THERMAL HETEROCYCLIZATION IN PYROLYTIC REACTIONS: SYNTHETIC AND MECHANISTIC STUDY

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Abstract. *In this review chapter we will provide a detailed mechanistic study and utilities of pyrolytic reactions with emphasis on flash vacuum pyrolysis (FVP)in heterocyclic synthesis.*

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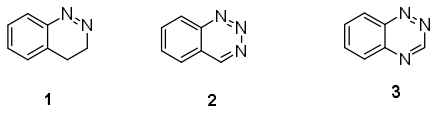
1. Introduction

Flash vacuum pyrolysis (FVP) offers valuable routes for heterocyclization reactions, and represents a powerful alternative in heterocyclic synthesis. FVP has been successfully used by our research group for the synthesis of various heterocyclic compounds. Very recently we reported on the FVP of ethers, acetylenic esters and amides in which reaction pathways and mechanisms were postulated based on the analysis and characterization of the products of the reactions.

2. Thermal heterocyclization

FVP of cinnolines **1**,[1-3] 1,2,3-benzotriazines **2**,[4] and 1,2,4-benzotriazines **3**[4] (Scheme 1) is a preparative important process that provides direct and easy access to many interesting heterocyclic compounds. Upon elimination of N2, diradical intermediates are usually generated, which then intramolecularly cyclize to give new heterocyclic systems.



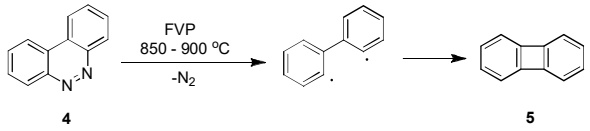
1 2 3

Scheme 1. Cinnoline, 1,2,3-benzotriazene and 1,2,4-benzotriazene.

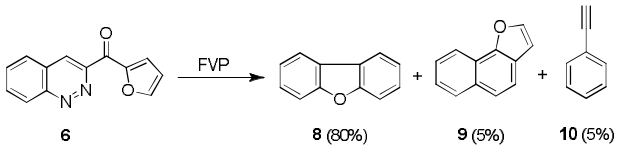
2.1. FVP of cinnolines

In general, FVP of benzo[*c*]cinnoline **4** requires high temperatures to yield biphenylene **5** (Scheme 2).[2,5] The synthetic potential of this reaction has been extensively utilized and has provided an easy direct access to the aza-analogues of **5** which are otherwise difficult to make.[6-9]

Our group has used this approach for the synthesis of angular heteroarenes. We have reported the FVP of 3-(2-furoyl)-cinnoline **6** and 3-(2-thienoyl)-cinnoline **7**.[1] FVP of **6** resulted in high yield of dibenzofuran **8** together with naphtho[1,2-*b*]furan **9** and phenylacetylene **10** (Scheme 3).

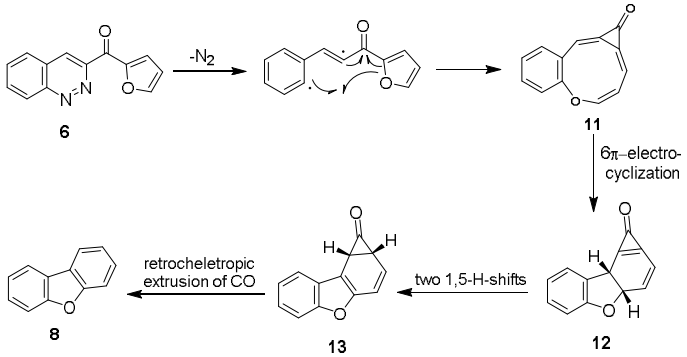


Scheme 2. FVP of benzo[*c*]cinnoline **4**.



Scheme 3. FVP of 3-(2-furoyl)-cinnoline **6**.

The mechanism of the pyrolytic reaction of **6** suggests the formation of a diradical that rearranges into benzononatetraene **11**, which electrocyclizes into **12**. Then, the latter undergoes a double 1,5-H-shifts to produce **13**. The extrusion of CO from **13** results in **8** (Scheme 4).



Scheme 4. Mechanism for the formation of dibenzofuran **8**.

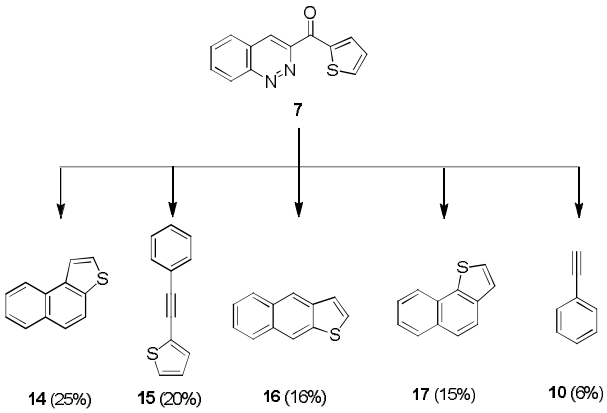
Under the same reaction conditions, FVP of 3-(2-thienoyl)-cinnoline **7** resulted in phenylacetylene **10**, naphtho[2,1-*b*]thiophene **14**, phenyl-2-thienylacetylene **15**, naphtho[2,3-*b*]thiophene **16** and naphtho[1,2-*b*]thiophene **17** (Scheme 5).

2.2. FVP of [1,2,3]-triazines

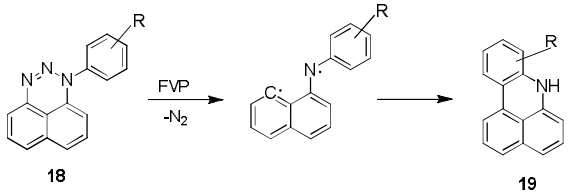
The FVP of substituted [1,2,3]-triazines **18** is a very convenient method for the synthesis of condensed naphthoheterocyclic ring systems **19** (Scheme 6).[10] The mechanism of their pyrolytic behavior resemble very much that of substituted benzotriazoles (Scheme 7) that has been extensively and successfully used for the preparation of many interesting heterocyclic systems.[11-14] The mechanism involves thermal extrusion of N_2 leading to reactive 1,3-biradical intermediates which interact with aryl or heteroaryl substituent to afford cyclic products.

Our group has investigated[15] the potential application of substituted 1-aroylnaphtho[1,8-*de*][1,2,3]triazenes **20a-f** in the synthesis of condensed naphtho[1,8-*de*] heterocyclic ring systems **21a-f** (Scheme 8).

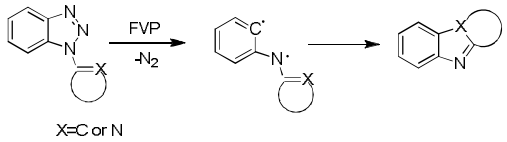
The diradicals, resulted from the initial extrusion of N_2, undergoes intramolecular cyclization to give the oxazines **21a-f** (Scheme 9). This study has offered a simple direct routes toward many condensed heterocyclic systems condensed on the *peri* positions of the naphthalene ring.



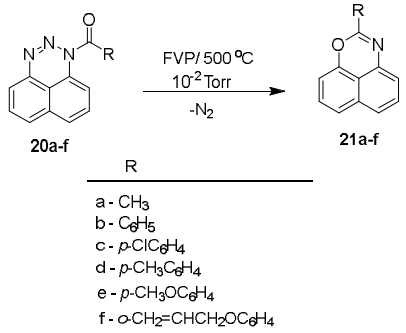
Scheme 5. Product distribution after the FVP of 3-(2-thienoyl)-cinnoline **7**.



Scheme 6. FVP of substituted [1,2,3]-triazines **18**.



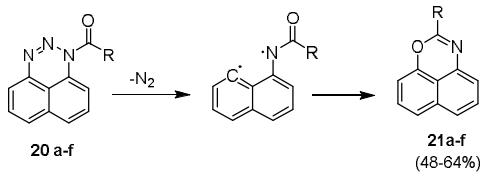
Scheme 7. General pyrolytic behaviour of benzotriazole derivatives.



Scheme 8. FVP of substituted 1-aroylnaphtho[1,8-*de*][1,2,3]triazenes **20a-f**.

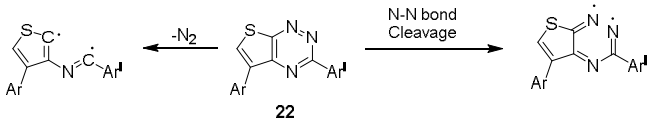
2.3. FVP of [1,2,4]-triazines

Rees *et al.* have investigated the pyrolytic reactions of 1,2,4-benzotriazines[4] and have shown that their pyrolysis involves mainly N_2 elimination, generating diradical intermediates which then cyclize to condensed heterocyclic systems.



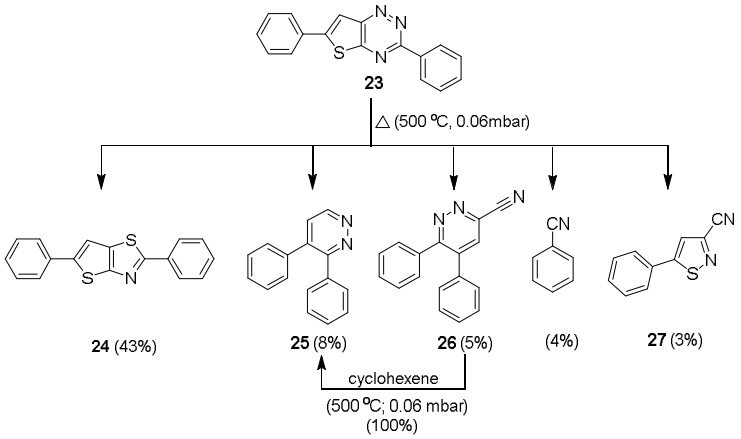
Scheme 9. Suggested mechanism for the formation of oxazine derivatives **21a-f**.

Pyrolysis of thieno[3,2-*e*]-[1,2,4]-triazines **22** involves two major pathways. In addition to the N_2 extrusion, the cleavage of the N–N bond takes place, thus leading to new reactive diradicals, consequently leading to formation of new heterocyclic products (Scheme 10).



Scheme 10. FVP of thieno[3,2-*e*]-[1,2,4]-triazines **22**.

We have also reported the formation of the products **24**-**27** by pyrolysis of thieno[2,3-*e*]-[1,2,4]-triazine **23** (Scheme 11).[16] The formation of the products **24**-**27** is shown in Scheme 12. It involves: i) elimination of N_2 leading to **24**; ii) cleavage of C3–N4 bond leading to the pyridazines **25**; iii) N–N bond cleavage leading to **27** (Scheme 12).



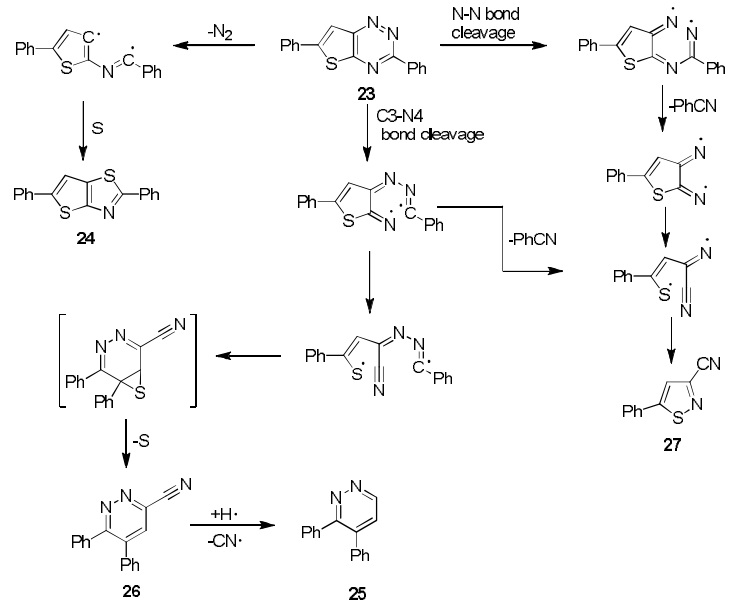
Scheme 11. FVP of thieno[2,3-*e*]-[1,2,4]-triazine **23** with product distribution.

The formation of product **24** might possibly formed by cycloaddition of sulfur with the substrate triazine **23** and subsequent elimination of N_2 (Scheme 13).

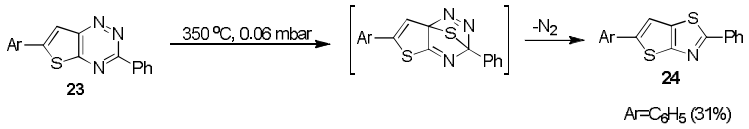
3. Pyrolysis of acetylenic compounds

3.1. Acetylenic ethers

Aryl propynyl ethers undergo thermal rearrangement to benzofuran and/or benzopyran derivatives.[17] It is noteworthy that non-thermal cyclization of arene-alkyne ethers were conducted using cesium fluoride. Claisen rearrangement of propargyl ether **28** has selectively produced 2-methylbenzofurans **29**.[18] On the other hand, using catalytic amount of gold(I) complexes gave chromene derivative **30** (Scheme 14).[19]



Scheme 12. Mechanism for the formation of **24-27** by the pyrolysis of **23**.



Scheme 13. Suggested mechanism for the formation of **24** from **23**.

It is of special interest to note that benzofuran derivatives, especially naphthofurans, are potentially powerful for the development of anticancer drugs[20,21] and for their bioactivities.[22,23] On the other hand, chromene possess valuable medicinal and pharmaceutical properties.[24,25]

Moreover we have investigated the contribution of acetylenic moiety in intramolecular reaction of acetylenic ether.[26]

The absence of substituent in the *ortho* position of the aryl group of propargyl ethers **31**, **32** and **33** makes them undergo Claisen-rearrangement to produce 2-indanone and benzocyclobutene derivatives (Scheme 15).

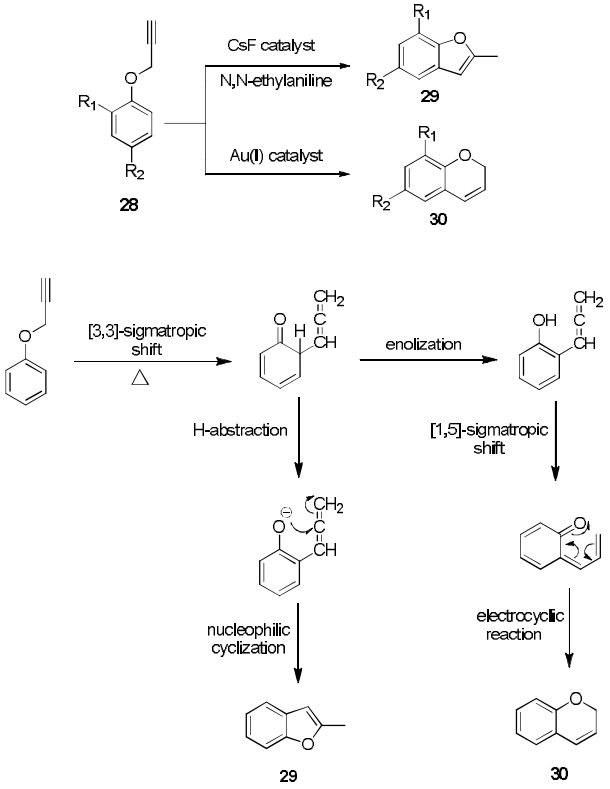
In the presence of an active substituent in the *ortho* position of the aryl group **34**, **35**, **36** and **37**, interesting unexpected products were characterized and identified as a result of the interaction of these substituents with the carbene intermediate (Schemes 16-19).

The presence of methoxy group in the *para* position of **38** and **39** resulted into quinones (Scheme 20).

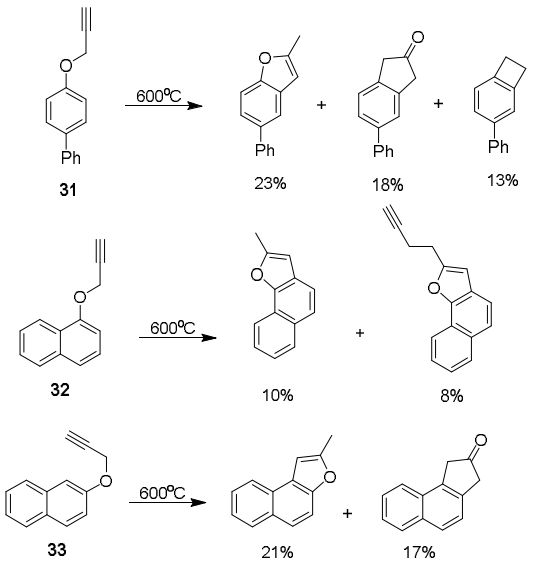
3.2. Acetylenic esters

Taking advantage of the acetylenic tendency to arrange cleanly in gas phase pyrolytic reactions, more than 40 years ago, Trahansovsky *et al.*[27] pyrolyzed phenyl propiolate **40** and found that these esters rearrange cleanly and in a fair yield into the tropolone derivative 2*H*-cyclohepta[*b*]furan-2-one **41** (Scheme 21).

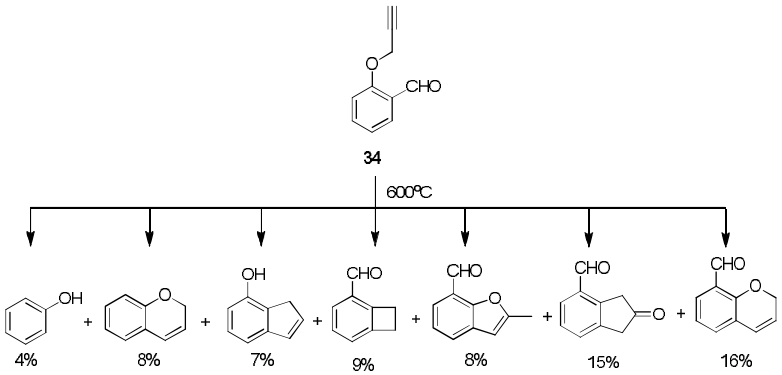
This was considered as the basis for the direct and convenient conversion of phenols to cycloheptane derivatives and has opened the way to a practical approach to polyalkylated 2*H*-cyclohepta[*b*]furan-2-ones **41**. The mechanism proposed for the rearrangement of **40** into **41** was a Claisen-type rearrangement that results in the formation of intermediate **42** (Scheme 22).



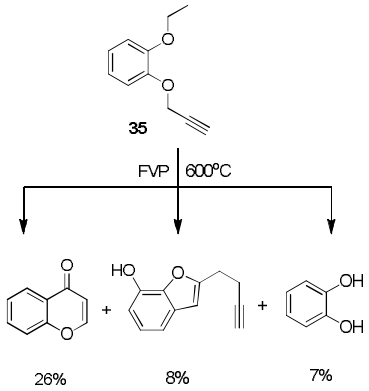
Scheme 14. Formation of benzofuran and chromene *via* Claisen rearrangement.



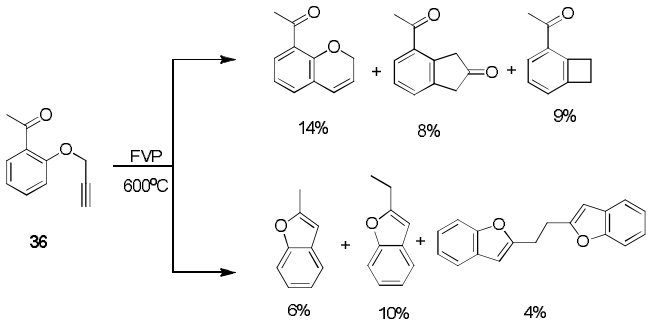
Scheme 15. FVP of propargyl ether **31**, **32** and **33**.



Scheme 16. FVP of propargyl ether **34**.



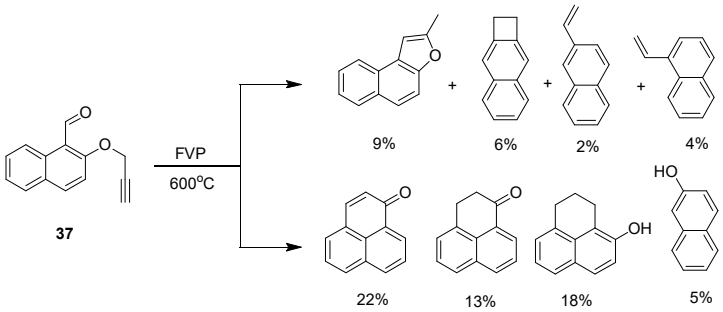
Scheme 17. FVP of propargyl ether **35**.



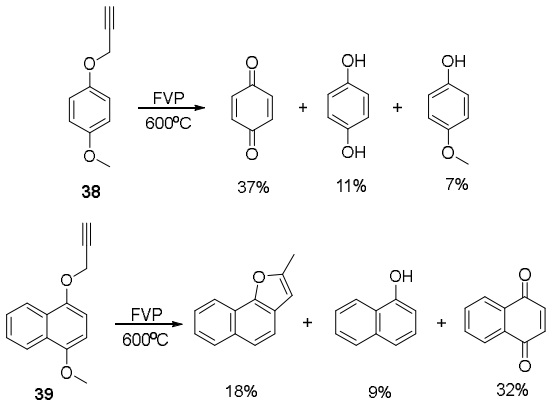
Scheme 18. FVP of propargyl ether **36**.

The authors confirmed their findings by investigating the FVP of **43** that resulted in **44** and **45** as shown in Scheme 23.

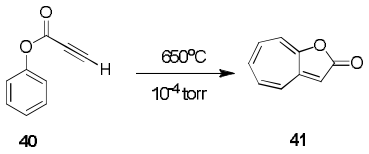
This approach has inspired Hansen *et al.*[28] in the preparation of six highly alkylated cyclohepta[b]furan-2(2*H*)-ones **47** by FVP pyrolysis of polyalkylated aryl propiolates **46** at 650-790 ºC and 10^{-2} Torr *via* carbene intermediate (Scheme 24). This process allows high number of substituents at the seven membered ring.



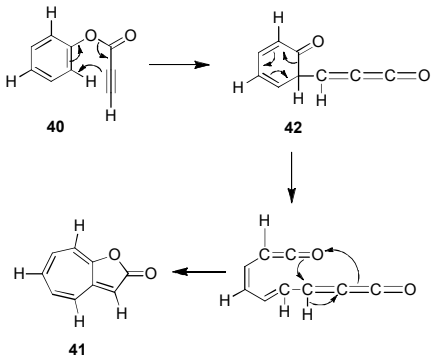
Scheme 19. FVP of propargyl ether **37**.



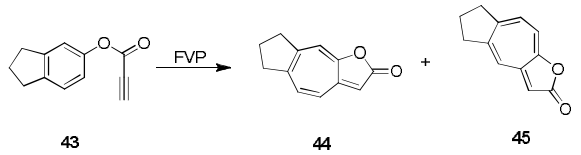
Scheme 20. FVP of propargyl ethers **38** and **39**.



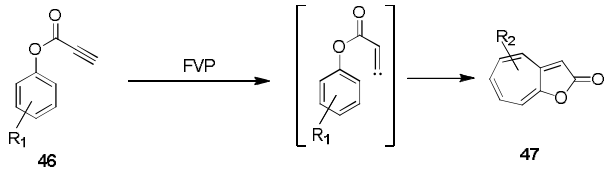
Scheme 21. FVP of **40**.



Scheme 22. Mechanism for the formation of **41** *via* the intermediate **42**.



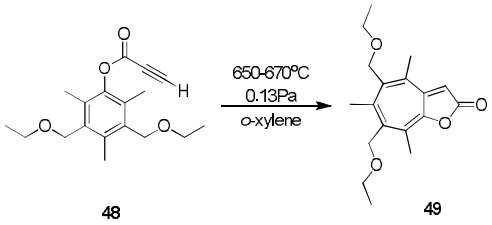
Scheme 23. FVP of **43**.



R_1	R_2	Yield(%)
None	None	35-50
2,4,6-Me_3	4,6,8-Me_3	30-50
2,3,4,5,6-Me_5	4,5,6,7,8-Me_5	15-40
2,3,4,6-Me_4	4,5,7,8-Me_4	25-45
3,4,5-Me_3	5,6,7-Me_3	30-45
3,5-Et_2	5,7-Et_2	33-45

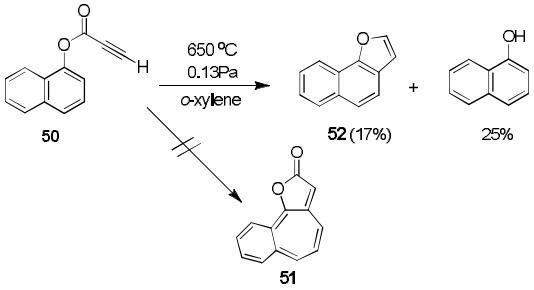
Scheme 24. Formation of highly alkylated cyclohepta[b]furan-2(2*H*)-ones **47** from **46**.

Accordingly, when **48** was pyrolyzed the expected cyclohepta[*b*]furan **49** was formed.[31] This indicates that the C–O bond in benzylic position survives the FVP at 650 °C (Scheme 25).

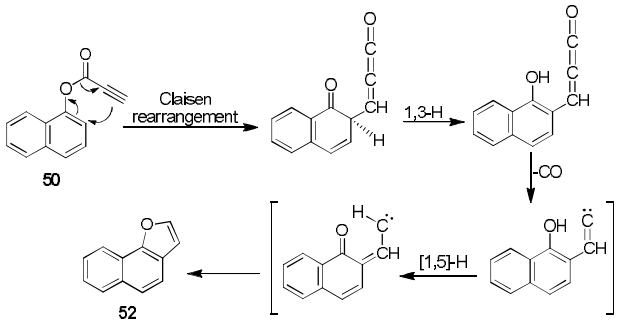


Scheme 25. FVP of **48**.

When 1-naphthalenyl 2-propynoate **50** was pyrolyzed, no indication for the formation 2*H*-benzo[6,7] cyclohepta[1,2-b]furan-2-one **51** was found; instead naphtho[1,2-b]furan **52** and 1-naphthol in moderate yield was observed (Scheme 26). The mechanism for the formation of **52** is shown in Scheme 27.



Scheme 26. FVP of 1-naphthalenyl 2-propynoate **50**.

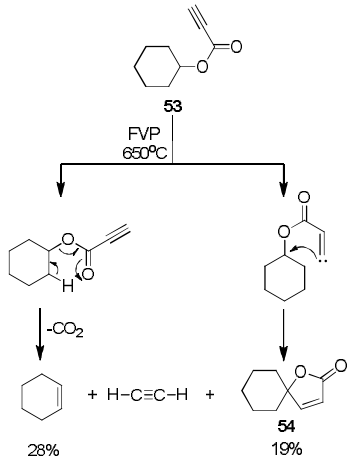


Scheme 27. Mechanism for the formation of **52** by FVP of **50**.

We further examined[30] the FVP of propiolate esters that have been categorized as esters with β-hydrogen atom(s) and esters without β-hydrogen and have concluded that the first category undergoes FVP by retro-ene reaction while propiolate esters with no β-hydrogen pyrolyze *via* carbene intermediate.

3.2.1. Propiolate esters with β-hydrogen(s)

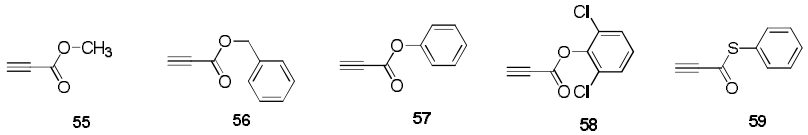
FVP of cyclohexyl propiolate **53** at 650 °C produced 1-oxaspiro[4.5]dec-3-en-2-one **54**. The proposed mechanism suggests the formation of a carbene intermediate followed by C-H insertion. Other products detected are cyclohexene and acetylene which formed *via* six-membered transition state (Scheme 28).



Scheme 28. Suggested mechanism for the FVP of **53**.

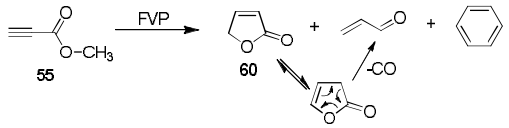
3.2.2. Propiolate esters without β-hydrogen

Methyl propiolate **55**, benzyl propiolate **56**, phenyl propiolate **57**, 2,6-dichlorophenyl propiolate **58**, S-phenyl prop-2-ynethioate **59** were considered (Scheme 29).



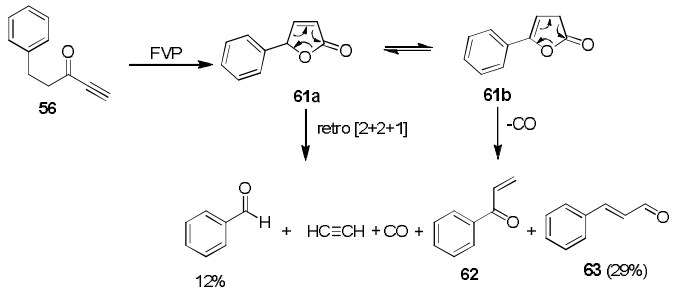
Scheme 29. Propiolate esters without β-hydrogen

The products identified from FVP of **55** at 550 °C at 10^{-2} Torr were γ-lacton **60** that resulted from an intramolecular insertion of the methylene carbene intermediate into C-H. Loss of CO from **59** produced acrolein. At a higher temperature, acrolein was the major product (Scheme 30).



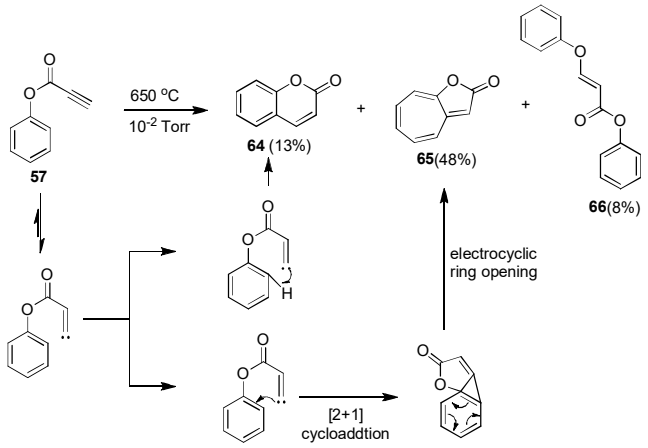
Scheme 30. Suggested mechanism for the FVP of **55**.

Two major products identified out of FVP of **56** at 650 °C and 10^{-2} Torr: 1-phenylprop-2-en-1-one cinnamaldehyde **63** (29%) and benzaldehyde (12%). The suggested mechanism involves the formation of a methylene carbene derivative generated from the 1,2-hydrogen shift of the substrate, which would then cyclize to produce the lacton **61b**. Upon decarbonylation, compounds **62** and **63** are formed. Benzaldehyde might be produceed from elimination of acetylene from **61a** as shown in Scheme 31.



Scheme 31. Suggested mechanism for the FVP of **56**.

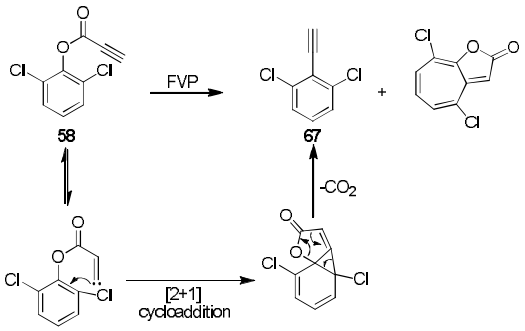
2*H*-Chromen-2-one **64** and (4Z,6Z,8E)-2*H*-cyclohepta[6]furan-2-one **65** resulted from FVP of phenyl propionate **57** supports the carbene intermediate formation followed by the insertion at the C–H bond as shown in Scheme 32.



Scheme 32. Suggested mechanism for the FVP of **57**.

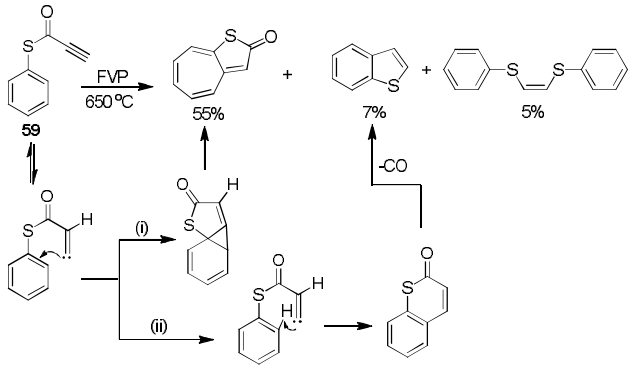
Formation of **66** was explained by the addition of the phenol produced from the fragmentation of **57** to another substrate molecule. This has been observed in the FVP of naphthalene-1-yl propiolate at 650 °C that produced 1-naphthol (Scheme 32).[29]

FVP of 2,6-dichlorophenyl propiolate **58** at 650 °C and 10^{-2} Torr resulted the unexpected formation of 1,3-dichloro-2-ethynylbenzene **67** as a major product. This compound could be formed through carbene insertion followed by 6-electron pericyclic elimination of CO_2 as shown in Scheme 33.



Scheme 33. Suggested mechanism for the FVP of **58**.

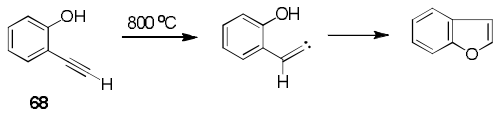
This study was completed by FVP of S-phenyl-prop-2-ynethioate **59**. Analysis of the products is in support of the mechanism suggested for its oxygen analogue **57** (Scheme 34).



Scheme 34. Suggested mechanism for the FVP of **59**.

3.3. Acetylenic alcohols

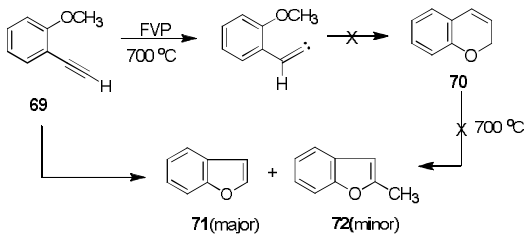
FVP of 2-ethynylphenol **68** at 800 °C resulted in quantitative conversion to benzofuran suggesting the formation of vinylidene carbene intermediate as shown in Scheme 35.[31,32]



Scheme 35. FVP of **68**.

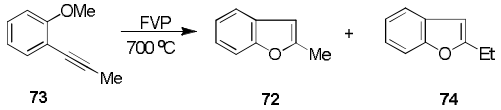
In an attempt to extend the vinylidene cyclization from intramolecular C-H insertion to the synthesis of benzopyran, Barton and co-workers pyrolyzed 2-ethynylanisol **69** at 700 °C (Scheme 36). None of the desired

pyran **70** was produced.[34] Benzofuran **71** was the major product with 2-methylbenzofuran **72** as a minor product. The possibility that **72** was produced from **70** was ruled out as this compound was found to be stable by FVP at 700 °C.



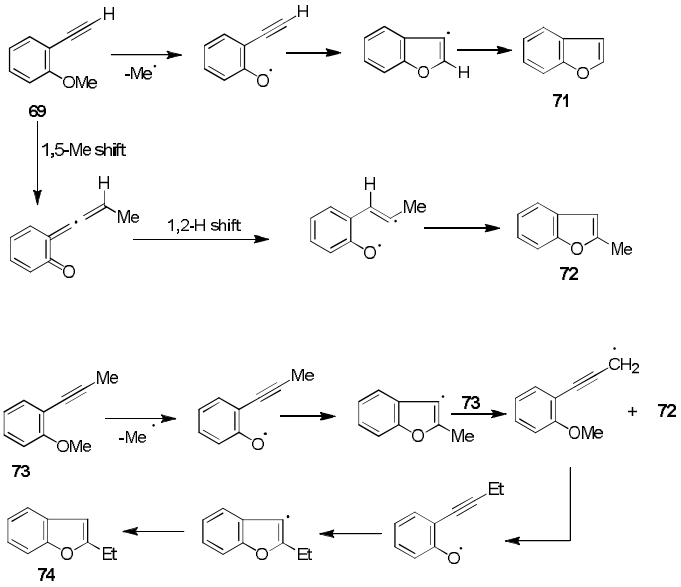
Scheme 36. FVP of **69** showing the product formation.

Similarly, FVP at 700 °C of 1-propynylanisole **73** afforded 2-methyl- **72** and 2-ethylbenzofuran **74**. Benzopyrans were not detected (Scheme 37).



Scheme 37. FVP of **73**.

It was suggested that the initially formed thermally activated **74** leads to **72** in pyrolysis of anisol **73** *via* homolytic cleavage of C-C and the loss of methyl radical. 2-Methylbenzofuran **72** is not a source of benzofuran. Barton proposed two mechanistic pathways for pyrolysis of anisol **69** (Scheme 38).[32]

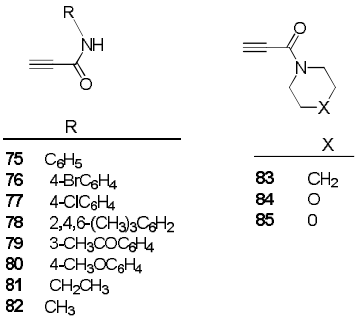


Scheme 38. FVP of **69** and **73** and suggested mechanisms for the formation of **71**, **72** and **74**.

The formation of benzofuran is a result of homolytic loss of methyl radical followed by intramolecular cyclization (Scheme 38). It is noteworthy that loss of methyl radical from anisol is reported to produce phenol at 640 °C in 52% yield in flow pyrolysis.[33] This pathway also accounts for the formation of **72** from **73**. The formation of **72** is also possible by O-C insertion by vinylidene intermediate. The formation of **74** would be explained by radical rearrangement.

3.4. Acetylenic amides

The only study on the pyrolysis of acetylenic amides was performed recently.[34] We reported details of eleven different types of acetylenic amides **75-85** that provides a useful application for the synthesis of 1-azaazulen-2-ones, ene-lactams and bicyclic lactams (Scheme 39). The nature of the substituent at the nitrogen atom of the amide moiety showed a pronounced effect on the reaction mechanism.

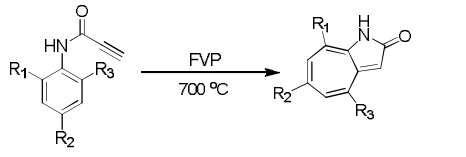


	R
75	C_6H_5
76	4-BrC_6H_4
77	4-ClC_6H_4
78	2,4,6-$(CH_3)_3C_6H_2$
79	3-$CH_3COC_6H_4$
80	4-$CH_3OC_6H_4$
81	CH_2CH_3
82	CH_3

	X
83	CH_2
84	O
85	0

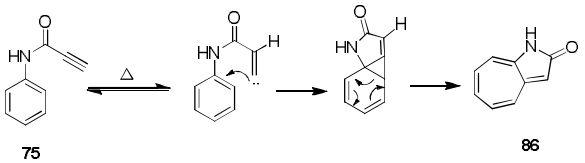
Scheme 39. Acetylenic amides.

FVP of *N*-arylpropiolamide **75-78** at 700 °C resulted in cyclohepta[*b*]pyrrol-2-(1*H*)ones **86-89**. The formation of these products suggests the mechanism shown in Scheme 40, which involves an intramolecular insertion by the methylene carbene intermediate followed by the electrocyclic ring opening to form the ene-lactams **86-89**.



	R_1	R_2	R_3
75	H	H	H
76	H	Br	H
77	H	Cl	H
78	CH_3	CH_3	CH_3

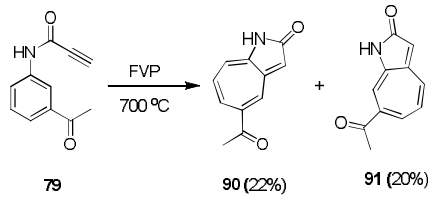
	R_1	R_2	R_3	%Yield
86	H	H	H	67
87	H	Br	H	38
88	H	Cl	H	45
89	CH_3	CH_3	CH_3	49



75 **86**

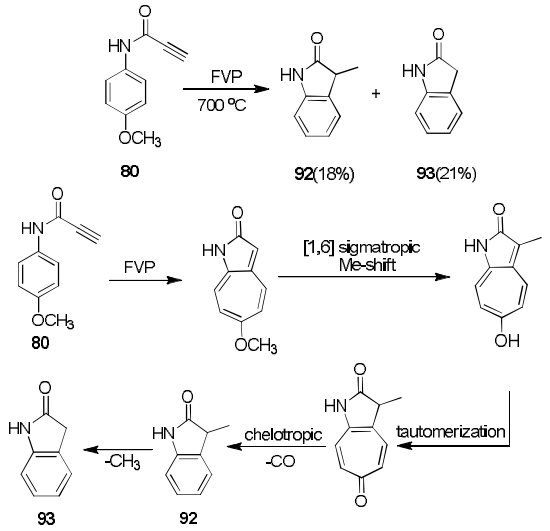
Scheme 40. FVP of **75-78** and suggested mechanisms for the formation of **86** from **75**.

Two isomers of the ene-lactams **90** and **91** were identified from the FVP of **79** at 700 °C as a result of the methylene carbene insertion into the C=C bonds of the two different *ortho* positions of the aryl moiety (Scheme 41).



Scheme 41. FVP of **79**.

The formation of the unexpected products **92** and **93**, obtained from the FVP of amide **80**, was hypothesized according to the mechanism shown in Scheme 42, involving an intramolecular insertion of the carbene intermediate, followed by [1,6]-sigmatropic methyl shift. Then, the product tautomerizes to the tropone, which undergoes a cheletropic extrusion of CO to give **92**. The latter loses a methyl group and extracts a hydrogen atom to produce **93**.



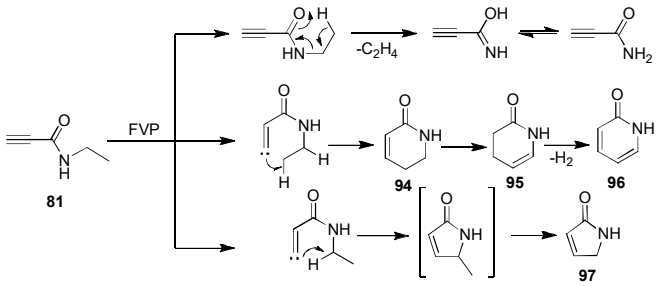
Scheme 42. FVP of **80** and suggested mechanisms for the formation of **92** and **93**.

Pyridinones **94**-**96** were detected as a result of carbene insertion at C-H of the methyl group of **81** followed by isomerization and aromatization. Only a 6% yield of lactam **97** was obtained, which suggest a carbene insertion into the C-H of the methylene group (Scheme 43).

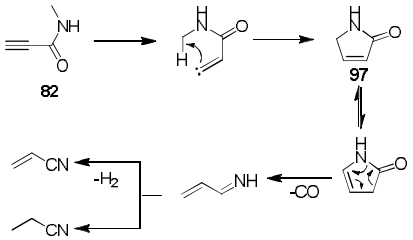
The absence of β-hydrogen atom in amide **82** rules out the retro-ene reaction. The formation of lactam **97** suggests the insertion of carbine intermediate, followed by the loss of CO group to give imine, that dehydrogenate to acrylonitrile or isomerize to propionitrile (Scheme 44).

FVP of propiolamides **83** and **84** at 550 °C resulted in new bicyclic lactams **98**-**99** and **100**-**101**, respectively, *via* carbene intermediate. (Scheme 45).

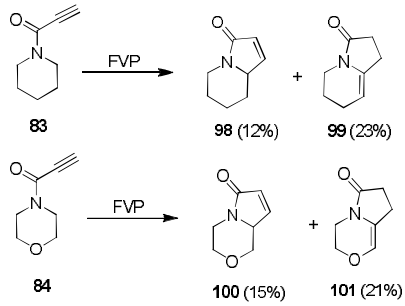
FVP of propiolamide **85** gave 5-vinyl-3,4-dihydro-2*H*-pyrrol **102** (Scheme 46).



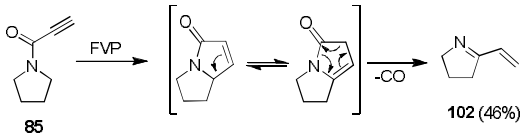
Scheme 43. FVP of **80** and suggested mechanisms for the formation of **94-97**.



Scheme 44. Suggested mechanism for the FVP of **82**.



Scheme 45. FVP of **83** and **84**.



Scheme 46. Suggested mechanism for the FVP of **85**.

4. Conclusion

The behavior of N=N heterocyclic compounds in pyrolytic reaction usually starts with elimination of N_2 molecule leading to a diradical intermediates that then combine intramolecularly into condensed heterocyclic molecules. The general applicability of acetylenic moieties to arrange cleanly and in a good yield in gas-phase pyrolytic reaction made them valuable precursors for a convenient one-step synthetic tool and has been used as preparative route to various heterocyclic compounds.

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