Are flash pyrolytic reactions useful?

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Abstract - Four groups of flash vacuum pyrolytic reactions are proposed as being useful in synthetic organic methodology: 1,2- and 1,4-eliminations; fragmentations of carbonyl compounds; Diels-Alder and retro-Diels-Alder reactions; acetylene - methylenecarbene rearrangements.

INTRODUCTION

Pyrolytic reactions must have some virtues; there has after all been a flood of papers on flash vacuum pyrolysis (FVP) in the chemical literature of the last 25 years. These virtues have, however, rarely shown up in the area of multi-step synthesis. Instead FVP has mostly been used for the generation of small, highly reactive or transient molecules such as $\underline{1}$ - $\underline{6}$. The pyrolytic generation of 1-methylpentalene $\underline{1}$ (ref. 1) is clearly one of the chemical triumphs of this century, but it contributed more to the theory of aromaticity than to synthesis. In the context of the present Symposium my rhetorical title question must be re-defined to ask whether pyrolytic methods can usefully be added to standard synthetic methodology.
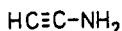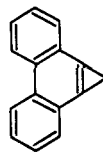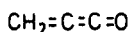

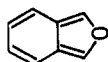
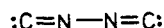The following schemes outline four groups of reactions which are sufficiently general and reliable to have synthetic value. Not all of the examples are new; many beautiful but too specialized reactions have been omitted.

A significant barrier to the general use of FVP in synthesis has been that some special equipment is required; however most reactions can be run with simple glass and silica ware, commercial (ref. 2) or laboratory-constructed (ref. 3). *The cost is much below that of most photochemical gear because the equipment is long-lived.*

ELIMINATIONS

The 1,2-elimination of acetic or benzoic acid to form alkenes can proceed smoothly by FVP at modest temperatures. Scheme 1 shows an example from the group of Dr. D.J. Collins (ref. 4) in which the elimination is unambiguous, both protecting groups survive, and the workup to remove benzoic acid is trivial.

Scheme 1

620° / 0.03 torr

Packed silica tube

− Ph-COOH
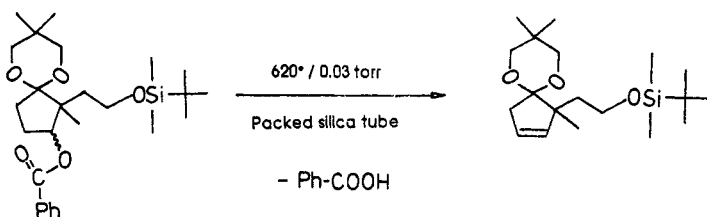
1,4-Elimination in o-disubstituted aromatic compounds is of particular value for the preparation of benzocyclobutene derivatives which are in turn valuable synthetic intermediates. In the first reaction in Scheme 2 a useful intermediate is produced in good yield (ref. 5); in the second example the bis-methylene species forms smoothly, but dimerization competes with its trapping with acrylic ester (ref. 6). Such competition is, unfortunately, common with highly reactive intermediates.

Scheme 2

590-610°C
0.01 torr
−Me₃SiCl

73%   (+ 7% bis-SiMe₃)

620°
10⁻⁴ torr

collect at −196°

−78°

30-40%

dimers
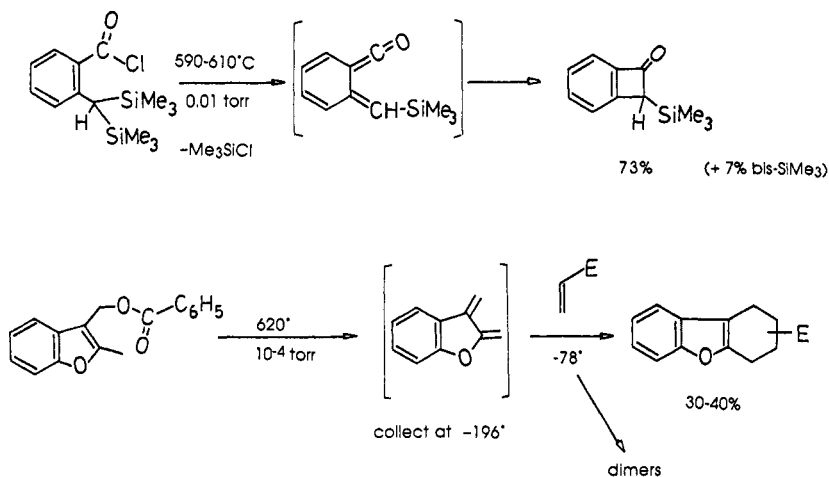
FRAGMENTATIONS

Fragmentations of carbonyl compounds are at the heart of pyrolytic chemistry, and the reactions below have been selected from myriad examples. Scheme 3 shows the pyrolytic synthesis of the diene 7, for which we had ambitions (unfulfilled!) as a synthon for rings A and B in steroid synthesis (ref. 7). Note that the ethylenedioxy group survives 630°, but that at 740° the diene 7 is destroyed by aromatization to p-cresol.

Scheme 3

FVP 740°

630°/0.1 torr

+ CO

65%

7 72%
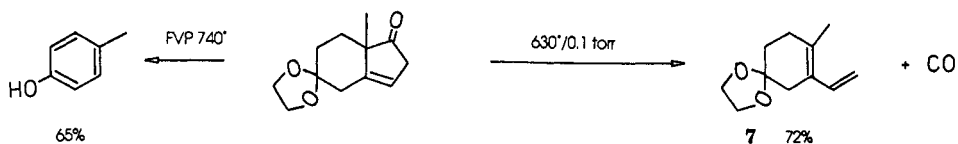
The pyrolysis of unsaturated derivatives of Meldrum's acid is a fertile area of chemistry which grew out of our early efforts to make methyleneketene, $CH_2=C=C=O$. Our most useful reaction is the conversion of o-tolualdehyde, by condensation with Meldrum's acid to give **8** and then FVP, into 2-naphthol in essentially quantitative pyrolytic yield (Scheme 4). This pyrolysis I shall refer to as the McMullen reaction after its discoverer, Dr. Gabrielle McMullen (ref. 8).

Scheme 4
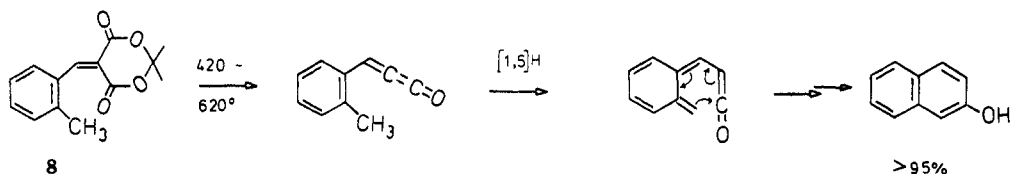
The McMullen reaction is very versatile and can be used for the synthesis of phenols, 2-naphthols, and naphthalenones. The dibenzofuranol **10** has been synthesised in a double application of the McMullen reaction, starting from the furan **9**, Scheme 5 (ref. 9).

Scheme 5
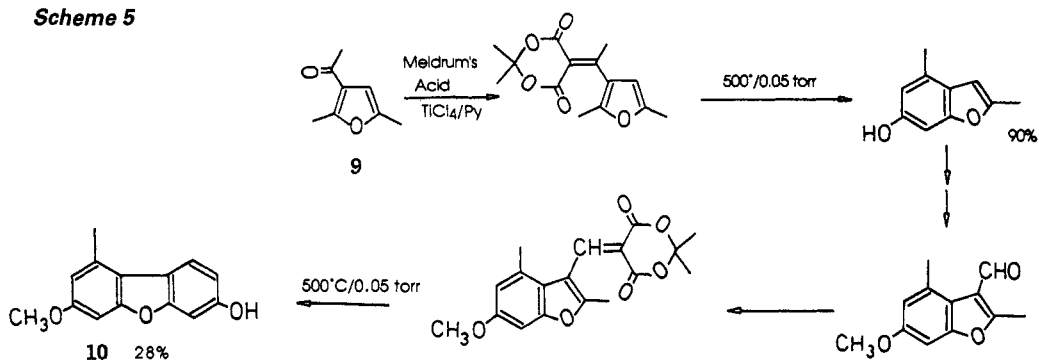
Related reactions leading to nitrogen heterocycles have been developed by the groups of Chuche, McNab, and Wentrup, and give access to a range of heterocyclic carbonyl compounds not readily prepared in other ways. Scheme 6 shows a typical synthesis of an azepinone **11** by McNab's group (ref. 10). Such reactions require dipolar intermediates, however they are formulated. Lower vinylogues give pyrrolones.
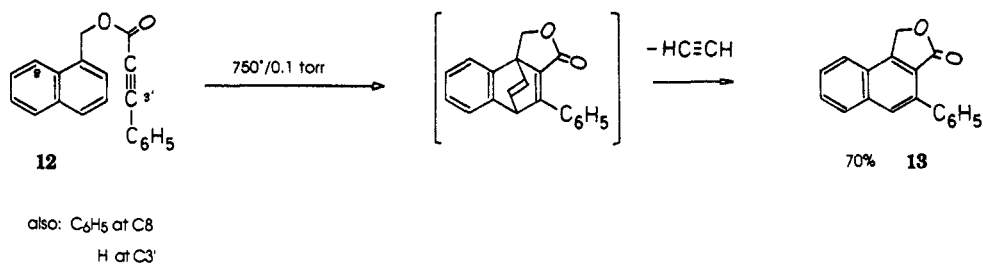
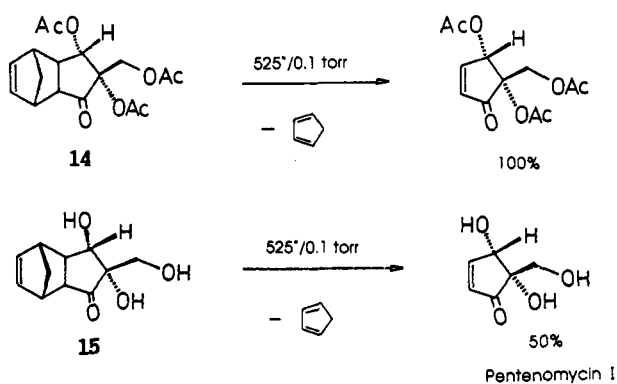*Scheme 6*
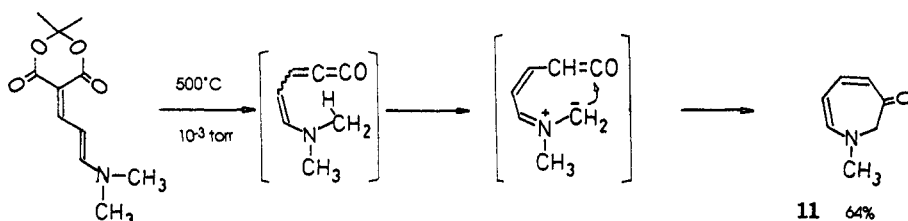
DIELS–ALDER AND RETRO-DIELS–ALDER REACTIONS

The importance of the Diels-Alder reaction in modern synthesis can scarcely be over-emphasised, and the intramolecular variant is currently widely used. Intermolecular Diels-Alder reactions are unlikely to be helped by FVP conditions, but we have recently developed an intramolecular Diels-Alder/retro-Diels-Alder sequence (ref. 11) which in a single step converts a 1-substituted naphthalene 12 into a 1,2-di or 1,2,3-trisubstituted product (13, Scheme 7). The same reaction occurs only to a minor extent in the benzene series.

Scheme 7


also: C_6H_5 at C8
     H at C3'

The sequence of Diels-Alder protection of a double bond, structural modification of the adduct, and ultimate deprotection by retro-Diels-Alder elimination of a diene is well established. FVP conditions may be essential for this deprotection. Scheme 8 shows the work of Zwanenburg's group on pentenomycin I synthesis (ref. 12), where the triacetate 14 behaved impeccably, but the triol 15 gave only 50% yield. The same effect appears in Scheme 9, from our work on an alternative approach to mycorrhizin A (ref. 13). The secondary alcohol 16 eliminated cyclopentadiene smoothly, but its epimer gave only 31% yield; silylation to 17, however, led to 100% yield of deprotected enone 18. The message from these examples is that hydrogen bonding substituents are to be avoided if possible in FVP; if they are protected with non-polar groups then quite complex molecules can be sublimed smoothly into the hot zone.

Scheme 8

Scheme 9
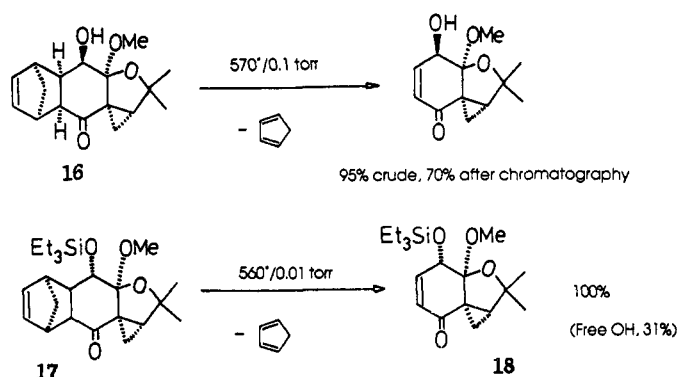
There is an alternative for use with compounds with hydrogen-bonding and polar substituents, and for compounds which decompose on attempted sublimation. Magrath and Fowler (ref. 14) have shown that such compounds can be dissolved in a solvent stable to pyrolysis (e.g. benzene or water), frozen, and subjected to a <u>very rapid</u> vacuum sublimation which leads to entrainment of the solute with the solvent vapour. Thus the sensitive bicyclic system <u>19</u> was co-sublimed with benzene and the mixed vapour was pyrolysed at 450° to give the product of 1,2-elimination and aza-Cope rearrangement, <u>20</u> (Scheme 10). Even the nucleoside thymidine could be co-sublimed with water; at a pyrolysis temperature of 350° it was unchanged, but at 500° it lost the deoxyribose moiety to give thymine (80%).
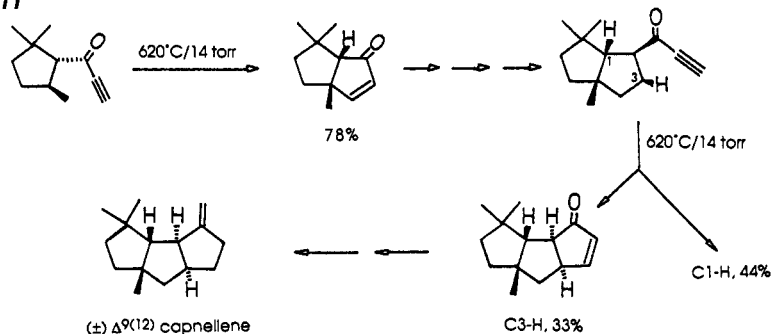
Scheme 10
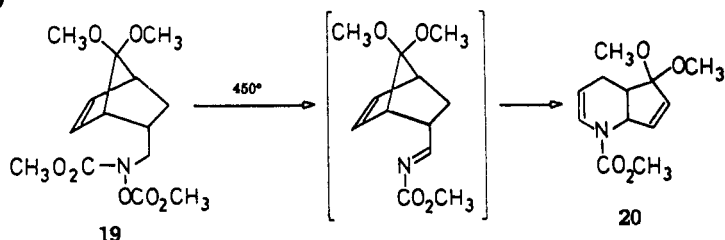
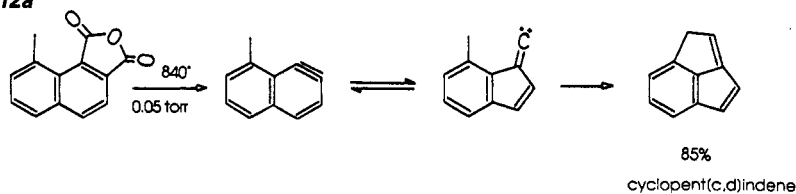## ACETYLENE–METHYLENECARBENE REARRANGEMENTS

The high temperature equilibration of an acetylene R-C≡C-R' with the methylenecarbene RR'=C: was first achieved at Monash (review, ref. 15). The most useful application, however, is due to Dreiding's group, which found that the equilibration is very facile in acetylenic ketones on pyrolysis at <u>ca</u> 600°/14 torr. Intramolecular insertion of the carbene centre in suitable ketones gives cyclopentenones in good yield. Scheme 11 shows a double application of this procedure to $(\pm)\Delta^{9(12)}$ capnellene synthesis (ref. 16).
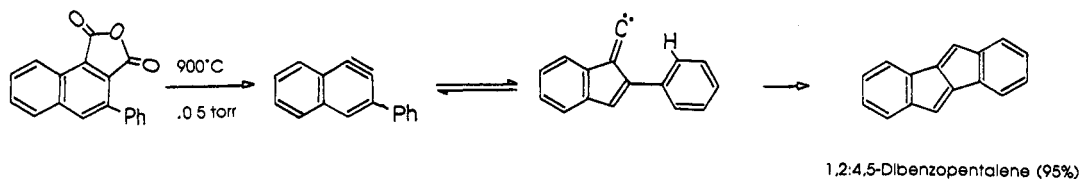
Scheme 11

A similar equilibration, from aryne to ring-contracted carbene, is probably involved in the FVP of some aromatic anhydrides bearing <u>peri</u> or <u>ortho</u> substituents. Scheme 12 shows insertion into a <u>peri</u>-methyl group (ref. 17) and into an <u>ortho</u>-phenyl substituent (ref. 11). These are very high temperature reactions, remote from natural product synthesis, but they do produce hydrocarbons which are less easy to make by conventional synthesis.

Scheme 12a

85%

cyclopent(c,d)indene

Scheme 12b

1,2:4,5-Dlbenzopentalene (95%)

This story began with some transient species, and finishes with an application of methylenecarbene rearrangement to generation of a transient, dimethylbutatrienone, **21**. Scheme 13 shows a rational synthesis of **21**, based on our experience of 1,2-elimination methyleneketene decarbonylation, methylenecarbene rearrangement and retro-Diels-Alder fission (ref. 18). This is obviously **not** a synthetically useful reaction, but this account has shown that from time to time the spin-off from such chemistry can lead to useful synthetic procedures.

Scheme 13
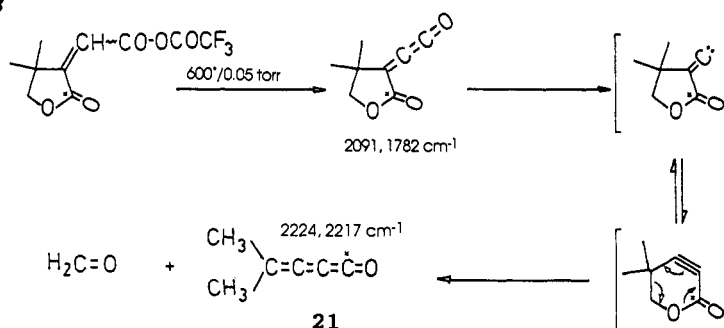
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