A mild and efficient four component one-pot synthesis of 2,4,5-triphenyl-(1H-1-imidazolyl)isoxazoles catalyzed by ceric ammonium nitrate

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Ceric ammonium nitrate (CAN) acts as an efficient catalyst for the synthesis of 2,4,5-triphenyl-1H-1-imidazolyl isoxazoles in a four component one-pot condensation of benzil or benzoin, aromatic aldehyde, isoxazole amine and ammonium acetate. This one-pot procedure is very simple, affording excellent yields in shorter reaction time at ambient temperature. Isoxazole amines are employed as one of the synthon in this multi-component condensation for the first time.

Keywords: Ceric ammonium nitrate, triphenyl imidazolyl isoxazoles, one-pot synthesis

Multi-component reactions (MCRs) have proved to be highly successful in generating products in a one-pot synthetic operation. The development of new multi component reactions is an area of considerable current interest, because a large number of new products could be synthesized by these methods. Tetrasubstituted imidazole is frequently found in many biological systems such as Losartan and Olmesartan. Imidazoles like lepidilines A and B exhibit cytotoxicity against several human cancer cell lines. Trifenagrel is a 2,4,5-triaryl imidazole derivative, that reduces platelet aggregation in several animal species and humans. The presence of an imidazole ring in natural products and pharmacologically active compounds has created interest for the development of new synthetic approaches to these heterocycles. However, despite intensive efforts, only few general methods exists for the synthesis of tetra substituted imidazoles catalyzed by silical gel or Zeolite HY, silica gel/NaHSO₄ (ref. 8), molecular iodine, K₃CoW₁₂O₄₀.3H₂O (ref.10), heteropolyacids and HClO₄·SiO₂ (ref.12). Many of these methods are associated with one or more disadvantages such as expensive or toxic reagents, long reaction times, tedious work up and low yields. Thus, development of new methods using cheap and commercially available less toxic reagents to afford high yields of products in short reaction times are required.

Ceric ammonium nitrate (CAN) is a convenient reagent for affecting a number of synthetic transformations due to its ready solubility in organic solvents, low toxicity, and high reactivity. The use of CAN as Lewis acid in C–C bond forming reactions has attracted synthetic chemists. As a sequel to our study in exploring application of different reagents for the development of simple and efficient methods for the synthesis of isoxazole containing heterocyclic compounds, we herein report a simple, mild and efficient protocol for synthesis of 2,4,5-triphenyl-1H-imidazolyl isoxazoles using ceric ammonium nitrate catalyst.

Results and Discussion

The four component condensation of benzil 1, aromatic aldehyde 2a, 3-amino-5-methylisoxazole 3a and ammonium acetate was carried out in methanol in the presence of 10 mol % ceric ammonium nitrate at ambient temperature for 30 min. The reaction resulted in the formation of the desired 5-methyl-3-(2,4,5-triphenyl-1H-imidazolyl)isoxazole 4a in 95% yield. Similarly, the reaction of other aromatic aldehydes 2b/2c/2d with 3-amino-5-methylisoxazole 3a, benzil and ammonium acetate in the presence of ceric ammonium nitrate at ambient temperature afforded the corresponding imidazolyl isoxazoles 4b/4c/4d respectively. We have also utilized different isoxazole amines 3b and 3c in this transformation to study the generality of the reaction (Scheme I). The structures of the products 4a-l were established on the basis of elemental analyses and by spectral data (IR, ¹H NMR and MS) (Table I). All the products 4a-l reported are new.

This four component reaction was also carried out using benzoin in place of benzil under the same reaction conditions. The reaction resulted in the formation of similar products as were obtained with benzoin. Probably, the formation of imidazoles using benzoin has advantage, because benzil is obtained from benzoin by oxidation using reagents like HNO₃, chlorine, thallium nitrate and ammonium chloro
Scheme I

**Table I** — One-pot synthesis of 2,4,5-triphenyl-1H-1-imidazolyl isoxazoles using CAN as catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-CHO</th>
<th>Amine</th>
<th>Products</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, R’ = H</td>
<td>3a</td>
<td>4a, R’ = H</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>2b, R = 2-Cl</td>
<td>3a</td>
<td>4b, R = 2-Cl</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>2c, R = 2-CH₃</td>
<td>3a</td>
<td>4c, R = 2-CH₃</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>2d, R’ = 4-CH₂O</td>
<td>3a</td>
<td>4d, R’ = 4-CH₂O</td>
<td>40</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>2a, R = H</td>
<td>3b</td>
<td>4e, R = H</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>2b, R = 2-Cl</td>
<td>3b</td>
<td>4f, R = 2-Cl</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>2c, R = 2-CH₃</td>
<td>3b</td>
<td>4g, R’ = 2-CH₃</td>
<td>40</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>2d, R = 4-CH₂O</td>
<td>3b</td>
<td>4h, R’ = 4-CH₂O</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>2a, R’ = H</td>
<td>3c</td>
<td>4i, R’ = H</td>
<td>35</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>2b, R = 2-Cl</td>
<td>3c</td>
<td>4j, R = 2-Cl</td>
<td>35</td>
<td>96</td>
</tr>
<tr>
<td>11</td>
<td>2c, R = 2-CH₃</td>
<td>3c</td>
<td>4k, R = 2-CH₃</td>
<td>40</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>2d, R = 4-CH₂O</td>
<td>3c</td>
<td>4l, R = 4-CH₂O</td>
<td>45</td>
<td>85</td>
</tr>
</tbody>
</table>
chromate, which are toxic, costly and also requires the drastic experimental conditions. By employing benzoin in place of benzil, we could able to avoid the oxidation step and the method is environmentally benign (Scheme II). The product yield is found to be almost identical, when the reaction is run either with benzil or benzoin in this multi-component synthesis.

The scope and generality of this one-pot, four-component synthesis of imidazolyl isoxazoles either by using benzil or benzoin is further illustrated by conducting the reaction with different aromatic aldehydes and different isoxazole amines. This method has the ability to tolerate a variety of functional groups such as chloro, methyl and methoxy groups on benzene ring. Our results demonstrate that CAN is an efficient, environmentally friendly catalyst for the one-pot, four component condensation of benzil or benzoin, aromatic aldehyde, ammonium acetate and isoxazole amine to prepare triphenyl imidazolyl isoxazoles in excellent yields in short reaction times.

The plausible mechanism for the synthesis of imidazolyl isoxazoles, involves the formation of intermediate 5, by the reaction of an aldehyde, isoxazole amine and ammonium acetate in the presence of ceric ammonium nitrate catalyst. Intermediate 5 condenses with benzil to form another intermediate 6, which in turn liberates a water molecule to afford the imidazole 4 (Scheme III).

Conclusion

In conclusion, we have reported the synthesis of pharmacologically important triphenyl imidazolyl isoxazoles using inexpensive CAN as an efficient and alternative catalyst either from benzil or benzoin. This protocol offers many attractive features such as (a) the use of cheap, mild and easily available catalyst (b) easy work-up (c) better yields, and (d) reduced reaction time. To the best of our knowledge, isoxazole amines are employed as one of the synthon in this multi-component condensation for the first time. In view of the potential biological activity of imidazole and isoxazole nuclei, we predict that the newly synthesized compounds may be drug candidates and the activity data will be published elsewhere.
Experimental Section

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as an internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of 2,4,5-triphenyl-1H-1-imidazoyl isoxazoles, 4a-l

A mixture of ceric ammonium nitrate (10 mol %), benzil or benzen 1 (1 mmol), aromatic aldehyde 2 (1 mmol), isoxazole amine 3 (1 mmol) and ammonium acetate (1 mmol) was dissolved in methanol (15 mL) and the contents are stirred at ambient temperature for 30 min. After the completion of the reaction (monitored by TLC), the reaction-mixture was poured into ice cold water. The separated solid was filtered, washed with water. The products were purified by recrystallization from ethanol.

Compound 4a: Brown solid, m.p. 225°C, IR (KBr): 1620, 1480, 1420 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.20 (s, 3H, CH_3), 5.80 (s, 1H, isoxazole-H), 7.22-8.15 (m, 15H, Ar-H); MS (EI): m/z 378 [M+H]^+; Anal. Calcd. for C_{26}H_{19}N_2O: C, 79.57; H, 5.03; N, 11.14; Found: C, 79.60; H, 5.00; N, 11.17%.

Compound 4b: Brown solid, m.p. 215°C, IR (KBr): 1615, 1483, 1418 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 5.86 (s, 1H, isoxazole-H), 7.25-8.18 (m, 14H, Ar-H); MS (EI): m/z 412 [M+H]^+; Anal. Calcd. for C_{29}H_{18}N_3OCl: C, 72.99; H, 4.37; N, 10.21; Found: C, 73.02; H, 4.35; N, 10.25%.

Compound 4c: Brown solid, m.p. 202°C, IR (KBr): 1620, 1475, 1415 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.22 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 5.90 (s, 1H, isoxazole-H), 7.20-8.12 (m, 14H, Ar-H); MS (EI): m/z 392 [M+H]^+; Anal. Calcd. for C_{39}H_{23}N_2O: C, 79.79; H, 5.37; N, 10.74; Found: C, 79.83; H, 5.34; N, 10.70%.

Compound 4d: Brown solid, m.p. 194°C, IR (KBr): 1610, 1485, 1426 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.20 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.90 (s, 1H, isoxazole-H), 7.28-8.20 (m, 14H, Ar-H); MS (EI): m/z 408 [M+H]^+; Anal. Calcd. for C_{32}H_{21}N_2O: C, 76.65; H, 5.15; N, 10.31; Found: C, 76.62; H, 5.17; N, 10.34%.

Compound 4e: Brown solid, m.p. 210°C, IR (KBr): 1610, 1490, 1430 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.05-7.85 (m, 15H, Ar-H); MS (EI): m/z 392 [M+H]^+; Anal. Calcd. for C_{33}H_{23}N_2O: C, 79.79; H, 5.37; N, 10.74; Found: C, 79.80; H, 5.41; N, 10.77%.

Compound 4f: Brown solid, m.p. 186°C, IR (KBr): 1620, 1480, 1425 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.20 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.00-7.81 (m, 14H, Ar-H); MS (EI): m/z 426 [M+H]^+; Anal. Calcd. for C_{38}H_{22}N_2OCl: C, 73.41; H, 4.70; N, 9.88; Found: C, 73.36; H, 4.73; N, 9.90%.

Compound 4g: Brown solid, m.p. 192°C, IR (KBr): 1595, 1485, 1410 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.01-7.84 (m, 14H, Ar-H); MS (EI): m/z 406 [M+H]^+; Anal. Calcd. for C_{38}H_{23}N_2O: C, 80.00; H, 5.67; N, 10.37; Found: C, 80.05; H, 5.65; N, 10.34%.

Compound 4h: Brown solid, m.p. 176°C, IR (KBr): 1620, 1490, 1430 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.05-7.82 (m, 14H, Ar-H); MS (EI): m/z 442 [M+H]^+; Anal. Calcd. for C_{39}H_{23}N_2OCl: C, 76.95; H, 5.46; N, 9.97; Found: C, 76.99; H, 5.40; N, 9.73%.

Compound 4i: Brown solid, m.p. 168°C, IR (KBr): 1610, 1580, 1480, 1425 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 6.80 (d, 1H, CH=CH, J = 12Hz), 7.05(d, 1H, CH=CH, J = 12Hz), 7.21-8.23 (m, 20H, Ar-H); MS (EI): m/z 470 [M+H]^+; Anal. Calcd. for C_{49}H_{32}N_2O: C, 82.67; H, 5.21; N, 8.76; Found: C, 82.69; H, 5.22; N, 8.73%.

Compound 4j: Brown solid, m.p. 190°C, IR (KBr): 1600, 1585, 1480, 1420 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.22 (s, 3H, CH_3), 6.84 (d, 1H, CH=CH, J = 12Hz), 7.08(d, 1H, CH=CH, J = 12Hz), 7.20-8.20 (m, 19H, Ar-H); MS (EI): m/z 514 [M+H]^+; Anal. Calcd. for C_{52}H_{33}N_3OCl: C, 77.19; H, 4.67; N, 8.18; Found: C, 77.22; H, 4.65; N, 8.15%.

Compound 4k: Brown solid, m.p. 225°C, IR (KBr): 1610, 1585, 1485, 1420 cm^{-1}; ^1H NMR (200 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.70 (d, 1H, CH=CH, J = 12Hz), 6.97(d, 1H, CH=CH, J = 12Hz), 7.18-8.20 (m, 19H, Ar-H); MS (EI): m/z 494 [M+H]^+; Anal. Calcd. for C_{55}H_{37}N_3O: C, 82.75; H, 5.47; N, 8.51; Found: C, 82.71; H, 5.50; N, 8.54%.
Compound 4l: Brown solid, m.p. 198°C, IR (KBr): 1595, 1580, 1480, 1415 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 2.20 (s, 3H, CH\(_3\)), 3.83 (s, 3H, OCH\(_3\)), 6.80 (d, 1H, CH=CH, \(J = 12\)Hz), 6.98 (d, 1H, CH=CH, \(J = 12\)Hz), 7.05-8.01 (m, 19H, Ar-H); MS (El): \(m/z\) 510 [M+H]+; Anal. Calcd. for C\(_{34}\)H\(_{27}\)N\(_3\)O\(_2\): C, 80.15; H, 5.30; N, 8.25; Found: C, 80.10; H, 5.28; N, 8.29%.

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References