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Sodium Bisulfite as an Efficient and Inexpensive Catalyst for the One-pot Synthesis of 2,4,5-Triaryl-1*H*-imidazoles from Benzil or Benzoin and Aromatic Aldehydes

Jaiprakash N. Sangshetti[1], **Nagnnath D. Kokare**[1,2], **Sandeep A. Kotharkar**[1], and **Devanand B. Shinde**[1,*]

[1] Department of Chemical Technology, Dr. *Babasaheb Ambedkar* Marathwada University, Aurangabad, India
[2] New Drug Discovery, Wockhardt Research Centre, Aurangabad, India

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Summary. 2,4,5-Triaryl-1*H*-imidazoles were efficiently synthesized from benzoin or benzil, ammonium acetate, and aromatic or heteroaromatic aldehydes in the presence of sodium bisulfite as catalyst. The present protocol offers significant improvements for the synthesis of 2,4,5-triaryl-1*H*-imidazoles with regard to yield of products, simplicity in operation, and cheap catalyst.

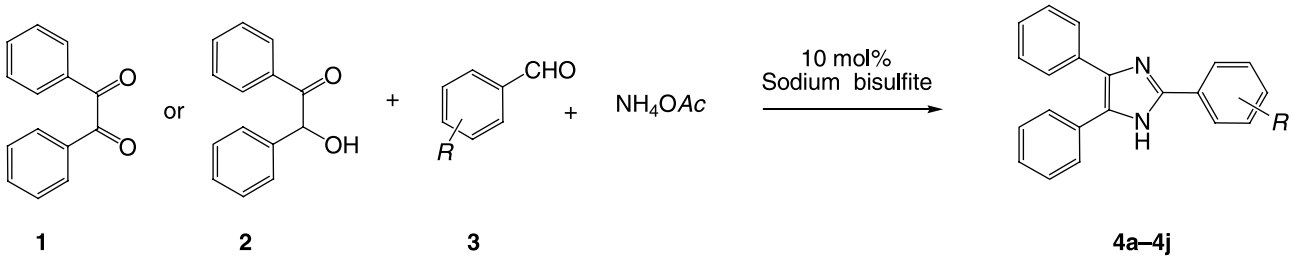
Keywords. Triaryl-1*H*-imidazoles; Sodium bisulfite; Benzoin; Benzil; Ammonium acetate.

Introduction

Over the century, imidazoles have received significant attention due to their reactions and biochemical properties. Even today, research in imidazole chemistry continues. Compounds with an imidazole moiety have biological and pharmaceutical importance [1]. Several substituted imidazoles are known as inhibitors of P 38 kinase [2]. Eprosartan is one of the series of 1-(carboxybenzyl)imdazole-5-acrylic acids, which is a potent and selective angiotensin II receptor antagonist [3]. Highly substituted imidazoles like lepidilines A and B [4] exhibit micromolar cytotoxicity against several human cancer cell lines. Trifenagrel [5] is a potent 2,4,5-triarylimidazole that reduces platelet aggregation in several animal species and humans. In recent years, substituted imidazoles are substantially used in ionic liquids [6] that have been given a new approach to 'Green Chemistry'. The imidazole compounds are also used in photography as photosensitive compound [7].

In literature several methods for synthesizing them are reported, mainly using nitriles and esters [8, 9] as the starting substrates. *Japp* and *Radziszewski* proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes, and ammonia, to obtain 2,4,5-triphenylimidazoles [10, 11]. Subsequently, many other syntheses of this important heterocycle have been published [12]. For example, 2,4-diaryl-1*H*-imidazoles are often obtained from amidines and α-bromoarylketones [13]. Moreover, *Zhang* and *Chen* described an efficient procedure to obtain unsymmetrical, C5 unsubstituted 2,4-diarylimidazoles. In this approach acetophenones are oxidized *in situ* to α-(tosyloxy)-acetophenones, which then condense with arylamidines to obtain the desired compounds [14]. Recently, some methods for synthesis of substituted imidazoles have been reported [15, 16]. However, some of these methods suffer from one or more drawbacks like high temperature requirement, highly acidic conditions, and the use of metal cyanides for preparation of the nitrile compounds that limit their uses

* Corresponding author. E-mail: dbshinde.2007@rediffmail.com



Scheme 1

[17, 18]. Some of the methods have resorted to harsh conditions (*e.g.*, the formamide synthesis, which requires excess reagents, H_2SO_4 as a condensing agent, 150–200°C, 4–6 h resulting in yields of 40–90%) [19–21]. Therefore, the development of a mild, efficient, and versatile method is still strongly desirable.

In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds [22], herein we wish to report a simple, economic, and efficient one-pot method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzoin or benzil, ammonium acetate, and aromatic aldehydes using sodium bisulfite as the catalyst.

Results and Discussion

Initially, we studied the catalytic efficiency of sodium bisulfite for the synthesis of 2,4,5-triphenyl-1*H*-imidazole (**4a**) using benzil, ammonium acetate, and benzaldehyde in different solvents and various mol% of sodium bisulfite (Scheme 1). The title compound **4a** was isolated with 98% yield using optimized reaction conditions (Table 1), ethanol:water (1:1) as solvent, and 10 mol% sodium bisulfite as catalyst. Using the standardized reaction conditions, a range of 2-aryl-4,5-diphenylimidazoles were synthesized. The same methodology was extended for the synthesis of 2-heteroaryl-4,5-diphenylimidazoles using hetero-aromatic aldehydes. The results are summarized in Table 2.

Table 1. Optimization of reaction conditions for synthesis of 2,4,5-triphenyl-1*H*-imidazole using 10 mol% sodium bisulfite as catalyst

Solvent	Reaction time/min	Yield/%
Acetonitrile	45	93
THF	50	79
Ethanol	30	98
THF/water (1/1)	50	78
Acetonitrile/water (1/1)	50	89
Ethanol/water (1/1)	30	98

1,2-Diketones (like benzil) are usually prepared from the α-hydroxy ketones (like benzoin) catalyzed by various oxidants. Some of these catalysts are toxic, costly, and also require tedious experimental procedures [23]. To avoid the preparation of starting

Table 2. Synthesis 2,4,5-triaryl-1*H*-imidazoles using benzil or benzoin, ammonium acetate, aromatic aldehydes, and 10 mol% sodium bisulfite

Product	Aldehyde	Rection time/min		Yield/%		mp/°C	
		Benzil	Benzoin	Benzil	Benzoin	Found	Reported [Ref.]
4a	benzaldehyde	30	40	98	96	277–279	276–77 [9]
4b	4-methylbenzaldehyde	35	50	98	95	231–233	231–232 [9]
4c	4-methoxybenzaldehyde	30	40	96	93	229–231	227–228 [9]
4d	4-hydroxybenzaldehyde	35	50	95	92	268–270	268–269 [24]
4e	2-chlorobenzaldehyde	30	30	92	90	195–196	197–198 [24]
4f	4-(dimethylamino)benzaldehyde	30	40	95	90	255–258	257–258 [9]
4g	4-chlorobenzaldehyde	30	40	98	94	259–262	261–263 [9]
4h	4-nitrobenzaldehyde	40	60	90	85	232–233	236–238 [9]
4i	3,4-dimethoxybenzaldehyde	30	50	96	92	220–221	216–218 [25]
4j	furan-2-carbaldehyde	30	40	95	92	199–201	202–203 [25]

material 1,2-diketones like benzil, the synthesis of **4a** was studied using benzoin. Surprisingly, using similar reaction conditions, **4a** was isolated in 96% yield. Encouraged by this result, we extended the methodology for the synthesis of various 2,4,5-triaryl-1*H*-imidazoles using benzoin and various aromatic aldehydes. The yields obtained were in the range of 85–96%.

In conclusion, using 10 mol% sodium bisulfite as catalyst, 2,4,5-triaryl-1*H*-imidazoles were efficiently synthesized with better yields from benzil and even as well as benzoin. For all the presented reactions, the ethanol–water solvent was used, which is relatively environmentally benign.

Experimental

^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as ppm downfield from internal standard *TMS*. Mass spectra were taken with Micromass-QUATTRO-II of WATERS mass spectrometer. Melting points were determined in capillary tubes.

General Method for the Synthesis of 2,4,5-Triaryl-1H-imidazoles

A mixture of 0.104 g sodium bisulfite (10 mol%), 2.8 g ammonium acetate (40 mmol), and 10 mmol benzil or benzoin was dissolved in 20 cm^3 ethanol/water (1/1, *v*/*v*) and to this mixture, 12 mmol aromatic aldehyde were added. Then, the reaction mixture was heated at 80°C till completion of reaction (TLC). The reaction mixture was cooled to room temperature and poured on 50 cm^3 ice-water to get the solid precipitated. It was collected by filtration, washed with water, and dried to give the corresponding 2,4,5-triaryl-1*H*-imidazoles.

All synthesized compounds were characterized with ^{1}H NMR and mass. Also the melting points recorded were compared with the corresponding literature melting points and found to be matching.

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