Glutamic acid as an efficient and green catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles under thermal, solvent-free conditions

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A high-yielding synthesis of 1,2,4,5-tetrasubstituted imidazoles is described, involving the reaction of 1,2-dicarbonyl compounds, aryl aldehydes, amines and ammonium acetate in the presence of a catalytic amount of glutamic acid under thermal, solvent-free conditions. The salient features of this protocol are aerobic conditions, a non-hazardous green catalyst, short reaction times and mild reaction conditions.

Keywords: glutamic acid, 1,2,4,5-tetrasubstituted imidazoles, solvent-free, green catalyst, ammonium acetate, 1,2-dicarbonyl compounds

Multi-component reactions (MCRs) have been demonstrated to be highly successful in generating products in a single synthetic operation.[1] The development of new MCRs[2] and the modification of existing MCRs are areas of notable current interest. One such reaction is the synthesis of imidazole rings. Tetrasubstituted imidazoles are core parts of many biologically active molecules, such as Losartan and Olmesartan.[3] The presence of an imidazole ring in natural products and pharmacologically active compounds has established a diverse array of synthetic methods for obtaining these heterocycles.[4] The synthesis, reactions and biological attributes of substituted imidazoles constitute an important part of modern heterocyclic chemistry.[5] However, despite substantial efforts, only a handful of general techniques exist for the construction of tetrasubstituted imidazoles. Recently, the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been catalysed by silica gel or Zeolite HY,[6] silica gel/$NaHSO_4$,[7] molecular iodine,[8] $InCl_3$-$3H_2O$,[9] $K_5CoW_{12}O_{40}.3H_2O$,[10] $[bmim]_3[CdCl_6]$,[11] $NaNO_2$,[12] L-proline,[13] $HClO_4$–SiO_2,[14] $SbCl_5.SiO_2$[15] and 1,4-diazabicyclo[2.2.2]octane (DABCO).[16]

The methods reported previously for the synthesis of 1,2,4,5-tetrasubstituted imidazoles suffer from severe disadvantages, such as long reaction times, hazardous organic solvents, complex work-up and purification, strongly acidic conditions, high temperatures, use of toxic metal catalysts and inadequate yields. Based on the above information and because of our interest in developing synthetic strategies for the construction of heterocyclic compounds, we have now used a glutamic acid-catalysed condensation as a new and rapid method affording excellent yields for the synthesis of 1,2,4,5-tetrasubstituted imidazoles under thermal, solvent-free conditions.

Results and discussion

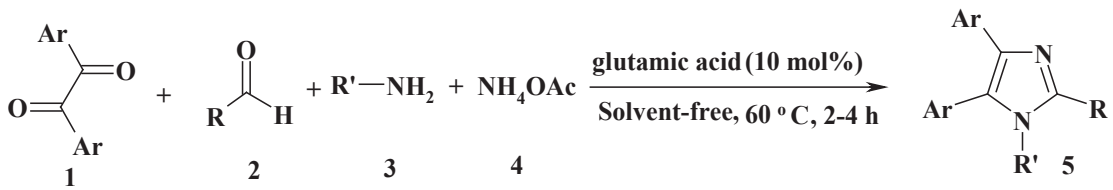
In continuation of our studies on MCRs,[17–19] we report here the reaction between 1,2-dicarbonyl compounds **1**, aryl aldehydes **2**, amines **3** and ammonium acetate **4** in the presence of a catalytic amount of glutamic acid under thermal, solvent-free conditions (Scheme 1).

Initially, we began with the condensation of benzil (1 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and ammonium acetate (1 mmol) in solvent-free conditions at 30 °C for 24 h in the absence of catalyst, which led to a very poor yield (10%) of 1,2,4,5-tetraphenylimidazole. To enhance the yield of the desired product, the temperature of the reaction was increased to 60 °C, but no appreciable increment in the product yield was observed. It was then thought worthwhile to carry out the reaction in the presence of an organocatalyst, glutamic acid. We also increased the amount of catalyst required for this transformation, and it was found, from using 5 mol%, 10 mol%, 15 mol%, 20 mol% and 25 mol% catalyst, that the maximum yield (90%) was obtained when the reaction mixture was loaded with 10 mol% of the catalyst (Table 1). Further increasing the amount of catalyst adversely affected the yield and slowed down the reaction slightly. The detailed results obtained are given in Table 1.

The substrate scope of the reaction was then evaluated using a variety of structurally diverse 1,2-dicarbonyl compounds, aryl aldehydes and primary amines (Table 2). The strategy was tolerant of electron-donating and electron-withdrawing groups in the aryl aldehyde. Both aromatic and aliphatic primary amines have been successfully subjected to this protocol.

Table 1 Optimisation of the reaction conditions for synthesis of **5a**

Entry	Catalyst (mol%)	Solvent/conditions	Time (h)	Yield (%)
1	Glutamic acid (0)	Solvent-free/30 °C	24	10
2	Glutamic acid (0)	Solvent-free/60 °C	24	25
3	Glutamic acid (5)	Solvent-free/30 °C	10	55
4	Glutamic acid (5)	Solvent-free/60 °C	6	70
5	Glutamic acid (10)	Solvent-free/60 °C	4	90
6	Glutamic acid (15)	Solvent-free/60 °C	4	90
7	Glutamic acid (20)	Solvent-free/60 °C	4	80
8	Glutamic acid (25)	Solvent-free/60 °C	4	65
9	Glutamic acid (10)	Solvent-free/30 °C	7	60
10	Glutamic acid (10)	Solvent-free/90 °C	4	45



Scheme 1 Synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of glutamic acid under thermal, solvent-free conditions.

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Table 2 Reaction between 1,2-dicarbonyl compounds, aryl aldehydes, amines and ammonium acetate in the presence of a catalytic amount of glutamic acid under thermal, solvent-free conditions

Product	Ar	R	R'	Time (h)	Yield (%)[a]	M.p. (°C)	
						Found	Reported
5a	C_6H_5	C_6H_5	C_6H_5	4	90	217–219	216–218 (Ref. 20)
5b	C_6H_5	4-Cl-C_6H_4	C_6H_5	2	95	165–167	164–166 (Ref. 21)
5c	C_6H_5	4-No_2-C_6H_4	C_6H_5	3	85	186–188	184–186 (Ref. 22)
5d	C_6H_5	4-Br-C_6H_4	C_6H_5	2	90	155–157	152–154 (Ref. 23)
5e	C_6H_5	4-OMe-C_6H_4	C_6H_5	4	80	187–189	185–188 (Ref. 24)
5f	C_6H_5	4-Me-C_6H_4	C_6H_5	4	85	189–191	186–188 (Ref. 24)
5g	C_6H_5	4-OH-C_6H_4	C_6H_5	4	75	290–292	287–289 (Ref. 25)
5h	C_6H_5	C_6H_5	$C_6H_5CH_2$	3	92	161–163	163–165 (Ref. 14)
5i	C_6H_5	4-Cl-C_6H_4	$C_6H_5CH_2$	2	90	163–165	162–164 (Ref. 22)
5j	C_6H_5	4-OH-C_6H_4	$C_6H_5CH_2$	3	80	131–133	134–135 (Ref. 14)
5k	C_6H_5	3-OMe-C_6H_4	$C_6H_5CH_2$	3	85	129–131	128–130 (Ref. 20)
5l	C_6H_5	4-OMe-C_6H_4	$C_6H_5CH_2$	3	80	165–167	164–165 (Ref. 26)
5m	C_6H_5	4-Me-C_6H_4	$C_6H_5CH_2$	4	75	162–164	165–166 (Ref. 20)
5n	C_6H_5	4-Br-C_6H_4	$C_6H_5CH_2$	2	95	171–173	172–174 (Ref. 14)
5o	4-Cl-C_6H_4	4-Me-C_6H_4	$C_6H_5CH_2$	3	91	186–188	185–186 (Ref. 26)
5p	4-Me-C_6H_4	4-OMe-C_6H_4	$C_6H_5CH_2$	3	86	181–183	183–184 (Ref. 26)
5q	C_6H_5	2-OH-4-NO_2-C_6H_3	$C_6H_5CH_2$	3	80	220–222	-

[a]Yields refer to the pure isolated products.

The compounds **5a–p** were characterised by their ^{1}H NMR and IR spectra and also by elemental analyses.[20–26]

Compound **5q** was new, and its structure was deduced by elemental and spectral analysis. The mass spectrum of **5q** showed the molecular ion peak at *m/z* 447. The ^{1}H NMR spectrum of **5q** exhibited a methylene proton signal at 5.03 ppm, and the OH proton was observed at 9.43 ppm, which disappeared after addition of some D_2O. Also observed were multiplets between 6.70 and 7.44 ppm, which are related to the aromatic protons. The ^{13}C NMR spectrum of **5q** showed 22 signals, in agreement with the proposed structure, while the IR spectrum also supported the suggested structure.

Conclusions

In summary, we have shown that glutamic acid has several advantages in the preparation of 1,2,4,5-tetrasubstituted imidazoles, such as short reaction times, simple work-up, aerobic conditions, and is a non-hazardous, green catalyst that affords excellent yields. Also, the present method does not involve any hazardous organic solvent. Therefore, this procedure can be classified as green chemistry.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a JASCO FT/IR-460Plus spectrophotometer. The NMR spectra were obtained on a Bruker Avance DRX-400 FT spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard.

Synthesis of 1,2,4,5-tetrasubstituted imidazoles; general procedure

Glutamic acid (0.1 mmol) was added to a mixture of the 1,2-dicarbonyl compound (1 mmol), aryl aldehyde (1 mmol), amine (1 mmol) and ammonium acetate (1 mmol). The reaction mixture was heated to 60 °C and maintained for the appropriate time (Table 2). The progress of the reaction was followed by TLC (*n*-hexane–ethyl acetate). After completion of the reaction, the mixture was washed with H_2O (3 × 10 mL) and filtered to remove the catalyst. The crude product was recrystallised from hot ethanol to obtain the pure compound.

1-Benzyl-2-(2'-hydroxy-5'-nitrobenzyl)-4,5-diphenyl-1H-imidazole (**5o**): Pale yellow solid; FTIR (ν_{max}/cm^{-1}): 3425, 3032, 2940, 2867, 1619, 1468; MS (*m/z*, %): 447 (5); ^{1}H NMR ($CDCl_3$): δ 5.03 (s, 2H), 6.70–7.44 (m, 18H), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 48.3, 118.9, 119.4, 125.9, 126.2, 126.7, 127.4, 127.9, 128.7, 128.8, 129.1, 129.8, 130.3, 130.5, 131.2, 131.8, 134.0, 139.6, 140.4, 146.4, 159.9, 166.2; Anal. calcd for $C_{28}H_{21}N_3O_3$: C, 75.15; H, 4.73; N, 9.39; found: C, 75.31; H, 4.90; N, 9.27%.

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