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Synthesis of 2,4,5-Triaryl-*1H*-Imidazoles using anhydrous $PbCl_2$

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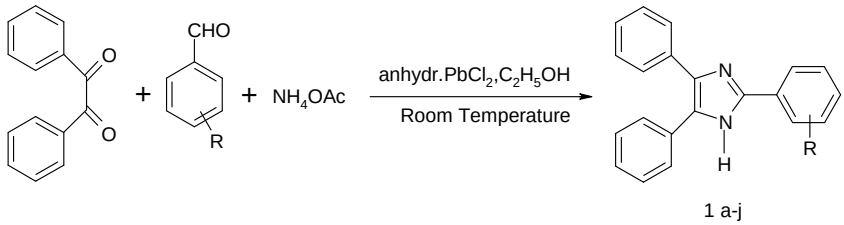
ABSTRACT

A simple and versatile synthesis of 2,4,5-Triaryl-1H-imidazole derivatives is achieved by pathway of Multicomponent reaction involving cyclocondensation of 1,2-dicarbonyl compound, aromatic aldehyde and ammonium acetate as a source of ammonia in presence of anhydrous $PbCl_2$ as a catalyst in ethyl alcohol. The remarkable features of this synthetic pathway are simple workup, short reaction time, high yields and use of anhydrous $PbCl_2$ as an effective catalyst.

Keywords: 2, 4, 5-Triaryl-1H-imidazole, Multicomponent reaction, anhydrous $PbCl_2$, high yields, effective catalyst.

INTRODUCTION

Multi-component reactions (MCRs) are selective and high atom economy reactions [1, 2] that have emerged as important tools to obtain complex and biologically active organic compounds [3-5]. Imidazoles have displayed a wide range of biological activities, such as inhibitors of P38 MAP kinase [6] and B-Rafkinase [7]. They are also useful as herbicides [8], pesticides [9], glucagon receptors[10] as well as anti-inflammatory[11], anti-tumor[12] and anti-thrombotic[13] agents. A number of methods for the preparation of 2,4,5-triaryl-1H-imidazoles have been reported and include the use of sulfuric acid immobilized on silica gel[14], KH_2PO_4[15], microwave irradiation (solvent and catalyst free)[16], ionic liquids [17], ceric ammonium nitrate (CAN)[18], oxalic acid[19], $Eu(OTf)_3$[20], [Hmim]HSO_4[21], $ZrCl_4$[22], $Yb(OTf)_3$[23], $NiCl_2.6H_2O$[24], sodium bisulfate[25], iodine[26], nano-crystalline magnesium oxide[27], silica sulfuric acid[28], acetic acid[29], L-proline[30], PEG-400[31], $Cu(TFA)_2$[32], tetra(*n*-butyl)ammonium bromide (TBAB)[33], $(NH_4)_6Mo_7O_{24}.4H_2O$[34], $InCl_3.6H_2O$ [35], $Zr(acac)_4$ [36], anhydrous $FePO_4$ [37] and uranyl nitrate supported on acidic alumina [38]. These processes suffer from one or more drawbacks such as harsh reaction conditions, difficult work-up procedures, long reaction times, poor yields, use of expensive and hazardous catalyst. We now report a simple, mild and high yield giving methodology for the preparation of 2, 4, 5-triaryl-1H-imidazoles involving the use of a cost-effective and efficient catalyst.



1 a-j

Scheme 1

EXPERIMENTAL SECTION

All chemicals were obtained from Sigma-Aldrich, Merck and used without purification. Open capillary method involving use of Thiele tube was used to determine melting points. IR spectra were recorded with Perkin-Elmer FTIR spectrometer as KBr pellets. ^{1}HNMR spectra were acquired on a 400 MHz Varian FT-NMR spectrometer. The chemical shift values were expressed in δ with reference to tetra methyl silane (TMS) as an internal standard. The progress of reaction was monitored using TLC (Silica gel 200-475 mesh, a mixture of Pet ether and Ethyl acetate in 5:1 proportion as solvent system) and the products were purified by recrystallization from suitable solvent. The synthesized 2,4,5-triaryl-1H-imidazoles were known compounds. Their formation was confirmed by comparison of their melting points, IR and ^{1}H NMR with the corresponding data in literature (*Table 3*).

Preparation of 2, 4, 5-Triaryl-1H-imidazoles: Typical Procedure

Anhydrous $PbCl_2$ (0.0278 gm, 0.1mmol) to a mixture of benzil (0.210 gm,1mmol), aromatic aldehyde (1mmol) and ammonium acetate (0.154 gm, 2 mmol) in ethanol (4.0 ml) and the reaction mixture was stirred using magnetic needle over magnetic stirrer. After the completion of reaction (as indicated by TLC), the reaction mixture was carefully filtered to separate heterogeneous catalyst and filtrate was poured in cold water (10.0 ml). The precipitated solid was collected, washed with water and further purified by recrystallization from hot ethanol. All the derivatives were characterized by melting point data, IR and ^{1}H NMR.

Spectral analysis of selected 2, 4, 5-Triaryl-1H-imidazoles:

Entry (1b) 2-(p-tolyl)-4, 5-diphenyl-1H-imidazole

^{1}HNMR (400 MHz, DMSO): δ= 2.33 (s,3H), 7.19 (t,1H,J=7.3 Hz), 7.33 (t,4H,J=7.3Hz), 7.36 (t,1H, J=7.2Hz), 7.46 (t, 2H, J=7.3Hz), 7.50 (d, 2H, J=7.1Hz), 7.58 (d, 2H, J=7.7Hz), 8.00 (d,2H, J=8.1 Hz), 12.45 (br,1H) ppm.

IR (KBr, cm^{-1}) = 3419,3029,1594,1500,1450,1126,1069,971,824,763,670.

Entry (1h) 2-(4-bromophenyl)-4, 5-diphenyl-1H-imidazole

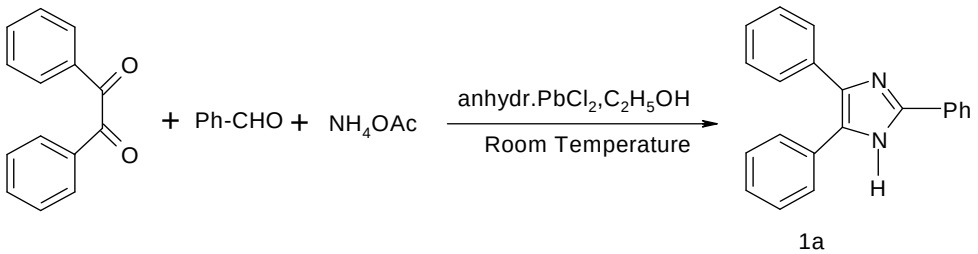
^{1}HNMR (400 MHz, DMSO): δ= 7.21 (t,1H,J=7.3Hz), 7.34 (t,2H,J=7.2Hz), 7.41(t,1H,J=7.9Hz), 7.42(t,2h,j=7.3Hz), 7.49-7.56 (m,6H), 8.10 (d,2H,J=7.1Hz), 12.83 (br,1H) ppm

IR (KBr, cm^{-1}) = 3442,3029,1600,1520,1490,1450,1430,1130,1070,827,690.

RESULTS AND DISCUSSION

The optimum conditions for the synthesis of 2, 4, 5-Triaryl-1H-imidazole derivatives were established by examining the reaction between benzil, benzaldehyde and ammonium acetate as model reaction (*Scheme 2*).

An appropriate solvent for the reaction was selected by investigating the effect of different solvents on reaction time and yield of product for model reaction. Low yield and long reaction time was observed when the reaction was performed in solvents of low polarity (Table 1, Entries 1 and 2). Even in CH_3CN, the reaction time and yield were not satisfactory (Table 1, Entry 3). When reaction was performed in C_2H_5OH, a polar solvent maximum yield was obtained in short reaction time (Table1, Entry-4).



1a

Scheme 2

Table 1 Investigation of solvent effect for the synthesis of 2, 4, 5-Triaryl-1H-imidazole (1a)

Entry	Catalyst	Solvent	Time (min.)	Yield[a] (%)
1	anhydrous $PbCl_2$	$CHCl_3$	65	52
2	anhydrous $PbCl_2$	CH_2Cl_2	50	58
3	anhydrous $PbCl_2$	CH_3CN	45	62
4	anhydrous $PbCl_2$	C_2H_5OH	15	91

[a]*Isolated Yields*

On the basis of results (Table 1), C_2H_5OH was selected as the most appropriate solvent for Scheme1**.**

The efficiency of anhydrous $PbCl_2$ as a catalyst was determined with respect to its loading amount. There was no improvement in yield with increment in loading amount from 0.01 mmol to 0.05 mmol. A satisfactory yield in short reaction time was obtained with 0.1 mmol of catalyst (Table 2, Entry 3). There was no appreciable improvement in yield even if loading amount was increased to 0.2 mmol.

Table 2 Investigation of catalytic effect of anhydr. $PbCl_2$ on synthesis of 2, 4, 5-Triaryl-1H-imidazole(1a)

Entry	anhydrous $PbCl_2$ (mmol)	Time (min.)	Yield[b] (%)
1	0.01	45	52
2	0.05	40	58
3	0.1	15	91
4	0.2	15	91

[b]*Isolated yields*

The scope of ***Scheme1*** was further investigated by reacting benzil with different aromatic aldehydes and ammonium acetate under the condition thus established.

Table 3 Synthesis of 2,4,5-Triaryl-1H-imidazoles (1a-j) *

Entry	R-	Product	Time (min.)	Yield (%)	M.P.(^{0}C) (Literature Value)
1	H	1a	15	91	273-275 (272-274)[39]
2	4-CH_3	1b	30	89	226-227 (227-228)[39]
3	4-OCH_3	1c	25	90	227 (227-228)[39]
4	2-OCH_3	1d	30	88	211-212 (210-211)[25]
5	4-Cl	1e	20	90	260-262 (261-262)[39]
6	2-Cl	1f	20	88	194-195 (195-196)[25]
7	4-OH	1g	15	91	259-260 (260-261)[40]
8	4-Br	1h	30	89	243-245 (244-246)[39]
9	4-NO_2	1i	20	93	237-239 (235-238)[24]
10	3-NO_2	1j	15	91	299-300 (>290)[39]

**Reaction condition: Benzil (1.0 mmol), aldehyde (1.0 mmol), ammonium acetate (2mmol), anhydrous $PbCl_2$ (0.1 mmol) in C_2H_5OH (4.0 ml) at room temperature*

The above results have shown that all the three components reacted smoothly in presence of anhydrous $PbCl_2$ in C_2H_5OH as a catalyst and gave moderate to good yields of corresponding products (Table 3). Thus, anhydrous $PbCl_2$, a Lewis acid was proved to be an efficient catalyst under mild conditions. Moreover, various aromatic aldehydes containing either electron donating or electron withdrawing substituents at different position reacted well under present reaction condition (Table 3) proving the wide scope and generality of the protocol. The nature and substitution pattern of different substituents affected the course of reaction in terms of time and yields. Those aromatic aldehydes with electron withdrawing groups gave maximum yields in short reaction time (Table 3, Entries 1g, 1i). On the other hand, those with electron donating substituents gave comparatively low yields with slow reaction rate (Table 3, Entries 1b, 1c, 1e, 1h). Further, aromatic aldehydes with ortho-substitution were found to be less reactive (Table 3, Entries 1d, 1f). There was no reaction when aliphatic aldehydes were used. On the basis of these observations, the plausible mechanism for the present protocol can be given (Fig. 1).

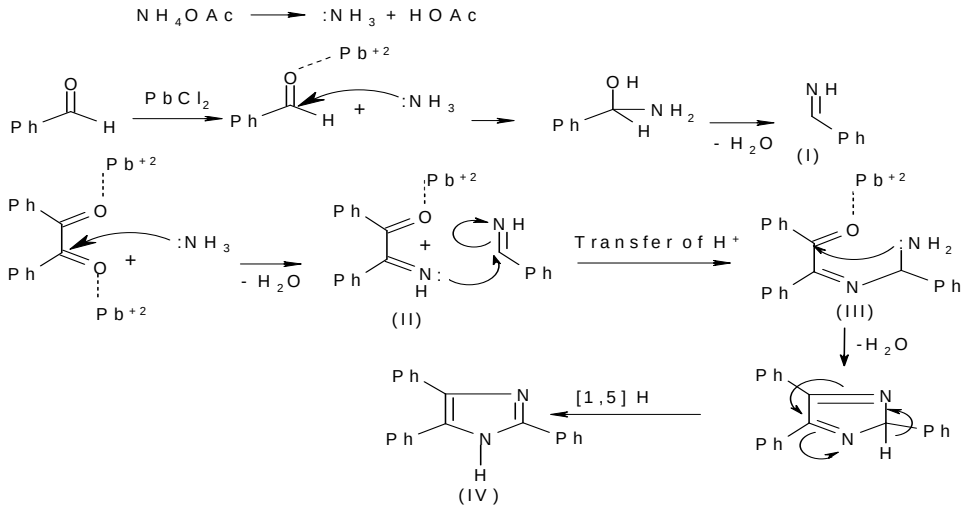


Fig.1

During the reaction, NH_4OAc served as source of $:NH_3$. Pb^{+2} from anhydrous $PbCl_2$ served as Lewis acid which facilitated formation of imine derivatives (I, II and III). The cyclization of intermediate (III) was promoted by Pb^{+2}. The final transfer of H^+ resulted in formation of product (IV).

CONCLUSION

In conclusion, anhydrous $PbCl_2$ in C_2H_5OH was found to be an excellent catalyst for the three component, one pot synthesis of 2, 4, 5-Triaryl-1H-imidazoles. The catalyst was found to be heterogeneous and easily separable from reaction mixture. The catalyst and solvent were inexpensive, readily available. Anhydrous $PbCl_2$ was found to be stable towards moisture which made its handling easy. Different aromatic aldehydes reacted smoothly in presence of small amount (0.1 mmol) of anhydrous $PbCl_2$ as a catalyst giving satisfactory yields of the corresponding 2, 4, 5-Triaryl-1H-imidazole derivatives in short reaction time.

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