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AN ALTERNATIVE SYNTHETIC APPROACH TOWARDS 2, 4, 5-TRISUBSTITUTED-1H-IMIDAZOLES

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ABSTRACT: A simple and reliable synthetic method has been developed for 2, 4, 5-trisubstituted imidazoles by the condensation reaction between benzil, ammonium acetate, and various aromatic aldehyde in the presence of $ZrO(NO_3)_2$ catalyst under neat condition. The key advantages of this method are catalyst free, solvent free, purification of products by non-chromatographic methods, good yield and short reaction time.

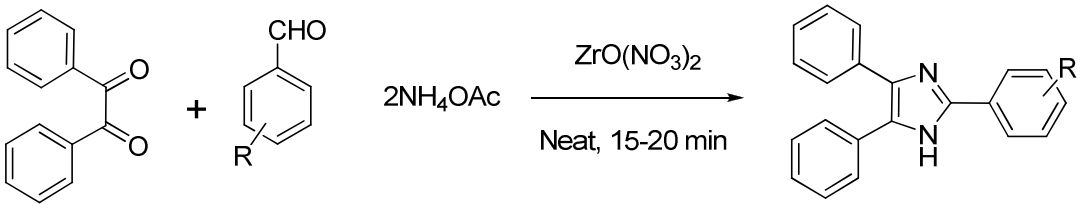
KEYWORDS: Benzil, 2, 4, 5-trisubstituted imidazole, Zirconylnitrite, neat condition

INTRODUCTION

The imidazole nucleus is a fertile source of biologically important heterocyclic molecules has many pharmacological properties and play important roles in biochemical processes[1]. Specifically the multi-substituted imidazole have received significant attention as a result of their diverse medicinal application such as therapeutic agent[2], herbicidal[3], antibacterial[4], antitumor[5], glucagon receptors[6].fungicididal[7], antithrombotic activitity[8], CB1cannabinoid receptor antagonists[9] and used in photography as photosensitive compound[10]. The synthesis of tri substituted imidazole by the condensation of aldehyde, benzil, ammonium acetate in acetic acid or phosphoric acid under reflux condition is a classical and well-established procedure. Recently some methods for synthesis of substituted imidazole has been reported by using various catalysts such as Al_2O_3, $ZrCl_4$[11], $NiCl_2.6H_2O$[12], Zeolite HY[13], $InCl_3.3H_2O$[14], DABCO[15], and PEG-400[16]. Each of the above methods has its own merits and some of the methods were plagued by the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution. Therefore, the development of simple and efficient method to overcome those disadvantages is still a challenge for organic chemists. Here in we described the synthesis of tri-substituted imidazolese in presence of $ZrO(NO_3)_2$ under neat condition.

RESULTS AND DISCUSSION

The benzil (one equivalent), substituted aldehyde (one equivalent) and ammonium acetate (two equivalent) involved in three component one-pot reaction produced corresponding 2, 4, 5-tri-substituted imidazole in the presence of $ZrO(NO_3)_2$ under solvent free condition (**Scheme-1**).



1 **2a-j** **3** **4a-j**

Scheme-1

The Structural features of synthesized compounds have been confirmed by the comparism of their Melting point, IR, ^{1}H-NMR and ^{13}C-NMR spectra with authentic sample reported in literature and physical data of compounds 4a-4j are given in **table-1**. To optimize the reaction conditions, we examined effects of different solvents (EtOH, CH_3CN and H_2O) in the presence of $ZrO(NO_3)_2$ on model reaction (Where R=H, Scheme-1) and the results are summarized in **Table-2**. We found that when the reaction was carried out at 100-110^{O}C in presence of $ZrO(NO_3)_2$ under solvent free condition provided good yield within 20 min. We also performed the model reaction in different mole % of $ZrO(NO_3)_2$ catalyst and observed that 15 mole% suitable to obtained maximum yield at neat condition (**Table-3**).

Table-1: physical and analytical data of 2,4,5-trisbstituted imidazoles 4a-4j

Entry	R (substituent)	Time (Min)	Yield (%)	M.p^{o}C (Obs/report[17])
1	H	10	87	270 (275)
2	2-OH	15	80	206(209)
3	4-OMe	15	75	222(226)
4	4-Me	20	60	225(230)
5	4-Cl	20	75	260(262)
6	4-NO_2	25	70	235(238)
7	2-OH, 4-OMe	30	82	222(226)
8	2-OMe, 3-OMe	30	72	222(226)
9.	3-NO_2	20	74	262 (268)
10	3-OH, 4-OH	20	70	268 (272)

Table-2: Synthesis of 2,4,5-trisubstituted imidazole in presence of 15 mol% $ZrO(NO_3)_2$ at different solvent medium.

Entry	Solvents	Time (min)	Yield (%)
1	Ethanol	30	70
2	Water	30	70
3	Acetonitrile	30	64
4	Without solvent	10	87

Table-3: Synthesis of **4a** in the presence of various mol% of $ZrO(NO_3)_2$ at neat condition.

Entry	Catalyst (mol %)	Time (min)	Yield (%)
1	5	20	70
2	10	15	72
3	15	10	87
4	20	20	80
5	25	20	80

EXPERIMENTAL

The chemicals were used without any further purification and the melting points were determined in capillary tubes which are uncorrected. The IR spectra were recorded using KBr pellet with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance ultra shield spectrometer where DMSO-d^6 used as solvent and TMS as standard.

General procedure for 2, 4, 5-trisubstituted imidazole 4a-4j

A mixture of aromatic aldehyde (5mmol), benzil (5 mmol), ammonium acetate (10mmol) were stirred at 100-110^{O}C in solvent free condition with 15 mol% $ZrO(NO_3)_2$. The progress of reaction was monitored by TLC where 7:3 hexane and ethyl acetate used as eluents. After completion of reaction, the mixture was cooled to room temperature and was dissolved in cold water. The formed solid was filtered, dried and was purified by crystallization from hexane and ethyl acetate (6:4) mixture.

CONCLUSION

We developed simple and efficient method for 2,4,5-trisubstituted imidazole promoted by $ZrO(NO_3)_2$ in solvent free condition. The operationally simple, readily available and good yield with short time are salient features of our method.

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