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

Although amino heterocyclic compounds 8 can behave as enamines, 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).

Aldehyde hydrazones can be considered as azaenamines. Nitrogen lone pair resonance renders aldehyde carbon electron rich (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 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.
Enamine chemistry has been surveyed in a volume of prestigious Patai’s chemistry of functional group series on 1994.\textsuperscript{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,\textsuperscript{38a} Ferraz,\textsuperscript{38b} Elassar,\textsuperscript{39} Stanovnik\textsuperscript{40} and Negri.\textsuperscript{41} Chemistry of cyclic enaminonitriles and enaminooesters has been also surveyed by Wamhoff.\textsuperscript{42} Stanovnik's report\textsuperscript{40} is basically concerned with his work. The same applies more or less to Negri work.\textsuperscript{41} Elassar's review\textsuperscript{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

2.1.1. CONDENSATION WITH AMIDE ACETAL

The condensation of amide acetals with active methyl and methylene ketones is a general efficient route to enamines.\textsuperscript{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\textsuperscript{44-65} to adopt \textit{trans} form 13A rather than \textit{cis} isomeric form 13B. The reaction was initially conducted by refluxing both reagents in xylene or toluene or acetic acid for 10-20 h.\textsuperscript{66} However, it could be recently shown that shorter reaction times can be adopted by refluxing neat reagents\textsuperscript{67} (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. 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 heating54 (Scheme 5).

Methyl function in indoles 22 condenses readily with DMF-DMA to yield carbazoles 2569 (Scheme 6).
Although α-picoline failed to condense with DMF-DMA, methyl functions in nitrotoluene \(26^{,20,71}\), 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).

\[
\begin{align*}
\text{NO}_2 & \quad \text{Me} \\
\text{DMF-DMA} & \quad \text{Me} \\
\text{26} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{27} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{28} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{29} & \quad \text{Me} \\
\text{26} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{30} & \quad \text{Me} \\
\text{Et} & \quad \text{Me} \\
\text{27} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{31} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{28} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{32} & \quad \text{Me} \\
\text{NMe}_2 & \quad \text{Me} \\
\text{29} & \quad \text{Me} \\
\text{26} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{33} & \quad \text{Me} \\
\text{Et} & \quad \text{Me} \\
\end{align*}
\]

Scheme 7

Stanovnik \textit{et al.}\textsuperscript{40} have reported that condensation of acylaminoacid esters with DMF-DMA gave the corresponding enaminones. Elnagdi \textit{et al.}\textsuperscript{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\textsuperscript{44-65} (Scheme 8).

\[
\begin{align*}
\text{X} = \text{CH}, \text{N} \\
\text{34} & \quad \text{35} \\
\text{34} & \quad \text{36} \\
\text{36} & \quad \text{37} \\
\end{align*}
\]

Scheme 8
Al-Mousawi et al.\textsuperscript{57} have reported that condensation of 38a with DMF-DMA affords the \textit{trans} enaminone 39A. Ignoring this report Al-Omran and Abou El-khair have reported the same synthesis and assigned \textit{cis}-form for the resulting enaminones 39B\textsuperscript{78} based on observed coupling of olefinic protons. Condensation 38b with DMF-DMA afforded 40 under the same condition (Scheme 9).

![Scheme 9](image)

Cyclic ketones\textsuperscript{57,79,80} also condense with DMF-DMA to yield enamines 41\textit{a,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](image)
Nitroalkanes 46,75 nitrotoluenes 47,81 and p-nitrophenylacetic acid 4882 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-(1H)-quinolones 54 (Scheme 11).

The acetamide 55 condensed with DMF-DMA to yield 5683 (Scheme 12).

2.1.II. CONDENSATION WITH TRIETHYLOLTHOFORMATE

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).

![Scheme 13](image)

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).

![Scheme 14](image)

Similar way was applied for condensation of 62 with primary amines to give the corresponding enamines $63^{88}$ (Scheme 15).

![Scheme 15](image)
Microwave irradiation of ketones with secondary amines in the absence of a solvent has been reported to afford enamines in excellent yields.\textsuperscript{64} Ketones \textsuperscript{64} condense with silyl carbamate \textsuperscript{65} to yield enamines \textsuperscript{66} (Scheme 16).

\begin{equation}
\text{\textsuperscript{64}R}^1\text{CO}_2 + \text{\textsuperscript{65}Me}_2\text{N}\text{OSiMe}_3 \rightarrow \text{\textsuperscript{66}R}\text{NMe}_2
\end{equation}

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\textsuperscript{90} (Scheme 17).

\begin{equation}
\text{\textsuperscript{67}HO}_2\text{C} = \text{\textsuperscript{68}ArN} \rightarrow \text{\textsuperscript{69}NH}_2\text{Ar}
\end{equation}

Scheme 17

Cyclohexanone condensed with morpholine in the presence of 20 % molar InCl\textsubscript{3} in acetonitrile to yield \textit{in situ} enamine \textsuperscript{69} which added to Schiff's bases \textsuperscript{70} to yield \textsuperscript{71} \textsuperscript{91} (Scheme 18).

\begin{equation}
\text{\textsuperscript{70}O} = \text{\textsuperscript{71}NHR} \rightarrow \text{\textsuperscript{72}O}
\end{equation}

Scheme 18

An interesting synthesis of 2-aminocyclohexadienes \textsuperscript{74} from reaction of \textsuperscript{72} with amines has been reported. Intermediate \textsuperscript{73} was also prepared on conducting condensation in refluxing benzene and acetic acid for 7 h\textsuperscript{92} (Scheme 19).
Aminonaphthalenes 77 were obtained via condensing tetralone 75 with amines and subsequent oxidation of resulted enamines 76\textsuperscript{93} by Pd/C (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\textsuperscript{94} (Scheme 21).

Anticonvulsant enamine 83 was prepared via condensing 81 and 82\textsuperscript{95} (Scheme 22).
Fernando et al.\textsuperscript{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\textsuperscript{96} (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\textsuperscript{97} (Scheme 24).

The condensation of β-diketones 87 with secondary amines in the presence of TMSOTf\textsuperscript{98} has been reported to afford enaminones 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 (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 (Scheme 27).

![Scheme 27]

2.1.IV. MISCELLANEOUS CONDENSATION

Compound 94 reacts with phosphonium imines to yield sulphonylenamines 95 (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 (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\textsuperscript{103} (Scheme 30).

Reaction of \( \alpha,\beta \)-unsaturated ketones 102 with POCl\(_3\)/DMF affords \( \beta \)-chloroenones 103. The latter reacted with eliminated amine to afford the expected enamines 104\textsuperscript{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\textsuperscript{105} (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 (Scheme 33).

\[
\text{Ph-N=C=S} \quad \text{KOH / DMF} \quad \text{Ph-N=C=S} \quad \text{KOH / DMF} \quad \text{Ph-N=C=S} \quad \text{KOH / DMF}
\]

\[
\text{110} \quad \text{111} \quad \text{112}
\]

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

\[
\text{40} \quad \text{base} \quad \text{113}
\]

2.2. II. ADDITION OF ACTIVE METHYLENE TO NITRILES

Katritzky et al. could successfully affect addition of nitriles to benzotriazoles to yield in presence of BuLi in THF (Scheme 35). Even methyl function in oxazolines and 1,5-dimethyl-1,2,3,4-tetrazoles add to simple nitriles yielding enamines and , respectively (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).

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).
2.2. III. MISCELLANEOUS SYNTHESIS

Addition of $\beta$-ketoesters 87 to $\alpha$-cyanoesters yields the corresponding adducts 125\textsuperscript{116} (Scheme 38).

![Scheme 38](image)

Similar addition of thioglycolic acid 126 and thiosalicylic acid 128 to active methylene nitriles affords 127 and 129 respectively\textsuperscript{117,118} (Scheme 39).

![Scheme 39](image)

The synthesis of 2,3-dihydropiperidine enamines\textsuperscript{119,120} has typically been carried out by one of the following methods: oxidation of saturated piperidines with mercuric acetate,\textsuperscript{121} reduction of aromatic heterocycles\textsuperscript{122} and amides,\textsuperscript{123} addition of Grignard reagents to lactams,\textsuperscript{124} and base catalyzed isomerizations of 1,2,5,6-tetrahydropyridines.\textsuperscript{125} It has recently been found that perhydropyrido[1,2-\text{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\textsuperscript{126} (Scheme 40).

![Scheme 40](image)

Silyl $\beta$-enaminones 135 have been synthesized by reductive cleavage of silylisoaxazoles 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).

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 \((1,1'-\text{binaphthalene}-2,2'-\text{diyl})\text{bis}(\text{diphenylphosphine})\) (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).

Treatment of \((2\text{-methyl-1-azabuta-1,3-diene})\text{tricarbonyliron}(0)\) 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).
Imines 141 and bis-imine 144 react via their enamine tautomers with terminal perfluorinated epoxides, e.g. hexafluoropropene oxide to produce fluorinated enamine ketones 143 and 145, respectively \(^{132}\) (Scheme 44).

\[
\begin{align*}
\text{R}_2\text{NR} + \text{R}_1\text{O} &\rightarrow \text{HF} \\
\text{141} &\rightarrow \text{143} \\
\text{144} &\rightarrow \text{145}
\end{align*}
\]

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).

\[
\begin{align*}
\text{N}_\text{Ph} \quad \text{R} \\ n-\text{Bu}_3\text{SnH} / \text{AIBN} &\rightarrow \\text{PhCOCl} \\
\text{146} &\rightarrow \text{147}, \text{148, 149}
\end{align*}
\]

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
Cheletropic [2+2] cycloaddition\textsuperscript{134} (Scheme 46).

![Scheme 46](image)

The usefulness of the reaction of $\beta,\beta$-dimethylenamines 153 with vinylketene for the synthesis of cyclobut-2-enones 155 was investigated\textsuperscript{135} (Scheme 47).

![Scheme 47](image)

Nour et al.\textsuperscript{136} reported formation of 157 via reacting 156 with electrophilic alkenes (Scheme 48).

![Scheme 48](image)

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\textsuperscript{137} (Scheme 49).

![Scheme 49](image)
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 intermediate138,139 (Scheme 50).

![Scheme 50]

Quite similar formation of benzene derivatives 162a,b via refluxing enaminoesters 13a and enaminals 13b in acetic acid has been reported140 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 mixture141 (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\textsuperscript{142} and tetrahydro-dicyanonaphthalene 169\textsuperscript{143-146} (Scheme 53).

Reaction of vinylketenes 170 with enamines 171 gives ethyl benzoate derivatives 173 via non-isolable intermediate 172\textsuperscript{147} (Scheme 54).

Several reports on synthetic applications of the TiCl\textsubscript{4}/Et\textsubscript{3}N reagent system have been published. For
examples i) conversion of ketimines to pyrroles,\textsuperscript{148} trialkylamines and ketones to $\alpha,\beta$-unsaturated aldehydes,\textsuperscript{149} ii) the reductive coupling of aromatic aldehydes and imines to the corresponding diols and diamines,\textsuperscript{150} iii) the conversion of 1-alkynes to diynes,\textsuperscript{151} $N,N$-dialkylarylamines to $N,N,N',N'$-tetraalkylbenzidines,\textsuperscript{152} iv) the enantioselective oxidative coupling of the chiral 1,1-$bi$-2-naphthyl ester of phenylacetic acid,\textsuperscript{153} v) the synthesis of cyclobutanone derivatives via iminium ions,\textsuperscript{154} and vi) the intramolecular reductive coupling of chiral diimines to chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes.\textsuperscript{155} Srinivas \textit{et al.} reported\textsuperscript{156} that enamines 174 react with TiCl$_4$/Et$_3$N at 0–25 °C to give the corresponding aromatized products 175 (Scheme 55).

![Scheme 55](image)

Enamine 177 was reduced by sodium borohydride triacetate to produce amines 178\textsuperscript{157} (Scheme 56).

![Scheme 56](image)

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\textsuperscript{158} (Scheme 57).

![Scheme 57](image)
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).

![Scheme 58](image)

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 \(\alpha\)-alkyl-\(\alpha\)-nitroalkenes **184** has been reported\(^{160}\) (Scheme 59).

![Scheme 59](image)

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).

![Scheme 60](image)

The recent developments in utility of enamines as precursors to pyrrole have been reported by Stanovnik
et al.\textsuperscript{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.

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{EtO}_2\text{C}\text{CN}};
\node (b) at (2,0) {\text{HCl / EtOH}};
\node (c) at (4,0) {\text{EtO}_2\text{C}};
\node (d) at (6,0) {\text{NH}_2};
\node (e) at (4,-2) {\text{AcOH}};\node (f) at (6,-2) {\text{(CF}_3\text{CO})_2\text{O}};
\node (g) at (8,-4) {\text{EtO}_2\text{C}};
\node (h) at (9,-4) {\text{NHCOCF}_3};
\node (i) at (11,-6) {\text{EtO}_2\text{C}};
\node (j) at (13,-6) {\text{NHCOCF}_3};
\node (k) at (15,-8) {\text{PhCOCl}};
\node (l) at (17,-10) {\text{COPh}};
\node (m) at (0,-1) {\text{188}};
\node (n) at (2,-1) {\text{189}};
\node (o) at (4,-1) {\text{190}};
\node (p) at (6,-1) {\text{191}};
\node (q) at (8,-1) {\text{192}};
\node (r) at (10,-1) {\text{193}};
\draw [-latex] (a) -- (b);
\draw [-latex] (b) -- (c);
\draw [-latex] (c) -- (d);
\draw [-latex] (e) -- (f);
\draw [-latex] (f) -- (g);
\draw [-latex] (g) -- (h);
\draw [-latex] (h) -- (i);
\draw [-latex] (i) -- (j);
\draw [-latex] (j) -- (k);
\draw [-latex] (k) -- (l);
\end{tikzpicture}
\end{center}
\caption{Scheme 61}
\end{scheme}

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{EtO}_2\text{C}\text{NHMe}_2};
\node (b) at (2,0) {\text{AcOH}};\node (c) at (4,0) {\text{(CF}_3\text{CO})_2\text{O}};
\node (d) at (6,0) {\text{Me}};
\node (e) at (8,0) {\text{PhCO}};
\node (f) at (10,0) {\text{COPh}};
\node (g) at (0,-2) {\text{192}};
\node (h) at (2,-2) {\text{193}};
\draw [-latex] (a) -- (b);
\draw [-latex] (b) -- (c);
\draw [-latex] (c) -- (d);
\draw [-latex] (d) -- (e);
\draw [-latex] (e) -- (f);
\end{tikzpicture}
\end{center}
\caption{Scheme 62}
\end{scheme}

3.3. I. 2. FURANS

Anodic oxidation of enamiones 13A gives a mixture of 194 and 195\textsuperscript{164} (Scheme 63).

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{R}};
\node (b) at (2,0) {\text{R}};
\node (c) at (4,0) {\text{PhOC}};
\node (d) at (6,0) {\text{COMe}};
\node (e) at (8,0) {\text{Me}};
\node (f) at (10,0) {\text{COPh}};
\node (g) at (0,-2) {\text{13A}};
\node (h) at (2,-2) {\text{194}};
\node (i) at (4,-2) {\text{195}};
\draw [-latex] (a) -- (b);
\draw [-latex] (b) -- (c);
\draw [-latex] (c) -- (d);
\draw [-latex] (d) -- (f);
\draw [-latex] (f) -- (e);
\draw [-latex] (e) -- (g);
\draw [-latex] (g) -- (h);
\draw [-latex] (h) -- (i);
\end{tikzpicture}
\end{center}
\caption{Scheme 63}
\end{scheme}

Chiral lactone compounds 198\textsuperscript{165a} are produced from reaction of 196 with 197 (Scheme 64).
3.3. I. 3. THIOPHENES

Recently, Al-Mousawi et al.\textsuperscript{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).

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\textsuperscript{166-169} (Scheme 66).
A useful reaction for synthesis of nitropyrazoles 207 is the reaction of nitroenaminones 206 with hydrazine\(^{170}\) (Scheme 67).

![Scheme 67]

Intramolecular cyclocondensation of 208 gives pyrazole derivatives 209\(^{171}\) (Scheme 68).

![Scheme 68]

Enamines 210 are converted into pyrazole 211 via reaction with hydrazine hydrate\(^{172,173}\) (Scheme 69).

![Scheme 69]

Nitrilimines are versatile reagents for synthesis of pyrazoles via reactions with enamines\(^8\) or enaminones.\(^{174}\) Thus hydrazonoyl halide 212 has afforded 213 and 214 upon treatment with enaminones and enamines respectively (Scheme 70).

![Scheme 70]
3.3. II. 2. IMIDAZOLES

Imidazole derivatives 216 can be synthesized from reaction of 215\textsuperscript{175} with active methylene reagents (Scheme 71).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{HN} \quad \text{Y} \quad \text{Z} \\
\text{O} \quad \text{Ph} & \quad \text{N} \quad \text{215} \\
\text{X} = \text{S}, \text{O} & \\
\end{align*}
\]

**Scheme 71**

3.3. II. 3. ISOXAZOLES

Isoxazoles 217\textsubscript{a,b} and 218 are synthesized from the corresponding enaminones via reactions with hydroxylamine\textsuperscript{166-169} (Scheme 72).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{Y} \\
\text{O} & \quad \text{202a,b} \\
\text{a: } Y = \text{benzothiazol-2-yl} & \\
\text{b: } Y = \text{pyran-3-yl} \\
\end{align*}
\]

**Scheme 72**

Hydroximoyl chloride reacts with enaminones 13A to give isoxazole derivatives 219\textsuperscript{176} (Scheme 73).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{Y} \\
\text{O} & \quad \text{204} \\
\text{R} & \quad \text{Y} = \text{benzotriazol-1-yl} \\
\text{NMe}_2 & \\
\end{align*}
\]

**Scheme 73**

Enamines 210 are converted into isoxazole 220 via reaction with hydroxylamine\textsuperscript{172,173} (Scheme 74).
3.3. II. 4. THIAZOLES
Enamines 221 react with Br₂ in presence of ammonium thiocyanate yielding thiazoline derivatives 222\(^{177}\) (Scheme 75).

\[
\begin{align*}
\text{Me} & \quad \text{NH}_2 \\
\text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Et} & \quad \text{EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{NH}_2 \\
\text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Et} & \quad \text{EtOH}
\end{align*}
\]

Scheme 74

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).

\[
\begin{align*}
\text{ArCHO}_2 & \quad \text{AcOH} \\
\text{NH}_4\text{OAc} & \quad \text{NH}_3
\end{align*}
\]

Scheme 76

Also enaminonitrile 13c reacted with enamines 181 to yield 225. Intermediacy of a cyanodiene 224 was postulated\(^{179}\) (Scheme 77).

\[
\begin{align*}
\text{R}_2\text{N} & \quad \text{CN} \\
\text{R} & \quad \text{NR}_2
\end{align*}
\]

Scheme 77
Reactions of enaminones 13A with malononitrile 226 in ethanolic basic solution afforded the corresponding pyridine 227 and 228 according to reaction condition\textsuperscript{180,181} (Scheme 78).

![Scheme 78]

The enamines 229 react typically as electron rich diene with acetylenes giving pyridines 230\textsuperscript{182} (Scheme 79).

![Scheme 79]

A combinatorial library of several thousand derivatives of 233 was prepared via reacting 231 and 232\textsuperscript{183} (Scheme 80).

![Scheme 80]

Dioxopyrimidine derivative 234 reacts with enaminoester 235 (1:2) to afford pyridine derivative 238\textsuperscript{184} (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. 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, the reactivity of methyl acetoacetate 87 with the α,β-unsaturated nitriles 239 in the presence of SnCl4 was investigated (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\(^6\) in good yield (Scheme 83).

\[
\begin{align*}
\text{NC} & \quad \text{Ph} \\
\text{\textbullet} & \quad \text{CN} \\
\text{243} & \quad + \quad \text{6} \\
& \quad \text{pyridine} \quad \Delta \\
& \quad \text{PhCN} \\
& \quad \text{244} \\
\end{align*}
\]

Scheme 83

Enamines 13A react with hippuric acid to afford acylaminopyrane derivatives 245\(^{180}\) (Scheme 84).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{COR} \\
\text{\textbullet} & \quad \text{PhCONHCH}_2\text{CO}_2\text{H} \\
\text{13A} & \quad \text{Ac}_2\text{O} \quad \Delta \\
& \quad \text{R} \\
& \quad \text{245} \\
\end{align*}
\]

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-2H-thiopyranes 247, and 4H-thiopyranes 248 respectively\(^{188}\) (Scheme 85).

\[
\begin{align*}
\text{Ar} & \quad \text{N} \\
\text{S} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{246} & \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
& \quad \text{H}_2\text{C} \quad \text{X} \\
& \quad \text{CN} \\
& \quad \text{247} \\
& \quad \text{248} \\
\end{align*}
\]

Scheme 85
3.4. II. SIX-MEMBERED RINGS WITH TWO HETEROATOMS

3.4.II. 1. PYRIDAZINES

Recently, Elnagdi et al.\textsuperscript{189} has noted that 249 reacts with \(\alpha,\beta\)-unsaturated nitriles 6a-c to yield aminopyridazine derivatives 250a-c (Scheme 86).

![Scheme 86](image)

The enaminone 251 reacts with aromatic diazonium salts to yield 252 that readily cyclized into 253 in refluxing ethanol\textsuperscript{190} (Scheme 87).

![Scheme 87](image)

3.4.II. 2. PYRIMIDINES

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

![Scheme 88](image)
Pyrimidine derivatives 259-261 can be synthesized from the corresponding enaminones via reactions with guanidine, urea or thiourea and imines respectively (Scheme 89).

\[
\begin{align*}
\text{Me}_2N&-\text{CN} \xrightarrow{\text{H}_2\text{N}+\text{NH}_2} \text{Y} = \text{benzothiazol-2-yl} \\
\text{Y} &= \text{259} \\
\text{X} &= \text{O, S} \\
\text{R} &= \text{260} \\
\text{R} &= \text{261}
\end{align*}
\]

**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 (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 (Scheme 91).
The addition of ethyl propiolate to enamines 268 has been well investigated\textsuperscript{195} in the past to give imidazo[1,2-\(a\)]pyridinone derivative 270 (Scheme 92).

The reaction of salicylaldehyde 271 with enaminonitriles affords benzopyrane derivative 273 in good yield\textsuperscript{196} (Scheme 93).

The enaminoester 274 reacts with DMAD in DMSO in the presence of molecular sieves (4A\textsuperscript{o}) at 135 °C
for one day to yield 275\textsuperscript{197} via [2+2] cycloaddition reaction (Scheme 94).

\begin{align*}
\text{EtO}_2\text{C} & \quad \text{MeO}_2\text{C} & \\
\longrightarrow & \quad \longrightarrow & \\
\text{N} & \quad \text{CO}_2\text{Me} & \\
\text{R} & \quad \text{R} & \\
& \quad \text{MeO}_2\text{C} & \\
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Me} & \\
\longrightarrow & \quad \longrightarrow & \\
\text{N} & \quad \text{MeO}_2\text{C} & \\
\text{R} & \quad \text{CO}_2\text{Me} & \\
& \quad \text{CH}_2\text{CO}_2\text{Et} & \\
\text{H} & \quad \text{H} & \\
\text{274} & \quad \text{276} & \\
\text{n} = 1, 2, 3 & \quad \text{R} = \text{H}, \text{Me}, \text{Ph} & \\
\text{DMSO} & \quad \text{DMSO} & \\
\text{Scheme 94} & \quad \text{Scheme 94} & \\
\end{align*}

Nitrooxazoles 277 obtained via heating nitroisooxazoles 276 in presence of FeCl\textsubscript{3} / SiO\textsubscript{2} react with 1-diethylaminopropyne to yield 278\textsuperscript{198} (Scheme 95).

\begin{align*}
\text{Ph} & \quad \text{Me} & \\
\text{NO}_2 & \quad \text{NO}_2 & \\
\text{N} & \quad \text{N} & \\
\text{O} & \quad \text{O} & \\
\text{O} & \quad \text{O} & \\
\text{R} & \quad \text{R} & \\
\text{276} & \quad \text{277} & \\
\text{FeCl}_3 / \text{SiO}_2 & \quad \text{CHCl}_3 / \text{rt} & \\
\text{D} & \quad \text{D} & \\
\quad & \quad & \\
\text{Ph} & \quad \text{Me} & \\
\text{O} & \quad \text{O} & \\
\text{N} & \quad \text{N} & \\
\text{C} & \quad \text{C} & \\
\text{CON} & \quad \text{C} & \\
\text{Et}_2 & \quad \text{Et}_2 & \\
\text{Ph} & \quad \text{Me} & \\
\text{278} & \quad \text{278} & \\
\text{Scheme 95} & \quad \text{Scheme 95} & \\
\end{align*}
Several cyclization reactions involving intramolecular alkylation have been reported. For example, compound 279 gives 280 on treatment with HMPA\textsuperscript{199} (Scheme 96).

Scheme 96

Intramolecular attack of electron rich moiety in 281 at C-3 gives 282\textsuperscript{200} (Scheme 97).

Scheme 97

Reaction of cyclic enamine 283 with 284 afforded two isomeric 1,4-benzothiazine 285A and pyrido-[2,1-c]thiazine 285B\textsuperscript{201} (Scheme 98).
The reaction of enamines 13A with 1,4-benzoquinones and 1,4-naphthoquinones has been reported\textsuperscript{169,202,203} to yield bezofurans 286 and naphtho[b]furans 287 (Scheme 99).

Nitroenamines 288 also add to 1,4-benzoquinone yielding a mixture of benzofuran 290 and indoles 292\textsuperscript{204} (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\textsuperscript{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\textsuperscript{207} (Scheme 102).
The manganese (III) acetate initiated oxidative free radical reaction between 2-hydroxy-1,4-naphthoquinone \(304\) and \(\beta\)-enamino ketone \(89\) to afford spirolactam \(305\) (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(1H, 3H, 7H)-trione derivative 307 along with 1,4-dihydropyridine derivative 308 (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 (Scheme 105).
Reaction of 1,3-dimethyl-5-thioformyl-6-aminouracil 314 with enamines gave 315 and 316\(^{210}\) (Scheme 106).

\[
\begin{align*}
\text{MeC} &= \text{N} \text{O} \\
\text{O} &= \text{N} \text{H}_2 \\
\text{Me} &= \text{S} \\
\text{R}^1 &= \text{MeCN} \\
\text{R}^2 &= \text{Me}
\end{align*}
\]

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).

\[
\begin{align*}
\text{CO}_2\text{E} &= \text{NMe}_2 \\
\text{Cl} &= \text{N} \\
\text{Cl} &= \text{O} \\
\text{CO}_2\text{Et} &= \text{NMe}_2\text{Cl} \\
\text{TEA} &= \text{RNH}_2 \\
\text{R} &= \text{R}_2
\end{align*}
\]

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-2H-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).
Fused heterocycles which developed by Stanovnik’s laboratories\textsuperscript{162,163,216} are summarized in Schemes 111, 112.

\begin{center}
\includegraphics[width=\textwidth]{scheme111}
\end{center}

\textbf{Scheme 111}

\begin{center}
\includegraphics[width=\textwidth]{scheme112}
\end{center}

\textbf{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\textsuperscript{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 enamiones 200 with 3-aminobenzimidazole and 2-cyanomethylbenzimidazole respectively. Moreover, azoloazines 347, 348 are prepared via reaction of enamiones 200 with aminoazoles\textsuperscript{166,218} (Scheme 114).

**Scheme 114**

The behavior of simple enamiones with heterocyclic amines could be established in a series of papers\textsuperscript{166,203,219} (Scheme 115).
Enaminones 202b react with 2-aminothiazole to afford pyrano[4,3-b]pyridinone derivative 353\textsuperscript{169} (Scheme 116).

Reacting 354 with 355 gives 356 and 357 via [4+2] cycloaddition\textsuperscript{220} (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\textsuperscript{221} (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\(^\text{222}\) (Scheme 119).

An improved method for the synthesis of 2-aminoquinolines utilizing microwave-assisted synthesis was recently developed.\(^\text{223}\) 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).
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).

The enaminones 369 cyclized readily into 370\(^{225}\) (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).

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).
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.\(^{229}\)
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REFERENCES


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