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ENAMINES AS PRECURSORS TO POLYFUNCTIONAL HETEROAROMATIC COMPOUNDS; A DECADE OF DEVELOPMENT

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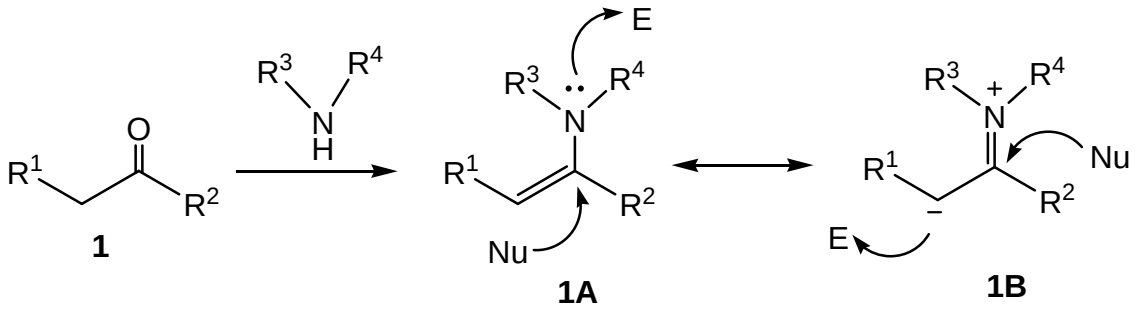
Abstract – Recent synthesis and utilization of enamines as precursors for heterocyclic and carbocyclic compounds are reviewed. Two general synthetic routes for preparation of enamines based on condensation and addition reactions. Enamines and azaenamines can be used as building blocks for carbocyclic, five- and six-membered heterocyclic as well as fused heterocyclic compounds.

INTRODUCTION

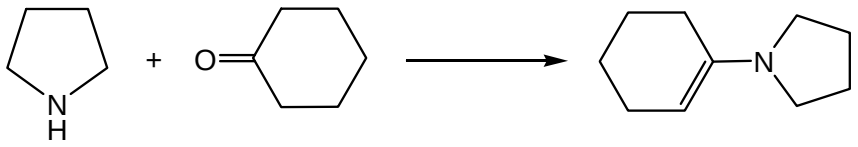
The condensation of alkyl aldehydes or ketones with secondary amines affords the corresponding amino alkenes **1A**. The term enamine was given by Wittig and Blumenthal for these compounds.[1-3] Enamines are polydentate electrophiles. Amine nitrogen and as a result of nitrogen lone pair resonance α–carbon is electrophilic while β-carbon is nucleophilic (Scheme 1).



Scheme 1

The alkene double bond can also be a part of carbocyclic ring or a non aromatic heterocyclic ring. The best known example for carbocyclic enamines **4** is the product of condensation of pyrrolidines **2** with

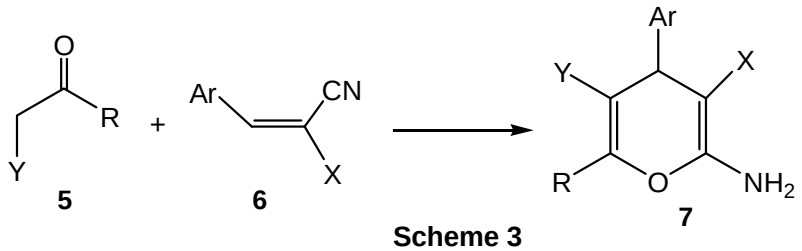
cyclohexanone **3** prepared by Stork[4] (Scheme 2).



2 **3** **4**

Scheme 2

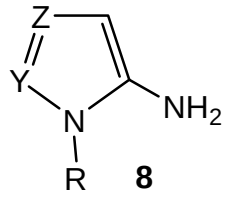
The addition of aryl active methylene ketones **5** to functionally substituted α,β-unsaturated nitriles **6** affords also heterocyclic enamines **7**[5-23] (Scheme 3).



5 **6** **7**

Scheme 3

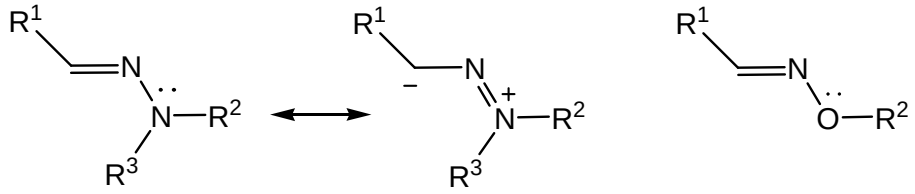
Although amino heterocyclic compounds **8** can behave as enamines,[24] we believe that treating these as enamines is not quite proper as their chemistry in fact can be better correlated with that of aromatic amines in most cases. Thus, in this article, chemistry of enamines in which the double bond is part of heteroaromatic system will not be considered (Figure 1).



8

Figure 1

Aldehyde hydrazones can be considered as azaenamines. Nitrogen lone pair resonance renders aldehyde carbon electron rich[25-30] (Chart 1). Reactivity of these compounds as azaenamines has been recently investigated. Even hydrazone carbon of some ketone hydrazones is also electron rich and nucleophilicity of these carbons has, long time since, been recognized[31-36] but to our knowledge no trial to survey such activities has ever been made. On the other hand, the electron donation to oxime carbon in oxime ethers **11** (cf. Chart 1) is weak because of electronegativity of oxygen atom and thus their chemistry will not be surveyed.



9 **10** **11**

Chart 1

Enamine chemistry has been surveyed in a volume of prestigious Patai's chemistry of functional group series on 1994.[37] However because of the enormous achievement in enamine chemistry, the publication of recent review article seems mandatory. Chemistry of enaminones has been surveyed by Greenhill,[38a] Ferraz,[38b] Elassar,[39] Stanovnik[40] and Negri.[41] Chemistry of cyclic enaminonitriles and enaminoesters has been also surveyed by Wamhoff.[42] Stanovnik's report[40] is basically concerned with his work. The same applies more or less to Negri work.[41] Elassar's review[39] is rather incomplete and has ignored some important achievements of even his colleagues.

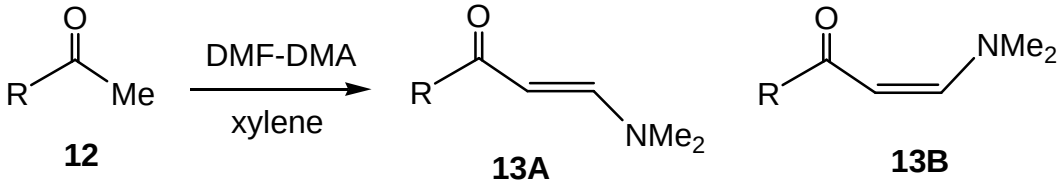
Enamines have been extensively utilized in the past as precursors to polyfunctional aromatics and heteroaromatics. The following article is intended to demonstrate recent work aimed at utilizing enamines as precursors to heterocyclic as well as alicyclic compounds. We believe that this survey will be of value to chemists involved in synthetic chemistry in general and will also be of interest to instructors of advanced organic chemistry.

2. SYNTHETIC APPROACHES TO ENAMINES AND AZAENAMINES

2.1. CONDENSATION REACTIONS

2.1.I. CONDENSATION WITH AMIDE ACETAL

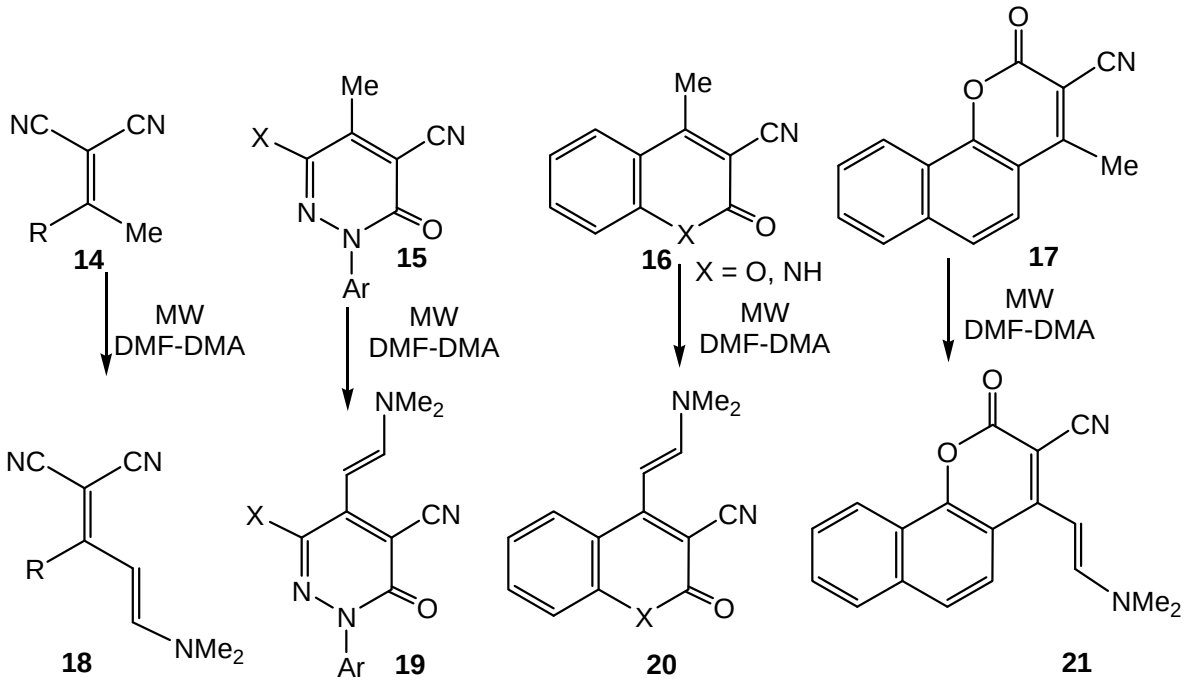
The condensation of amide acetals with active methyl and methylene ketones is a general efficient route to enamines.[43] The reaction of methyl ketones **12** with dimethylformamide dimethyl acetal (DMF-DMA) gives enaminones **13** which has generally been shown by Elnagdi and co-workers[44-65] to adopt *trans* form **13A** rather than *cis* isomeric form **13B**. The reaction was initially conducted by refluxing both reagents in xylene or toluene or acetic acid for 10-20 h.[66] However, it could be recently shown that shorter reaction times can be adopted by refluxing neat reagents[67] (Scheme 4).



12 **13A** **13B**

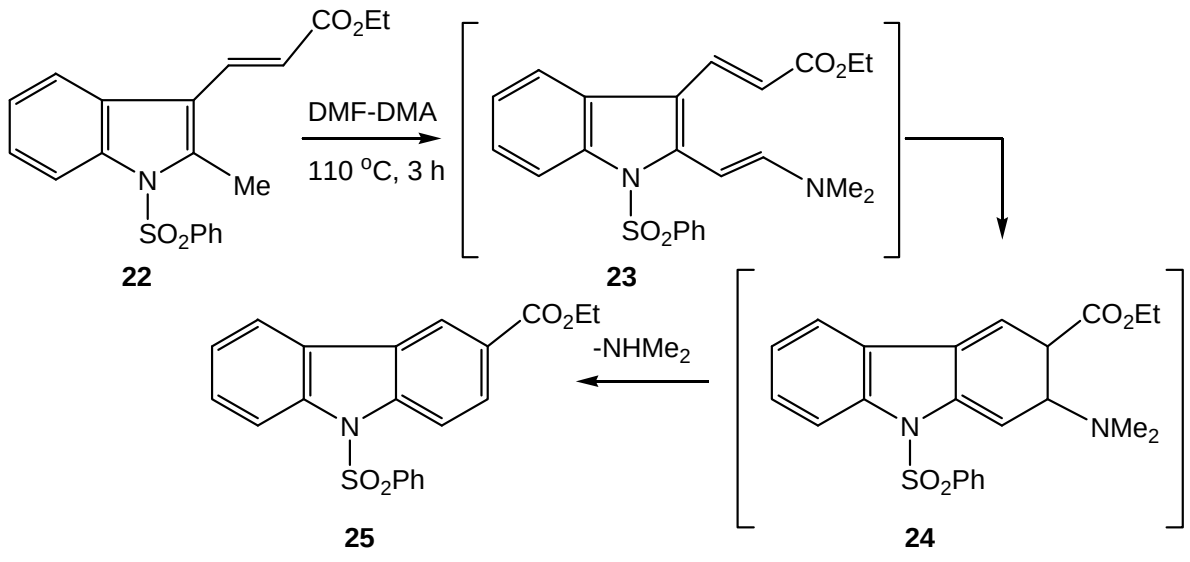
Scheme 4

The reaction of methyl function in 2-butenenitriles **14** and heterocyclic carbonitriles **15-17** with DMF-DMA proceeds much faster and is generally conducted in refluxing toluene for 6 h and yields, in each case, *trans* enamines **18-21** in good yields.[68] Preparation of enamines **18-21** under microwave irradiation in the presence of acetic acid was also investigated. Reactions under these conditions proved much faster (5-10 minutes) and gave better yields than conventional heating[54] (Scheme 5).



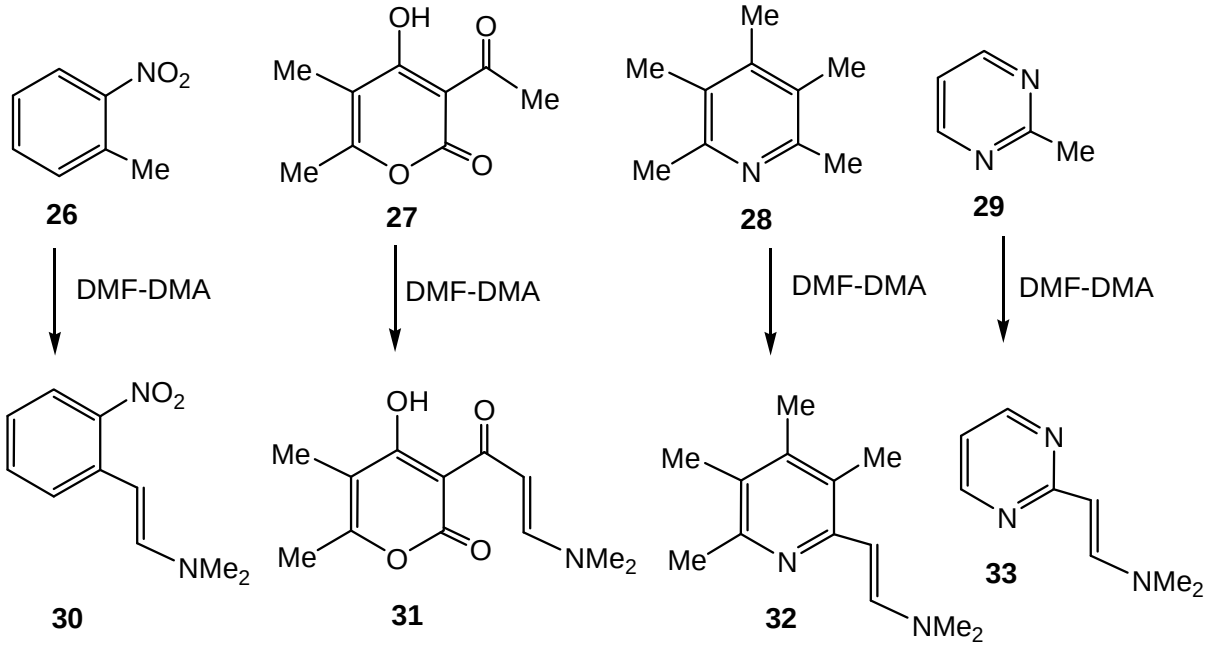
Scheme 5

Methyl function in indoles **22** condenses readily with DMF-DMA to yield carbazoles **25**[69] (Scheme 6).



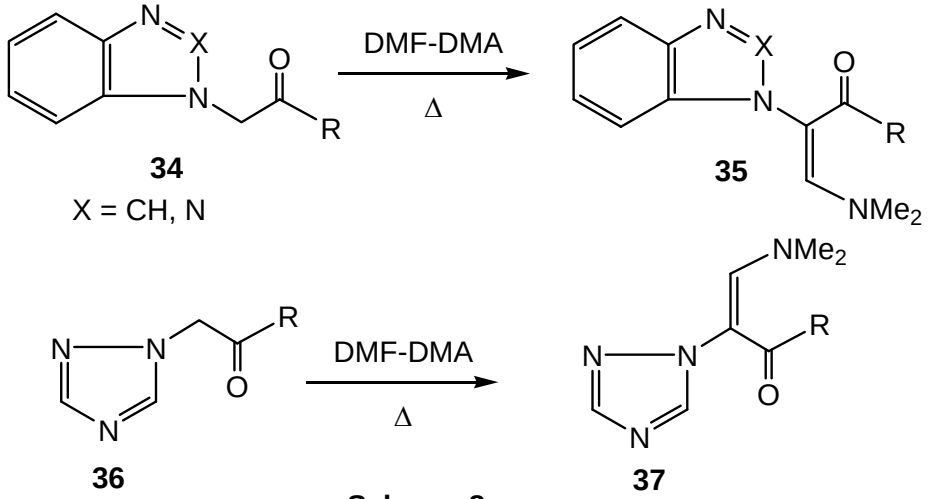
Scheme 6

Although α-picoline failed to condense with DMF-DMA, methyl functions in nitrotoluene **26**,[70,71] pyranone **27**,[66] pyridine **28**,[72-74] and pyrimidine **29**[75,76] have been successfully condensed with DMF-DMA to yield **30**-**33** respectively (Scheme 7).



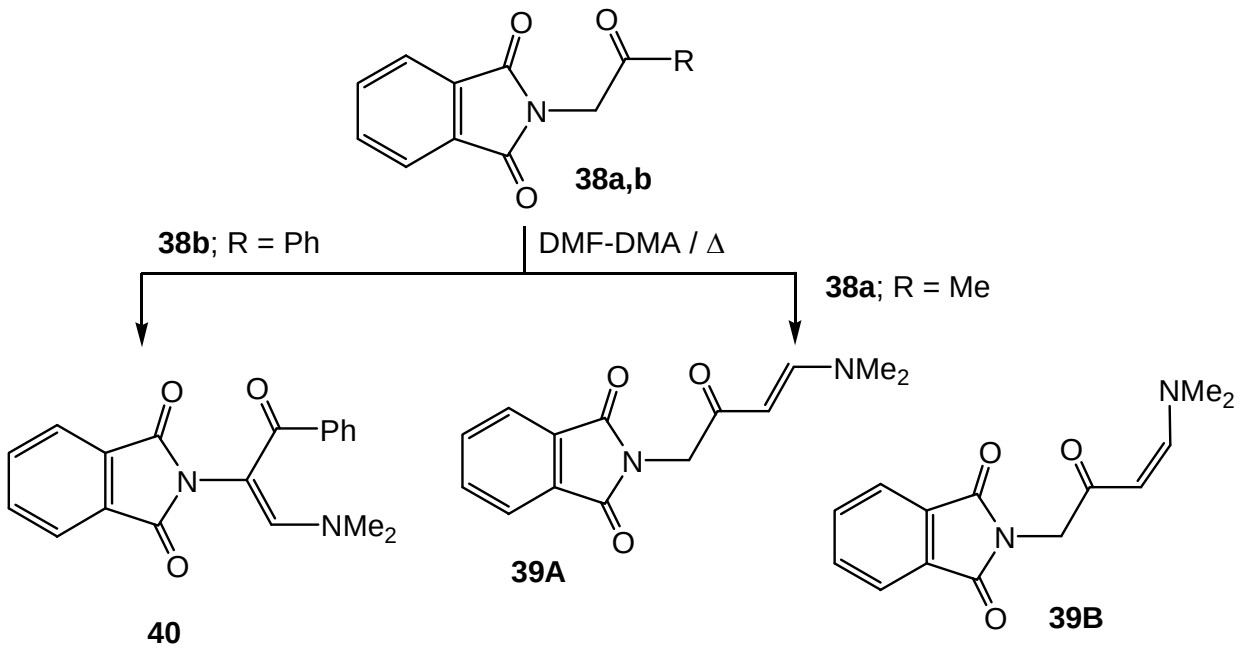
Scheme 7

Stanovnik *et al.*[40] have reported that condensation of acylaminoacid esters with DMF-DMA gave the corresponding enaminones. Elnagdi *et al.*[77] have also condensed azolylmethyl ketones **34** and **36** with DMF-DMA to obtain corresponding condensation products **35** and **37** respectively. Applying microwave irradiation in a domestic microwave oven enabled obtaining better yields of the enamines in much shorter time[44-65] (Scheme 8).



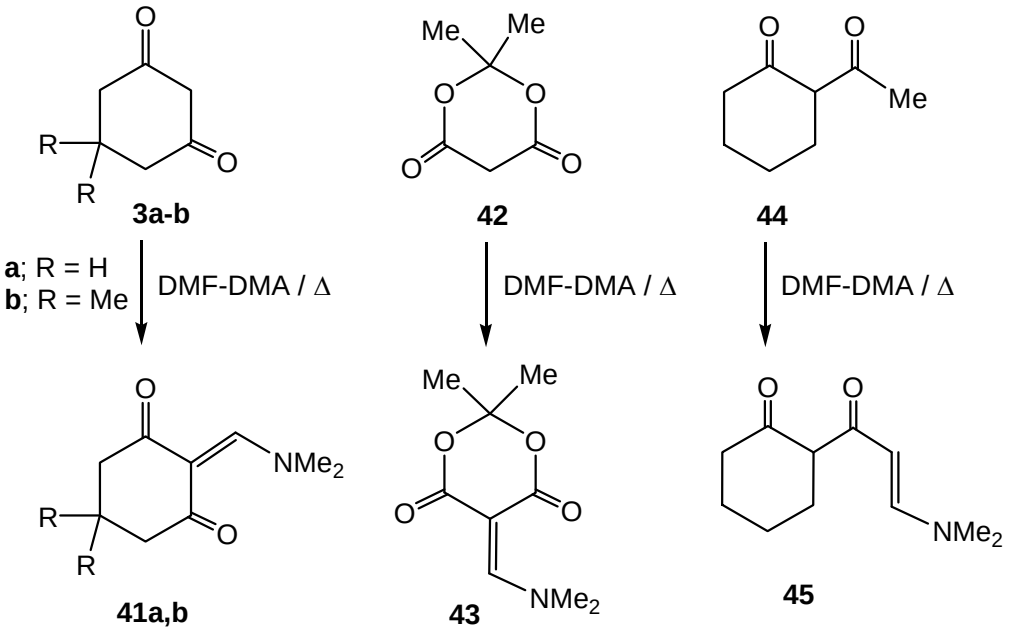
Scheme 8

Al-Mousawi *et al.*[57] have reported that condensation of **38a** with DMF-DMA affords the *trans* enaminone **39A**. Ignoring this report Al-Omran and Abou El-khair have reported the same synthesis and assigned *cis*-form for the resulting enaminones **39B**[78] based on observed coupling of olefinic protons. Condensation **38b** with DMF-DMA afforded **40** under the same condition (Scheme 9).



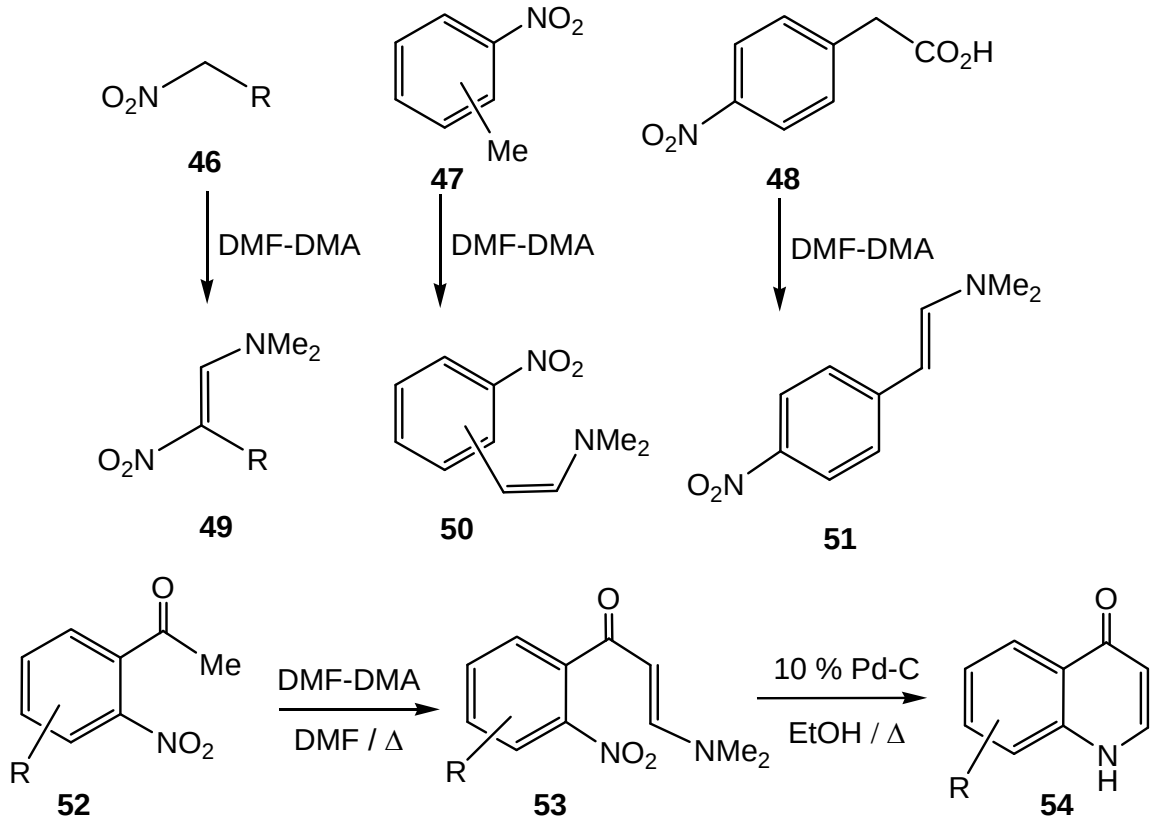
Scheme 9

Cyclic ketones[57,79,80] also condense with DMF-DMA to yield enamines **41a,b** and **43**. The methyl function rather than methylene function was the site of reaction of **44** with DMF-DMA yielding **45** (Scheme 10).



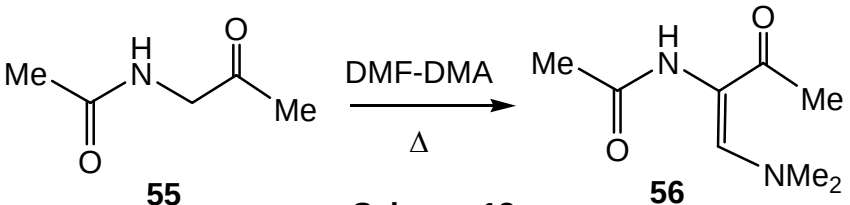
Scheme 10

Nitroalkanes **46**,[75] nitrotoluenes **47**,[81] and *p*-nitrophenylacetic acid **48**[82] also condense readily with DMF-DMA to yield enamines **49**, **50** and **51**, respectively (Scheme 11). Tois *et al.*[71] used DMF-DMA to prepare enamines through condensation with *o*-nitroacetophenone. This reaction was also extended to produce 4-(1*H*)-quinolones **54** (Scheme 11).



Scheme 11

The acetamide **55** condensed with DMF-DMA to yield **56**[83] (Scheme 12).

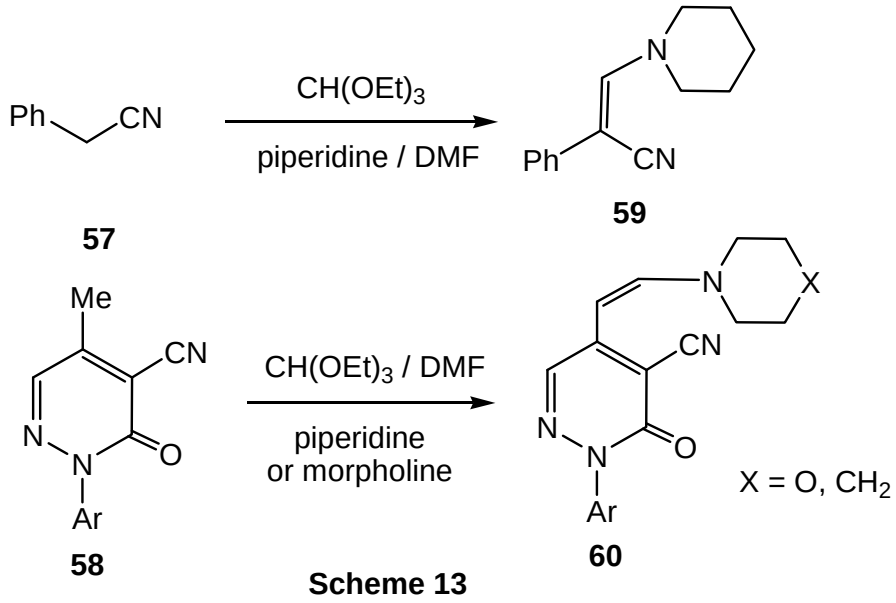


Scheme 12

2.1.II. CONDENSATION WITH TRIETHYLORTHOFORMATE

To avoid utility of expensive and toxic DMF-DMA Elnagdi *et al.*[84] reported an alternative way which depends on refluxing active methylenes with a mixture of triethylorthoformate and piperidine in DMF. The authors suggested initial *in situ* formation of amide acetal that condenses subsequently with active methylene compound to yield enamine. Thus, benzyl cyanide **57**, 4-methylpyridazine derivative **58** were

condensed with triethylorthoformate and piperidine to give **59**[85] and **60**[86] respectively (Scheme 13).

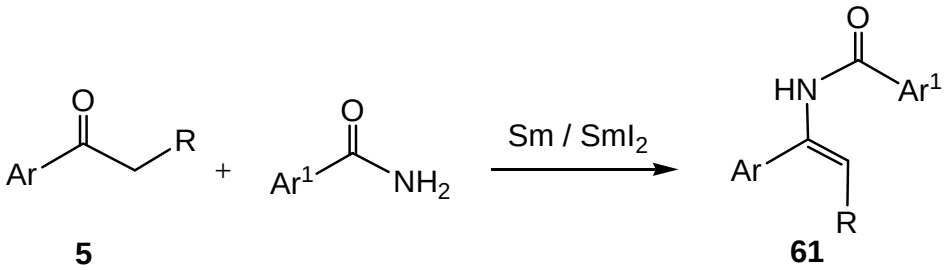


57 **59** **58** **60**

Scheme 13

2.1.III. CONDENSATION OF CARBONYL COMPOUNDS WITH AMINES AND AMIDES

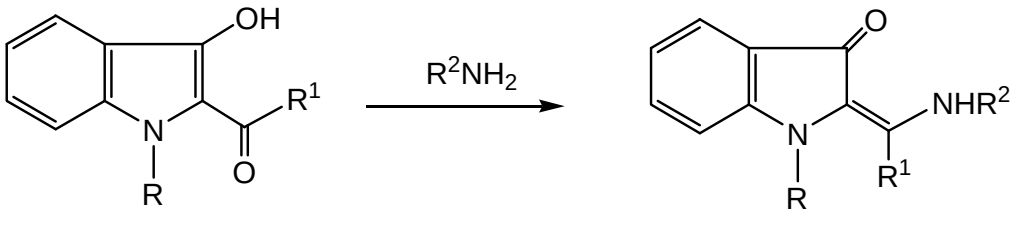
The condensation of carbonyl compounds with amino compounds in the presence of a dehydrating agent is other extensively utilized route to enamines. For example, amides condense with arylmethylene ketones **5** in presence of Sm/SmI_2 to yield enamine amides **61**[87] (Scheme 14).



5 **61**

Scheme 14

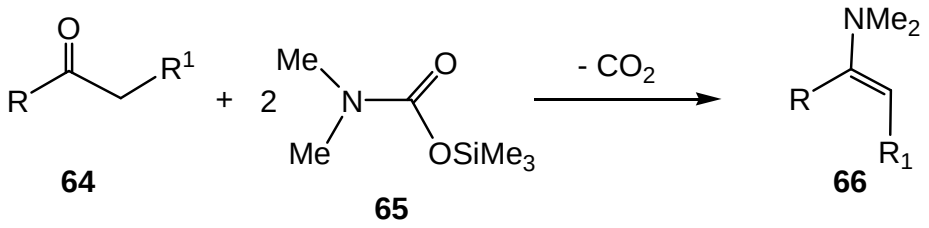
Similar way was applied for condensation of **62** with primary amines to give the corresponding enamines **63**[88] (Scheme 15).



62 **63**

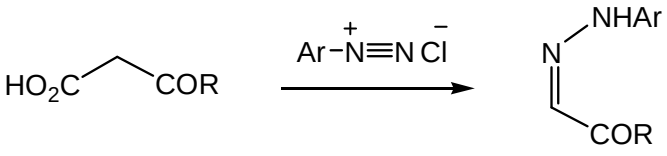
Scheme 15

Microwave irradiation of ketones with secondary amines in the absence of a solvent has been reported to afford enamines in excellent yields.[64] Ketones **64** condense with silyl carbamate **65** to yield enamines **66**[89] (Scheme 16).



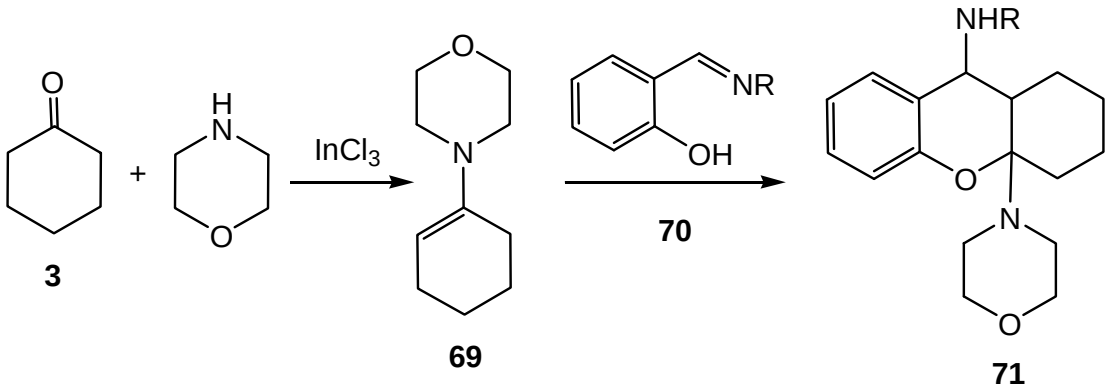
Scheme 16

Condensation of aldehydes or ketones with hydrazines gives hydrazones in good yields. This is the most efficient condensation procedure for azaenamines. Other approach is the coupling reaction of β-keto acids with aromatic diazonium salts and subsequent decarboxylation[90] (Scheme 17).



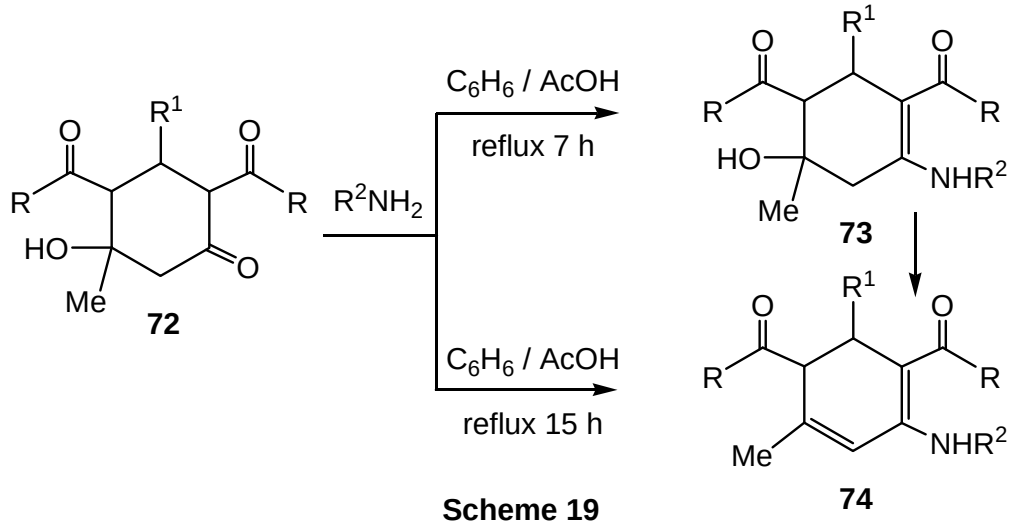
Scheme 17

Cyclohexanone condensed with morpholine in the presence of 20 % molar $InCl_3$ in acetonitrile to yield *in situ* enamine **69** which added to Schiff's bases **70** to yield **71**[91] (Scheme 18).



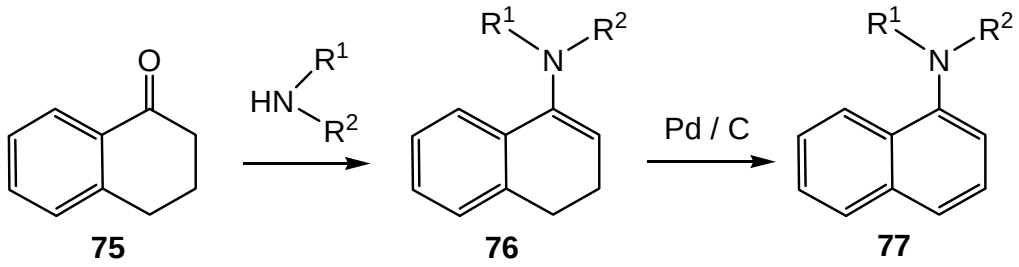
Scheme 18

An interesting synthesis of 2-aminocyclohexadienes **74** from reaction of **72** with amines has been reported. Intermediate **73** was also prepared on conducting condensation in refluxing benzene and acetic acid for 7 h[92] (Scheme 19).



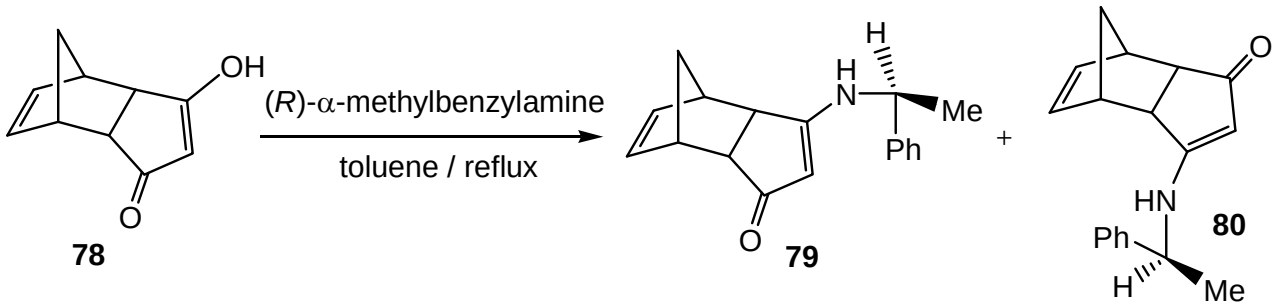
Scheme 19

Aminonaphthalenes **77** were obtained *via* condensing tetralone **75** with amines and subsequent oxidation of resulted enamines **76**[93] by Pd/C (Scheme 20).



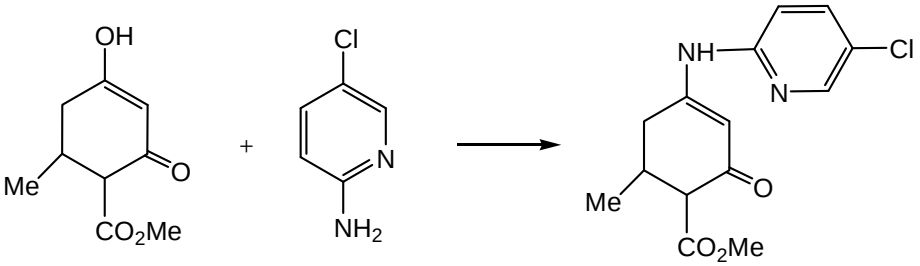
Scheme 20

The tricyclic compound **78** condense with (*R*)-α-methylbenzylamine in the presence of toluene under reflux to yield a mixture of **79** and **80**[94] (Scheme 21).



Scheme 21

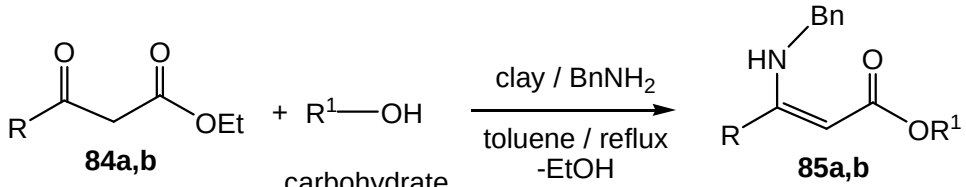
Anticonvulsant enamine **83** was prepared *via* condensing **81** and **82**[95] (Scheme 22).



81 **82** **83**

Scheme 22

Fernando *et al.*[96] have reported that clay catalyzed efficiently *trans*-esterifications and enaminoesters formation in *one-pot* reaction from β-ketoesters, carbohydrate derivatives and amines, in good to excellent yields without decomposition of the carbohydrate moieties[96] (Scheme 23).



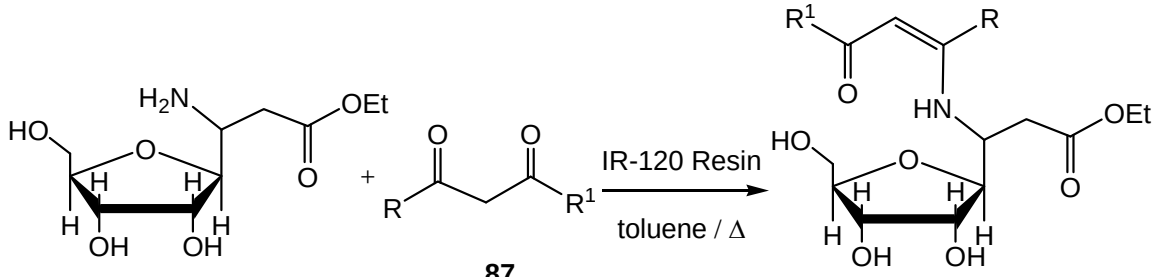
84a,b

a; R = Me
b; R = Ph

85a,b

Scheme 23

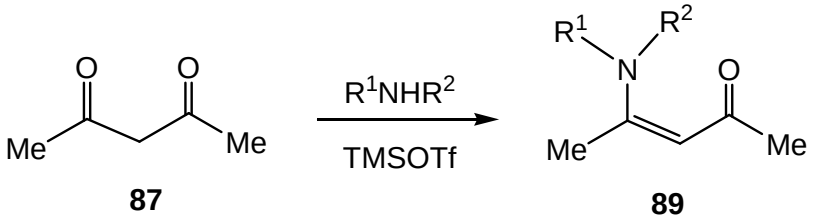
β-Ketoesters and acetylacetone **87** on condensation with glycosylated aminoesters **86** in the presence of IR-120 resin resulted in high yields of glycosyl enaminoesters or ketones **88**[97] (Scheme 24).



86 **87** **88**

Scheme 24

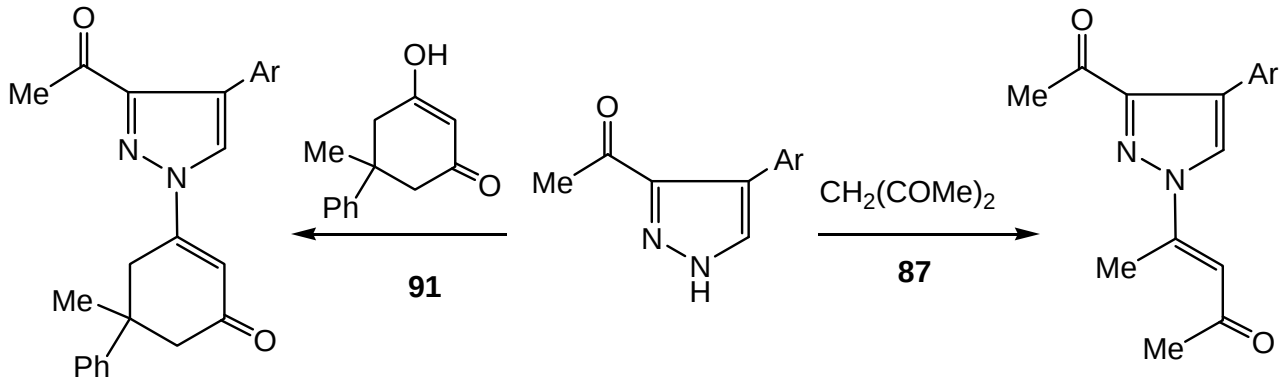
The condensation of β-diketones **87** with secondary amines in the presence of TMSOTf[98] has been reported to afford enaminones **89** (Scheme 25).



87 **89**

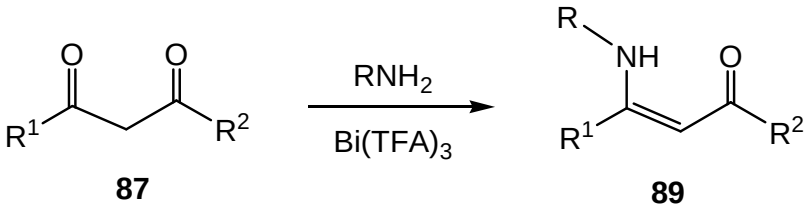
Scheme 25

Pyrazolylenamines **92** and **93** are prepared from condensation of 3-acetylpyrazole derivative **90** with pentane-2,4-dione **87** and cyclohexene derivative **91** respectively[99] (Scheme 26).



Scheme 26

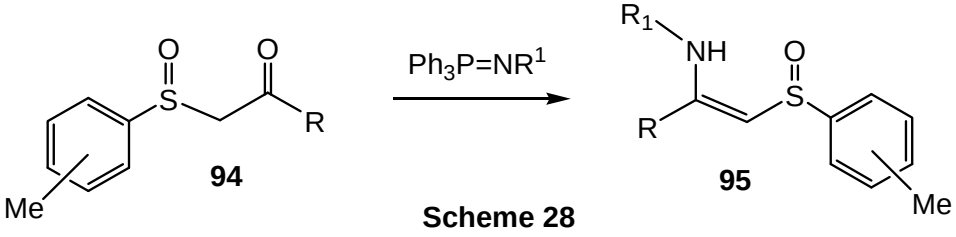
Recently Bismuth (III) trifluoroacetate has been found to be an extremely efficient catalyst for the preparation of β-enaminones. In addition this catalyst is highly regio- and chemo-selective[100] (Scheme 27).



Scheme 27

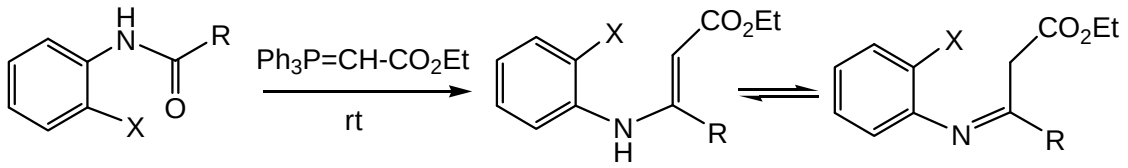
2.1.IV. MISCELLANEOUS CONDENSATION

Compound **94** reacts with phosphonium imines to yield sulphinylenamines **95**[101] (Scheme 28).



Scheme 28

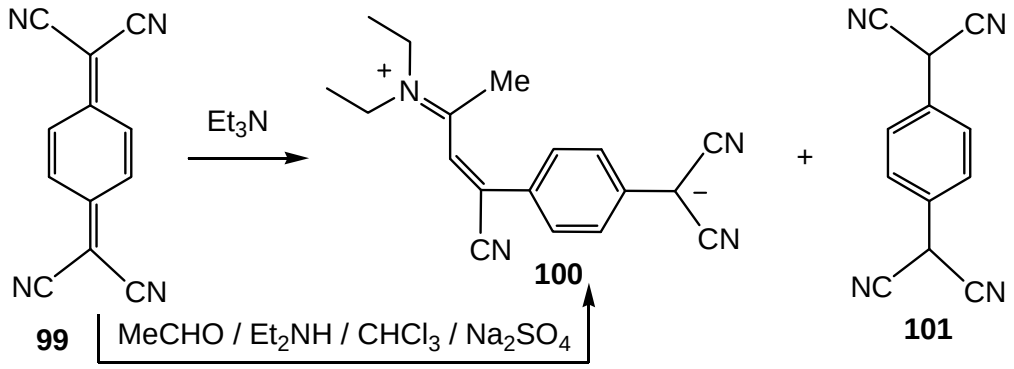
Amides **96** reacted with phosphoranes to yield a mixture of enamines **97** which is thought to exist in equilibrium with **98**[102] (Scheme 29).



96 **97** **98**

Scheme 29

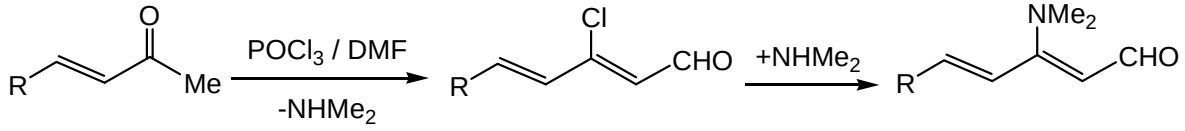
The reaction of **99** with triethylamine gives **100** and **101**. On the other hand, compound **100** can be produced *via* reaction of **99** with acetaldehyde and diethylamine[103] (Scheme 30).



99 **100** **101**

Scheme 30

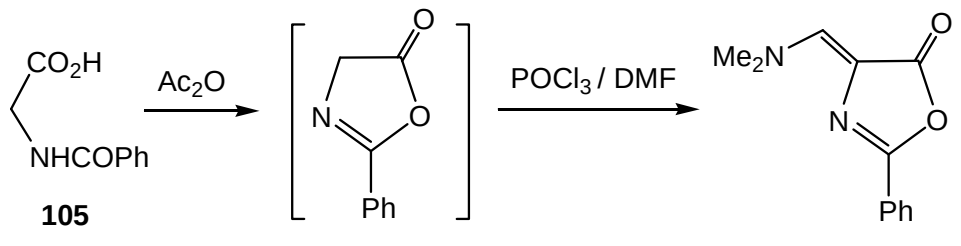
Reaction of α,β-unsaturated ketones **102** with $POCl_3$/DMF affords β-chloroenones **103**. The latter reacted with eliminated amine to afford the expected enamines **104**[104] (Scheme 31).



102 **103** **104**

Scheme 31

Reaction of hippuric acid with acetic anhydride gives non-isolable oxazolone derivative which was trapped by Vilsmeier reagent to afford the corresponding enamine **106**[105] (Scheme 32).



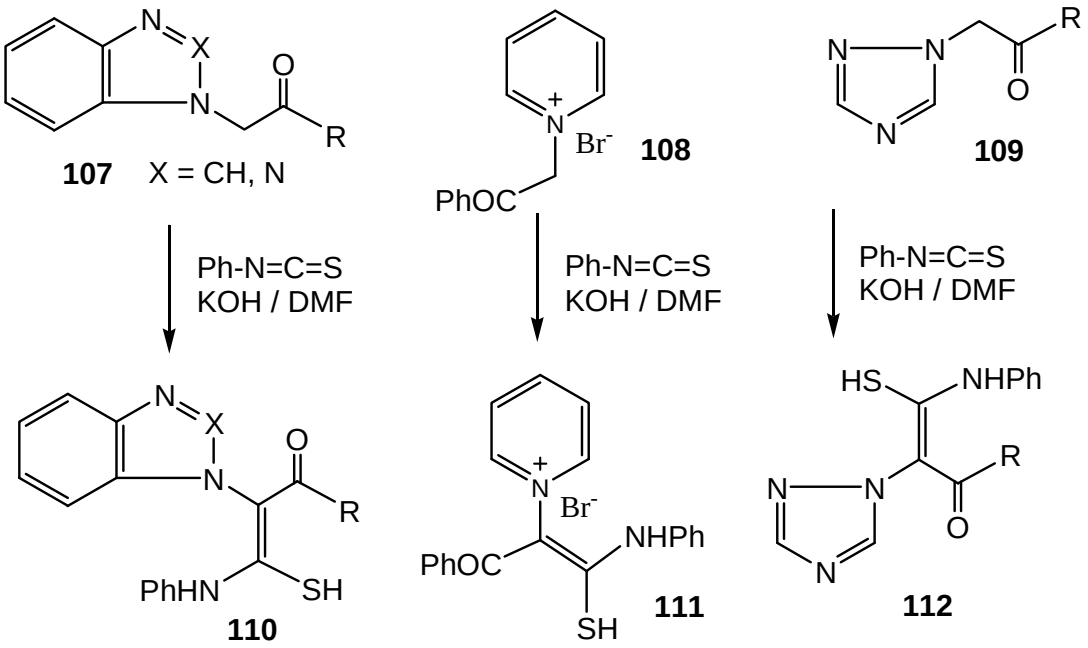
105 **106**

Scheme 32

2.2. ADDITION REACTIONS:

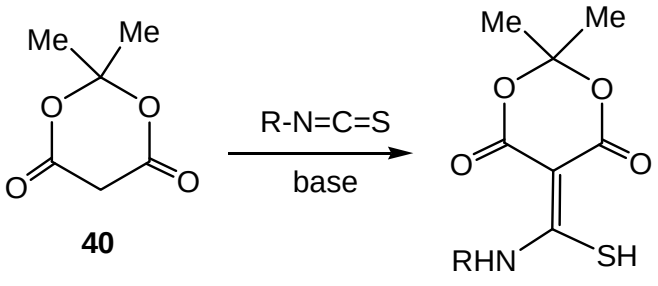
2.2. I. ADDITION OF ACTIVE METHYLENE TO ISOTHIOCYANATE

The addition of active methylene nitriles to isocyanates and isothiocyanates is the most general route to enamines *via* addition reactions. Recent application of this approach is the addition of isothiocyanate to azolylacetone and azolylacetophenone in presence of potassium hydroxide[77] (Scheme 33).



Scheme 33

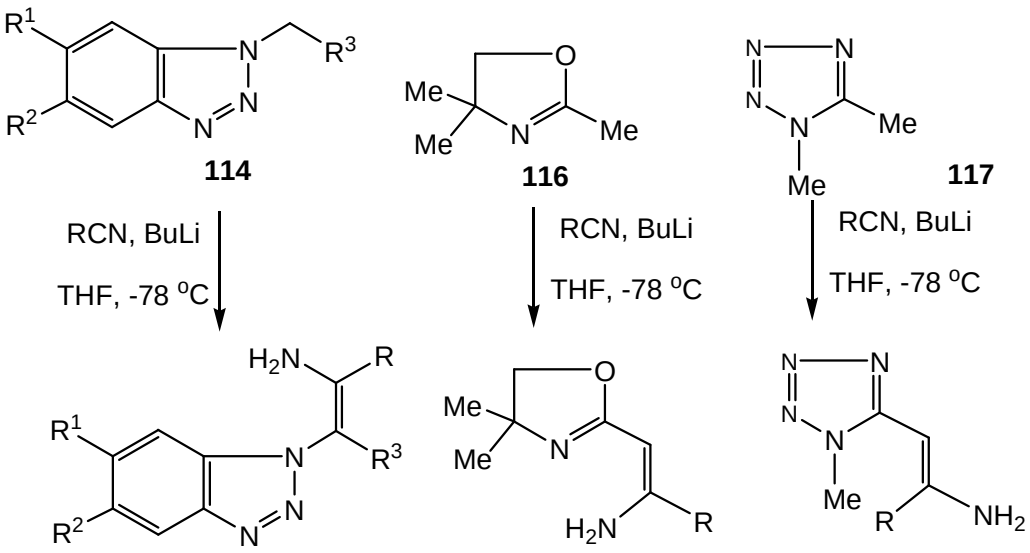
Reactions of isothiocyanates with active methylenes **40** have been surveyed by Beit-Yannai and Rappoport[106] (Scheme 34).



Scheme 34

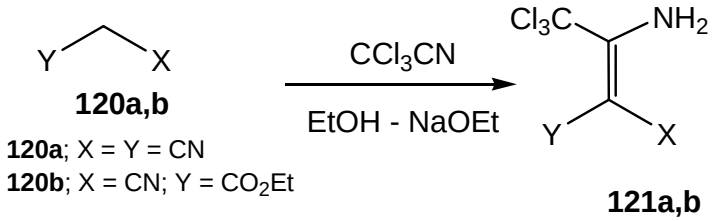
2.2. II. ADDITION OF ACTIVE METHYLENE TO NITRILES

Katritzky *et al.* could successfully affect addition of nitriles to benzotriazoles **114** to yield **115** in presence of BuLi in THF[107] (Scheme 35). Even methyl function in oxazolines **116** and 1,5-dimethyl-1,2,3,4-tetrazoles **117** add to simple nitriles yielding enamines **118** and **119**, respectively[108] (Scheme 35).



Scheme 35

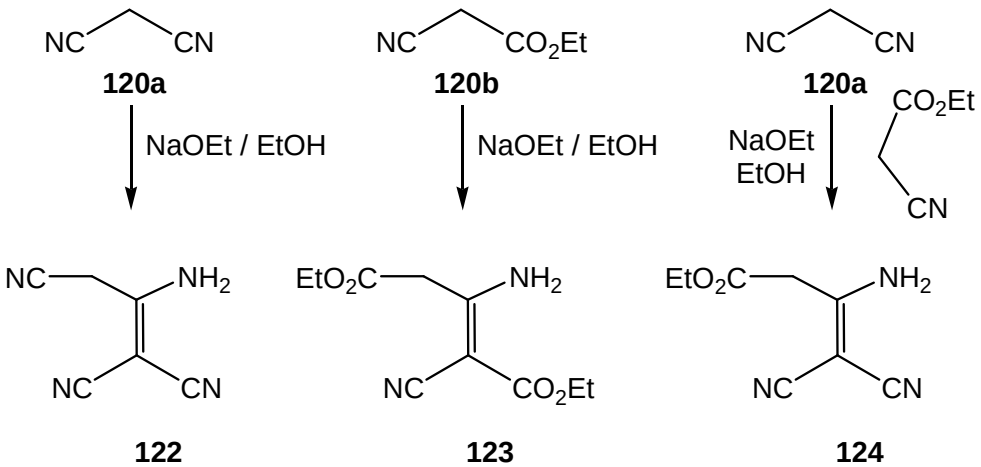
Reactions of trichloroacetonitrile with active methylenes **120a,b** to yield enamines **121a,b** in presence of bases has been surveyed by Erian and Sherief[109] (Scheme 36).



120a; X = Y = CN
120b; X = CN; Y = CO_2Et

Scheme 36

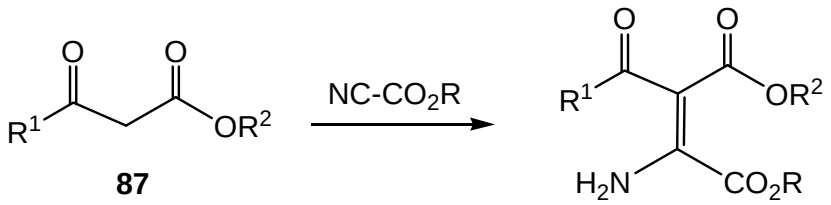
Strong bases affect dimerization of active methylenes. For example, malononitrile **120a** readily affords **122** on treatment with sodium ethoxide,[110,111] ethyl cyanoacetate **120b** produced **123**[112,113] and sodium ethyl cyanoacetate adds malononitrile yielding **124**[114,115] (Scheme 37).



Scheme 37

2.2. III. MISCELLANEOUS SYNTHESIS

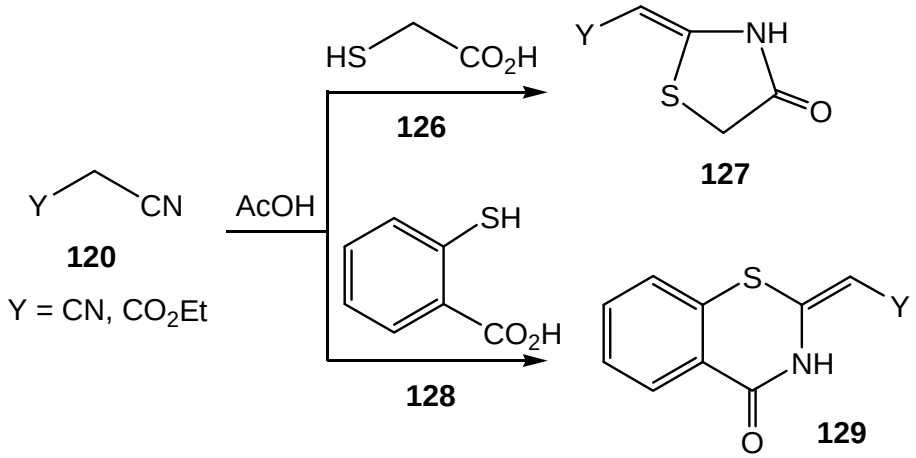
Addition of β-ketoesters **87** to α-cyanoesters yields the corresponding adducts **125**[116] (Scheme 38).



87 **125**

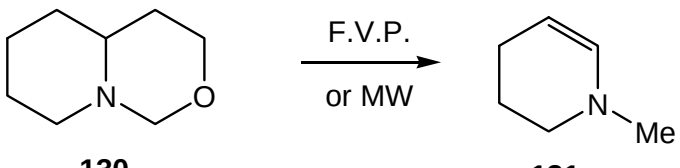
Scheme 38

Similar addition of thioglycolic acid **126** and thiosalicylic acid **128** to active methylene nitriles affords **127** and **129** respectively[117,118] (Scheme 39).



Scheme 39

The synthesis of 2,3-dihydropiperidine enamines[119,120] has typically been carried out by one of the following methods: oxidation of saturated piperidines with mercuric acetate,[121] reduction of aromatic heterocycles[122] and amides,[123] addition of Grignard reagents to lactams,[124] and base catalyzed isomerizations of 1,2,5,6-tetrahydropyridines.[125] It has recently been found that perhydropyrido[1,2-*c*]-[1,3]oxazine **130** is a good source of various *N*-methyl-4,5,6,7-tetrahydropiperidine enamines **131** using only the green reactions of flash vacuum thermolysis or microwave excitation of this oxazine[126] (Scheme 40).

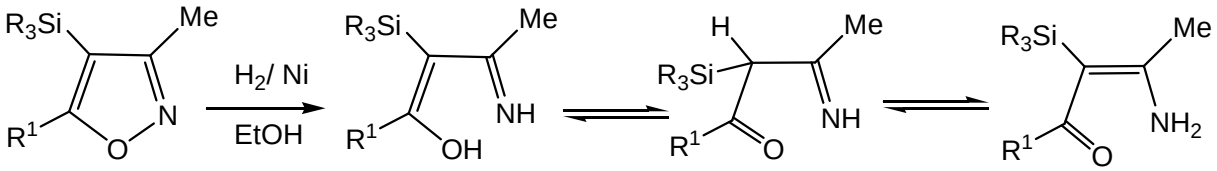


130 **131**

Scheme 40

Silyl β-enaminones **135** have been synthesized by reductive cleavage of silylisoxazoles **132**. These synthons bearing the silyl group in different positions of the enamine ketonic system are of great interest

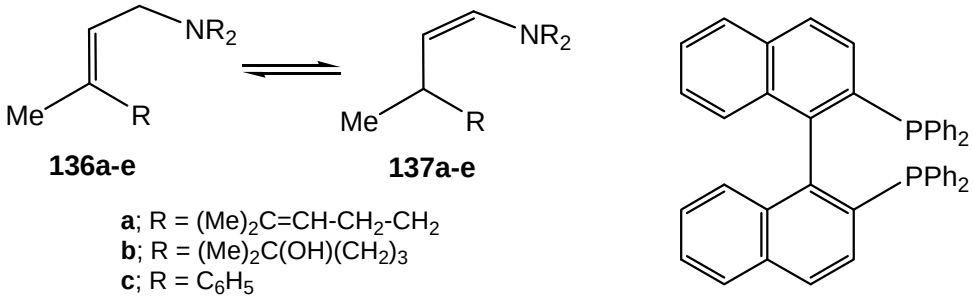
in the construction of a variety of heterocycles[127] (Scheme 41).



132 **133** **134** **135**

Scheme 41

The rhodium metal catalyzed isomerization of asymmetric allylamines **136a-e** to enamines **137a-e**. This methodology was developed by Otsuka, Tani, Noyori and co-workers.[128] Cationic Rh complexes containing (1,1'-binaphthalene-2,2'-diyl)*bis*(diphenylphosphine) (BINAP) **138** have been found to be excellent catalysts both in terms of chemo-selectivity as well as enantio-selectivity for these isomerizations[129,130] (Scheme 42).



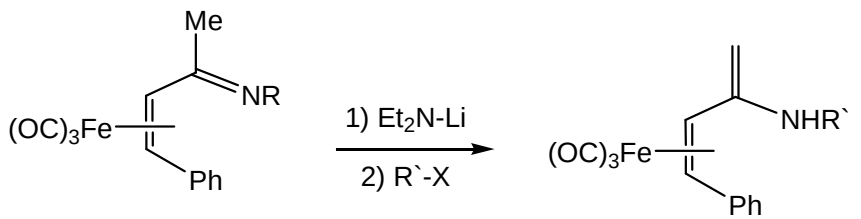
136a-e **137a-e**

a; R = $(Me)_2C{=}CH{-}CH_2{-}CH_2$
b; R = $(Me)_2C(OH)(CH_2)_3$
c; R = C_6H_5
d; R = $MeOCH_2$
e; R = $CH(OMe)_2$

138 (BINAP)

Scheme 42

Treatment of (2-methyl-1-azabuta-1,3-diene)tricarbonyliron(0) complexes **139a-d** with lithium diethylamide followed by alkylation leads to the formation of tertiary (enamine)tricarbonyl iron(0) complexes **140a-c** in good yield[131] (Scheme 43).



139a-d

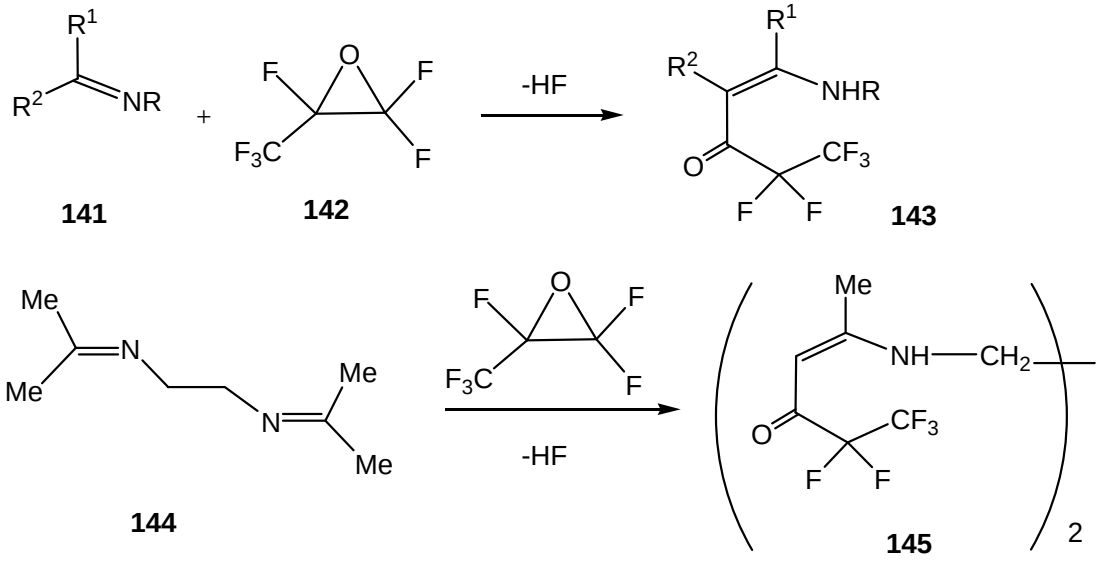
a; R = C_6H_5 **b**; R = $C_6H_5CH_2$
c; R = $(Me)_2CH$ **d**; R = 4-$MeOC_6H_4$

140a-c

a; R` = $C_6H_5$ **b**; R` = $C_6H_5CH_2$
c; R` = $CH_2{=}CHCH_2$

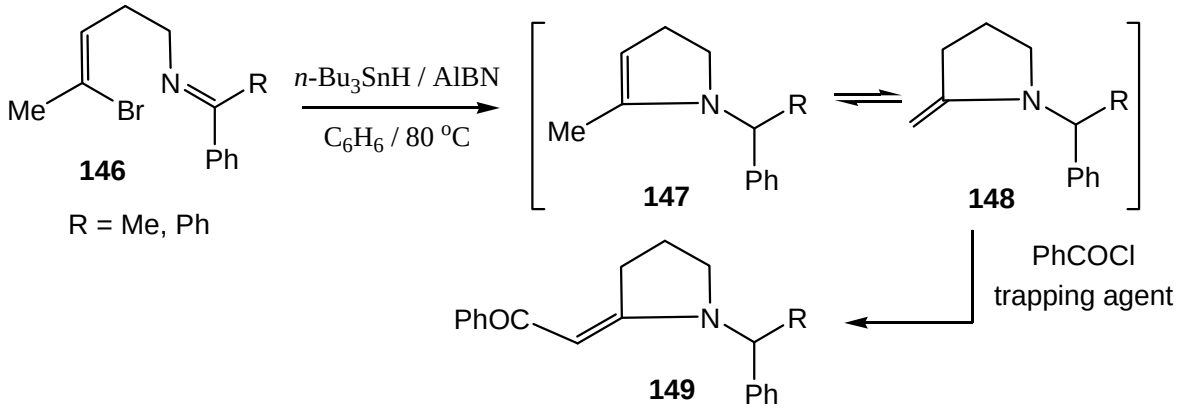
Scheme 43

Imines **141** and *bis*-imine **144** react *via* their enamine tautomers with terminal perfluorinated epoxides, e.g hexafluoropropene oxide to produce fluornated enamine ketones **143** and **145**, respectively[132] (Scheme 44).



Scheme 44

Free radical-mediated vinyl amination is a new scope that has been discussed for the preparation of pyrrolidine enamines using 5-*exo*-*trig* cyclizations of vinyl radicals to the nitrogen of azomethines. The research mainly focuses on *N*,*N*-dialkyl enamines since their nucleophilicity renders them the most challenging enamines to synthesize using redox conditions[133] (Scheme 45).



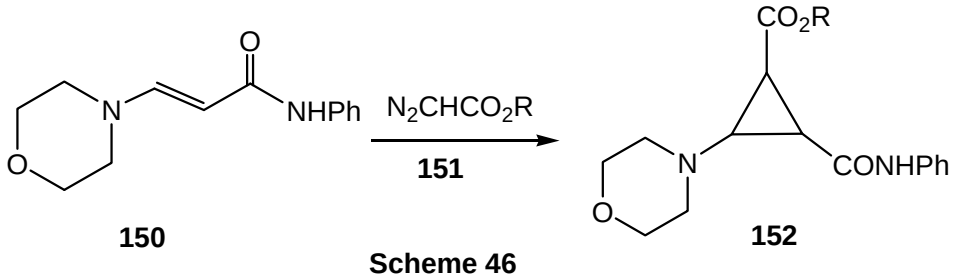
Scheme 45

3. ENAMINES AND AZAENAMINES AS PRECURSORS TO CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS

3.1. POLYFUNCTIONAL CARBOCYCLIC

Carbenes, generated *in situ via* thermolysis of diazoacetals **151** affords cyclopropanyl amines **152** *via* a

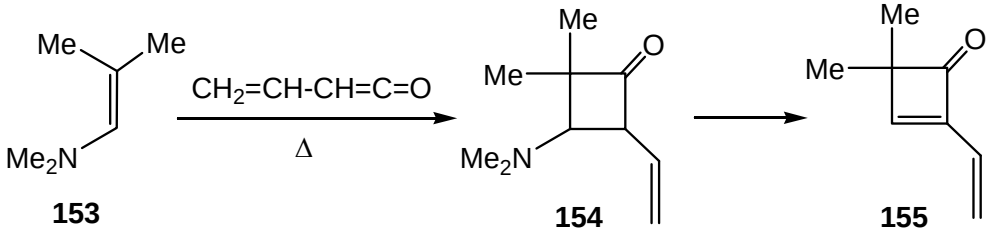
cheleotropic [2+2] cycloaddition[134] (Scheme 46).



150 **152**

Scheme 46

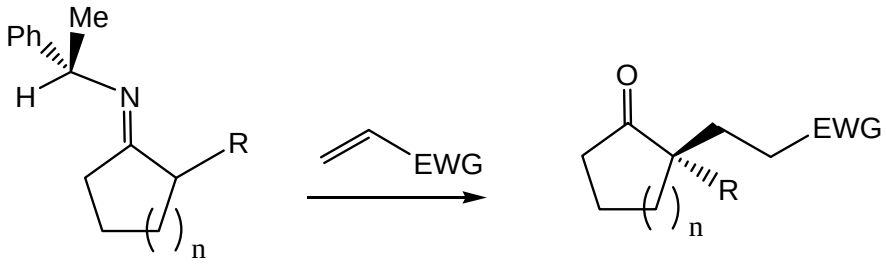
The usefulness of the reaction of β,β-dimethylenamines **153** with vinylketene for the synthesis of cyclobut-2-enones **155** was investigated[135] (Scheme 47).



153 **154** **155**

Scheme 47

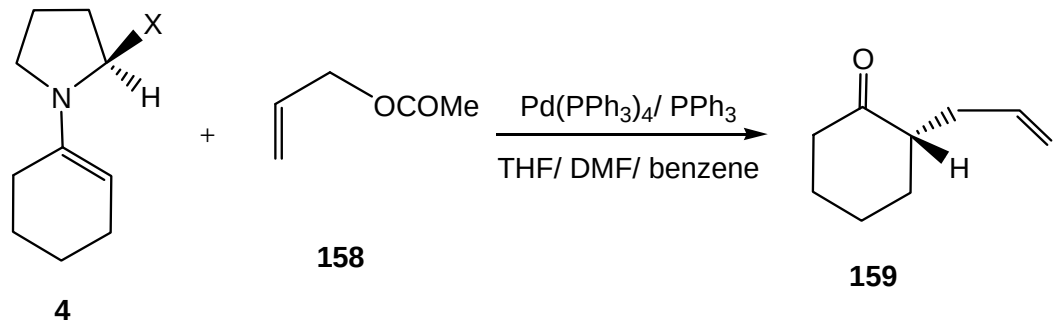
Nour *et al.*[136] reported formation of **157** *via* reacting **156** with electrophilic alkenes (Scheme 48).



156 **157**

Scheme 48

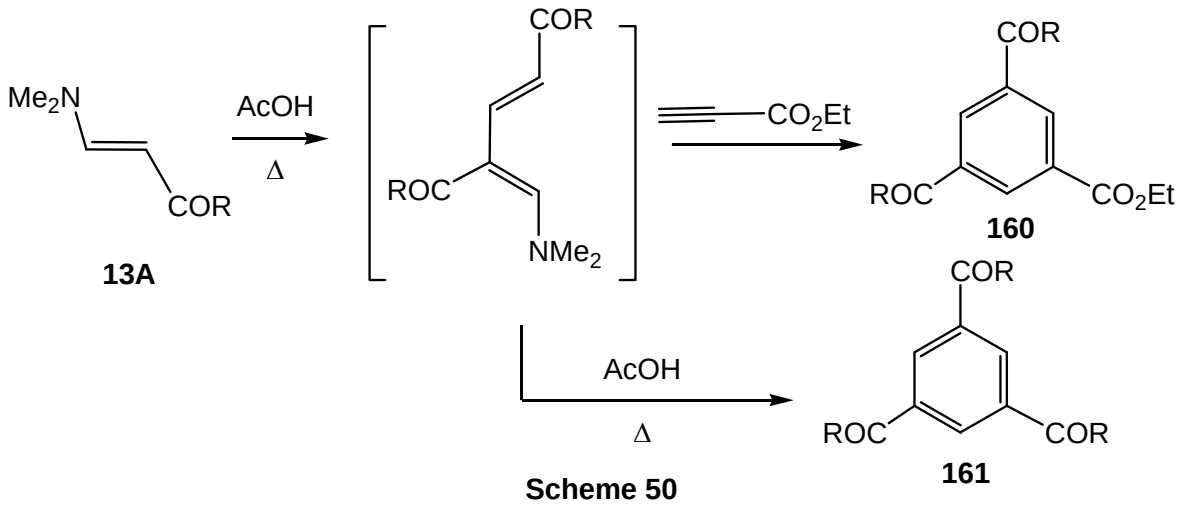
Reacting the chiral (*S*)-enamine **4** derived from (*S*)-proline allyl ester and cyclohexanone with allyl acetate **158** in the presence of palladium catalyst and subsequent hydrolysis gave (*S*)-(-)-2-allyl cyclohexanone **159**[137] (Scheme 49).



4 **158** **159**

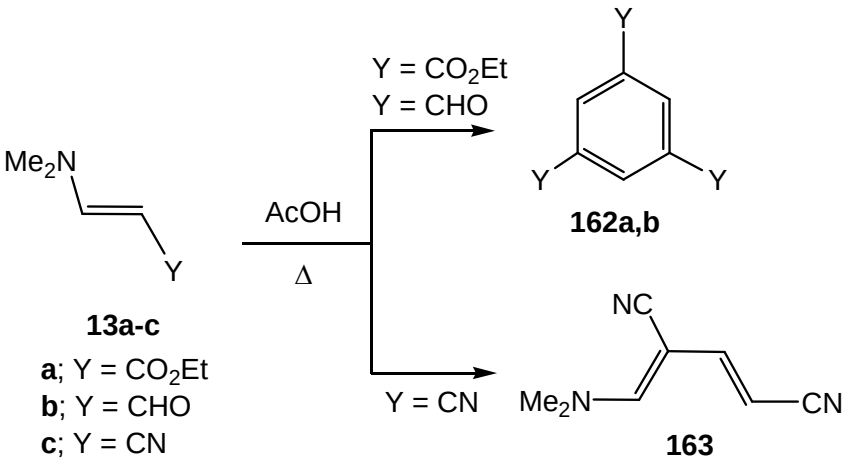
Scheme 49

Attempted addition of ethyl propiolate to enaminones **13A** resulted in formation of ethyl benzoate derivatives **160**. It is believed that under reaction conditions enaminone **13A** initially undergo self condensation and the formed self condensation product then adds to ethyl propiolate to give the desired product. In support of this, refluxing enaminone **13A** in acetic acid gives triacylbenzene **161** most likely *via* self condensation intermediate[138,139] (Scheme 50).



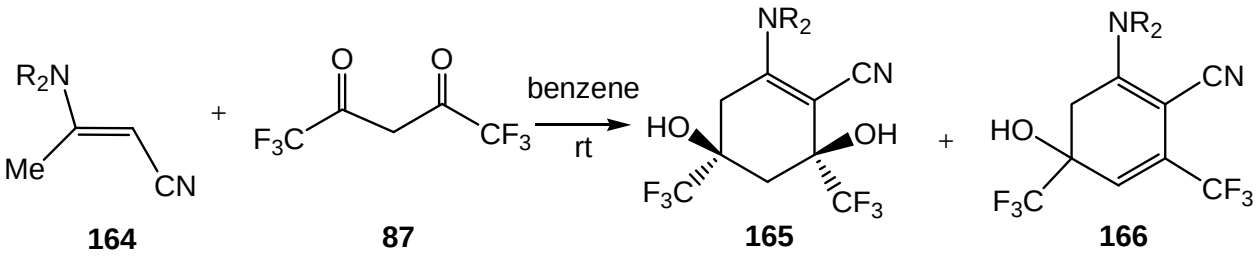
Scheme 50

Quite similar formation of benzene derivatives **162a,b** *via* refluxing enaminoesters **13a** and enaminals **13b** in acetic acid has been reported[140] while enaminonitriles **13c** afforded only self condensation product **163** (Scheme 51).



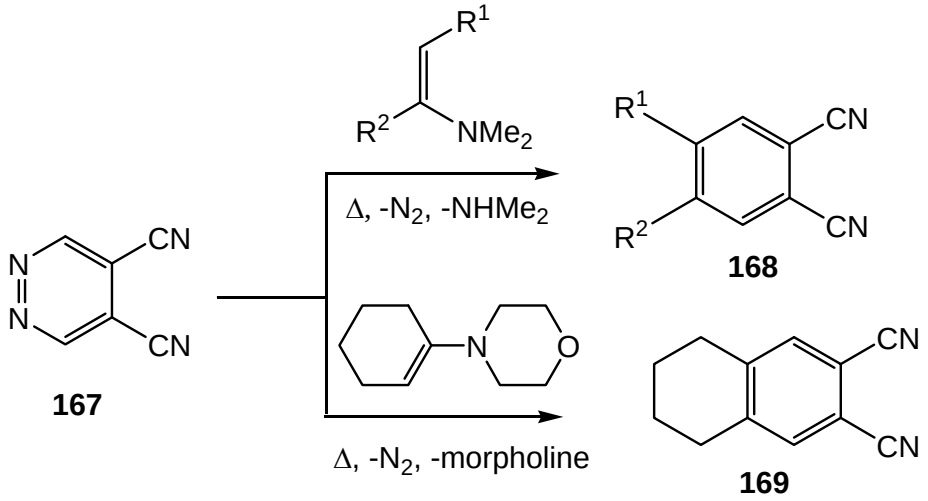
Scheme 51

Enamine derivatives of β-aminocrotonitrile **164** react with 1,1,1,5,5,5-hexafluoroacetylacetone **87** in benzene at room temperature for 2–3 days affording a mixture of cyclohexene **165** and cyclohexadiene **166** derivatives in combined yield 35–40%, precipitated from the reaction mixture[141] (Scheme 52).



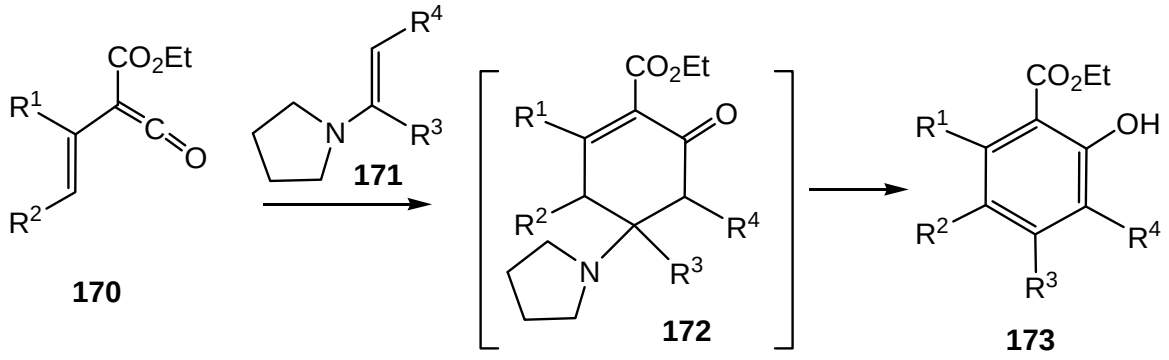
Scheme 52

Simple enamines behave as typical electron rich double bond and thus add electron poor diene systems in a typical inverse electron demand Diels-Alder reaction. Thus, reacting enamines with 3,4-dicyanopyridazine **167** gives dicyanobenzene **168**[142] and tetrahydro-dicyanonaphthalene **169**[143-146] (Scheme 53).



Scheme 53

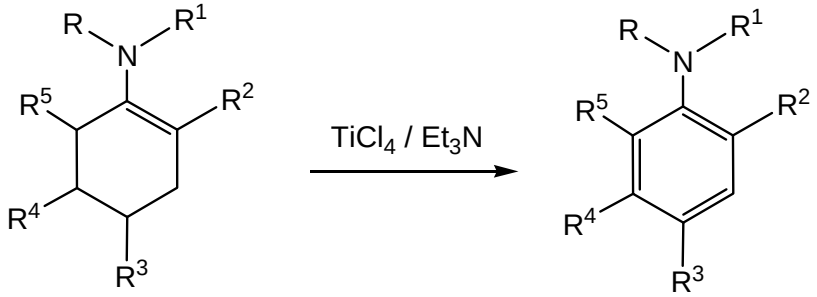
Reaction of vinylketenes **170** with enamines **171** gives ethyl benzoate derivatives **173** *via* non-isolable intermediate **172**[147] (Scheme 54).



Scheme 54

Several reports on synthetic applications of the $TiCl_4/Et_3N$ reagent system have been published. For

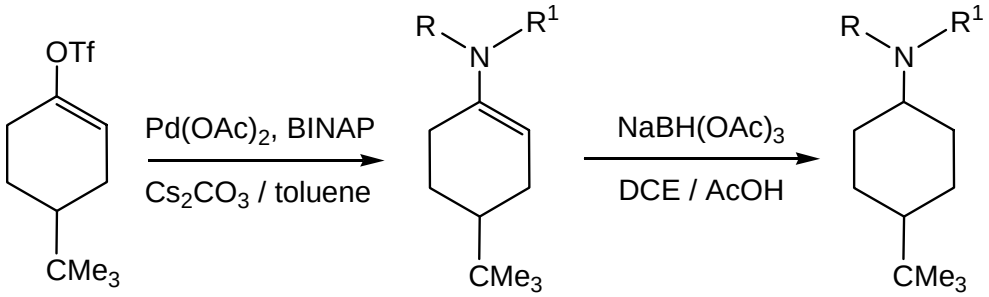
examples i) conversion of ketimines to pyrroles,[148] trialkylamines and ketones to α,β-unsaturated aldehydes,[149] ii) the reductive coupling of aromatic aldehydes and imines to the corresponding diols and diamines,[150] iii) the conversion of 1-alkynes to diynes,[151] *N*,*N*-dialkylarylamines to *N*,*N*,*N*`,*N*`-tetra-alkylbenzidines,[152] iv) the enantioselective oxidative coupling of the chiral 1,1-*bi*-2-naphthyl ester of phenylacetic acid,[153] v) the synthesis of cyclobutanone derivatives *via* iminium ions,[154] and vi) the intramolecular reductive coupling of chiral diimines to chiral 3,4-disubstituted-2,5-diazabicyclo [4.4.0]decanes.[155] Srinivas *et al.* reported[156] that enamines **174** react with $TiCl_4/Et_3N$ at 0–25 °C to give the corresponding aromatized products **175** (Scheme 55).



174 **175**

Scheme 55

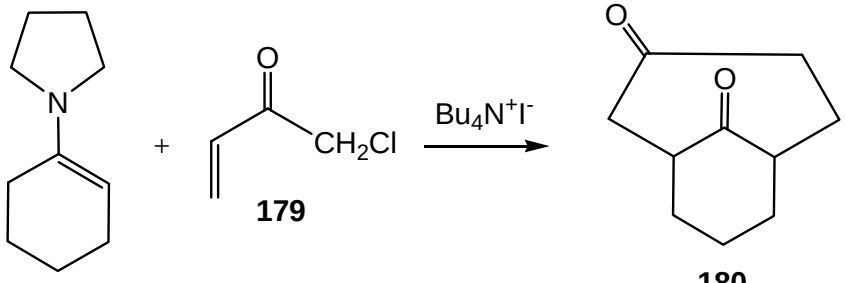
Enamine **177** was reduced by sodium borohydride triacetate to produce amines **178**[157] (Scheme 56).



176 **177** **178**

Scheme 56

An interesting alkylation that leads to a bicyclic compound **180** is the reaction of **4** with 1-chlorobut-3-ene-2-one **179** in tetrabutyl ammonium iodide[158] (Scheme 57).

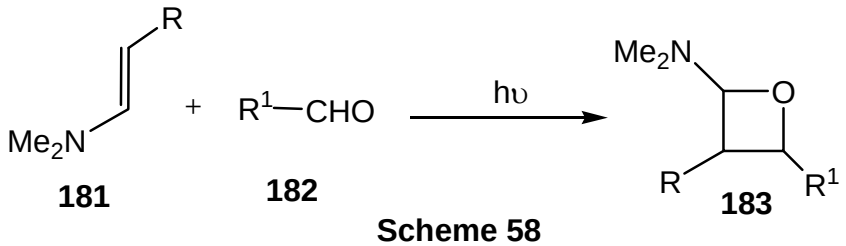


4 **179** **180**

Scheme 57

3.2. FOUR-MEMBERED RING WITH ONE HETEROATOM

Enamines **181** undergo allowed photochemical [2+2] cycloaddition with aldehydes **182** (Paterno-Büchi reaction)[159] to yield oxetane derivatives **183** (Scheme 58).



181 **182** **183**

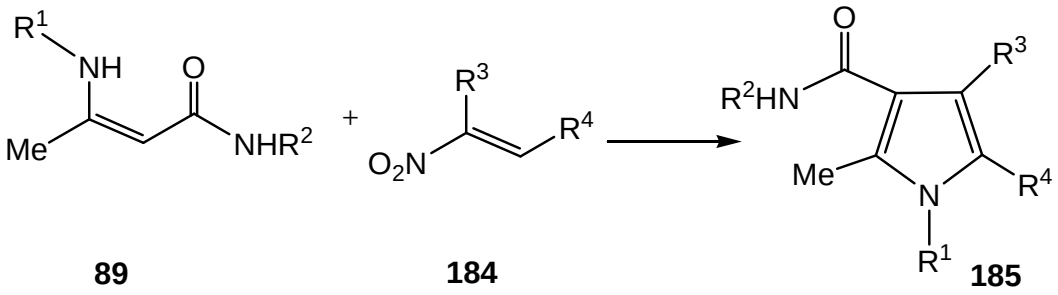
Scheme 58

3.3. FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

3.3. I. FIVE-MEMBERED RINGS WITH ONE HETEROATOM

3.3. I. 1. PYRROLES

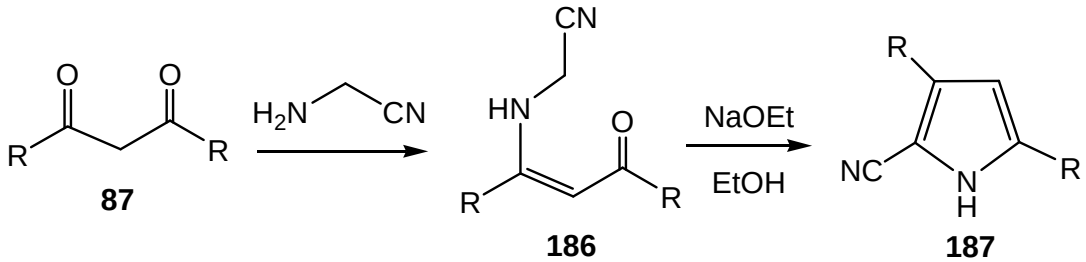
A versatile solid-phase synthesis of pyrrole-3-carboxamides **185** from enaminones **89** and α-alkyl-α-nitroalkenes **184** has been reported[160] (Scheme 59).



89 **184** **185**

Scheme 59

The reaction of 1,3-dicarbonyl compounds **87** with aminoacetonitrile afforded enaminones **186**. Cyclization of the latter product **186** upon treatment with ethanolic solution containing sodium ethoxide gave the corresponding pyrrole derivatives **187**[161] (Scheme 60).

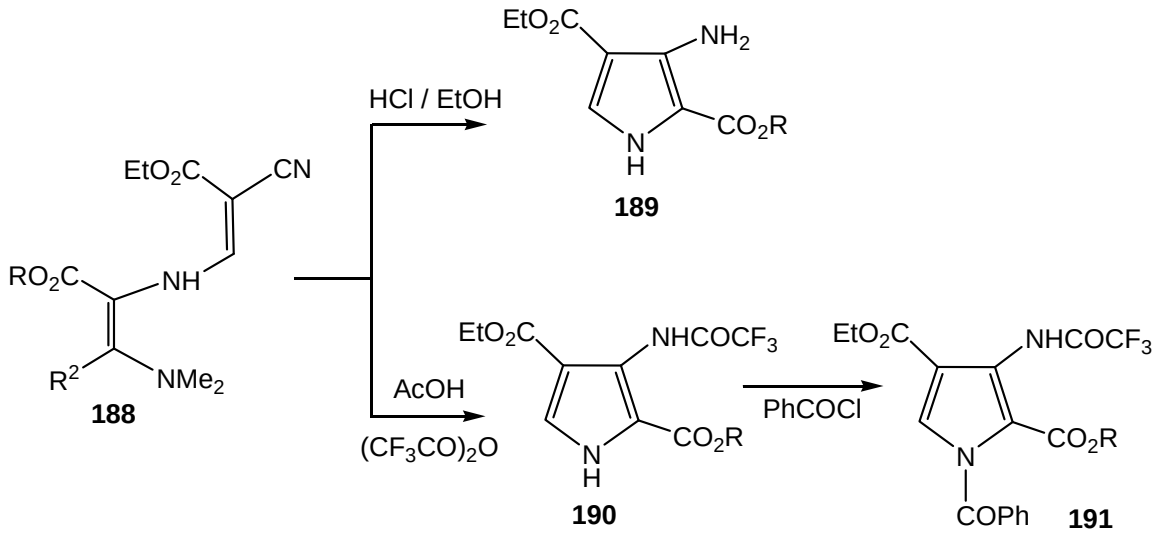


87 **186** **187**

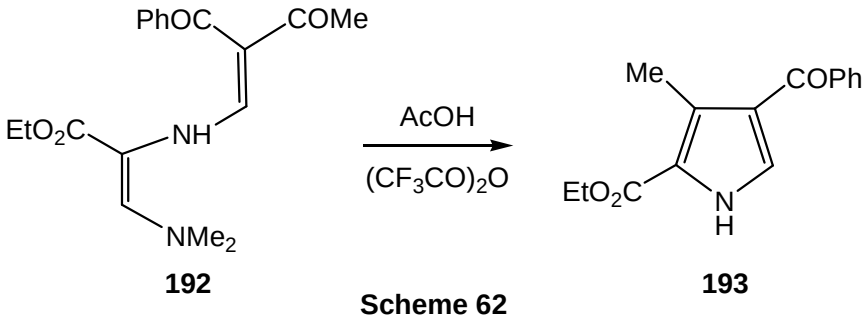
Scheme 60

The recent developments in utility of enamines as precursors to pyrrole have been reported by Stanovnik

et al.[162,163] (Schemes 61, 62). Thus **188** afforded **189** upon reflux in ethanol in presence of hydrochloric acid. On the other hand, **188** afforded **190** upon treatment with acetic acid in presence of trifluoroacetic anhydride. Compound **190** could be benzoylated to yield **191**. Heating **192** in acetic acid afforded **193**.



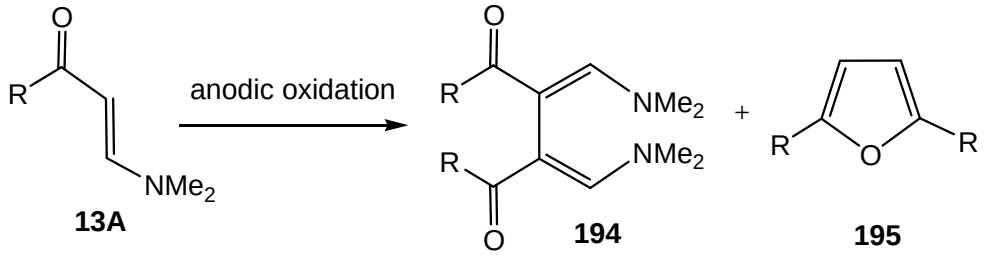
Scheme 61



Scheme 62

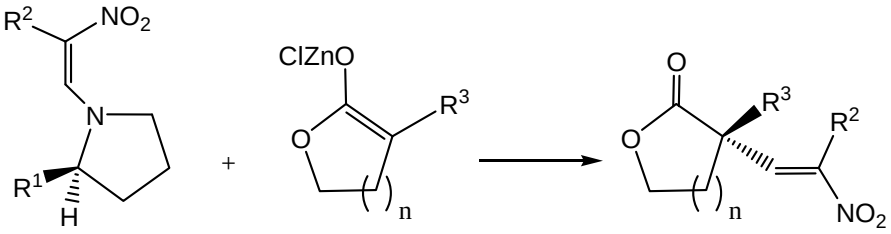
3.3. I. 2. FURANS

Anodic oxidation of enaminones **13A** gives a mixture of **194** and **195**[164] (Scheme 63).



Scheme 63

Chiral lactone compounds **198**[165a] are produced from reaction of **196** with **197** (Scheme 64).

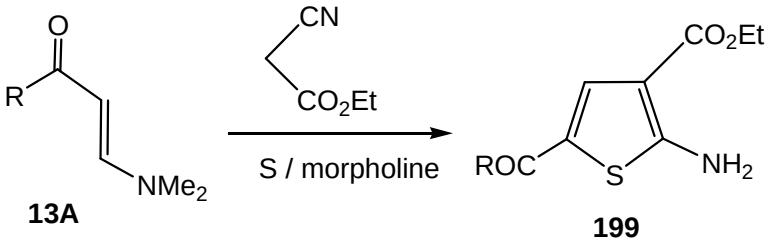


196 **197** **198**

Scheme 64

3.3. I. 3. THIOPHENES

Recently, Al-Mousawi *et al.*[165b] reported that the reaction of enaminones **13A** with ethyl cyanoacetate and elemental sulfur in presence of a base affords thiophenes **199** in good yield (Scheme 65).



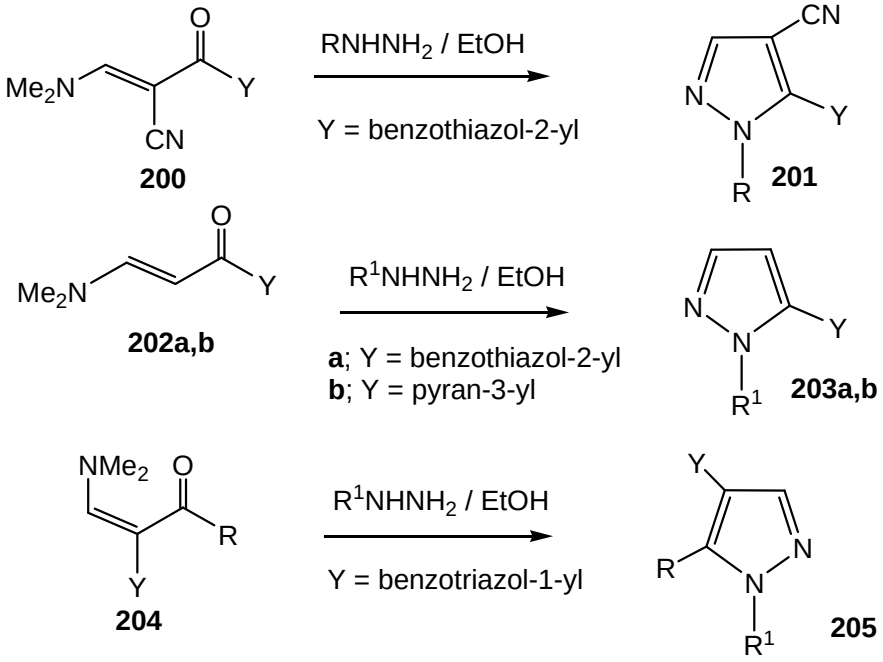
13A **199**

Scheme 65

3.3. II. FIVE-MEMBERED RINGS WITH TWO HETEROATOMS

3.3. II. 1. PYRAZOLES

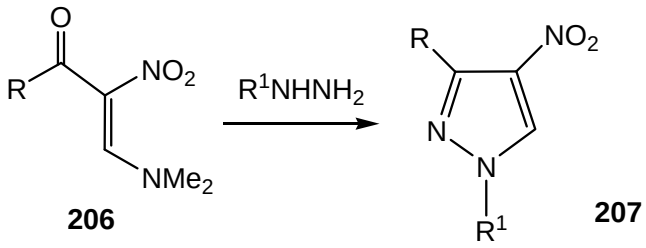
Pyrazoles **201, 203a,b** and **205** are produced from reaction of hydrazines with enaminones **200, 202a,b** and **204** respectively[166-169] (Scheme 66).



200 **201** **202a,b** **203a,b** **204** **205**

Scheme 66

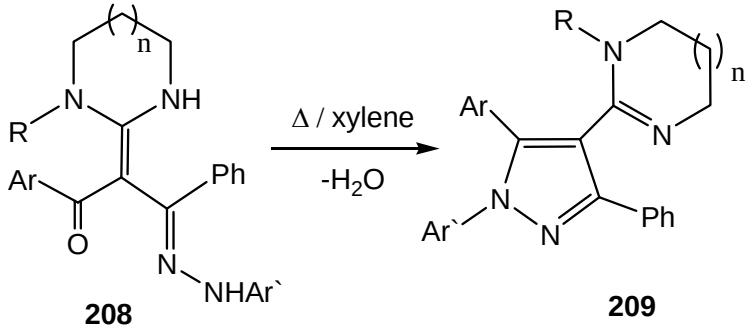
A usefull reaction for synthesis of nitropyrazoles **207** is the reaction of nitroenaminones **206** with hydrazine[170] (Scheme 67).



206 **207**

Scheme 67

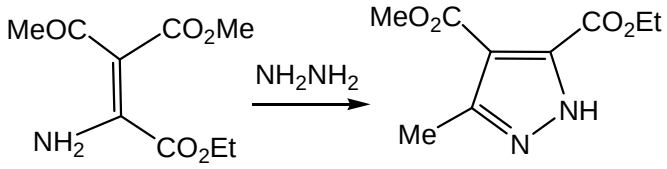
Intramolecular cyclocondensation of **208** gives pyrazole derivatives **209**[171] (Scheme 68).



208 **209**

Scheme 68

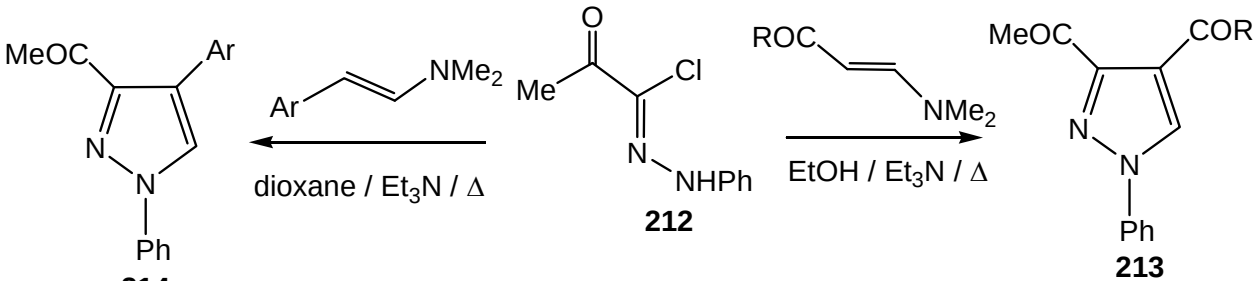
Enamines **210** are converted into pyrazole **211** *via* reaction with hydrazine hydrate[172,173] (Scheme 69).



210 **211**

Scheme 69

Nitrilimines are versatile reagents for synthesis of pyrazoles *via* reactions with enamines[82] or enaminones.[174] Thus hydrazonoyl halide **212** has afforded **213** and **214** upon treatment with enaminones and enamines respectively (Scheme 70).

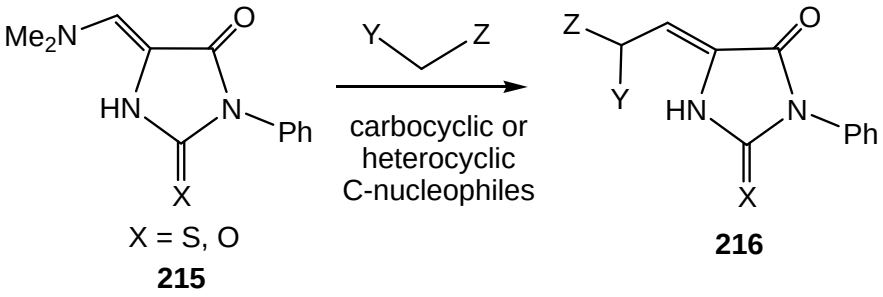


214 **212** **213**

Scheme 70

3.3. II. 2. IMIDAZOLES

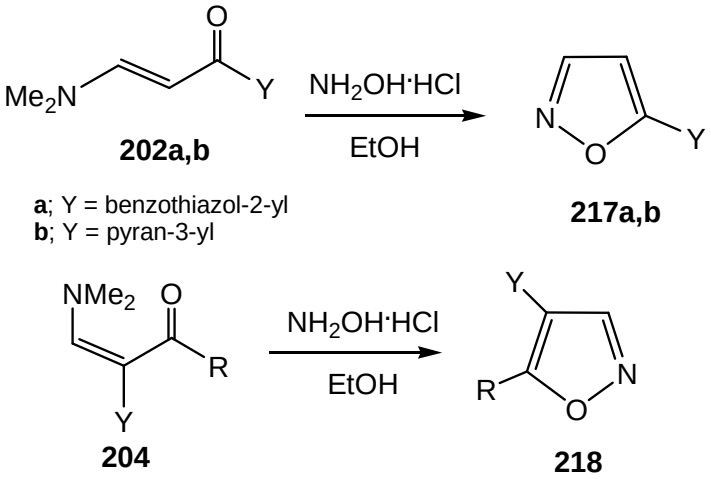
Imidazole derivatives **216** can be synthesized from reaction of **215**[175] with active methylene reagents (Scheme 71).



Scheme 71

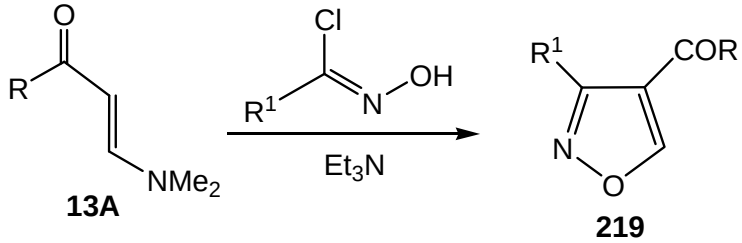
3.3. II. 3. ISOXAZOLES

Isoxazoles **217a,b** and **218** are synthesized from the corresponding enaminones *via* reactions with hydroxylamine[166-169] (Scheme 72).



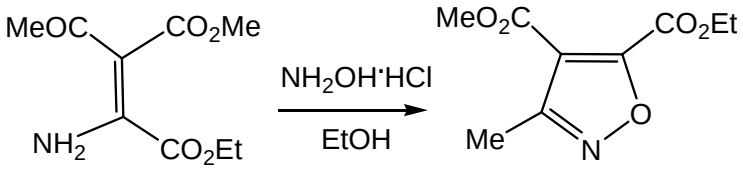
Scheme 72

Hydroximoyl chloride reacts with enaminones **13A** to give isoxazole derivatives **219**[176] (Scheme 73).



Scheme 73

Enamines **210** are converted into isoxazole **220** *via* reaction with hydroxylamine[172,173] (Scheme 74).

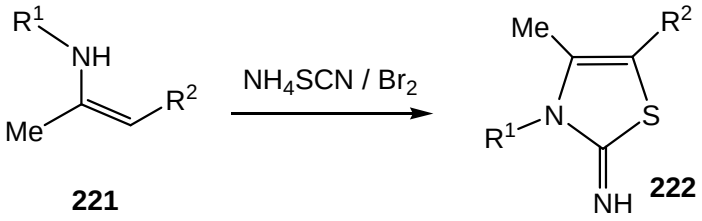


210 **220**

Scheme 74

3.3. II. 4. THIAZOLES

Enamines **221** react with Br_2 in presence of ammonium thiocyanate yielding thiazoline derivatives **222**[177] (Scheme 75).



221 **222**

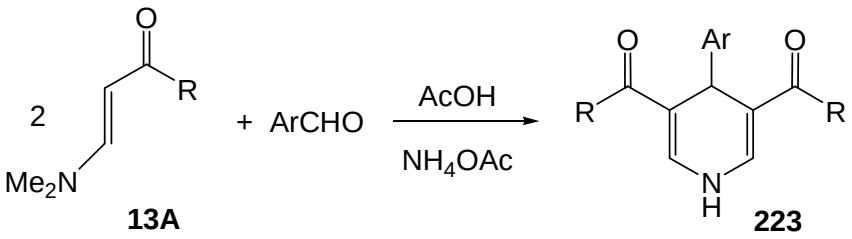
Scheme 75

3.4. SIX-MEMBERED HETEROCYCLIC COMPOUNDS

3.4. I. SIX-MEMBERED RINGS WITH ONE HETEROATOM

3.4. I. 1. PYRIDINES

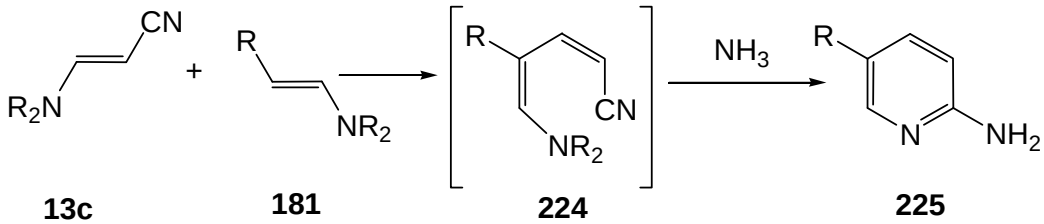
Elnagdi *et al.* reported that aromatic aldehydes reacted with enaminones **13A** (1:2) in acetic acid in presence of ammonium acetate to yield **223**[178] (Scheme 76).



13A **223**

Scheme 76

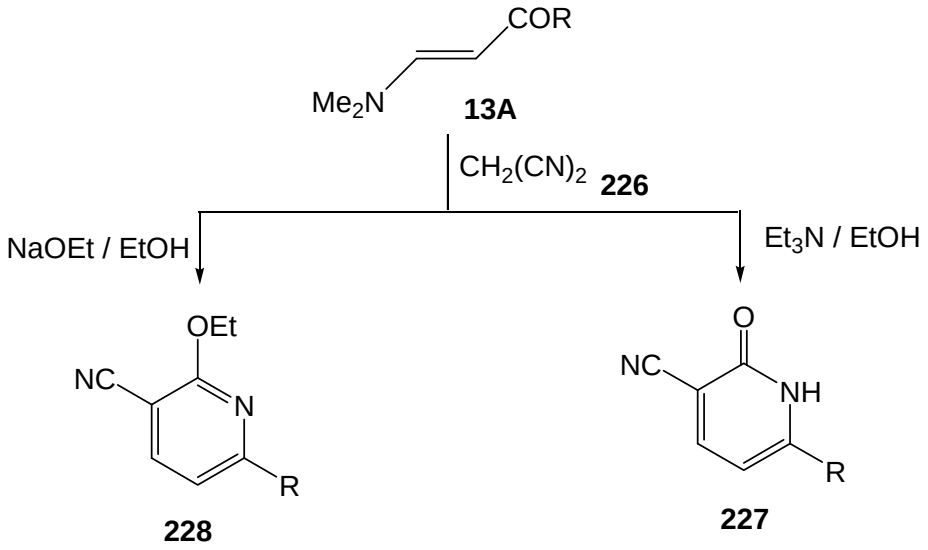
Also enaminonitrile **13c** reacted with enamines **181** to yield **225**. Intermediacy of a cyanodiene **224** was postulated[179] (Scheme 77).



13c **181** **224** **225**

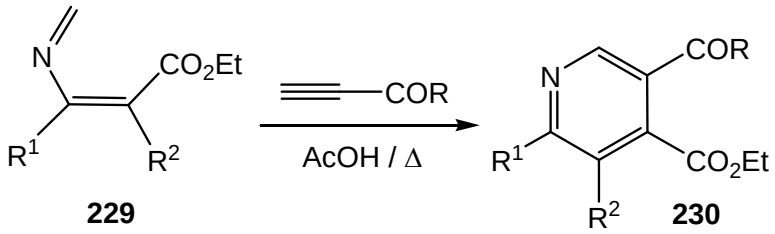
Scheme 77

Reactions of enaminones **13A** with malononitrile **226** in ethanolic basic solution afforded the corresponding pyridine **227** and **228** according to reaction condition[180,181] (Scheme 78).



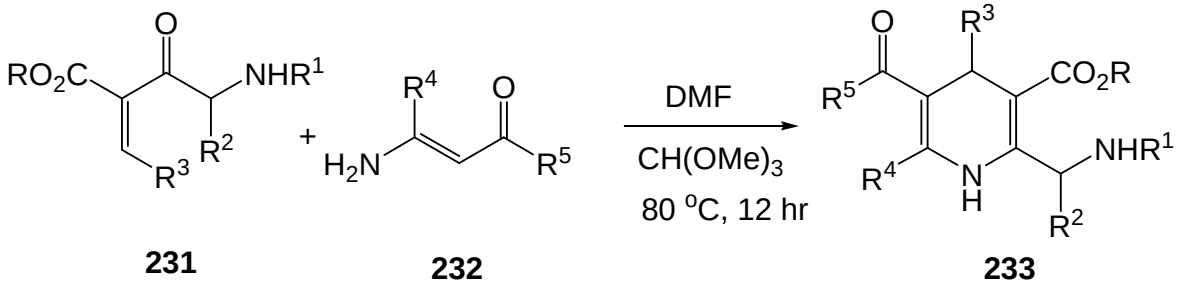
Scheme 78

The enamines **229** react typically as electron rich diene with acetylenes giving pyridines **230**[182] (Scheme 79).



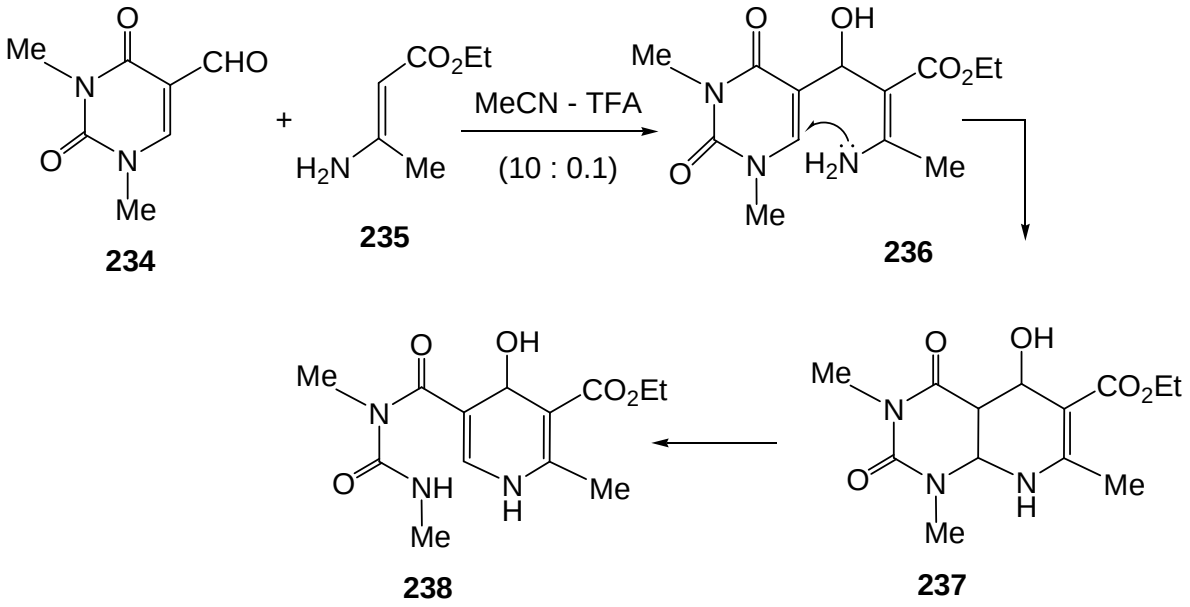
Scheme 79

A combinatorial library of several thousand derivatives of **233** was prepared *via* reacting **231** and **232**[183] (Scheme 80).



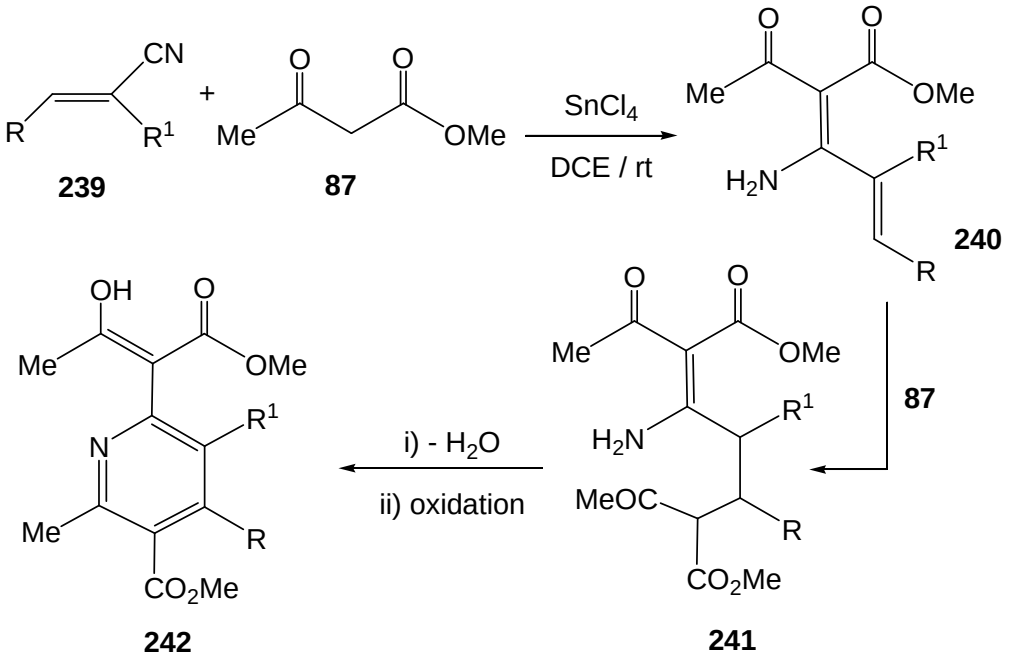
Scheme 80

Dioxopyrimidine derivative **234** reacts with enaminoester **235** (1:2) to afford pyridine derivative **238**[184] (Scheme 81).



Scheme 81

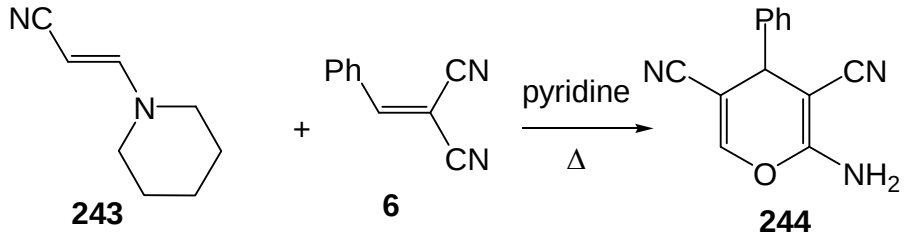
Tin (IV) chloride selectively promotes the nucleophilic attack of methyl acetoacetate **87** to the cyano group instead of the olefinic carbon atom of α,β-unsaturated nitriles **239** to give enaminoketoesters **240**.[185] In the presence of an excess of ketoester a second C–C bond formation occurs followed by cyclization affording substituted pyridines **242** in a selective cascade sequence. Taking into account the specific activation of the cyano group discovered by Veronese *et al.* in the metal promoted reaction of nitriles with β-dicarbonyl compounds,[178,186,187] the reactivity of methyl acetoacetate **87** with the α,β-unsaturated nitriles **239** in the presence of $SnCl_4$ was investigated (Scheme 82).



Scheme 82

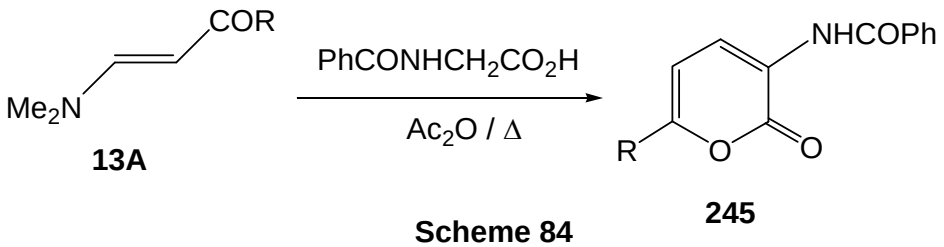
3.4. I. 2. PYRANES

Recently Elnagdi *et al.* reported first Michael type addition of enaminonitrile **243** to benzylidene-malononitrile **6** to yield 2-aminopyrane derivative **244**[63] in good yield (Scheme 83).



Scheme 83

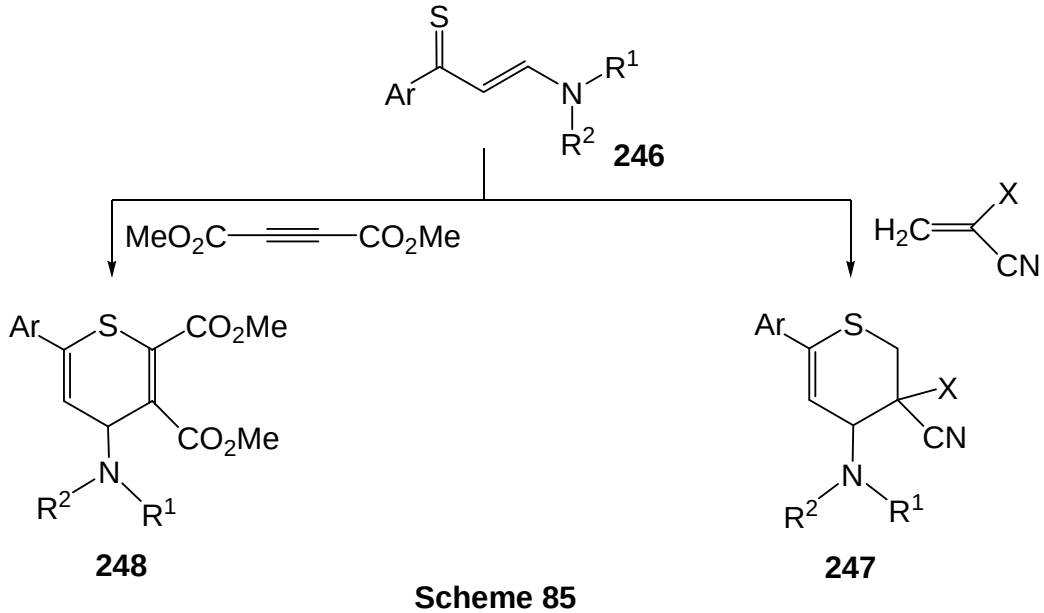
Enamines **13A** react with hippuric acid to afford acylaminopyrane derivatives **245**[180] (Scheme 84).



Scheme 84

3.4. I. 3. THIOPYRANES

Enaminothiones **246** prepared from the corresponding enaminones by thiation with Lawesson's reagent, react with 2-chloroacrylonitrile and dimethyl acetylenedicarboxylate giving dihydro-2*H*-thiopyranes **247**, and 4*H*-thiopyranes **248** respectively[188] (Scheme 85).

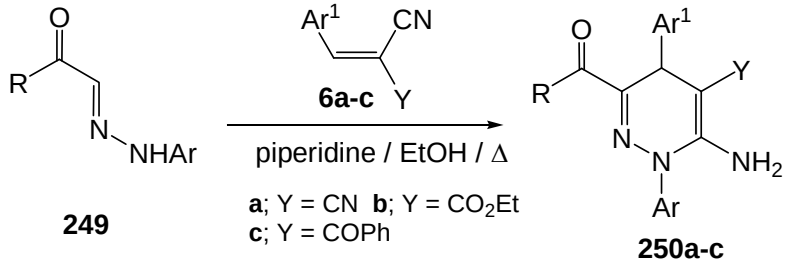


Scheme 85

3.4. II. SIX-MEMBERED RINGS WITH TWO HETEROATOMS

3.4.II. 1. PYRIDAZINES

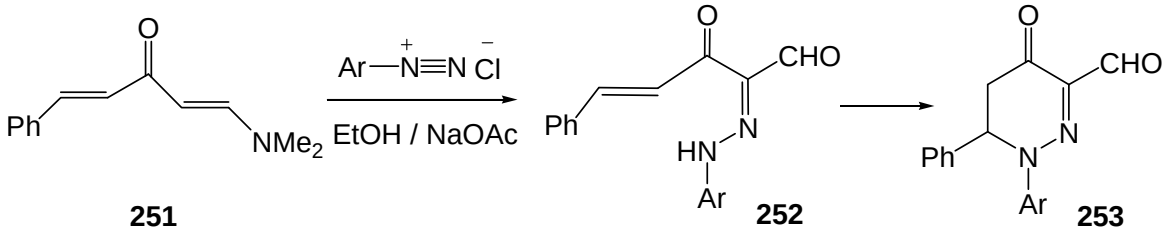
Recently, Elnagdi *et al.*[189] has noted that **249** reacts with α,β-unsaturated nitriles **6a-c** to yield aminopyridazine derivatives **250a-c** (Scheme 86).



249 **250a-c**

Scheme 86

The enaminone **251** reacts with aromatic diazonium salts to yield **252** that readily cyclized into **253** in refluxing ethanol[190] (Scheme 87).

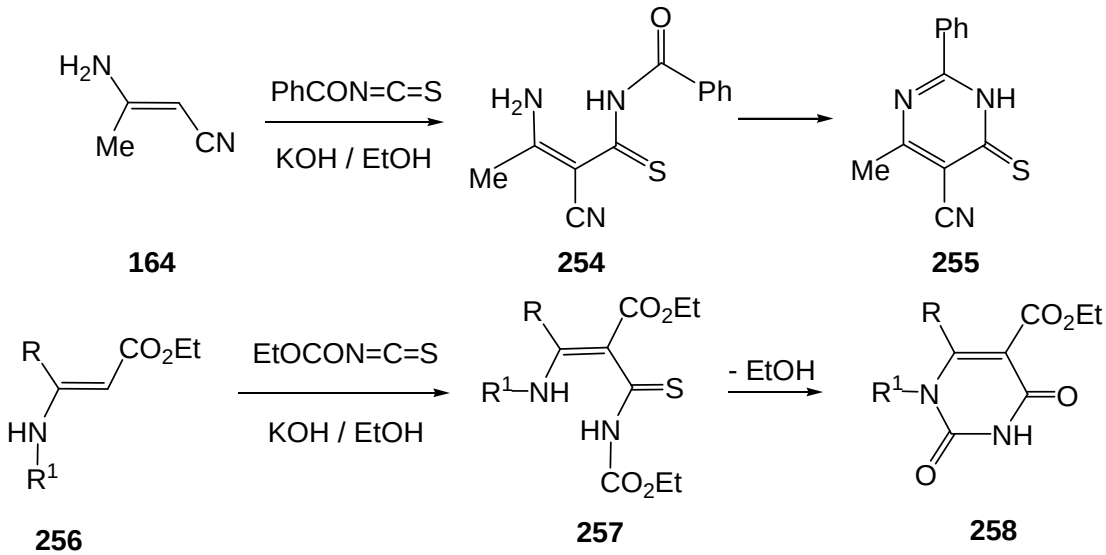


251 **252** **253**

Scheme 87

3.4.II. 2. PYRIMIDINES

Enamines readily add isothiocyanates and benzoyl isothiocyanate. For example the pyrimidine thione **255**[191] is prepared from the reaction **164** and benzoyl isothiocyanate in presence of potassium hydroxide (Scheme 88). Also enaminoesters **256** react with ethoxycarbonyl isothiocyanate to yield **258**.[192]

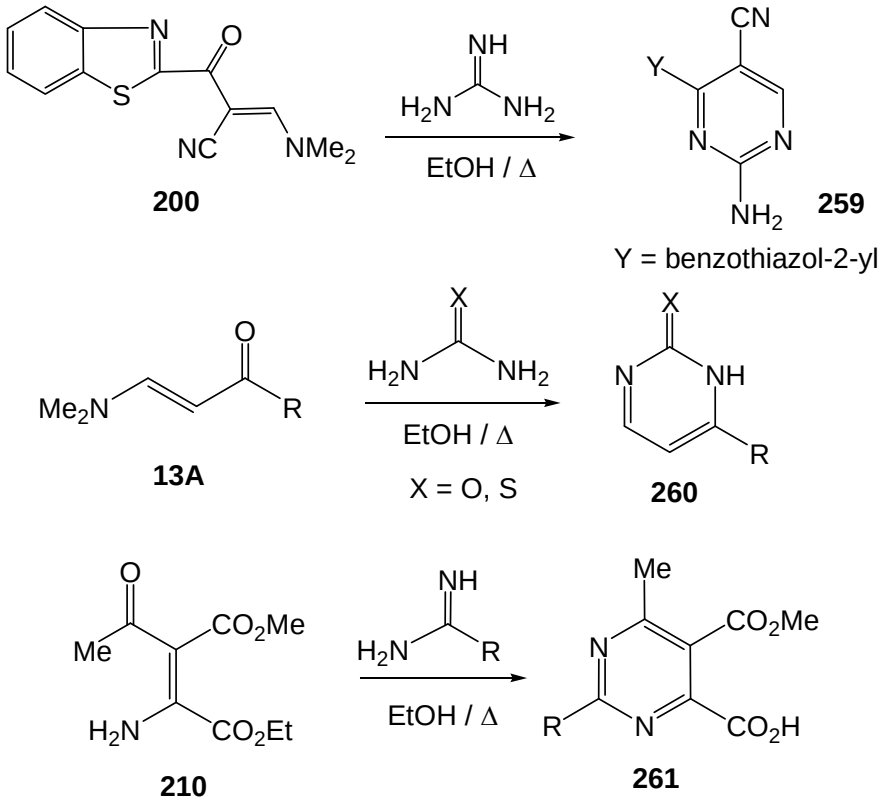


164 **254** **255**

256 **257** **258**

Scheme 88

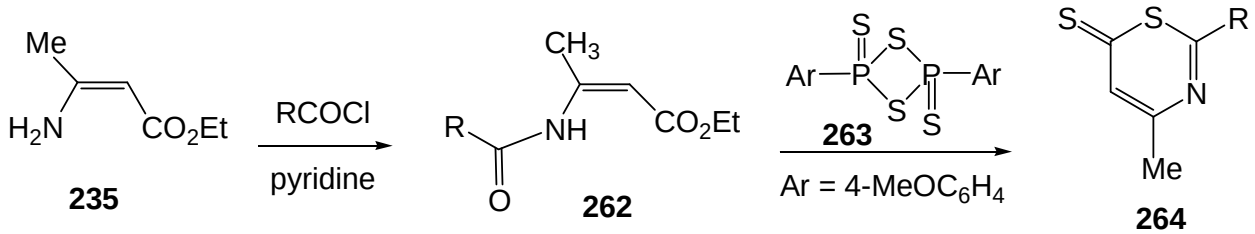
Pyrimidine derivatives **259-261** can be synthesized from the corresponding enaminones *via* reactions with guanidine, urea or thiourea and imines respectively[166-169,172,173] (Scheme 89).



Scheme 89

3.4.II. 3. 1,3-THIAZINES

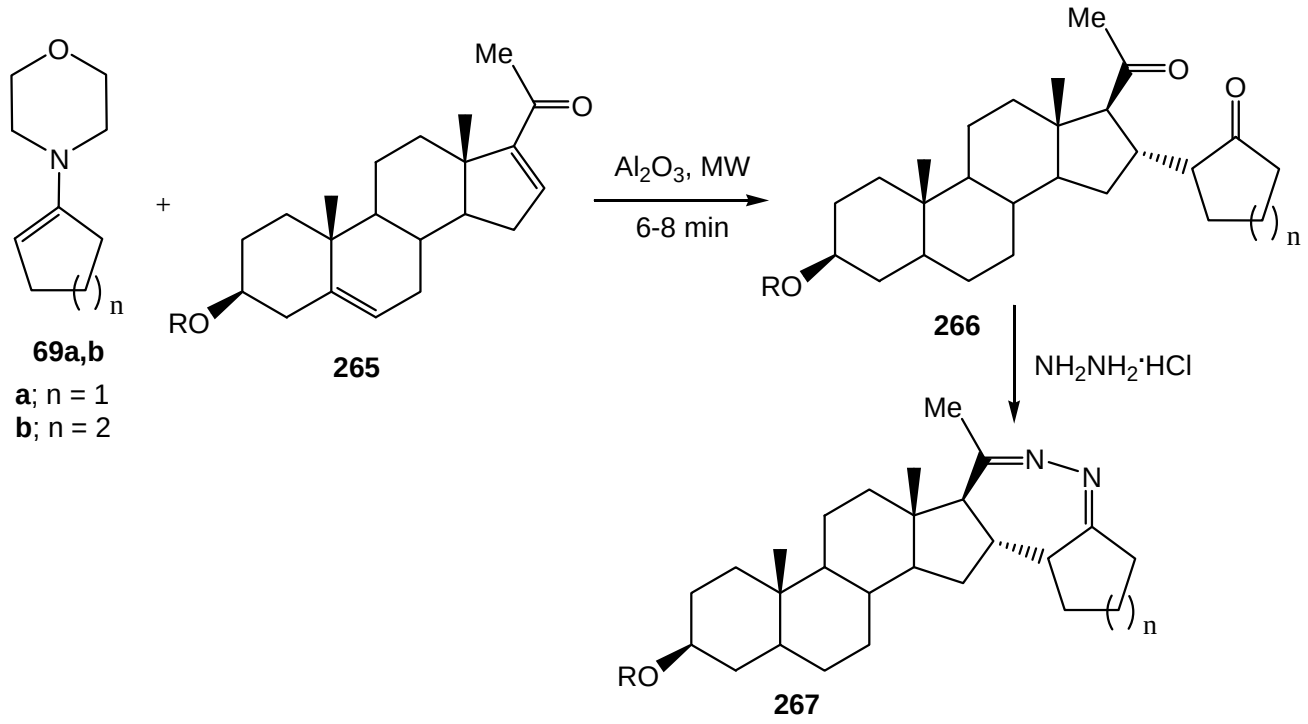
Acylation of enaminoester **235** with different acid chlorides gives only *N*-acylated products **262**. The latter compounds were cyclized by Lawesson's reagent **263** to give thiazine derivatives **264**[193] (Scheme 90).



Scheme 90

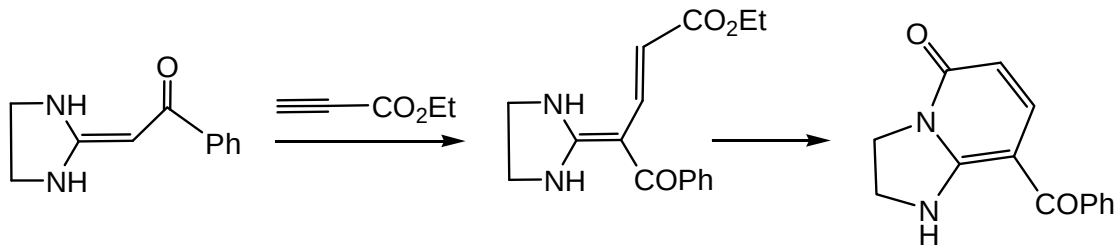
3.5. POLYCYCLIC HETEROCYCLES

Michael addition of enamines **69a,b** to conjugated enones **265** is affected in high yield by microwave irradiation. The 1,5-diketo Michael adducts have been converted into a novel class of 1',2'-diazepino(17,16-d') steroids **267**[194] (Scheme 91).



Scheme 91

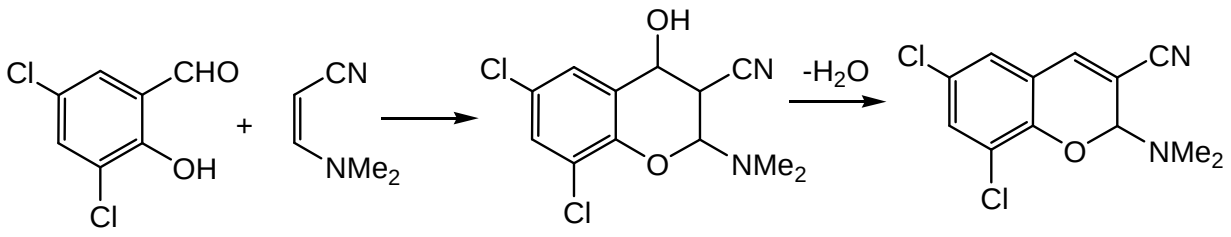
The addition of ethyl propiolate to enamines **268** has been well investigated[195] in the past to give imidazo[1,2-*a*]pyridinone derivative **270** (Scheme 92).



268 **269** **270**

Scheme 92

The reaction of salicylaldehyde **271** with enaminonitriles affords benzopyrane derivative **273** in good yield[196] (Scheme 93).

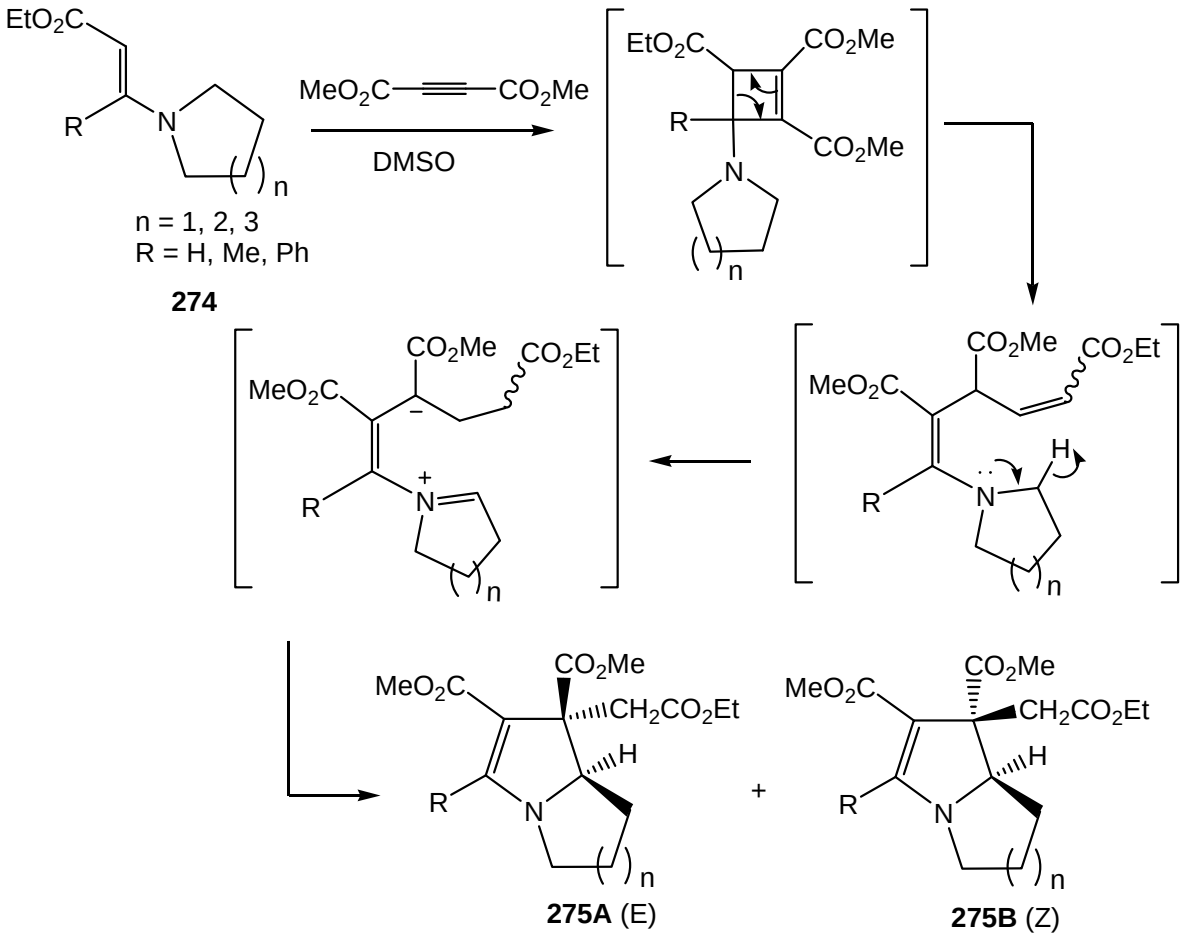


271 **272** **273**

Scheme 93

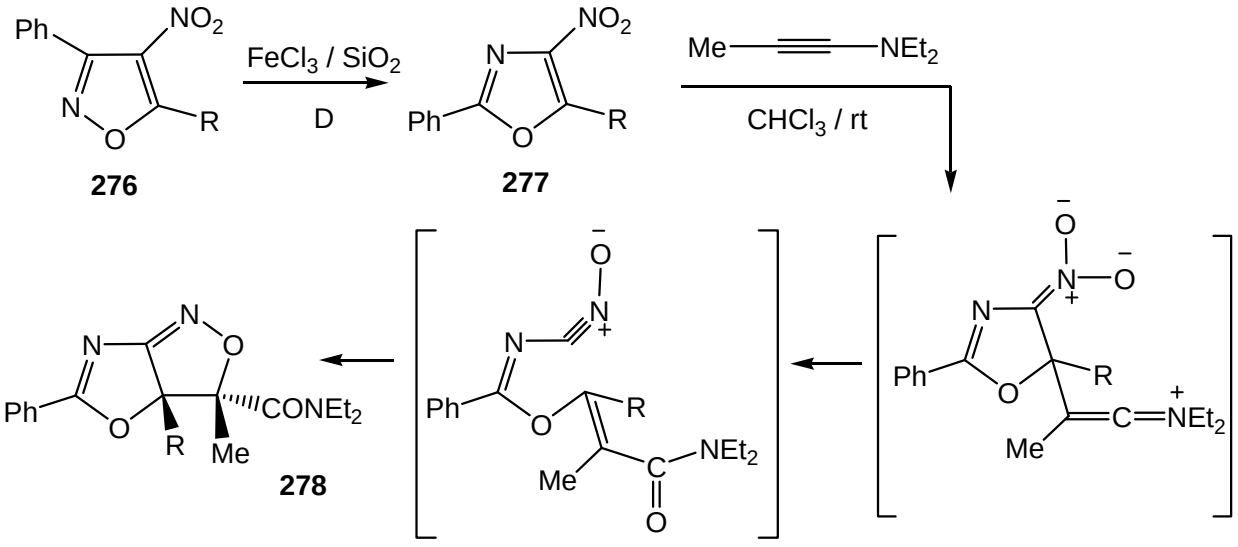
The enaminoester **274** reacts with DMAD in DMSO in the presence of molecular sieves (4A^{o}) at 135 ^{o}C

for one day to yield **275**[197] *via* [2+2] cycloaddition reaction (Scheme 94).



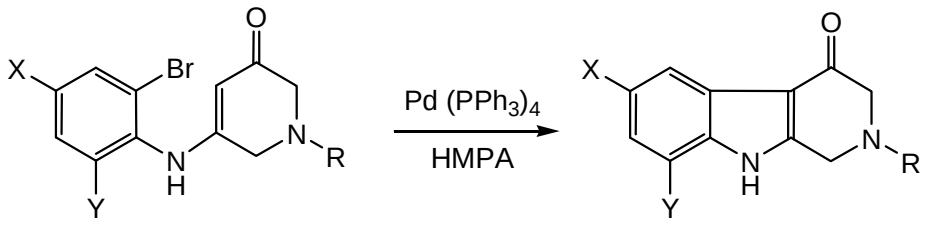
Scheme 94

Nitrooxazoles **277** obtained *via* heating nitroisooxazoles **276** in presence of $FeCl_3$ / SiO_2 react with 1-diethylaminopropyne to yield **278**[198] (Scheme 95).



Scheme 95

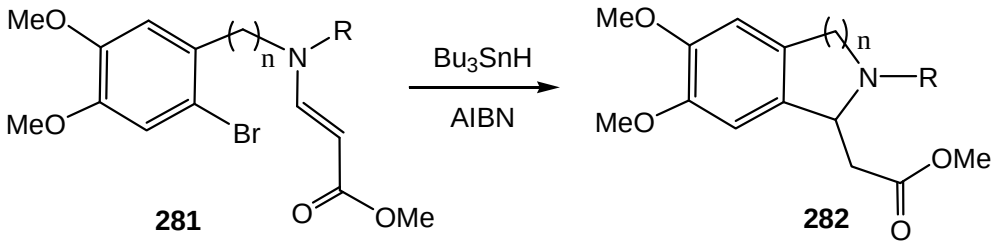
Several cyclization reactions involving intramolecular alkylation have been reported. For example compound **279** gives **280** on treatment with HMPA[199] (Scheme 96).



279 **280**

Scheme 96

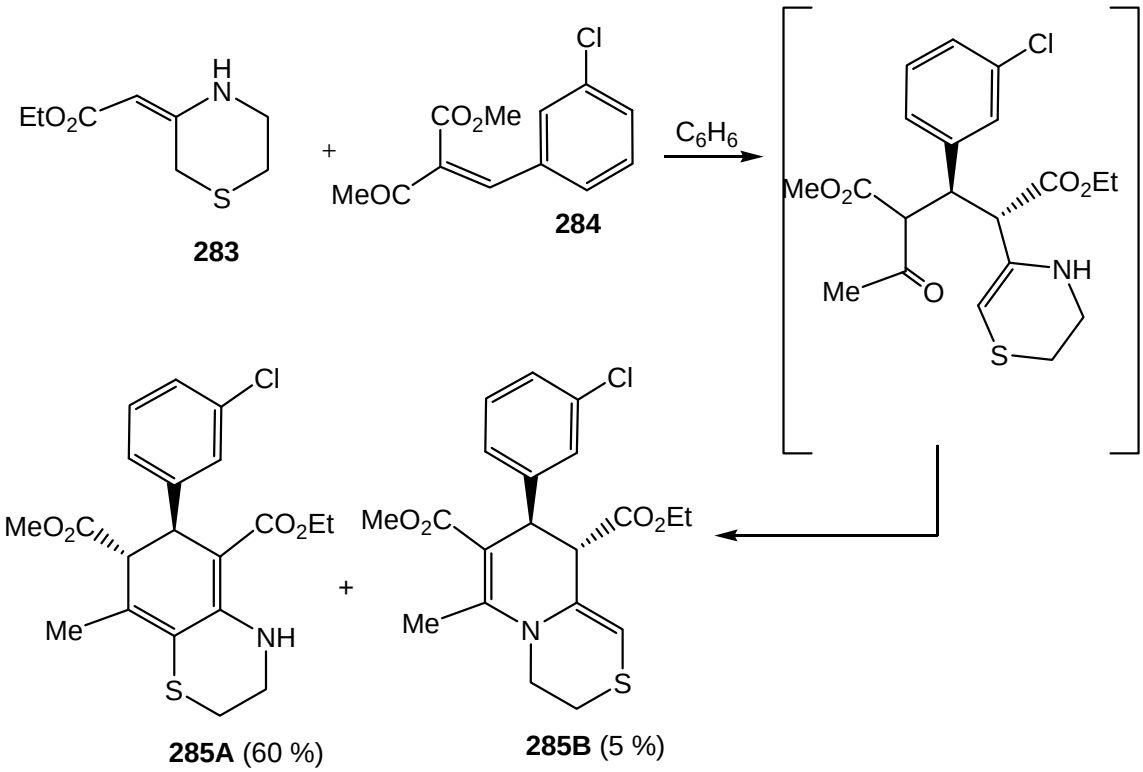
Intramolecular attack of electron rich moiety in **281** at C-3 gives **282**[200] (Scheme 97).



281 **282**

Scheme 97

Reaction of cyclic enamine **283** with **284** afforded two isomeric 1,4-benzothiazine **285A** and pyrido-[2,1-*c*]thiazine **285B**[201] (Scheme 98).

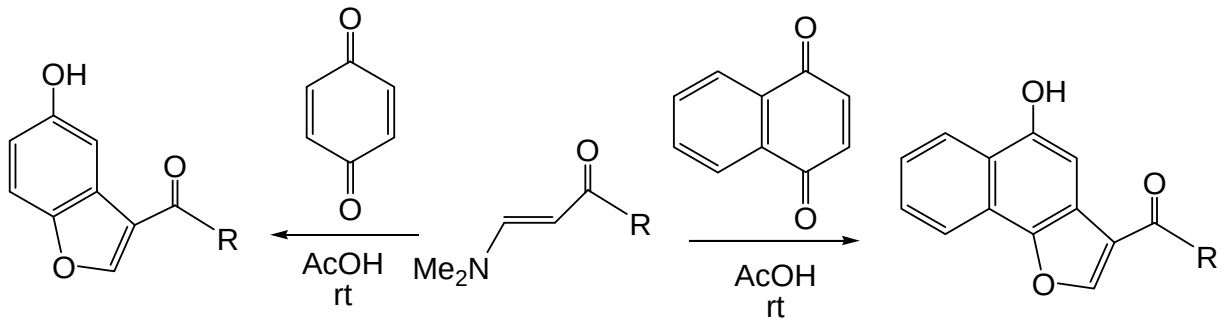


283 **284**

285A (60 %) **285B** (5 %)

Scheme 98

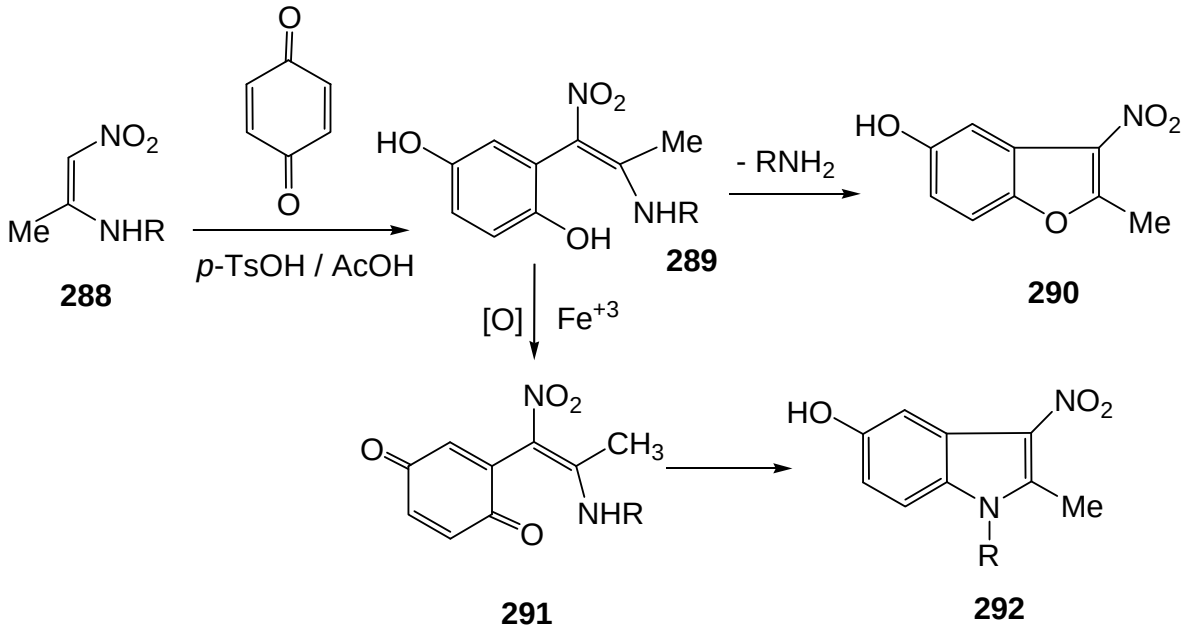
The reaction of enamines **13A** with 1,4-benzoquinones and 1,4-naphthoquinones has been reported[169,202,203] to yield bezofurans **286** and naphtho[b]furans **287** (Scheme 99).



286 **13A** **287**

Scheme 99

Nitroenamines **288** also add to 1,4-benzoquinone yielding a mixture of benzofuran **290** and indoles **292**[204] (Scheme 100).

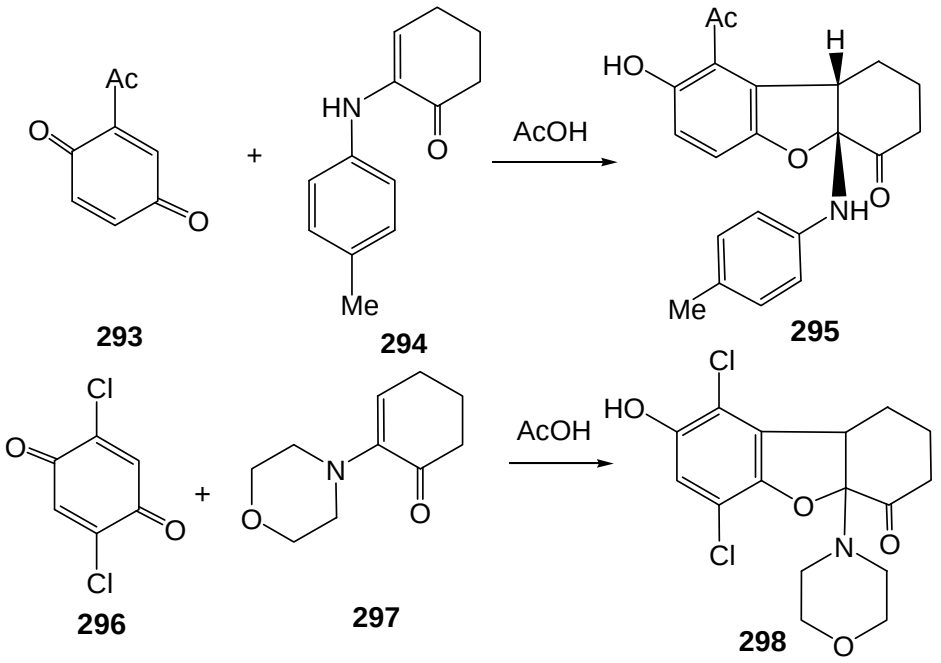


288 **289** **290** **291** **292**

Scheme 100

The behavior of 2-acetyl-1,4-benzoquinone **293** and 2,5-dichloro-1,4-benzoquinone **296** towards enamines **294** and **297** was investigated respectively[205,206] (Scheme 101).

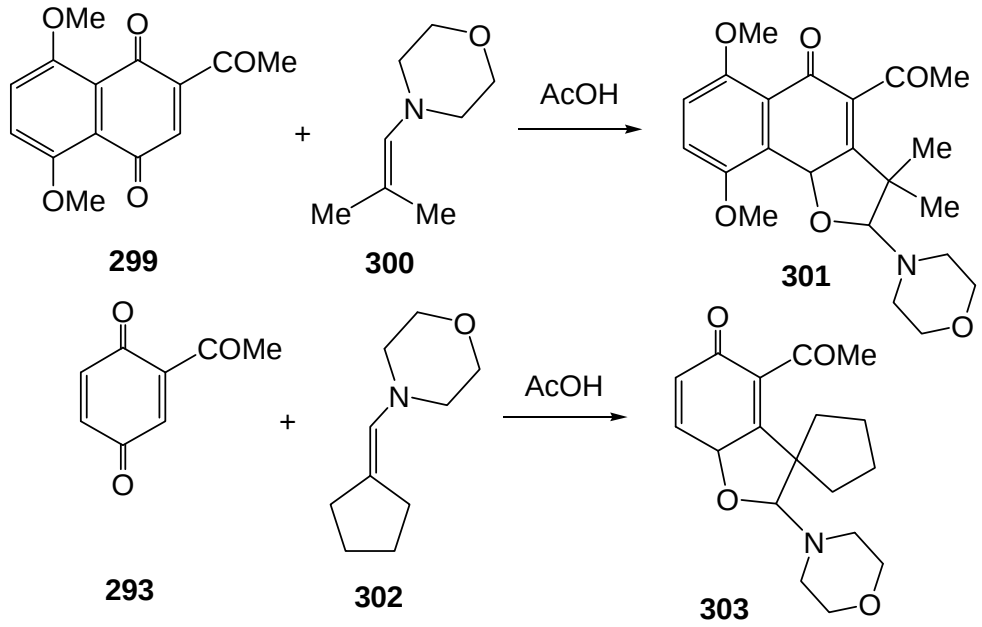
2-Acetyl-5,8-dimethoxy-1,4-naphthoquinone **299** reacts with 4-isobutenylmorpholine **300** to yield condensed naphthoquinone **301**. Also 2-acetyl-1,4-benzoquinone **293** forms of **303** on treatment with enamine **302**[207] (Scheme 102).



293 **294** **295**

296 **297** **298**

Scheme 101

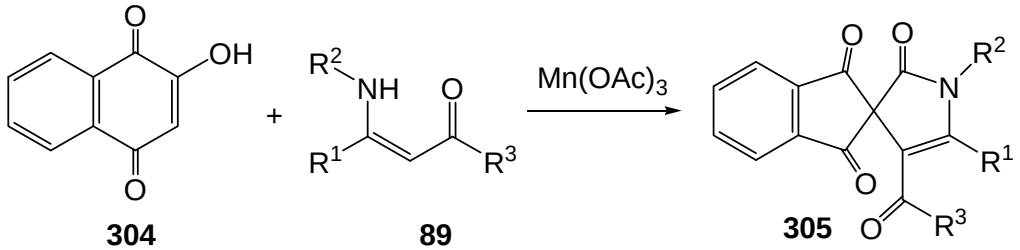


299 **300** **301**

293 **302** **303**

Scheme 102

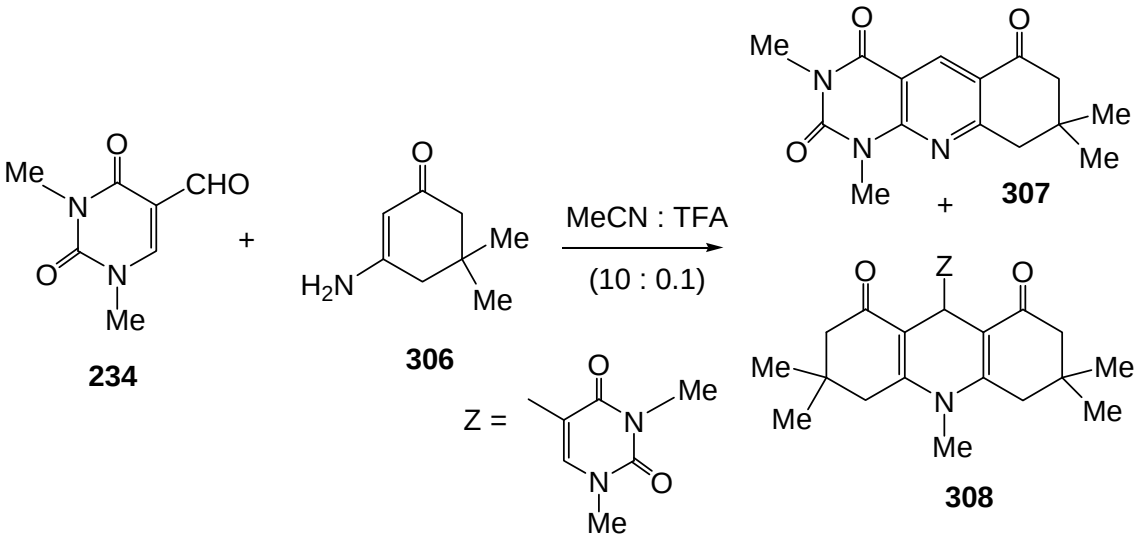
The manganese (III) acetate initiated oxidative free radical reaction between 2-hydroxy-1,4-naphtho-quinone **304** and β-enamino ketone **89** to afford spirolactam **305**[208] (Scheme 103).



304 **89** **305**

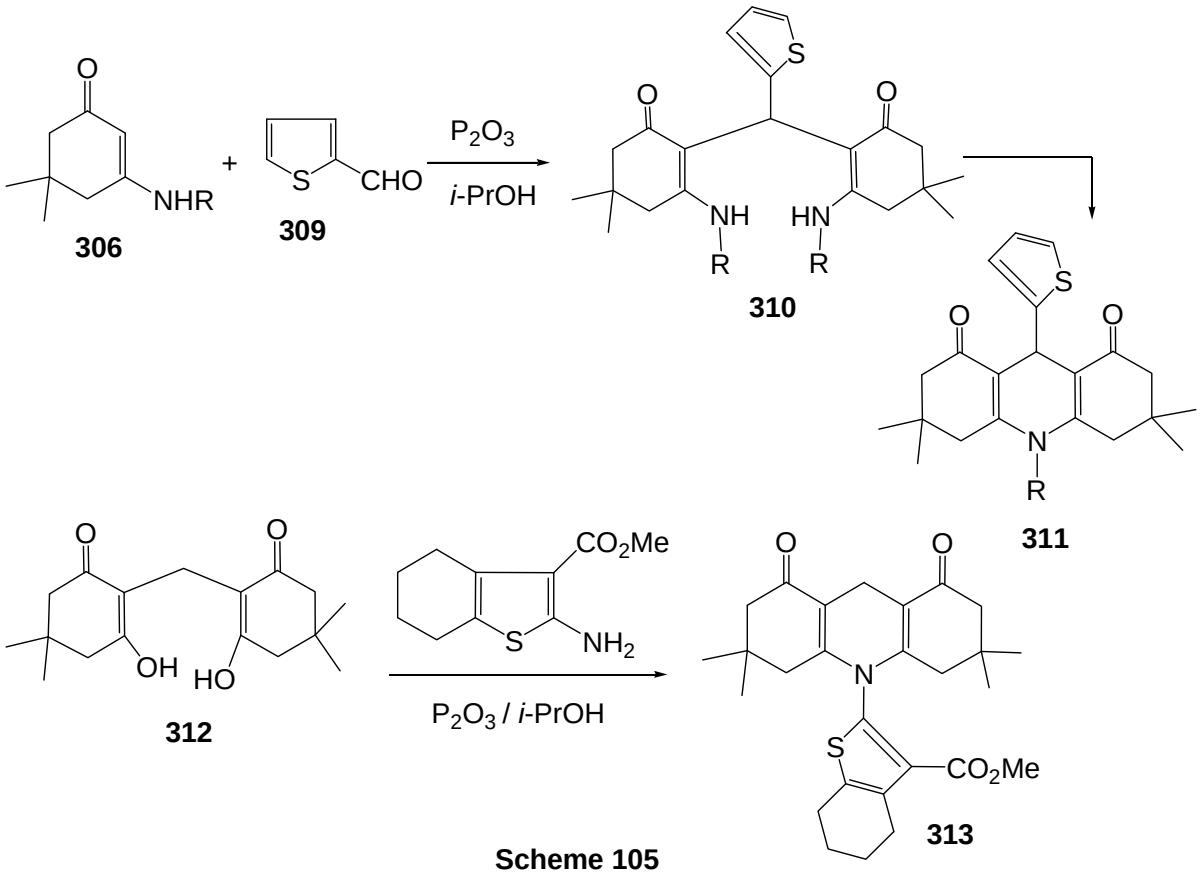
Scheme 103

1,3-Dimethyl-5-formyluracil **234** reacts with 3-amino-5,5-dimethylcyclohex-2-enone **306** to produce pyrimido[4,5-*b*]quinolin-2,4,6(1*H*, 3*H*, 7*H*)-trione derivative **307** along with 1,4-dihydropyridine derivative **308**[184] (Scheme 104).



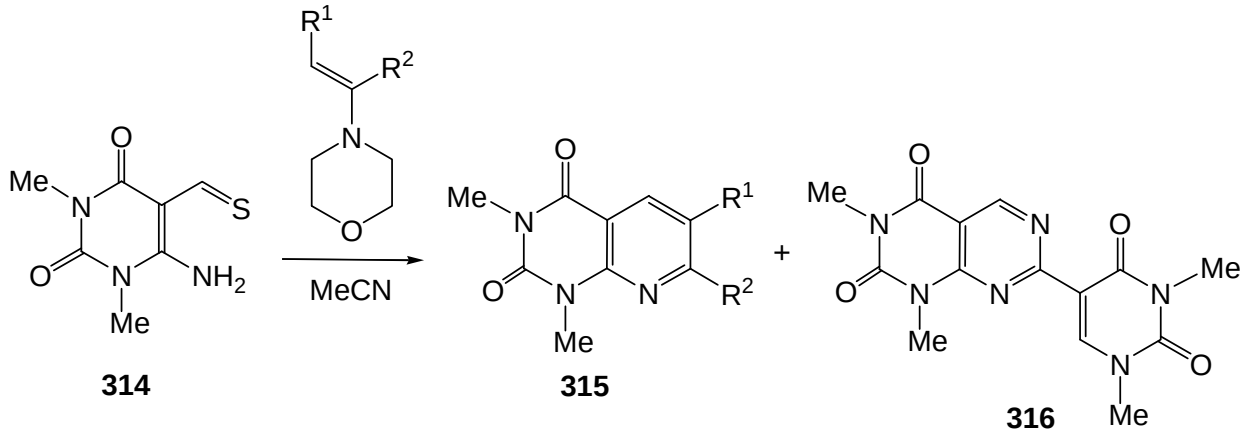
Scheme 104

The reaction of enamine **306** with thiophene-2-aldehyde **309** in presence of phosphorous trioxide gives **310** which readily cyclized into acridine derivative **311**. Similar reaction has been conducted with **312** and gave **313**[209] (Scheme 105).



Scheme 105

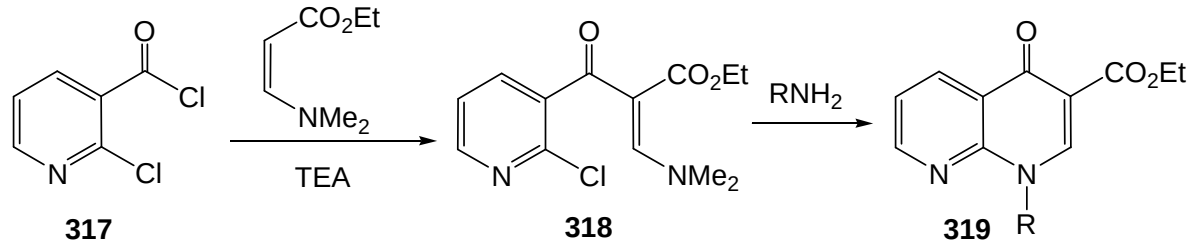
Reaction of 1,3-dimethyl-5-thioformyl-6-aminouracil **314** with enamines gave **315** and **316**[210] (Scheme 106).



314 **315** **316**

Scheme 106

Springfield *et al.*[211] have recently disclosed an efficient *one-pot* procedure for the preparation of substituted 1,8-naphthyridin-4-one analogues **319** (Scheme 107).

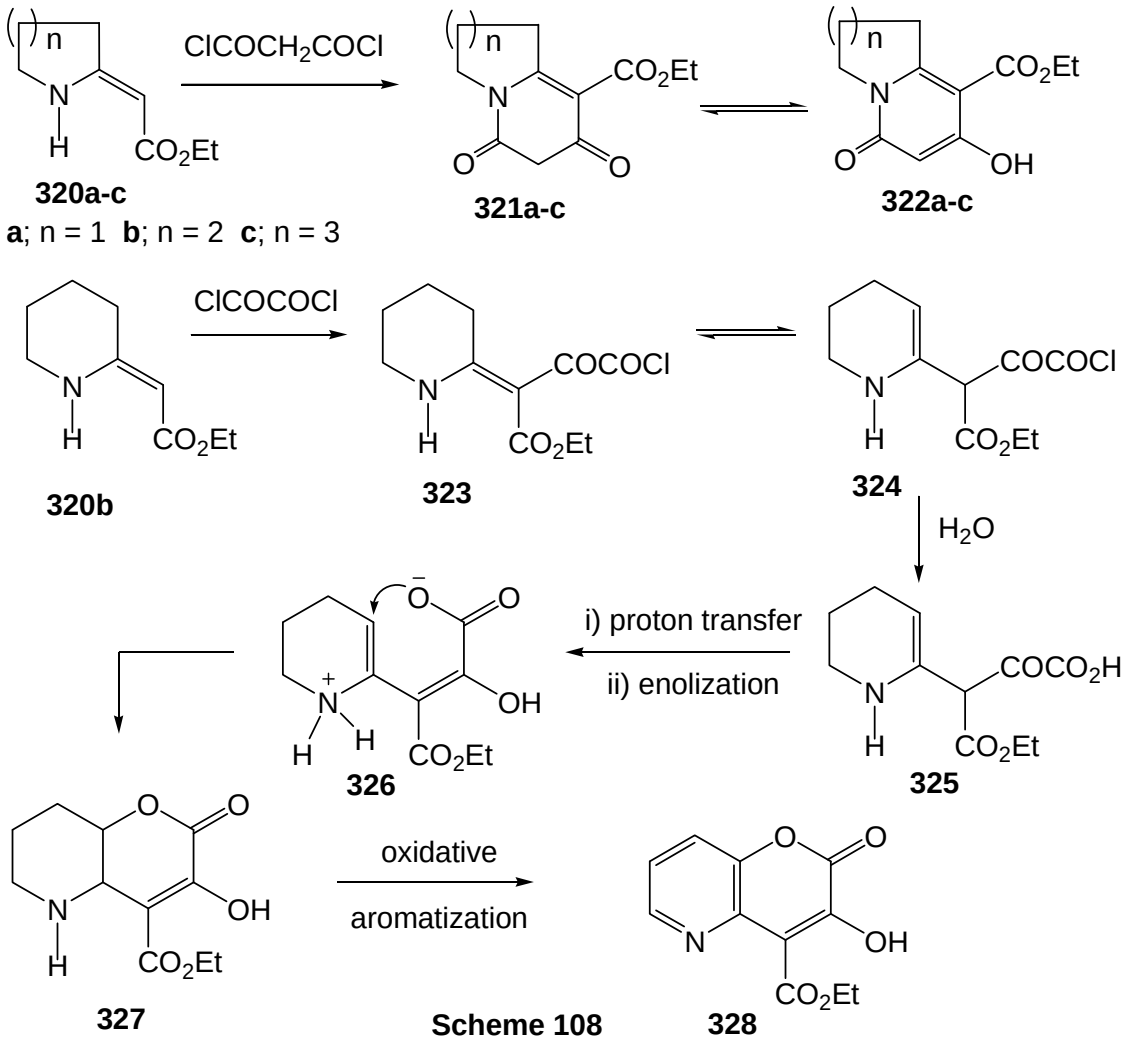


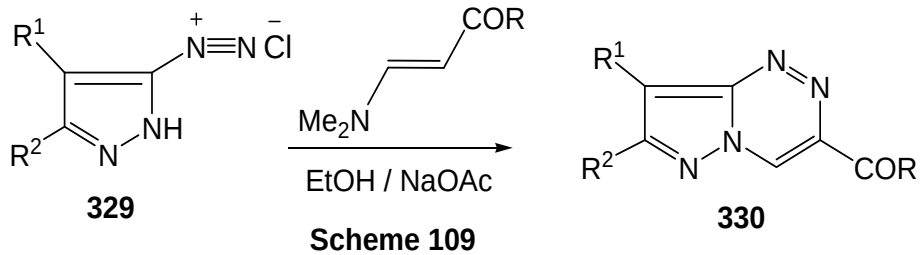
317 **318** **319**

Scheme 107

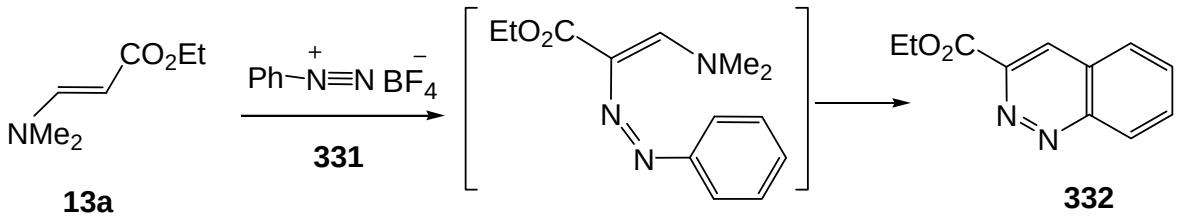
A general method for the preparation of hydroxylated 2-pyridinone-fused heterocycles **322a-c** is based on reaction of heterocyclic secondary enamines **320a-c** with malonyl chloride as the *bis* electrophilic reagent under very mild conditions. Similarly, the reaction of heterocyclic secondary enamines with oxalyl chloride has been shown to give different products depending on the heterocyclic structure of the enamines. 2-Oxo-5,6,7,8-tetrahydro-2*H*-pyrido[3,2-*b*]pyran **328** was produced as the sole product from the six-membered heterocyclic enamine **320b**[212] (Scheme 108).

Elnagdi *et al.*[213,214] has extensively investigated the reactivity of enaminones toward aromatic diazonium salts. It has been established that diazotized aminopyrazoles **329** couple with a diversity of enaminones to yield pyrazolo[5,1-*c*]-1,2,4-triazines **330**[213,214] (Scheme 109).



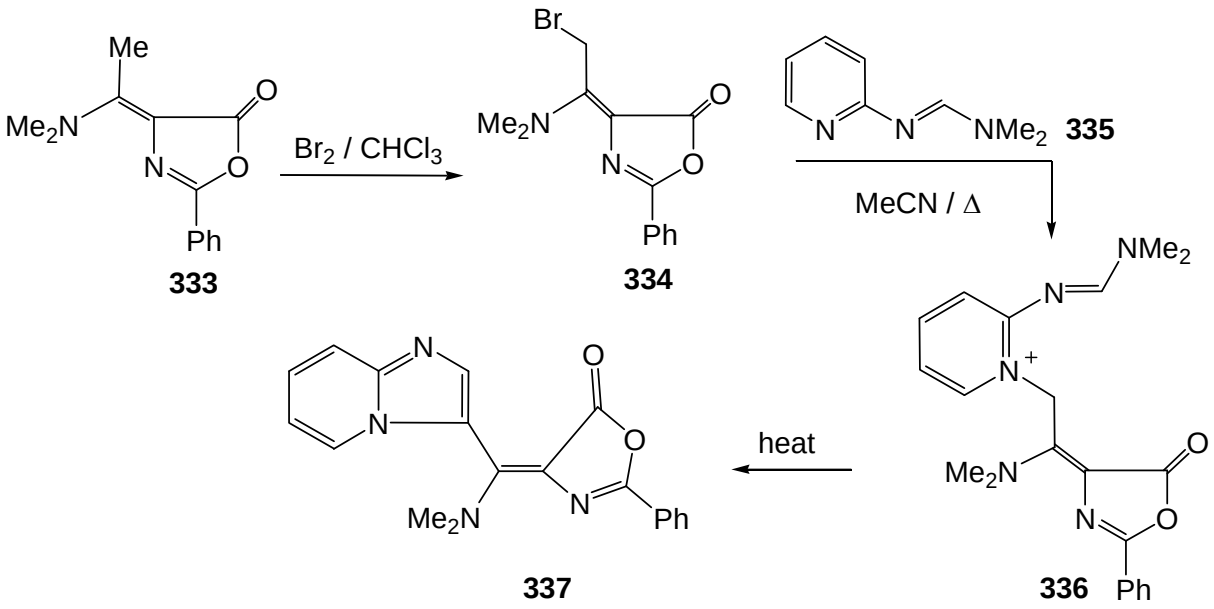


Coupling of enaminoesters **13a** with benzenediazonium tetrafluoroborate **331** gives cinnolines **332**[215] (Scheme 110).

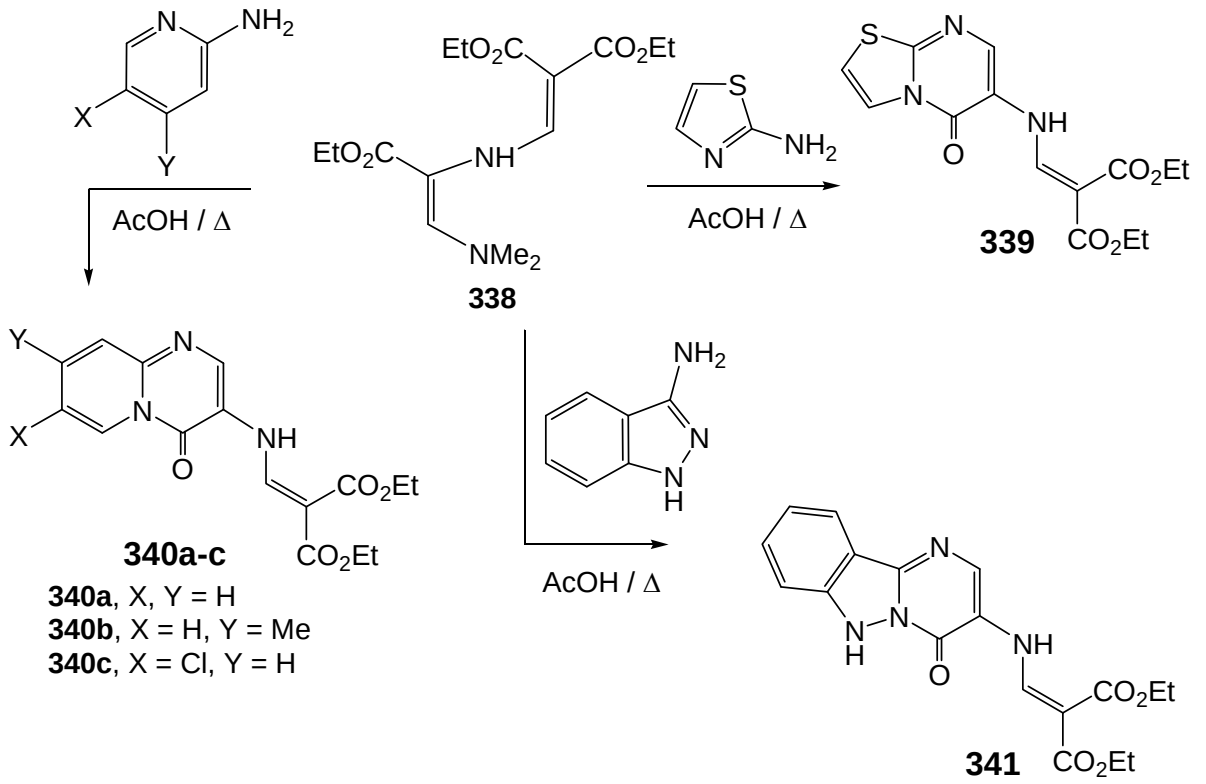


Scheme 110

Fused heterocycles which developed by Stanovnik's laboratories[162,163,216] are summarized in Schemes 111, 112.



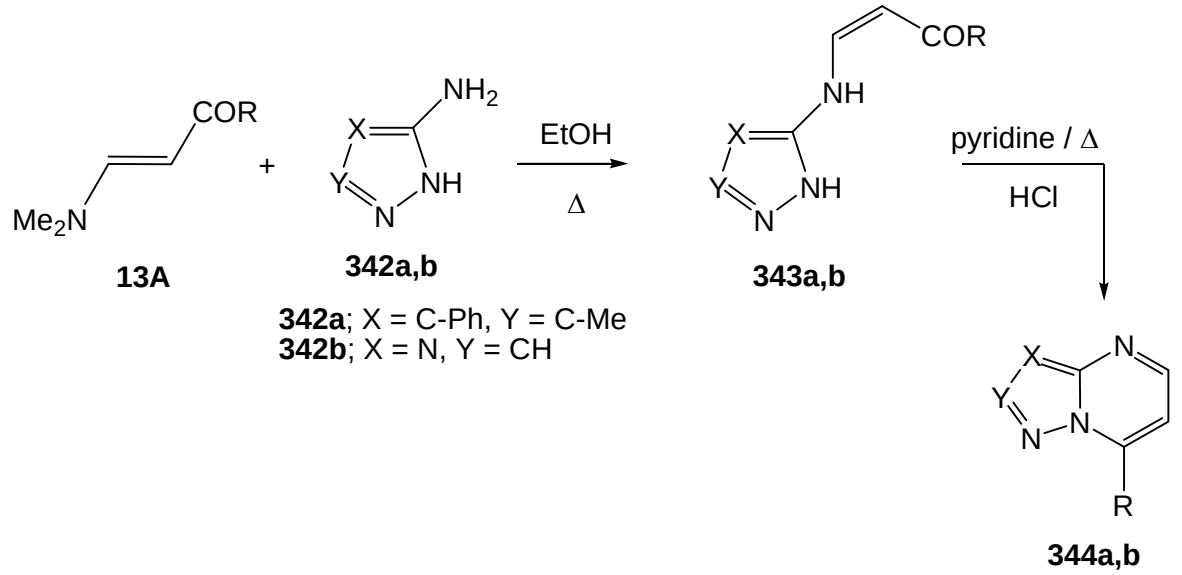
Scheme 111



Scheme 112

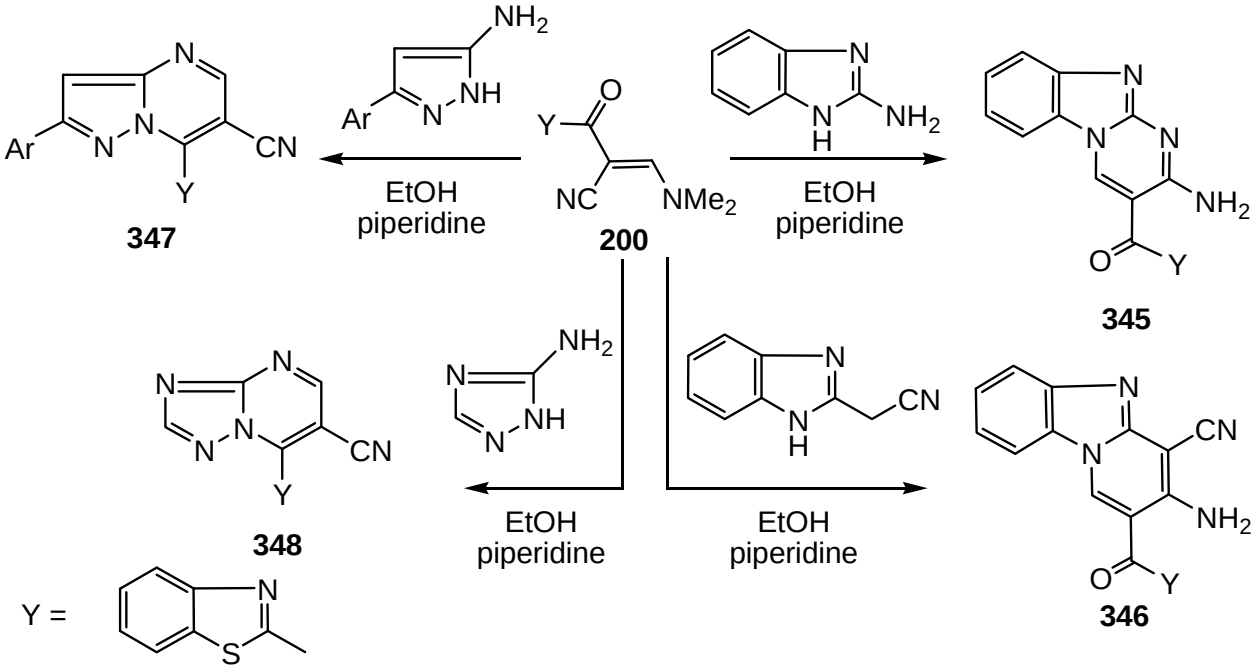
Enaminones **13A** reacted with aminoazoles **342a,b** to yield the corresponding enaminones **343a,b**. The latter products were readily cyclized into azolopyrimidines **344a,b**[167,217] on refluxing pyridine solution in

the presence of concentrated hydrochloric acid (Scheme 113).



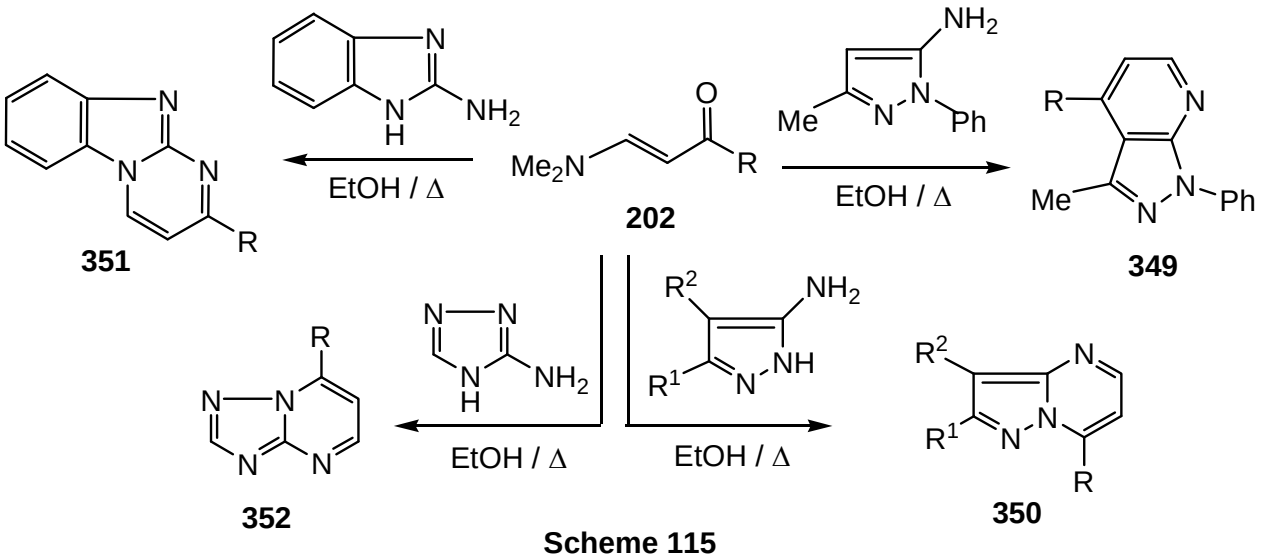
Scheme 113

Benzazoloazines **345** and **346** are produced from reactions of enaminones **200** with 3-aminobenzimidazole and 2-cyanomethylbenzimidazole respectively. Moreover, azoloazines **347**, **348** are prepared *via* reaction of enaminones **200** with aminoazoles[166,218] (Scheme 114).



Scheme 114

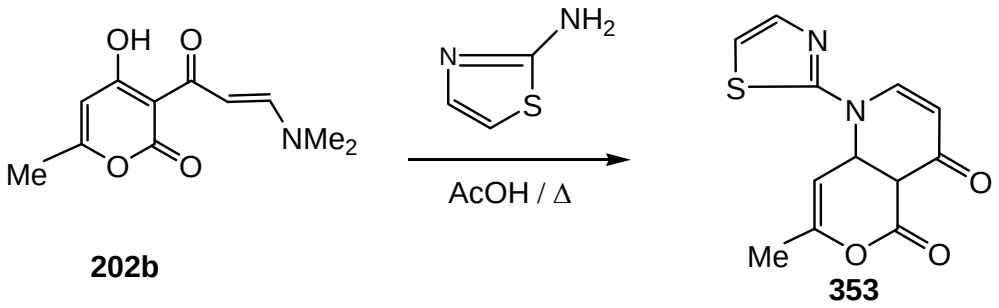
The behavior of simple enaminones with heterocyclic amines could be established in a series of papers[166,203,219] (Scheme 115).



351 **202** **349** **352** **350**

Scheme 115

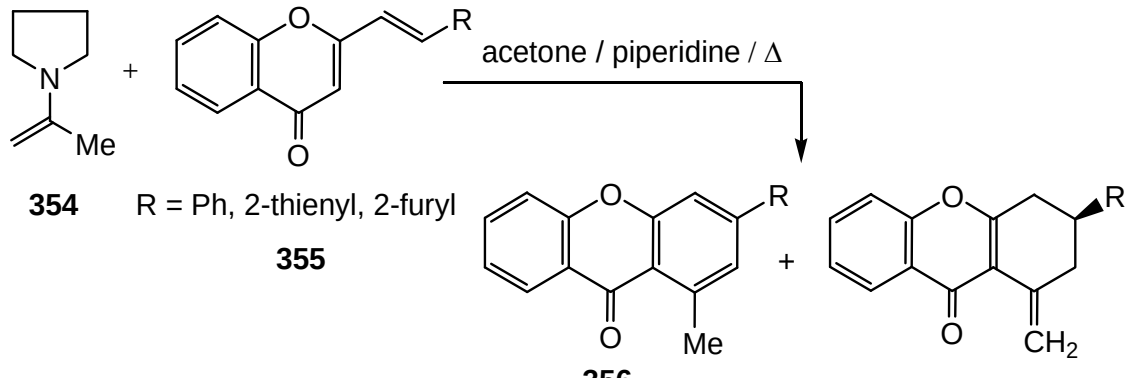
Enaminones **202b** react with 2-aminothiazole to afford pyrano[4,3-*b*]pyridinone derivative **353**[169] (Scheme 116).



202b **353**

Scheme 116

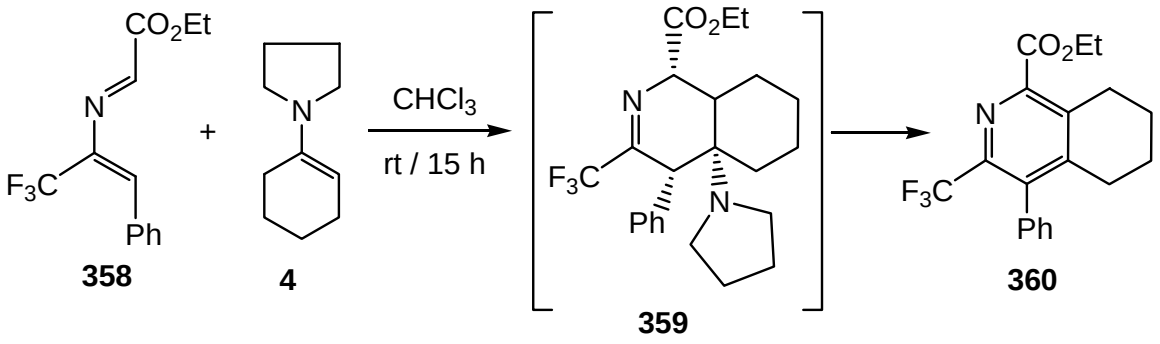
Reacting **354** with **355** gives **356** and **357** *via* [4+2] cycloaddition[220] (Scheme 117).



354 **355** **356** **357**

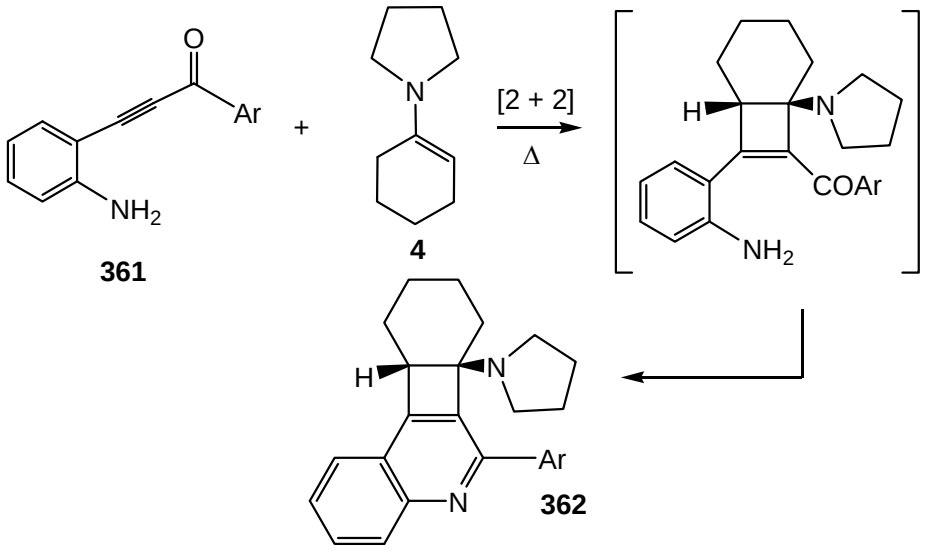
Scheme 117

[4+2] Cycloaddition reaction of 3-trifluoromethyl-4-phenyl-2-aza-1,3-butadienes **358** with enamines **4** gives fluoroalkyl substituted isoquinoline derivatives **360**[221] (Scheme 118).



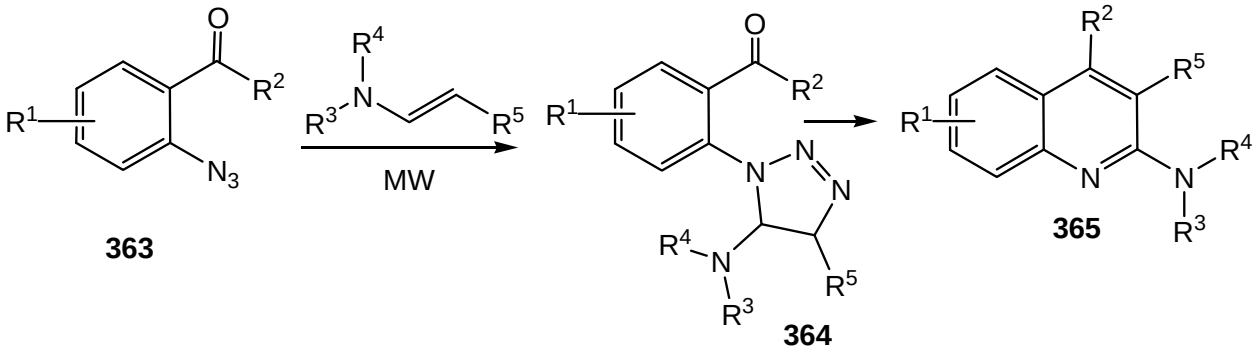
Scheme 118

β-(2-Aminophenyl)-α,β-ynones **361** react with enamine of cyclic ketones **4** by domino [2+2] cycloaddition/annulation reaction, giving rise to fused bicycloquinolines **362**[222] (Scheme 119).



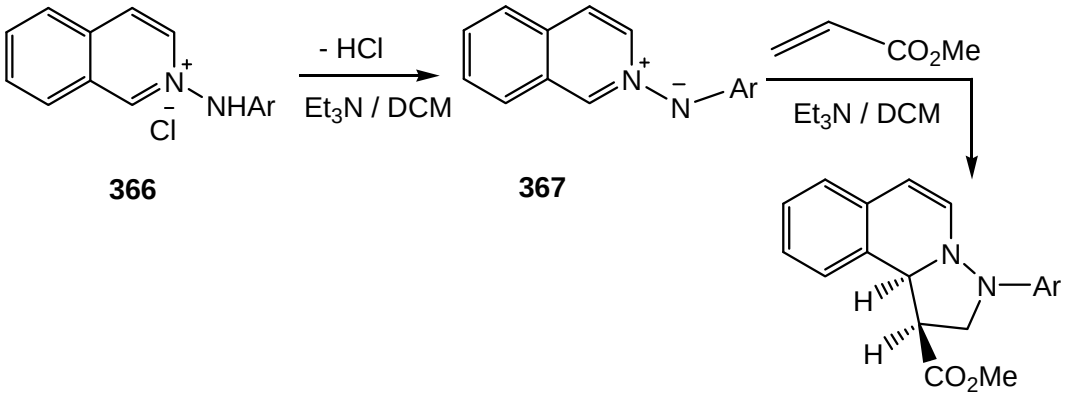
Scheme 119

An improved method for the synthesis of 2-aminoquinolines utilizing microwave-assisted synthesis was recently developed.[223] The process involves rapid microwave irradiation of secondary amines and aldehydes to form enamines followed by the addition of 2-azidoacetophenones **363** with subsequent irradiation to produce 2-aminoquinoline derivatives **365** (Scheme 120).



Scheme 120

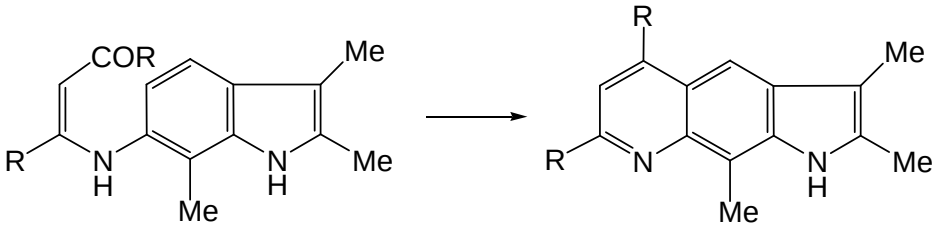
Deprotonation of *N*-arylaminoisoquinolinium salts **366** furnishes the deep red isoquinolinium *N*-arylimides **367** which undergo 1,3-dipolar cycloadditions to afford pyrazolo[5,1-*a*]isoquinoline derivatives **368**[224] (Scheme 121).



366 **367** **368**

Scheme 121

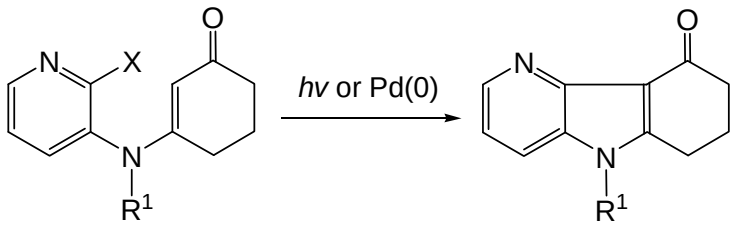
The enaminones **369** cyclized readily into **370**[225] (Scheme 122).



369 **370**

Scheme 122

Enaminones have been reported to efficiently react under photochemical conditions.[226] Example to these assumptions is the photocyclization of *N*-(halopyridinyl)enaminones **371** that were the most efficient paths for the elaboration of the pyridoindolic framework. Thus 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-ones **372** were obtained regioselectively, without formation of by-products[226] (Scheme 123).

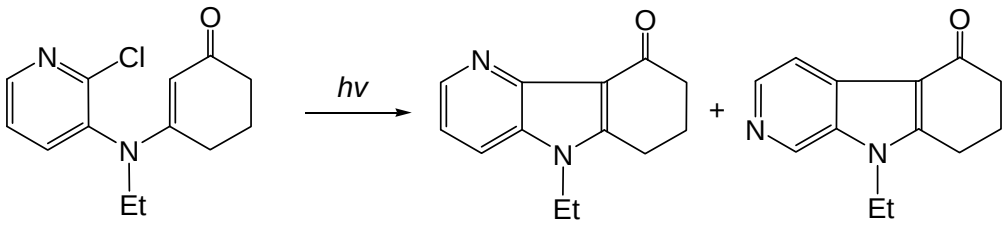


X = H, Hal
R^1 = H, Et, Bn

371 **372**

Scheme 123

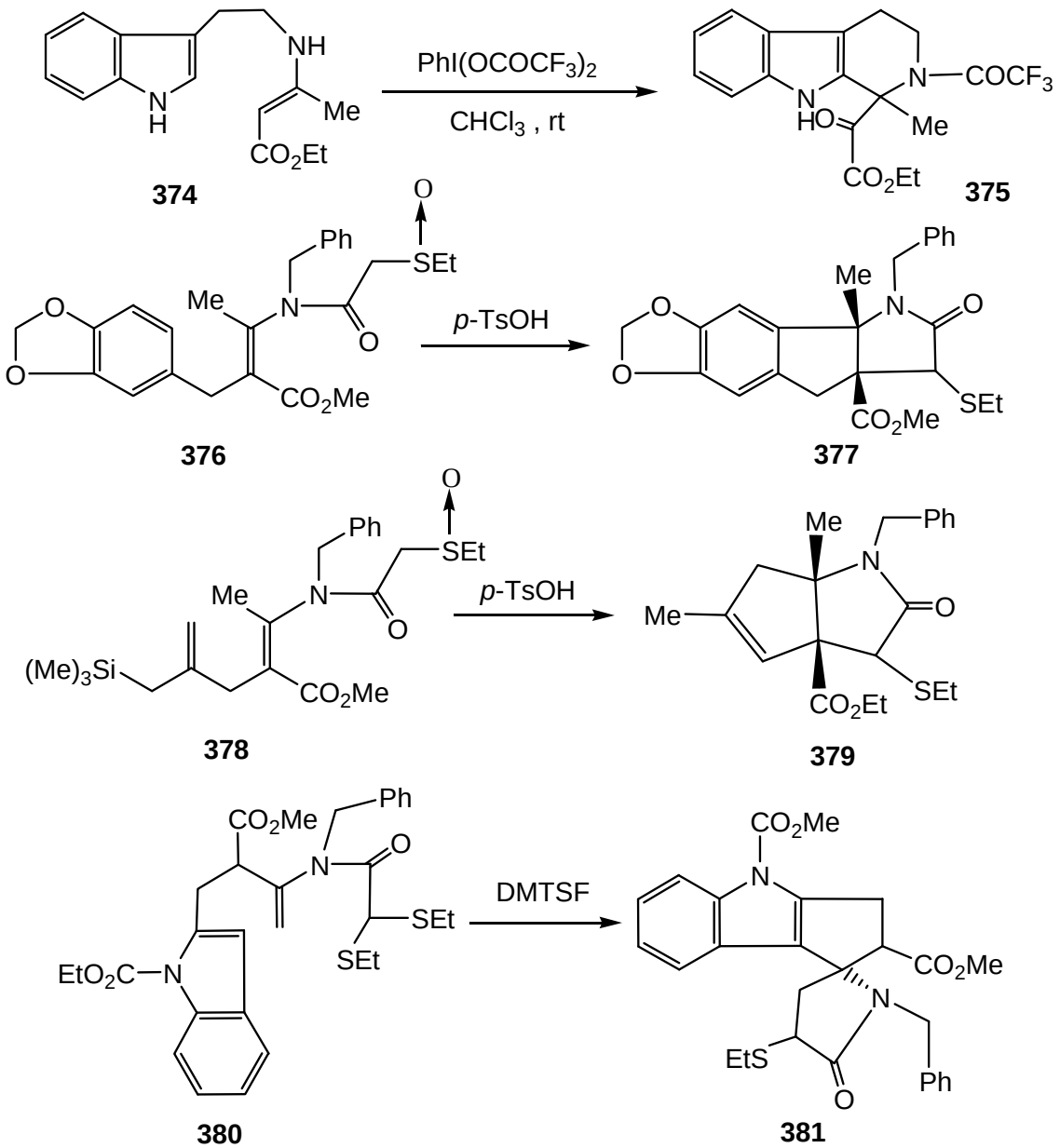
Also the application of such methodologies was suggested.[227] Thus Photochemical cyclization of enaminone **371** derived from 3-amino-2-halopyridines using palladium catalyst led to the synthesis of 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-ones **372** and its isomeric structure **373** (Scheme 124).



371 **372** **373**

Scheme 124

Treatment of enaminoester **374** with *bis*(trifluoroacetoxy)iodobenzene furnishes fused heterocyclic compound **375**[228] (Scheme 125). Similarly, *p*-toluenesulfonic acid and dimethyl(methylthio)sulfonium fluoroborate (DMTSF) affect cyclization of **376**, **378** and **380** into **377, 379** and **381** respectively.[229]



374 **375**

376 **377**

378 **379**

380 **381**

Scheme 125

ACKNOWLEDGEMENT

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