Development of methodologies for the regioselective synthesis of four series of regioisomer isoxazoles from β-enamino diketones

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1. **General Information:**

Reagents were used as obtained from commercial suppliers without further purification. The solvents were dried and purified according to recommended procedures. The reactions were monitored by thin-layer chromatography using Merck TLC silica gel plates and visualized with UV light. The column chromatography used was silica gel 60, with 230-400 mesh (Merck). All melting points were measured with MQAPF-307 Microquímica apparatus using benzoic acid as internal standard. $^1$H and $^{13}$C NMR, HSQC and HMBC experiments were run on VARIAN Mercury Plus apparatus operating at $^1$H 300 MHz and $^{13}$C 75 MHz, and Bruker avance III HD apparatus operating at $^1$H 500 MHz and $^{13}$C 125 MHz. Chemical shifts are reported in ppm using TMS as the internal standard for CDCl$_3$ and DMSO-d$_6$. ESI(+)-MS and tandem ESI(+)-MS/MS were acquired using a hybrid high-resolution and high accuracy microTof (Q-TOF) mass spectrometer (Bruker). For ESI(+)-MS, the energy for the collision induced dissociations (CDI) was optimised for each component. For data acquisition and processing, the Q-TOF-control data analysis software (Bruker Scientific) was used. Single Crystal X-ray diffraction studies: X-ray intensity data measurements of compounds 2a (CCDC-1589617), 3a (CCDC-1589618), 4a (CCDC-1589619) and 5a (CCDC-1589620) were collected with a Bruker APEX II CCD area-detector diffractometer and graphite-monochromatized Mo-Kα radiation. The structure was solved by direct methods using SHELXS. Subsequent Fourier-difference map analyses yielded the positions of the non-hydrogen atoms. Refinements were carried out the SHELXS package. All refinements were made by full matrix least squares on F2 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions but the atoms (of hydrogens) that are commenting performing special bond were located in the Fourier map. The ORTEP diagram were drawn with 50% probability displacement ellipsoids using ORTEP-3 for Windows.

2. **General synthetic procedure and spectra data:**

2.1. **β-enamino diketone substrates 1a-e:**

The β-enamino diketone substrates 1a-e were prepared according to the literature.

2.2. **4,5-disubstituted isoxazoles 2a-e (method A):**

![Chemical Structure](image)

To a solution of β-enamino diketone 1 (1a: 160.1 mg; 1b: 146.6 mg; 1c: 137.6 mg; 1d: 144.6 mg; 1e: 152.6 mg, 0.5 mmol, 1.0 equiv) in acetonitrile (4 mL) were added hydroxylamine hydrochloride (41.7 mg, 0.6 mmol, 1.2 equiv) and pyridine (48 μL, 0.6 mmol, 1.2 equiv). The mixture was stirred at room temperature for 2 h. Then, the reaction mixture was concentrated under reduced pressure, poured into distilled H$_2$O (10 mL), extracted with dichloromethane (3 x 5 mL), washed with a solution of H$_2$O–HCl (10:1; 2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure to give the corresponding isoxazoles, which
were purified by chromatography column on a silica gel column (hexane/ethyl acetate, 20:80) to afford pure compounds 2a-e.

4-(2-ethoxy-2-oxoacetyl)-5-(4-nitrophenyl) isoxazole (2a): Yellow solid; 65% yield (94.3 mg); mp 112.1-113.2°C; ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.43 (t, 3H, J = 7.16 Hz, OCH₂CH₃), 4.43 (q, 2H, J = 7.16 Hz, OCH₂CH₃), 8.30 (d, 3H, J = 9.20 Hz, 4-NO₂C₆H₄), 8.38 (d, 2H, J = 9.20 Hz, 4-NO₂C₆H₄), 9.12 (s, 1H, H₃); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 14.1 (OCH₂CH₃), 63.5 (OCH₂CH₃), 114.2 (C4), 123.9, 130.5, 131.4, 149.9 (4-NO₂C₆H₄), 152.0 (C3), 161.3 (CO₂Et), 172.0 (C5), 176.9 (CO₂Et); HRMS (ESI⁺): calcd for C₁₃H₁₂NO₄⁺, [M+H]⁺: 291.0612, found 291.0553.

4-(2-ethoxy-2-oxoacetyl)-5-(4-fluorophenyl) isoxazole (2b): Yellow solid; 53% yield (69.7 mg); mp 78.0-78.8°C; ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.40 (t, 3H, J = 7.15 Hz, OCH₂CH₃), 4.39 (q, 2H, J = 7.15 Hz, OCH₂CH₃), 7.22 (dd, 2H, J = 9.03 Hz, 4-FC₆H₄), 8.16 (dd, 2H, J = 9.09, J₆H = 5.25 Hz, 4-FC₆H₄), 9.02 (s, 1H, H₃); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 14.1 (OCH₂CH₃), 63.2 (OCH₂CH₃), 114.2 (C4), 116.2 (d, 3J₄C = 22.32 Hz, 4-FC₆H₄), 122.2 (d, 4J₄C = 3.25 Hz, 4-FC₆H₄), 131.9 (d, 3J₄C = 8.95 Hz, 4-FC₆H₄), 151.9 (C3), 161.8 (CO₂Et), 165.3 (d, 3J₄C = 255.29 Hz, 4-FC₆H₄), 173.6 (C5), 177.1 (CO₂Et); HRMS (ESI⁺): calcd for C₁₃H₁₂FNO₄⁺, [M+H]⁺: 264.0667, found 264.0670.

4-(2-ethoxy-2-oxoacetyl)-5-phenyl isoxazole (2c): Light yellow viscous liquid; 57% yield (69.9 mg); ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.35 (t, 3H, J = 7.15 Hz, OCH₂CH₃), 4.34 (q, 2H, J = 7.15 Hz, OCH₂CH₃), 7.50-7.63 (m, 3H, Ph), 8.03-8.07 (m, 2H, Ph), 9.00 (s, 1H, H₃); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 14.0 (OCH₂CH₃), 63.1 (OCH₂CH₃), 112.8 (C4), 125.9, 128.8, 129.3, 132.6 (Ph), 151.7 (C3), 161.8 (CO₂Et), 174.6 (C5), 177.3 (CO₂Et); HRMS (ESI⁺): calcd for C₁₃H₁₂NO₄⁺, [M+H]⁺: 246.0761, found 246.0698.
4-(2-ethoxy-2-oxoacetyl)-5-(4-methylphenyl) isoxazole (2d): Light yellow solid; 52% yield (67.4 mg); mp 70.2-70.6 °C; \(^1\)H NMR (300.06 MHz, CDCl\(_3\)) \(\delta\) (ppm) 1.36 (t, 3H, J = 7.15 Hz, OCH\(_2\)CH\(_3\)), 2.44 (s, 3H, 4-CH\(_3\)C\(_6\)H\(_4\)), 4.35 (q, 2H, J = 7.14 Hz, OCH\(_2\)CH\(_3\)), 7.33 (d, 2H, J = 8.04 Hz, 4-CH\(_3\)C\(_6\)H\(_4\)), 7.98 (d, 2H, J = 8.29 Hz, 4-CH\(_3\)C\(_6\)H\(_4\)), 8.97 (s, 1H, H3); \(^13\)C NMR (75.46 MHz, CDCl\(_3\)) \(\delta\) (ppm) 14.0 (OCH\(_2\)CH\(_3\)), 21.8 (4-CH\(_3\)C\(_6\)H\(_4\)), 63.0 (OCH\(_2\)CH\(_3\)), 112.4 (C4), 123.2, 129.2, 129.5, 143.6 (4-CH\(_3\)C\(_6\)H\(_4\)), 151.8 (C3), 161.9 (COCO\(_2\)Et), 174.8 (C5), 177.3 (COCO\(_2\)Et); HRMS (ESI+): calcd for C\(_{14}\)H\(_{14}\)NO\(_3\)^+: \([\text{M+H}]^+\): 260.0917, found 260.0849.

4-(2-ethoxy-2-oxoacetyl)-5-(4-methoxyphenyl) isoxazole (2e): Yellow solid; 50% yield (68.8 mg); mp 66.7-66.6 °C; \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \(\delta\) (ppm) 1.39 (t, 3H, J = 7.15 Hz, OCH\(_2\)CH\(_3\)), 3.90 (s, 3H, 4-OCH\(_3\)C\(_6\)H\(_4\)), 4.38 (q, 2H, J = 7.17 Hz, OCH\(_2\)CH\(_3\)), 7.03 (d, 2H, J = 8.95 Hz, 4-OCH\(_3\)C\(_6\)H\(_4\)), 8.16 (d, 2H, J = 8.99 Hz, 4-OCH\(_3\)C\(_6\)H\(_4\)), 8.97 (s, 1H, H3); \(^13\)C NMR (125.77 MHz, CDCl\(_3\)) \(\delta\) (ppm) 14.1 (OCH\(_2\)CH\(_3\)), 55.6 (4-OCH\(_3\)C\(_6\)H\(_4\)), 63.0 (OCH\(_2\)CH\(_3\)), 111.7 (C4), 114.2, 118.4, 131.3 (4-OCH\(_3\)C\(_6\)H\(_4\)), 151.9 (C3), 162.1 (COCO\(_2\)Et), 163.2 (4-OCH\(_3\)C\(_6\)H\(_4\)), 174.4 (C5), 177.1 (COCO\(_2\)Et); HRMS (ESI+): calcd for C\(_{14}\)H\(_{14}\)NO\(_3\)^+: \([\text{M+H}]^+\): 276.0860, found 276.0876.

2.3. 4,5-disubstituted isoxazoles 3a-e (method B):

To a solution of \(\beta\)-enamino diketone 1 (1a: 160.1 mg; 1b: 146.6 mg; 1c: 137.6 mg; 1d: 144.6 mg; 1e: 152.6 mg, 0.5 mmol, 1.0 equiv) in ethanol (4 mL) was added hydroxylamine hydrochloride (41.7 mg, 0.6 mmol, 1.2 equiv), and stirred under reflux for 1 h. Then, the reaction mixture was concentrated under reduced pressure, poured into distilled H\(_2\)O (10 mL), extracted with dichloromethane (3 x 5 mL) and washed with a solution of brine (2 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure to give the corresponding isoxazoles, which were purified by chromatography column on a silica gel column (hexane/ethyl acetate, 20:80) to afford pure compounds 3a-e.
5-(ethoxycarbonyl)-4-(4-nitrobenzoyl) isoxazole (3a): Yellow solid; 58% yield (84.1 mg); mp 118.3-193.2 °C; $^1$H NMR (300.06 MHz, CDCl$_3$) δ (ppm) 1.17 (t, 3H, J = 7.15 Hz, OCH$_2$CH$_3$), 4.25 (q, 2H, J = 7.15 Hz, OCH$_2$CH$_3$), 7.99 (d, 2H, J = 9.02 Hz, 4-NO$_2$C$_6$H$_4$), 8.35 (d, 2H, J = 9.01 Hz, 4-NO$_2$C$_6$H$_4$), 8.60 (s, 1H, H3); $^{13}$C NMR (75.46 MHz, CDCl$_3$) δ (ppm) 13.8 (OCH$_2$CH$_3$), 63.3 (OCH$_2$CH$_3$), 121.6 (C4), 124.1, 130.3, 141.5 (4-NO$_2$C$_6$H$_4$), 150.5 (C3), 150.9 (4-NO$_2$C$_6$H$_4$), 155.7 (CO$_2$Et), 158.6 (C5), 185.7 (CO).

5-(ethoxycarbonyl)-4-(4-fluorobenzoyl) isoxazole (3b): Yellow solid; 65% yield (85.5 mg); mp 108.5-109.0 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) δ (ppm) 1.13 (t, 3H, J = 7.15 Hz, OCH$_2$CH$_3$), 4.25 (q, 2H, J = 7.15 Hz, OCH$_2$CH$_3$), 7.18 (dd, 2H, J = 8.89, J$_{F-H}$ = 8.34 Hz, 4-FC$_6$H$_4$), 7.86 (dd, 2H, J = 8.99, J$_{F-H}$ = 5.30 Hz, 4-FC$_6$H$_4$), 8.52 (s, 1H, H3); $^{13}$C NMR (125.77 MHz, CDCl$_3$) δ (ppm) 13.7 (OCH$_2$CH$_3$), 63.0 (OCH$_2$CH$_3$), 116.2 (d, $^3$J$_{C-F}$ = 22.10 Hz, 4-FC$_6$H$_4$), 122.0 (C4), 132.2 (d, $^3$J$_{C-F}$ = 9.61 Hz, 4-FC$_6$H$_4$), 133.4 (d, $^3$J$_{C-F}$ = 2.94 Hz, 4-FC$_6$H$_4$), 150.4 (C3), 155.9 (CO$_2$Et), 158.0 (C5), 166.5 (d, $^3$J$_{C-F}$ = 257.42 Hz, 4-FC$_6$H$_4$), 185.5 (CO); HRMS (ESI$^+$): calcd for C$_{13}$H$_{12}$FNO$_4$*, [M+H]$^+$: 264.0667, found 264.0676.

4-benzoyl-5-(ethoxycarbonyl) isoxazole (3c): White solid; 64% yield (78.4 mg); mp 83.8-85.0 °C; $^1$H NMR (300.06 MHz, CDCl$_3$) δ (ppm) 1.06 (t, 3H, J = 7.15 Hz, OCH$_2$CH$_3$), 4.20 (q, 2H, J = 7.16 Hz, OCH$_2$CH$_3$), 7.47-7.54 (m, 2H, Ph), 7.62-7.68 (m, 1H, Ph), 7.81-7.84 (m, 2H, Ph), 8.54 (s, 1H, H3); $^{13}$C NMR (75.46 MHz, CDCl$_3$) δ (ppm) 13.6 (OCH$_2$CH$_3$), 62.9 (OCH$_2$CH$_3$), 122.1 (C4), 128.9, 129.5, 134.3, 137.0 (Ph), 150.6 (C3), 156.0 (CO$_2$Et), 158.2 (C5), 187.1 (CO); HRMS (ESI$^+$): calcd for C$_{13}$H$_{12}$NO$_4$*, [M+H]$^+$: 246.0761, found 246.0708.

5-(ethoxycarbonyl)-4-(4-methylbenzoyl) isoxazole (3d): Light yellow solid; 63% yield (81.6 mg); mp 77.6-78.3 °C; $^1$H NMR (300.06 MHz, CDCl$_3$) δ (ppm) 1.09 (t, 3H, J = 7.14 Hz, OCH$_2$CH$_3$), 2.44 (s, 3H, 4-CH$_3$C$_6$H$_4$), 4.22 (q, 2H, J = 7.14 Hz, OCH$_2$CH$_3$), 7.28-7.31 (m, 2H, 4-CH$_3$C$_6$H$_4$), 7.72 (d, 2H, J = 8.24 Hz, 4-CH$_3$C$_6$H$_4$), 8.51 (s, 1H, H3); $^{13}$C NMR (75.46 MHz,
CDCl₃ δ (ppm) 13.6 (OCH₂CH₃), 21.9 (4-CH₃C₆H₄), 62.8 (OCH₂CH₃), 122.4 (C4), 129.6, 129.6, 134.5, 145.6 (4-CH₃C₆H₄), 150.5 (C3), 156.0 (CO₂Et), 157.9 (C5), 186.6 (CO); HRMS (ESI⁺): calcd for C₁₄H₁₄NO₄⁺, [M+H]⁺: 260.0917, found 260.0863.

5-(ethoxycarbonyl)-4-(4-methoxybenzoyl) isoxazole (3e): White solid; 52% yield (71.5 mg); mp 84.0-84.7 °C; ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.12 (t, 3H, J = 7.14 Hz, OCH₂CH₃), 3.90 (s, 3H, 4-CH₃C₆H₄), 4.25 (q, 2H, J = 7.16 Hz, OCH₂CH₃), 6.96 (d, 2H, J = 9.00 Hz, 4-OCH₃C₆H₄), 7.81 (d, 2H, J = 8.92 Hz, 4-OCH₃C₆H₄), 8.49 (s, 1H, H3); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 13.7 (OCH₂CH₃), 62.8 (OCH₂CH₃), 114.2 (4-OCH₃C₆H₄), 122.6 (C4), 129.9, 132.0 (4-OCH₃C₆H₄), 150.5 (C3), 156.1 (CO₂Et), 157.6 (C5), 164.7 (4-OCH₃C₆H₄), 185.5 (CO); HRMS (ESI⁺): calcd for C₁₄H₁₄NO₅⁺, [M+H]⁺: 276.0866, found 276.0888.

2.4. 3,4-disubstituted isoxazoles 4a-e (method C):

To a solution of β-enamino diketone 1 (1a: 160.1 mg; 1b: 146.6 mg; 1c: 137.6 mg; 1d: 144.6 mg; 1e: 152.6 mg, 0.5 mmol, 1.0 equiv) in acetonitrile (4 mL) were added hydroxylamine hydrochloride (41.7 mg, 0.6 mmol, 1.2 equiv), boron trifluoride diethyl etherate solution 46.5% (270 µL, 1.0 mmol, 2.0 equiv) and pyridine (56 µL, 0.7 mmol, 1.4 equiv). The mixture was stirred at room temperature for 5 h. Then, the reaction mixture was concentrated under reduced pressure, poured into distilled H₂O (10 mL), extracted with dichloromethane (3 x 5 mL), washed with a solution of H₂O–HCl (10:1; 2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure to give the corresponding isoxazoles, which were purified by chromatography column on a silica gel column (hexane/ethyl acetate, 20:80) to afford pure compounds 4a-e.

3-(ethoxycarbonyl)-4-(4-nitrobenzoyl) isoxazole (4a): Light yellow solid; 70% yield (101.5 mg); mp 90.4-92.4 °C; ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.30 (t, 3H, J = 7.15 Hz, OCH₂CH₃), 4.35 (q, 2H, J = 7.14 Hz, OCH₂CH₃), 8.01 (d, 2H, J = 8.96 Hz, 4-NO₂C₆H₄), 8.36 (d, 2H, J = 8.95 Hz, 4-NO₂C₆H₄), 8.89 (s, 1H, H5); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 13.9
(OCH₃CH₃), 63.2 (OCH₃CH₃), 120.1 (C4), 124.2, 130.1, 141.8, 150.8 (4-NO₂C₆H₄), 154.4 (C3), 158.9 (CO₂Et), 161.7 (C5), 184.5 (CO); HRMS (ESI+): calcd for C₁₃H₁₃N₂O₆⁺, [M+H]⁺: 291.0612, found 291.0544.

3-(ethoxycarbonyl)-4-(4-fluorobenzoyl) isoxazole (4b): Yellow viscous liquid; 71% yield (93.4 mg); ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.27 (t, 3H, J = 7.15 Hz, OCH₃CH₃), 4.35 (q, 2H, J = 7.14 Hz, OCH₃CH₃), 7.19 (t, 2H, J = 8.57 Hz, 4-FC₆H₄), 7.88 (dd, 2H, J = 8.87, J=8= 5.29 Hz, 4-FC₆H₄), 8.79 (s, 1H, H5); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 13.9 (OCH₃CH₃), 63.0 (OCH₃CH₃), 116.2 (d, 1J=CF = 22.02 Hz, 4-FC₆H₄), 120.3 (C4), 132.0 (d, 1J=CF = 9.46 Hz, 4-FC₆H₄), 133.7 (d, 1J=CF = 3.00 Hz, 4-FC₆H₄), 154.6 (C3), 159.1 (CO₂Et), 160.8 (C5), 166.4 (d, 1J=CF = 256.71 Hz, 4-FC₆H₄), 184.4 (CO); HRMS (ESI+): calcd for C₁₃H₁₃FNO₆⁺, [M+H]⁺: 264.0676, found 264.0679.

4-benzoyl-3-(ethoxycarbonyl) isoxazole (4c): Yellow viscous liquid; 64% yield (78.4 mg); ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.24 (t, 3H, J = 7.15 Hz , OCH₃CH₃), 4.32 (q, 2H, J = 7.14 Hz, OCH₃CH₃), 7.48-7.55 (m, 2H, Ph), 7.62-7.68 (m, 1H, Ph), 7.83-7.87 (m, 2H, Ph), 8.80 (s, 1H, H5); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 13.8 (OCH₃CH₃), 62.9 (OCH₃CH₃), 120.5 (C4), 129.0, 129.3, 134.1, 137.3 (Ph), 154.8 (C3), 159.2 (CO₂Et), 161.1 (C5), 185.9 (CO); HRMS (ESI+): calcd for C₁₃H₁₃NO₆⁺, [M+H]⁺: 246.0761, found 246.0695.

3-(ethoxycarbonyl)-4-(4-methylbenzoyl) isoxazole (4d): White viscous liquid; 65% yield (84.2 mg); ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.25 (t, 3H, J = 7.15 Hz, OCH₃CH₃), 2.45 (s, 3H, 4-CH₃C₆H₄), 4.33 (q, 2H, J = 7.14 Hz, OCH₃CH₃), 7.29-7.32 (m, 2H, 4-CH₃C₆H₄), 7.75 (d, 2H, J = 8.20 Hz, 4-CH₃C₆H₄), 8.77 (s, 1H, H5); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 13.8 (OCH₃CH₃), 21.8 (4-CH₃C₆H₄), 62.8 (OCH₃CH₃), 120.6 (C4), 129.4, 129.7, 134.8, 145.2 (4-CH₃C₆H₄), 154.8 (C3), 159.2 (CO₂Et), 160.8 (C5), 185.5 (CO); HRMS (ESI+): calcd for C₁₃H₁₃NO₆⁺, [M+H]⁺: 260.0917, found 260.0843.

3-(ethoxycarbonyl)-4-(4-methoxybenzoyl) isoxazole (4e): White viscous liquid; 74% yield (101.8 mg); ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.26 (t, 3H, J = 7.15 Hz, OCH₃CH₃), 3.90 (s, 3H, 4-OCH₃C₆H₄), 4.34 (q, 2H, J = 7.18 Hz, OCH₃CH₃), 6.98
(d, 2H, J = 8.88 Hz, 4-OCH3C6H4), 7.84 (d, 2H, J = 8.88 Hz, 4-OCH3C6H4), 8.75 (s, 1H, HS); 13C NMR (125.77 MHz, CDCl3) δ (ppm) 13.9 (OCH3C6H5), 55.7 (4-OCH3C6H5), 62.8 (OCH2C6H5), 114.2 (4-OCH3C6H5), 120.6 (C4), 130.2, 131.7 (4-OCH3C6H5), 154.7 (C3), 159.2 (COEt), 160.4 (C5), 164.4 (4-OCH3C6H5), 184.4 (CO); HRMS (ESI+): calcd for C14H12NO5•, [M+H]⁺: 276.0866, found 276.0880.

2.5. 3,5-disubstituted 4-formyl isoxazoles 5a-e (method D):

![Diagram](image-url)

A mixture of compound 1 (1a: 160.1 mg; 1b: 146.6 mg; 1c: 137.6 mg; 1d: 144.6 mg; 1e: 152.6 mg, 0.5 mmol, 1.0 equiv) and tert-butylamine (38.5 mg, 0.525 mmol, 1.05 equiv) in acetonitrile (4 mL) was stirred at room temperature for 2 h. Next, hydroxylamine hydrochloride (41.7 mg, 0.6 mmol, 1.2 equiv) and boron trifluoride diethyl etherate solution 46.5% (270 µL, 1.0 mmol, 2.0 equiv) were added to mixture and stirred under reflux for 3 h. Then, the reaction mixture was concentrated under reduced pressure, poured into distilled H2O (10 mL), extracted with dichloromethane (3 x 5 mL), washed with a solution of H2O–HCl (10:1; 2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure to give the corresponding isoxazoles, which were purified by chromatography column on a silica gel column (hexane/ethyl acetate, 20:80) to afford pure compounds 5a-e.

3-(ethoxycarbonyl)-4-formyl-5-(4-nitrophene) isoxazole (5a): Light orange solid; 75% yield (108.8 mg); mp 123.0-124.2 °C; 1H NMR (500.13 MHz, CDCl3) δ (ppm) 1.50 (t, 3H, J = 7.16 Hz, OCH2CH3), 4.57 (q, 2H, J = 7.17 Hz, OCH2CH3), 8.40 (d, 2H, J = 9.19 Hz, 4-NO2C6H4), 8.43 (d, 2H, J = 9.24 Hz, 4-NO2C6H4), 10.47 (s, 1H, C=O); 13C NMR (125.77 MHz, CDCl3) δ (ppm) 14.3 (OCH2CH3), 63.5 (OCH2CH3), 116.8 (C4), 124.1, 130.3, 130.9, 150.1 (4-NO2C6H4), 156.0 (C3), 159.4 (CO2Et), 170.9 (C5), 184.5 (CHO); HRMS (ESI+): calcd for C13H11N2O5•, [M+H]⁺: 291.0612, found 291.0540.

3-(ethoxycarbonyl)-5-(4-fluorophenyl)-4-formyl isoxazole (5b): Yellow solid; 65% yield (85.5 mg); mp 72.9-74.0°C; 1H NMR (500.13 MHz, CDCl3) δ (ppm) 1.48 (t, 3H, J = 7.17 Hz, OCH2CH3), 4.55 (q, 2H, J = 7.17 Hz, OCH2CH3), 7.23-7.26 (m,
2H, 4-FC₆H₄), 8.27 (dd, 2H, J = 9.06, J₂=2 = 5.25 Hz, 4-FC₆H₄), 10.42 (s, 1H, CHO); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 14.2 (OCH₃CH₂), 63.2 (OCH₃CH₂), 115.1 (C₄), 116.3 (d, J₁C-F = 21.88 Hz, 4-FC₆H₄), 121.8 (d, J₂C-F = 3.23 Hz, 4-FC₆H₄), 131.7 (d, J₂C-F = 9.09 Hz, 4-FC₆H₄), 155.9 (C₅), 159.6 (CO₂Et), 166.5 (d, J₂C-F = 255.69 Hz, 4-FC₆H₄), 172.6 (C₅), 184.5 (CHO); HRMS (ESI+): calcd for C₁₃H₁₂FNO₅⁺, [M+H]⁺: 264.0667, found 264.0684.

3-{ethoxycarbonyl}-4-formyl-5-phenyl isoxazole (5c): Yellow viscous liquid; 62% yield (76.0 mg); ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.48 (t, 3H, J = 7.14 Hz, OCH₃CH₂), 4.55 (q, 2H, J = 7.15 Hz, OCH₃CH₂), 7.53-7.65 (m, 3H, Ph), 8.14-8.18 (m, 2H, Ph), 10.40 (s, 1H, CHO); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 14.2 (OCH₃CH₂), 63.1 (OCH₃CH₂), 115.3 (C₄), 125.5, 129.0, 129.0, 132.9 (Ph), 155.7 (C₃), 159.7 (CO₂Et), 173.8 (C₅), 184.3 (CHO); HRMS (ESI+): calcd for C₁₃H₁₂FNO₅⁺, [M+H]⁺: 246.0761, found 246.0695.

3-{ethoxycarbonyl}-4-formyl-5-(4-methylphenyl) isoxazole (5d): White solid; 70% yield (90.7 mg); mp 57.2-57.7 °C; ¹H NMR (300.06 MHz, CDCl₃) δ (ppm) 1.48 (t, 3H, J = 7.14 Hz, OCH₃CH₂), 2.46 (s, 3H, 4-CH₃C₆H₄), 4.54 (q, 2H, J = 7.15 Hz, OCH₃CH₂), 7.34-7.37 (m, 2H, 4-CH₃C₆H₄), 8.07 (d, 2H, J = 8.30 Hz, 4-CH₃C₆H₄), 10.39 (s, 1H, CHO); ¹³C NMR (75.46 MHz, CDCl₃) δ (ppm) 14.2 (OCH₃CH₂), 21.9 (4-CH₃C₆H₄), 63.1 (OCH₃CH₂), 114.9 (C₄), 122.7, 129.0, 129.7, 143.9 (4-CH₃C₆H₄), 155.7 (C₃), 159.8 (CO₂Et), 173.9 (C₅), 184.3 (CHO); HRMS (ESI+): calcd for C₁₃H₁₄NO₅⁺, [M+H]⁺: 260.0917, found 260.0856.

3-{ethoxycarbonyl}-4-formyl-5-(4-methoxyphenyl) isoxazole (5e): White solid; 68% yield (93.5 mg); mp 112.3-113.7°C; ¹H NMR (500.13 MHz, CDCl₃) δ (ppm) 1.47 (t, 3H, J = 7.14 Hz, OCH₃CH₂), 3.89 (s, 3H, 4-OCH₃C₆H₄), 4.53 (q, 2H, J = 7.15 Hz, OCH₃CH₂), 7.02 (d, 2H, J = 9.03 Hz, 4-OCH₃C₆H₄), 8.21 (d, 2H, J = 9.08 Hz, 4-OCH₃C₆H₄), 10.37 (s, 1H, CHO); ¹³C NMR (125.77 MHz, CDCl₃) δ (ppm) 14.1 (OCH₃CH₂), 55.6 (4-OCH₃C₆H₄), 62.9 (OCH₃CH₂), 114.1 (C₄), 114.3, 118.0, 131.0 (4-OCH₃C₆H₄), 155.8 (C₃), 159.8 (CO₂Et), 163.3 (4-OCH₃C₆H₄), 173.4 (C₅), 184.3 (CHO); HRMS (ESI+): calcd for C₁₃H₁₄NO₅⁺, [M+H]⁺: 276.0866, found 276.0876.

3. References:

(1) Perrin, D. D.; Armarego L. F. in Purification of Laboratory Chemicals, Pergamon Press, New York, 3rd edn, 1996.
(2) Sheldrick, G. M. Acta Cryst. 2008, A64, 112.

(3) Farrugia, L. J. J. Appl. Crystallogr. 1997, 30, 565.

(4) Rosa, F. A.; Machado, P.; Rossatto, M.; Vargas, P. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. Synlett 2007, 3165.
Table SI-1. X-ray crystallographic data of compound 2a

| Bond precision: | C–C = 0.0024 Å | Wavelength=0.71073 |
|----------------|----------------|---------------------|
| Cell:          | a=12.6326(13)  | b=14.5578(13)       | c=7.3585(7) |
| alpha=90       | beta=106.635(3)| gamma=90            |
| Temperature:   | 297 K          |                     |
| Volume         | Calculated     | Reported            |
|                | 1296.6(2)      | 1296.6(2)           |
| Space group    | P 21/c         | P21/c               |
| Hall group     | -P 2ybc        | -P2ybc              |
| Moiety formula | C13 H10 N2 O6  | C13 H10 N2 O6       |
| Sum formula    | C13 H10 N2 O6  | C13 H10 N2 O6       |
| Mr             | 290.23         | 290.23              |
| Dx, g cm-3     | 1.487          | 1.487               |
| Z               | 4              | 4                   |
| Mr (mm-1)      | 0.120          | 0.120               |
| F000           | 600.0          | 600.0               |
| F000'          | 600.37         | 600.37              |
| h.k,lmax       | 18.20,10       | 18.20,10            |
| Nref           | 4003           | 3988                |
| Tmin,Tmax      | 0.955,0.972    | 0.967,0.989         |
| Tmin’          | 0.955          |                     |

Correction method- # Reported T Limits: Tmin=0.967 Tmax=0.989
AbsCorr - MULTI-SCAN

Data completeness= 0.996  Theta(max)= 30.580
R(reflections)= 0.0563( 2971)  wR2(reflections)= 0.1774( 3988)
S = 0.974  Npar= 190

The crystal structure 2a has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC-1589617.
The crystal structure 3a has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC-1589618.
Figure SI-3. ORTEP plot of compound 4a

| Bond precision | C-C = 0.0020 A | Wavelength=1.54178 |
|---------------|----------------|-------------------|
| Cell          | a=7.3487(2)   | b=17.1804(4)      | c=10.4509(3) |
|               | alpha=90      | beta=98.167(1)    | gamma=90     |
| Temperature   | 296 K         |                   |               |
| Volume        | Calculated    | 1306.07(6)        | Reported      |
|               | 1306.07(6)    |                   |               |
| Space group   | P 21/c        | P21/c             |               |
| Hall group    | -P 2ybc       | -P2ybc            |               |
| Moiety formula| C13 H10 N2 O6 | C13 H10 N2 O6     |               |
| Sum formula   | C13 H10 N2 O6 | C13 H10 N2 O6     |               |
| Mr            | 290.23        | 290.23            |               |
| D, g cm-3     | 1.476         | 1.476             |               |
| Z              | 4             | 4                 |               |
| Mr (mm-1)     | 1.025         | 1.025             |               |
| F000          | 600.0         | 600.0             |               |
| F000’         | 602.27        |                   |               |
| h,k,lmax      | 9,21,12       | 9,21,12           |               |
| Nref          | 2573          | 2565              |               |
| Tmin,Tmax     | 0.704,0.751   | 0.691,0.762       |               |
| Tmin’         | 0.639         |                   |               |

Correction method= # Reported T Limits: Tmin=0.691 Tmax=0.762
AbsCorr = MULTI-SCAN
Data completeness= 0.997    Theta(max)= 72.240
R(reflections)= 0.0403( 2260)    wR2(reflections)= 0.1095( 2565)
S = 1.050     Npar= 190

The crystal structure 4a has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC-1589619.
**Figure SI-4.** ORTEP plot of compound 5a

**Table SI-4.** X-ray crystallographic data of compound 5a

| Bond precision: | C-C = 0.0028 Å | Wavelength=0.71073 |
|-----------------|-----------------|--------------------|
| Cell:           |                 |                    |
| a=5.8104(5)    | b=8.2881(8)     | c=13.1190(12)      |
| alpha=89.312(3)| beta=82.695(3)  | gamma=85.322(3)    |
| Temperature:    | 100 K           |                    |
| Volume          | 624.56(10)      | 624.56(10)         |
| Space group     | P-1             | P-1                |
| Hall group      | -P 1            | -P 1               |
| Moity formula   | C13 H10 N2 O6   | C13 H10 N2 O6      |
| Sum formula     | C13 H10 N2 O6   | C13 H10 N2 O6      |
| Mr              | 290.23          | 290.23             |
| D, g cm-3       | 1.543           | 1.543              |
| Z               | 2               | 2                  |
| Mu (mm-1)       | 0.125           | 0.125              |
| F000            | 300.0           | 300.0              |
| F000’           | 300.0           | 300.0              |
| h,k,lmax       | 0,11,18         | 0,11,18            |
| h,k,lmax’      | 3637            | 3625               |
| Tmin,Tmax      | 0.935,0.969     | 0.935,0.969        |
| Tmin’          | 0.944           |                    |

Correction method= # Reported T Limits: Tmin=0.935 Tmax=0.969  
AbsCorr = MULTI-SCAN  
Data completeness= 0.997  
Theta(max)= 29.980  
R(reflections)= 0.0560 (2149)  
wr2(reflections)= 0.1556 (3625)  
S = 1.045  
Npar= 190

The crystal structure 5a has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC-1589620.
Figure SI-5. $^1$H NMR spectrum of 2a (CDCl$_3$, 300.06 MHz)
Figure SI-6. $^{13}$C NMR spectrum of 2a (CDCl$_3$, 75.46 MHz)
Figure SI-7. $^1$H NMR spectrum of 2b (CDCl$_3$, 500.13 MHz)
Figure SI-8. $^{13}$C NMR spectrum of 2b (CDCl$_3$, 125.77 MHz)
Figure SI-9. $^1$H NMR spectrum of 2c (CDCl$_3$, 300.06 MHz)
Figure SI-10. $^{13}$C NMR spectrum of 2c (CDCl$_3$, 75.46 MHz)
Figure SI-11. $^1$H NMR spectrum of 2d (CDCl$_3$, 300.06 MHz)
Figure SI-12. $^{13}$C NMR spectrum of 2d (CDCl$_3$, 75.46 MHz)
Figure SI-13. $^1$H NMR spectrum of 2e (CDCl$_3$, 500.13 MHz)
Figure SI-14. $^{13}$C NMR spectrum of 2e (CDCl$_3$, 125.77 MHz)
Figure SI-15. $^1$H NMR spectrum of 3a (CDCl$_3$, 300.06 MHz)
Figure SI-16. $^{13}$C NMR spectrum of 3a (CDCl$_3$, 75.46 MHz)
Figure SI-17. $^1$H NMR spectrum of 3b (CDCl$_3$, 500.13 MHz)
Figure SI-18. $^{13}$C NMR spectrum of 3b (CDCl$_3$, 125.77 MHz)
Figure SI-19. \(^1\)H NMR spectrum of 3c (CDCl\(_3\), 300.06 MHz)
Figure SI-20. $^{13}$C NMR spectrum of 3c (CDCl$_3$, 75.46 MHz)
Figure SI-21. $^1$H NMR spectrum of 3d (CDCl$_3$, 300.06 MHz)
Figure SI-22. $^{13}$C NMR spectrum of 3d (CDCl$_3$, 75.46 MHz)
**Figure SI-23.** \(^1\)H NMR spectrum of 3e (CDCl₃, 500.13 MHz)
Figure SI-24. $^{13}$C NMR spectrum of 3e (CDCl$_3$, 125.77 MHz)

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Figure SI-25. $^1$H NMR spectrum of 4a (CDCl$_3$, 500.13 MHz)
Figure SI-26. $^{13}$C NMR spectrum of 4a (CDCl$_3$, 125.77 MHz)
Figure SI-27. $^1$H NMR spectrum of 4b (CDCl$_3$, 500.13 MHz)
Figure SI-28. $^{13}$C NMR spectrum of 4b (CDCl$_3$, 125.77 MHz)
Figure SI-29. $^1$H NMR spectrum of 4c (CDCl$_3$, 300.06 MHz)
Figure SI-30. $^{13}$C NMR spectrum of 4c (CDCl$_3$, 75.46 MHz)
Figure SI-31. $^1$H NMR spectrum of 4d (CDCl$_3$, 300.06 MHz)
Figure SI-32. $^{13}$C NMR spectrum of 4d (CDCl$_3$, 75.46 MHz)
Figure SI-33. $^1$H NMR spectrum of 4e (CDCl$_3$, 500.13 MHz)
Figure SI-34. $^{13}$C NMR spectrum of 4e (CDCl$_3$, 125.77 MHz)
Figure SI-35. $^1$H NMR spectrum of 5a (CDCl$_3$, 500.13 MHz)
Figure SI-36. $^{13}$C NMR spectrum of 5a (CDCl$_3$, 125.77 MHz)
Figure SI-37. $^1$H NMR spectrum of 5b (CDCl$_3$, 500.13 MHz)
Figure SI-38. $^{13}$C NMR spectrum of 5b (CDCl$_3$, 125.77 MHz)
Figure SI-39. $^1$H NMR spectrum of 5c (CDCl$_3$, 300.06 MHz)
Figure SI-40. $^{13}$C NMR spectrum of 5c (CDCl$_3$, 75.46 MHz)
Figure SI-41. $^1$H NMR spectrum of 5d (CDCl$_3$, 300.06 MHz)
Figure SI-42. $^{13}$C NMR spectrum of 5d (CDCl$_3$, 75.46 MHz)
Figure SI-43. $^1$H NMR spectrum of 5e (CDCl$_3$, 500.13 MHz)
Figure SI-44. $^{13}$C NMR spectrum of 5e (CDCl$_3$, 125.77 MHz)