Synthetic applications of flash vacuum pyrolysis

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Reviewing the literature published between 1990 and 1995

1 Introduction

This review is concerned with the synthetic applications of gas-phase pyrolysis reactions carried out under low pressure flow conditions, a technique commonly known as flash vacuum pyrolysis (FVP) or flash vacuum thermolysis (FVT). In its simplest form, FVP involves vacuum distillation of a substrate through an empty hot tube with the products collected afterwards in a cold trap, and this simple apparatus is increasingly used as an alternative to high boiling solvents or sealed-tube reactions as a means of carrying out preparative pyrolysis chemistry.

The main problem with condensed-phase methods in that reactive intermediates are generated in the presence of precursor, products and (usually) solvent, so that many unwanted secondary reactions can take place; there are added – often insurmountable – difficulties if the required product is itself thermally unstable. Under FVP conditions, however, the reactive intermediate is generated under unimolecular conditions in the gas phase, and the low pressure flow conditions ensure that individual molecules spend only a short time (of the order of milliseconds) in the reaction zone, so that even thermally unstable products can be quenched without decomposition. The method is therefore ideal for unimolecular reactions but is often inefficient for gas-phase bimolecular reactions. However, reactive molecules which have sufficient lifetime to survive to the cold trap can be trapped chemically in the condensed phase by added reagents, and this can be a useful synthetic procedure.

Work in this field prior to 1980 has been comprehensively surveyed in R.F.C. Brown's monograph;[1] more recent general reviews which emphasise the preparative features of the method include those by Wiersum,[2,3,4] Schaden,[5,6] Karpf[7] and Brown.[8] The well-known application of FVP for the small-scale generation and spectroscopic characterisation of highly reactive species by matrix isolation is specifically excluded from this survey. Other related techniques such as 'flow' pyrolysis at atmospheric pressure, vacuum gas–solid reactions (VSGR)[9] and 'microsecond' FVP[10] are also excluded.

Although almost any organic molecule can be thermally decomposed under FVP conditions if a high enough furnace temperature is used, the most constructive use of the technique for preparative purposes involves the intentional use of a reaction with low activation energy. This can either generate a product directly, or generate a reactive intermediate in an appropriate environment for intramolecular trapping. Such reactions fall into three categories:

(i) Pericyclic processes. Because of entropy factors, these are most favourable in the 'reverse' direction *i.e.* retro Diels–Alder reactions, retroene reactions *etc.* Even intramolecular Diels–Alder reactions in the 'forward' direction are relatively rare under FVP conditions because of the precise constraints of the transition state, and similar considerations can often favour radical processes over retroene reactions.

(ii) Cleavage of 'small' molecules. The driving force behind this mode of reaction is the thermodynamic stability of small molecules such as N_2, CO, CO_2 *etc.*, and consequently can lead to the formation of 'high-energy' intermediates such as carbenes, nitrenes or diradicals, as well as controlling the direction of fragmentation of heterocyclic systems.

(iii) Cleavage of the weakest single bond in the molecule to generate free radicals. Although this is conceptually the simplest FVP mechanism, it is by far the least studied, and relatively few useful synthetic methods have emerged.

Since these processes are dominated by cleavage mechanisms, it follows that most FVP reactions are oxidative rather than reductive, and *often* involve the creation of unsaturated centres. This is reflected in the examples quoted in later sections, which are

arranged according to the functionality which is actually generated in the pyrolysis step. The selection is, of course, a personal one, and is representative of about one third of the relevant articles published during the period. In many examples, the utility of the gas-phase methodology is specifically emphasised by comparison with the results of corresponding solution thermolyses.

2 Apparatus

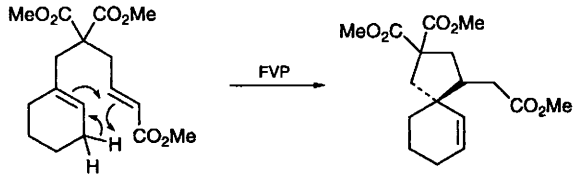
The majority of the reactions described in later sections can be carried out with the simple apparatus shown in **Figure 1**, versions of which are commercially available. The substrate is contained in the inlet, and is heated under a vacuum of 10^{-2}–10^{-3} Torr (1 Torr = 133.322 Pa = 1.31×10^{-3} bar) until it sublimes (or distils) into the furnace tube.

The chemistry takes place in the furnace tube, which is generally made from silica, is either empty or packed loosely with silica wool or silica chips, and can be heated electrically up to *ca.* 1000 °C. The optimum temperature for any reaction is dependent on the tube dimensions, and in practice is determined empirically by small-scale trial reactions. Both temperature and pressure conditions are quoted where possible in the examples given in later sections. Because of the short contact time of the molecules in the hot zone, furnace temperatures are usually outside the normal temperature range of organic chemistry. In our apparatus, most 'useful' reactions take place in the temperature range 450–700 °C, though it must be emphasised that these are 'mild' conditions since most functional groups and chiral centres will survive unchanged.

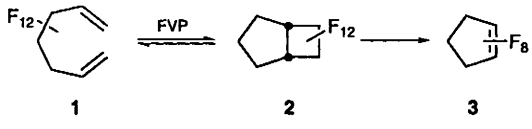
After reaction, the products are quenched in a trap cooled by liquid nitrogen, and can be worked up in the usual way when the pyrolysis is complete. Traps of modified design can be used for rapid quenching of reactive products for subsequent chemical trapping.[1] Provided the substrate can volatilise without decomposition, FVP can be carried out on an unlimited scale – certainly tens of grams – and for most preparative purposes with standard lab equipment a throughput rate of at least 1–2 grams per hour is typical.

3 Alkanes

C–C single bonds are not commonly created by FVP methods, though one reaction – the pyrolysis of macrocyclic sulfones – is almost universally employed for C–C bond formation in cyclophane chemistry (see below). Other isolated examples which have been reported recently include the intramolecular ene reaction shown in **Scheme 1**;[11] whereas pyrolysis of the precursor in mesitylene led either to no reaction or to decomposition, FVP at 550 °C (0.1 Torr) gave the product as a single diastereoisomer in 80% yield. In contrast, the primary pyrolytic process which occurs on FVP of perfluorohepta-1,6-diene **1** is a formal [2+2] cycloaddition leading to its [3.2.0] bicyclic isomer **2**, though at high temperatures the final product is the cyclopentene **3** (90%) formed by retro [2+2] cleavage of tetrafluoroethylene (**Scheme 2**).[12] The corresponding hydrocarbon displays quite different thermal behaviour, dominated by a retroene reaction.[12]



Scheme 1



Scheme 2

The use of sulfone pyrolysis in cyclophane chemistry was first reviewed by Vögtle and Rossa in 1979[13a] and later in 1992[13b] and is now almost universally employed in this field. The basic strategy involves initial reaction of a dibromo compound

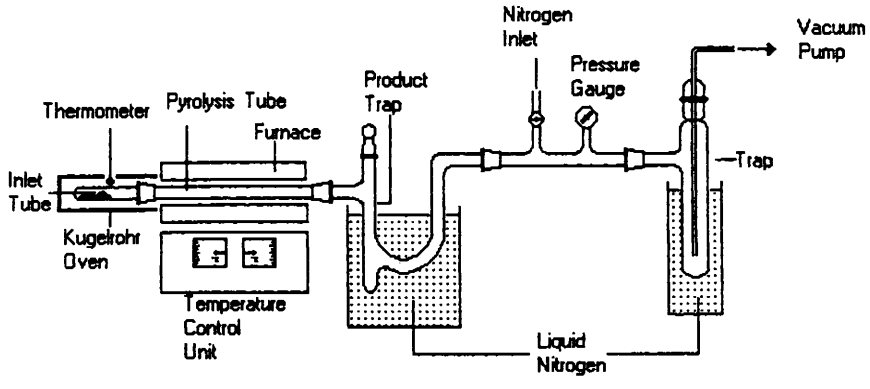
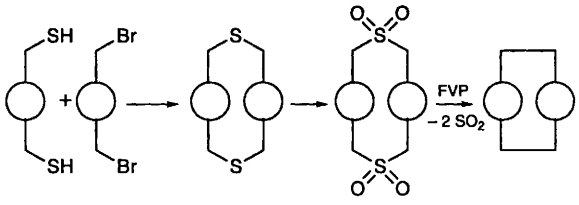


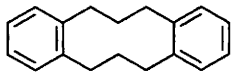
Figure 1

with a dithiol to give a macrocyclic disulfide, which is then oxidised to the disulfone and subjected to FVP (**Scheme 3**). In the key thermolysis step, loss of SO_2 generates a diradical which couples in intramolecular fashion to create the new alkane system.



Scheme 3

The examples which follow have been chosen to illustrate the wide structural diversity which can be accommodated by this strategy, including aromatic, heterocyclic and even aliphatic cyclophanes. Thus the simple orthocyclophane **4**[14] was made from an appropriate bis-sulfone in 56% yield by FVP at 700 °C (0.05 Torr). The synthesis of the more complex 'cuppedophanes' (*e.g.* **5**, 27% at 500 °C and 0.01 Torr) and 'cappedophanes' (*e.g.* **6**, 24% under similar conditions) illustrate the applicability of the method to polysulfones.[15]



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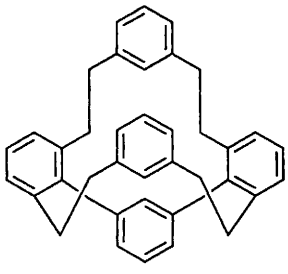

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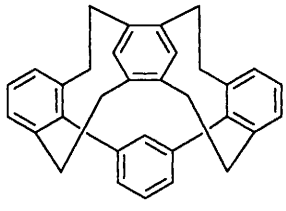

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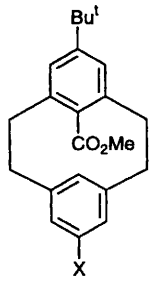
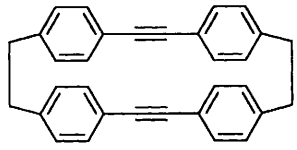
Simple metacyclophanes which have been made include compounds **7** and **8**;[16,17] the presence of the functional groups X allows the possibility of elaboration to 'molecular tweezers' which are capable of selectively binding guest molecules. Vögtle's group has also successfully synthesised the tolanophane **9** by this method,[18] though the yield was low owing to the poor volatility of the sulfone, and alternative routes were developed. Mixed orthoparacyclophanes (*e.g.* **10**; 75%) and orthometacyclophanes (**11**; 58%) are also available from disulfones (600 °C, 0.001 Torr).[19]

Polycyclic aromatic cyclophanes include the *anti*-metapyrenophanes **12**, which are obtained as the exclusive cyclophane products upon pyrolysis



7 X = NO_2
8 X = Br



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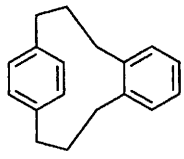

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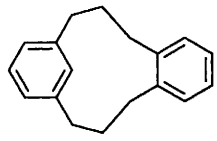
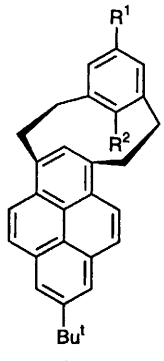


11

(480 °C, 0.8 Torr) of either the *syn*- or the *anti*-isomer of the disulfone (**13** and **14** respectively).[20]

In the heterocyclic series, the synthesis of [2_4](2,3,4,5)thienophane (superthienophane) **15** is a notable achievement.[21] The strategy involves two consecutive sulfone pyrolysis steps at 550 °C and 470 °C (0.5–2 Torr) respectively (**Scheme 4**). Although the overall yield is very low – particularly due to a poor conversion (3%) in the second pyrolysis step – two other potential routes were completely unsuccessful.



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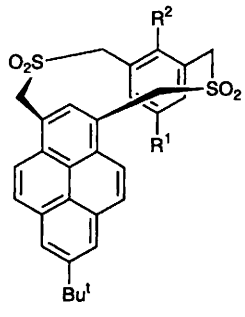

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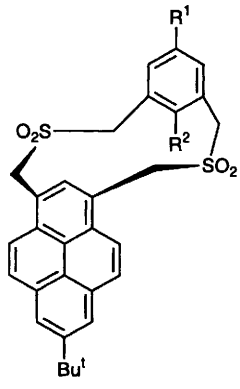

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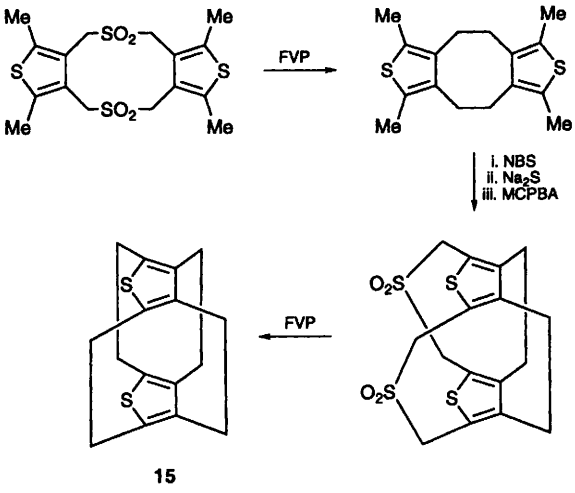
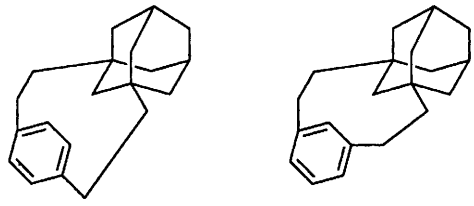


Scheme 4

The adamantane unit has been employed as a building block for new cyclophanes – so-called 'araliphanes'.[22–24] Pyrolysis conditions of 550–600 °C (10^{-4}–10^{-5} Torr) which lead to both the *para*-isomer **16** and *meta*-isomer **17** (50%) are similar to those developed for the aromatic series. In both cases the aromatic rings of the products are severely distorted, showing that even highly strained systems can survive FVP conditions.

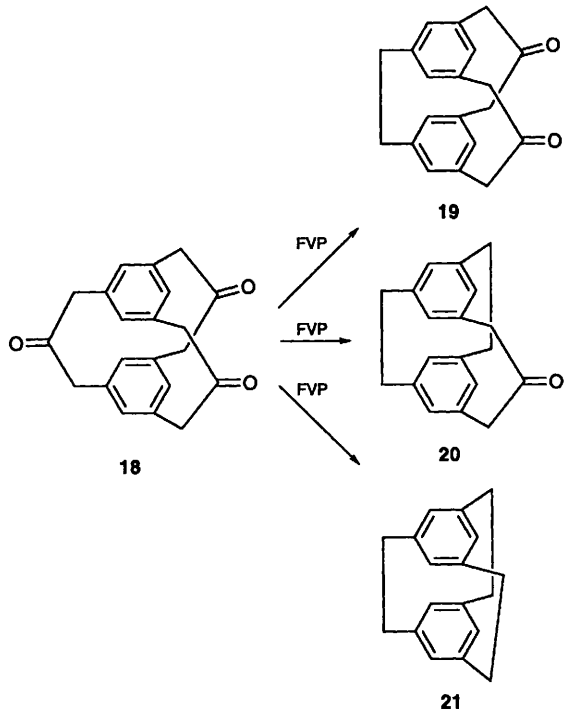


16 **17**

Despite the versatility of the sulfone pyrolysis method exemplified above, Vögtle has recently developed alternative precursors, owing to the poor volatility of complex sulfones and the sensitivity of some thiols and sulfides. The pyrolysis of macrocyclic dibenzyl ketone derivatives (*e.g.* **18**) proved to be a satisfactory alternative[25–27] which had the added advantage that conditions could be optimised over the range 610–650 °C (10^{-5} Torr) to give reasonable yields of successively partially decarbonylated products such as **19–21** (**Scheme 5**). The precursor ketones are made using TOSMIC methodology, which, unlike the synthesis of sulfones, is compatible with the presence of oxidisable groups in the molecule.

The mechanism of the formation of [8]paracyclophane by FVP of methylenespirocyclohexadienes has been studied in detail.[28]

The synthesis of benzocyclobutene by pyrolysis of α-chloro-*o*-xylene has been optimised on a 10 g scale and a detailed recipe published.[29]



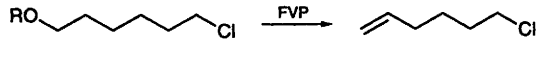
Scheme 5

4 Alkenes

The formation of an alkene unit is a common FVP transformation, which is often accomplished in preparative fashion either by retro heteroene reactions such as acetate or xanthate pyrolysis (which have been reviewed recently[30]) or by retrocycloaddition processes. In this section, the formation of monoenes is considered before that of dienes (and allenes), and the section is completed with a brief consideration of xylylene formation. Heteroene reactions are considered before cycloaddition methods.

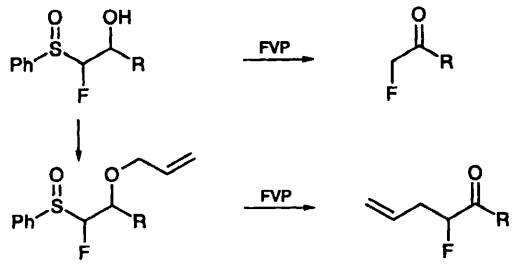
A comparative study of acetate, xanthate and tosylate pyrolysis has been used to optimise the preparation of 6-chlorohex-1-ene (**Scheme 6**).[31] The main problem here is to avoid secondary elimination of HCl to give hexa-1,5-diene; yields of up to 80% of the required product were obtained from the xanthate **22**, which has a lower pyrolysis temperature than the alternative precursors.

The mechanism of sulfoxide pyrolysis is isoelectronic with that of acetate elimination, and two complementary methods involving sulfoxide pyrolysis at *ca.* 500 °C and 0.1 Torr have been employed to give α-fluoromethyl ketones in around 50% yield (**Scheme 7**).[32,33] Although both methods



22 R = MeCO, $ArSO_2$ or MeSCS

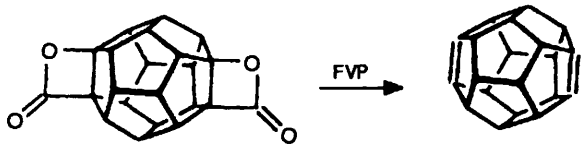
Scheme 6



Scheme 7

involve sulfenate elimination, the second has a subsequent fluorine-facilitated Claisen rearrangement which extends its scope. The gas-phase procedure is a great improvement over earlier methods such as solution pyrolysis (no products) or sealed-tube conditions (very low yields due to instability of products and difficulties in separating by-products).

The formation of alkenes by stereospecific decarboxylation of β-lactones has been reviewed,[34] and the reaction has been applied to the generation of the pyramidalised dodecahedradiene **24** (70%) by pyrolysis of the dilactone **23** at 500 °C (0.01 Torr) (**Scheme 8**).[35] Allenes can also be prepared in this way (see below).

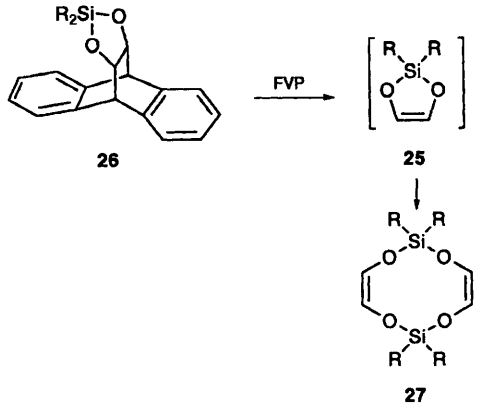


23 **24**

Scheme 8

Retro Diels–Alder reactions have been employed extensively in alkene formation. Part of the attraction of the method lies in the fact that a sensitive alkene unit can be protected during a synthetic sequence as a Diels–Alder adduct and then released when required under very mild FVP conditions. Owing to its reactivity, cyclopentadiene is the diene component most often used, but dienes which generate aromatic systems on their release such as furan or anthracene often require lower furnace temperatures for this reverse process.

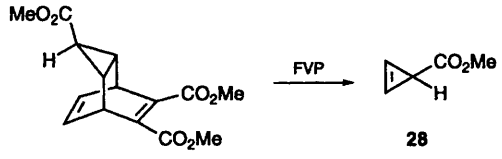
Aromatic leaving groups have been used to generate silicon-protected *Z*-ethene-1,2-diols **25**. These could not be released from their anthracene adducts **26** by distillation at 300 °C, but they were successfully generated by FVP at 560 °C (0.01 Torr) and isolated as their dimers **27** (**Scheme 9**).[36] Under the trapping conditions employed, it was not possible to obtain the monomers **25**. Methyl cyclopropene-3-carboxylate **28** has a room temperature half-life of 1–2 h but a carefully optimised procedure involving retro Diels–Alder cleavage of dimethyl phthalate at 390–430 °C (0.01 Torr) has been applied to the synthesis of ^{13}C-



26 **25** **27**

Scheme 9

labelled isotopomers in up to 85% yield (**Scheme 10**).[37a] In contrast, cyclopropene–anthracene adducts **29** undergo ring opening of the cyclopropane ring to give bridged alkenes **30** (71–87%) under mild FVP conditions (400 °C, 0.05 Torr).[37b]



28

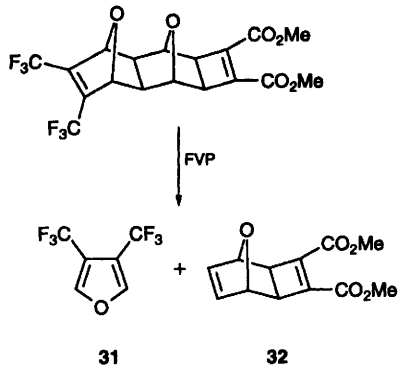
Scheme 10

29 **30**

(R = electron withdrawing group)

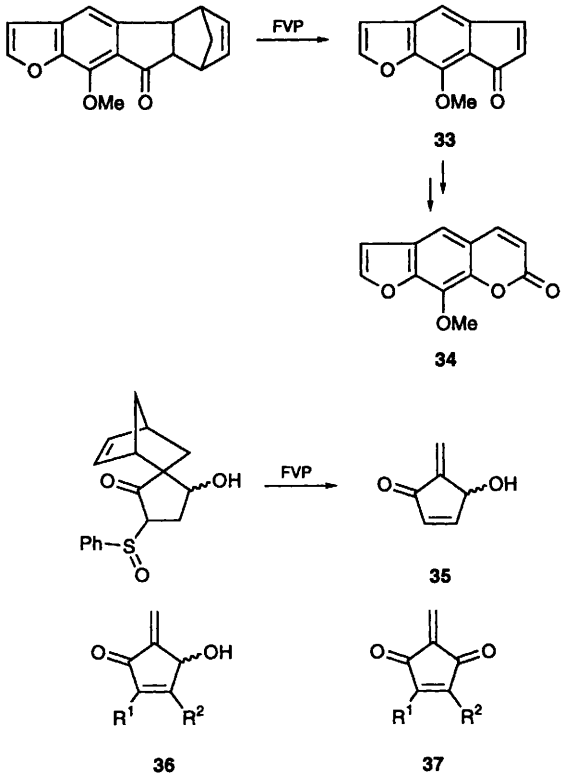
3,4-Bis(trifluoromethyl)furan **31** is a much better leaving group in retro Diels–Alder reactions than cyclopentadiene, and it has been employed by Warrener and co-workers to give the cyclobutadiene-1,2-dicarboxylate transfer reagent **32** in 90% yield at 490 °C and 17 Torr (**Scheme 11**).[38] The corresponding *endo,exo,exo* precursor is much more thermally stable, but pyrolysis at higher temperatures leads to undesired electrocyclic ring opening of the cyclobutene function.

Three recent examples of FVP mediated retro Diels–Alder reactions in cyclopentenone chemistry may be quoted (**Scheme 12**). The benzocyclopentenone **33** was obtained as shown in quantitative yield *en route* to methoxsalen **34**,[39] and a similar route has been employed by the same group to generate the 2,3-double bond of 1,4-anthraquinones.[40] Both retro Diels–Alder and sulfoxide elimination methodologies were used in a general route to prostanoid precursors **35** (57–88% at



31 32

Scheme 11

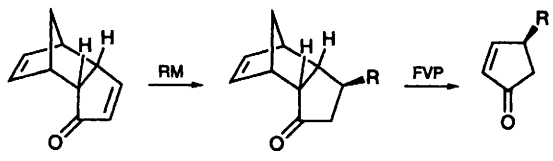


36 37

Scheme 12

350–400 °C and 0.03–0.05 Torr).[41] Closely related anthracene adducts were used to obtain 2-methylene-1,3-dioxygenated cyclopentenes **36** and **37** in 'near-quantitative' yield.[42]

Application of the retro Diels–Alder cleavage of cyclopentadiene or furan in natural product synthesis has been extensively employed in recent years by Zwanenburg and co-workers. Much of this work has involved the tricyclic cyclopentenone **38** as a key intermediate. This compound is in effect a masked cyclopentadienone, and is available in both homochiral forms by enzymatic resolution of a precursor.[43] Chemical transformation of the remaining enone system usually occurs with high regio- and stereo-selectivity, the latter due to



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Scheme 13

shielding of the concave *endo* face by the norbornene system (**Scheme 13**); retro Diels–Alder reaction then yields functionalised cyclopentenones.

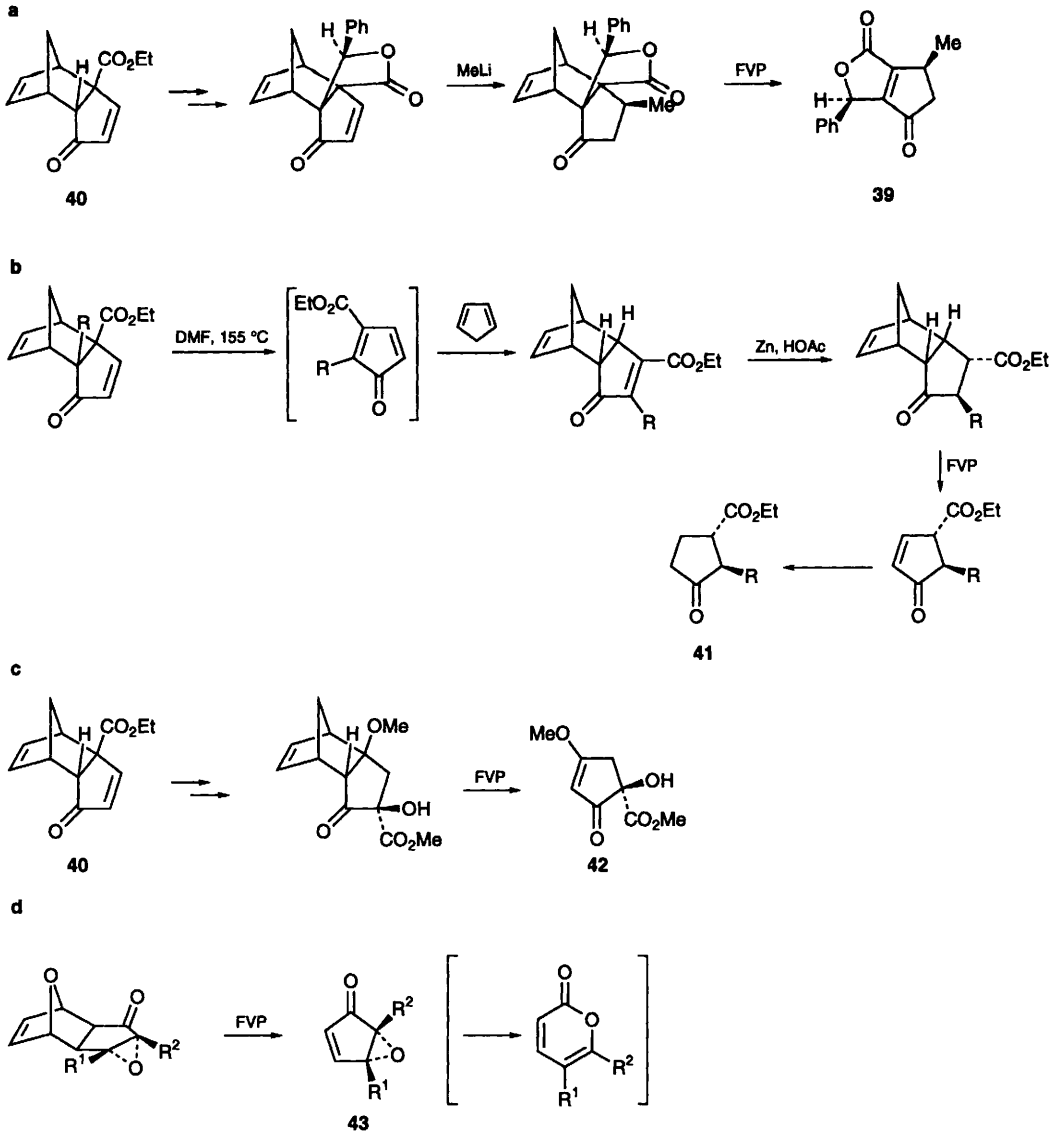
A number of related examples based on this methodology are shown in **Scheme 14**. Thus, annelated cyclopentenones **39** have been constructed from the ester **40** *via* stereospecific conjugate addition of methyllithium (**Scheme 14a**); FVP at 520 °C (0.01 Torr) gave >90% yields of the products.[44] Dihydrosarkomycin esters **41** have been made by a related strategy in which a solution-phase pyrolysis and recombination is a key step (**Scheme 14b**).[45] It is noteworthy that no isomerisation of the double bond to the more stable fully conjugated isomer takes place during the penultimate FVP step, carried out at 510 °C and 0.02 Torr. An enantioselective total synthesis of the natural product (−)-kjellmanianone **42** has been accomplished, again using the ester **40** as the initial starting material (**Scheme 14c**).[46]

For the epoxides **43**, however, careful control of the pyrolysis conditions was required, in order to avoid secondary thermal ring opening to α-pyrones. The use of furan rather than cyclopentadiene adducts was crucial in lowering the furnace temperature of the retro Diels–Alder reaction to 300–375 °C, and under these conditions >90% yields of **43** are routinely obtained (**Scheme 14d**).[47] α-Methylene cyclopentenoids have also been made in this way.[48]

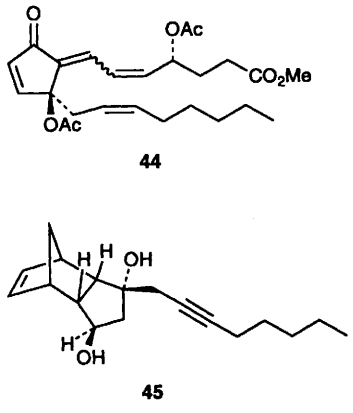
Related epoxides have provided, after reductive ring opening, a stereo- and enantio-selective formal synthesis of clavulone **44** *via* the key intermediate **45**.[49,50] The work has now been extended to the cyclohexene series and total syntheses of conduritols F and A (**46** and **47**) have been accomplished (**Scheme 15**).[51]

Other examples of this strategy include the generation of the enone **48** (which 'worked beautifully') in 95% yield *en route* to pilocarpine **49**,[52] (**Scheme 16**), and an enantioselective route to indolizidine and pyrrolizidine alkaloids[53] where efficient removal of the controlling cyclopentadiene unit at 450–500 °C (0.1 Torr) is a key step in the overall strategy (*e.g.* **Scheme 17**).

The procedure in which furan is used as the retro Diels–Alder component has been elegantly exploited by Bloch and his group. The general strategy again utilises a thermolabile group which can also provide stereocontrol of a variety of reactions. Examples include diastereoselective reduction of the homochiral ketone **50** with lithium



Scheme 14



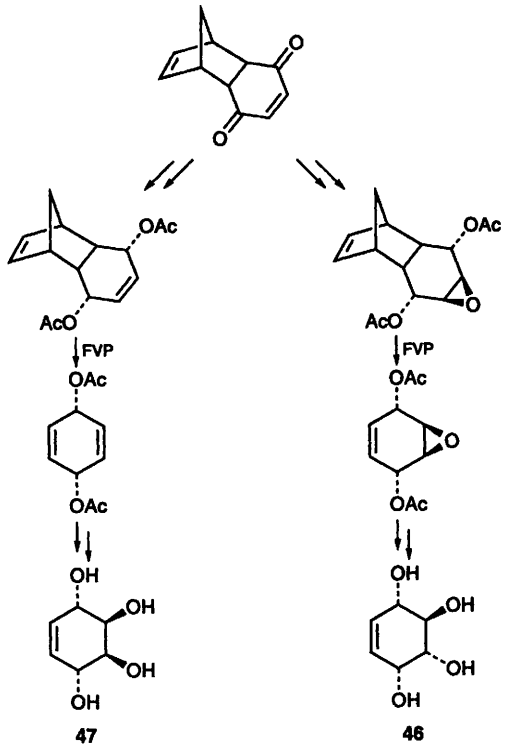
aluminium hydride to give the alcohol **51** and hence the dihydrofuran **52** (82%) by FVP at 500 °C. This compound was used as an intermediate in the synthesis of **53**, which is a host specific substance for the ambrosia beetle (**Scheme 18**).[54] Similarly, release of the homochiral *Z*-alkene **54** is a key step in a total syntheis of (+)-indolizidine 195B **55** (**Scheme 19**).[55]

Other examples of the application of retro Diels–Alder methodology are given in Sections 6 and 8 below.

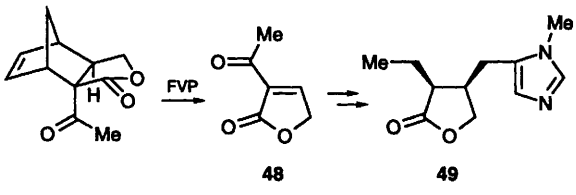
Dienes may be obtained by extension of the methods used for monoenes, or by specific routes such as retrocheletropic processes.

Free radical mediated retro [2+2] cleavage of fused cyclobutanes at 500–550 °C (0.5 Torr) has been used in the terpene field to give α,ω-dienes. Thus, for example, the epoxide **56** of the abundant sesquiterpene caryophyllene gave the β-farnesene epoxide **57** in *ca.* 45% yield in high chemical and optical purity, though fractional distillation and chromatography was required (**Scheme 20**).[56]

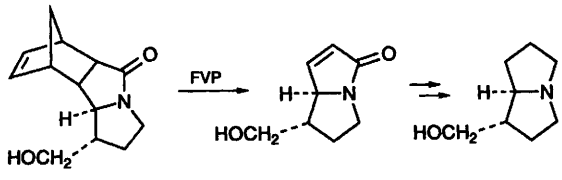
Cross-conjugated trienes (dendralenes) are of current interest. Trahanovsky has employed traditional acetate pyrolysis at 860–900 °C (10^{-4}



Scheme 15

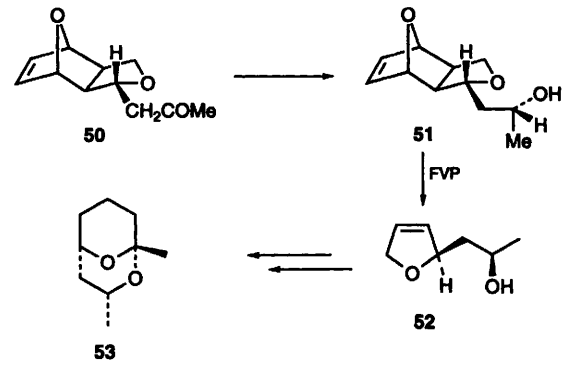


Scheme 16

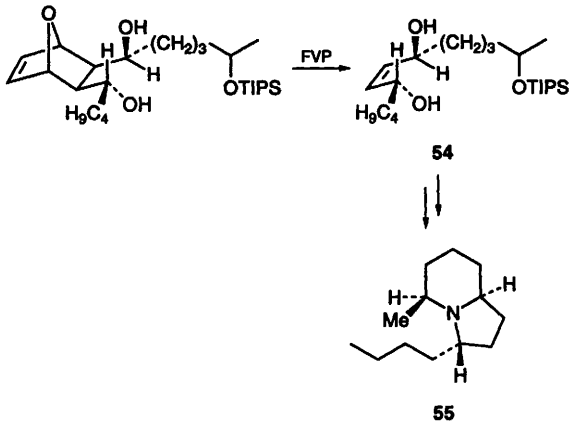


Scheme 17

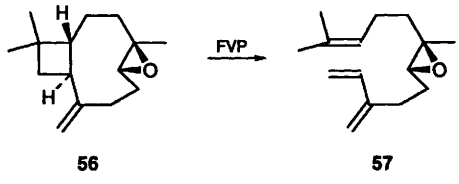
Torr) to give the parent [3]dendralene **58** in 'relatively high purity' in >70% yield (**Scheme 21**), and its highly reactive cyclic analogue **59** in 45% yield.[57] The parent compound **58** can also be made under milder conditions (550 °C, 0.001 Torr, 87%) by cheletropic elimination of SO_2 from the sulfone **60** (**Scheme 21**).[58] The closely related dienyne **61** is also best prepared by gas-phase methodology, but the only preparatively useful procedure involves dehydration of the pentynol **62** at the rate of 10 g per hour over 5 Å molecular sieves at 300 °C (0.001 Torr) (63% isolated yield).[59]



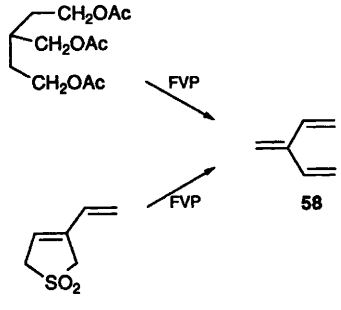
Scheme 18



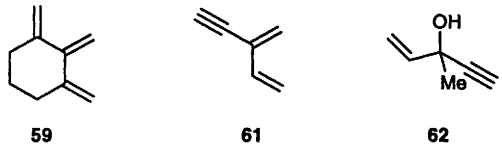
Scheme 19



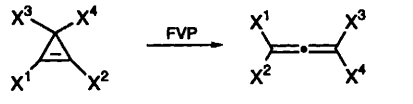
Scheme 20



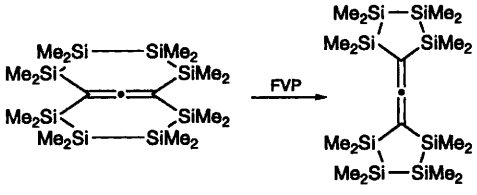
Scheme 21



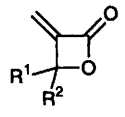
FVP of halocyclopropenes at 375–650 °C gives up to 85% yields of halogenated allenes generally uncontaminated with the isomeric alkyne (**Scheme 22**).[60] A range of silylated allenes has been obtained in high yield by thermal isomerisation of a series of bicyclic, doubly bridged allenes at 500–600 °C in a nitrogen flow (*e.g.* **Scheme 23**).[61–63] The reaction is thought to involve a concerted 1,3-shift with inversion at silicon.[61] Thermal decarboxylation of α-methylene β-lactones **63** represents potentially a more general synthetic route to the allene system, but only two examples are reported.[64]



Scheme 22

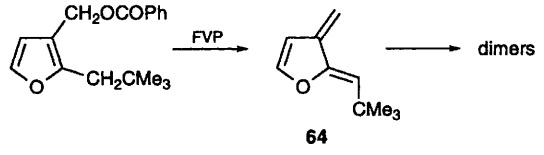


Scheme 23



63

FVP of paracyclophane at 650 °C has been used to generate *p*-xylylene for copolymerisation experiments with C_{60}.[65] Heterocyclic *o*-xylylenes represent an important class of reactive diene which are often efficiently made by FVP methods. Recent examples include the extension of the acetate elimination reaction to generate *tert*-butyl substituted furan-based xylylenes such as **64** (50% at 550 °C and 10^{-5} Torr) (**Scheme 24**), and the effect of the bulky substituent on the dimerisation properties of the ring system has been studied.[66,67] The method has been extended to the generation and trapping of reactive thiazole, oxazole and imidazole analogues,[68] though attempts to make corresponding pyrazole analogues failed. Much of this work depends on the discovery of convenient trapping reagents which can compete with inevitable polymerisation reactions; the thiophene xylylene **65**, generated by FVP of 2-chloromethyl-3-methylthiophene and quenched at -196 °C, has been found to react smoothly with co-condensed sulfur dioxide on warming, to give the adduct **66** in 62% yield.[69]



64

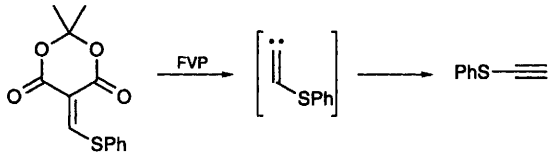
Scheme 24

65 **66**

5 Alkynes

Most of the recent work on the generation of the alkyne unit by FVP has centred on the preparation of functionalised (particularly halo-) alkynes, and the use of phosphorus compounds in alkyne synthesis.

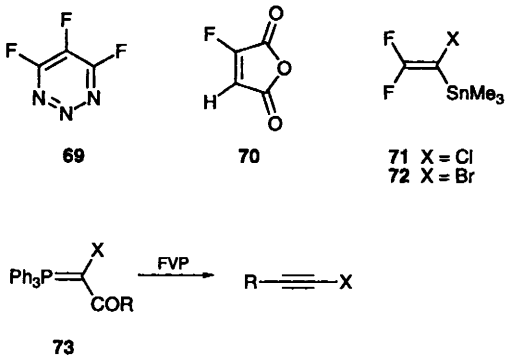
The pyrolysis of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) derivatives has been known for some time as a route to alkynes *via* their methylenecarbene isomers.[1] A recent application is the preparation of phenylthioacetylene **67** in two steps from readily available starting materials, with the key step being the thermal decomposition of the Meldrum's acid derivative **68** (68%, at 600 °C and 0.001–0.1 Torr) (**Scheme 25**).[70] Routes to haloalkynes include the decomposition of the perfluoro-1,2,3-triazine **69** at 700 °C (0.1 Torr) to give a mixture of difluoroacetylene and cyanogen fluoride, which was fractionated at low temperature to give the acetylene in a pure state.[71] It has a half-life of *ca.* 15 min at 300 K and 2 Torr. Fluoroacetylene has been obtained by pyrolysis of the maleic anhydride **70**, but was characterised only by matrix isolation.[72] Chlorofluoroacetylene and bromofluoroacetylene have been obtained by β-elimination of trimethyltin fluoride at 800 °C from the vinyl derivatives **71** and **72** respectively.[73]



68 **67**

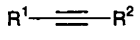
Scheme 25

A range of aryl and *tert*-alkyl chloro- and bromo-acetylenes has been made in 37–55% yield by extrusion of triphenylphosphine oxide from the phosphoranes **73** (X = Cl or Br) by FVP at 800 °C (0.001 Torr) (**Scheme 26**); only traces of the acetylenes were obtained under 'static' pyrolysis conditions.[74] The overwhelming advantages of gas-phase methodology for such extrusions have been emphasised in an extensive series of papers by



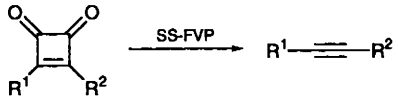
Scheme 26

Aitken *et al.*,[75-79] wherein a structurally diverse series of phosphoranes has been subjected to FVP at 500–750 °C (0.01 Torr) on a scale of up to 20 g. The method is particularly suitable for alkynes **74** [R^1 = H, R^2 = alkyl or aryl; R^1 = R^2 = alkyl or aryl (59–93% yield),[75] or R^1 = aryl, R^2 = CO_2R (83–92% yield)],[76] but yields are more variable for the formation of conjugated diynes (6–68%),[77] diacylalkynes (0–67% yield)[78] and conjugated enynes (0–85%),[79] for which *E*–*Z* isomerisation is an added complication.



74

A new method of 'solution-spray' flash pyrolysis (SS-FVP) has been developed to overcome disadvantages of involatile substrates in the formation of poly-ynes from cyclobutenedione pyrolyses (**Scheme 27**).[80] The method involves direct introduction of a solution of the compound in benzene as a sprayed aerosol within the quartz pyrolysis tube, which is filled with quartz rings and maintained at a pressure of 1–2 Torr. A range of linear poly-ynes containing from one to six acetylene units has been made using this strategy in yields ranging from 31–99%; these yields are particularly impressive given the high molecular weight and low thermal stability of the precursors, and it is hoped that further applications of this method will be reported in the future.

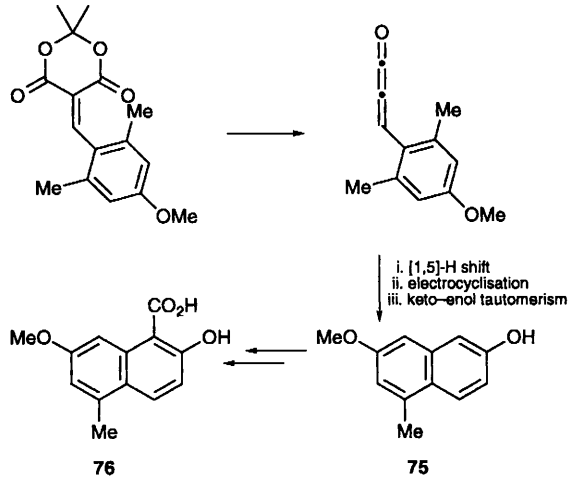


Scheme 27

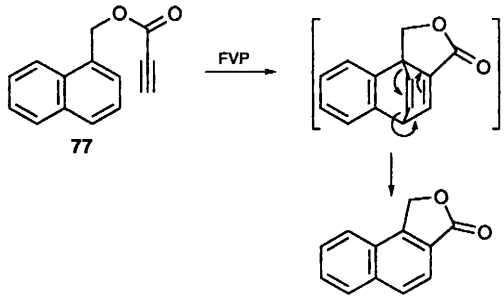
6 Aromatics

Although FVP methods are rarely used to make benzene derivatives, there has been much recent interest in fused polycyclic systems, particularly as possible fullerene fragments. In addition, FVP has long been used in generation of cyclic polyenes (non-benzenoid aromatics), many of which are highly sensitive compounds, and a number of these systems are also considered in this section.

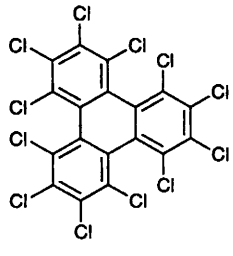
The Meldrum's acid pyrolysis route to β-naphthols[1] has been recently applied to the methoxy compound **75** (99% yield at 650 °C and 0.01 Torr), which can be easily transformed to the carboxylic acid **76** which is the intercalating moiety of neocarzinostatin (**Scheme 28**).[81] The Brown–Eastwood group have also developed a useful route to 1,2-disubstituted naphthalenes (*ca.* 70% yield) which involves a Diels–Alder – retro Diels–Alder sequence on pyrolysis of 1-naphthylmethyl-propynoates **77** at 750 °C (0.02 Torr) (**Scheme 29**).[82] This is a relatively unusual case of a cycloaddition in the *forward* direction which leads to useful products under FVP conditions. Perchlorotriphenylene **78** has



Scheme 28



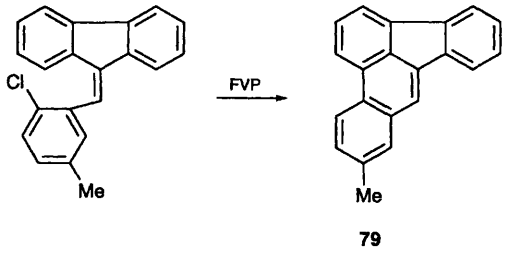
Scheme 29



78

proved to be 'unusually elusive'.[83,84] After a number of failed attempts, the compound was finally obtained in <1% yield *via* tetrachlorobenzyne trimerisation, by FVP of tetrachlorophthalic anhydride under relatively high pressure conditions (0.25 Torr) to encourage the intermolecular coupling.[83,84]

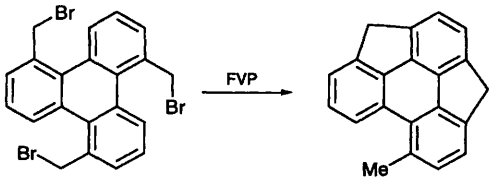
In the field of polycyclic aromatics, two key reactions have been employed to construct new rings under FVP conditions, both involving pyrolysis of halogen compounds at very high temperatures. The first is exemplified by the reaction shown in **Scheme 30**[85] in which regiospecific cyclisation with loss of HCl occurred at 800 °C (0.005 Torr) to give the methyl derivative **79** of the highly tumourogenic benzo[*e*]acephenanthrylene system in 63% yield. The mechanism probably involves electrocyclic ring closure followed by elimination; a similar mechanism, preceded by well-known thermal *E*–*Z* isomerisation has also been proposed to rationalise the formation of phenanthrenes in reasonable yield from *o*-chlorostilbenes at 950 °C.[86] (Dehydrogenative cyclisation can also take place, and though the yields are less impressive, the ease of preparing the precursor can be an advantage in more complex cases.[87]) Five membered rings can also be formed from *o*-halopolycyclics, and although temperatures of over 1000 °C are required, the thermodynamic stability of the products allows reasonable yields (38–53%) to be obtained (**Scheme 31**).[88] Fluorene systems can be made by pyrolysis of benzyl bromides at 950 °C (10^{-4} Torr) (**Scheme 32**),[89] though in this case the mechanism almost certainly involves homolytic cleavage of the halogen atom followed by free radical cyclisation or hydrogen atom capture.



79

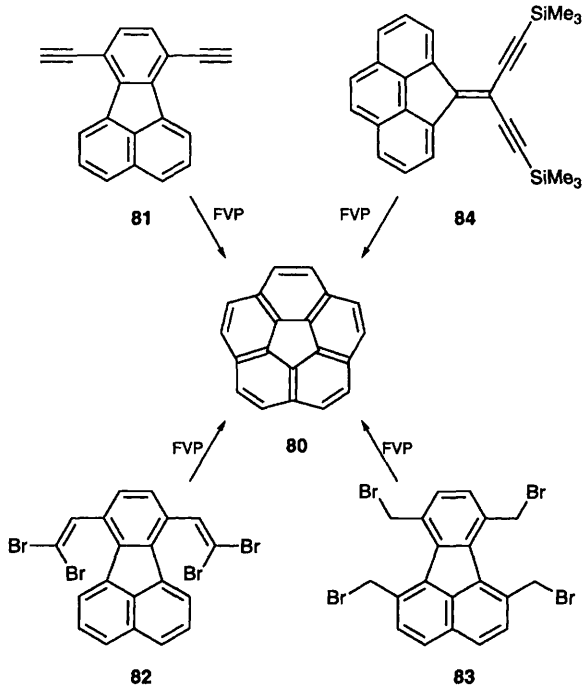
Scheme 30

Scheme 31



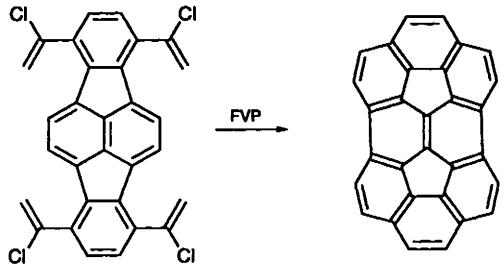
Scheme 32

The second key process capitalises on fundamental work by Brown[1] who showed that under FVP conditions terminal alkynes are in equilibrium with isomeric methylenecarbenes (*cf.* Section 5). This reaction has also been exploited by Dreiding and Karpf in natural product synthesis,[7] but its recent use has followed from a concise synthesis of corannulene **80** from the dialkyne **81** discovered by Scott and co-workers (**Scheme 33**).[90] Although the initial yield was low (10% on a 30–50 mg scale), and the pyrolysis conditions were fierce (1000 °C and 10^{-4} Torr) the synthesis was still attractive owing to an easy route to the precursor. It was then found possible to increase the yield to *ca.* 40% by using the dibromide **82** as precursor, though this mechanism is probably an electrocyclisation–aromatisation sequence as discussed in the previous paragraph. Later work supports this mechanism,[91] since brominated corannulenes can be isolated on variation of the pressure conditions. Corannulene has also been obtained (18%) by FVP of the tetrabromo compound **83** at 1000 °C,[92] and by flow pyrolysis at 900 °C of the silylated compound **84** in the presence of hydrogen carrier gas (15%).[93]

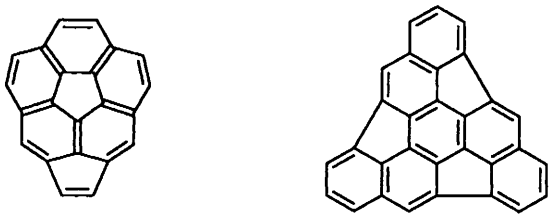


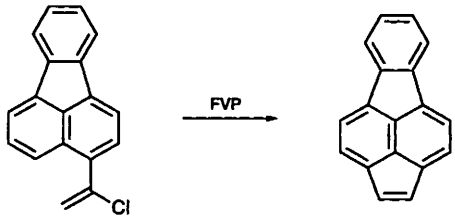
Scheme 33

In a slight modification of the original approach, α-chlorostyrenes have been employed as thermal precursors to the key alkyne intermediate, and a typical example is shown in **Scheme 34** (5% after FVP at 1000 °C).[94] Other compounds which have been made by this strategy include the cyclopentacorannulene **85**[95] and the $C_{30}H_{12}$ hydrocarbon **86**, albeit in very low yield.[96] Five membered rings can



Scheme 34



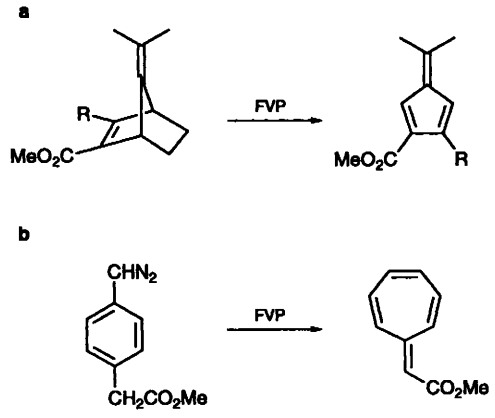


Scheme 35

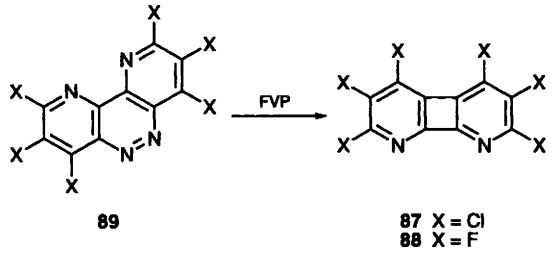
be made efficiently by this method,[97-100] as shown in **Scheme 35** (60% yield after FVP at 1050 °C and 0.01 Torr),[97] but the possibility of secondary rearrangement to isomeric, more stable hydrocarbons at the very high temperatures required must not be ignored (*e.g.* ref 100).

Although the majority of the activity in synthesis of 'non-benzenoid' aromatics has been in the area of polycyclics, new routes to fulvene[101] and heptafulvene[102] derivatives by retro Diels–Alder and phenylcarbene ring expansion routes have been published (**Scheme 36**). The retro Diels–Alder process takes place at 580 °C (0.006 Torr) to give the fulvenes in 68–99% yield (2 examples), but the carbene ring expansion is less efficient (17% from the *p*-isomer at 350 °C and 10^{-5} Torr).

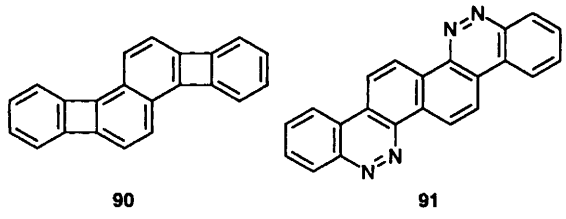
The preparation of biphenylenes by nitrogen extrusion from fused pyridazines is a well known process.[1] Recent examples include the perchloro-1,8-diazabiphenylene **87** (14%),[103] and its perfluoro analogue **88** (80%),[104] obtained by pyrolysis of the appropriate precursor **89** at 850–900 °C (0.03 Torr) (**Scheme 37**). The polycyclic derivative **90** has also been made as the 'only identifiable product' after 900 °C pyrolysis of **91**, though the unstable product could only be isolated in 4% yield after chromatography.[105]



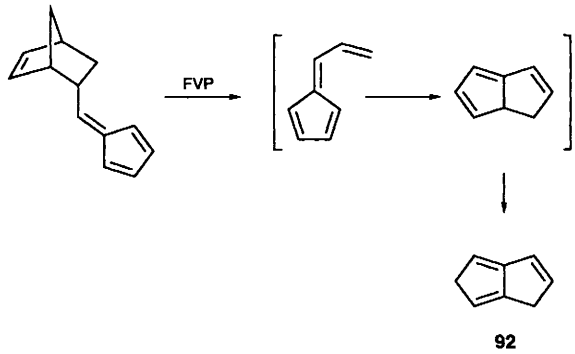
Scheme 36



Scheme 37

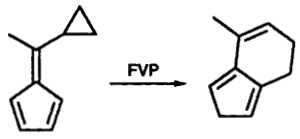


There is much current interest in the pentalene system. Griesbeck has reported extensively on a retro Diels–Alder electrocyclisation approach to dihydropentalenes,[106-109] shown in **Scheme 38**. In the parent case, pyrolysis of the precursor at 520 °C (0.01 Torr) led to the 1,5-dihydro (dendralene-like) isomer **92** in 58% yield on a multi-gram scale, after



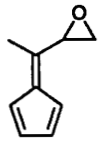
Scheme 38

a sequence of 1,5-hydrogen shifts subsequent to the ring closure step.[106,107] Methyl[107] and phenyl[109] analogues have been made by a similar process, which has also been extended to dihydroindenes such as **93** using a cyclopropylpentafulvene precursor **94** (overall yield 90–94% as a mixture of three isomers at 600 °C and 0.08 Torr) (**Scheme 39**).[108] No ring-annelated products were formed from the corresponding epoxide **95**, which instead underwent quantitative decarbonylation above 600 °C (0.01 Torr) to vinylcyclopentadienes.[108]



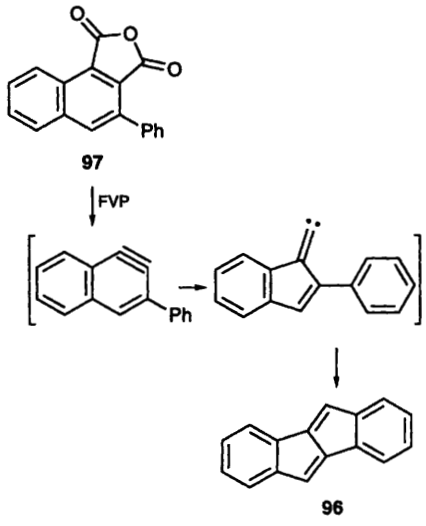
94 **93**

Scheme 39



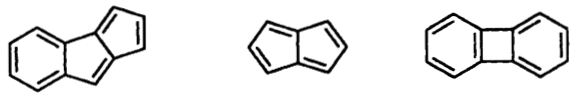
95

The pyrolysis of *o*-phenyl substituted phthalic anhydrides is a general route to benzannelated pentalenes.[82,110,111] An early example, shown in **Scheme 40**, gave a 95% yield of the stable [1,2:4,5]-dibenzopentalene **96** on FVP of the anhydride **97** at 900 °C (0.04 Torr).[82] As shown, the mechanism can be rationalised by ring contraction of an intermediate benzyne, followed by CH insertion of the resulting carbene.[82] The corresponding reaction of 3-phenylphthalic anhydride and 3-vinylphthalic anhydride under similar conditions gave benzopentalene **98** and pentalene **99**



97 **96**

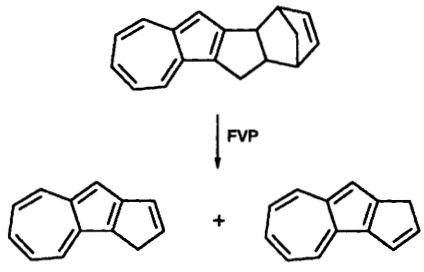
Scheme 40



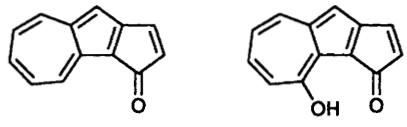
98 **99** **100**

respectively,[111] which were isolated as their dimers under normal conditions. The benzopentalene dimer was also obtained by FVP of biphenylene **100** or its precursors at 900 °C.[110–112]

A number of potentially unstable fused azulenes have been prepared by Yasunami and co-workers,[113–116] in which the key step is the release of the final unit of unsaturation by retro Diels–Alder methodology. This key reaction, shown in **Scheme 41**,[113] has also been applied to the cyclopentazulen-3-one **101**[114,115] and the 4-hydroxy compound **102**.[116] The yield of this final step is invariably above 80% at pyrolysis temperatures of 400–550 °C (0.1 Torr).



Scheme 41

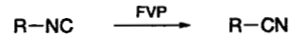


101 **102**

7 Heteroatom-containing functional groups

Surprisingly, FVP methods are not often used to create common heteroatom-containing functional groups, so there is considerable scope here for future development. With the exception of nitrile generation by the isocyanide–cyanide rearrangement (see below), most of the activity in this area is focussed on 'unstable' functionalities such as thiones and ketenes where the absence of reagents and convenient low temperature trapping of the pyrolysates are attractive features of the FVP technique.

The isocyanide–cyanide rearrangement (**Scheme 42**) has been reviewed.[117] It is in essence a chain



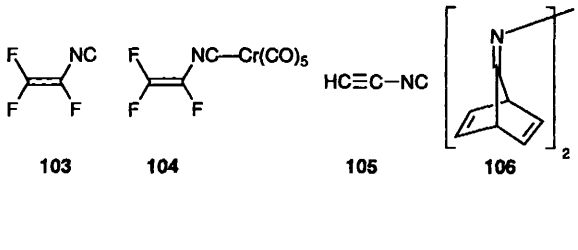
Scheme 42

extension sequence, which, after appropriate functional group transformations, allows the elaboration of an amine into a carboxylic acid containing one more carbon atom. The preparative aspects of the process require suppression of free radical chain side reactions, and this is efficiently accomplished under the dilute conditions of FVP, so that yields can be 'almost quantitative'.[117] The use of FVP has a number of other advantages for this reaction. Thus, most isocyanides rearrange under standard conditions of 520–550 °C (0.01 Torr), and high throughput rates (>0.5 g min^{-1} on a 20 g scale) are possible. Sterically hindered isonitriles react under these standard conditions,[118] allyl and propargyl derivatives react without allyl isomerisation[119] and homochiral isocyanides rearrange without racemisation.[120]

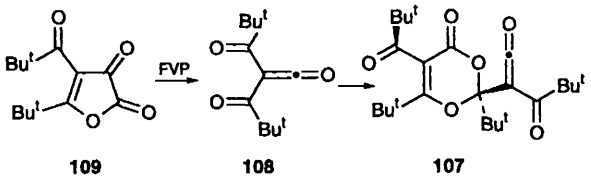
FVP methods at lower temperatures have been used to synthesise unstable isocyanides, notwithstanding the above rearrangement. Examples include the fluorinated compound **103**, released from its chromium pentacarbonyl complex **104** by FVP at 240 °C (0.02 Torr),[121] and acetylene isocyanide **105**, prepared similarly and identified by photoelectron spectroscopy.[122] FVP of norbornadienone azine **106** does not give diisocyanogen (CNNC) but rather isocyanogen (CNCN) is obtained, possibly *via* one isocyanide–cyanide rearrangement; further conversion to cyanogen (NCCN) is found at higher temperatures.[123]

FVP is a classic method for generating unusual ketenes; partly this is due to their distinctive infrared chromophores which render the functional group attractive for matrix isolation, but much useful preparative chemistry can also be accomplished. The Wentrup group is foremost in this area, and an extensive review (203 references) on the preparation and chemistry of α-oxoketenes has recently appeared.[124] An unusually stable α-oxoketene **107** is formed by dimerisation of dipivaloylketene **108** which is itself obtained in 90% yield by FVP (500 °C, 10^{-3} Torr) of the furandione **109** (**Scheme 43**).[125] Dipivaloylketene **108** itself is relatively stable in solution at −20 °C and trapping reactions with heterocumulenes have been investigated.[126]

The heterocyclic oxoketene **110** has been made by FVP of the diazo compound **111** at 400 °C (10^{-3} Torr), identified in a matrix, and isolated as its dimer **112** (74%) whose structure was proved by X-ray crystallography (**Scheme 44**).[127] This structure confirmed that the isomeric ketene **113** was not formed in the carbene ring contraction. Many heterosubstituted methyleneketenes are unusually stable so that they can be isolated at low temperatures and trapped with added reagents. The dithia compound **114**, for example, prepared by FVP of the Meldrum's acid derivative **115**, has a half-life in solution of 20 min at −50 °C,[128] and can be trapped by [2+2] cycloaddition with chloral.[129]

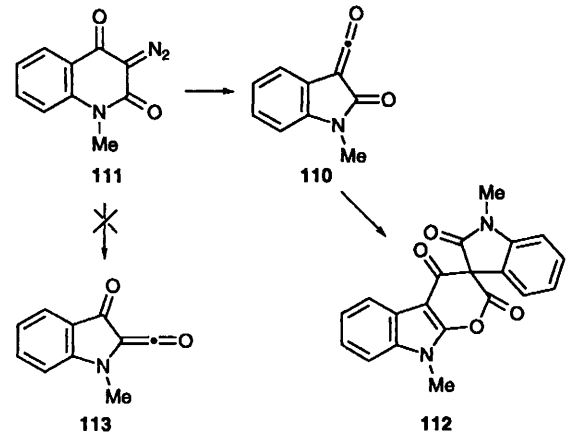


103 104 105 106

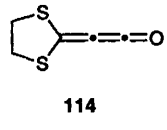


109 108 107

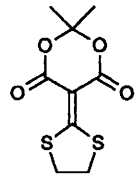
Scheme 43



Scheme 44

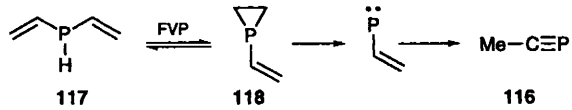


114



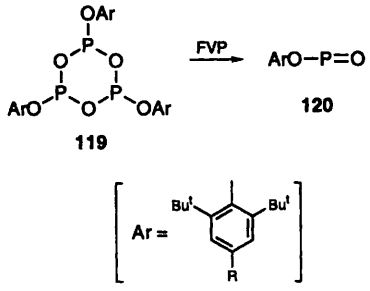
115

There has been considerable interest in recent years in phosphorus compounds with low coordination numbers. Phosphapropyne **116** can be made in pure form by FVP (700 °C, 0.001 Torr) of either the divinylphosphine **117** or the phosphirane **118**, which exist in equilibrium at high temperature (**Scheme 45**).[130] Remarkably, **116** is stable in solution for at least one week at room temperature. The triaryloxytrioxatriphosphorinane **119** can be cracked to the monomeric aryl phosphenite **120** at 350 °C (10^{-5} Torr) (**Scheme 46**) which rapidly dimerises.[131]



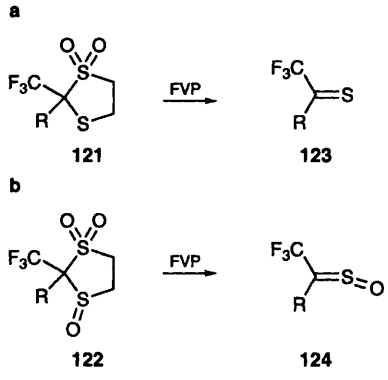
117 118 116

Scheme 45

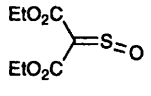


Scheme 46

FVP is an ideal method for the synthesis of sensitive thiocarbonyl compounds, and many different routes have been studied.[1] Recent examples include the pyrolysis of oxidised 1,3-dithiolanes **121** and **122** at 550 °C with loss of SO_2 and ethylene to give trifluoromethyl substituted thioketones **123** and sulfines **124** respectively in yields of 53–80% (**Scheme 47**).[132] The same type of precursor has been used to generate prop-2-enethial intermediates which can undergo a number of secondary thermal reactions.[133] Diethyl thioxomalonate *S*-oxide **125** has been released from its anthracene adduct by retro Diels–Alder reaction at 500 °C (10^{-4} Torr) and trapped by reaction with cyclopentadiene (47%).[134]

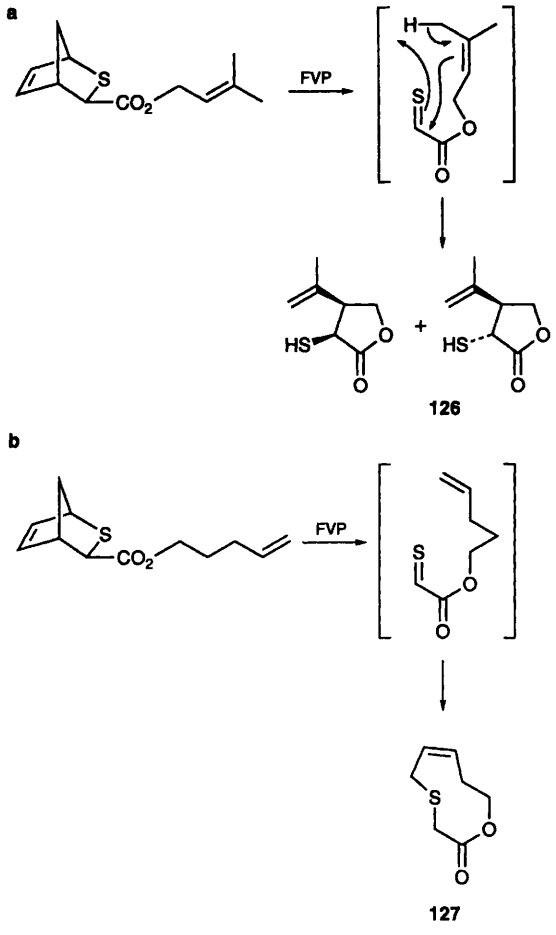


Scheme 47

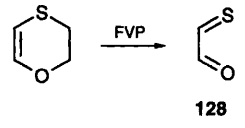


125

A similar strategy has been employed to generate thioaldehydes capable of intramolecular ene reactions. Typical examples are shown in **Scheme 48**; the yield of the mixture of *E* and *Z* lactones **126** was >95% from a 600 °C pyrolysis[135] whereas the related reaction leading to thialactones (*e.g.* **127**) is applicable to 6–11 membered rings.[136] α-Oxothiones, including the parent compound **128**, have been generated at 850 °C (10^{-5} Torr) by the unusual retro hetero Diels–Alder process shown in **Scheme 49**,



Scheme 48

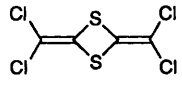


128

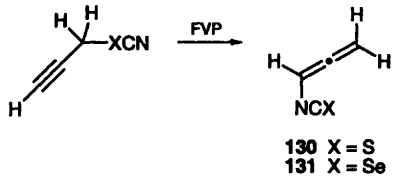
Scheme 49

identified by matrix isolation and trapped in 21–53% yield by reaction with a range of dienes.[137,138]

Sulfur-containing heterocumulenes can also be generated by FVP. Thus, dichlorothioketene ($Cl_2C{=}C{=}S$) was prepared and trapped in quantitative yield by FVP of the dimer **129** at 820 °C (0.001 Torr).[139] Allenyl isothiocyanates **130**[140] and their seleno analogues **131**[141] are both obtained by FVP of the appropriate cyanate at 350–400 °C (0.01–0.75 Torr) – the former in almost quantitative yield on a daily scale of up to 1 mol (**Scheme 50**). Both classes of compound are useful substrates for heterocyclisation reactions by treatment with nucleophilic reagents.



129

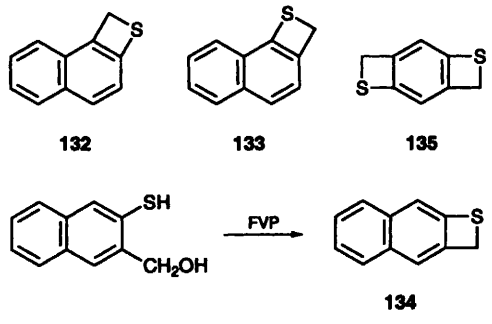


Scheme 50

8 Heterocycles

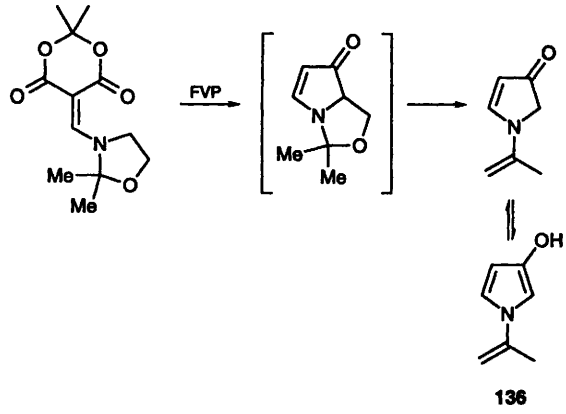
In contrast to the preceding section, FVP reactions provide an increasingly important route to many types of heterocyclic compounds. From the point of view of the heterocyclisation process, gas-phase methods provide the advantages of easily controlled conditions with no necessity for high boiling solvents, and in addition the work-up and isolation of sensitive products is particularly straightforward. In this section, the systems are considered in order of increasing ring size, with subdivisions according to the atomic number of the heteroatom(s) and their number. Annelated compounds are considered directly after the parent ring systems.

FVP routes to stable three-membered rings are rare, though annelated heterocyclic four-membered rings can be generated *via* the appropriate xylylene. Recent examples involve the pyrolysis of α-mercaptoarylmethanols, which provides the best general route to benzo-annelated thietes.[142,143] Full details have been published of the routes to all three isomeric naphthothietes **132–134**,[142] which are obtained in yields varying from 50% to almost quantitative from FVP of the appropriate precursors at 750 °C (0.001 Torr) (*e.g.* **Scheme 51**). The highly reactive bisthiete **135** has been synthesised in 60% yield by a similar strategy.[143]



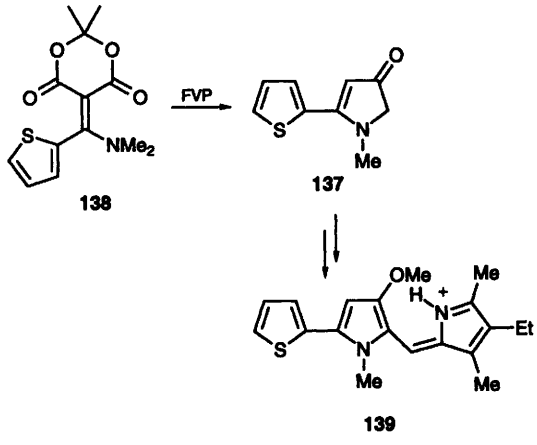
Scheme 51

In the five-membered ring series, the amino-methylene Meldrum's acid route to 3-hydroxy-pyrroles[144a] has been extended to unusual *N*-alkenyl derivatives **136**, formed at 600 °C (0.001 Torr) by an unexpectedly facile cleavage of formaldehyde from the initial bicyclic product (**Scheme 52**).[144b] The 5-thienyl substituted pyrrol-3(2*H*)-one **137**, available in 70% yield from FVP (600 °C, 0.001 Torr) of the Meldrum's acid **138**, has been elaborated to an



Scheme 52

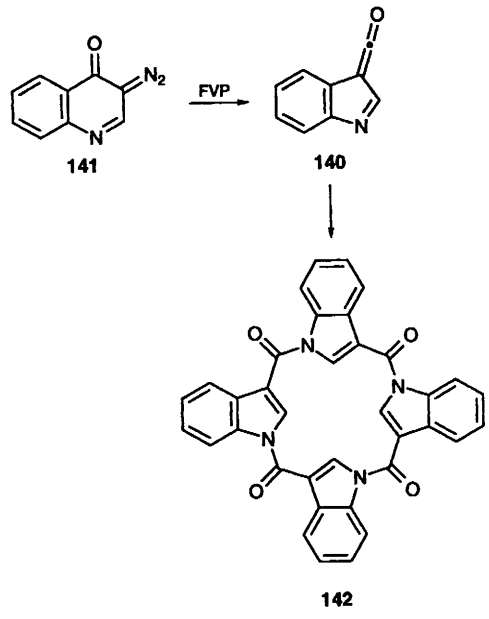
analogue **139** of the natural product prodigiosin (**Scheme 53**).[145] The indolyl ketene **140** is formed under similar conditions by FVP of the diazo compound **141** (*cf.* **Scheme 44**); under preparative conditions it is isolated as the tetramer **142** in 75% yield (**Scheme 54**).[146] The novel indeno[1,2-*b*]indole system **143** has been isolated by FVP (800 °C, 0.06 Torr) in 30–40% yield using a similar strategy to that employed for the benzopentalenes (**Scheme 55**; *cf.* **Scheme 40**).[147]



Scheme 53

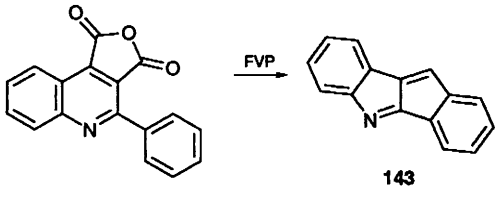
FVP is an excellent route to bridgehead nitrogen systems such as pyrrolizin-3-ones and their benzo-analogues. Examples of the former include a short synthesis of the natural product 3,8-didehydroheliotridin-5-one **144**, in which FVP methods were employed to generate the ring system at *two* key points in the synthesis (**Scheme 56**).[148] Yields of the pyrolysis steps, carried out at 600 or 650 °C, were 90% and 60% respectively. The related indole derivative **145** yielded the pyrrolo[1,2-*a*]indolone **146** (97%), upon FVP at 750 °C (0.03 Torr).[149]

A route to the pyrrolizidine system has been developed, in which the key step is an intramolecular 1,3-dipolar cycloaddition of a thermally generated azomethine ylide to an allyl function (**Scheme 57**).[150] The generation of the ylide **147**



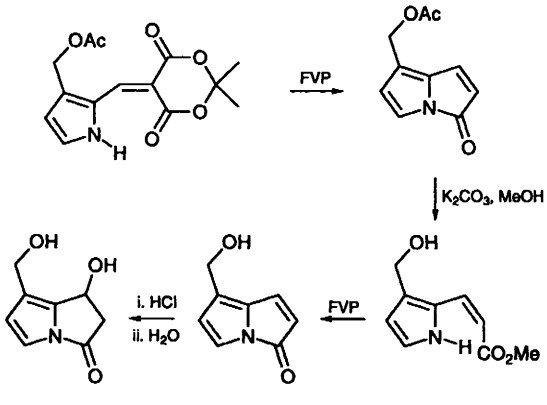
141 140 142

Scheme 54



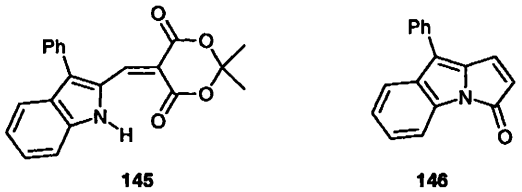
143

Scheme 55

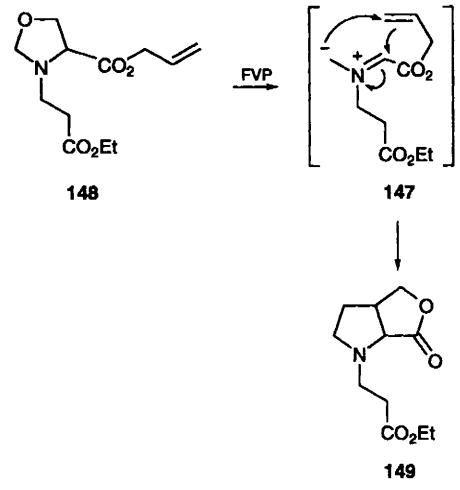


144

Scheme 56



145 146



148 147 149

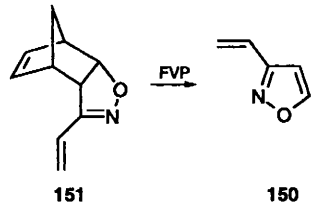
Scheme 57

from the oxazolidine **148** further emphasises the propensity for carbonyl compounds to act as thermal leaving groups (*cf.* **Scheme 52**), and the pyrrolidine **149**, which can be further elaborated to pyrrolizidines, is obtained in 82% yield after *in situ* cycloaddition.[150]

A simple example of the use of the retro Diels–Alder reaction in heterocyclic chemistry, shown in **Scheme 58**, is the generation of the 4,5-double bond of 3-vinylisoxazole **150** (99%) from the cyclopentadiene adduct **151** at 475 °C (0.001 Torr).[151] Pyrolysis of **151** in solution was ineffective. At higher temperatures, the N–O bond of such compounds may be cleaved, and the FVP reactions of isoxazolones have been studied by Prager and coworkers. These compounds undergo CO_2 cleavage leading to imino carbene intermediates which can be trapped by adjacent lone pairs rather than undergoing insertion reactions.[152] A typical example is shown in **Scheme 59**; the yield of the fused imidazole obtained from a 530 °C (0.01 Torr) pyrolysis is 92%.

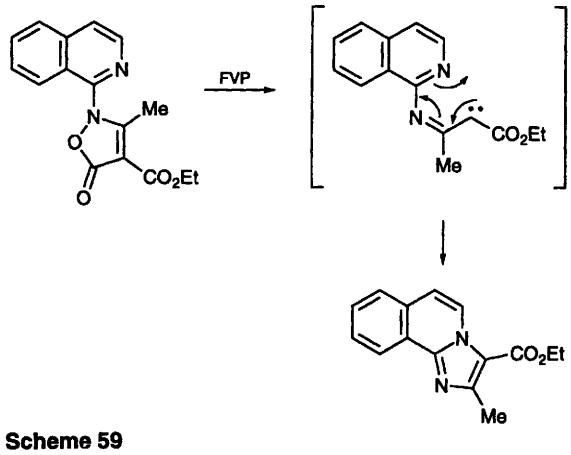
3-Hydroxythiophenes and thiophen-3(2*H*)-ones, including the unstable parent compound **152**, can be prepared in generally excellent yield *via* methyleneketene intermediates by FVP of alkylthiomethylene Meldrum's acid derivatives **153** at 600–625 °C (0.001 Torr) (**Scheme 60**),[145,153–155] and full experimental details are now available.[154]

Gas-phase free radical chemistry has been employed in a new synthesis of benzofurans **154**,[156] in which the ability of the carboxylic ester function

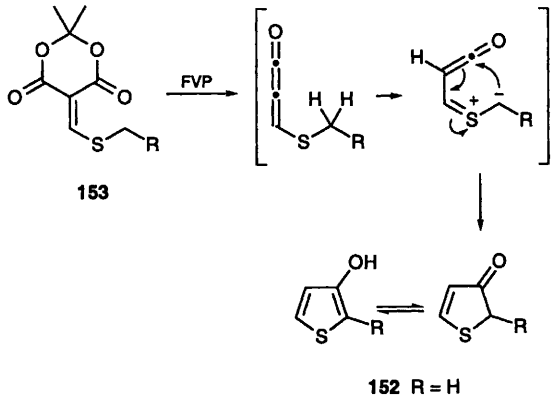


151 150

Scheme 58



Scheme 59

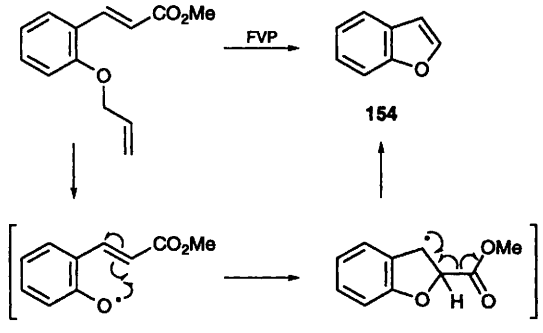


153

152 R = H

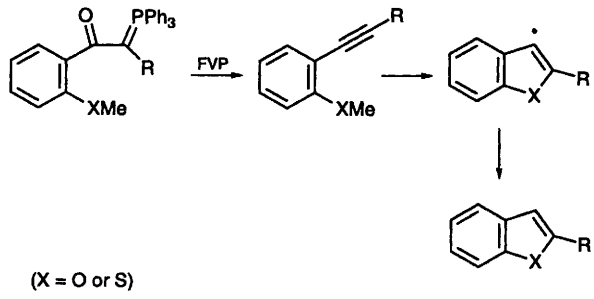
Scheme 60

to act as a radical leaving group under FVP conditions is underlined (**Scheme 61**). Conditions are mild (650 °C and 0.01 Torr), yields are generally in the range 60–90% and the precursors are easily synthesised by Knoevenagel or Wittig methodology. An alternative radical approach to benzofurans which is also applicable to benzothiophenes involves addition to a pendant alkyne function generated *in situ*, (**Scheme 62**), though with the exception of some specific examples yields are lower and mixtures are often obtained.[157] An extension to polycyclics, including the previously unknown benzothieno[3,2-*b*]benzofuran **155**,[158] has also been reported.



154

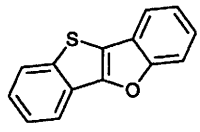
Scheme 61



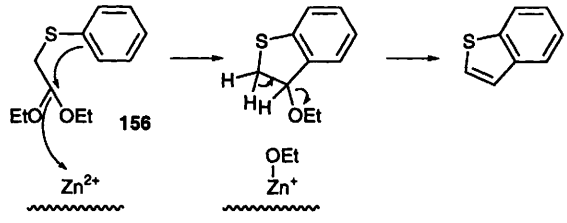
(X = O or S)

Scheme 62

An unusual example of heterolytic reactions taking place in only a short contact time also leads to the benzothiophene system. In this case, the cyclisation of thio acetal **156** is promoted by employing a furnace (200–300 °C, 0.05 Torr) containing a plug of zinc chloride-modified montmorillonite clays; yields were in the range 67–98% for benzothiophene and a range of derivatives, but were seldom >50% for the corresponding process in solution (**Scheme 63**).[159]



155

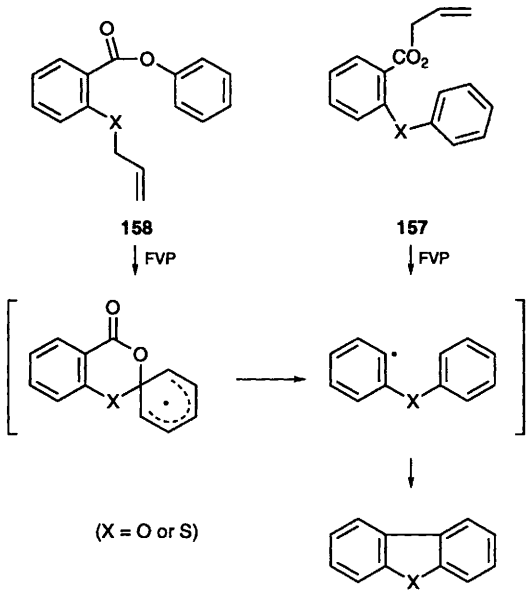


156

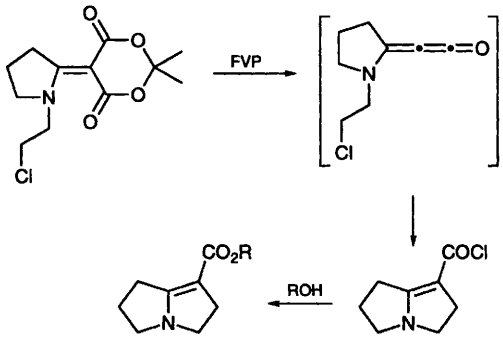
Scheme 63

Two complementary radical routes to dibenzofurans and dibenzothiophenes have been developed (**Scheme 64**).[160,161] In the first, an aryl radical is generated directly by FVP of an allyl ester **157** at 900 °C (0.001 Torr), but results in only moderate yields (up to 63%) after cyclisation. The same key intermediate is generated indirectly in the alternative method (**Scheme 64**), which involves pyrolysis of readily available aryl salicylates (or thio salicylates) **158** under more moderate conditions (650 °C, 0.001 Torr). Better yields are usually obtained by this latter route (70–94% for a range of esters derived from *p*-substituted phenols).

Another cyclisation mechanism of methyleneketene intermediates can give rise to fused bicyclic products of variable ring size (*e.g.* **Scheme 65**) in moderate yield,[162] by variation of the size of the N-containing ring and the length of the side-chain in the precursor. The method gives rapid entry to



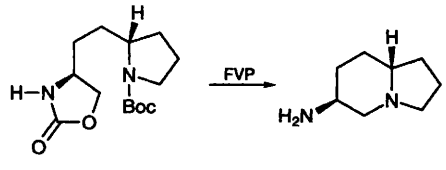
Scheme 64



Scheme 65

1-azabicyclo[*x*.*y*.0]alkane frameworks which are often encountered in the alkaloid field.

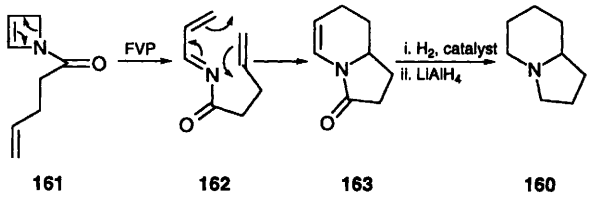
Surprisingly few FVP reactions have been developed to create monocyclic six-membered heterocycles, though there is considerable interest in fused systems. In one unusual example, (**Scheme 66**) a fused piperidine ring is created in 83% yield by FVP (270 °C, 3 Torr) of an oxazolidinone unit, with concomitant deprotection of a Boc group.[163] Oxazolidinones are the *products* from the FVP of *N*-ethoxycarbonylaziridines **159** under apparently more vigorous conditions (650 °C), though the pressure used (0.001 Torr) is indicative of a much shorter contact time.[164]



Scheme 66

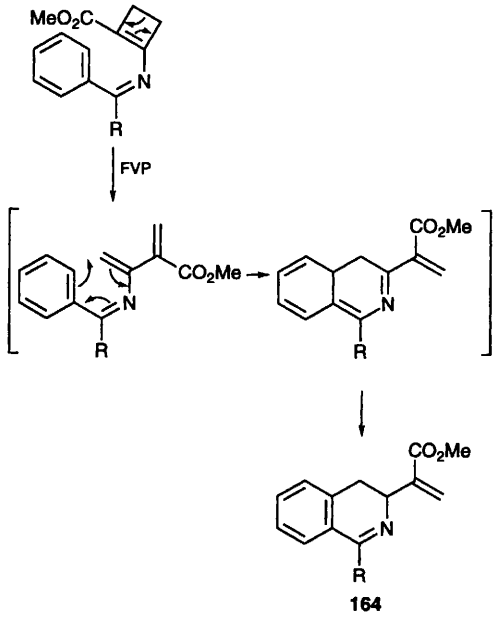
159

An electrocyclic ring opening is the key step in the route to (±)-δ-coniceine **160** from the azetine **161** (**Scheme 67**).[165] Under relatively low pressure conditions for this study (540 °C, 5 Torr), the intermediate azadiene **162** is isolated, which is converted to the bicycle **163** by heating in benzene. Under higher pressure (20–30 Torr) and with a longer contact time, the cycloadduct **163** may be formed directly.[165] In similar fashion, conjugated imino cyclobutenes undergo ring opening, but in this case lead to dihydroisoquinolines **164** by electrocyclic ring closure and 1,5-H shift at 500–550 °C (10^{-4} Torr) (**Scheme 68**). Yields are in the range 50–68%, even in the presence of a sensitive cyclopropyl substituent (*e.g.* **Scheme 68**, R = cyclopropyl).[166] FVP of conjugated hydrazones such as **165** at 600 °C (0.001 Torr) gave the fused pyridines **166** in *ca.* 50% yield;[167,168] this cyclisation could not be effected in solution. An electrocyclisation mechanism has been proposed,[167] but homolysis of the N–N bond and cyclisation of the resulting intermediate iminyl radical are also possible.



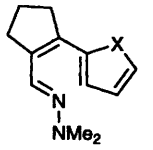
161 162 163 160

Scheme 67



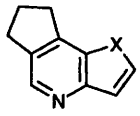
164

Scheme 68



(X = O or S)

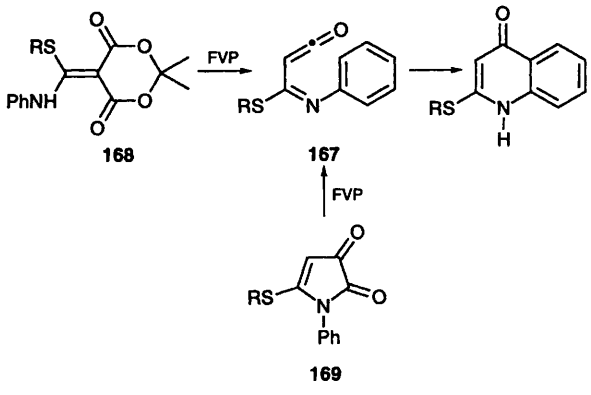
165



(X = O or S)

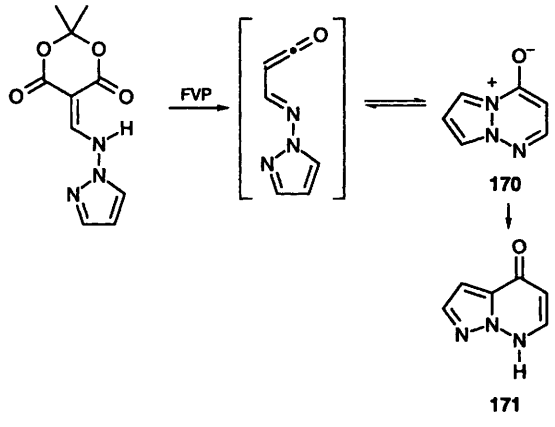
166

The electrocyclisation of aryl- or heteroaryl-iminoyl ketenes **167** has become a standard route to fused pyridin-4-one structures and some examples are given in references 169–172 (**Scheme 69**). For preparative purposes, Meldrum's acid derivatives such as **168** are often the most readily accessible precursors, but pyrrole-2,3-diones **169** can also be used.[169,170] Trapping of the ketene by an adjacent lone pair gives rise to the novel betaine structure **170** (50–55% by FVP at 550 °C and 8×10^{-5} Torr) whose structure was proved by X-ray crystallography (**Scheme 70**).[171] At higher furnace temperatures this product rearranges to the isomeric structure **171**, presumably *via* regeneration of the ketene. Similarly, pyrimidoquinolinones **172** can be made 'with yields routinely in the range 95–98%' by FVP of the crotonate esters **173** at 530 °C (0.01 Torr), a vast improvement over the corresponding solution thermolysis procedure (**Scheme 71**).[172] An unusual rearangement (**Scheme 72**) provides a novel entry to this energy surface.[173]



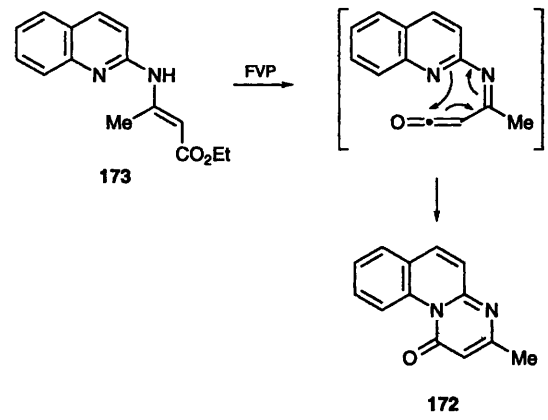
168 **167** **169**

Scheme 69



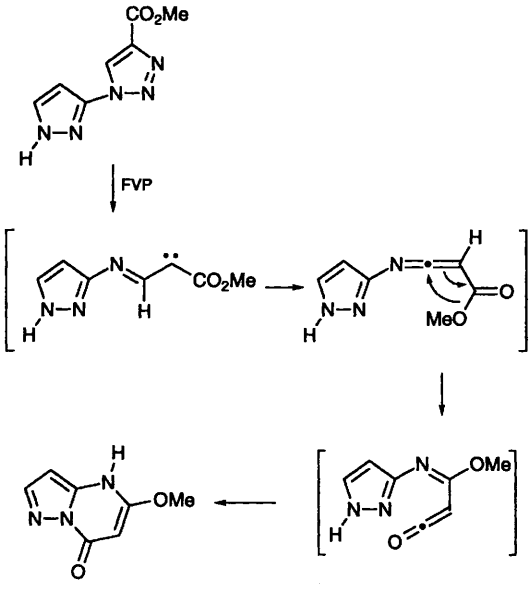
170 **171**

Scheme 70



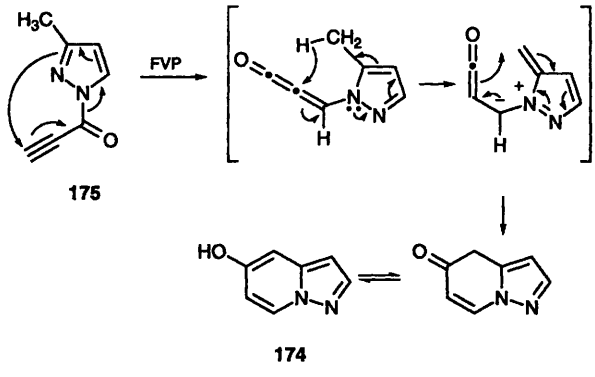
173 **172**

Scheme 71



Scheme 72

An interesting four step pyrolysis sequence (**Scheme 73**) provides 5-hydroxypyrazolo[1,5-*a*]pyridines **174**, often in yields of >90%, by FVP of the propynoylpyrazoles **175** at 650 °C (0.03 Torr).[174] Trapping of conjugated ketenes by adjacent

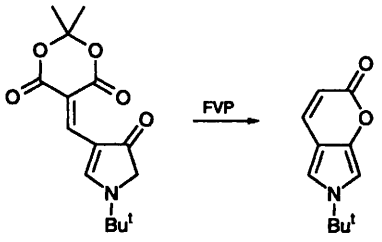


175 **174**

Scheme 73

carbonyl functions is an important route to α-pyrones, and some pyranopyrroles (*e.g.* **Scheme 74**) have been made by FVP of Meldrum's acid derivatives at 600–650 °C (0.001 Torr).[175]

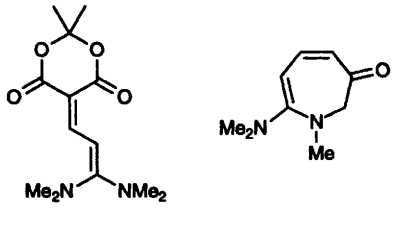
The parent phosphinine (phosphabenzene) **176** is formed 'almost exclusively' by FVP of vinyldiallylphosphine **177** at 700 °C (0.001 Torr) *via* a retroene–electrocyclisation–dehydrogenation mechanism.[176]



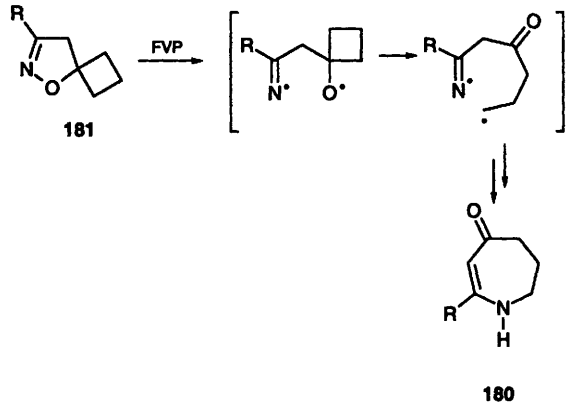
Scheme 74

176 **177**

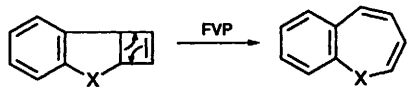
A number of FVP routes to seven-membered rings have been documented. Stable azepinones may be obtained by the vinylogous cyclisation sequence to that shown in **Scheme 53**, and FVP of the Meldrum's acid derivative **178** at 600 °C (0.005 Torr) gives the 7-dimethylamino substituted example **179** (90%) which shows unusual cycloaddition reactions with dienophiles.[177] Related 4,5,6,7-tetrahydro(1*H*)-azepin-4-ones **180** are obtained in moderate yield by FVP at 700 °C of the spirocyclobutane isoxazole derivatives **181** (**Scheme 75**).[178] Application of this strategy to products of other ring sizes has been reviewed.[179] Tsuchiya's group has employed an electrocyclic ring opening strategy to make a number of new benzoheterepine ring systems **182-185** with unusual heteroatoms (**Scheme 76**).[180,181] Optimum furnace temperatures are 500–550 °C at 10^{-5} Torr, and yields can be as high as 85%, whereas no reaction took place under solution pyrolysis conditions. The oxides **182** and **185** can be chemically reduced to the parent systems **186** and **187** respectively.



178 **179**



Scheme 75



182 X = POPh
183 X = $SiMe_2$
184 X = $GeMe_2$
185 X = AsOPh
186 X = PPh
187 X = AsPh

Scheme 76

9 Conclusions

It can be readily seen from this survey that FVP methods are no longer the province of specialist thermolysis chemists with interests in mechanisms or unusual intermediates, but are generally useful to the synthetic organic community as a whole. This position was admirably prophesied as follows by Boekelheide in 1980,[182] when FVP reactions were involved in the key steps of his 'superphane' synthesis:

'*...gas-phase pyrolysis is a synthetic method of general utility. It is usually clean, convenient and efficient, and frequently has advantages over other synthetic methods for accomplishing the same goals*'.[182]

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