PERKIN 1

3-Hydroxypyrroles and 1*H*-pyrrol-3(2*H*)-ones. Part 14.[1,2] Pyrolysis of oxazolidinylmethylene derivatives of Meldrum's acid – synthesis of *N*-alkenyl-3-hydroxypyrroles and related reactions

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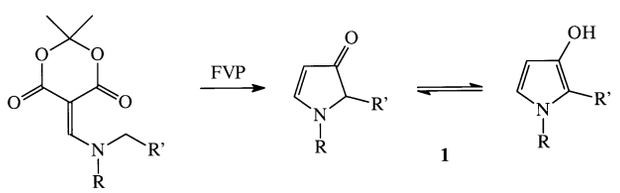
Flash vacuum pyrolysis (FVP) of the title compounds **14** and **17** at 600–625 °C (0.005 Torr) gives the *N*-alkenylpyrrolones **22** and **23** respectively. The mechanism is shown to involve hydrogen transfer and cyclisation of the methyleneketene intermediate (*e.g.* **25**) to a fused pyrrolone (*e.g.* **28**). This species fragments to create an azomethine ylide which provides the alkenyl substituent by a further hydrogen transfer. Similar reactions are shown by the thiazolidine derivatives **20** and **21**, though in the latter case the initial bicycles **35** and **37** can be observed by NMR spectroscopy. When the normal sites for hydrogen transfer are blocked by substituents (as in compound **16**) an alternative hydrogen transfer–cycloaddition sequence leads to the fused pyridin-4-one **43**.

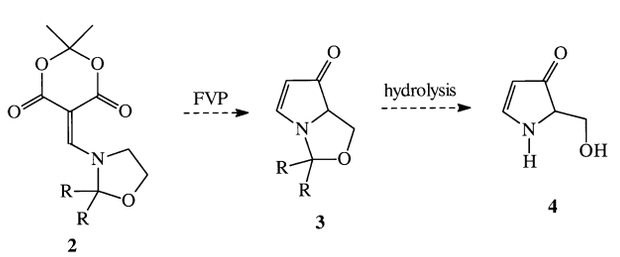
Introduction

The 'Meldrum's acid route' to 3-hydroxypyrroles and 1*H*-pyrrol-3(2*H*)-ones **1** (Scheme 1) has proved to be a flexible



Scheme 1

method for the preparation of 1-substituted or 1,2-disubstituted derivatives of this highly sensitive ring system.[3,4] Using flash vacuum pyrolysis (FVP) conditions, the products are collected at low temperature in the absence of air and so the high reactivity of the system to electrophilic reagents[1] and to oxidising agents[5] can be controlled. *N*-Unsubstituted pyrrolones cannot be made directly by this gas-phase route;[6] nevertheless, these are attractive synthetic targets, because of their relationship to the 3-alkoxypyrrole core of the prodigiosin series of antibiotics.[7,8] Although the pyrolysis of some simple *N*-protected Meldrum's acid precursors proved unsuccessful,[9] we anticipated that oxazolidinyl derivatives **2** could provide the bicycles **3** as primary pyrolysis products which could release the *N*-unsubstituted pyrrolone **4** functionality upon hydrolysis (Scheme 2). As we report here, pyrolyses of these substrates proceeded cleanly, but unexpectedly, and the products proved to



Scheme 2

be *N*-alkenyl-3-hydroxypyrroles rather than the anticipated bicycles.[2] Studies of the mechanism of this transformation and the syntheses and pyrolyses of some related precursors are also reported.

Results and discussion

The oxazolidines **5**–**8** and the related tetrahydro-1,3-oxazine **9** were prepared by standard methods (see Experimental section). Similarly, the hexahydropyrimidine **10** and the thiazolidines **11** and **12** were synthesised so that the effect of the second heteroatom on the thermal cyclisation could be assessed. The substrates **5**–**7** and **9**–**12** were reacted with methoxymethylene Meldrum's acid **13** in acetonitrile solution at room temperature to give the products **14**–**16** and **18**–**21** respectively, often in >80% yield. 2,2-Dimethyloxazolidine **8** was hydrolytically unstable under these conditions, but could be prepared and reacted with **13** *in situ* to give a good yield of the Meldrum's derivative **17**, and a similar method was used to make the deuterium-labelled compound **17D**. The products **14**–**21** were characterised by their spectra. In some cases, the NMR spectra showed that two rotamers were present in solution, as found previously for *N,N*-disubstituted aminomethylene Meldrum's acid derivatives in which the two *N*-substituents have rather similar steric requirements.[3] In other cases broad peaks were observed due to restricted rotation about the C–N bond. Molecular ions were observed in the electron impact mass spectra of each of the derivatives **14**–**21** (though some were of low intensity) and peaks due to some or all of the normal Meldrum's acid breakdown pattern (sequential loss of acetone, carbon dioxide and carbon monoxide) were detected in most cases.

Pyrolysis of the oxazolidine derivative **14** under FVP conditions at 600–625 °C proceeded relatively cleanly to give an unstable involatile oil which condensed at the mouth of the trap. The ^{1}H NMR spectrum of the crude pyrolysate (deuteriochloroform) clearly showed that a pyrrolone had been formed (from the characteristic[10] widely spaced doublets at δ_H 7.94 and 5.15) but a two-proton singlet at δ_H 3.82 was indicative of the product being a 2-unsubstituted pyrrolone. This assignment

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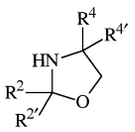
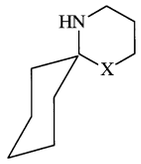
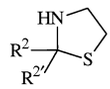


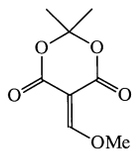




5 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = $R^{4'}$ = H
6 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = Ph, $R^{4'}$ = H
7 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = $R^{4'}$ = Me
8 R^2 = $R^{2'}$ = Me, R^4 = $R^{4'}$ = H
8D R^2 = $R^{2'}$ = [$^2H_3$]C, R^4 = $R^{4'}$ = H

9 X = O
10 X = NMe

11 R^2-$R^{2'}$ = -$(CH_2)_5$-
12 R^2 = $R^{2'}$ = H



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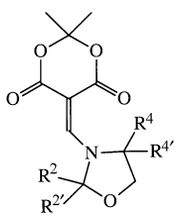
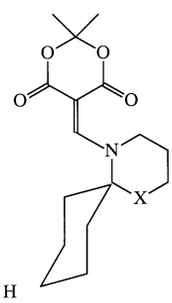
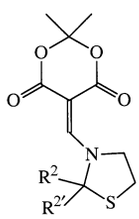




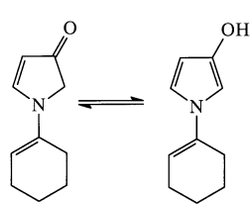


14 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = $R^{4'}$ = H
15 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = Ph, $R^{4'}$ = H
16 R^2-$R^{2'}$ = -$(CH_2)_5$-, R^4 = $R^{4'}$ = Me
17 R^2 = $R^{2'}$ = Me, R^4 = $R^{4'}$ = H
17D R^2 = $R^{2'}$ = [$^2H_3$]C, R^4 = $R^{4'}$ = H

18 X = O
19 X = NMe

20 R^2-$R^{2'}$ = -$(CH_2)_5$-
21 R^2 = $R^{2'}$ = H

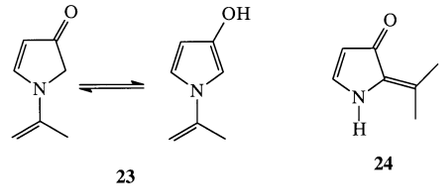
was confirmed by recording the spectrum in [$^2H_6$]DMSO, which promoted tautomerisation to the enol (hydroxypyrrole) form and showed three signals for the pyrrole ring protons. An unexpected one proton alkene signal was present in spectra recorded in both solvents. The mass spectrum showed a parent ion at *m*/*z* 163 ($C_{10}H_{13}NO$) consistent with the loss of CH_2O during the pyrolysis over and above the expected Meldrum's acid breakdown. This information is consistent with the product being the *N*-alkenylpyrrolone (hydroxypyrrole) **22**, obtained in *ca.* 70% yield. *N*-Alkenylpyrroles are generally obtained by reaction of ketoximes with acetylenes under basic conditions,[11] but the present method provides the first route to *N*-alkenylpyrrolones.



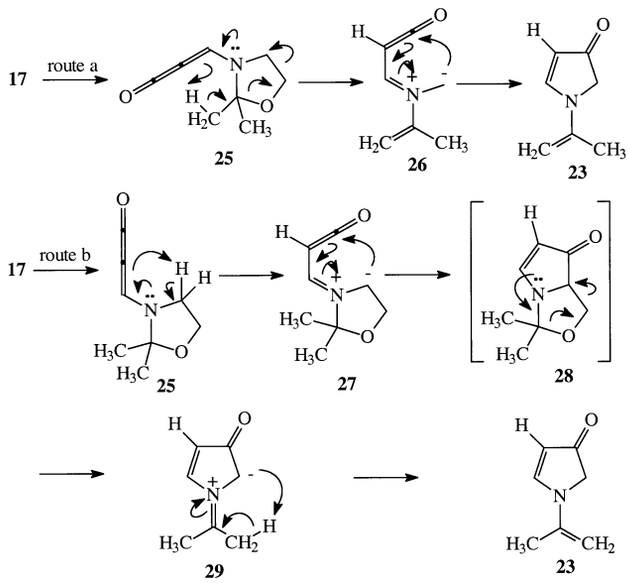
22

Pyrolysis of the dimethyloxazolidine **17** also provided the corresponding alkenylpyrrolone **23** (*ca.* 50%) (see Experimental section) but in this case a second product was identified as the 2-methylene isomer **24** (*ca.* 20%). The ratio of the two products (2.7 : 1) was essentially unchanged over the pyrolysis temperature range 500–750 °C. The ^{1}H NMR spectrum of the minor product showed typical pyrrolone signals but instead of the usual characteristic doublets, a triplet (δ_H 7.59; ^3J 3.6 Hz) and double doublet (δ_H 5.33; ^3J 3.6 and ^4J 1.6 Hz) was obtained as well as a one-proton broad signal (NH); the extra couplings are explained by the presence of the NH.

Assuming that the pyrolyses of the Meldrum's acid derivatives give methyleneketene intermediates[4] there are two reasonable mechanisms for the formation of the alkenylpyrroles, exemplified in Scheme 3 for the case of the formation of **23**. The



23 **24**



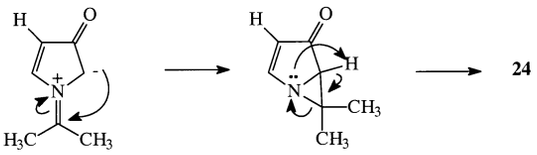
25 **26** **23** **25** **27** **28** **29** **23**

Scheme 3

first mechanism (route a) involves hydrogen abstraction by the methyleneketene **25** from the methyl group followed by concerted loss of CH_2O to generate the azomethine ylide **26** with the alkenyl substituent already in place. The product **23** is formed by electrocyclisation of **26**. Alternatively, pyrrolone formation by route b could take place by the standard hydrogen transfer mechanism[3] to give an alternative azomethine ylide **27** and hence the expected bicycle **28**, which can give the final product **23** by subsequent loss of CH_2O and consolidation of the azomethine ylide **29**. There is precedent for the final step of this sequence since loss of formaldehyde from oxazolidines under FVP conditions is a known route to azomethine ylides.[12]

The two mechanisms (Scheme 3) can be distinguished by identifying the source of the hydrogen atom in the 4-position of the final product (specified in the Scheme 3); in route a, it comes from the methyl substituent of the oxazolidine, whereas in route b it is transferred from the 4-position of the oxazolidine ring. The deuteriated substrate **17D** was therefore synthesised and the labelled **23** which was obtained from the pyrolysis revealed *no* deuterium incorporation at the 4-position of the ring by ^{1}H NMR spectroscopy. In addition the signal due to the proton(s) at the 2-position integrated to *ca.* 1H. Hence the concerted mechanism (route a) can be discounted and instead the product is apparently formed *via* collapse of the bicycle **28** (route b). In the experiment using the labelled substrate, the ratio of minor product **24** had substantially increased (deuteriated **23** : **24** = 1.3 : 1.0) which suggests that both products may be formed from the same intermediate and that the final hydrogen shift to generate **23** from **29** may be rate determining. In this interpretation, k_H/k_D = 2.1, which is in line with other values of kinetic isotope effects under FVP conditions.[13] The route to **24** could therefore involve collapse of the azomethine ylide **29** to the aziridine **30** followed by ring opening (Scheme 4). Thermal partition between azomethine ylides, aziridines and enamines has been reported.[12]

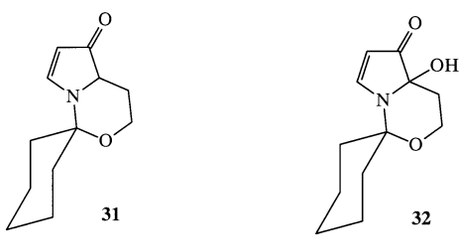
No tangible products were obtained from the pyrolysis of the phenyl-substituted compound **15**. It is possible that a 2-substituted *N*-alkenylpyrrolone was formed, but that it was too



Scheme 4

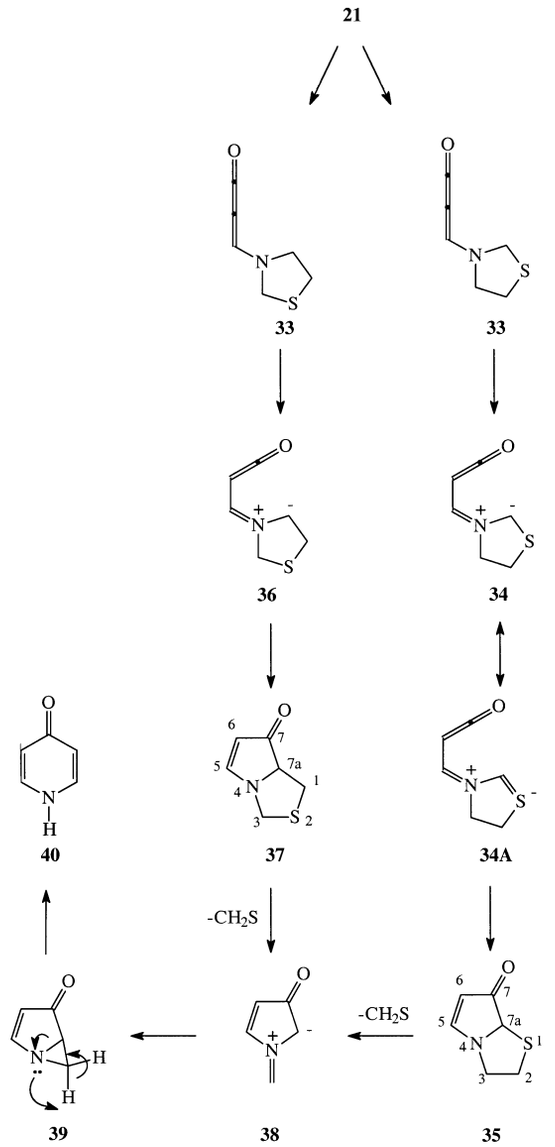
readily oxidised[5] to allow its isolation under our usual conditions.

In view of these results, the six-membered ring tetrahydrooxazinyl derivative **18** was pyrolysed. In this case, elimination of formaldehyde cannot occur from the initial cyclisation product to give an azomethine ylide and indeed the initial cyclisation product **31** was thermally stable and could be identified from the characteristic pyrrolone and hydroxypyrrole peaks in the complex ^{1}H NMR spectrum of the crude pyrolysate. Best results were obtained when the pyrolysate was condensed on a 'cold-finger' which was washed with [$^2H_6$]acetone and transferred directly to an NMR tube in the absence of air. Such 2-substituted pyrrolones are readily oxidised and both the pyrrolone **31** and its oxidation product **32** were subsequently characterised by mass spectrometry (see Experimental section). In contrast, pyrolysis of the tetrahydropyrimidine **19** was unsuccessful.



Pyrolysis of the thiazolidine **20** gave, as the major product, the same alkenylpyrrolone **22** which was obtained from the corresponding oxazolidine **14**. Clearly extrusion of thioformaldehyde from the bicyclic intermediate corresponding to **28** can take place by a similar mechanism. However, this process is less facile than in the oxazolidine series, since a second (unidentified) *N*-substituted pyrrolone (*ca.* half the amount of the major product) was also formed in competition. In addition, bicyclic products could be characterised from the spectra of the products formed by pyrolysis at 600 °C of the Meldrum's acid derivative **21** of the parent thiazolidine. Use of the 'cold-finger' trap was essential and the unstable products were identified by their NMR spectra in [$^2H_6$]acetone at −20 °C. Three products **35**, **37** and **40** were formed in 55 : 18 : 27 ratio (Scheme 5). The major bicycle was identified as the pyrrolo[2,1-*b*]-thiazole **35** by the characteristic pyrrolone resonances (δ_H 7.97 and 5.25; ^3J 3.6 Hz) the singlet due to the 7a-proton (δ_H 4.71) and the four signals due to the non-equivalent protons at the 2- and 3-positions (δ_H 2.7–4.1). The minor bicycle showed similar alkene signals (δ_H 8.10 and 5.35, ^3J 3.6) but the pattern of aliphatics was different, consistent with the isomeric pyrrolo-[1,2-*c*]thiazole structure **37**. The third product showed only two signals in the ^{1}H NMR spectrum and three in the ^{13}C NMR and was identified as pyridin-4-one **40** by comparison with literature data. This compound was the sole product at 750 °C.

The likely mechanism for the formation of these products is also shown in Scheme 5. Hydrogen transfer from the methyleneketene **33** can take place from either the 2- or the 4-positions of the thiazolidine to give the azomethine ylides **34** and **36** respectively which then cyclise to the isomeric products **35** and **37**. Loss of CH_2S from either of these provides another dipolar structure, **38**, which can collapse to **40** *via* the aziridine **39**. This mode of breakdown from the aziridine is apparently more

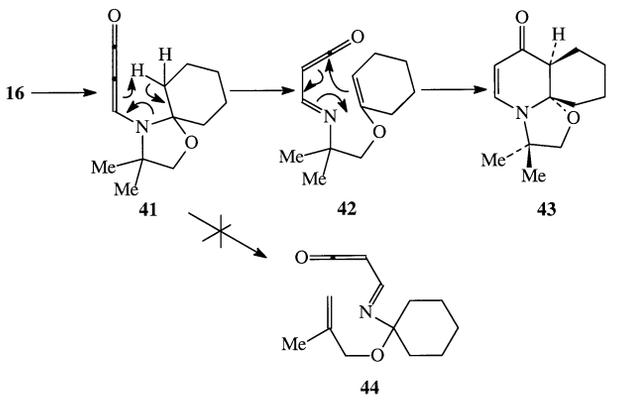


Scheme 5

favourable than hydrogen transfer from the bridgehead, as found in the formation of **24** from **30**. The regioselectivity observed in the formation of **35** and **37** may be due to additional stabilisation of the dipolar intermediate by interaction with the adjacent sulfur atom (as in **34A**) but preferential cleavage of **37** to **38** cannot be ruled out at this stage. The relative stability of **35** and **37** over the oxazolidine-derived products reported in this paper, may be due to the longer C–S bonds which impose less strain on the bicycle. It is of interest that none of the hydroxy tautomers of **35** and **37** were observed in [$^2H_6$]acetone solution, which may also be due to the increase in strain of the more planar bicycle.

Next, the substrate **16** was designed to discover whether the hydrogen transfer mechanism of Scheme 3 route a, could take place when no hydrogen atoms α- to the nitrogen atom are present. FVP of **16** at 625 °C, gave a single product (M^+ 221 Da) in 50% yield, which was isomeric with the methyleneketene intermediate **41** (*i.e.* no loss of CH_2O had taken place). The ^{1}H NMR spectrum showed the presence of an enaminone unit (δ_H 6.98 and 4.99) whose vicinal coupling constant (^3J 7.1 Hz) is indicative of a six-membered ring (rather than a five-membered ring) framework. The ^{13}C NMR (DEPT) spectrum showed the presence of three quaternaries, three methine, five methylene and the two methyl groups, which suggests that hydrogen atom transfer to the methyleneketene from the cyclohexane ring has taken place to generate the enone unit and that subsequent

cyclisation at the site of hydrogen atom removal has created the third methine group. The remainder of the carbon skeleton of the methyleneketene is unchanged. The most likely structure consistent with these features is the tricycle **43**, which could be formed by an initial retro-ene-type fragmentation to give the imidoylketene intermediate **42** followed by intramolecular cycloaddition with the co-formed enol ether moiety (Scheme 6).



Scheme 6

The regioselectivity of hydrogen transfer from the cyclohexane ring rather than the methyl groups (despite a 6 : 4 statistical ratio in the opposite direction) would then be explained by the reactivity of the enol ether **42** compared with the isomeric alkene **44** in the inverse electron demand cycloaddition with the electron deficient imidoylketene component.

If this mechanism is correct, the stereochemistry at the fusion of the two six-membered rings should be *cis*, owing to the suprafacial nature of the cycloaddition. This was confirmed in two ways. First the single proton at the ring junction (identified by proton–carbon correlation) shows no large couplings and is therefore unlikely to be in an axial position as required for a *trans* fusion. Second, NOE experiments (Fig. 1) confirm that the

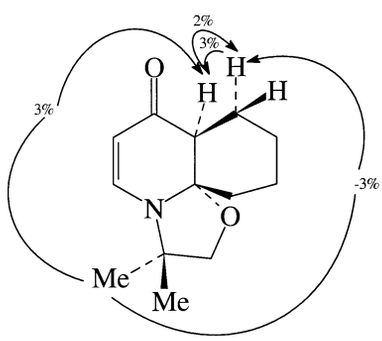


Fig. 1 Selected NOE data for **43**.

fused oxazolidine ring is on the same side of the molecule as the hydrogen atom at the bridgehead.

Finally the chemistry of the new 1-alkenylpyrrolones **22** and **23** was briefly explored. As previously mentioned, tautomerisation to the hydroxypyrrole form is promoted by polar solvents such as DMSO, but this is relatively disfavoured by comparison with simple model compounds. Thus, whereas the *N*-phenylpyrrolone **45** exists to the extent of 95% in the enol form in DMSO, **22** and **23** remain partially in their keto tautomers (20% and 37% respectively).

A series of NOE experiments on the 3-hydroxypyrrole tautomer of **22** (Fig. 2) has shown that the chemical shifts of the three pyrrole ring protons are in the same order and the coupling constants are of similar magnitudes as previously observed for simple 3-hydroxypyrroles [**22**: δ_H 6.69 (5-position) > 6.43 (2-position) > 5.65 (4-position); $^3J_{4,5} = 2.9$; $^4J_{2,5} = 2.5$; $^4J_{2,4} = 1.9$ Hz].[14] The NOE results also prove that there is facile rotation

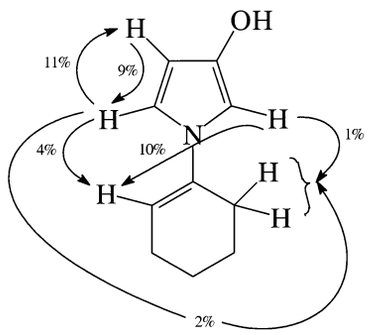
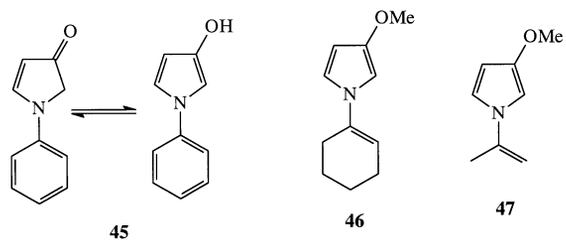


Fig. 2 NOE data for the hydroxypyrrole form of **22**.

about the *N*-cyclohexenyl bond, since both the methine and the adjacent methylene signals of the cyclohexenyl substituent are enhanced by irradiation of the hydroxypyrrole 2- and 5-proton resonances.

Both the alkenylpyrrolones **22** and **23** could be regioselectively *O*-alkylated directly from the pyrolysis in moderate yield under conditions we have previously developed,[15] to provide the methoxypyrroles **46** and **47**. The pyrrolones are therefore stable enough to survive basic conditions (NaH) in a dipolar aprotic solvent (dimethylimidazolidinone). In contrast to the corresponding pyrrolones, the *O*-alkyl compounds are stable oils which can be purified and handled easily at room temperature. A number of preliminary attempts were made to hydrolyse the enamine unit of the methoxypyrroles **46** or **47** under dilute acid conditions to provide the parent 3-methoxypyrrole but no products could be isolated.



Conclusions

This work has provided the first synthetic route to *N*-alkenylpyrrol-3(2*H*)-ones (1-alkenyl-3-hydroxypyrroles), by employing the standard Meldrum's acid route to the pyrrolone and the known thermal breakdown of oxazolidine rings to give azomethine ylide intermediates. After formation of the methyleneketene by Meldrum's acid fragmentation, the overall process requires a hydrogen transfer (to generate an azomethine ylide), electrocyclisation (to a fused pyrrolone), fragmentation of the oxazolidine ring (to create a second azomethine ylide) and hydrogen transfer to give the final product. Corresponding thiazolidines may be more stable to fragmentation. The *N*-alkenylpyrrol-3(2*H*)-ones were shown to behave in a broadly similar way as other pyrrol-3(2*H*)-ones with respect to tautomerism and *O*-alkylation reactions. When pyrrolone formation is blocked, an alternative hydrogen transfer to the methyleneketene by a retro-ene reaction can take place, followed by an intramolecular reverse electron demand cycloaddition to provide the fused tricyclic pyridin-4-one **43**.

Experimental

^{1}H And ^{13}C NMR spectra were recorded at 250 (or 200) and 63 (or 50) MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants are quoted in Hz. ^{13}C NMR signals refer to CH resonances unless otherwise stated; in most cases assignments were confirmed by appropriate DEPT

experiments. Mass spectra were obtained under electron impact conditions.

Oxazolidines and related compounds

The general method of Hancock and Cope was used,[16] whereby the appropriate ethanolamine or diamine (1 equivalent) was heated with cyclohexanone (1.1 equivalent) in toluene solution in the presence of a small amount of toluene-*p*-sulfonic acid using a Dean and Stark trap. The following products were prepared.

1-Oxa-4-azaspiro[4.5]decane (2,2-pentamethyleneoxazolidine) 5. (82%), bp 93–95 °C (15 Torr) [lit.,[17] 89–90 °C (16 Torr)].

3-Phenyl-1-oxa-4-azaspiro[4.5]decane (2,2-pentamethylene-4-phenyloxazolidine) 6. (78%), bp 140–142 °C (0.2 Torr) [characterised as its Meldrum's acid derivative **15** (see below)].

3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane (4,4-dimethyl-2,2-pentamethyleneoxazolidine) 7. (62%), bp 106–109 °C (34 Torr) [lit.,[16] 95–97.5 °C (20 Torr)].

1-Oxa-5-azaspiro[5.5]undecane (2,2-pentamethylenetetrahydro-1,3-oxazine) 9. (80%) mp 44–45 °C (lit.,[18] 44–45 °C); δ_H 3.75 (2H, m), 2.87 (2H, m) and 1.3–1.8 (12H, m); δ_C 83.96 (quat), 60.21 (CH_2), 38.55 (CH_2), 34.54 ($2CH_2$), 27.64 (CH_2), 26.34 (CH_2) and 22.30 ($2CH_2$).

1-Methyl-1,5-diazaspiro[5.5]undecane (1-methyl-2,2-pentamethylenehexahydropyrimidine) 10. (85%) bp 50–60 °C (0.9 Torr) [lit.,[19] 112 °C (70 Torr)].

2,2-Pentamethylene-1,3-thiazolidine 11. Made by the general method of Schmolka and Spoerri[20] bp 106–107 °C (11 Torr) [lit.,[21] 125–127 °C (20 Torr)], δ_H 3.18 (2H, t), 2.78 (2H, t) and 1.3–1.8 (10H, m); δ_C 81.75 (quat), 49.93 (CH_2), 39.93 ($2CH_2$), 34.96 (CH_2), 25.00 (CH_2) and 24.33 ($2CH_2$).

1,3-Thiazolidine 12. Compound **12** was made in 75% yield by the standard route[22] bp 60–65 °C (10 Torr) [lit.,[22] 60–62 °C (10 Torr)]; δ_H 4.01 (2H, s), 3.03 (2H, t) and 2.71 (2H, t); δ_C 55.73, 53.12 and 34.30 (all CH_2).

Meldrum's acid derivatives

A solution of the relevant oxazolidine or related substrate (22 mmol) in acetonitrile (5 cm^3) was added to a stirred solution of 2,2-dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione **13** (3.72 g, 20 mmol) in acetonitrile (25 cm^3) and the reaction was allowed to stir at room temperature for 3 h. The product was isolated as a precipitate or by removal of the solvent under reduced pressure. The following derivatives were prepared by this method.

2,2-Dimethyl-5-(2,2-pentamethyleneoxazolidin-3-ylmethylene)-1,3-dioxane-4,6-dione 14. (87%) mp 147–149 °C (from ethanol) (Found: C, 61.3; H, 7.4; N, 4.7. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.1; N, 4.75%); δ_H 8.05 (1H, s), 4.00 (2H, br d, ^3J 5.6), 3.94 (2H, br d, ^3J 5.6), 1.77–1.55 (10H, m) and 1.63 (6H, s); δ_C 165.60 (quat), 160.13 (quat), 150.87, 102.81 (quat), 99.05 (quat), 85.07 (quat), 63.38 (CH_2), 50.51 (CH_2), 35.17 ($2CH_2$), 26.47 ($2CH_3$), 24.14 (CH_2) and 22.89 ($2CH_2$); *m*/*z* 295 (M^+, 15%), 238 (28), 237 (89), 194 (30), 150 (40), 141 (36), 140 (21), 139 (100), 122 (50), 96 (25) and 95 (27).

2,2-Dimethyl-5-(2,2-pentamethylene-4-phenyloxazolidin-3-ylmethylene)-1,3-dioxane-4,6-dione 15. (27%) mp 141–143 °C (from cyclohexane) (Found: C, 68.2; H, 6.8; N, 3.8. $C_{21}H_{25}NO_5$ requires, C, 67.9; H, 6.75; N, 3.8%); δ_H 8.08 (1H, d, ^4J 1.4), 7.31–7.10 (5H, m), 5.93 (1H, m), 4.48 (1H, d of d, ^3J 7.4 and ^2J 9.2), 3.87 (1H, d of d, ^3J 5.8 and ^2J 9.2), 2.19–1.16 (10H, m), 1.48 (3H, s) and 0.77 (3H, s); δ_C 165.41 (quat), 159.90 (quat), 149.41, 136.15 (quat), 128.77, 128.21, 127.42, 102.81 (quat), 100.31 (quat), 87.16 (quat), 71.57, 63.99, 37.48, 33.22, 27.37, 24.30, 23.92, and 23.04 (2C's overlapping; full assignments not confirmed by DEPT); *m*/*z* 313 (M − C_3H_6O, 23%), 215 (100), 143 (48), 104 (66), and 91 (13), (M^+ not detected).

2,2-Dimethyl-5-(4,4-dimethyl-2,2-pentamethyleneoxazolidin-3-ylmethylene)-1,3-dioxane-4,6-dione 16. (82%) mp 185–187 °C (from ethanol) (Found: C, 63.4; H, 8.0; N, 4.45. $C_{17}H_{25}NO_5$ requires C, 63.2; H, 7.75; N, 4.35%); δ_H (all signals broad) 8.00 (1H, s), 3.66 (2H, s), 1.59–1.35 [22H, m including 1.58 (s), and 1.51 (s)]; δ_C (signals broadened) 163.58 (two quat), 150.18, 102.30 (quat), 102.13 (quat), 84.39 (quat), 77.72 (CH_2), 65.50 (quat), 36.14 (CH_2), 26.50 (CH_3), 23.91 (CH_2) and 22.97 (CH_2) (some signals overlapping); *m*/*z* 323 (M^+, 25%), 266 (27), 265 (74), 193 (29), 178 (58), 169 (60), 166 (28), 154 (55) and 150 (88).

2,2-Dimethyl-5-(2,2-pentamethylenetetrahydrooxazinylmethylene)-1,3-dioxane-4,6-dione 18. (85%) mp 155–156 °C (from ethanol) (Found: C, 61.7; H, 7.5; N, 4.3. $C_{16}H_{23}NO_5$ requires C, 62.15; H, 7.45; N, 4.55%); δ_H 8.34 (1H, s), 3.8–4.0 (4H, m), 2.28 (2H, m), 1.94 (2H, m) and 1.7–1.5 (14H, m); δ_C 156.04, 103.24 (quat), 92.34 (quat), 84.17 (quat), 58.79 (CH_2), 47.65 (CH_2), 34.76 ($2CH_2$), 27.12 ($2CH_3$), 25.24 (CH_2), 25.17 (CH_2) and 22.64 ($2CH_2$) (2 quat signals expected at *ca.* δ_C 160 are broadened by exchange); *m*/*z* 309 (M^+, 7%), 251 (66), 153 (41), 137 (44), 127 (100), 109 (70) and 81 (84).

2,2-Dimethyl-5-(3-methyl-2,2-pentamethylenehexahydropyrimidin-1-ylmethylene)-1,3-dioxane-4,6-dione 19. (82% crude), decomposed on attempted crystallisation and was not fully characterised δ_H 8.03 (1H, s), 3.50 (2H, t), 2.64 (2H, t), 2.34 (3H, s), 2.24 (3H, m), 1.76 (6H, m), 1.65 (3H, m) and 1.60 (6H, s); δ_C 165.63 (quat), 164.55 (quat), 159.74, 116.93 (quat), 104.64 (quat), 84.29 (quat), 49.90 (CH_2), 49.47 (CH_2), 42.28 ($2CH_2$), 36.45 (CH_3), 29.53 (CH_2), 27.34 ($2CH_2$), 27.13 ($2CH_3$) and 25.27 (CH_2); *m*/*z* 322 (M^+, 2%), 264 (3), 221 (5), 168 (49), 139 (26) and 125 (100).

2,2-Dimethyl-5-(2,2-pentamethylenethiazolidin-3-ylmethylene)-1,3-dioxane-4,6-dione 20. (85%) mp 134–136 °C (from ethanol) (Found: C, 57.05; H, 6.9; N, 4.25. $C_{15}H_{21}NO_4S{\cdot}0.25\ H_2O$ requires C, 57.05; H, 6.8; N, 4.45%); δ_H 8.25 (1H, s), 4.13 (2H, t, ^3J 6.4), 2.98 (2H, br d, ^3J 6.4), 2.2–1.4 (16H, m); δ_C 165.64 (quat), 160.10 (quat), 152.54, 102.83 (quat), 85.39 (quat), 82.21 (quat), 57.58 (CH_2), 39.11 ($2CH_2$), 27.58 (CH_2), 26.45 ($2CH_3$), 24.88 ($2CH_2$) and 24.22 (CH_2); *m*/*z* 253 (M^+, 2%), 181 (15), 168 (100), 152 (21), 138 (65), 125 (26) and 110 (46).

2,2-Dimethyl-5-(thiazolidin-3-ylmethylene)-1,3-dioxane-4,6-dione 21. (80%) mp 114–116 °C (from ethanol) (Found: C, 49.4; H, 5.25; N, 5.7. $C_{10}H_{13}NO_4S$ requires C, 49.4; H, 5.35; N, 5.75%); δ_H (2 rotamers present in 62 : 38 ratio) 8.21 (minor, 1H, s), 8.17 (major, 1H, t, ^4J 0.8), 4.71 (minor, 2H, s), 4.58 (major, 2H, d, ^4J 0.8), 4.01 (major, 2H, t, ^3J 6.4), 3.89 (minor, 2H, t, ^3J 6.5), 3.10 (minor, 2H, t, ^3J 6.5), 3.02 (major, 2H, t, ^3J 6.4) and 1.63 (both rotamers, 6H, s); δ_C 165.02 (both rotamers, quat), 160.33 (major, quat), 160.20 (minor, quat), 155.63 (major), 155.56 (minor), 102.96 (major, quat), 102.88 (minor, quat), 86.19 (major, quat), 85.83 (minor, quat), 59.20 (major, CH_2), 58.70 (minor, CH_2), 54.35 (minor, CH_2), 53.51 (major, CH_2), 30.63 (minor, CH_2), 26.36 (major, CH_2) and 26.38 (both rotamers, CH_3); *m*/*z* 243 (M^+, 2%), 185 (100), 157 (37), 129 (23), 113 (28), 87 (25) and 53 (47).

2,2-Dimethyl-5-(2,2-dimethyloxazolidinylmethylene)-1,3-dioxane-4,6-dione 17. The acetone-derived oxazolidines showed variable amounts of hydrolysis product using the standard

conditions and so an alternative 'one-pot' method was devised as follows. Ethanolamine (2-aminoethanol) (2.44 g, 40 mmol) was dissolved in acetone (50 cm^3) and a catalytic amount of toluene-*p*-sulfonic acid was added. The solution was then heated at reflux for 3 h. After the solution had cooled a solution of freshly prepared 2,2-dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione **13** (7.44 g, 40 mmol) in acetone (25 cm^3) was added. The reaction mixture was then stirred overnight at room temperature. The product was obtained by removal of solvent under reduced pressure to give *2,2-dimethyl-5-(2,2-dimethyloxazolidinylmethylene)-1,3-dioxane-4,6-dione* **17** (85%) mp 135–137 °C (from ethanol) (Found: C, 56.3; H, 6.7; N, 5.6. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%); δ_H (all signals broad), 8.93 (1H, s), 4.11–3.98 (4H, m), 1.69 (6H, s) and 1.56 (6H, s); δ_C 165.52 (quat), 160.10 (quat), 151.03, 102.95 (quat), 97.96 (quat), 85.40 (quat), 63.63 (CH_2), 50.34 (CH_2), 26.54 and 26.31 (both $2CH_3$); *m*/*z* 255 (M^+, 10%), 198 (17), 197 (26), 139 (100), 138 (46), 96 (23), 95 (45), 68 (23) and 67 (89).

Under similar conditions, 2,2-dimethyl-5-(2,2-[$^2H_6$]dimethyloxazolidinylmethylene)-1,3-dioxane-4,6-dione, **17D** *m*/*z* 261 (M^+, 2%), 203 (10), 139 (100), 111 (11), 95 (35), 68 (16) and 67 (64) was prepared in 80% yield.

Flash vacuum pyrolysis experiments

Conditions for the pyrolyses were established in small scale experiments in which the product(s) were dissolved in a deuteriated solvent and analysed immediately by ^1H NMR spectroscopy. On a larger scale the crude products could not be further purified because of decomposition. The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), pressure range (P) and pyrolysis time (t)] and, where appropriate, approximate yields are given.

FVP of the 5-(2,2-pentamethyleneoxazolidinyl)- derivative 14. (158 mg, T_f 600 °C, T_i 140 °C, P 5 × 10^{-3} Torr, t 2 h) gave *1-(cyclohex-1-enyl)-1H-pyrrol-3(2H)-one*, **22** (*ca.* 70%) decomposes on attempted distillation [140 °C (0.2 Torr)] (Found: M^+ 163.0997. $C_{10}H_{13}NO$ requires M 163.0997); δ_H 7.94 (1H, d, ^3J 3.4), 5.15 (1H, d, ^3J 3.4), 5.01 (1H, br t, ^3J 1.2), 3.82 (2H, s) and 2.20–1.45 (8H, m); δ_C 198.16 (quat), 158.20, 134.49 (quat), 105.55, 100.49, 55.07 (CH_2), 24.27 (CH_2), 23.54 (CH_2), 21.88 (CH_2) and 21.65 (CH_2); *m*/*z* 163 (M^+, 100%), 162 (27) and 135 (23).

FVP of the 5-(2,2-dimethyloxazolidinyl)- derivative 17. (90 mg, T_f 625 °C, T_i 140 °C, P 1 × 10^{-3} Torr, t 30 min) gave *1-(1-methylethenyl)-1H-pyrrol-3(2H)-one* **23** (*ca.* 50%), decomposes on attempted distillation [100 °C (0.2 Torr)] (Found: M^+, 123.0683. C_7H_9NO requires M 123.0684); δ_H 9.45 (1H, d, ^3J 3.6), 5.22 (1H, d, ^3J 3.6), 4.11 (2H, s), 3.84 (2H, s) and 1.96 (3H, s); δ_C 198.50 (quat), 158.62, 139.24 (quat), 102.71, 91.84 (CH_2), 55.17 (CH_2) and 18.30 (CH_3); *m*/*z* 123 (M^+, 100%), 108 (37), 95 (11), 94 (15), 83 (56), 80 (14) and 67 (11); a second product formed during this pyrolysis, (*ca.* 20%), which decomposed on attempted recrystallisation. A small sample of this compound was adventitiously obtained in reasonable purity, allowing it to be identified as *2-(dimethylmethylene)-1H-pyrrol-3(2H)-one* **24** (Found: M^+, 123.0690. C_7H_9NO requires M, 123.0684); δ_H 7.59 (1H, t, ^3J 3.6), 7.25 (1H, br s), 5.33 (1H, d of d, ^3J 3.6 and ^4J 1.6), 2.35 (3H, s) and 1.97 (3H, s); *m*/*z* 123 (M^+, 100%), 108 (54), 80 (20), 53 (14) and 41 (20).

FVP of the 5-(2,2-pentamethylenetetrahydrooxazinyl) derivative 18. (200 mg, T_f 600 °C, T_i 185 °C, P 10^{-2} Torr, t 15 min) with standard work-up gave a mixture whose spectra showed only decomposition products. However, when the pyrolysate was trapped on a 'cold-finger' at −80 °C and an aliquot was washed directly into an NMR tube under a nitrogen atmosphere, the ^1H NMR spectrum at −20 °C showed evidence of the formation of the fused pyrrolone **31** δ_H ([$^2H_6$]acetone) (pyrrolone tautomer) 8.29 (1H, d, ^3J 3.4) and 5.00 (1H, d, ^3J 3.4); (hydroxypyrrole tautomer) 6.44 (1H, d, ^3J 3.0) and 5.65 (1H, d, ^3J 3.0). The keto and enol tautomers were present in 47 : 53 ratio under these conditions. The assignment was confirmed by mass spectrometry (**31**, Found: M^+, 207.1256. $C_{12}H_{17}NO_2$ requires M 207.1259) which also showed the presence of the oxidation product **32** (Found: M^+, 223.1206. $C_{12}H_{17}NO_3$ requires M 223.1208). This oxidation behaviour is characteristic of 2-substituted pyrrolones.[5]

FVP of the 5-(2,2-pentamethylenethiazolidinyl)- derivative 20. (200 mg, T_f 600 °C, T_i 185 °C, P 10^{-2} Torr, t 15 min) gave *1-(cyclohex-1-enyl)-1H-pyrrol-3(2H)-one* **22** as above, (*ca.* 30%) δ_H 7.97 (1H, d, ^3J 3.4), 5.21 (1H, d, ^3J 3.4), 5.04 (1H, br t, ^3J 1.2), 3.88 (2H, s) and 2.30–1.5 (8H, m); δ_C 198.44 (quat), 157.87, 134.59 (quat), 105.65, 100.91, 55.23 (CH_2), 24.50 (CH_2), 23.71 (CH_2), 22.07 (CH_2) and 21.84 (CH_2); a second unidentified component (*ca.* 20%) showed characteristic pyrrolone signals at δ_H 7.91 (1H, d, ^3J 3.9) and 5.18 (1H, d, ^3J 3.9); δ_C 163.47 and 101.07.

FVP of the 5-(thiazolidinyl) derivative 21. (100 mg, T_f 600 °C, T_i 165 °C, P 10^{-2} Torr, t 15 min) gave no significant products except acetone. However, when a 'cold-finger' trap was used as described for compound **18** above, three products **35**, **37** and **40** formed in 55 : 18 : 27 ratio could be identified from the NMR spectra of an aliquot of the mixture. The major product was 2,3-dihydropyrrolo[2,1-*b*]thiazol-7(7a*H*)-one **35** (55% of the mixture) δ_H ([$^2H_6$]acetone) 7.97 (1H, d, ^3J 3.6), 5.25 (1H, d, ^3J 3.6), 4.71 (1H, s), 4.03 (1H, dd, ^2J 12.1 and ^3J 5.6), 3.29 (1H, td, ^2J and ^3J 11.8, ^3J 5.3), 3.05 (1H, dd, ^2J 10.5 and ^3J 5.4) and 2.82 (1H, td, ^2J and ^3J 11.0, ^3J 5.7); δ_C ([$^2H_6$]acetone) 202.73 (quat), 170.29, 105.68, 66.70, 53.14 (CH_2) and 32.44 (CH_2). The minor bicycle was 1,3-dihydropyrrolo[1,2-*c*]thiazol-7(7a*H*)-one **37** (18% of the mixture) δ_H ([$^2H_6$]acetone) 8.10 (1H, d, ^3J 3.6), 5.35 (1H, d, ^3J 3.6), 4.70 (1H, d, ^2J 10.5), 4.37 (1H, d,^2J 10.5), 3.97 (1H, overlapping m), 3.38 (1H, overlapping m) and 2.97 (1H, overlapping m); δ_C ([$^2H_6$]acetone) 204.19 (quat), 171.54, 109.20, 69.37, 54.52 (CH_2) and 31.63 (CH_2). The presence of the pyrrolothiazoles was confirmed by mass spectrometry (Found: M^+, 141.0249. C_6H_7NS requires M 141.0248). The third product was 1*H*-pyridin-4-one **40** (27% of the mixture) δ_H ([$^2H_6$]acetone) 7.87 (1H, d, ^3J 7.4) and 6.37 (1H, d, ^3J 7.4); δ_C ([$^2H_6$]acetone) (CH's only) 140.36 and 117.70 (Found: M^+ 95.0370. C_5H_5NO requires M 95.0371). FVP at 750 °C gave pyridin-4-one **40** δ_H ([$^2H_6$]acetone) 7.83 (1H, d, ^3J 7.4) and 6.39 (1H, d, ^3J 7.4) as the only product.

FVP of the 5-(4,4-dimethyl-2,2-pentamethyleneoxazolidinyl-) compound 16. (148 mg, T_f 625 °C, T_i 150 °C, P 10^{-3} Torr, t 1 h), gave *3,3-dimethyl-2,3,8,9,10,11-hexahydro-7aH-oxazolo[2,3-j]-quinolin-7-one* **43** (50%) bp 165–167 °C (0.2 Torr) (Found: M^+, 221.1416. $C_{13}H_{19}NO_2$ requires M 221.1414); δ_H 6.98 (1H, d, ^3J 7.1), 4.99 (1H, br d, ^3J 7.1), 3.95 (1H, d, ^2J 9.0), 3.87 (1H, br d, ^2J 9.0), 2.63 (1H, m), 2.43 (1H, m), 1.70 (1H, m), 1.88–1.28 (6H, m), 1.38 (3H, s) and 1.35 (3H, s); δ_C 193.29 (quat), 142.66, 97.77, 95.79 (quat), 76.71 (CH_2), 59.91 (quat), 50.07, 29.06 (CH_3), 26.51 (CH_2), 24.68 (CH_3), 22.56 (CH_2) and 21.28 (2 CH_2 signals superimposed); *m*/*z* 221 (M^+, 28%), 206 (43), 192 (39), 179 (100), 150 (14), 124 (22) and 55 (26).

FVP of the 5-(2,2-pentamethylene-4-phenyloxazolidinyl-) derivative **15** and the hexahydropyrimidinyl compound **19** failed repeatedly to give any identifiable products.

1-Cyclohex-1-enyl-3-methoxypyrrole 46

The pyrrolone precursor **14** (0.5 g, 1.7 mmol) was pyrolysed under FVP conditions as described above. The entire pyrolysate

was dissolved in dimethylimidazolidinone (10 cm^3), sodium hydride (50%, 0.24 g, *ca.* 3 × excess) was added and the mixture was stirred for 15 min under an atmosphere of nitrogen. Methyl toluene-*p*-sulfonate (0.32 g, 1.7 mmol) was added and the stirring was continued at room temperature for 2 h. Standard work-up[14] gave a dark oil which was distilled (Kugelrohr) to give *1-cyclohex-1-enyl-3-methoxypyrrole* **46** (0.090 g, 30% overall for the two steps), bp 138–140 °C (0.1 Torr) (Found: M^+, 177.1148. $C_{11}H_{15}NO$ requires *M* 177.1154); δ_H 6.67 (1H, dd, ^3J 3.1 and ^4J 2.5), 6.47 (1H, dd, ^4J 2.5 and 2.0), 5.90 (1H, dd, ^3J 3.1 and ^4J 2.0), 5.63 (1H, m), 3.72 (3H, s), 2.44–2.37 (2H, m), 2.21–2.13 (2H, m) and 1.83–1.61 (4H, m); δ_C 149.40 (quat), 135.92 (quat), 115.50, 110.78, 99.41, 98.04, 57.53 (CH_3), 26.41 (CH_2), 24.00 (CH_2), 22.50 (CH_2) and 21.95 (CH_2); *m*/*z* 177 (M^+, 100%), 162 (58), 134 (16) and 81 (20).

1-(1-Methylethenyl)-3-methoxypyrrole 47

The pyrrolone precursor **17** (0.37 g, 1.5 mmol) was pyrolysed under FVP conditions as described above. The entire pyrolysate was dissolved in dimethylimidazolidinone (8 cm^3) containing a suspension of sodium hydride (50%, 0.22 g, *ca.* 3 × excess) and the mixture was stirred for 15 min under an atmosphere of nitrogen. Methyl toluene-*p*-sulfonate (0.19 g, 1 mmol) was added and the stirring was continued at room temperature for 1 h. Standard work-up[14] gave a brown oil which was distilled (Kugelrohr) to give *1-(methylethenyl)-3-methoxypyrrole* **47** (0.066 g, 32% overall for the two steps), bp 142–145 °C (20 Torr) (Found: M^+, 137.0843. $C_8H_{11}NO$ requires *M* 137.0841); δ_H 6.74 (1H, dd, ^3J 3.1 and ^4J 2.5), 6.53 (1H, dd, ^4J 2.5 and 2.0), 5.94 (1H, dd, ^3J 3.1 and ^4J 2.0), 4.81 (1H, br s), 4.46 (1H, br s), 3.74 (3H, s) and 2.17 (3H, d, ^4J 1.2); δ_C 150.01 (quat), 140.44 (quat), 116.27, 99.42 (2CH), 95.88 (CH_2), 57.52 (CH_3) and 19.64 (CH_3); *m*/*z* 137 (M^+, 100%), 122 (70), 82 (75) and 41 (62).

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