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Review

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

Concetta Montanile Kascheres

Instituto de Química, Universidade Estadual de Campinas, CP 6154, 13083-970 Campinas-SP, Brazil

Universidade Paulista, Instituto de Ciências da Saúde, Avenida Independência, 412, 130087-050 Sorocaba, SP, Brazil

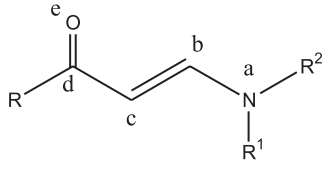
Depois de trinta e dois anos no Brasil e de aposentada da Universidade Estadual de Campinas, a autora gostaria de apresentar este resumo representando uma grande parte da pesquisa em metodologia sintética desenvolvida pelos grupos de pesquisa de Albert J. Kascheres e da autora no Instituto de Química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

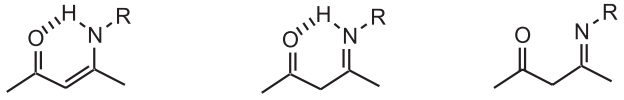
1. Enaminones

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

* e-mail: conniek@uol.com.br

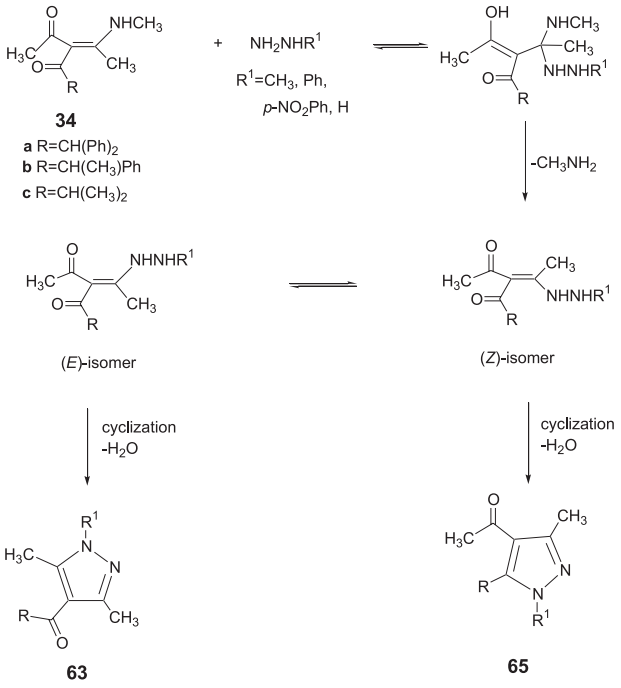
I dedicate this work to Al Kascheres (with whom I have the joy of sharing this wonderful life) on the occasion of his 60th birthday (May 24, 2003).

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

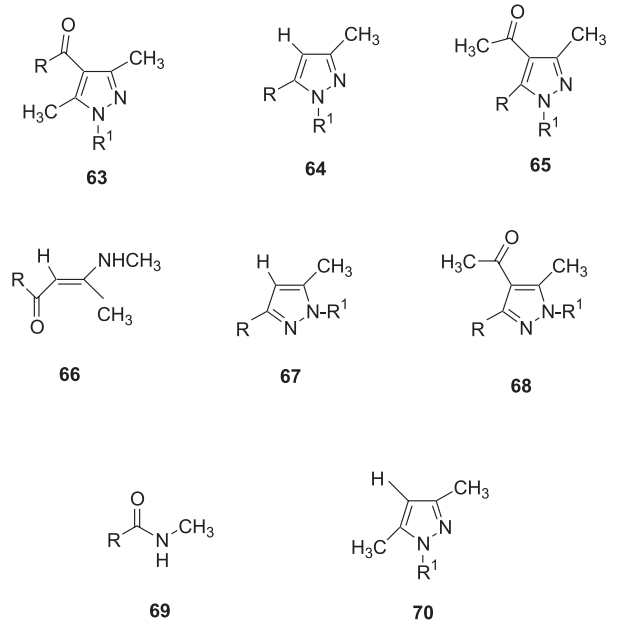
Enaminones react with hydrazines to form substituted pyrazoles.[48] As already seen, diazoketone **33a** reacts with enaminones via ketenes under noncatalytic thermal conditions to form nucleophilic addition products. The same reaction occurs with **33b** and **33c** to form the α-acylenaminoketones **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-acyl-enaminoketones **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



Scheme 17.

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**).



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]

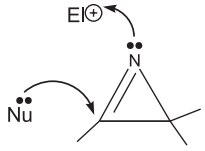
Simple eye inspection of the distribution of the eight products, shown above, especially those obtained in low yields, did not enable detection of consistent differences between solvents or nucleophiles. Therefore, in an attempt to understand how these factors could be correlated, we utilized principal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

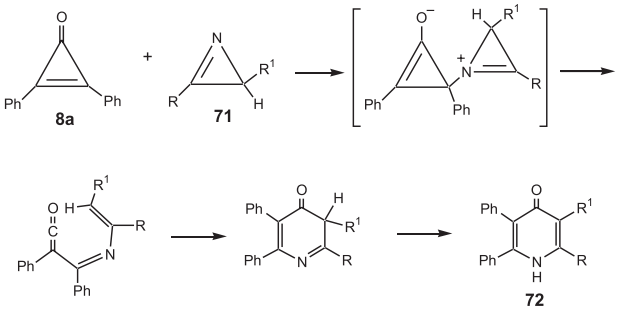
1.4 Small rings

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]

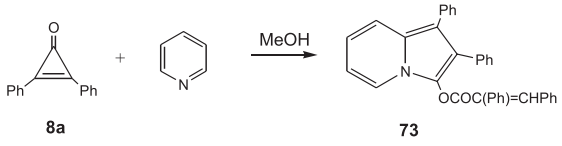


Scheme 18.

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]

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