3-Hydroxy-1*H*-pyrrole

Lawrence Hill,[a] S. Haider Imam,[a] Hamish McNab,*[b] William J. O'Neill[b]

[a] Durham Organics Ltd., Units 12-14, Langley Moor Industrial Estate, Langley Moor, Durham, DH7 8JE, UK

[b] School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK
Fax +44(131)6504743; E-mail: H.McNab@ed.ac.uk

Received 8 April 2009

Abstract: Flash vacuum pyrolysis (FVP) of *tert*-butyl {[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino}acetate at 600 °C gives the unstable 3-hydroxy-1*H*-pyrrole in ca. 55% yield as the only significant product. It exists as the enol tautomer in dimethyl sulfoxide solution, and predominantly as the keto tautomer in water. 3-Hydroxy-1*H*-pyrrole reacts readily with mild electrophiles, exclusively at the 2-position. FVP of the product obtained from one such reaction with methoxymethylene-substituted Meldrum's acid gives pyrano[3,2-*b*]pyrrol-5(1*H*)-one in 77% yield.

Key words: gas-phase reactions, heterocycles, pyrroles, electrophilic aromatic substitutions, tautomerism

Pyrroles with oxygen-containing functionalities are of interest in opto-electronic applications because of their highly electron-rich nature.[1] The parent 3-hydroxy-1*H*-pyrrole (**1E**) [1*H*-pyrrol-3(2*H*)-one (**1K**)] has been reported only once,[2] generated by a multistep sequence culminating in hydrogenolysis, decarboxylation, and in situ silylation of benzyl 3-hydroxy-1*H*-pyrrole-2-carboxylate. The silyl protecting group was removed by treatment with methanol to give **1E** in ca. 1% overall yield from commercially available precursors. Spectroscopic details and rate and equilibrium studies of ketonisation of **1E** were reported (Figure 1),[2] but nothing is known of the chemical properties of this compound.

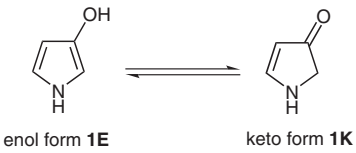
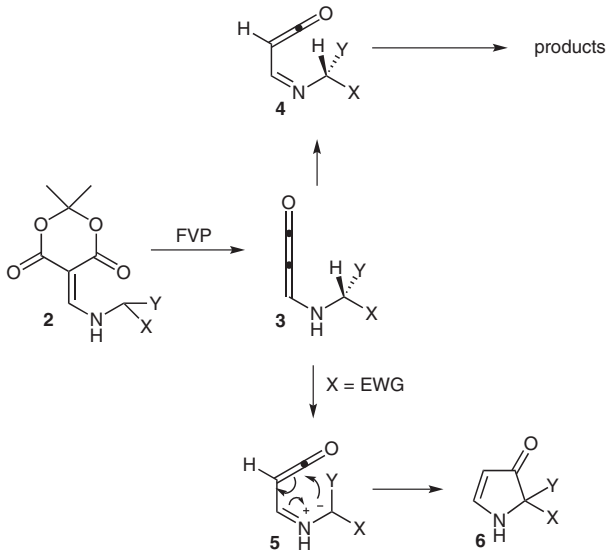


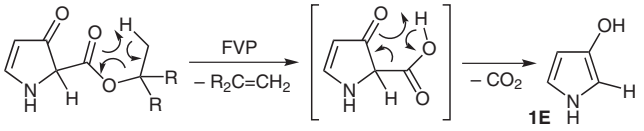
Figure 1

In the previous paper,[3] we have shown that the 'normal' 1,3-H shift of N-unsubstituted methyleneketenes[4] **3** [generated by flash vacuum pyrolysis (FVP) of aminomethylene derivatives of Meldrum's acid **2**] leading to imidoylketenes **4** can be circumvented when an electron-withdrawing group (X) is present in the α-position of the side chain.[3] In such cases, a 1,4-H shift takes place, leading to azomethine ylides **5** which collapse to N-unsubstituted 1,2-dihydropyrrol-3-ones (3-hydroxypyrroles when Y = H) **6** (Scheme 1). This is the normal thermal behaviour of the corresponding N,N-disubstituted aminomethylene Meldrum's acid derivatives.[4,5] In this paper, we show how this strategy can be extended to provide a convenient two-step route to 3-hydroxypyrrole **1E** itself, and report the first studies of its chemical properties.



Scheme 1

In order to fulfil these requirements, a group X (Scheme 1) is required that can be thermally eliminated under the conditions of the pyrolysis. In principle, any ester group (X = CO_2R) in which the group R bears a β-hydrogen atom, should be capable of retro-ene elimination[6] to provide the 2-carboxylic acid; it is well known that decarboxylation of 3-hydroxypyrrole-2-carboxylic acids takes place under very mild conditions (Scheme 2).[7]

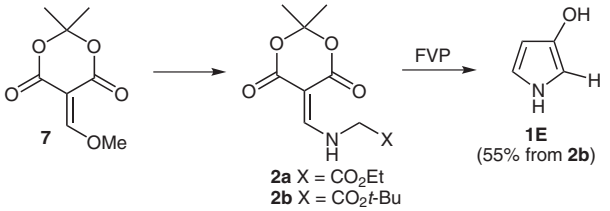


Scheme 2

In practice, the aminomethylene Meldrum's acid derivatives **2a** and **2b** derived respectively from glycine ethyl ester[3] and glycine *tert*-butyl ester (89%) were readily made from methoxymethylene-substituted Meldrum's acid **7** under standard conditions (Scheme 3).[8] FVP of the ethyl ester **2a** at 850 °C gave some 3-hydroxypyrrole **1E**,

SYNTHESIS 2009, No. 15, pp 2535–2538
Advanced online publication: 23.06.2009
DOI: 10.1055/s-0029-1217422; Art ID: P05309SS

but many impurities were present. However, FVP of the *tert*-butyl ester **2B** at 600 °C gave a clean sample of **1E** (55%) whose ^{1}H NMR spectrum in DMSO-d_6 is consistent with the published data of the hydroxy tautomer [Figure 2 (a)].[2] HSQC extension to the carbon dimension gives the data shown in Figure 2 (b); assignments are consistent with those of 1-substituted 3-hydroxypyrroles previously reported.[9]

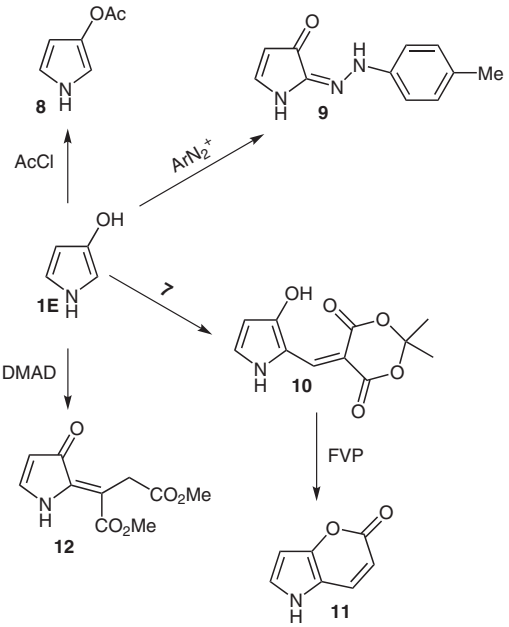


Scheme 3

3-Hydroxypyrrole **1E** is reported to 'resinify very rapidly'[2] and, in our hands, it cannot be purified by distillation or chromatography. It is best generated immediately before reactions. In polar organic solvents (e.g., DMSO), it exists exclusively as the hydroxy tautomer, as found for 1-substituted analogues;[10] in aqueous solution it is present in the keto form.[2] 3-Hydroxypyrrole **1E** is moderately stable in acid solution (e.g., TFA) for a few hours, where it is quantitatively protonated at the 2-position;[11] in trifluoroacetic acid-*d*, rapid deuterium exchange takes place at the 2- and 4-positions.

Figure 2 (a) ^{1}H NMR chemical shifts (δ) of **1E**; (b) ^{13}C NMR chemical shifts (δ) of **1E**.

In reactions of 3-hydroxypyrrole **1E**, the yield is quoted for the two steps from **2b**. Thus, 3-hydroxypyrrole **1E** is readily acylated with acetyl chloride in the presence of triethylamine to provide the *O*-acetoxy compound **8** (49%). 3-Hydroxypyrrole **1E** reacts rapidly with soft electrophiles at the 2-position (Scheme 4). For example, coupling with diazonium salts provides the hydrazone **9** (56%)[12] and reaction with methoxymethylene-substituted Meldrum's acid **7** gives **10** (61%). Compound **10** is transformed into the previously unknown parent member **11** of the rare pyrano[3,2-*b*]pyrrol-5(1*H*)-one ring system by FVP at 600 °C in 77% yield.[13] As found previously,[13] the alternative cyclisation onto the nitrogen atom to provide a pyrrolizin-3-one is not observed. Treatment of **1** with dimethyl acetylenedicarboxylate gives the conjugate addition product **12** (41%) which adopts the tautomer shown exclusively. The analogous tautomer is obtained when dimethyl acetylenedicarboxylate is reacted with indoxyl,[14] but an alternative tautomer is formed when dimethyl acetylenedicarboxylate is reacted with 1-substituted 3-hydroxypyrroles.[15]



Scheme 4

In conclusion, 3-hydroxypyrrole **1E** can now be made reproducibly in 49% overall yield by a two-step method; the key step is an FVP-mediated, one-pass cyclisation, dealkylation, and decarboxylation. 3-Hydroxypyrrole **1E** is highly reactive; it can be O-acylated under basic conditions and reacts readily with soft electrophiles at the 2-position.

^{1}H and ^{13}C NMR spectra were recorded at 250 MHz and 63 MHz respectively unless otherwise stated. Chemical shifts are given relative to TMS. Mass spectra were recorded under electron impact conditions. UV/Vis gives ε in $dm^3\ mol^{-1}\ cm^{-1}$.

Flash vacuum pyrolysis (FVP) reactions were carried out by distillation of the substrate in vacuo through an electrically heated silica furnace tube (35 × 2.5 cm). Products were trapped in a U-tube situated at the exit point of the furnace and cooled with liquid N_2. Pyrolysis conditions are quoted as follows: substrate, quantity (*w*), furnace temperature (T_f), inlet temperature (T_i), pressure range (*P*), pyrolysis time (*t*), and product(s).

***tert*-Butyl {[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-methyl]amino}acetate (2b)**

Et_3N (0.70 mL) was added to a soln of glycine *tert*-butyl ester hydrochloride (0.419 g, 2.5 mmol) in MeCN (40 mL). Methoxymethylene-substituted Meldrum's acid **7** (0.465 g, 2.5 mmol) was added and the soln was stirred at r.t. for 2.5 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 and washed with 2 M HCl. The organic layer was dried ($MgSO_4$) and the solvent removed to give **2b** (0.634 g, 89%) as a yellow solid; mp 135–136 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 9.61 (br m, 1 H), 8.07 (d, ^3J = 14.6 Hz, 1 H), 4.09 (d, ^3J = 5.8 Hz, 2 H), 1.70 (s, 6 H), 1.49 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 166.07 (q), 165.07 (q), 165.53 (q), 159.94, 104.61 (q), 85.72 (q), 83.65 (q), 56.61 (CH_2), 27.74 (3 CH_3), 26.71 (2 CH_3).

MS: *m*/*z* (%) = 285 (M^+, 29), 229 (14), 184 (23), 172 (32), 126 (100).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.75; H, 6.65; N, 4.9. Found: C, 54.95; H, 6.65; N, 4.95.

3-Hydroxy-1*H*-pyrrole (1E)

FVP of **2b** (*w* 0.0988 g, T_f 600 °C, T_i 200 °C, *P* 2.6–2.8 × 10^{-2} Torr, *t* 5 min) gave 3-hydroxypyrrole **1E**[2] (ca. 55%; NMR yield based on a cyclohexane standard) as an orange-brown oil.

^{1}H NMR (360 MHz, DMSO-d_6): δ (enol tautomer **1E**) = 9.95 (br s, 1 H), 7.79 (br s, 1 H), 6.43 (td, ^3J = 2.7 Hz, ^4J = 1.7 Hz, 1 H), 6.16 (td, ^3J = 2.7 Hz, ^3J = 2.4 Hz, 1 H), 5.61 (td, ^3J = 2.4 Hz, ^4J = 1.7 Hz, 1 H); data consistent with literature values.[2]

^{13}C NMR (90 MHz, DMSO-d_6): δ (enol tautomer **1E**) = 143.72 (q), 114.99, 100.51, 98.19.

^{1}H NMR (500 MHz, H_2O + D_2O): δ (keto tautomer **1K**) = 8.27 (m, 1 H), 5.20 (d, ^3J = 2.9 Hz, 1 H) 3.94 (d, ^4J = 1.4 Hz, 2 H).

^{13}C NMR (125 MHz, H_2O + D_2O): δ (keto tautomer **1K**) = 204.21 (q), 170.83, 99.23, 55.55 (CH_2).

Protonation of 3-Hydroxypyrrole 1E

A freshly prepared sample of 3-hydroxypyrrole **1E** was dissolved in TFA and the NMR spectra recorded.

^{1}H NMR (500 MHz, TFA): δ = 8.92 (s, 1 H), 6.34 (d, ^3J = 2.0 Hz, 1 H), 5.03 (d, ^3J = 2.0 Hz, 2 H); signals at δ = 6.34 and 5.03 were not observed when **1** was dissolved in TFA-*d*.

^{13}C NMR (125 MHz, TFA): δ = 189.23 (q), 173.17, 100.17, 54.83 (CH_2).

3-Acetoxy-1*H*-pyrrole (8)

The product **1E** from FVP of **2b** (*w* 0.208 g, T_f 600 °C, T_i 200 °C, *P* 2.9–3.2 × 10^{-2} Torr, *t* 17 min) was dissolved in DMF (2.5 mL). Et_3N (0.5 mL) and AcCl (0.4 mL) were added and the mixture was stirred at r.t. for 1 h. The mixture was diluted with H_2O, acidified, and extracted with EtOAc (3 × 20). The combined organic fractions were washed with 2 M HCl and sat. $NaHCO_3$ (2 × 20) and then dried ($MgSO_4$) and the soln concentrated to give the crude material as a brown oil. The oil was purified by Kugelrohr distillation to give **8** (0.045 g, 49%) as an orange oil; bp 88–90 °C/0.5 Torr).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.03 (br s, 1 H), 6.82 (m, 1 H), 6.63 (td, ^3J = 3.0 Hz, ^3J = 2.3 Hz, 1 H), 6.09 (ddd, ^3J = 3.0 Hz, ^4J = 1.6 Hz, 1 H), 2.24 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.90 (q), 137.40 (q), 115.68, 107.01, 101.14, 20.90 (CH_3).

MS: *m*/*z* (%) = 125 (M^+, 37), 83 (100).

HRMS: *m*/*z* $[M]^+$ calcd for $C_6H_7NO_2$: 125.04713; found; 125.04709.

2-(4-Tolylhydrazono)-1,2-dihydropyrrol-3-one (9)

The pyrolysate **1E** from FVP of **2b** (*w* 0.094 g, T_f 600 °C, T_i 200 °C, *P* 2.3–2.4 × 10^{-2} Torr, *t* 13 min) was dissolved in DMF (2.5 mL). 4-Tolyldiazonium tetrafluoroborate (0.062 g, 0.33 mmol) was added and the resulting deep red soln was stirred for 20 min. The soln was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (2 × 20 mL) and brine (20 mL) and dried ($MgSO_4$); the solvent was removed to give a brown solid. Purification by dry flash chromatography (hexane–EtOAc, 3:2) gave **9** (0.039 g, 56%) as an orange-red solid; mp 188–190 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.66 (t, ^3J = 3.6 Hz, 1 H), 7.26–7.12 (m, 4 H), 5.53 (d, ^3J = 3.6 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 177.88 (q), 147.93, 140.10 (q), 133.52 (q), 132.60 (q), 129.85 (2 CH), 114.12 (2 CH), 101.45, 29.58 (CH_3).

UV/Vis (MeOH): λ_{max} (ε) = 456 (11,100), 373.0 (7,750), 260.0 nm (6,400).

MS: *m*/*z* (%) = 201 (M^+, 100), 106 (26).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}N_3O$: 201.08966; found: 201.08964.

5-(3-Hydroxy-1*H*-pyrrol-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (10)

FVP of **2b** (*w* 0.108 g, T_f 600, T_i 200 °C, *P* 2.3–2.5 × 10^{-2} Torr, *t* 23 min) gave an orange-brown oil, which was dissolved in a mixture of DMF and Et_3N (10:1, 4 mL). Methoxymethylene-substituted Meldrum's acid **7** (0.067 g, 0.36 mmol) was added and the soln was stirred at r.t. for 1 h. The mixture was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The combined organics were washed with 2 M HCl, brine (2 × 20 mL) and dried ($MgSO_4$) and the solvent was removed to give **10** (0.0547 g, 61%) as a brown solid; mp 199–201 °C (dec.).

^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.64 (br s, 2 H), 8.10 (s, 1 H), 7.63 (t, ^3J = 2.7 Hz, 1 H), 5.90 (t, ^3J = 2.7 Hz, 1 H), 1.71 (s, 6 H).

^{13}C NMR (90 MHz, DMSO-d_6): δ = 164.30 (q), 164.01 (q), 162.17 (q), 137.26, 133.89, 117.60 (q), 103.15 (q), 98.32, 92.74 (q), 26.57 (2 CH_3).

MS: *m*/*z* (%) = 237 (M^+, 40), 179 (72), 135 (38), 107 (100).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}NO_5$: 237.06317; found: 237.06274.

Pyrano[3,2-*b*]pyrrol-5(1*H*)-one (11)

FVP of **10** (*w* 0.115 g, T_f 600 °C, T_i 220 °C, *P* 2.4–2.6 × 10^{-2} Torr, *t* 24 min) gave **11** (0.0507 g, 77%) as an orange-brown solid; mp 155–157 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.58 (d, ^3J = 9.5 Hz, 1 H), 7.05 (t, ^3J = 2.9 Hz, 1 H), 6.23 (t, ^3J = 2.9 Hz, 1 H), 6.05 (d, ^3J = 9.5 Hz, 1 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 163.25 (q), 147.84 (q), 132.62, 123.27 (q), 115.16, 107.13, 97.65.

MS: *m*/*z* (%) = 135 (M^+, 100), 107 (36).

HRMS: *m*/*z* $[M]^+$ calcd for $C_7H_5NO_2$: 135.03148; found: 135.03123.

Dimethyl 2-[(*E*)-3-Oxo-1,3-dihydro-2*H*-pyrrol-2-ylidene]succinate (12)

FVP of **2b** (*w* 0.0995 g, T_f = 600 °C, T_i 200 °C, *P* 2.4–2.6 × 10^{-2} Torr, *t* 17 min) gave an orange-brown oil that was dissolved in DMF (2.5 mL). DMAD (0.05 mL) was added and the soln stirred at r.t. for 1 h. The mixture was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (2 × 20 mL) and brine (20 mL) and dried ($MgSO_4$); the solvent was removed to give a brown solid. Purification by column chromatography (hexane–EtOAc, 3:2) gave **12** (0.0324 g, 41%) as a red solid; mp 107–109 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.03 (br s, 1 H), 7.80 (dd, ^3J = 3.9 Hz, ^3J = 3.4 Hz, 1 H), 5.33 (dd, ^3J = 3.9 Hz, ^4J = 1.9 Hz, 1 H), 4.10 (s, 2 H), 3.82 (s, 3 H), 3.71 (s, 3 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 190.03 (q), 171.23 (q), 168.64 (q), 154.82, 138.41 (q), 108.91 (q), 101.88, 52.51 (CH_3), 51.93 (CH_3), 29.38 (CH_2).

MS: *m*/*z* (%) = 225 (M^+, 46), 193 (100), 165 (39), 134 (22) and 106 (21).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}NO_5$: 225.06317; found: 225.06258.

Acknowledgment

We are grateful to Durham Organics and the Engineering and Physical Sciences Research Council (EPSRC) UK, for a CASE award (to W.J.O'N.).

References

(1) For example: Zotti, G.; Zecchin, S.; Schiavon, G.; Groenendaal, L. B. *Chem. Mater.* **2000**, *12*, 2996.
(2) (a) Capon, B.; Kwok, F. C. *Tetrahedron Lett.* **1986**, *27*, 3275. (b) Capon, B.; Kwok, F. C. *J. Am. Chem. Soc.* **1989**, *111*, 5346.
(3) Hill, L.; Hunter, G. A.; Imam, S. H.; McNab, H.; O'Neill, W. J. *Synthesis* **2009**, 2531.
(4) Review: Gaber, A. M.; McNab, H. *Synthesis* **2001**, 2059.
(5) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 863.
(6) De Puy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.
(7) Review: McNab, H.; Monahan, L. C. In *Pyrroles*, Vol. 2; Jones, R. A., Ed.; Wiley: New York, **1992**, 525.
(8) McNab, H.; Withell, K. *ARKIVOC* **2000**, *(v)*, 806.
(9) (a) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1999. (b) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1459.
(10) Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1455.
(11) Cf.:Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1463.
(12) Cf.: Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 701.
(13) Cf.: Derbyshire, P. A.; Hunter, G. A.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2017.
(14) Kawasaki, T.; Tang, C.-Y.; Nakanishi, H.; Hirai, S.; Ohshita, T.; Tanizawa, M.; Himori, M.; Satoh, H.; Sakamoto, M.; Miura, K.; Nakano, F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 327.
(15) Hunter, G. A. *Ph. D. Thesis*; The University of Edinburgh: Scotland, **1990**.