Neighboring-Group Effect: DBU-Promoted Ring Transformation of Substituted Isoxazoles to Substituted Pyrroles

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Abstract: A novel DBU-promoted ring transformation of substituted isoxazoles to substituted pyrroles is described.

Key words: isoxazole, pyrrole, Baylis–Hillman, DBU, ring transformation, neighboring-group effect

Recently, we have described the synthesis of 5,8-dihydroisoxazolo[4,5-c]azepin-4-ones (A) from the acetates of Baylis–Hillman adducts of 3-aryl-5-formylisoxazole-4-carboxylate (Scheme 1). During this study, a few attempts to carry out direct intramolecular cyclization of the secondary amines, obtained from Baylis–Hillman adducts, involving the NH group and the ester group present on the isoxazole ring, were unsuccessful. However, it was envisioned that a strong base may trigger the desired cyclization to yield the isoxazole annulated system B and this consideration prompted us to study the possibility of desired intramolecular ring closure by DBU. Interestingly, this reaction, instead of yielding the desired bicyclic derivatives, led to the formation of a substituted pyrrole. The details of this observation are described herein.

The required amino derivatives 4–8a,b,c were obtained by the Michael addition of several primary amines on the Baylis–Hillman adducts 2a–c and 3a–c prepared from 3-aryl-5-formylisoxazole-4-carboxylates 1a–c as described earlier. All amines were obtained as diastereoisomeric mixtures and no attempts were made to separate them. These secondary amines were subsequently refluxed in the presence of DBU in THF (Scheme 2). The starting material disappeared in five hours as evident by TLC. Column chromatography of the reaction products led to isolation of the pure products 9–13a,b,c, which exhibited a mass of 44 amu less than the expected azepinones. The one- and two-dimensional NMR experiments of a model product 13a indicated the product to be a pyrrole derivative. In order to confirm the structure of the product unambiguously, the X-ray crystal structure of a representative compound 13b was examined. The ORTEP diagram (Figure 1) shows the crystal structure of compound 13b and its conformation with atomic numbering scheme.

During the optimization studies, the reaction was carried out in different solvent systems. It was observed that though dioxane and dimethylformamide gave similar pyrrole derivatives, the best yields were achieved when the reaction was performed in THF. The reaction failed to occur in methanol. In order to evaluate the generality of this reaction several analogues of substituted pyrroles 9–13a,b,c were synthesized (Table 1).

Scheme 1

Scheme 2 Reagents and conditions: a) CH₂=CHEWG, DABCO, THF, r.t., 5 min; b) RNH₂, MeOH, r.t., 8–12 h; c) DBU, THF, reflux, 5 h.
The formation of such pyrroles can be explained on the basis of mechanism shown in Scheme 3. Initially in the presence of base, due to the neighboring-group participation of the secondary hydroxyl group hydrolysis of the ester present on the ring occurs followed by concomitant fission of the isoxazole ring to yield the acetylene intermediate III. The acetylene bond undergoes an intramolecular attack of the NH group leading to the dihydro pyrrole system IV which rearranges by a 1,5-shift to furnish the substituted pyrroles 9–13. It was observed that the oxime with E stereochemistry was obtained.

In order to establish that the secondary hydroxyl group facilitates the de-esterification of the ester present on the isoxazole ring through neighboring-group participation, in a model reaction the methoxy analogue 14b of compound 4b was prepared (Scheme 4). This was then subjected to Michael addition in the presence of benzylamine to yield the amino derivative 15b. The product 15b, upon refluxing in the presence of DBU was recovered unreacted even after 24 hours, thereby proving the role of the hydroxyl group in cyclization.

Thus we have described a novel DBU-promoted ring transformation of substituted isoxazoles to pyrrole derivatives. We have also provided the experimental evidence for the neighboring-group effect that is responsible for this rearrangement.

### Table 1  Pyrroles 4–8 Prepared

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Ar</th>
<th>EWG</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Physical appearance, mp (°C)</th>
<th>HPLC (t_R in min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Ph</td>
<td>CO_2Me</td>
<td>CH_2Ph</td>
<td>9a</td>
<td>50</td>
<td>white solid, 170–172</td>
<td>18.7</td>
</tr>
<tr>
<td>4b</td>
<td>2-ClC_6H_4</td>
<td>CO_2Me</td>
<td>CH_2Ph</td>
<td>9b</td>
<td>58</td>
<td>white solid, 134–135</td>
<td>19.2</td>
</tr>
<tr>
<td>4c</td>
<td>2-Cl_2C_6H_3</td>
<td>CO_2Me</td>
<td>CH_2Ph</td>
<td>9c</td>
<td>52</td>
<td>white solid, 153–154</td>
<td>20.7</td>
</tr>
<tr>
<td>5a</td>
<td>Ph</td>
<td>CO_Bu</td>
<td>CH_2Ph</td>
<td>10a</td>
<td>55</td>
<td>white solid, 168–169</td>
<td>21.7</td>
</tr>
<tr>
<td>5b</td>
<td>2-ClC_6H_4</td>
<td>CO_Bu</td>
<td>CH_2Ph</td>
<td>10b</td>
<td>36</td>
<td>light brown solid, 93–95</td>
<td>22.3</td>
</tr>
<tr>
<td>5c</td>
<td>2-Cl_2C_6H_3</td>
<td>CO_Bu</td>
<td>CH_2Ph</td>
<td>10c</td>
<td>49</td>
<td>pale yellow solid, 114–115</td>
<td>23.7</td>
</tr>
<tr>
<td>6a</td>
<td>Ph</td>
<td>CO_Bu</td>
<td>CH_2C_6H_4F-4</td>
<td>11a</td>
<td>57</td>
<td>white solid, 166–168</td>
<td>21.2</td>
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<tr>
<td>6b</td>
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<td>CO_Bu</td>
<td>CH_2C_6H_4F-4</td>
<td>11b</td>
<td>42</td>
<td>light brown solid, 97–99</td>
<td>22.3</td>
</tr>
<tr>
<td>6c</td>
<td>2-Cl_2C_6H_3</td>
<td>CO_Bu</td>
<td>CH_2C_6H_4F-4</td>
<td>11c</td>
<td>53</td>
<td>white solid, 151–152</td>
<td>22.3</td>
</tr>
<tr>
<td>7a</td>
<td>Ph</td>
<td>CO_Bu</td>
<td>CH_2-furan-2-yl</td>
<td>12a</td>
<td>51</td>
<td>white solid, 142–144</td>
<td>19.8</td>
</tr>
<tr>
<td>7b</td>
<td>2-ClC_6H_4</td>
<td>CO_Bu</td>
<td>CH_2-furan-2-yl</td>
<td>12b</td>
<td>45</td>
<td>brown oil</td>
<td>21.1</td>
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<tr>
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<td>CO_Bu</td>
<td>CH_2-furan-2-yl</td>
<td>12c</td>
<td>53</td>
<td>pale yellow solid, 107–109</td>
<td>22.5</td>
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<tr>
<td>8a</td>
<td>Ph</td>
<td>CO_Bu</td>
<td>cyclopropyl</td>
<td>13a</td>
<td>55</td>
<td>white solid, 97–98</td>
<td>19.9</td>
</tr>
<tr>
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<td>CO_Bu</td>
<td>cyclopropyl</td>
<td>13b</td>
<td>56</td>
<td>white solid, 80–81</td>
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</tr>
<tr>
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<td>2-Cl_2C_6H_3</td>
<td>CO_Bu</td>
<td>cyclopropyl</td>
<td>13c</td>
<td>50</td>
<td>white solid, 148–149</td>
<td>22.7</td>
</tr>
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</table>

*The HPLC was carried out using a 0–100% gradient of MeCN–H_2O containing 0.1 TFA at the rate of 1 mL/min in a RP-18E column (250 × 4.5 mm, 5μ) over a period of 30 min.*
fers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. The HRMS were recorded on JEOL-JMS-600H at 70eV. Elemental analyses were performed on a Elementar’s Vario EL III microanalyzer. All amines 4–8a,b,c were prepared as described. Compounds 4a–c, 5a–c, 6a–c, 7a–c, 8a–c, 14b and 15b were prepared by following reported procedures.

Scheme 3 Mechanism for the formation of pyrroles

Scheme 4 Reagents and conditions: a) MeI, Ag2O, CH2Cl2, r.t., 12 h; b) BnNH2, MeOH, r.t., 12 h; c) DBU, THF, reflux, 24 h.

5-(3-Benzylamino-1-hydroxy-2-methoxycarbonylpropyl)-3-phenylisoxazole-4-carboxylic Acid Methyl Ester (4a)

Yield: 81%; colorless oil.

IR (neat): 3449 (OH and NH), 1732 cm–1 (C=O).

Yield: 73%; colorless oil.

IR (neat): 3492 (OH and NH), 1732 cm–1 (C=O).

Yield: 75%; colorless oil.

IR (neat): 467.20 (M+ + 1), 488.80 (M+ + Na).

Yield: 76%; light brown oil.

IR (neat): 492.93 (M+ + 1), 514.60 (M+ + Na).

Yield: 73%; colorless oil.

IR (neat): 476.50 (M+ + 1), 498.80 (M+ + Na).

Yield: 76%; light brown oil.

Yield: 71%; pale yellow oil.

Yield: 81%; colorless oil.

Yield: 76%; light brown oil.

Yield: 71%; pale yellow oil.

Yield: 81%; colorless oil.
7.51 (m, 18 H, 2 × MS (ES+): 3.4 (m, 2 H, 2 × IR (neat): 3320 (OH and NH), 1730 cm–1 (C=O). Yield: 73%; pale yellow oil.

5-([2-Butoxycarbonyl-3-[(furan-2-ylmethyl)amino]-1-hydroxypropyl]-3-phenylisoxazole-4-carboxylic Acid Methyl Ester (7a) IR (neat): 3323, 1729 cm–1 (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.86–0.93 (m, 6 H, 2 × CH3), 1.25–1.37 (m, 4 H, 2 × CH2), 1.54–1.61 (m, 4 H, 2 × CH2), 2.99–3.04 (m, 2 H, CH, 2 × 1 H of CH3), 3.25–3.27 (m, 2 H, 2 × CH2), 3.33–3.39 (m, 2 H, CH, 2 × 1 H of CH3), 3.77 (s, 6 H, 2 × OCH3), 3.90–4.05 (m, 4 H, 2 × CH2), 4.13 (m, 4 H, 2 × OCH3), 5.75 (br s, 1 H, CH3), 5.90 (1 d, J = 3.0 Hz, CHO), 6.32–6.33 (m, 4 H, 2 × 2 Haryl), 7.40–7.47 (m, 8 H, 2 × 4 ArH), 7.56–7.62 (m, 4 H, 2 × ArH and 2 × 1 Haryl), 8.31 (br s, 2 H, 2 × NH).

13C NMR (CDCl3, 50 MHz): δ = 14.1, 19.4, 30.8, 45.7, 47.2, 47.5, 52.5, 65.9, 69.3, 108.6, 109.2, 110.8, 128.3, 128.6, 129.7, 130.4, 143.1, 151.1, 162.5, 171.5, 177.8.

MS (ES+): m/z = 457.00 (M+ + 1), 479.00 (M+ + Na).

5-([2-Butoxycarbonyl-3-[(furan-2-ylmethyl)amino]-1-hydroxypropyl]-3-phenylisoxazole-4-carboxylic Acid Methyl Ester (7b) IR (neat): 3326 (OH and NH), 1729 cm–1 (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.85–0.97 (m, 6 H, 2 × CH3), 1.28–1.41 (m, 4 H, 2 × CH2), 1.55–1.68 (m, 4 H, 2 × CH2), 2.70–2.81 (m, 2 H, CH, 2 × 1 H of CH3), 3.13–3.15 (m, 2 H, 2 × CH2), 3.31–3.37 (m, 2 H, 2 × 1 H of CH3), 3.65–3.70 (m, 8 H, 2 × OCH3 and 2 × 1 CH of CH3), 3.84–3.90 (m, 2 H, 2 × 1 CH of CH3), 4.05–4.21 (m, 4 H, 2 × OCH2), 5.72 (d, 1 H, J = 4.4 Hz, CHO), 5.97 (d, 1 H, J = 4.8 Hz, CHO), 6.82–6.93 (m, 2 H, 2 × 1 Haryl), 6.93 (d, 1 H, J = 4.8 Hz, CHO), 7.63 (m, 2 H, 2 × 1 Haryl), 7.68, 8.31 (br s, 2 H, 2 × NH).

MS (ES+): m/z = 490.93 (M+ + 1), 513.00 (M+ + Na).

5-([2-Butoxycarbonyl-3-[(furan-2-ylmethyl)amino]-1-hydroxypropyl]-3,4-dichlorophenyl]isoxazole-4-carboxylic Acid Methyl Ester (8a) Yield: 72%; light brown oil.

IR (neat): 3324 (OH and NH), 1729 cm–1 (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.78–0.90 (m, 6 H, 2 × CH3), 1.14–1.35 (m, 4 H, 2 × CH2), 1.53–1.57 (m, 4 H, 2 × CH2), 2.60–2.70 (m, 2 H, 2 × 1 H of CH3), 3.01–3.10 (m, 2 H, 2 × CH3), 3.15–3.30 (m, 2 H, 2 × 1 H of CH3), 3.57–3.64 (m, 8 H, 2 × OCH3 and 2 × 1 CH of CH3), 3.67–3.79 (m, 2 H, 2 × 1 CH of CH3), 4.00–4.10 (m, 4 H, 2 × OCH2), 5.62 (d, 1 H, J = 4.0 Hz, CHO), 5.88 (d, 1 H, J = 5.0 Hz, CHO), 6.11–6.14 (m, 2 H, 2 × 1 Haryl), 6.22–6.23 (m, 2 H, 2 × 1 Haryl), 7.19–7.29 (m, 6 H, 2 × 3 ArH), 7.40–7.43 (m, 2 H, 2 × 1 Haryl).

MS (ES+): m/z = 525.00 (M+ + 1), 546.80 (M+ + Na).

5-([2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxypropyl]-3-phenylisoxazole-4-carboxylic Acid Methyl Ester (8a) Yield: 77%; pale yellow oil.

IR (neat): 3319 (OH and NH), 1730 cm–1 (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.48–0.52 (m, 8 H, 2 × 2 CH2 of cyclopropane), 0.88–0.98 (m, 6 H, 2 × CH3), 1.31–1.46 (m, 4 H, 4 × CH2), 1.59–1.69 (m, 4 H, 2 × 2 CH2 of cyclopropane), 2.85–2.99 (m, 8 H, 2 × CH of CH3), 3.10–3.13 (m, 2 H, 2 × CH3), 3.45–3.57 (m, 2 H, 2 × CH of CH3), 3.78 (s, 6 H, 2 × OCH3 and 2 × 1 CH of CH3), 4.08–4.18 (m, 4 H, 2 × OCH3).
2 × OCH3), 5.65 (br s, 1 H, CHOH), 5.93 (d, 1 H, J = 4.0 Hz, CHOH), 7.47–7.65 (m, 10 H, 2 × ArH).

1°C NMR (CDCl3, 50 MHz): δ = 6.3, 6.6, 14.0, 19.4, 30.9, 31.1, 47.7, 48.5, 52.3, 65.6, 70.6, 108.1, 128.5, 129.7, 130.3, 162.4, 162.8, 171.9, 178.4.

MS (ES+): m/z = 417.13 (M+ + 1), 438.73 (M+ + Na).

5-(2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxypropyl)-3-(2-chlorophenyl)isoxazole-4-carboxylic Acid Methyl Ester (8b)

Yield: 68%; pale yellow oil.

IR (neat): 3318 (OH and NH), 1729 cm⁻¹ (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.58–0.73 (m, 8 H, 2 × CH2 of cyclopropane), 0.89–0.97 (m, 6 H, 2 × CH3), 1.29–1.39 (m, 4 H, 2 × CH2), 1.56–1.63 (m, 4 H, 2 × CH2), 2.15–2.28 (m, 1 H, CH of cyclopropane), 2.32–2.41 (m, 1 H, CH of cyclopropane), 3.0–3.15 (m, 2 H, 2 × CH of CH3), 3.20–3.30 (m, 2 H, 2 × CH3), 3.37–3.50 (m, 2 H, 2 × CH of CH3), 3.69, 3.70 (2 s, 6 H, 2 × OCH3), 4.10–4.19 (m, 4 H, 2 × OCH2), 5.79 (d, 1 H, J = 3.58 Hz, CHOH), 5.91 (d, 1 H, J = 5.18 Hz, CHOH), 7.35–7.47 (m, 8 H, 2 × ArH).

MS (ES+): m/z = 452.27 (M+ + 1), 474.87 (M+ + Na).

5-(2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxypropyl)-3-(2,4-dichlorophenyl)isoxazole-4-carboxylic Acid Methyl Ester (8c)

Yield: 65%; pale yellow oil.

IR (neat): 3407 (OH and NH), 1729 cm⁻¹ (C=O).

1H NMR (CDCl3, 200 MHz): δ = 0.49–0.52 (m, 8 H, 2 × CH2 of cyclopropane), 0.88–0.98 (m, 6 H, 2 × CH3), 1.25–1.42 (m, 4 H, 2 × CH2), 1.62–1.69 (m, 4 H, 2 × CH2), 2.14–2.18 (m, 2 H, 2 × CH of cyclopropane), 2.90–2.98 (m, 2 H, 2 × CH of CH3), 3.13–3.15 (m, 2 H, 2 × CH), 3.39–3.47 (m, 2 H, 2 × CH of CH3), 3.69, 3.73 (2 s, 6 H, 2 × OCH3), 4.04–4.22 (m, 4 H, OCH2), 5.71 (d, 1 H, J = 4.2 Hz, CHOH), 5.95 (d, 1 H, J = 4.2 Hz, CHOH), 7.37 (s, 4 H, 2 × ArH), 7.51 (m, 2 H, 2 × ArH).

MS (ES+): m/z = 484.67 (M+ + 1), 506.93 (M+ + Na).

Pyroles 9–13a,b,c; General Procedure

To a stirred solution of compound 4–8a,b,c (2 mmol) in THF (10 mL) was added DBU (0.32 mL, 2 mmol) at rt. and the mixture was refluxed for 5 h. On completion, the mixture was extracted with EtOAc (3 × 20 mL) and H2O (25 mL). The organic layers were combined, dried (Na2SO4), and evaporated to yield an oily residue which was purified by chromatography over silica gel. Elution with hexane–EtOAc (8:2) afforded the pure product.

1-Benzyl-5-(2-hydroxyimino-2-phenylethyl)-1H-pyrrole-3-carboxylic Acid Methyl Ester (10a)

IR (KBr): 3244 (OH), 1665 cm⁻¹ (C=O).

1H NMR (CDCl3, 300 MHz): δ = 0.92 (t, 3 H, J = 7.2 Hz, CH3), 1.35–1.42 (m, 2 H, CH2), 1.64 (br s, 2 H, CH2), 3.49 (s, 2 H, CH2), 4.15 (t, 2 H, J = 6.5 Hz, OCH3), 5.12 (s, 2 H, CH2), 6.33 (s, 1 H, =CH), 7.01–7.05 (m, 2 H, ArH), 7.22–7.43 (m, 7 H, ArH and =CH), 8.38 (br s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.2, 19.6, 23.9, 31.3, 51.5, 63.9, 110.2, 115.8, 126.9, 127.4, 128.3, 128.6, 129.9, 129.3, 135.3, 137.2, 156.0, 160.4.

MS (FAB+): m/z = 391 (M+ + 1).

HRMS: m/z calc for C2H13N1O2: 346.0695; found: 346.0671.

1-Benzyl-5-(2,2-dichlorophenyl)-1H-pyrrole-3-carboxylic Acid Butyl Ester (10b)

IR (KBr): 3371 (OH), 1691 cm⁻¹ (C=O).

1H NMR (CDCl3, 300 MHz): δ = 0.93 (t, 3 H, J = 7.2 Hz, CH3), 1.31–1.48 (m, 2 H, CH2), 1.55–1.69 (m, 2 H, CH2), 4.01 (s, 2 H, CH2), 4.15 (t, 2 H, J = 6.3 Hz, OCH3), 4.96 (s, 2 H, CH2), 6.32 (s, 1 H, =CH), 7.12–7.44 (m, 7 H, ArH and =CH), 9.55 (br s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.2, 19.7, 25.8, 31.3, 51.3, 63.4, 110.9, 115.7, 127.1, 127.8, 128.2, 129.3, 130.2, 130.6, 131.3, 133.0, 134.9, 137.1, 156.7, 165.4.

MS (FAB+): m/z = 425 m/z (M+ + 2).

HRMS: m/z calc for C23H20N1O2: 424.1554; found: 424.1551.

1-Benzyl-5-(2,2-dichlorophenyl)-1H-pyrrole-3-carboxylic Acid Butyl Ester (10c)

IR (KBr): 3316 (OH), 1683 cm⁻¹ (C=O).

1H NMR (CDCl3, 300 MHz): δ = 0.94 (t, 3 H, J = 7.5 Hz, CH3), 1.34–1.49 (m, 2 H, CH2), 1.56–1.70 (m, 2 H, CH2), 3.99 (s, 2 H, CH2), 4.17 (t, 2 H, J = 6.6 Hz, OCH3), 4.99 (s, 2 H, NCH3), 6.32 (s, 1 H, =CH), 6.92–6.97 (m, 2 H, ArH), 7.12–7.36 (m, 7 H, ArH and =CH), 8.31 (br s, 1 H, OH).

13C NMR (CDCl3, 75 MHz): δ = 14.2, 19.7, 25.7, 31.3, 51.3, 64.1, 110.9, 115.8, 126.9, 127.5, 127.9, 128.2, 129.3, 130.1, 132.2, 133.4, 133.9, 135.9, 137.0, 155.9, 165.4.
1-(4-Fluorobenzyl)-5-(2-hydroxyimino-2-phenylethyl)-1H-pyrrole-3-carboxylic Acid Butyl Ester (11a)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.44 (br s, 1 H, OH).

13C NMR (CDCl₃, 75 MHz):
1H, =CH), 8.44 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylic Acid Butyl Ester (11b)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 340.1807.

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-4-fluoro-pyrrole-3-carboxylic Acid Butyl Ester (11c)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 340.1807.

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-furan-2-yl-pyrrole-3-carboxylic Acid Butyl Ester (12a)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-furan-2-yl-pyrrole-3-carboxylic Acid Butyl Ester (12b)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic Acid Butyl Ester (12c)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic Acid Butyl Ester (13a)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic Acid Butyl Ester (13b)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

1-Cyclopropyl-5-(2-hydroxyimino-2-phenylethyl)-1H-pyrrole-3-carboxylic Acid Butyl Ester (13a)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic Acid Butyl Ester (13b)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).

5-[2-(2-Chlorophenyl)-2-hydroxyiminoethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic Acid Butyl Ester (13c)

IR (KBr): 3348 (OH), 1682 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): ²H 8.10 (br s, 1 H, OH).

HRMS: m/z 443 (M+ + 1).
1-Cyclopropyl-5-[2-(2,4-dichlorophenyl)-2-hydroxyiminoethyl]-1H-pyrrole-3-carboxylic Acid Butyl Ester (13c)

IR (KBr): 3245 (OH), 1667 cm⁻¹ (C=O).

1H NMR (CDCl₃, 200 MHz): δ = 0.85–0.99 (m, 7 H, 2 CH₂ of cyclopropyl and CH₃), 1.25–1.49 (m, 2 H, CH₂), 1.58–1.72 (m, 2 H, CH₂), 2.96–3.03 (m, 1 H, CH of cyclopropyl), 4.16 (t, 2 H, J = 6.5 Hz, OCH₂), 4.24 (s, 2 H, CH₂), 6.26 (s, 1 H, =CH), 7.09–7.22 (m, 3 H, ArH and =CH), 7.39–7.40 (m, 1 H, ArH)

13C NMR (CDCl₃, 75 MHz): δ = 6.7, 13.8, 19.2, 25.5, 28.4, 30.9, 63.6, 109.6, 114.4, 121.6, 127.2, 128.9, 129.7, 131.8, 133.4, 155.4, 165.1.

MS (FAB+): m/z = 409 (M⁺ + 1).

HRMS: m/z calcd for C₂₀H₂₂Cl₂N₂O₄: 408.1008; found: 408.1007.

3-(2-Chlorophenyl)-5-(1-methoxy-2-methoxycarbonylallyl)isoxazole-4-carboxylic Acid Methyl Ester (14b)

Yield: 78%; colorless oil.

IR (neat): 1713 cm⁻¹ (C=O).

1H NMR (CDCl₃, 300 MHz): δ = 3.51 (s, 3 H, CH₃), 3.73 (s, 3 H, CO₂CH₃), 3.74 (s, 3 H, CO₂CH₃), 5.98 (s, 1 H, =CHH), 6.26 (s, 1 H, CHOCH₃), 6.61 (s, 1 H, =CHH), 7.34–7.49 (m, 4 H, ArH).

MS (ES⁺): m/z = 388.07 (M⁺ + Na).

Anal. Calcd for C₁₇H₁₆ClNO₆: C, 55.82; H, 4.41; N, 3.83. Found: C, 56.02; H, 4.44; N, 3.85.

5-(3-Benzylamino-1-methoxy-2-methoxycarbonylpropyl)-3-(2-chlorophenyl)isoxazole-4-carboxylic Acid Methyl Ester (15b)

Yield: 82%; colorless oil.

IR (neat): 3347 (NH), 1734 cm⁻¹ (CO₂Me).

1H NMR (CDCl₃, 300 MHz): δ (diastereoisomers) = 3.02–3.08 (m, 2 × 1 H of CH₂), 3.15–3.21 (m, 2 H, 2 × 1 H of CH₂), 3.33–3.38 (m, 8 H, 2 × 3 H of OCH₃), and 2 × 1 H of CH), 3.63 (s, 6 H, 2 × 3 H of CO₂CH₃), 3.68–3.72 (s merged with d, 10 H, 2 × 3 H of CO₂CH₃ and 2 × 1 H of CH₂), 3.77–3.80 (m, 2 H, 2 × 1 H of CHOCH₃), 5.44 (d, 2 H, J = 7.5 Hz, 2 × 1 H of CHOCH₃), 7.22–7.31 (m, 18 H, 2 × 9 H, ArH).

MS (ES⁺): m/z = 472.87 (M⁺), 495.07 (M⁺ + Na).

Anal. Calcd for C₂₄H₂₅ClN₂O₆: C, 60.95; H, 5.33; N, 5.92. Found: C, 61.11; H, 5.64; N, 3.79.

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References

(1) CDRI Communication No. 6618.
(3) Crystal data for compound 13b: C₂₀H₂₂Cl₂N₂O₄, M = 409.30, monoclinic, P2₁/c, a = 10.891 (1) Å, b = 17.066 (1) Å, c = 11.343 (1) Å, β = 95.31 (1)°, V = 2 099.2 (3) Å³, Z = 4, Dc = 1.2951 (2) g cm⁻³, µ (Mo-Kα) = 0.331 mm⁻¹, F(000) = 857.51, rectangular colorless crystal, size = 0.2 × 0.2 × 0.275 mm, 4628 reflections measured [R(int) = 0.05], 3688 unique, wR2 = 0.111 for all data, conventional R = 0.062 [(Δ/σ)max = 000] on F-values of 1274 reflections with I>2σ(I), S = 0.907 for all data and 247 parameters. Unit cell determination and intensity data collection (2θ = 50°) was performed on a Bruker P4 diffractometer at 293(K). Structure solutions by direct methods and refinements by full-matrix least-squares methods on F². Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (deposit No: 284175) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

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