

Application of Flow Thermolysis in Organic Synthesis: Easy Access to α,ω -Bis Thienyl- and Bis Pyrrolyl- Alkanes from Methylene Derivatives of Meldrum's Acid

Jean Claude Pommelet ^{1,*}, Fanck Jourdain¹ and Hamid Dhimane²

¹ Laboratoire de Chimie Moléculaire et Thioorganique, UMR 6507, ISMRA, Université de Caen, 6 Bd Maréchal Juin, 14050 Caen, France. Tel (33) 2 31 45 28 53, Fax (33) 2 31 45 28 77

² Laboratoire de Chimie des Hétérocycles, UMR 7611, Université Pierre et Marie Curie, 4 Place Jussieu, 75252 Paris 05, France

* Author to whom correspondence should be addressed; E-mail: pommelet@ismra.fr

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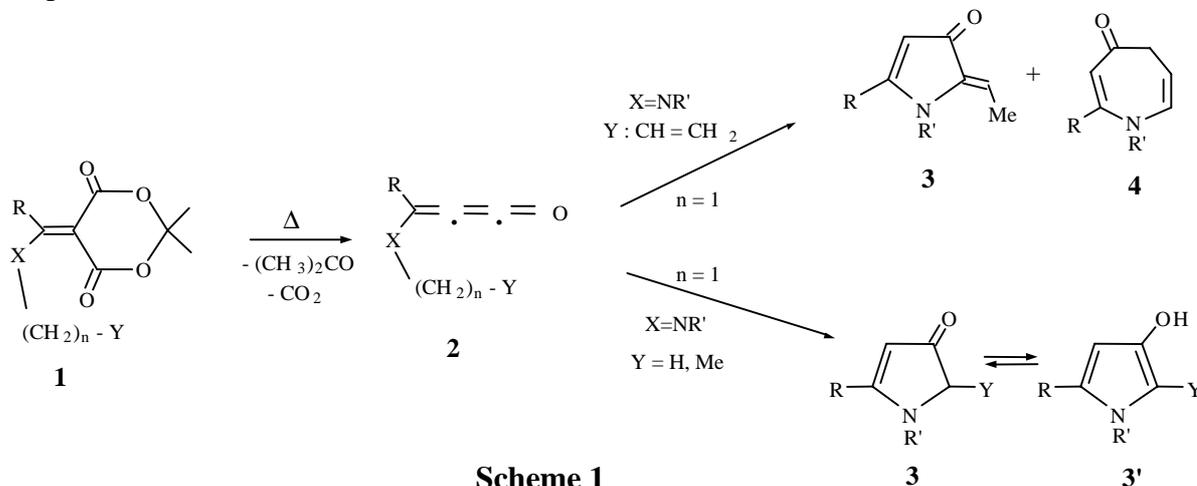
Abstract: Thermal decomposition of Meldrum's acid derivatives and rearrangement of (alkylsulfanyl) or (propargylamino)methylene ketene intermediates leads in one step to bis thienyl- or bis pyrrolyl-alkanes.

Keywords: Thermolysis, organic synthesis, Meldrum's acid, thiophenes, pyrroles

Introduction

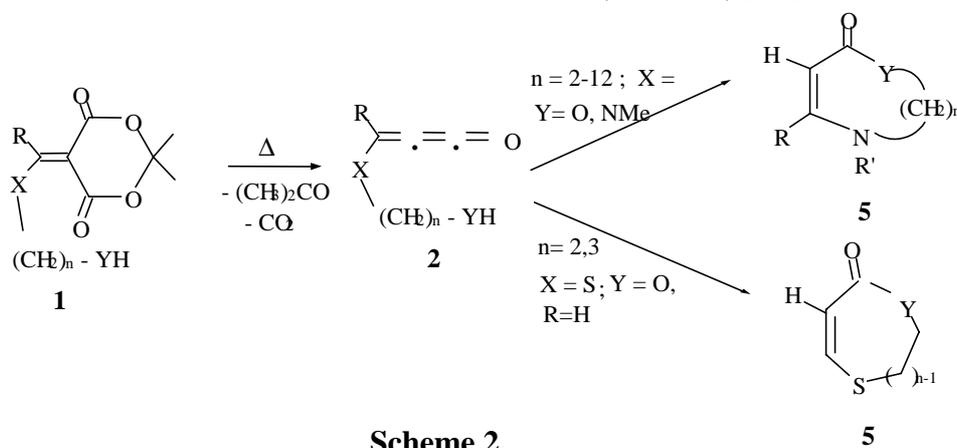
The highly reactive hetero-substituted methyleneketene intermediates **2** can be easily generated by thermolysis of the corresponding Meldrum's acid derivatives **1** [1-4] and can undergo various thermal reactions depending on the nature of both the heteroatom X and the chain $(\text{CH}_2)_n\text{Y}$. Alkoxy-methyleneketenes **2** (X=O; Y=H; R=H,CH₃) are reasonably stable in solution at room temperature, and seem to be the most stable ones [3].

A 1,4-hydrogen shift takes place during the thermolysis of methyleneketenes **2** bearing a tertiary alkylamino or allylamino substituent ($X=NR'$; $Y=H, Me, CH=CH_2$) [5,6] and the cyclisation of the ketenic ylides thus formed yields 1H-pyrrol-3(2H)-ones **3** ($X=NR'$), possibly accompanied by dihydroazepinones **4** (Scheme 1).



Scheme 1

On the other hand, an intramolecular addition to the central double bond of the aminomethyleneketenes **2** ($X=NR'$) can also be observed when a nucleophilic group ($Y=O, NMe$) is present at the ω -position of the side chain (Scheme 2). This cyclisation, which is performed under reduced pressures, constitutes an efficient access to the macrolactones and macrolactams **5** ($n=2-12$) [7,8].

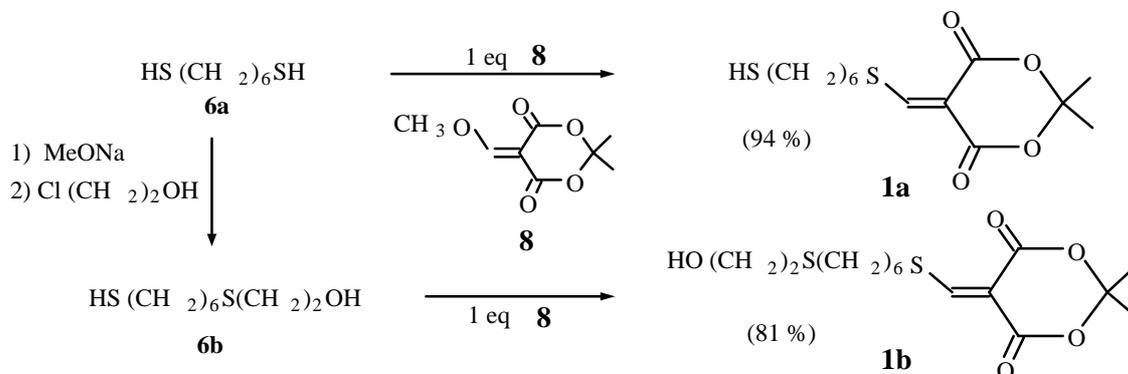


Scheme 2

We have also observed such an intramolecular nucleophilic addition with alkylsulfanyl methyleneketenes **2** ($X=S$) bearing on the sulfur atom an ω -hydroxy or ω -mercaptoethyl- or propyl substituent ($Y=O, S$; $n=2,3$) [9]. In order to extend this methodology to the synthesis of large sized sulfur heterocycles ($n>3$), we decided to examine the thermal behaviour of Meldrum's acid derivatives **1a** ($X=S$; $n=6$; $Y=S$) and **1b** ($X=S$; $n=6$; $Y=S(CH_2)_2O$).

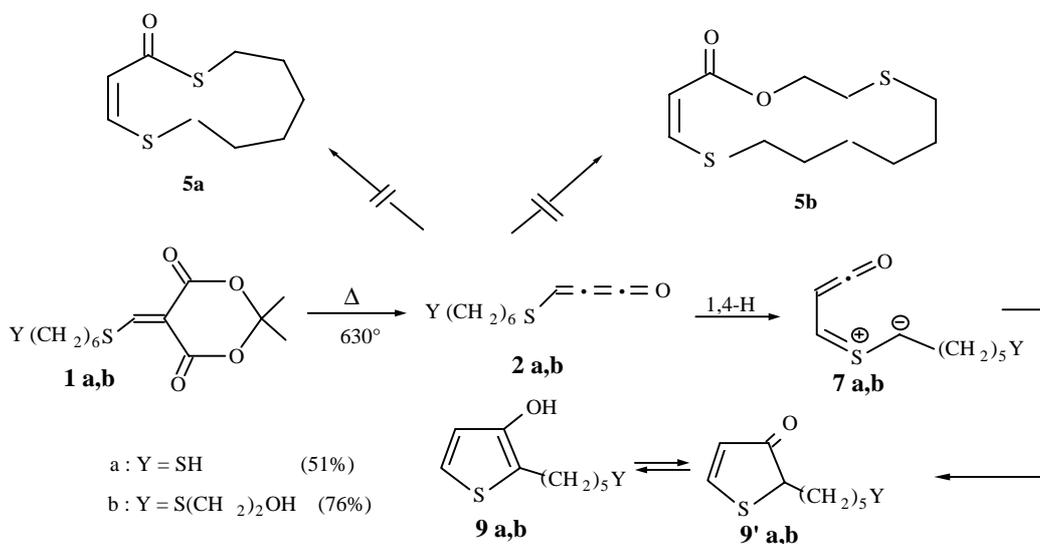
Results and discussion

The derivatives **1a,b** were easily prepared from the methoxymethylene Meldrum's acid derivative **8** and 1,6-hexanedithiol **6a** or 9-mercapto-3-thianonanol **6b** (Scheme 3).



Scheme 3

The thermolysis of **1a** at 630°C (5×10^{-2} Torr) did not give the expected thiolactone **5a**; instead a mixture of 3-hydroxythiophene **9a** and its tautomer **9'a** (Scheme 4) was isolated after flash chromatography on silica gel ($9a/9'a = 9/1$, 51% yield).

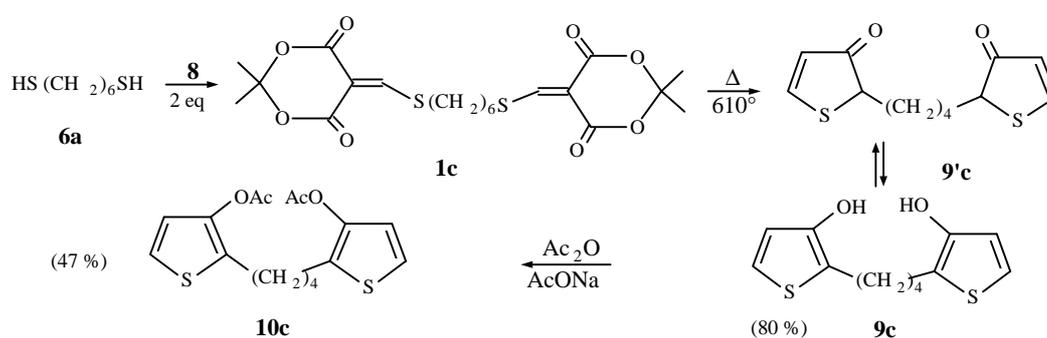


Scheme 4

The thermolysis of **1b**, under the same conditions, gave a similar result: the lactone **5b** was never detected and a mixture of thiophenes **9b** and **9'b** (Scheme 4) was obtained in 76% yield ($9b/9'b = 9/1$). Thus, whereas the ω -aminoalkyl or hydroxyalkyl aminomethyleneketenes ($\text{X} = \text{NR}'$; $\text{Y} = \text{NMe}, \text{O}$; $n = 2-12$) essentially led to enamino-lactams or lactones **5** [7,8] the alkylsulfanyl methyleneketenes **2** bearing a large functionalised hydrocarbon chain ($\text{X} = \text{S}$; $n > 3$) only provided hydroxythiophenes **9**. The absence of large sized lactones or thiolactones **5a,b** well illustrates the specific thermal behaviour of

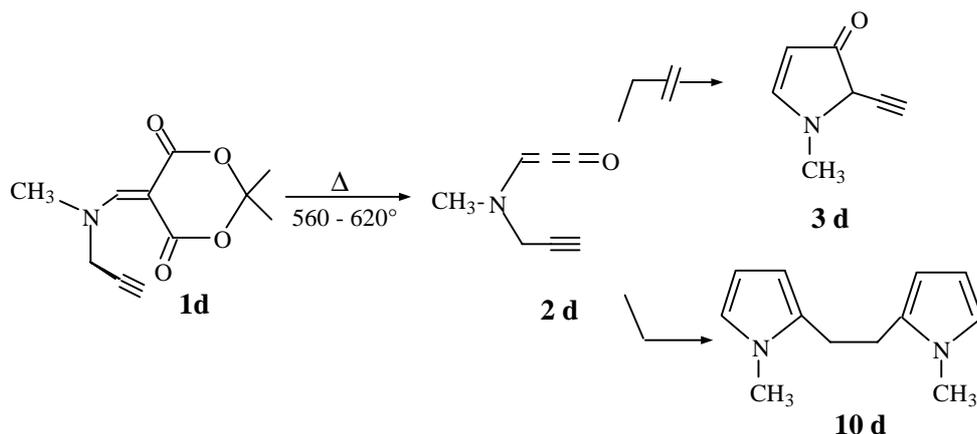
these alkylsulfanyl methyleneketenes **2a,b**: the 1,4-hydrogen migration involving the rearrangement of **2a,b** into planar dipolar species **7a,b** [3,10] seems to be favored in that case; on the contrary, the intramolecular addition was favored in the case of alkylsulfanyl intermediates **2** with smaller ω -mercapto or ω -hydroxyalkyl chains ($n=1-2$) [9].

The symmetrically substituted hexane **1c** was prepared by treatment of 1,6-hexanedithiol **6a** with two equivalents of enol ether **8** (Scheme 5). The derivative **1c** exhibited similar thermal behaviour and afforded at 610°C the 1,4-bis(2'-(3'-hydroxythienyl)) butane **9c**, in equilibrium with its tautomeric keto form **9'c** (80% yield). These compounds reacted with an excess of acetic anhydride to give exclusively the 1,4-bis(2'-(3'-O-acetylated thienyl)) butane **10c** (47%). This method constitutes an easy access to the α - ω bis thienyl alkanes.



Scheme 5

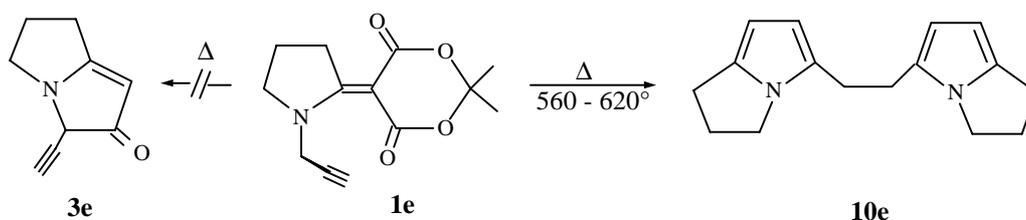
In order to compare the thermal behaviour of N-propargylamino methyleneketenes to that of N-allylamino methyleneketenes giving five and seven membered cyclic enaminones **3** and **4** (Scheme 1; X = NR'; n = 1; Y: CH=CH₂) [5], we have also examined the thermal decomposition of Meldrum's acid derivatives **1d,e** (X = NR'; n=1; Y = C≡CH). N-propargyl aminomethylene Meldrum's acid derivative **1d** was prepared from N-methylpropargylamine and enol ether **8** (70% yield). Flash-vacuum pyrolysis of **1d** was investigated in the temperature range 560-620°C ($p=10^{-5}$ Torr, pyrolysis products trapped in methanol matrix at -196°C). An unexpected thermal rearrangement was observed during the pyrolysis of **1d**: the aza-analogue of hydroxythiophene (2-ethynyl-3-hydroxypyrrole **3d**) was never observed, but the unexpected 1,2-bis(2'-(N-methylpyrrolyl)) ethane **10d** (Scheme 6) was the only product isolated from methanol matrix (42% after purification by liquid chromatography).



Scheme 6

The $^1\text{H-NMR}$ spectrum (two doublets at 6.06 and 6.18 ppm, and only one signal at 6.65 ppm for aromatic protons), supported this structure and confirmed the link at the C_2 position of the two pyrrole moieties. In mass spectroscopy, the molecular ion M^+ (188) was recorded in presence of the base peak at m/e 94 which indicates the symmetrical structure of **10d**. $^{13}\text{C-NMR}$ data also confirmed this structural assignment (cf. Experimental Section: quaternary carbon at 132.8 ppm).

This methodology was extended to the preparation of bis pyrrolizinyloethane (Scheme 7). The derivative **1e**, easily obtained from N-propargylpyrrolidin-2-one [11], was submitted to thermolysis ($T = 560\text{--}620^\circ\text{C}$; $p = 10^{-5}$ Torr) and afforded also the 1,2-bis(2,3-dihydro-1H-pyrrolizinyl)ethane **10e** (34 %: significant formation of tar on the inner side of apparatus).



Scheme 7

In the $^1\text{H-NMR}$ spectrum only two aromatic protons were detected at 5.77 and 6.0 ppm for **10e**, that indirectly corroborated the structure of **10d** which in addition exhibited an aromatic proton at 6.65 ppm. Both of these results indicated that a new thermal rearrangement had taken place during the thermolysis of these N-propargylamino methyleneketenes. *A priori*, the derivatives **1d,e** were expected to behave like the N-allyl analogues which after thermal decomposition lead to the enaminones **3** and **4** (Scheme 1) [5]. In reality, the corresponding ethynylaminone **3d,e** was never detected in the crude product. The bis-pyrrolyl ethanes **10d,e** were necessarily formed by dimerisation of two molecules of

the aminomethyleneketenes **2d,e** and were formally obtained after elimination of two molecules of carbon monoxide and addition of two hydrogen atoms .

Conclusions

In summary, alkylsulfanylmethyleneketenes **2a,b** bearing a large ω -hydroxy or mercaptoalkyl chain did not give access to lactone or thiolactone **5a,b** but rather yielded the 3-hydroxythiophenes **9a,b**. This reaction was extended to the synthesis of 1,4- bis-thienylbutane **9c**. The N-propargylamino methyleneketenes **1d,e** did not react like N-allyl analogues to yield enamines **3** or **4** but the formation of 1,2-bis-pyrrolylethanes **10d,e** was observed. Therefore the thermal decomposition of derivatives **1c-e** provides a simple and new route for synthesis of α,ω -heterocyclic substituted alkanes and further investigations are planned to extend these reactions.

Experimental Section

General

NMR spectra (CDCl_3 solutions) were recorded on a Bruker 250 instrument operating at 250 and 62.5 MHz or a Bruker 80 instrument operating at 80 and 15.08 MHz respectively for ^1H and ^{13}C -NMR spectra. Mass spectra were performed on a Nermag Riber R10 spectrometer operating at $IE=70\text{eV}$. IR spectra (reported in cm^{-1}) were recorded on Perkin Elmer 16PC FT-IR or Philips SP 2000 instruments.

Synthesis of Meldrum's acids **1a-e**

6-Mercapto hexylsulfanyl methylene Meldrum's acid (**1a**)

Enol ether **8** [3] (0.62 g, 33×10^{-4} mol) and 1,6 hexanedithiol (0.5 g, 33×10^{-4} mol) in acetonitrile (50mL) were placed in a two necked flask equipped with a reflux condenser. The solution was refluxed for 12-15 h and the solvent was then evaporated under vacuum. The crude product was purified by chromatography on silica gel (elution with 1:1 CH_2Cl_2 /petroleum ether) to give 0.95 g (31×10^{-4} mol, 94%) of a white solid. $\text{Mp} = 160^\circ\text{C}$. $^1\text{H-NMR}$: $\delta = 1.25$ -1.50 (m, 5H); 1.55 (m, 2H); 1.65 (s, 6H); 1.75 (m, 2H); 2.45 (m, 2H); 2.95 (t, 2H, $J = 7.1\text{Hz}$); 8.95 (s, 1H). MS m/z (%): 304 (M^+ , 3), 247 (8), 246 (31), 203 (16), 202 (4), 150 (31), 148 (27), 126 (34), 117 (12), 116 (40), 87 (91), 69 (37), 67 (59), 60 (48), 57 (59), 55 (94), 443 (100). IR (KBr): 1716($\nu_{\text{C=O}}$), 1520($\nu_{\text{C=C}}$).

9-Hydroxy-7-thianonylsulfanyl methylene Meldrum's acid (**1b**)

1b was prepared by a similar procedure from enol ether **8** (0.48 g, 26.10^{-4} mol) and 9-mercapto-2-thianonanol (0.5 g, 26×10^{-4} mol). The purification was performed by chromatography with acetone/methanol: (10:1); 0.73 g of **1b** was obtained (81%). $^1\text{H-NMR}$: δ = 1.39 (m, 4H); 1.55 (m, 2H); 1.67 (s, 6H); 1.72 (m, 2H); 2.2 (s, 1H); 2.47 (t, 2H, $J = 7.3\text{Hz}$); 2.65 (m, 2H); 2.95 (t, 2H, $J = 7.3\text{Hz}$); 3.66 (t, 2H, $J = 6.0\text{Hz}$); 8.94 (s, 1H). MS m/z (%): 348 (M^+ , 2), 246 (3), 161 (40), 86 (100), 84 (49), 61 (85), 55 (76), 43 (95), 41 (63). IR (KBr): 1712 ($\nu_{\text{C=O}}$), 1520 ($\nu_{\text{C=C}}$).

Hexamethylenedithio-bis-methylene Meldrum's acid (**1c**)

1c was prepared by a similar procedure from enol ether **8** (2.48 g, 132×10^{-4} mol) and hexanedithiol (1 g, 66×10^{-4} mol). Purification was performed by chromatography using chloroform/acetone (2:1); 2.65 g of **1c** was obtained (87%). Mp = 162°C . $^1\text{H-NMR}$: δ = 1.5 (m, 4H); 1.73 (s, 12H); 1.8 (m, 4H); 3.02 (t, 4H, $J = 7.3\text{Hz}$); 8.98 (s, 2H). MS m/z (%): 458 (M^+ , 2), 400 (5), 296 (22), 246 (49), 241 (29), 165 (20), 139 (36), 1321 (19), 43 (100). IR (KBr): 1716 ($\nu_{\text{C=O}}$), 1518 ($\nu_{\text{C=C}}$).

N-Methylpropargylaminomethylene Meldrum's acid (**1d**)

1d was prepared by a similar procedure from enol ether **8** (6.7 g, 36×10^{-3} mol) and N-methylpropargylamine (2.5 g, 36×10^{-3} mol). Recrystallisation of the crude mixture from ethanol gave 5.6 g (25×10^{-3} mol, 70%) of **1d**. Mp = 123°C . $^1\text{H-NMR}$ showed two isomers: δ = 1.72 (s, 6H); 2.43 (t, 1H, $J = 3.0\text{Hz}$); 3.52 (s, 3H); 4.77 (d, 2H, $J = 3.0\text{Hz}$); 8.10 (s, 1H); and 1.73 (s, 6H); 2.65 (t, 1H, $J = 3.0\text{Hz}$); 3.42 (s, 3H); 4.31 (d, 2H, $J = 3.0\text{Hz}$), 8.32 (s, 1H). MS m/z (%): 223 (M^+ , 5), 208 (17), 166 (50), 165 (19), 122 (100), 121 (33), 93 (30), 82 (53), 68 (10), 67 (17), 66 (35), 65 (18). IR (CHCl_3): 3280 ($\nu_{\text{H-C}}$), 2100 ($\nu_{\text{C+C}}$), 1680 ($\nu_{\text{C=O}}$), 1590 ($\nu_{\text{C=C}}$).

1-(Propargyl)-2-pyrrolidinylmethylene Meldrum's acid (**1e**)

1e was prepared from N-propargylpyrrolidin-2-one following the procedure previously reported [6,11] $^1\text{H-NMR}$: δ = 1.76 (s, 6H); 2.15 (qt, 2H, $J = 8.0\text{Hz}$); 2.42 (t, 1H, $J = 3.0\text{Hz}$); 3.53 (t, 2H, $J = 8.0\text{Hz}$); 3.97 (t, 2H, $J = 8.0\text{Hz}$); 4.45 (d, 2H, $J = 3.0\text{Hz}$). MS m/z (%): 249 (M^+ , 1), 234 (12), 192 (20), 149(10), 148(95), 147(9), 119(38), 86(100). IR (CHCl_3): 3300 ($\nu_{\text{H-C}\equiv}$), 2130 ($\nu_{\text{C}\equiv\text{C}}$), 1710 ($\nu_{\text{C=O}}$), 1550 ($\nu_{\text{C=C}}$).

Thermolysis of Meldrum's acids **1a-c**

Thermolysis of derivatives **1a,c** were carried out under flow conditions. Solutions of **1** were vaporised at the top of an electrical heated quartz column filled with quartz beads. The temperature was held

constant during the thermolysis; the pressure was maintained at 5×10^{-2} Torr. Products were condensed at -196°C and analysed after purification.

Thermolysis of 1a: $T=630^\circ\text{C}$; **9a** and **9'a** were purified by chromatography on silica gel with CH_2Cl_2 /acetone (66/34). Yield: 68 mg (3.36×10^{-4} mol, 51%) from 200 mg (6.58×10^{-4} mol) of **1a**. $^1\text{H-NMR}$ of **9a**: $\delta = 1.3$ -1.6 (m, 9H); 2.65 (m, 3H); 6.56 (d, 1H, $J = 5.4\text{Hz}$); 6.85 (d, 1H, $J = 5.4\text{Hz}$); $^1\text{H-NMR}$ of **9'a**: $\delta = 1.3$ -1.6 (m, 9H); 2.65 (m, 2H); 3.60 (m, 1H); 6.12 (d, 1H, $J = 5.7\text{Hz}$); 8.28 (d, 1H, $J = 5.7\text{Hz}$). MS m/z (%): 202 (M^+ , 14), 139 (32), 113 (100), 87 (32), 55 (20).

Thermolysis of 1b: $T=540^\circ\text{C}$; **9b** and **9'b** were purified by chromatography on silica gel with acetone. Yield: 107 mg (4.35×10^{-4} mol, 76%) from 200 mg (5.74×10^{-4} mol) of **1b**. $^1\text{H-NMR}$ of **9b**: $\delta = 1.36$ (m, 4H); 1.52 (m, 5H); 2.47 (t, 2H, $J = 6.0\text{ Hz}$); 2.65 (m, 3H); 3.65 (t, 2H, $J = 6.0\text{Hz}$); 6.55 (d, 1H, $J = 5.6\text{Hz}$); 6.85 (d, 1H, $J = 5.6\text{Hz}$); $^1\text{H-NMR}$ of **9'b** showed two specific signals for this tautomer: 6.13 (d, 1H, $J = 5.7\text{Hz}$); 8.3 (d, 1H, $J = 5.7\text{Hz}$). MS m/z (%): 246 (M^+ , 3), 159 (15), 55 (100), 45 (30), 43 (51).

Thermolysis of 1c: 610°C ; **9c** and **9'c** purified by chromatography with CH_2Cl_2 . Yield: 80%. $^1\text{H-NMR}$ of **9c** (CDCl_3): $\delta = 1.6$ -1.7 (m, 6H); 2.65 (m, 4H); 6.55 (d, 2H, $J = 5.4\text{Hz}$); 6.86 (d, 2H, $J = 5.4\text{Hz}$); $^1\text{H-NMR}$ of **9'c**: $\delta = 1.66$ (m, 4H); 2.65 (m, 4H); 3.6 (m, 2H); 6.11 (d, 2H, $J = 6.0\text{Hz}$); 8.28 (d, 2H, $J = 6.0\text{Hz}$). **10c**, purified by chromatography with CH_2Cl_2 /acetone (90:10). Yield: 80 mg (2.36×10^{-4} mol, 47%) from 230 mg (5×10^{-4} mol) of **1c**. $^1\text{H-NMR}$: $\delta = 1.60$ (m, 4H); 2.19 (s, 6H); 2.60 (m, 4H); 6.73 (d, 2H, $J = 5.5\text{Hz}$); 6.98 (d, 2H, $J = 5.5\text{Hz}$); $^{13}\text{C-NMR}$: $\delta = 20.8(\text{q})$; 25.7(t); 30.1(t); 120.8(d); 121.9(d); 129.7(s); 142.9(s); 169.1(s). MS m/z (%): 340 (3), 338 (3), 336 (6), 294 (28), 293 (100), 292 (48), 140 (25), 139 (75), 136 (28), 43 (34).

Thermolysis of Meldrum's Acids 1d,e

Pyrolyses of **1d,e** were carried out at low pressures (10^{-4} - 10^{-5} Torr) in a apparatus previously described [6,12] and the products were collected on a cold finger, cooled in liquid N_2 at the exit of the horizontal quartz tube heated by an electrical oven. An entrance port placed between the exit of the tube and the cold finger permits the coating of the cold finger with methanol.

Bis 2'-(N-methylpyrrolyl) -1,2 -ethane (10d).

Purified by chromatography on silica gel with ether/petroleum ether/methanol (50:40:10). Yield of **10d**: 146 mg (7.76×10^{-4} mol, 42%) from 819 mg (36.7×10^{-4} mol) of **1d**. $\text{Mp} = 97^\circ\text{C}$. $^1\text{H-NMR}$: $\delta = 2.96$ (s, CH_2); 3.55 (s, CH_3); 6.06 (d, 1H, $J = 3.5\text{Hz}$); 6.18 (d, 1H, $J = 3.5\text{Hz}$); 6.65 (s, 1H); $^{13}\text{C-NMR}$: $\delta = 26.3$ (t) ; 33.5 (q) ; 105.7 (d) ; 106.8 (d) ; 121.3 (d); 132.8 (s); MS m/z (%): 189 (M^+ , 17),

188 (M^{+} , 98), 95 (67), 94 (100); IR ($CHCl_3$): $\nu = 3010, 2960, 2950, 1500, 1455, 1420, 1305, 1090$; Anal. Found: C, 76.49; H, 8.71; N, 14.75. Calc. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.56; N, 14.88%.

Bis 5'-(2,3-dihydro-1H-pyrroliziny) -1,2 -ethane (10e).

Purified by chromatography on silica gel with petroleum ether/ether (60:40). Yield of **10e**: 123 mg (5.12×10^{-4} mol, 34%) from 760 mg (30.5×10^{-4} mol) of **1e**. 1H -NMR: $\delta = 2.47$ (qt, 2H, $J = 7.1$ Hz); 2.85 (s, CH_2); 2.87 (t, 2H, $J = 7.1$ Hz); 3.68 (t, 2H, $J = 7.1$ Hz); 5.77 (sl, 1H); 6.0 (sl, 1H); ^{13}C -NMR: $\delta = 24.5$ (t); 27.6 (t); 28.1 (t); 44.3 (t); 98.2 (d); 108.5 (d); 127.4 (s); 135.5 (s); MS m/z (%) = 240 (M^{+} , 10); 121 (12); 120 (100)

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Sample Availability: Available from the authors.