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COMPARATIVE STUDY OF SYNTHESIS OF 2, 4, 5-TRIARYL SUBSTITUTED IMIDAZOLES UNDER SOLVENT FREE CONDITIONS USING DIFFERENT LEWIS ACIDS AS CATALYSTS

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ABSTRACT

A range of 2, 4, 5-triaryl substituted imidazoles have been synthesized in very good yields under solvent-free conditions by grinding 1, 2-diketone, aromatic aldehydes and ammonium acetate in the presence of I_2, NaH_2PO_4 and $SnCl_2.2H_20$ as catalysts. Optimization of reaction conditions were carried out using different amount of catalysts. 10 mol% catalysts were found to be sufficient catalyze the reaction with high yield. Rate of synthesis of imidazoles and yield of the products were found to be directly proportional to the acidity of Lewis acid catalysts. The short reaction time, green reaction, and simple operation make this protocol practical and economically attractive. Effectiveness of catalysts was found to be of the order of $SnCl_2.2H_2O>NaH_2PO_4>I_2$.

KEY WORDS: Triaryl imidazoles, Lewis acids, catalysts, solvent free.

INTRODUCTION

The chemistry of the heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. The variety of heterocyclic compounds is enormous, their chemistry is complex and synthesizing them requires great skill. Heterocyclic systems are encountered in many groups of organic compounds possessing great applicability in industry as well as in our life in various ways. Heterocyclic compounds have a great applicability as drugs because they have a specific chemical reactivity and resemble essential metabolism and can provide false synthons in biosynthetic process.

Imidazoles are heterocycles with a wide range of applications and are receiving growing attention.[1 - 2] The imidazole ring system is of particular interest because it is a component of histidine and its decarboxylation metabolite histamine.[3] To design and conduct chemical reaction with "green" experimental protocol is an enormous challenge that chemists have to confront to improve the quality of the environment for present and future generations. Many articles about solid-state reactions with grinding have been reported, such as the Grignard reaction[4], Aldol Condensations[5] and other reactions.[6-9] There are several methods reported in the literature for the synthesis of imidazoles using Zeolite HY/silica gel[10], $ZrCl_4$[11], $NiCl_2.6H_2O$[12], iodine[13], sodium bisulfite[14], Boric acid[15]; however these methods require prolonged reaction time and exotic reaction condition. In recent years, $SnCl_2.H_2O$[16], NaH_2PO_4[17] have gained special attention as a catalysts in organic synthesis because of many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature.

Multi-component condensations (MCCs) constitute an especially attractive synthesis strategy for rapid and efficient generation of molecules due to the fact that the products are formed in a single step and also the diversity could be achieved simply by varying the reacting components. Lewis acids have wide range of applications in carbonyl group chemistry. Lewis acids used to increase electron deficiency of carbonyl carbon and thus increase reactivity of carbonyl compounds. Herein, we explored simple green route and the feasibility and effectiveness of I_2, NaH_2PO_4 and $SnCl_2.2H_2O$ as catalysts in the synthesis of imidazole derivatives, in place of tedious, expensive and less effective methods. Comparative study of these catalysts were also been carried out.

MATERIALS AND METHODS

MATERIALS

Aldehydes used: Benzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde and salicylaldehyde.

1, 2-diketo compound used: Benzil

Other chemicals: Ammonium acetate, iodine crystals, sodium dihydrogen phosphate, stannous chloride, sodium thiosulphate, petroleum ether, ethyl acetate and ethanol.

Chemicals were purchased from S. D. Fine and Merck chemical companies.

METHODS

Optimization of reaction conditions

To optimize the reaction conditions, a mixture of benzaldehyde (1 mmol), benzil (1 mmol), NH_4OAc (2.5 mmol) were ground together in a mortar with a pestle at room temperature for appropriate time to its corresponding imidazole under solvent-free conditions with different amount of catalysts. This has given the idea of maximum amount of catalyst needed to obtain maximum yield. (Table 1)

General procedure of synthesis of imidazole derivatives

A mixture of benzaldehyde (1 mmol), benzil (1 mmol), NH_4OAc (2.5 mmol), and iodine (10 mol %) were ground together in a mortar with a pestle at room temperature for appropriate time (Table 2). After completion of reaction confirmed by TLC, the mixture was treated with aqueous $Na_2S_2O_3$ to furnish the crude products. The crude was further purified by column chromatography by using petroleum ether: ethyl acetate (9:1) eluent and recrystallized from ethanol. (Figure 1)

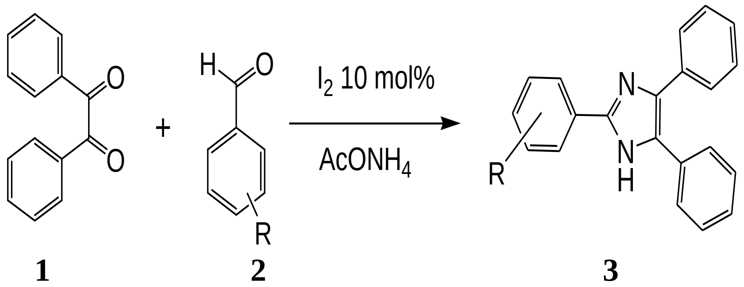

Figure -1: Synthetic Route of 2, 4, 5-triaryl substituted imidazole

Similar synthetic procedures of benzimidazoles were carried out with optimized amount of NaH_2PO_4 and $SnCl_2.2H_2O$ catalysts. Here treatment of $Na_2S_2O_3$ was not needed.

The characterization of products was done by IR and ^1H NMR spectra. IR Spectra: Instrument: BRUKER-FTIR- Spectrophotometer, Frequency range: 4000-400cm^{-1}, Sample technique: KBr disc. ^1H NMR Spectra: Instrument: BRUKER Spectrometer (300 MHz), Internal reference: TMS, Solvent: $CDCl_3$

RESULTS AND DISCUSSION

A rate enhancement with high yield was observed when higher molar ratios of iodine were used. However, no product formation was observed in absence of iodine. However, 10 mol% catalysts were sufficient to catalyze the reaction with high yield. (Table 1)

Reactions were carried out simply by mixing 1, 2-diketone with an aldehyde and ammonium acetate in the presence of a catalytic amount (10 mol%) of catalyst under solvent-free condition. The mixture was ground together in a mortar with a pestle at room temperature for appropriate time. 2, 4, 5 - triaryl substituted imidazole derivatives were obtained in excellent yields. (Table 2).

Table -1: Optimization of reaction condition using different catalyst

Entry	I_2 Catalyst			NaH_2PO_4 Catalyst			$SnCl_2.2H_2O$ Catalyst		
	I_2 (mol%)	Time (min)	Yield (%)	NaH_2PO_4 (mol%)	Time (min)	Yield (%)	$SnCl_2$ (mol%)	Time (min)	Yield (%)
1	0	60	0	0	60	0	0	60	0
3	2	50	17	2	40	19	2	30	25
3	5	30	81	5	15	81	5	10	81
4	10	15	87	10	7	92	10	4	94
5	15	10	88	15	7	92	15	4	94

This protocol is rapid and efficient for the preparation of several 2, 4, 5 - triaryl substituted imidazoles from both electrons efficient as well as electron deficient aromatic aldehydes. Electron-withdrawing groups enhance the rate of the reaction as compare to the electron-donating group. Physical data is given in Table 2.

Table - 2: Physical data of the products for different catalyst

Product	R	I_2 Catalyst		NaH_2PO_4 Catalyst		$SnCl_2.2H_2O$ Catalyst		M.P. (^{o}C)	R_f
		Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)		
1	H	10	87	7	92	4	94	268	0.55
2	m-NO_2	15	81	10	87	6	92	195	0.45
3	p-NO_2	10	88	5	90	4	95	256	0.49
4	o -OH	10	90	7	92	4	95	208	0.47

The possible mechanism of this reaction with molecular iodine as a catalyst is shown in Figures 2 and 3.

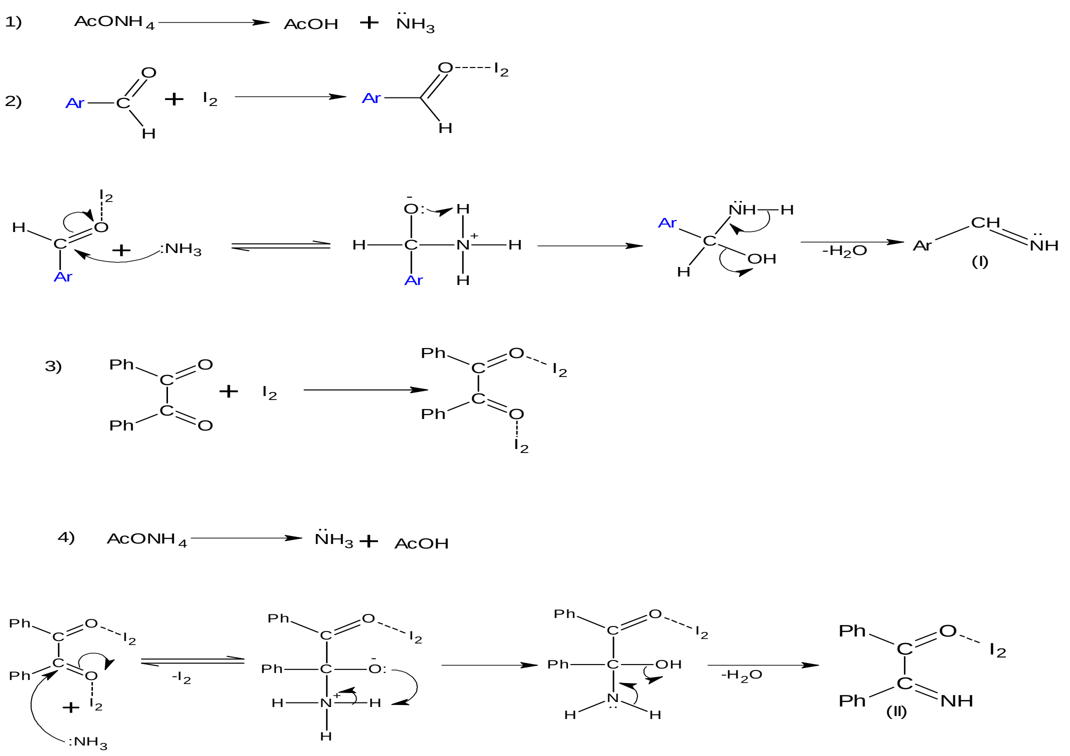

Figure - 2: Formation of intermediates (I) and (II).

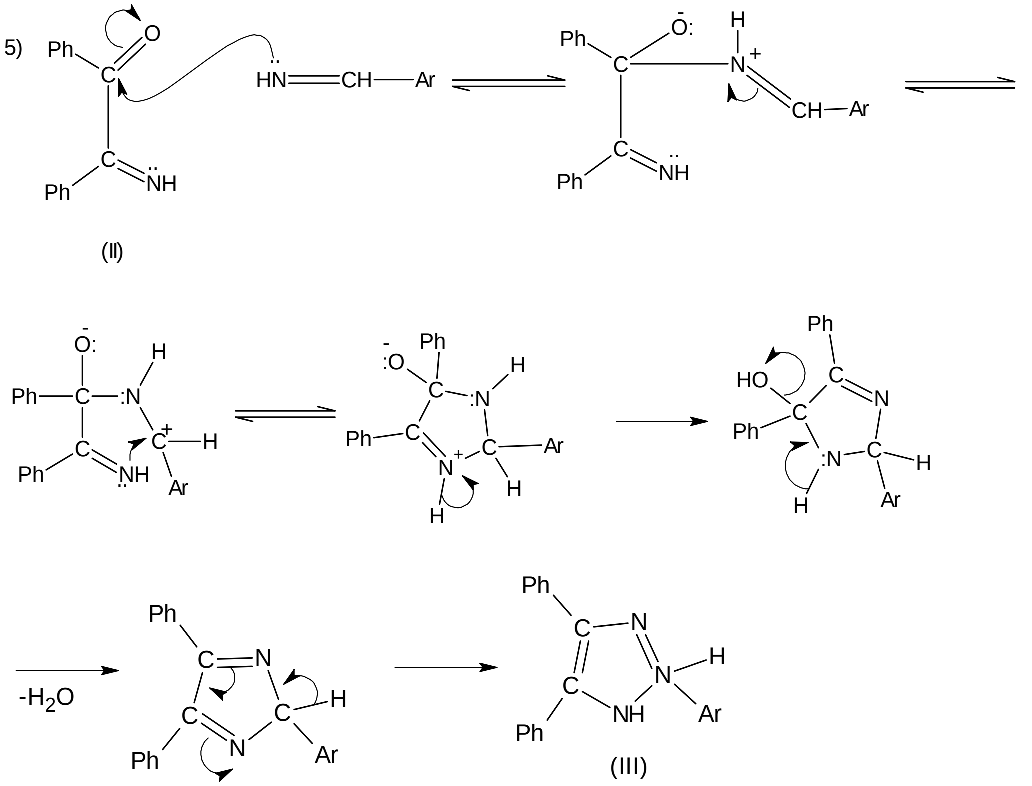

Figure -3: Cyclisation of intermediates into 2, 4, 5 - triaryl substituted imidazole (III).

The Lewis acidic nature of molecular I_2 catalyst makes it capable of binding with the carbonyl oxygen of aromatic aldehyde increasing the reactivity of the parent carbonyl compound and facilitates the formation of imines intermediate (I). Further catalyst iodine condenses with the carbonyl oxygen of the 1, 2-diketone, which on dehydration afford the intermediate (II). Intermediates I and II combine for the formation of intermediate, which on dehydration and further cyclisation gives 2, 4, 5 - triaryl substituted imidazoles (III).

Similar kinds of Lewis acidic character were shown by other catalyst use under study i.e. for NaH_2PO_4 and $SnCl_2.2H_2O$.

Aliphatic aldehyde and ketones were also used as starting carbonyl compounds for the same reaction. No product formation took place in this reaction by grinding the reagents for more than 30 minutes. The aryl groups substituted with different groups did not show any effect on the formation of imidazoles. The ortho and para substituents activate the aromatic ring of aldehydes and increase the rate of the reaction while meta substituents required somewhat greater time as compared to the o/p substituents.

The rate of reaction and the respective yield of the products are depends upon the Lewis acidity shown by the catalyst. It was observed that more the Lewis acidic character of catalyst faster the reaction and higher the yields obtained in such cases. Also Lewis acidic character increases the electron deficiency of carbonyl carbon to the greater extent and thus the attack of lone pair of electron of ammonia became faster.

Order of Lewis acidic character used under study is: $SnCl_2.2H_2O > NaH_2PO_4 > I_2$.
Thus rate of reaction and yield of products obtained for the catalyst is of the order of $SnCl_2.2H_2O > NaH_2PO_4 > I_2$.

All the above observations indicate the limited scope of this method, which is only applicable efficiently for aromatic aldehydes.

Spectral Studies of Products

2, 4, 5-Triphenyl-1H-imidazole (1)

IR (cm^{-1}): 1116, 1504, 1628, 3003, 3425; ^1H NMR ($CDCl_3$/ DMSO - d_6, 300 MHz): δ 10.24 (s, 1H), 7.22- 8.04 (m, 15H).

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

IR (cm^{-1}): 1118, 1498, 1560, 1626, 3022, 3418; ^1H NMR ($CDCl_3$/DMSO - d_6, 300 MHz): δ 11.04 (s, 1H), 8.90 (s, 1H), 8.50- 8.53 (d, J = 9 Hz, 1H), 8.25- 8.28 (d, J = 9 Hz, 1H), 7.75-7.78 (t, 1H), 7.30-7.65 (m, 10H).

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

IR (cm^{-1}): 790, 1111, 1495, 1553, 1620, 3071, 3418; ^1H NMR ($CDCl_3$/DMSO - d_6, 300 MHz): δ 10.16 (s, 1H), 8.38-8.41 (d, 2H), 8.06- 8.09 (d, 2H), 7.26-8.02 (m, 10H)

2-(4, 5-Diphenyl-1H-imidazol-2-yl)-phenol (4)

IR (cm^{-1}): 1196, 1563, 1645, 2460, 3310, 3421, 3577; ^1H NMR ($CDCl_3$/DMSO - d_6, 300 MHz): δ 10.81 (s, 1H), 7.20-7.68 (m, 10H), 7.14-7.17 (t, 1H), 7.08 - 7.11 (t, 1H), 7.03-7.06 (d, J = 8.05 Hz, 1H), 6.90-6.92 (d, J =7.4Hz, 1H), 4.88 (s, 1H).

CONCLUSION

Molecular iodine, NaH_2PO_4, and $SnCl_2.2H_2O$ were found to be effective catalyst for the formation of 2, 4, 5-triaryl substituted imidazoles in excellent yields. The uses of these inexpensive and easily available catalysts under solvent-free conditions make this protocol practical and economically attractive. The simple work-up procedure, mild reaction conditions, selectivity, and very good yields make our methodology a valid contribution to the existing processes in the field of 2,4,5-triaryl substituted imidazole derivatives synthesis. Feasibility and effectiveness of catalysts under study were found to be of the order of $SnCl_2.2H_2O > NaH_2PO_4 > I_2$ and was depend on the Lewis acidity of catalysts.

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