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ScienceDirect
Tetrahedron 63 (2007) 2684–2688
Tetrahedron

Modular syntheses of isoxazoloazepinones and pyrazoloazepinones

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Received 23 October 2006; revised 4 January 2007; accepted 11 January 2007
Available online 14 January 2007

Abstract—Herein we described an optimised synthesis of isoxazoloazepinone and novel heterocycle pyrazoloazepinone. These syntheses are modular in nature and fast to execute. The title compounds were obtained pure without the intervention of chromatography.

1. Introduction

The chemistry of heterocycles lies at the heart of drug discovery.[1] Many known active compounds contain heterocyclic cores, which are indespensable elements for bioactivity.[2] Additionally, some heterocyclic nuclei such as isoxazoles display a wide range of organic reactivities and could be used as an effective means of preparing new molecular scaffolds.[3] Isoxazoles have been repeatedly shown as useful synthons in organic synthesis.[4] As part of our ongoing efforts in developing multicomponent one-pot procedures using commercially available materials,[5–8] we became interested in the reaction of 3-methyl-4-nitro-5-styrylisoxazoles **1a–e** and diethyl malonate **2** (Scheme 1).

In a previous report, Sarti-Fantoni and co-workers have reported that **1a–e** reacted with an excess of diethyl malonate **2** (10 equiv) in the presence of piperidine to furnish the corresponding Michael adducts **3a–e** in good yields.[9] Compounds **3a–e** were subsequently elaborated to produce the isoxazoloazepinones **5a–e**. The synthesis of **5a–e** from **3a–e** involved hydrolysis and decarboxylation to obtain **4a–e** and a sequential tandem reduction–lactamisation to furnish bicyclic **5a–e**. The yield reported for the conversion of acids **4a–e** to isoxazoloazepinones **5a–e** did not exceed 15–20%.[9] Considering the ongoing interest in heterocycles, such as **5**,[10] we revisited this synthesis in order to: (i) make the preparation of acids **4** more practical by developing a one-pot procedure; (ii) enlarge the range of compounds obtainable from acids **4** and (iii) improve the yield of the tandem reduction–lactamisation steps. Here, we report a detailed study on the improved synthesis of compound **5a** and the preparation of the novel heterocyclic core pyrazoloazepinone **6** (Fig. 1). We have shown that all except one of the five steps required can be carried out in one-pot, thus making this two-step procedure a simple and an efficient way of accessing these compounds.

2. Results and discussion

Our first objective was the establishment of a one-pot procedure to access adducts **3a** and **4a** from commercially available materials **7**, **8a** and **2** (Scheme 2).

We have recently shown some synthetic application of 3,5-dimethyl-4-nitroisoxazole **7** in which spiroisoxazolines[5,7] or 3-arylpropionic acids[8] were obtained in one-pot from commercially available materials. These syntheses are based on the ability of compound **7** to undergo sequential Knoevenagel–Michael tandem reactions when reacted with aromatic aldehydes **8a–c** and a suitable Michael donor. We first studied the reaction of **7**, **8a** and **2** with respect to ratio of reactant, solvent, reaction time and catalyst loading. Critical to the establishment of a one-pot procedure were the findings that only 1.2 equiv of diethyl malonate and 0.3 equiv of piperidine were necessary. The optimised conditions involved reacting 1 equiv of **7** with 1 equiv of **8a–c** in the presence of 0.3 equiv piperidine in ethanol, at 65 °C for 1 h followed by addition of 1.2 equiv of **2** and continuation of the reaction for 3 h. Typically, adducts **3a–c** were obtained in 70–83% yields (Scheme 2 and Table 1). We considered then to extend the one-pot procedure developed for **3a–c** to include the transformation of **3a–c** to **4a–c**. Thus we reacted **7**, **8a–c** and **2** in the presence of 0.3 equiv of

Keywords: Fused isoxazoles; Polyfunctional scaffold; Fused pyrazoles.
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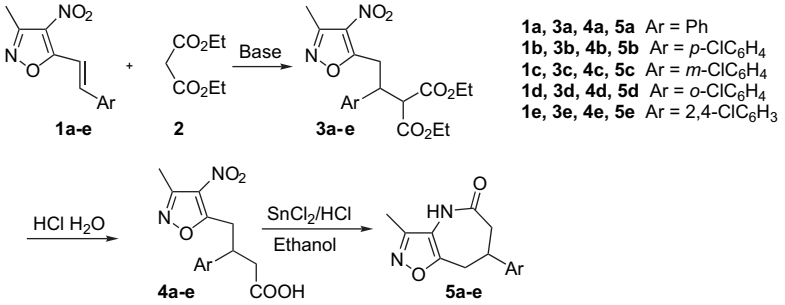
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.018



Scheme 1. Synthesis of the isoxazoloazepinones **5a–e**.

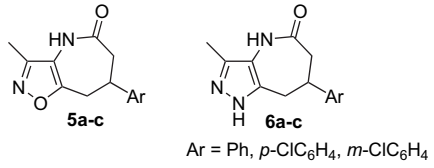
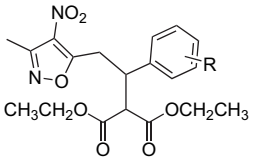
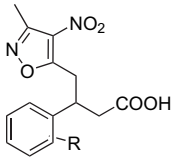
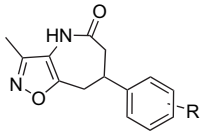


Figure 1. Target molecules **5a–c** and **6a–c**.

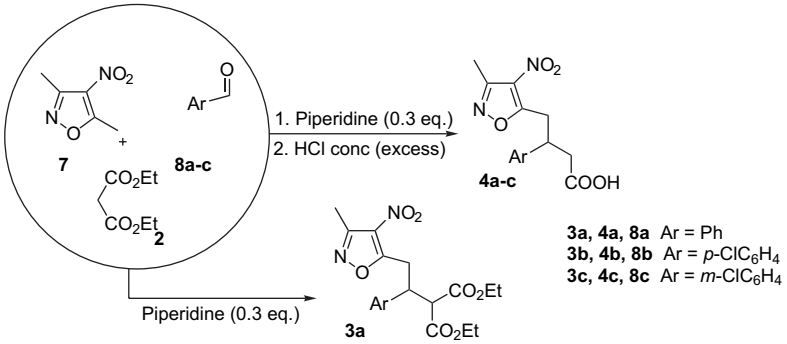
piperidine, then we added an excess of HCl and refluxed the reaction mixture for 18 h. We were pleased to find that carboxylic acids **4a–c** could be synthesised, using this simplified one-pot procedure, in very good yields (Scheme 2 and Table 1). The one-pot synthesis of compounds **4a–c** was implemented by a simple purification method that involved an acid base extraction. The carboxylic acids **4a–c** were extracted from the organic layer as the sodium salt using a saturated aqueous solution of $NaHCO_3$ and were subsequently precipitated by increasing the pH to 4.

The second objective of this study was the improvement of the tandem reduction–lactamisation sequence to obtain compounds **5**. We repeated the procedure reported for the preparation of **5a** (Scheme 3) and confirmed that under the reaction conditions used, compound **5a** was obtained in low yield. We found that the main product of this reaction was the *O*-ethyl azepinone **9a**, which we isolated in 61% yield. It was observed that compound **9a** was formed by alkylation of **5a**, which occurred due to the presence of large excess of ethanol and HCl. In order to maximise the yield of **5a** it was decided to avoid the use of ethanol. We studied the transformation of **4a** to **5a** under a number of diverse solvents, which included dichloromethane, toluene, acetonitrile, tetrahydrofuran and mixtures of acetonitrile/water or

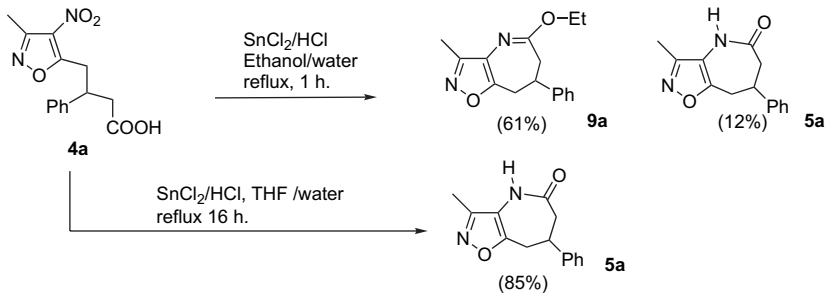
Table 1. Percentage yields for the one-pot syntheses of compounds **3a–c** and **4a–c** and for the stepwise synthesis of compounds **5a–c**

Compound	Structure	**a**, R=H	**b**, R=*p*-Cl	**c**, R=*m*-Cl
3		70	83	76
4		88	73	79
5		85	78	86

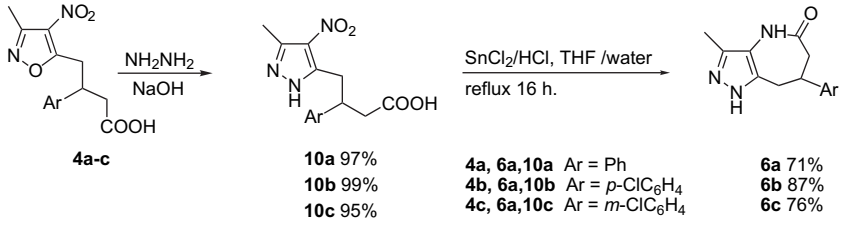
tetrahydrofuran/water. During these studies, we found that the reaction temperature and reaction time were equally important to obtain **5a** in high yields. We found that reduction of the nitro group in **4a** to the amino group was a fast process, and full conversion of **4a** was observed after an hour. Full conversion of **4a** was also observed at room temperature. However, we found that appearance of **5a** only occurred when the reaction was carried out at high temperatures (>70 °C) and after prolonged reaction times. This study identified a 1:1 mixture of tetrahydrofuran/water as the optimum solvent system, a minimum amount of 2.5 equiv of



Scheme 2. One-pot preparation of compounds **3a** and **4a–c**.



Scheme 3. Synthesis of isoxazoloazepinone **5a**.



Scheme 4. Synthesis of triaza-azulenones **6a–c**.

$SnCl_2$, and a reaction time of 16 h. This optimised procedure furnished compounds **5a–c** in 76–85% yields (Scheme 2 and Table 1).

Our last goal was to enlarge the range of compounds obtainable from acids **4a–c**. One important feature of 4-nitroisoxazoles lies in their ability to react with equimolar quantities of hydrazine, alkyl-hydrazines or aryl-hydrazines to generate the corresponding pyrazoles.[11] We demonstrated that it is possible to convert **4a–c** into their pyrazole derivatives **10a–c** in yields typically over 90% (Scheme 4). Compounds **10a–c** served to access the pyrazole-azulenone core **10a–c** via reduction–lactamisation sequence.

In conclusion, we have optimised a procedure for the preparation of isoxazoloazepinones **5a–c** in which intermediates **3a–c** and **4a–c** were prepared directly from commercially available materials in a one-pot fashion. The key points of the optimised procedure are the catalytic use of the piperidine base, the use of minimal amount of solvent and the use of a limited amount of diethyl malonate. The improved reaction conditions are complemented by a simple purification method that affords pre-intermediates without the need for chromatography. We enlarged the range of compounds available from acids **4a–c**, which were used to access the novel heterocyclic pyrazoloazepinones **6a–c**. These reactions are modular in nature, fast to execute and can be run without the need for chromatography. We believe that this study will be of interest to those involved in drug discovery and in the preparation of novel heterocyclic cores.

3. Experimental

3.1. General experimental

^1H and ^{13}C NMR spectra were recorded on a 200 or a 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 and br, broad. Coupling constants (J) were recorded in hertz (Hz) to the nearest 0.5 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 and 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 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) appropriately. Retention factors (R_f) are reported to ±0.5.

3.1.1. One-pot procedure for the preparation of adducts 3a–c. To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **7** (426 mg, 3.0 mmol) in ethanol (10 mL) were added piperidine (78 mg, 0.9 mmol, 0.3 equiv) and aromatic aldehydes **8a–c** (3 mmol, 1 equiv). The resulting solution was reacted at 65 °C for 2 h, before diethyl malonate **2** (580 mg, 3.6 mmol, 1.2 equiv) was added. The reaction was continued at 65 °C for further 3 h. The solvent was then evaporated in vacuo and the product was isolated by column chromatography. The spectroscopic data of compounds **3a–c** were reported in a previous communication.[9]

3.1.2. One-pot procedure for the preparation of adducts 4a–c. To a stirred solution of 3,5-dimethyl-4-nitroisoxazole **7** (426 mg, 3.0 mmol) in ethanol (10 mL) were added piperidine (78 mg, 0.9 mmol, 0.3 equiv) and aromatic aldehydes **8a–c** (3 mmol, 1 equiv). The resulting solution was reacted

at 65 °C for 2 h, before diethyl malonate **2** (580 mg, 3.6 mmol, 1.2 equiv) was added. The reaction was continued at 65 °C for further 3 h, then diluted with 36% w/v HCl (20 mL) and refluxed for 24 h. The reaction mixture was then cooled to room temperature and extracted with diethyl ether (100 mL×2). The organic layer was concentrated in vacuo and the sodium salt of the carboxylic acids **4a–c** was then extracted from the organic layer using a saturated aqueous solution of $NaHCO_3$ (20 mL). The water layer was acidified to pH 4 by dropwise addition of concd HCl. The product was finally extracted into chloroform, dried over $MgSO_4$ and concentrated in vacuo. The spectroscopic data of compounds **4a–c** were reported in a previous communication.[9]

3.1.3. Procedure for the preparation of compounds 10a–c. In a round-bottomed flask were put compounds **4a–c** (3.0 mmol), NaOH (120 mg, 3.0 mmol, 1 equiv) and hydrazine hydrate (0.15 mL, 3.0 mmol, 1 equiv). The reaction mixture was stirred at 75 °C for 8 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.

3.1.3.1. 4-(5-Methyl-4-nitro-2*H*-pyrazol-3-yl)-3-phenyl-butyric acid 10a. Colourless solid (280 mg, 97% yield), R_f=0.4 (ethyl acetate/petroleum ether 50:50), mp 181–182 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3445–3220b, 1687s; δ_H (400 MHz, $CDCl_3$) 7.29–7.18 (5H, m, Ph), 6.78 (2H, br, O*H* and N*H*), 3.76–3.69 (1H, m, C*H*Ph), 3.62–3.50 (2H, m, PyrCH_2), 2.78–2.74 (2H, m, CH_2COOH), 2.47 (3H, s, CH_3C=N); δ_C (100 MHz, $CDCl_3$) 172.4 (C=O), 155.0, 140.8, 129.9, 128.4, 127.0, 126.6, 40.2 (CH_2), 39.5 (*C*H), 33.4 (*C*H_2), 11.2 (*C*H_3). HRMS found: (M−H$^+$) 288.0988, $C_{14}H_{14}N_3O_5$ requires 288.0984; *m*/*z*: 289 (100%, M$^+$).

3.1.3.2. 3-(4-Chloro-phenyl)-4-(5-methyl-4-nitro-2*H*-pyrazol-3-yl)-butyric acid 10b. Colourless solid (969 mg, 100% yield), R_f=0.6 (ethyl acetate), mp 188–190 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3445–3220b, 1687s; δ_H (400 MHz, acetone-d_6) 7.31 (2H, d, *J*=8, *p*-ClC_6H_4), 7.29 (2H, d, *J*=8, *p*-ClC_6H_4), 3.73–3.65 (1H, m, C*H*C_6H_4(*p*-Cl)), 3.36 (1H, dd, *J*=14, *J*=7, Pyr–CH_aH_b), 3.26 (1H, dd, *J*=14, *J*=8, Pyr–CH_aH_b), 2.77 (1H, dd, *J*=15, *J*=6, CH_aH_bCOOH), 2.70 (1H, dd, *J*=15, *J*=9, CH_aH_bCOOH), 2.50 (3H, s, CH_3C=N); δ_C (100 MHz, acetone-d_6) 172.1 (C=O), 165.2, 145.2, 142.8, 142.1, 131.2, 128.8, 127.8, 39.5 (*C*H), 39.0 (*C*H_2), 33.4 (*C*H_2), 11.5 (*C*H_3). HRMS found: (M−H$^+$) 322.0582, $C_{14}H_{13}ClN_3O_4$ requires 322.0595; *m*/*z*: 322 (100%, M−H$^+$).

3.1.3.3. 3-(3-Chloro-phenyl)-4-(5-methyl-4-nitro-2*H*-pyrazol-3-yl)-butyric acid 10c. Colourless solid (920 mg, 95% yield), R_f=0.6 (ethyl acetate/petroleum ether 50:50), mp 168–171 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3415–3195b, 1688s; δ_H (400 MHz, acetone-d_6) 7.28–7.21 (4H, m, *m*-ClC_6H_4), 3.75–3.67 (1H, m, C*H*C_6H_4(*m*-Cl)), 3.35 (1H, dd, *J*=14, *J*=7, Pyr–CH_aH_b), 3.27 (1H, dd, *J*=14, *J*=8, Pyr–CH_aH_b), 2.82 (1H, dd, *J*=15, *J*=6, CH_aH_bCOOH), 2.75 (1H, dd, *J*=15, *J*=9, CH_aH_bCOOH), 2.53 (3H, s, CH_3C=N); δ_C (100 MHz, acetone-d_6) 171.8 (C=O), 157.3, 145.1, 142.1, 132.6, 114.0, 113.0, 112.6, 112.5, 40.2 (*C*H), 39.1 (*C*H_2), 33.3 (*C*H_2), 11.8 (*C*H_3). HRMS found: (M−H$^+$) 322.0582, $C_{14}H_{13}ClN_3O_4$ requires 322.0595; *m*/*z*: 322 (100%, M−H$^+$).

3.1.4. Procedure for the preparation of compounds 5a–c and 6a–c. Compound **4a–c** or **10a–c** (1 mmol) was combined with $SnCl_2\cdot 2H_2O$ (490 mg, 6.6 mmol, 2.2 equiv), THF (20 mL), water (20 mL) and concd HCl (1 mL). The reactants were refluxed at 80 °C for 16 h and were then cooled to room temperature. The THF was evaporated in vacuo and the water layer was extracted with diethyl ether (100 mL×5). The ether layer was dried over $MgSO_4$, concentrated in vacuo and the product was crystallised from ethanol.

3.1.4.1. 3-Methyl-7-phenyl-4,6,7,8-tetrahydro-1*H*-1,2,4-triaza-azulen-5-one 6a. Colourless solid (171 mg, 71% yield), R_f=0.3 (acetone/petroleum ether 4:6), mp 225–227 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3460–3320b, 1681s; δ_H (400 MHz, d_6-DMSO) 13.31 (1H, s, *H*NC=O), 11.93 (1H, s, *H*N–N), 7.19–7.06 (5H, m, Ph), 3.45 (1H, app. t, *J*=7, C*H*Ph), 3.10–3.05 (2H, m, CH_2, CH_2C=O), 2.40 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.28 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.00 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 171.9 (C=O), 154.3, 153.1, 135.5, 132.8, 132.0, 129.9, 121.1, 39.8 (*C*H), 39.1 (*C*H_2), 32.0 (*C*H_2), 8.2 (*C*H_3C=N). HRMS found: (M−H$^+$) 240.1125, $C_{14}H_{14}N_3O$ requires 240.1137; *m*/*z*: 242.1 (50%, M+H$^+$).

3.1.4.2. 7-(4-Chloro-phenyl)-3-methyl-4,6,7,8-tetrahydro-1*H*-1,2,4-triaza-azulen-5-one 6b. Colourless solid (280 mg, 76% yield), R_f=0.34 (ethyl acetate/acetone/petroleum ether 1:1:2), mp 228–230 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3460–3341b, 1665s; δ_H (400 MHz, d_6-DMSO) 13.4 (1H, s, *H*NC=O), 12.06 (1H, s, *H*N–N), 7.31 (2H, d, *J*=8, *p*-ClC_6H_4), 7.24 (2H, d, *J*=8, *p*-ClC_6H_4), 3.52 (1H, app. t, *J*=7, C*H*(*p*-ClC_6H_4)), 3.14 (2H, d, *J*=3, CH_2C=O), 2.64 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.44 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.50 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 171.8 (C=O), 154.5, 153.9, 140.5, 132.3, 128.3, 128.2, 121.6, 39.5 (*C*H), 39.2 (*C*H_2), 32.3 (*C*H_2), 9.2 (*C*H_3C=N). HRMS found: (M−H$^+$) 274.0742, $C_{14}H_{13}N_3OCl$ requires 274.0747; *m*/*z*: 274 (100%, M−H$^+$).

3.1.4.3. 7-(3-Chloro-phenyl)-3-methyl-4,6,7,8-tetrahydro-1*H*-1,2,4-triaza-azulen-5-one 6c. Colourless solid (239 mg, 87% yield), R_f=0.16 (acetone/petroleum ether 4:6), mp 218–219 °C (ethanol); ν_{max} (Film)/cm^{-1}: 3460–3341b, 1675s; δ_H (400 MHz, d_6-DMSO) 12.2 (1H, s, *H*NC=O), 9.18 (1H, s, *H*N–N), 7.41 (1H, s, *m*-ClC_6H_4), 7.36 (1H, app. t, *J*=7, *m*-ClC_6H_4), (2H, d, *J*=7, *m*-ClC_6H_4), 3.50–3.46 (1H, m, C*H*(*m*-ClC_6H_4)), 3.12 (2H, d, *J*=3, CH_2C=O), 2.57 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.49 (1H, dd, *J*=15, *J*=6, PyrCH_2), 2.1 (3H, s, CH_3); δ_C (100 MHz, d_6-DMSO) 171.8 (C=O), 154.5, 145.9, 133.1, 130.4, 126.7, 126.4, 125.5, 117.0, 121.6, 42.5 (*C*H_2), 39.3 (*C*H_2), 32.7 (CH), 9.1 (*C*H_3). HRMS found: (M−H$^+$) 274.0739, $C_{14}H_{13}N_3OCl$ requires 274.0747; *m*/*z*: 274.1 (100%, M−H$^+$).

3.1.5. 5-Ethoxy-3-methyl-7-phenyl-7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepine 9a. Compound **4a** (1 mmol) was combined with $SnCl_2\cdot 2H_2O$ (490 mg, 6.6 mmol, 2.2 equiv), ethanol (20 mL), water (20 mL) and concd HCl (1 mL). The

reactants were refluxed for 1 h and then cooled to room temperature. The ethanol was evaporated in vacuo and the water layer was extracted with diethyl ether (100 mL×5). The ether layer was dried over $MgSO_4$, concentrated in vacuo and **9a** was purified by flash chromatography. Colourless solid (167 mg, 62% yield), R_f=0.4 (acetone/petroleum ether 4:6); δ_H (400 MHz, d_6-DMSO) 8.27 (1H, s, *H*N), 7.39–7.17 (5H, m, Ph), 4.04 (2H, q, J=7, OCH_2), 3.57–3.53 (1H, m, C*H*Ph), 3.05 (1H, dd, J=15, J=7, CH_2), 2.93 (1H, dd, J=15, J=7, CH_2), 2.73 (1H, dd, J=15, J=7, CH_2), 2.65 (1H, dd, J=15, J=7, CH_2), 2.16 (3H, s, CH_3), 1.16 (1.5, 1H, t, J=7, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 170.2 (C═O), 154.5, 153.1, 137.1, 131.7, 128.6, 126.9, 127.8, 60.6 (*C*H_2), 39.9 (*C*H), 39.6 (*C*H_2), 31.5 (*C*H_2), 14.0 (CH_3), 9.2 (CH_3). HRMS found: (M+H$^+$) 271.3334, $C_{16}H_{19}N_2O_2$ requires 271.3342; *m*/*z*: 271 (50%, M+H$^+$).

Acknowledgements

We would 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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