

## Potassium aluminum sulfate (alum): an efficient catalyst for the one-pot synthesis of trisubstituted imidazoles

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**Abstract** Trisubstituted imidazoles were synthesized in high yields in the presence of potassium aluminum sulfate (alum) as a non-toxic, reusable, inexpensive, and easily available reagent at 70°C.

**Keywords** Imidazole; Multicomponent condensations; Benzil; Benzoin;  $KAl(SO_4)_2 \cdot 12H_2O$  (alum).

### Introduction

Multi-component condensations (MCCs) constitute an especially attractive synthesis strategy for rapid and efficient generation of molecules due to the fact that the products are formed in a single step and also the diversity could be achieved simply by varying the reacting components.

Multi-substituted imidazoles are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activities [1–3]. Owing to the versatile biological activities of these compounds, numerous classical methods for their synthesis have been reported [4–16]. In a typical procedure, a 1,2-diketone, an aldehyde, and ammonium acetate are condensed in the presence

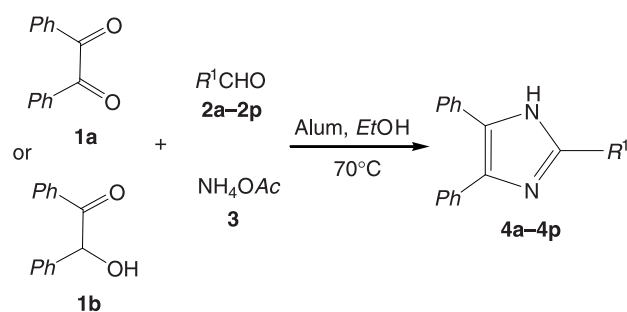
of strong protic acid, such as  $H_3PO_4$  [17],  $H_2SO_4$  [18],  $AcOH$  [19] as well as an organo catalyst in  $AcOH$  [19] under reflux conditions; isolation of product requires neutralization of the reaction mixture. Since solid acids are environmentally friendly with respect to corrosiveness, safety, less waste, and ease of separation and recovery, replacement of these liquid acids is desirable in the chemical industry.

Recently, a few research groups have reported one-pot condensation of  $\alpha$ -hydroxy ketone,  $\alpha$ -ketoamide, or 1,2-diketone, aldehyde, and  $NH_4OAc$  on solid supports under microwave irradiation [20–23]. However, in spite of their potential utility, most of these methods not only need high temperatures (180–200°C) but also the reactions were conducted in  $AcOH$ .

### Results and discussion

During the course of our studies toward development of new routes for the synthesis of highly substituted heterocycles [24–26] using potassium aluminum sulfate (alum) catalysts [27, 28], we wish to introduce an efficient procedure for the synthesis of trisubstituted imidazoles **4a–4p** via one-pot condensation of 1,2-diketone **1a** or  $\alpha$ -hydroxy ketone **1b** with aldehyde **2a–2p** and  $NH_4OAc$  in the presence of  $KAl(SO_4)_2 \cdot 12H_2O$  (alum) as a non-toxic, reusable,

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Scheme 1

**Table 1**  $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$  (alum)-catalyzed condensation of benzil (1), benzaldehyde (2a), and  $\text{NH}_4\text{OAc}$  (3), under different reaction conditions<sup>a</sup>

| Entry | Solvent                           | Yield of 3a/% <sup>b</sup> |
|-------|-----------------------------------|----------------------------|
| 1     | $\text{H}_2\text{O}$              | 70                         |
| 2     | $\text{CH}_3\text{CH}_2\text{OH}$ | 93                         |
| 4     | $\text{CH}_3\text{CN}$            | 60                         |
| 5     | None                              | 40                         |

<sup>a</sup> The reaction were carried out in the presence of 1 mmol benzil, 1 mmol benzaldehyde, 4 mmol  $\text{NH}_4\text{OAc}$ , and 0.3 g  $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$  at 70°C for 150 min

<sup>b</sup> Isolated yield

inexpensive, and easily available catalyst in ethanol under classical heating conditions (Scheme 1).

We found that this condensation might be conducted in various solvents as is evident from Table 1. Most excitingly, the condensation could also be carried out in ethanol with an excellent yield.

When a mixture of benzil (1a), benzaldehyde (2a), and  $\text{NH}_4\text{OAc}$  (3) was stirred in ethanol at 70°C in the presence of a catalytic amount of alum, the reaction was completed within 2.5 h. Workup of the reaction mixture showed that imidazole 4a was prepared in 93% yield.

Encouraged by this achievement, we extended the reaction of benzil (1a) or benzoin (1b) and  $\text{NH}_4\text{OAc}$  with a range of other aldehydes 2b–2p under similar conditions, furnishing the respective imidazoles 4b–4p in good yields. The optimized results are summarized in Table 2.

In conclusion, we were able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active trisubstituted imidazoles *via* condensation of 1,2-diketone or  $\alpha$ -hydroxy ketone with various aromatic aldehydes and

**Table 2** One-pot synthesis of trisubstituted imidazoles in the presence of alum under classical heating conditions at 70°C<sup>a</sup>

| Entry           | $R^1$   | Products 4 | Yield/% <sup>b</sup> | Time/h | mp/°C   |                  |
|-----------------|---|------------|----------------------|--------|---------|------------------|
|                 |   |            |                      |        | Found   | Reported         |
| 1               | $\text{C}_6\text{H}_5$                          | <b>a</b>   | 93                   | 2.5    | 272–273 | 269 [1]          |
| 2               | 4- $\text{CH}_3\text{C}_6\text{H}_4$            | <b>b</b>   | 94                   | 2.5    | 226–228 | 232–235 [2]      |
| 3               | 4- $\text{CH}_3\text{OC}_6\text{H}_4$           | <b>c</b>   | 87                   | 3.5    | 228–231 | 230–232 [29]     |
| 4               | 2- $\text{CH}_3\text{OC}_6\text{H}_4$           | <b>d</b>   | 85                   | 4      | 212–214 | 210–210.5 [29]   |
| 5               | 4- $\text{ClC}_6\text{H}_4$                     | <b>e</b>   | 93                   | 3      | 259–261 | 262–264 [29]     |
| 6               | 4- $\text{BrC}_6\text{H}_4$                     | <b>f</b>   | 89                   | 3      | 252–254 | 261.5–263.5 [29] |
| 7               | 3- $\text{ClC}_6\text{H}_4$                     | <b>g</b>   | 90                   | 3      | 282–286 | 285–287 [29]     |
| 8               | 2- $\text{MeC}_6\text{H}_4$                     | <b>h</b>   | 95                   | 2.5    | 198–202 | 205–207 [29]     |
| 9               | 4- $\text{OHC}_6\text{H}_4$                     | <b>i</b>   | 92                   | 3      | 230–232 | 233 [1]          |
| 10              | 1-naphthyl                                      | <b>j</b>   | 90                   | 4      | 285–286 | 291.5–292 [29]   |
| 11              | 4- $\text{CH}_3\text{SC}_6\text{H}_4$           | <b>k</b>   | 82                   | 3.5    | 242–244 | –                |
| 12              | 4- $\text{CH}_3\text{O}_2\text{CC}_6\text{H}_4$ | <b>l</b>   | 85                   | 3      | 246–248 | –                |
| 13              | 4- $\text{NO}_2\text{C}_6\text{H}_4$            | <b>m</b>   | 92                   | 3      | 242–244 | 241–242 [30]     |
| 14              | 3- $\text{NO}_2\text{C}_6\text{H}_4$            | <b>n</b>   | 82                   | 3.5    | > 280   | > 260 [30]       |
| 15              | 2-furyl   | <b>o</b>   | 86                   | 4      | 208–209 | 202–203 [31]     |
| 16              | 2-thienyl                                       | <b>p</b>   | 89                   | 4      | 249–251 | – [18]           |
| 17 <sup>c</sup> | $\text{C}_6\text{H}_5$                          | <b>a</b>   | 88                   | 3      | 272–273 | 269 [1]          |
| 18 <sup>c</sup> | 4- $\text{CH}_3\text{C}_6\text{H}_4$            | <b>b</b>   | 89                   | 3      | 226–228 | 232–235 [2]      |
| 19 <sup>c</sup> | 4- $\text{CH}_3\text{OC}_6\text{H}_4$           | <b>c</b>   | 83                   | 3.5    | 228–231 | 230–232 [29]     |
| 20 <sup>c</sup> | 4- $\text{ClC}_6\text{H}_4$                     | <b>e</b>   | 91                   | 3.5    | 259–261 | 262–264 [29]     |
| 21 <sup>c</sup> | 3- $\text{ClC}_6\text{H}_4$                     | <b>g</b>   | 88                   | 3.4    | 282–286 | 285–287 [29]     |

<sup>a,c</sup> Reaction conditions: benzil or benzoin (for entry 17–21) (1 mmol), aldehyde (1 mmol),  $\text{NH}_4\text{OAc}$  (4 mmol), and  $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$  (0.3 g), 70°C

<sup>b</sup> Isolated yield

ammonium acetate using potassium aluminum sulfate (alum) as a non-toxic, reusable, inexpensive, and easily available reagent at 70°C. Corrosiveness safety, less waste, ease of separation, and replacement of liquid acids as well as a solid acid are all among desirable factors for the chemical industry, which we have considered in our green chemistry approach.

## Experimental

Melting points were obtained in open capillary tubes by means of an electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. The IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

### General procedure for preparation of imidazoles

A mixture of 1 mmol benzil or benzoin, 1 mmol aldehyde, 4 mmol NH<sub>4</sub>OAc, 0.3 g KAl(SO<sub>4</sub>)<sub>2</sub> · 12H<sub>2</sub>O, and 10 cm<sup>3</sup> ethanol was stirred at 70°C. After completion of the reaction, as was indicated by TLC, the solvent was evaporated to give the crude product which was washed with water and acetone. For further purification it was crystallized from a 9:1 = acetone: H<sub>2</sub>O mixture to afford the pure product.

### 2-(4-(Methylthio)phenyl)-4,5-diphenyl-1H-imidazole

(**4k**, C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>S)

Cream powder; mp 242–244°C; IR (KBr):  $\bar{\nu}$  = 3440 (NH), 3034 (C–H), 1602 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  = 2.46 (s, CH<sub>3</sub>), 7.21–7–30 (m, 8H, Ar-H), 7.51 (d, 4H, *J* = 7.7 Hz, Ar-H), 7.99 (d, 2H, *J* = 6.8 Hz, Ar-H) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  = 15.3, 125.6, 1256.0, 126.9, 127.2, 128.0, 128.2, 133.2, 138.5, 145.8 ppm; MS: *m/z* (%) = 342 (M<sup>+</sup>, 100), 165 (45), 89 (25), 77 (25), 67 (20), 39 (20).

### Methyl 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoate

(**4l**, C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>)

White powder; mp 246–248°C; IR (KBr):  $\bar{\nu}$  = 3345 (NH), 3045 (C–H), 1694 (C=O), 1607 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  = 3.82 (s, CH<sub>3</sub>), 7.17–7.25 (m, 6H, Ar-H), 7.47 (d, 4H, *J* = 7.0 Hz, Ar-H), 7.96 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.11 (d, 2H, *J* = 8.3 Hz, Ar-H) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  = 52.5, 125.3, 127.3, 128.1, 128.3, 129.2, 129.8, 132.7, 134.2, 144.7, 166.4 ppm; MS: *m/z* (%) = 354 (M<sup>+</sup>, 100), 165 (50), 89 (20), 77 (15), 67 (15).

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