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Ceric ammonium nitrate catalysed three component one-pot efficient synthesis of 2,4,5-triaryl-1H-imidazoles

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Abstract. Ceric ammonium nitrate (CAN) is used as an efficient catalyst for the synthesis of 2,4,5-triaryl-1H-imidazoles via condensation of benzoin/benzil, ammonium acetate, and aromatic aldehydes. The easy work-up, higher yields and shorter reaction time are the advantages of the method presented here.

Keywords. Ceric ammonium nitrate; triarylimidazoles; benzoin; benzil; ammonium acetate; aromatic aldehydes.

1. Introduction

Interest in imidazole-containing structures stems from their widespread biological activities and their use in synthetic chemistry. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds.[1–5] In recent years, substituted imidazoles are substantially used in ionic liquids,[6] that has been given a new approach to 'Green Chemistry'. Triarylimidazole derivatives have many biological activities, for example, herbicidal,[7] fungicidal,[8] antiinflammatory,[9] and antithrombotic activities.[10] In addition, they are used in photography as photosensitive compound.[11] Literature survey reveals that there are several methods for synthesizing them, mainly using nitriles and esters[12–14] as the starting materials. The first synthesis of the imidazole core 2,4,5-triphenylimidazoles using 1,2-dicarbonyl compounds aldehydes and ammonia, was proposed by Japp and Radziszewski.[15,16] Subsequently, many other methods for synthesis of this important heterocycle have been published.[17–18] Recently some methods for synthesis of tetra-substituted imidazoles are reported.[19] However, some of these previous methods have suffered 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 utility.[20,21] Some 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, 40–90%).[22–24] For this reason, the development of mild, efficient and versatile method is still important.

Ceric (IV) ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a wide array of synthetic transformations due to its many advantages such as solubility in organic solvents, low toxicity, high reactivity, and ease of handling. Although Ce (IV) derivatives are generally employed as one electron oxidants, the use of CAN as lewis acid in C–C bond forming reaction has attracted great deal of attention.[25] In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds[26] here, we present a simple, mild and efficient protocol for synthesis of 2,4,5-triaryl-1H-imidazoles using CAN catalyst.

2. Experimental

^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsi-

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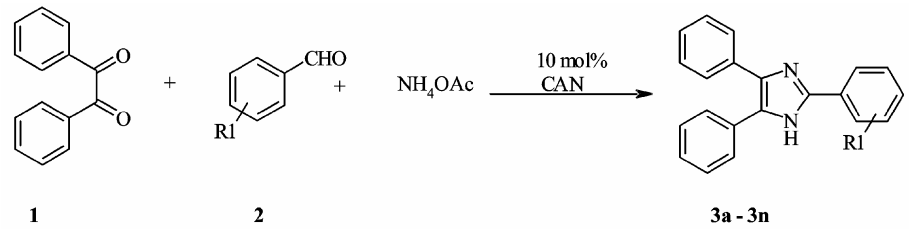
lane internal standard. The following abbreviations are used; singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), multiplate (*m*) and broad (*br*). Mass spectra were taken with Micromass – QUATTRO-II of WATER mass spectrometer. HPLC was performed using Zorbax SB-C18 reverse phase column (0·46 × 25 cm) on Shimadzu instrument equipped with an automatic injector with UV-PDA detector. Detection was carried out at 254 nm. The mobile phase consists of 0·05% TFA and acetonitrile (1 : 1, v/v). The products were eluted at flow rate of 1 ml/min using isocratic method. Flash column chromatography was performed with 300 and 400 meshes silica gel and analytical thin layer chromatography was performed on pre-coated silica gel plates (60F-254) with system (v/v) indicated. Melting points were determined in capillary tubes and are uncorrected.

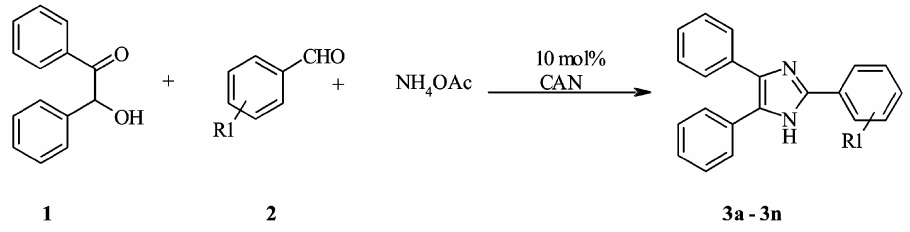
2.1 *Typical procedure*

A mixture of ceric ammonium nitrate (10 mol%), ammonium acetate (40 mmol), and benzil or benzoin (10 mmol) was dissolved in ethanol-water (20 ml, 1 : 1, v/v) and to the reaction mixture, aromatic aldehyde (12 mmol) was added. Then, the reaction mixture was heated at 65°C till completion of reaction as indicated by TLC. The reaction mixture was cooled to room temperature and poured on ice-water (50 ml) to get the precipitated solid. It was collected by filtration, washed with water and dried to give the corresponding 2,4,5-triaryl-1H-imidazoles.

All synthesized compounds were characterized with ^{1}H NMR and mass. Also the melting points recorded and compared with the corresponding literature m.p. and found to be matching with those. The representative analytical data for 2,4,5-triphenyl-1H-



Scheme 1. Synthesis of 2,4,5-triarylimidazoles using benzil, aromatic aldehydes, ammonium acetate and 10 mol% CAN catalyst.



Scheme 2. Synthesis of 2,4,5-triarylimidazoles using benzoin, aromatic aldehydes, ammonium acetate and 10 mol% Cerric ammonium nitrate catalyst.

Table 1. Optimization of reaction conditions and mol% of CAN for the synthesis of 2,4,5-triphenyl-1H-imidazole (**3a**).

Solvent	Mol% CAN	Reaction time (min)	Yield (%)
Acetonitrile	20	70	75
Ethanol	20	50	98
Acetonitrile-water (1 : 1)	20	70	75
Ethanol-water (1 : 1)	20	50	98
Ethanol-water (1 : 1)	15	50	98
Ethanol-water (1 : 1)	10	50	98
Ethanol-water (1 : 1)	5	70	87
Ethanol-water (1 : 1)	2·5	90	80

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

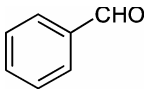
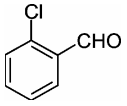
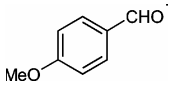
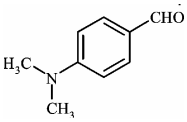
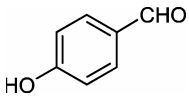
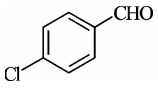
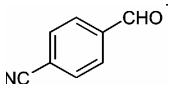
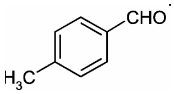
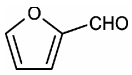
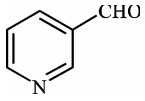
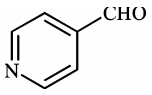
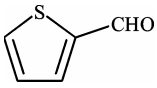
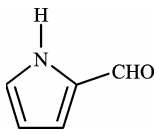
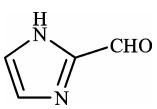
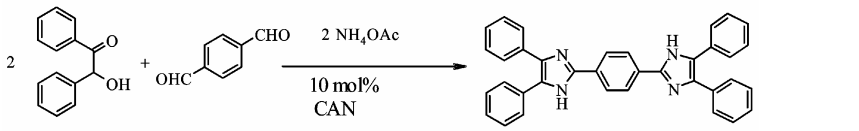
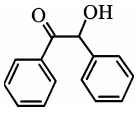
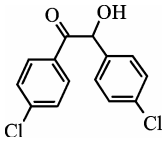
			Reaction time (min)		Yield (%) (Literature yield)[29]	
Entry	Product	Ar-CHO	Benzil	Benzoin	Benzil	Benzoin
1	**3a**		50	70	98 (97)	90 (88)
2	**3b**		50	80	96 (93)	85 (85)
3	**3c**		50	70	96 (86)	87 (81)
4	**3d**		70	110	85 (86)	65 (70)
5	**3e**		60	70	95 (93)	90 (91)
6	**3f**		50	70	95 (93)	85 (76)
7	**3g**		60	70	95 (95)	86 (88)
8	**3h**		50	70	98 (92)	88 (84)
9	**3i**		50	70	98 (98)	90 (93)
10	**3j**		50	80	98 (95)	90 (91)
11	**3k**		50	70	95 (94)	85 (84)
12	**3l**		50	70	94 (94)	80 (85)
13	**3m**		50	70	95 (92)	84 (80)
14	**3n**		50	70	90 (88)	80 (76)

Table 3. Synthesis of *bis*-2,4,5-triaryl-1H-imidazoles using benzil or benzoin, ammonium acetate, benzene-1,4-dicarboxaldehyde and 10 mol% CAN.



Entry	Product	Benzoin/Benzil	Reaction time (min)	Yield (%)
1	**3o**		80	82
2	**3p**		90	89

imidazole (**3a**): Off-white solid, m.p. 276–277°C; HPLC purity – 98·5%; ^{1}H NMR (400 MHz, DMSO): δ = 7·51–7·64 (*m*, 6H), 7·67–7·73 (*m*, 3H), 7·85–7·90 (*m*, 6H), 8·9 (*bs*, 1H); MS (EI, 70 eV): *m/z* = 296 $[M + H]^+$.

2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (**3f**): Off-white solid, m.p. 196–198°C; HPLC purity – 97·0% ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7·4–7·60 (*m*, 6H), 7·67–7·70 (*m*, 2H), 7·93–8·0 (*m*, 6H), 8·71 (*bs*, 1H); MS (EI, 70 eV): *m/z* = 330 $[M + H]^+$.

1,4-di[4,5-di (4-chloro phenyl) imidazol-yl] benzene (**3p**) m.p. 232–233°C; HPLC purity – 97·5% ^{1}H NMR (400 MHz, DMSO): δ = 7·6 (*d*, *J* = 8·39 Hz, 8H), 7·37 (*d*, *J* = 8·43 Hz, 8H), 7·56 (*s*, 4H), 7·67 (*m*, 2H); MS (EI, 70 eV): *m/z* = 515 $[M + H]^+$.

3. Results and discussion

Initially, to study the catalytic efficiency of CAN, and to establish optimum quantity of CAN, synthesis of 2,4,5-triphenyl-1H-imidazole (**3a**) was carried out using benzil, ammonium acetate and benzaldehyde in different solvents and various mol% of CAN (scheme 1). The title compound **3a** was isolated with 98% yield using optimized reaction conditions (table 1), (ethanol-water (1 : 1) solvent and 10 mol% CAN catalyst). Using the standardized reaction conditions, a range of 2-aryl-4,5-diphenylimidazoles were synthesized and the results were summarized in table 2. The method was found to be effective for heteroaromatic aldehydes for the synthesis 2-heteroaryl-4,5-diphenylimidazoles with better yields (**3i**–**3n**). The easy work-up is advantageous aspect of this method, which includes the pouring of the reaction mixture over ice-water to get the precipitated solid which on filteration gave the sufficiently pure compound in good yield. The present method is superior to the available methods with regard to yields and reaction time.[14] Especially, for the preparation of 4-methylphenyl-2,4-diphenylimidazole (**3h**) was synthesized in 98% while the reported yield was 74% and also 2-chlorophnyl-2,4-diphenylimidazole (**3b**) was synthesized in 96% while the reported yield was 85%.[27]

1,2-diketones (like benzil) are usually prepared from the α-hydroxy ketones (like benzoin) catalysed by various oxidants. Some of these catalysts are toxic, costly and also required the tedious experimental procedures.[28] To avoid the preparation of starting material 1,2-diketones like benzil, the synthesis of 2,4,5-triphenyl-1H-imidazole was studied using benzoin (scheme 2). Surprisingly, using the similar reaction conditions, 2,4,5-triphenyl-1H-imidazole was isolated in 90% yield. Encouraged by this result, we extended the methodology for synthesis of various 2,4,5-triaryl-1H-imidazoles using benzoin and various aromatic aldehydes. The yields obtained were in the range of 65% to 90%.

Also same methodology was extended for the synthesis of the substituted 1,4-di(4,5-diphenylimidazolyl) benzene (**3o–3p**) in the similar reaction conditions using benzoin, benzene 1,4 di-carboxaldehyde, ammonium acetate, and 10 mol% CAN (table 3).

In conclusion we have presented use of CAN as a catalyst for efficient synthesis of 2,4,5-triaryl-1H-imidazoles with moderate to excellent yields from

benzil as well as benzoin. For all the presented reactions, the ethanol-water solvent was used which is relatively environmentally benign and supporting to Green Chemistry. The advantages of the reported method are the use of cheap, mild, and easily available catalyst, easy work-up, and better yields.

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