**.

In addition, use of environmentally friendly reaction medium is one of the fundamental principles of green chemistry. Water as a reaction solvent has received much attention in synthesis of organic compounds, because it would be considerably safe, non-toxic, environmentally friendly, green, clean, readily biodegradable, and cheap compared to the organic solvents, Moreover, when a water soluble catalyst is used, the insoluble products can be separated by simple filtration.

the development of a highly suitable methodology for the synthesis of fine chemicals

Experimental

General information

All chemicals were obtained commercially and used without further purification. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube procedure with a Thermal scientific 1900 apparatus. The progress of reactions was controlled by thin-layer chromatography (TLC) on 0.2 mm silica gel F-252 (Merck) plates using *n*-hexane/ethyl acetate as eluent.

General procedure for the synthesis of benzimidazole derivatives

The aromatic aldehyde (2 mmol) and 1,2-phenylenediamine (1 mmol) were added to a solution of SLES (15 mol%) in H_2O (5 ml), and the mixture stirred at ambient temperature for the given time (**Table 3**). The reaction progress was controlled by TLC (Eluent: 7:3 *n*-hexane-aceton). After the completion of the reaction, the resulting precipitated product was filtered, washed with water, and dried. The pure products were obtained by recrystallization from hot ethanol.

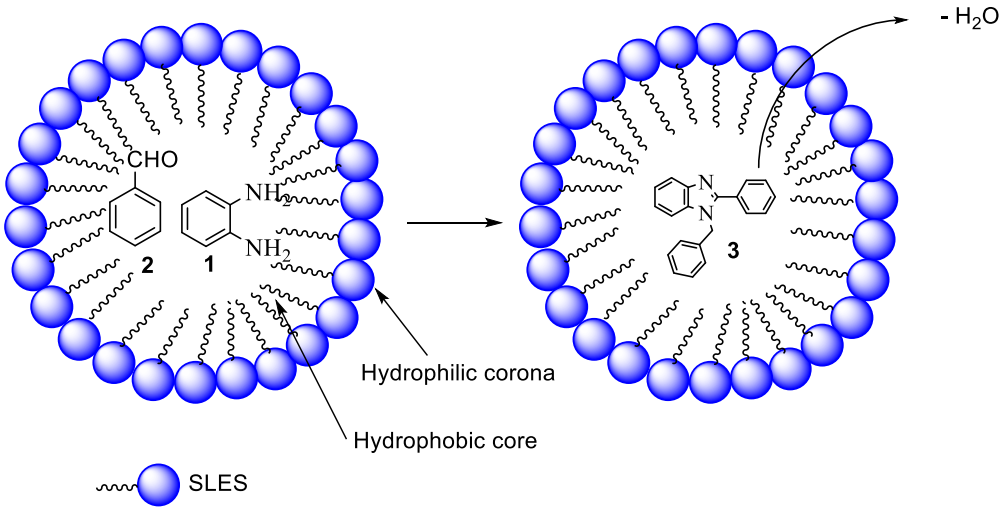
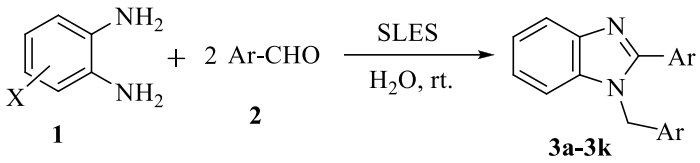


Figure 1. Suggested model for the synthesis of benzimidazoles in the presence of SLES in protic solvent



Scheme 1. Synthesis of benzimidazole derivatives (**3a**-**3k**)

Results and Discussion

We report a simple and efficient procedure for the synthesis of benzimidazole derivatives through the reaction of 1,2-ortho phenylendiamin 1 with aromatic aldehyde 2 in aqueous micellar media using sodium lauryl ether sulfate (SLES) which simultaneously function as a catalyst to promote the reactions and as a surfactant to assist in solubilizing the organic substrates (**Scheme 1**). In the micellar solution, 1,2-*o*-phenylenediamine 1 and aromatic aldehyde 2, which are both hydrophobic, are forced inside the hydrophobic core of micelles, and thus allowing the reaction to take place more easily. The IR spectrum of compound **3a** is showed in the **Figure 2**.

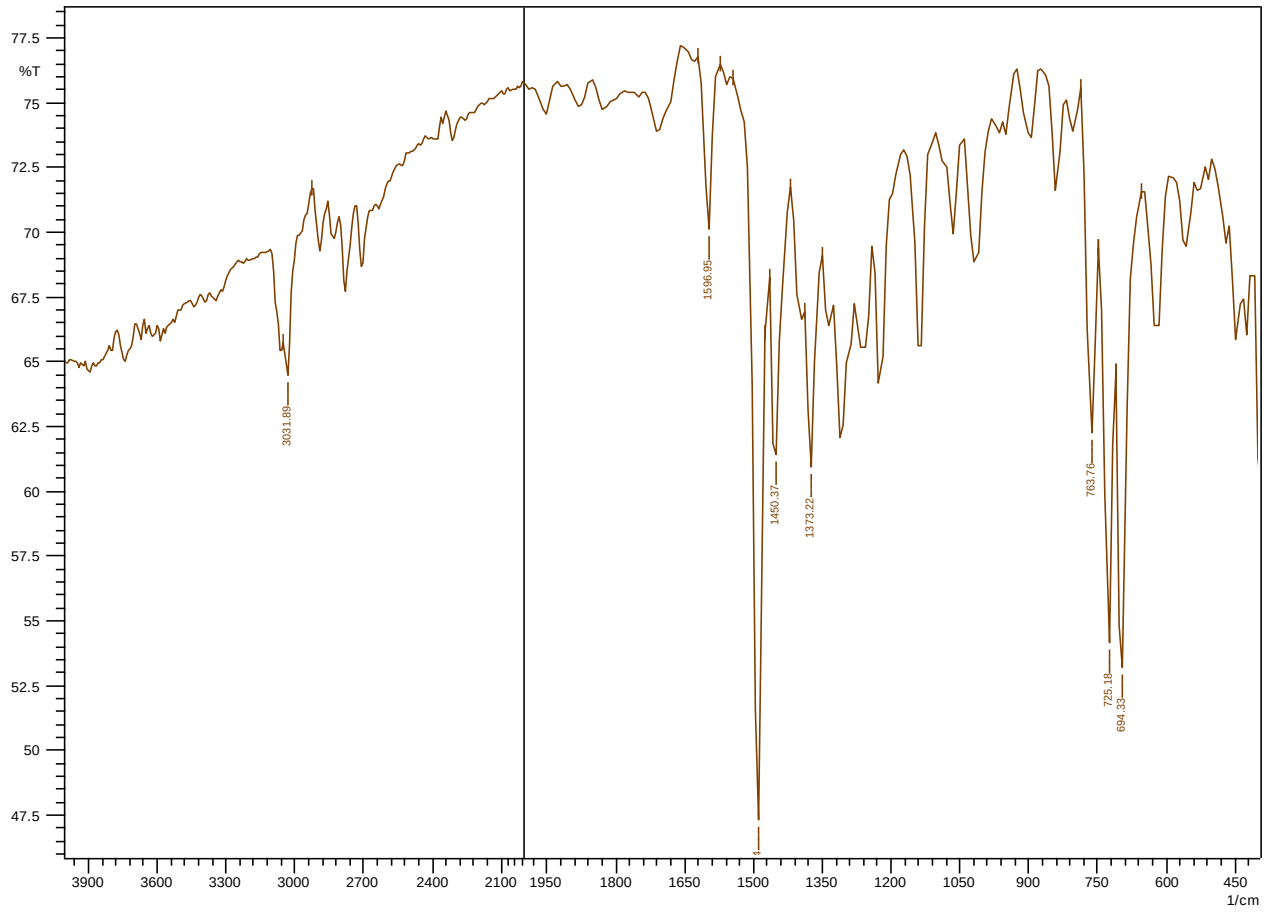


Figure 2. IR spectrum of compound **3a**

Table 1. Effect of the amount of SLES in the synthesis of compound **3a** as a model reaction[a]

Entry	Mol%	Yield(%)[b]
1	0	23
2	5	85
3	7	78
4	10	87
5	15	92

[a]Diamin (1.0 mmol), benzaldehyde (2.0 mmol) in the presence of different amount of SLES.
[b]Yields refer to isolated products.

To find the optimum value of surfactant, different amounts of SLES (0, 5, 7, 10, and 15 mol%) were used in the model reaction to obtain and compare the yields of product. The results were presented in **Table 1**. According to the results, it can be concluded that the optimum amount of surfactant was 15 mol%, led to form the desired product in 92% yield within 75 min. In addition, we screened the effect of other surfactants such as dodecyl trimethyl ammonium bromide (*DTAB*), tetradecyl trimethyl ammonium bromide (TTAB), cetyl trimethylammonium bromide (CTAB), and DBSA (dodecyl benzene solfunic acid) on the time and yield of the model reaction. As listed in **Table 2**, SLES include better performs than other surfactants with respect to the time and yield of the reaction. Based on these observations, we extended the study to the reaction of diamin (**1**) with other benzaldehydes (**2**) and the results were summarized in **Table 3**. In this procedure, SLES forms micelles in water and can dissolve insoluble starting materials. The dissolved material reacted gradually on stirring the reaction mixture at ambient temperature and was completed in 20-180 min giving 85-100% yields of 1,2-disubstituted benzimidazoles (**3a-3k**). The resulting solid products were characterized by comparison with their authentic samples.

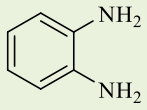
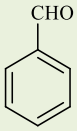
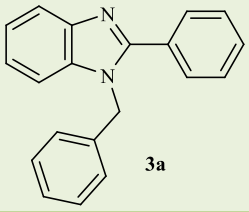
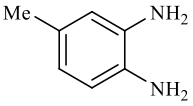
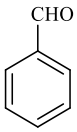
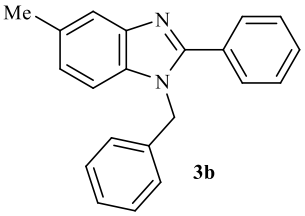
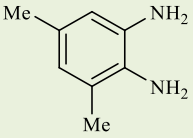
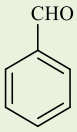
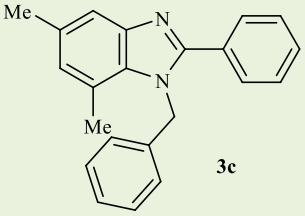
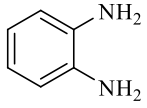
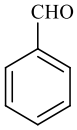
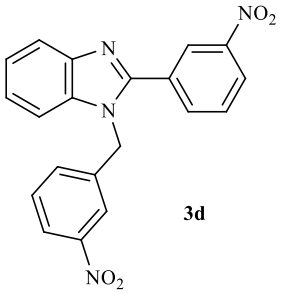
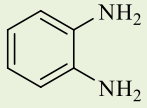
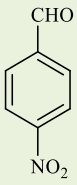
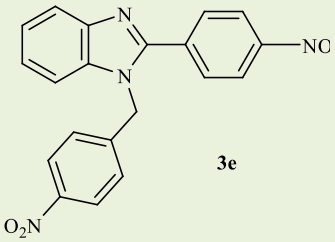
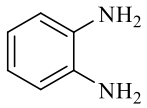
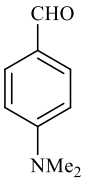
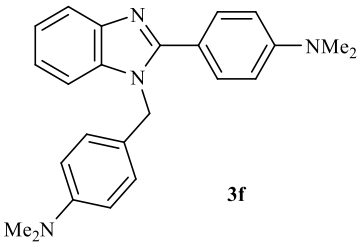
Table 2. Effect of different surfactants in the synthesis of compound **3a** as a model reaction

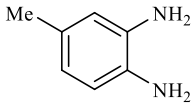
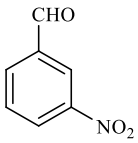
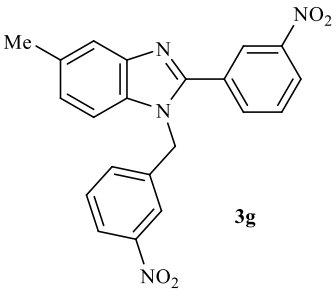
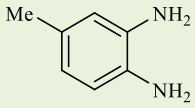
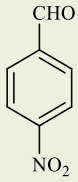
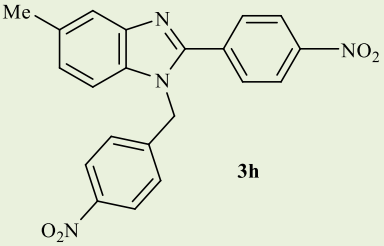
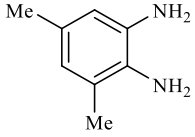
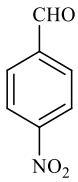
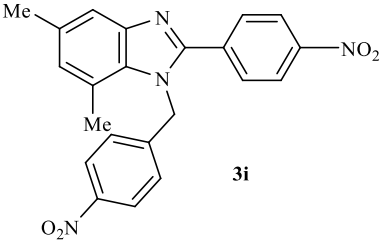
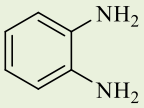
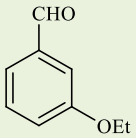
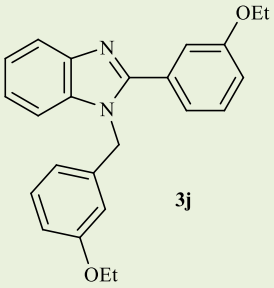
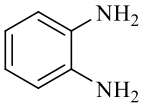
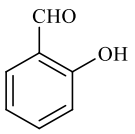
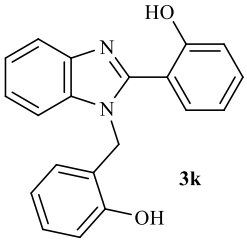
Entry	Surfactant (10 mol%)	Time (h)	Yield[a] (%)
1	TTAB	10	70
2	DETAB	10	70
3	CTAB	10	62
4	DBSA	-	-
5	SLES	1.15	92

[a]Diamin (1.0 mmol), benzaldehyde (2.0 mmol) in the presence of different surfactants.

[b]Yields refer to isolated products.

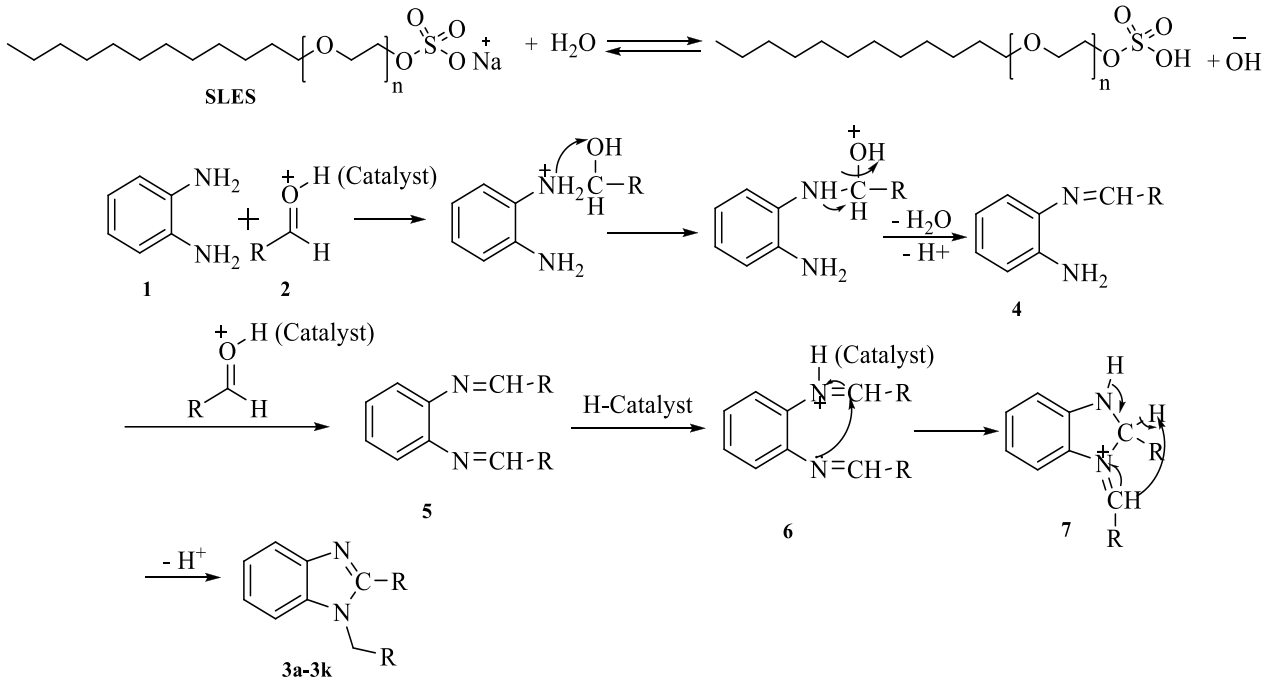
Table 3. Synthesis of 1,2-disubstituted benzimidazole derivatives (**3a-3k**) *via* the condensation of diamin with benzaldehydes using SLES

Entry	Diamin	Benzaldehyde	product	Time (min)	Yield (%)[a]	Melting point (°C) [28]
1			 **3a**	75	92	132-133 [28]
2			 **3b**	60	90	-
3			 **3c**	50	85	-
4			 **3d**	30	99	-
5			 **3e**	20	99	119-120 [28]
6			 **3f**	180	98	254-255 [28]

7			 **3g**	40	90	-
8			 **3h**	40	92	-
9			 **3i**	40	92	-
10			 **3j**	30	95	-
11			 **3k**	30	90	207-208 [28]

[b]Yields refer to isolated products.

A plausible mechanism and critical role of sodium lauryl ether sulfate (SLES) as surfactant and thus activating the carbonyl group of benzaldehydes for nucleophilic addition is depicted in **Scheme 2**. In this method, intermediate imine 4 attacked to another molecule of activated benzaldehyde (**2**) to produce compound **5**. Finally, the desired products (**3a-3k**) were obtained by a cyclization procedure.



Scheme 2. A possible mechanism for synthesis of benzimidazole derivatives

Conclusion

In this study, a green method was presented for the synthesis of 1,2-disubstituted benzimidazoles from diamin and aryl aldehydes in the presence of SLES in water as green and protic solvent. The present method has many advantages such as easy operation procedures, mild conditions, high yields, environment friendly, and no side reactions.

Orcids

Eskandar Kolvari
https://orcid.org/0000-0003-0484-5273

Parvin Hajiabbasi Tabar Amiri
https://orcid.org/0000-0001-9065-1779

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