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Tetrabutylammonium bromide (TBAB) in isopropanol: An efficient, novel, neutral and recyclable catalytic system for the synthesis of 2,4,5-trisubstituted imidazoles

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ABSTRACT

A simple, efficient and eco-friendly procedure has been developed using tetrabutylammonium bromide (TBAB, 10 mol%) as novel neutral ionic liquid catalyst for the synthesis of 2,4,5-triaryl imidazoles by a three-component, one-pot condensation of benzil, aryl aldehydes and ammonium acetate in refluxing isopropanol. The present methodology offers several advantages such as excellent yields, shorter reaction times (15–30 min) and environmentally benign milder reaction conditions; moreover, the catalyst in isopropanol solvent exhibited reusable activity.

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1. Introduction

Synthesis of imidazole ring system and its derivatives occupy an important place in the realm of natural and synthetic organic chemistry, because of their therapeutic and pharmacological properties [1,2]. They have emerged as an integral part of many biological systems [3,4] viz., histidine, histamine and biotin; an active backbone in existing drugs such as losartan, olmesartan, eprosartan [5] and trifenagrel [6]; agrochemical [7], fungicides, herbicides [8] and plant growth regulators [9] and large classes of imidazole derivatives are also used as ionic liquids [10,11]. In addition to these important applications imidazole derivatives are ideal scaffolds to make libraries of anti-inflammatory, anti-allergic and analgesic [12] drug like compounds and to generate inhibitors of P38 MAP kinase [13]. Thus, syntheses of this heterocyclic nucleus have rekindled our interest in obtaining trisubstituted imidazole. Various methods have been reported [14] for the synthesis of 2,4,5-trisubstituted imidazoles are by condensation of benzil, aldehyde and ammonium acetate. Preparation of 2,4,5-triphenyl imidazole **3a** (Lophine) [15] was first reported by Radziszewski [16] and simultaneously by Japp and Robinson [17] in 1882 and are synthesized by the reaction of benzil with aryl aldehyde in alcoholic ammonia solution. The procedure was later modified by Cook and Jones [18] by refluxing benzil with substituted aldehydes and ammonium acetate in glacial acetic acid. Recently, the synthesis of 2,4,5-trisubstituted imidazoles are carried out by condensation of benzil, aldehyde and ammonium acetate in the presence of acetic acid [6], some common Lewis acid catalysts (Table 1) like $Yb(OTf)_3$ [22], $NdCl_3$ [22], $LaCl_3$ [22], $FeCl_3$ [22], $AlCl_3$ [22], Al_2O_3 [27], $NiCl_2$ [37], $[HBim]BF_4$ [23] and molecular iodine [36]. Although these methods were derived from the early success [19–24], the reaction suffered from low yields, harsh conditions, high temperature and side reactions leading to mixture of products. Additionally, reagents for these procedures are not readily or commercially available. A majority of theses procedures also involve microwave-assisted synthesis [25–29], apart from recently reported ionic liquids [23]. Moreover, the synthesis of these heterocyclic compounds have been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. Hence, the development of clean safe, effective, economical, high-yielding and mild environmental benign protocols is still desirable and is in demand (Scheme 1).

Recently tetrabutylammonium bromide (TBAB) has immerged as an extremely useful homogeneous catalyst in various organic transformations [30], including conjugate addition of thiols to electron deficient alkenes [31], transthioacetalisation of acetals [32], trimethylsilylation of alcohols [33] and in the synthesis of aryl-14*H*-dibenzo[*a*,*j*]xanthenes [38]. TBAB is an inexpensive readily

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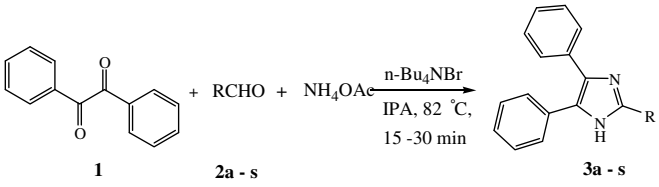
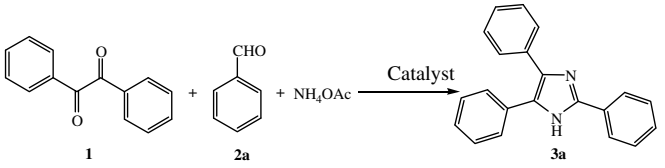
Table 1
Synthesis of 2,4,5-triphenyl imidazole **3a** using different catalysts and reaction conditions

Entry	Catalyst	Amount of catalyst (mol%)	Solvent	Temp. (°C)	Time (min)	Yield (%)	Ref.
1	AcOH	–	AcOH	70	120	42	[22]
2	AcOH	–	AcOH	180/MW	20	88	[6]
3	$Yb(OTf)_3$	5	AcOH	70	120	95	[22]
4	$AlCl_3$	20	AcOH	70	240	60	[22]
5	$FeCl_3$	20	AcOH	70	240	45	[22]
6	$NdCl_3$	25	AcOH	70	180	82	[22]
7	$LaCl_3$	15	AcOH	70	180	78	[22]
8	$NiCl_2$	–	Ethanol	Reflux	25	94	[37]
9	Al2O3	–	CH_2Cl_2	130/MW	20	78	[27]
10	I_2	5	–	75	25	99	[36]
11	$[Hbim]BF_4$		$[Hbim]BF_4$	100	60	95	[23]
12	No catalyst	–	Isopropanol	82	120	14	–
13	$SnCl_2 \cdot 2H_2O$	10	Isopropanol	82	120	35	–
14	IR-120 (H^+)	10	Isopropanol	82	120	38	–
15	Amberlist-H^+	10	Isopropanol	82	120	36	–
16	$NaHSO_4/SiO_2$	10	Isopropanol	82	120	41	–
17	TBAB	10	Solvent free	100	60	62	–
18	TBAB	10	Isopropanol	82	20	95	–
19	TBAB	5	Isopropanol	82	20	86	–
20	TBAB	2.5	Isopropanol	82	20	73	–
21	TBAB	10	Ethanol	80	20	70	–
22	TBAB	10	Methanol	65	20	65	–
23	TBAB	10	THF	65	20	56	–
24	TBAB	10	1,4-Dioxane	100	20	62	–
25	TBAB	10	Isopropanol	82	20	55	–



Scheme 1.



Scheme 2.

available ionic liquid with inherent properties like environmental compatibility, greater selectivity, operational simplicity, non-corrosive nature and ease of reusability. It is therefore of interest to examine the behavior of TBAB as catalyst in the synthesis of 2,4,5-trisubstituted imidazole derivatives. To the best of our knowledge, the generality and applicability of TBAB in the preparation of 2,4,5-trisubstituted imidazoles is not known. In continuation of our efforts towards synthesis of 2-(*n*-butyl)-5-chloro-3*H*-imidazole-4-carboxaldehyde [34], an intermediate for the preparation of an anti-hypertensive drug, losartan-K, and development of new methodologies in organic synthesis [35]. We herein describe a new efficient and practical route for the one-pot three-component synthesis of trisubstituted imidazoles **3a**–**s** by the condensation of benzil 1, aryl aldehyde **2a**–**s** and ammonium acetate catalyzed by TBAB in refluxing isopropanol (Scheme 1).

2. Results and discussion

In order to evaluate the catalytic efficiency of TBAB catalyst and to determine the most appropriate reaction conditions; initially a model study was carried out on the synthesis of Lophine **3a** (Scheme 2) by the condensation of benzil, benzaldehyde and ammonium acetate in different sets of reaction conditions (Scheme 2, Table 1).

Among the tested solvents such as methanol, ethanol, isopropanol, tetrahydrofuran, 1,4-dioxane, solvent free conditions and various catalysts ($SnCl_2 \cdot 2H_2O$, IR-120-H^+, Amberlist-H^+, $NaHSO_4/SiO_2$, TBAB), the condensation of benzil, benzaldehyde and ammonium acetate was best catalyzed by 10 mol% of TBAB in IPA at reflux temperature (Table 1, entry 13–18). It is also found to be novel, one-pot combination and exclusively gave 2,4,5-triphenyl imidazole **3a** in 95% in 20 min (Table 1, entry 18). Formation of bi-products like *N*-desylbenzamide or 2,4,5-triphenyloxazole was not observed [1]. In order to improve the yields, we performed reaction using different quantities of reagents. The best results were obtained with 0.1:1:1:10 ratios of TBAB, benzil, aryl aldehyde and ammonium acetate, respectively.

In a typical general experimental procedure a mixture of benzil, aryl aldehyde and ammonium acetate in the presence of catalytic amount of TBAB was refluxed in isopropanol for appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to 10 °C and precipitated solid was filtered to give analytically pure 2,4,5-trisubstituted imidazoles in good to excellent yields. Moreover, the catalyst and solvent could be quantitatively recovered from the reaction mixture (filtrate) and reused for successive reactions. For example the catalyst containing filtrate was reused in case of 2-(3,4,5-trimethoxyphenyl)-4,5-diphenylimidazole (**3g**) for 10 times without appreciable loss of activity (Table 3). To study the generality of this process several examples illustrating this novel and practical general method for the synthesis of 2,4,5-trisubstituted imidazoles were studied and are summarized in Table 2.

In order to introduce pharmacologically relevant substitution patterns; several diversified examples illustrating the present method for the synthesis of 2,4,5-trisubstituted imidazoles 3 was studied. An increase in the rate of reaction was observed with aldehyde bearing electron donating groups (Table 2, entries 2, 7 and 12) in comparison to the unsubstituted aldehyde (Table 2, entry

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