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Facile Three-component Synthesis of imidazo[4,5-*b*]indoles

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ABSTRACT

A rapid, efficient and high yielding synthetic procedure to 3,4-dihydro-2-arylimidazo[4,5-b]indole by the multicomponent reaction of aromatic aldehydes, indoline-2,3-dione and ammonium acetate catalyzed by L-proline under ultrasonic irradiation is described.

Keywords: imidazo[4,5-*b*]indole, one-pot, L-proline

INTRODUCTION

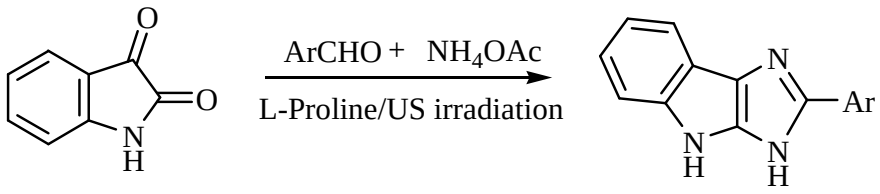
A survey of the pertinent literature reveals that aryl imidazoles have been found to possess a wide spectrum of biological activity such as antibacterial [1], antirheumatoid arthritis [2], antitubercular [3], antiviral [4], anti-inflammatory [5] and anticancer activities [6-8]. Specifically, it has been revealed from the literature that imidazoles fused with indole nucleus possess various biological activities [9-11] including anticancer activity especially against breast cancer.

Imidazole and its derivatives are receiving growing attention for their pharmacologically properties such as herbicidal, fungicidal, analgesic, antiinflammatory and antithromobotic activities [12]. 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 [13], $Yb(OTf)_3$ [14], elemental iodine [15], $ZrCl_4$ [16] and $HClO_4$-SiO_2 [17] were screened. Some procedures also involve ionic liquid-promoted or microwave assisted synthesis [18].

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 [19,20]. Additionally, due to its experimental simplicity, ease of handling, cost 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 [21].

As a part of our ongoing research in developing a versatile and efficient methodology for synthesis of heterocyclic compounds [22, 23], herein, we wish to describe an ultrasound accelerated synthesis of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole and from aldehydes, indoline-2,3-dione and ammonium acetate catalyzed by L-proline (Scheme 1).



Scheme 1. Synthetic route to substituted imidazoles

EXPERIMENTAL SECTION

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 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 pre-coated silica gel plates (60F-254). Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyser.

Typical procedure for preparation of the imidazole derivatives

A mixture of aromatic aldehyde (1 mmol), indoline-2,3-dione 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:

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-d6): δ 7–7.25 (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+).

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-d6): 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+).

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). ^{1}H NMR (100 MHz, DMSO-d6): 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+).

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). ^{1}H NMR (100 MHz, DMSO-d6): 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+).

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). ^{1}H NMR (100 MHz, DMSO-d6): 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+).

RESULTS AND DISCUSSION

At first, three component reaction of indoline-2,3-dione, ammonium acetate and *p*-nitrobenzaldehyde to synthesize the 3,4-dihydro-2-(4-nitrophenyl)imidazo[4,5-*b*]indole as the model reactions were chosen to find the optimum solvent for each reaction. (Tables 1). We screened different solvents such as ethanol, methanol, dichloromethane, acetonitrile, chloroform, dioxane at room temperature under ultrasonication. As shown in the Table 1, the best yield was obtained when ethanol was used as the solvent. In the case of the protic solvents the yields are better than aprotic solvents. Therefore, further synthesis of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole derivatives was performed in ethanol.

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

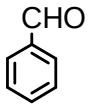
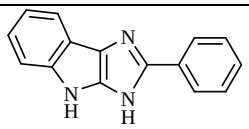
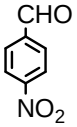
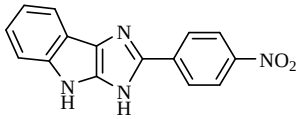
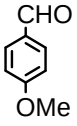
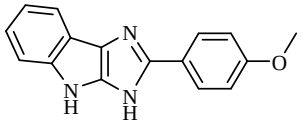
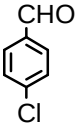
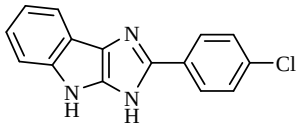
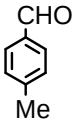
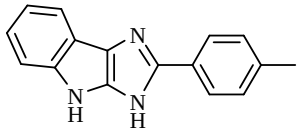
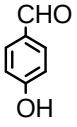
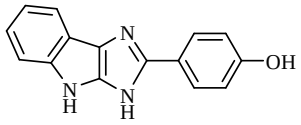
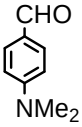
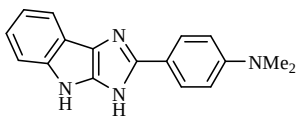
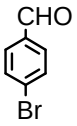
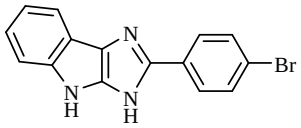
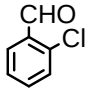
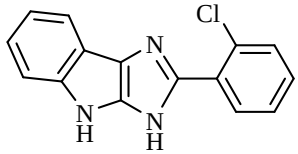
Solvent	Ethanol	Methanol	Dichloromethane	Chloroform	Acetonitrile	Dioxane
Yield[a,b]	91	78	72	77	76	63

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

To evaluate the effect of ultrasound for the model reactions (Table 2, compounds 2), we first examined the model reactions without ultrasound in the presence of 5 mol% L-proline at room temperature using the optimum solvent found before. Moderate yields of 65% with almost prolonged reaction times (50 min) were obtained for the compound 2 at reflux condition, while using ultrasound at room temperature, excellent yields of 91% with short reaction times (17 min) were found for the compound 2. Therefore, in order to describe an efficient and time-saving protocol, all derivatives of 3,4-dihydro-2-arylimidazo[4,5-b]indole 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.

Table2. Results of the synthesis of imidazol derivatives.

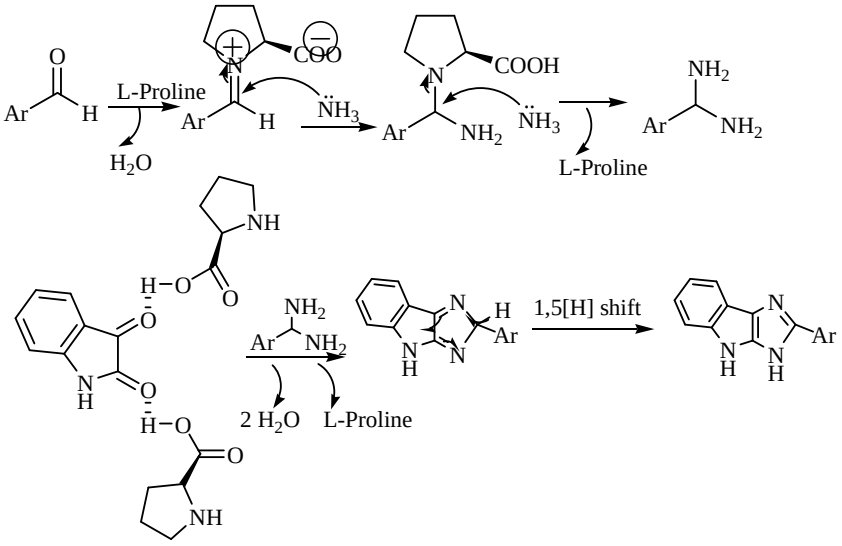
Entry	Aldehyde	Product	Time (min)	Yield (%)[b]
1			**14**	**96**
2			**17**	**91**
3			**15**	**93**
4			**16**	**92**
5			**15.5**	**90**
6			**15.5**	**88**
7			**16**	**85**
8			**15**	**91**
9			**17.5**	**74**

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

A series of substituted aromatic aldehydes were treated with indoline-2,3-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 2. 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.

The proposed mechanism of this reaction is as shown in Scheme 2. The probable mechanism involves the formation of a diamine intermediate, condensation with indoline-2,3-dione, intramolecular cyclization and subsequently [1,5] sigmatropic proton shift to afford the corresponding 3,4-dihydro-2-arylimidazo[4,5-b]indole derivatives.



Scheme 2. The proposed mechanism

CONCLUSION

In conclusion, a clean, one-pot, fast and efficient procedure for the preparation of 3,4-dihydro-2-arylimidazo[4,5-*b*]indole compounds through the three-component reaction of aromatic aldehydes, indoline-2,3-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 and applicability of the novel method for the wide range of substrates.

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