AIPO₄ MEDIATED ONE-POT, FOUR-COMPONENT SYNTHESIS OF 1, 2, 4, 5-TETRASUBSTITUTED IMIDAZOLES UNDER CONVENTIONAL HEATING AND MICROWAVE IRRADIATION

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ABSTRACT

An efficient method has been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by four-component condensation of benzil or benzoin, aldehydes, amines, and ammonium acetate under microwave irradiation or classical heating conditions using Aluminium Phosphate (AIPO₄: a heterogeneous catalyst). The catalyst exhibited remarkable reusable activity.

Keywords: Aluminium phosphate, tetrasubstituted imidazoles, solvent-free conditions, classical heating or microwave irradiation.

INTRODUCTION

Trifenagrel¹ is a potent 2,4,5-triaryl imidazole that reduces platelet aggregation in several animal species and humans. Thus the prevalence of imidazole moiety in several naturally occurring and synthetic biologically active compounds has rekindled an increased interest in obtaining tri- and tetra-substituted imidazoles via regiocontrolled process. Over the century, imidazole has received significant attention due to their synthesis, reactions and biochemical properties. Even today, research in imidazole chemistry continues undebated. Compounds with imidazole moiety have biological and pharmaceutical importance². Several substituted imidazoles are known as inhibitors of P 38 kinase³. Eprosartan is one of a series of 1-(carboxy benzyl) imidazole-5-acrylic acids, which is a potent and selective angiotensin II receptor antagonist⁴. Highly substituted imidazoles like lepidilines A and B⁵ exhibit micromoles cytotoxicity against several human cancer cell lines.

In the literature there exist few reports on the direct synthesis of tetrasubstituted imidazoles. General methods rely on the synthesis of trisubstituted imidazoles followed by installation of the fourth substituent via N-alkylation⁶, metal activated coupling⁷ or imidazole-N-oxides⁸. Tetra substituted imidazoles can be directly prepared from cycloaddition of munchnone derivatives but this methodology is limited to N-methyl imidazoles⁹. Another direct method involves a four component condensation of 1,2-
diketones, aldehydes, amines and NH₂OAc in AcOH or on various supports such as acidic, basic and neutral alumina, bentonite, montmorillonite K10, montmorillonite KSF, silica gel florisil under microwave irradiation and PDTC. The condensation of α-hydroxy ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in the presence of microwave has been reported recently. AlPO₄ can be used as a catalyst and support. As a catalyst, AlPO₄ is known to be active in several chemical processes, such as dehydration, isomerization, alkylation, rearrangement, retroaldolization, condensation and Diels-Alder cycloaddition. Moreover, AlPO₄ is also used as a support for polymerization, oxidation, hydrogenation, reductive cleavage or hydration catalysts. In continuation of our work on the development of useful synthetic methodologies, we have developed a method, for solvent free synthesis of 1,2,4,5-tetrasubstituted imidazoles by using inexpensive and reusable AlPO₄ (1 mol %) catalyst under microwave irradiation or classical heating in a highly efficient manner.

To the best of our knowledge, however, the generality and applicability of AlPO₄ to accomplish these reactions has not been reported in the literature. This method not only affords the products in excellent yield but also avoids the problems with catalyst cost, handling, safety and pollution. This catalyst is water tolerant, recoverable, reusable, non-explosive, easy to handle and thermally robust. In view of emerging importance of the heterogeneous catalyst, we wish to explore the use of AlPO₄ as a recoverable and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Scheme-1).

**Scheme-1**

**EXPERIMENTAL**

Typical procedure for the synthesis of tetra-substituted imidazoles: A solution of benzyl or benzoin(2 mmol), aldehyde (2 mmol) and amine (2 mmol) in of methylene chloride (3 mL), was added to a mixture of ammonium acetate (250 mg) and catalyst AlPO₄. The contents were cooled to room temperature and mixed thoroughly with 2×15 mL of acetone. The mixture was filtered to separate the catalyst and the solvent was removed under reduced pressure to afford the crude product, which was purified by recrystallization from acetone-water (15:1 v:v).

**Spectroscopic data of products:**

**1,2-Bis(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (4a):** M.p. 187-189 °C; FAB MS: 441 [M+H]⁺, 281, 221, 175, 165, 147, 121, 87, 73, 55.; IR (KBr): vmax 1599, 1497, 1412 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 6.92-7.63 (m, 18 H Ar-H).

**1-Benzyl-4,5-diphenyl-2-phenyl-1H-imidazole (4b):** M.p. 163-165 °C; FAB MS: 387 [M+H]⁺, 309, 296, 193, 178, 165, 91, 55.; IR (KBr): vmax 1599, 1496, 1474, 1414 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-d₆, 300 MHz) δ 5.10 (s, 2H, CH₂), 6.72-7.61 (m, 20 H Ar-H).

**1-Benzyl-4,5-diphenyl-2-(3-chlorophenyl)-1H-imidazole (4c):** M.p. 144-146 °C; FAB MS: 421 [M+H]⁺, 387, 343, 295, 165, 91, 55.; IR (KBr): vmax 1599, 1497, 1412 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 5.16 (s, 2H, CH₂), 6.76-7.69 (m, 19 H Ar-H). ¹³C NMR (DMSO-d₆, 75 MHz) δ: 48.20 (CH₃), 126.06, 126.58, 126.88, 127.34, 127.75, 128.60, 129.07, 129.49, 130.40, 130.75, 130.96, 131.25, 133.09, 133.71, 134.71, 137.54, 145.92.

**1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (4d):** M.p. 156-158 °C; FAB MS: 421 [M+H]⁺, 387, 204, 165, 154, 136, 109, 91, 69, 55.; IR (KBr): vmax 1596, 1474, 1443, 1411 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 5.15 (s, 2H, CH₂), 6.73-7.69 (m, 19 H Ar-H). ¹³C NMR (DMSO-d₆, 75 MHz) δ:
2-(4-Chlorophenyl)-1-(4-fluorophenyl)-4,5-diphenyl-1H-imidazole (4e): M.p. 196-198 °C; FAB MS : 425 [M+H]⁺, 182, 164, 111, 75, 43. ; IR (KBr) : 1594, 1479, 1418 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) : δ 7.17-7.49 (m, 18 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz) : δ: 116.49, 116.79, 126.76, 127.05, 128.67, 128.84, 129.02, 129.51, 130.40, 130.57, 131.32, 131.44, 131.57, 132.10, 135.22, 133.26, 133.67, 134.60, 137.39, 145.50.

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4f): M.p. 167-169 °C; FAB MS : 421 [M+H]⁺, 307, 228, 165, 154, 136, 77, 57 ; IR (KBr) : 1596, 1505, 1471, 1436, 1411 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) : δ 2.20 (s, 3H, CH₃), 6.92-7.63 (m, 18 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz ) δ: 21.22 (CH₃ ), 127.01, 127.53, 127.99, 128.267, 128.45, 129.97, 130.02, 130.30, 131.10, 131.21, 133.34, 133.83, 134.71, 137.59, 138.77, 145.50.

1-Benzyl-4,5-diphenyl-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (4g): M.p. 155-157 °C; FAB MS: 401 [M+H]⁺, 310, 178, 165, 121, 103, 91, 69. ; IR (KBr) : ν(max) 1601, 1497, 1452 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.31(s, 3H, CH₃), 5.14 (s, 2H, CH₂), 6.73-7.66 (m, 19 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz ) δ: 21.30 (CH₃), 48.08 (CH₂), 126.01, 126.55, 126.68, 127.05, 128.37, 128.54, 128.88, 129.98, 129.38, 129.98, 130.47, 131.09, 131.26, 131.35, 137.84, 138.80, 147.64.

1-Benzyl-4,5-diphenyl-2-(4-bromophenyl)-4,5-diphenyl-1H-imidazole (4h): M.p. 149-151 °C; FAB MS : 432 [M+H]⁺, 386, 359, 239, 165, 154, 136, 95, 55. ; IR (KBr) : ν(max) 1599, 1497, 1412 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.26 (s, 3H, CH₃), 7.15-8.95 (m, 18 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz ) δ: 21.11 (CH₃), 122.86, 123.28, 126.80, 127.15, 127.81, 128.82, 129.02, 129.01, 129.12, 130.39, 130.47, 131.55, 132.23, 132.70, 134.01, 134.30, 134.47, 137.73, 137.89, 144.15, 148.02.

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4i): M.p. 188-191 °C; FAB MS: 401 [M+H]⁺, 311, 267, 194, 165, 152, 91, 55. ; IR (KBr) : ν(max)1595, 1508, 1473, 1438 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.32, (s, 3H, CH₃) 6.91-7.61 (m, 18 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz ) δ: 21.22, 21.34 (2 CH₃), 126.74, 127.99, 128.07, 128.19, 128.36, 128.86, 129.93, 129.74, 130.44, 130.72, 131.13, 134.25, 138.29, 138.45, 146.96.

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4j): M.p. 219-220 °C; FAB MS : 432 [M+H]⁺, 386, 359, 289, 194, 136, 95, 69, 55. ; IR (KBr) : ν(max)1591, 1507, 1334 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz) δ 2.15 (s, 3H, CH₃), 7.17-7.49 (m, 18 H, Ar-H ). ¹³C NMR (DMSO-d₆, 75 MHz ) δ: 21.13 (CH₃), 123.97, 126.8, 127.22, 128.77, 128.99, 129.24, 130.39, 131.53, 133.29, 134.05, 134.39, 136.83, 138.22, 139.16, 144.33, 147.03.

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4k): M.p. 226-228 °C; FAB MS : 403 [M+H]⁺, 310, 297, 282, 166, 91, 51.; IR (KBr) : ν(max)1601, 1535, 1479, 1401 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-d₆, 300 MHz) δ 2.33 (s, 3H, CH₃), 6.54-7.49 (m, 18 H, Ar-H ), 9.01 (s, 1H, OH).

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4l): M.p. 231-233 °C; FAB MS: 403 [M+H]⁺, 310, 297, 282, 166, 91, 51.; IR (KBr) : ν(max)1605, 1564, 1481, 1401cm⁻¹; ¹H NMR (CDCl₃ + DMSO-d₆, 300 MHz) δ 2.33, (s, 3H, CH₃), 6.54-7.49 (m, 18 H, Ar-H ), 9.01 (s, 1H, OH).

1-Benzyl-4,5-diphenyl-2-p-tolyl-1H-imidazole (4m): M.p. >275 °C; FAB MS: 403 [M+H]⁺, 340, 385, 339, 282, 165, 136, 91, 55. ; IR (KBr) : ν(max)1594, 1479, 1418 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-d₆, 300 MHz) δ 2.11 (s, 3H, CH₃), 6.79-7.55 (m, 19 H, Ar-H).
Table-1: AlPO₄ catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles 4a-o

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<th>Yield %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Time&lt;sup&gt;c&lt;/sup&gt; 140°C (hr)</th>
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² All the compounds were characterized by IR, NMR, MS and mp.

³ Isolated yields under thermal and microwave conditions.

⁴ Time under thermal and microwave conditions.

RESULTS AND DISCUSSION

The typical procedure<sup>15</sup> for 1,2,4,5-tetrasubstituted imidazoles involve impregnating the mixture of AlPO₄ (1 mol%) and ammonium acetate (ammonia source) with a dichloromethane solution of benzil, aldehyde and amine, evaporating the solvent, and heating the solid residue in a microwave oven or oil bath (at 140°C). The reactions proceeded in high yields and the results are summarized in Table-1. Aldehydes bearing various functional groups such as Cl, F, Br, OMe, OH, NO₂, etc have been used and reactions proceeded smoothly with high yields. Under the same conditions, this approach can be repeated for synthesis of these imidazoles when the benzoin was used instead of benzil as a starting material (Scheme-1) Thus, benzoin effectively participated in the condensation with aldehyde, amine, and ammonium acetate in presence of AlPO₄ to
give corresponding tetrasubstituted imidazoles but the yields were found to be low (10-30%). The structures of the imidazoles were confirmed from 1H NMR, IR, mass spectral data and melting point. The four-component condensation of benzil, p-chlorobenzaldehyde, benzyl amine and ammonium acetate was also performed in the absence of AlPO$_4$ under microwave irradiation; however, the yield of 4d was low (30%). Carrying out the condensation in refluxing CH$_3$CN or EtOH for 3 h catalyzed by AlPO$_4$ resulted 4d with 48% yield.

The possibility of recycling the catalyst is of concern, especially for large-scale operations. For this purpose the reaction of benzil, p-chlorobenzaldehyde, benzyl amine and ammonium acetate at 140 °C as a model reaction was again studied. When the reaction completed, the catalyst was recovered and reused for the similar reaction. This process was carried out over four runs without appreciable reduction (90% to 80%) in the catalytic activity of the catalyst.

**CONCLUSION**

In conclusion, we have reported here in several noteworthy features of a new catalyst for the synthesis of tetra-substituted imidazoles through the four-component condensation of benzil, aldehydes, amines and ammonium acetate using AlPO$_4$. This protocol offers many attractive features such as reduced reaction times, higher yields and economic viability of the catalyst. The reaction proceeds under solvent free conditions and isolation of the catalyst is easily achieved. This method can be applied to large-scale processes with high efficiency and the catalyst is recoverable and in few (four) runs without loss of catalytic activity. This makes the method economic, benign, simple, and convenient process for the synthesis of 1,2,4,5-tetrasubstituted imidazoles of biological and medicinal importance.

**REFERENCES**


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1, 2, 4, 5-TETRASUBSTITUTED IMIDAZOLES 340 Padi Pratap Reddy et al.