COMMUNICATION

Pyrolytic cascades: a convenient entry to 5*H*-pyrrolo[2,1-*a*]-isoindol-5-ones and related heterocyclic systems

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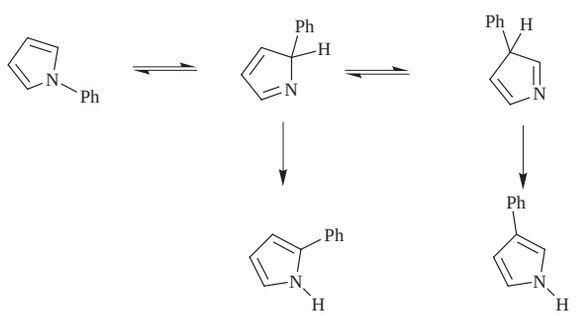
Received (in Cambridge) 6th April 1999, Accepted 18th June 1999

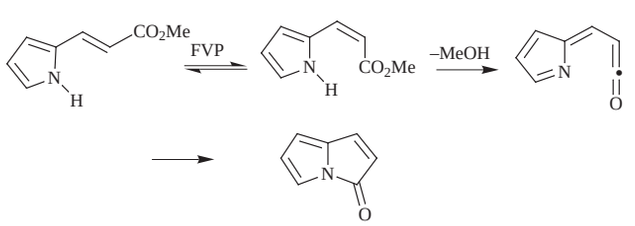
Flash vacuum pyrolysis (FVP) of 1-(2-methoxycarbonylphenyl)pyrrole 2 at 925 °C (0.001 Torr) gives pyrrolo-[2,1-*a*]isoindol-5-one 1 (79%) by a cascade process involving rate determining 1,5-aryl migration, elimination of methanol and electrocyclisation of the resulting ketene intermediate 3; the related heterocyclic systems 6, 9 and 12 were made by analogous methods.

The thermal rearrangement of 1-substituted pyrroles to 2- (and 3-) substituted isomers by sequential [1,5]-shifts has been known for more than 100 years,[1] and studied extensively by Patterson and co-workers in the 1960's and 1970's.[2,3] We have used the thermal rearrangement of 1-phenylpyrrole under extreme flash vacuum pyrolysis (FVP) conditions (1000 °C, 0.01 Torr) as a straightforward route to small quantities of the 2- and 3-phenyl isomers (Scheme 1).[4] We have also shown that



Scheme 1

3-(pyrrol-2-yl)propenoate esters and related compounds undergo concerted elimination of alcohols under FVP conditions to give pyrrolizin-3-ones by electrocyclisation of a pyrrol-2-ylideneketene intermediate (Scheme 2).[5,6] We have now discovered that these two processes can be combined in a convenient three step, one-pass FVP route to the unusual pyrrolo[2,1-*a*]isoindol-5-one system **1** from readily available 1-(2-methoxycarbonylphenyl)pyrrole **2**, and discuss the mechanism and scope of this novel pyrolytic cascade process.



Scheme 2

Thus, when the pyrrole **2** is subjected to FVP at 925 °C (0.01 Torr) a single heterocyclic product is obtained in 79% yield, whose spectroscopic data are in accord with those of the pyrroloisoindolone **1**.[7] The structure was also proved unambiguously by X-ray crystallography† (Fig. 1). We believe that the

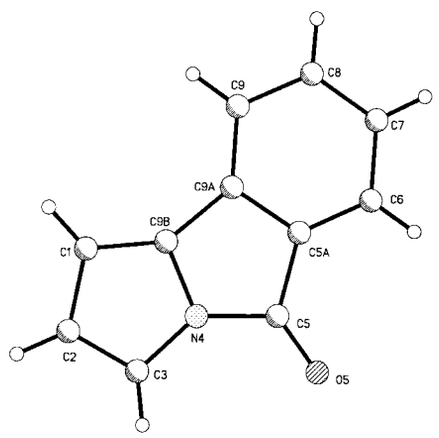
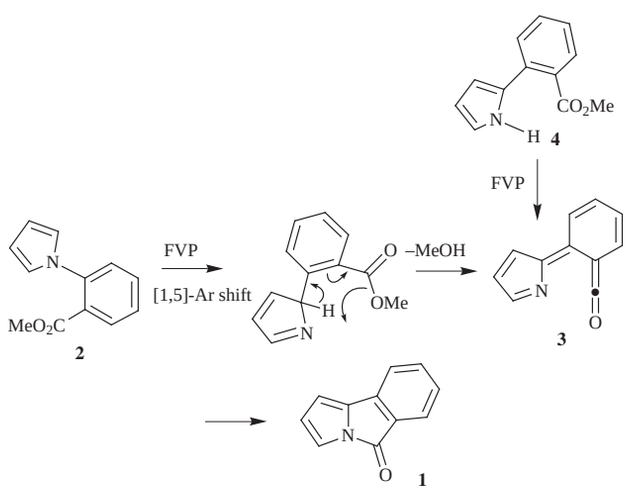


Fig. 1 Molecular structure of **1** as determined by X-ray crystallography.

mechanism of our pyrolysis is a cascade involving an initial 1,5-shift of the aryl group, followed by elimination and electrocyclisation of the ketene intermediate **3** (Scheme 3). The absence



Scheme 3

of any products derived from a 3-arylpyrrole suggests that the elimination step may be fast relative to a further 1,5-aryl shift. In agreement with this proposal, pyrolysis of the 2-arylpyrrole **4** (obtained by methanolysis of the pyrroloisoindolone **1** in the presence of Hünig's base) gives **1** under much milder conditions than its isomer **2** (total conversion at 800 °C and 0.01 Torr). Finally, the remarkable thermal stability of **1** (and its ketene valence isomer **3**) should be noted.

Because few general synthetic routes to pyrrolo[2,1-*a*]-isoindol-5-ones are currently available (*cf.* ref. 7) we have explored the potential of the sequence shown in Scheme 3 for the synthesis of other heterocyclic systems related to **1**. Thus

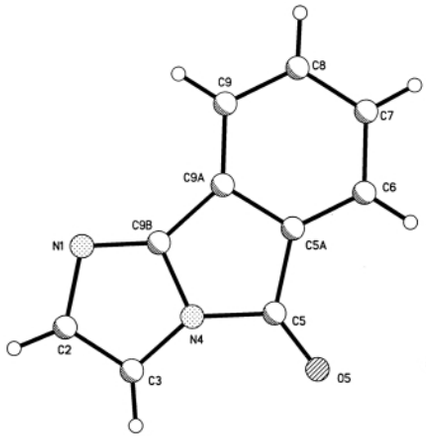
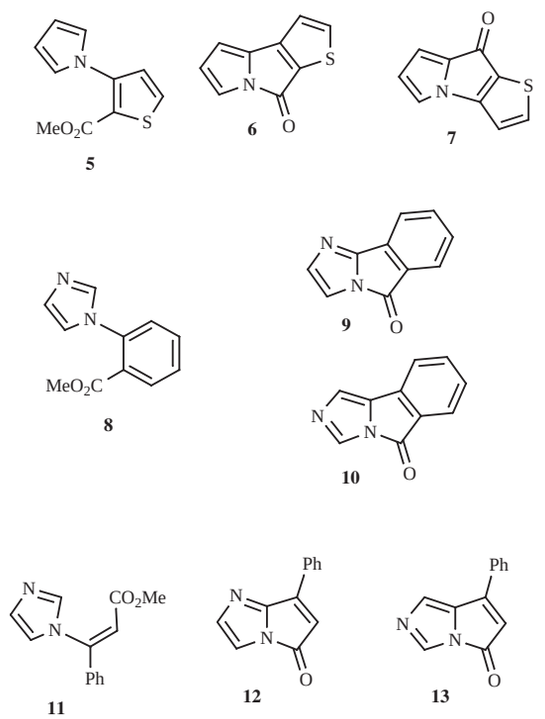


Fig. 2 Molecular structure of **9** as determined by X-ray crystallography.



the commercially available 1-thienylpyrrole **5** gives the new ring system ‡ **6** (79%) in one step at 925 °C (0.01 Torr), showing that the presence of the benzene ring is not required for the process to be successful. The known isomeric ring system **7** was unambiguously excluded on the basis of its spectra.[8]

Pyrolysis of the 1-arylimidazole **8** (obtained by reaction of imidazole with methyl 2-fluorobenzoate under basic conditions[9]) could give either of the tricycles **9** or **10**, *via* initial migration of the aryl group to the 2- or 5-position of the imidazole respectively. It is known that pyrolysis of 1-phenylimidazole under flow conditions gives both 2-phenylimidazole and 4-phenylimidazole in a 15:1 ratio,[10] and we therefore anticipated that the imidazo[2,1-*a*]isoindol-5-one **9** should predominate. These expectations were realised in practice, and the identification of **9** [67% at 925 °C (0.01 Torr)] was confirmed by X-ray crystallography † (Fig. 2). A trace of the isomeric heterocycle **10** (≤10%) was tentatively identified from minor signals in the expected region[11] of the ^{1}H NMR spectrum of the crude pyrolysate.

Finally, we have shown that the cascade strategy is also compatible with the presence of a 1-vinyl substituent in place of the 1-aryl group. Pyrolysis of the known[12] 1-vinylimidazole **11** at 800 °C (0.01 Torr) gave the expected pyrrolo[1,2-*a*]imidazolone **12** in 73% yield (identified by comparison of its NMR spectra with those of other examples of this ring system[6,11]) and only a trace (*ca.* 9%) of the isomeric product **13** was obtained. It is noteworthy that the conditions required for sigmatropic migration of the vinyl substituent are significantly milder than for migration of the aryl group, as previously found in the indene series.[13]

In conclusion, we have developed a convenient and flexible cascade process employing readily available precursors which gives pyrrolo[2,1-*a*]isoindol-5-one and related heterocyclic systems which are either previously unknown or are awkward to prepare by traditional methods. However, very high reaction temperatures are needed for the *N*-aryl examples, and so the success of the cascade process in these cases relies on the remarkable thermal stability of the products (*cf.* ref. 14).

Acknowledgements

We are grateful to the EPSRC for the award of a diffractometer.

Notes and references

† Crystal data for **1**, $C_{11}H_7NO$, $M = 169.18$, orthorhombic, *Pbca*, $a = 5.3646(5)$, $b = 13.6245(14)$, $c = 22.3766(19)$ Å, $V = 1635$ Å^3, $T = 220$ K, $Z = 8$, μ(Cu-Kα) = 0.719 mm^{-1}, $R1$ [1266 data with $F > 4\sigma(F)$] = 3.57%, $wR2$ (1516 unique F^2) = 9.64%.

Crystal data for **9**, $C_{10}H_6N_2O$, $M = 170.17$, orthorhombic, $Pna2_1$, $a = 13.055(4)$, $b = 5.5116(14)$, $c = 21.840(5)$ Å, $V = 1571$ Å^3, $T = 220$ K, $Z = 8$, μ(Cu-Kα) = 0.791 mm^{-1}, $R1$ [1403 data with $F > 4\sigma(F)$] = 3.43%, $wR2$ (1516 unique F^2) = 9.09%.

Structure solution and refinement were performed with the SHELX-97 suite of programs.[15]

CCDC reference number 207/340. See http://www.rsc.org/suppdata/p1/1999/2047 for crystallographic files in .cif format.

‡ All new compounds were characterised by their spectra and by elemental analysis or accurate mass measurement.

1 P. Crepieux and A. Pictet, *Ber. Dtsch. Chem. Ges.*, 1895, **28**, 1905.
2 For example, J. M. Patterson and L. T. Burka, *J. Am. Chem. Soc.*, 1966, **88**, 3671.
3 J. M. Patterson, *Synthesis*, 1976, 281.
4 C. L. Hickson and H. McNab, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 339.
5 S. E. Campbell, M. C. Comer, P. A. Derbyshire, X. L. M. Despinoy, H. McNab, R. Morrison, C. C. Sommerville and C. Thornley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2195.
6 H. McNab and C. Thornley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2203.
7 R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam and T. Worakun, *Tetrahedron*, 1990, **46**, 4003.
8 S. Rault, J. -C. Lancelot, Y. Effi and M. Robba, *Heterocycles*, 1983, **20**, 477.
9 *cf.* M. Artico, R. Silvestri, G. Stefancich, L. Avigliano, A. DiGiulio, M. Maccarrone, E. Agostinelli, B. Mondovi and L. Morpurgo, *Eur. J. Med. Chem.*, 1992, **27**, 219.
10 C. G. Begg, M. R. Grimmett and P. D. Wethey, *Aust. J. Chem.*, 1973, **26**, 2435.
11 H. McNab, *J. Chem. Soc.*, *Perkin Trans. 1*, 1987, 657.
12 C. Kashima, M. Shimizu and T. Tajima, *Heterocycles*, 1981, **15**, 961.
13 D. J. Field and D. W. Jones, *J. Chem. Soc.*, *Perkin Trans. 1*, 1980, 714.
14 B. A. J. Clark, X. L. M. Despinoy, H. McNab, C. C. Sommerville and E. Stevenson, following communication.
15 G. M. Sheldrick, SHELX-97, Programs for the solution and refinement of crystal structures, University of Göttingen, 1997.

Communication 9/04885E