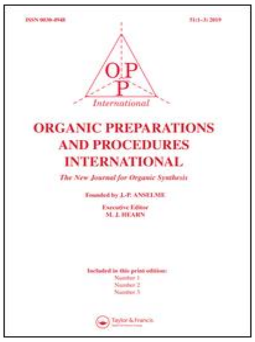

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EXPERIMENTAL PAPER

An Efficient Synthesis of Substituted Imidazoles Catalyzed by 3-N-Morpholinopropanesulfonic Acid (MOPS) under Ultrasound Irradiation

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Imidazoles are a major class of five-membered, nitrogen-containing heterocyclic compounds possessing a wide spectrum of biological and physical activities.[1–5] Because of its importance, numerous methods have been reported in the literature for the synthesis of the imidazole moiety. For example, the synthesis of 1,2,4,5-tetraarylimidazoles is generally carried out by using 1,2-diphenylethanedione, an aromatic aldehyde and an amine in the presence of ammonium acetate and a number of catalysts, reagents and solvents.[6–21] Following a recent trend in organic synthesis, considerable research activity has centered on using catalysts with the sulfonic acid functionality.[22–26] In view of this, we sought to develop a new, mild, simple and nontoxic method for the preparation of substituted imidazoles. We also tried to find a method that would replace lengthy heating with ultrasound and would be greener.[27–30] In continuation of our research on developing green methods and catalysts,[31–32] we examined the activity of the readily available and environmentally benign 3-(N-morpholino)propane sulfonic acid (MOPS) as a catalyst for the one-pot four-component synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives in aqueous ethanol under ultrasound (Schemes 1 and 2).

In search of suitable reaction conditions, we chose the model reaction of 1,2-diphenylethanedione, 4-hydroxy benzaldehyde and ammonium acetate in ethanol in the presence of a number of additives, as shown in Table 1. In the presence of MOPS it was found that the desired product was formed in 85% yield in just 30 min.

To probe the role of the solvent, the model reaction was carried out with MOPS under different solvent conditions. The studies in Table 2 showed that ethanol-water (1:1 v/v) was the best choice of solvent for this transformation.

The model reaction was tested at different temperatures. The reaction at reflux temperature gave a high yield of 90% in 20 min (Table 2). The reaction was also carried out using different amounts of the catalyst and the results showed that 10 mol % of catalyst was the best choice for completing the reaction in the ethanol-water (1:1) system. See the Experimental section for details on catalyst recovery and re-cycling. After optimizing the reaction conditions, the model reaction was also performed using ultrasonic

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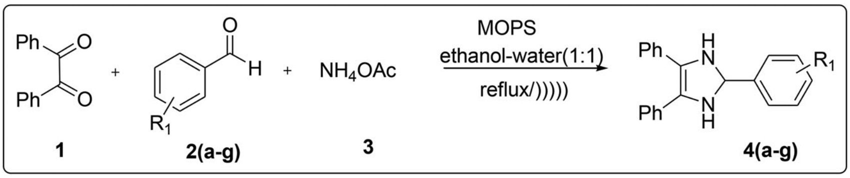
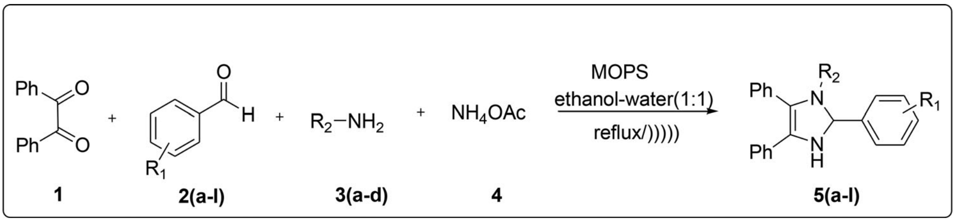


Scheme 1. Synthesis of 2,4,5-tetrasubstituted imidazoles catalyzed by MOPS.



Scheme 2. Synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by MOPS.

irradiation. The reaction was found to proceed smoothly within a very short reaction time and delivered the desired product in excellent yield (Tables 3 and 4).

In summary, we found that MOPS serves as an effective catalyst for the preparation of imidazoles in high yields. Our method avoids the use of harsh reagents, and the use of ultrasonic irradiation greatly shortens the over-all reaction time.

Experimental section

All reagents were obtained from Sigma Aldrich. The reaction was monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). Ethyl acetate and n-hexane were used as eluting solvents. Chemicals used were SD Fine or Sigma Aldrich and used without further purification. Melting points were measured in open glass capillaries and are uncorrected. ^{1}H NMR was recorded on a Varian 200 MHz instrument in $CDCl_3$ using TMS as internal standard. All of the products were known compounds, characterized by comparison of their melting points with literature values in the references cited. An Equitron ultrasonic cleaner (50 KHz and 170 W) was used for ultrasonication.

Synthesis of 2,4,5-Trisubstituted Imidazoles

General Procedure: 1,2-Diphenylethanedione (0.210 g, 1.00 mmol), aromatic aldehyde (1.00 mmol), and ammonium acetate (0.308 g, 4.00 mmol) were dissolved in 10 mL of ethanol-water (1:1). Then 10 mol % of the MOPS was added to the reaction mixture and heated at reflux with constant stirring for the appropriate time, as monitored by TLC. The reaction mixture was cooled to room temperature and poured onto crushed ice to get the solid product. This crude product was filtered and washed several times with water and dried. Further purification was carried out by recrystallization from ethanol.

Procedure using ultrasound irradiation: The same reaction was carried out using ultrasound irradiation. We used the Equitron ultrasonic cleaner with 50 KHz and 170 W power. The same stoichiometry of reactants was taken in a round bottom flask and

Table 1. Influence of different catalysts and solvents on the model reaction.

Entry	Catalyst	Solvent	Isolated yield (%)	Time (min)
1.	–	Ethanol	20	300
2.	Ferric sulfate	Ethanol	55	120
3.	$CuSO_4$	Ethanol	50	120
4.	Sulfamic acid	Ethanol	65	90
5.	Sulfinilic acid	Ethanol	68	60
6.	Methane sulfonic acid	Ethanol	80	60
7.	MOPS	Ethanol	85	30
8.	MOPS	Methanol	78	60
9.	MOPS	Water	65	90
10.	MOPS	DMSO	48	120
11.	MOPS	DMF	40	120
12.	MOPS	Acetonitrile	42	100
13.	MOPS	PEG 400	60	120
14.	MOPS	Ethanol -Water (1:1)	90	20
15.	MOPS	Ethanol -Water (2:1)	80	30
16.	MOPS	Ethanol -Water (1:2)	75	45

Reaction Conditions: 1,2-diphenylethanedione (1 mmol), 4-hydroxy benzaldehyde (1 mmol), NH_4OAc (3 mmol), catalyst (20 mol%), in solvent (10 mL) at reflux.

Table 2. The effect of temperature and catalyst concentration.[a]

Entry	Catalyst	Temperature (°C)	Time(min)	Isolated yield (%)
1.	**MOPS (20%)**	**Reflux**	**20**	**90**
2.	MOPS (20%)	80	20	80
3.	MOPS (20%)	60	45	78
4.	MOPS (20%)	40	80	60
5.	MOPS (20%)	RT	120	32
6.	MOPS (15%)	**Reflux**	20	90
7.	**MOPS (10%)**	**Reflux**	**20**	**90**
8.	MOPS (5%)	**Reflux**	80	88
9.	MOPS (3%)	**Reflux**	120	70
10.	**MOPS (10%)**[b]	**Reflux**	**20**	**90, 90, 88**

[a]Reaction Conditions: 1,2-diphenyl ethanedione (1 mmol), 4-hydroxy benzaldehyde (1 mmol), NH_4OAc (3 mmol) and catalyst in 10 mL of ethanol-water (1:1 v/v) at specified temperature.

[b]The reaction was carried out on 50 mmol scale and catalyst was reused three times.

kept in the ultrasonic bath containing water at 40 °C. The surface of the reaction mixture was adjusted vertically to achieve the optimum position at the point at which the maximum surface disturbance occurred. The reaction mixture was continuously sonicated (20 to 60 min.) for the appropriate time, as monitored by TLC. After completion of the reaction, work-up and purification followed as above.

The catalyst was recovered from the aqueous filtrate by evaporating the water; the catalyst was washed with acetone and then air dried and could be reused in subsequent cycles. A similar method was applied for the synthesis of 1,2,4,5-tetrasubstituted-1H-imidazole derivatives by the condensation of 1,2-diphenylethanedione, aromatic aldehydes, aromatic amines and ammonium acetate. Representative spectrometric data are shown below.

2,4,5-Triphenyl-1H-imidazole (4b)

^1H NMR (200 MHz, DMSO-d_6): δ 7.56–7.22 (m, 13H), 8.09 (d, J = 7.8 Hz, 2H), 12.69 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): d 145.6, 137.2, 135.2, 131.2, 130.4, 128.7, 128.5, 128.3, 128.2, 127.8, 127.2, 126.6, 125.3; ESI MS (m/z): 297.3 (M^++1).

Table 3. Synthesis of 2-Aryl-4,5-Diphenyl-1H-Imidazoles.

		With US[a]		Without US[b]		
Entry	R_1	Time (min)	Yield[c] (%)	Time (min)	Yield[c](%)	Mp Obs (lit)[ref]
4a	4-OH	15	90	20	90	264-266 (260-262)[13]
4b	H	20	84	40	80	270-272 (274-276)[13]
4c	4-CH_3	30	84	50	86	228-230 (227-228)[13]
4d	4-OCH_3	20	90	30	86	230-232 (228-230)[12]
4e	4-$N(CH_3)_2$	15	92	25	88	260-262 (258-260)[12]
4f	4-NO_2	30	85	40	82	230-232 (229-231)[12]
4g	4-Cl	20	90	30	85	258-260 (260-262)[12]

[a] Reaction conditions: 1,2-diphenyl ethanedione (1 mmol), aromatic aldehyde (1 mmol), NH_4OAc (3 mmol), catalyst (10 mol %), in 10 mL of ethanol-water (1:1) under ultrasonic waves.

[b] Reaction conditions: 1,2-diphenyl ethanedione (1 mmol), aromatic aldehyde (1 mmol), ammonium acetate (3 mmol), catalyst (10 mol %), in 10 mL of aqueous ethanol (1:1) at reflux.

[c] Isolated yield.

Table 4. Synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives.

			With US[a]		Without US[b]		
Entry	R_1	R_2	Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]	mp Obs (lit)[ref]
5a	4-CH_3	4-Cl C_6H_4	20	88	50	80	170-172 (168-170)[11]
5b	4-Cl	4-Cl C_6H_4	25	94	30	82	186-188 (188-190)[11]
5c	4-Cl	C_6H_5	20	90	40	85	162-164 (162-164)[7]
5d	4-OCH_3	C_6H_5	25	92	45	76	180-182 (179-181)[7]
5e	H	C_6H_5	30	92	40	84	216-218 (213-215)[11]
5f	4-OH	C_6H_5	10	90	20	90	280-282 (283-285)[7]
5g	4-$N(CH_3)_2$	C_6H_5	25	90	40	88	256-258 (261-264)[7]
5h	4-CH_3	C_6H_5	20	90	60	85	184-186 (183-184)[11]
5i	H	C_6H_5 CH_2	25	92	55	88	162-164 (161-163)[11]
5j	4-Cl	C_6H_5 CH_2	20	94	45	80	165-166 (162-163)[21]
5k	4-OH	C_6H_5 CH_2	30	90	40	90	132-134 (134-136)[21]
5l	4-CH_3	C_6H_5 CH_2	20	90	40	80	190-192 (190-192)[12]

[a] Reaction conditions: 1,2-diphenylethanedione (1 mmol), aromatic aldehyde (1 mmol), aromatic amine (1 mmol), NH_4OAc (3 mmol), catalyst (10 mol %), in 10 mL of ethanol-water (1:1) under ultrasonic irradiation.

[b] Reaction conditions: Reflux temperature.

[c] Isolated yield.

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (4d)

^1H NMR (200 MHz, DMSO-d_6): δ 3.82 (s, 3H), 7.05 (d, J = 8.4 Hz, 2H), 7.50–7.33 (m, 10H), 8.03 (d, J = 8.1 Hz, 2H), 12.50 (s, 1H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.2,114.1,123.1,126.58,127.7, 128.4, 145.7, 159.5; ESI MS (m/z): 327.2 (M^++1).

1,2-bis(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (5b)

^1H NMR (200MHz,$CDCl_3$) δ 6.93 (d,1H), 6.98(d,1H), 7.07 (d,1H), 7.11 (d,1H), 7.18-7.37 (m,12H),7.51 (d,1H), 7.55(d,1H) ppm; ^{13}C NMR (100MHz,$CDCl_3$) δ96.16, 126.94, 127.94, 128.27, 128.38, 128.55, 128.62, 129.51, 129.53, 130.10, 130.17, 130.79, 131.06, 133.71, 134.53, 134.59, 140.71, 145.61 ppm; ESI MS M/Z 441.2 (M^+)

1,4,5-Triphenyl-2-p-tolyl-1H-imidazole (5h)

^1H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 3H) 7.31–7.02 (m, 17H), 7.60 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3): d 147.1, 138.1, 137.2, 134.5, 131.1, 130.7, 130.6, 128.9, 128.8, 128.4, 128.2, 128.1, 127.8, 127.6, 127.4, 126.5, 21.3; ESI MS (m/z): 387.3 (M^++1).

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