Recent Development in Preparation Reactivity and Biological Activity of Enaminoketones and Enaminothiones and Their Utilization to Prepare Heterocyclic Compounds

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Enaminoketones and esters are gaining increased interest, particularly cyclic-β-enaminoesters, which are known as important intermediates for the synthesis of heterocycles and natural products, because the enantioselective preparation of highly functionalized compounds is of central importance in synthetic chemistry. Enaminones are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident eletrophilicity of enones. Enaminoketones and enaminonitriles have proven to be versatile building blocks for the synthesis of various heterocycles such as pyridine, pyrimidine and pyrrole derivatives. Enaminones systems have "enone" character, and may act as acceptors in both 1,2 and 1,4-additions. In this way the enaminone serves as a scaffold for annulation, and can gain access to systems such as pyrroles indolizidines, quinolizidines and perhydroindoles, all of which are common motifs in alkaloid structures. Enaminones are frequently employed as building blocks for the preparation of a variety of bicyclic compounds of biological interest and have been recently recognized as potential anticonvulsant compounds. Since a large number of developments in the use of enaminones in heterocyclic synthesis have occurred, a review of the recent developments in the synthetic approaches, covering the literature since 1995 until 2004, to these interesting molecules and their useful chemical transformations and biological activity can be considered of considerable value.

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Enaminoketones.

Introduction.

The term enaminone was introduced by Greenhill to define the enamine of a 1,3-diketone, β-ketoester or similar 1,3-difunctional reagents, and is used to indicate any compound containing the conjugated system N-C=C-C=O [1]. Enaminones are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident eletrophilicity of enones. The chemistry of the enaminocarbonyl group **1** 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) [2-4] (Figure 1).

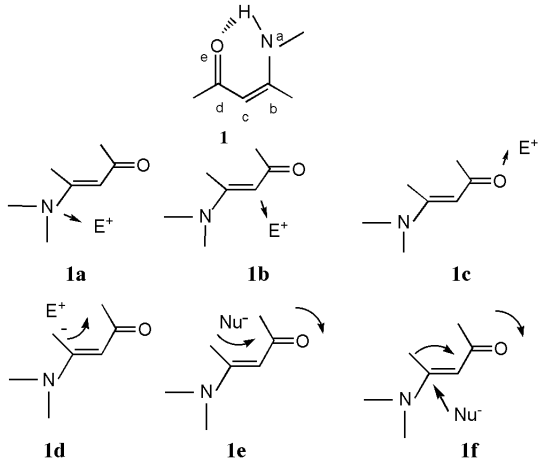

Figure 1

Theorically, primary and secondary acyclic enaminones can exist in three tautomeric forms: ketamino form, iminoenol form and oxoimino form [1-3]. There is also evidence that cyclic enaminones exist primarily in the enaminoketo form. A study of cyclic enaminoketones shows that these compounds have a significant steric fator in the six-membered ring. The six-membered ring enaminoketones are only slightly stronger bases than the saturated amines, whereas five-and-seven membered rings are much stronger bases than saturated amines. This has been attributed to a large steric strain present in six-membered enaminoketones [5].

β-Aminoenones or enaminoketones can exist in four conformations owing to restricted rotations around the C=C double and C-C=O single bonds [3]. Enaminones with primary or secondary amino groups can exist in both *Z*- and *E*- forms. If there is at least one hydrogen atom at the nitrogen, then the *Z*-isomer contains an intramolecular hydrogen bond. The *E*-isomer (without this intramolecular hydrogen bond) containing two different substituents at nitrogen can exist as a pair of isomers of limited stability (their stability lies between that of conformers and the geometrical isomers) as a consequence of partial double bond character of the C-N bond [6,7]. The conjugation of the system facilitates the interconversion between the *Z* and the *E* forms.

In general, spectroscopic methods have shown that primary and secondary enaminones exist predominantly, and in many cases completely, in the *Z*, s-*Z* form in solution of apolar solvents. 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 [3]. 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).

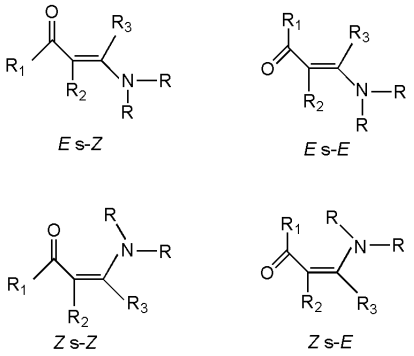

Figure 2

The ^{17}O NMR chemical shifts of enaminones depended upon the type, number and position of the substituents. The chemical shift differences between the *E* and *Z* forms of enaminones, is mainly attributed to intramolecular hydrogen bonding [8]. Correlations of ^{17}O and ^{13}C chemical shifts of the carbonyl groups with those of the corresponding N-acylanilines indicate that the enaminone moiety as a whole has electronic properties similar to those of the RCONH group [9,10]. The more extended delocalization of enaminones resulting from the n, π conjugation of the amino group with the C=C-C=O system is described by the mesomeric formulae A, B and C (Figure 3). The "enamine" nucleophilicity at N and C can be extended to the carbonyl group by conjugation [11].

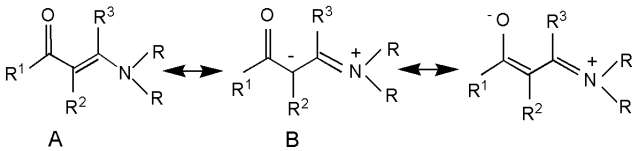

Figure 3

The *E* and *Z* forms of enaminones can be easily distinguished by their ^1H NMR spectra: the N-H signals of the *E*-form (4 – 8 ppm) appear at much higher field than those of the *Z*-form (9 - 13 ppm) indicating the presence of strong intramolecular hidrogen bonding in the latter [3,9,12]. The only common interfering band will be from carboxylic acids (most likely dimeric) which appear at the same chemical shifts about δ=10-13 ppm. In the infrared, the NH- "free" infrared stretching frequency differs appreciably from that of the "free" OH. Chemical shift of the acidic proton is an excellent guide to the extent of tautomeric interaction and resulting hydrogen bonding [12].

2-Propenal-3-amine is the simplest "enaminone", and its tautomers and conformers were investigated in a search for the most likely reactive form [13]. The heteronuclear N–H---O is ever more important than the homonuclear O–H---O bond, because of its outstanding importance in protein folding and DNA pairing [14]. The resonance-assisted intramolecular N–H---O bond formed by the heterodienic fragments of β-enaminone have the correct geometry to form potentially strong N–H---O bond [15].

When the HOMO/LUMO interaction is the major factor governing reactivity, the reaction is said to be frontier-orbital controlled [16]. The AM1 molecular orbital calculations showed that enaminones **2** (Figure 4) have HOMOs with large coeficients on both the α-carbon and nitrogen atoms and have LUMOs with large coeficients on both the β-carbon atom and carbonyl carbon of the acetyl group [3,17]. X-Ray crystallographic data indicated good agreement with AM1 calculated geometries indicating that, whichever the configuration, the volumous group tends to be approximately perpendicular to the plane of the enaminone, most likely because of steric factors [18,19]. Both *Ab initio* 6-31G** and AM1 geometry optimizations indicated a tendency for one intramolecular hydrogen bond with the carbonyl carbon of the acetyl group, favouring *E* configuration and conjugation of the acetyl group with the double bond [20].

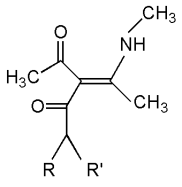

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Figure 4

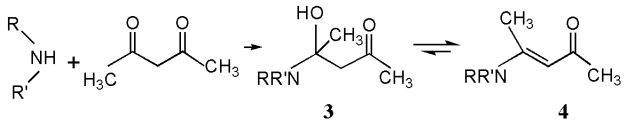
Preparation of Enaminoketones.

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 most direct route for the synthesis of enamino compounds is the condensation of a primary amine and a

1,3-diketone or 3-ketoester [1,2,21]. The reaction is usually facile when uncrowded primary amines are involved. Aromatic or hindered amines reacted more sluggishly and necessitate azeotropic removal of the water formed [2]. Depending on the basicity of the amine and the steric environment of both the keto compound and the amine, equilibrium may exist in such way that it may become necessary to trap the water formed in order to shift the equilibrium towards the enaminone [2]. In addition, enaminones can be prepared through various other methods.

Synthesis of Enaminones and Enaminoester Through Condensation and Addition Reactions.

Chemical and physical activation methods, such as BF_3 catalysis, heterogeneous clay catalysis and microwave irradiation have been proposed in order to improve the chemical yield of enaminone. The synthesis of enaminoketone **4** from the condensation of bulky amines with ethyl acetoacetate or 2,4-pentanedione (Figure 5) can be activated either by high pressure or catalysis by ytterbium triflate. The reaction can simply be depicted as a sequence of an addition reaction followed by elimination of a molecule of water. The method is limited by the kinetic competition between the formation of the intermediate aminoalcohol **3** and the dehydration step [22].

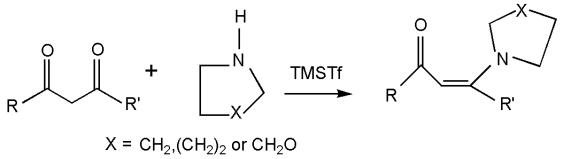


3 **4**

R= *n*-Pr, Ph, *n*-Bu, *i*-Bu
R'= H, Me, *n*-Bu, *i*-Bu

Figure 5

Enaminones **6** were synthesized in high yields (70-90%) by the reaction of β-diketones **5** and secondary cyclic amines in the presence of trimethylsilyl trifluoromethanesulfonate (TMSTF) as an activator (Figure 6). In the presence of TMSTF, the yields of the enaminones are increased considerably as compared to yields obtained without TMSTF [23]. It is not clear how TMSTF activates the reaction, but one possibility involves complexation of TMSTF with one of the carbonyls of the diketone **6**, making the carbonyl carbon more electrophilic and therefore more susceptible to nucleophilic attack by the secondary amine [23].

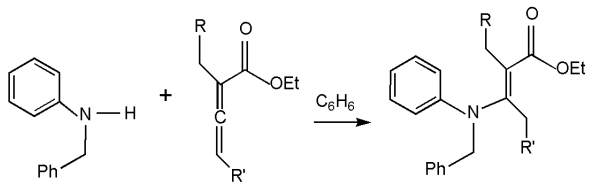


X = CH_2,$(CH_2)_2$ or CH_2O

5 R= Ph and R'= Ph, Me **6**

Figure 6

Michael addition of *N*-benzylaniline to conjugated allenic compounds **7** in refluxing benzene led to (*E*)-β-enaminoesters **8** (Figure 7) with a moderate to good yield. The experimental and molecular modelling results clearly showed that Michael addition of amines on allenic esters was kinetically controlled [24].

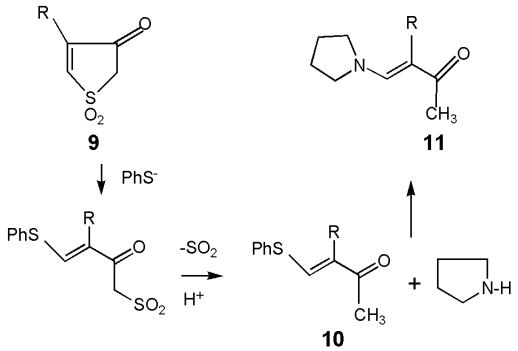


7 **8**

R=R'= CH_2Ph, *n*-Bu

Figure 7

Thiophene-1,1-dioxide **9** are very reactive, being sensitive to acidic and basic conditions. Heating a solution of **9** and benzenethiol in toluene under reflux, in the presence of a catalytic amount of pyridine, proceeded with extrusion of sulfur dioxide and formation of a 5:1 mixture of (*E*)- and (*Z*)-4-phenylthiobut-3-en-2-one **10**. The ratio of stereoisomers was determined from the ^{1}H NMR spectra by the vicinal coupling constants of the olefinic protons. Amines reacted readily with the ketones **10** affording high yields of the corresponding enaminones **11** (Figure 8), exclusively as the *E*-isomers according to the ^{1}H NMR spectra [25].



9 **11**

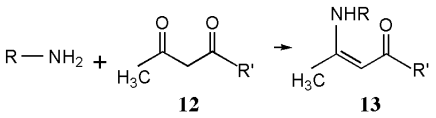
10

R= H, Me

Figure 8

Enaminones **13** were prepared from β-ketoester or 1,3-diketones **12** and primary amines in water as solvent (Figure 9). The probable explanation for the formation of enaminones in water is their tautomeric forms (A and C –

Figure 3) associated with the hydrogen bond. Enaminones of all types exist predominantly in the carbonyl form A and are stabilized by the contribution of the zwitterionic form (C – Figure 3) which can be solvated by water preventing hydrolysis of the formed enaminone. When the enaminone is formed, it is stabilized by resonance, blocking the formation of other products [26].

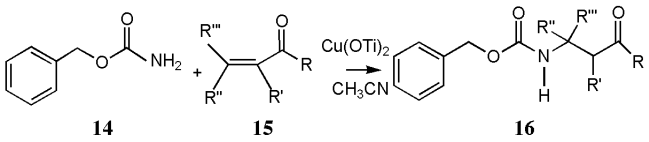


12 **13**

R= -OCH_2CH_3, Me
R'= -CH_2CH_3, Ph, -CH_2CH_2OH, $CH_2CH{=}CH_2$

Figure 9

The conjugate addition of benzyl carbamate **14** to α,β-unsaturated ketones **15** catalysed by Cu (II) – $Cu(OTf)_2$ complexes, leads to β-aminoketones **16** bearing a benzyloxy carbonyl moiety (Figure 10), which can easily undergo further conversions using well-established protective group chemistry [27].



14 **15** **16**

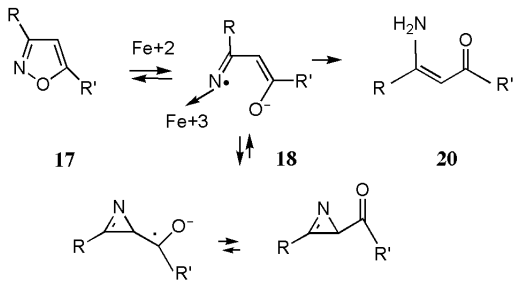
R=R'=R"= H, Me
R'"= CH_3CO, PhCO

Figure 10

Synthesis of Enaminones Through Ring-opening of Isoxazoles.

Isoxazoles are generally considered as useful synthons in organic synthesis, and 5-alkyl or 5-aryl isoxazole in the presence of iron dichloride, as catalyst, undergo reductive cleavage to enaminoketones [21,28]. Reduction of isoxazoles gave enaminoketones as the only products. The metal cation coordinates the nitrogen atom of the isoxazole ring **17**, giving a complex, which subsequently undergo NO bond cleavage by one-electron transfer from the metal to give the radical anion **18**, which is in equilibrium with **19** (Figure 11). When R' is an alkyl or aryl group, isoxazole does not isomerize to azirine, but undergos reductive cleavage to the enaminoketone **20** [28].

Five enaminones **23** were obtained from the reaction of 2,4,4-trimethyl-2-oxazoline anion **22** with ethyl acetate, ethyl benzoate, ethyl cyclohexanoate, ethyl hexanoate and ethyl-*p*-methyl benzoate **21**, respectively (Figure 12). All five enaminones were found to have an extensive π elec-



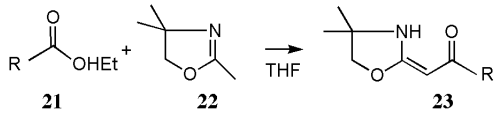
17 **18** **20**

19

R= Ph, *p*-NO_2-C_6H_4, *p*-MeO-C_6H_5
R'= -OMe, -NMePh, -NMe_2

Figure 11

tron delocalization and to have the same configuration where the double bond is trapped by an internal hydrogen bond between the NH and the C=O. The double bond is stabilized in the configuration *E*, due to the internal hydrogen bond, either in the solid state or in non-polar solvents. From the analysis of bond orders, ^{13}C chemical shifts, and C=O, C=C stretching frequencies, it was possible to detect an extensive delocalization of the lone electron pairs of the enaminone nitrogen and oxygen atoms over the adjacent vinyl and carbonyl π sistem [29].



21 **22** **23**

R= Me, Ph, cyclohexyl, *n*-pentyl, *p*-tolyl

Figure 12

Several enantiomerically pure β'-hydroxy-β-enaminoketones were prepared from the corresponding isoxazolic carbinols, which were obtained by enzymatic kinetic resolution of the racemic β-hydroxy-isoxazoles catalyzed by commercial lipases, such as, *Pseudomonas cepacia* lipase, *Porcine pancreatic* lipase, *Candida cylindracea* lipase, *Candida antarctica* lipase and *Aspergillus niger* lipase [4,30]. The enzymatic transesterification of racemic alcohols was studied with respect to the influence of experimental variables such as the enzyme used, the acylating agent or the solvent on the enantioselectivity of the reaction. Hydrogenation, using Pd/C of the optically pure isoxazolic carbinols (*S*)-**24**, yielded the β-hydroxy-β-enaminoketone (*S*)-**25** without racemization of the stereogenic center. When the same reaction (Figure 13) was applied to (*R*)-**24**, the enaminoketone (*R*)-**25** was also obtained [30]. A series of long-chain compounds containing the β-enaminone functionality were prepared in yields ranging from 71 to 88% from their corresponding long-chain 3,5-disub-

stituted isoxazole precursors utilizing a Raney nickel-catalyzed reductive ring-opening procedure [31]. These multifunctional compounds were subsequently hydrolyzed under mild acidic conditions (pH 4 – 5) to give their corresponding long-chain β-diketones in yields ranging from 79 to 98%. Long-chain β-diketone compounds are known to be relatively common constituents of some plant waxes [31]. A series of optically active β-enaminones had been prepared regio-and-stereoselectively from primary and secondary amines [pyrrolidine, cytisine, salsoline, 2-amino-1-(4-nitrophenyl)-propane-1,3-diol and (+)-3-carene-derived-β-chlorovinylketone] [32].

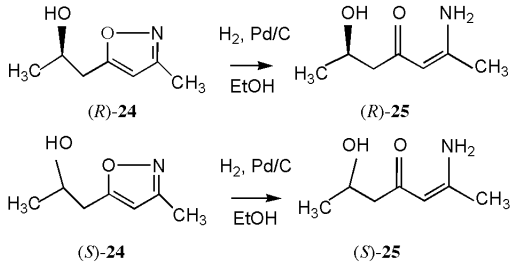
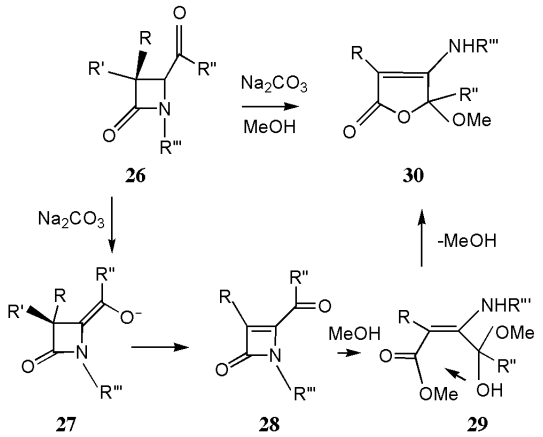


Figure 13

Miscellaneous.

Enaminones derived from tetronic acid are valuable synthetic intermediates for the construction of biologically active nitrogen heterocycles through aza-annulation reactions with acrylate derivatives [33]. The reaction of compounds **26** with Na_2CO_3 in methanol at room temperature, smoothly gave the corresponding substituted cyclic enaminones **30** (Figure 14). The formation of compounds **29** may be rationalized through a tandem E1cβ-elimination-rearrangement process of the enolate **27** generated initially, followed by ring opening of the resulting highly strained 2-azetinones **28**. Further intramolecular transesterification of the resulting hemiacetal enaminoester **29** gives enamine lactones **30** [33].



R= Et, Me, Cl, H
R'= Br, Cl, OPh
R"= H, Me, Ph
R'"= PMP, propargyl

Figure 14

The enaminones **32** were prepared by Eschenmoser sulfide contraction of thiolactam **31** with bromoacetonitrile, ethyl bromoacetate and phenacyl bromide (Figure 15), respectively. The preferred geometry of these types of enaminones appeared to depend on whether the nitrogen atom was secondary or tertiary. Secondary enaminones had been shown to exist in the *cis*-s-*cis* configuration, which allowed intramolecular hydrogen bonding resulting in a very stable six-membered ring. Tertiary enaminones were shown to exist in the *trans*-s-*trans* conformation. Comparison of ^{1}H NMR data with literature values showed that enaminones **3 2** were obtained as the *E*-isomers [34].

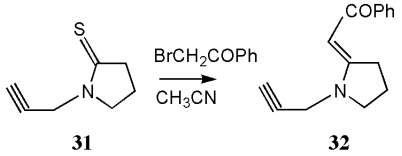
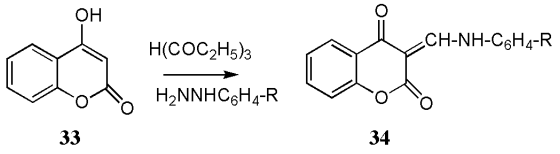


Figure 15

Reaction of 4-hydroxycoumarin **33** with ethylorthoformate, phenylhydrazine and *p*-tolyl-hydrazine yielded the anilino-methylene chromandiones (enaminoketone) **34**, which indicated a reductive N-N bond cleavage to aniline and ammonia under mild conditions (Figure 16) [35].



R= 3-MePh, CONHPh, Ph, Me

Figure 16

Schiff bases derived from tryptophan methyl ester **35** reacted with differently substituted electron-rich siloxy dienes **36** in a domino Mannich-Michael process in the presence of achiral or chiral boric acid and gave enaminones (vinylogous amides) **37** and **38** (Figure 17). In this sequential transformation the silylenol ether of the diene attacked the imine first and gave rise to a vinylogous ester which cyclizes by conjugated attack of the amine on the carbonyl group [36].

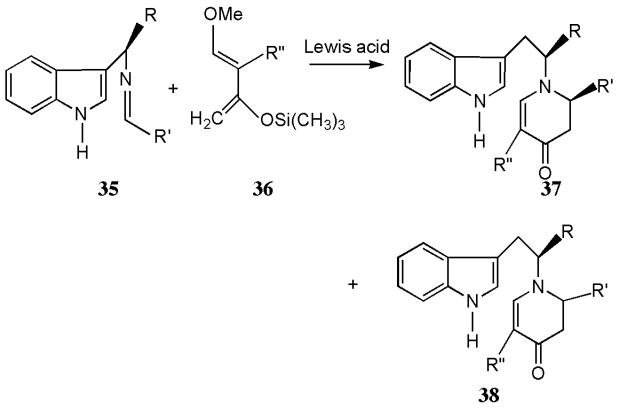


Figure 17

E,Z β-chloroacroleine derivatives **39** reacted with secondary amine to produce enaminoketone **40** (Figure 18). Only the *E* diastereoisomer was formed. Chloroacroleines are easily obtained by a Vilsmeier reaction [37].

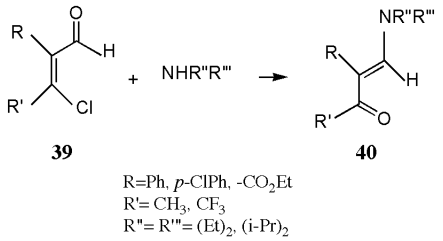


Figure 18

5-Hydroxytricyclodecadienone **41** undergoes a dynamic kinetic resolution to tricyclic enaminoketones **43** applying prolinol **42** or its methyl ether as chiral mediator. This approach, which constitutes an asymmetric desymmetrization of Diels-Alder adduct is an attractive alternative for the existing enzymatic methodology to obtain enantiopure tricyclodecadienones (Figure 19). In addition, the tricyclic enaminoketones **43** are interesting structures as they may possess pharmacological activity and furthermore they act as conceivable synthons for aminocyclopentenoids and aza-cubanes [38].

Irradiation of β-aminopropiophenones **44** in methanol and in the presence of oxygen led to the formation of 2-aminocyclopropanols **45**, which undergo oxidative ring opening and β-aminovinyl aryl ketones **47** are formed as the main photoproducts. The stereoselectivity of the cyclopropanol formation was found to be highly dependent on α- or β-substituents on the alkyl chain of the β-aminoketones. Substituents at the α- or β-position of **44** determine

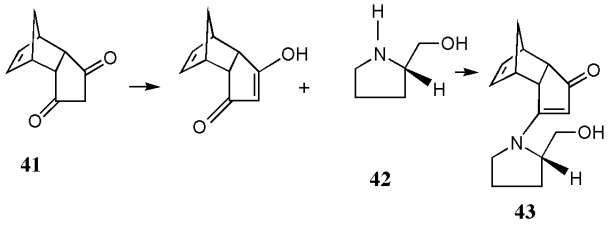


Figure 19

the stereoselectivity of the photocyclization presumablely due to repulsive interaction during the ring closure of the intermediate 1,3-hydroxybiradicals [39]. The enaminones **47** are formed by C(1)-C(2) ring opening of the 2-aminocyclopropanols **45** and subsequent reaction with oxygen (Figure 20). The formation of enaminones reflected the reactivity of **46** towards oxygen and in the case of an aryl group at the C(2) ring carbon, the regioselectivity in ring opening probably is due to the localization of the excitation energy [39].

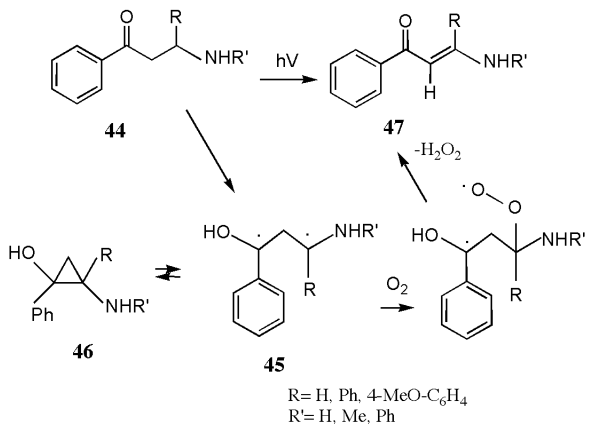


Figure 20

The introduction of an alkyl side chain containing a hydroxyl function at the α' or γ-position of a 1,3-diketone represented an important synthetic goal since the added functionality would increase the synthetic scope of the enaminones. Reaction of α'-trimethylsilyl enaminones resulted in a stereoselective synthesis of α',β'-unsaturated enaminones. The stereochemistry of the new double bond depends on the reaction time. The most relevant feature of the reaction is the prevalent formation of the *cis* isomer [40]. The reaction of secondary α-ketoenamines **48** with dibenzoyldiazine (DBD) furnished exclusively the corresponding enamine type adducts **49**, which rearranged in acidic medium to the more stable enaminone isomers **50** (Figure 21) [41].

Aldimines of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine **51** reacted with 1-methoxy-3-trimethylsilyloxybuta-

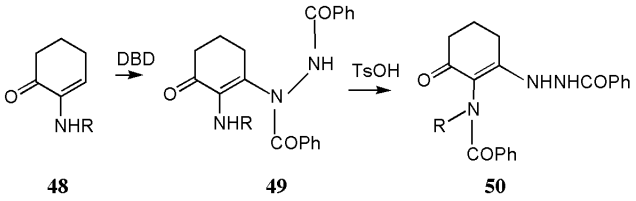


Figure 21

1,3-diene **52** in a Mannich-Michael condensation reaction sequence and gave 2-substituted-*N*-galactosyl-5,6-dehydropiperidin-4-ones **53** with high diastereoselectivity. The X-ray analysis of **53** proved (*R*) configuration of the major diastereomer (Figure 22). Despite their low reactivity, these enaminones can be converted into chiral 2,6-disubstituted piperidinones with high stereoselectivity by reaction with organo-cuprates in combination with hard electrophiles [42].

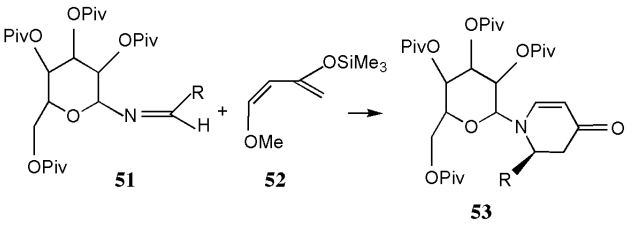


Figure 22

Condensations of the *N*,*N*-dibenzyl-α-amino esters with the anion of acetonitrile, yielded compound **54**, which was followed by the addition of a Grignard reagents and afforded rapid access to the peptidomimetic α-amino enaminones **55** in one pot from the esters. The use of methyl and phenyl Grignard reagents gave enaminones **55** (Figure 23) with an asymmetric center adjacent to the carbonyl. The enantiomeric purities and yields for the isolated enaminones **55** were excellent [43].

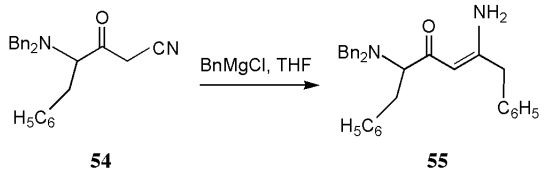


Figure 23

The two-step replacement of a vinylic β-hydrogen in an α,β-unsaturated ketone by an unsubstituted amino group can produce an enaminoketone. Methoxyamine has been found to be a highly efficient aminating agent not only for nitroolefins, but also for 1,3-diaryl-2-propen-1-one. The base treatment of β-methoxyaminoketones gave enaminoketones and/or aziridineketone with high selectivity depending on the base and solvent use. The use of ^{t}BuOK in THF or DMF predominantly gave enaminoketone. The high basicity, which depended on the combination of the bases and the solvents, was needed to obtain enaminoketones with high selectivity, since ^{t}BuOH was favored over NaOMe or KOH, and the relatively polar aprotic solvents were preferable to non-polar or protic solvents in this system [44]. The amination of the α,β-unsaturated ketones **56** with methoxyamine followed by treatment of intermediate **57** with ^{t}BuOK in DMF furnished the corresponding enaminoketones **58** (Figure 24) [44].

Reaction of α and β-ionones **59** with the Vilsmeier reagent

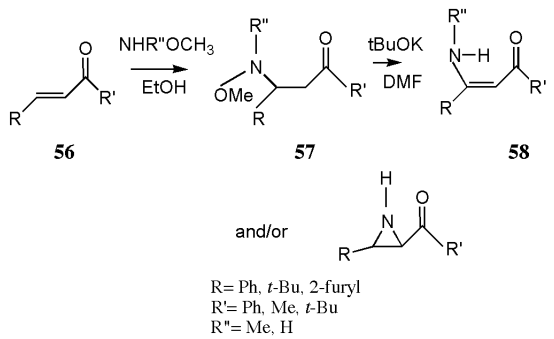


Figure 24

$(R_2N{=}CHCl)PO_2Cl_2$ afforded the unexpected enaminones **60** along with the expected chloro derivatives **61**, which come from the expected Vilsmeier-reaction course (Figure 25). This one-pot reaction opens up new possibilities for the synthesis of stable enaminones, which, in turn, could be very useful key intermediates to synthesize promising derivatives. These enaminones can be used as key intermediates in the synthesis of synthetic retinoids [45].

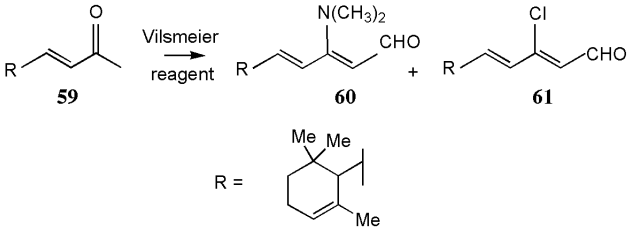
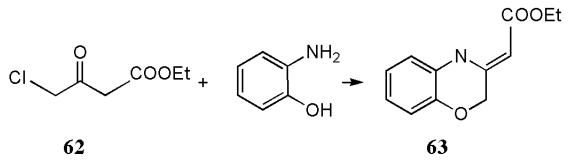


Figure 25

Enaminones are widely employed in the synthesis of heterocycles, however heterocyclic enaminones and their use

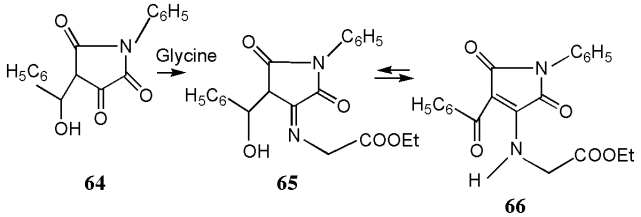
in the synthesis of more complex systems have been less studied. The reaction of the primary amines with ethyl-4-chloroacetate accompanied by intramolecular displacement of the chlorine atom by the other heteroatom (O, S or N) of the amino reagent, is a very useful methodology for the preparation of heterocyclic enaminones in high yield. The reaction between chloroacetylacetate and aliphatic or aromatic 1,2-aminoalcohols, 1,2-aminothiols or 1,2-diamines, yielded in one pot six-membered 1,4-heterocyclic systems containing the enaminone moiety. The rigidity imposed by the benzene ring of the aminophenol and its higher nucleophilic character accounts for the cyclization in this case [46]. The reaction of compound **62** with *o*-aminophenol and some drops of triethylamine gave ethyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-ylidenacetate **63** containing the enaminone moiety (Figure 26) in 93% yield [46].



62 **63**

Figure 26

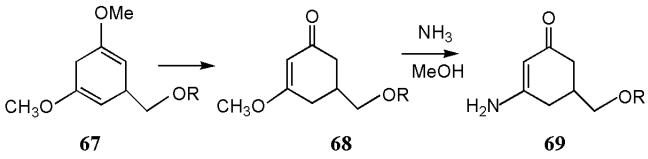
In the reaction of 1-phenyl-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione **64** with glycine ethyl ester hydrochloride, carried out in boiling ethanol, condensation unexpectedly occurred at C-3 and two tautomeric forms (keto-enamine **65** and enol-imino **66**) were obtained (Figure 27). The condensation of compound **64** with bases can take place either at C-6 or C-3 depending on the solvent used. When the reaction of **64** take place at C-6, the two tautomers are formed at the same ratio, whereas the condensation at C-3 gives a product for which the equilibrium is shifted towards the enaminone form. ^{1}H NMR data showed that the keto-enamine form predominated at equilibrium (76%) [47].



64 **65** **66**

Figure 27

A convenient method for the synthesis of a series of butyrophenone quinoline derivatives, which were potential CNS agents, includes the preparation of 3-amino-5-methoxymethyl-2-cyclohexen-1-one a potentially useful synthon for the synthesis of other β-substituted cycloalkanones with fused heterocycles containing N as practical ambident nucleophiles [48]. Methylation of hydroxyl group in 1,4-dihydro-3,5-dimethoxy benzyl alcohol, followed by mild acidic hydrolysis of the resulting enolether **67** provided the β-methoxyenone **68**. The ammonolysis of β-methoxyenone **68** in methanol afforded the enaminone 3-amino-5-methoxymethyl-2-cyclohexen-1-one derivative **69** (Figure 28) [48].

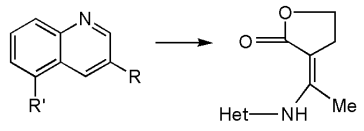


67 **68** **69**

R= Me, H

Figure 28

The synthesis of the tricyclic derivatives of quinoline or isoquinoline possessing an additional pyridinic ring, which were potential antimalarial agents, is focused on the use of heterocyclic enaminones as synthetic intermediates, which can then undergo regioselective heterocyclizations [49]. Treatment of the different aminoquinolines **70** with 2-acetylbutyrolactone in refluxing toluene with a catalytic amount of *p*-toluene sulfonic acid gave the corresponding enaminofuranone **71** in moderate to good yield (Figure 29) [49].



70 **71**

R=R'= NH_2, H
Het = 3-quinolinyl, 5-quinolinyl, 6-quinolinyl

Figure 29

The reaction of halogenated quinones **72** with a variety of secondary amines in the presence of acetaldehyde proceeded *via* formation of enamines **73** and produced mono quinonic enaminones **75**. The reaction proceeded *via* formation of intermediate **74**, which cyclized to produce the mono quinonic enaminones **75** (Figure 30) [50].

The reactions of the α-iodoenone **76** with mono- or dimethylamine consisted in the substitution of the ethoxy group of enone by amine moieties producing the corresponding α-iodoenaminones **77**. The N-monosubstituted

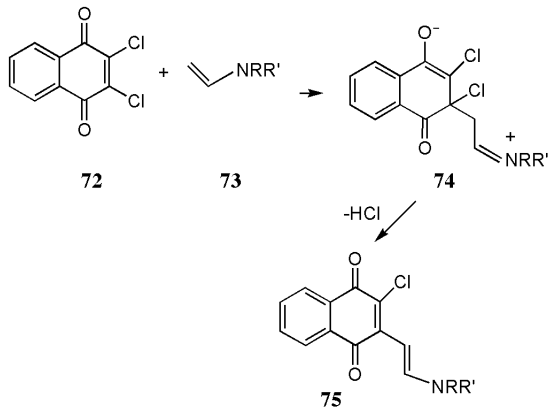


Figure 30

enaminones **77** exist in low polarity solvents predominantly in a *Z* configuration (*cis* position between the trifluoroacetyl and the amino groups) due to C=O—HN hydrogen bonding (Figure 31) [51].

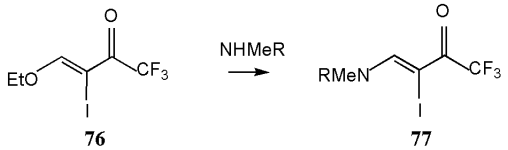


Figure 31

The reaction of 2,6-dimethyl-phenyl isocyanide **78** with dimethyl acetylene dicarboxylate **79** was trapped by *N*,*N*'-dimethylbarbituric acid **80** and afforded the isomeric products **83** and **84** in a nearly 1:1 ratio and an overall yield of 85%. It is reasonable to assume that compounds **83** and **84** resulted from an initial addition of the aryl isocyanide to the acetylenic ester resulting in the formation of intermediate **81**. The direct addition of the enolate anion to the positive ion **81**, produced the heterodienes **82** and these addition products undergoes an imine to enamine tautomerism to generate the enaminone system [52]. Dynamic NMR effects are observed in the ^{1}H NMR spectra of isomeric products and are attributed to restricted rotation around the aryl-nitrogen single bond and polarized carbon-carbon double bond. The *E* configuration is based on the chemical shift of the olefinic proton. (Figure 32) [52].

The regioselective preparation of enaminones **86** had been developed from 1,3-diketonatoboron difluorides **85** (Figure 33). This methodology is of particular use, especially when one has to deal with a low boiling amine or an

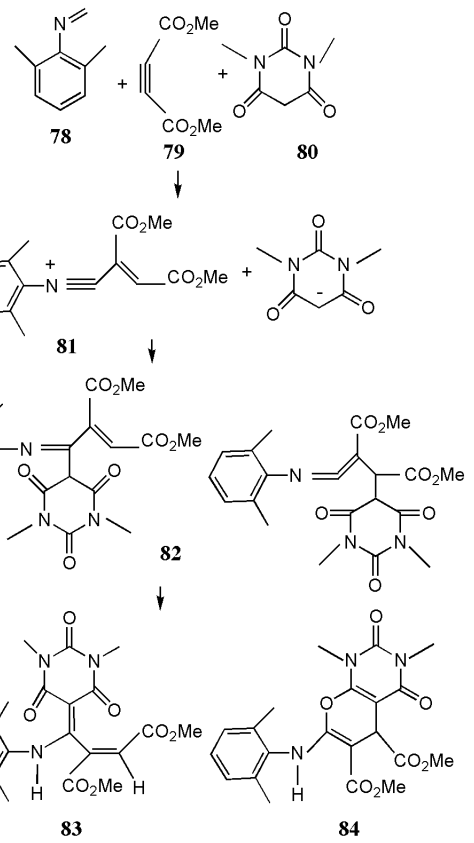


Figure 32

amine containing other nucleophilic functional groups. The reactions proceed smoothly under mild reaction conditions producing enaminones in high yields. Initially, 1,3-diketonatoboron difluorides were prepared in good yields by treatment of the corresponding 1,3-diketones with BF_3•OEt_2 at room temperature [53]. The reaction of cyclic, acyclic and α-chloro-substituted-β-dicarbonyl compounds with amines or their corresponding ammonium acetates was carried out using K-10 as solid support and a domestic microwave oven as the radiation source to give β-enamino carbonylic compounds in good yields [54].

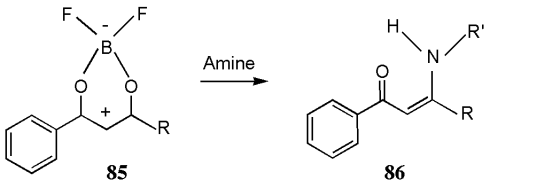
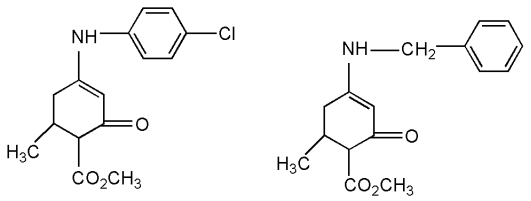


Figure 33

Medicinal Properties of Enaminones.

Due to the variety of nucleophilic and electrophilic sites in the enaminone system, enaminone esters possess great potential as reaction intermediates and medicinal compounds. Preliminary evalution of the enaminone esters revealed a histaminergic effect, uterine relaxant properties and anticonvulsant activity [55]. Enaminones are widely used synthons in organic synthesis and their structural features are part of anticonvulsive and histaminergic systems [56]. Terpenoid-based chiral enaminones are considered to be potential biologically active compounds (enaminones comprising biologically active amines are regarded as prodrugs) as well as ligands for diastereoselective synthesis [57]. A series of enaminones has been synthesized from cyclic β-dicarbonyl precursors, which were condensed with morpholine, pyrrolidine, penethylamine, hydrazine substituted benzyl amines and substituted anilines and several of these compounds exhibited potent anticonvulsant activity with a remarkable lack of neurotoxicity [58,59]. Methyl-4-(*p*-chlorophenylamino)-6-methyl-2-oxocyclohex-3-en-1-oate **87** and methyl 4-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-oate **88** are two anticonvulsant enaminones (Figure 34) [58-60]. Enaminones with anticonvulsant activity, in animal tests exhibited anticonvulsant activity similar to phenytoin and carbamazepine, which are known and used for their biological activity [61].

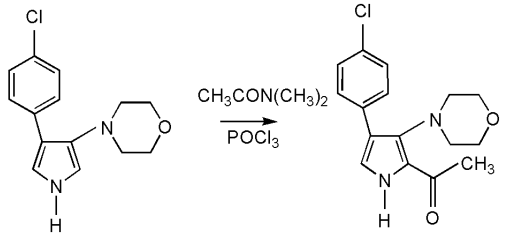


87 **88**

Figure 34

The ultraviolet (UV) spectra of enaminones were determined in acidic, alkaline and neutral media and compared to their anticonvulsant activities. The UV spectra of the enaminones had hypsochromic shifts in acidic media in comparison with neutral media. Generally, a small hypsochromic shift occurred in alkaline media when compared to neutral solutions of the enaminones [62]. Tertiary enaminones absorbed UV light at longer wavelength than the secondary enaminones in acidic, neutral and alkaline media. The tertiary enaminones displayed absorption at the higher end and secondary enaminones towards the lower end of the UV wavelength range 292-315 nm in aqueous media. Tertiary enaminones that were devoid of the NH proton were found to be uniformly inactive in a mouse model of electroshock seizures, while some secondary enaminones had anticonvulsant activity. Thus the NH group of secondary enaminones is very important for anticonvulsant activity. In addition, the para-substitution on the phenyl group in some enaminones result in higher molar absorptivity (epsilon) values that enhance the biological activity [62]. These results indicate that the anticonvulsant activity of enaminones is not due to electronic effect alone, but is probably due to a combination of factors including electronic and steric effects, lipophilicity, and hydrogen bonding [63-65].

Among substances reported in the literature to possess anticonvulsant activity a class that could have structural similarity to the aroyl (aminoacyl) pyrroles was the series of *N*-aryl and *N*-benzyl enaminones **90** (Figure 35). The 2-acetyl-4-(4-chlorophenyl)-3-morpholinopyrrole **90** was synthesized by acylation of **89** with dimethylacetamide. The enaminones with a keto group, such as **90** are very active as anticonvulsant [66,67]. Substituted aniline enaminones displayed exceptional anticonvulsant activity [68]. For conduction of biological studies to anticonvulsant activity of enaminones in animals, a sensitive and selective high-performance liquid chromatography-mass spectrometry (LC/MS) was developed for the determination of the selected enaminones in rat serum [69]. The potential anticonvulsant activity of the enaminones was attempted to discern the possible role of metabolites as the active/co-active entities of the esters of the enaminones. The most active compound was ethyl-4-(4-chlorophenyl-1)-amino-6-methyl-2-oxocyclohex-3-ene-1-carboxylate, which displayed an ED50 of 16.7 mg/Kg and pharmacokinetic evaluation of this compound in rats using LC/MS analysis, unequivocally provides evidence that this compound is converted into the decarboxylated analogue in the brain and the urine [70].



89 **90**

Figure 35

Enaminones have been reported as having synthetic utility in pharmaceutical development, *e.g.* of cardiotonic compounds [71], $GABA_A$ – receptor agonists [72] and HIV protease inhibitors [73]. The biologically active

enaminones also include, the 2-alkylideneindole **91**, which has antiinflammatory potential [74-76], the fused polycyclic compound **92** (Figure 36), and a synthetic analogue of the duocarmycin class of antitumour agents [75,76]. However, the most important chemotherapeutic agents to contain an embedded enaminone component are without doubt the quinolone antibacterials. In particular, the fluorinated quinolones are amongst the most effective broad-spectrum oral antibacterial agents developed to date [76].

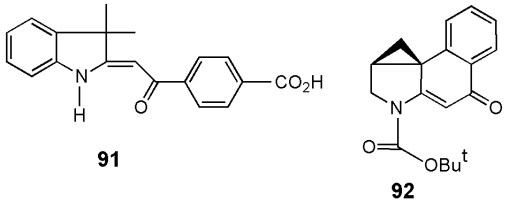


Figure 36

One-pot transformations of pyrrolidine enaminones **93** into 5-(3-aminopropyl)isoxazoles and the corresponding pyrazoles were achieved with hydroxylamine in an acetate-buffered solution and with hydrazine sulfate, respectively (Figure 37). The ring transformation sequence allowed simple access to heterocycles which are histamine analogues and both enaminones and heterocycles possess histaminergic activity [77,78].

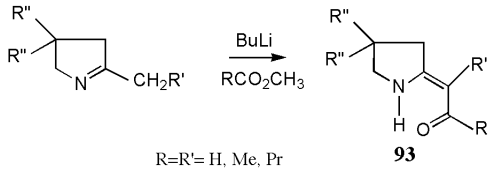


Figure 37

(-)-Multiflorine has an enaminone type conjugation on the A-ring, which is unusual in lupine alkaloids and produced a hypoglicemic effect when administered to mice with streptozotocin-induced diabetes [79, 80].

Reactions of Enaminoketones.

The reactivity of this system depends on the amine moiety and on the degree of substitution at the α or β positions [1-4]. Enaminoketones and esters are gaining increased interest, particularly cyclic-β-enaminoesters which are known as important intermediates for the synthesis of natural products [81]. The densely functionalised cyclic enaminones **94-97** (Figure 38) are suitable for a number of further synthetic transformations, namely hydrolisis to diones, reduction and condensation to fused heterocycles [82]. Benzyltrimethylammonium dichloroiodate was an efficient α-iodinating agent for enaminones [83].

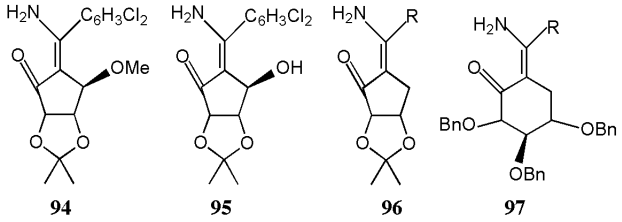


Figure 38

The use of β-acylated enamines (enaminones) has been explored in alkaloid synthesis. These readily accessible compounds can function both as nucleophiles and as electrophiles, their versatility in either case being extended by their ability to show ambident reactivity [81]. They are easily incorporated into structures that contain the gross skeletal features found in many alkaloidal systems, and offer ample opportunity for exploiting nuances associated with the control of diastereoselectivity and enantioselectivity [81,84]. The amphibian indolizidines are convenient targets for exploring and applying all these aspects of enaminone reactivity [84]. An efficient and modular synthetic route for the preparation of linked bis- and tris-(1,3,5-triaroylbenzenes) had been established in which an enamine-directed alkyne cross-cyclotrimerization is the key transformation [85]. The enaminonitrile [β-amino-β-(pyrid-4-yl)acrylonitrile] is an attractive starting material for the preparation of pyridine derivatives [86].

Reactions of Enaminones with Electrophiles

Reactions of enaminones with electrophiles can occur through eletrophilic attack on the α-carbon of enaminones. Diazoketones reacted with 4-(methylamine)-3-penten-2-one under thermal conditions. The reactions occurred through the ketene intermediate to form α-acyl-enaminoketones **2** (Figure 4) as the principal product, *i.e.*, a product of reaction at the Cα of the enaminone. The HOMO of the enaminones **2** corresponds to a π molecular orbital with the largest coefficients on the Cα and nitrogen atoms [3,17,18,19]. Cyclic enamino esters and enaminoketones were reacted with 5,7-dinitro-3-diazo-1,3-dihydro-2*H*-indol-2-one and gave bicyclic triazoles in good to excellent yields [3]. The reactions of carbethoxycarbene with several acyclic enaminones led to the unexpected formation of pyrroles and the pyrrole structure indicated that the initial step of the reaction mechanism occurred through an electrophilic attack of carbene at the α-carbon of enaminones leading to the net result of Cα-H insertion [3]. Quinone diazides were reacted with enaminones and produced azo-enaminones [3].

Primary, secondary and tertiary enaminones were reacted with bis-pyridine-iodonium(I) tetrafluoroborate [$I(Py)_2BF_4$] in methylene chloride at room temperature and gave the α-iodo-enaminones in almost quantitative yields [87]. The corresponding iodo-derivates **99** are obtained from the enaminone **98** (Figure 39).

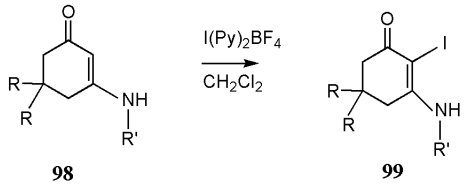


Figure 39

Upon reaction of 1-[hydroxy(tosyloxy)iodo]-2,2,2-trifluoroethane **101** with cyclic enaminones **100**, stable iodonium tosylates **103** were obtained. The reaction of trifluoroethyliodination followed by thermal decomposition of the iodonium tosylate constitute an iodination methodology for cyclic enaminones, in view of the fact that iodination at sp2 carbon α- to the carbonyl group of certain enaminones presents some difficulties [88]. Both products were obtained by column chromatography: iodo enaminones **102** together with their precursors 2,2,2-trifluoroethyl tosylate **103** (Figure 40).

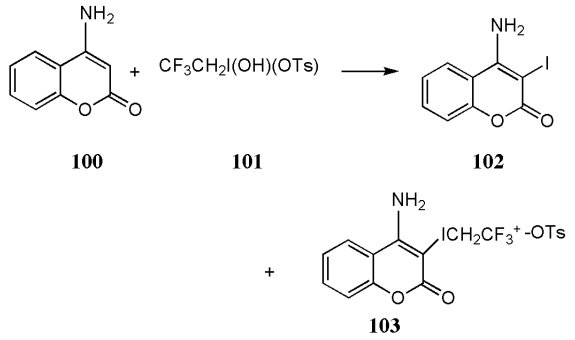


Figure 40

The regiochemistry of aza-annulation of enaminones with α,β-unsaturated acid chlorides bearing hydrogen atoms on the γ-carbon was reversed when triethylamine was used as mediator. Acylation may be performed through the aza-annulation of enaminones with α,β-insaturated acid chlorides or esters, which is a very efficient method for the formation of nitrogen heterocycles, such as piperidine, contained in alkaloids [89]. The aza-annulation of enaminone **104** is mechanistically interesting in that the enaminone is an ambident nucleophile, which can react at N or Cα position and the α,β-unsaturated acid chloride **105** is an ambident electrophile which can react at carbonyl group or Cβ carbon giving the intermediates **106**, which subsequently cyclize to give pyridine **107** (Figure 41) [89].

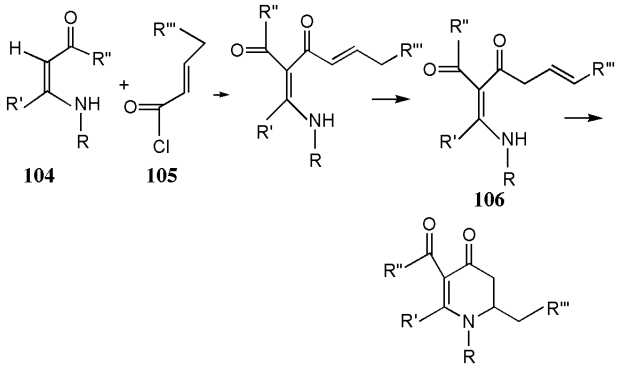


Figure 41

5-Amino-endo-tricyclo[5.2.1.0]-deca-4,8-dien-3-ones undergo a surprisingly effective regioselective halogenation using *N*-halosuccinimides under electrophilic conditions [90]. Most importantly halogenation of the C8 – C9 norbonene bound is not observed. Exclusive α-halogenation is observed treating tertiary enaminone of **108** with one equivalent of *N*-halosuccinimide (NBS) and this reaction gave single monohalogenated compound **109**. When two equivalents of NBS was used in dichloromethane a fast dibromination took place to afford α,γ-dibromo enaminone **110** in quantitative yield (Figure 42). These bridgehead halo substituted tricyclodecadienones are suitable synthons for β-functionalized cyclopentenoids [90].

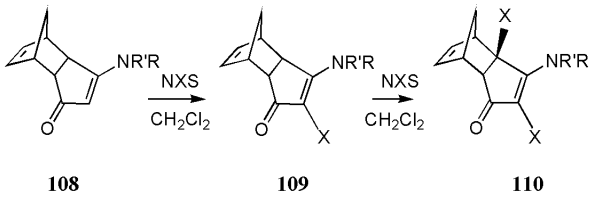
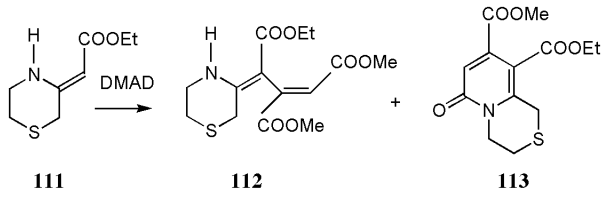


Figure 42

The Michael addition of heterocyclic enaminones to α,β-unsaturated carbonyl compounds, followed by aza-annulation represented a simple and efficient approach to the synthesis of 1,4-benzothiazines and thiazines [91]. The

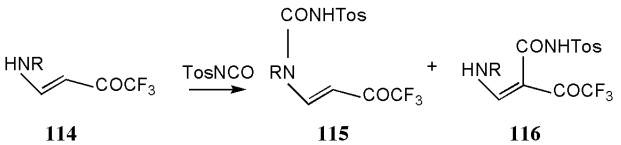
condensation and aza-annulation sequence was especially attractive when heterocyclic enaminones **111** were used in the reaction with dimethyl acetylene dicarboxylate (DMAD) and were found a mixture of the Michael addition product **112** (62%) and the cyclization product **113** (16%) (Figure 43) [91].



DMAD - dimethyl acetylene dicarboxylate

Figure 43

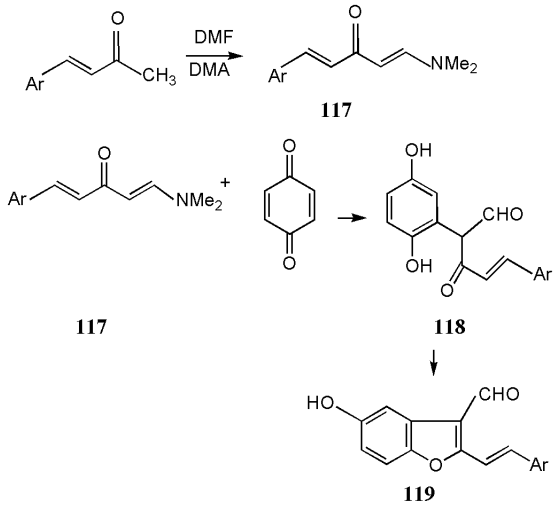
The electrophilic center of the sulfur atom of chlorosulfonylureas reacted with enaminones and provided the chromone-3-sulfonylureas. This reaction is applicable for the preparation of different substituted heterocyclic sulfonylureas [92]. The development the NH and αCH insertion reaction of the TosNCO into N-monosubstituted fluorinated enaminones, which was sensitive to reaction conditions: temperature, solvents and catalysts afforded the highly functionalized trifluoromethyl containing sulphonyl ureas and vinylogous sulphonylureas. The fluorinated substances can be utilized as practical building blocks for effective synthesis of bioactive fluorinated compounds [92]. The regioselectivity of the reaction depends on the temperature, the nature of the solvent and catalyst. High temperatures or basic catalysts direct in favour of NH insertion, while low temperatures direct the process in favour of αCH insertion [93]. N-Monosubstituted β-aminovinyl trifluoromethylketones **114** reacted with TosNCO and mixtures of ureas **115** and vinylogous sulphonylureas **116** were obtained (Figure 44) [93].



R= Me, *n*-Bu, *t*-Bu, Ph

Figure 44

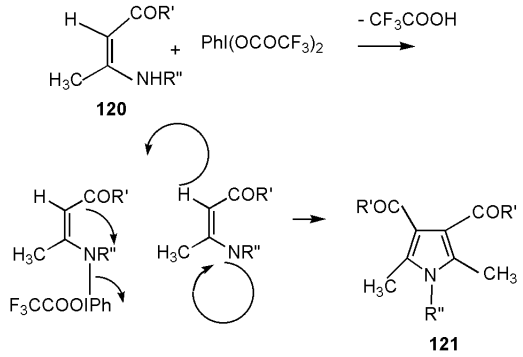
Condensation of 1-substituted-1-butene-3-one with dimethyl-formamide and dimethylacetal (DMF/DMA) afforded the enaminodienones **117** in good yield. No trace of the *Z*-form is observed, only the *E*-forms were isolated, as had been indicated from the coupling values for olefinic doublets. Several enaminodienones were used as precursors for synthesis of pyridines, pyranones and benzofurans [94]. These reactions occurred through initial attack of α-carbon of enaminodienones **117** on *p*-benzoquinone, yielding acyclic intermediate **118**, with subsequent cyclization exclusively into **119**, which is apparently thermodynamically more stable because of its extended conjugated double bond system (Figure 45) [94].



Ar= Ph,4-$OCH_3C_6H_4$, 2-furyl

Figure 45

A Tandem dimerisation-cyclocondensation of enaminones **120** with bis-(trifluoroacetoxy)-iodo-benzene provided an effective method for the synthesis of highly substituted pyrroles **121**, because bis-(trifluoroacetoxy)-iodo-benzene is a stronger oxidising agent and has a weaker nucleophilic group CF_3COO^-. A plausible mechanism of the

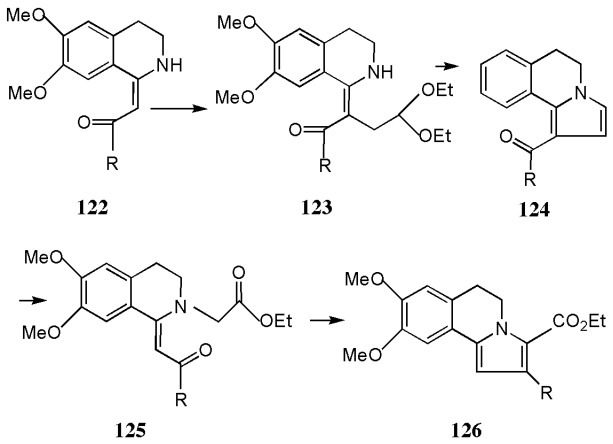


R'= Ph, Me
R"= Bn, Me, *p*-ClC_6H_4

Figure 46

reaction is analogous to the oxidation of the β-aminocinnamates with diacetoxyiodobenzene (Figure 46) [95].

Study of annulation reactions of enaminones with various one- and two carbon electrophilic synthons has yielded direct one-pot convergent routes to a variety of functionalized pyrrolo[2,1-α]isoquinolines and indolo[2,1-α]isoquinolines, and some of them may prove useful precursors for biologically important natural products possessing these structural frameworks [96]. The cyclocondensation of **122** with bromoacetaldehyde diethylacetal appears to follow the enamine reactivity pattern *via* initial C-alkylation to form **123** followed by intramolecular ring closure with elimination of ethanol to afford compounds **124**. However, the reaction takes a different course with more reactive ethyl bromoacetate involving N-alkylation of enaminones **122** followed by acid-assisted intramolecular Aldol condensation of the aminoacetate intermediate **125** and the formation of compounds **126** (Figure 47). The ambident reactivity of enaminones **122** toward bromoacetaldehyde diethylacetal and ethyl bromoacetate can be rationalized in terms of soft and hard electrophilic character of their bromine-bearing carbon atoms resulting in the attack by respective softer (C) and harder (N) nucleophilic terminus of **122** [96].



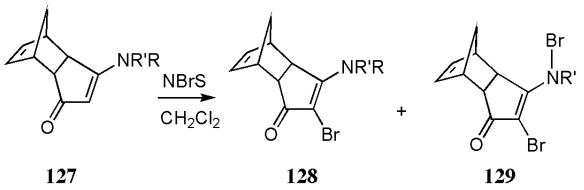
122 **123** **124**

125 **126**

R= Ph, Me

Figure 47

When enaminone **127** was treated with a slight excess of NBS (1.1 equivalent), two products were formed, namely, the expected α-haloenaminone **128** and a minor less polar compound identified as a α,N-dibrominated product **129** (Figure 48). Interestingly, the second halogenation did not occur on the norbonene double bond, but on nitrogen instead. This is quite surprising, as once the monohalogenated product **128** is formed, the electron density on the nitrogen of the enaminone moiety will be considerably reduced due to the electron withdrawing nature of the bromine. Hence, the second bromination might be expected to take place on the norbonene double bond [97].



127 **128** **129**

R = H; R'= benzyl, cyclohexyl, *n*-pentyl

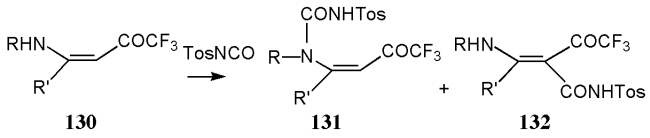
Figure 48

The regioselectivity of N-tosylcarbomoylation of N-monosubstituted β-aminovinyl trifluoromethyl ketones depends on the structure of enaminones, the reaction temperature, the nature of solvent and catalyst [98]. N-monosubstituted trifluoromethyl containing enaminones exist as a mixture of *cis*- and *trans*-isomers, which obviously have different reactivity toward to TosNCO. Thus, the α-position of double C=C bond of the *cis*-isomer is more sensitive to electrophilic attack than nitrogen or oxygen atoms, which participated in intramolecular hydrogen bond formation, whereas in the *trans*-isomer, the nitrogen atom is most preferable to eletrophilic attack [98]. The effects of steric hindrance caused by a N-substituent (N-alkyl group) on the regioselectivity, results in decreased availability of the NH group of enaminones for electrophilic attack by TosNCO. N-Monosubstituted-β-amino-vinyl trifluoromethyl ketones **130** reacted with TosNCO not only at the α-carbon atom of the carbon-carbon double bond, but also at the nitrogen atom, and mixtures of two products, ureas **131** and vinylogous sulphonylureas **132** (Figure 49) were obtained in high yield [98].

The reaction of acyclic enaminones **134** with methoxymethylene Meldrum's acid **133** afforded C-adduct and/or N- adduct of enaminones in moderate to good yields. The regiochemistry of this reaction depends on the N-amino substituent of the enaminone. C-Adducts are obtained with NR_2 substituents (R = Alkyl) and N-adducts with the NH_2 group. Better results were obtained when dichloromethane was used as solvent instead of acetonitrile and with this modification N-adduct **135** and C-adduct **136** were obtained in a 2:1 ratio, respectively (Figure 50) [99].

Reactions of Enaminones with Nucleophiles.

Reactions of enaminones with nucleophiles can occur through nucleophilic attack on β-carbon. 4,5-Diarylisoxazoles **139** was efficiently prepared by submitting

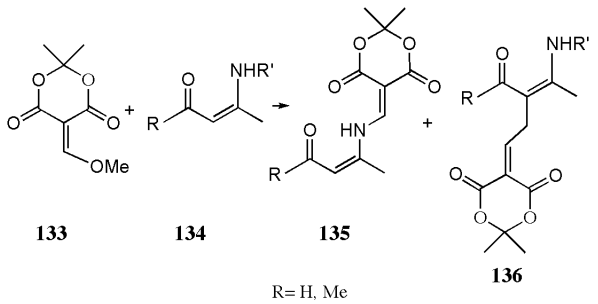


130 **131** **132**

R= H, Me, Et,*n*-Pr, *n*-Bu, -CH_2Ph
R' = H, Me, Ph

Figure 49

enaminones **137** readily obtained from deoxybenzoins, to oximation conditions (Figure 51). This conversion implies an uncommon amine group exchange reactions on β-carbon [100]. The mechanism proposed for the formation of the isoxazoles involved an amine exchange reaction in the first step. Subsequent nucleophilic attack of the so-obtained hydroxylamine on the carbonyl group to give the intermediate **138**, followed by elimination yielded the target heterocycle **139** [100].

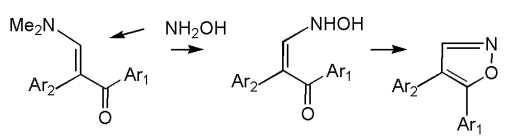


133 **134** **135** **136**

R= H, Me

Figure 50

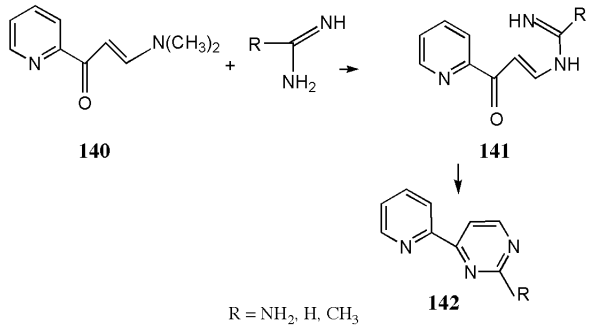
A simple and efficient synthetic method to polyaza heterocyclic structures containing 1,3-pyrimidine units was based on the enaminones with the appropiate carboxamidines. By this procedure several polyaza heterocycles have been prepared in good yields. The reaction of enamino-oxoquinoline **140** with amidines such as guanidine and formamidine occurred readily under basic conditions leading to pyrimidine **142** in high yields. One of the most important characteristics in the reactivities of the enaminones is the displacement of the N,N-dimethylamino groups by different nucleophiles [101]. One probable mechanism might be the attack of the amidine on β-carbon atom of enaminone to give **141**, which on subsequent intramolecular cyclisation followed by elimination of water yielded pyrimidine **142** (Figure 52) [101].



137 **138** **139**

Ar_1 = 3,4-$(MeO)_2$Ph; 2,3,4-$(MeO)_3$Ph
Ar_2 = Ph; 3,4-$(MeO)_2$Ph

Figure 51

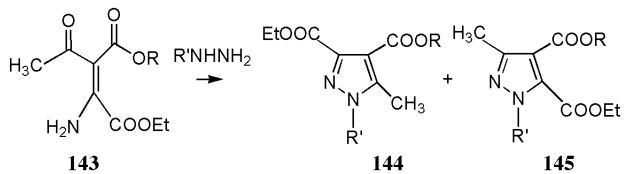


140 **141** **142**

R = NH_2, H, CH_3

Figure 52

β-Alkoxycarbonyl-β-enaminoketoesters **143** reacted with methyl, ethyl and phenyl hydrazine and gave two pyrazole *ortho*-dicarboxylic acid derivatives **144** and **145**. The two series of compounds showed similar analytical and ^{1}H NMR spectroscopic data that agreed with the structure of the isomeric pyrazole derivatives **144** and **145**, bearing two *ortho* ester groups. (Figure 53) [102]. The formation of these pyrazoles can be explained by a Michael type reaction in which the initial nucleophilic amino group attacks the β-carbon atom of enaminone with elimination of ammonia followed by intramolecular attack of the second amino group on the ketonic carbonyl group and subsequent ring closure [102]. In the reactions of α-acylenaminoketones **2** (Figure 4) with hydrazine reagents, the formation of isomeric principal pyrazoles and deacetylated pyrazoles formed by a deacetylation process, can also be explained by an initial Michael-type reaction [3,19,20].



143 **144** **145**

R= Me, CH_2Ph
R'= Et, Ph

Figure 53

Treatment of β-enaminones having modified carane and p-menthane skeletons with aryl- and alkylhydrazines

resulted in regioselective formation of stable pyrazolinols or *N*-substituted pyrazoles depending on the nature of the substituent at the hydrazine nitrogen. The reaction of enaminone **146** with arylhydrazines was found to require quite rigid conditions and proceed with the formation of both positional isomers **147** and **148** (Figure 54) [103].

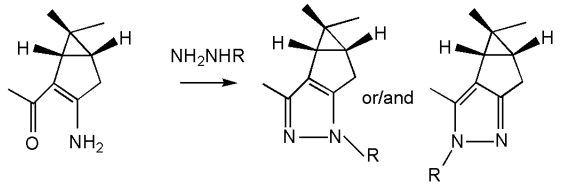


Figure 54

Ethyl-3-amino-3-(*p*-phenyl-substituted)-2-propenoates **149** were reacted with hydrazines and methylhydrazines using solid support K-10/ultrasound and homogeneous media (reflux in ethanol or dichloromethane) yielding pyrazole **150** and **151** (Figure 55). The regiochemistry of the cyclization showed dependence of the reaction conditions employed as well as the substituent in the aromatic ring [4,104,105].

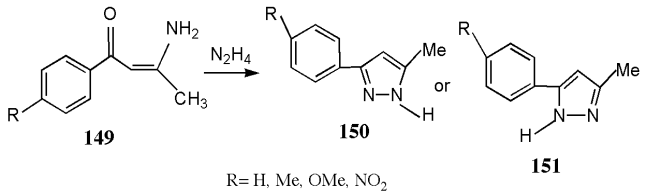


Figure 55

The condensation of bis(enaminone) **152** with 2,2'-bipyridil-6-carboxamidines under basic conditions, provided the formation of **153**, creating an oppportunity to extend the number of heterocyclic units in the system (Figure 56). Using this procedure, several new, optically active polyaza heterocycles had been prepared in good yields, from enantiomerically pure *N*α-Boc-L-arginine as guanidine reagents [106].

4-(2-Pyridil)pyrimidines **155** had been synthesized in high yields, reacting enaminones **154** with the appropriate carboxamidine or guanidine under basic conditions (Figure 57) [107].

A series of *O*-(butylsilyloxy)-benzoylchlorides generated from the corresponding silyl esters were coupled with

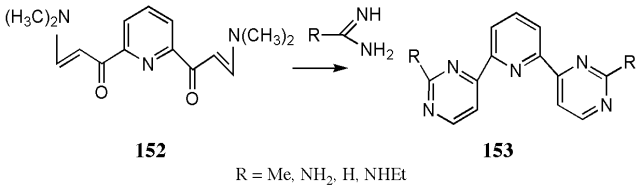


Figure 56

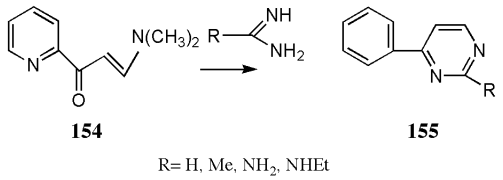


Figure 57

a range of terminal alkynes to afford the corresponding alkynyl ketones, which were converted to enaminoketones. The alkynones, when converted to enaminones and subjected to TBS deprotection, the system would prove to undergo Michael addition followed by elimination of secondary amine to exclusively yield benzopyrones [108]. Pure samples of the enaminoketones **157** were prepared by stirring an alcoholic solution of the alkynone **156** with secondary amine for two hours. These enaminoketones when refluxed with excess of diethylamine formed benzopyrones **158** (Figure 58) [108].

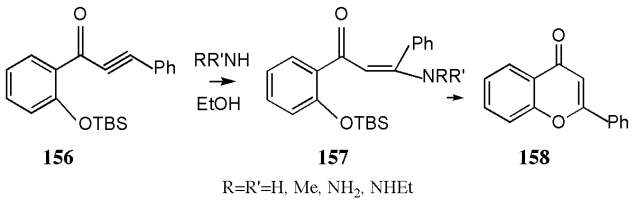


Figure 58

The identification of some intermediates of the reactions between β-aminoenones and malonitrile to give 2(1*H*)-pyridinones had been allowed to obtain valuable information concerning its mechanism [109]. These reactions began with a conjugated addition of the nitrile to the enone followed by elimination. The compounds thus obtained,

cyclize to nonisolable 2*H*-pyran-2-imine and afforded 2(1*H*)-pyridinones by ring opening to unsaturated aminoamides followed by cyclization (Dimroth-type-rearrangement). This process began with a conjugated addition-elimination of the malonic dinitrile to the β-enaminone **159** and gave the intermediate **160**. The reaction mechanism supposed the existence of an easily reversible equilibrium between the geometric isomers *Z* and *E* of **162** with respect to the double bond C2-C3. The opening of the iminopyrone **161** must lead to (2*Z*) **162**, but the configuration of the intermediates **162**, isolated and identified by X-ray, is 2*E* [109]. On the other hand, the formation of product **163** starting from **159** demands that the last process of the conjugated addition-elimination takes place in the isomer (2*Z*) **162**. The conversion of **160** in a 2*H*-pyran-2-imine intermediate **161** whose opening by action of a nucleohile afforded **162**, gave 2(*H*)-pyridinone **163** by cyclization from **162** (Figure 59) [109].

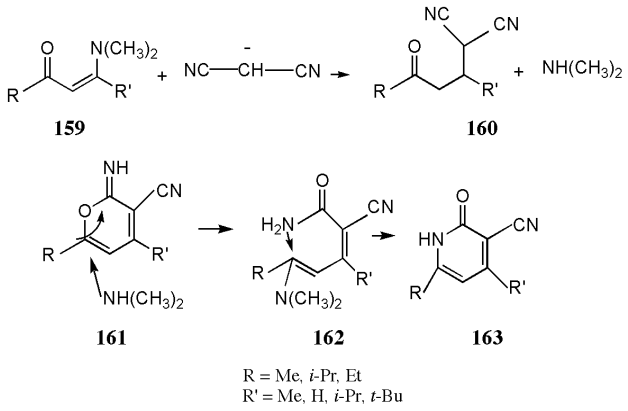


Figure 59

The tandem amine-exchange/heterocyclization of enaminoketones was successfully applied to the regioselective preparation of a series of 4,5 diarylpyrazoles by reaction of phenylhydrazine and several 3-*N,N*-(dimethylamino)-1,2-diaryl-propenones [110]. Enaminoketones **164** were reacted with phenylhydrazine and the corresponding *N*-phenyl-4,5-diarylpyrazoles **165** were obtained as the only isomers (Figure 60). A plausible mechanism involved an initial amine-exchange process.

The synthesis of chiral polyaza heterocyclic structures containing pyridines and 1,3-pyrimidine units is based on the reaction of the appropriate enaminones with optically pure carboxamidine derived from the commercially available (R)-(-)-myrtenal [111]. Condensation of enaminopyridine **166** with compound **167** gave the annelated (pyrimidyl)pyridine **168** (Figure 61).

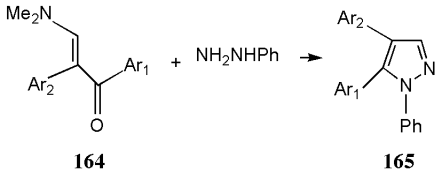


Figure 60

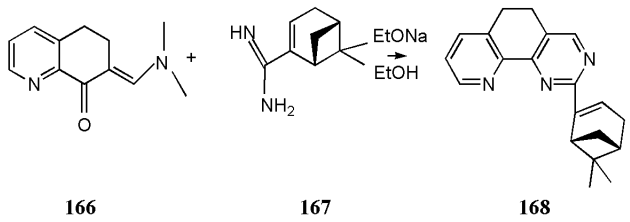


Figure 61

3-Acetylcoumarine was condensed with dimethylformamide dimethylacetal (DMF/DMA) to yield the enaminone **169** which reacted readily with benzamidine hydrochloride and afforded the 4-coumarinoyl pyrimidine **170** (Figure 62) [112].

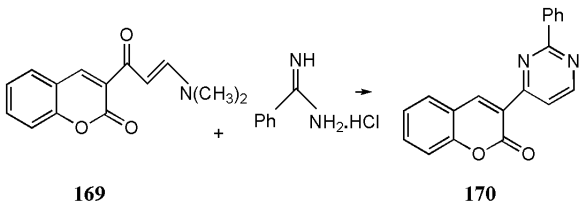


Figure 62

Introduction of trifluoromethyl groups into bioactive molecules is known to improve their therapeutic efficacy. This result was related to an increased lipophilicity brought by the substituent. The high electronegativity of fluorine and the great strength of the C-F bond were also contributing factors [113]. Enamines were directly trifluoroacylated to enaminoketones **171** and subsequent cyclocondensation of these enaminones with O-methylisourea afforded the 2-methoxypyrimidine **172** in good yields (Figure 63) [113].

The readily obtainable 3-phenylhydrazon-indan-1-one **173** was reacted with dimethylformamide dimethylacetal (DMF/DMA) in refluxing xylene and yielded the enaminone **174**, which was reacted with hydrazine hydrate in acetic acid at reflux temperature to yield the indenopyrazole derivative **175**, which was formed *via* initial Michael addition of hydrazine to the β-carbon of double

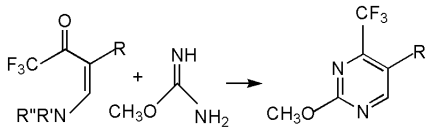


Figure 63

bond followed by elimination of dimethylamine and water molecules (Figure 64) [114].

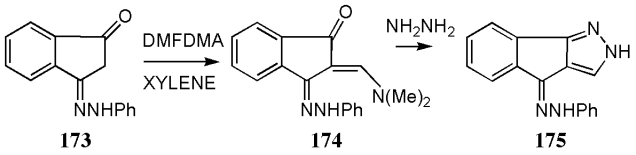


Figure 64

The reaction of enaminone **176** with diethyl-3-amino-2-cyanopenten-1,5-dicarboxylate **177** yielded a product of condensation *via* dimethylamine elimination, the intermediate **178**, which cyclized and gave the ethyl-2-amino-5-aroyl-3-cyano-4-hydroxybenzoate derivate **179** (Figure 65) [115].

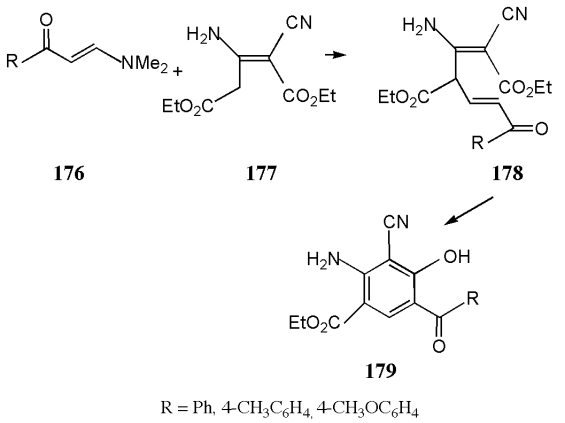


Figure 65

A variety of polyfunctionally substituted condensed pyridines and pyrazolo tetrahydroquinazolines have been synthesized utilizing cyclic enaminones as starting materials. The enaminones **180** reacted with malononitrile in refluxing acetic acid and yielded products of condensation *via* dimethylamine elimination, which may give an intermediate, such as **181**. Thus, initial Michael addition at the activated double bond can afford **181** that would then clyclise into **182** or isomerise into **183** (Figure 66) [116].

The reactions of enaminones with nucleophiles can also occur through nucleophilic attack on the carbonyl group. A

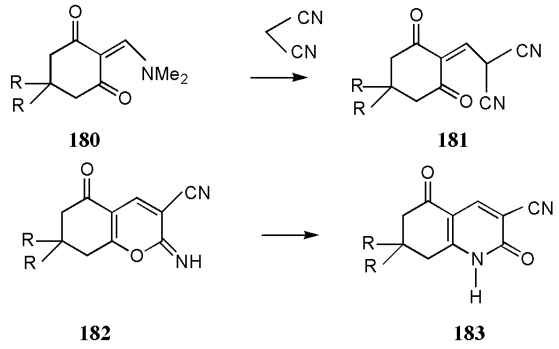


Figure 66

series of 5-arylpyrrolo[3,2-*b*]pyridines **187** was synthesized by addition of 3-aminopyrroles **184** to aryl enaminones **185**. The reactions may proceed by a mechanism involving the orientation shown in Figure 67, in which the amine group of **184** reacts directly with the ketone (CO group) of aryl enaminones **185** followed by cyclization. Another possibility is that the enaminone reacts at the α-position of the pyrrole and then cyclizes. Some 5-arylpyrrolo[3,2-*b*]pyridines are active in CNS screens indicative of anxiolytics [117].

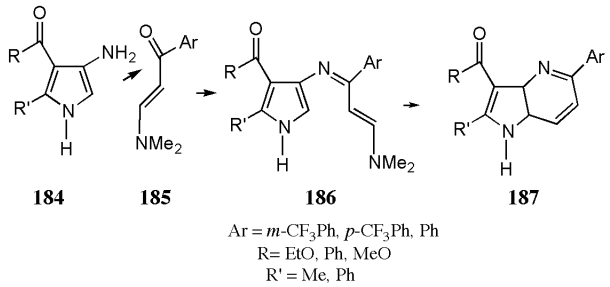


Figure 67

4,5-*o*,*o*-Dihaloarylpyrimidines readily obtained from the corresponding enaminoketones were transformed into phenanthro[9,10-*d*]pyrimidines by means of a high yielding Tandem stannylation/biaryl coupling procedure. Phenanthrene derivatives are good DNA-chain intercalators mainly due to their planarity [118]. Enaminones **188** were submitted to Leuckart reductive amination conditions and afforded 4,5-*o*,*o*-dihaloarylpyrimidines with good yields. The formation of 4,5-*o*,*o*-dihaloarylpyrimidines were obtained through nucleophilic attack of formamide on the carbonyl group of enaminone giving the intermediate **189**, which cyclized to give 4,5-*o*,*o*-dihaloarylpyrimidines **190** (Figure 68). Intermediate **189**

was isolated as a mixture of diastereoisomers, providing additional proof of the amine-exchange [118,119].

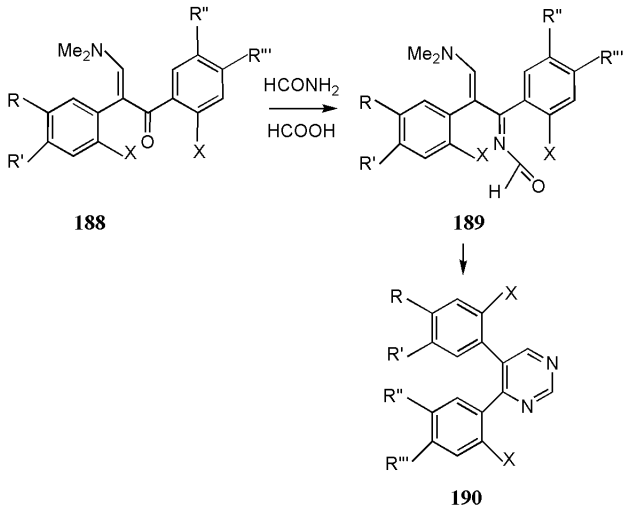


Figure 68

Reactions of Enaminones with Bases.

Deprotonation with strong bases (and, in some cases, acid-induced tautomerism) provides a further nucleophilic site β to N. The trifluoromethylated enaminoketones are good precursors for the synthesis of trifluoromethylated pyrroles [120]. The treatment of trifluoromethylated enaminoketones **191** with base afforded a mixture of isomeric pyrroles **192** and **193** (Figure 69).

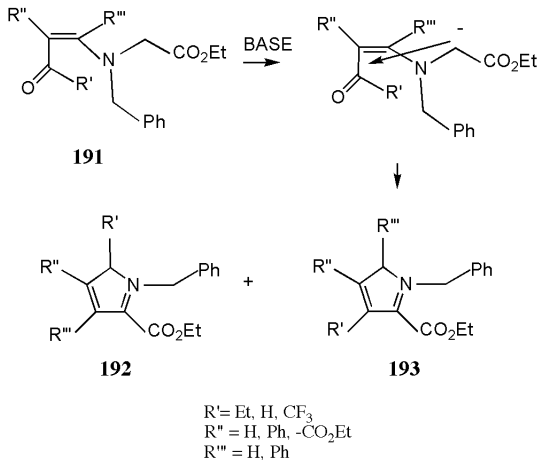


Figure 69

Two principal strategies, both proceeding *via* enaminone intermediates, have been reported for the construction of the quinolin-4-one nucleus of the quinolone antibacterials [76]. In the route developed by chemists at Bayer AG, the quinoline nucleus **195** is formed by base-induced cyclisation of 2-(2-halobenzoyl)-3-aminoacrilates **194** (Figure 70). The alternative route employs a thermal or acid-catalysed Gould-Jacobs cyclisation of anilinomethylenemalonates **196** [76].

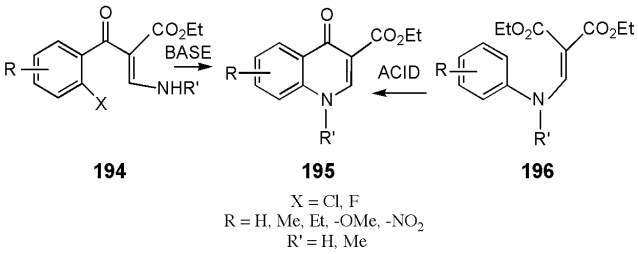
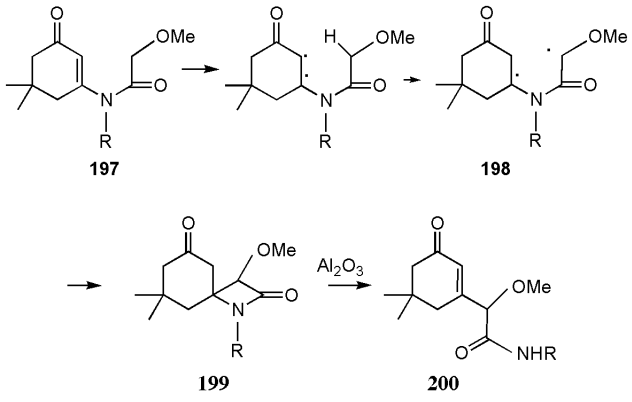


Figure 70

Photochemical or Radicalar Reactions Involving Enaminones.

Enaminoketones have various electrophilic and nucleophilic sites. In addition these compounds exibit the ability to participate in pericyclic and radical processes, opening the doors to a sumptuous, and still relatively unexplored chemistry. The acyl group serves to modulate both the stability and the reactivity of the enamine unit, which is usually sensitive to hydrolysis and oxidation. The irradiation of *N*-alkanoyl-β-enaminones **197** were conducted at 366 nm in acetonitrile solutions and led to the formation of spiranic β-lactams **199** which undergo C-N bond cleavage during chromatography on alumina. The photorearrangement occurred and gave cycloalkenones functionalized at position 3, which possess the expected α-amino-β,γ-unsaturated amide functionality. Thus, this rearrangement was applied to the synthesis of α-amino-β,γ-unsaturated amides **200** in one step in convenient yields [121]. Mechanistically, the hydrogen atom abstraction has occurred from intermediate **197** leading to a spiranic keto-β-lactam **199** (Figure 71). Due to its amidoketone structure and to the strain of the four membered ring, this spiranic β-lactam is highly sensitive to base and could undergo β-elimination during chromatography on alumina. Whatever the size or the nature of the substituents of the starting materials, the photorearrangement occurs and led to cycloalkenones, which possess the expected α-amino-β,γ-unsaturated amide functionality [121].

Irradiation of 3-[(2-chloro-3-pyridinyl)-amino]cyclohex-2-en-1-one **201** in a benzene/methanol solution for 45 min afforded a mixture of two regioisomers **202** and **203**. Optimal conditions for obtaining **202** included the use of acetonitrile in a pyrex reactor. Surprisingly, using



R = Bn

Figure 71

methanol in a quartz reactor reversed the regioselectivity of the cyclization and compound **203** was isolated in moderate yield (Figure 72) [122].

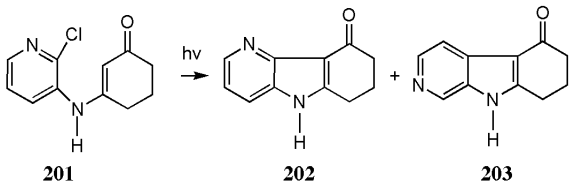
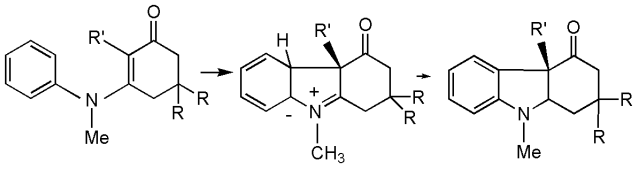


Figure 72

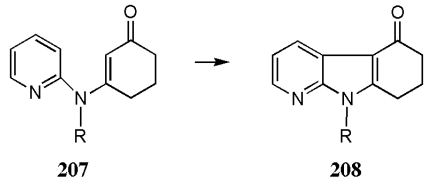
Photoreaction of *N*-phenyl enaminones such as the *N*-methyl-*N*-phenyl-3-amino-2-cyclohexen-1-one derivatives **204** to the corresponding *N*-methylhexahydro-4-carbazolones **206**, *via* the dipolar ionic intermediate **205** produced by a conrotatory ring closure was a useful synthon for building interesting heterocyclic compounds such as indole alkaloids (Figure 73) [123].



R=R'= H, Me

Figure 73

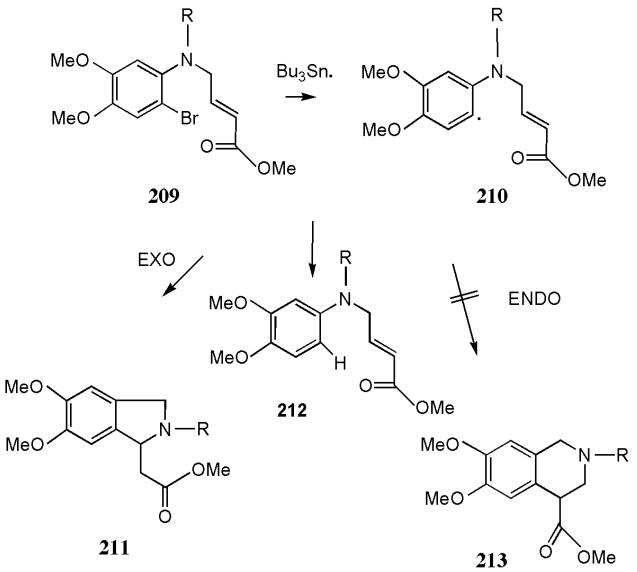
The synthesis of 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]-indol-9-ones from arylenaminones have been investigated using two "routes": a radical process through a photochemical reaction and a catalytic process through an arylpalladium complex. Irradiation of secondary enaminone **207** using a pyrex immersion well aparatus and a medium pressure mercury UV lamp (400 W) in benzene led to 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-9-ones **208** (Figure 74). Considering charge and orbital control of the reaction as outlined in the frontier molecular concept from HOMOC-2enaminone/LUMOC-13pyridine controlled process as well as from net atomic charge estimations, the reaction produced 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-9-ones **208** [124].



R = H, Et

Figure 74

Electronically, enaminone esters can be described as push-pull systems, with extensive charge donation from the nitrogen to the carbonyl group. The aryl radical cyclization of *N*-benzyl or *N*-phenethyl enaminones **209** afforded 5-exo products **211**. Direct reduction of intermediate **210** by tributyltin hydride led to the reduced products **212**. The other reaction path leading to endo cyclization products **213** onto the enaminone double bonds were not favoured (Figure 75) [125]. PM3 calculations suggested that the non-occurrence of endo and 4-exo cyclizations is

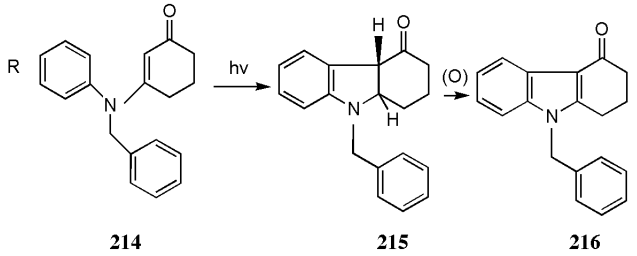


R= H, Me, Et

Figure 75

due to the corresponding transition structures involving significant distortion of the conjugated enaminone system and confirmed that the course of the reaction is strongly dependent on the initial configuration of the starting enaminones, because endo-type cyclizations requiring s-(*Z*)-conformation. Since, the secondary and tertiary enaminones as were shown by NMR experiments to exist mainly in s-(*E*)-conformation, only exo cyclization products were obtained [125].

Tricyclic keto-indoles were synthesized by photocyclization of easily obtained enaminones in an electrocyclic photochemical reaction. The most general procedures using one-step synthesis was carried out in a benzene-methanol solution in the presence of sodium methylate. The substituted tricyclic keto-indoles **216** were synthesized in excellent yield from *N*-arylenaminones **214** by an oxidative process from compound **215** (Figure 76) [126].

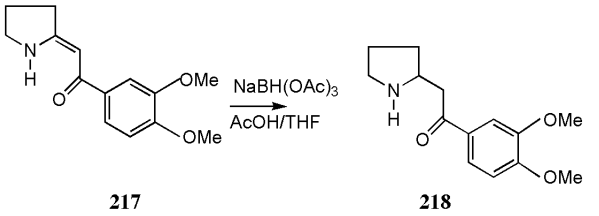


214 **215** **216**

Figure 76

Reduction of Enaminone.

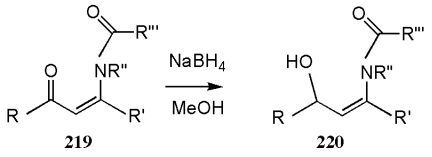
Ruspolinone **218**, one of the three pyrrolidine alkaloids isolated in the racemic form from *Ruspollia hypercrateri - formis* and possessing the pyrrolidinyl-acetophenone skeleton, can be readily obtained by chemoselective reduction of the C=C unit of the enaminoketone **217** with sodium triacetoxyborohydride (Figure 77) [127].



217 **218**

Figure 77

Enaminoketones and enaminoesters can be reduced to γ-aminoalcohols or β-aminoacids, important classes of organic compounds of proved biological and pharmacological activity. Cyclic *N*-acylenaminones or acyclic ones **219** could be reduced regioselectively under mild conditions with sodium borohydride in methanol to the corresponding β-hydroxyenamides **220** (Figure 78) [128]. The problematic reduction of enaminones is possible through a previous treatment with an acylating agent that allows the carbonyl group to become electrophilic enough to be attacked by hydride. The synthesis of 2-pyranone can occur through an unknown isomerization mechanism of the hydroxytetrahydro-2-pyridinone, an accessible starting material obtained by reduction of acylated enaminones [128].



219 **220**

R = Me, Ph R' = Me
R" = Me, (R)-CHPhMe
R'" = Ph, Me

Figure 78

An efficient enantioselective synthesis of 4-amino-cyclopenten-2-ene-1-one from enaminones and its diastereomer had been accomplished *via* a one step electron transfer reduction of the enaminone double bond and concomitant removal of an α-methylbenzyl group, followed by a [4 + 2] cycloreversion strategy. The key step in this route is the electron transfer reaction of *N*-α-methylbenzyl substituted enaminone and its diastereomer, with lithium in liquid ammonia, which not only reduces the enaminone double bond but concurrently removes the chiral auxiliary. The reluctance of the enaminone moiety to undergo hydride reduction is probably due to its extended π-delocalization, which requires reduction conditions that are not suitable to retain the β-amino group [129]. The γ-aminocyclopentenones have great potential as building blocks for 5'-norcarbocyclic nucleosides as well as for related antiviral compounds. Reacting diastereomerically pure **221** with lithium in liquid ammonia as the reducing agent and ^{t}BuOH as the proton donor, a mixture of diastereomeric-γ-aminocyclopentenones **222** and **223** were obtained in excellent yield and with a remarkably high diastereoselectivity (de 94%) (Figure 79) [129].

The regiochemistry of the reduction of *N*-acylated tricyclic enaminones can be directed by choosing the appropriate reductive conditions. An efficient synthesis of both (1*S*,4*R*) and (1*R*,4*S*)-4*N*-acetylamino-1-benzoylcyclopent-2-enes **226** has been accomplished starting from enantiopure 5-(1'-phenylethylamino)-endo-tricyclo-[5.2.1.0]-deca-4,8-dien-3-ones **224** and **225** (Figure 80) [130].

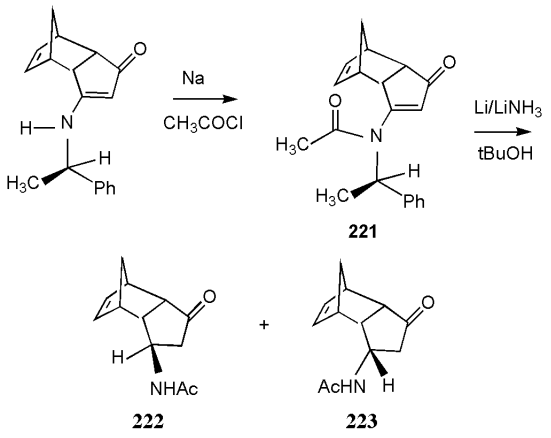


Figure 79

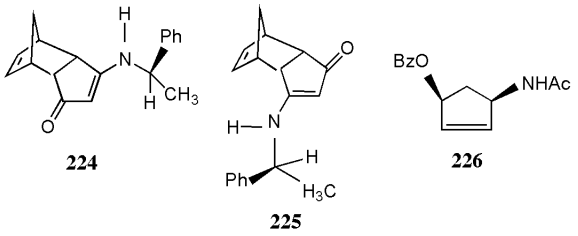


Figure 80

The stereochemistry and regiochemistry of di-, tri- and tetracyclic enaminones upon catalytic hydrogenation on Pd and Pt catalysts seems to be mainly a function of the catalyst and the medium. The highest stereoselectivity was observed for multiflorine on Pd/C in which 99% of equatorial alcohol was obtained [131]. The diastereoselective synthesis of 2,6-disubstituted piperidinic alkaloids can be obtained from an easily available chiral lactam [132].

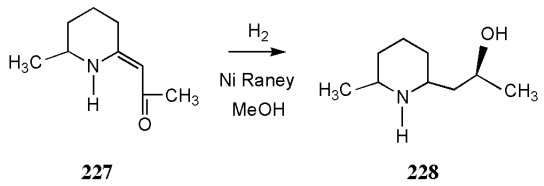
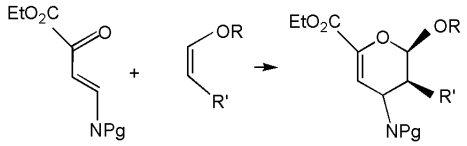


Figure 81

Direct condensation of chiral lactim ether with acetylacetone in the presence of catalytic nickel acetylacetonate gave the *Z*-isomer of the β-enaminoketone stereoselectively in 60% yield, based on the chemo- and diastereocontrolled reductions. Catalytic hydrogenation conditions of β-enaminoketone **227** using Raney Ni or Pd/C as catalysts, diastereoselectively led to only one diastereomer (-)-epiinidinol **228** (Figure 81) [132].

Hetero Diels-Alder Reactions from Enaminones.

A simple and convenient procedure for the formation of optically active amino sugars **231** could be the catalytic enantioselective inverse-electron demand hetero Diels-alder reaction of γ-amino-protected β,γ-unsaturated-α-keto-esters **229** with vinyl ethers **230** using a chiral Lewis acid (Figure 82). The catalytic reactions proceeded in good yield with high diastereo- and enantioselectivity and full control of the stereochemistry at the amino-carbon center [133].



R = NHPh
R' = H, Me

Figure 82

Enaminones undergo inverse electron demand Diels-Alder reaction with 1,3,5-triazine allowing access to functonalised quinazolinones as intermediates in the synthesis of CNS agents. The inverse electron demand Diels-Alder reaction is controlled mainly by the interaction of HOMO dienophile and LUMO diene and it requires an electron-rich dienophile and an electron-poor diene. This reaction is highly dependent of the solvent [134]. The [4 + 2] cycloaddition reactions of enaminones **232** with 1,3,5-triazine in acetic acid afforded 7-methoxymethyl-5,6,7,8-tetrahydro-5-quinazolinones **233** (Figure 83).

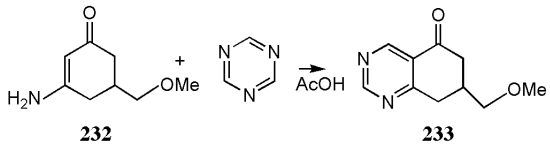
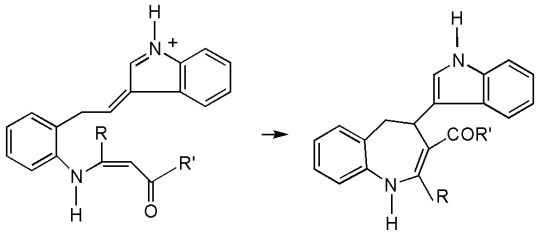


Figure 83

Cyclization of Enaminones

The condensation of trimer of indole with β-diketones and β-keto esters was followed by the cyclization of the intermediate enaminoketones **234** by means of acetic acid to yield 4,5-dihydro-1*H*-1-benzazepines **235** (Figure 84) [135].

Under acidic conditions, biselectrophilic chromophore -CH=C-CHO of 1,3-dimethyl-5-formyluracyl reacted with bisnucleophilic unit CH=CH-N of enaminone derivatives

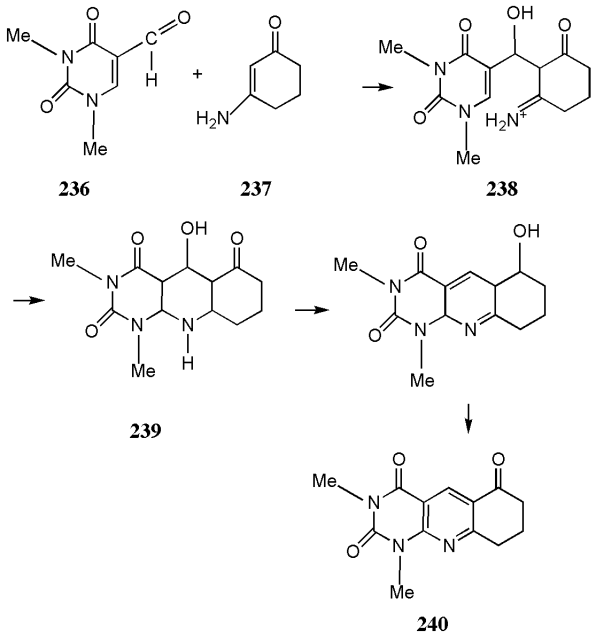


234 **235**

R= H, Me, Et, Pr, Bu
R'= Me, Et

Figure 84

to undergo an unprecedent reaction to provide annulation or subsequent transformation products along with Hantzsch type 1,4-dihydropyridine derivatives. The reaction of 1,3-dimethyl-5-formyluracyl **236** with enaminones **237** in CH_3CN-TFA gave intermediates **238** and **239** which afforded annulation products, such as pyrimido[4,5-*b*]quinolin-2,4,6(1*H*,3*H*,7*H*)-trione derivatives **240** and 1,3-dimethyluracil [136]. The formation of the products could be visualised to proceed through nucleophilic attack of enaminone at the formyl group to give an intermediate **238**, which undergoes intramolecular addition at C-6 of the uracil unit to give other intermediate **239**, which undergo enolisation, dehydration and oxidation to give compound **240** (Figure 85) [136].



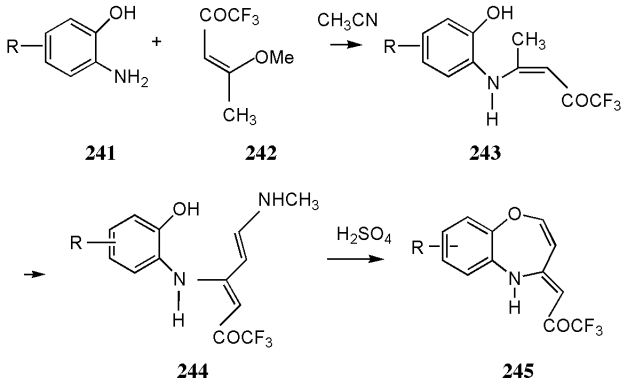
236 **237** **238**

239

240

Figure 85

High yields of enaminones **243** were obtained by reacting commercially accessible aminophenols **241** and the trifluoroacetylvinyl ether **242**. Functionalization of the methyl group with DMA/DMF gave rise to dieneamines **244** that were cyclized in acidic environment to benzoxazepine derivatives **245** (Figure 86) [137].



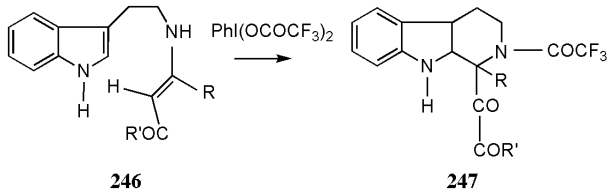
241 **242** **243**

244 **245**

R = H, 5-CH_3, 4-CH_3, 5-Cl, 5-NO_2, 4-NO_2

Figure 86

The reaction of enamino carbonyl derivatives of tryptamine **246** with bis[(trifluoroacetoxy)iodo] benzene provided an easy route to 1,1-bis-functionalised *N*-trifluoroacetylated-β-carbolines **247**. The reaction proceeded through Pictet-Spengler-type cyclisation, trifluoroacetylation and oxidation steps (Figure 87) [138].



246 **247**

R = Me, Ph, Pr
R'= OEt, Me

Figure 87

Quinolizine derivatives have attracted a great deal of interest, due to their biological activities, such as anti-HIV, anti-tumor, anti-hypertensive, anti-allergic, anti-ulcer, anti-mycobacterial, anti-bacterial, anti-inflammatory and as potent selective human steroid [139]. Human steroid 5α-reductase (5αR) is a family of two isoenzymes (types 1 and 2) that convert testosterone to the more potent androgen dihydrotestosterone (DHT). Selective inhibition of (5αR) is currently investigated as a potential therapeutic tool for the treatment DHT-related skin disorders, such as acne, alopecia, male baldness and hirsutism [139]. Reactions of enaminones **248** with malononitrile in refluxing ethanol and in the presence of catalytic amounts of piperidine afforded aminoquinolizinone derivatives. The

formation of aminoquinolizinone derivatives **251** is assumed to proceed *via* initial attack of the anion of the first malononitrile molecule on the cyclic carbonyl carbon of compound **248** to form the ylidene malonitrile derivative **249** that then cyclizes into **250** with addition of a second malonitrile molecule to the enaminone double bond of **250**, which loses a molecule of dimethylamine and cyclizes to afford the quinolizinone derivative **251** (Figure 88) [139].

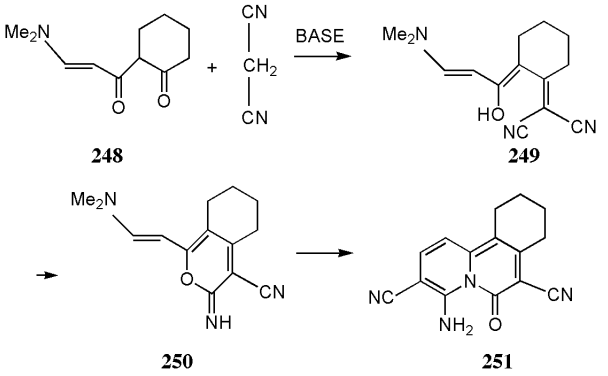
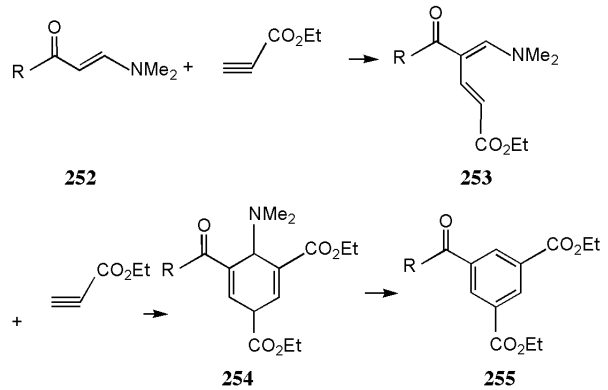


Figure 88

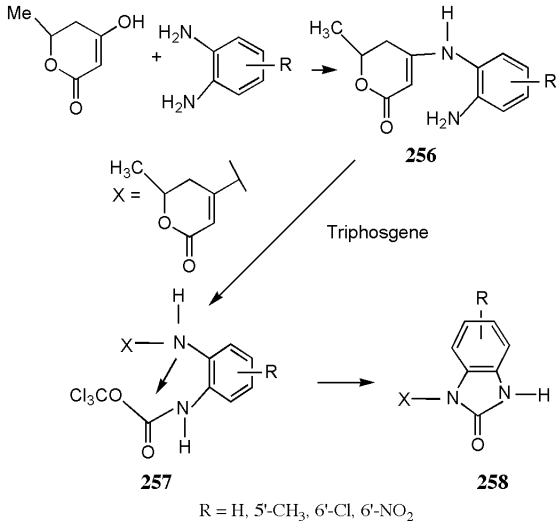
Enaminones undergo self-condensation on reflux in acidic media yielding 1,3,5-trisubstituted benzenes in very high yields. Reaction of enaminones **252** with ethyl propiolate afforded 5-aroyl-1,3-benzene dicarboxylate derivatives **255**. It is possible to assume that the product is formed *via* a [2 + 2+ 2] concerted cycloaddition mechanism yielding **254**, which loses dimethylamine to yield the product **255**. However, possible initial formation of intermediate **253**, which then adds further one molecule of ethyl propiolate to yield **254** that aromatize into **255** cannot be ruled out (Figure 89) [140].



R = 2-furyl, 2-thienyl, 2-pyridyl, Ph, Me

Figure 89

Reaction of pyrone or tetronic acid with *o*-phenylenediamine derivatives gave enaminones **256**. The reactions of enaminones **256** with triphosgene allowed access to benzimidazolones **258**, bearing as X group either a pyrone or a tetronic acid moiety. Intramolecular cyclization reactions of intermediate compounds **257** to gain access to heterocyclic compounds, because this reaction results from the harder nucleophile nitrogen attack on the hard electrophilic center, the carbonyl group in the intermediate **257** (Figure 90) [141].



R = H, 5'-CH_3, 6'-Cl, 6'-NO_2

Figure 90

Aza-annulation Reactions of Enaminones.

The stereoselective formation of six-membered nitrogen heterocycles that contained an asymmetic quaternary carbon center was achieved through asymmetric aza-annulation of β-enamino amide substrates **259** with activated acrylate derivatives **260**. Condensation of a racemic β-keto amide with an optically active primary amine, either (*R*)-α-methylbenzylamine or α-amino esters **259**, resulted in aza-annulation and gave the corresponding δ-lactam **261** with high diastereoselectivity (Figure 91) [142].

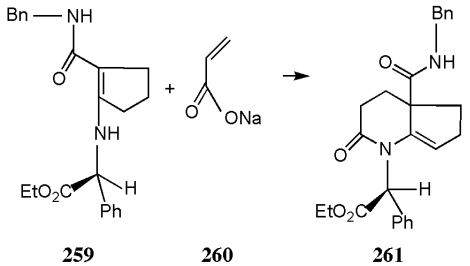


Figure 91

Enaminones reacted with itaconic anhydride (2-methylene-succinic anhydride) in methylene chloride at room temperature and gave exocyclic enamides as the major products, which can be readily equilibrated to the thermodynamically more stable endocyclic enamides. Reaction of enaminone **262** with itaconic anhydride proceeded smoothly in methylene chloride and gave a 5:1 mixture of cyclic compounds **263** and **264** (Figure 92) [143]. The most remarkable aspect of this reaction is that the major isomer is the thermodynamically less stable β,γ-unsaturated carbonyl compound with the double bond outside the ring. This is an example of an aza-annulation reaction on an enaminone bearing a hydrogen atom α to the electron withdrawing group in which β, γ-unsaturated isomer is observed as the major isomer. The good correlation of the relative stereochemistry of aza-annulation with itaconic anhydride involved formal 1,2-additions [143].

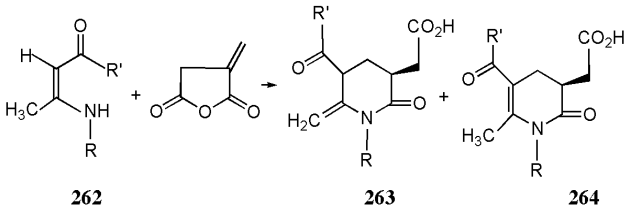


Figure 92

Concomitant enaminone-directed benzannulation-macrocyclization can be developed into a general method for the construction of functionalized cyclophanes and, in turn, new molecular hosts and/or metal-ligating species. The key cyclophane-forming macrocyclization reaction was accomplished during the course of a regioselective cross-benzannulation between bis arylethynyl ketone and enaminone reactants. Macrocyclic products with ring sizes ranging from 18- to 22-membered were successfully constructed [144].

Reactions of Enaminones with Organometallics.

Enaminones may be reacted with organocadmium reagents such as dibutylcadmium to effect the deprotonation and cyclization directly at room temperature. A series of selected Lewis acid salts, which included zinc chloride, zinc bromide, cadmium chloride and copper acetate were found to be capable of promoting the cyclization of enaminone **265** to afforded the pyrazolopyridine **266** (Figure 93) [145]. The mechanism proposed for the enaminone cyclization involve coordination of cadmium to the nitrile as a critical step. Activation of the nitrile toward nucleophilic addition by the enaminone anion then becomes facilitated. A subsequent symmetry allowed 6-π electron electrocyclization would then complete the central ring closure. The organocadmium reagents are sufficiently basic to depronate the enaminones to form the corresponding anions and provide a means to introduce the cadmium counterion [145].

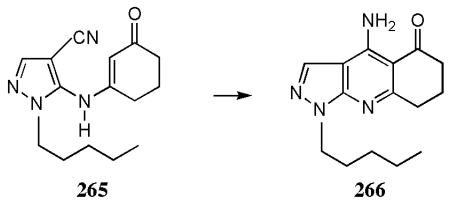


Figure 93

The synthesis of substituted cycloalkenones was carried out by the addition of organometalic compounds such as Grignard Reagents to enaminones derived from cycloalkane-1,3-diones. Grignard reagents were added to cyclic s-*trans* enaminones **267** and cycloalkenone **268** were obtained after aqueous hydrolysis (Figure 94). These reactions have been found to be solvent and reagent-selective. In some cases, a disubstituted aminocycloalkene **269** is also formed by a double addition reaction [146].

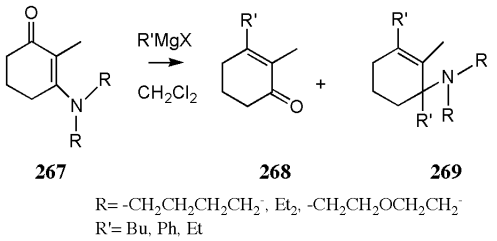
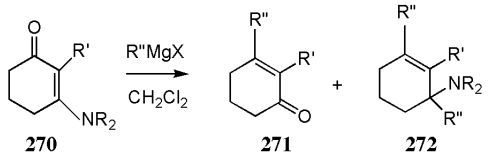


Figure 94

Enaminone **270** was treated with an excess of ethereal solution of phenylmagnesium bromide and the use of dichloromethane as solvent gave cycloalkenones **271**. A second addition takes place in some instances to give bis-adducts **272** (Figure 95). Factors that have been identified as influencing this process include solvent polarity and coordinating ability [147].

The α,β-unsaturated carbonyl compounds are amongst the most important intermediates and one useful for many synthetic purposes. Furthermore, this bifunctional moiety is present in a large number of molecules of biological relevance [148]. Enaminones **273** dissolved in toluene reacted with Grignard reagents in tetrahydrofuran to gave selectively and with high yields of cyclic and aliphatic α,β-unsaturated ketones **275** (Figure 96). The alkylations

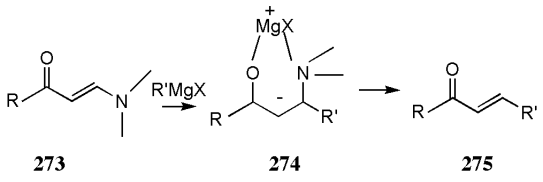


270 **271** **272**

R= -$CH_2CH_2CH_2CH_2$-, Et_2, -$CH_2CH_2OCH_2CH_2$-
R'= H, Me
R"= Ph, Bu, Et

Figure 95

take place *via* intermediates, such as **274**, which have no propensity for additional attack by nucleophiles [148]. The use of "dry"cerium (III) chloride allows the addition of organolithiums to enaminones [149].

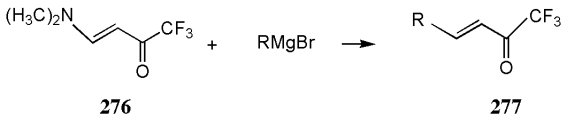


273 **274** **275**

R= Me, n-Bu, Ph, -$(CH_2)_3$Ot-Bu
R'= Ph, Bu, Et

Figure 96

Enaminones **276** were available by reaction of 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one with amines, such as dimethylamine and they reacted with Grignard reagents to gave α,β-unsaturated trifluoromethylketones **277** in good yield by 1,4-addition followed by elimination (Figure 97) [150]. Cyclic tertiary enaminones and (2-phenylalkynyl)-carbene tungsten complex gave cross-conjugated carbiminium carbonyl metalates, which isomerized to pyrilium carbonylmetalates in 62-90% yields [151].

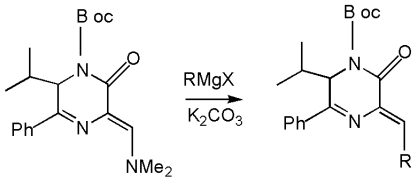


276 **277**

R = n-$C_{11}H_{21}$, n-$C_{12}H_{25}$, Ph, p-MeOPh, m-CH_3Ph

Figure 97

The α,β-didehydroaminoacids (DDAAS) are one of the conformationally constrained noncoded aminoacids. They acted as antimicrobial and phytotoxic agents and, once incorporated in the peptidic sequence, an enhanced resistance of enzymatic and chemical degradation of the resulting proteins occurred [152]. The didehydroalanine derivative and enaminone can give DDAA derivative using Heck olefination and vinylic nucleophilic substitution. Enaminones **278** underwent vinylic nucleophilic substitution, acting as β-acylvinyl cation by organomagnesium compounds affording diastereoselectively (*Z*)-DDAA derivatives **279** in moderate yields (Figure 98) [152].



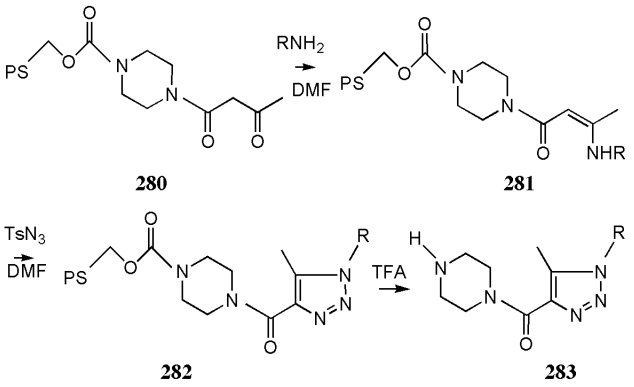
278 **279**

R= -$CHMe_2$, -CMe_3, Ph, naphthyl

Figure 98

Solid-phase Synthesis from Enaminoketones.

Solid-phase synthesis is playing a decisive role in the on going development of combinatorial chemistry, mainly because it offers high synthetic flexibility as well as the possibility of automation [153,154]. Diversely substituted 1,2,3-triazoles have been synthesized on a solid support. A resin-bound 3-oxobutyramide **280** could be effectively condensed with primary aliphatic amines. The resulting 3-amino-2-butenoic acid amides **281** were then cyclized by treatment with tosylazide in the presence of a tertiary amine to give **282**. Acidolytic cleavage from the support yielded the corresponding 1,2,3-triazoles **283** in purities up to 82% (Figure 99) [153,154].



280 **281**

282 **283**

R= -$CH_2CO_2CH_2$Ph, 4-methoxybenzyl, 2-(4-nitrophenyl)ethyl

Figure 99

A versatile solid-phase synthesis of pyrrole–3-carboxamides **287** from enaminones **284** was performed either in a two or three component pathway by treating a polymer bound enaminone with a nitroalkene **285**. In the first step rink amides PS resin was acetoacetylated with diketene

and converted into polymer bound enaminones **284** upon treatment with primary amines [155]. The reaction conditions for the subsequent cyclization to give compound **286** with nitroalkenes were then evaluated by using 2-phenylethylamine and 1-phenyl-2-nitroprop-1-ene (Figure 100).

The remarkable range of biological activities exhibited by indole containing molecules and natural products pro-

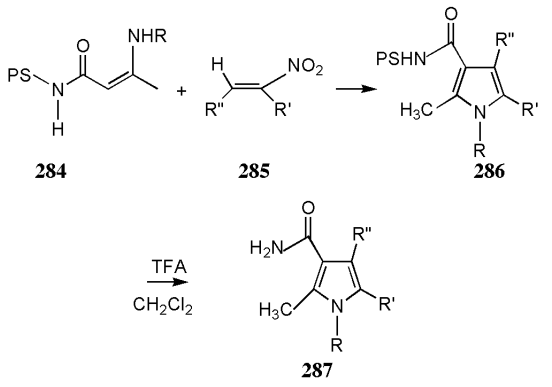


Figure 100

vides compelling impetus for development of improved methods for the construction of this heterocycle as well as the need to adapt classic ring-forming reactions to the solid-phase. The solid-phase version of the Nenitzescu indole synthesis of 5-hydroxyindole-3-carboxamides involved initial acetoacetylation of Argopore-Rink-NH_2 Resin with diketone to afford a polymer bound acetoamide [156]. Formation of the corresponding enaminones **288** *via* condensation with primary amines in the presence of the trimethylortoformate followed by addition of 1,4-benzo-

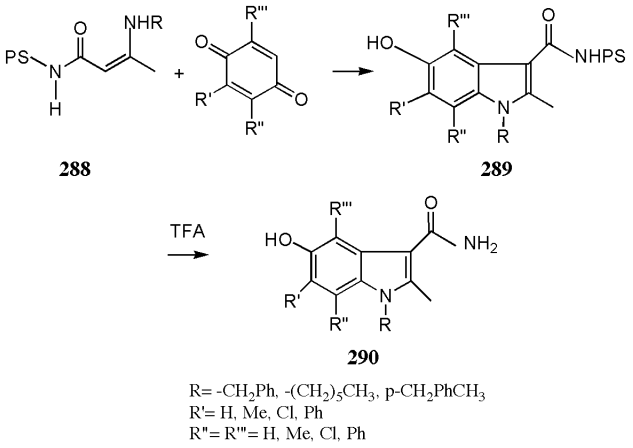


Figure 101

quinones led to the formation of indoles **290** after TFA induced cleavage from the resin compond **289** (Figure 101) [156].

Enaminothiones.

The principal difference in reactivity of enaminothione 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 [3]. Enaminothiones are not known to react as nucleophiles through Cα. Thus, enaminothiones react through sulfur, while enaminones react through Cα or N. Diphenylcyclopropenone reacted with enaminothiones and afforded 4,5-dimethylene cyclopentenone derivatives, in which the sulfur atom of enaminothiones acted as a nucleophile at the phenyl group [3]. Enaminothione exists exclusively in the intramolecularly hydrogen bonded *E*-configuration in nonpolar solvents like benzene and chloroform, while in polar solvents there is a significant population of the *Z*-isomers [157].

Benzylation of compound **291** with bromomethyl benzene in acetone using K_2CO_3 as base, followed by a rapid isolation of the product yielded a mixture of two stereoisomers **292a** and **292b**. The major isomer was isolated and proved to have *Z*-configuration (**292a**) by NOE experiments. The minor product had *E*-configuration (**292b**) (Figure 102). Acid-catalysed equilibration of pure **292a***Z* (benzene, reflux, catalytic amount of PTSA) drastically altered the stereochemical composition, *i.e.* the final *Z*/*E* ratio of the product [158]. This dramatic change proved that **292a***Z* has the kinetically preferred configuration, while **292b***E* had lower energy and was therefore the predominant isomer under thermodynamic control [158].

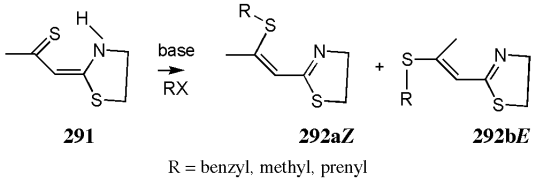
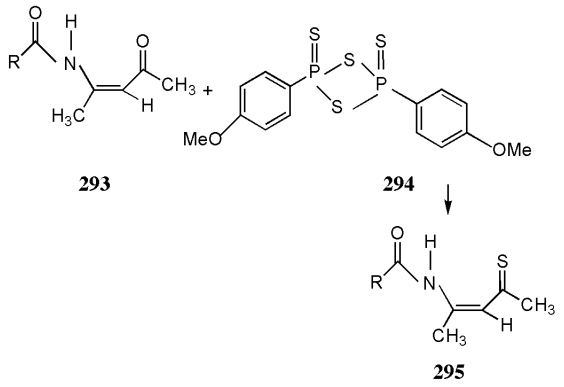


Figure 102

The 4-acylaminopent-3-en-2-ones **293** were reacted with 2,4-bis-(4-methoxyphenyl)-1,3,2,4,dithiadiphosphetane-2,4-disulfide **294** under mild conditions in dimethyl ethane (DME) and gave the corresponding enaminothione **295** in high yields (Figure 103) [159].

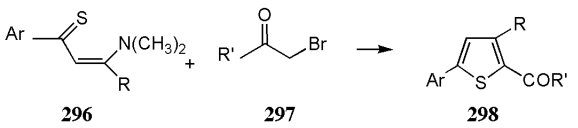
Enaminothiones have been shown to be highly reactive synthons for the preparation of thiopyran derivatives *via* [4 + 2] cycloaddition reactions with carbon-carbon dienophiles [160]. The enaminothiones have been shown



R = Me, Ph, $(CH_3)_2HC$-, $(CH_3)_3C$-

Figure 103

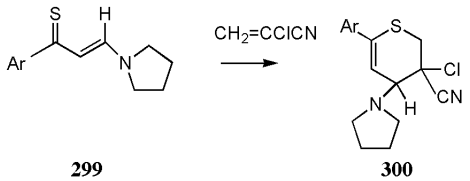
to participate as 4π component in Diels-Alder cycloaddition reactions with a large variety of carbon-carbon dienophiles. Diels-Alder cycloaddition reactions of enaminothiones with nitroalkenes resulted in very good yields of thiopyrans as exclusive stereoisomers. 2-Aminovinyl thioketones **296** reacted with α-bromoketones **297** to give substituted 2-acylthiophenes **298** by a cycloaddition process (Figure 104). The cyclization was favored by addition of triethylamine [160].



R= H, Me
Ar= Ph, p-CH_3OPh
R'= Me, p-BrPh, Ph, p-ClPh

Figure 104

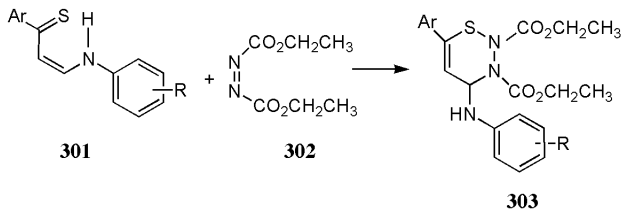
The enaminothione **299** reacted with acrylonitrile and 2-chloroacrylonitrile at room temperature and gave 3,4-dihydro-4-(1-pyrrolidinyl)-2*H*-thiopyrans **300** (Figure 105) [161].



Ar = Ph, p-MeOPh, p-BrPh

Figure 105

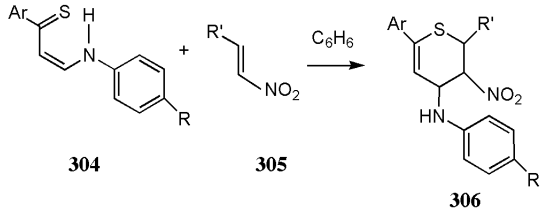
The reactions of enaminothiones with ethyl azodicarboxylate participate in Diels-Alder cycloadditions as a 4π as well as 2π component. Treatment of 3-Arylamino-1-phenyl-propene-1-thione **301** with ethyl diazenedicarboxylate **302** yielded 4-arylamino-6-phenyl-2,3-dihydro-4*H*-1,2,3-thiadiazine-2,3-dicarboxylates **303** (Figure 106) [162].



Ar = Ph
R= H, 2"-Cl, 3"-Cl, 4"-Cl, 2"-Me, 4"-Me

Figure 106

The reactions of nitroalkenes **305** with 3-*N*-aryl-amino-1-phenylpropene-1-thiones **304**, which has the preferred *Z* configuration due of attraction between NH and sulphur of thione in anhydrous benzene, yielded 2-aryl-4-arylamino-3-nitro-6-phenyl-3,4-dihydro-2*H*-thiopyran **306** (Figure 107) [163].



R= Me, Cl, H Ar = Ph
R'=Ph, p-MeOPh

Figure 107

Reaction of the enaminothione **307** with NaOBr in water-THF gave the acetylene derivative **308** (Figure 108) [164].

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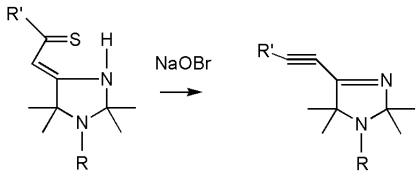

307 **308**

R=OMe, H
R'= Ph, SMe, Me, $N(CH_3)_2$

Figure 108

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