L-Proline as an Efficient Catalyst for the Synthesis of 2,4,5-Triaryl-1*H*-Imidazoles

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L-Proline has been found to be an efficient organocatalyst for one-pot synthesis of 2,4,5-triaryl substituted imidazole by the reaction of an aldehyde, a benzil and an ammonium acetate. The short reaction time and excellent yields making this protocol practical and economically attractive.

Key Words: L-Proline, 2,4,5-Triaryl substituted imidazoles, Aromatic aldehydes, Ammonium acetate, Benzil

Introduction

Imidazole nucleus is of significant importance to medicinal chemistry and plays important role in biochemical process[1]. Several imidazole containing compounds are known to possess significant biological activities such as, antiulcerative-Cimetidine,[2] proton pump inhibitor-Omeprazole,[3] fungicide-Ketoconazole.[4] In addition to this, imidazoles are substantially used in the synthesis of ionic liquids[5] that have been given a new approach to green chemistry. They are also used in photography as a photosensitive compound.[6] Thus, synthesis of the imidazole nucleus has been received extensive attention to the researchers.

Due to their great importance, many synthetic strategies have been developed for the synthesis of imidazoles. In 1882, Radziszewski reported the first synthesis of imidazoles from 1,2-dicarbonyl compound using various aldehydes and ammonia, to obtain the 2,4,5-trisubstituatedimidazoles.[7] It also has been synthesized using nitriles and esters.[8] Recently, various reports on the synthesis of 2,4,5-triaryl-1*H*-imidazoles starting from an aldehyde, a benzil, and an ammonium acetate in presence of catalysts such as HY-zeolite/silica gel,[9] $ZrCl_4$,[10] $NiCl_2{\cdot}6H_2O$,[11] ionic liquid,[12] iodine,[13] sodium bisulfite,[14] excess H_2SO_4,[15] AcOH,[16] NH_4OAc,[17] $Yb(OTf)_3$,[18] *p*-toluenesulfonic acid (*p*-TSA),[19] potassium aluminum sulfate (Alum)[20] and $InCl_3{\cdot}3H_2O$.[21] However, these methods have its own merit while some of these are plagued by the limitation of prolonged reaction time, exotic reaction conditions and lower yields. Hence, the development of a new method for the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives would be highly desirable.

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents large amounts of solvents and expensive purification techniques represents a fundamental target of the modern organic synthesis.[22]

Recently, the commercially available and inexpensive amino acid L-proline has been elegantly used to catalyze many reaction such as the Mannich reaction and the direct asymmetric Aldol reaction.[23] The proline function has been proposed to act like a 'microaldolase' that facilitates each step of the mechanism including the formation of the intermediate imine and the carbon-carbon bond. Very recently, L-proline has also been effectively used as a versatile organocatalyst in various organic transformations.[24] L-proline exploited as an efficient organocatalyst in the organic synthetic routes for carbon-carbon, carbon-heteroatom bonds and heterocycles.[25] In the present study, we extend the scope of the L-proline-catalyzed synthesis of 2,4,5-triaryl substituted imidazoles and the results from our study are presented herein. Obviously the chirality of the catalyst is not necessary for the procedure, because 2,4,5-triaryl substituted imidazoles does not possess any chiral center.

Experimental

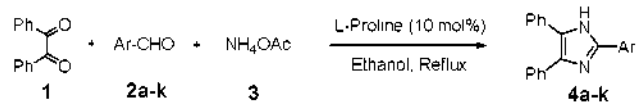
All the melting points were determined in open capillaries in an paraffin bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. ^{1}H NMR spectra were recorded on Mercury plus Varian in DMSO or $CDCl_3$ at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique. The progress of the reactions was monitored by TLC.

General experimental procedure synthesis of 2,4,5-triaryl-1*H*-imidazole (4a-j). A mixture of an aromatic aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (3 mmol) and L-Proline (10 mol%) in ethanol (20 mL) was stirred at reflux temperature for 2 ~ 3 hr. The progress of the reaction was monitored by TLC. After completion of reaction conversion, the reaction mixture was cooled to room temperature and poured on crushed ice. The obtained crude solid product was filtered, dried and crystallized from ethanol.

Results and Discussion

In continuation of our research work on the development of novel synthetic methodologies,[26] herein, we would like to report a highly efficient route for the synthesis of 2,4,5-triaryl imidazoles catalyzed by an commercially available, inexpensive, mild organocatalyst L-proline. This protocol is a one-pot three component coupling of aldehyde, benzil and ammonium acetate in ethanol (Scheme 1).

In our search for the better solvent and the best experimental reaction conditions in the preparation of 2,4,5-triarylimidazoles,



Scheme 1

Table 1. Screening of solvents for the synthesis of 4a[a]

Entry	Solvent	Yield (%)[b]
1	Dioxane	38
2	Acetonitrile	43
3	Tetrahydrofuran	49
4	Dichloromethane	54
5	Chloroform	57
6	Methanol	82
7	2-Propanol	87
8	Ethanol	93

[a]Reaction condition: **1** (1 mmol), **2a** (1 mmol), **3** (3 mmol), L-proline (10 mol%) at reflux temperature. [b]Isolated yield.

Table 2. Screening of catalyst for the synthesis of 4a[a]

Entry	Catalyst	Time (min)	Yield (%)[b]
1	Without catalyst	180	37
2	Glycine	150	77
3	3-aminopropanoic acid	135	84
4	L-proline	125	93

[a]Reaction conditions: **1** (1 mmol), **2a** (1 mmol), **3** (3 mmol), catalyst (10 mol%) in ethanol at reflux temperature. [b]Isolated yield.

Table 3. Effect of concentration of L-Proline[a]

Entry	Concentration (mol%)	Yield (%)[b]
1	5	82
2	7.5	88
3	10	93
4	12.5	93

[a]Reaction condition: **1** (1 mmol), **2a** (1 mmol), **3** (3 mmol) in ethanol at reflux temperature. [b]Isolated yield.

we have determined that the reaction of benzaldehyde **2a**, benzoin **1** and ammonium acetate **3** in ethanol at reflux is the standard model reaction.

To evaluate the effect of solvent, we have screened different solvents such as dichloromethane, tetrahydrofuran, acetonitrile, chloroform, dioxane, methanol, 2-propanol and ethanol at reflux temperature. Ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (93%) of desired product, whereas the product formed in lower yields (38 ~ 87%) by using other solvents (Table 1, Entry 1 ~ 7). In case of the protic solvents the yields are better than aprotic solvent. (Table 1, Entry 6 ~ 8).

We screened a number of different catalysts, such as glycine, 3-aminopropanoic acid afforded the desired product in low yields 77% and 84%, respectively (Table 2, Entry 2 and 3). However, L-proline provided the best results, yielding 93% of product yield within 125 min (Table 2, Entry 4). To determine

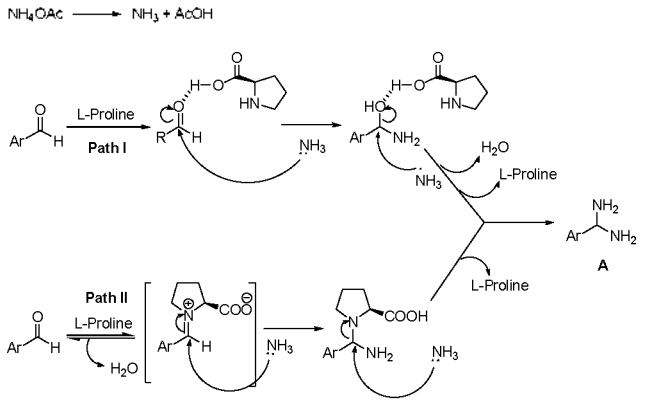


Figure 1. Step I.

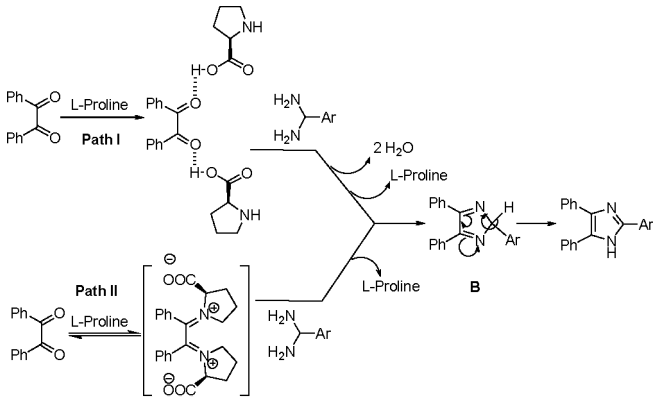


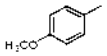
Figure 2. Step II.

the role of catalyst, the same reaction was carried out in the absence of catalyst at same condition, which resulted in 37% yield formation, after 180 min. These results indicate that catalyst exhibits a high catalytic activity in this transformation.

To determine the optimum concentration of catalyst, we have investigated the model reaction at 5, 7.5, 10 and 12.5 mol% of L-proline in ethanol at reflux temperature. The product was obtained in 82, 88, 93 and 93% yield, respectively. This indicates that the use of 10 mol% of L-proline is sufficient to promote the reaction forward (Table 3).

The catalyst plays a crucial role in the success of the reaction in terms of the rate and yield of product. The chirality of the catalyst is not necessary for the described procedure, but the L-proline in comparison with the corresponding racemic amino acid [d,l-Proline] makes the choice of catalyst. The proposed mechanism for the L-proline catalyzed synthesis of 2,4,5-triaryl-imidazoles is occurs *via* a tandem sequence of reaction as depicted in Figure 1. In the first step, formation of the intermediate-diamine **A** takes place by two different paths (Figure 1). Path I involves the activation of the carbonyl oxygen by the acid part of L-proline through intermolecular hydrogen bonding[27] whereas Path II involves the formation of imindium by the amine part of L-proline.[28] Similarly, Step II follows these two paths by reaction of intermediate A and benzil to form a common intermediate **B** (Figure 2), which on rearrangement through a [1,5] hydrogen shift[29] gives rise to 2,4,5-triarylimidazoles.

Table 4. L-proline catalyzed synthesis of 2,4,5-triaryl substituted imidazoles[a]

Entry	Compound	Ar-CHO	Time (min)	Yield (%)[b]	M.P. (°C)	
					Found	Literature
1	**4a**		125	93	274 ~ 276	276 ~ 277[9]
2	**4b**		115	94	231 ~ 232	231 ~ 232[9]
3	**4c**		120	90	229 ~ 231	227 ~ 228[9]
4	**4d**		135	92	268 ~ 270	268 ~ 270[14]
5	**4e**		140	90	257 ~ 259	257 ~ 258[9]
6	**4f**		145	91	194 ~ 196	195 ~ 196[14]
7	**4g**		140	88	262 ~ 264	260 ~ 262[14]
8	**4h**		130	91	190 ~ 192	190[10]
9	**4i**		150	75	230 ~ 232	232 ~ 233[14]
10	**4j**		145	89	198 ~ 200	199 ~ 201[14]
11	**4k**		140	84	258 ~ 260	260 ~ 261[13]

[a]*Reaction condition:* **1** (1 mmol), **2a-k** (1 mmol), **3** (3 mmol), L-proline (10 mol%) in ethanol at reflux temperature. [b]Isolated yield.

Table 5. Compares some of our results with some of the aforementioned methods for the synthesis of 2,4,5-triaryl-1*H*-Imidazoles

Entry	Catalyst	Reaction condition	Time (h)	Yield (%)	Reference
1	L-proline	EtOH/reflux	2 ~ 5	75 ~ 94	present
2	Excess H_2SO_4	150 ~ 200 °C	4	40 ~ 90	15
3	*p*-TSA / TBAI	145 °C	1 ~ 4	75 ~ 95	19
4	Alum	EtOH / 70 °C	2.5 ~ 4	82 ~ 94	20
5	$InCl_3 \cdot 3H_2O$	MeOH / RT	8.3 ~ 9.4	54 ~ 82	21

To differentiate these two paths the reaction was carried out in the presence of pyrrolidine. The pyrrolidine does not contain the carboxylic acid functional group to promote the path I. hence the reaction follows the path II. Similarly the same reaction is carried out in benzoic acid it does not contain the amine group hence it follow path I. But in case of pyrrolidine and benzoic acid the rate of reaction is slow as well as % yield is lower 68% and 76% respectively compared to L-proline.

To study the generality of this process, variety of examples were illustrated for the synthesis of 2,4,5-triaryl imidazoles and results are summarized in Table 4. The reaction is compatible for various substituents such as CH_3, OCH_3, OH, $N(CH_3)_2$, Cl and F. This method is also effective for the heteroaromatic aldehydes which form their corresponding 2,4,5-triarylimidazole derivatives in 74 ~ 89% of yields (Table 3, Entry 10 and 11). The formation of desired product was confirmed by ^{1}H NMR, IR and mass spectroscopic analysis technique.[30] Also the melting points were recorded and compared with the corresponding literature data.

In order to show the merit of this method in Table 5, we have compared our result with results obtained by some other reported procedures for the synthesis of 2,4,5-triaryl-1*H*-imidazoles. The data presented in this table show the promising feature of this method in terms of reaction rate and the yield of product compared with those reported in the literature.

Conclusion

In conclusion, we have described a general and highly efficient procedure for the preparation of 2,4,5-triaryl substituted imidazoles derivatives using commercially available inexpensive L-proline as an organocatalyst in ethanol. The remarkable advantage of this protocol is mild reaction conditions, excellent yields of product, operational and experimental simplicity. We believe that, this methodology will be a valuable addition to the existing methods for the synthesis of 2,4,5-triaryl substituted imidazoles.

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30. **Spectroscopic data of principle compounds.**
2,4,5-Triphenyl-1*H*-imidazole (4a): IR (KBr, cm^{-1}): 3430 (N-H), 3050 (C-H), 1600 (C = C), 1580 (C = N). ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz, δ ppm): 7.6-8.1 (m, 15 H, Ar-H), 12.50 (1 H, brs, NH). ES-MS (m/z): 297 (M + 1).
2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4c): IR (KBr, cm^{-1}): 3436 (N-H), 2950 (C-H), 1610 (C = C), 1575 (C = N), 1385 (C-O). ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz, δ ppm): 3.90 (s, 3 H), 7.05 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.90 (d, 2 H, *J* = 8.4 Hz, Ar-H). 7.30-7.80 (m, 10 H, Ar-H), 12.21 (1 H, brs, NH). ES-MS (m/z): 327 (M + 1).
2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4g): IR (KBr, cm^{-1}): 3435 (N-H), 1600 (C = C), 1580 (C = N). ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz, δ ppm): 7.35 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.85 (d, 2 H, *J* = 8.4 Hz, Ar-H) 7.20-7.70 (m, 10 H, Ar-H) 12.16 (1 H, brs, NH). ES-MS (m/z): 331 (M + 1), 332 (M + 3).
2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (4i): IR (KBr, cm^{-1}): 3421 (N-H), 1580 (C = N), 1515 (-NO_2), 1335 (-NO_2). ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz, δ ppm): 7.90 (d, 2 H, *J* = 8.4 Hz, Ar-H), 8.2 (d, 2 H, *J* = 8.4, Ar-H) 7.15-7.70 (m, 10 H, Ar-H) 12.10 (1 H, brs, NH). ES-MS (m/z): 342 (M + 1).
2-(2-Furyl)-4,5-diphenyl-1*H*-imidazole (4k): IR (KBr, cm^{-1}): 3316. (N-H), 2993 (C-H), 1660 (C = C), 1210, (C-O), ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz, δ ppm): 11.21 (brs, 1 H, NH), 7.15-7.6 (m, 10 H, Ar-H) 7.46-7.58 (m, 4 H). ES-MS (m/z): 287 (M + 1).