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A brief review on synthesis & applications of β-enamino carbonyl compounds

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Abstract : Owing to the wide range applications of β-enamino esters (enamines of β–dicarbonyl compounds) in pharmaceuticals and as building blocks for the synthesis of a variety of heterocyclic compounds, β-amino esters, β-amino acids, γ-amino alcohols, peptides and alkaloids a number of methods have been developed so far for the synthesis of these compounds. Due to the importance of these compounds as intermediates in organic synthesis, a concised review is presented.

Keywords: Building blocks; concised review; β-enamino esters; heterocyclic and intermediates in organic synthesis.

1. Introduction

β-enamino esters are the attractive synthones for the construction of bio-active heterocycles such as pyrazoles, oxazoles, quinolines, dibenzodiazepines, pyridinones, tetrahydrobenzoxazines, tetronic acids and tetrahydro phenanthridines.[1-5] They have been used for the preparation of different important antibacterial,[6] anti inflammatory,[7] anticonvulsant,[8] and antitumour agents.[9] They are also important precursors for the synthesis of 3-amino sugar derivatives,[10] azo compounds,[11] β-amino ketones,[12] hexahydroazulenes,[13] and indolizidine alkaloids.[14] Thus it is highly desirable to review on these compounds. The versatility of enaminones is in great part due to their promptness to both electrophilic and nucleophilic attack.[15] For this reason, they have been used in the synthesis of various heterocycles and natural products[3] and hence several methodologies have been recently developed towards their synthesis, representing great achievements compounds to the original procedures. Besides reducing the reaction time and increasing the yield and efficiency of the process, most of them focused on a cleaner way to obtain enaminones.

Enaminones or enamine of β-dicarbonyl compounds and their chemistry has been reviewed.[1, 16] These enaminones have demonstrated a potential as multipurpose synthetic intermediates in organic synthesis,[17-21] in the pharmaceutical development[18-21] and in heterocyclic synthesis.[18] The most important and straight forward method involves the direct condensation of β–dicarbonyl compounds

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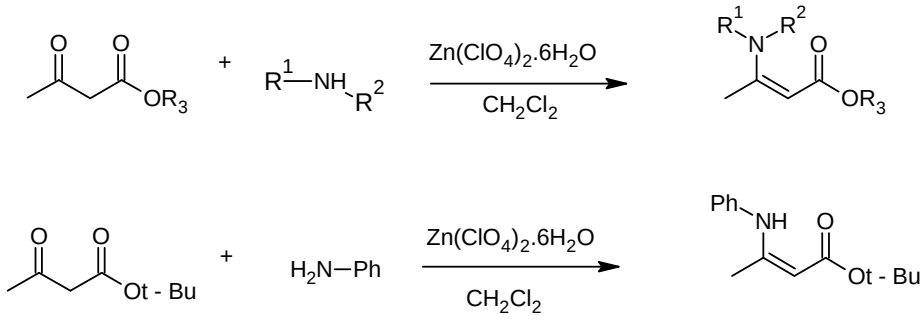
with amines at reflux in an aromatic solvent with azeotropic removal of water.[22,23] A few current examples of preparation of enaminones and their chemistry will be discussed.

2. Sytnthetic Approaches

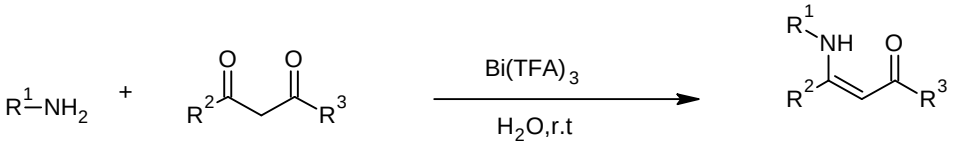
2.1. Conventional Catalytic methods

Bartoli & Sambri et al,[24] reported the synthesis of *N*-substituted β-amino esters by the condensation of primary and secondary amines with keto esters by using $Zn(ClO_4)_2.6H_2O$ as catalyst(yields > 70%).



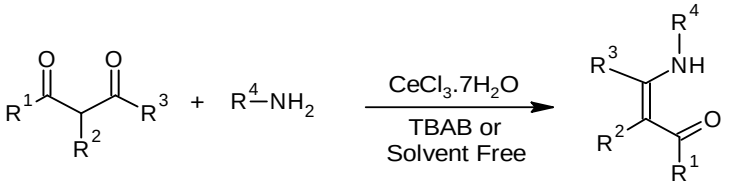
Scheme 1. Synthesis of enaminones using $Zn(ClO_4)_2$ as catalyst

Khosropour & M. Khodaei et al,[25] reported the synthesis of β-enaminones in water by using bismuth (III) trifluoroacetate as catalyst. By employing this catalyst in water, high regio- and chemo-selective enamination of carbonyl compounds was achieved with about 63-98% of yields.



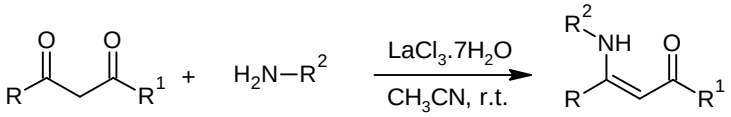
Scheme 2. Synthesis of enaminones using $Bi(TFA)_3$ as catalyst

M.Khodaei's et al,[26] proposed the enamination of various primary amines, which was carried out in the presence of catalytic amount of cerium chloride hepta hydrate in ionic liquids as solvent media under mild reaction conditions(yields > 70%).



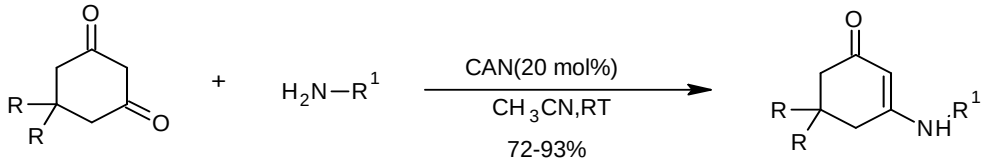
Scheme 3. Synthesis of enaminones using $CeCl_3$ as catalyst

Lenin et al,[27] synthesized a series of various β-keto carbonyl compounds rapidly form enaminone derivatives with a variety of amines at room temperature with 85-93% of yields, in the presence of a catalytic amount of lanthanum trichloride hepta hydrate. The reaction proceeds smoothly at room temperature in methylene dichloride solvent.



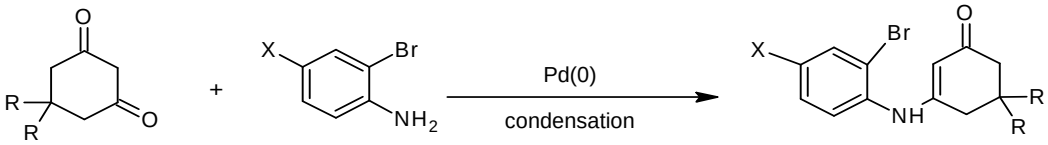
Scheme 4. Synthesis of enaminones using $LaCl_3$ as catalyst

Paira et al,[28] reported β-enaminones in good yields (about 70-93%) from 1, 3-dicarbonyl compounds and activated amines in the presence of ceric ammonium nitrate as catalyst.



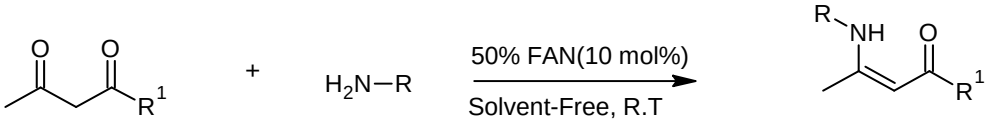
Scheme 5. Synthesis of enaminones using CAN as catalyst

Hideo et al,[29] obtained 3-(2-bromoaryl) amino) cyclohexa-2-en-1-ones with a catalytic amount of Pd(0) species. They condensed 2-bromo-p-toluidine with cyclohexane-1-3-dione yielded the bromo enaminones (Yields between 05-38% only).



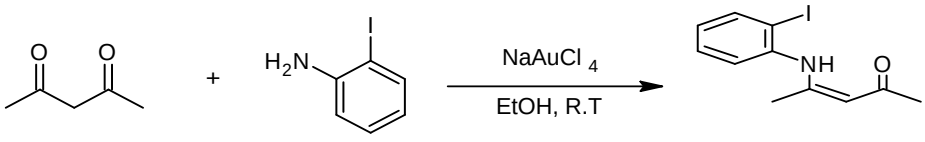
Scheme 6. Synthesis of enaminones using Lead as catalyst

Murthy et al,[30] reported that a variety of β-enamino esters and β-enaminones are synthesized by the reaction of 1, 3-dicarbonyl compounds and various primary amines in the presence of catalytic amount of ferric (III) ammonium nitrate at room temperature under solvent free conditions with 69-92% of yields.

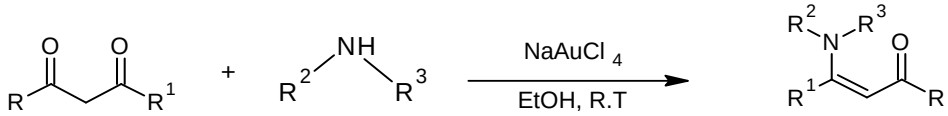


Scheme 7. Synthesis of enaminones using FAN as catalyst

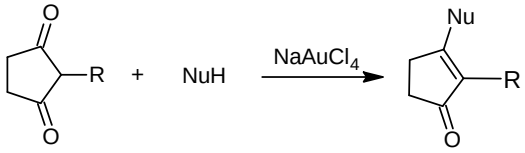
Arcadi et al,[31] developed a new and efficient synthesis of β-enaminones from 1, 3-dicarbonyl compounds and ammonia/amines providing an attractive and environmental friendly alternative to the more vigorous reagents and drastic conditions of the existing methodologies reporting 61-98% yields, which are described using gold (III) catalyst. This catalyst is also extended to reaction of cyclic1, 3-dicarbonyls with O-,P- and S-nucleophiles.



Scheme 8. Synthesis of enaminones from primary amines

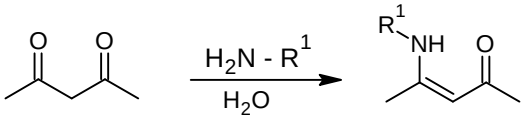


Scheme 9. Synthesis of enaminones from secondary amines



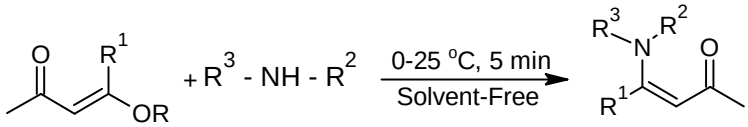
Scheme 10. Synthesis of enaminones using $NaAuCl_4$ as catalyst

Stefani et al,[32] published the synthesis of enaminones from β-keto esters or 1, 3-Diketones and primary amines in water as solvent system(yields > 60%).



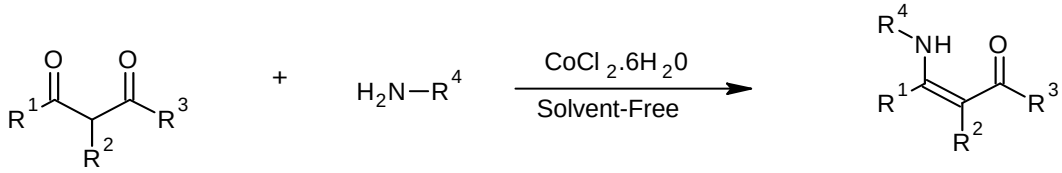
Scheme 11. Synthesis of enaminones using H_2O as solvent

Martins et al,[33] described important studies and published an efficient green procedure to prepare a series of twenty six 4-amino-1,1,1-trihalo-3-alkene-2-ones from the solvent-free reaction of 1, 1, 1-trihalo-4-alkoxy-3-alkene-2-ones with 1^0 and 2^0 amines(yields of 73-99%).



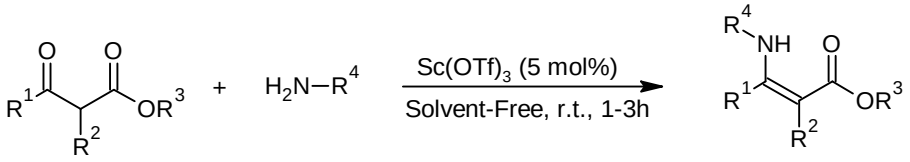
Scheme 12. Synthesis of enaminones under solvent-free condition

Zhang and Hu,[34] reported synthesis of various β-enaminones and β-enamino esters by the reaction of 1,3-dicarbonyl compounds with amines in the presence of a catalytic amount of cobalt(II) chloride at room temperature under solvent-free conditions. The experimental procedure is simple and the products are straight forwardly isolated in high yields(about 75-95%).



Scheme 13. Synthesis of enaminones using $CoCl_2$ as catalyst

Yadav et al,[35] published the synthesis of enaminones using β-keto esters and an amine under solvent-free conditions in the presence of a catalytic amount of $Sc(OTf)_3$(5 mol%) for a certain period of time required to complete the reaction. The resulting *N*-substituted β-enamino esters (yields of 70-95%) was extracted from the reaction mixture and the catalyst was recovered and re-used for three to four times without loss of activity, even after fourth cycle the product was obtained with the similar yield and purity of those obtained in the first cycle.

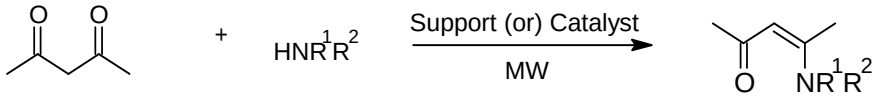


Scheme 14. Synthesis of enaminones using $Sc(OTf)_3$ as catalyst

2.2. Microwave-Assisted Synthesis of Enaminones

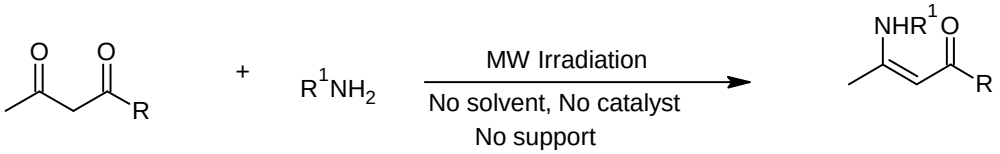
There are major advancements in the last few years in the methodology of synthetic chemistry, but one element of the process has not much changed since its inception i.e., the use of conventional heating to perform chemical transformations. However, with the advent of microwave assisted synthesis, for the first time, a technology that will dramatically, change the way chemical synthesis is performed by offering a new energy source, powerful enough to complete reactions in minutes instead of hours or even days. Microwave heating is a different process. The microwaves couple directly with the molecules that are heating, leading to a rapid rise in temperature, because the process is not dependent upon the thermal conductivity of the materials. The result is, an instantaneous heating of anything that will react to either dipole rotation or ionic conduction, the two fundamental mechanisms for transferring energy from microwave to the substance being heated. Microwave enhanced chemical reactions can be faster by as much as 1000 fold this is based on experimental data, from numerous works, that have been performed over the last 15 years. In recent years there has been considerable interest in the application of microwave heating upon chemical reactions. After much debate there seems to be general agreement that in most cases microwave heating can only give rise to different temperatures regimes, which can be used in a profitable way. For instance when the reaction need to be rapid increase of the synthesis of radiopharmaceuticals or when high temperature need to be reached for the preparation of some inorganic compounds. In addition, microwave heating is ideal for solvent-free reaction systems, so called "dry reactions".[36] Temperature effects are also the origin of the fact that a power input change can cause a different. Herein, some of the microwave approaches for the synthesis of enaminones are described.

Hamelin et al,[37] synthesized a series of enamino ketones and acylamines, starting from β-diketones and primary or secondary amines and amino esters by using clay K_{10} or silica under microwave condition (yields of 60-93%).



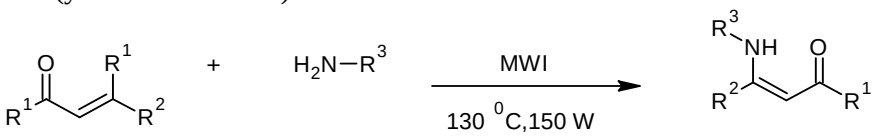
Scheme 15. Synthesis of enaminones using clay K_{10} or silica

Andrade et al,[36] reported microwave irradiation of different sources were used to prepare various enaminones from the corresponding free amines and β-dicarbonyl compounds under solvent-free conditions with greater than 90% yields.

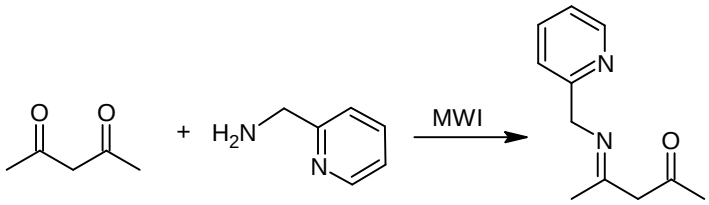


Scheme 16. Synthesis of enaminones under neat reaction conditions

Lee et al,[38] presented a new and efficient methodology for the β-ketoimine ligands with microwave heating system. They studied the comparison between microwave and conventional synthetic methods (yields of 60-100%).

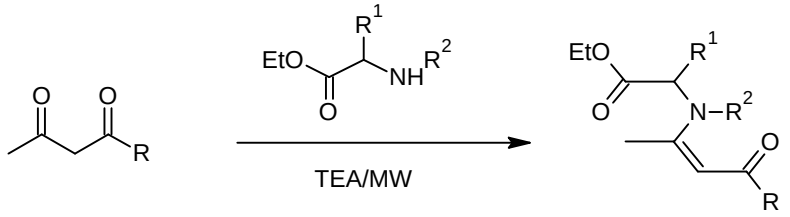


Scheme 17. Synthesis of enaminones under MW heating

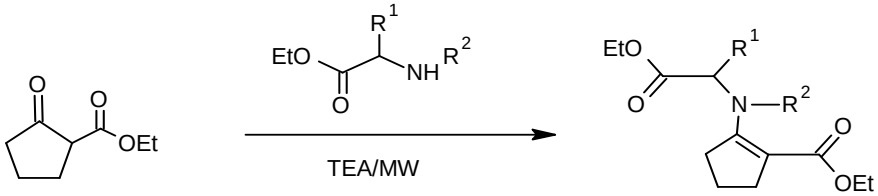


Scheme 18. Synthesis of enaminones under MW heating

Braibante et al,[39] published a series of β-amino esters, α, β-unsaturated ketones and esters derived from α-amino acids have been prepared starting from α-amino esters hydrochlorides with 1,3-dicarbonyl compounds in the presence of triethyl amine. These compounds have been prepared using domestic microwave oven (yields of 50-93%), under solvent-free condition with and without solid support of K_{10} or KSF (MW/ K_{10} - yields of 36-86%; MW/ KSF- yields of 45-94%).

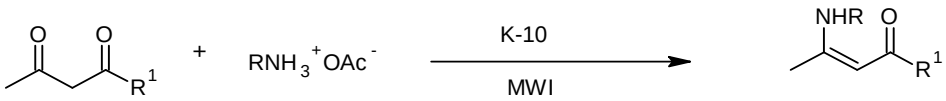


Scheme 19: Synthesis of Enaminones using K_{10} or KSF

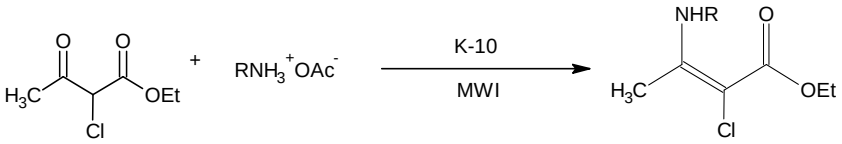


Scheme 20. Synthesis of enaminones in presence of TEA

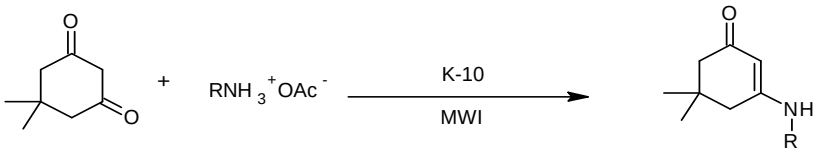
Braibante et al,[40] prepared β-Enamino ketones and esters using the methodology of the reactions on solid support coupled with microwave irradiation. The reaction of cyclic, acyclic and α-chloro-substituted β-dicarbonyl compounds with amines or their corresponding ammonium acetates was carried out using K-10 to yield β-enamino carboxylic compounds in good yields of about 47-97%.



Scheme 21. Synthesis of enaminones using K_{10} as solid support



Scheme 22. Synthesis of β-enamino esters



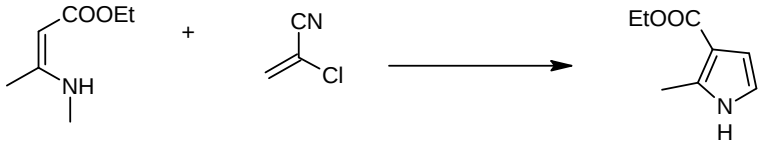
Scheme 23. Synthesis of β-enamino ketones

3. Applications of B-Enamino Carbonyl Compounds in Organic Synthesis

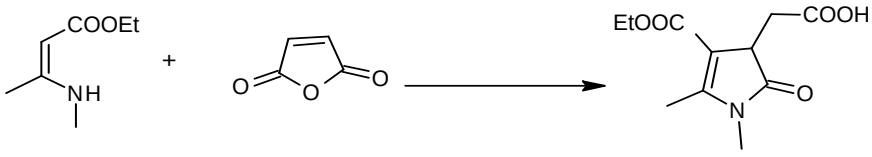
β-enamino carbonyl compounds represent an important class of functionalized building blocks. The β-enamino carbonyl unit can be converted to region- and stereo-selective synthesis of a variety of biologically active compounds, such as α and β-amino acids, γ-aminols, alkaloids, peptides and a variety of heterocyclic and pharmaceutical compounds. The structure-activity relationship (SAR) studies with enaminones[41-46] have uncovered remarkable anticonvulsant activity for several analogues. The cellular mechanism studies conducted by Kombian and co-workers showed that some anticonvulsant anilines and benzyl amino enaminones reversibly suppressed glutamated-mediated excitatory postsynaptic currents(EPSCs) recorded in the nucleus accumbens and hippocampus regions which is analogous to GABA activity.[47-48]

3.1. Enaminones in the Synthesis of Heterocycles.

Jakobsen et al,[49] described the Michael type condensations of enamino esters to electrophilic α-chloro acrylonitrile to furnish the pyrrole derivatives (scheme-24).Bean et al,[50] reported the condensation of enamino esters with maleic anhydride which derived the pyrrolinone (scheme-25).

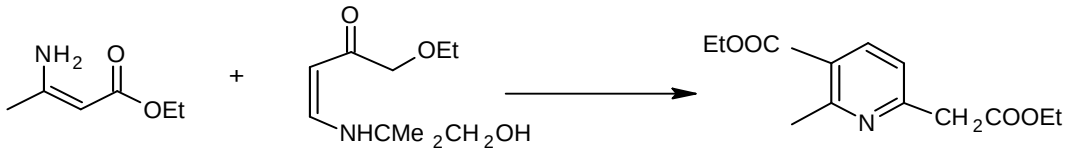


Scheme 24: Michael type condensations of enamino esters



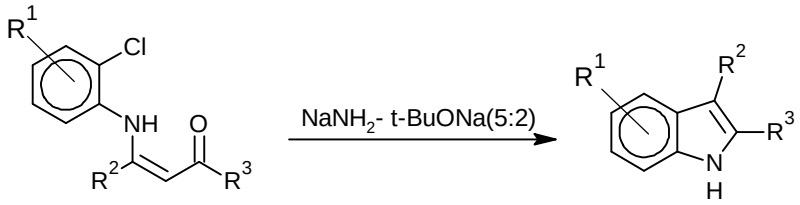
Scheme 25: Pyrrolinone synthesis by Michael type condensation

Singh et al,[51] published the synthesis of 2, 3, 6-substituted pyridine derivatives by the reaction of enamino esters with enaminones.



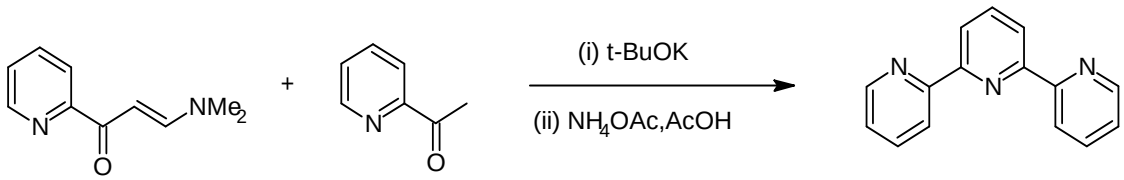
Scheme 26. Synthesis of pyridine derivatives from enaminones

Caubere et al,[52] reported the synthesis of indole derivatives by intramolecular cyclisation of enaminone derivatives mediated by the complex base $NaNH_2$-tBuONa(5:2).



Scheme 27. indole synthesis by intramolecular cyclisation of enaminones

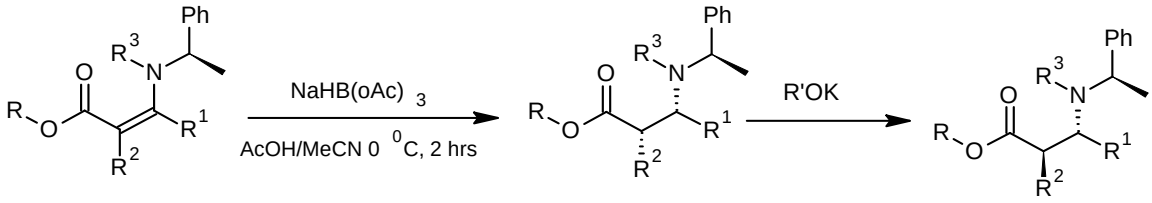
Livoreil et al,[53] developed an interesting synthesis of the linear tris{terpyridine} ligand from the reaction of the enaminone with the acyl pyridine. This reaction involves an initial addition of the acyl methyl function to the α, β-unsaturated moiety in the enaminones.



Scheme 28. Synthesis of the linear tris{terpyridine} from enaminones

3.2. In the Synthesis of β-amino Esters

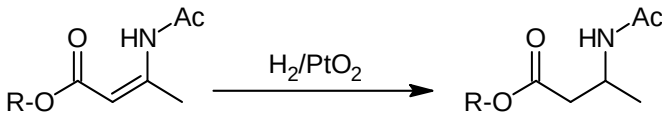
Cimarelli et al,[54] described the synthesis of enantiopure β-amino esters by the reduction of enantiopure β-enamino esters with sodium triacetoxyborohydride in the acetic acid medium.



Scheme 29. Reduction of enantiopure β-enamino esters in synthesis of enantiopure β-amino esters

3.3. In the Synthesis of Chiral α-amido Esters

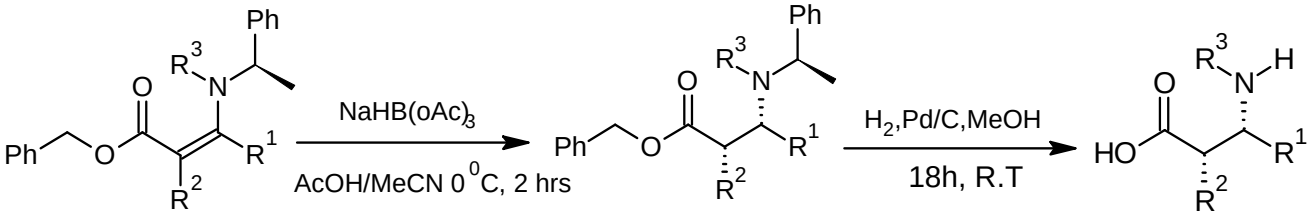
Potin et al,[55] synthesized a series of chiral amido esters with high diastereo isomeric excess by asymmetric hydrogenation (H_2/PtO_2) of stereogenic β-acetamido crotonates in which the chirality is present in the alkyl of the ester part. For this purpose, new efficient chiral auxiliaries such as 2, 2-diphenyl cyclopentanol and 1, 1-diphenyl-3-methyl-2-butanol was used.



Scheme 30. synthesis of chiral amido esters

3.4. In the Synthesis of Chiral β-amino Acids

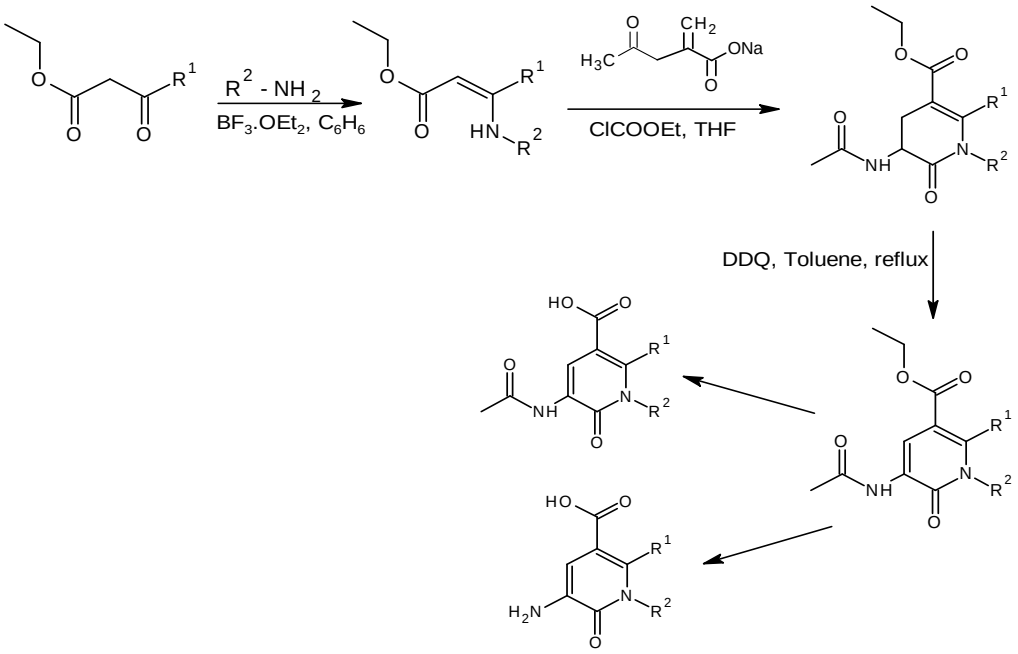
Cimarelli et al,[56] reported the preparation of both the enantiomers of β-amino acids by the stereoselective reduction of diastereomers of β-enaminoesters.



Scheme 31. Stereoselective reduction of β-enaminoesters

3.5. In the Synthesis of Peptides

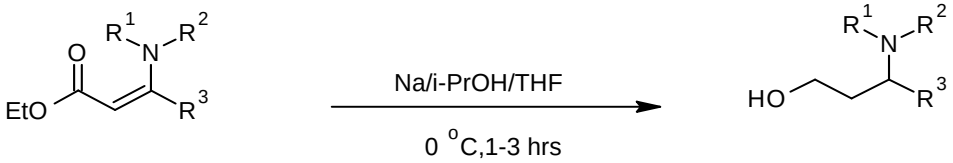
Beholz et al[57] developed a conventional method for the formation of dihydropyridone and pyridine based peptide analogs through Aza-annulation of β-enamino esters and amide substrates with α-amino acrylate derivatives.



Scheme 32. Aza-annulation of β-enamino esters

3.6. In the Synthesis of γ-amino Alcohols

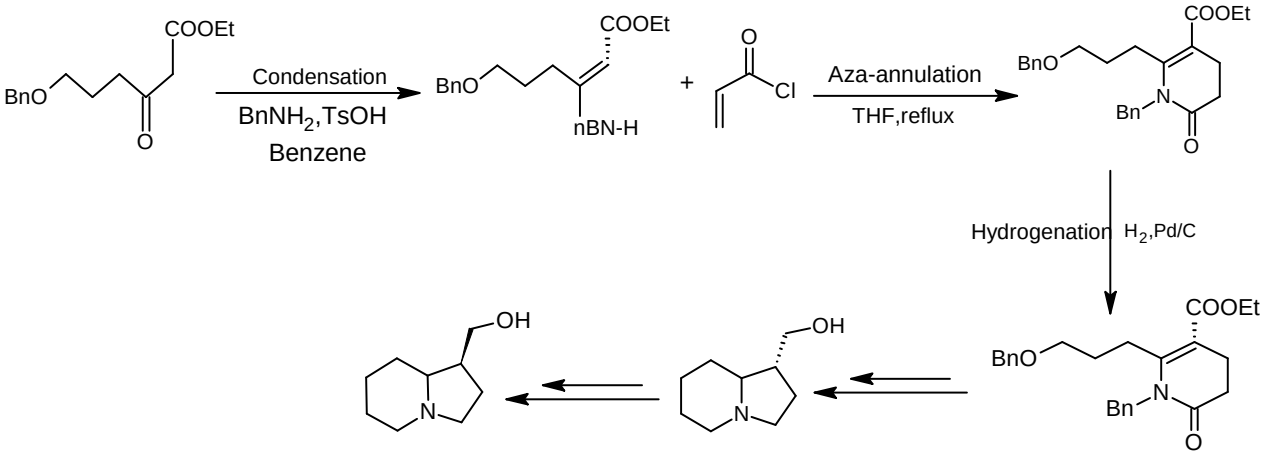
Bartoli et al,[58] reported the synthesis of both cis-and trans γ-amino alcohols by chemo- and diastereo selective reduction of β-enamino esters with the use of inexpensive reagent Na/i-PrOH under appropriate reduction conditions.



Scheme 33. Chemo- and diastereo selective reduction of β-enamino esters

3.7. In the Synthesis of Alkaloids

Paulvannan et al,[59] described the stereochemically controlled synthesis of nitrogen containing six membered heterocyclic indolizidine alkaloids namely Tashiromine and 5-epitashiromine by the application of the condensation/aza-annulations/ hydrogenation sequence as the key for construction.



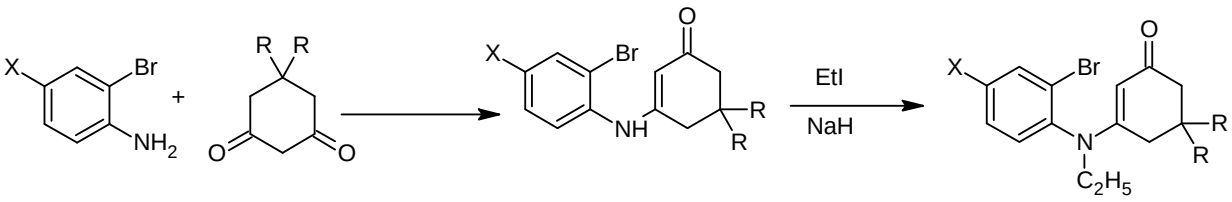
Scheme 34. Stereochemical synthesis of Tashiromine and 5-epitashiromine

3.8. Intramolecular Cyclization of Enaminones for the Synthesis of Carazoles

Iida et al,[60] treated the 3-{(2-bromoaryl) amino} cyclohex-2-en-1-ones with a catalytic amount of Pd(0) species, yielded 1,2-dihydrocarbazol-4(*3H*)-ones by the intramolecular cyclization via aryl palladium complexes. By the catalysis of $Cu(OAc)_2$ and oxygen, analogous products were also obtained by the similar cyclization of 3-aminocyclohex-2-en-ones using a stoichiometric amount of $Pd(OAc)_2$.

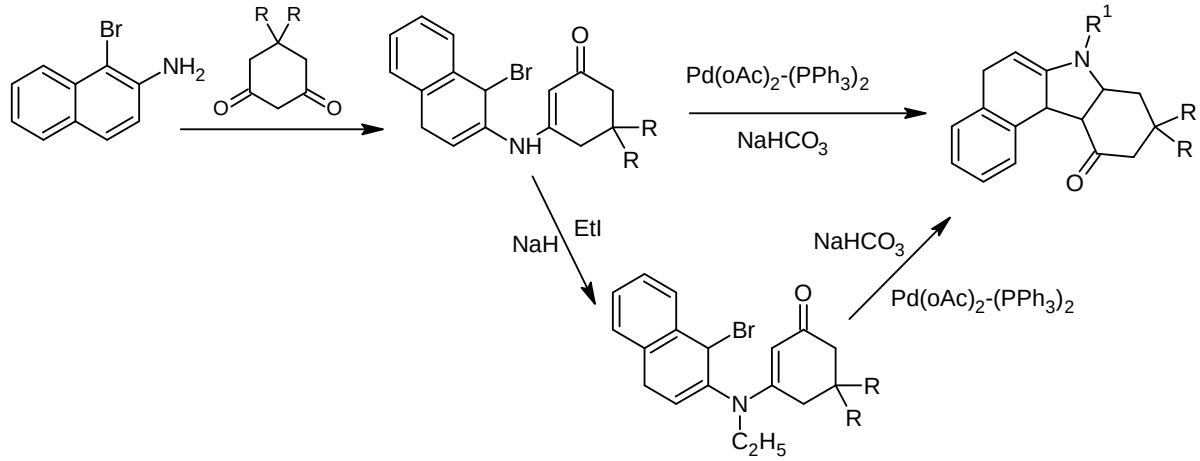
3.8.1. Catalytic Cyclization

The condensation of 2-bromo-p-toluidine with cyclohexane-1, 3-dione or dimedone resulted the bromo enaminones respectively.[61]



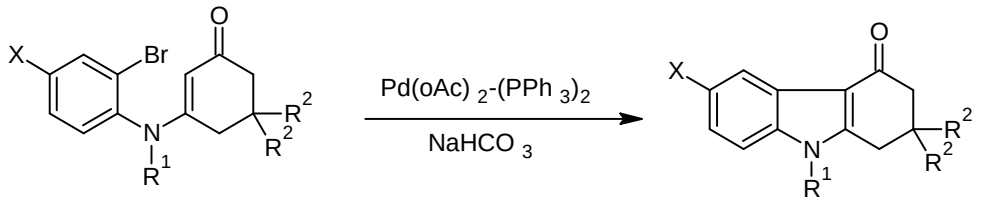
Scheme 35. Synthesis of bromo enaminones by condensation of 2-bromo-p-toluidine

Various tertiary enaminones were synthesized by *N*-ethylation with ethyl iodide and sodium hydride. In the same manner, 1-bromo-β-naphthylamine is condensed with the β-diketones to give the *N*-β-naphthyl enaminones which were converted to the corresponding *N*-ethyl derivatives by a similar method described in the below Scheme-36.[60]



Scheme 36. Synthesis of tertiary enaminones

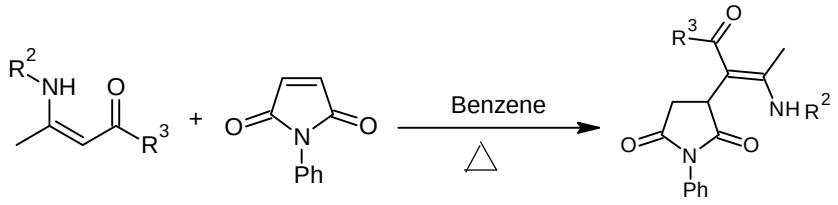
When bromo enaminone was treated with 2 mol% 2:1 triphenyl phosphine-palladium acetate complex in dimethyl formamide in the presence of sodium bicarbonate, the enaminone system was subject to palladium-catalyzed to yield the carbazole.[60]



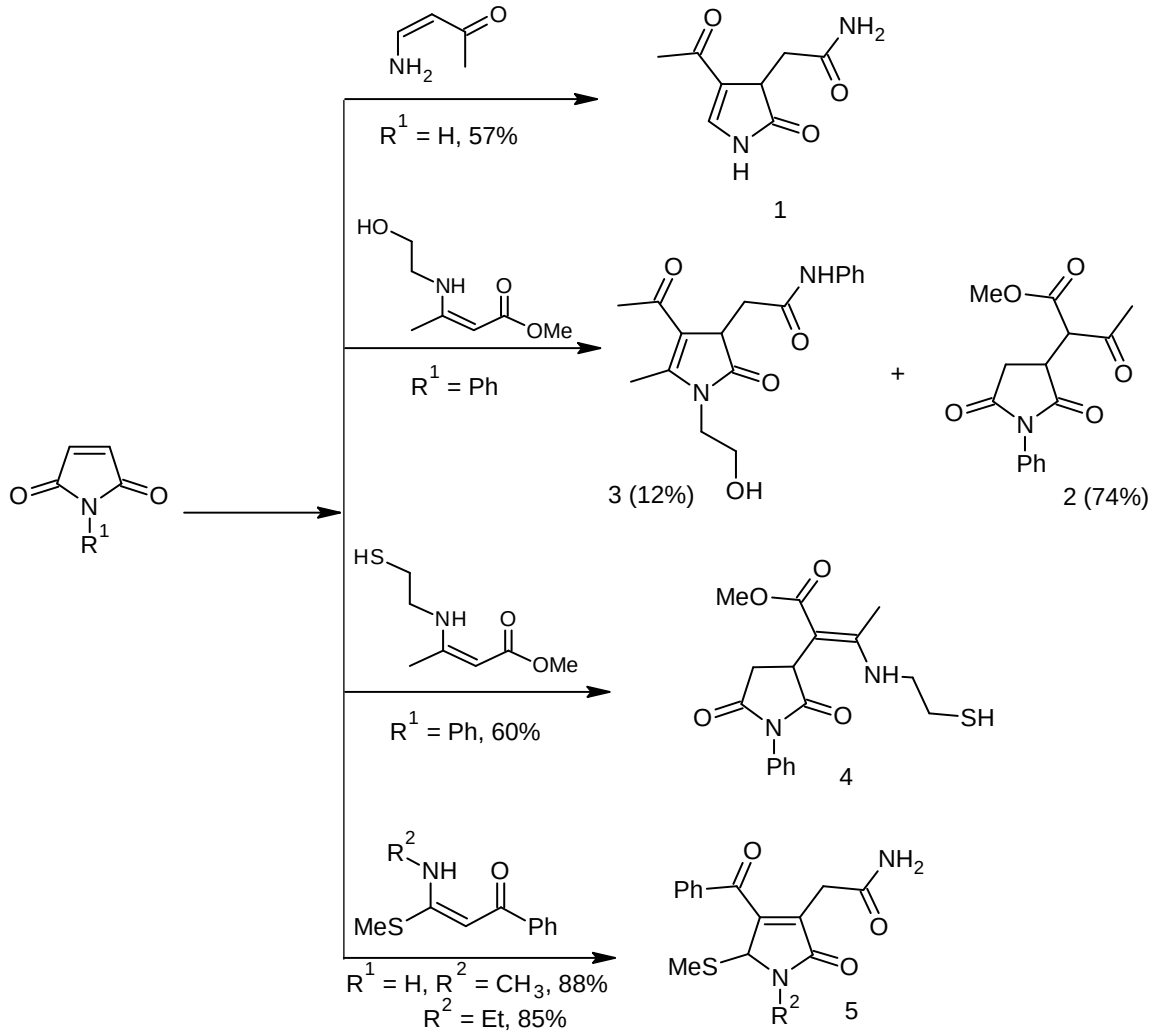
Scheme 37. Synthesis of carbazoles

3.9. Enaminones with N-(p-tolyl)-maleimide in Michael Reaction

Cunha et al,[61] described the reaction of *N*-(*p*-tolyl)-maleimide with enaminones afforded succinimide-containing enaminones in moderate to good yields and these compounds were evaluated against *E-coli* and *S.aureaus*, but no significant antibacterial activity was reported in this work. The regiochemistry of the compounds was examined mechanistically within frontier molecular orbital considerations.



Scheme 38: Synthesis of succinimide-containing enaminones



Scheme 39. Michael reaction with enaminones

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