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ORIGINAL ARTICLE

L-Proline-catalyzed three-component synthesis of condensed imidazoles

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KEYWORDS

Imidazo[4,5-*b*]indole;
Imidazo[4,5-*f*]phenanthroline;
L-Proline

Abstract A one-pot, efficient and high yielding procedure for the synthesis of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole and 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline is reported. The procedure proceeded by the multicomponent reaction of aromatic aldehydes, indoline-2,3-dione or 1,10-phenanthroline-5,6-dione and ammonium acetate catalyzed by L-proline under ultrasonic irradiation. Conveniency, simplicity, rapidity and cleanliness of the procedure for the synthesis of imidazole derivatives are the advantages of this study.

1. Introduction

Recently "ideal synthesis" has been defined as one in which the target compound is generated in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process (Jin et al., 2004; wender et al., 1997). One-pot multicomponent condensations represent a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity (Hudlicky, 1996). Significant progress has been achieved in this discipline; many powerful single bond forming reactions and asymmetric variants have been developed. These discoveries have paved the way for the stereoselective assembly of complex organic molecules, a task deemed inconceivable by early practitioners (Toure and Hall, 2009).

Imidazole and its derivatives are receiving growing attention for their pharmacologically properties such as herbicidal, fungicidal, analgesic, antiinflammatory and antithromobotic activities (Dömling and Ugi, 2000). During the course of studies on the development of new procedures to synthesize 2,4,5-triarylimidazoles, a number of catalysts, such as copper (II) acetate (Lipshutz and Morey, 1983), $Yb(OTf)_3$ (Wang et al., 2006), elemental iodine (Kidwai et al., 2006), $ZrCl_4$ (Sharma et al., 2006), $HClO_4$–SiO_2 (Srinivas et al., 2006), $NiCl_2{\cdot}6H_2O$ (Heravi et al., 2006) were screened. Some procedures also involve ionic liquid-promoted or microwave assisted synthesis (Shaabani and Rahmati, 2006; Balalaie et al., 2003).

Recently, the commercially available and inexpensive aminoacid L-proline has been used to catalyze many reactions such as the Mannich reaction and the direct asymmetric Aldol reaction (Dalko and Moisan, 2004; Lacoste, 2006). Additionally, due to its experimental simplicity, ease of handling, cost

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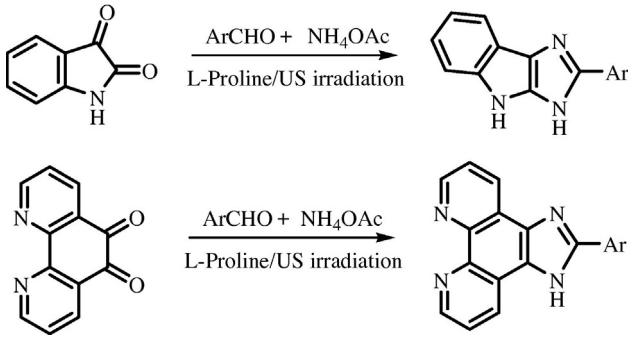


Scheme 1 Synthetic route to substituted imidazoles.

effectiveness and excellent solubility in water and organic solvents, L-proline has been found to be a very efficient catalyst in different transformations as a versatile organocatalyst (Luche, 1998).

Ultrasound has increasingly been used in organic synthesis in the last three decades. It has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under ultrasound irradiation (Rajagopal et al., 2002; Song et al., 2001; Shindalkar et al., 2005; Shelke et al., 2008; Gaplovsky et al., 2000).

As a part of our ongoing research in developing a versatile and efficient methodology for synthesis of heterocyclic compounds (Damavandi 2011), herein, we wish to describe an ultrasound accelerated synthesis of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole and 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline from aldehydes, indoline-2,3-dione or 1,10-phenanthroline-5,6-dione and ammonium acetate catalyzed by L-proline (Scheme 1).

1.1. Materials and methods

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker 100-MHz spectrometer in chloroform as the solvent and TMS as internal standard. Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Sonication was performed in a Shanghai Branson-CQX ultrasonic cleaner with a frequency of 40 kHz and a nominal power of 100 W. The reaction vessel was placed in side the ultrasonic bath. Flash column chromatography was performed with 300 and 400 meshes silica gel and analytical thin layer chromatography was performed on precoated silica gel plates (60F-254). Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyser.

1.2. Typical procedure for preparation of the imidazole derivatives

A mixture of aromatic aldehyde (1 mmol), indoline-2,3-dione or 1,10-phenanthroline-5,6-dione (1 mmol) and ammonium acetate (4 mmol) in ethanol (10 mL) in the presence of L-proline (5 mol %) was stirred at room temperature under ultrasonic waves for the appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction was diluted with water and extracted with ethyl acetate. Organic layer was dried over anhydrous $MgSO_4$ and then solvent was removed under reduced pressure. Crude product was washed with *n*-hexane and recrystallized from ethanol to obtain the pure product. The spectra data of the selected compounds are as follows:

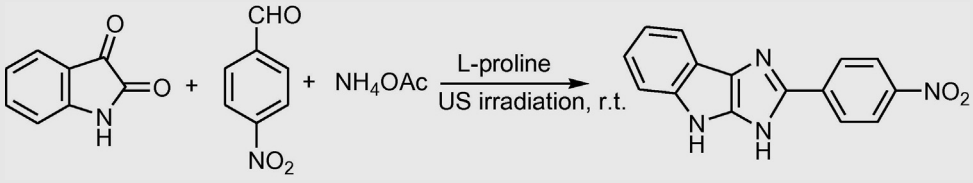
1.3. 3,4-Dihydro-2-phenylimidazo[4,5-b]indole (**1**)

IR (KBr, cm^{-1}): 3405 (N–H), 1552 (C=C), 1590 (C=N). ^{1}H NMR (100 MHz, DMSO-d_6): δ 7.00–7.25 (m, 4H, Ar), 7.30–7.70 (m, 5H), 8.45 (s, NH). 12.25 (s, NH). Found for $C_{15}H_{11}N_3$: C, 76.25; H, 4.71; N, 17.95; Calcd.: C, 77.23; H, 4.75; N, 18.01. Mass *m*/*z*: 233 (M+).

1.4. 3,4-Dihydro-2-(4-nitrophenyl)imidazo[4,5-b]indole (**2**)

IR (KBr, cm^{-1}): 3435 (N–H), 1555 (C=C), 1585 (C=N), 1340 (NO_2), 1525 (NO_2). ^{1}H NMR (100 MHz, DMSO-d_6): δ 7.05–7.10 (m, 2H, Ar), 7.30–7.65 (m, 4H, Ar), 8.05 (d, 2H, J = 8 Hz, Ar), 8.45 (s, 1H, NH), 11.95 (s, 1H, N–H). Found for $C_{15}H_{10}N_4O_2$: C, 63.66; H, 3.58; N, 20.08; Calcd.: C, 64.74; H, 3.62; N, 20.13. Mass *m*/*z*: 278 (M+).

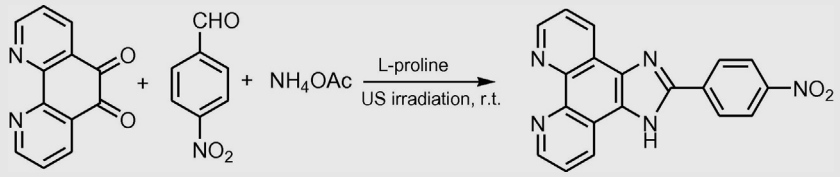
Table 1 Influence of solvent on L-proline/US-catalyzed reaction of indoline-2,3-dione, ammonium acetate and *p*-nitrobenzaldehyde.



Solvent	Ethanol	Methanol	2-Butanol	Dichloromethane	Chloroform	Acetonitrile	Dioxane	THF
Yield[a,b]	91	78	80	72	77	76	63	72

[a] All the reactions were carried out under ultrasonication at r.t. for 30 min.
[b] Isolated yields.

Table 2 Influence of solvent on L-proline/US-catalyzed reaction of 1,10- phenanthroline-5, 6-dione, ammonium acetate and *p*-nitrobenzaldehyde.



Solvent	Ethanol	Methanol	2-Butanol	Dichloromethane	Chloroform	Acetonitrile	Dioxane	THF
Yield[a],[b]	92	84	80	70	78	95	70	75

[a] All the reactions were carried out under ultrasonication at r.t. for 30 min.
[b] Isolated yields.

*1.5. 3,4-Dihydro-2-(4-methoxyphenyl)imidazo[4,5-b]indole (**3**)*

IR (KBr, cm^{-1}): 3405 (N–H), 1552 (C=C), 1590 (C=N). ^1H NMR (100 MHz, DMSO-d_6): δ 3.72 (s, 3H, OMe), 6.95 (d, 2H, J = 6 Hz, Ar), 7–7.25 (m, 2H, Ar), 7.30–7.60 (m, 4H, Ar), 10.55 (s, NH), 12.30 (s, NH). Found for $C_{16}H_{13}N_3O$: C, 72.45; H, 4.90; N, 15.78; Calcd.: C, 72.99; H, 4.98; N, 15.96. Mass m/z: 263 (M+).

*1.6. 3,4-Dihydro-2-p-tolylimidazo[4,5-b]indole (**5**)*

IR (KBr, cm^{-1}): 3418 (N–H), 1425–1525 (C=C), 1605 (C=N). ^1H NMR (100 MHz, DMSO-d_6): δ 2.30 (s, 3H, Me), 7.10–7.35 (m, 5H, Ar), 7.35–7.60 (m, 3H, Ar), 10.05 (s, NH), 12.10 (s, NH). Found for $C_{16}H_{13}N_3$: C, 77.60; H, 5.23; N, 16.87; Calcd.: C, 77.71; H, 5.30; N, 16.99. Mass m/z: 247 (M+).

*1.7. 2-(4-Bromophenyl)-3,4-dihydroimidazo[4,5-b]indole (**8**)*

IR (KBr, cm^{-1}): 3410 (N–H), 1415–1530 (C=C), 1608 (C=N). ^1H NMR (100 MHz, DMSO-d_6): 7.07–7.25 (m, 5H, Ar), 7.30–7.70 (m, 3H, Ar), 10.15 (s, NH), 12.12 (s, NH). Found for $C_{15}H_{10}BrN_3$: C, 56.42; H, 3.15; N, 13.29; Calcd.: C, 57.71; H, 3.23; N, 13.46. Mass m/z: 311 (M+).

*1.8. 2-(4-Chlorophenyl)-1H-imidazo[4,5-f][1,10] phenanthroline (**14**)*

IR (KBr, cm^{-1}): 3400 (N–H), 1405–1540 (C=C), 1575 (C=N). ^1H NMR (100 MHz, DMSO-d_6): 7.45–7.85 (m, 6H), 8.15 (dd, 2H), 8.95 (d, 2H), 13.10 (s, NH). Found for: $C_{19}H_{11}ClN_4$: C, 68.90; H, 4.11; N, 16.89; Calcd.: C, 68.99; H, 3.35; N, 16.94. Mass m/z: 332 (M+).

*1.9. 4-(1H-Imidazo[4,5-f][1,10] phenanthrolin-2-yl)phenol (**15**)*

IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 3412 (O-H, N–H), 1410–1555 (C=C), 1580 (C=N). ^1H NMR (100 MHz, DMSO-d_6): 7.05–7.55 (m, 4H), 7.80 (dd, 2H), 8.22 (d, 2H), 8.97 (d, 2H), 9.85 (s, OH), 13.20 (s, NH). Found for: $C_{19}H_{12}N_4O$: C, 67.24; H, 4.45; N, 16.51%. Calcd: C, 73.07; H, 3.87; N, 17.94%. Mass m/z: 312 (M+).

2. Results and discussion

In our initial search for appropriate reaction conditions, three component reaction of indoline-2,3-dione or 1,10-phenanthroline-5,6-dione, ammonium acetate and *p*-nitrobenzaldehyde to synthesize the 3,4-dihydro-2-(4-nitrophenyl)imidazo[4,5-*b*]indole and 2-nitrophenyl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline as model reactions were chosen to find the optimum solvents for each reaction. (Tables 1 and 2). We screened different solvents such as ethanol, methanol, 2-butanol, dichloromethane, tetrahydrofuran, acetonitrile, chloroform, dioxane at room temperature under ultrasonication. As shown in the Table 1, the best yield was obtained when ethanol was used as a solvent in the presence of 5 mol % catalyst under ultrasonication. In the case of the protic solvents the yields are better than aprotic solvent. In addition, as can be seen in Table 2, acetonitrile was found to be the best solvent for the one-pot condensation of 1,10-phenanthroline-5, 6-dione, ammonium acetate and *p*-nitrobenzaldehyde in the presence of 5 mol % catalyst under ultrasonication. Therefore, synthesis of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole and 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline derivatives was performed in ethanol and acetonitrile respectively.

To evaluate the effect of ultrasound for the model reactions (Table 2, compounds **2** and **12**), we first examined these model reactions without ultrasound in the presence of 5 mol % L-proline at room temperature using the optimum

Table 3 Comparative study of some aminoacid as catalysts.[a]

Entry	Catalyst	Yield (%)[b]	Time (min)
1	No catalyst	58	35
2	Glycine	76	34
3	Alanine	72	31
4	Tyrosine	78	25
5	L-proline	91	17

[a] Reaction condition: as shown in Table 1.

Table 4 Results of the synthesis of imidazol derivatives.

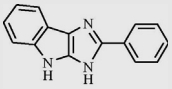
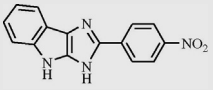
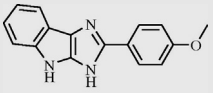
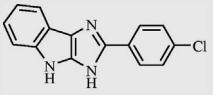
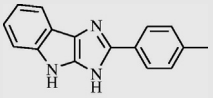
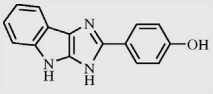
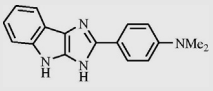
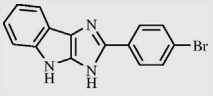
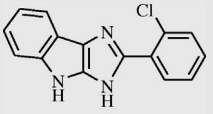
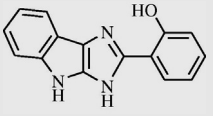
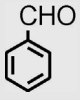
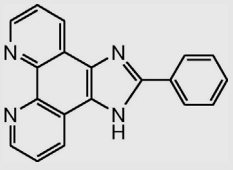
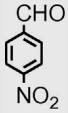
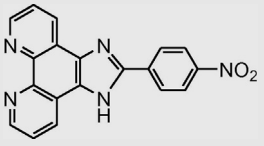
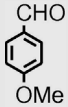
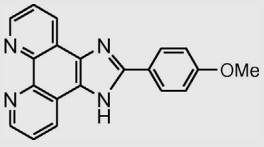
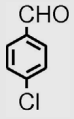
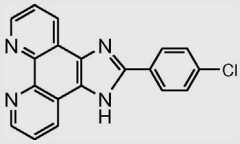
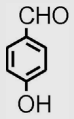
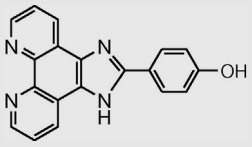
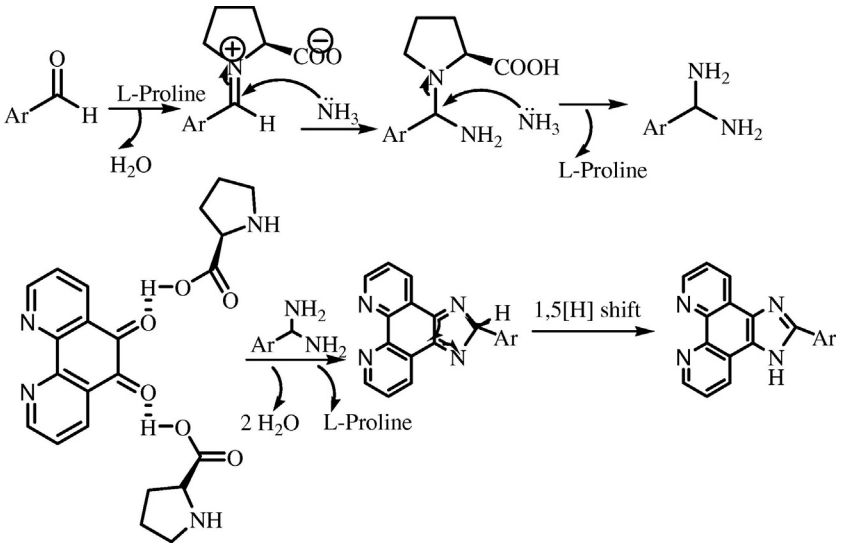
Entry	Aldehyde	Product	Time (min) (min)	Yield[b] (%)
1			14	96
2			17	91
3			15	93
4			16	92
5			15.5	90
6			15.5	88
7			16	85
8			15	91
9			17.5	74
10			13.5	84
11			12	96
12			10	95
13			11	94

Table 4 (*continued*)

Entry	Aldehyde	Product	Time (min) (min)	Yield[b] (%)
14			11	96
15			13	93

Reaction condition: EtOH and acetonitrile as solvents, aromatic aldehyde (1 mmol), diketone (1 mmol), ammonium acetate (4 mmol), catalytic amount 5 mol %, room temperature and under US irradiation.
[b] Isolated yield.



Scheme 2 The proposed mechanism.

solvents found before. Moderate yields of 65% and 74% with almost prolonged reaction times (50 min and 42 min) were obtained for the compounds **2** and **14** respectively, while using ultrasound at room temperature, excellent yields of 91% and 95% with short reaction times (17 min and 14 min) were found for the compounds 2 and 14 respectively. Therefore, in order to describe an efficient and time-saving protocol, all derivatives of 3,4-dihydro-2-arylimidazo[4,5-b]indole and 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline were performed under ultrasound irradiation.

To determine the role of the used catalyst, the model reaction using indoline-2,3-dione, ammonium acetate and *p*-nitrobenzaldehyde was carried out in ethanol in the absence of L-proline under US irradiation, which resulted in 58% yield, after 35 min. Therefore, the catalyst plays a key role in the success of the reaction in terms of yield and rate. Additionally, a number of different catalysts, such as Glycine, Alanine and Tyrosine afforded the desired product in lower yields (Table 3). However, L-proline provided the best results, yielding 91% of product yield within 17 min (Table 3, entry 5).

A series of substituted aromatic aldehydes were treated with indoline-2,3-dione or 1,10-phenanthroline-5,6-dione and ammonium acetate in the presence of L-proline under ultrasonic irradiation, the products were obtained in high to excellent yields. All of the results are shown in Table 4. As shown, aromatic aldehydes bearing either electron-donating or electron-withdrawing groups as well as heterocyclic aldehydes reacted successfully and the corresponding products were isolated in high to excellent yields.

This protocol was further extended by using 1,10-phenanthroline-5,6-dione as a diketone to synthesise various 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthrolines. The one-pot three component condensations of 1,10-phenanthroline-5,6-dione, ammonium acetate and aromatic aldehydes were carried out using the same conditions in acetonitrile as the optimum solvent. Several substituted imidazoles were obtained in excellent yields.

In general, 1,10-phenanthroline-5,6-dione reacted faster and gave excellent yields of the desired imidazoles in shorter reaction times.

The proposed mechanism of this reaction is as shown in Scheme 2. The probable mechanism involves the formation of a diamine intermediate, condensation with 1,10-phenanthroline-5,6-dione, intramolecular cyclization and subsequently [1,5] sigmatropic proton shift to afford the corresponding 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives. In the case of indoline-2,3-dione, reaction proceeds in the same fashion as above.

It is worth mentioning that the model reaction was carried out in the presence of pyrrolidine and benzoic acid separately. Pyrrolidine does not contain the carboxylic acid functional group to promote the reaction by activating the carbonyl groups, while benzoic acid does not contain the amine group to form iminium ion or diamine intermediate. The results revealed that two parts of the catalysts are crucially involved in promoting the reaction since in the case of pyrrolidine and benzoic acid, the rate of reactions were slower and chemical yields were lower, 70% and 78% yields in 32 and 30 min were afforded respectively compared to L-proline.

3. Conclusion

In summary, a clean, one-pot, fast and efficient procedure for the preparation of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole and 2-aryl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline compounds through the three-component reaction of aromatic aldehydes, indoline-2,3-dione or 1,10- phenanthroline-5, 6-dione and ammonium acetate using a catalytic amount of L-proline as catalyst under ultrasonic irradiation has been described. This procedure offers several advantages including mild reaction conditions, high yields of products as well as a simple experimental procedure and applicability of the novel method for a wide range of substrates.

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