A facile multicomponent synthesis of tetrasubstituted imidazoles using Fe\textsuperscript{3+}-K10 catalyst under solvent-free microwave conditions

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An efficient, microwave assisted, multi-component synthesis of 1,2,4,5-tetrasubstituted imidazoles has been achieved by the one-pot condensation of benzil, aromatic aldehyde, aliphatic/aromatic amine and ammonium acetate using Fe\textsuperscript{3+}-K10 heterogeneous catalyst under solvent-free conditions. This approach offers a number of advantages such as excellent yield, solvent-free conditions, short reaction time, an eco-friendly and low loading catalyst, mild reaction temperature, and an easy work-up.

Keywords: Multi-component reactions, microwave-assisted organic synthesis, imidazoles, Fe\textsuperscript{3+}-K10 heterogeneous catalyst, solvent-free conditions

Multicomponent reactions (MCRs) have opened a new dimension in synthetic organic chemistry creating diverse structures in one-pot fashion\textsuperscript{1,2}. One such important target is the highly substituted imidazole. The imidazole is a core moiety in many biological and pharmaceutical systems. Substituted imidazoles manifest wide range of biological activities such as anti-inflammatory, anti-allergic and analgesic\textsuperscript{3,4}. Thus, the presence of imidazole moiety as a core section of various biological systems has aroused a diverse array of synthetic approaches in obtaining substituted imidazoles.

The outcome of MCRs is often crucially dependent on the nature of the catalyst. Among various transition metal catalysts, ferric chloride\textsuperscript{5} is of great synthetic potential due to its easy availability, mild reaction conditions and easy work-up. The leading contenders for environmentally acceptable processes are supported reagents. In recent years, Lewis acid-impregnated Montmorillonite K10 has been identified to exhibit high catalytic activity, particularly the Fe\textsuperscript{3+}-K10 catalyst. Coupling of microwave irradiation\textsuperscript{6} with the use of catalyst or mineral support, under solvent-free conditions, provides a clean chemical process with an advantageous merit of enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation. Use of catalysts such as silica gel or zeolite-HY (Ref 7), silica gel/NaHSO\textsubscript{4} (Ref 8) molecular iodine (Ref 9), K\textsubscript{2}CoW\textsubscript{12}O\textsubscript{40}.3H\textsubscript{2}O (Ref 10), heteropoly acids (Ref 11), HClO\textsubscript{4}-SiO\textsubscript{2} (Ref 12) BF\textsubscript{3}-OE\textsubscript{t} (Ref 13), BF\textsubscript{3}-SiO\textsubscript{2} (Ref 14), ionic liquid (Ref 15), and microwave/acetic acid\textsuperscript{16} has been successfully made for the synthesis of highly substituted imidazoles.

In view of the above and considering the intrinsic properties of Fe\textsuperscript{3+}-K10 catalyst such as environmental compatibility, greater selectivity, operational simplicity, non-corrosive nature and ease of isolation, it was thought worthwhile to exploit the use of this heterogeneous catalyst in the synthesis of tetra-substituted imidazoles under solvent-free conditions using microwave irradiation.

Results and Discussion

In the present course of reaction, the Fe\textsuperscript{3+}-K10 catalyst has been prepared using an acetonitrile solution of iron(III) chloride and is subsequently used to catalyze the cyclocondensation of benzil, aromatic aldehyde, aliphatic/aromatic amine and ammonium acetate. In order to explore the optimum conditions, a representative reaction using suitable reactants to afford 4i has been examined in the presence as well as in the absence of the MW. When the reaction is carried out without the aid of MW irradiation using conventional method in refluxing ethanol, the reaction of benzil, benzaldehyde, and ethyl amine in the presence of ammonium acetate gave rise to the product 4i in 70% yield in 60 minutes. In contrast, however, under solvent-free MW irradiation conditions, the product 4i is obtained in just 3 minutes with 85% yield. As a result MW irradiation in conjunction with Fe\textsuperscript{3+}-K10 catalyst emerged as a method of choice and was applied for the synthesis of a wide range of highly substituted imidazoles (4a-m) using variant structural features under solvent-free conditions (Scheme I).

The yields obtained were reasonably good to excellent without the formation of any side product. The outcome of the investigations is described in Table I. It is evident from the Table that the aromatic aldehydes with electron withdrawing groups undergo
fast reaction as compared to aromatic aldehydes having electron donating groups.

All the reactions were monitored by TLC. After the completion of the reaction, CH$_2$Cl$_2$ was added to the reaction-mixture and the catalyst was filtered. The filtrate was then concentrated under diminished pressure to afford the crude product which was purified either by recrystallization from ethanol or by column chromatography using dichloromethane as eluent. All the products 4 exhibited physical and spectral data consistent with their structures.

**Experimental Section**

**General Procedures.** Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. $^1$H NMR spectra were run on a JEOL AL300 FTNMR spectrometer (chemical shift in δ ppm, relative to TMS as internal reference). All commercially available chemicals were procured from E. Merck, Germany and were used as received. Microwave irradiation was made using a CEM Discover single mode microwave reactor (Benchmate Model, USA) with infrared temperature probe and adjustable 0-300 W output power. The catalyst Fe$_3^+$-K10 was prepared according to a literature procedure$^{17}$.

**General procedure for preparation of 1,2,4,5-tetra substituted imidazoles 4**

Equimolar quantities (2 mmoles) of Benzil 1, amine 2 and aldehyde 3 along with ammonium acetate were blended with Fe$_3^+$-K10 (37% w/w) and then transferred into the 10 mL closed Pyrex reaction vessel and irradiated at 200 W (80°C) for 3-4 min. Upon completion of the reaction, as checked by TLC, the mixture was cooled to RT and was extracted with CH$_2$Cl$_2$ (3 × 15 mL) and filtered. The organic phase was washed with H$_2$O and the solvent was removed at rotary evaporator. The crude product thus obtained was purified by column chromatography using CH$_2$Cl$_2$ as eluent.

**1,2,4,5-Tetraphenylimidazole 4a:** Yellow solid, m.p. 214-16ºC; IR (KBr): 2925, 1595, 1575, 1495 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 6.82-7.64 (m, 20 H).
2-(4-Methylphenyl)-1,4,5-triphenylimidazole 4b: Solid, m.p. 186-87°C; IR (KBr): 2930, 1596, 1570, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 2.17 (s, 3H), 6.82-7.60 (m, 19H).

2-(3-Nitrophenyl)-1,4,5-triphenylimidazole 4c: Yellow solid, m.p. 242-44°C; IR (KBr): 2945, 1597, 1570, 1495 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.28-7.65 (m, 15H), 7.80-8.21 (m, 4H).

1,4,5-Triphenyl-2-thiophen-2-ylimidazole 4d: Solid, m.p. 248-50°C; IR (KBr): 2975, 1596, 1570, 1485 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 6.73-7.60 (m, 18H).

1-Benzyl-2,4,5-triphenylimidazole 4e: Solid, m.p. 159-61°C; IR (KBr): 2992, 1600, 1578, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 4.92 (s, 2H), 6.62-7.66 (m, 20H).

1-Benzyl-2-(4-methylphenyl)-4,5-diphenylimida-zole 4f: Solid, m.p. 164-66°C; IR (KBr): 2920, 1600, 1574, 1495 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.10 (s, 3H), 5.00 (s, 2H), 6.68-7.62 (m, 19H).

1-Benzyl-2-(2-nitrophenyl)-4,5-diphenylimidaz-ole 4g: Solid, m.p. 153-54°C; IR (KBr): 2975, 1600, 1590, 1496 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 5.0 (s, 2H), 6.80-7.62 (m, 19H).

1-Benzyl-2-(3,4,5-trimethoxyphenyl)-4,5-diphenylimidazole 4h: Solid, m.p. 183-85°C; IR (KBr): 2950, 1640, 1582,1520 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.60 (s, 6H), 3.74 (s, 3H), 5.07 (s, 2H), 6.85-7.54 (m, 17H).

1-Ethyl-2,4,5-triphenylimidazole 4i: Yellow solid, m.p. 114-16°C; IR (KBr): 2945, 1600, 1570, 1495 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.10 (t, 3H, J = 7.5 Hz), 4.00 (q, 2H, J = 7.2 Hz), 7.10-7.90 (m, 15H).

1-Ethyl-2-(4-methylphenyl)-4,5-diphenylimidaz-ole 4j: Solid, m.p. 121-23°C; IR (KBr): 2985, 1600, 1580, 1485 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.95 (t, 3H, J = 7.3 Hz), 2.40 (s, 3H), 3.86 (q, 2H, J = 7.2), 7.10-7.87 (m, 14H).

4-Bromophenyl-1-ethyl-4,5-diphenylimidazole 4k: Solid, m.p. 128-30°C; IR (KBr): 2960, 1600, 1570, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.98 (t, 3H, J = 7.2), 3.90 (q, 2H, J = 7.1), 7.10-7.85 (m, 14H).

1-Cyclohexyl-2,4,5-triphenylimidazole 4l: Solid, m.p. 168-69°C; IR (KBr): 2900, 1595, 1568, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.65-1.93 (m, 10H), 3.70-4.10 (m, 15H).

1-Cyclohexyl-2-(4-methylphenyl)-4,5-diphenylimidazole 4m: Solid, m.p. 162-63°C; IR (KBr): 2930, 1600, 1570, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.60-2.10 (m, 10H), 2.32 (s, 3H), 3.62-4.26 (m, 1H), 6.87-7.52 (m, 14H).

Conclusion
The findings clearly demonstrate that FeCl₃ supported montmorillonite K10 is a highly efficient catalyst to bring about a one-pot, four component synthesis of 1,2,4,5-tetrasubstituted imidazoles under solvent-free MW irradiation and the present method is convincingly superior to the other reported procedures with respect to the ease of operation, reaction time, amount of catalyst and yield of the products.

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References