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ORIGINAL ARTICLE

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

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KEYWORDS

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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

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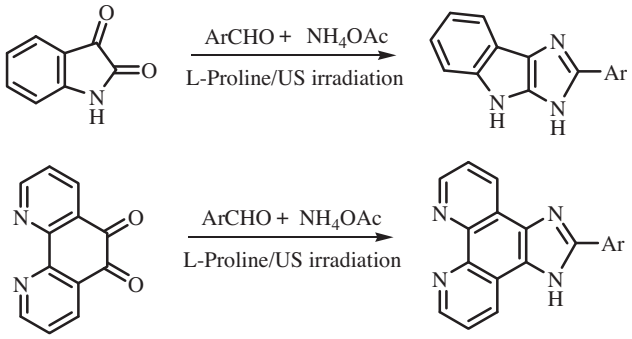


Scheme 1 Synthetic route to substituted imidazoles.

reaction (Dalko and Moisan, 2004; Lacoste, 2006). 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 (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:

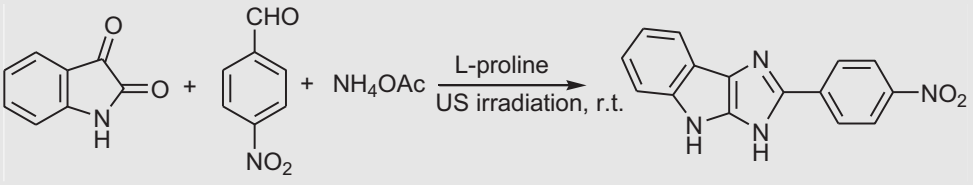
1.3. 3,4-Dihydro-2-phenylimidazo[4,5-b]indole (**1**)

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.

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