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Review

The Chemistry of Enaminones, Diazocarbonyls and Small Rings: Our Contribution

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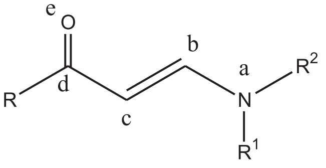
Depois de trinta e dois anos no Brasil e de aposentada da Universidade Estadual de Campinas, a autora gostaria de apresentar este resumo representando uma grande parte da pesquisa em metodologia sintética desenvolvida pelos grupos de pesquisa de Albert J. Kascheres e da autora no Instituto de Química da Universidade Estadual de Campinas. Contribuições foram feitas nas áreas de enaminonas, diazocarbonilas, ciclopropenonas e azirinas.

After thirty two years in Brazil and retired from Universidade Estadual de Campinas the author wishes to present this account, a summary of a large part of the research in synthetic methodology developed by the research groups of Albert J. Kascheres and the author at Universidade Estadual de Campinas Chemistry Institute. Contributions have been made to the area of enaminones, diazocarbonyls, cyclopropenones and azirines.

Keywords: enaminones, diazocarbonyls, cyclopropenones, azirines

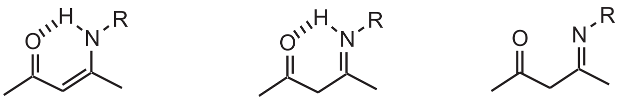
1. Enaminones

Enaminones are chemical compounds consisting of an amino group linked through a C=C to a carbonyl group. They are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident eletrophilicity of enones. They are typical push-pull ethylenes in which the amine group pushes and the carbonyl pulls electron density. The carbonyl group, conjugated to the enamine moiety, gives this system enough stability to be easily prepared, isolated and stored under atmospheric conditions at room temperature. The chemistry of the enamino carbonyl group (**A**) is potentially an area of considerable scope when one considers that there are present in this moiety three nucleophilic sites (a, c and e) and two electrophilic sites (b and d).[1,2]



A

There are structural questions that have to be addressed concerning these systems; the first involves tautomerism. Primary and secondary acyclic enaminones can exist in three tautomeric forms (**I-III**), as shown in Figure 1. There has been collected a great deal of evidence using NMR, UV, IR and X-ray analyses, showing that the ground state of enaminones is best characterized by tautomeric form **I**.[3] There is also evidence that cyclic enaminones exist primarily in the enaminoketo form (**I**).[4] Our theoretical calculations comparing the AM1 and MNDO methods showed that AM1 gives results consistent with this experimental data.[5]



I **II** **III**

Figure 1. The tautomeric forms of acyclic secondary enaminones.

Once the correct tautomer has been established, the geometric form of enaminones must be determined. These compounds are known to exist in the following geometric forms: *Z,s-Z; Z,s-E; E,s-Z; and E,s-E* (Figure 2). The conjugation of the system facilitates the interconversion between the *Z* and the *E* forms. In general, spectroscopic

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I dedicate this work to Al Kascheres (with whom I have the joy of sharing this wonderful life) on the occasion of his 60th birthday (May 24, 2003).

methods have shown that primary and secondary enaminones exist predominantly, and in many cases completely, in the *Z,s-Z* form in solution in apolar solvents. This allows for intramolecular hydrogen bonding. An increase in solvent polarity, particularly solvents that form strong intermolecular hydrogen bonds, increases contribution of the *E* forms. Tertiary enaminones tend to adopt the *E* forms which are sterically less hindered.[6]

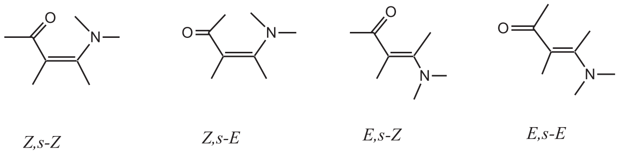

Z,s-Z *Z,s-E* *E,s-Z* *E,s-E*

Figure 2. The four possible geometric forms of enaminones.

1.2 Reaction with electrophiles

For most of our studies the following enaminones, presented in Figure 3, were used:

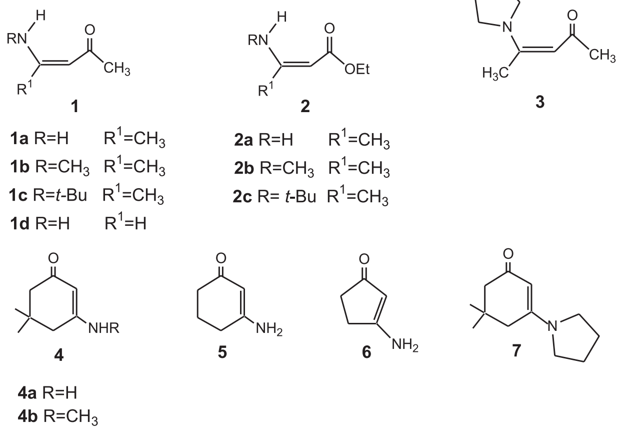
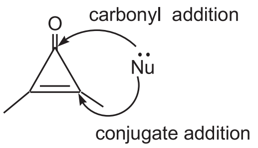


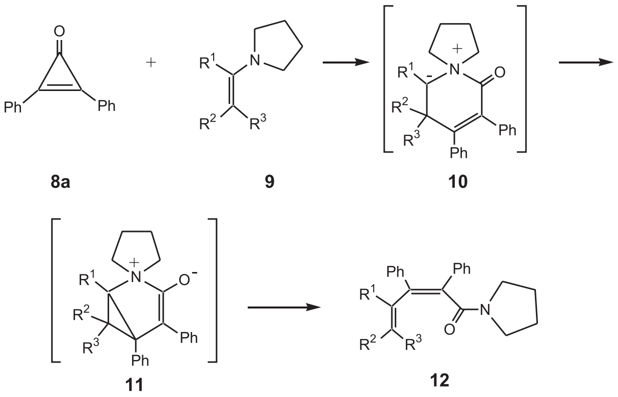
Figure 3. Enaminone structures used in most of the studies.

1.2.1 Reaction with diphenylcyclopropenone

Cyclopropenones are strained ring ambident electrophiles with a tendency to form ring opened products. In reaction with nucleophiles one has to consider the possibility of carbonyl or conjugate addition.



The reaction of diphenylcyclopropenone (**8a**) with a variety of tertiary enamines (**9**) was suggested to proceed through ylide (**10**) and ammonium enolate (**11**) intermediates to afford the C-N insertion products (**12**) (Scheme 1).[7] Intermediates analogous to **10** and **11** were also proposed in the reaction of tertiary enaminones (**9**, R^2=COR).[8]

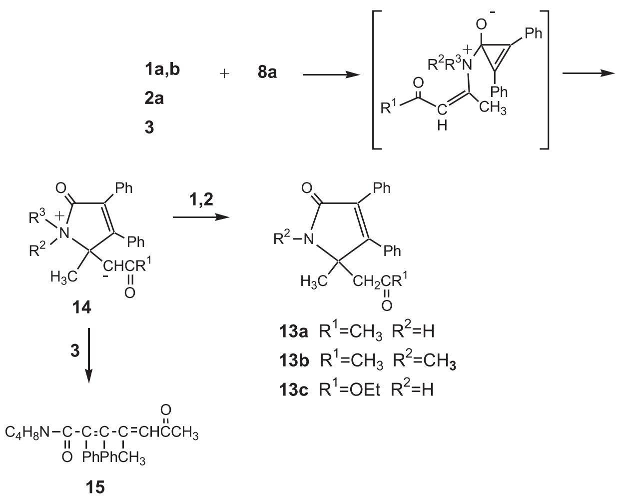


Scheme 1.

Although primary and secondary enaminones were known at the time of the above studies, their utilization as mechanistic probes in the above reaction, where rapid proton transfer in intermediates might permit the isolation of interesting heterocycles, was not explored. Therefore we undertook the study of primary and secondary enaminones with diphenylcyclopropenone (**8a**).

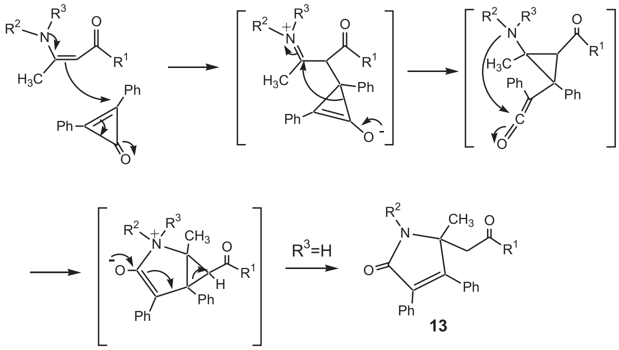
The reaction of the acyclic enaminones **1a, b**, **2a** and **3** with diphenylcyclopropenone (**8a**) led to the formation of 5-functionalized 1,5-dihydropyrrol-2-ones (**13**) for enaminones **1** and **2**. The results permitted an alternative representation (Scheme 2) of the reaction of **8a** with acyclic enaminones as a cycloaddition at NC$_\beta$ of the enaminone to afford intermediate (**14**), which could also account for the products **15** obtained from tertiary enaminones.[9] This would require that the reaction be initiated by attack at the carbonyl carbon of **8a**.

According to perturbation theory, the major contributions to bond making when two reagents approach each other involve opposite charge attraction (*i.e.*, electrostatic interactions) at the reaction sites and interactions between the filled orbitals of one reagent and the unfilled orbitals of the other, with HOMO's and LUMO's corresponding to the most important interactions because of the proximity of their energy levels. When the HOMO/LUMO interaction is the major factor governing reactivity, the reaction is said to be frontier-orbital controlled.[10] Since **8a** acts as an electrophile, its LUMO should be important if the reaction is frontier-orbital



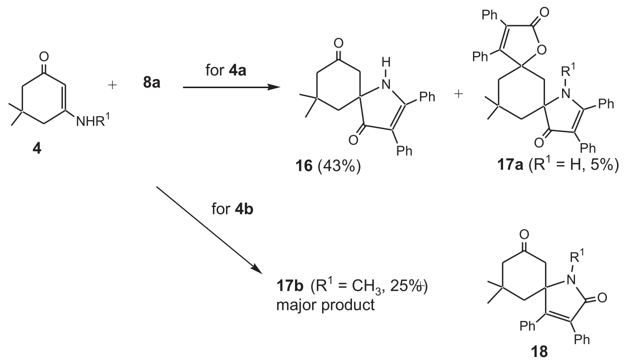
Scheme 2.

controlled. The LUMO coefficients for this system were obtained using the AM1 approach. The results of this calculation, 0.455 for phenyl-C versus 0.0001 for C_{CO}[11] suggest that the reaction should involve the phenyl-C of **8a.** Thus, another suggestion (Scheme 3) is now presented for this reaction.



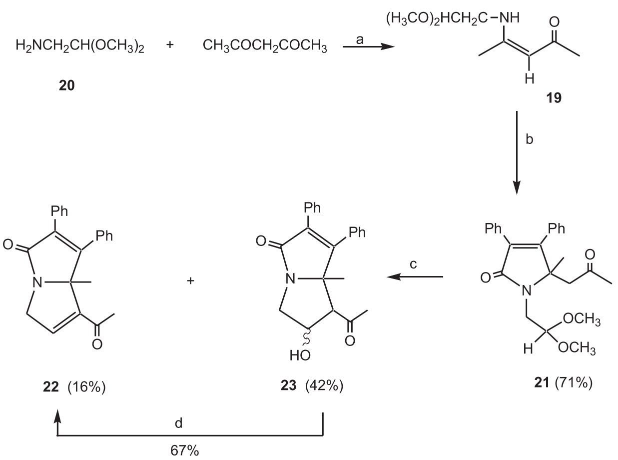
Scheme 3.

The cyclic enaminones **4** proved to be much less reactive toward **8a**. The principal product of the reaction of **4a**, a 1:1 adduct, was assigned the 1,5-dihydro-4H-pyrrol-4-one structure **16**. In the case of **4b**, the 2:1 product (**17b**) was the principal cycloadduct. A 1:1 adduct was also isolated, and was eventually identified as the 1,5-dihydro-2*H*-pyrrol-2-one **18**. Thus, of the one to one adducts isolated in this study, **16** was the only 1,5-dihydro-4*H*-pyrrol-4-one observed.[9] While products **13** seem to envolve reaction of the enaminone at the C_α position, these products suggest reaction of the cyclic enaminone **4** at N (Scheme 4).



Scheme 4.

Compound **13** or a derivative of it was envisioned as a starting point for preparing bicyclic [3.3.0] systems. Thus, the presence of an activated methylene in the C-5 substituent might permit construction of a second ring through intramolecular aldol condensation involving an appropriately situated carbonyl group on nitrogen. Therefore, enaminone **19** was prepared quantitatively by the reaction of the aminoacetal **20** with acetylacetone. The reaction of **19** with diphenylcyclopropenone (**8a**) afforded derivative **21** in 71% yield. Hydrolysis of **21** with concentrated hydrochloric acid afforded compounds **22** and **23** (Scheme 5). Compounds **22** and **23** contain the nucleus present in the pyrrolizidine alkaloids. Many pyrrolizidine derivatives are known,[13] but few with a carbonyl group in the 2 position of the rings as in **22** and **23** have been documented.[14]

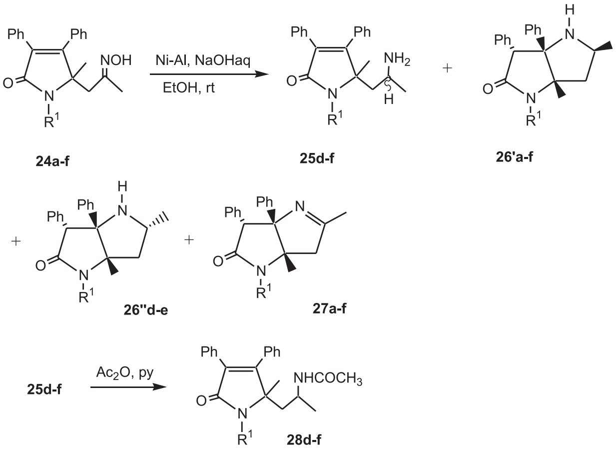


a) rt, 15 h; b) toluene, **8a**, 6 days, heat; c) conc HCl, 2 h, rt;
d) TsOH, benzene, Dean-Stark, reflux, 23 h.

Scheme 5.

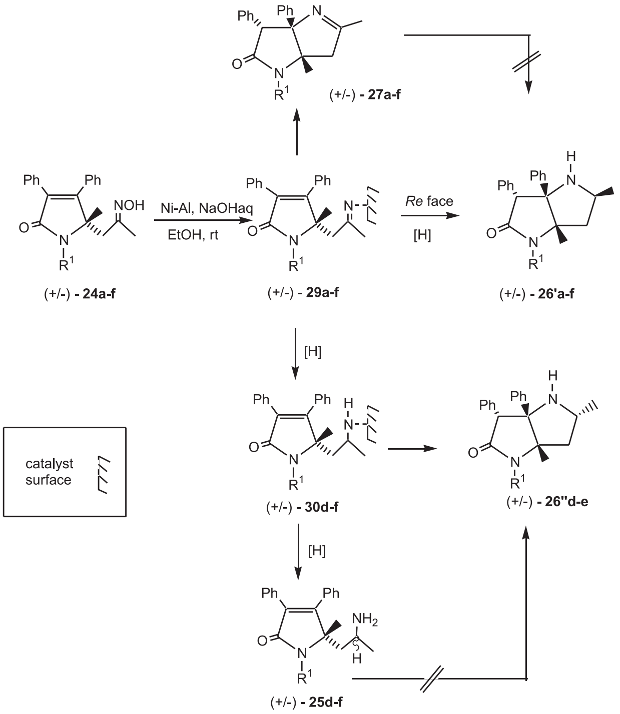
Another approach was to convert the ketone fragment in **13** to other versatile functional groups, such as a primary amine. A well established procedure toward this end involves submitting the oxime to Raney nickel generated *in situ*.[15] However, the reduction of oximes **24a-f** under these conditions gave only bicyclic compounds **26a-f** and **27a-f**, obtained as single diastereomers (Table 1), while hydrogenation using W7 Raney nickel produced only amines **25** (as 1:1 mixtures of diastereomers) which upon acetylation formed **28d-f**. The high diastereoselectivity observed in the transformation of **24** to **26** was understood in terms of participation of intermediate **29** as shown in Scheme 6. Formation of the new C4-N8 bond requires approach of N8 from below the heterocycle plane thus favoring transfer of hydrogen from the catalyst surface to the imine fragment via the *Re* face in the stereoisomer shown. Competing reductions to **30** and, eventually to **25**, without selectivity, occurs when R^1 in **24** is small.[16] Compounds **26** and **27** are pyrrrolo[3,2b]pyrrole derivatives. Several examples containing this nucleus have been cited,[17] but few oxo derivatives have been documented.[18]

Table 1. Products of reduction of **24** with Raney nickel generated *in situ*



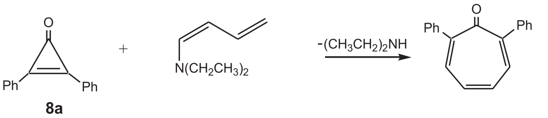
24 R¹	**26** (%)	(**26'**: **26"**)	**27** (%)	**28** (%)	**26**:**27**
a' *tert*-butyl	16	(1:0)	42	-	1:2.6
b *iso*-propyl	36	(1:0)	47	-	1:1.3
c benzyl	41	(1:0)	48	-	1:1.2
d ethyl	27	(6.3:1)	26	29	1:1
e methyl	28	(5:1)	26	28	1.1:1
f H	13	(1:0)	04	37	3.3:1

The principal difference in reactivity of enaminothiones **31** when compared to enaminones resides in the observed heterodiene character of the enaminothione in Diels-Alder reactions with electron deficient olefins, as well as behavior as a nucleophile almost exclusively through sulfur.[19]



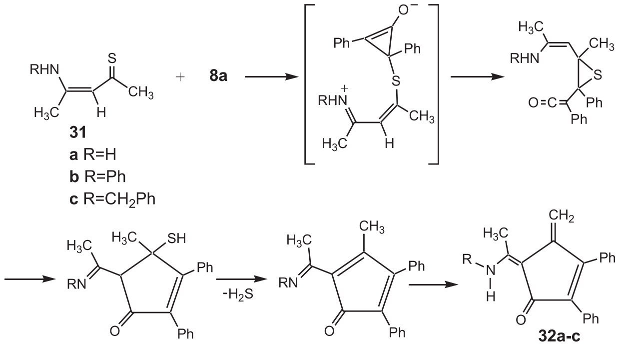
Scheme 6.

The observed participation of **8a** as a dienophile in reaction with (diethylamino)butadiene (equation1)[20] together with our results with enaminones (Scheme 3 and 4) prompted us to examine the reactivity of enaminothiones **31**, wherein the effect of the β-thione substituent might be compared with that of the β-ketone and β-vinyl derivatives previously studied.



(1)

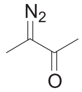
The reactions of **8a** with **31a-c** occurred slowly in refluxing benzene to afford 4-methylenecyclopentenones **32a-c** in good yield (Scheme 7). The most straightforward mechanistic interpretation of the formation of **32** involves initial nucleophilic attack of **31** at the carbonyl carbon (C_1) of **8a** through C_α, with subsequent ring expansion to the thione carbon. The problem here is that enaminothiones are not known to react as nucleophiles through C_α and, as discussed above, C1 of **8a** should not be the reactive electrophilic center. With the objective of gaining further insight into the electronic distribution in **31**, an AM1 calculation as implemented in the AMPAC package was performed on geometrically optimized **31a** in the Z, s-cis-configuration. For the purpose of comparison, a similar calculation was performed on the oxygen analog. The fronteir orbital treatment calls attention to the importance of the HOMO of **31a** in the reactions of this system as a nucleophile. This HOMO is essentially a nonbonding orbital on sulfur. In contrast, the corresponding orbital of the oxygen analog is the p-system with largest coefficients at C_α and N. Interestingly, the chemical behavior of these systems toward electrophiles, reflects exactly these differences. Thus, as mentioned above, enaminothiones react through sulfur, while enaminones react through C_α or N. A mechanism for the formation of **32** wherein the nucleophilic site is sulfur, is presented in Scheme 7. While more round-about, this pathway is more coherent with regard to the expected behavior of **31**.[21]



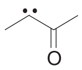
Scheme 7.

1.2.2 Reaction with diazocarbonyls

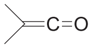
Diazocarbonyls, like enaminones, have added stability when compared to the parent compounds because of the carbonyl group. They are known to react through the starting compound, through ketocarbenes formed by the loss of molecular nitrogen and through ketenes formed by loss of nitrogen followed by the Wolff rearrangement. Ketocarbenes and ketenes are electrophilic intermediates.



diazocarbonyl



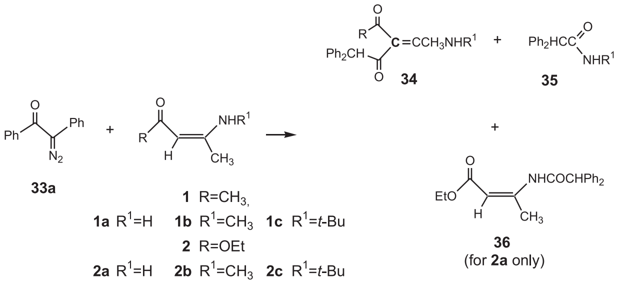
ketocarbene



ketene

As already mentioned, enaminones have three nucleophilic and two electrophilic centers. A systematic study of diazocarbonyl compounds with enaminones was undertaken based upon the variety of reactions that would be possible which could lead to new and interesting compounds.

Benzyldiazoketone (**33a**) was reacted with enaminones **1** and **2** under thermal conditions. The reactions occurred through the ketene intermediate to form α-acylenaminoketones (**34**) as the principal product; *i.e.*, a product of reaction at C_α of the enaminone. Amides **35** and in the case of **2a**, compound **36,** were also formed (Scheme 8). Compounds **35** and **36** suggest reaction at the nitrogen of the enaminone.[22]

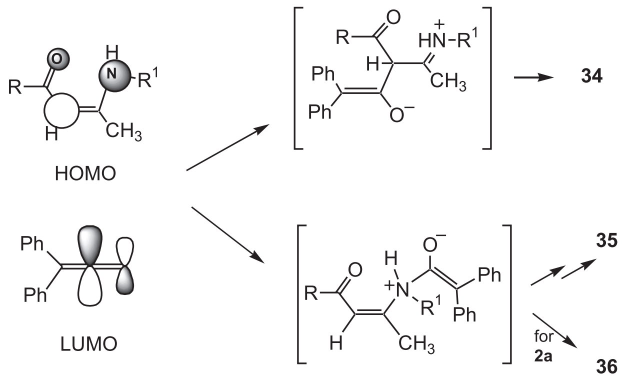


Scheme 8.

In all cases, competitive formation of decomposition products of **33a** occurs. It was observed that for both enaminoketones **1a-c** and enaminoesters **2a-c**, the total yield of products and the relative yields of the products of reaction at the C_α carbon [proportion **34**:(**35** + **36**] increase in going from R^3 = H to Me to t-Bu while the yield of decompostion products of diazoketone **33a** decreases, suggesting that the order of reactivity for the enaminones is **1a** > **1b** > **1c** and **2a** > **2b** >**2c**. For a given substitution on nitrogen, the total yield of products is greater for the enaminoesters. Molecular orbital calculations using the HAM/3[23] semi-empirical method shows that for equal substitution on nitrogen, the HOMO energy of the enaminoester is greater than for the enaminoketone and within each series the HOMO energy follows the order R^3=H < R^3=Me < R^3=t-Bu. If one considers that by frontier orbital theory a higher energy HOMO implies greater reactivity of the enaminone as nucleophile, we can see an excellent agreement between HAM/3 HOMO energies and the reactivity observed.[22]

The HOMO of the enaminones corresponds to a π molecular orbital with the largest coefficients on the C_α and nitrogen (see Scheme 9). The absolute magnitude of the two coefficients is somewhat greater at C_α. Therefore, the products formed are consistent with a HOMO-controlled process in which initial attack by diphenylketene occurs at these centers (Scheme 9).

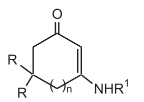
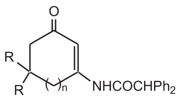
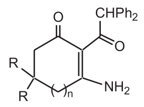
The primary and secondary acyclic enaminones **1** and **2** are known to exist in the *Z,s-Z* form. The reactions of diphenylketene with the cyclic enaminones **4**, **5** and **6** were also carried out to see the effect of fixing the enaminone in the *E,s-E* form. The principal products obtained in the case of the cyclic enaminones **4**, **5** and **6**



Scheme 9.

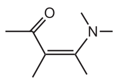
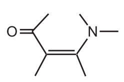
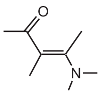
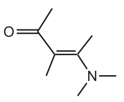
correspond to reaction at nitrogen; *i.e.* products **37**. In the case of **4a** there was a small amount of product of reaction at C_α (**38**, Table 2).

Table 2. Products and yields of the reaction of **33a** ($PhCOCN_2Ph$) with cyclic enaminones **4**, **5**, and **6**

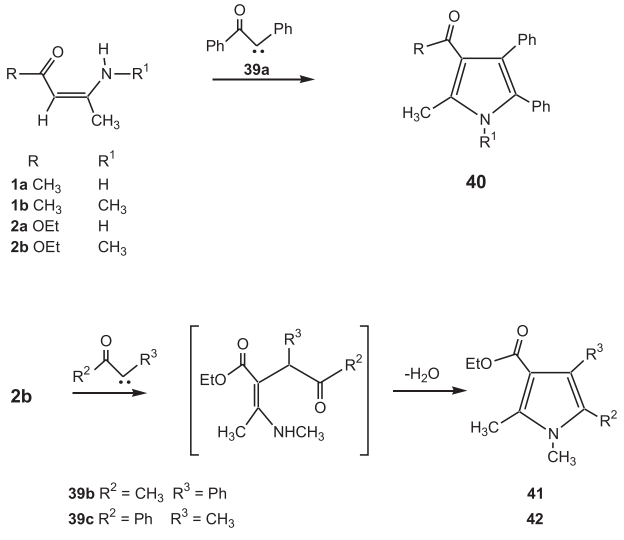
starting enaminone		products (yield)	
		 +	
4a	R = CH_3 R^1 = H, n = 1	**37a** (73%)	**38a** (6%)
5	R = H R^1 = H, n = 1	**37b** (73%)	
6	R = H R^1 = H, n = 0	**37c** (73%)	
4b	R = CH_3 R^1 = CH_3, n = 1		

For these fixed *E,s-E* enaminones, intramolecular hydrogen bonding is not possible, which can decrease conjugation when compared to acyclic *Z,s-Z* enaminones. This would increase the electron density on nitrogen and thus favor reaction at this site. At the same time, attack at the C_α carbon might be slowed down because of the development of substantial 1,3-diaxial interaction in the transition state, which we expect to be important for the volumous diphenylketene. Further information was obtained using AM1 geometric optimization, which shows that while the nitrogens of the *Z,s-Z* acyclic enaminones are planar, those of the cyclic systems are not. This is an indication of the decreased conjugation in the cyclic enaminones. HAM/3 molecular orbital calculations show a high energy second HOMO which corresponds to a non-bonded electron pair on oxygen for the cyclic enaminones. Thus, this orbital would also have to be considered in any analysis of reactivity. In fact, this might explain the greater tendency for cyclic *E,s-E* enamino ketones to give high yields of O-alkylated salts upon alkylation and to give O-acylated products or Cα-acyl derivatives via unstable O-acylated intermediate salts upon acylation. Calculation on compound **1a** using standard geometric models and fixed in the four possible geometric forms show that the high energy of the second HOMO is a function of the *s-E* conformation (Table 3). Thus, to explain the reaction of the cyclic enaminones **4**, the possibility of prior reaction of the diphenylketene on oxygen to form an unstable intermediate that then reacts further with another molecule of the enaminone cannot be dismissed. However at some point during the reaction a greater preference for reaction on nitrogen would have to be explained.[22]

Table 3. HOMO and second HOMO energy levels (in eV) of **1a** in four geometric forms

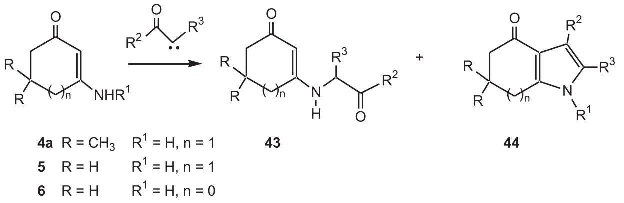
				
	Z,s-Z	*Z,s-E*	*E,s-Z*	*E,s-E*
HOMO	-8.355	-8.376	-8.554	-8.317
second HOMO	-9.603	-8.804	-9.495	-8.817
$\Delta\mathcal{E}$, eV	1.248	0.428	0.941	0.500

Under $Cu(acac)_2$ catalytic conditions the acyclic enaminones **1**and **2** react with **33a** to form pyrroles **40** by the inital formation of the ketocarbene of **33a** (*i.e.* **39a**). Upon further investigation with the ketocarbenes from **33b** and **33c**, we discovered that these pyrroles were also formed by initial reaction at the α-carbon of the enaminone as can be seen from the formation of **41** as the main product from **39b** and **42** as the only product from **39c** (Scheme 10).



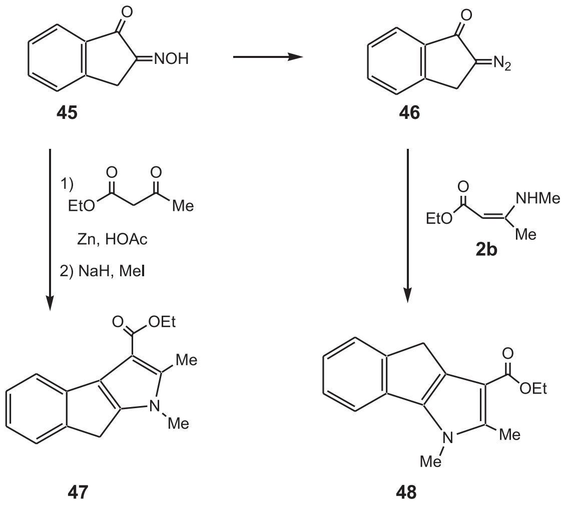
Scheme 10.

In the case of cyclic enaminones **4a**, **5** and **6**, compounds **43** were initially formed and then converted to pyrroles **44** (except for **43** formed from **6**) by the action of base (Scheme 11). Again the acyclic enaminones react mainly through C_α and the cyclic ones through nitrogen (see Schemes 3 and 4).[24]



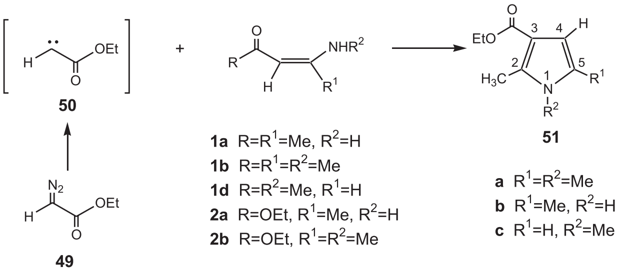
Scheme 11.

To the best of our knowledge, these results represented the first example of the use of ketocarbenes in pyrrole synthesis. Therefore with this in mind we decided to look at other diazo systems to test the generality of the reaction and to be able to synthesize more complex pyrroles. The reaction of 2-diazo-1-indanone (**46**) was examined. This compound is prepared from 2-oxime-1-indanone (**45**) which forms 3-carboethoxy-2-methyl-1,8-dihydro-indene[2,1-b]pyrrole (**47**) with ethyl acetoacetate under Knorr conditions, followed by methylation. The reaction of **46** could form the same product **47** with enaminoester **2b** if the reaction occurred on the nitrogen of the enaminone or it could form the isomer 1,4-dihydro-indene[1,2-b]pyrrole **48**, if it reacted on C_α. The product actually formed was **48** (Scheme 12) which again shows reaction of the acyclic enaminone at C_α and the possibility of forming isomeric systems from the same starting material; *i.e.* the oxime **45** (used to prepare **46**).[25]



Scheme 12.

We next looked at the reactions of ethyl diazoacetate **49** under catalytic conditons. Again pyrroles **51** were formed from the carboethoxycarbene **50**, but they were unexpected ones and the mechanism of their formation was not obvious. Results from varying the structures of the enaminones allowed us to determine that in these pyrroles the C(3)-CO_2Et structural fragment comes from the carboethoxycarbene formed from **49** and that the fragment originating from the enaminone is C(4)H-C(5)-R^1NR^2. The position of the C3-CO_2Et fragment in the pyrrole indicates that the initial step of the reaction mechanism occurs through an electrophilic attack of the carbene at the C_α of the enaminones, leading to the net result of C_α-H insertion. To investigate the origin of the C(2)-Me fragment, the reaction of **49** with enaminoketone **1d** (no substituent at both C_α and $C\beta$) was performed. Work-up of the reaction mixture revealed pyrrole **51c** as the only product which could be isolated and identified indicating that the C(2)-Me fragment originated from a second molecule of carboethoxycarbene. These results show that the COR groups from **1** and **2** are eliminated during the course of the reaction (Scheme 13). Even with this data in hand, a reasonable mechanism for the process could not be proposed. However, the driving force for the reaction is undoubtedly the formation of the stable aromatic pyrrole system.[26]

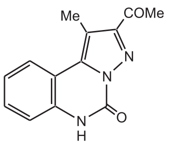


Scheme 13.

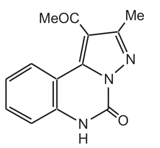
1.2.3 Reaction of 3-diazo-1,3-dihydro-2H-indol-2-ones and related compounds with enaminones

The reaction of 3-diazo-1,3-dihydro-2H-indol-2-one (**52a**, Table 4) with **1b** led to the easy isolation of a product that precipitated from the reaction mixture and which we identified as a pyrazoloquinazolinone (60% yield) (Scheme 14).

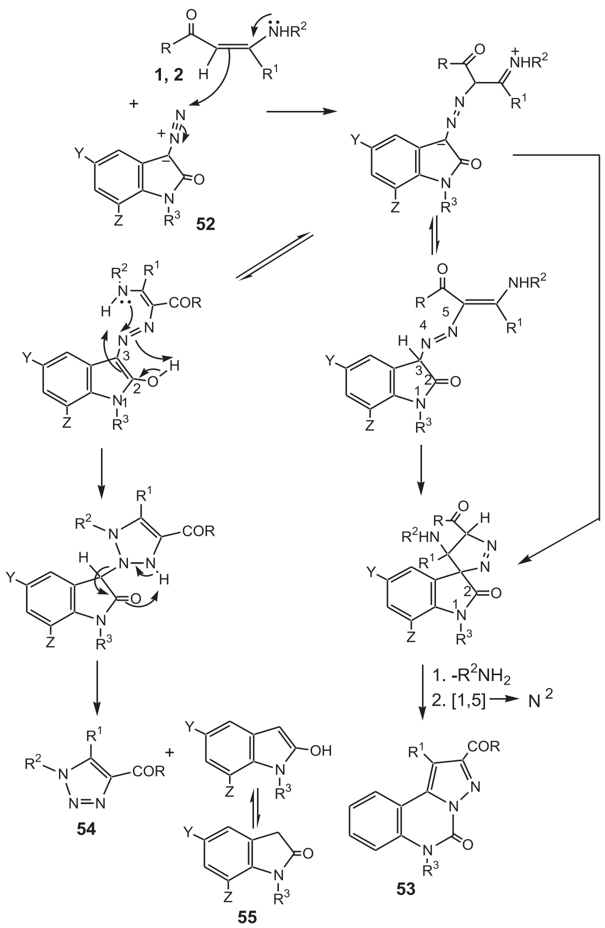
We had a characterization problem at hand though, *i.e.* which isomer was formed (**53a** or **53a'**).



53a



53a'

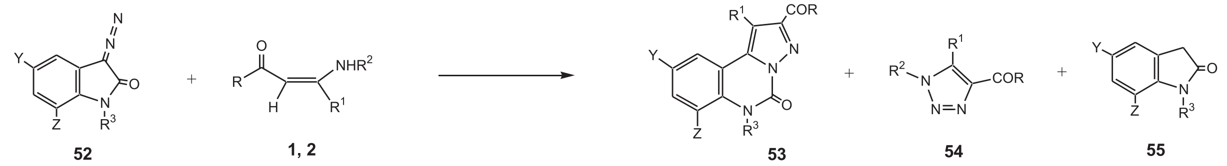


Scheme 14.

Mass analyzed ion kinetic energy spectroscopy (MIKES), a mass spectrometric technique which determines the products of metastable ions formed in the second field free region of a mass spectrometer with reverse Nier-Johnson geometry,[27] was used in a first attempt to establish the structure. The MIKES spectrum (Figure 4) showed the loss of CH_3COCN, which would only be reasonable for isomer **53a**.[28] However, the intensity of this transition was very low and this was a relatively new type of spectroscopy. We had doubts as to the reliability of the results. Thus we waited until a detailed NMR study could be accomplished and in fact COLOC confirmed **53a** as the correct isomer. A more detailed look at the reaction mixture produced the triazole (**54**) as another product in low yield (6%).[29] Both systems are of interest from the biological viewpoint. Thus, pyrazolquinazolinones belong to a class of compounds with antiallergenic and anti-inflammatory activity[30] and there are a number of examples of 1,2,3-triazoles with important biological activity such as the inhibition of the growth, mobility, and adhesion of cancerous cells in cultures and in rats[31], herbicides,[32] fungicides,[33] anti-allergenics,[34] anticonvulsants[52] and interference in the metabolism of prostaglandins.[36]

This reaction shows the diazocarbonyl compound reacting by way of the starting material. A detailed study with substituted 3-diazo-1,3-dihydro-2H-indol-2-ones **52b-f** showed that electron withdrawing groups on the diazo compound favored reaction (Table 4). Both

Table 4. Reactions of substituted 3-diazo-1,3-dihydro-2*H*-indol-2-ones (**52**) with enaminones



52 +	**enaminone** →	**53** (%) +	**54** (%) +	**55** (%)
a Y = Z = H	**1b** R = R^1 = R^2 = CH_3	**a** (60)	**a** (06)	
b Y = CH_3, Z = R^3 = H	**1b**	**b** (35)	trace	
b	**2b** R = OEt, R^1 = R^2 = CH_3	**c** (17)	**b** (10)	
c Y = OCH_3, Z = R^3= H	**2b**	**d** (04)	**b** (11)	
d Y = NO_2, Z = R^3 = H	**2b**	**e** (39)	**a** (27)	
d	**1c** R = R^1 = CH_3, R^2 = *t*-Bu	**f** (08)	**c** (25)	
d	**2b**		**b** (54)	**a** (11)
d	**2c** R = OEt, R^1 = CH_3, R^2 = *t*-Bu		**d** (73)	
e Y = NO_2, Z = H, R^3 = CH_3	**1b**		**a** (55)	**b** (23)
e	**1c**		**c** (59)	
e	**2b**		**b** (59)	**b** (17)
e	**2c**		**d** (82)	
f Y = Z = NO_2, R^3 = H	**1b**		**a** (55)	**c** (08)
f	**1c**		**c** (61)	
f	**2b**		**b** (67)	**c** (21)
f	**2c**		**d** (81)	

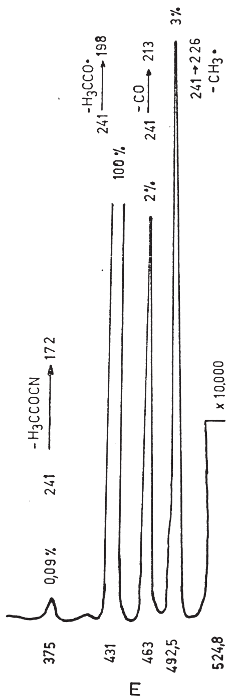
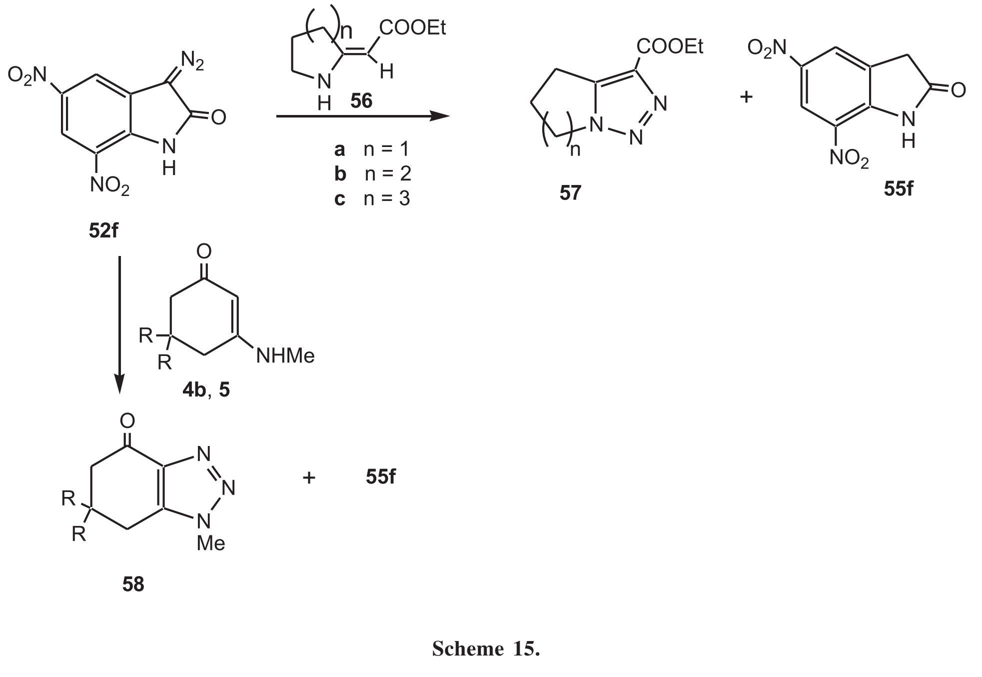


Figure 4. MIKES of the molecualr ion of compound **53a** (or **53a'**).

compounds could be explained by frontier orbital theory considering an initial reaction of the C_α of the enaminone (HOMO) on the terminal nitrogen of the diazo compound as shown in Scheme 14 (LUMO of the diazo compounds show large coefficients on the two diazo nitrogens). The reaction was more easily directed toward the formation of the triazoles.[29] The most important methods of 1,2,3-triazole synthesis involves reaction of azides with acetylenes. These triazoles would require the use of *N*-alkyl azides which are hazardous to work with.

We envisioned the use of this novel reaction in the preparation of bicyclic 1,2,3-triazole systems. The ability to form more highly nitrogenated analogs of aromatic compounds, like pyrroles and imidazoles, becomes important when one considers that as the number of heteroatoms in the ring increases, the tendency toward electrophilic attack decreases as does the reactivity of the benzylic leaving groups toward substitution. Pyrrole metabolites of pyrrolizidine alkaloids represent examples of compounds in which the high reactivity (and toxicity) of the pyrrole ring precludes their use in cancer chemotherapy. Thus, various attempts have been used to synthesize triazole analogs which modulate the reactivity downward.[36] With this in mind the reactions of enamino esters **56** (Scheme 15) and cyclic enamino ketones **4b** and **5** were undertaken.[37]

The reaction of **52f** with **56a** (n=1) formed 3-carboethoxy-5,6-dihydro-4H-pyrrolo-[1,2,3]-triazole **57a** in 78% yield. This product can be used as a synthon to prepare triazole analogs of the tumor inhibitory pyrrolizidine alkaloid pyrrole metabolites.[38] Enamino ester **56b** (n=2) reacts similarly to form 3-carboethoxy-4,5,6,7-tetrahydro-[1,2,3]- triazolo-[1,5a]-pyridine (**57b**) in 83% yield. This is a triazole analog of the indolizidine alkaloid skeleton. Enamino ester **56c** (n=3) reacts with **52f** to form 3-carboethoxy-5,6,7,8-tetrahydro-[1,2,3]- triazolo-[1,5a]-



Scheme 15.

azepine (**57c**) in 73% yield. In the reactions of **4b** and **5,** there is the formation of **58** in approximately 50% yield. Dihydroisatin **55c** was isolated in many of the reactions.[37] This compound can be oxidized to the starting dinitroisatin which can then be used to form **52f**, the starting diazocompound. Thus, even though most of the atoms of **52f** are not incorporated in the triazoles, a recyclable product is obtained.

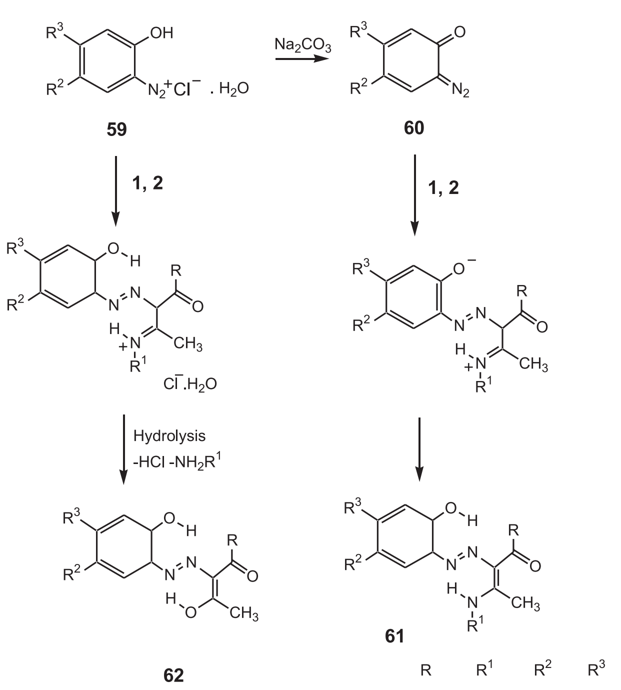
1.2.4 Reaction of enaminones with diazoquinones. Non-linear optical properties

Quinone diazides are compounds that have intermediate reactivity between diazonium salts and aliphatic diazoketones.[38] They can react by either loss or retention of molecular nitrogen, depending on reaction conditions. An example of the first case involves the formation of dihydrobenzofurans by a regiospecific route in reactions of o-quinone diazides with vinyl ethers under thermal conditions.[39] On the other hand, retention of nitrogen in azo-coupling reactions is often observed.[40] This type of reaction is widely used in industry for the synthesis of hydroxyazo dyes.[41]

Since quinone diazides, especially nitro-substituted ones, are very sensitive to light we decided to try a one-pot procedure in the reactions with enaminones in order to avoid contact of the reacting mixture with light. The quinine diazides **60** were generated in the reaction media by nitrosation of the proper *o*-aminophenol to form diazonium salt **59** which is then neutralized to form **60**. The quinone diazides formed were reacted with enaminones **1** and **2** to produce the novel azo-enaminones **61** which were not formed when **59** was reacted directly with the enaminones. In that case deaminated azo compounds **62** were formed instead (Scheme 16).[42]

AM1 geometry optimization of **61** indicate a tendency for two intramolecular hydrogen bonds with the azo group and a planar structure for the azo-conjugated skeleton. X-ray crystallographic data for **61d**[43] indicate good agreement between X-ray and AM1 calculated geometries. Based on these data all azo-compounds synthesized are assumed to have the two hydrogen bonds linked to the azo group. The planarity of the azo skeleton leads to extensive conjugation throughout the molecule, and when the phenyl ring is attached to electron-withdrawing groups, like chlorine or nitro, a push-pull conjugation is observed.

Organic compounds containing push-pull conjugation can present large optical second-order molecular polarizabilities and have important applications in second-order nonlinear optical (NLO) devices. Delocalization and intramolecular charge transfer effect of π-electrons in these molecules can cause large and fast nonlinear responses.[44] Extensive calculations using semi-empirical models have been reported for many varieties of molecular architectures, and many of these calculations have not only determined numerical values for nonlinear response, but have also dealt with interpretation of the molecular geometry and the electronic structure of such organic conjugated molecules.[45,46]



	R	R^1	R^2	R^3
a	OEt	CH_3	CH_3	H
b	OEt	CH_3	NO_2	H
c	CH_3	*t*-Bu	NO_2	H
d	OEt	H	Cl	NO_2
e	OEt	CH_3	Cl	NO_2
f	OEt	H	Cl	NO_2
g	OEt	*t*-Bu	Cl	NO_2
h	OEt	*t*-Bu	Cl	NO_2
i	OEt	CH_3	H	NO_2
j	CH_3	*t*-Bu	H	NO_2

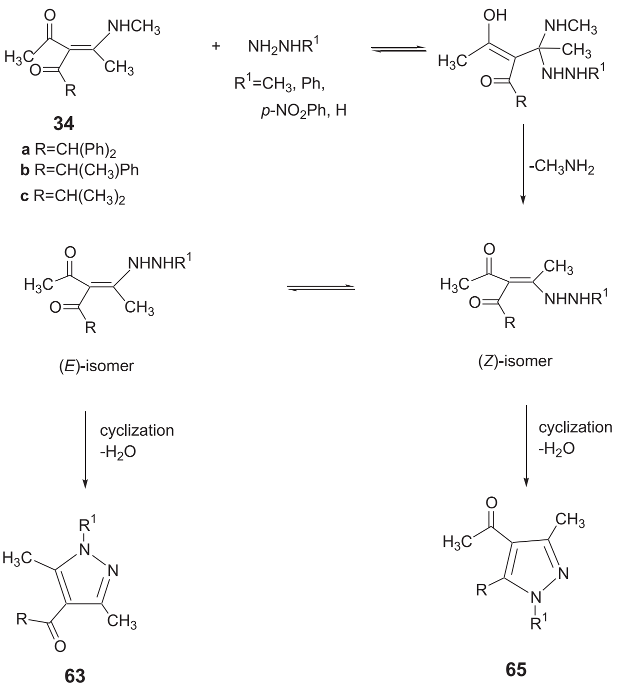
Scheme 16.

We decided to evaluate the molecular polarizability of these azo compounds theoretically because we did not have conditions for measuring them experimentally. The AM1/finite-field method was chosen as our first approach since it is reasonably fast and has been used successfully for determining trends of molecular hyperpolarizabilities.[47] Results from these calculations show that the push-pull conjugation is essential for a significant value of the molecular coefficient of hyperpolarizability, β. Thus, compound **61a** has no electron-withdrawing groups on the phenyl and has the smallest value for the molecular coefficient of hyperpolarizability, β. Intermediate values were found for **61b**,**c**, and **e**, and for compounds **62b**,**c** which have a poor donating group (OH). The other six azo-enaminones seem promising for second harmonic generation; they have significant values for second harmonic generation and are almost planar. The *p*-nitroazoenaminones have the largest value for β and therefore show most promise in non-linear optics. In conclusion, our procedure allowed us to obtain novel azo compounds in good yields, especially azo-enaminones containing push-pull conjugation. In addition, we proposed the potential usefulness of the push-pull azo-enaminones (**61**) in nonlinear optics, as second harmonic generators, based on theoretical finite-field static calculations.[42]

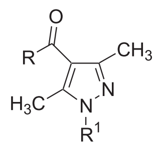
1.3 Reaction with nucleophiles

Enaminones react with hydrazines to form substituted pyrazoles.[48] As already seen, diazoketone **33a** reacts with enaminones via ketenes under noncatalytic thermal conditions to form nucleophilic addition products. The same reaction occurs with **33b** and **33c** to form the α-acylenaminoketones **34b** [3-acetyl-1-phenyl-1-methyl-4-(methylamino)-3-penten-2-one] and **34c** [3-acetyl-1,1-dimethyl-4-(methylamino)-3-penten-2-one]. The study of the reactivity of α-acylenaminoketones **34a-c** interested us because of the differences in the two ketonic carbonyls, especially since X-ray analysis of **34a** showed that 1,1-diphenylacetyl group is perpendicular to the planar methylaminopentenone system.[49] Both *ab initio* 6-31G** and AM-1 geometry optimizations of **34a-c** give results which go along with the X-ray analysis of **34a.** [49] Solvent effects were also of interest to us. Thus, benzene, methylene chloride, tetrahydrofuran, methanol and *N,N*-dimethylformamide were utilized in the reactions of α-acylenaminoketones **34a-c** (Scheme 17) with hydrazine reagents (methylhydrazine, phenylhydrazine, p-nitrophenylhydrazine and hydrazine hydrate). Besides verifying which of the two carbonyls would preferentially be attacked during a nucleophilic attack, we wished to obtain information on the solvent dependence of the regiochemistry of the pyrazole formed. The reaction mixtures were submitted to gas chromatography/mass spectrometry analyses, in an attempt to identify all the products and possible intermediates formed during the reactions.

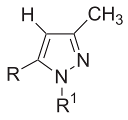
The formation of the principal pyrazoles **63** (the product formed by nucleophilic attack on the acetyl group), **64** (deacetylated pyrazoles, with the substituent R in the 5 position) and **65** (4-acetylpyrazoles formed by nucleophilic attack on RCO) can be explained by an initial Michael-type reaction (Scheme 17). The pyrazoles **64** and the deacetylated enaminones **66** (4-methylamine-2-pentenones) were formed by a deacetylation process. Small amounts of isomeric pyrazoles (**67,** isomer of **64** and **68,** isomer of **65**)) were also formed (perhaps by initial reaction on the carbonyl) together with acetamides (**68**) and 3,5-dimethylpyrazoles (**70**).



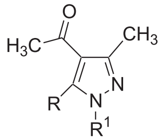
Scheme 17.



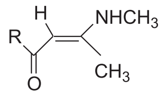
63



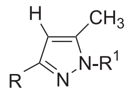
64



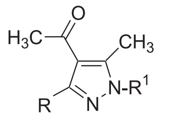
65



66



67



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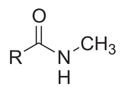

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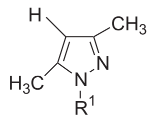


70

With methylhydrazine, the main product is **63**, except for **34b** and **34c** in dimethylformamide, in which case, **65** is the main product. With phenylhydrazine, the formation of **64** becomes important, as is the case with *p*-nitrophenylhydrazine. With hydrazine hydrate, the main product is **65**, except for **34a** and **34b** in methanol, in which case, **63** is the main product.[50]

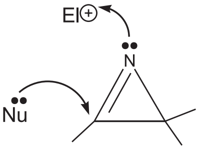
Simple eye inspection of the distribution of the eight products, shown above, especially those obtained in low yields, did not enable detection of consistent differences between solvents or nucleophiles. Therefore, in an attempt to understand how these factors could be correlated, we utilized principal component analysis (PCA).

Three principal components describe 87% of the total variance in the original data set. Thus, the pyrazole **64**, which was obtained by a mechanism involving a deacetylation process was separated from pyrazoles **63** and **65** in the first principal component. The second component, on the other hand, has information about the structural characteristic of the α-acylenaminoketones. In this component **63** is separated from **65** which correspond to pyrazoles formed by attack at different carbonyls.

These reactions were separated into four groups, according to the nucleophile used in the reaction. The data suggest that the utilization of methanol, the only protic solvent used, favors nucleophilic attack on the acetyl carbonyl group to form **63**. Products obtained via a deacetylation process were favored by a decrease in the nucleophilicity of the secondary amino group of the hydrazine.[51]

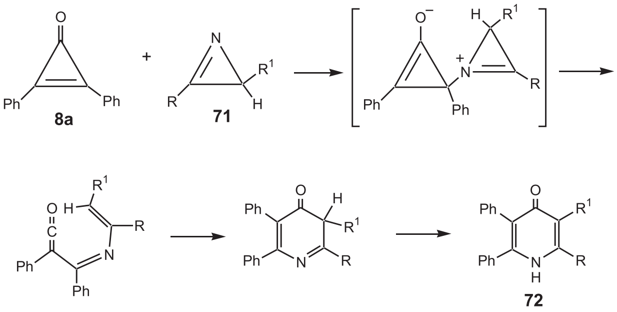
1.4 Small rings

We have already mentioned the reactions of diphenylcyclopropenone with enaminones and have seen that both these systems are ambident substrates. 1-azirines represent another versatile small ring system containing a nucleophilic reaction site on nitrogen and an electrophilic one on C2.



1-azirine

Thus, the reaction of diphenylcyclopropenone **8a** with mono and disubstituted azirines **71** in refluxing toluene led to the formation of 4(1H) pyridones **72**. These compounds can be pictured as forming by way of nucleophilic attack of the weakly basic azirine nitrogen on the C2 position of the electrophilic diphenylcyclopropenone ring followed by an electrocyclization, as illustrated in Scheme 18.[52]

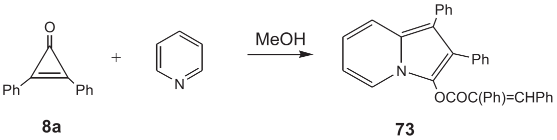


Scheme 18.

1.5 Cyclopropenone and derivatives

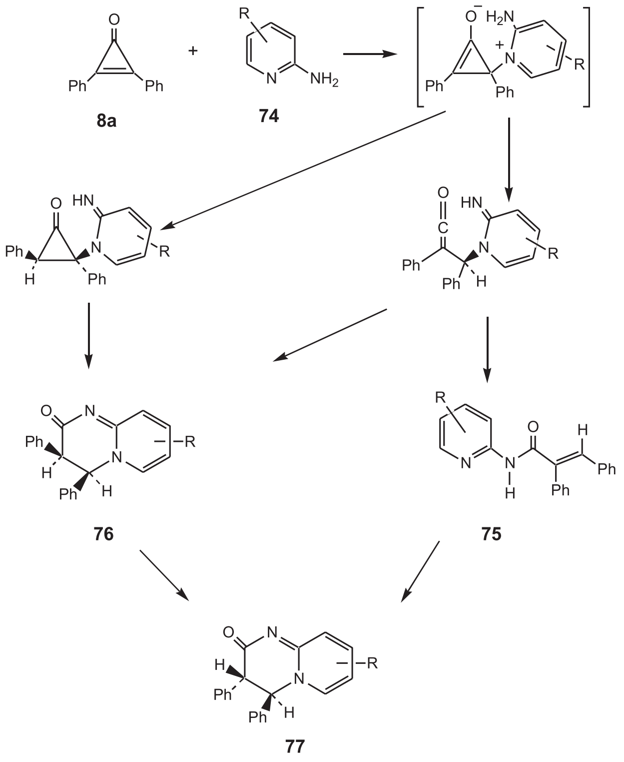
1.5.1 Reaction of cyclopropenones with aminoaromatics

A carbonyl addition product **73** (40% yield) had been identified in the reaction of diphenylcyclopropenone (**8a**) with pyridine[53] (equation 2). Interest in the chemical behavior of **8a** made it desirable to explore the possibility of participation of a "conjugate addition" mode in the reacton of pyridine with appropriately substituting the nucleus with a second functional group capable of intercepting a reactive (ketene) intermediate. The 2-aminopyridine system (**74**) was chosen as a probe for this pathway.

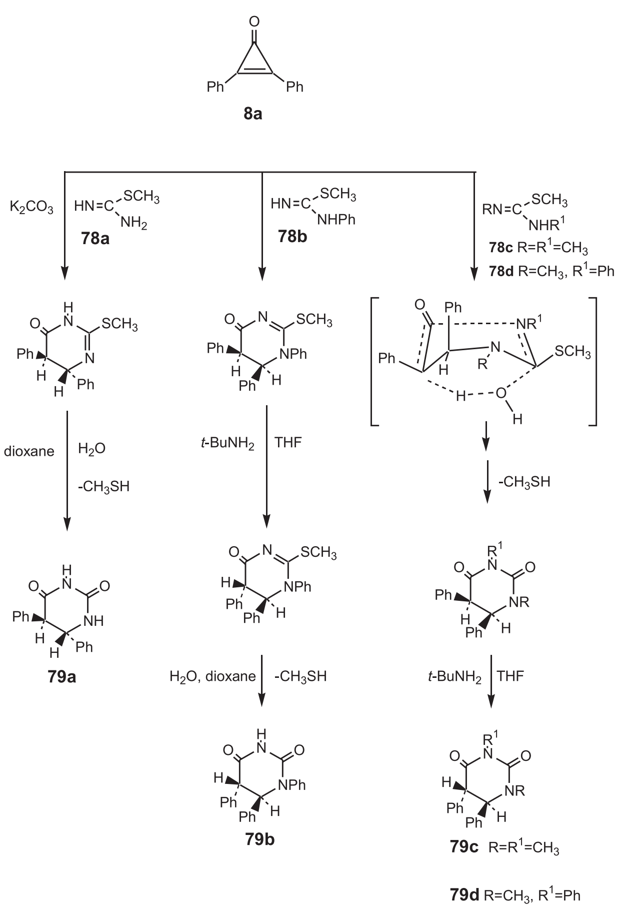


(2)

Diphenylcyclopropenone underwent a smooth reaction with a variety of 2-aminopyridines at room temperature to form **75** and **76**. Isomerization of compound **76** was observed to be solvent dependent. The lack of reactivity of aniline and other studies to understand the mechanism of formation of **75,** led to a visualization of the reaction as a conjugate addition pathway involving initial nucleophilic attack of the ring nitrogen of **74** on the electrophilic cyclopropenone ring to eventually form **76** and **77** as shown in Scheme 19. The formation of **76** and **77** in this study apparently represented the first report of a 3,4-disubstituted 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one.[54]



Scheme 19.

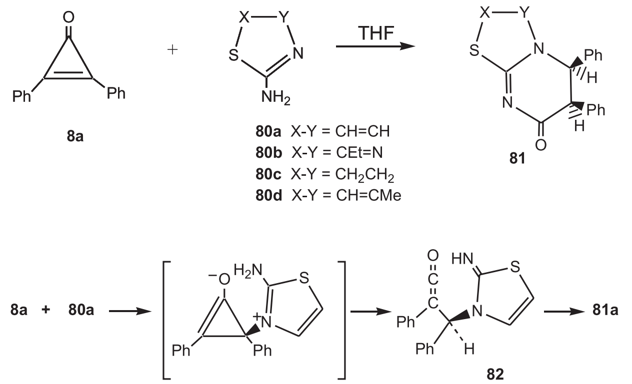


Scheme 20.

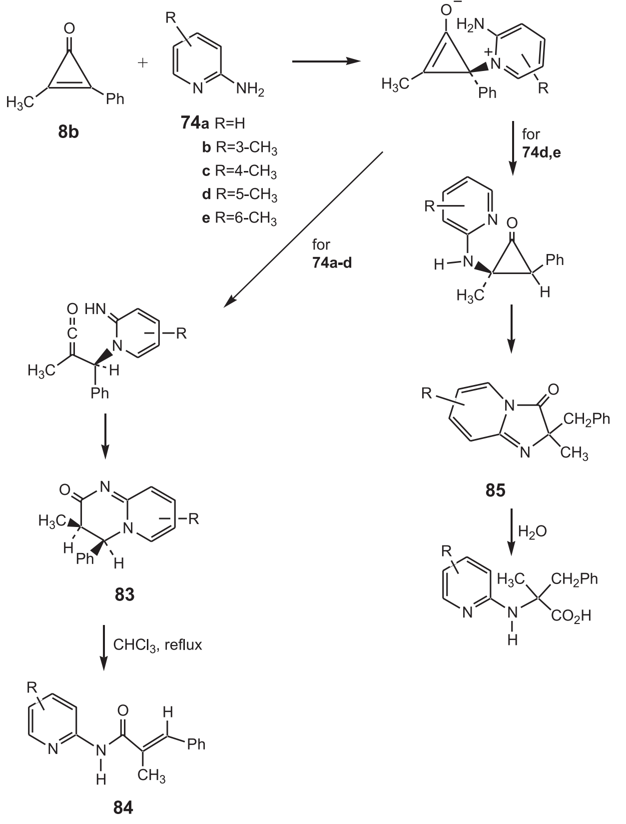
Among the factors contributing to the facility of the ring-opening process to form **75**, an unfavorable H-6:phenyl interaction and the tendency toward the benzenoid-like aromatic nucleus were mentioned.[54] Analogous reactions were later observed with amidines and guanidines.[55] The above results led to the conclusion that this reaction could be applied to the synthesis of 5,6-diphenyl-5,6-dihydrouracils by reaction of diphenylcyclopropenone with thiopseudoureas as masked urea fragments. Therefore, thiopseudoureas **78** were reacted with **8a** and formed the expected dihydrouracils **79** as shown in Scheme 20. It is interesting to note that urea does not react with **8a** under the reaction conditions.[56]

With the objective of evaluating the potential of the above reaction in the synthesis of bicyclic systems, a study of the reactivity of **8a** with 2-aminothiazoles (**80**) and related compounds was undertaken.[57] The reactions of **80** with diphenylcyclopropenone led to the formation of **81** in average to very high yields. In comparison with **76**, **81a-c** demonstrated a remarkable stability in solution. The formation of **81** may be visualized as occurring by way of a highly stereospecific and efficient intramolecular interception of a ketene intermediate **82**, formed by initial conjugate addition as in the case shown above.[57]

Unsymmetrical cyclopropenones such as methylphenyl-cyclopropenone **8b** (Scheme 21) can react with nucleophiles at either of the two conjugate positions. Cyclopropenone **8b** proved to be less reactive than **8a** in reaction with 2-aminopyridines. Analogous pyridopyrimidinones **83** were formed and proved to be more stable than the diphenyl analog **76**. These compounds (**83**) could be transformed to **84** in refluxing chloroform. An unstable primary product **85** was detected in the case of **74d** and **74e**. The reaction was first thought to occur by initial nucleophilic reaction of the ring nitrogen on the



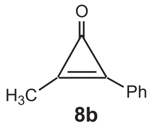
electrophilic C-Ph of the cyclopropenone as shown in Scheme 21.[58] However, HOMO-LUMO coefficients obtained from AM1 calculations of geometrically optimized **8b** show that both HOMO and LUMO coefficients are largest at methyl-C (Table 5)[59] suggesting that reaction of nucleophiles with **8b** is kinetically favored at methyl-C. Thus, the possibility that the reaction of **8b** with 2-aminopyridines actually proceeds via an initial fast and reversible reaction at methyl-C in conjunction with a slow and irreversible ketene-forming sequence involving attack at phenyl-C, as shown in Scheme 22 has to be considered.[59]



Scheme 21.

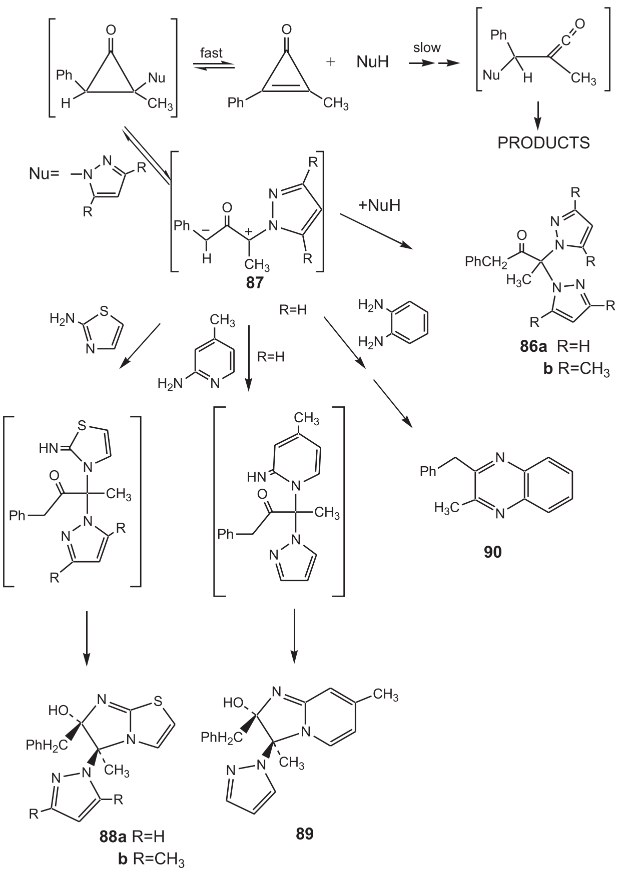
Reaction of **8b** with pyrazole, wherein hydrogen transfer in intermediates involves no loss of heterocyclic aromaticity, shed new light on this question. An equimolar mixture of these reagents afforded ketone **86a** (98% yield) together with unreacted **8b**, confirming the participation of a cyclopropanone intermediate resulting from initial nucleophilic attack at methyl-C. A second equivalent of pyrazole may be incorporated via dipolar species **87**. The viability of interception of **87** by other nitrogen nuclephiles was studied. The use of 2-aminothiazole, 2-amino-4-methylpyridine and *o*-diphenylenediamine (which does not react with **8b** in the absence of pyrazole) formed **88**, **89** (and **86a**) and **90**, respectively, as shown in Scheme 22.

Table 5. HOMO – LUMO coefficients for **8b**



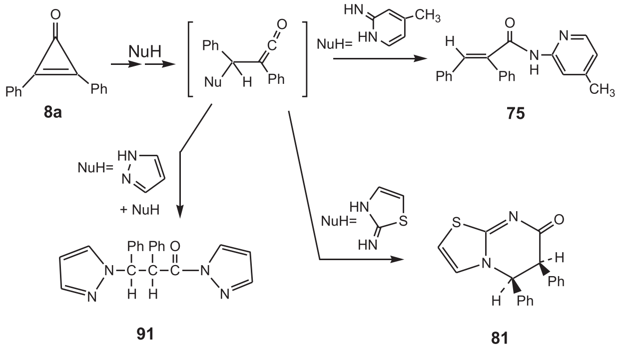
8b

	1st HOMO (p_z)	1stLUMO (p_z)
Methyl – C	0.437	-0.500
Phenyl – C	0.297	0.438



Scheme 22.

With the objective of comparing these results with those involving the possible participation of a ketene intermediate, the above reactions of pyrazole were repeated with **8a** in substitution of **8b**. In the case of 2-aminothiazole, formation of previously reported **81** (78%) was observed, in addition to **91** (20%, mixture of diastereoisomers). In the presence of 2-amino-4-methylpyridine, the previously reported **75** (a ketene rearrangement product, 83%) was produced, in addition to **91** (11%) (Scheme 23). These results reflect the inherent nucleophilic superiority of aminothiazoles and aminopyridines, which may only be brought to light in irreversible ketene-forming processes. The extensive incorporation of pyrazoles in the competitive studies of **8b** may be attributed to the formation of relatively stable cyclopropanone intermediates resulting from reaction at methyl-C.[59]

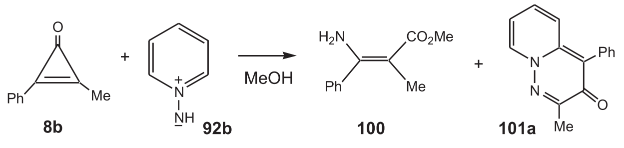


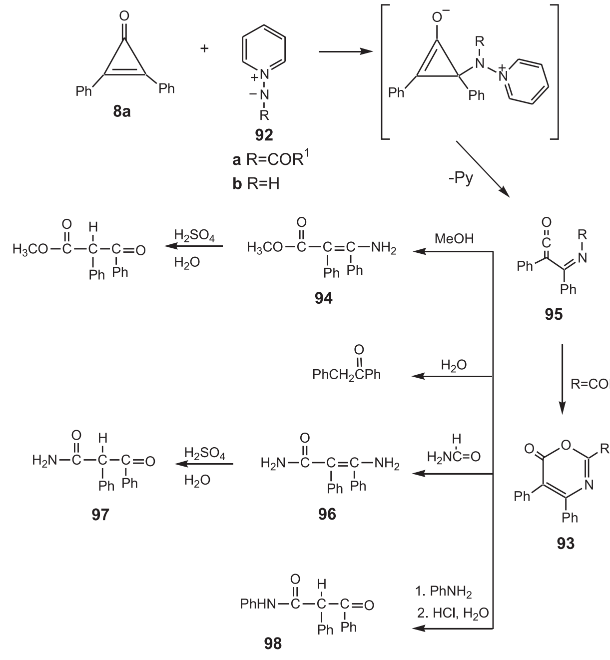
Scheme 23.

1.5.2 Reaction of cyclopropenones with pyridinium N-Imines and other ylides

As a continuation of the study of cyclopropenones with pyridine derivatives, the reactions of cylopropenones with pyridinium *N*-imines and other ylides were examined. A ketene intermediate was invoked for the reaction of diphenylcyclopropenone (**8a**) with *N*-acylpyridinium imines (**92a**) which formed 2,4,5,-trisubstituted 6H-1,3-oxazin-6-ones (**93**).[60] The reaction of diphenylcyclopropenone (**8a**) with *N*-aminopyridinium iodide, in methanol, in the presence of a tertiary amine, led to the formation of **94** which can be visualized as occurring by way of a 1,2 or 1,4 addition of methanol to an iminoketene intermediate (**95**), formed by initial conjugate additiion of **92b** on **8a** with imine acting as a nucleophile, as shown in Scheme 24. The interception of **95** was also accomplished in aqueous dioxane to form deoxybenzoin, in formamide to form **96** (hydrolyzed to the known **97**) and in aniline to form **98**.[61]

When methylphenylcyclopropenone (**8b**) was reacted with pyridine *N*-imine **92b** in methanol, formation of both enamino ester **100** and the 3H-pyrido[1,2b]pyridazine-3-one **101a** was observed.



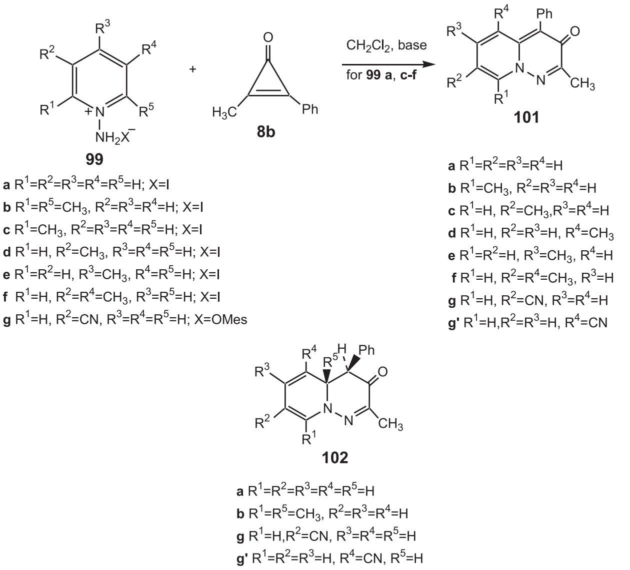


Scheme 24.

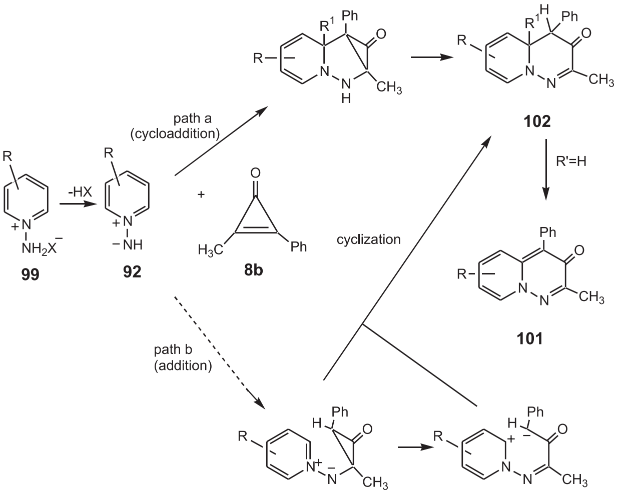
When the reaction was carried out in dichloromethane an intermediate **102** was isolated in addition to **101**. On standing **102** was readily oxidized to **101**. This reaction apparently involves participation of **92b** not only as a nucleophile, as in the case of diphenylcyclopropenone, but also as a 1,3 dipolar compound. Thus, this work represents the first example of a possible 1,3-dipolar addition of a pyridine *N*-imine to a cyclopropenone, further illustrating the effects of substituents on the reactivity of the cyclopropenone ring.[62] As a continuation to this study, methylphenylcyclopropenone was reacted with substituted pyridinium *N*-imino salts **99** in methylene chloride in the presence of triethylamine or potassium carbonate at room temperature. The results are summarized in Scheme 25. The reaction of di-*n*-propylcyclopropenone needed reflux conditions. The results show nucleophilic reaction for the diphenylcyclopropenone (Scheme 24) and cycloadditions for the methylphenyl and dipropylcyclopropenones (Scheme 26).[63]

1.5.3 Reaction of cyclopropenones with N-acylamidine derivatives

N-acylamidines can be envisioned as enaminone aza analogs (an aza-enaminone). Reactions of **8a** with *N*-benzoylacetamide (**103**) and *N*-(methoxycarbonyl) benzamide (**104**) afforded the1,2-dihydro-3H-pyrrol-3-ones consistent with reaction of the *N*-acylamidine from the external nitrogen as shown in Scheme 27. Calculations



Scheme 25.



Scheme 26.

show that the coefficients of the HOMO are principally on the two nitrogens and largest on the external imino group in tautomer **B** (Figure 5 and Scheme 28). Thus, it appears that the reaction is kinetically favored for the tautomeric forms of **103** and **104** and frontier orbital controlled. A slow and irreversible attack at the conjugate position of **8a** followed by an electrocyclic five-membered ring formation results in the regiochemistry observed for compounds **105** and **106**. Thus while acyclic enaminones react mainly through C$_\alpha$, the "aza-enaminones" react through the external nitrogen, consistent with a frontier-orbital controlled reaction. Methylphenylcyclopropenone and isopropylphenylcyclopropenone did not react with **103** and **104** under the reaction conditions employed, consistent with the higher energy LUMO's found for these systems when compared to **8a**. Therefore, all the results

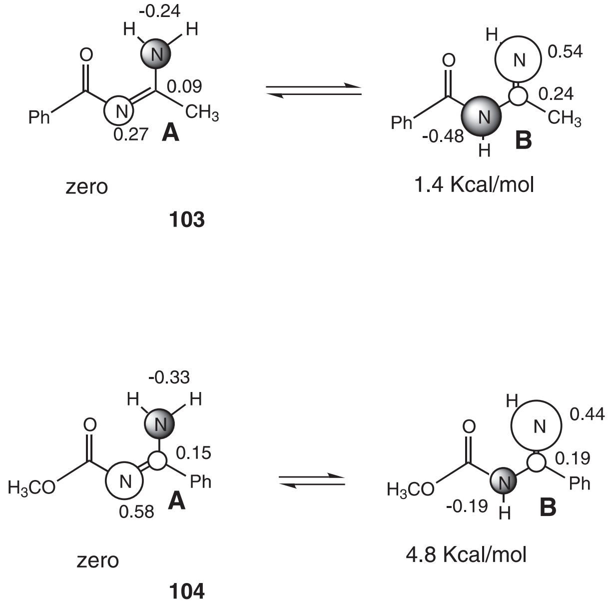
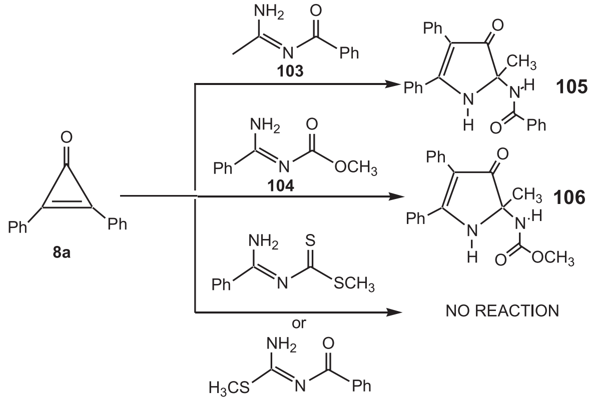
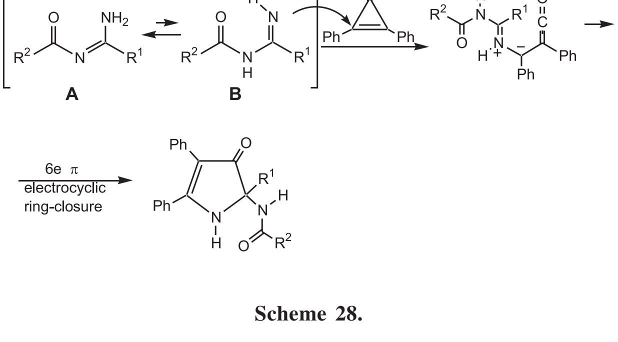


Figure 5. HOMO coefficients and relative energies for **103** and **104** and their tautomers.



Scheme 27.

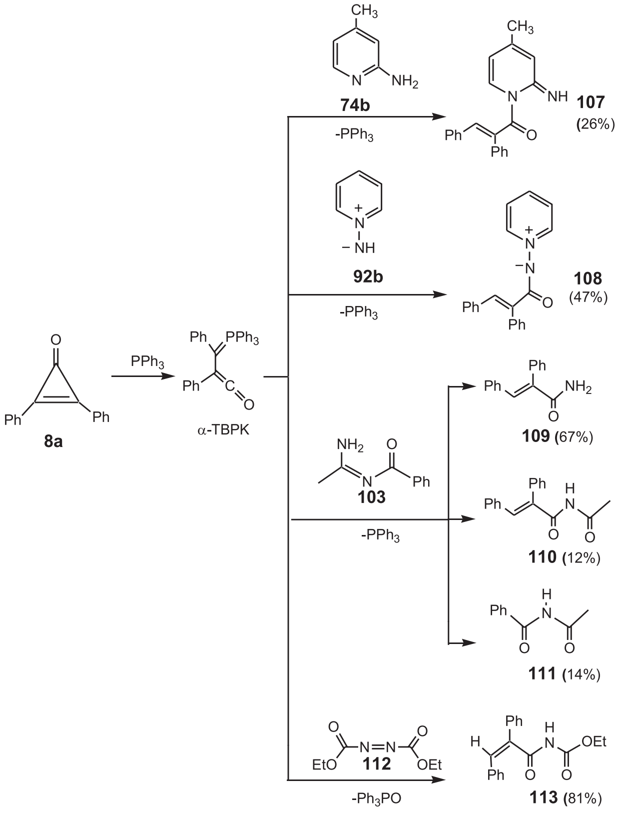


Scheme 28.

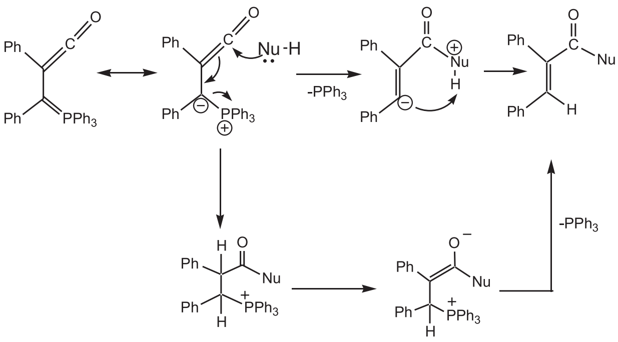
obtained in this study can be understood using a frontier-orbital approach.[64]

1.5.3.1 *Reaction of α-TBPK, a derivative of* **8a**

α-(Triphenylphosporanylidene)-benzylphenylketene (α-TBPK) is a derivative of **8a** prepared by its reaction with triphenylphosphine. Since this solid is stable only under anhydrous conditions it is generated *in situ*. The α-TBPK thus formed was reacted with 2-amino-4-methylpyridine **74b**, pyridinium *N*-imine **92b** and *N*-benzoylacetamidine **103,** compounds that had already been reacted with the parent diphenylcyclopropenone (**8a**). The products formed are presented in Scheme 29 In each case triphenylphosphine was also recovered.[65] From a mechanistic viewpoint, the formation of **107-111** may be visualized as occurring through attack of the nitrogen nucleophile at the electrophilic carbon of the ketene portion of α-TBPK, followed by triphenylphosphine elimination and proton transfer (Scheme 30). The presence of this good leaving group changes the direction of the reaction when compared to the reaction of the parent **8a** as shown in Scheme 24**.** Reaction with diethyl azodicarboxylate **112,** which does not have a transferable hydrogen, formed *N*-acylcarbamate **113** in excellent yield together with triphenylphosphine oxide. The formation of **113** provides a new route to polysubstituted *N*-acylcarbamates which are versatile intermediates in the synthesis of nucleoside analogues. Their preparation is not a trivial task.[66]

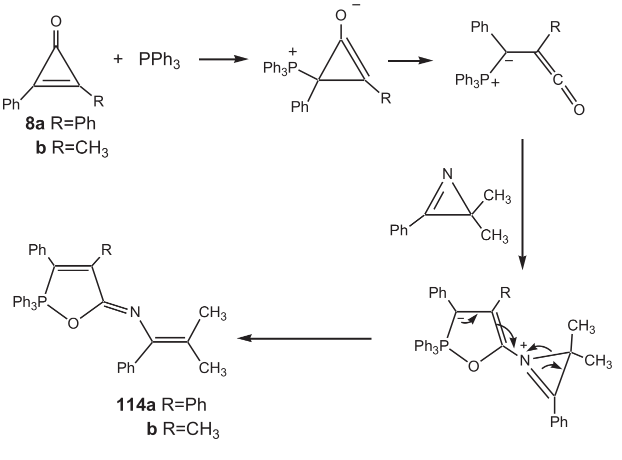


Scheme 29.



Scheme 30.

The above studies show elimination of the phosphine group in the final product. Earlier, in a study involving the reaction of α-TBPK with 3,3-dimethyl-2-phenyl-1-azirine, it was found that oxaphospholene **114** was formed, representing a case in which there was no loss of the phosphine group. Analogous results were obtained with **8b** as a starting material as seen in Scheme 31.[67]

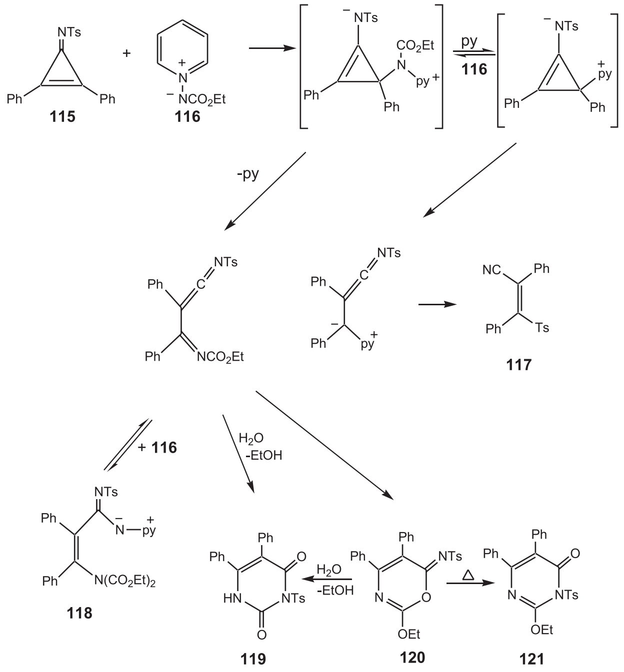


Scheme 31.

1.5.3.2 *Reactions of tosyl analog of* **8a**

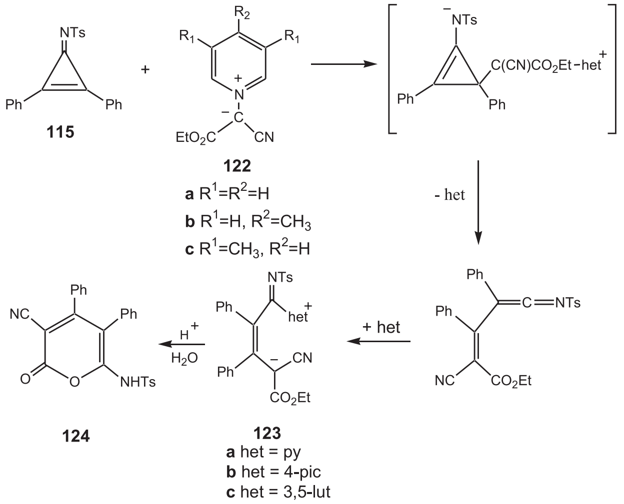
While considerable attention had been given to the study of the reactions of diphenylcyclopropenone with pyridinium *N*-amines and pyridinium methylides, the chemistry of the *N*-tosyl analogue had been ignored. Thus a study was undertaken with the objective of comparing the reactivity of *N*-(*p*-tolylsulfonyl)diphenylcyclopropenimine **115** in reactions with mono- and disubstituted pyridinium and isoquinolinium ylides. The reaction of

115 and **116** in refluxing benzene (no reaction at room temperature) afforded **117** as the major product and **118** as the secondary product. In Scheme 32, the formation of **118** is depicted as involving a second equivalent of **116** on an initally formed ketenimine intermediate, with migration of a carboethoxy group. A heated toluene solution of **118** afforded **116** (19%), a uracil derivative **119** (28%), and the pyrimidinone **121** (41%), the latter two being other products isolated from the original reaction of **115** with **116.** The thermal behavior of **118** suggests a reversibility for this process, with possible participation of a thermally unstable iminooxazine **120**, in the formation of **119** and **121**.[68]

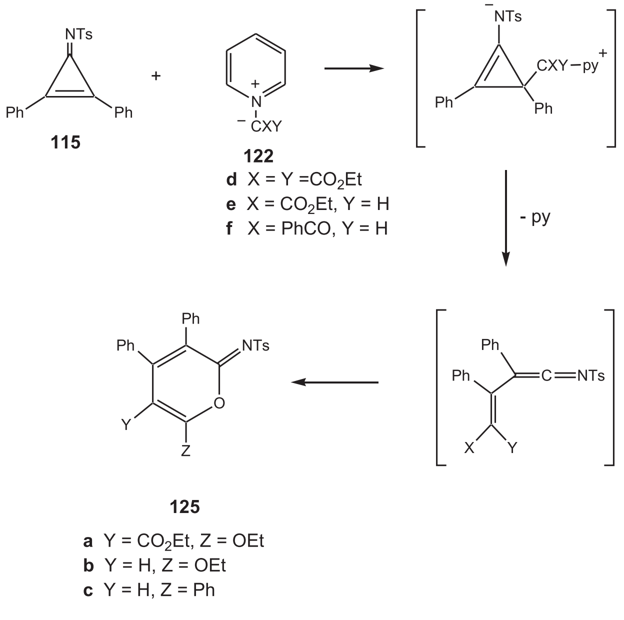


Scheme 32.

While no reaction occurred between **115** and pyridinium dicyanomethylide, a smooth reaction was observed with the cyanocarboethoxy analogues **122a-c** producing internal salts **123a-c** in high yields, which upon hydrolysis formed **124** (Scheme 33). The reaction of the dicarbethoxymethylide **122d** and **115** gave a product **125** (Scheme 34), reminiscent of the product[61] of mono-substituted methylides and **8a** (as seen in Scheme 24). The products obtained from the reactions of **115** with pyridinium ylides were accounted for by considering pathways involving ketenimine intermediates depicted in Schemes 33 and 34. While the ketene counterparts suggested in the reactions of **8a** with certain pyridinium ylides show a tendency to undergo cyclization, these results with **115** demonstrate that further reaction with nucleophiles present in the medium would be expected in this case.[68]

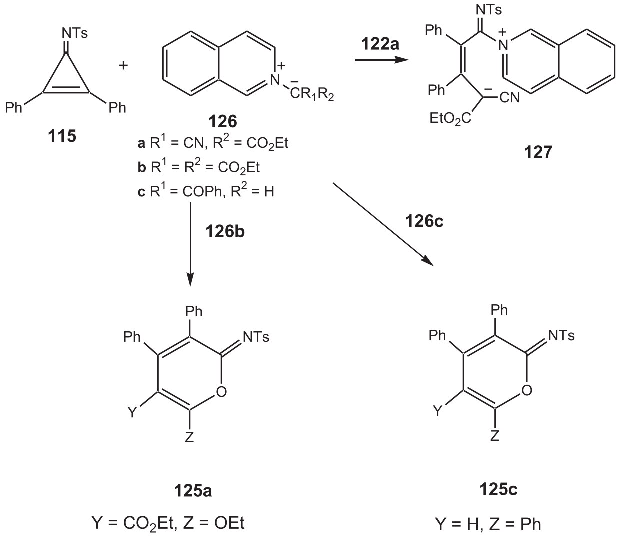


Scheme 33.

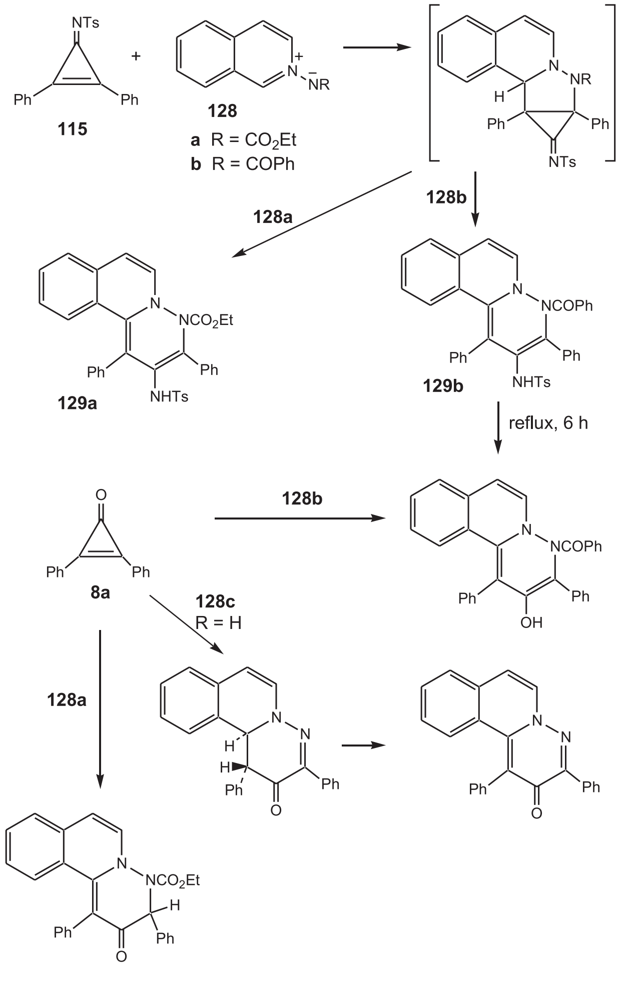


Scheme 34.

Reaction of **115** with isoquinolinium methylides **126a-c** paralleled that of pyridinium analogues, producing **127**, **125a** and **125c**, respectively (Scheme 35). The isoquinoline *N*-amide derivatives **128** however, differed markedly in their reactivity toward **115**. With these systems, high yields of cycloadducts **129a,b** were obtained (Scheme 36). Cycloaddition products were obtained when **8a** was reacted with **128a,b**. This result contrasts with the reaction



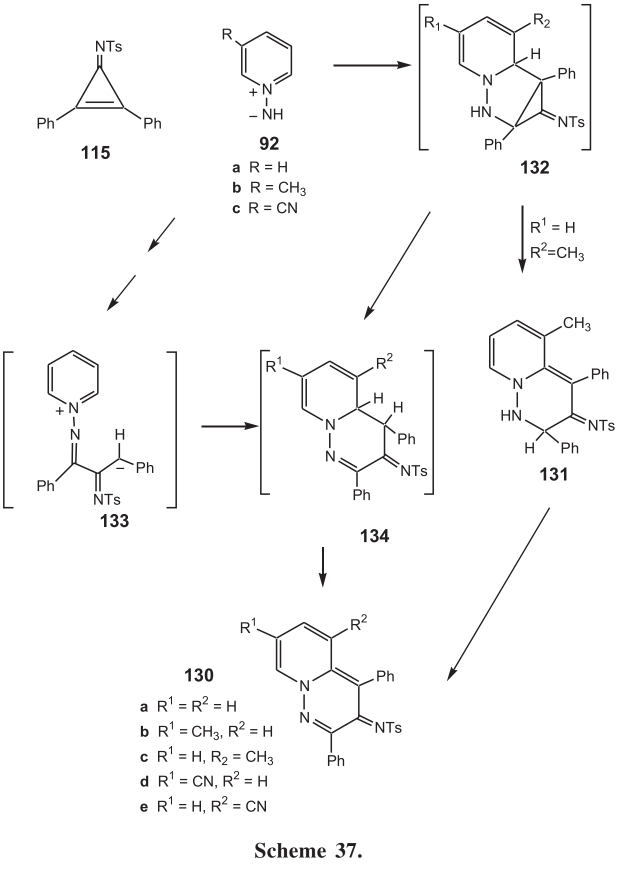
Scheme 35.



Scheme 36.

of diphenylcyclopropenone **8a** with pyridinium *N*-amines where the reaction is nucleophilic (Scheme 24).[68] These results show that cyclopropenimine **115** is capable of differentiating nucleophilic and dipolar character in a homologous series of cycloiminium methylides and imines.

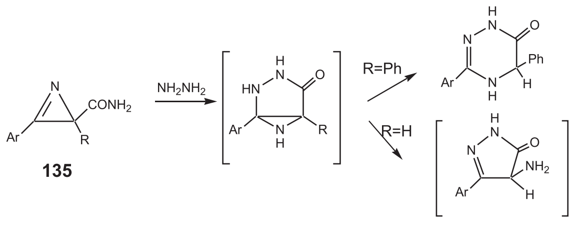
The reactions of pyridinium *N*-imines with **8a** formed products consistent with a pathway involving initial nucleophilic attack on the cyclopropenone ring with subsequent ellimination of pyridine (Scheme 24). A similar behavior was seen in the reaction of **115** upon reaction with pyridinium *N*-carboethoxyimine **116** (Scheme 32). On the other hand, cycloaddition products **129** were obtained with isoquinoline *N*-amide derivatives **128**. These results prompted the study of the reactions of **115** with pyridinium *N*-imines **92**. The reaction of **115** with **92a** yielded the cycloadduct **130a**. The reaction of **92b** in methylene chloride afforded the stable intermediate **131** as the major product. When **92c** was used, the stable intermediate **131** was isolated, along with **130c**. The formation of **131** provides direct evidence for the participation of **132**. However, since a 1,2-dihydro intermediate was isolated in one case only, an alternative pathway to other **130** products involving inverse hydrogen transfer to **132** or a stepwise process with participation of **133** to produce a 4,4a-dihydro intermediate **134** cannot be excluded (Scheme 37).[69]



Scheme 37.

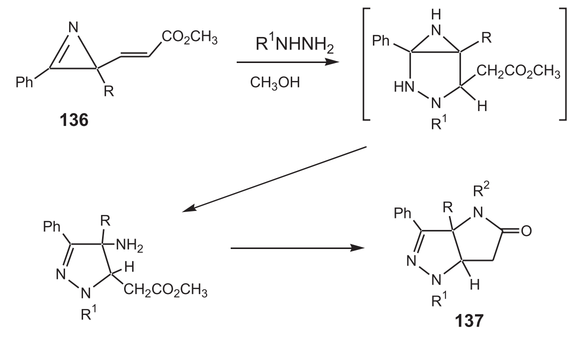
2. 1-Azirines

While the behavior of simple 1-azirines toward a variety of nucleophilic reagents has received considerable attention in the literature, that of such systems containing additional electrophilic centers attached to the 3-position has been largely ignored. One example involving 1-azirine-3-carboxamides **135** with hydrazine was suggested to proceed through bicyclic aziridine intermediates with subsequent C-C or C-N bond cleavage to afford tetrahydro1,2,4-triazin-6-ones or unstable 4-amino-2-pyrazol-5-ones, depending on the nature of the 3-substituent (equation 3).[70] Although this result would suggest a promising role for azirine systems containing three electrophilic centers in the preparation of new heterocycles, no studies demonstating this potential had appeared by 1990. Therefore, studies of 1-azirines **136a** and **136b** with hydrazines and amidines were undertaken. Reaction of **136a** with hydrazine in methanol afforded the bicyclic system **137**. Similarly, **136b** produced **137b** (Table 6), the reaction pathway being unaffected by the presence of a substituent other than hydrogen at the 3-position. The process was represented as involving intramolecular interception of a C-N cleavage product derived from a bicyclic aziridine intermediate analogous to that depicted in equation 3. The absence of unsaturation adjacent to the aziridine portion of this intermediate should disfavor C-C bond cleavage. To address the question of initial nucleophilic attack at C-2 versus a Michael type at the 3-substituent, the behavior of **136a** with substituted hydrazines was examined. The observed formation of **137c** (Table 6) suggested initial attack at C-2. In an attempt to incorporate an additional carbon atom into the bicyclic products, reactions of **136** with formamidine and guanidine were studied (Scheme 38). In methanol only complex mixtures were obtained. However, in dimethyl sulfoxide, it was possible to observe the selective formation of imidazole **138**, pyrimidones **139a-b** or amino-*s*-triazine **140**. The reaction pathway reflects a strong directive effect of the 3-substituent on the azirine ring. This effect was explained by considering that the reaction occurs from different tautomers (Scheme 38) resulting from C-C bond cleavage in aziridine intermediate **141**, wherein product formation is thermodynamically controlled. These results represent the first example of a solvent-controlled C-N versus C-C bond cleavage process in the reactions of azirine derivatives.[71]

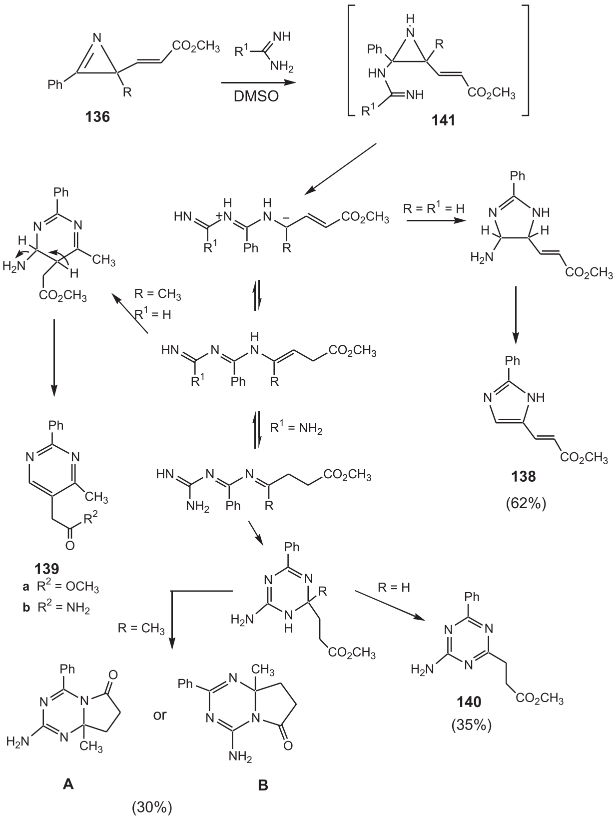


(3)

Table 6. Bicyclics formed in the reaction of azirines **136** with hydrazines in ethanol

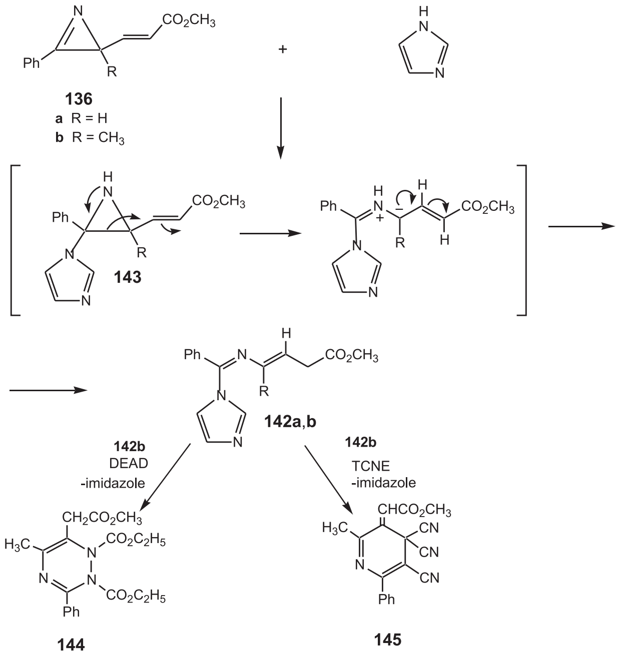


R	R¹	R²	136	137	Yield (%)
H	H	H	**a**	**a**	43
CH_3	H	H	**b**	**b**	32
H	Ph	H	**a**	**c**	38
CH_3	CH_3	CH_3	-	**d**	44
H	Ph	CH_3	-	**e**	51



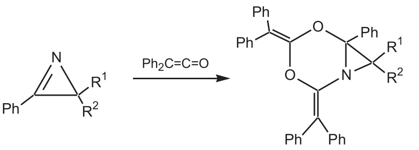
Scheme 38.

After two days, the reaction of imidazole, another nucleophile studied, with 1-azirine-3-methyl acrylate **136a** (methylene chloride, room temperature) demonstrated the total consumption of reagents with formation of two new systems, one of which disappeared after an additional five days in solution. The final product obtained was 2-aza-1,3-diene **142a** in 45% yield, obtained as a 10:1 mixture of *Z*/*E* isomers after column chromatography. The participation of a highly reactive aziridine intermediate **143** as the second system in the two day reaction was suggested by the NMR spectrum of the crude reaction product. Reaction of the more hindered **136b** with imidazole afforded **142b** (60%) as a 1:12 mixture of the *Z*/*E* isomers. Interestingly, in this case, the *E*-isomer predominates (Scheme 39). The reactions of these and other nucleophiles improved with the presence of catalytic amounts of the non-nucleophilic base sodium carbonate which shows that the ring opening of the aziridine intermediate is base catalyzed. The most interesting aspect of the chemistry of azadiene systems has been the constuction of heterocycles through the use of the hetero Diels-Alder reaction. The reaction of **142b** with the electron deficient diethylazodicarboxylate (DEAD) and tetracyanoethylene (TCNE) formed cycloadducts **144** and **145**, respectively (Scheme 39) In both cases, the diazole nucleus serves as an efficient leaving group in the initial Diels-Alder adduct. This observation calls attention to this potentially valuable feature in the azadienes **142** prepared in the present study.[72]



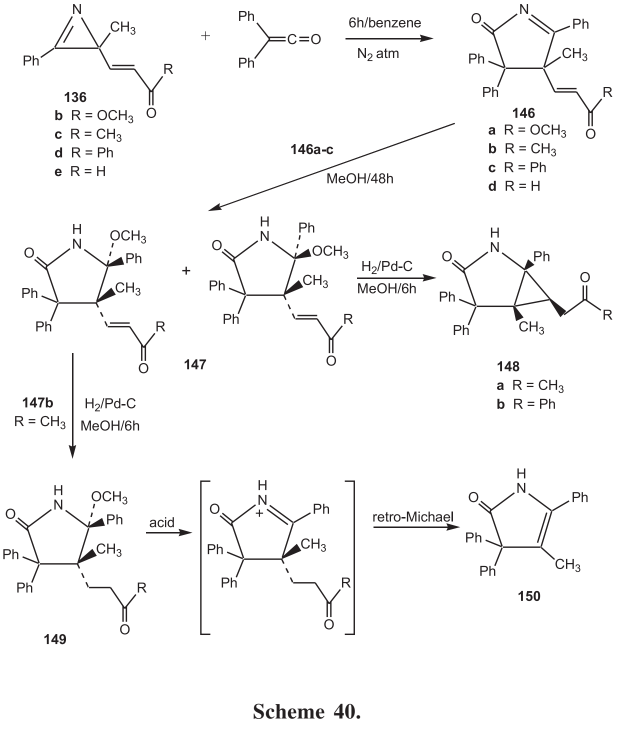
Scheme 39.

Reaction of simple azirines with diphenylketene forms bicyclic aziridines by way of addition of two equivalents of ketene to the imine moiety (equation 4).[73]

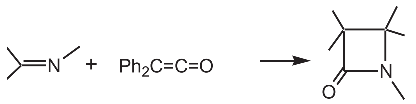


(4)

Continued interest in the effect of higher order functionality at the 3-position of the 1-azirine nucleus led to the study of the reaction of 1-azirine-3-acrylates as nucleophiles with the electrophilic diphenylketene formed from 1,2-diphenyldiazoethanone **33a**. Formation of 5-pyrrolin-2-ones **146** in good yields was observed for the azirines **136b-e** (Scheme 40). Alcohols added readily to the imine fragment in **146**, as illustrated for the reactions of methanol with **146a-c**, wherein methoxy pyrrolidinones **147a-c** were obtained as mixtures of diastereomers. Under conditions of catalytic hydrogenation (H_2/Pd-C/MeOH/6H), diastereomeric mixtures of **147b-c** suffered concomitant hydrogenolysis of the C_5 methoxy with intramolecular Michael addition to afford 2-azabicyclo[3.1.0]hexanes **148a-b**, respectively. This reaction represents a new approach to cyclopropane ring formation.[74] When diastereomer **147b** (that which contains C-4Me *cis* to C-5Ph) was submitted to this condition (catalytic hydrogenation), a smooth reduction to **149** was observed without any indication of hydrogenolysis. Under acidic conditions **149** forms **150** exclusively, most likely through initial loss of methanol, with no sign of an intramolecular aldol process. Extensive substitution at C-4 and C-5 in **149** appears to be responsible for this observation.

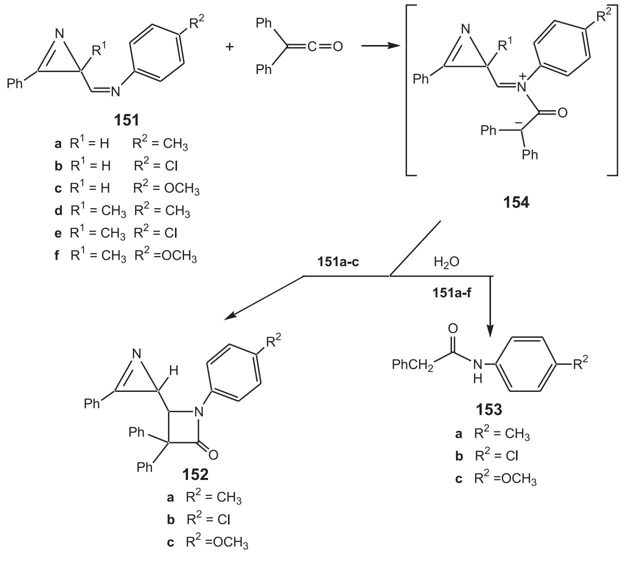


Scheme 40.



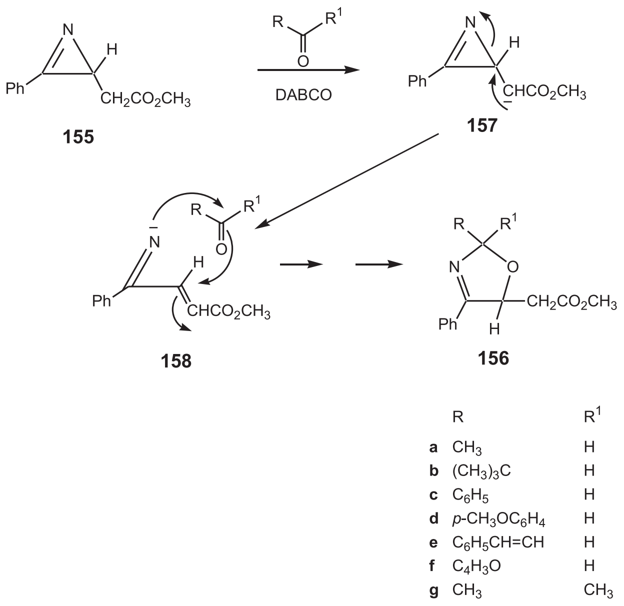
(5)

While 1-azirines react with diphenylketene according to equation 4, simple imines afford 2-azetidinones upon reaction with diphenylketene (equation 5).[74] The ready availability of 2-formyl-2H-azirine-*N*-aryl-imines **151**, wherein both imine types are encountered, prompted the investigation of the behavior of **151** in the above reaction. Compounds **151a-c** reacted with diphenylketene to form 2H-2-azirinyl-2-azetidinones **152a-c** and some *N*-aryldiphenylacetamides **153a-c** (Scheme 41). Formation of *N*-aryldiphenylacetamides **153a-c** may be attributed to the interception by intermediate **154** of trace quantities of water in the reaction medium, in competition with ring closure to **152**. The results demonstrate the enhanced reactivity of the *exo*-imine group in **151**, furnishing a convenient route to the previously unknown 2H-2-azetidinone system in a highly diastereoselective fashion.[75]



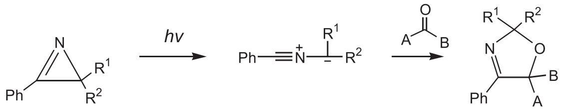
Scheme 41.

All the above reactions involve azirines with electron withdrawing groups on the 3-position (referred to as the "3-Z mode"). The next study focuses on an electron-rich substituent at the 3-position (referred to as the "3-X mode") which exerts a pushing effect on the three membered ring. To the extent that this process results in C-N bond cleavage, the resulting imino anion might be induced to undergo reaction with electrophiles.The 3-acetate derivative **155** was chosen as a simple precursor to a 3-X substituted 1-azirine. Mild base-catalyzed reaction of **155** with aldehydes and ketones is reported here. While no reaction occurred between methyl 2-phenyl-1-azirine-3-acetate **155** and a series of aldehydes and ketones used as solvents in the absence of base, the presence of DABCO in the reaction medium resulted in a smooth conversion to 3-oxazolines **156**, as a 1:1 mixture of diastereomers (where these exist). Formation of **156** is consistent with participation of the intermediate 3-X substituted 1-azirine **157** generated in low concentration through proton extraction from **155** by DABCO with ring opening to **158** (Scheme 42). A nucleophilic role for DABCO in this reaction, which would invoke the participation of aziridine intermediates, was discarded inasmuch as potassium carbonate also produces **156**, albeit at a slower rate. In contrast to the well-known 2-oxazoline isomers, 3-oxazolines are a rare class of compounds and only a few methods have been elaborated for their preparation.[76] Of these methods, one approach is extremely pertinent to the present discussion.[76] Aldehydes and ketones react with nitrile ylides produced from 1-azirines by photochemically promoted C-C bond cleavage (equation 6). In this case, the carbonyl moiety becomes the 1,5-fragment in the resulting 3-oxazoline. In the present study, the 1,2-fragment in **156** originates from the carbonyl component. The two methodolgies are therefore complementary, although it should be noted that acceptable yields of 3-oxazolines in the photochemical process require the presence of electron-withdrawing substituents on the carbonyl moiety. The mild reaction conditions employed in the present study permit, for the first time, construction



Scheme 42.

of a 3-oxazoline nucleus containing versatile functional groups at the 2-position (*i.e.* styryl (**156e**) and furyl (**156f**)).[77]



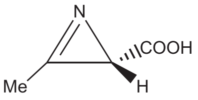
(6)

3. Retrospective

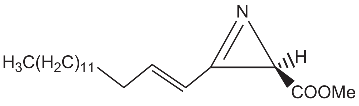
This account represents a good part of our published work with enaminones, diazocarbonyls and small rings. There is a considerable amount of unpublished data which was not included here, nor were reactions of diazocarbonyl related compounds with nucleophiles[78] other than enaminones. Basically we started with the concepts of nucleophiles reacting with electrophiles using systems that are ambident and/or ambiphilic or can form interesting intermediates with these properties, and used structure considerations to generate chemical possibilities. A mechanistic approach was used to understand the reactivity. The addition of the more subtle notions of molecular orbital theory, principally the concept that frontier orbitals are important to reactivity, came when some of the experimental data had already been obtained. Having found that the reactions are, in general, frontier-orbital controlled, this additional concept added a new dimension to our studies, allowing us to make more well founded suggestions about reaction mechanisms. For example, as suggested by frontier-orbital treatment, acyclic enaminones tend to react at the C_α position and diphenylcyclopropenone reacts by conjugate addition. Also, molecular orbital calculations suggest that the Me-C of methyl phenylcyclopropenone (**8b**) should be the kinetically favored position for reaction with nucleophiles.

These studies have shown that the reactions of diphenylcyclopropenone seem to involve ketene intermediates formed from ring opening of primary adducts of nucleophilic attack. Reactions with pyridinium *N*-imines, **8b** show more tendency toward cycloaddition than does diphenylcyclopropenone. Also, reactions of **8a** and diphenylcyclopropenyl tosylimine (**115**) with isoquinoline *N*-amide derivatives are more likely to form cycloadducts than with pyridinium *N*-amide derivatives.

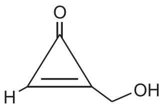
As already mentioned, many of the chemical systems obtained by us in these and other works have medicinal and biological possibilities. Besides preparing compounds with possible biological activity, recently there has appeared in the literature examples of enaminones, azirines and cyclopropenones (our starting reagents) with medicinal activity. Thus, methyl 4-(p-chlorophenylamino)-6-methyl-2-oxocyclohex-3-ene-1-oate and methyl 4-(benzylamino)-6-methyl-2-oxocyclohex-3-ene-1-oate are two anticonvulsant enaminones.[79] Azirinomicine, the first naturally occurring 1-azirine (isolated from the *Steptomyces aureaus* bacteria) is an antibiotic[80] and dysidazirine, the first example of this strained ring class of heterocycles from a marine source, has citotoxic activity.[80] The cyclopropenone penitricine has antibiotic activity and has been used as a model for other biologically active cyclopropenones.[81]



azinomicine



dysidazirine



penitricine

The chemical understanding obtained from these and other studies should help researchers understand the mode of action of these and related biologically active compounds and help produce more effective drugs. With this, we can see that the continuation of this research along the medicinal line presents itself as an exciting possibility for the future.

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