



# Synthesis of Trisubstituted Imidazoles Using Lewis and Bronsted Acid Catalysts

Rahim HEKMATSHOAR<sup>1\*</sup>, Hajar JAHANBAKHSI<sup>1</sup>, Farnoosh MOUSAVIZADEH<sup>1</sup>,  
Reyhane RAHNAMAFAR<sup>1</sup>

<sup>1</sup> Alzahra University, School of Science, Department of Chemistry, Vanak, Tehran, IRAN

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## ABSTRACT

An efficient and one-pot method for the preparation of trisubstituted imidazoles by condensation of benzil, different aldehydes and ammonium acetate in the presence of a catalytic amount of NiSO<sub>4</sub>·7H<sub>2</sub>O or H<sub>3</sub>BO<sub>3</sub> under different conditions is reported.

**Key Words:** Trisubstituted imidazoles, Multi-component reactions, NiSO<sub>4</sub>·7H<sub>2</sub>O, H<sub>3</sub>BO<sub>3</sub>, one-pot reactions, solid acid catalysts.

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\*Corresponding author, e-mail: rhekmatu@yahoo.com.

## 1. INTRODUCTION

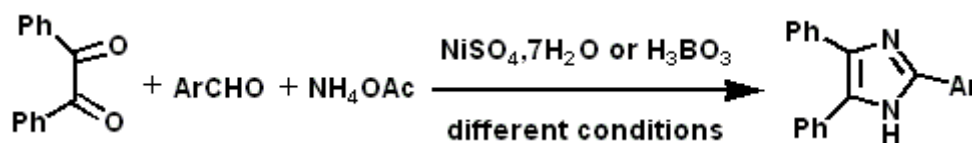
Multi-component reactions (MCRs) are one-pot processes in which three or more components come together to form a product containing substantial elements of all the reactants [1,2]. They provide an inherently more efficient approach to chemical synthesis than conventional bimolecular reactions, since they are performed without the need to isolate any intermediate and save both energy and raw materials and also reduce time. Considerable current effort is focused on the development of new MCRs or improvement of already reported methods [3,4].

Imidazoles are an important class of heterocyclic compounds with an ability to behave as ligands in metalloenzymes [3,5], non-natural metal complexes[6], and highly significant biomolecules such as the essential amino acid histidine, biotin and the pilocarpine alkaloids[7]. In view of the numerous biological, pharmacological and material properties associated with this five-membered heterocyclic moiety, the development of new

synthetic protocols under varied mild reaction conditions is always a matter of interest[8,9]. Because of this, a large number of classical methods for their synthesis have been reported [10-14]. In these procedures, a 1,2-diketone, an aldehyde and ammonium acetate are condensed in the presence of a strong protic acid (such as  $H_3PO_4$ [15],  $H_2SO_4$  [16] and  $HOAc$  [17]) or other catalysts in  $HOAc$  [12] under reflux conditions.

In recent years, the use of solid acid catalysts [18], have received considerable importance in organic synthesis. Such catalysts offer many advantages including: no need for solvents or the use of less toxic ones (e.g., hydrocarbons), milder reaction conditions, easier separation of the catalyst from the reaction mixture, and its possible regeneration and reuse, reducing the production of waste and thus harm to the environment.

To our best of knowledge the  $H_3BO_3$  and  $NiSO_4$  have not been used in organic synthesis. Herein, we wish to report the three-component condensation of benzil, benzaldehyde derivatives and ammonium acetate catalyzed by  $H_3BO_3$  or  $NiSO_4 \cdot 7H_2O$ , as efficient and facile one-pot synthesis of tri-substituted imidazoles (Scheme 1).



Scheme 1

## 2. EXPERIMENTAL

All the chemicals were purchased from Merck company. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus.  $^1H$  NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard (DMSO solution). IR spectra were recorded on the FT-IR Bruker

Tensor 27. All products were known compounds and identified by comparison of their spectral and physical data on the literature description [19-25].

### Synthesis of tri-substituted imidazoles: General procedure

**Method A:** A mixture of benzil (0.21 g, 1 mmol), aldehyde (1 mmol), ammonium acetate (0.38 g, 5 mmol) and  $NiSO_4 \cdot 7H_2O$  (0.02 g, 7 mol%) was refluxed in acetic acid (3 cc). After completion of the reaction (monitored by TLC), the solution was poured into water (15 ml). The resulting solid product was then removed by filtration and recrystallized from ethyl acetate.

### Recycling of $NiSO_4$ :

After collection of products the catalyst could be recycled by evaporation of residual solution, washing with acetone and reactivation at 100 °C for 3h. In the case of model

reaction the recycled catalyst was used for three times without observation of appreciable loss in its catalytic activities.

**Method B:** A mixture of benzil (0.21 g, 1 mmol), aldehyde (1 mmol), ammonium acetate (0.38 g, 5 mmol) and boric acid (0.01 g, 15 mol%) was refluxed in ethanol (3 cc). After completion of the reaction (monitored by TLC), the obtained solid product, was washed with water to separate the catalyst and excess amount of ammonium acetate. The resulting solid residue was purified by recrystallization from ethyl acetate.

**Method C:** A mixture of benzil (0.21 g, 1 mmol), aldehyde (1 mmol), ammonium acetate (0.38 g, 5 mmol) and boric acid (0.01 g, 15 mol%) was heated at 140 °C under solvent-less conditions. After completion of reaction (monitored by TLC), the obtained solid product was washed with water to separate the catalyst and the excess amount of ammonium acetate. The resulting crude product was purified by recrystallization from ethyl acetate.

### 3. RESULTS AND DISCUSSION

In order to get the best reaction condition for both of these catalysts in this heterocyclization reaction, condensation of 4-hydroxy-benzaldehyde, benzil and ammonium acetate, has been chosen as a model reaction. To illustrate the need of catalyst, the model reaction performed in the absence of any catalyst in refluxing acetic acid and ethanol. The reactions were not completed even after 24 h. Clearly, the catalyst is an essential component for this reaction. We carried out the model reactions under solvent-free condition at room temperature using a catalytic amount of Boric acid or Nickle Sulfate. The reactions were not completed in any case. The temperature of the reaction mixture was gradually risen. In the case of Boric acid, at 140 °C, the desired product was obtained in good yield in a relatively short reaction time, but for Nickle sulfate the reaction was not completed after 24 h.

The effect of temperature was studied by carrying out both model reactions at different temperatures. It was observed (Table 1) that yield is a function of temperature and it was increased as the reaction temperature was raised. So in other studies all reactions were carried out under reflux conditions in solvents or at 140 °C under solvent-free conditions.

A screening of three different solvents was done in order to find the best solvent as a solvent of choice. As reported in Table 1, Ethanol was found to be the superior one affording the desired product in 88% yield in the case of H<sub>3</sub>BO<sub>3</sub>, but for NiSO<sub>4</sub>, acetic acid selected as solvent of choice.

Table 1. Condensation of 4-hydroxy-benzaldehyde, benzil and ammonium acetate.

Entry	Solvent	Catalyst(mol%)	Temperature(°C)	Time(min)	Yield(%) <sup>a</sup>
1	Solvent-less	H <sub>3</sub> BO <sub>3</sub> ( 15%)	64	60	40
2	Solvent-less	H <sub>3</sub> BO <sub>3</sub> (15 %)	140	22	83
3	H <sub>2</sub> O	H <sub>3</sub> BO <sub>3</sub> ( 15%)	100	300	0
5	EtOH	H <sub>3</sub> BO <sub>3</sub> (15 %)	25	80	45
6	EtOH	H <sub>3</sub> BO <sub>3</sub> ( 15%)	78	60	88
7	Solvent-less	NiSO <sub>4</sub> (7%)	64	24h	40
8	Solvent-less	NiSO <sub>4</sub> (7%)	140	24h	70
9	EtOH	NiSO <sub>4</sub> (7%)	78	100	85
10	CH <sub>3</sub> COOH	NiSO <sub>4</sub> (7%)	70	100	99
11	CH <sub>3</sub> COOH	NiSO <sub>4</sub> (7%)	117	60	99

a) Yields are related to isolated pure products.

To examine the scope and generality of these approaches, a number of aldehydes were used to synthesis of 1,2,4-trisubstituted imidazoles in reasonable to good yields. As shown in Table 2 and 3, for both catalysts, reactions

tolerated both electron withdrawing groups and electron donating groups. The method has also the ability to tolerate other functional groups such as methoxy, hydroxy, halides and nitro.

Table 2. Synthesis of 2,4,5-triaryl-imidazoles in the presence of a catalytic amount (7 mol%) of NiSO<sub>4</sub>·7H<sub>2</sub>O in acetic acid at 117 °C.

Entry	Ar	Yield (%) <sup>a</sup>	m.p.	
			Obtained	Reported[Ref.]
a	ph	99	271	272-273[20]
b	4-OH-Ph	99	263	260-261[19]
c	2-OH-Ph	97	210	203-205[19]
d	4-OMe-Ph	99	230	226- 228[20]
e	4-NO <sub>2</sub> -Ph	94	240	235-238[20]
f	3-NO <sub>2</sub> -Ph	94	310	313-315[20]
g	4-Cl-Ph	98	259-262	258[20]
h	4-Br-Ph	98	260	259[20]

a) Yields are related to isolated pure products.

Table 3. Synthesis of 2,4,5-triaryl-imidazoles in the presence of a catalytic amount (15 mol%) of H<sub>3</sub>BO<sub>3</sub>.

Entry	Ar	Temperature(°C)		Time		Yield (%) <sup>a</sup>	
		B <sup>b</sup>	C <sup>c</sup>	B	C	B	C
a	Ph	78	140	60	20	83	82
b	4-OH-Ph	78	140	60	22	88	83
c	2-OH-Ph	78	-	60	-	80	-
d	4-OMe-Ph	78	140	60	21	88	85
e	4-NO <sub>2</sub> -Ph	78	140	60	18	80	86
f	3-NO <sub>2</sub> -Ph	78	140	60	18	81	86
g	4-Cl-Ph	78	-	60	-	87	-
h	4-Br-Ph	78	140	60	20	86	82

a) Yields are related to isolated pure products. b) Method B c) Method C

Table 4. Reusability of NiSO<sub>4</sub>.7H<sub>2</sub>O in the case of model reaction.

Entry	Number of recycling	Time(min)	Yield(%) <sup>a</sup>
1	1	60	99
2	2	60	92
3	3	60	87

a) yields are related to isolated pure products.

We also found that NiSO<sub>4</sub>.7H<sub>2</sub>O is reusable. In the case of model reaction the recycled catalyst could be used in the same reaction without significant loss of activity (Table 4).

All products are known and were identified by comparison with those reported in the literature [19-25].

In conclusion, a facile preparation of a variety of 1,2,4-trisubstituted imidazoles from condensation of benzil, different aldehydes and ammonium acetate in the presence of a catalytic amount of H<sub>3</sub>BO<sub>3</sub> or NiSO<sub>4</sub> has been demonstrated. The main advantages of this methodology are: (a) operational simplicity, (b) relatively short reaction times, (c) high yields of products, (d) the use of relatively non-toxic reagents and solvents and also performing the reaction under solvent-free conditions using H<sub>3</sub>BO<sub>3</sub> as catalyst and (e) the recyclability of NiSO<sub>4</sub>.

#### 2,4,5-Triphenyl-1H-imidazole (a)

m.p: 271°C; FTIR (KBr, cm<sup>-1</sup>): 3432, 1660, 1550, 1486, 1462; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.55 (1H, br s), 7.50–7.90 (15H, m).

#### 4-(4,5-Diphenyl-1H-imidazol-2-yl)-phenol(b)

m.p: 263°C; FTIR (KBr, cm<sup>-1</sup>): 3590, 3454, 3284, 3064, 1701, 1283; <sup>1</sup>H NMR(300 MHz, DMSO-*d*<sub>6</sub>): δ 12.40 (s, 1H), 9.70 (s, 1H), 7.90 (d, *J*=8.4 Hz, 2H), 7.54–7.21 (m, 10H), 6.86 (d, *J*=8.4 Hz, 2H).

#### 2-(4,5-Diphenyl-1H-imidazol-2-yl)phenol(c)

m.p: 210°C; FTIR (KBr, cm<sup>-1</sup>): 3428, 3215, 1602, 1532; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.51 (1H, br s), 7.2–7.52 (10H, m), 6.97–7.01(2H, d, *J*/47.8 Hz), 6.86–6.93 (2H, d, *J*/47.5 Hz).

#### 2-(4-Methoxyphenyl)-4,5-diphenylimidazole(d)

m.p: 230°C; FTIR (KBr, cm<sup>-1</sup>): 3402, 3056, 1612, 1492, 1450; <sup>1</sup>H NMR(300 MHz, DMSO-*d*<sub>6</sub>): δ 12.51 (1H, br s), 8.01 (2H, dt, *J*/48.8 Hz), 7.52 (4H, d, *J*/47.2 Hz), 7.37 (4H, t, *J*/47.2 Hz), 7.29 (2H, t, *J*/47.2 Hz), 7.05 (2H, dt, *J*/48.8 Hz, 2.0 Hz), 3.81 (3H, s).

#### 2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole(e)

m.p: 240°C; FTIR (KBr, cm<sup>-1</sup>): 3402, 2928, 1598, 1519, 1346, 856; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.81 (s, 1H), 8.01–7.42 (m, 14H).

#### 2-(3-Nitrophenyl)-4,5-diphenylimidazole(f)

m.p: 310°C; FTIR (KBr, cm<sup>-1</sup>): 3382, 3064, 1605, 1519, 1348; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 13.10 (1H, br s), 8.96 (1H, t, *J*/42.0 Hz), 8.50–8.55 (1H, m), 8.15–8.25 (1H, m), 7.78 (1H, t, *J*/48.0 Hz), 7.24–7.60 (10H, m).

#### 2-(4-Chlorophenyl)-4,5-diphenylimidazole(g)

m.p: 259-262°C; FTIR (KBr, cm<sup>-1</sup>): 3405, 3060, 1603, 1485, 1448, 1433; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ

12.79 (1H, br s), 7.21–7.56 (12H, m), 8.11(2H, d, J/4.8 Hz).

**2-(4-Bromophenyl)-4,5-diphenylimidazole(h)**

m.p: 260°C; FTIR (KBr, cm<sup>-1</sup>): 3400, 3060, 1601, 1482, 1450,1429; <sup>1</sup>H NMR(300 MHz, DMSO-*d*<sub>6</sub>): δ 12.79 (1H, br s), 8.04 (2H, d, J/4.8 Hz),7.68 (2H, d, J/4.8 Hz), 7.55–7.23 (10H, m).

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