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One pot three-component synthesis of imidazole derivatives using NH_3/NH_4Cl

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ABSTRACT

Imidazole is a planar, five membered heteroaromatic molecule with pyrrole type and pyridine type annular nitrogens. Several approaches are available of imidazoles from alpha halo ketones, aminonitrile, aldehyde ect. Reactivity of imidazole and benzimidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance.

Imidazoles among the principal groups of heterocyclic compounds that have biological properties. Due to the presence of imidazole rings in natural products and active pharmaceutical ingredients, different ways for the synthesis of heterocyclic compounds of this type investigated. The aim of this project is substituted derivatives 2,4,5-Imidazoles.

In this study, three-substituted imidazole compounds synthesized using ammonium chloride as a catalyst cost in terms of reflux were studied. Reaction with aldehydes and ammonium acetate Acenaphthene quinone in crowding conditions in the presence of ammonium chloride was performed successfully and imidazole derivatives were prepared with good yields. The key advantages of this process are high yields,cost effectiveness of catalyst,easy work-up and purification of products by non-chromatographic method.

Key words: 2,4,5-Trisubstituted imidazoles, Ammonium chloride, Heterogeneous catalysts.

INTRODUCTION

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity [1-4]. MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery[5,6]. The imidazole nucleus is a fertile source of biologically important molecules. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes. They are well known as inhibicides,anti-inflammatory agents, antithrombotic agents, plant growth regulators and therapeutic agents. In addition, they are used in photography as photosensitive compounds. Some substituted triarylimidazoles are selective antagonists of the glucagons receptor and inhibitors of IL-1 biosynthesis [7] . Radziszewski and Jaap proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds,aldehydes and ammonia to obtain 2,4,5-triphenylimidazole [8,9] .One of the aims we have in mind is to introduce a new catalyst for synthesis of 2,4,5-trisubstituted imidazoles with cost effectiveness and mild condition in high yields.

We examined a wide variety of aromatic aldehydes with various substituents to establish the catalytic importance of NH_4Cl for this reaction. A wide range of ortho-meta and para substituted aromatic aldehydes undergo this one-pot multicomponent synthesis with Acenaphthene quinone and ammonium acetate to afford 2,4,5-trisubstituted imidazoles in good yields.

EXPERIMENTAL

All materials and reagents were purchased from Merck and Aldrich and used without further purification. Melting points were determined on an Electro thermal type 9100 melting point apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet AVATAR-370 FT-IR spectrophotometer and 1H NMR spectra were obtained on a Bruker DRX400 spectrometer.

General procedure for preparation of 4a-k

A miture of aldehyde (1 mmol), Acenaphthene quinone (1mmol), ammonium acetate (5 mmol) and ammonium chloride (3 mmol) as a catalyst in ethanol (10 ml) was stirred.The mixture was refluxed for described time. After completion of the reaction was cooled to room temperature

and solid materials washed with water and the solvent was evaporated to give the crude product. For further purification it was recrystallized from ethanol to afford pure product.

Analytical data for selected compounds:

8-(3-nitro-phenyl)-7H-acenaphtho[1,2-d]imidazole
,m.p.=229°C. IR(KBr) :ῡ =3195, 1535, 1345cm^{-1}. ^{1}HNMR (300MHz, DMSO-d$_6$): δ=7.63-7.5(m,7H, Ar-H), 8.2 (d, 1H)ppm, 8.4 (d, 1H)ppm, 8.8 (s, 1H)ppm, ^{13}C NMR(DMSO-d$_6$): δ= 148.8 ,148.0 , 132.8 ,131.7 ,131.1 ,129.6 ,128.9 ,128.2 ,127.5 ,127.1 ,122.8 ,120.4 ,119.3ppm

8-(4-methyl-phenyl)-7H-acenaphtho[1,2-d]imidazole
m.p.=231-233°C. IR(KBr) :ῡ =3420, 1606, 1259cm^{-1}.^{1}HNMR (300MHz, DMSO-d$_6$):δ=2.47(s, 3H, CH_3), 7.1-8.2(m, 10 H, Ar-H), 13.1(s, 1H, NH)ppm. , ^{13}C NMR(DMSO-d$_6$): δ=138.1, 136.3, 131.5, 131.2, 129.5, 129.2, 128.7, 128.2, 126.8, 126.5, 125.2, 122.5, 120.1,119.7ppm

8-(2-chloro-phenyl)-7H-acenaphtho[1,2-d]imidazole
m.p.=190-191°C.IR(KBr) :ῡ =3039.8, 1694, 1281cm^{-1}.^{1}HNMR (300MHz, DMSO-d$_6$):δ=7(d, 1H),7. 2(d, 1 H), 7.4-7.6(m, 1H),7.8-7.7(t , 3H), 7.98-7.95 (d, 1H) ppm. , ^{13}C NMR(DMSO-d$_6$): δ=132.7, 131.6, 130.8, 130.4, 129.5, 128.7, 128.1, 127.9, 126.9, 121.7, 120.4ppm

Results and Discussion

In this study we wish to report the synthesis of imidazole derivatives (4a–4k) via an one-pot three-component condensation of Acenaphthene quinone (1), aromatic aldehyde (2a-k), and ammonium acetate in the presence of ammonium chloride as catalyst.

Efficiency of this reaction is mainly affected by the amount of catalyst, temperature and reaction time.For getting the best conditions, initially we started the condensation of Acenaphthene quinone (1mmol), 4 nitro benzaldehyde (1mmol) and ammonium acetate (5 mmol) in presence of ammonium chloride (1 mmol) as a catalyst at 30°C, which led to low yield of 2,4,5-trisubstituted imidazole.To enhance the yield of the desired product the temperature of the reaction was increased to Reflux condition . With increasing the temperature, the productivity of the reaction increased but was not very high, yet. Then, it was thought worthwhile to carry out the reaction in the presence of higher amount of the catalyst. As indicated in Table 1. A further increasing of catalyst loading does not affect the yield(Table 1).

After optimizing the conditions, we applied this catalyst for synthesis of trisubstituted imidazoles by using different aromatic aldehydes with a wide range of ortho – meta and para-substitutions under reflux conditions to establish the catalytic importance of NH_4Cl for this reaction.

Generally, the synthetic procedure involves stirring the mixture of Acenaphthene quinone (1mmol), aldehyde (1mmol) , ammonium acetate (5 mmol) and ammonium chloride (3 mmol) for 180 min at under reflux conditions. The corresponding results are given in Table 2. We found that the reaction proceeded very efficiently either electron-releasing or electron-withdrawing substituents on aryl ring of aldehyde.

Table1.Effect of catalyst on the one-pot three component synthesis of substituted imidazole

Entry	Catalyst/mmol	Temperature (°C)	Time (min)	Yield (%)
1	1	r.t.	?	Trace
2	1	reflux	200	45
3	2	30	720	30
4	2	reflux	200	60
5	3	50	720	60
6	3	reflux	180	90
7	4	reflux	180	92
8	5	reflux	180	94

Reaction conditions: 4-nitro benzaldehyde (1mmol), Acenaphthene quinone (1mmol), ammonium acetate (5 mmol) in ethanol.

Table 2: Synthesis of 2,4,5-triaryl-1H-imidazoles (4a-k) using ammonium chloride(3 mmole) under reflux conditions

Entry	Ar	product	Yield(%) reflux	m.p. (°C) found/reported[ref]
1	C_6H_5	**4a**	80	270-273 / 270-273[11]
2	4-$NO_2C_6H_5$	**4b**	90	240-242 / 242[10]

3	3-$NO_2C_6H_5$	**4c**	87	229
4	3-MeC_6H_5	**4d**	77	230
5	4-MeC_6H_5	**4e**	78	231-233 / 232-233[11]
6	2-BrC_6H_5	**4f**	83	296-298
7	3-$BrOC_6H_5$	**4g**	84	289-292
8	2-ClC_6H_5	**4h**	88	190-191
9	3-$MeOC_6H_5$	**4i**	73	269-271
10	4-$MeOC_6H_5$	**4j**	75	249-253/248-251[11]
11	4-CNC_6H_5	**4k**	89	203-205

All the synthesized imidazoles have been characterized on the basis of elemental and studies

Possible mechanism for the NH_4Cl catalyzed synthesis of trisubstituted imidazoles has been proposed in Fig 2.In summary, this paper describes a convenient and efficient process for synthesis of trisubstituted imidazoles through the three-components coupling of Acenaphthene quinone, aldehydes and ammonium acetate using ammonium chloride as a catalyst. Reaction profile is very clean and no side products are formed. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of trisubstituted imidazoles of biological and medicinal importance.

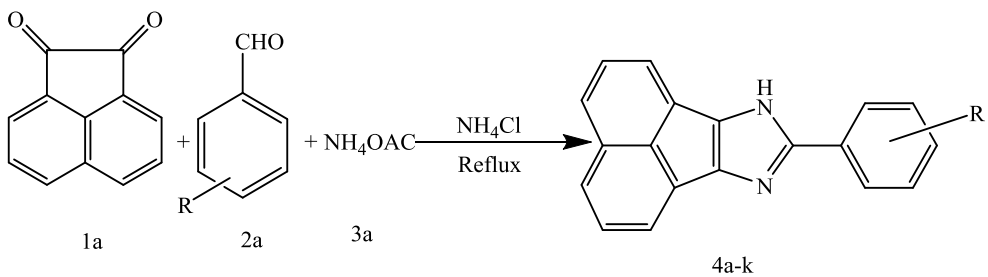

Fig 1 : Ammonium chloride catalyzed synthesis of 2,4,5-trisubstituted imidazoles

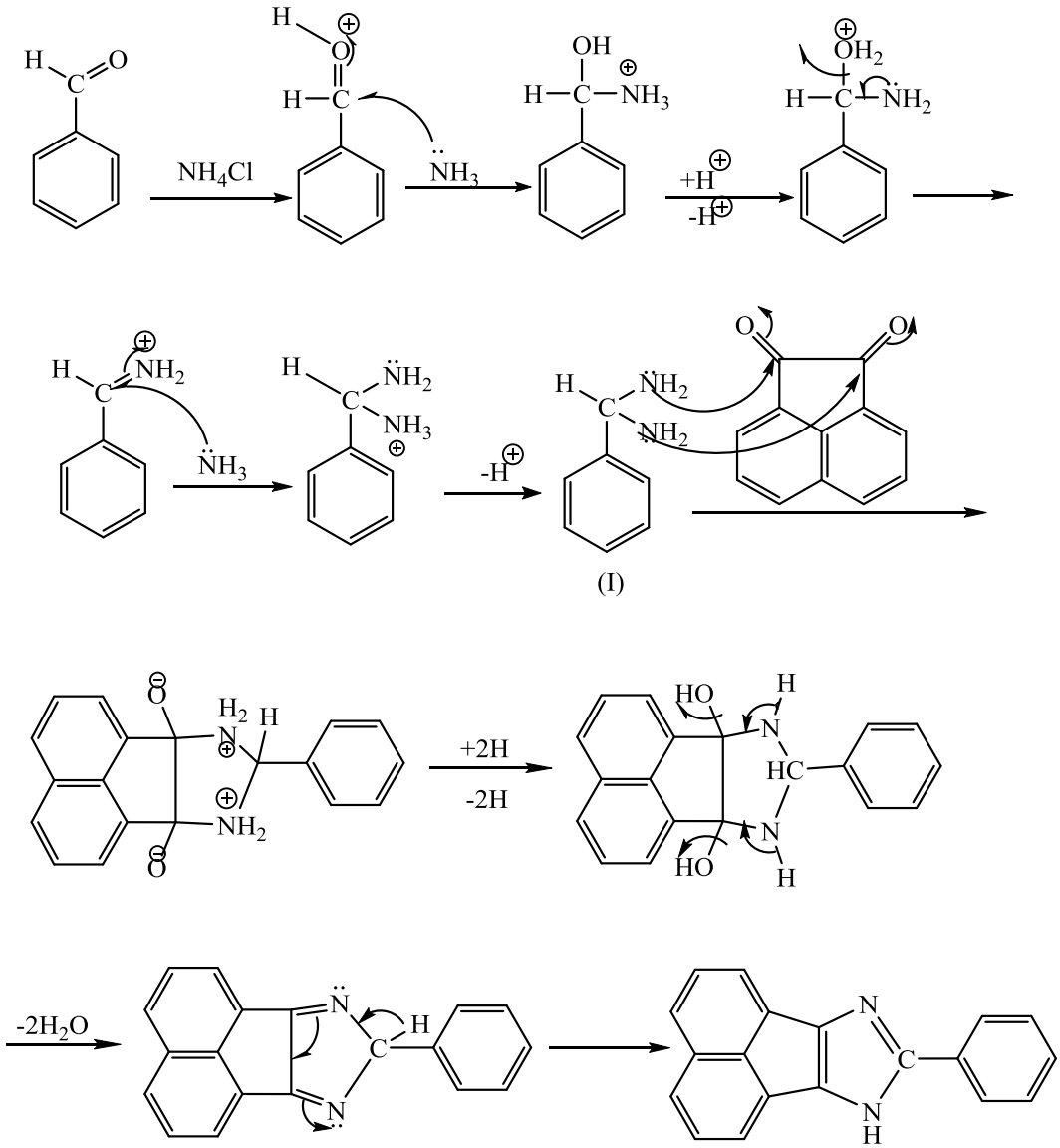

Fig 2: Probable mechanism for the formation of imidazole derivatives using Acenaphthene quinone ,aromatic aldehydes ,ammonium acetate and ammonium chloride as a catalyst

Conclusions

We have been able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active trisubstited imidazoles via condensation of Acenaphthene quinone with various aromatic aldehydes and ammonium acetate using ammonium chloride as a catalyst.

High yields, easy work-up and purification of compounds by non-chromatographic method (crystallization only) are the key advantages of this method.

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