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Novel approach to the synthesis of aliphatic and aromatic α-keto acids

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ABSTRACT

A new practical and efficient synthesis of α-keto acids was accomplished starting from the synthon 1,4-diacetylpiperazine-2,5-dione. The synthesis encompasses both aromatic and aliphatic substrates proving to be versatile and innovative with excellent carbon economy and recycling of the glycine by-product.

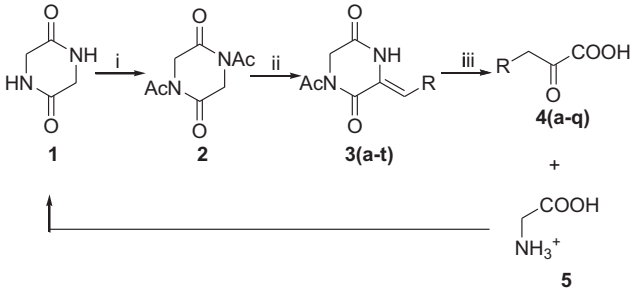
1. Introduction

α-Keto acids are of major importance in biological processes. This class of compounds plays a key role both in the biosynthesis and metabolism of amino acids and provides interesting intermediates for chemical synthesis.[1,2] The successful and efficient production of keto acids is an appealing synthetic objective as they can be, for example, employed in the synthesis of chiral amino acids when appropriate biocatalysts are applied.[3–5] The development of suitable methods for the synthesis of α-keto acids has been of interest for more than a century since the synthesis of pyruvic acid was achieved by Berzelius in 1835.[6] A variety of preparative methods for aliphatic[7–14] and aromatic[14–17] substrates have been previously reported in the literature for α-keto compounds, although these methods are somewhat limited to either aliphatic or aromatic substrates.

We have now developed a simple and reliable synthetic route, which is applicable to both aliphatic and aromatic substrates, generating α-keto acids in very good yields.

2. Results and discussion

Aiming at minimising waste and sustainability of the overall process, we started from a diketopiperazine synthon **2**, which is easily obtained from the commercially available glycine anhydride **1**. The synthesis allows for the recycling of the glycine by-product resulting in excellent carbon economy (Scheme 1).



Scheme 1. Synthesis of α-keto acids. (i) Ac_2O/DMF, (ii) *t*BuOK/*t*BuOH/CH_2Cl_2 (or THF)/RCHO, (iii) 6 M HCl, reflux. R: (a) phenyl, (b) 2-methylphenyl, (c) 3-methylphenyl, (d) 2-methoxyphenyl, (e) 3-methoxyphenyl, (f) 2-thiophenyl, (g) 1-naphtyl, (h) 2-naphtyl, (i) 2,3-difluorophenyl, (j) 2,4-difluorophenyl, (k) 2,5-difluorophenyl, (l) phenyl-ethyl, (m) cyclohexyl, (n) 2-propenyl, (o) ethyl, (p) 3-cyclohexenyl, (q) *tert*-Butyl, (r) 2-furanyl, (s) 2-*N*-methylpyrrolyl, (t) *N*-Boc-3-indole.

The 3-arylalkylidene-2,5-piperazine-diones **3** were prepared following the Gonzalez protocol where the reaction between **2** and an aromatic aldehyde was performed in a *t*-BuOH/CH_2Cl_2 mixture with *t*-BuOK as a base.[18] For the aliphatic derivatives the synthesis was accomplished by a modified procedure, which employed THF as a solvent and a stoichiometric ratio of aldehyde.[19] In both cases the reaction was performed at room temperature and was promoted by the anchimeric assistance of the vicinal *N*-acetyl group as described by Gallina and co-workers.[20] The reaction displays total diastereoselectivity in favour of the *Z*-isomer justified via the Zimmerman–Traxler[21] model (Fig. 1).

We believe that the reaction proceeds through the transition state **a**, in which interactions between the acetyl group and the R substituent on the aldehyde are minimised. This transition state

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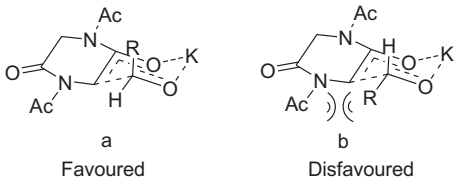
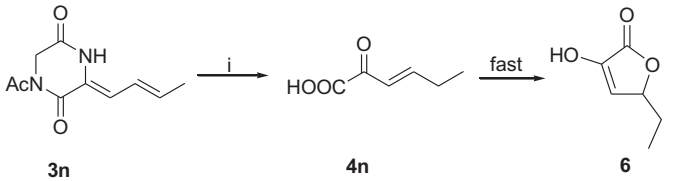


Fig. 1. Zimmerman–Traxler model.



Scheme 2. Intramolecular cyclization in the formation of **6** (i) 6 M aqueous HCl, reflux.

generates the aldol intermediate, which leads to the formation of the *Z*-isomer. The configuration of the double bond has been confirmed by NMR[18,19] spectroscopy and where possible, by X-ray analysis as for compounds **3q** and **3b** (Fig. 2).

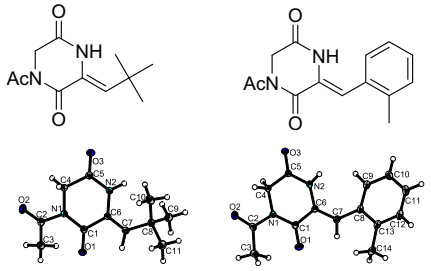


Fig. 2. X-ray analysis for compounds **3q** and **3b**.[22]

The intermediates **3** were hydrolysed by heating at reflux in a 6 M aqueous HCl solution for 2 h generating the corresponding keto acid and glycine by-product in good yield. The glycine by-product was easily recovered from the aqueous phase in quantitative yield, and a protocol to recycle it to glycine anhydride **1** in two steps is reported in the literature.[23] Results are summarised in Table 1.

Table 1
% Yields of condensation and hydrolysed products

Aldehyde R group (RCHO)	Diketopiperazine	Yield (%)	Keto acid	Yield (%)
Phenyl	**3a**	92	**4a**	95
2-Methylphenyl	**3b**	87	**4b**	91
3-Methylphenyl	**3c**	93	**4c**	95
2-Methoxyphenyl	**3d**	89	**4d**	83
3-Methoxyphenyl	**3e**	92	**4e**	80
2-Thiophenyl	**3f**	85	**4f**	48
1-Naphtyl	**3g**	79	**4g**	95
2-Naphtyl	**3h**	73	**4h**	92
2,3-Difluorophenyl	**3i**	93	**4i**	91
2,4-Difluorophenyl	**3j**	93	**4j**	91
2,5-Difluorophenyl	**3k**	92	**4k**	90
Phenyl-ethyl	**3l**	68	**4l**	85
Cyclohexyl	**3m**	88	**4m**	88
2-Propenyl	**3n**	75	**4n**	—
Ethyl	**3o**	82	**4o**	89
3-Cyclohexenyl	**3p**	78	**4p**	—
tert-Butyl	**3q**	90	**4q**	96
2-Furanyl	**3r**	87	—	—
2-*N*-Methylpyrrolyl	**3s**	81	—	—
N-Boc-3-indole	**3t**	67	—	—

Under hydrolytic conditions, which have been previously discussed, unsaturated aliphatic (**3n** and **3p**) and heteroaromatic (**3r**–**t**) diketopiperazines do not yield the corresponding keto acids. In the case of compound **3p** the reaction products found were a mixture of unidentified compounds, while for compound **3n** the product **6** was identified. The presence of **6** indicates that rapid addition of water to the double bond had occurred, subsequently followed by an intramolecular cyclization (Scheme 2).

In the case of the heteroaromatic DKP, similar product decomposition was observed but no compounds were identified. None of the 2-furan **3r**, *N*-methylpyrrole **3s** or 3-indole **3t** diketopiperazines yielded a product. An exception was the 2-thiophene **3f** diketopiperazine for which the hydrolysis step yielded the desired 2-thiophene α-keto acid **4f**.

Compounds **3** could undergo a further condensation reaction to generate a symmetric product the hydrolysis of which would yield 2 equiv of **4** without a glycine by-product. Unfortunately, while the second condensation can be easily achieved, the hydrolysis of such compounds failed even under extremely harsh conditions.

3. Conclusions

In conclusion a new, practical and efficient synthesis of aromatic and aliphatic keto acids has been accomplished through the use of a diketopiperazine synthon, which is easily obtained from commercially available glycine anhydride **1**. The condensation step results in excellent yields both with the use of aromatic aldehydes with a variety of substituents on the aromatic ring, and with the use of aliphatic aldehydes. Compounds **4g** and **4h** were also synthesised following previously reported protocols (via azlactone[3] and hydantoin[24]) with much lower isolated yields for the azlactone (17% and 35%, respectively) and for the hydantoin (24% and 20%, respectively).[25] These results were in line with what was previously reported in the literature. Furthermore, these methods were unsuccessful when applied to the synthesis of aliphatic keto acids, as the harsh reaction conditions required for the condensation step were responsible for self-condensation of the aldehydes. In contrast, our procedure is versatile and innovative, yielding up to 93% of the condensation product and 96% of the desired keto acid upon hydrolysis, with excellent atom economy that allows for effective recycling of the glycine by-product.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich except where stated. All reactions were performed under an atmosphere of nitrogen using oven dried glassware. Oxygen-free nitrogen was obtained from BOC gases and used without further drying. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR, respectively) were recorded on 300 MHz, 400 MHz and 500 MHz FT spectrometers. Tetramethylsilane was used as an internal reference in the deuterated chloroform ($CDCl_3$) (δ=0.00 ppm) for ^{1}H NMR spectra. The middle $CDCl_3$ solvent peak was referenced to 77.0 for ^{13}C NMR spectra. The coupling constants (J) are in hertz and the chemical shifts (δ) are given in parts per million (ppm). High resolution mass spectra were obtained on a Waters/Micromass instrument. Melting points were determined using a Gallenkamp melting point apparatus. Melting points are uncorrected. Elemental analyses were performed by Mr. Adam Coburn and Ms. Ann Connolly, School of Chemistry and Chemical Biology, University College Dublin.

4.2. 1,4-Diacetyl-piperazine-2,5-dione (2)[26]

A mixture of glycine anhydride (11.4 g, 100 mmol) in acetic anhydride was stirred under reflux for 7 h. The solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate/ether to yield **2** (17.2 g, 87%) as a brown solid. Mp 99 °C. δ_H (500 MHz, $CDCl_3$) 2.60 (s, 6H), 4.66 (s, 4H).

*4.2.1. (Z)-1-Acetyl-3-benzylidenepiperazine-2,5-dione (**3a**).*[18] 1,4-Diacetyl-piperazine-2,5-dione **2** (11.7 g, 50 mmol) was dissolved in dry CH_2Cl_2 (50 mL) under N_2 atmosphere. Benzaldehyde (5 mL, 50 mmol) and potassium *tert*-butoxide (5.61 g, 50 mmol), dissolved in a minimum amount of *tert*-butanol (~25 mL), were added to this solution. The reaction mixture was stirred for 3 h, then a saturated aqueous solution of NH_4Cl (100 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated in vacuo. The product **3a** (11.2 g, 92%) was obtained as a white solid. Mp 199–200 °C. δ_H (500 MHz, $CDCl_3$) 2.67 (s, 3H), 4.53 (s, 2H), 7.19 (s, 1H), 7.35–7.42 (m, 3ArH), 7.45–7.52 (m, 2ArH), 7.97 (br s, 1H, NH).

*4.2.2. (Z)-1-Acetyl-3-(2-methyl-benzylidene)-piperazine-2,5-dione (**3b**).* Prepared as described for **3a** using 2-methylbenzaldehyde (5.78 mL, 50 mmol) to give the title compound **3b** (11.2 g, 87%) as a white solid. Mp 173–174 °C. δ_H (500 MHz, $CDCl_3$) 2.32 (s, 3H), 2.67 (s, 3H, $-NCOCH_3$), 4.49 (s, 2H), 7.22–7.38 (m, 4ArH+1H), 7.84 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 19.9, 27.3, 46.2, 119.2, 126.1, 126.7, 127.4, 129.4, 131.2, 131.3, 137.6, 159.6, 162.5, 172.5; ν_{max} 3260 (NH), 1708 ($COCH_3$), 1668 (C=O), 1612 (C=C); Elemental analysis found: C, 65.40; H, 5.44; N, 10.80. $C_{14}H_{14}N_2O_3$ requires C, 65.11; H, 5.46; N, 10.85.

*4.2.3. (Z)-1-Acetyl-3-(3-methyl-benzylidene)-piperazine-2,5-dione (**3c**).* Prepared as described for **3a** using 3-methylbenzaldehyde (5.89 mL, 50 mmol) to give the title compound **3c** (12 g, 93%) as a white solid. Mp 187–188 °C (dec). δ_H (300 MHz, $CDCl_3$) 2.39 (s, 3H), 2.65 (s, 3H, $-NCOCH_3$), 4.49 (s, 2H), 7.15–7.46 (m, 4ArH+1H), 8.12 (br s, 1H, NH); δ_C (101 MHz, $CDCl_3$) 21.4, 27.1, 46.0, 120.2, 125.5, 125.6, 129.1, 129.4, 130.2, 132.4, 139.4, 160.0, 162.8, 172.5; ν_{max} 3248 (NH), 1679 ($COCH_3$), 1627 (C=O), 1618 (C=C); Elemental analysis found: C, 64.80; H, 5.45; N, 10.80. $C_{14}H_{14}N_2O_3$ requires C, 65.11; H, 5.46; N, 10.85.

*4.2.4. (Z)-1-Acetyl-3-(2-methoxy-benzylidene)-piperazine-2,5-dione (**3d**).* Prepared as described for **3a** using 2-methoxybenzaldehyde (5.9 mL, 50 mmol) to give the title compound **3d** (12.2 g, 89%) as a white wax. Mp 183–184 °C. δ_H (500 MHz, $CDCl_3$) 2.67 (s, 3H, $-NCOCH_3$), 3.96 (s, 3H), 4.49 (s, 2H), 6.98–7.09 (m, 2ArH), 7.18 (s, 1H), 7.25–7.42 (m, 2ArH), 8.45 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 27.1, 46.1, 56.0, 112.0, 117.2, 121.6, 121.7, 125.7, 131.0, 156.3, 160.3, 162.5, 172.5; ν_{max} 3192 (NH), 1721 ($COCH_3$), 1677 (C=O), 1628 (C=C), 1280 (O–Me); Elemental analysis found: C, 61.60; H, 5.13; N, 10.20. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21.

*4.2.5. (Z)-1-Acetyl-3-(3-methoxy-benzylidene)-piperazine-2,5-dione (**3e**).*[27] Prepared as described for **3a** using 3-methoxybenzaldehyde (6.09 mL, 50 mmol) to give the title compound **3e** (12.6 g, 92%) as a white solid. Mp 199–200 °C. δ_H (500 MHz, $CDCl_3$) 2.65 (s, 3H, $-NCOCH_3$), 3.81 (s, 3H), 4.50 (s, 2H), 6.91–6.97 (m, 3ArH), 7.14 (s, 1H), 7.32–7.41 (m, 1ArH), 8.05 (br s, 1H, NH).

*4.2.6. (Z)-1-Acetyl-3-thiophen-2yl-methylene-piperazine-2,5-dione (**3f**).* Prepared as described for **3a** using thiophene-2-carbaldehyde (4.67 mL, 50 mmol) to give the title compound **3f** (10.6 g, 85%) as a yellow solid. Mp 174–175 °C. δ_H (500 MHz, $CDCl_3$) 2.65 (s, 3H, $-NCOCH_3$), 4.54 (s, 2H), 7.18 (dd, 1ArH, *J* 5.1, 3.6), 7.32 (d, 1ArH, *J* 3.6), 7.34 (s, 1H), 7.54 (d, 1ArH, *J* 5.1), 7.88 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 27.0, 46.0, 113.3, 123.4, 128.5, 128.9, 131.0, 135.4, 160.2, 162.8, 172.3; ν_{max} 3232 (NH), 1689 ($COCH_3$), 1658 (C=O), 1625 (C=C); Elemental analysis found: C, 52.72; H, 4.04; N, 11.21. $C_{11}H_{10}N_2O_3S$ requires C, 52.79; H, 4.03; N, 11.19.

*4.2.7. (Z)-1-Acetyl-3-(naphthalene-1-yl-methylene)-piperazine-2,5-dione (**3g**).* Prepared as described for **3a** using 1-Naphthaldehyde (7.8 mL, 50 mmol) to give the title compound **3g** (11.6 g, 79%) as a yellow solid. Mp 162 °C (dec). δ_H (500 MHz, DMSO) 2.55 (s, 3H, $-NCOCH_3$), 4.37 (s, 2H), 7.43 (d, 1ArH, *J* 6.3), 7.52–7.59 (m, 2ArH+1H), 7.65 (d, 1ArH, *J* 7.1), 7.94 (d, 2ArH, *J* 7.5), 7.96–8.00 (m, 1ArH), 10.17 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 27.3, 45.5, 110.0, 119.9, 124.7, 126.1, 126.6, 127.1, 127.6, 129.0, 129.1, 130.5, 131.6, 133.8, 161.3, 164.1, 172.5; ν_{max} 3196 (NH), 1690 ($COCH_3$), 1652 (C=O), 1632 (C=C); Elemental analysis found: C, 69.39; H, 4.92; N, 9.51. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52.

*4.2.8. (Z)-1-Acetyl-3-(naphthalene-2-yl-methylene)-piperazine-2,5-dione (**3h**).* Prepared as described for **3a** using 2-Naphthaldehyde (4.8 mL, 50 mmol) to give the title compound **3h** (10.7 g, 73%) as a yellow solid. Mp 229–231 °C. δ_H (500 MHz, DMSO) 2.51 (s, 3H, $-NCOCH_3$), 4.39 (s, 2H), 7.10 (s, 1H), 7.50–7.58 (m, 2ArH), 7.68 (d, 1ArH, *J* 8.2), 7.93 (d, 3ArH, *J* 8.1), 8.14 (s, 1ArH), 10.17 (br s, 1H, NH); δ_C (126 MHz, DMSO) 27.2, 46.2, 110.0, 119.2, 126.9, 127.3, 127.4, 128.0, 128.4, 128.7, 130.0, 131.2, 133.1, 133.3, 162.1, 164.7, 172.3; ν_{max} 3194 (NH), 1688 ($COCH_3$), 1675 (C=O), 1621 (C=C); Elemental analysis found: C, 69.45; H, 4.83; N, 9.75. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52.

*4.2.9. (Z)-1-Acetyl-3-(2,3-difluorobenzylidene)-piperazine-2,5-dione (**3i**).* Prepared as described for **3a** using 2,3-difluorobenzaldehyde (5.5 mL, 50 mmol) to give the title compound **3i** (13 g, 93%) as a white solid. Mp 195–196 °C. δ_H (500 MHz, DMSO) 2.51 (s, 3H, $-NCOCH_3$), 4.35 (s, 2H), 6.86 (s, 1H), 7.16–7.31 (m, 1ArH), 7.34–7.43 (m, 2ArH), 10.46 (br s, 1H, NH); ν_{max} 3221 (NH), 1691 ($COCH_3$), 1648 (C=O), 1618 (C=C); δ_C (126 MHz, DMSO) 27.3, 46.4, 109.3, 117.6, 123.8, 125.2, 126.2, 130.3, 148.1, 150.5, 160.1, 164.2, 172.4; Elemental analysis found: C, 55.61; H, 3.50; N, 10.00; F, 13.56. $C_{13}H_{10}F_2N_2O_3$ requires C, 55.72; H, 3.60; N, 10.00; F, 13.56.

*4.2.10. (Z)-1-Acetyl-3-(2,4-difluorobenzylidene)-piperazine-2,5-dione (**3j**).* Prepared as described for **3a** using 2,4-difluorobenzaldehyde (5.5 mL, 50 mmol) to give the title compound **3j** (13 g, 93%) as a white solid. Mp 157–158 °C. δ_H (500 MHz, DMSO) 2.50 (s, 3H, $-NCOCH_3$), 4.34 (s, 2H), 6.84 (s, 1H), 7.09–7.20 (m, 1ArH), 7.28–7.36 (m, 1ArH), 7.59–7.69 (m, 1ArH), 10.42 (br s, 1H, NH); ν_{max} 3218 (NH), 1711 ($COCH_3$), 1686 (C=O), 1611 (C=C); δ_C (126 MHz, DMSO) 27.4, 46.3, 104.8, 109.9, 112.3, 118.1, 129.3, 132.3, 160.6, 161.2, 162.7, 164.3, 172.4; Elemental analysis found: C, 55.60; H, 3.73; N, 9.82; F, 13.81. $C_{13}H_{10}F_2N_2O_3$ requires C, 55.72; H, 3.60; N, 10.00; F, 13.56.

*4.2.11. (Z)-1-Acetyl-3-(2,5-difluorobenzylidene)-piperazine-2,5-dione (**3k**).* Prepared as described for **3a** using 2,5-difluorobenzaldehyde (5.5 mL, 50 mmol) to give the title compound **3k** (12.9 g, 92%) as a white solid. Mp 186–187 °C. δ_H (500 MHz, DMSO) 2.50 (s, 3H, $-NCOCH_3$), 4.35 (s, 2H), 6.84 (s, 1H), 7.21–7.26 (m, 1ArH), 7.28–7.33 (m, 1ArH), 7.41–7.45 (m, 1ArH), 10.54 (br s, 1H, NH); ν_{max} 3186 (NH), 1722 ($COCH_3$), 1695 (C=O), 1615(C=C); δ_C (126 MHz, DMSO) 27.3, 46.3, 109.3, 117.3, 122.8, 130.1, 156.6, 158.3, 161.0, 164.4, 172.3; Elemental analysis found: C, 55.63; H, 3.84; N, 9.72; F, 13.57. $C_{13}H_{10}F_2N_2O_3$ requires C, 55.72; H, 3.60; N, 10.00; F, 13.56.

*4.2.12. (Z)-1-Acetyl-3-(2-Phenyl-propiliden)-piperazine-2,5-dione (**3l**).* Prepared as described for **3a** using 2-Phenyl-propionaldehyde

(6.7 mL, 50 mmol) to give the title compound **3l** (9.3 g, 68%) as a white solid. Mp 161–162 °C. δ_H (300 MHz, $CDCl_3$) 1.47 (d, 3H, *J* 6.6), 2.60 (s, 3H, −NCO*CH*$_3$), 3.72–3.85 (m, 1H), 4.41 (s, 2H), 6.49 (d, 1H, *J* 9.3), 7.24–7.35 (m, 5ArH), 8.54 (br s, 1H, NH); δ_C (126 MHz, DMSO) 22.2, 27.1, 36.5, 45.9, 125.0, 126.9, 127.1, 128.4, 129.0, 143.2, 159.9, 164.1, 172.6; ν_{max} 3280 (NH), 1723 ($COCH_3$), 1681 (C=O), 1615 (C=C); Elemental analysis found: C, 66.40; H, 5.90; N, 10.25. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29.

*4.2.13. (Z)-1-Acetyl-3-cyclohexylmethylene-piperazine-2,5-dione (**3m**).* 1,4-Diacetyl-piperazine-2,5-dione **2** (11.7 g, 0.05 mol) was dissolved in dry THF (50 mL) under N_2 atmosphere. Cyclohexanecarbaldehyde (6.1 mL, 50 mmol) and potassium *tert*-butoxide (5.61 g, 50 mmol), dissolved in a minimum amount of *tert*-butanol (25 mL), were added to this solution. The reaction mixture was stirred for 3 h, then an aqueous solution of NH_4Cl (100 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated in vacuo. The product **3m** (11 g, 88%) was obtained as a white solid. Mp 198–200 °C. δ_H (300 MHz, $CDCl_3$) 1.17–1.42 (m, 5H), 1.64–1.82 (m, 5H), 2.22–2.41 (m, 1H), 2.61 (s, 3H, −NCO*CH*$_3$), 4.44 (s, 2H), 6.19 (d, 1H, *J* 9.9), 8.26 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 25.3, 25.6, 27.1, 31.8, 35.5, 46.0, 124.7, 129.7, 160.1, 163.8, 172.7; ν_{max} 3197 (NH), 1710 ($COCH_3$), 1678 (C=O), 1624 (C=C); Elemental analysis found: C, 62.09; H, 7.22; N, 11.24. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19.

*4.2.14. (3Z,2′E)-1-Acetyl-3-but-2-enylidene-piperazine-2,5-dione (**3n**).* Prepared as described for **3m** using *trans*-crotonaldehyde (4.1 mL, 50 mmol) to give the title compound **3n** (7.8 g, 75%) as a yellow solid. Mp 217–218 °C (dec). δ_H (500 MHz, $CDCl_3$) 1.94 (d, 3H, *J* 6.0), 2.62 (s, 3H, −NCO*CH*$_3$), 4.47 (s, 2H), 6.21–6.32 (m, 1H), 6.33–6.44 (m, 1H), 6.77 (d, 1H, *J* 11.7), 8.92 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 19.3, 27.1, 46.0, 121.8, 122.2, 123.1, 140.8, 160.3, 164.0, 172.6; ν_{max} 3281 (NH), 1718 ($COCH_3$), 1682 (C=O), 1656 (C=C), 1624 (C=C); Elemental analysis found: C, 57.39; H, 5.84; N, 13.50. $C_{10}H_{12}N_2O_3$ requires C, 57.68; H, 5.81; N, 13.45.

*4.2.15. (Z)-1-Acetyl-3-propylidene-piperazine-2,5-dione (**3o**).* Prepared as described for **3m** using propionaldehyde (3.6 mL, 50 mmol) to give the title compound **3o** (8 g, 82%) as a white solid. Mp 158–159 °C. δ_H (300 MHz, $CDCl_3$) 1.15 (t, 3H, *J* 6.9), 2.16–2.26 (m, 2H), 2.61 (s, 3H, −NCO*CH*$_3$), 4.44 (s, 2H), 6.30 (t, 1H, *J* 7.5), 8.21 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 12.9, 19.5, 27.1, 45.9, 125.8, 126.5, 160.0, 164.2, 172.6; ν_{max} 3383 (NH), 1715 ($COCH_3$), 1693 (C=O), 1643 (C=C); Elemental analysis found: C, 55.35; H, 5.99; N, 14.10. $C_9H_{12}N_2O_3$ requires C, 55.09; H, 6.16; N, 14.28.

*4.2.16. (Z)-1-Acetyl-3-cyclohex-3enyl-methylene-piperazine-2,5-dione (**3p**).* Prepared as described for **3m** using cyclohex-3-enecarbaldehyde (5.85 mL, 50 mmol) to give the title compound **3p** (9.7 g, 78%) as a white solid. Mp 175–176 °C. δ_H (300 MHz, $CDCl_3$) 1.54–1.61 (m, 2H), 1.76–1.84 (m, 1H), 1.92–2.02 (m, 1H), 2.12–2.21 (m, 2H), 2.54–2.66 (m, 1H), 2.62 (s, 3H, −NCO*CH*$_3$), 4.44 (s, 2H), 5.67–5.75 (m, 2H), 6.27 (d, 1H, *J* 9.9), 8.37 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 23.9, 27.1, 27.6, 30.3, 31.4, 46.0, 124.8, 125.3, 127.1, 129.0, 160.1, 164.0, 172.6; ν_{max} 3341 (NH), 1708 ($COCH_3$), 1678 (C=O), 1666 (C=C), 1618 (C=C); Elemental analysis found: C, 62.60; H, 6.52; N, 11.31. $C_{13}H_{16}N_2O_3$ requires C, 62.89; H, 6.50; N, 11.28.

*4.2.17. (Z)-1-Acetyl-3-(2,2-dimethyl-propylidene)-piperazine-2,5-dione (**3q**).* Prepared as described for **3m** using 2,2-Dimethyl-propionaldehyde (5.5 mL, 50 mmol) to give the title compound **3q** (10.1 g, 90%) as a white solid. Mp 161–162 °C. δ_H (300 MHz, $CDCl_3$) 1.26 (s, 9H), 2.60 (s, 3H, −NCO*CH*$_3$), 4.43 (s, 2H), 6.27 (s, 1H), 7.62 (br s, 1H, NH); δ_C (126 MHz, $CDCl_3$) 27.1, 29.8, 32.5, 45.6, 128.2, 132.5, 160.3, 162.7, 172.5; ν_{max} 3252 (NH), 1718 ($COCH_3$), 1668 (C=O), 1642 (C=C); Elemental analysis found: C, 58.99; H, 7.20; N, 12.45. $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19; N, 12.49.

*4.2.18. (Z)-1-Acetyl-3-(furan-2-ylmethylene)piperazine-2,5-dione (**3r**).* Prepared as described for **3a** using 2-furaldehyde (4.2 mL, 50 mmol) to give the title compound **3r** (10.2 g, 87%) as a yellow solid. Mp 192–194 °C. δ_H (500 MHz, DMSO) 2.64 (s, 3H, −NCO*CH*$_3$), 4.51 (s, 2H), 6.56 (dd, *J* 3.5, 1.9, 1ArH), 6.66 (d, *J* 3.5, 1ArH), 6.89 (s, 1H), 7.61 (d, *J* 1.8, 1ArH), 9.11 (s, 1H, NH); δ_C (126 MHz, DMSO) 27.2, 107.6, 110.2, 110.5, 119.3, 142.5, 154.1, 162.2, 164.6, 172.5; ν_{max} 3248 (NH), 1701 ($COCH_3$), 1687 (C=O), 1622 (C=C); HRMS (ES^+): calcd for $C_{11}H_{11}N_2O_4^+$ $(M+H)^+$: 235.0719; found: 235.0718.

*4.2.19. (Z)-1-Acetyl-3-((1-methyl-1H-pyrrol-2-yl)methylene) piperazine-2,5-dione (**3s**).* Prepared as described for **3a** using *N*-methyl-pyrrole-2-carboxaldehyde (5.1 mL, 50 mmol) to give the title compound **3s** (10 g, 81%) as a yellow solid. Mp 187–189 °C. δ_H (400 MHz, DMSO) 2.54 (s, 3H, −NCO*CH*$_3$), 3.67 (s, 3H), 4.48 (s, 2H), 6.02–6.16 (m, 1ArH), 6.11–6.23 (m, 1ArH), 6.52–6.67 (m, 1ArH), 6.81 (s, 1H), 9.80 (s, 1H, NH); δ_C (126 MHz, DMSO) 27.2, 33.7, 56.6, 106.7, 108.8, 110.2, 119.2, 123.5, 131.9, 162.2, 164.6, 172.5; ν_{max} 3235 (NH), 1700 ($COCH_3$), 1691 (C=O), 1652 (C=C); Elemental analysis found: C, 58.31; H, 5.29; N, 16.97. $C_{12}H_{13}N_3O_3$ requires C, 58.29; H, 5.30; N, 16.99.

*4.2.20. (Z)-tert-Butyl 3-((4-acetyl-3,6-dioxopiperazin-2-ylidene) methyl)-1H-indole-1-carboxylate (**3t**).* Prepared as described for **3a** using a Boc protected indole-3-carboxaldehyde[28] (12.3 g, 50 mmol) to give the title compound **3t** (12.8 g, 67%) as a beige solid. Mp 234 °C (dec). δ_H (300 MHz, $CDCl_3$) 1.70 (s, 9H), 2.58 (s, 3H, −NCO*CH*$_3$), 4.52 (s, 2H), 7.43–7.32 (m, 2ArH), 7.66 (d, *J* 7.6, 1ArH), 7.91 (s, 1H), 8.14 (d, *J* 8.2, 1ArH), 8.31 (s, 1H); δ_C (101 MHz, $CDCl_3$) 27.2, 28.3, 46.1, 85.4, 110.1, 115.3, 119.5, 121.5, 122.2, 124.8, 126.1, 126.3, 135.8, 136.64, 149.8, 162.2, 164.5, 172.4; ν_{max} 3180 (NH), 1721 ($COCH_3$), 1679 (C=O), 1644 (C=C), 1154 (C–O); HRMS (ES^+): calcd for $C_{11}H_{11}N_2O_4^+$ $(M-H)^+$: 384.1559; found: 384.1563.

*4.2.21. (Z)-2-Hydroxy-3-phenyl-acrylic acid (**4a**).*[26] (*Z*)-1-Acetyl-3-benzylidenepiperazine-2,5-dione **3a** (5 g, 20 mmol) was dissolved in 6 N aqueous HCl (25 mL) and heated to reflux for 4 h. The reaction was then cooled to room temperature and extracted with CH_2Cl_2 (150 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated in vacuo. The product **4a** (3.2 g, 95%) was obtained as a white solid. Mp 151–153 °C. δ_H (300 MHz, DMSO) 6.38 (s, 1H), 7.17–7.28 (m, 1ArH), 7.31–7.39 (m, 2ArH), 7.74 (d, 2ArH, *J* 7.8), 9.22 (br s, 1H), 13.20 (br s, 1H).

*4.2.22. 2-Oxo-3-o-tolyl-propanoic acid (**4b**).* Prepared as described for **4a** using **3b** (5 g, 19 mmol) to give the title compound **4b** (3.1 g, 91%) as a white solid. Mp 138.4–139.2 °C. δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H), 4.17 (s, 2H), 7.08–7.19 (m, 4ArH); δ_C (101 MHz, $CDCl_3$) 19.6, 42.2, 126.3, 128.0, 130.1, 130.6, 137.2, 138.2, 160.9, 192.5; ν_{max} 3462 (OH), 1742 (C=O), 1618 (C=O), 1584 (C=C); HRMS (ES^-): calcd for $C_{10}H_9O_3^-$ $(M-H)^-$: 177.0552; found: 177.0549.

*4.2.23. (Z)-2-Hydroxy-3-m-tolyl-acrylic acid (**4c**).* Prepared as described for **4a** using **3c** (5 g, 19 mmol) to give the title compound **4c** (3.2 g, 95%) as a white solid. Mp 141–142 °C. δ_H (300 MHz, $CDCl_3$) 2.37 (s, 3H), 6.69 (s, 1H), 7.11–7.21 (m, 1ArH), 7.24–7.32 (m, 1ArH), 7.56–7.68 (m, 2ArH); δ_C (101 MHz, $CDCl_3$) 21.4, 114.0, 127.5, 128.5, 129.5, 130.9, 133.6, 138.1, 170.4; ν_{max} 3389 (OH), 1734 (C=O), 1690 (C=O), 1590 (C=C); HRMS (ES^-): calcd for $C_{10}H_9O_3^-$ $(M-H)^-$: 177.0552; found: 177.0566.

*4.2.24. (Z)-2-Hydroxy-3-(2-methoxy-phenyl)-acrylic acid (**4d**).*[26] Prepared as described for **4a** using **3d** (5 g, 18 mmol) to give the title

compound **4d** (2.9 g, 83%) as an orange wax. δ_H (300 MHz, DMSO) 3.80 (s, 3H), 6.78 (s, 1H), 6.91–7.02 (m, 2ArH), 7.16–7.24 (m, 1ArH), 8.15 (d, 1ArH, *J* 7.0), 9.03 (br s, 1H).

*4.2.25. 3-(3-Methoxy-phenyl)-2-oxopropionic acid (**4e**).*[26] Prepared as described for **4a** using **3e** (5 g, 18 mmol) to give the title compound **4e** (2.8 g, 80%) as a white solid. Mp 151–152 °C. δ_H (300 MHz, $CDCl_3$) 3.79 (s, 3H), 4.18 (s, 2H), 6.77–6.87 (m, 3ArH), 7.21–7.30 (m, 1ArH).

*4.2.26. (Z)-2-Hydroxy-3-thiophen-2-yl-acrylic acid (**4f**).*[3] Prepared as described for **4a** using **3f** (5 g, 20 mmol) to give the title compound **4f** (1.6 g, 48%) as a yellow solid. Mp 165–166 °C. δ_H (300 MHz, DMSO) 6.74 (s, 1H), 6.98–7.06 (m, 1ArH), 7.22 (d, 1ArH, *J* 3.5), 7.50 (d, 1ArH, *J* 5.7), 9.24 (br s, 1H), 12.6 (br s, 1H).

*4.2.27. (Z)-2-Hydroxy-3-(naphthalen-1-yl)-acrylic acid (**4g**).* Prepared as described for **4a** using **3g** (5 g, 17 mmol) to give the title compound **4g** (3.5 g, 95%) as a yellow solid. Mp 149 °C (dec). δ_H (500 MHz, CD_3OD) 7.26 (s, 1H), 7.48 (t, 2ArH *J* 7.7), 7.53 (t, 1ArH, *J* 7.5), 7.77 (d, 1ArH, *J* 8.2), 7.86 (d, 1ArH, *J* 8.0), 8.15 (d, 1ArH, *J* 8.4), 8.32 (d, 1ArH, *J* 7.3); δ_C (126 MHz, CD_3OD) 105.3, 122.9, 125.9, 125.2, 125.8, 127.5, 127.6, 128.3, 130.5, 131.5, 133.8, 144.9, 166.9; HRMS (ES^-): calcd for $C_{13}H_9O_3^-$ $(M-H)^-$: 213.0552; found 213.0545.

*4.2.28. (Z)-2-Hydroxy-3-(naphthalen-2-yl)-acrylic acid (**4h**).* Prepared as described for **4a** using **3h** (5 g, 17 mmol) to give the title compound **4h** (3.4 g, 92%) as a yellow solid. Mp 155 (dec). δ_H (500 MHz, CD_3OD) 6.66 (s, 1H), 7.40–7.49 (m, 2ArH), 7.76–7.86 (m, 3ArH), 7.92 (d, 1ArH, *J* 8.6), 8.26 (s, 1ArH); δ_C (126 MHz, CD_3OD) 110.2, 125.7, 127.1, 127.2, 127.8, 128.5, 132.6, 132.7, 133.6, 141.3, 166.9; HRMS (ES^-): calcd for $C_{13}H_9O_3^-$ $(M-H)^-$: 213.0552; found 213.0546.

*4.2.29. (Z)-3-(2,3-Difluorophenyl)-2-hydroxyacrylic acid (**4i**).* Prepared as described for **4a** using **3i** (5 g, 18 mmol) to give the title compound **4i** (3.2 g, 91%) as a pale yellow solid. Mp 119–120 °C (dec). δ_H (500 MHz, DMSO) 6.48 (s, 1H), 7.12–7.31 (m, 2ArH), 7.98–8.04 (m, 1ArH), 9.88 (br s, 1H); δ_C (126 MHz, DMSO) 98.6, 116.0, 125.0, 125.4, 125.7, 144.9, 147.1, 150.0, 166.0; ν_{max} 3471 (OH), 1760 (C=O), 1734 (C=O), 1668 (C=C); HRMS (ES^-): calcd for $C_9H_5F_2O_3^-$ $(M-H)^-$: 199.0207; found: 199.0206.

*4.2.30. (Z)-3-(2,4-Difluorophenyl)-2-hydroxyacrylic acid (**4j**).* Prepared as described for **4a** using **3j** (5 g, 18 mmol) to give the title compound **4j** (3.2 g, 91%) as a pale brown solid. Mp 117–118 °C (dec). δ_H (500 MHz, DMSO) 6.45 (s, 1H), 7.08–7.27 (m, 2ArH), 8.21–8.29 (m, 1ArH), 9.67 (br s, 1H); δ_C (126 MHz, DMSO) 99.1, 104.1, 112.0, 119.7, 131.7, 143.6, 159.6, 161.4, 166.2; ν_{max} 3462 (OH), 1722 (C=O), 1698 (C=O), 1642 (C=C); HRMS (ES^-): calcd for $C_9H_5F_2O_3^-$ $(M-H)^-$: 199.0207; found: 199.0205.

*4.2.31. (Z)-3-(2,5-Difluorophenyl)-2-hydroxyacrylic acid (**4k**).* Prepared as described for **4a** using **3k** (5 g, 18 mmol) to give the title compound **4k** (3.1 g, 90%) as a pale yellow solid. Mp 116–117 °C (dec). δ_H (500 MHz, DMSO) 6.46 (s, 1H), 7.06–7.12 (m, 1ArH), 7.19–7.25 (m, 1ArH), 7.90–8.03 (m, 1ArH), 9.98 (br s, 1H); δ_C (126 MHz, DMSO) 98.9, 115.4, 116.2, 116.7, 124.5, 145.0, 155.7, 158.4, 165.9; ν_{max} 3456 (OH), 1702 (C=O), 1622 (C=O), 1591 (C=C); HRMS (ES^-): calcd for $C_9H_5F_2O_3^-$ $(M-H)^-$: 199.0207; found: 199.0198.

*4.2.32. 2-Oxo-4-phenylpentanoic acid (**4l**).* Prepared as described for **4a** using **3l** (5 g, 18 mmol) to give the title compound **4l** (3 g, 85%) as a pale wax. δ_H (300 MHz, $CDCl_3$) 1.34 (d, 3H, *J* 6.9), 3.18 (dd, 1H, *J* 6.9, 17.1), 3.33 (dd, 1H, *J* 6.9, 17.1), 3.36–3.42 (m, 1H), 7.18–7.40 (m, 5ArH); δ_C (101 MHz, $CDCl_3$) 22.1, 35.2, 45.3, 126.7, 128.7, 144.9, 159.2, 194.8; ν_{max} 3474 (OH), 1756 (C=O), 1634 (C=O); HRMS (ES^-): calcd for $C_{11}H_{11}O_3^-$ $(M-H)^-$: 191.0708; found 191.0703.

*4.2.33. 3-Cyclohexyl-2-oxo-propionic acid (**4m**).*[3] Prepared as described for **4a** using **3m** (5 g, 20 mmol) to give the title compound **4m** (3 g, 88%) as a pale wax. δ_H (300 MHz, $CDCl_3$) 0.88–1.31 (m, 5H), 1.66–1.72 (m, 5H), 1.93–2.01 (m, 1H), 2.80 (d, 2H, *J* 7.1).

*4.2.34. 2-Oxo-pentanoic acid (**4o**).*[26] Prepared as described for **4a** using **3o** (5 g, 25 mmol) to give the title compound **4o** (2.6 g, 89%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 0.99 (t, 3H, *J* 7.5), 1.68–1.75 (m, 2H), 2.94 (t, 2H, *J* 7.2).

*4.2.35. 4,4-Dimethyl-2-oxo-pentanoic acid (**4q**).*[26] Prepared as described for **4a** using **3q** (5 g, 22 mmol) to give the title compound **4q** (3.1 g, 96%) as a yellow solid. Mp 55–57 °C. δ_H (300 MHz, $CDCl_3$) 1.05 (s, 9H), 2.85 (s, 2H), 8.93 (br s, 1H), δ_C (126 MHz, DMSO) 29.6, 31.2, 50.2, 164.0, 197.1.

4.3. 4-Ethyl-2-hydroxy-cyclopenten-2-one (6)[29]

δ_H (300 MHz, DMSO) 0.85 (t, 3H, *J* 7.0), 1.52–1.82 (m, 2H), 4.86 (m, 1H), 6.24 (s, 1H), 10.26 (br s, 1H).

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