Chemical Methodologies 4(2020) 324-332

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research article

One-pot Synthesize of Phenyl Phenanthro Imidazole Derivatives Catalyzed by Lewis Acid in the Presence of Ammonium Acetate

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ARTICLE INFORMATION

Received: 27 June 2019
Received in revised: 01 November 2019
Accepted: 18 December 2019
Available online: 01 May 2020

DOI: 10.33945/SAMI/CHEMM.2020.3.9

KEYWORDS

Multicomponent
One-pot
Imidazoles
Ammonium acetate
Lewis acid

ABSTRACT

Tri substituted imidazole derivatives were synthesized with the combinations of phenanthroquinone, benzealdehyde derivatives at the presence of ammonium acetate that catalyzed by Lewis acid. In all reactions, polar solvent was used and the reactions were carried out under the reflux conditions. The structure of all compounds was confirmed using the IR and ^{1}HNMR. This method revealed several advantages including, excellent yields, simplicity of operation and easy separation. The results showed that, products formed in high yields and low reaction times. Also, the metal atom of Lewis acid catalyst increased the reactivity of substrate and the reaction time.

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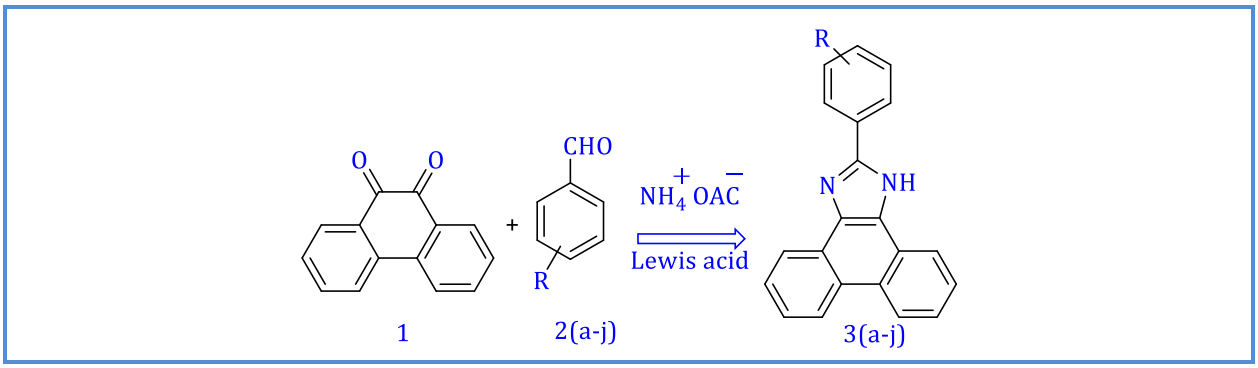
Graphical Abstract



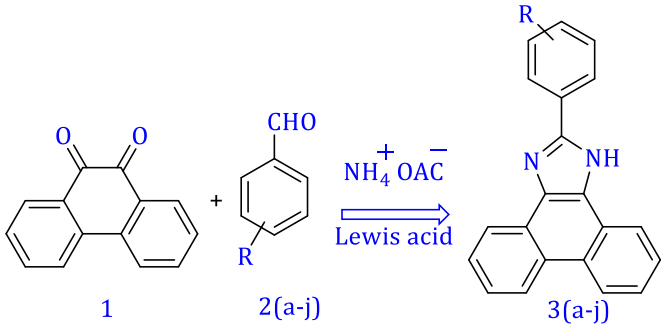
Introduction

Multicomponent reactions (MCRs) have been widely used in modern organic synthesis and medicinal chemistry. Multicomponent reactions are one-pot processes with three or more components that cased to produce organic compounds in high yields, short reaction times 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]. Recently, heterocyclic compounds have been very important due to their biological and chemicals activities. Imidazoles are well known heterocyclic compounds with the variety of medicinal effects [7]. Imidazole nucleus is an important synthetic strategy in pharmaceutical industry. For synthesis of imidazole, there are many ways including, reaction of alpha halo ketones, aminonitrile, and aldehyde [8].

Imidazole derivatives are an important group of heterocyclic compounds that have some superior biological and chemical properties [9]. Nowadays these compounds are used in pharmacology. They have different capacity such as anti-bacterial, anti-viral, and anti-cancer, and anti-inflammatory properties [10-12]. Also, the imidazole ring system is one of the main substructures found in most of natural products and pharmacologically active compounds, such as the hypnotic agent [13]. Therefore, many synthetic methods have been reported for the synthesis of multi substituted imidazoles [14].

Several methods have been used for synthesis of imidazoles including, ammonium chloride (NH_4Cl) and other methods using $ZrCl_4$, zeolites HY/silica gel, $NaHSO_3$, sulphanilic acid, iodine, ceric ammonium nitrate, oxalic acid, ionic liquids and also by microwave irradiation using acetic acid [15]. Each of the aforementioned methods for has its own merits, while some of the methods are plagued by the limitations of poor yield, longer reaction time, difficult work-up, and effluent

pollution [16-20]. Therefore, developing a new mild method to overcome these disadvantages still remains a challenge in organic chemistry. In this research study we aimed at introducing a new catalyst for synthesis of 2,4,5-trisubstituted imidazoles with cost effectiveness and mild condition in high yields. In constitution of our works in the synthesis of new heterocyclic compounds, [13, 21-23] we used an aromatic aldehydes with various substituents to synthesis of new phenanthro imidazole derivatives. A wide range of *ortho*-, *meta*- and *para*-substituted aromatic aldehydes undergo this one-pot multicomponent synthesis with phenanthroquinone and ammonium acetate to afford substituted acenaphtho imidazole derivatives in good yields (Scheme 1).



Scheme1. One-pot three component synthesis of substituted imidazoles in the presence of ammonium acetate under reflux conditions

Experimental

Materials and instruments

All the materials purchased from Merck and Aldrich and used without further purification. The melting point was recorded using an electro-thermal type 9100 melting point apparatus. The IR spectra recorded using a thermo Nicolet AVATAR-370 FT-IR spectrophotometer. A Bruker DRX250 spectrometer was used to obtain ^{1}HNMR and ^{13}CNMR spectra. The reactions performed under the reflux condition.

Typical procedure for synthesis of imidazole derivatives in microwave condition

A mixture of benzaldehyde (1 mmol), acenaphthenequinone (1 mmol), ammonium acetate (3 mmol) and 1 g Lewis acid ($FeCl_3$ or $CuCl_2$) in 10 mL ethanol was stirred. The resulted mixture was refluxed for described time (24-48 h). At the end of the reaction (the reaction progress was monitored by TLC using *n*-hexan:ethyl acetate as an eluent solution), catalyst was separated and the residue separated with filtering. The solid product washed with cold water (3×20 cm^3), and recrystallized in ethanol to provide the pure product. After cooling, product mixture was filtered, then, it was dried in oven for 1 h at 100 °C

to synthesis of pure product (**3a**, m.p. = 286-288/>300 °C [17]. For other derivatives, this procedure can use without any change. At the end of the reaction, weight of the dried products was determined and the melting points recorded for each product.

Selected spectral data

2-(4-nitrophenyl)-1H-phenanthro[9,10-d]imidazole (3b)

Yellow crystal, m.p. = 316 °C. IR (KBr): $\bar{\upsilon}$=3260 (N-H), 1591 (C=N), 1536 (NO_2), 1450 (C=C), 1383 (NO_2) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 7.63-8.83 (m, 12H, Ar-H), 13.80 (s, 1H, NH) ppm.

2-(2-chlorophenyl)-1H-phenanthro[9,10-d]imidazole (3e)

Yellow crystal, m.p. = 232-234 °C. IR (KBr): $\bar{\upsilon}$=3435 (N-H), 1594 (C=N), 1450 (C=C) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 7.37-8.88 (m, 12H, Ar-H), 13.57 (s, 1H, NH) ppm.

2-(4-chlorophenyl)-1H-phenanthro[9,10-d]imidazole (3f)

Yellow crystal, m.p. = 228-230 °C. IR (KBr): $\bar{\upsilon}$=3432 (N-H), 1592 (C=N), 1673 (C=C) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 5.11 (s, 2H, CH_2), 7.16-8.83 (m, 17H, Ar-H), 9.83 (s, 1H, NH) ppm.

2-(3-nitrophenyl)-1H-phenanthro[9,10-d]imidazole (3c)

Yellow crystal, m.p. = 269-271 °C. IR (KBr): $\bar{\upsilon}$=3212 (N-H), 1591 (C=N), 1562 (C=C) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 2.08 (s, 3H, CH_3), 7.28-8.82 (m, 12H, Ar-H), 10.17 (s, 1H, NH), 13.40 (s, 1H, NH) ppm.

2-(4-boromophenyl)-1H-phenanthro[9,10-d]imidazole (3i)

Yellow crystal, m.p. = 228-230 °C. IR (KBr): $\bar{\upsilon}$=3260 (N-H), 1595 (C=N), 1670 (C=C) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 7.63-8.83 (m, 12H, Ar-H), 13.80 (s, 1H, NH) ppm.

2-(4-methylphenyl)-1H-phenanthro[9,10-d]imidazole (3H)

White crystal, m.p. = 290-292 °C. IR (KBr): $\bar{\upsilon}$=3350 (N-H), 1590 (C=N), 1665 (C=C) cm^{-1}. ^{1}HNMR (250 MHz, DMSO-d_6): δ = 7.63-8.83 (m, 12H, Ar-H), 13.80 (s, 1H, NH) ppm.

Results and discussion

Substituents with electronegative atoms (-C=O, -CN) are electron withdrawing groups. They deactivate the aromatic ring by decreasing the electron density on the ring through a resonance withdrawing effect. Alkyl substituents (-CH_3, -CH_2CH_3) are also electron donating groups they activate the aromatic ring by augmenting the electron density on the ring through an inductive donating effect.

Table 1. One-pot three component synthesis of substituted imidazoles

Entry	Ar	Product	Yield (%) microwave conditions	m.p. (°C) Found/reported [Ref.]
1	C_6H_5	**3a**	89	286-288/>300 [17]
2	4-$NO_2C_6H_4$	**3b**	92	>300/>300 [17]
3	3-$NO_2C_6H_4$	**3c**	89	269-271/278-280 [18]
4	4-CNC_6H_4	**3d**	86	>300/>300 [17]
5	2-ClC_6H_4	**3e**	87	232-234/236-237 [17]
6	4-ClC_6H_4	**3f**	94	268-270/263-265 [18]
7	4-$MeOC_6H_4$	**3g**	83	258-260/265-267 [18]
8	4-MeC_6H_4	**3h**	84	290-292/292-294 [18]
9	4-BrC_6H_4	**3i**	68	228-230/ new
10	2-$NO_2C_6H_4$	**3j**	74	246-248/ new

[a] Reaction conditions: aldehyde (1 mmol), [9,10] phenanthraquinone (1 mmol), ammonium acetate (2.5 mmol) and $Fecl_3$ catalyst (0.04 gr) at reflux condition in ethanol

Examination of the effects of temperature, amount of catalyst and effects of various solvents on the synthesis of the three-substituted phenyl acenaphto derivatives of imidazole in reflux conditions.

Electron-withdrawing groups such as cyano (CN), nitro (NO_2) and halogens (Cl, F) can activate the carbonyl group of aromatic ring. Therefore, aromatic ring is going to be an affective site for reaction with amino groups. For example, aldehydes that had the electron-withdrawing substituent reacted effectively with ammonium acetate and electrophile (NH_4OAC) attack on the carbonyl group of benzaldehyde simply. Other groups such as electron donating like methyl (-CH_3) and methoxi (-OCH_3) reduce the activity of the carbonyl group of aromatic ring of benzaldehyd, as a result, the aromatic ring with electron-donating substituents that does not affect the attack of ammonium acetate well. In all reactions that benzaldehyd was carried electron withdrawing group, products were manufactured with high-yield (80-95%); however, the reactions that had electron-donating substituents products were made at a lower yield, 70-80%).

In this work we studied dicarbonyl compound like phenanthroquinone, ammounium acetate, and aldehyde derivatives to be good starting materials for synthesis of imidazole derivatives at the presence of Lewis acid under reflux conditions. This technique has several advantages including, excellent yields, simplicity of operation, and easy separation. Also, the metal atom of Lewis acid catalysis decreased the reactivity of the substrate and the reaction time. There are different methods for synthesis of the imidazole. It may be prospered by the following reaction.

Reactivity of imidazole and benzo imidazole is referred from their resonance structure in which the dipolar contributors have finite importance.

Lewis acids with activate the pair electrons of primary materials, can increase the reaction rate. In other words, the metal atom forms an adduct with a lone-pair bearing electronegative atom in the substrate, like oxygen (both sp^2 and sp^3), nitrogen, sulfur, and halogens. The complication has partial charge-transfer character and makes the lone-pair donor useful and effective and working correctly electronegative, activating the substrate toward nucleophilic attack.

For optimization, we selected 3-nitro phenyl phenanthro imidazole combination as a sample to investigate the effect of temperature, amount of catalyst and various solvents on the chemical reactions, we changed one of the variables in each reaction.

Solvent has one of the most important roles in these reactions. In this part, reaction with following conditions (3-nitro benzaldehyde (1 mmol), phenanthro quinone (1 mmol), ammonium acetate (2.5 mmol) and $FeCl_3$ catalyst at reflux condition after 48 h tested in presence different solvents. Results are presented in Table 2. We noticed that protic solvent like ethanol and methanol have higher yield in this method. The best result was obtained when using ethanol (Entry 3).

Table 2. Effect of solvent on the one-pot three component synthesis of substituted imidazole[a]

Entry	Solvent	Yield (%)
1	$CHCl_3$	64
2	MeOH	78
3	EtOH	94

[a] Reaction conditions: 3-nitro benzaldehyde (1 mmol), [9,10] phenanthraquinone (1 mmol), ammonium acetate (2.5 mmol) and $Fecl_3$ catalyst (0.04 gr) at reflux condition after 48 h

For optimization of Lewis acid amounts, the reaction carried out with different amounts of Lewis acid catalyst. Obtained results in Table 3 indicated that the best result obtained with 0.04 gr. Amount of catalyst, but increase the amount of catalyst, did n't have significant effects in the yield of products.

Table 3. Effect of catalyst on the one-pot three component synthesis of substituted imidazole[a]

Entry	Catalyst/gr	Temperature (°C)	Time (h)	Yield (%)
1	$Fecl_3$/0.02	Reflux	48	85
2	$Fecl_3$/0.03	Reflux	48	75
3	$Fecl_3$/0.04	Reflux	48	67
4	$Fecl_3$/0.05	Reflux	48	60

[a] Reaction conditions: 3-nitro benzaldehyde (1 mmol), [9,10] phenanthraquinone (1 mmol), ammonium acetate (2.5 mmol) in ethanol at reflux condition after 48 h

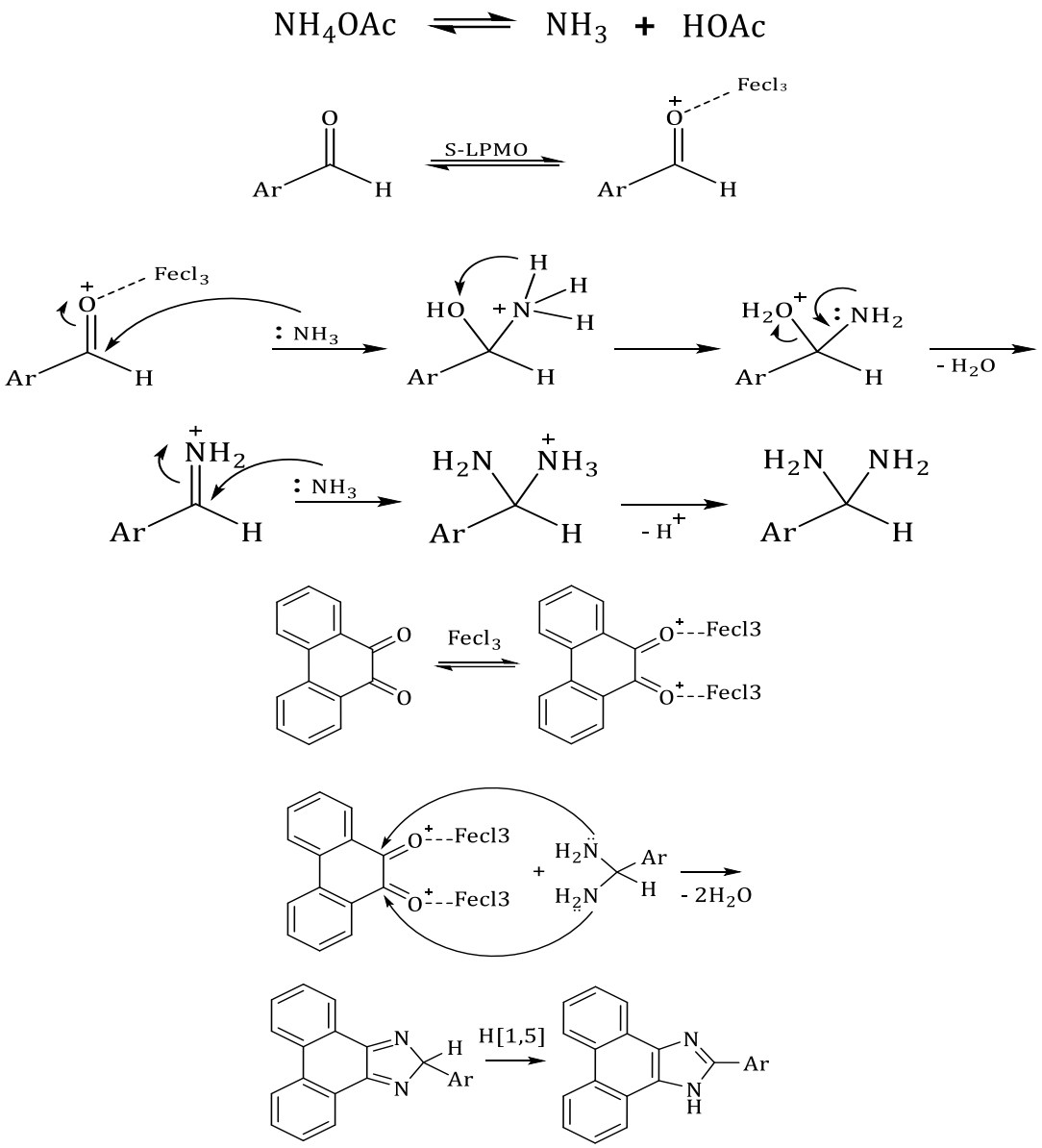
In the next step, temperature studied as a main variable. The reaction mixture was carried out at three different temperatures. In all three cases, the product structure was confirmed by the IR spectra and the measurements of the melting point. The results are shown in the Table 4. The best result was obtained with the reaction at 78 °C.

Table 4. Effect of temperature on the one-pot three component synthesis of substituted imidazole[a]

Entry	Temperature (°C)	Yield (%)
1	60	60
2	78	90
3	95	30

[a] Reaction conditions: 3-nitro benzaldehyde (1 mmol), [9,10] phenanthraquinone (1 mmol), ammonium acetate (2.5 mmol) and $FeCl_3$ catalyst (0.04 gr) in ethanol at reflux condition after 48 h

The mechanism of the reaction was showed in Scheme 2. Ammonia molecules are obtained from ammonium acetate. We think that the aldehyde and 1,2-dicarbonyl compounds including [9,10] phenanthraquinone at first activated by $FeCl_3$ as Lewis acid, in the rate determining step.



Scheme 2. Plausible mechanism for the formation of imidazole derivatives in the presence of $FeCl_3$ catalyst

Conclusions

Imidazole is a five-membered heterocyclic compound. There were so many different conventional methods for synthesis of imidazole and its derivatives. The method for synthesis of final products is new and not reported elsewhere. Imidazole derivatives have many properties especially in medicinal chemistry applications. These compounds are have been used as anti-bacterial, anti-viral, anti-cancer, and anti-allergic drugs. There were many different methods to synthesize imidazole and its derivatives by researchers. In this research study we found that dicarbonyl compounds such as phenanthro quinone, ammonium acetate, and aldehyde derivatives can be good starting materials for synthesis of imidazole at the present of Lewis acid under reflux conditions. This technique has several advantages including, excellent yields, simplicity of operation, and easy separation. Also, the results revealed that, the metal atom of Lewis acid catalyst increased the reactivity of substrate and the reaction time.

Acknowledgements

The authors are grateful to the Islamic Azad University, Ahvaz Branch for its financial support.

Conflict of Interest

We have no conflicts of interest to disclose.

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How to cite this manuscript: Elham Haddadzadeh, Mohammad Kazem Mohammadi*, One-pot Synthesize of Phenyl Phenanthro Imidazole Derivatives Catalyzed by Lewis Acid in the Presence of Ammonium Acetate. Chemical Methodologies 4(3), 2020, 324-332. DOI:10.33945/SAMI/CHEMM.2020.3.9.