“4-MC synthesis of 3-heteroarylpropionic acids”

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General experimental: $^1$H and $^{13}$C Spectra were recorded on a 400 MHz spectrometers at ambient temperatures. For $^1$H NMR recorded in CDCl$_3$ chemical shifts ($\delta$) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants ($J$) were recorded in Hertz (Hz) to the nearest 0.5Hz.

Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum ($\nu_{max}$) was reported in wave numbers (cm$^{-1}$) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad.

Flash chromatography was carried out using silica gel 60 (0.040-0.063mm, 230-400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with silica gel 60, which were visualized by quenching of u.v. fluorescence ($\lambda_{max} = 254$ nm) or by staining with either 10% w/v ammonium molybdate in 2M sulphuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors ($R_f$) are reported to ±0.5.

General one-pot procedure for the preparation of compounds 1a-i (Table 1):

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole 5 (426 mg, 3 mmol) in ethanol (10 mL), was added piperidine (26 mg, 0.3 mmol, 0.1 eq.) and an aromatic aldehyde 6 (3 mmol, 1 eq.). The resulting solution was reacted at 60°C for 1 hours, before acetylacetone 10 (4.5 mmol, 1.5 eq.) was added. The reaction mixture was heated at 60°C for 6 hours and was cooled to room temperature. Then a dinucleophile 9 (3 mmol, 1 eq.) was added and the reaction mixture was heated at 65°C for 7 hours. Finally, to the reaction mixture was added water (10 mL) and sodium hydroxide (0.480 g, 12 mmol) and refluxed at 130°C for 6 hours. The reaction mixture was cooled to room temperature and evaporated en vacuo. The brown oil so obtained was diluted with water (10 mL) and washed with chloroform (10 mL). The aqueous layer was acidified to pH≈5 by addition of 1M hydrochloric acid and subsequently extracted with chloroform (2 x 10 mL). This latter organic layer was dried over MgSO$_4$, filtered and evaporated to yield pure carboxylic acids.
3-(3,5-Dimethyl-isoxazol-4-yl)-3-phenyl-propionic acid 1a:

Brown oil (662 mg, 90% yield); \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 3220-2950, 1733; \( \delta_H \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.35-7.17 (5H, m, Ph), 4.44 (1H, app. t, \( J = 8 \), CHPh), 3.18 (1H, dd, \( J = 16 \), \( J = 8 \), CH\(_2\)COOH), 2.98 (1H, dd, \( J = 16 \), \( J = 9 \), CH\(_2\)COOH), 2.38 (3H, s, CH\(_3\)), 2.11 (3H, s, CH\(_3\)); \( \delta_C \) (100 MHz, CD\(_3\)COCD\(_3\)) 175.7 (C OO), 165.2 (OCOC=C), 158.9 (C=N), 140.2, 128.3 (Ar), 126.6 (Ar), 114.6 (Ar), 37.6 (CH\(_2\)), 34.7 (CH), 11.2 (CH\(_3\)), 10.4 (CH\(_3\)); HRMS found: [M-H] 244.0963, C\(_{14}\)H\(_{14}\)NO\(_3\) requires 244.0974; m/z: 244 (100%, M-H\(^+\)).

3-(3,5-Dimethyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1b:

Brown oil (352 mg, 48% yield), \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 3250-2950, 1738; \( \delta_H \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.35-7.14 (5H, m, Ph), 4.58 (1H, app. t, \( J = 7 \), CHPh), 3.16 (1H, dd, \( J = 16 \), \( J = 7 \), CH\(_2\)COOH), 2.97 (1H, dd, \( J = 8 \), \( J = 16 \), CH\(_2\)COOH), 2.38 (6H, s, 2CH\(_3\)); \( \delta_C \) (100 MHz, CD\(_3\)COCD\(_3\)) 171.0 (C OO), 142.0, 140.3, 128.3 (Ar), 126.5 (Ar), 126.4, 118.3 (Ar), 37.8 (CH\(_2\)), 35.1 (CH), 10.3 (2CH\(_3\)); HRMS found: M-H\(^+\) 243.1125, C\(_{14}\)H\(_{15}\)N\(_2\)O\(_2\) requires 243.1134, m/z: 245.2 (100%, MH\(^+\)).
3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1c:

Brown oil (816 mg, 85% yield), $\nu_{\text{max}}$ (Film)/cm$^{-1}$: 3135-2940b, 1728s; $\delta_{\text{H}}$ (400 MHz, CD$_3$COCD$_3$) 7.41-7.24 (10H, m, 2Ph), 4.59 (1H, app. t, $J = 8$, CHPh), 3.22 (1H, dd, $J = 16$, $J = 7$, CH$_2$COOH), 3.04 (1H, dd, $J = 16$, $J = 9$, CH$_2$COOH), 2.25 (3H, s, CH$_3$), 2.23 (3H, s, CH$_3$); $\delta_{\text{C}}$ (100 MHz, CD$_3$COCD$_3$) 176.5 (COOH), 147.4, 142.2, 139.2, 137.0, 128.9, 128.4, 127.5, 126.3, 125.4, 125.2, 118.9 (Ar), 38.6 (CH), 36.3 (CH$_2$), 12.7 (CH$_3$), 11.2 (CH$_3$); HRMS found: M-H$^+$ 319.1451, C$_{20}$H$_{19}$N$_2$O$_2$ requires 319.1447, $m/z$: 319 (100%, M-H$^+$).

3-(4-Chloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)- propionic acid 1d:

Brown oil (544 mg, 65% yield), $\nu_{\text{max}}$ (Film)/cm$^{-1}$: 3100-2945b, 1730s; $\delta_{\text{H}}$ (400 MHz, CD$_3$COCD$_3$) 7.31 (2H, d, $J = 8$, Ar), 7.11 (2H, d, $J = 8$, Ar), 4.40 (1H, app. t, $J = 9$, ArCH), 3.13 (1H, dd, $J = 16$, $J = 7$, CH$_2$C=O), 2.95 (1H, dd, $J = 16$, $J = 9$, CH$_2$C=O), 2.37 (3H, s, CH$_3$CO), 2.10 (3H, s, CH$_3$C=N); $\delta_{\text{C}}$ (100 MHz, CD$_3$COCD$_3$) 175.8 (COOH), 165.3 (OCC=C), 158.7 (C=N), 138.6 (Ar), 132.5 (Ar), 128.5 (Ar), 127.9 (Ar), 114.4 (Ar), 37.6 (CH$_2$), 34.2 (CH), 11.2 (CH$_3$CO), 10.4 (CH$_3$C=N) HRMS found: M-H$^+$ 278.0572, C$_{14}$H$_{13}$NO$_3$Cl requires 278.0584, $m/z$: 278 (100%, M-H$^+$).
3-(4-Chloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1e:

Brown oil (590 mg, 71% yield), \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 3160-2915\(b\), 1735s; \( \delta_{\text{H}} \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.31 (4H, s, \( p\)-Cl-Ph), 4.50 (1H, app t, \( J = 8 \), CH(\( p\)-Cl-Ph)), 3.14 (1H, dd, \( J = 15 \), \( J = 7 \), CHCOOH), 2.96 (1H, dd, \( J = 15 \), \( J = 9 \), CHCOOH), 2.16 (3H, s, CH\(_3\)) 2.06 (3H, s, CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz, CD\(_3\)COCD\(_3\)) 171.9 (CO), 142.3 (C=N), 140.6 (C=N), 130.6, 128.6 (CH), 127.6 (CH), 115.7, 37.7 (CH\(_2\)), 35.4 (CH, \( p\)-Cl-ph), 10.37 (2CH\(_3\)); HRMS found: M-H\(^+\) 277.0831, C\(_{13}\)H\(_{14}\)N\(_2\)O\(_3\)Cl requires 277.0822, m/z: 277 (100%, M-H\(^+\)).

3-(4-Chloro-phenyl)-3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-propionic acid 1f:

Colourless solid (752 mg, 71% yield), m.p. 74-76\(^{\circ}\)C (ethanol); \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 3210-2975\(b\), 1730s; \( \delta_{\text{H}} \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.44-7.16 (9H, m, Ph + \( p\)-Cl-Ph), 4.54 (1H, app. t, \( J = 8 \), CH(\( p\)-Cl-Ph)), 3.17 (1H, dd, \( J = 16 \), \( J = 7 \), CH\(_3\)C=O), 3.00 (1H, dd, \( J = 16 \), \( J = 9 \), CH\(_3\)C=O), 2.25 (6H, s, 2CH\(_3\)C=O); \( \delta_{\text{C}} \) (100 MHz, CD\(_3\)COCD\(_3\)) 175.6 (COOH), 146.7 (C=N), 140.2, 136.7, 131.8, 128.6 (Ar),128.2 (Ar), 128.1 (Ar), 127.3 (Ar), 124.8 (Ar), 118.2 (Ar), 38.0 (CH\(_2\)), 35.4 (CH), 12.3 (CH\(_3\)), 10.8 (CH\(_3\)); HRMS found: M-H\(^+\) 353.1053, C\(_{20}\)H\(_{18}\)N\(_2\)O\(_2\)Cl requires 353.1057, m/z: 353 (100%, M-H\(^+\)).
3-(2,4-Dichlorophenyl)-3-(3,5-dimethyl-isoxazol-4-yl)propionic acid 1g:

![Chemical structure]

Colourless solid (789 mg, 84% yield); m.p. = 168-170°C (ethanol); $\nu_{\text{max}}$ (Film)/cm$^{-1}$: 3200-2955b, 1728s; $\delta_H$ (400 MHz, CD$_3$COCD$_3$) 7.52 (1H, d, $J = 8$, o-Cl,p-Cl-Ph), 7.50 (1H, d, $J = 2$, o-Cl,p-Cl-Ph), 7.45 (1H, dd, $J = 8$, J = 2, o-Cl,p-Cl-Ph); 4.66 (1H, dd, $J = 9$, J = 6, CH$_2$); 3.07 (1H, dd, $J = 16$, J = 6, CH$_3$COOH); 2.35 (CH$_3$N), 2.15 (CH$_3$CO); $\delta_c$ (100 MHz, CD$_3$COCD$_3$) 174.8 (COOH), 165.7 (OCC=C), 158.7 (C=N), 135.8, 134.3, 133.2, 129.7 (Ar), 128.2 (Ar), 126.7 (Ar), 112.3 (Ar), 37.1 (CH$_2$), 32.3 (CH), 11.5 (CH$_3$), 10.5 (CH$_3$); HRMS found: M-H$^+$ 312.0196, C$_{14}$H$_{12}$NO$_3$Cl$_2$ requires 312.0194, m/z: 312 (100%, M-H$^+$).

3-(2,4-Dichlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)propionic acid 1h:

![Chemical structure]

Colourless solid (571 mg, 61% yield), m.p. 226-227°C; $\nu_{\text{max}}$ (Film)/cm$^{-1}$: 3210-2975b, 1730s; $\delta_H$ (400 MHz, CD$_3$COCD$_3$) 7.53 (1H, d, $J = 2$, o-Cl,p-Cl-Ph), 7.50 (1H, d, $J = 8$, o-Cl,p-Cl-Ph), 7.45 (1H, dd, $J = 8$, J = 2, o-Cl,p-Cl-Ph); 4.57 (1H, app. t, J = 8, CH$_2$Ar), 2.96 (1H, dd, J = 15, J = 9, CH$_3$COOH), 2.83 (1H, dd, J = 15, J = 8, CH$_3$COOH), 2.50 (1H, s, NH), 2.04 (6H, s, 2CH$_3$); $\delta_c$ (100 MHz, CD$_3$COCD$_3$) 206.6 (COOH), 172.4 (C=N), 140.8, 139.2, 134.0, 131.4, 129.9 (Ar), 128.9 (Ar), 126.8 (Ar), 113.5 (Ar), 38.1 (CH$_2$), 33.6 (CH), 11.3 (CH$_3$); HRMS found: M-H$^+$ 311.0343, C$_{14}$H$_{13}$N$_2$O$_2$Cl$_2$ requires 311.0354, m/z: 312 (100%, M-H$^+$).
3-(2,4-Dichloro-phenyl)-3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-propionic acid 1i:

Brown oil (1001 mg, 86% yield), \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 3110-2975, 1732; \( \delta_{\text{H}} \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.40-7.27 (8H, m, Ph + o-Cl,p-Cl-Ph), 4.78 (1H, app. t, \( J = 8 \), CHPh), 3.10 (1H, dd, \( J = 16, J = 7 \), CH\(_2\)COOH), 3.00 (1H, dd, \( J = 16, J = 9 \), CH\(_2\)COOH), 2.22 (6H, s, 2CH\(_3\)); \( \delta_{\text{c}} \) (100 MHz, CD\(_3\)COCD\(_3\)) 174.9 (COOH), 146.7 (C=N), 138.4, 137.3, 137.2, 134.4, 132.6, 129.5, 128.6 (Ar), 127.5 (Ar), 126.4 (Ar), 124.9, 115.9 (Ar), 37.6 (CH\(_2\)), 33.8 (CH), 12.6 (CH\(_3\)), 10.9 (CH\(_3\)); HRMS found: M-H\(^+\) 387.0651, C\(_{20}\)H\(_{17}\)N\(_2\)O\(_2\)Cl\(_2\) requires 387.0667, \( m/z \): 387 (100%, M-H\(^+\)).

**General one-pot procedure for the preparation of compounds 2a-i (Table 2)**

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole 5 (426 mg, 3 mmol) in ethanol (10 mL), was added piperidine (26 mg, 0.3 mmol, 0.1 eq.) and an aromatic aldehyde 6 (3 mmol, 1 eq.). The resulting solution was reacted at 60°C for 2 hours, before acetylacetone 10 (4.5 mmol, 1.5 eq.) was added. The reaction mixture was heated at 60°C for 6 hours, then a dinucleophile 9 (3 mmol, 1 eq.) was added. The reaction mixture was heated at 65°C for 7 hours. It was then cooled to room temperature and the solvent was evaporated en vacuo. The product was purified by recrystallisation from hot ethanol.
5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-phenylethyl]-3-methyl-4-nitroisoxazole

2a:

Coulourless solid (863 mg, 88% yield), \( R_f = 0.6 \) (ethyl acetate : petroleum spirits 1 : 4), m.p. 94-95 °C (ethanol); \( \nu_{\text{max}} \) (Film)/cm\(^{-1}\): 1519 cm\(^{-1}\) s; \( \delta_H \) (200 MHz, CD\(_3\)COCD\(_3\)) 7.13-6.97 (5H, m, Ph), 4.37 (1H, t, \( J = 8 \), CHPh), 3.71 (2H, d, \( J = 8 \), CH\(_2\)Is), 2.30 (3H, s, CH\(_3\)Is), 2.00 (3H, s, CH\(_3\)CO), 1.86 (3H, s, CH\(_3\)C=N); \( \delta_c \) (100 Mhz, CD\(_3\)COCD\(_3\)) 171.9 (OC=CON\(_2\)), 165.4 (CH\(_3\)CO), 158.6 (CH\(_3\)C=N), 155.3 (CH\(_3\)C=N), 139.1 (Ph), 131.5 (NO\(_2\)C=C-O) 128.4 (Ph), 126.9 (Ph), 126.5 (Ph), 113.5 (C\(_iv\)), 36.2 (CHPh), 30.9 (CH\(_2\)), 11.2 (CH\(_3\)C=N), 11.1 (CH\(_3\)C=N), 10.4 (CH\(_3\)CO); HRMS found: M+H\(^+\) 328.1313, C\(_{17}\)H\(_{18}\)N\(_3\)O\(_4\)Cl\(_2\) requires 328.1297, \( m/z \): 328 (100%, MH\(^+\)).

5-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-phenylethyl]-3-methyl-4-nitro-isoxazole

2b:

Colourless solid (831 mg, 85% yield), \( R_f = 0.56 \) (ethyl acetate), m.p.148-149 °C (ethanol); \( \nu_{\text{max}} \) (Film)/cm\(^{-1}\): 3200-2810, 1600m; \( \delta_H \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.27-7.25 (5H, m, Ph), 4.69 (1H, m, CHPh), 3.99 (1H, dd, \( J = 15 \), \( J = 10 \), CH\(_3\)Is), 3.95 (1H, dd, \( J = 15 \), \( J = 7 \), CH\(_3\)Is), 2.52 (3H, s, CH\(_3\)C=N), 2.16 (6H, s, CH\(_3\)C=C and CH\(_3\)C=N); \( \delta_c \) (100 Mhz, CD\(_3\)COCD\(_3\)) 172.2 (C-O), 155.1 (CH\(_3\)C=N), 142.3 (CH\(_3\)C=N), 140.4 (Ph), 131.4 (NO\(_2\)C=C-O), 128.2 (Ph), 127.9 (CH\(_3\)CNH), 126.7 (Ph), 126.2 (Ph), 115.3 (C\(_iv\)), 36.1 (CH), 31.4 (CH\(_2\)), 11.2 (CH\(_3\)), 10.7 (CH\(_3\)) 10.6
5-[2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitroisoxazole 2c:

Colourless solid (732 mg, 61% yield), Rf = 0.27 (ethyl acetate : petroleum spirits 1 : 3), m.p. = 86-88 °C (ethanol); νmax (Film)/cm⁻¹: 1600m; δH (200 MHz, CD3COCD3) 7.36–7.25 (10H, m, Ar), 4.74 (1H, t, J = 7, CH), 4.03 (2H, d, J = 8, CH2), 2.54 (3H, s, IsCH3), 2.20 (3H, s, CH2C=N), 2.15 (3H, s, CH3C=N); δc (100 Mhz, CD3COCD3) 172.8 (C-O), 155.2 (CH3C=N), 146.7, 140.6 (Ph), 131.2, 128.6 (Ph), 128.2 (Ph), 127.4 (Ph), 126.7 (Ph), 126.5 (Ph), 124.8 (Ph), 124.7 (Ph), 117.2, 37.5 (CH), 31.1 (CH2), 12.6 (CH3), 11.7 (CH3), 11.2 (CH3); HRMS found: M+H⁺ 403.1782, C23H23N4O3 requires 403.1770, m/z: 403 (100%, MH⁺).

5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(4-chlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2d:

Colourless solid (867 mg, 80% yield), Rf = 0.46 (ethyl acetate : petroleum ether 1 : 4); m.p. 133-135 °C (ethanol); νmax (Film)/cm⁻¹: 1600m; δH (400 MHz, CD3COCD3) 7.40 (2H, d, J = 8, p-Cl-Ph), 7.18 (2H, d, J = 8, p-Cl-Ph), 4.58 (1H, t, J = 8, CH(p-Cl-Ph)), 3.93 (1H, d, J = 8, CH2Is), 3.92 (1H, d, J = 8, CH2Is), 2.55 (3H, s, CH3Is), 2.32 (3H, s, CH3CO), 2.09 (3H, s, CH3C=N); δc (100 Mhz, CD3COCD3) 171.5 (O Ayrıca N=O2),
165.5 (CH₃CO), 158.4 (CH₃C=N), 155.4 (CH₃C=N), 137.6, 132.9, 128.6 (p-Cl-Ph), 127.9 (p-Cl-Ph), 113.1, 35.7 (CH), 30.8 (CH₂), 11.2 (CH₃C=N), 11.1 (CH₃C=N), 10.4 (CH₃CO); HRMS found: MH⁺ 360.0756, C₁₇H₁₅N₃O₄Cl requires 360.0751; m/z: 360 (100%, MH⁺).

5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitroisoxazole 2e:

Colourless solid (1,021 mg, 95% yield), Rᵣ = 0.25 (ethyl acetate : acetone : petroleum ether 1 : 1 : 8), m.p. 138-143 °C (ethanol); νₑₓₙ (Film)/cm⁻¹: 3220-2820b, 1602m; δ_H (400 MHz, CD₃COCD₃) 7.30 (2H, d, J = 8, p-Cl-Ph), 7.18 (2H, d, J = 8, p-Cl-Ph), 4.65 (1H, t, J = 7, CH p-Cl-Ph), 3.99-3.88 (2H, m, CH₂), 2.53 (3H, s, CH₃C=C), 2.15 (6H, s, CH₃C=N); δ_c (100 Mhz, CD₃COCD₃) 172.3 (OC=CNO₂),155.2 (CH₃C=N), 142.6 (CH₃C=N), 138.1 (p-Cl-Ph), 132.3 (NO₂C=C=O), 128.3 (p-Cl-Ph), 128.1 (p-Cl-Ph), 128.0 (p-Cl-Ph), 127.9 (CH₃CNH), 115.7 (Civ), 36.4 (CH) 31.2 (CH₂), 11.2 (C=CCH₃), 11.1 (N=CCH₃), 10.9 (N=CCH₃); HRMS found: M-H⁺ 359.0916, C₁₇H₁₆N₄O₃Cl requires 359.0911, m/z: 361 (100%, MH⁺).
5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2f:

Colourless solid (938 mg, 72% yield), R<sub>f</sub> = 0.32 (ethyl acetate : petroleum spirits 1 : 4), m.p. 143-144 °C (ethanol); <i>v</i><sub>max</sub> (Film)/cm<sup>-1</sup>: 1601m; <i>δ</i><sub>H</sub> (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 7.34-7.24 (9H, m, Ph + p-Cl-Ph), 4.69 (1H, t, J = 8, CH<sub>p</sub>-Cl-Ph), 4.05 (1H, d, J = 8, CH<sub>2</sub>Is), 3.98 (1H, d, J = 8, CH<sub>3</sub>C=N), 2.55 (3H, s, CH<sub>3</sub>CO), 2.17 (3H, s, CH<sub>3</sub>C=N), 2.14 (3H, s, CH<sub>2</sub>C=N); <i>δ</i> (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 172.4 (OC=CNO<sub>2</sub>), 155.3 (CH<sub>3</sub>C=N), 146.6 (Ar), 139.1 (Ar), 138.6 (Ar), 136.7 (Ar), 132.3 (Ar), 131.5 (OC=CNO<sub>2</sub>), 128.7 (Ar), 128.4 (Ar), 128.1 (Ar), 127.4 (Ar), 124.8 (Ar), 116.7 (Ar), 37.0 (CH), 31.1 (CH<sub>2</sub>), 12.2 (CH<sub>3</sub>C=C), 11.2 (CH<sub>3</sub>C=N), 10.8 (CH<sub>3</sub>C=N); HRMS found: MH<sup>+</sup> 435.1219, C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>Cl requires 435.1224; m/z: 435 (100%, MH<sup>+</sup>).

5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(2,4-dichlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2g:

Colourless solid (1,002 g, 85% yield), R<sub>f</sub> = 0.25 (ethyl acetate : petroleum spirits 1 : 4), m.p. 125-126 °C (ethanol); <i>v</i><sub>max</sub> (Film)/cm<sup>-1</sup>: 1601; <i>δ</i><sub>H</sub> (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 7.43 (1H, d, J = 2, CH-<i>o</i>-Cl, p-Cl-Ph), 7.41 (1H, d, J = 8, Ar), 7.33 (1H, dd, J = 8, J = 2, Ar), 4.85 (1H, t, J = 8, CH(<i>o</i>-Cl,p-Cl-Ph)), 4.01 (1H, dd, J = 15.0, J = 8, CH<sub>2</sub>Is), 3.80 (1H, dd, J = 15, J = 8 CH<sub>2</sub>Is), 2.55 (3H, s, CH<sub>3</sub>), 2.32 (3H, s, CH<sub>3</sub>), 2.09 (3H, s,
5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2h:

Colourless solid (720 mg, 61% yield), Rf = 0.2 (ethyl acetate : petroleum spirits 1 : 4), m.p. 151-152 °C (ethanol); νmax (Film)/cm⁻¹: 3230-2860b, 1601m; δH (400 MHz, CD3COCD3) 7.42 (1H, d, J = 8, o-Cl,p-Cl-Ph), 7.40 (1H, d, J = 2, o-Cl,p-Cl-Ph), 7.30 (1H, dd, J = 8, J = 2, o-Cl,p-Cl-Ph), 4.91 (1H, t, J = 9, CHCH2), 4.02 (1H, dd, J = 14, J = 9, CH3Is), 3.80 (1H, dd, J = 14, J = 9, CH3Is), 2.54 (3H, s, CH3), 2.17 (6H, s, 2CH3); δc (100 MHz, CD3COCD3) 171.7 (OC=CON2), 155.3 (CH3C=N), 142.0, 136.3, 134.3, 133.1, 130.9, 129.6 (Ar), 128.5 (Ar), 126.5 (OC=CON2), 113.1 (Ar), 34.5 (CH), 31.1 (CH2), 11.2 (CH3), 11.1 (CH3), 10.7 (CH3); HRMS found: MH⁺ 393.0523, C17H15N4O4Cl2 requires 393.0521, m/z: 395(100%, MH⁺).
5-{2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2i:

\[
\text{\includegraphics[width=0.2\textwidth]{5-(2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2i.png}}
\]

Colourless solid (1.039 g, 74% yield), \( R_f = 0.4 \) (ethyl acetate : petroleum spirits 1 : 4), m.p. 72-73 °C (ethanol); \( \nu_{\text{max}} \) (Film)/cm\(^{-1} \): 1601m; \( \delta_{\text{H}} \) (400 MHz, CD\(_3\)COCD\(_3\)) 7.51 – 7.30 (8H, m, Ar), 4.94 (1H, t, \( J = 8 \), ArCH\(_2\)), 4.08 (1H, dd, \( J = 15, J = 8 \), CH\(_2\)), 3.87 (1H, dd, \( J = 15, J = 8 \), CH\(_2\)), 2.55 (3H, s, CH\(_3\)C=N), 2.22 (3H, s, CH\(_3\)), 2.18 (3H, s, CH\(_3\)); \( \delta_{\text{c}} \) (100 Mhz, CD\(_3\)COCD\(_3\)) 171.7 (OC\(_{\text{O}}\)=CNO\(_{\text{2}}\)), 155.29 (CH\(_3\)C=N), 146.5, 138.3, 137.3, 136.1, 134.4, 133.2, 130.3 (Ar), 129.7 (Ar), 128.7 (Ar), 128.6 (Ar), 127.6, 126.6 (Ar), 125.0 (Ar), 115.0 (Ar), 35.1 (CH), 31.0 (CH\(_2\)), 12.5 (CH\(_3\)), 11.2 (CH\(_3\)), 10.8 (CH\(_3\)); HRMS found: M-H\(^+\) 469.0826, \( C_{23}H_{19}N_4O_3Cl_2 \) requires 469.0834, \( m/z \): 471 (100%, MH\(^+\)).
3-(3,5-Dimethyl-isoxazol-4-yl)-3-phenyl-propionic acid 1a

3-(3,5-Dimethyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1b:
3-(3,5-Dimethyl-1phenyl-1H-pyrazol-4-yl)-3-phenyl-propionic acid 1c

3-(4-Chloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)- propionic acid 1d:
3-(4-Chloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)-propionic acid 1e:

3-(4-Chloro-phenyl)-3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-propionic acid 1f:
3-(2,4-Dichloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl)-propionic acid 1g:

3-(2,4-dichloro-phenyl)-3-(3,5-dimethyl-1H-pyrazol-4-yl)- propionic acid 1h:
3-(2,4-Dichloro-phenyl)-3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-propionic acid 1i:

5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-phenylethyl]-3-methyl-4-nitroisoxazole 2a:
5-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole 2b:

![Chemical Structure Image]

5-[2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole 2c:

![Chemical Structure Image]
5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(4-chlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2d:

5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitroisoxazole 2e:
5-[2-(4-Chloro-phenyl)-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2f:

5-[2-(3,5-dimethyl-4-nitroisoxazol-5-yl)-2-(2,4-dichlorophenyl)-ethyl]-3-methyl-4-nitroisoxazole 2g:
5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2h:

5-[2-(2,4-Dichloro-phenyl)-2-(3,5-dimethyl-1phenyl-1H-pyrazol-4-yl)-ethyl]-3-methyl-4-nitro-isoxazole 2i: