Electronic Supplementary Information: McNab, Morrow, Parsons, Shannon and Withell

Synthetic routes to pyrrolizine-1,5-dione derivatives by flash vacuum pyrolysis of amidomethylene derivatives of Meldrum's acid

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Supplementary Information

The following products were made using Method A, described in the main paper:

2,2-Dimethyl-5-[*N*-(2-oxopiperidin-1-yl)methylene]-1,3-dioxane-4,6-dione 14
(piperidin-2-one, 8 h), (59%), mp 143-144 °C (from hexane/toluene), (Found: C, 56.7; H, 6.05; N, 5.45. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 5.95; N, 5.55%); δ_H 9.00 (1H, s), 3.78 (2H, t, ^3J 5.8), 2.68 (2H, t, ^3J 6.7), 1.96-1.86 (4H, m) and 1.70 (6H, s); δ_C 170.52 (quat), 163.59 (quat), 159.07 (quat), 152.59, 103.80 (quat), 96.28 (quat), 51.87, 32.76, 26.86, 22.69 and 19.76; *m/z* 195 [$(M-C_3H_6O)^+$, 93%], 167 (43), 151 (26), 139 (71), 127 (34), 123 (47), 109 (31), 95 (71), 94 (60), 82 (32) and 67 (100).

2,2-Dimethyl-5-[*N*-(1-oxo-3,4-dihydroisoquinolin-2-yl)methylene]-1,3-dioxane-4,6-dione 15
[3,4-dihydroisoquinolin-1(2*H*)-one, 18 h], (64%), mp 186-187 °C (from toluene), (Found: C, 63.65; H, 5.05; N, 4.5. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.0; N, 4.65%); δ_H 9.24 (1H, s), 8.09 (1H, m), 7.59-7.25 (3H, m), 4.14 (2H, t, ^3J 6.0), 3.10 (2H, t, ^3J 6.0), and 1.75 (6H, s); δ_C 163.60 (quat), 163.25 (quat), 159.39 (quat), 153.41, 139.61 (quat), 134.33, 130.10, 127.73, 127.35, 126.41 (quat), 103.89 (quat), 95.88 (quat), 50.27, 27.94 and 27.09; *m/z* 243 [$(M-C_3H_6O)^+$, 100%], 214 (81), 199 (42), 198 (25), 171 (38), 170 (56), 132 (37) and 118 (30).

Reactions with 6-methylpiperidin-2-one and 6-phenylpiperidin-2-one under these sets of conditions failed to give any identifiable products other than unreacted starting material and 5-hydroxymethylene Meldrum's acid.

2,2-Dimethyl-5-(*N*-methyl-*N*-methylcarbamoylaminomethylene)-1,3-dioxane-4,6-dione 16
(*N,N′*-dimethylurea, 7 h), (48%), mp 158-159 °C (from toluene/ethyl acetate), (Found: C, 49.5; H, 5.85; N, 11.3. $C_{10}H_{14}N_2O_5$ requires C, 49.6; H, 5.85; N, 11.55%); δ_H 8.84 (1H, s), 6.65 (1H, br), 3.39 (3H, s), 2.92 (3H, d, ^3J 4.8) and 1.71 (6H, s); δ_C 164.63 (quat), 159.71 (quat), 155.65, 154.83 (quat), 103.85 (quat), 91.47 (quat), 38.20, 28.24 and 26.80; *m/z* 185 [$(M-C_3H_5O)^+$, 38%], 140 (10), 128 (31), 127 (33), 99 (38), 84 (25), 83 (100), 82 (31).

2,2-Dimethyl-5-(*N,N,N′*-trimethylcarbamoylaminomethylene)-1,3-dioxane-4,6-dione 17
(*N,N,N′*-trimethylurea,[1,2] 6 h), (10%), bp 70 °C (0.6 Torr), (Found: M^+, 256.1054. $C_{11}H_{16}N_2O_5$ requires *M*, 256.1059); δ_H 8.07 (1H, br), 3.38 (3H, s), 2.94 (6H, s) and 1.66 (6H, s); δ_C (measured at -60 °C due to the broadness of the room temperature spectrum) 164.82 (quat), 161.17 (quat), 156.85, 156.09 (quat), 103.99 (quat), 90.01 (quat), 44.16, 38.36, 36.23, 26.94 and 25.99; *m/z* 256 (M^+, 46%), 212 (38), 199 (41), 198 (66), 180 (20), 154 (38), 142 (27), 141 (30), 126 (56), 97 (43) and 72 (100).

2,2-Dimethyl-5-[*N*-(2-oxoimidazolidin-1-yl)methylene]-1,3-dioxane-4,6-dione 18
(imidazolidin-2-one, 7 h), (58%), mp 192-193 °C (dec.) (from ethanol/ acetonitrile), (Found: C, 49.75; H, 5.35; N, 11.4. $C_{10}H_{12}N_2O_5$ requires C, 50.0; H, 5.05; N, 11.65%); δ_H ([$^2H_6$]DMSO) 8.58 (1H, br), 8.47 (1H, s), 4.12 (2H, t, ^3J 7.5), 3.45 (2H, t, ^3J 7.5) and

1.66 (6H, s); δ_C ([$^2H_6$]DMSO) 164.45 (quat), 159.49 (quat), 155.27 (quat), 148.78, 103.62 (quat), 89.87 (quat), 45.68, 37.26 and 26.48; *m/z* 240 (M^+, 8%), 183 (29), 182 (100), 139 (37), 138 (23), 110 (53), 82 (29), 70 (22) and 67 (34).

The following products were made using Method B, described in the main paper:

Methyl 3-[*N*-(2-oxopiperidin-1-yl)]prop-2-enoate 23[3]
(piperidin-2-one, 54 h, chromatography), (50%), mp 91-93 °C (from hexane/toluene), (Found: C, 58.7; H, 7.4; N, 7.35. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.65%); δ_H 8.55 (1H, d, ^3J 14.5), 5.21 (1H, d, ^3J 14.5), 3.67 (3H, s), 3.38 (2H, t, ^3J 6.3), 2.50 (2H, t, ^3J 6.3) and 1.94-1.76 (4H, m); δ_C 169.12 (quat), 167.64 (quat), 140.68, 99.18, 52.12, 45.39, 32.90, 22.09 and 19.98; *m/z* 183 (M^+, 4%), 152 (16), 124 (100), 96 (11), 95 (11), 82 (23) and 55 (12).

Methyl 3-[*N*-(3,4-dihydro-1-oxoisoquinolin-2-yl)]prop-2-enoate 24
(3,4-dihydroisoquinolin-1(2*H*)-one, 120 h, chromatography), (26%), mp 140-141 °C (from hexane/toluene), (Found: C, 67.8; H, 6.05; N, 6.0. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%); δ_H 8.66 (1H, d, ^3J 14.5), 8.05 (1H, m), 7.45 (1H, m), 7.32 (1H, m), 7.20 (1H, m), 5.36 (1H, d, ^3J 14.5), 3.70 (3H, s), 3.73 (2H, t, ^3J 6.6) and 3.06 (2H, t, ^3J 6.6); δ_C 167.71 (quat), 162.50 (quat), 140.82, 138.05 (quat), 132.93, 129.08, 127.66 (quat), 127.25, 127.00, 99.35, 51.16, 42.88 and 26.78; *m/z* 231 (M^+, 14%), 200 (46), 173 (37), 172 (100), 130 (13), 118 (12), 91 (11), 90 (22) and 89 (13).

Methyl 3-(*N*-methyl-*N*-carbamoylamino)prop-2-enoate 25 (*N,N′*-dimethylurea, 96 h, recrystallisation), (48%), mp 114-115 °C (from hexane/ethyl acetate), (Found: C, 48.6; H, 7.1; N, 16.4. $C_7H_{12}N_2O_3$ requires C, 48.85; H, 7.05; N, 16.25%); δ_H 8.21 (1H, d, ^3J 13.7), 5.85 (1H, br), 5.06 (1H, d, ^3J 13.7), 3.68 (3H, s), 3.06 (3H, s) and 2.85 (3H, d, ^3J 4.4); δ_C 168.52 (quat), 155.44 (quat), 143.21, 95.17, 51.10, 31.11 and 27.80; *m/z* 172 (M^+, 3%), 141 (9), 115 (62), 84 (100), 83 (19), 82 (15) and 58 (27).

Methyl 3-(*N*-dimethylcarbamoyl-*N*-methylamino)prop-2-enoate 26 (*N,N,N′*-trimethylurea,[1,2] 16 h, chromatography), (8%), bp 65 °C (0.2 Torr), (Found: M^+, 186.1009. $C_8H_{14}N_2O_3$ requires *M*, 186.1004); δ_H 7.72 (1H, d, ^3J 13.6), 4.99 (1H, d, ^3J 13.6), 3.65 (3H, s), 2.96 (3H, s) and 2.87 (6H, s); δ_C 168.29 (quat), 160.52 (quat), 146.36, 94.13, 51.04, 38.53, 36.22 and 33.44; *m/z* 186 (M^+, 52%), 155 (46), 132 (27), 127 (50), 113 (54), 112 (51), 102 (43), 86 (74), 84 (87), 82 (40) and 72 (100).

Methyl 3-[*N*-(2-oxoimidazolidin-1-yl)]prop-2-enoate 27
(imidazolidin-2-one, 192 h, recrystallisation), (58%), mp 147-148 °C (from hexane/ethyl acetate), (Found: C, 49.45; H, 6.0; N, 16.75. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.45%); δ_H 8.01 (1H, d, ^3J 14.3), 6.5 (1H, br), 4.94 (1H, d, ^3J 14.3), 3.68 (3H, s) and 3.66-3.60 (4H, m); δ_C 167.85 (quat), 157.35 (quat), 138.86, 95.45, 51.04, 41.79 and 37.32; *m/z* 170 (M^+, 49%), 139 (81), 138 (100), 111 (27), 96 (24), 95 (66), 82 (88), 70 (28), 69 (25) and 68 (43).

FVP Reactions
General conditions are described in the main paper.

FVP of 2,2-dimethyl-5-(*N*-formyl-*N*-methylaminomethylene)-1,3-dioxane-4,6-dione 8
[0.19 g (0.89 mmol), T_f 600 °C, T_i 180 °C, P 0.01 Torr, t 15 min] Examination of the pyrolysate by ^{1}H NMR spectroscopy showed no identifiable products. Repeat pyrolyses at higher and lower furnace temperatures (500-800 °C) gave the same result.

FVP of 2,2-Dimethyl-5-[*N*-(1-oxo-3,4-dihydroisoquinolinyl)methylene]-1,3-dioxane-4,6-dione 15
Initial small scale pyrolyses carried out over a range of furnace temperatures (500-750 °C) showed little consistency when pyrolysates were examined by ^{1}H NMR spectroscopy. The most promising temperature was therefore selected and the pyrolysis scaled-up [2.72 g (9.0 mmol), T_f 700 °C, T_i 210 °C, P 0.02 Torr, t 120 min]. Dry flash chromatography of the soluble portion of the pyrolysate (using *n*-hexane and ethyl acetate as eluents) gave one identifiable product which was assigned as 2-ethenylsoquinolin-1(2*H*)-one[4] **A** (see discussion below), (0.031 g, 2%), bp 80-85 °C (0.5 Torr); δ_H (360 MHz) 8.41 (1H, m), 7.70 (1H, dd, ^3J 9.2 and 16.1), 7.62 (1H, m), 7.46 (2H, m), 7.33 (1H, d, ^3J 7.6), 6.52 (1H, d, ^3J 7.6), 5.20 (1H, dd, ^2J 1.7 and ^3J 16.1) and 4.97 (1H, dd, ^2J 1.7, ^3J 9.2); δ_C (90 MHz) 160.67 (quat), 136.31 (quat), 132.64, 131.67, 128.23, 127.19, 126.10 (quat), 125.99, 125.90, 107.11 and 101.19 (consistent with literature data[4]) *m/z* 171 (M^+, 74%), 170 (91), 169 (52), 147 (37), 146 (38), 145 (51), 130 (36), 129 (32), 128 (47), 119 (47), 118 (57), 117 (49), 116 (51), 115 (54), 102 (41) and 86 (100).

FVP of 2,2-dimethyl-5-(*N*-methyl-*N*-methylcarbamoylaminomethylene)-1,3-dioxane-4,6-dione 16
[0.30 g (1.2 mmol), T_f 700 °C, T_i 190 °C, P 0.02 Torr, t 55 min] The pyrolysate was removed from the trap with acetone from which a dark brown solid slowly precipitated. This was collected by filtration and shown to be *N,N′*-dimethyluracil **B** (see discussion below) (0.02 g, 11%), mp 122-123 °C (from ethanol) (lit.,[5] 123-124 °C); δ_H ([$^2H_6$]DMSO) 7.72 (1H, d, ^3J 7.9), 5.72 (1H, d, ^3J 7.9), 3.35 (3H, s) and 3.21 (3H, s).

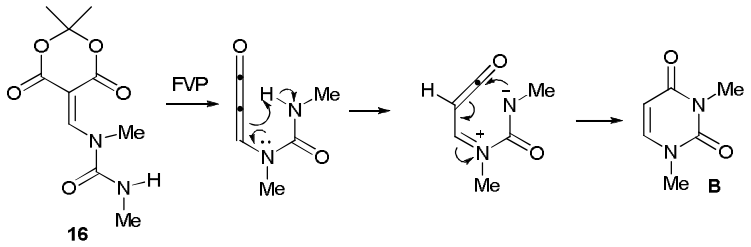
FVP of 2,2-Dimethyl-5-(*N*-methyl-*N*-dimethylcarbamoylaminomethylene)-1,3-dioxane-4,6-dione 17
[0.10 g (0.39 mmol), T_f 700 °C, T_i 150 °C, P 0.01 Torr, t 28 min] The pyrolysis produced mainly insoluble brown polymer.

FVP of 2,2-Dimethyl-5-[*N*-(2-oxoimidazolidinyl)methylene]-1,3-dioxane-4,6-dione 18
Pyrolysis of this compound [0.1 g (0.42 mmol), T_f 700 °C, T_i 240 °C, P 0.02 Torr, t 27 min] proved difficult due to its poor volatility. On a 0.1 g scale, a 40% residue remained in the inlet tube, and mainly insoluble polymeric material in the trap. Examination of the minor soluble portion of the pyrolysate by ^{1}H NMR spectroscopy showed it to be 1-ethenyl-1,3-dihydroimidazol-2(2*H*)-one[6,7] **C** see discussion below), (4%), bp 100 °C (0.3 Torr), (Found: M^+, 110.0482. $C_5H_6N_2O$ requires *M*, 110.0480); δ_H 6.90 (1H, dd, ^3J 16.1 and 9.2), 6.48 (1H, m), 6.33 (1H, m), 4.89 (1H, dd, ^3J 16.1 and ^2J 1.1) and 4.65 (1H, dd,

^3J 9.2 and ^2J 1.1); δ_C ([$^2H_6$]DMSO) 164.32 (quat), 127.33, 110.56, 107.15 and 95.62; *m/z* 110 (M^+, 83%), 86 (93), 85 (16), 81 (60), 73 (16), 68 (34) and 54 (100)**.**

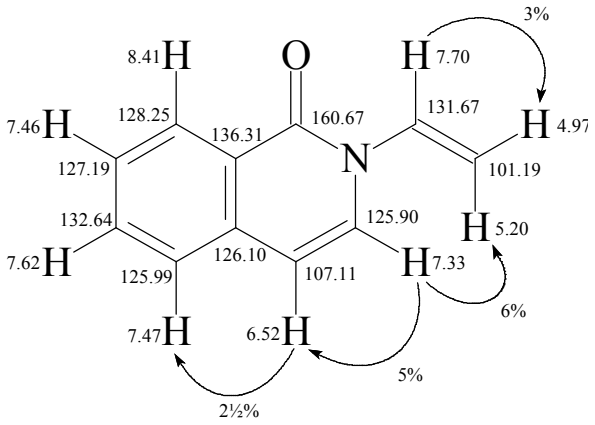
Formation of 1,3-dimethyluracil B from 16

Rather than undergo a 1,4-hydrogen shift from the methyl group attached to the aminomethylene position (*c.f.* Scheme 1 of the main paper), the methyleneketene derived from **16** appears to undergo an inefficient hydrogen transfer from the free NH to provide a dipolar species which collapses to 1,3-dimethyluracil **B** (11%).

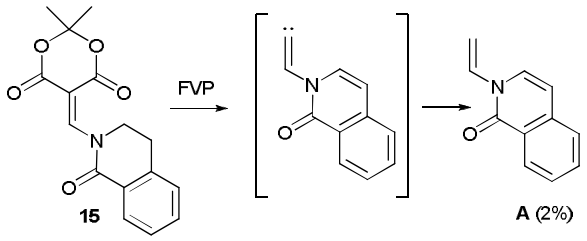


Identification of products from FVP of 15 and 18

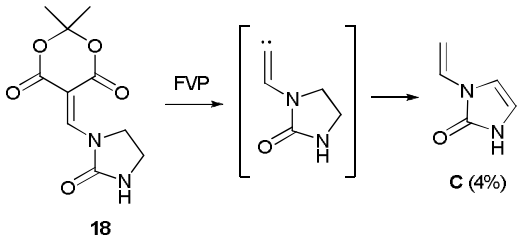
The isoquinoline derivative, **15** was subjected to FVP over a range of temperatures (500-800 °C) but gave highly complex mixtures of products; the temperature giving the least complex mixture (700 °C) was pyrolysed on a larger scale and the products were subjected to dry flash chromatography. Only one product was isolated from the column (2%). The ^{13}C NMR spectrum indicated the compound contained 11 carbon atoms, comprised of 3 quaternary carbon atoms, 7 CH carbon atoms and 1 CH_2 carbon atom. The ^1H NMR spectrum showed doublets of doublets at 4.97, 5.20 and 7.70 p.p.m. corresponding to an ethenyl group, with coupling constants of 1.7, 9.2 and 16.1 Hz. Mass spectrometry indicated a molecular ion of *m/z* 171 ($C_{11}H_9NO$), and the breakdown pattern confirmed the presence of the ethenyl group with a peak at $(M-27)^+$. Combining all the information led to the assignment of the structure as **A**; the complete NMR assignments for the proton and carbon atoms (which were confirmed by an HSQC experiment); and significant NOE enhancements are shown below.



Compound **A** may be formed by vicinal hydrogen atom abstraction[8] from a methylenecarbene intermediate:



An identical type of reaction was observed when the Meldrum's acid derivative **18** was pyrolysed:



The *N*-ethenylimidazolidinone **C** was isolated from the pyrolysis, but in a yield of only 4%.

Table 1. Crystallographic experimental data[9]

	10	**12**	**19**	**32**	**34**
CSD REFCODE	**OCAVAQ**	**OCARUG**	**OCAVEU**	**OCASOB**	**OCAREQ**
Crystal data					
Chemical formula	$C_{12}H_{15}NO_5$	$C_{21}H_{17}NO_5$	$C_8H_{11}NO_3$	$C_8H_9NO_2$	$C_{17}H_{11}NO_2$
M_r	253.25	363.36	169.18	151.16	261.27
Cell setting, space group	Monoclinic, *P*2(1)/*c*	Monoclinic, *P*2(1)/*c*	Monoclinic, *P*2(1)/*n*	Monoclinic, *P*2(1)/*n*	Monoclinic, $P2_1/c$
Temperature (K)	150 (2)	220 (2)	293 (2)	293 (2)	220 (2)
a, *b*, *c* (Å)	7.5098 (10), 17.549 (2), 9.2149 (10)	17.452 (2), 6.9642 (10), 16.402 (2)	7.8763 (8), 11.8734 (9), 9.4875 (7)	9.8974 (8), 7.1505 (5), 11.2656 (8)	12.370 (3), 8.3166 (14), 12.570 (2)
β (°)	100.521 (7)	116.631 (9)	106.367 (6)	111.738 (6)	104.60 (2)
V (Å^3)	1194.0 (2)	1782.0 (4)	851.30 (12)	740.58 (10)	1251.4 (4)
Z	4	4	4	4	4
D_x (Mg m^{-3})	1.409	1.354	1.320	1.356	1.387
Radiation type	Cu *K*α	Cu *K*α	Cu *K*α	Cu *K*α	Mo *K*α
μ (mm^{-1})	0.93	0.81	0.85	0.81	0.09
Crystal form, colour	Lath, colourless	Block, colourless	Block, colourless	Irregular block, colourless	Block, colourless
Crystal size (mm)	0.47 × 0.23 × 0.16	0.47 × 0.39 × 0.31	0.23 × 0.12 × 0.08	0.39 × 0.31 × 0.27	0.35 × 0.23 × 0.12
Data collection					
Diffractometer	Stoe Stadi-4 diffractometer with Oxford Cryosystems variable temperature device.	Stoe Stadi-4 diffractometer with Oxford Cryosystems variable temperature device.	Stoe Stadi-4 diffractometer with Oxford Cryosystems variable temperature device.	Stoe Stadi-4 diffractometer with Oxford Cryosystems variable temperature device.	Stoe Stadi-4 diffractometer with Oxford Cryosystems variable temperature device.
Data collection method	ω–θ	ω with learnt profile	ω–2θ	ω–2θ	ω–θ
No. of measured, independent and observed reflections	2057, 1751, 1540	4131, 2599, 2437	1271, 1240, 721	1572, 1084, 995	3102, 2197, 1194
Criterion for	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$

observed reflections					
R_{int}	0.008	0.018	0.042	0.045	0.036
θ_{max} (°)	60.0	59.9	60.1	60.0	25.0
No. and frequency of standard reflections	3 every 120 min				
Intensity decay (%)	0	15	0	0	0
Refinement					
Refinement on	F^2	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.032, 0.083, 1.04	0.033, 0.094, 1.09	0.051, 0.131, 1.02	0.039, 0.113, 1.03	0.053, 0.110, 0.96
No. of relections	1750 reflections	2594 reflections	1238 reflections	1081 reflections	2195 reflections
No. of parameters	167	245	111	101	182
H-atom treatment	calc	calc	calc	calc	calc
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0417P)^2 + 0.4363P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.040P)^2 + 0.7272P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0555P)^2 + 0.1931P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0611P)^2 + 0.2137P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0416P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.18, –0.16	0.19, –0.18	0.18, –0.15	0.20, –0.14	0.25, –0.19
Extinction method	SHELXL	SHELXL	SHELXL	SHELXL	SHELXL
Extinction coefficient	0.0031 (4)	0.0054 (3)	0.0113 (13)	0.0296 (26)	0.0127 (16)

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9. Crystallographic Computer programs: *Stoe DIF4*; *Stoe REDU4*; *SHELXS-86* (Sheldrick, 1990); *SHELXTL*; *SHELXL-93* (Sheldrick, 1993).