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Tetrahedron
Tetrahedron 63 (2007) 2047–2052

Modular synthesis of isoxazolopyridones and pyrazolopyridones

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Received 12 October 2006; revised 29 November 2006; accepted 14 December 2006
Available online 17 December 2006

Abstract—Herein we described the preparation of two novel heterocyclic nuclei isoxazolopyridone and pyrazolopyridone. The syntheses are modular in nature and fast to execute. The title compounds were obtained pure without intervention of chromatography.

1. Introduction

Fused heterocycles have a wide variety of uses in medicinal chemistry.[1] Despite the wealth of fused heterocycles developed to date, there is a continuing demand for novel fused heterocycles due to the plethora of medicinal applications which these molecular types have.[2] As a part of our ongoing efforts in developing multicomponent one-pot procedures using commercially available materials,[3–9] we envisaged a novel modular synthesis leading to fused isoxazolopyridones **1** and pyrazolopyridones **2** (Fig. 1). We are now pleased to report a detailed study on the preparation of a small family of compounds **1** and **2**. We have shown that all except one of the five synthetic steps can be carried out in one pot, thus making this two-step procedure a simple and efficient way of accessing these molecules.

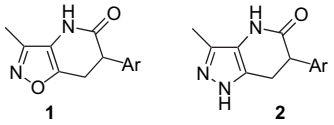

Figure 1. Target compounds **1** and **2**.

2. Results and discussion

Our approach to the development of multicomponent one-pot syntheses is based on the generation of building blocks containing multiple functionalities, each of which can be selectively reacted.[3–9] We have recently shown some synthetic applications of 3-methyl-4-nitro-5-styrylisoxazoles **3** (Fig. 2), in which spiroisoxazolines,[3,6] 3-heteroarylpropionic acids,[7] or 3-indolepropionic acids[8] were obtained in one-pot from commercially available components **4** and **5** and a suitable Michael donor. In these syntheses, a number of components reacted together in a Knoevenagel–Michael tandem sequence.[3,6–9] Considering the ease of reaction of **3** as a Michael acceptor, we decided to explore the reaction of **3** with the anion of nitromethane **6**, which has been repeatedly reported as an excellent nucleophile (Scheme 1).[10]

We reasoned that if nitromethane **6** was reacted with **3** in a Michael reaction, then adducts **7** could easily be prepared through a one-pot procedure involving a sequential Knoevenagel–Michael reaction from commercially available components **4**, **5** and **6**. Adducts **7** could then be elaborated to obtain two novel heterocyclic types isoxazolopyridones **1** and pyrazolopyridones **2** (Scheme 1).

This involved transformation of **7** to carboxylic acid **8** using the Victor-Meyer reaction,[11] and a subsequent tandem reduction–lactamisation sequence to cyclise **8** to **1**.[12] Significantly, compound **8** could serve as a precursor of pyrazole acid **9**. This transformation is viable only for 4-nitroisoxazoles where position 5 of the heterocycle is rendered electrophilic by conjugation to a nitro group.[13] Application of the tandem reduction–lactamisation sequence to **9** would then lead to scaffolds **2**.

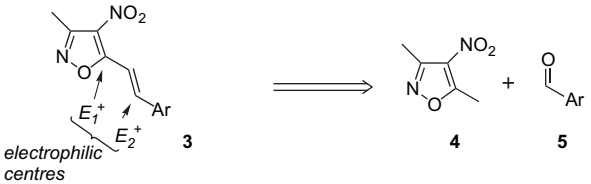

Figure 2. A polyfunctional scaffold: 3-methyl-4-nitro-5-styryl-isoxazoles **3**.

Keywords: Fused isoxazoles; Polyfunctional scaffold; Fused pyrazoles.
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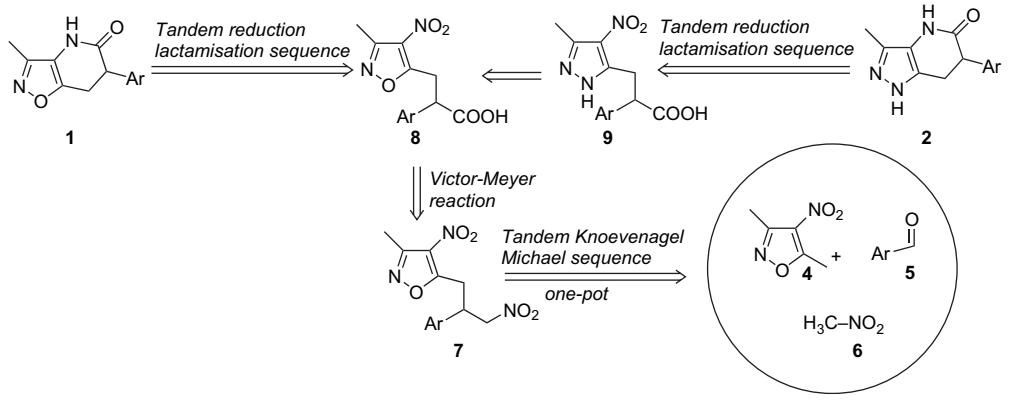
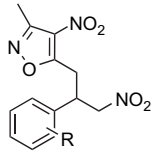
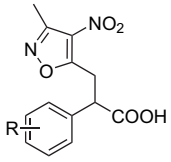
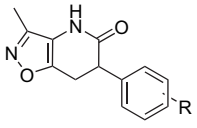
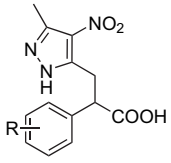
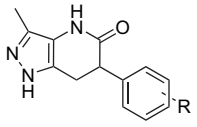
doi:10.1016/j.tet.2006.12.044



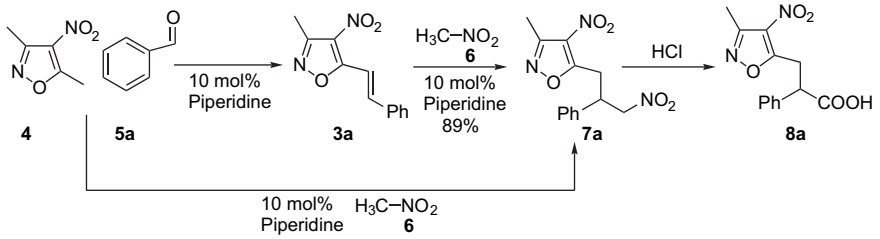
Scheme 1. A disconnection of compounds **1** and **2**.

In our first experiment, styrylisoxazole **3a** was prepared and subsequently reacted with 3 equiv of nitromethane **6**. We were delighted to find that a limited amount of piperidine was sufficient to obtain adduct **7a** in 89% yield (Scheme 2). We then optimised this reaction procedure and found that only 1.1 equiv of **6** was required to obtain **7a** in similar high yields. This was an important finding, as a limited catalyst loading and a ratio of reagents close to one usually maximises the purity of the resultant products and is actually a requirement of tandem reaction processes. We then confirmed that components **4**, **5a** and **6** could be reacted in a one-pot fashion to give adduct **7a** in high yields (Scheme 1 and Table 1). The optimised conditions involved: (a) reacting 1 equiv of **4** with 1 equiv of **5a** in the presence of 0.1 equiv piperidine in ethanol, at 65 °C for 2 h; (b) addition of 1.1 equiv of nitromethane and continuation of the reaction for 4 h. Compound **7a** was obtained in 85% isolated yield after chromatography. Alternatively, compound **7a** could be purified by crystallisation from hot ethanol in 60–75% isolated yield. Adduct **7a** was then subjected to the Victor-Meyer reaction,[11] and it was confirmed that acid **8a** could be obtained in high yields (Scheme 2). We then considered extending the one-pot preparation of **7a** to include the transformation of **7a** to **8a**. Thus, we reacted **4**, **5a–c** and **6** in the presence of 0.1 equiv of piperidine, then we added an excess of 36% w/v HCl and heated at reflux the reaction mixture. Compounds **8a–c** were obtained through this one-pot procedure in good yield (Scheme 3 and Table 1).

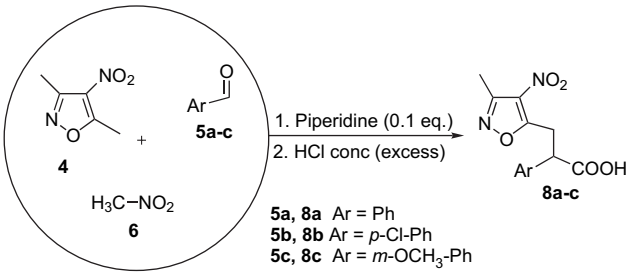
Table 1. Yields (%) for the one-pot synthesis of **7a–c** and **8a–c** and for the preparation of **9a–c**, **1a–c** and **2a–c**

Compound	Structure	**a** R=H (%)	**b** R=*p*-Cl (%)	**c** R=*m*-OCH_3 (%)
7		94	82	80
8		80	96	75
1		84	81	77
9		99	95	95
2		81	89	86

With compounds **8a–c** in hand we turned our attention to the reduction of the aromatic nitro group. One very common methodology for the reduction of nitroisoxazoles involves the use of $SnCl_2$ as the reductant under strongly acidic conditions (Scheme 4). We selected this procedure as it presents the additional advantage of promoting a subsequent lactamisation of the resulting δ-aminoacid **10a** to cyclic lactam **1a** due to the ability of Sn^{4+} formed during the reaction to act as a Lewis acid.[12] Cyclisation of δ-aminoacids has been repeatedly reported to occur either under strongly acidic



Scheme 2. Stepwise preparation of **7a** and **8a** and one-pot preparation of **7a**.



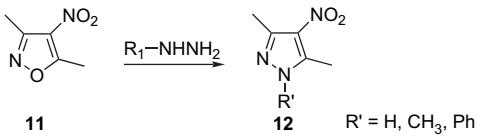
Scheme 3. One-pot synthesis of carboxylic acid **8a–c**.

conditions [14] or in the presence of a suitable Lewis acid catalyst.[15] The reaction is believed to involve a dehydration of the carboxylic acid to generate a reactive acylium ion, which then undergoes nucleophilic attack by the amine functionality.[14,15] Therefore compound **8a** was reacted in the presence of 2.2 equiv of $SnCl_2$ under acidic conditions (HCl). We observed that the solvent used, the reaction temperature and reaction time were all critical to obtain the desired product **1a** (Scheme 4).

We found that reduction of the nitro group in **8a** to the amino group was a fast process, and full conversion of **8a** was observed after an hour. Full conversion of **8a** was also observed at room temperature. However, we found that appearance of **1a** only occurred when the reaction was carried out at high temperatures (>70 °C) and after prolonged reaction times. We did not attempt to isolate **10a**, which is probably the intermediate formed during the synthesis of **1a**. In order to optimise this sequence the transformation of **8a** to **1a** was studied under a number of different conditions, including different solvent systems (methanol, ethanol, methanol/water, ethanol/water, dichloromethane, toluene, tetrahydrofuran and tetrahydrofuran/water) and different reaction times. This study identified a 1:1 mixture of water/tetrahydrofuran as the optimum solvent system. Typically, in an optimised procedure, 1 mmol of **8a–c** was heated at reflux with 2.2 equiv of $SnCl_2$ and 1 mL of concd HCl in 20 mL of 1:1 THF/water for 16 h.

One important characteristic of nitroisoxazoles is the activation of position 5 to nucleophilic attack due to the electron withdrawing effects of the nitro functionality. In particular, hydrazine and alkyl or aryl hydrazines have been shown by Musante to convert the 4-nitroisoxazolyl core **11** into a 4-nitropyrazolyl core **12** (Scheme 5).[13] Musante also reported that this reaction usually proceeded to completion when nitroisoxazoles were reacted with equimolar quantities of hydrazine. This is a notable feature and qualifies this transformation as a click reaction.[16]

Significantly, this reaction expands the range of diverse products achievable from a 4-nitroisoxazole core. Therefore, we reacted **8a** with an equimolar quantity of hydrazine and



Scheme 5. Conversion of 4-nitroisoxazoles to 4-nitropyrazoles.

found that **9a** was obtained in nearly quantitative yield (Scheme 6). Compound **9a** was obtained in sufficient purity to be used directly in the following step without the need for further purification, and was reacted to obtain the pyrazolopyridinone **2a** following the procedure developed for compound **1a**.

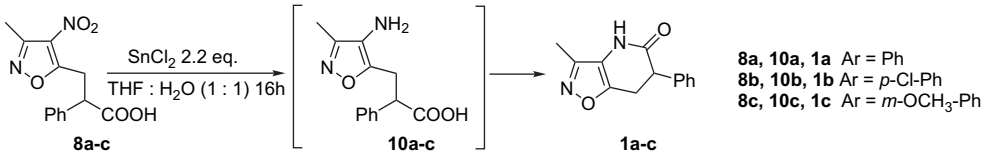
The generality of these newly developed syntheses has been demonstrated with respect to variation in the aldehyde component by synthesising a small family of compounds (Table 1). Compounds **1a–c** and **2a–c** were all obtained in good isolated yields without the use of chromatography.

In conclusion we have developed two novel one-pot syntheses in which 3,5-dimethyl-4-nitroisoxazole **4**, aromatic aldehydes **5a–c** and nitromethane **6** were reacted to furnish adducts **7a–c** or **8a–c**. We elaborated on **7a–c** and **8a–c** to obtain two novel heterocyclic cores **1a–c** and **2a–c**. These reactions are modular in nature, fast to execute and can be run without the intervention of chromatography. We believe that this study will be of interest for those involved in drug discovery and in the preparation of novel heterocyclic cores.

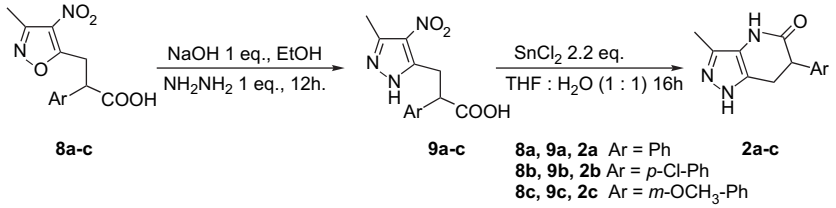
3. Experimental

3.1. General experimental

^1H and ^{13}C spectra were recorded on 200 or 400 MHz spectrometers at ambient temperatures. ^1H NMR spectral assignments are supported by ^1H–^1H COSY and ^{13}C–^1H COSY where necessary. For ^1H NMR recorded in $CDCl_3$, chemical shifts (δ_H) 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; br, broad. Coupling constants (J) were recorded in hertz (Hz) to the nearest 0.1 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (ν_{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; br, broad. Flash chromatography was carried out using *silica gel 60* (0.040–0.063 mm, 230–400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with *silica gel 60*, which



Scheme 4. Synthesis of isoxazolopyridones **1a–c**.



Scheme 6. Preparation of pyrazolopyridinone **2a–c**.

were visualised by quenching of UV fluorescence (λ_{max}= 254 nm) or by staining with either 10% w/v ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to be ±0.5.

3.2. General procedure for the preparation of 7a–c

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **4** (426 mg, 3 mmol) in ethanol (10 mL), were added piperidine (26 mg, 0.3 mmol, 0.1 equiv) and an aromatic aldehyde **5a–c** (3 mmol, 1 equiv). The resulting solution was reacted at 65 °C for 2 h, before nitromethane **6** (200 mg, 3.3 mmol, 1.1 equiv) was added. The reaction was continued at 65 °C for a further 4 h. The solvent was then evaporated in vacuo and the product was isolated by column chromatography.

3.2.1. 3-Methyl-4-nitro-5-(3-nitro-2-phenylpropyl)isoxazole 7a. Colourless solid (820 mg, 94% yield); R_f=0.2 (ethyl acetate/petroleum ether 1:9); mp 116–118 °C (ethanol); ν_{max} (Film)/cm^{-1}: 1581m, 1576m; δ_H (400 MHz, DMSO-d_6) 7.31–7.20 (5H, m, Ph), 4.78–4.69 (2H, m, CH_2NO$_2$), 4.21–4.10 (1H, m, CHPh), 3.76 (1H, dd, J=15.0, 9.0, Is-CH_aH$_b$), 3.55 (1H, dd, J=15.0, 6.5, CH$_a$$H_b$CHPh), 2.50 (3H, s, C$H_3$C=N); δ_C (100 MHz, DMSO-d_6) 170.5 (O–C=C–NO$_2$), 155.3 (CH$_3$$C$=N), 136.2 (Ph), 131.5 (O–C=C–NO$_2$), 128.9 (Ph), 128.5 (Ph), 126.7 (Ph), 78.7 (CH$_2$NO$_2$), 41.1 (CHPh), 30.8 (Is-CH$_2$), 11.1 (CH$_3$C=N). HRMS (EI) found [M−H]$^+$: 290.0763, $C_{13}H_{12}N_3O_5$ requires: 290.0777; m/z (EI) 290 (100%, [M−H]$^+$).

3.2.2. 5-[2-(4-Chlorophenyl)-3-nitropropyl]-3-methyl-4-nitroisoxazole 7b. Colourless solid (819 mg, 82% yield); R_f=0.3 (ethyl acetate/petroleum ether 15:85); mp 119–121 °C (ethanol); ν_{max} (Film)/cm^{-1}: 1580m, 1575m; δ_H (400 MHz, CDCl$_3$) 7.32 (2H, d, J=7.9, p-Cl–Ph), 7.19 (2H, d, J=7.9, p-Cl–Ph), 4.71 (2H, d, J=8.0, CH_2NO$_2$), 4.20–4.12 (1H, m, CHPh(p-Cl)), 3.76 (1H, dd, J=15.0, 9.1, Is-CH_aH$_b$), 3.56 (1H, dd, J=15.0, 6.5, CH$_a$$H_b$CHPh-($p$-Cl)), 2.52 (3H, s, C$H_3$C=N); δ_C (100 MHz, DMSO-d_6) 170.1 (O–C=C–NO$_2$), 155.3 (CH$_3$$C$=N), 134.6 ($p$-Cl–Ph), 134.6 ($p$-Cl–Ph), 134.2 (O–C=$C$–NO$_2$), 129.1 ($p$-Cl–Ph), 128.1 ($p$-Cl–Ph), 78.5 ($CH_2NO_2$), 40.5 ($C$HPh), 30.6 (Is-$CH_2$), 11.1 ($CH_3$C=N). HRMS (EI) found [M−H]$^+$: 324.0381, $C_{13}H_{11}ClN_3O_5$ requires: 324.0387; m/z (EI) 324 (100, [M−H]$^+$).

3.2.3. 5-[2-(3-Methoxyphenyl)-3-nitropropyl]-3-methyl-4-nitroisoxazole 7c. Colourless solid (781 mg, 80% yield); R_f=0.2 (ethyl acetate/petroleum ether 10:90); mp 112–114 °C (ethanol); ν_{max} (Film)/cm^{-1}: 1581m, 1575m; δ_H (400 MHz, CDCl$_3$) 7.28–7.25 (1H, m, m-CH$_3$O–Ph), 7.23–6.75 (3H, m, m-CH$_3$O–Ph), 4.73 (2H, dq, J=13.2, 7.8, CH_2NO$_2$), 4.17–4.09 (1H, m, CHPh(m-CH$_3$O)), 3.80 (3H, s, CH$_3$O), 3.78 (1H, dd, J=15.0, 9.1, Is-CH_aH$_b$), 3.58 (1H, dd, J=15.0, 6.5, CH$_a$$H_b$CHPh($p$-Cl)), 2.51 (3H, s, C$H_3$C=N); δ_C (100 MHz, DMSO-d_6) 170.6 (O–C=C–NO$_2$), 165.6 (m-CH$_3$O–Ph), 155.2 (CH$_3$$C$=N), 137.7 ($m$-CH$_3$O–Ph), 132.1 (O–C=$C$–NO$_2$), 129.9 ($m$-CH$_3$O–Ph), 118.7 ($m$-CH$_3$O–Ph), 113.3 ($m$-CH$_3$O–Ph), 112.7 ($m$-CH$_3$O–Ph), 78.7 ($CH_2NO_2$), 54.8 ($CH_3$O), 41.1 ($C$HPh), 30.7 (Is-$CH_2$), 11.1 ($CH_3$C=N). HRMS (EI) found [M−H]$^+$: 320.0898, $C_{14}H_{14}N_3O_6$ requires: 320.0883; m/z (EI) 320 (50, [M−H]$^+$).

3.3. General procedure for the one-pot preparation of compounds 8a–c

To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **4** (426 mg, 3 mmol) in ethanol (10 mL), were added piperidine (26 mg, 0.3 mmol, 0.1 equiv) and an aromatic aldehyde **5a–c** (3 mmol, 1 equiv). The resulting solution was reacted at 65 °C for 2 h, before nitromethane **6** (200 mg, 3.3 mmol, 1.1 equiv) was added. The reaction was continued at 65 °C for a further 4 h, then diluted with 36% w/v HCl (20 mL) and heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and extracted with chloroform (100 mL×2). The sodium salt of the carboxylic acid **8a–c** was extracted from the organic layer using a saturated aqueous solution of NaHCO$_3$ (20 mL). The water layer was slowly acidified to pH=4 by dropwise addition of concd HCl. The product was then precipitated with cooling to 4 °C or alternatively extracted into chloroform and concentrated in vacuo.

3.3.1. 3-(3-Methyl-4-nitroisoxazol-5-yl)-2-phenylpropionic acid 8a. Colourless solid (662 mg, 80% yield); R_f=0.1 (ethyl acetate/petroleum ether 40:60); mp 145–146 °C; ν_{max} (Film)/cm^{-1}: 3420b, 1701s; δ_H (400 MHz, CDCl$_3$) 7.36–7.27 (5H, m, Ph), 4.32 (1H, t, J=8.1, CHPh), 3.96 (1H, dd, J=15.0, 8.1, Is-CH_aH$_b$), 3.71 (1H, dd, J=15.0, 8.1, Is-CH$_a$$H_b$), 2.54 (3H, s, C$H_3$C=N); δ_C (100 MHz, CDCl$_3$) 174.7 (C=O), 171.3 (O–C=C–NO$_2$), 155.2 (CH$_3$$C$=N), 135.5 (Ph), 131.7 (O–C=C–NO$_2$), 128.7 (Ph), 128.0 (Ph), 127.3 (Ph), 46.9 (CHPh), 29.5 (Is-CH$_2$), 11.1 (CH$_3$C=N). HRMS (EI) found [M−H]$^+$: 275.0675, $C_{13}H_{11}N_2O_5$ requires: 275.0668; m/z (EI) 275 (50, [M−H]$^+$).

3.3.2. 2-(4-Chlorophenyl)-3-(3-methyl-4-nitroisoxazol-5-yl)propionic acid 8b. Colourless solid (894 mg, 96% yield); R_f=0.2 (ethyl acetate/petroleum ether 40:60); mp 151–152 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3412b, 1698s; δ_H (400 MHz, CDCl$_3$) 7.34 (2H, d, J=7.8, p-Cl–Ph), 7.27 (2H, d, J=7.8, p-Cl–Ph), 4.28 (1H, t, J=7.5, CHPh(p-Cl)),

3.92 (1H, dd, J=15.1, 7.5, Is-CH_aH_b), 3.69 (1H, dd, J=15.1, 7.5, Is-CH$_a$$H_b$), 2.54 (3H, s, C$H_3$C=N); δ_C (100 MHz, $CDCl_3$) 176.6 (C=O), 170.8 (O–*C*=C–NO_2), 155.3 (CH_3*C*=N), 134.1 (*p*-Cl–Ph), 133.7 (*p*-Cl–Ph), 130.3 (O–C=*C*–NO_2), 128.9 (*p*-Cl–Ph), 128.3 (*p*-Cl–Ph), 46.6 (*C*HPh(*p*-Cl)), 30.3 (Is-*C*H_2), 11.1 (*C*H_3C=N). HRMS (EI) found $[M-H]^+$: 309.0269, $C_{13}H_{10}ClN_2O_5$ requires: 309.0278; *m*/*z* (EI) 309 (20, $[M-H]^+$).

3.3.3. 2-(3-Methoxyphenyl)-3-(3-methyl-4-nitroisoxazol-5-yl)propionic acid 8c. Colourless solid (689 mg, 75% yield); R_f=0.2 (ethyl acetate/petroleum ether 50:50); mp 138–139 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3450b, 1699s; δ_H (400 MHz, DMSO-d_6) 7.28–7.24 (1H, m, *m*-CH_3O–Ph), 6.89–6.84 (3H, m, *m*-CH_3O–Ph), 4.17 (1H, t, J=7.0, C*H*Ph(*m*-CH_3O)), 3.86 (1H, dd, J=15.1, 7.0, Is-CH_aH_b), 3.73 (3H, s, *m*-CH_3O–Ph), 3.59 (1H, dd, J=15.1, 7.0, Is-CH$_a$$H_b$), 2.44 (3H, s, C$H_3$C=N); δ_C (100 MHz, DMSO-d_6) 173.0 (C=O), 172.8 (O–*C*=C–NO_2), 165.5 (*m*-CH_3O–Ph), 155.3 (CH_3*C*=N), 139.3 (*m*-CH_3O–Ph), 130.3 (O–C=*C*–NO_2), 128.6 (*m*-CH_3O–Ph), 119.8 (*m*-CH_3O–Ph), 113.6 (*m*-CH_3O–Ph), 113.0 (*m*-CH_3O–Ph), 55.1 (*C*H_3O), 47.2 (*C*HPh(*m*-CH_3O)), 31.30 (Is-*C*H_2), 11.1 (*C*H_3C=N). HRMS (EI) found $[M-H]^+$: 305.0787, $C_{14}H_{13}N_2O_6$ requires: 305.0774; *m*/*z* (EI) 305 (20, $[M-H]^+$).

3.4. General procedure for the preparation of compounds 9a–c

In a round bottom flask were put compounds **8a–c** (3 mmol), NaOH (120 mg, 3 mmol, 1 equiv), ethanol (10 mL), and hydrazine hydrate (0.15 mL, 3 mmol). The reaction mixture was stirred at 75 °C for 12 h. It was then transferred into a large beaker, diluted with water (120 mL) and cooled with an ice-bath. It was acidified with 3 M HCl until a white precipitate was obtained. The precipitate was extracted into ethyl acetate (50 mL×2), washed with water (50 mL), dried over Na_2SO_4 and evaporated in vacuo.

3.4.1. 3-(5-Methyl-4-nitro-2*H*-pyrazol-3-yl)-2-phenyl-propionic acid 9a. Colourless solid (810 mg, 99% yield); R_f=0.6 (ethyl acetate/petroleum ether 90:10); mp 181–183 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3247–3083b, 1708s; δ_H (400 MHz, acetone-*d*) 7.25–7.14 (5H, m, Ph), 3.84 (1H, dd, J=9.0, 7.5, C*H*Ph), 3.51 (1H, dd, J=15.1, 9.0, Is-CH_aH_b), 3.20 (1H, dd, J=15.1, 7.5, Is-CH$_a$$H_b$), 2.39 (3H, s, C$H_3$C=N); δ_C (100 MHz, $CDCl_3$) 175.4 (C=O), 145.7 (N–*C*=C–NO_2), 143.6 (CH_3*C*=N), 141.7 (HN–C=*C*–NO_2), 129.7 (Ph), 127.9 (Ph), 127.8 (Ph), 126.0 (Ph), 51.4 (*C*HPh), 30.9 (Is-*C*H_2), 13.0 (*C*H_3C=N). HRMS (EI) found $[M-H]^+$: 274.0821, $C_{13}H_{12}N_2O_5$ requires: 274.0828; *m*/*z* (EI) 274 (20, $[M-H]^+$).

3.4.2. 2-(4-Chlorophenyl)-3-(5-methyl-4-nitro-2*H*-pyrazol-3-yl)propionic acid 9b. Colourless solid (880 mg, 95% yield); R_f=0.1 (ethyl acetate/petroleum ether 1:1); mp 188–190 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3250–3083b, 1710s; δ_H (400 MHz, DMSO-d_6) 7.41 (2H, d, J=8.5, *p*-Cl–Ph), 7.37 (2H, d, J=8.5, *p*-Cl–Ph), 4.28 (1H, t, J=8.0, C*H*Ph(*p*-Cl)), 3.72 (1H, dd, J=15.0, 7.5, Py–CH_aH_b), 3.33 (1H, dd, J=15.0, 7.5, Py–CH$_a$$H_b$), 2.54 (3H, s, C$H_3$C=N); δ_C (100 MHz, $CDCl_3$) 172.8 (C=O), 157.7 (C=N), 145.0 (N–*C*=C–NO_2), 142.4 (HN–C=*C*–NO_2), 137.6, 132.1, 130.0, 129.3 (*p*-Cl–Ph), 128.1 (*p*-Cl–Ph), 47.7 (*C*H), 30.5 (*C*H_2), 11.2 (*C*H_3C=N). HRMS (EI) found $[M-H]^+$: 308.0433, $C_{13}H_{11}N_3O_4Cl$ requires: 308.0438; *m*/*z* (EI) 308 (95, $[M-H]^+$).

3.4.3. 2-(3-Methoxyphenyl)-3-(5-methyl-4-nitro-2*H*-pyrazol-3-yl)propionic acid 9c. Colourless solid (869 mg, 95% yield); R_f=0.6 (acetone/petroleum ether 40:60); mp 163–165 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3214–3065b, 1707s; δ_H (400 MHz, DMSO-d_6) 7.13–7.09 (1H, m, *m*-CH_3O–Ph), 6.82–6.69 (3H, m, *m*-CH_3O–Ph), 3.78 (1H, t, J=7.2, C*H*Ph(*m*-CH_3O)), 3.70 (3H, s, CH_3O), 3.47 (1H, dd, J=15.1, 7.2, Is-CH_aH_b), 3.22 (1H, dd, J=15.1, 7.2, Is-CH$_a$$H_b$), 2.38 (3H, s, C$H_3$C=N); δ_C (100 MHz, $CDCl_3$) 175.3 (C=O), 157.8 (*m*-CH_3O–Ph), 145.6 (N–*C*=C–NO_2), 143.7 (CH_3*C*=N), 143.4 (HN–C=*C*–NO_2), 129.7 (*m*-CH_3O–Ph), 128.8 (*m*-CH_3O–Ph), 120.1 (*m*-CH_3O–Ph), 113.5 (*m*-CH_3O–Ph), 111.3 (*m*-CH_3O–Ph), 54.8 (*C*H_3O), 51.6 (*C*HPh), 30.8 (Pyr-*C*H_2), 13.1 (*C*H_3C=N). HRMS (EI) found $[M-H]^+$: 304.0920, $C_{14}H_{13}N_3O_5$ requires: 304.0933; *m*/*z* (EI) 304 (50, $[M-H]^+$).

3.5. Procedure for the preparation of compounds 1a–c and 2a–c

Compounds **8a–c** or **9a–c** (1 mmol) were combined with 2.2 equiv of $SnCl_2\cdot 2H_2O$ (490 mg, 6.6 mmol), THF (20 mL), water (20 mL) and 36% w/v HCl (1 mL). The reactants were heated at reflux for 16 h and then cooled to room temperature. THF was evaporated in vacuo and the water layer was extracted with diethyl ether (100 mL×5). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a colourless solid.

3.5.1. 3-Methyl-6-phenyl-6,7-dihydro-4*H*-isoxazolo[4,5-*b*]pyridine-5-one 1a. Colourless solid (192 mg, 84% yield); R_f=0.2 (ethyl acetate/acetone/petroleum ether 25:15:60); mp 179–180 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3440–3158b, 1667s; δ_H (400 MHz, acetone-d_6) 12.85 (1H, s, *H*NC=O), 7.37–7.29 (5H, m, Ph), 4.19 (1H, t, J=8.0, C*H*Ph), 3.87 (1H, dd, J=15.6, 8.0, CH_aH_bCHPh), 3.59 (1H, dd, J=15.6, 8.0, CH_aH_bCHPh), 2.44 (3H, s, CH_3C=N); δ_C (100 MHz, DMSO-d_6) 173.1, 172.7, 155.5, 137.8, 129.9, 128.8, 127.7, 47.2, 31.1, 11.5. HRMS (EI) found $[M+H]^+$: 229.9761, $C_{13}H_{13}N_2O_2$ requires: 229.0977; *m*/*z* (EI) 229 (100, $[M+H]^+$).

3.5.2. 6-(4-Chlorophenyl)-3-methyl-6,7-dihydro-4*H*-isoxazolo[4,5-*b*]pyridin-5-one 1b. Colourless solid (213 mg, 81% yield); R_f=0.2 (ethyl acetate/petroleum ether 20:80), mp 181–182 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3440–3158b, 1705s; δ_H (400 MHz, DMSO-d_6) 13.0 (1H, s, *H*NC=O), 7.23 (2H, d, J=7.3, *p*-ClPh), 7.16 (2H, d, J=7.3, *p*-ClPh), 4.22 (1H, t, J=8.0, C*H*Ph(*p*-Cl)), 3.87 (1H, dd, J=15.6, 8.0, CH_aH_bCH), 3.58 (1H, dd, J=15.6, 8.0, CH$_a$$H_b$CH), 2.44 (3H, s, C$H_3$C=N); δ_C (100 MHz, DMSO-d_6) 173.1, 172.6, 155.5, 136.7, 132.2, 129.7, 128.7, 46.7 (*C*H), 30.8 (*C*H_2), 9.2 (*C*H_3C=N). HRMS (EI) found $[M+H]^+$: 263.0588, $C_{13}H_{12}ClN_2O_2$ requires: 263.0587; *m*/*z* (EI) 263 (20, $M+H^+$).

3.5.3. 6-(3-Methoxyphenyl)-3-methyl-6,7-dihydro-4*H*-isoxazolo[4,5-*b*]pyridine-5-one 1c. Colourless solid (199 mg, 77% yield); R_f=0.2 (ethyl acetate/petroleum ether

20:80); mp 164–166 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3480–3120b, 1707s; δ_H (400 MHz, DMSO-d_6) 13.2 (1H, s, *H*NC=O), 7.13–7.07 (1H, m, *m*-CH_3O–Ph), 6.85–6.71 (3H, m, *m*-CH_3O–Ph), 4.25 (1H, t, *J*=7.8, C*H*Ar), 3.88 (1H, dd, *J*=15.8, 8.0, CH_aH_bCH), 3.70 (3H, s, CH_3O), 3.57 (1H, dd, *J*=15.8, 8.0, CH$_a$*H*$_b$CH), 2.42 (3H, s, CH_3C=N); δ_C (100 MHz, DMSO-d_6) 173.0, 172.6, 139.9, 155.5, 136.7, 130.5, 122.3, 115.7, 112.8, 57.9, 45.7 (*C*H), 30.3 (*C*H_2), 9.2 (*C*H_3C=N). HRMS (EI) found [M+H]$^+$: 259.1079, $C_{14}H_{15}N_2O_3$ requires: 259.1082; *m*/*z* (EI) 259 (80, [M+H]$^+$).

3.5.4. 6-Phenyl-3-methyl-1,4,6,7-tetrahydropyrazolo-[4,3-*b*]pyridin-5-one 2a. Colourless solid (183 mg, 81% yield); R_f=0.1 (acetone/petroleum ether 3:7); mp 272–275 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3460–3120b, 1665s; δ_H (400 MHz, DMSO-d_6) 12.00 (1H, s, *H*NC=O), 9.92 (1H, s, *H*N–N), 7.15–7.00 (5H, Ph), 3.87 (1H, t, *J*=7.0, C*H*Ph), 3.46 (1H, dd, *J*=15.2, 7.0, CH_aH_bCHPh), 3.11 (1H, dd, *J*=15.2, 7.0, CH_aH_bCHPh), 2.41 (3H, s, CH_3C=N); δ_C (100 MHz, DMSO-d_6) 169.6 (C=O), 140.3 (Ph), 136.7, 128.1, 128.0, 126.1, 122.4, 118.6, 46.9 (*C*HPh), 27.6 (*C*H_2CH), 8.2 (*C*H_3C=N). HRMS (EI) found [M−H]$^+$: 226.0986, $C_{13}H_{12}N_3O$ requires: 226.0980; *m*/*z* (EI) 226 (100, [M−H]$^+$).

3.5.5. 6-(4-Chlorophenyl)-3-methyl-1,4,6,7-tetrahydropyrazolo[4,3-*b*]pyridin-5-one 2b. Colourless solid (233 mg, 89% yield); R_f=0.4 (ethyl acetate/acetone/petroleum ether 15:15:70); mp 290–291 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3480–3190b, 1658s; δ_H (400 MHz, DMSO-d_6) 12.02 (1H, s, *H*NC=O), 9.95 (1H, s, br, *H*N–N), 7.37 (2H, d, *J*=7.5, *p*-ClPh), 7.26 (2H, d, *J*=7.5, *p*-ClPh), 3.88–3.84 (1H, m, C*H*Ph(*p*-Cl)), 3.10–3.01 (2H, m, CH_2CHPh(*p*-Cl)), 2.14 (3H, s, CH_3C=N); δ_C (100 MHz, DMSO-d_6) 169.3 (C=O), 139.2 (*p*-ClPh), 136.8, 131.3 (*p*-ClPh), 130.2 (*p*-ClPh), 128.1 (*p*-ClPh), 122.4, 118.8, 46.3 (*C*H), 27.5 (*C*H_2), 8.2 (*C*H_3). HRMS (EI) found [M−H]$^+$: 260.0599, $C_{13}H_{11}ClN_3O$ requires: 260.0591; *m*/*z* (EI) 260 (100, [M−H]$^+$).

3.5.6. 6-(3-Methoxyphenyl)-3-methyl-1,4,6,7-tetrahydropyrazolo[4,3-*b*]pyridin-5-one 2c. Colourless solid (222 mg, 86% yield); R_f=0.5 (acetone/petroleum ether 6:4); mp 255–257 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3420–3165b, 1655s; δ_H (400 MHz, acetone-d_6) 7.24 (1H, t, *J*=7.1, Ar), 6.82–6.85 (3H, m, Ar), 4.07 (1H, app. t, *J*=7.0, C*H*Ar), 3.73 (3H, s, OCH_3), 3.55 (1H, dd, *J*=14.7, 7.9, CH_aH_bCHPh), 3.42 (1H, dd, *J*=14.7, 7.9, CH_aH_bCHPh), 3.35 (1H, s, br, *H*NC=O), 2.50 (3H, s, CH_3C=N), 2.46 (1H, s, br, NH); δ_C (100 MHz, DMSO-d_6) 172.3 (C=O), 165.3, 140.5, 136.8, 128.6, 122.5, 121.7, 119.8, 113.5, 112.5, 56.0 (*C*H_3), 48.3 (*C*HPh), 30.7 (*C*H_2CH), 8.0 (*C*H_3C=N). HRMS (EI) found [M−H]$^+$: 256.1100, $C_{14}H_{14}N_3O_2$ requires: 256.1086; *m*/*z* (EI) 256 (50, [M−H]$^+$).

Acknowledgements

We like to acknowledge The Royal Society of Chemistry for a grant to M.F.A.A., the RCSI Research Committee and PTRLI cycle III for a grant to E.F.D.

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