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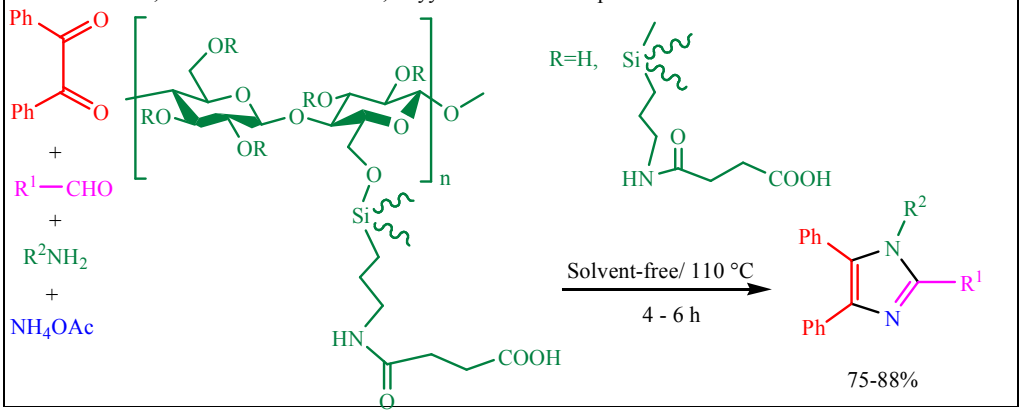

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(carboxy-3-oxopropylamino)-3-propylsilylcellulose as a novel organocatalyst for synthesis of substituted imidazoles under solvent-free condition

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(carboxy-3-oxopropylamino)-3-propylsilylcellulose (COPAPSC) as a novel organocatalyst has been prepared by synthesis grafting of –COOH functionalized organosilane on cellulose by using surface hydroxyl groups as anchor point. $–CO_2H$ group functionalized cellulose via consecutive surface functionalization with 3-aminopropyltriethoxysilane (3-APTES) followed by the condensation of the surface $–NH_2$ groups with the succinic anhydride. COPAPSC is used as a catalyst for the synthesis of tri- and tetrasubstituted imidazoles from the reaction of benzil, aromatic aldehydes, ammonium acetate, and amines under solvent-free conditions. The key advantages of this process are high yields, easy work-up, purification of products by non-chromatographic method and the reusability of the catalyst.

Keywords: (carboxy-3-oxopropylamino)-3-propylsilylcellulose, 2,4,5-Trisubstituted imidazoles, 1,2,4,5-Tetrasubstituted imidazoles, Solvent-free synthesis

Introduction

Nowadays, owing to increasing concern about environmental consciousness, more attention has been focused on the development of new processes that minimize pollution and maximize sustainable development in chemical synthesis [1].

In this respect, immobilization of catalysts on solid supports has several important potential advantages such as removal, recovery, and reutilization of catalysts; reduced environmental contamination; good thermal and chemical stabilities; and good dispersion of the active catalytic site [2]. For this purpose, exploring heterogeneous catalysis is obviously on the rise, especially in industry [3]. Many solid materials as supports, such as silica [4], zeolites [5], metal oxides [6], graphene [7], magnetic-materials [8], and polymers [9] have broadly been investigated for catalytic applications. A considerable stimulation of scientific and technological research has been triggered over the past 10 years in response to the growing global importance of renewable resources and environmentally compatible materials [10]. In the field, natural biopolymers especially cellulose could be utilized as a support for catalytic applications.

Cellulose is the most widely spread organic polymer that is found in nature because it constitutes the main component of the plants' cell walls. It is well-known that cellulose is a fascinating, inexhaustible biopolymer and renewable raw material. It was widely applied as an efficient support and/or template for synthesis of inorganic and organic materials. For example, sulfuric acid was supported on the cellulose, and the acid modified cellulose was used as an activated catalyst for the synthesis of α-amino amide derivatives through Ugi reactions, synthesis of 1,4-dihydropyridines through Hantzsch reaction, and synthesis of 3,4-dihydropyrimidin-2(1H)-ones/-thiones through Biginelli reaction [11-13]. On the other hand, carboxylate-functionalized cellulose was prepared by succinic anhydride and cellulose and used as an effective biosorbent for heavy metals remediation [14]. In recent years, cellulose has gained renewed as a raw material and still possesses a high potential for future applications The imidazole nucleus is a fertile source of biologically important molecules [15] and is the core structural skeleton in many important biological molecules like histidine, histamine, biotin, as well as several drug moieties [16, 17] such as Trifenagrel, Eprosartan, and Losartan. In addition, they are used in photography as photosensitive compounds. Some substituted triarylimidazoles are selective antagonists of the glucagon receptors and inhibitors of IL-1 biosynthesis [18].

The recent development of green chemistry and organometallic chemistry expands the utility of imidazoles as ionic liquids [19–21] and N-heterocyclic carbenes [19, 22, 23]. Radziszewski and Jaap [24, 25] proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes, and ammonia to obtain 2,4,5-triphenylimidazole.

by these foregoing discussion and with given our interest and experience in the area of heterogeneous catalysis in organic synthesis [26–28], we report a new surface –CO2H group functionalized cellulose via consecutive surface functionalization with 3-aminopropyltriethoxysilane (3-APTES) followed by the condensation of the surface $–NH_2$ groups with the succinic anhydride (Scheme 1). Previously $–CO_2H$ and $–SO_3H$ functionalized cellulose has been reported, but the incorporation of the $–CO_2H$ group on cellulose by condensation between an anhydride and a primary amine has not been studied so far. Increasing importance of metal-free catalysis, on the contrary, motivated us to use this organically modified acid functionalized cellulose (COPAPSC) as a catalyst for the synthesis of imidazole from a mixture of aromatic aldehyde, amine and α diketone. To the best of our knowledge, organocatalysis promoted by a $–CO_2H$ functionalized cellulose for the synthesis of imidazole has not been explored so far.

Experimental

General

Chemicals were purchased from Merck and Fluka chemical companies. IR spectra were recorded in KBr pellets in reflection

mode on an Avata Therma Nicolet FTIR. ^{1}HNMR spectra were recorded on a Bruker Avance DPX-250 MHz spectrometer using TMS as an internal standard and $CDCl_3$ or DMSO as solvent. ^{13}CNMR spectra were recorded on a Bruker Avance DPX-62.5 MHz spectrometer ($CDCl_3$ or DMSO solution). Mass spectra were recorded on GC 17A, MS QP 5050 Shimadzu. Elemental analysis for C, H, and N were obtained using an Elementar, Vario EL III. All the reactions were monitored by thin layer chromatography (TLC) on pre-coated sheets of silica gel G/UV-254 using UV light for visualization. Melting points were determined with Electrothermal 9100 melting point apparatus.

Preparation of COPAPSC

To a magnetically stirred cellulose (5.0 g) was suspended in dry toluene (50 ml) and then an excess of 3-APTES (5.0 ml) was added. The suspension was mechanically stirred as it was heated under reflux for 24 h under Ar atmosphere. The resulting white solid was filtered, washed repeatedly with toluene, ethanol-water, deionized water and methanol and finally dried under vacuum at 60 °C for 4 h to give 3-aminopropylsilylcellulose (3-APSC (5.2 g). This 3-APSC functionalized cellulose was stirred with 0.15 g (15 mmol) of succinic anhydride dissolved in dry chloroform (20 ml) for 4 h at 50 °C, and the final product was collected by filtration, washed sequentially with chloroform, ethanol and diethyl ether. The produce was dried in a vacuum desiccator to give COPAPSA as a white powder (5.39 g).

General procedure for the preparation of imidazole derivatives

A mixture of 1,2-diketone (1 mmol), aromatic aldehyde (1 mmol), amine (1 mmol), ammonium acetate (1.5 mmol), and COPAPSA (0.2 g equal to 0.05 mmol of H^+) was stirred at 110 °C under solvent-free conditions for the given time (Tables 2 and 3). After completion of the reaction, appropriate amounts of hot EtOH (96%) was added and the mixture was stirred for 10 min and then the catalyst was separated by filtration. The catalyst was washed with warm ethanol (3 ml × 3) to effectively clean. The filtrate was concentrated in vacuum to remove the ethanol. The residue was washed with cold water and crystallized from hot ethanol to afford the pure products. Recovered catalyst was dried and reused in the subsequent runs.

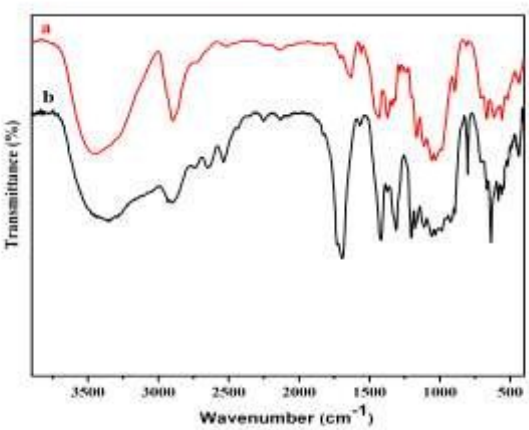

Fig. 1 FT-IR spectra of: (a) Cellulose and (b) COPAPSA

Results and discussion

Catalyst characterization

Figure 1 shows the FT-IR spectra of the cellulose and COPAPSA. The absorbance at 3200–3500 cm^{-1} can be attributed the O–H and N-H amid stretching vibration of CBPAOBA. Two bonds at 2933 and 2898 cm^{-1} are attributed to $–CH_2–$ asymmetric and symmetric stretching vibration. The absorbance at 1728 and 1693 cm^{-1} are due to carbonyl groups of acidic and amide respectively. Another band at 1419 cm^{-1} is attributed to the C–N stretching vibration which was overlapped with the –C–C–H vibration of cellulose. The absorbance at 1058 cm^{-1} is assigned –C–O– stretching vibration [29]. The OH vibration of carboxylic groups is overlapped with the OH vibration of cellulose.

The nitrogen content in COPAPSA was determined to be 0.32% (0/23 mmol g^{-1}) by elemental analysis. The number of H^+ sites of COPAPSA was determined to be 0.25 mmol g^{-1} by acid–base titration, which was very close to the nitrogen content. These results indicated that most of the nitrogen species on the sample were in the form of amide groups.

In continuation of our work on the development of useful synthetic methodologies toward the synthesis of heterocyclic compounds, the catalytic activity of the Bronsted acid COPAPSA was tested for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles under solvent-free condition (Scheme 2).

We attempted to find technically simple, high yielding, and solvent-free condition for the synthesis of these compounds. Therefore, we studied COPAPSA as a catalyst in the cyclocondensation of benzil, aldehyde, ammonium acetate, and amine. First of all, the reaction of 4-chlorobenzaldehyde (1 mmol), ammonium acetate (1.5 mmol) and benzil (1 mmol) catalyzed by COPAPSA was investigated in different solvents as well as under solvent-free condition in which the results are shown in Table 1.

Initial screening studies confirmed that solvent-free technique is the optimal condition for this reaction. Another important point which could be elicited evidently from these results is that raising the reaction temperature from 80 to 110 °C and amount of catalyst from 0.08 to 0.2 g increased the yield and also improved the reaction rates (Table 1, Entries 2-10). A further increasing of catalyst loading does not affect the yield (Table 1,entry 11). Moreover, it is worth mentioning that application of solvents such as H_2O, EtOH, CH_3OH, ethylene glycol, and glycerol did not lead to better results. Under these conditions, longer reaction times and lower yields can be observed clearly (Table 1, Entries 12-16). On the contrary, due to the growing concern for the influence of the organic solvent on the environment as well as on the human body, organic reactions without the use of conventional organic solvents have attracted the attention of synthetic organic chemists. It is observed that the solvent-free conditions gave an excellent yield of product and the shortest reaction time than in the presence of solvents. The development of solvent-free organic reactions is thus gaining prominence.

As a control experiment, cyclocondensation of benzil, aldehyde, and ammonium acetate was also carried out at 110 °C in the presence cellulose for 6 hour under solvent-free condition resulted in a yield of 15% (Table 1, Entry 1).

After determining the optimum reaction conditions, we turned our attention to studying the scope of this method. We applied this catalyst for the synthesis of trisubstituted and tetrasubstituted imidazoles by using different aromatic aldehydes with a wide range of substitutions under solvent- free heating conditions to establish the catalytic importance of COPAPSA for this reaction. The corresponding results are given in Table 2 and 3.

The proposed mechanism for the formation of the products can be explained by the pathway presented in Scheme 2. The reaction commenced through the acid catalyzed formation of imine (**7**) which underwent nucleophilic attack by aniline to give the in situ intermediate (**8**). An acid catalyzed condensation between this intermediate (**8**) and diketone (**1**) produced another in situ intermediate (**9**) which on subsequent aromatization produces the tetrasubstituted imidazole (**6a**) and releases the catalyst for the next catalytic cycle (Scheme 3) [15].

Recyclability of the catalyst was also examined. To this end, the catalyst which was recovered from the reaction between benzil, aniline, benzaldehyde, and ammonium acetate by filtration was washed three times with warm ethanol and dried at 80 °C for a period of 5 h in a vacuum oven. The recovered catalyst can be reused four times in subsequent reactions without any significant loss in its activity. The results with the recyclable COPAPSA are summarized in Fig. 2.

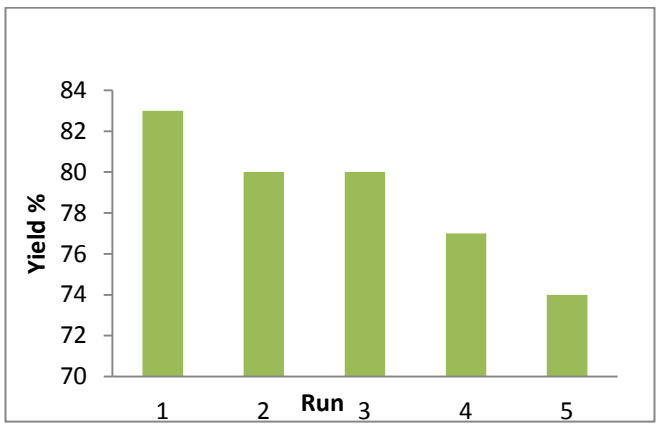

Fig. 2 Reusability of COPAPSA in condensation of benzaldehyde, ammonium acetate, aniline and benzyl at 110 °C under solvent-free conditions in 5 h.

In Table 4, the efficiency of our method for the synthesis of imidazoles is compared with some other published works in literature. The reaction of 4-choloro benzaldehyde, benzil, and ammonium acetate was used as a model reaction. Each of these methods have their own advantages, but they often suffer from some troubles including the use of organic solvent, (entries 2- 5) and long reaction time (entries 6–9).

In summary, COPAPSA, an efficient, reusable, green and solidly supportive biodegradable acid catalyst, has been prepared and utilized for the synthesis of imidazole derivatives by a one-pot coupling reaction of benzil, benzaldehyde compounds, ammonium acetate, and primary amine. Moreover, the broad scope, operational simplicity, and practicability render it an attractive approach for the generation of different compounds with potential properties for the use in medicinal chemistry programs.

Selected experimental data

2-(4-Methoxyphenyl)-4, 5-diphenyl-1H-imidazole (4b). White solid, (85%, 0.277 g) mp: 231–233 °C (Lit[30]. mp 228-230 ° C). IR (KBr, υ: cm^{-1}): 3425, 3029, 2956, 1610, 1495, 1249; ^{1}HNMR (250 MHz, DMSO-d_6) (δ, ppm): 3.79 (s, 3H) , 7.05 (d, J = 8.4 Hz, 2H), 7.50–7.28 (m, 10H), 8.03 (d, J = 8.1 Hz, 2H), 12.50 (s, 1H); ^{13}C NMR (62.9MHz, DMSO-d_6) (δ, ppm): 55.2, 114.1, 123.5, 126.8, 127.7, 128.4, 129, 131.6, 135.7, 137.2, 146.1, 159.8; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.90; H, 5.51; N, 8.63.

1-(4-Methylphenyl)-2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole (6k). Yellow solid, (87%, 0.375 g) mp: 150-152 °C (Lit[33]. 149-151 ° C). IR (KBr, υ: cm^{-1}): 3052, 1596, 1525, 1350; ^{1}H NMR (250 MHz, DMSO-d_6) (δ, ppm): 2.34 (s, 3H), 7.45–6.94 (m, 14H), 7.50 (t, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) (δ, ppm): 21.2, 122.7, 123.4, 126.9, 127.3, 127.9, 128.2, 128.8, 129.1, 131.0, 132.0, 132.2, 133.7, 134.3, 138.7, 139.1, 144.3, 148.0; Anal. Calcd for $C_{28}H_{21}N_3O_2$: C, 77.94; H, 4.91; N, 9.74. Found: C, 77.89; H, 4.97; N, 9.78.

Acknowledgements

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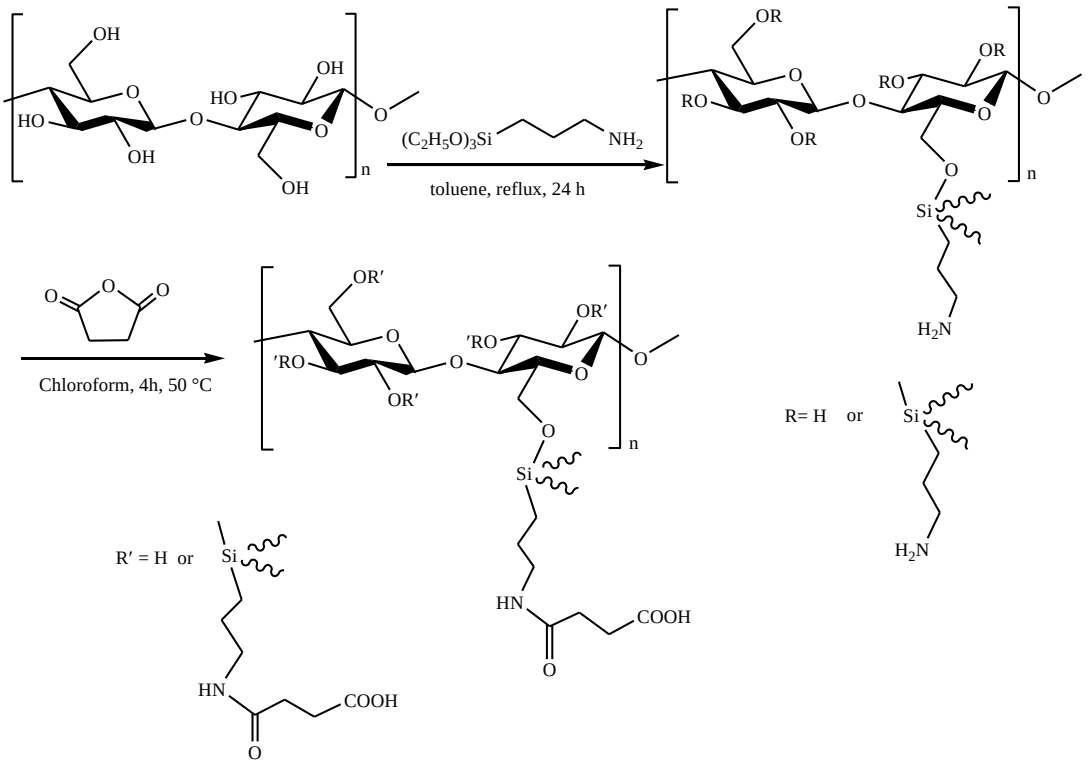
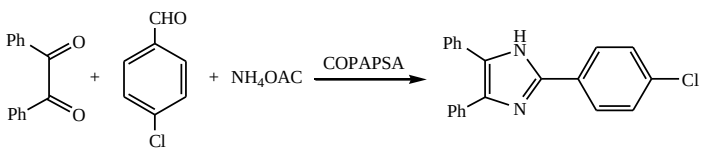


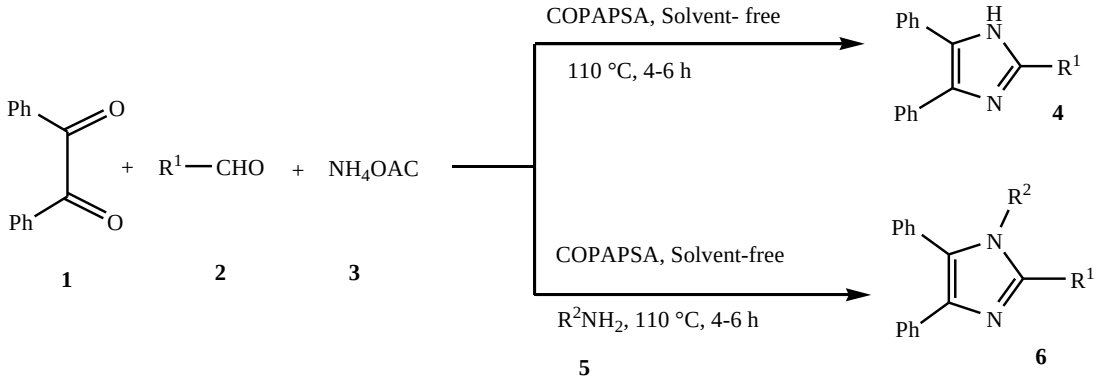
Scheme 1 Preparation of (carboxy-3-oxopropylamino)-3-propylsilylcellulose

Table 1 Effect of solvent, temperature and amount of catalyst on the synthesis of 4d[a]



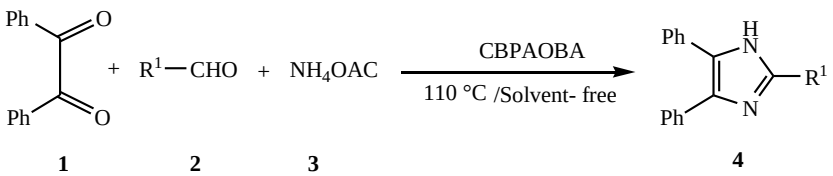
Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (h)	Yield [b] (%)
1	Cellulose (0.2)	Solvent free	110	6	15
2	COPAPSA (0.08)	Solvent free	80	7	40
3	COPAPSA (0.10)	Solvent free	80	7	52
4	COPAPSA (0.20)	Solvent free	80	5	63
5	COPAPSA (0.08)	Solvent free	100	5	55
6	COPAPSA (0.10)	Solvent free	100	5	73
7	COPAPSA (0.20)	Solvent free	100	5	80
8	COPAPSA (0.08)	Solvent free	110	5	60
9	COPAPSA (0.10)	Solvent free	110	4	72
10	COPAPSA (0.2)	Solvent free	110	4	84
11	COPAPSA (0.3)	Solvent free	110	4	84
12	COPAPSA (0.20)	Water	Reflux	7	-
13	COPAPSA (0.20)	Methanol	Reflux	7	72
14	COPAPSA (0.20)	Ethanol	Reflux	5.5	70
15	COPAPSA (0.20)	Ethylene glycol	140	9	70
16	COPAPSA (0.20)	Glycerol	140	8	75

[a] Reaction condition: 4-chlorobenzaldehyde (1 mmol), ammonium acetate (1.5 mmol), and benzil (1 mmol) in the presence of cellulose and COPAPSA.
[b] Isolated yields.



Scheme 2 COPAPSA catalyzed synthesis of trisubstituted and tetrasubstituted imidazoles

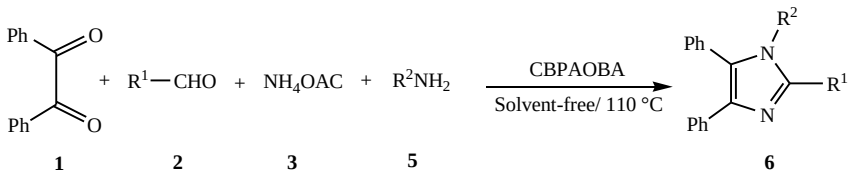
Table 2 Synthesis of 2, 4, 5-trisubstituted imidazoles [a]



Entry	R^1	Product	Time (h)	MP◦C (lit.) [Ref.]	Yield [b] (%)
1	C_6H_5	4a	4	270-273 (274-276) 30	77
2	4-$OMeC_6H_4$	4b	4	226-228 (228-230) 30	85
3	4-MeC_6H_4	4c	4	227-229 (232-234) 30	82
4	4-ClC_6H_4	4d	4	260-261(260-262) 30	84
5	4-$NO_2C_6H_4$	4e	4	235-238 (234-236) 30	82
6	3-$NO_2C_6H_4$	4f	4	263-265 (>300) 31	78
7	4-OHC_6H_4	4g	5	230-233 (234-236) 30	77
8	2-OHC_6H_4	4h	4	207-210 (202-205) 31	79
9	4-BrC_6H_4	4j	4	244-246 (254-256) 30	88
10	2-$NO_2C_6H_4$	4k	5.5	228-230 (230-231) 31	80
11	4-$N(Me)_2C_6H_4$	4l	6	256-259 (256-259) 31	75

[a]Reactions were performed with the benzil (1 mmol), aromatic aldehyde (1 mmol), ammonium acetate (1.5 mmol) and COPAPSA (0. 2 g equal to 0.05 mmol H^+) at 110 °C under solvent-free conditions.
[b] Isolated yields of pure products.

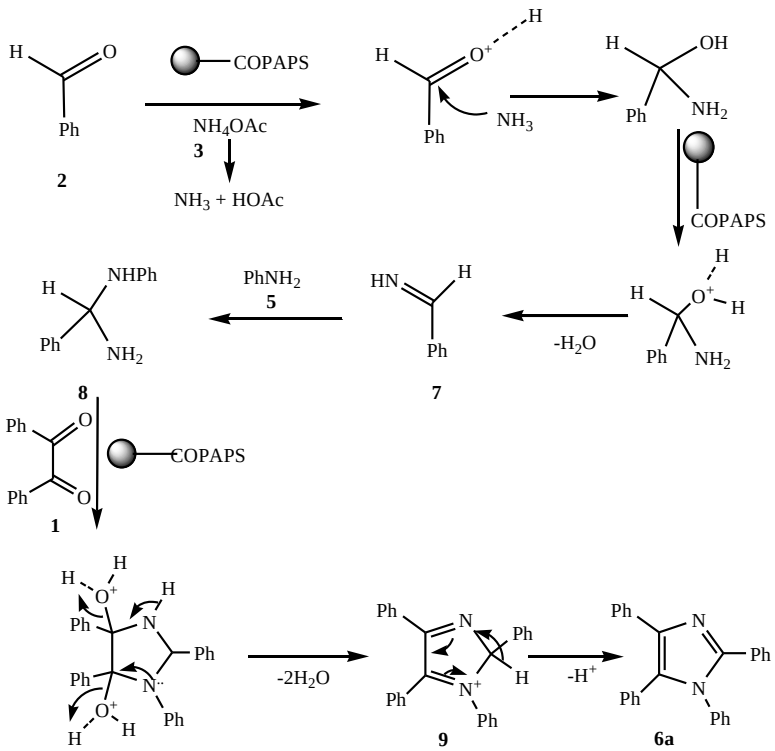
Table 3 Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles [a]



1 2 3 5 6

Entry	R^1	R^2	Product	Time (h)	MP°C (lit.) [Ref.]	Yield [b] (%)
1	C_6H_5	C_6H_5	6a	5.5	210-211 (214-216) 15	83
2	3-ClC_6H_4	Benzyl	6b	5	148-150 (144-146) 32	85
3	4-ClC_6H_4	Benzyl	6c	5	156-158 (160-162) 15	82
4	4-$OMeC_6H_4$	4-MeC_6H_4	6d	3.5	180-181 (176-178) 33	85
5	4-$OMeC_6H_4$	Benzyl	6e	4	160-163 (162-164) 15	87
6	2-ClC_6H_4	Benzyl	6f	5	137-139 (140-141) 34	75
7	4-OHC_6H_4	Benzyl	6g	4	137-138 (134-135) 34	84
8	4-BrC_6H_4	Benzyl	6h	5	175-178 (170-172) 34	75
9	4-$NO_2C_6H_4$	4-MeC_6H_4	6i	4	223-226 (219-220) 32	75
10	4-OHC_6H_4	Benzyl	6j	4.5	253-254 (257-259) 15	78
11	3-$NO_2C_6H_4$	4-MeC_6H_4	6k	4	150-152 (149-151) 32	87
12	4-MeC_6H_4	4-MeC_6H_4	6l	4	192 194 (188-191) 32	80

[a]Reactions were performed with the benzil (1.0 mmol), aromatic aldehyde (1.0 mmol), ammonium acetate (1.0 mmol), amine (1.0 mmol), and COPAPSA (0. 2 g equal to 0.05 mmol H^+) at 110 °C under solvent-free conditions.
[b] Isolated yields of pure products.



Scheme 3. Probable mechanism for the formation of 6a using COPAPSA as catalyst

Table 4 Comparison of results using COPAPSA with results obtained by other works for the synthesis of 4d

Entry	Catalyst	Condition	Yield (%)[a]	Ref.
1	COPAPSA	Solvent free, 110 °C, 4 h	84	-
2	$Yb(OPf)_3$	HOAc, $C_{10}F_{18}$ 80 °C, 6h	83	35
3	Acetic acid	Chloroform, 160, MWI, 15 min	90	36
4	$InCl_3 \cdot 3H_2O$	MeOH, r.t., 9.4 h	71	37
5	diethyl bromophosphate	CH_3CN, ultrason., 30 min	95	38
6	DABCO	t-BuOH, 65°C, 12 h,	92	39
7	CSC-Star-SO_3AlCl_2	EtOH, 80°C, 10 h,	94	40
8	L-proline	MeOH, 60 °C, 9 h	88	31
9	MCM-41	Reflux in AcOH, 32 min	82	41

