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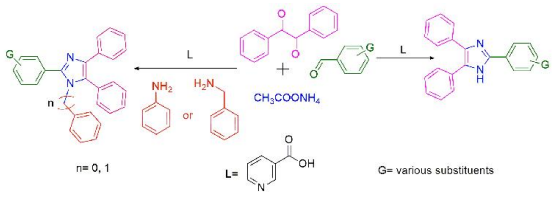
Highly efficient and environmentally benign synthesis of tri- and tetrasubstituted imidazoles catalyzed by 3-picolinic acid

Harendra Nath Roy,[a] Abu Zafar Sarker[a, *], Masud Rana[a], Kee-In Lee[b]



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Highly efficient and environmentally benign synthesis of tri- and tetrasubstituted imidazoles catalyzed by 3-picolinic acid

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ABSTRACT

3-Picolinic acid has been found to be an efficient organocatalyst for one-pot synthesis of 2, 4, 5-triaryl substituted imidazoles. Moreover, the utility of this protocol has further been explored for the four components synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles. The key advantages of this process are high yield, cost effectiveness, easy purification and above all environmentally benign.

Introduction

Today the synthesis, reactions and biological properties of substituted imidazoles covers a significant area of modern heterocyclic chemistry.[1] Notably, compounds with imidazole core units have many pharmacological properties and play an important role in different biochemical processes.[2] Modern research revealed that, highly substituted imidazoles derivatives possess a good photophysical properties, which result in their potential application in material chemistry.[3] Moreover, appropriately substituted imidazoles are extensively used as glucagon receptors,[4] CB1 cannabinoid receptor antagonists[5] and in some cases antibacterial,[6] antitumor[7] and pesticides.[8] Recent advances in green chemistry and organometallic catalysis have extended the utility of imidazoles as ionic liquids[9] and N-heterocyclic carbenes.[10, 11] Based on the above facts, a variety of synthetic routes are available in the literature to synthesis imidazoles analogues including ionic liquids,[12] [Hmim]TFA,[13] ceric ammonium nitrate(CAN),[14] $InCl_3.3H_2O$,[15] $NiCl_2.6H_2O$,[16] ZnO-nano tubes,[17] nano-$TiCl_4$ SiO_2,[18] BF_3•SiO_2,[19] ammonium metavanadate,[20] cellulose sulfuric acid,[21] boric acid,[22] $Yb(OTf)_3$,[23] potassium aluminum sulfate,[24] *p*-tolune sulfonic acid (*p*-TSA),[25] $ZrOCl_2$•$8H_2O$,[26] $K_5CoW_{12}O_{40}$•$3H_2O$,[27] AcOH,[28] KH_2PO_4,[29] PEG-400,[30] zeolite-HY/silica gel,[31] $ZrCl_4$,[32] sodium bisulfite,[33] NH_4OAc,[34] iodine[35] and microwave irradiation[36] are most notable. But, by considering the current application of different tri-and tetrasubstituted imidazoles in many aspects and to obviate the problems of the avilable procedures, chemists are adopting newer methods comparatively better in the sense of cost, yield and to the environment. Recently, organocatalysts[37] has drawn much attention in different organic transformations owing to its' experimental simplicity, ease of handling, cost efffectiveness and above all excellent solubility in organic solvents or in water. Moreover, multicomponents reactions have created unusual sensation especially in the field of organic synthesis[38] because of this reaction some straightforward outcomes are obtained today. But, few examples of multicomponent reactions mediated by organocatalysts towards imidazole synthesis are reported in the literature. So, in view to obtain tri- and tetrasubstituted imidazoles herein, we have adopted a multicomponent strategy to condense benzil, aldehydes, ammonium acetate, aniline / benzylamine mediated by 3-picolinic acid.[39] Although 3-picolinic acid is not familiar as organocatalyst in the organic transformation but its presence in this reaction, has brought an elegant transformation to various imidazoles with great ease and high yields.

Result & Discussion

This is an extension[40] of our earlier attempts in synthesizing biologically active molecules by screening organocatalyst via multicomponent scaffold. Initially, we attempted to synthesise substituted imidazoles from benzil, benzaldehyde and ammonium acetate mediated by some small bifunctional molecules like o-aminophenol, *p*-aminophenol, 2-picolinic acid and aspartic acid in ethanol. Reacting components were mixed thoroughly with the mentioned molecules (2.5~10 mol%) and it was gently heated over an oil bath to different temperatures. But, TLC monitoring has indicated a tiny conversion of the starting materials with the exception observed for 2- picolinic acid. Notably, the use of 2-picolinic acid converted the starting materials to the desired product **1** in 65 % yields. But, we were hopeful to increase the yield of the product **1** by changing the catalyst (table 1), catalyst

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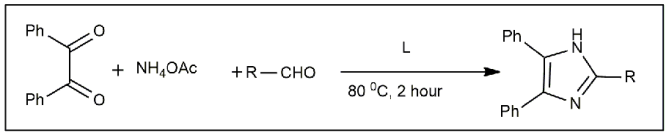
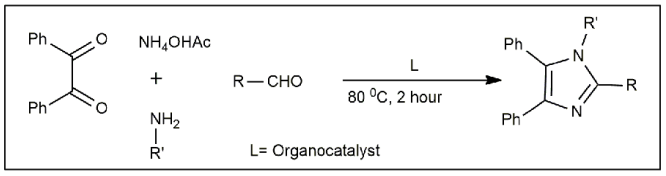
loading, solvents (table 2) and temperatures. Subsequently, by changing the mentioned parameters the required product **1** was produced albeit in low yield. May be the incipient location of –COOH group in pyridine ring discouraged 2-picolinic acid to release its proton towards aldehyde for necessary activation. Therefore, from the optimistic result, we opted to use 3-picolinic acid to the same reaction and by this catalyst (10 mole %) full conversions of the starting materials were observed after 2 hours reflux at 80 ^{0}C. The feasibility of the reaction was investigated with the changes of catalyst loading (table 3) and it was observed that 10 mol% catalysts is appropriate for the desired target in excellent yields. With the optimised conditions in hand, we have studied the scope and limitations with benzil / benzoin, ammonium acetate and various benzaldehydes. It is remarkable that the aryl chloride and bromide were compatible substrates with the yield of 90% & 88% respectively, and these molecules could provide a convenient access to metal-catalysed cross coupling reactions. Heterocyclic aldehydes (1H-indole-3-carbaldehyde & furan-2-carbaldehyde) were well tolerated under similar conditions to obtain the compounds **8** & **10** in 85 % & 87% yield. In all the cases reaction went on smoothly without any difficulties observed. With the success of a three component reaction in hand, we further extended our methodology for the construction of various substituted imidazole scaffolds by utilizing four component reactions. Under identical reaction conditions (table 4), with stoichiometric ratio of aniline derivatives as the fourth component, to our delight the reaction underwent smooth conversion to obtain the desired compounds in good to excellent yields (table 4). Reaction mechanism may follow the same pattern as mentioned in the literature.[41] But, in our case, 3-picolinic acid is donating its proton to aldehydes for necessary activation and N-atom on the other hand, abstracts protons where it is necessary to complete the reaction. By this way, the catalyst has played a dual role in the success of the present reaction both rate and the yield of the products. Some aldehydes like, resorcaldehyde, salicylaldehyde, chloralhydrate and cinamaldehyde did not afford the expected imidazoles. Failure of the reaction may arise due to excessive electron pushing functionalities present in the aromatic ring make the aldehydic carbon less electrophilic. With the same catalyst and standardized reaction conditions, seventeen different tri- and tetrasubstituted imidazoles (table 4) were synthesised without any sophisticated purification techniques. Interestingly, benzoin also reacted in the same fashion and afforded imidazoles with high yields and thereby makes the reaction path shorter. Some of the products are known in the literature, so for such cases only melting points were compared with the literature values given.[11, 24(a), 26, 32]



Scheme-1: synthesis of trisubstituted imidazoles in ethanol using 3-picolinic acid as a catalyst.



Scheme-2: synthesis of tetrasubstituted imidazoles in ethanol using 3-picolinic acid as a catalyst.

Table-1: Effect of catalyst on the reaction of benzil, benzaldehyde, and ammonium acetate in ethanol.

Entry	Catalyst	Time (hour)	Yield (%)[a]
I	no catalyst	48	25
II	*o*-aminophenol	47	27
III	*p*-aminophenol	47.5	43
IV	Aspartic acid	48	30
V	2-picolinic acid	12-18	50
VI	3-picolinic acid	2	90

[a] Isolated yield

Table-2: Effect of catalyst on the reaction of benzil, benzaldehyde, and ammonium acetate in various solvents.

Entry	Solvent	Yield (%)[a]
I	no solvent	35
II	water	40
III	methanol: water (1:1)	45
IV	methanol	50
V	ethanol : water (1:1)	65
VI	ethanol	90

[a] Isolated yield

Table-3: Effect of concentration of 3-picolinic acid on the reaction of benzil, benzaldehyde, and ammonium acetate in ethanol.

Entry	Concentration (mol%)	Yield (%)[a]
I	2.5	60
II	5	72
III	7.5	85
IV	10	90
V	12.5	90

[a] Isolated yield

Table-4: Synthesis of imidazoles by the reaction of benzil, aldehyde, and ammonium acetate in the presence of 3-picolinic acid in ethanol.

Entry	Compound	R		Benzil		Mp(^{0}C)	
				Yield(%)[a]	Time(min)	Found	Reported
I	**1**	2-ClC_6H_4		90	135	195-197	195-196[26]
II	**2**	4-$CH_3OC_6H_4$		92	130	229-231	227-228[24(a)]
III	**3**	$C_{10}H_7$		92	120	215-217	215[32]
IV	**4**	$C_6H_3O_2CH_2$		94	125	295-297	
V	**5**	4-HOC_6H_4		92	135	269-270	268-270[32]
VI	**6**	3-BrC_6H_4		88	120	200-201	199-200[32]
VII	**7**	4-$(CH_3)_2NC_6H_4$		97	125	259-261	257-258[24(a)]
VIII	**8**	$C_6H_3C_2H_2(NH)$		85	110	281-282	
IX	**9**	3-$O_2NC_6H_4$		97	115	>300	>300[32]
X	**10**	C_4H_3O		87	120	200-202	199-201[26]
For four component		R	R´				
XI	**11**	4-ClC_6H_4	$C_6H_5CH_2$	92	130	160-162	162-163[11]
XII	**12**	$C_6H_3O_2CH_2$	$C_6H_5CH_2$	92	120	130-132	
XIII	**13**	4-$(CH_3)_2NC_6H_4$	$C_6H_5CH_2$	90	125	180-182	
XIV	**14**	4-$O_2NC_6H_4$	$C_6H_5CH_2$	92	120	170-172	
XV	**15**	4-$CH_3OC_6H_4$	C_6H_5	90	130	174-176	
XVI	**16**	$C_6H_3C_2H_2(NH)$	C_6H_5	90	125	247-249	
XVII	**17**	4-$(CH_3)_2NC_6H_4$	C_6H_5	92	120	238-240	

[a] Isolated yield.

Conclusion

In conclusion, the study describes an efficient, rapid and convenient synthesis of tri- and tetrasubstituted imidazoles in a one-pot, three and four component coupling reaction strategy using inexpensive, less toxic and easily available 3-picolinic acid as an organocatalyst in ethanol. The present method offers several advantages especially easy experimental work-up procedure, tidy purification techniques, shorter reaction times, and higher yields. Besides, tolerability of the various substituents in the aromatic aldehydes were observed, Thus, this simple technique could be used as a contending method for the highly substituted imidazole motifs.

Acknowledgments

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39. General method for the synthesis of tri-substituted imidazoles: A mixture of benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol) and 3-picolinic acid (10 mol%) in ethanol (1 mL) was stirred at reflux temperature for 2 hour. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and by neutralization with 5% $NaHCO_3$ a white color solid was appeared. It was filtered, washed with water and dried over P_2O_5. Most of the products were sufficiently pure; however if necessary recrystallization were done from EtOH. Same procedures were adopted for aryl / benzyl amine bases.
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