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Polymer Supported DABCO as an Eco-Friendly and Green Catalyst for Synthesis of 2-arylbenzothiazole in Aqueous Media

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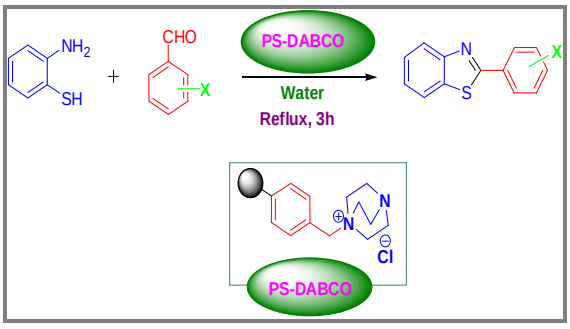
ABSTRACT

A new an efficient, high-yielding and rapid protocol has been developed for the synthesis of benzothiazoles via dehydrative C-N and C-S bond forming reaction of aryl aldehydes and 2-amino thiophenol by using PS-DABCO as green reusable heterogeneous catalyst in water as reaction solvent. An attempt is made to develop an environmentally friendly synthetic protocol representing a PS-DABCO catalyzed novel and very simple route for the preparation of 2-substituted benzothiazole derivatives. Absence of unwanted products, general applicability, reusability of the catalyst, green synthesis avoiding toxic reagents and improved and operational simplicity make this protocol a useful, greener, cost effective and practical for both academic as well as industrial purposes.

Graphical Abstract



Keywords: Heterogeneous catalyst, PS-DABCO, C-N bond forming reaction, Greener protocol, Benzothiazole.

INTRODUCTION

Heterocyclic benzothiazoles compounds have been attracted much attention of researchers because of their wide range of biological properties, such as their anti-HIV agents [**1**], antimicrobial [**2**], antiviral

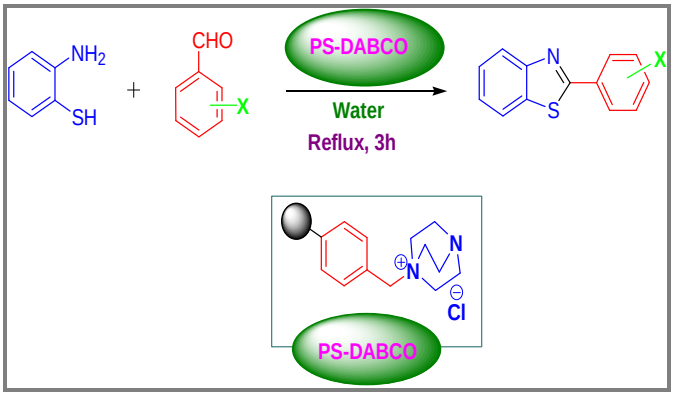
[3], anti-inflammatory [4], anticancer [5], antidiabetic [6], enzyme inhibitor (topoisomerase II inhibitory activity) [7]. They also can be used as potential photochromic compounds [8], plant growth regulators [9], in vivo imaging [10], fluorescence material [11] and dyes [12].

In addition, benzothiazole acts as core nucleus in various drugs due to their wide biological activities e.g. probenazole, pramipexole, lubeluzole, ethoxazolamide, zopolrestat and bentaluron etc. The high therapeutic properties of the heterocycles have been encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Benzothiazole derivatives catalyze the formation of sulphide linkages (reticulation) between unsaturated elastomeric polymers in order to obtain a flexible and elastic cross linked material. 2-Mercapto benzothiazole is mainly used for rubber accelerator in certain specialty products and tyre production.

Remarkably, amongst all these benzothiazole derivatives, 2-substituted benzothiazoles are privileged heterocyclic skeleton, because of their various biological properties and increasing applications in material fields [13]. The studies of SAR interestingly reveal that modification of the structure of substituent group at C-2 position commonly results the change in its bioactivity. These structural frameworks have potent utility as imaging agents for anti-tuberculotic [14] and anti-parasitic [15]. Consequently, development of new methods for the synthesis of 2-substituted benzothiazoles has drawn considerable attention.

Recently, several methods have been developed for the synthesis of benzothiazole scaffolds, for instance, condensation reaction of 2-amino thiophenol with acid derivatives [16], β-diketones [17] and aldehydes [18]. 2-substituted benzothiazoles also synthesized from cyclohexanones and thiourea as [19]. In addition, TBAB [20], p-TsOH [21], I_2 [22] and CdSe/MMT nanocomposites [23] catalyzed synthesis. However these procedures have suffered from the some drawbacks of green chemistry such as high reaction temperature, prolonged reaction time, low yields, requirement of expensive and excess catalysts, recovery and reusability of catalysts and co-occurrence of several side reactions etc. Therefore, the demand for green and eco-friendly procedure which uses reusable catalyst necessitated us to develop an alternative method for the synthesis of 2-substituted benzothiazoles.

Polymer supported heterogeneous catalyst has been of great interest due to several advantages in organic synthesis over homogeneous catalyst, such as ease of products separation, isolation and reuse of the catalyst. Literature survey revealed that, the Dabco based ionic liquid or salts are shows good catalytic activities in various C-C and C-N bond forming reactions [24-27]. Considering the advantages of the green chemistry, in continuation of our earlier work on the synthesis of biologically active heterocyclic compounds by using heterogeneous catalyst [28-30] and an importance of benzothiazoles molecules; we have used PS-DABCO catalyst for the synthesis of 2-substituted benzothiazoles derivatives (Scheme 1).



Scheme 1. PS-DABCO catalyzed multicomponent synthesis of pyranopyrazole.

MATERIALS AND METHODS

Chemicals required for the synthesis were obtained from Aldrich, Spectrochem, Loba-Company. Reactions have been monitored by Thin Layer Chromatography on 0.2 mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light or with an iodine vapour. Melting point ranges were determined in one end open capillaries and are uncorrected. All yields were referred to isolated products after purification. 1H NMR spectra were taken on a Bruker 400MHz DPX spectrometer with TMS as internal standard and the chemical shifts are reported in δ ppm units. Mass spectra (ES-MS, *m/z*) were recorded on Water-Micro QUATTRO-II mass spectrophotometer.

General procedure for the synthesis 2-substituted benzothiazoles (3a-m): A 25 mL round bottom flask containing 2-Aminothiophenol (**1**) (1.0 mmol) and aryl aldehyde (**2a-m**) (1.0 mmol) in 5 mL water in which PS-DABCO (3.0 mol %) was added. The reaction mixture was stirred at reflux temperature for 3h. The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ethyl acetate (10 mL) and separates the catalyst by simple filtration, washed the residue (catalyst) with hot ethyl acetate (2×5 mL), followed by concentrated under reduced pressure. The solid were filtered off and washed with water, dried and purified by recrystallization in aq. ethanol to give pure product. The selected products were characterized by PMR and Mass spectroscopy, whereas the remaining products characterized by their physical constants and were found to be in good agreement with the reported literature.

2-Phenylbenzothiazole [3a]: Yellow solid(Yield=92%); m.p. 114-116°C (lit. m.p. 115-116°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm8.03-8.16 (m, 3H), 7.91 (d, *J* = 8 Hz, 1H),7.46-7.60 (m, 4H), 7.34-7.44 (m, 1H); ESI-MS(MeOH): m/z: 212 $[M+H]^+$.

2-(2-Chlorophenyl)-benzothiazole [3b]: Orange solid(Yield=86%); mp 78-80^{o}C (lit. m.p. 76-78°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.18-8.29(m, 1H), 8.14 (d, *J* = 8.16 Hz, 1H), 7.96 (d, *J*= 7.91 Hz, 1H), 7.49-7.59 (m, 2H), 7.37-7.48(m, 3H); ESI-MS (MeOH): m/z: 246 $[M+H]^+$, 248 $[M+2+H]^+$.

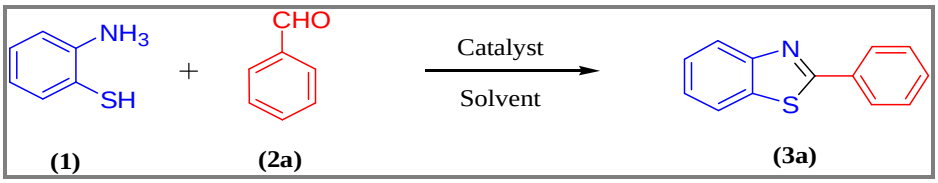
RESULTS AND DISCUSSION

The polymer supported DABCO catalyst was synthesized by modification of the reported method in a single step from Merrifield peptide resin (2 % cross linked, 2.3 mmol Cl g^{-1}, Aldrich) and 1,4-diaza bicyclo[2.2.2]octane (DABCO) [**28**].

At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported reactions. During the preliminary studies o-Aminothiophenol (**1**) (1 mmol) and benzaldehyde (**2**) in water used as a model system for this condensation reaction. A series of experiments were performed to optimize various reaction parameters, such as the catalyst, catalyst loading, solvent, temperature and time (Table 1). The proposed transformation was first examined by treating a mixture of model reaction components with various heterogeneous polymer supported catalysts were tested.

Among these heterogeneous catalysts examined PS-DABCO was found to be the best, providing excellent yields of the desired product **3a** (Table 1, **entries 1-3**). We further studied catalyst loadings ranging from 2 mol% to 4 mol%. The yield improved as the amount of PS-DABCO catalyst increased from 2 mol% to 3 mol% and became almost steady when the amount of catalyst was further increased beyond this (Table 1, **entries 3-5**). As the solvent will have an impact on the overall process, the effects of various solvents were examined; amongst the studied solvents, we found that water was the best solvent for the model reaction(Table 1, **entries 3, 6-9**), without solvent the product was obtained only 26% (Table 1**, entry 10**). A study of the effects of temperature showed that the yield of **3a** increased with increasing reaction temperature from 90°C to 100°C. Thus 100°C is the optimum temperature (Table 1**, entry 11**). The reaction time was optimized at water refluxed temperature for 3 h to give good yield of desired products (Table 1**, entries 12, 13**).

Table 1. Effect of catalyst screening and loading on 2-Phenylbenzothiazole synthesis reaction[a]

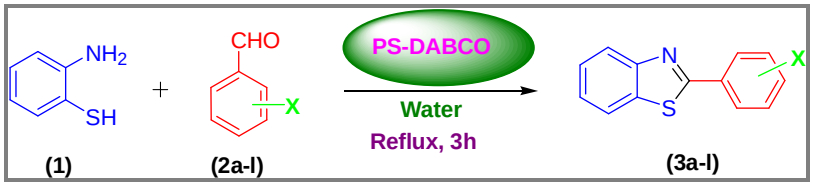


S. No.	Catalyst	Catalyst (mol%)	Solvent	Time (h)	Temp. (°C)	Yield (%)[b]
1	---	--	Water	24	100	18
2	PS-IMZ-Cl	3	Water	3	100	82
3	PS-DABCO	3	Water	3	100	92
4	PS-DABCO	2	Water	3	100	82
5	PS-DABCO	4	Water	3	100	92
6	PS-DABCO	3	Ethanol	3	78	92
7	PS-DABCO	3	AcOH	3	100	88
8	PS-DABCO	3	DMF	3	100	68
9	PS-DABCO	3	ACN	3	72	66
10	PS-DABCO	3	----	3	100	26
11	PS-DABCO	3	Water	3	90	68
12	PS-DABCO	3	Water	2	100	62
13	PS-DABCO	3	Water	4	100	92

[a]Reaction condition: o-Aminothiophenol (**1**) (1 mmol) and benzaldehyde (**2a**) (1.0 mmol), solvent (5 mL). [b]Isolated yields.

Having optimized reaction conditions in hand, we explored the substrate scope of the PS-DABCO catalysed 2-arylbenzothiazolel synthesis reaction. Various substituted aldehydes containing different functional groups were investigated. Products containing electron-donating as well as electron withdrawing groups were obtained in good to excellent yield. More importantly, aryl aldehydes with bearing electron withdrawing groups as well as electron donating groups reacted efficiently and did not influenced considerably effect on the yields of corresponding desired products. Satisfyingly a variety of communal functional groups, such as alkyl, ether, halo and nitro were tolerated note with

Table 2. PS-DABCO catalyzed synthesis of 2-arylbenzothiazole[a]

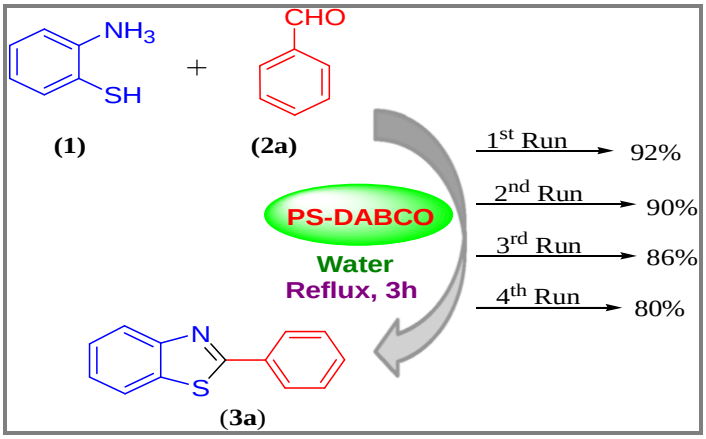


Entry	Aldehyde (-X)	Product	Yield[b] (%)	MP. (°C) (Obt.) [ref.]
1	-H	**3a**	92	114-116 (112-115) [20]
2	2-Cl	**3b**	86	78-80 (80-81) [20]
3	4-Cl	**3c**	92	114-116 (115-117) [20]
4	3,4-di-Cl	**3d**	90	152-154 (150-155) [7]
5	4- F	**3e**	92	104-106 (101-103) [20]
6	4- Me	**3f**	90	66-68 (62-66) [7]
7	4-OMe	**3g**	88	122-124 (121-123) [20]
8	3,4-di-OMe	**3h**	80	132-134 (132-133) [7]
9	4- CN	**3i**	84	122-124 (120-123) [7]
10	2-NO_2	**3j**	80	120-122
11	3-NO_2	**3k**	88	198-200 (200-203) [20]
12	4-NO_2	**3l**	88	230-230 (228-230) [20]
13	-CH=CH-Ph	**3m**	79	112-114

[a]Reaction condition: (1) (1.0 mmol), (2) (1.0 mmol), PS-DABCO (3 mol%), water (5 mL), reflux, 3h. [b]Isolated yields.

standing of the *meta*- or *para*-position, however *ortho*- substituted benzaldehyde gave lower yields, maybe due to steric hindrance. All the obtained results are summarized in table 2. Formation of desired product was confirmed with the help of FT-IR, PMR and mass spectroscopic data.

In terms of green chemistry principles, reusability of the catalyst is highly preferable. Hence the recyclability of the catalyst was studied taking PS-DABCO in the repeated experiments. In order to regenerate the catalyst, after the reaction it was separated from the reaction mixture by simple filtration and washed several times with deionized water and ethanol. Then it was dried at 100°C and reused for the further recycle reaction run. As shown in scheme 2**.** Therefore, the present catalyst is an interesting candidate for commercial exploitation and exhibited remarkable activity.



Scheme 2. Recyclability study of PS-DABCO catalyst.

APPLICATION

The present method was environmentally benign. The procedure offers advantages in terms of better yields, short reaction times, mild reaction conditions, and reusability of the catalyst. The easy separation, high thermal stability of catalyst and an environmentally benign procedure makes this methodology useful contribution to the existing procedures available for the synthesis of 2-aryl benzothiazolederivatives as a biologically and pharmaceutically relevant material.

CONCLUSION

We have developed a new eco-friendly procedure for the synthesis of 2-arylbenzothiazolevia condensation of aromatic aldehydes and o-aminothiaphenol using PS-DABCO as a polymer supported ionic liquid catalyst under aqueous solvent conditions. The wide variety of 2-arylbenzothiazolewere synthesized in good to excellent yields. The presented methodology includes an advantage such as simple procedure, excellent yields and easy separation of catalyst and its reusable behavior. This approach therefore represents a precious addition to the existing processes for the synthesis of 2-aryl benzothiazole.

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