

## Amberlyst A-15: Reusable catalyst for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1*H*-imidazoles under MW irradiation

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MS received 23 November 2010; revised 5 May 2011; accepted 11 May 2011

**Abstract.** One-pot multi-component condensation of benzyl, aldehydes, ammonium acetate and primary amines were used for synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives under MW radiation using amberlyst A-15 as a catalysts. This catalyst has several advantages (simple work-up, low cost and reusability).

**Keywords.** Amberlyst A-15; highly substituted imidazole; benzyl; aromatic aldehyde; amine; MW irradiation.

### 1. Introduction

Heterocyclic compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.<sup>1</sup> Highly substituted imidazole derivatives are also the key intermediates in the synthesis of many therapeutic agents. Omeprazole, Pimobendan, Losarton, Olmesartan, Eprosartan and Triphenagrel are some of the leading drugs in the market with diverse functionality.<sup>2</sup> Triarylimidazoles are used in photography as photosensitive compound.<sup>3</sup> In addition, they are of interest due to their herbicidal,<sup>4</sup> analgesic,<sup>5</sup> fungicidal,<sup>6</sup> antiinflammatory<sup>7</sup> and anti-thrombotic activities.<sup>8</sup> There are numerous methods in the literature for the synthesis of highly substituted imidazoles: (a) condensation of 1,2-diones, aldehydes, primary amines and ammonia,<sup>9</sup> (b) *N*-alkylation of trisubstituted imidazoles,<sup>10</sup> (c) condensation of benzoin or benzoin acetate with aldehydes, primary amines and ammonia in the presence of copper acetate<sup>11</sup> (d) cyclization of sulfonamides with mesoionic 1,3-oxazolium-5-olates,<sup>12</sup> (e) four component condensation of diones, aldehydes, primary amines and ammonium acetate in acetic acid under reflux conditions,<sup>13</sup> (f) condensation of  $\beta$ -carbonyl -*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing acetic acid<sup>14</sup> and

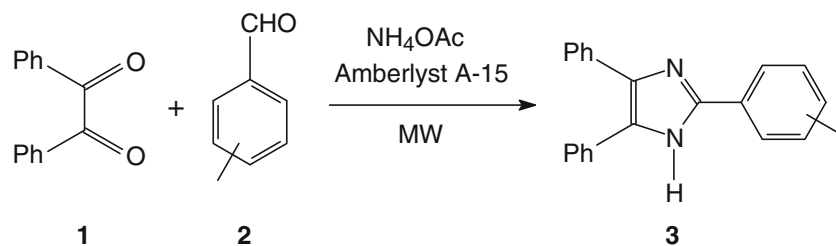
(g) conversion of *N*-(2-oxo)amides with ammonium trifluoroacetate under neutral conditions.<sup>15</sup>

The original synthesis of imidazole utilized glyoxal, formaldehyde and ammonia that involve the formation of four N–C bonds.<sup>16,17</sup> Recently, combination of the supported reagents and microwave irradiations were used under solvent less conditions.<sup>18</sup> Although, the reported methods are suffered by low yields, mixture of products, and lack of generality, harsh reaction conditions, excess of reagents.<sup>19</sup> We report here simple and green approach for the synthesis of 2,4,5-trisubstituted-1*H*-imidazole derivatives (scheme 1) by the condensation of benzyl, aldehydes, ammonium acetate and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives (scheme 2) by the condensation of benzyl, aldehydes, ammonium acetate and primary amines using Amberlyst A-15. This catalyst is mild, water tolerant, recoverable, non-explosive, easy to handle, and reusable. In view of emerging importance of heterogeneous catalyst, we wish to explore the use of Amberlyst A-15<sup>20</sup> under MW irradiation.

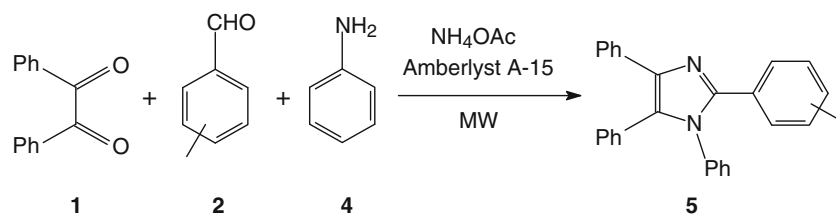
### 2. Results and discussion

The condensation of 1,2-diketones(1), aldehydes (2) and ammonium acetate on exposure to microwave irradiation gave good to excellent yields of 2,4,5-trisubstituted-1*H*-imidazole derivatives (3a–3i) (table 1)

\*For correspondence



**Scheme 1.** Synthesis of 2,4,5-trisubstituted-1*H*-imidazole derivatives.

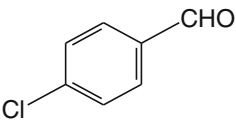
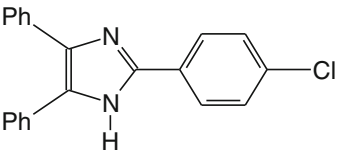
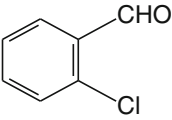
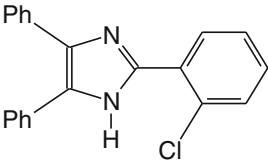
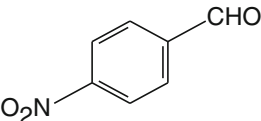
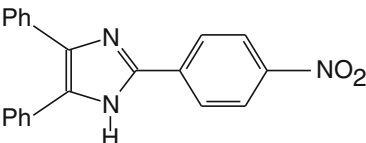
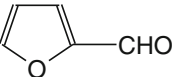
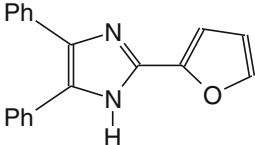


**Scheme 2.** Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives.

**Table 1.** Condensation of benzyl, aldehydes and ammonium acetate using amberlyst A-15 under MW irradiation.

Entry	Aldehyde 2	Product 3	Time (min.)	Yield <sup>ab</sup> (%)	MP (°C) <sup>c</sup>
a			15	87	271–272 (274–276) <sup>19</sup>
b			12	89	229–231 (234–236) <sup>8</sup>
c			12	88	251–251 (256–257) <sup>19</sup>
d			14	82	252–253 (256–257) <sup>20</sup>
e			13	83	200–201 (201–203) <sup>20</sup>

Table 1. Continued.

Entry	Aldehyde 2	Product 3	Time (min.)	Yield <sup>ab</sup> (%)	MP (°C) <sup>c</sup>
f			12	87	253–254 (256–258) <sup>20</sup>
g			12	85	179–181 (183–184) <sup>20</sup>
h			12	92	240–242 <sup>d</sup>
i			12	89	231–231 (233–235) <sup>19</sup>

<sup>a</sup>Isolated Products<sup>b</sup>All products are characterised by IR, <sup>1</sup>HNMR, and compared with authentic samples<sup>c</sup>Literature data of known compounds<sup>d</sup>Spectroscopic data of new synthesized compounds

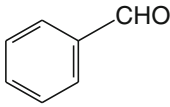
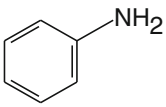
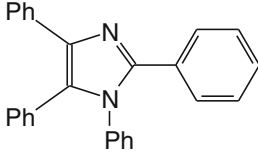
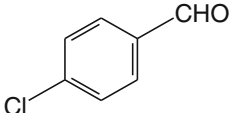
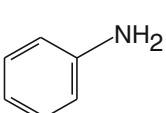
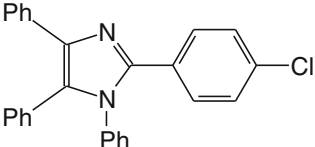
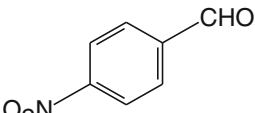
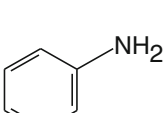
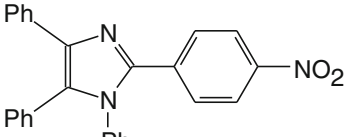
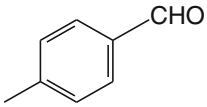
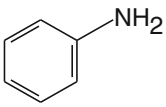
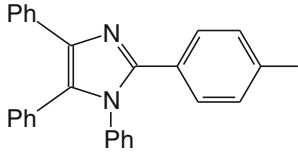
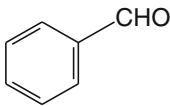
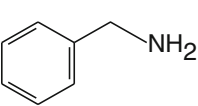
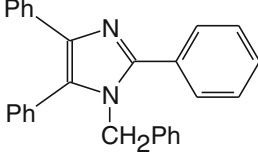
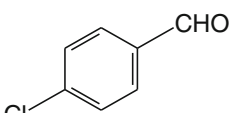
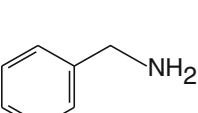
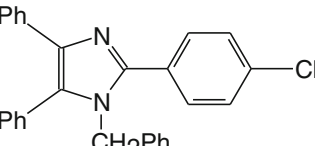
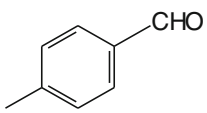
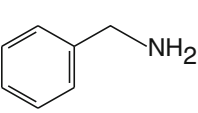
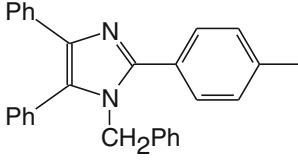
in presence of Amberlyst A-15. Similar methodology was applied for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives (5a–5g) which were also obtained in good to excellent yields by the condensation of benzil (1), aldehydes (2), aromatic amines (4) and ammonium acetate (table 2) in presence of Amberlyst A-15 under solvent-free conditions. The synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives using acetic acid for few hours is a well-established procedure.<sup>16</sup> However, this method suffering by several drawbacks such as drastic reaction conditions, difficult to handle, longer reaction time, tedious work-up, low yields, etc. All such drawbacks were overcome in the present procedure as amberlyst A-15 is easy to handle, short reaction time, yields are good, simple work-up procedure. We have carried out aldehydes consisting electron withdrawing groups or electron donating groups at different positions but it did not show any remarkable difference in the yield of product and time of the reactions. All the reactions

proceeded very efficiently and the results are summarized in table 1. Similarly, we have studied the condensation of benzyl, aldehydes, ammonium acetate with primary aromatic amines. The neat reactions were also attempted under conventional heating, keeping similar reaction conditions. The direct heating of reactants without solvent took more time for completion of reactions and gave the products with low yields. In some reactions decomposition of reactants took place.

## 2.1 Experimental

A domestic microwave oven (Bajaj, ET-B at 2450 MHz, 100% power, 1300 W) was used in all experiments. All melting points are uncorrected and were measured by open capillary method. IR spectra were run on Jasco-IR spectrometer. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> with TMS as internal reference on Bruker AC-300 NMR spectrometer.

**Table 2.** Condensation of benzyl, aldehydes, ammonium acetate and amine using Amberlyst A-15 under MW irradiation.

Entry	Aldehyde 2	Amine 4	Product 3	Time (min.)	Yield <sup>ab</sup> (%)	MP (°C) <sup>c</sup>
a				12	87	256–257 (261–262) <sup>19</sup>
b				10	89	152–153 (158–160) <sup>19</sup>
c				12	84	167–170 <sup>d</sup>
d				12	86	181–182 (184–185) <sup>19</sup>
e				15	78	156–157 (158–160) <sup>19</sup>
f				12	87	164–165 (164–165) <sup>19</sup>
g				15	76	158–160 (161–163) <sup>19</sup>

<sup>a</sup>Isolated products<sup>b</sup>All products are characterised by IR, <sup>1</sup>HNMR, and compared with authentic samples<sup>c</sup>Literature data of known compounds<sup>d</sup>Spectroscopic data of new synthesized compounds

## 2.2 Typical procedure

Mixture of benzyl (5 mmol), 4-Nitro- benzaldehyde (5 mmol) and NH<sub>4</sub>OAc (5 mmol), aromatic amine (5 mmol) and Amberlyst A-15 (350 mg) into 50 ml borosil beaker and irradiated with microwaves. The progress of reaction was monitored by TLC using pet.ether and ethyl acetate (9:1). After completion of the reaction the dichloromethane was added and the solid Amberlyst-A-15 was filtered and dried at 80°C and used for its reusability. The organic layer was extracted with H<sub>2</sub>O and dried by Na<sub>2</sub>SO<sub>4</sub>. The Organic layer was removed under reduced pressure. Further, the crude product was purified by column chromatography using pet. ether and ethyl acetate (9:1) on silica gel gave the product, 2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole and 2-(4-Nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole.

## 2.3 Spectroscopic data

2.3a 2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole (**3h**): IR KBr, (cm<sup>-1</sup>) 3400, 1580, 1515, 1335. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 7.1–7.6 (m, 10 H), 7.35 (d, 2 H, J = 10 Hz), 7.85 (d, 2 H, J = 10 Hz), 8.9 (bs, 1 H).

2.3b 2-(4-Nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole (**5c**): IR KBr, (cm<sup>-1</sup>) 1605, 1564, 1481, 1401. <sup>1</sup>H NMR(CDCl<sub>3</sub>, 300 MHz):7.17–7.84 (m, 19 H).

## 3. Conclusion

In conclusion, we have developed a general and most efficient one-pot multi-component reaction for the synthesis of 2,4,5-trisubstituted-1*H*-imidazole and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives using heterogeneous and reusable catalysts Amberlyst A-15 under MW irradiation method which is environmentally friendly.

## Acknowledgements

SSP thanks to University Grants Commission (UGC), New Delhi for financial assistance, wide letter no. f-47-503/08(WRO), dated 15.01.2009 and thanks are also due to the Principal, Padmashri Vikhe Patil College Pravaranagar for providing laboratory facilities.

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