GREEN SYNTHESIS OF 4-((UN)SUBSTITUTED BENZYLIDENE)-N-ARYLAMINO-2-((UN)SUBSTITUTED STYRYL)-1H-IMIDAZOLE-5(4H)-ONE DERIVATIVES

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We have achieved an efficient and green synthesis of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1H-imidazole-5(4H)-one derivatives in good yields by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst.

INTRODUCTION

Heterocyclic compounds containing imidazole moiety have many pharmacological properties and play an important role in biochemical processes. Highly substituted imidazoles are the key intermediates in the synthesis of various therapeutic agents and act as a subunit in drugs such as Olmesartan, Losartan, Eprosartan (angiotensin II receptor antagonist), Metronidazole (antibiotic), Trifenagrel (platelet aggregation inhibitor), Dacarbazine (antineoplastic), Etomidate (intravenous anesthetic) as well as plant growth regulators, fluorescence labeling agents, biological imaging and chromophores for non-linear optic systems. These moieties have been reported as antibacterial, anti-inflammatory, antihypertensive, antithrombotic, fungicidal, anti-allergic, antiviral and herbicidal properties. On the other hand, an ionic liquid catalyzed reaction have gained considerable attention because of their interesting properties like high thermal stability, non volatility, eco-friendly and easy method for the synthesis of imidazole derivatives.

Based on the literature, this prompted us to synthesize 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1H-imidazole-5(4H)-one derivatives from Schiff bases by making use of DBU as a catalyst.

EXPERIMENTAL

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. 1H NMR spectra were recorded in DMSO- d6 using TMS as internal standard with 400 MHz spectrometer. 13C NMR spectra were recorded in DMSO- d6 using TMS as internal standard with 100 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only.

Preparation of (Z)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (2a, 2b)

A mixture of 4-(benzylidene/substituted benzylidene)-2-methyl oxazolin-5-ones (1a, 1b) (10 mmol) and phenylhydrazine (10 mmol) was dissolved in ethanol and refluxed for 5 h at 80 °C. The completion of the reaction was monitored by TLC (1:3 of EtOAc:hexane). Then this reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL), separated solid product was collected, washed with water (10 mL) and dried. The product was recrystallised from ethanol to obtain (Z)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (2a, 2b). The formation of 2a and 2b from oxazolin-5-one derivatives (1a, 1b) has been confirmed from the spectral data.

The IR spectrum of the enamides showed peaks for NH group and C=O and absence of the peak for lactone ring. The 1H NMR spectra of the enamides showed signals for...
NHPH and NHCO groups. The mass spectra of the compounds exhibited molecular ion peaks (M⁺) corresponding to their molecular weights.

**Preparation of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styril/substituted styril)-1H-Imidazole-5(4H)-one derivatives (4a-i)**

Equimolar quantities of (Z)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (2a-2b) (10 mmol) and Schiff bases 3a and 3b (10 mmol) were mixed together in 20 mL of ethanol in the presence of DBU (1 mmol) as catalyst. The mixture was refluxed for 2 h. The completion of the reaction was checked by TLC (1:3 of EtOAc/hexane), then this reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). The separated solid product was collected, washed with water (10 mL) and dried. The product was recrystallized from ethanol to obtain 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styril/substituted styril)-1H-Imidazole-5(4H)-one derivatives (4a-4l). The physical (Table 1) and spectral analysis of the compounds is given below.

**Table 1. Physical data of the products 4a-4l.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Starting materials</th>
<th>Mol. formula of product</th>
<th>Yield* (%</th>
<th>M.P., °C</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, 3a</td>
<td>C₈H₁₀N₂O₄</td>
<td>68</td>
<td>165-166</td>
</tr>
<tr>
<td>2</td>
<td>2a, 3b</td>
<td>C₈H₁₀N₂O₂</td>
<td>65</td>
<td>168-169</td>
</tr>
<tr>
<td>3</td>
<td>2a, 3c</td>
<td>C₈H₁₀N₂OF</td>
<td>66</td>
<td>161-162</td>
</tr>
<tr>
<td>4</td>
<td>2a, 3d</td>
<td>C₈H₁₀N₂O₃</td>
<td>61</td>
<td>168-171</td>
</tr>
<tr>
<td>5</td>
<td>2a, 3e</td>
<td>C₈H₁₀N₂OCl</td>
<td>61</td>
<td>154-156</td>
</tr>
<tr>
<td>6</td>
<td>2a, 3f</td>
<td>C₈H₁₀N₂OCl</td>
<td>65</td>
<td>219-221</td>
</tr>
<tr>
<td>7</td>
<td>2a, 3b</td>
<td>C₈H₁₀N₂OCl</td>
<td>68</td>
<td>154-156</td>
</tr>
<tr>
<td>8</td>
<td>2b, 3b</td>
<td>C₈H₁₀N₂O₂Cl</td>
<td>68</td>
<td>171-172</td>
</tr>
<tr>
<td>9</td>
<td>2b, 3c</td>
<td>C₈H₁₀N₂OFCl</td>
<td>63</td>
<td>211-213</td>
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<tr>
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<td>2b, 3d</td>
<td>C₈H₁₀N₂OCl</td>
<td>63</td>
<td>211-212</td>
</tr>
<tr>
<td>11</td>
<td>2b, 3e</td>
<td>C₈H₁₀N₂OCl</td>
<td>64</td>
<td>206-208</td>
</tr>
<tr>
<td>12</td>
<td>2b, 3f</td>
<td>C₈H₁₀N₂OCl</td>
<td>69</td>
<td>210-212</td>
</tr>
</tbody>
</table>

* Refers to yields of crude products only.

**Spectral analysis of (4Z)-4-benzylidene-1-methyl-2-styril-1H-imidazol-5(4H)-one derivatives 4a-4l**

**4a: IR (KBr):** 3444 (-NH), 1668 (-C=O) cm⁻¹, 1HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, =CH-CH). 13CNMR δ = 109.5, 109.8, 116.1, 119.3, 123.3, 123.4, 123.7, 128.0, 128.8, 130.0, 130.3, 137.1, 137.1, 138.1, 138.6, 141.1, 141.3, 167.1. MS: M+H = 396.

**4b: IR (KBr):** 3436 (-NH), 1674 (-C=O) cm⁻¹, 1HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, =CH-CH). 13CNMR δ = 109.4, 109.5, 115.3, 114.2, 123.3, 123.4, 123.5, 126.2, 127.0, 128.4, 130.2, 130.4, 137.2, 137.4, 138.2, 138.5, 141.0, 141.3, 165.2. MS: M+H = 396.

**4c: IR (KBr):** 3432 (-NH), 1664 (-C=O) cm⁻¹, 1HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, =CH-CH). 13CNMR δ = 110.3, 110.8, 114.3, 118.2, 122.2, 123.2, 123.5, 125.2, 127.2, 130.4, 130.9, 137.2, 137.6, 138.4, 138.6, 141.8, 141.9, 165.8. MS: M+H = 385.

**RESULTS AND DISCUSSION**

As illustrated in scheme 1, the azaleactone (Z)-4-benzylidene-2-methylloxazol-5(4H)-one 1a-b were treated with phenylhydrazine and refluxed for 4-5 h in ethanol to produce (Z)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides 2a,2b. Then, 2a and 2b were reacted with the Schiff bases (benzylidene/substituted benzylidene)amines 3a,3f in the presence of DBU as a
catalyst in ethanol medium under reflux condition for 1-1.5 h to produce 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1H-Imidazole-5(4H)-one derivatives (4a-4l). A reasonable mechanism has been formulated for the formation of these imidazoline-5-ones (4a-4l). The IR spectrum of the compound showed absorption bands for NH, C=O, Ar, C=C, C-N and the 1H NMR showed the signals for aromatic, two distinct signals for olefinic protons and signals for amide protons. 13C NMR showed signals for –C=C, –(C=C) Ar, (C=N), (C=N) and (C=O). The mass spectrum of the compound 4a-4l showed the molecular ion peaks corresponding to molecular weight of the compounds. The spectral data confirms the structure of 4a-4l.

\[\text{Scheme 1. Synthesis of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1H-Imidazole-5(4H)-one derivatives.}\]

The IR spectra of 1a and 1b showed the presence of NH-stretching absorptions for NH and absence of stretching absorptions of lactone ring. The 1H NMR data showed signals for NH, which are D2O exchangeable and mass spectra which confirms the molecular weight of the compounds.

The cyclocondensation of 1a and 1b with Schiff bases to produce (4Z)-4-(benzylidene/ substituted benzylidene-N-aryl amino-2-(styryl/substituted styryl)-1H-imidazol-5(4H)-one derivatives (4a-4l) is supported by IR spectra showing the absence of N-H stretching absorptions of the amide group. The 1H NMR spectra showed the disappearance of peaks for NH and appearance of peaks for 2-styryl protons. 13CNMR spectra of the compound 3a-3l shows signals for the presence of C=C (C=C)Ar, C=N=C=N and C=O. Finally the mass spectrum of the compounds 4a-4l confirmed the molecular weight of the compounds there by supporting the presence of – C=C, (–C=C) Ar, (C=N), (–C=N) and (C=O). The IR spectra of 1a showed the absence of N-H stretching absorptions of the amide one derivatives

\[\text{Scheme 1. Synthesis of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1H-Imidazole-5(4H)-one derivatives.}\]

CONCLUSION

One pot green synthesis for the preparation of imidazole derivatives (4a-4l) in high purity and excellent yields has been developed by making use of DBU as a catalyst.

REFERENCES


Green synthesis of benzylidine and styryl-1H-imidazoles

Section A Research paper


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