PYROLYSIS, FLASH VACUUM

1. Introduction

In flash vacuum pyrolysis (FVP) [or flash vacuum thermolysis (FVT)] a substrate is distilled or sublimed under modest vacuum through a hot tube (where a chemical reaction takes place); the products of the reaction are collected in a cold trap at the exit point of the furnace. In essence, a laboratory-style vacuum distillation of the substrate is carried out with the condenser replaced by a hot tube (1-8).

The use of vacuum conditions (rather than, eg, pyrolysis of the substrate in a flow of inert carrier gas) has important ramifications that are at the core of the FVP experiment. First, other gaseous species (including oxygen) are essentially absent on a molecular scale in the hot tube and so intramolecular reactions are strongly favored. Second, contact times of substrate molecules in the hot zone are very short (of the order of milliseconds) by comparison with other pyrolysis methods, thus unstable or reactive species can be isolated provided they have sufficient lifetime to survive to the cold trap. Because such materials may be very difficult to obtain in any other way, FVP is the method of choice for the synthesis of many specific target molecules.

There is an extensive literature on applications of FVP and many reviews are available (1-8). Work in the field prior to 1980 has been comprehensively surveyed in R.F.C. Brown's classic monograph (1) and a more up to date account edited by Vallée appeared in 1998 (7). Reference (6) should be consulted for information on other review articles.

It is important at the outset to consider the FVP experiment described above in the context of other pyrolytic methods. In the simplest type of pyrolysis experiment, the substrate may be heated in solution or in a sealed tube. This technique is attractive because no specialized apparatus is required. However, reactive intermediates are generated in the presence of precursors, products, and solvent, potentially leading to the formation of intermolecular secondary products. Such methods are, however, much better than FVP for carrying out reactions of involatile substrates or for reactions that require an intermolecular component. Next, atmospheric pressure "flow" pyrolysis, which has been applied since the nineteenth century, involves introduction of the substrate to a packed vertical heated tube in a flow of carrier gas. Under these conditions it is possible to use involatile substrates (in solution in an inert solvent) and the relatively high pressures do not disfavor intermolecular processes. On the other hand, the extended contact times compared with FVP methods encourage decomposition of all but the most stable products and yields are often compromised as a result. Finally, many applications of the utility of microwave heating in synthetic organic chemistry are being discovered. Though reaction times are often short by comparison with "normal" solution chemistry, they are still many orders of magnitude longer than in the FVP experiment, again leading to the possibility of secondary reactions.

For organic chemists intuitively familiar with solution-phase reactions, the temperatures required for typical FVP processes can be surprising. "Mild" conditions (ie, those in which most functional groups and remote asymmetric centers survive unchanged) range from ∼350–650°C and many species remain stable at temperatures in excess of 900°C. Such very high temperatures are required because of the very short contact time of the molecules in the hot zone of the furnace; conditions are therefore very gentle by comparison with those obtained using the extended heating times commonly encountered in solution-phase pyrolyses. FVP should not be considered as a molecular sledgehammer, even if apparently extreme temperatures are employed.

2. Equipment

The preparative scale FVP experiment requires very simple equipment (Fig. 1). The substrate to be pyrolyzed is volatilized, by gentle heating under vacuum, from an inlet tube into the furnace tube that is heated at a constant temperature by a laboratory tube furnace. Products are condensed in a cold trap located at the exit point of the furnace. If the furnace tube is made of silica, reactions can be carried out at temperatures up to 1200°C; pyrex tubes begin to soften at ∼520°C, which is too low for many applications. The furnace tube may be empty, or packed with inert material such as silica chips or silica wool. Inert packing materials have the effect of increasing the contact time of the substrate molecules in the hot zone of the furnace, allowing lower furnace temperatures to be employed (9). Relatively little use has been made of catalytic packing materials under short contact time conditions, but the use of reagents as packing materials — the so-called “vacuum gas–solid reaction” (VGSR) technique — has been well documented (1g, and references cited therein).

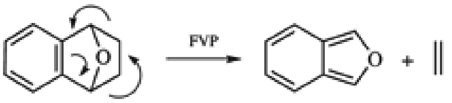
For preparative scale FVP, the relatively modest vacuum that can be obtained by a high capacity rotary pump (0.1 – 1.0 Pa or $\sim 10^{-2} - 10^{-3}$ Torr) is usually satisfactory, though a much lower pressure may be required for the in situ study of reactive intermediates described in the section Studies of Reactive intermediates.

The main FVP parameters are the temperature of the inlet (which controls the through-put rate), the furnace temperature, and the background pressure. In practice, the pressure delivered by the pump is often relatively constant and reactions are relatively little affected by through-put rate. Under these conditions, furnace temperature therefore becomes the sole variable; a plot of substrate conversion vs. furnace temperature is often a regular, sigmoid curve reflecting the Boltzmann distribution of molecular energies within the furnace (9).

The volatility of the substrate provides the most common limitation in the use of FVP methodology; it can also be difficult to scale up FVP reactions of substrates that are only just sufficiently volatile on a small scale. In order to tackle this problem, techniques such as “spray pyrolysis” (10) and “solution spray pyrolysis” (11) have been developed, but neither method has been particularly widely applied. Electron impact mass spectrometry also requires volatility of a compound at low pressure under vacuum so this technique can provide a useful guide to the suitability of a potential precursor for the classic FVP experiment. Although FVP is commonly encountered on a laboratory scale, in favorable cases pyrolysis of tens or even hundreds of grams is possible with little modification to the standard apparatus.

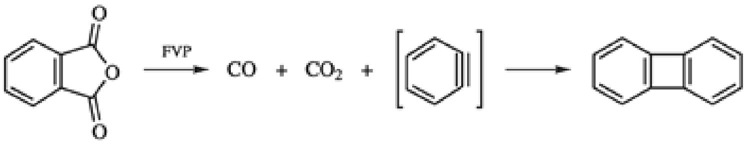
3. FVP Reactions

Most FVP reactions are either pericyclic (electrocyclic, sigmatropic shifts, or retro-Diels-Alder processes), radical reactions (initiated by cleavage of the weakest single bond in the substrate molecule), or involve the generation of diradicals (or carbenes, nitrenes, arynes) by cleavage of one or more single bonds, or of a formal double bond, often by extrusion of a small, stable molecule such as N_2, CO, or CO_2. Typical examples of each of these processes are shown in eq. 1 (Refs. 12-14, respectively). The generation and reactions of radicals and diradicals under FVP conditions has been reviewed (15). Because of the very dilute conditions in the furnace, intramolecular reactions (such as cyclizations or eliminations) are strongly favored, though coupling of radicals, carbenes, nitrenes, or arynes often takes place (cf. eqs. 1b and 1c). Intramolecular consolidation of diradicals is a particularly important route to closed-shell products (eq. 1d) 15, and references cited therein). Ionic intermediates are never encountered under FVP conditions due to high ionization energies in the absence of solvation.



(1a)

(1b)



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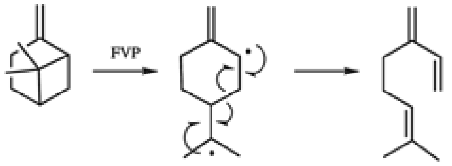
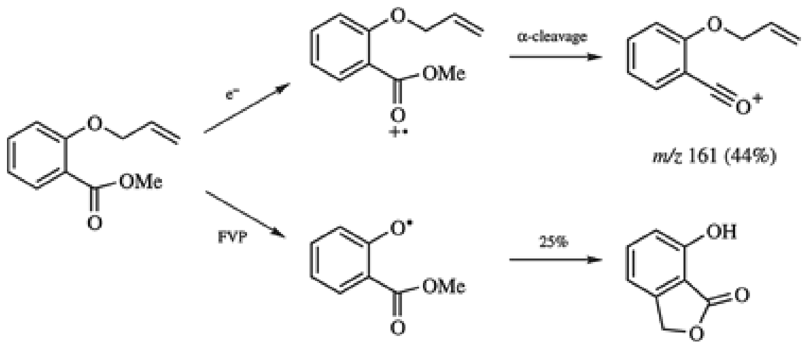


(1d)

Although superficially similar, the FVP experiment and the electron impact (EI) mass spectrometer (MS) experiment often produce quite different results. Whereas the FVP reaction is initiated by cleavage of the weakest bond in the molecule, the EI–MS experiment is driven by radical cation chemistry [and hence the location of the highest occupied molecular orbital (HOMO)]. An example of the contrasting behavior of one substrate under FVP and EI–MS conditions is shown in eq. 2 (16).



(2)

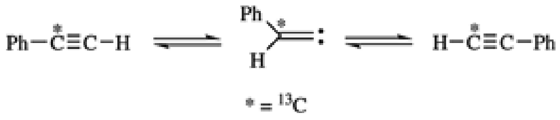
In the sections Studies of Reactive Intermediates and Application of FVP in Synthetic Organic Chemistry, specific examples of the use of FVP methods in mechanistic and synthetic organic chemistry are given. Inevitably, the choice of examples is highly selective—reference to >95% of the papers in the field has had to be omitted—but the intention has been to provide as balanced an account as possible, with emphasis on the strengths and limitations of the technique in organic synthesis.

4. Studies of Reactive Intermediates

Because reactions are carried out under short contact-time conditions in which the individual molecules are isolated from precursor, products (and atmospheric gases) in the absence of solvent, FVP methods provide idealized conditions for the study of reactive intermediates and reaction mechanisms.

4.1. Isotopic Labeling Studies. It is often possible to infer much about the mechanism of gas-phase processes by the use of isotopic labeling. The following three examples illustrate the utility of this approach. In each case, ^{13}C-labeling was used; labeling the molecular skeleton in this way tends to produce clearer results than, eg, deuterium labeling owing to secondary H(/D)-shifts that are sometimes remarkably facile.

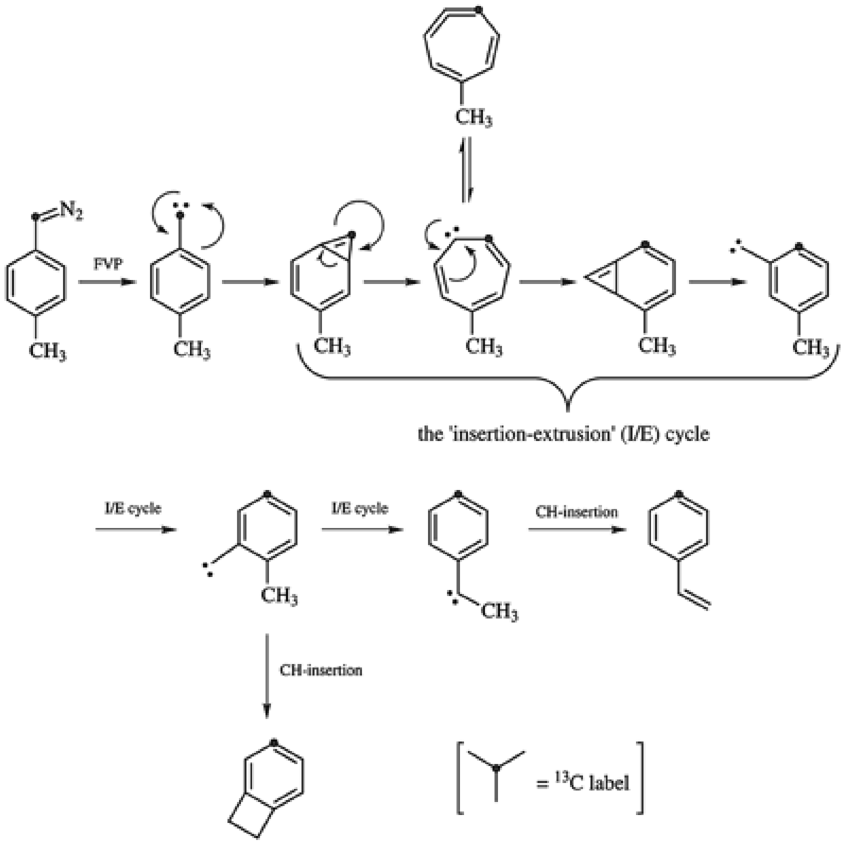
In a classic example, the interconversion of alkynes via a methylenecarbene experiment was established by the ^{13}C-labeling experiment shown in eq. 3 (17).



$$\mathrm{Ph{-}\overset{*}{C}{\equiv}C{-}H} \rightleftharpoons \mathrm{(Ph)(H)\overset{*}{C}{=}C:} \rightleftharpoons \mathrm{H{-}\overset{*}{C}{\equiv}C{-}Ph}$$

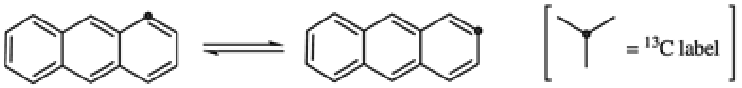
(3)

In a second application, the mechanism of the unexpected formation of benzocyclobutene and styrene from *p*-tolylcarbene under FVP conditions was shown to proceed by a carbene insertion-extrusion cycle, rather than by direct migration of the carbene around the periphery of the benzene ring (18) (eq. 4). There is still considerable interest in the precise mechanism of this and related rearrangements, in particular the relative energies of the various potential intermediates and transition states on the energy surface. Increasingly, experimental work in this, and related fields, is supported by theoretical calculations, often using density functional theory (DFT) (19).



(4)

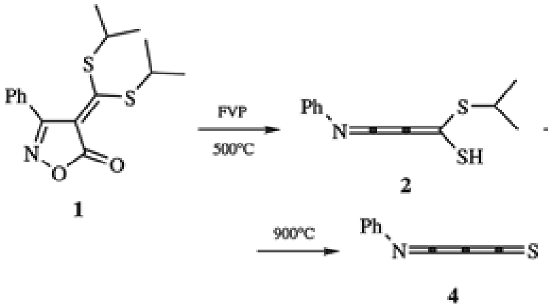
Skeletal rearrangements and automerization reactions of polycyclic (and other) aromatic systems (eg, eq. 5) have been revealed under FVP (and atmospheric pressure "flow") pyrolysis conditions. In the case of automerizations (in which the "product" of the reaction has the same structure as the starting material), labeled substrates are necessary to show the very existence of the reaction—and in addition to track the fate of individual atoms through the process (20).



(5)

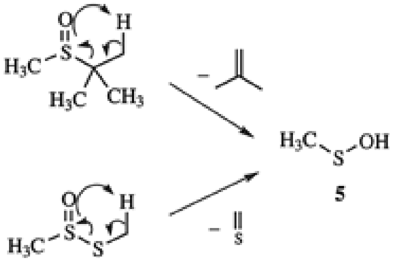
4.2. FVP in Conjunction with Gas-Phase Analytical Methods. When the hot gas-stream is analyzed *in situ* by a gas-phase analytical method, the resulting "hyphenated" techniques give direct information on the nature of the reactive intermediates generated in the FVP reaction. Thus, FVP–MS provides information on the molecular mass of species in the gas-stream whereas the ionisation patterns obtained by FVP–photoelectron spectroscopy (FVP–PES) provide another type of “molecular fingerprint”. The molecular structure and geometry of reactive intermediates can be determined by the use of FVP–microwave (FVP–MW) spectroscopy or FVP–gas electron diffraction (FVP–GED) methods.

As one example of the use of FVP–MS, the pyrolysate from the isoxazolone **1** was monitored at different furnace temperatures (21) and showed the dominant formation of thiols **2** and **3** at temperatures ~500°C, whereas temperatures of 800–900°C are required for complete conversion to the iminopropadienethione **4** (eq. 6).



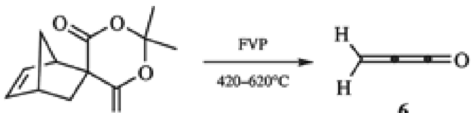
(6)

The use of FVP–PES was reviewed in 1981 (22). Like FVP–MS, this technique allows the determination and optimization of the temperature required for various thermal processes in real time. Products, including short-lived species, can be successfully characterized unambiguously. In a more recent example, it was possible to characterize the sulfenic acid **5** by PES, when generated by FVP-induced retro-ene reaction of two related precursors (eq. 7) (23).



(7)

Passing the effluent from the FVP furnace into a microwave chamber (FVP–microwave) has been used to determine the geometry of a number of short-lived species. Microwave spectroscopy is best for species containing a relatively small number of non-hydrogen atoms, but on the other hand spectra can be deconvoluted from gas streams in which the species of interest is only a minor component. In one example, the geometry of methyleneketene **6** has been determined (24) and shown to be nonlinear (eq. 8).



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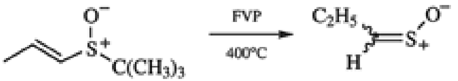
(8)

Similarly, the lacrymatory principle of onion, a property known for 6000 years, was generated and identified as the propanethial *S*-oxide **7** by FVP–MW methods (eq. 9) (25).



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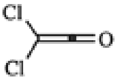
(9)

Provided the FVP process is efficient and only small amounts of by-products are obtained, gas-phase electron diffraction (GED) can be used to determine the geometry of reactive or short-lived species. Examples include dichloroketene (8) , the allyl radical (9) (27), and the imine (10) and enamine (11) (28) (eq. 9).



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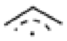


9

10

11

4.3. FVP in Conjunction with Matrix Isolation.

If the effluent from the FVP furnace is condensed onto a cold surface in the presence of a large excess of inert carrier gas, reactive intermediates or short-lived molecules can be trapped in the resulting matrix and examined by infrared (ir), ultraviolet (uv), or electron spin resonance (epr) spectroscopy. In particular ir spectroscopy has been used extensively in recent years because absorption frequencies of candidate species can be reliably calculated, often using DFT methods. The method has been recently reviewed (29). Matrix isolation has been employed to generate and characterize unusual functional groups (or combination of functional groups) and to probe reaction mechanisms. The groups of G. Meier and C. Wentrup have been particularly active in this field.

Examples of unusual functional groups include the iminopropadienethione **4** (eq. 6) (21) and many other examples of cumulated species related to ketenes. The novel 1,3-dipole, thioformaldehyde *S*-sulfide **(12)**, has been generated by FVP of 1,2,4-trithiolane (eq. 10) (30). In the area of reaction mechanisms, the results of matrix isolation experiments have made a huge impact on the understanding of the chemistry of phenylcarbene, phenylnitrene and related species (19) (c.f. eq. 4).

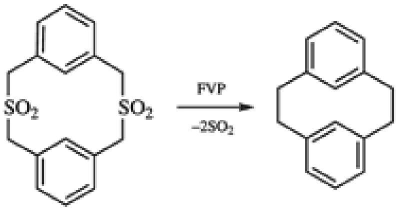
12

(10)

5. Application of FVP in Synthetic Organic Chemistry

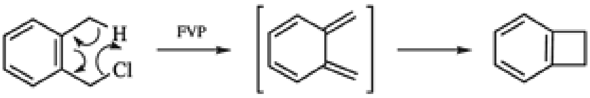
In the remainder of this article, the synthetic applications of FVP processes will be considered under the headings of the functional group created in the FVP reaction. The vast majority of useful FVP transformations are oxidative, involving either the creation of multiple bonds from saturated systems, or are cyclization reactions.

5.1. Alkanes. The FVP methods are not often used for the creation of C–C single bonds. However, the generation and intermolecular coupling of benzyl radicals by pyrolysis of oxalates (13) or sulfones (31) provides an excellent route to bibenzyl and its derivatives (cf. eq. 1b). Of greater importance, an intramolecular variant of benzyl sulfone pyrolysis has been widely employed in the synthesis of cyclophanes (32,33), in which the bridges do not contain any heteroatoms (eg, eq. 11). Countless examples of complex cyclophanes have been made in this way, including cases in which monobenzylic sulfones have been employed (32,33).



(11)

The sp^3–sp^3 bond of benzocyclobutene **(13)** (34) can be made by a number of FVP routes; that shown in eq. 12 (35) has been optimised for generation of **(13)** in 85% yield on a 10-g scale (36).



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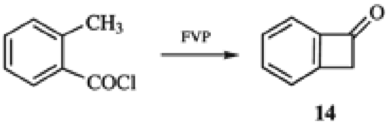
(12)

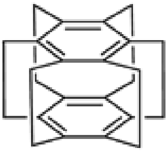
The formation of benzocyclobutenone **(14)** in 80% yield on a 200-g scale from *o*-toluoyl chloride (37) has been similarly optimised (38) (eq. 13).



14

(13)

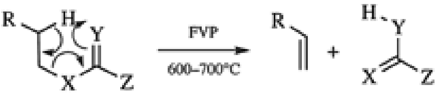
Multiple-bridged cyclophanes, including $[2_6]$ (1,2,3,4,5,6) cyclophane (superphane) (15) have been obtained by extensions of this strategy (39,40).



15

Formation of alkyl–alkyl bonds lacking benzyl stabilization is unusual under FVP conditions, but recent work has shown that it is possible to create macrocyclic rings by ring expansion or ring contraction strategies in this manner (41).

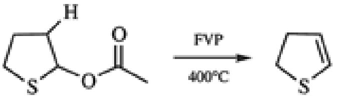
5.2. Alkenes. Alkenes are common products from FVP processes (42). The usual routes are by retro-ene reactions (of which hetero-analogues such as xanthate or acetate pyrolysis are the most important) (43,44) or by retro-cycloaddition reactions (45) (eg, eq. 14). The (*E*–*Z*) Isomerization of alkenes takes place under FVP conditions (46).



(14a)

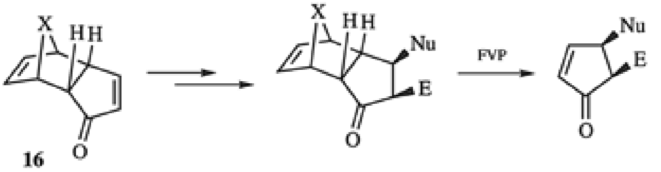
(14b)

Acetate pyrolysis (eq. 14a; X = Y = O, Z = CH_3) is traditionally carried out under “flow” conditions at atmospheric pressure (~500°C); FVP methods are equally successful though a slightly higher temperature is often required (600–700°C). Xanthates (eq. 14a; X = O, Y = S, Z = SCH_3) generally require lower furnace temperatures than corresponding acetates (47). In contrast to most solution-phase elimination mechanisms, the stereochemistry of the process is syn, as required by the cooperative, intramolecular nature of the mechanism. The advantages of the rapid quenching of products at the exit point of the hot zone are especially pronounced when the alkene product polymerizes or decomposes at normal temperatures. As one example, the unstable dihydrothiophene shown in eq. 15, could be obtained in >85% yield under FVP conditions (48).



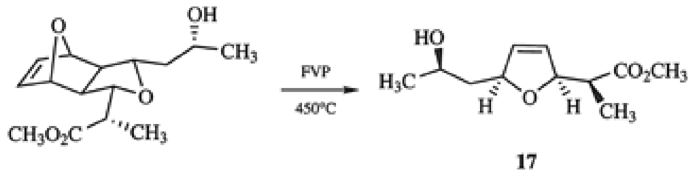
(15)

All aspects of the retro-Diels-Alder reaction (eq. 14b) were comprehensively reviewed by Rickborn in 1998 (45). In recent years, the Diels-Alder/retro-Diels-Alder sequence has been extensively employed as a protecting strategy for the alkene function in natural product syntheses, in particular by the groups of Bloch and Zwanenburg (49). One application of the general method is shown in eq. 16 ($X = CH_2$ or O). The tricyclic skeleton of **16** allows high levels of stereocontrol to be achieved during reactions of the enone function and the stereochemistry created in these steps is completely retained during the retro-Diels-Alder stage of the sequence (49).



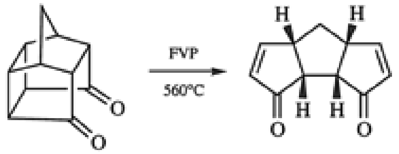
(16)

The related example shown in eq. 17 demonstrates the use of a furan adduct (cf. eq. 16, $X = O$) in the enantioselective synthesis of an immediate precursor **(17)** of (+)-methylnonactate (50). Furan adducts are advantageous since the retro-Diels-Alder reaction takes place at a lower furnace temperature than (eg, cyclopentadiene adducts).



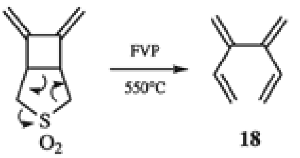
(17)

Another example of a retro-cycloaddition reaction, an efficient preparative route to benzo[*c*]furan, is shown in eq. 1a.



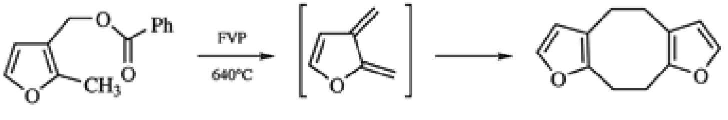
(18)

Dienes can be formed by ring-opening of cage structures (eg, eq. 18) (51) or by retro-cheletropic reactions, exemplified by the formation of [4]dendralene **(18)** (eq. 19) in which loss of SO_2 provides the driving force (52).



(19)

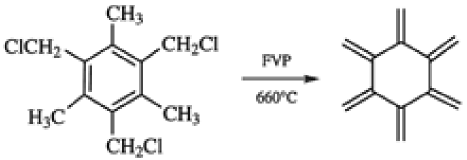
In a special case of polyene formation, xylylenes can be obtained as reactive intermediates en route to cyclobutenes by cyclic elimination reactions (eq. 12). In certain examples, often in the heterocyclic series, the diene form can prove to be more stable than the fused cyclobutene. Thus FVP of the furan derivative **(19)** gave the xylylene **(20)**, which was stable at −60°C in solution (53); at room temperature the head-to-head dimer **(21)** was obtained in 51% yield (eq. 20).



19 **20** **21**

(20)

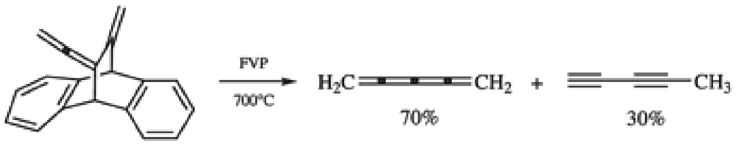
Similarly [6] radialene **(22)**, prepared by a similar method to that shown in eq. 12 (54) is more stable as the unsaturated valence isomer (eq. 21). It can be purified by sublimation at −10°C.



22

(21)

Cumulenes can be obtained by retro-Diels-Alder methods. In one spectacular example, pentatetraene, which has a half-life of 20 min in dilute solution at room temperature, was obtained in 70% yield by FVP of the anthracene adduct **(23)** (eq. 22) (55). This strategy has also been employed to generate reactive or transient alkenes such as vinyl alcohol (56,57).



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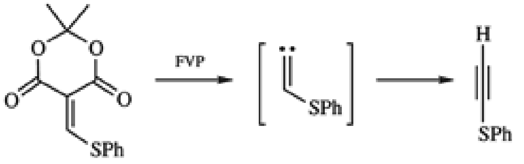
(22)

5.3. Alkynes. The best general FVP route to alkynes involves the generation and rearrangement of methylenecarbene intermediates (eq. 3) (17). Methylenecarbenes can obtained from some Meldrum's acid precursors (eg, eq. 23) (58), but the oxazolone route (eg, eq. 24) is much more general (59). This method provides the usual advantages of FVP for the synthesis of reactive and/or unstable alkynes.



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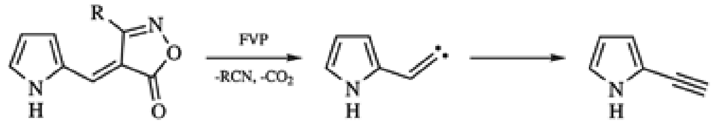


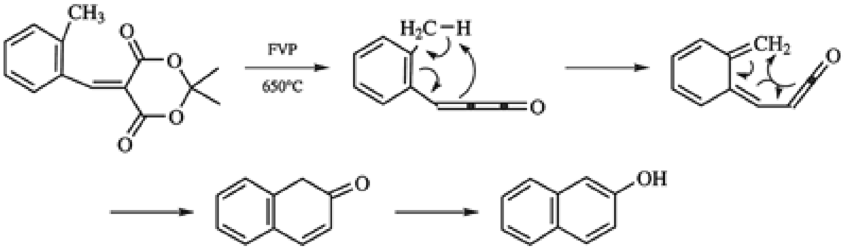
(24)

In addition, extrusion of triphenylphosphine oxide from phosphoranes at 500−750°C has provided a range of alkynes in up to 93% yield on a scale of up to 20 g (eq. 25) (60).

(25)

5.4. Aromatics. There are many examples of the annelation of benzene rings to a preformed aromatic template under FVP conditions. Many different reaction types have been used in these transformations, including electrocyclizations, carbene insertions, radical cyclizations, and collapse of diradical species. In the polycyclic aromatic field, many mechanistically intriguing skeletal rearrangements have been discovered under very high temperature conditions (cf, eq. 5). Much of this work has been stimulated by the discovery of fullerenes and the need for rational syntheses of bowl-shaped hydrocarbons, culminating in a logical route to C_{60} itself (see below) (61).

The formation of β-naphthol derivatives by FVP of *o*-tolualdehyde derivatives of Meldrum's acid—described as the McMullen reaction — is an important reaction of methyleneketene intermediates (eq. 26) (62). The method is very general and has been employed to create the phenol ring of natural products such as ruscodibenzofuran 24 (63).



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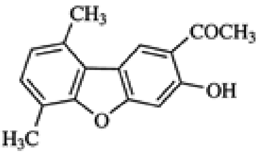
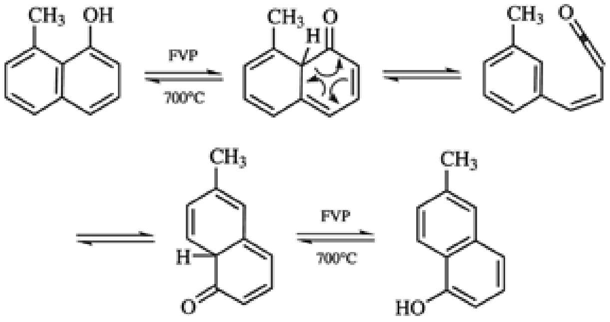


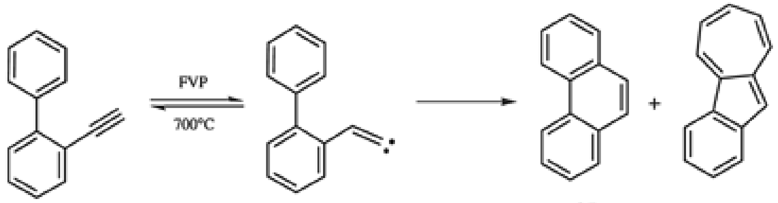
24

α-Naphthol derivatives also have interesting pyrolysis chemistry; in this case, tautomerism and retro-electrocyclization generates a ketene intermediate under surprisingly mild conditions, revealed by the thermal equilibration of 6-methyl- and 8-methyl-naphth-1-ol shown in eq. 27 (64).



(27)

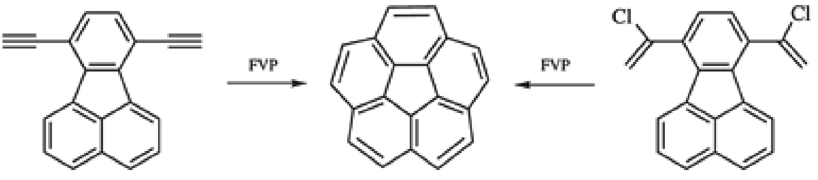
The synthesis of polycyclic aromatic systems under FVP conditions is based on two key reactions, namely, the *in situ* generation and cyclization of methylenecarbene intermediates by FVP of acetylenes or their precursors (the Brown reaction cf. eq. 3) and the generation and cyclization of aryl radicals.



25 **26**

(28)

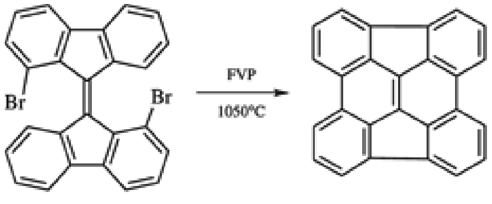
In an early example of the Brown reaction, both phenanthrene **(25)** (78%) and the benzazulene **(26)** (22%) were formed by FVP of biphenyl-2-ylacetylene at 700°C (eq. 28) (17). The benzazulene is formed by addition of the carbene to the adjacent aromatic ring followed by an electrocyclic ring expansion−contraction sequence. It was later found that this benzazulene pathway could be eliminated if the product was sufficiently strained. Thus, FVP of the diacetylene **(27)** at 1000°C gives corannulene **(28)** though in low preparative yield (10%), partly owing to the poor volatility of the precursor (eq. 29) (65). Optimization of this procedure using the chloro-compound **(29)** as a "protected" acetylene provided corannulene in 35−40% yield, as the final step in a three step sequence from commercially available starting materials (eq. 29) (66).



27 **28** **29**

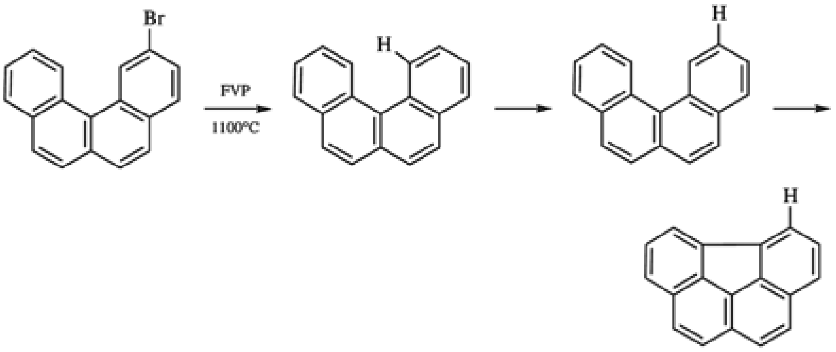
(29)

This general strategy has been extraordinarily productive in the synthesis of bowl-shaped hydrocarbons and fullerene fragments (67,68). However, extreme temperature conditions are usually required and yields are often low, especially for the more complex examples.



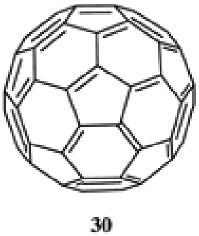
(30)

New Ar–Ar bonds can also be created by a free-radical cyclization process, employing aromatic halogen compounds (usually bromo derivatives) as the radical source. This thermal dehydrohalogenation procedure is usually much more efficient than the analogous dehydrogenation of the unsubstituted hydrocarbon. Although the halogen atom is usually located at the cyclization site [as in eq. 30 (69)] it has been established that 1,2-hydrogen shifts can occur in aryl radicals and so the precursor regiochemistry may not be critical (70) (eg, eq. 31).



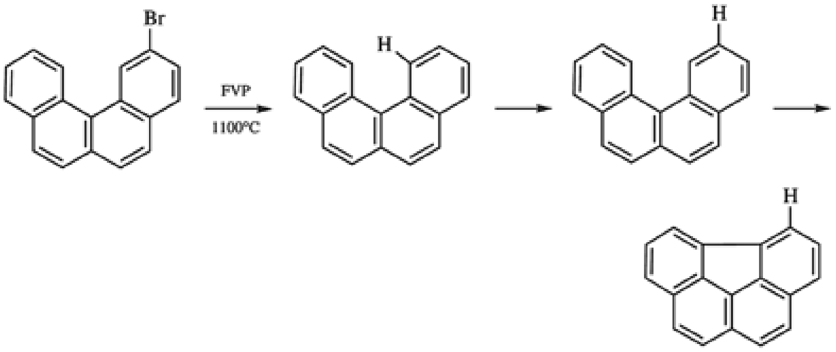
(31)

This radical cyclization approach has provided the first rational synthesis of [60]fullerene (C_{60}, **(30)**)] by FVP of a functionalized 16-ring, 60-carbon, precursor at 1100°C (61).



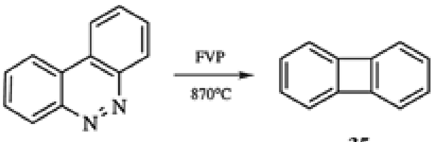
30

Polycyclic aromatic hydrocarbons can undergo complex skeletal rearrangements at high temperatures (cf. eq. 5) (20), which can complicate the analyses of many of the reactions in this area. One example of the sort of confusion that can arise is shown in eq. 32 in which the initial Brown cyclization product **(31)** subsequently rearranges at high temperature into the isomeric hydrocarbon **(32)**. At even higher temperatures, a third isomer **(33)** begins to appear (71). It appears that fused cyclopenta- (CP) units are particularly prone to rearrangements of this type, especially when the fusion is external (as in **(31)**) (20). The fundamental understanding of such reactions is important in the interpretation of high energy processes such as carcinogen formation in smoke (72), and the formation of fullerenes and carbon nanotubes (20).



(32)

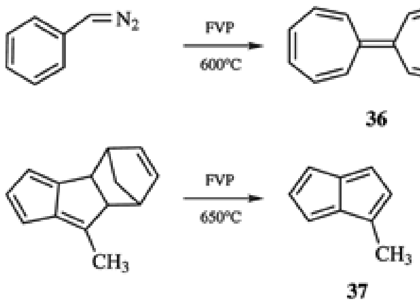
Unusual aromatic systems can be formed by extrusion reactions [eg, by loss of CO from polycyclic quinones (73) or by cleavage of N_2 from fused cinnolines]. As an example of the latter, FVP of benzo[*c*]cinnoline **(34)** provides the best synthetic route to biphenylene **(35)** (eq. 33) (74). The method is general and has been subsequently applied to various substituted and polycyclic examples.



34 **35**

(33)

FVP conditions are particularly advantageous for the preparation of reactive or unstable "non-benzenoid" aromatic compounds. Classic examples include the one-step formation of heptafulvalene **(36)** by ring expansion of phenylcarbene (cf. eq. 4) (75) and the generation of 1-methylpentalene **(37)**, which dimerises above −150°C by a retro-Diels-Alder strategy (76) (eq. 34).



(34)

On the other hand, unusual aromatic systems can also be destroyed at high temperatures, though with interesting mechanistic consequences. The mechanism of the puzzling isomerization of azulene to naphthalene (eq. 35) (77) has been recently worked out, predominantly by theoretical (DFT) methods (78).

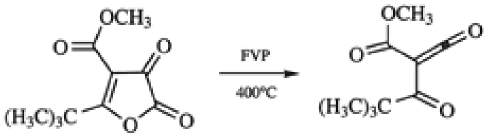
(35)

5.5. Heteroatom-Containing Functional Groups. In principle, the FVP method is an excellent way of creating multiple-bond functionality, but many other routes are also available for the formation of common functional groups. A few isolated FVP examples are given below, and the most important of these involve rearrangement reactions rather than eliminations. However, a number of unusual or highly reactive functional groups are best made in this way (cf. sections FVP in Conjunction with Gas-Phase Analytical Methods and FVP in conjunction with Matrix Isolation).

The isonitrile–nitrile rearrangement (eq. 36) is one example of a functional group interconversion that can be carried out with great efficiency under FVP conditions (79). Yields are high, a wide range of structurally diverse isonitrile derivatives rearrange under standard conditions and high throughput rates (>0.5 g/min) are possible. In addition, homochiral isonitriles rearrange with high levels of retention of configuration (80).

$$\mathrm{R{-}\overset{+}{N}{\equiv}\overset{-}{C}} \xrightarrow[550°\mathrm{C}]{\mathrm{FVP}} \mathrm{R{-}C{\equiv}N} \qquad (36)$$

FVP is an excellent method for generating ketenes, both as reactive intermediates and, in the presence of appropriate stabilizing features, as isolated products (81). For example, α-oxoketenes such as **(38)**, which are stabilized both sterically and electronically, can be prepared in 90% yield by decarbonylation of a precursor furan-2,3-dione. The ketene **(38)** dimerizes over a period of a few hours at room temperature (eq. 37) (83).



38

(37)

A series of functionalized allenes has been prepared by sigmatropic rearrangement of corresponding propargyl precursors under FVP conditions (84). The reaction shown in eq. 38 gives a flavor of the chemistry; the route to the allenyl isothiocyanate **(39)** has been extended to corresponding isoselenocyanates and thiocyanates (84). In a related process, propynal has been made in 80% yield by an FVP route involving a retro-ene decomposition of dipropargyl ether at 750°C (85).

39

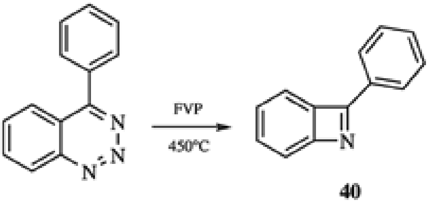
(38)

Many examples of unusual multiple-bonded functional groups have been generated by FVP methods, but most of these products are not stable entities (unless special electronic or steric features are incorporated in the target molecules) and the methods outlined in the section Studies of Reactive Intermediates have been used for their characterization. The "vacuum gas–solid reaction" (VGSR) technique (1g) has also been used extensively in this field, though the following examples are typical of the structures that can be obtained by conventional FVP methods. Thus, silanimines ($R_2Si{=}NR'$), phosphasilenes ($R_2Si{=}PR'$), and silanethiones ($R_2Si{=}S$) can be obtained, often by retro-ene reactions or by thermal cracking of their cyclic dimers (7). Retro-ene methods have also been used to obtain cycloalkanethiones ($R_2C{=}S$) (87). The first example of an isolated, sterically protected telluroketone ($R_2C{=}Te$) was obtained as a green crystalline solid by an FVP reaction (88). Phosphapropyne ($CH_3C\#P$) can be made by FVP of divinylphosphine at 700°C; this product is stable in solution for at least 1 week at room temperature (89).

There is considerable scope for development of FVP methods for functional group transformations, particularly for examples where the advantages of chemistry without reagents provide for convenient work-up and isolation.

5.6. Heterocycles. The FVP technique has been employed extensively in synthesis for heterocyclization reactions. As well as examples of rings with unusual heteroatoms and with unusual ring sizes, there are many cases where FVP has been used as an efficient method of making common heterocyclic systems. In the discussion below, the examples are arranged in order of increasing ring size of the cyclisation step.

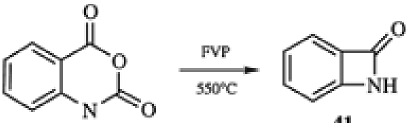
There are many cases of four-membered heterocycles being obtained efficiently at high temperatures. For example, the formation of the benzazete **(40)** by nitrogen extrusion from a benzotriazole precursor is a classic of early FVP chemistry (eq. 39). Careful temperature control was essential to stop benzyne formation by further extrusion of benzonitrile. The unstable azete **(40)** could be collected at −78°C and was shown to undergo cycloaddition reactions (90).



40

(39)

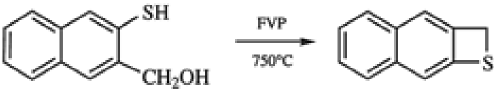
The formation of benzazetinone **(41)** in 80% yield by FVP of commercially available isatoic anhydride is noteworthy in its simplicity; the product was identified by nuclear magnetic resonance (nmr) spectroscopy at −90°C (eq. 40) (91).



41

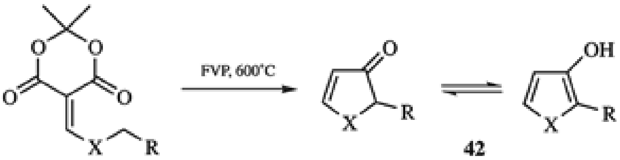
(40)

Benzo- and naphtho-thietes can be elegantly made via the corresponding xylylene by dehydration of (2-mercapto)arylmethanol derivatives at 750°C under FVP conditions (eg, eq. 41) (92,93).



(41)

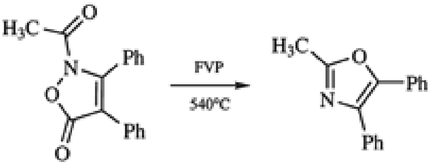
In the field of five-membered ring chemistry, the formation of benzo[*c*]furan has been previously mentioned (eq. 1a) (12) and a corresponding route to isoindole has also been developed (94). The versatile formation of reactive substituted 3-hydroxypyrroles (95) [and 3-hydroxythiophenes (96)] **(42)** (X = NR or S) by FVP of amino- (and thio-) methylene derivatives of Meldrum's acid (eq. 42) has been reviewed, together with other aspects of Meldrum's acid pyrolysis chemistry (97). The products **42** exist in solvent dependent equilibrium with their keto tautomers that are prone to aerial oxidation.



42

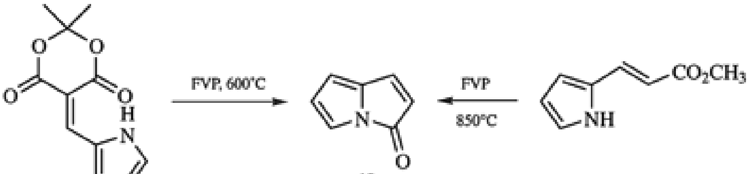
(42)

Decarboxylation of *N*-acylisoxazol-5-ones at ∼550°C provides a general and high yielding route to oxaxoles (eq. 43) (98).



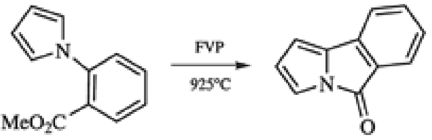
(43)

Pyrrolizin-3-ones **(43)** can be made from Meldrum's acid derivatives (94), but other FVP routes are available [eg, from pyrrol-2-ylacrylates after initial (*E–Z*) isomerization (eq. 44a) (100)]. The benzopyrrolizinone derivative **(45)** can be obtained from readily available precursors by high temperature pyrolysis of the *N*-arylpyrrole **(44)** (101); sigmatropic shift of the aryl group (102) precedes the cyclization (eq. 44b).



43

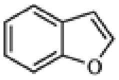
(44a)



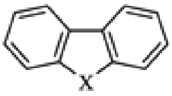
44 **45**

(44b)

Other fused five-membered rings that can be made by FVP include benzofurans (46) [by radical cyclization of 2-alkenylphenoxyls (102)], dibenzofurans (47), and dibenzothiophenes (48) [by cyclization of radicals derived from arylsalicylates or the corresponding thiosalicylates (104)] and carbazoles (49) [by extrusion of dinitrogen from 1-arylbenzotriazoles (105)].

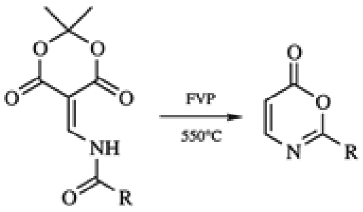


46

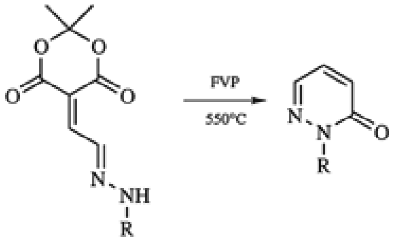


47 X = O
48 X = S
49 X = NH

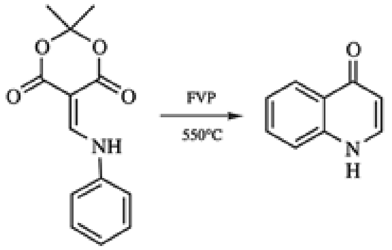
The FVP of Meldrum's acid derivatives has also provided a rich source of six-membered heterocyclic lactones, lactams, and ketones, and some examples are shown in eq. 45 (106–108).



(45a)

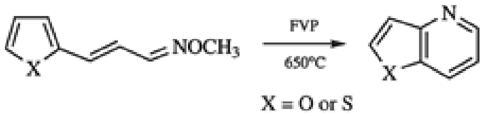


(45b)

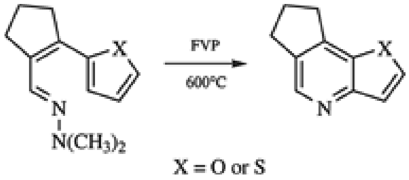


(45c)

Fused pyridines can be created by cyclization of iminyl radicals generated by FVP of oxime ether or hydrazone derivatives (eq. 46) (109,110), though in the latter case an electrocyclic mechanism has been proposed.

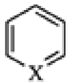


(46a)



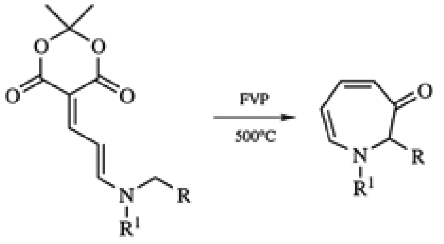
(46b)

Heterobenzenes in which the heteroatom is a second-row element have been generated by FVP methods, often employing a retro-ene reaction at some stage in the sequence. Examples include 1-methylsilabenzene (50) (111) and phosphabenzene (51) (112).



50 X = $SiCH_3$
51 X = P

In the seven-membered ring series, Meldrum's acid chemistry can also be applied to provide the azepin-3-ones shown in eq. 47 (113).

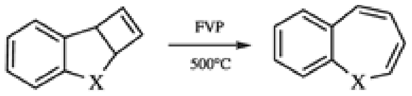


(47)

Though not strictly FVP chemistry, Meth-Cohn and co-workers (114) used their spray pyrolysis technique to provide reactive aza-azulenes by a ring expansion sequence and loss of N_2, CO_2, and HCl from azidoformates (eg, eq. 48).

(48)

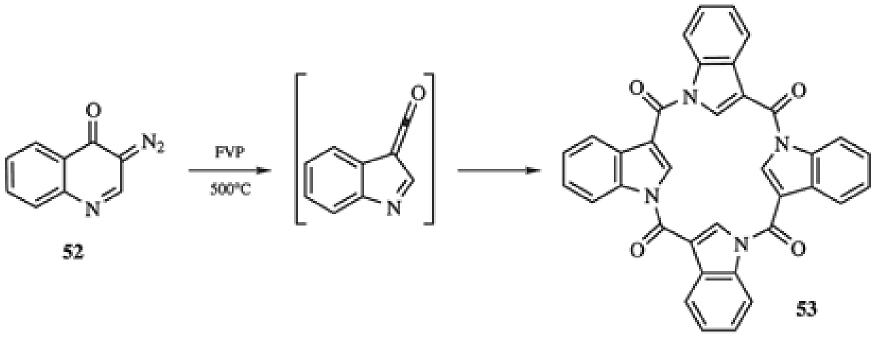
Tsuchiya and co-workers (115,116) prepared a series of new benzoheterepine ring systems with unusual heteroatoms (eq. 49). A thermal electrocyclic ring-opening strategy has been employed in all cases.



X = POPh, $Si(CH_3)_2$, $Ge(CH_3)_2$, AsOPh, PPh, AsPh

(49)

As one example of macrocycle formation under FVP conditions the generation of the indole tetramer **(53)** may be cited (117). It is obtained in 75% yield by FVP of the diazo-compound **(52)** via ring contraction and oligomerization of the resulting indolylketene (eq. 50).



(50)

6. Conclusions

The use of high temperature, short contact time (flash vacuum pyrolysis, FVP) conditions provides a useful addition to the armoury of the organic chemist. Reactive intermediates can be studied, either indirectly by isotopic labeling, or directly by matrix isolation. FVP is useful is synthesis, particularly for reactions such as eliminations and cyclizations that involve an oxidative component. Reactions take place in the absence of solvent and the absence of oxygen and products may be quenched at low temperatures only milliseconds after their formation. These are significant advantages if the product is likely to be unstable or reactive. Because high temperatures can be used to help surmount large energy barriers, the method is also useful for the creation of highly strained molecular architectures. Most of all, FVP provides generally useful conditions for chemistry without reagents with numerous applications in many areas of synthetic organic chemistry.

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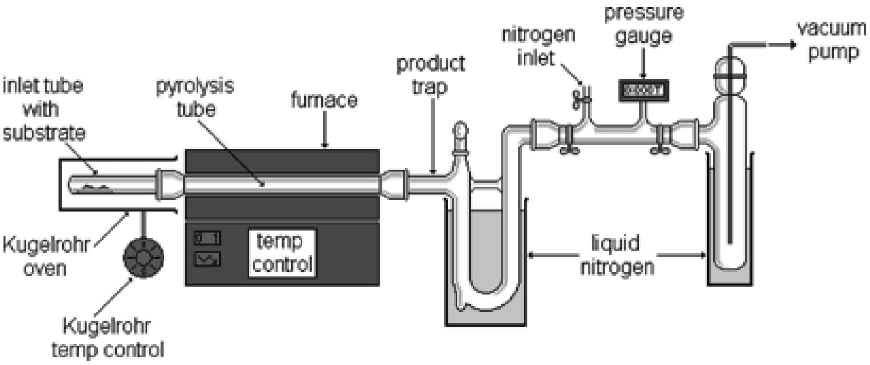

Fig. 1. Typical apparatus for preparative FVP.