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One-pot synthesis of 2,4,5- trisubstituted imidazoles using cupric chloride as a catalyst under solvent free conditions

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ABSTRACT

Three component condensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate under microwave irradiation in presence of cupric chloride ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$) as a catalyst give corresponding 2,4,5-trisubstituted imidazole's. The key advantages of this process are reaction proceeded smoothly and product obtained in excellent yield with high purity, cost effectiveness of catalyst, easy work-up.

Keywords: Benzil, 2, 4, 5-Trisubstituted imidazoles, Multicomponent reaction, CuCl_2 catalysts, microwave irradiation.

INTRODUCTION

Imidazole and their derivatives are unavoidable in the field of medicinal chemistry for their biologically active properties as they have been synthesized and evaluated for their potential as herbicides^[1], plant growth regulators^[2], antibacterial^[3], antitumor^[4] and therapeutic agents^[5]. They have been widely used as dye/fluorescent materials^[6] and Inhibitor of transforming Growth Factor β 1 type 1 activin receptor-like kinase^[7] and biosynthesis of interleukin-1. In recent years, several methods are reported for the preparation of 2, 4, 5-Trisubstituted imidazole such as cyclo-condensation between aromatic aldehydes, 1, 2-dicarbonyl compounds and ammonium acetate using different catalysts such as zeolite HY/silica gel^[8], ionic liquid^[9], iodine^[10], sodium bisulfite^[11], ZrCl_4 ^[12], $\text{Yb}(\text{OTf})_3$ ^[13]. Some other methods are synthesis of imidazoles from 1,2-diketone and aldehyde in presence of variety of catalysts by using microwave irradiation have been reported including MW/Silica-gel^[14], glyoxylic acid^[15], $\text{InCl}_3 \cdot 3\text{HO}_2$ ^[16]

Microwave technology offers a new and environmentally benign approach toward modern synthetic chemistry. Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformations in minutes, instead of hours or even days. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. A growing number of investigators are adopting microwave-assisted synthesis as a means to increase their productivity.

We report here a simple and efficient method for the synthesis of the 2,4,5-trisubstituted imidazoles using cupric chloride as catalyst that considered as efficient and readily available catalyst. The procedure reported herein is simple and the methodology represents a good addition to the list of methods available for the synthesis of 2, 4, 5-trisubstituted imidazoles.

MATERIALS AND METHODS

The chemicals used Benzaldehyde, Benzil, and Ammonium acetate were of analytical reagent grade. Methods used for synthesis of 2,4,5-trisubstituted imidazoles and their derivatives are conventional method and microwave method. Melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ¹H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in CDCl₃ as a solvent and chemical shift values are recorded in units δ (ppm) relative to TMS as an internal standard.

General procedure for preparation of 2a–j :

A mixture of aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (2.5 mmol) and cupric chloride (10 mol %) was taken in beaker (50 ml). The reaction mixture was mixed properly with the help of glass rod and exposed in a microwave oven at the power of 300 W and irradiated for a period of 15 min at a time. The progress of the reaction was followed by TLC (petroleum ether: ethyl acetate = 9:1 as eluent). After completion of the reaction, the reaction mixture was cooled to room temperature and poured in ice water, solid was filtered, washed with water and obtained the crude product. For further purification it was recrystallized from ethanol 96% to afford pure product. The experimental data, reaction time, yield and melting points of compounds were presented in **Table-1**.

Spectral data of selected compounds:**1,2,4,5-Triphenyl-1H-imidazole (3a):**

IR (KBr): 3390, 3120, 1621, 1601, 1510, 1506, 1480, 811, 735, 710 cm⁻¹. ¹H NMR 400 MHz (CDCl₃): δ 11.69 (s, 1H), 7.79–7.84 (m, 6H), 7.75–7.78 (m, 3H), 7.15–7.21 (m, 6H). LCMS: (M+1)=297.

2,2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (3d):

IR (KBr): 3409, 3032, 2912, 2856, 1642, 1614, 1592, 1502, 1470, 831 cm⁻¹. ¹H NMR 400 MHz (CDCl₃): δ 11.82 (s, 1H), 7.44 (m, 4H), 7.36 (d, 2H), 7.32–7.37 (m, 4H), 7.26–7.30 (d, 4H), 7.07–7.10 (m, 2H). LCMS: (M+1)=327.

3,2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (3e):

IR (KBr): 3411, 3035, 1648, 1621, 1590, 1502, 1465, 836 cm⁻¹. ¹H NMR 400 MHz (CDCl₃): δ 12.02 (s, 1H), 7.40–7.44 (m, 4H), 7.37 (d, 2H), 7.26–7.30 (m, 4H), 7.23–7.28 (m, 2H), 6.97–7.04 (d, 2H). LCMS: (M+1)=332.

4,2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (3h):

IR (KBr): 3405, 3091, 1615, 1602, 1596, 1590, 1522, 1521, 1467, 811, 735, 710 cm⁻¹. ¹H NMR 400 MHz (CDCl₃): δ 11.29 (s, 1H), 8.42 (d, 2H), 7.76 (d, 2H), 7.42–7.46 (m, 4H), 7.39–7.42 (m, 4H), 7.10–7.07 (m, 2H). LCMS: (M+1)=342.

RESULTS AND DISCUSSION

In view of the recent emphasis towards the development of new, selective and environmental friendly methodologies we have applied solvent-free and microwave conditions. As a part of continuation of our research effort to develop biologically active compounds^[17-19], herein we report an efficient method for the synthesis of 2,4,5-trisubstituted imidazoles by one pot condensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate under microwave irradiation in presence of cupric chloride (CuCl₂·2H₂O) as a catalyst (scheme-1). The reaction time, yield and melting points of 2,4,5-trisubstituted imidazoles has been shown in table-1.

In an initial experiment a mixture of 4-methoxybenzaldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2.5 mmol) was exposed in microwave oven in presence of cupric chloride (10 mol %) for 12 minutes. After the completion of reaction, the reaction mixture was cooled to room temperature and poured in ice water and the crude product was recrystallized from ethanol to afford 2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (entry-4, Table-1) in 92% yield.

With this result in hand, other substituted benzaldehydes have been reacted with benzil and ammonium acetate under similar experimental conditions and the results are listed in table-1. Benzaldehydes containing electron-donating groups (such as methoxy, hydroxy groups) or electron-withdrawing groups (such as nitro, halide) were employed and reacted well to give corresponding products in good to excellent yields. In all the cases, the reactions proceeded smoothly with 10 mol % of cupric chloride with respect to the total weight of all the reactants.

The structures of the products were confirmed from spectroscopic data and melting points found to be comparable with those of literature data.

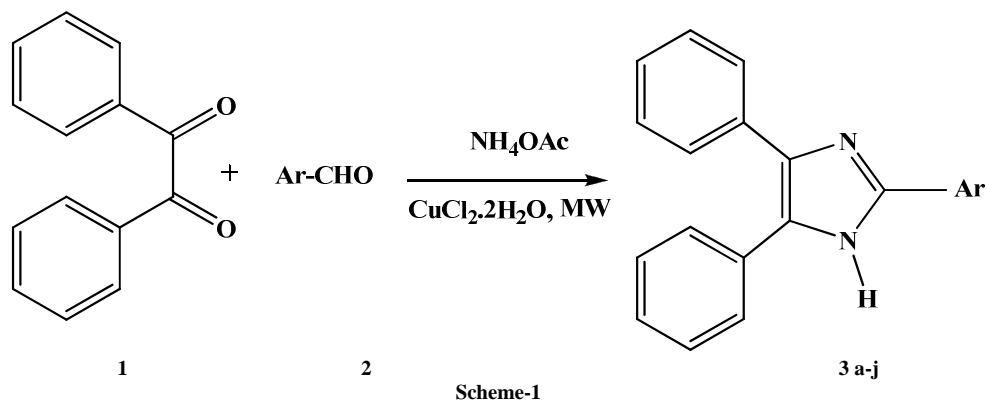
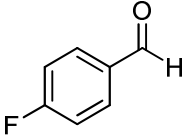
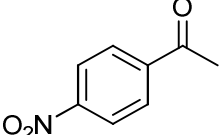
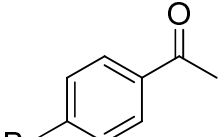
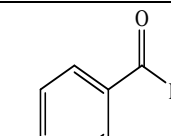


TABLE-1: Synthesis of 2,4,5-triaryl-1H-imidazoles (3a-j) using (10 mol%) cupric chloride under solvent-free conditions

Entry	Ar-CHO	Product	Microwave		Melting Point °C	
			Time(min)	Yield %	Obs	Lit
1		3a	13	87	276	276-277 ^[22]
2		3b	12	91	269	268-270 ^[21]
3		3c	13	88	230	230-231 ^[21]
4		3d	12	92	228	228-230 ^[20]
5		3e	14	90	261	260-262 ^[21]
6		3f	13	89	220	220-221 ^[20]

7		3g	13	87	190	190 ^[20]
8		3h	14	85	233	232-233 ^[21]
9		3i	14	91	210	261-263 ^[22]
10		3j	13	87	230	232-235 ^[22]

Reaction mechanism :

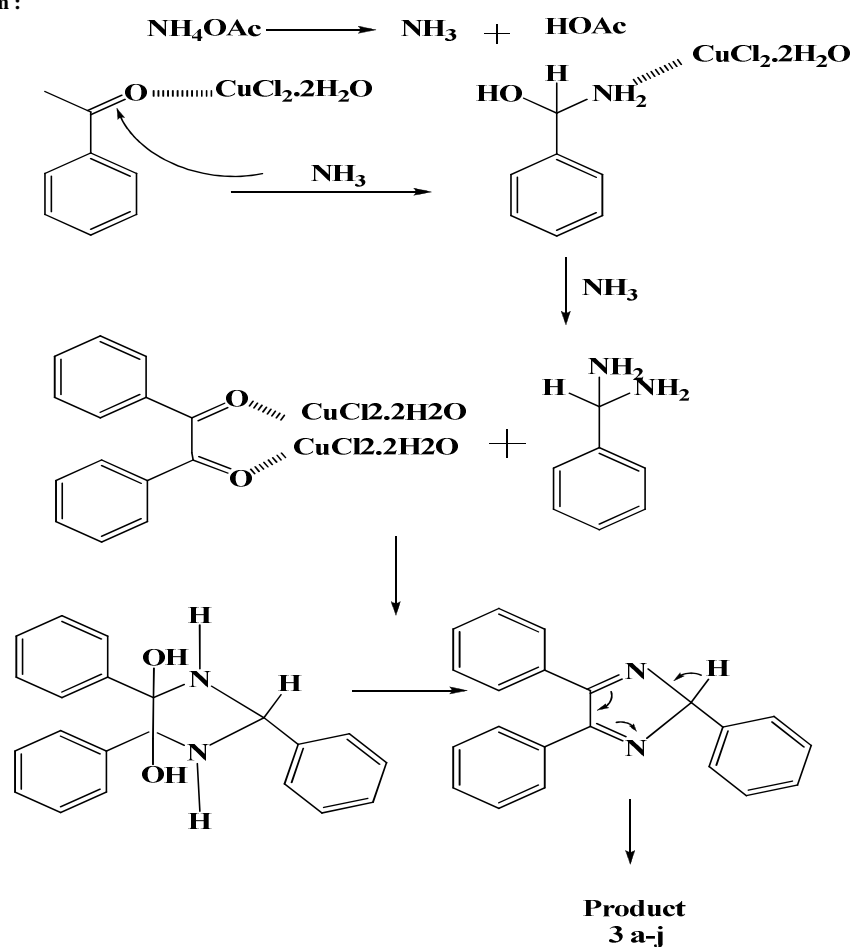


Fig-1: Mechanistic pathway for the formation of 2,4,5-trisubstituted imidazoles

CONCLUSION

We have shown an alternative method for the synthesis of 2,4,5-trisubstituted imidazoles using cupric chloride as catalyst. The reaction condition is nearly neutral and the reagent is readily available. Therefore, this novel method should find application in organic synthesis.

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