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DIVERGENT SYNTHESIS OF STEROID ANALOGS FROM STEROIDAL β-FORMYLENAMIDES, CONJUGATED ENONES AND β-FORMYLVINYL HALIDES

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Abstract – In the past two decades, our laboratory has been actively engaged in the design and synthesis of novel heterosteroidal analogues. Three functional groups namely β-formylenamide, conjugated enone and β-formylvinyl halide were primarily employed in various reactions to afford a library of novel heterosteroids. The synthetic strategies have been concomitantly utilized in the relevant non-steroidal β-formylenamides, conjugated enones and β-formylvinyl halides.

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1. INTRODUCTION

The chemistry of steroids is important because of their presence in animal and plant kingdom as crucial component of cell membrane and signaling molecules.[1] The steroidal domain is composed of several key molecules including corticosteroids and hormones. On the other hand, azasteroid is a type of steroid derivative obtained through incorporation of a nitrogen atom into the core structure of steroid by replacement of a carbon atom. Over the years, azasteroids and its fused analogs have played considerable role in drug design and formulation due to their broad spectrum of biological activities.[2,3] Azasteroids exhibit potent biological activities such as anti-tumor (abiraterone), benign prostatic hyperplasia (finasteride, dutasteride), anti-inflammatory (corticosteroid), anti-fungal (7-aza-des-*A*-steroid), cholesterol biosynthesis (lathosterol side chain amide) delivered *via* inhibition of enzymes like 5α-reductase, 17α-hydroxylase/17,20-lyase and lathosterol oxidase. Several functionally substituted steroid derivatives have been identified to be of colossal pharmaceutical importance.[4] Chemical properties of the steroidal molecules are affected by modifications in the ring of the steroid nucleus and this often opens up a doorway to useful biological activities (Figure 1). Due to this underlying fact, azasteroids and related heterosteroids have carved itself a niche in the present day drug discovery race.

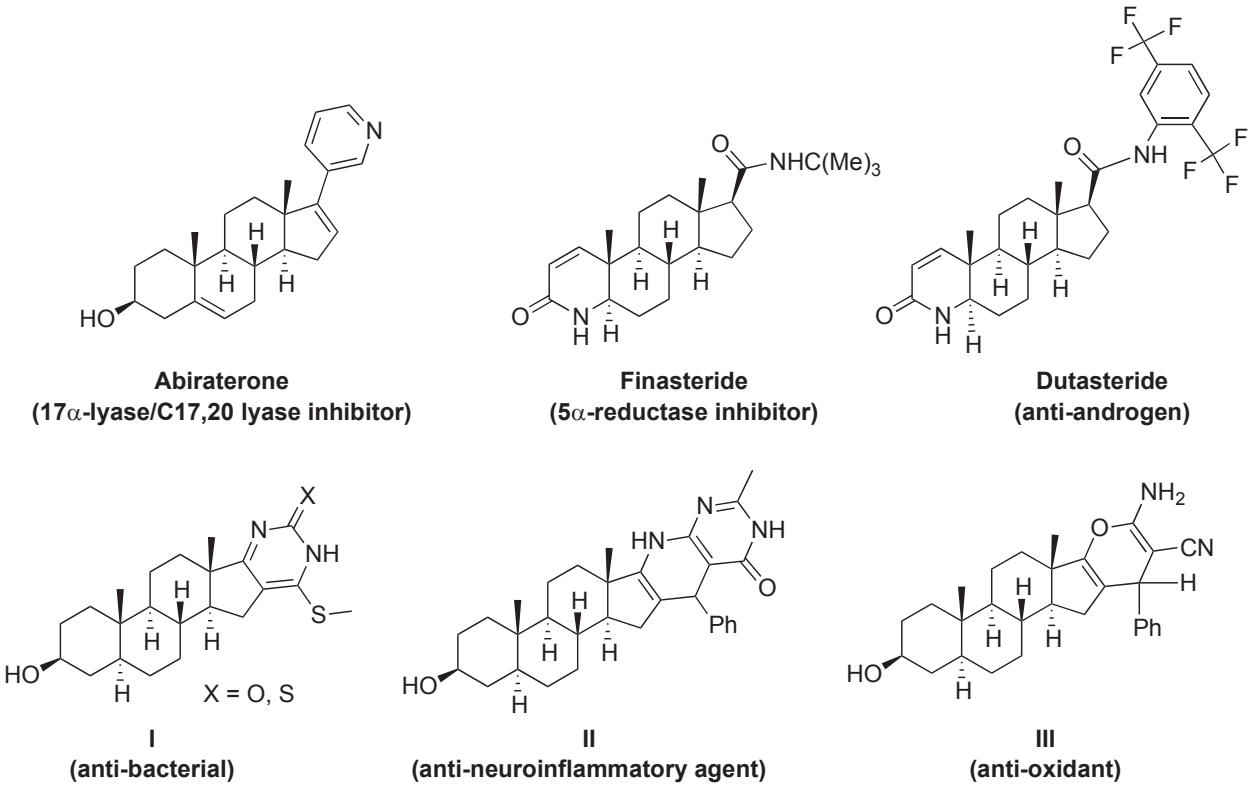


Figure 1. Some biologically active heterosteroids

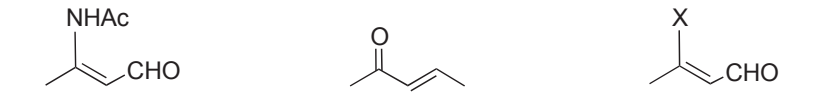
The functional diversity of steroidal moieties provides insights into the possibilities for developing a broad range of receptors by varying the pharmacophoric groups in the annulated rings.[5] Even amongst the

non-steroidal organic synthesis domain, the importance of polyfunctionalized heterocycles has been significantly emphasized.[6] Hydrophobic steroid moieties display excellent ability to interact with cell membranes, thereby proving its tenacity in solving several biological hurdles.[7] The existence of this vast pool of biological potential has continuously driven the medicinal chemist fraternity to annulate A- and D-rings of the core steroid nucleus with diverse aza-heterocyclic moieties. A number of these azasteroids provide a variety of scaffolds, the explorations of which have led to the identification of bio-molecules pertaining to anti-cancer, hypotensive, diuretic, anti-inflammatory, anti-microbial, hypocholesterolemic activities.[8–11]

Steroid semi-synthetic intermediate 16-dehydropregnenolone acetate (16-DPA), which could be derived from diosgenin,[12] is one of the most important precursors for anti-tumour drugs.[13,14] In addition, the conjugated acetyl group of 16-DPA provides immense opportunity for molecular modifications. The easy accessibility of a novel class of β-formylenamide from conjugated enone has opened up a new avenue for the design of several novel azasteroidal molecules. Conjugated enones and β-formylvinyl halides have contributed their fair share in the synthesis of heterosteroids. Although conjugated enones are the precursor of β-formylenamide, we are classifying it into two different categories with respect to its role as a synthon for the direct conversion to a large group of heterosteroids.

Ibrahim-Ouali *et al.* reviewed the partial and total synthesis of oxasteroids,[15] thiasteroids[16] and azasteroids[5] during 2006-2008; however, no attempt has been made thereafter to document the recent development of new and efficient routes to novel heterosteroids.

In this review, focus has been made on the synthetic application of three functional groups namely, β-formylenamide, conjugated enone and β-formylvinyl halide (Figure 2), which are suitably generated in the steroidal core, for exploring their enormous potential for synthesis of novel heterosteroids.



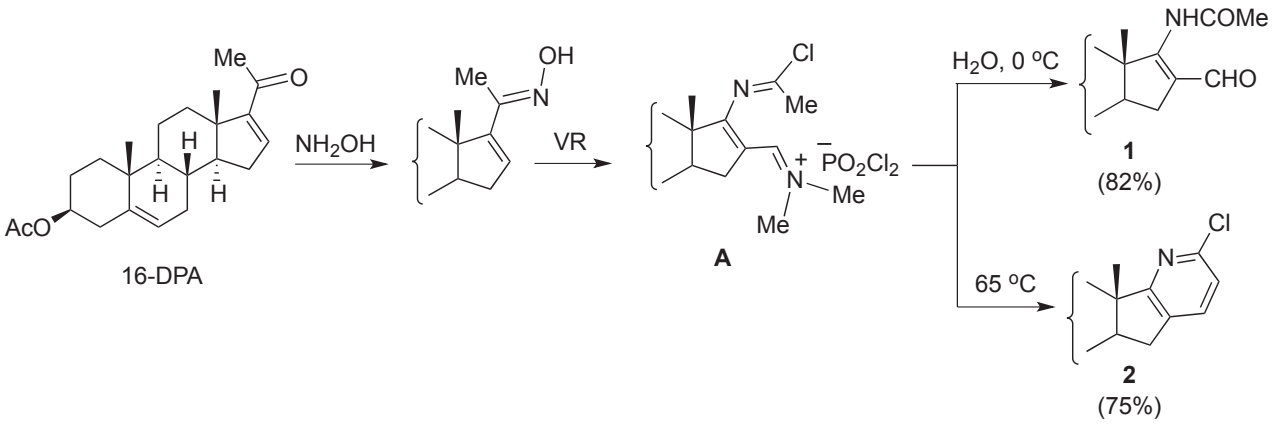
β-formylenamide **conjugated enone** **β-formylvinyl halide**

Figure 2. Synthons leading to novel azasteroids

2. STEROIDAL β-FORMYLENAMIDES

At the initial phase of our studies, pyridine functionalized steroidal molecules seized our attention since pyridines were reported to possess anti-tumor activities.[17,18] Taking into consideration that azadienes[19] or conjugated oximes[20] often played the role of synthetic precursors for pyridines, a schematic pathway was planned and executed for the synthesis of substituted steroidal pyridine from conjugated oximes under Vilsmeier condition. The starting molecule was 16-DPA which was initially subjected to oximation

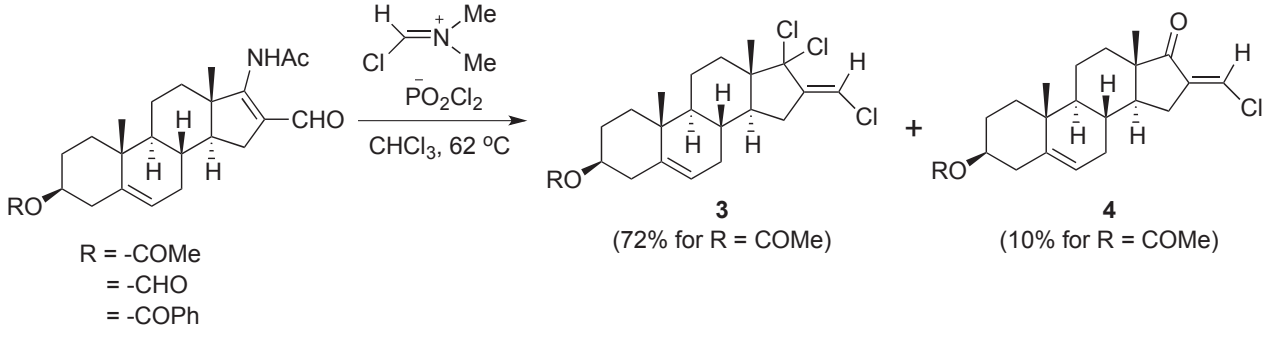
followed by treatment with Vilsmeier reagent. It was established that the intermediate **A** gave rise to two different products under varying temperature condition. On maintaining the temperature at 0 °C, intermediate **A** got converted to 3β-acetoxy-16-formyl-5,16-dehydropregnenolone-20-oxime,[21] which was later corrected as Beckmann rearrangement product 3β-acetoxy-17-acetamido-16-formylandrosta-5,16-diene (β-formylenamide, **1**) in our subsequent publication.[22] However, on increasing the temperature to 65 °C, androstano(17,16-*b*)pyridine (**2**) was formed (Scheme 1). A number of our succeeding ventures have been carried out using this β-formylenamide moiety and therefore, the aforementioned synthetic strategy has received utmost importance. Interestingly, β-formylenamide (**1**) exhibited anti-gastric ulcer activity[23] in addition to its enormous synthetic potential in our ventures.



Scheme 1. Synthesis of β-formylenamide

2.01. Geminal dichlorides from β-formylenamide

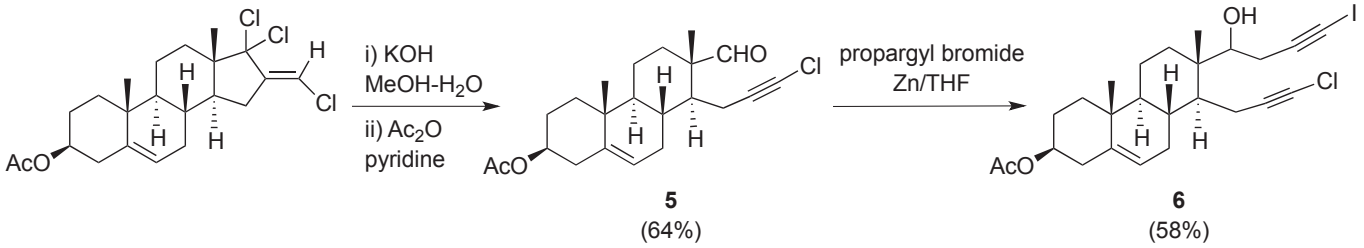
The chemistry of enamide has been an intriguing topic when it came to natural products[24] and synthesis of heterocycles.[25] Despite the enormous potential demonstrated by enamides, studies on D-ring steroidal enamides had been generally unexplored. Synthesis of geminal difluorides posed no difficulty; however, germinal dichlorides had limited accessibility.[26] Due to the importance of germinal dichlorides as synthons in several synthetic pathways, a process was developed by Ahmed *et al.* for preparation of



Scheme 2. Synthesis of geminal dichlorides from β-formylenamide

germinal dichlorides from β-formylenamide.[27] Here, a freshly prepared Vilsmeier reagent was reacted with β-formylenamide[22] under sub-zero temperature followed by raising the temperature to 65 °C to afford geminal dichloride moiety (**3**) and 17-ketosteroid (**4**) as major and minor products (Scheme 2).

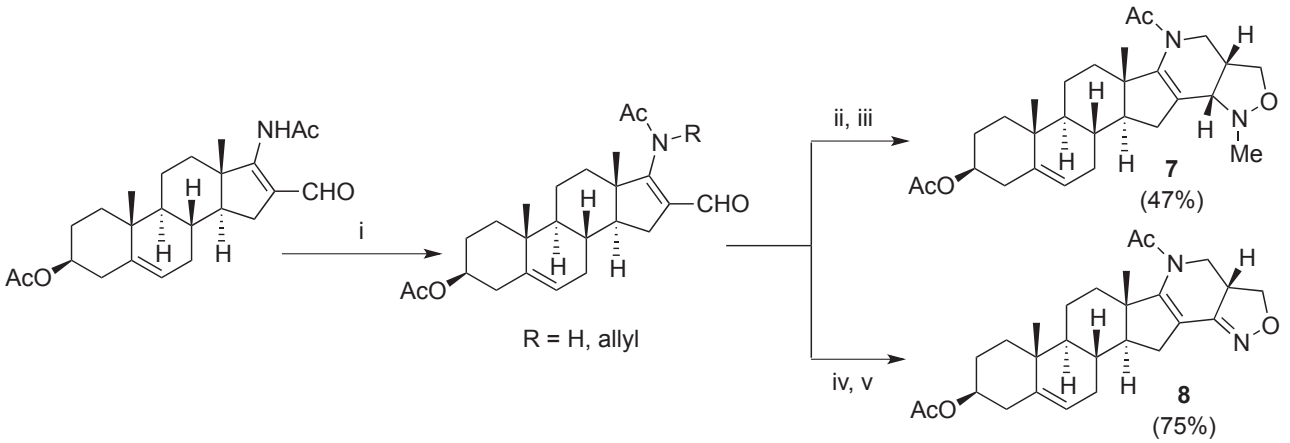
This geminal dichloride later became a forerunner of steroidal alkyne.[28] Cleavage of the D-ring was carried out by treating 3β-acetoxy-17,17-dichloro-16(*E*)-chloromethylene-androst-5-ene with methanolic KOH solution to afford alkyne (**5**) which was further converted to dialkyne (**6**) on treatment with propargyl bromide (Scheme 3).



Scheme 3. Synthesis of steroidal alkyne

2.02. Isoxazolidines from β-formylenamide

Isoxazolidines are another class of *N*-heterocycles which rose to prominence due to its role as reaction intermediates for the synthesis of several natural products, alkaloids, penem, carbepenem and amino acids. One of its earliest indispensable synthetic strategies was *via* 1,3-dipolar cycloaddition of nitrones and alkenes.[29] However, intramolecular nitrone-alkene cycloaddition of optically active steroidal molecule had not been explored adequately. Ahmed and coworkers made a successful attempt[30] on the synthesis of steroidal *cis*/*endo*-isoxazolidine (**7**) and isoxazoline (**8**) starting from β-formylenamide (Scheme 4).

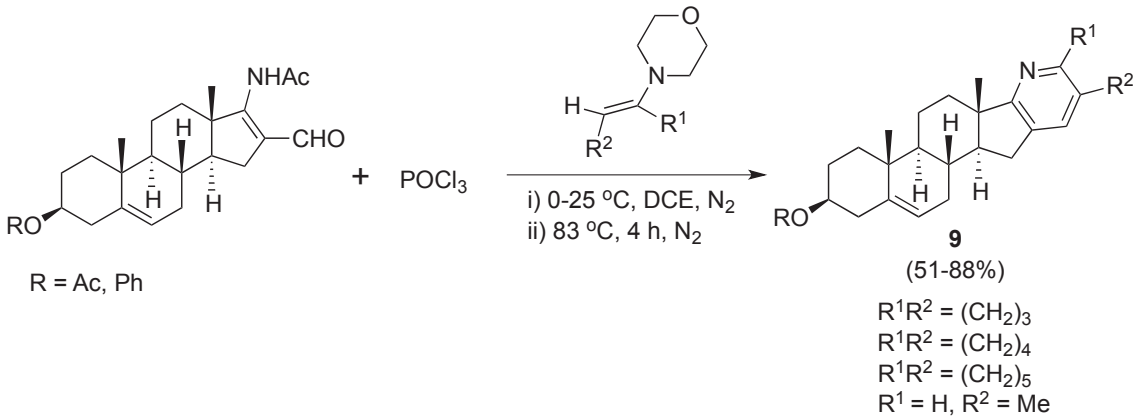


Reagents and Conditions: (i) allyl bromide, TBAB, CH_2Cl_2, KOH (40%), 5h (ii) MeNHOH, EtOH, rt, 5h (iii) toluene, 82 °C, 8h (iv) NH_2OH, EtOH, rt, 5h (v) Chloramine-T, EtOH, reflux, 4h

Scheme 4. Synthesis of isoxazolidines from β-formylenamide

2.03. Tetrahydroquinolino(17,16-*b*)- and pyrido(17,16-*b*)-steroids from β-formylenamide

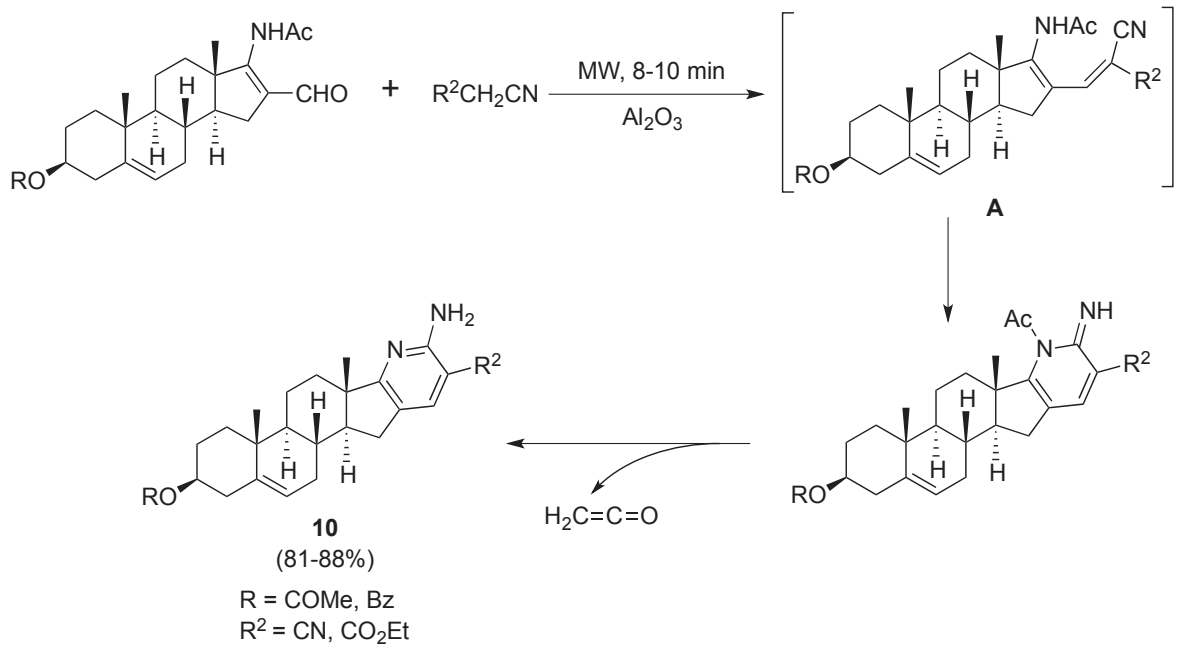
Endocyclic enamines which act as key intermediates for the preparation of natural products[31] have been generally prepared by Diels-Alder reaction of 1-azadienes.[32] In due course, we anticipated that certain substituted enamines or enamides could lead to 1-aza-1,3-diene system under treatment with $POCl_3$. Based on this conjecture, β-formylenamide was reacted with $POCl_3$ to yield *N*-acyl-1-aza-1,3-diene system which would further undergo IEDDA (inverse electron demand Diels-Alder) reaction with enamines to give D-ring annulated tetrahydroquinolino(17,16-*b*)- and pyrido(17,16-*b*)-steroids (**9**) (Scheme 5).[33]



Scheme 5. Synthesis of tetrahydroquinolino(17,16-*b*)- and pyrido(17,16-*b*)steroids from β-formylenamide

2.04. Substituted 2-aminopyridines from β-formylenamide

New strategies leading to pyridine functionalization involving hetero-annulation with *o*-amino-aldehydes has always been a topic of great interest.[34] Considering the importance of amino functionalized pyridines, Sharma *et al.* developed a microwave promoted synthetic protocol which relied on the catalytic activity of basic alumina. Here, a mixture of β-formylenamide, cyanomethylene (R^3 = CN) and basic alumina was irradiated under microwave for a duration of 8 minutes to afford 3β-acetoxy-6'-amino-5'-cyanopyrido(17,16-*b*)androsta-5,16-diene (**10**).[35] When the same reaction was repeated in the absence of basic alumina, the intermediate **A** was obtained as sole product. A thorough investigation has been reported for determining a probable mechanism for conversion of β-formylenamide to its 2-aminopyridine analogue. It was documented that the reaction proceeds *via* Knoevenagel condensation followed by intramolecular cyclisation reaction (Scheme 6).

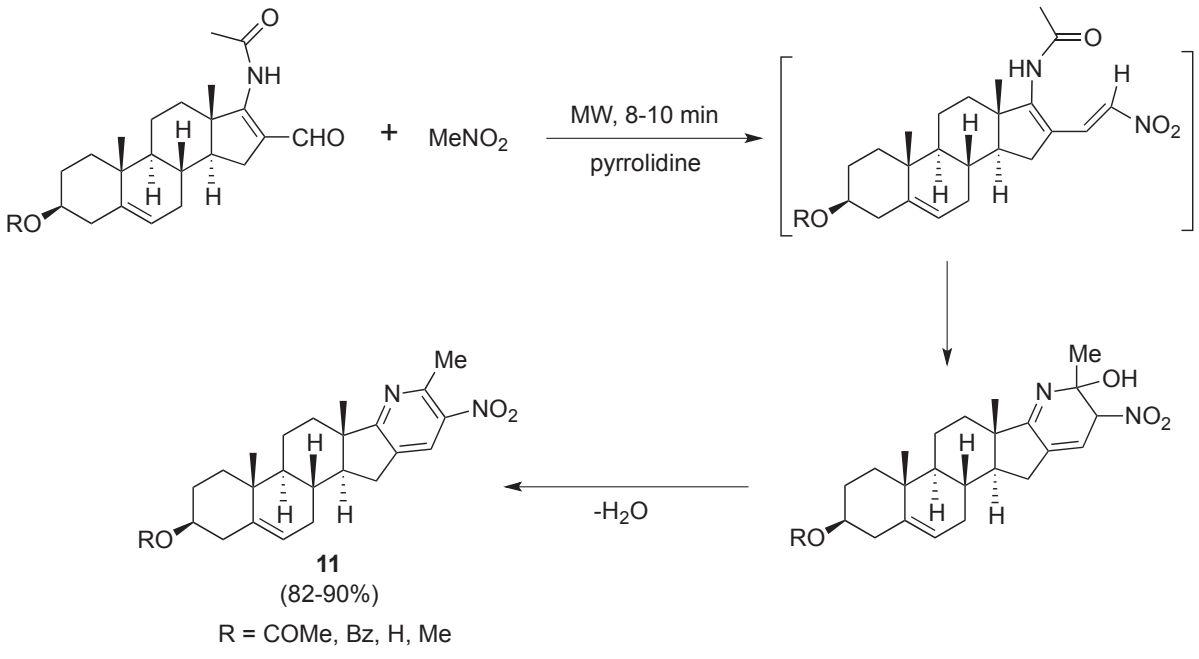


Scheme 6. Synthesis of substituted 2-aminopyridines from β-formylenamide

2.05. Annulated pyridine from nitroaldol condensation of β-formylenamide

Henry reaction or nitroaldol condensation has always been an important synthetic strategy for the fabrication of carbon-carbon bonds.[36] The reaction pathway is basically driven by a β-nitroalcohol or nitroalkene intermediate which ultimately aids in attaining several synthetic targets.[37]

The applicability of nitroaldol condensation on steroidal β-formylenamide for generation of novel



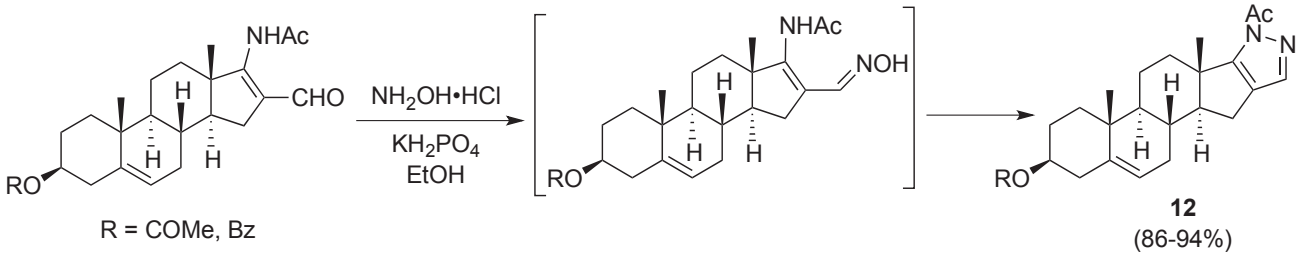
Scheme 7. Synthesis of annulated pyridine from nitroaldol condensation of β-formylenamide

azasteroidal molecule was investigated by Chetia *et al.*[38] and it has been reported that microwave irradiation of β-formylenamide and nitromethane in the presence of a base afforded annulated pyridines (**11**) (Scheme 7). The influence of a base on the reaction was also meticulously studied using several mild bases and pyrrolidine was found to be the most ideal candidate for the aforesaid transformation.

2.06. Pyrazoles from β-formylenamide

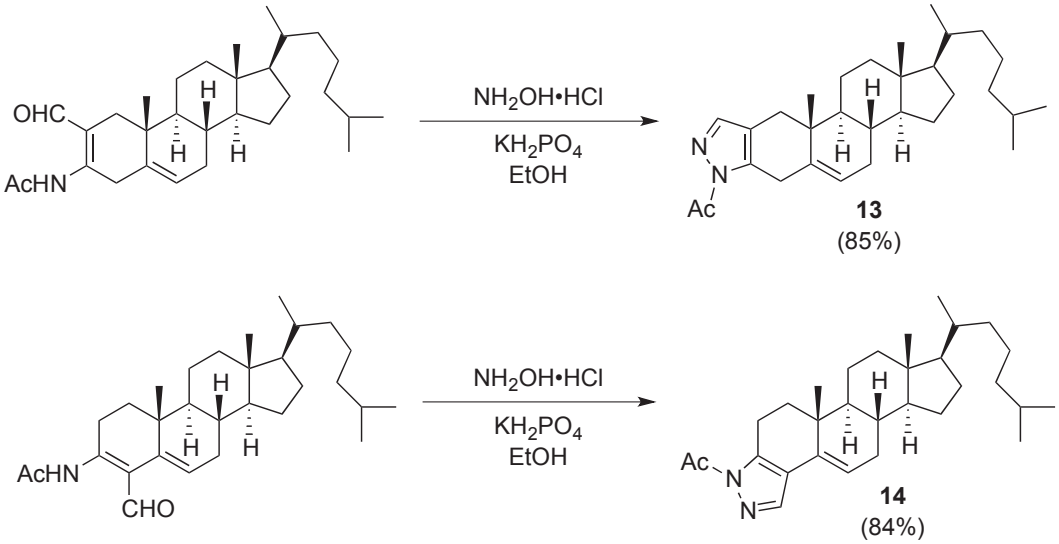
Pyrazoles are another class of *N*-heterocycles which have profound applications in pharmaceutical and agrochemical industries. The condensation of 1,3-dicarbonyls with hydrazine has been one of the simplest strategies for its preparation.[39] Nitrene insertion reactions have also been widely employed for designing versatile pyrazole analogues.[40]

In view of our studies on azasteroids, the feasibility of generating steroidal pyrazoles from β-formylenamide was also investigated.[41] The reaction of β-formylenamide with hydroxylamine hydrochloride under room temperature stirring condition afforded steroidal pyrazoles (**12**) (Scheme 8). Here, potassium dihydrogen phosphate was employed as a conjugate base catalyst. On replacing potassium dihydrogen phosphate with pyridine or sodium methoxide, the corresponding aldoxime was recovered exclusively. However, on employing pyrrolidine or morpholine as catalyst, pyrazole was formed as a minor product while the aldoxime was obtained as a major product. It was also found that when the reaction was repeated without any catalyst, a mixture of aldoxime and pyrazole was obtained.



Scheme 8. Synthesis of D-ring fused pyrazoles from β-formylenamide

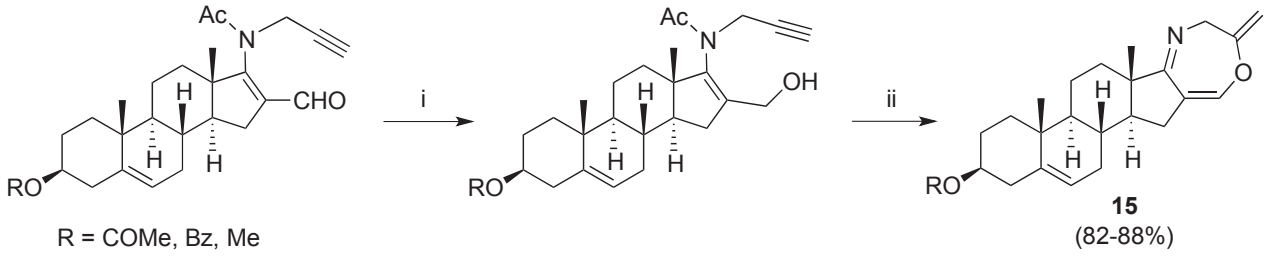
This synthetic pathway was also adopted for the preparation of A-ring fused steroidal pyrazole molecules (**13** and **14**) (Scheme 9).[41] The reactant β-formylenamide moiety was prepared from A-ring ketosteroid (3-cholestanone) *via* oximation, acetylation and acid catalysed rearrangement reaction.



Scheme 9. Synthesis of A-ring fused pyrazoles from β-formylenamide

2.07. 1,4-Oxazepines from *N*-propargyl-β-formylenamide

The role of 1,4-oxazepines in the pharmaceutical industry can be noted by its presence as a parent core moiety in biologically important compounds such as linadryl-H, loxapine and nitroxapine.[42] They have also been well documented in the asymmetric synthesis of secoiridoids and monoterpenoid alkaloids.[43] Bearing in mind the significance of this class of compounds in the medicinal chemistry domain, we designed and carried out the synthesis of steroidal 1,4-oxazepines from *N*-propargyl-β-formylenamide using I_2-$NaHCO_3$ system.[44] Firstly, the formyl group of *N*-propargyl-β-formylenamide was reduced using $NaBH_4$/MeOH. The resulting product was then subjected to cyclization by treatment with I_2-$NaHCO_3$ ultimately leading to the corresponding steroidal 1,4-oxazepine (**15**) (Scheme 10).



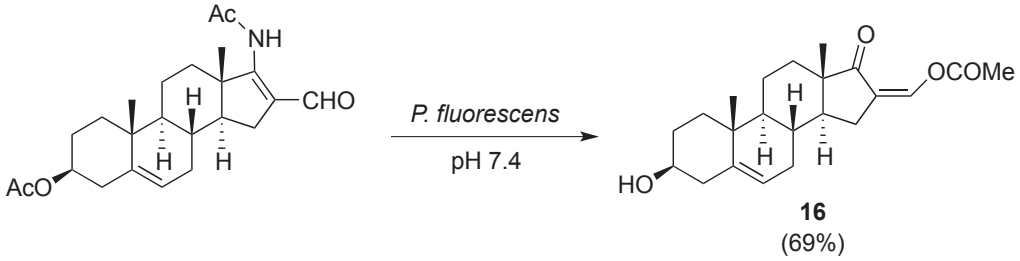
Reagents and Conditions: (i) $NaBH_4$, MeOH, 0-10 °C, N_2, 1 h (ii) I_2-$NaHCO_3$, Et_2O-H_2O, rt, 8 h

Scheme 10. Synthesis of 1,4-oxazepines from *N*-propargyl-β-formylenamide

2.08. Migration reaction of β-formylenamide

Enzymes have been extensively used in microbial transformation reactions[45] and based on this criterion, Bora *et al.* studied the utility of *Pseudomonas fluorescens*. It is a bacterial biocontrol agent mainly employed for dealing with soil-borne diseases.[46] Some explorations had been carried out on its applications

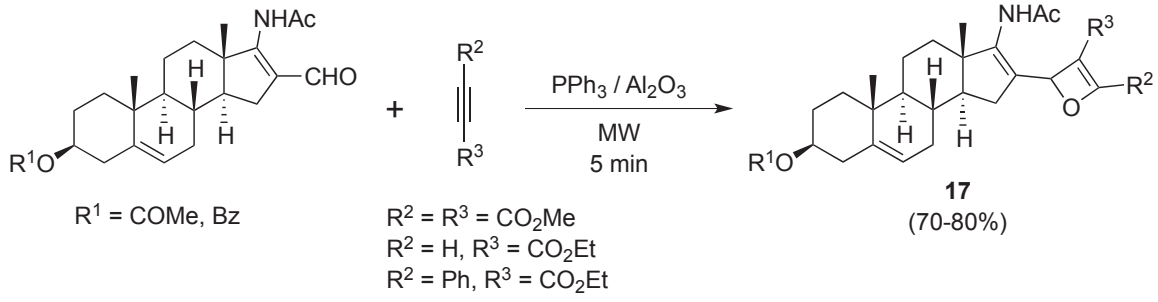
in hydroxylation of nicotinic acid[47] and aromatic compounds;[48] however, its full potential in biotransformation reactions has not been uncovered. Attempts were made on utilizing soil micro-organism *Pseudomonas fluorescens* strain RRLJ 134 and finally a facile 1,5-rearrangement reaction of the *N*-acetyl group of β-formylenamides was effectively conceived to afford rearrangement product (**16**).[49] In addition, acetate cleavage was also achieved using *Pseudomonas fluorescens* strain RRLJ 134 under neutral pH condition (Scheme 11).



Scheme 11. Migration reaction of β-formylenamide

2.09. Oxetene *via* [2+2] cycloaddition from β-formylenamide

It is well known that oxetanes are four membered oxygen heterocycles with profound biological activities *viz.* antibiotic[50] and anti-cancer.[51] It plays an integral role in the structural design of important compounds such as lipstatin, taxol and obafluorin. Several synthetic methodologies for oxetanes have been reported;[52] however, its corresponding unsaturated analogue oxetene received limited attention. Consequently, we took upon the task of developing newer strategies for the formulation of steroidal oxetene molecule.[53] Triphenylphosphine-alumina was found to be an excellent catalyst for reaction of β-formylenamide with alkyne to afford novel steroidal oxetenes (**17**) (Scheme 12). The reaction was carried out under microwave irradiation for 5 min.

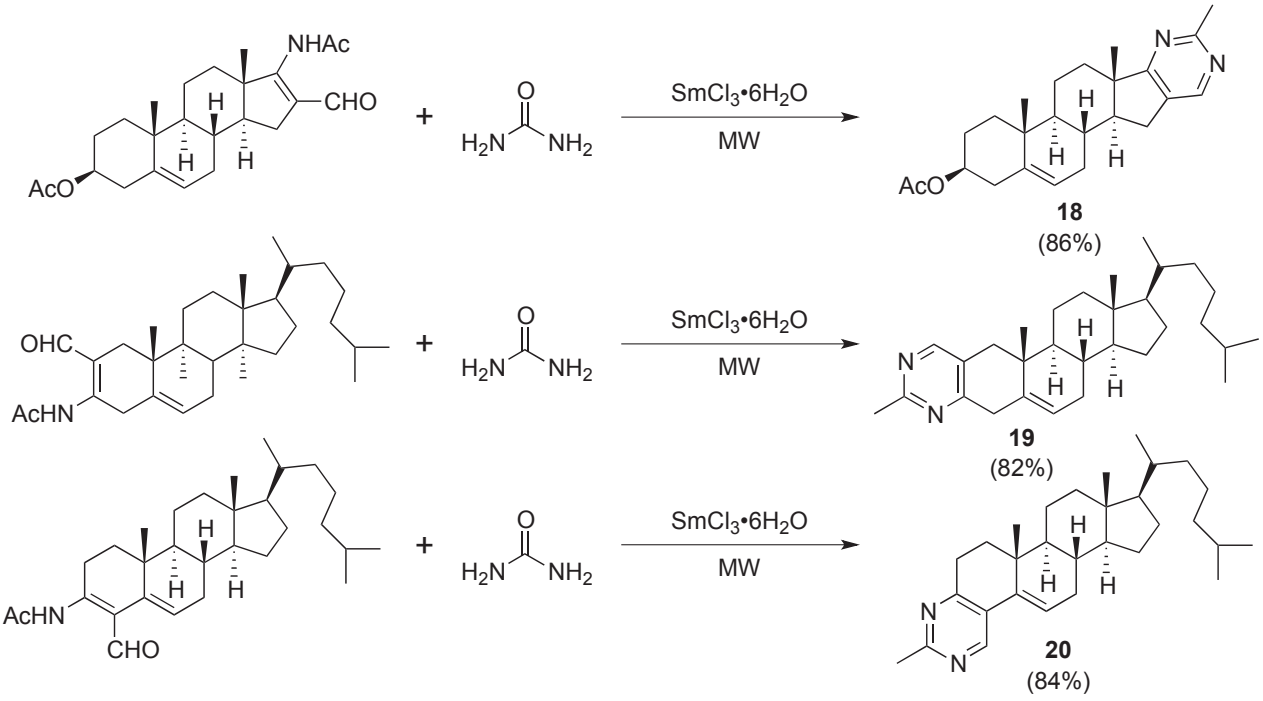


Scheme 12. Synthesis of oxetene *via* [2+2] cycloaddition from β-formylenamide

2.10. Pyrimidines from β-formylenamide

Pyrimidines are another class of nitrogen based heterocycles with anti-cancer, anti-bacterial, anti-mycotic,

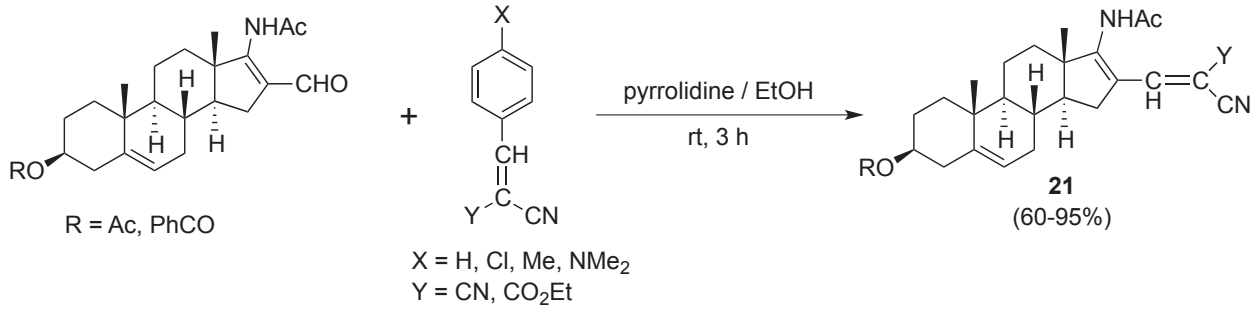
anti-microbial activities.[54] The pyrimidine ring as such is highly electron-deficient, therefore, syntheses of its derivatives are normally carried out by nucleophilic aromatic substitution of corresponding halopyrimidines.[55] In our venture for exploration of the synthetic aspects of β-formylenamides, we optimized a simple method for the preparation of steroidal pyrimidines from β-formylenamides and urea.[56] The reaction was carried out under microwave irradiation in the presence of samarium chloride hexahydrate, wherein, urea played the role of ammonia source under thermal condition. Both A-ring and D-ring functionalized steroidal pyrimidines (**18**, **19** and **20**) were achieved using this protocol (Scheme 13).



Scheme 13. Synthesis of pyrimidines from β-formylenamide

2.11. Dicyanomethylene group transfer between arylidenemalononitrile and aldehyde

Transfer reactions have been a valuable tool in transesterification, transalkylation, transetherification, transacetylation, transamination, transhydrogenation, and transamidation reactions. It has played a major role in the synthesis of important synthons such as arylidenemalononitrile derivatives.[57] Several reports on the synthesis of arylidenemalononitrile *via* Knovenagel condensation have been well documented,[58] but most of these methods utilizes harsh reaction conditions which is detrimental to molecules having alkali sensitive oxygen or nitrogen protecting functional groups. Ahmed and coworkers developed a milder method[59] for preparing (17-acetamido-steroidal-16-formylidene)malononitrile (**21**). It was carried out *via* transfer reaction of dicyanomethylene functional group from non-steroidal arylidenemalononitrile to steroidal β-formylenamide molecule (Scheme 14).



Scheme 14. Dicyanomethylene group transfer between arylidenemalononitrile and aldehyde

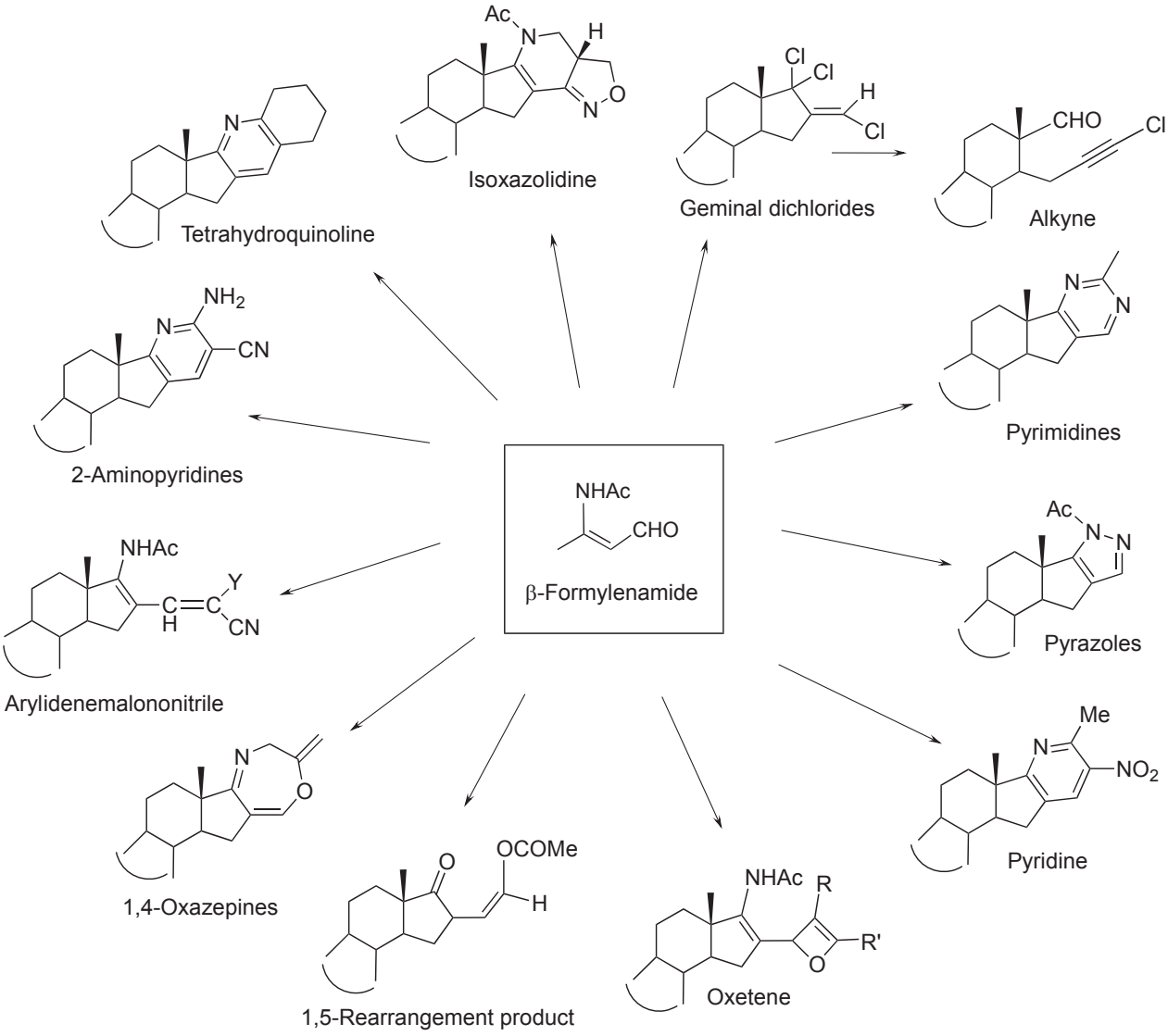


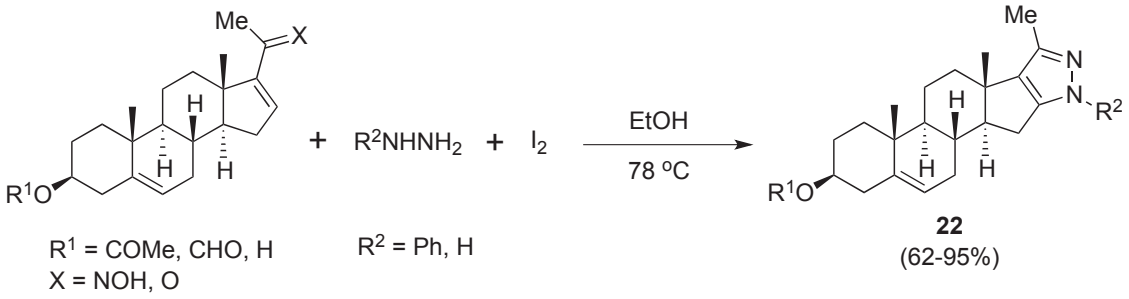
Figure 3. A summary of diverse steroidal molecules derived from β-formylenamide

3. STEROIDAL CONJUGATED ENONES

3.01. Pyrazoles from conjugated enones

Steroidal pyrazoles (**22**) have also been prepared by Ahmed and coworkers from steroidal conjugated

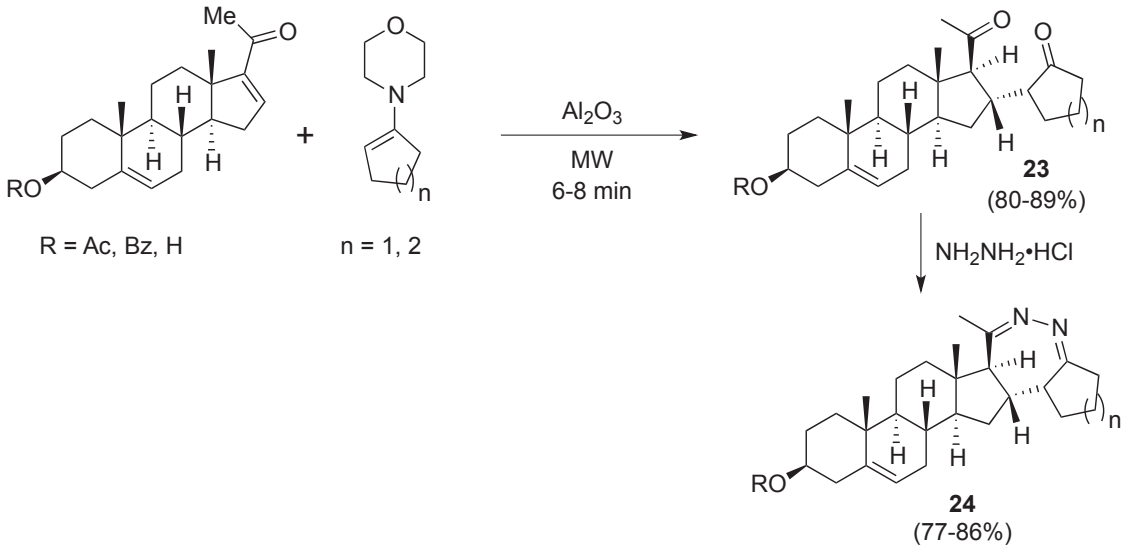
enones/oximes and hydrazine under ethanol reflux condition in the presence of iodine (Scheme 15).[60] In this case, inverse electron demand Diels-Alder reaction takes place where the electron-deficient heterodiene interacts with the diimide species. The diimide is generated from hydrazine when it undergoes oxidation in the presence of iodine.[61]



Scheme 15. Synthesis of pyrazoles from conjugated enones

3.02. 1',2'-Diazepino(17,16-*d*')steroids *via* Michael addition of enamines with conjugated enones

1,5-Diketo compounds are generally prepared from enolates and α,β-unsaturated carbonyl compounds by Michael addition under strongly basic conditions. However, the use of strong base often leads to unwanted auto-oxidation or retro-Michael type decomposition.[62] The search for alternative Michael donors has led to the exploitation of enamines in some complicated synthetic pathways,[63,64] but due to high susceptibility to hydrolysis,[65] their utility is significantly limited. In order to address this issue, Sharma *et al.* developed a method for the synthesis of 1,5-diketo compounds from conjugated enones and enamines.[66] The reaction was carried out under microwave irradiation in the presence of basic alumina. The resulting 1,5-diketones

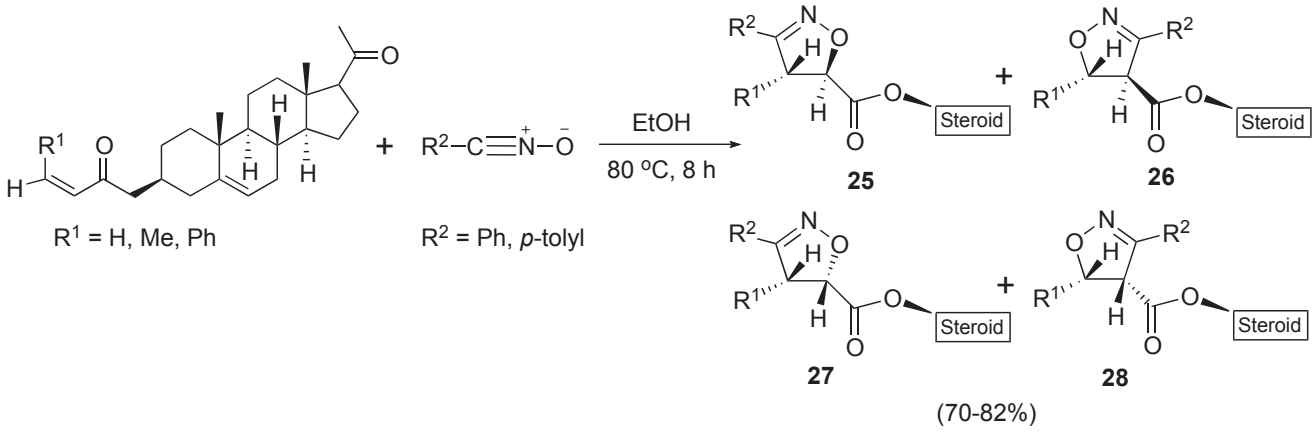


Scheme 16. Synthesis of 1',2'-diazepino(17,16-*d*')steroids *via* Michael addition of enamines with conjugated enones

(**23**) were further subjected to reaction with hydrazine hydrochloride under ethanol-reflux condition to afford 1,2-diazepine (**24**) derivatives (Scheme 16).

3.03. Isoxazolines from conjugated enones

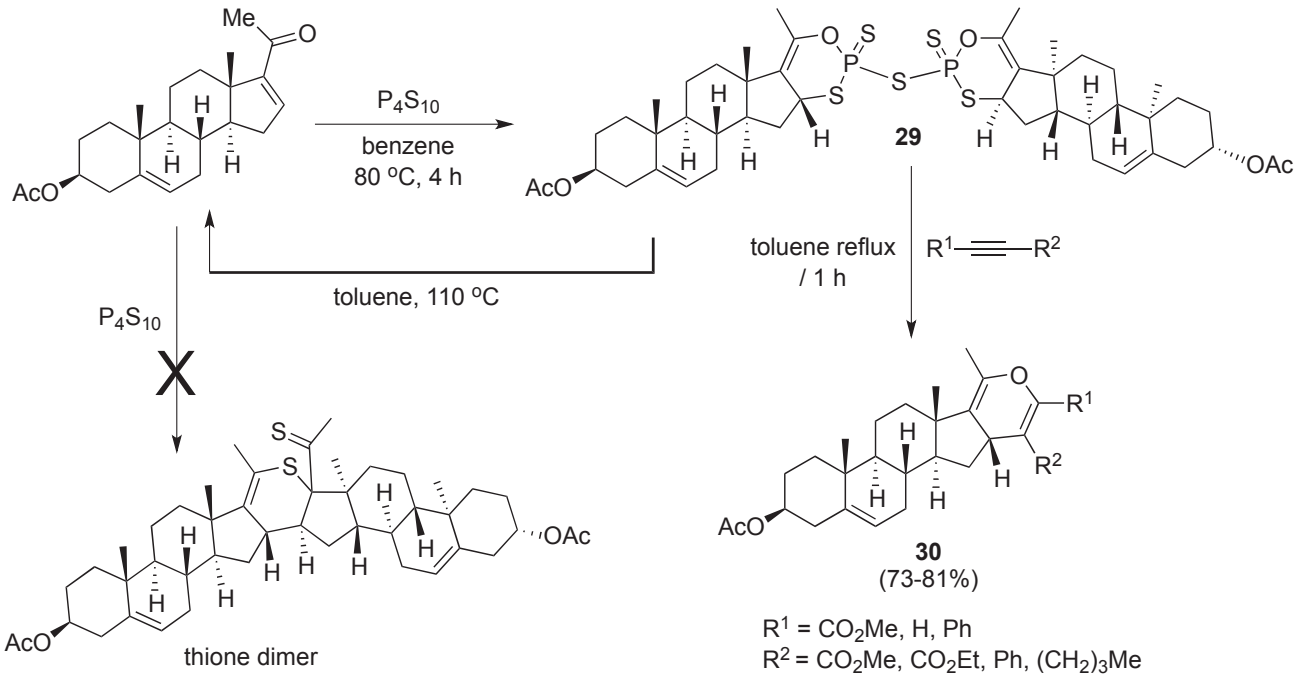
Isoxazolines can be prepared from several chiral auxiliaries such as camphor sultam substituted vinylboronic ester, Rebek's imide benzisoxazole, phenyl sulfones, (*R*,*R*)-diisopropyl tartrate (DIPT) and Oppolozer's chiral sultam.[67] The isoxazolines prepared from nitrile *N*-oxides and alkenes *via* asymmetric 1,3-dipolar cycloaddition have attracted considerable attention[68] due to its applicability as important versatile intermediates in organic synthesis. Sharma *et al.* worked on developing a regio- and stereoselective synthetic pathway for isoxazolines (**25**, **26**, **27** and **28**) using intermolecular nitrile *N*-oxide cycloaddition (INOC) reaction.[69] This was achieved by reacting pregnenolone acrylate with benzonitrile *N*-oxide under ethanol-reflux condition (Scheme 17).



Scheme 17. Synthesis of isoxazolines from conjugated enones

3.04. Pyrans from conjugated enones

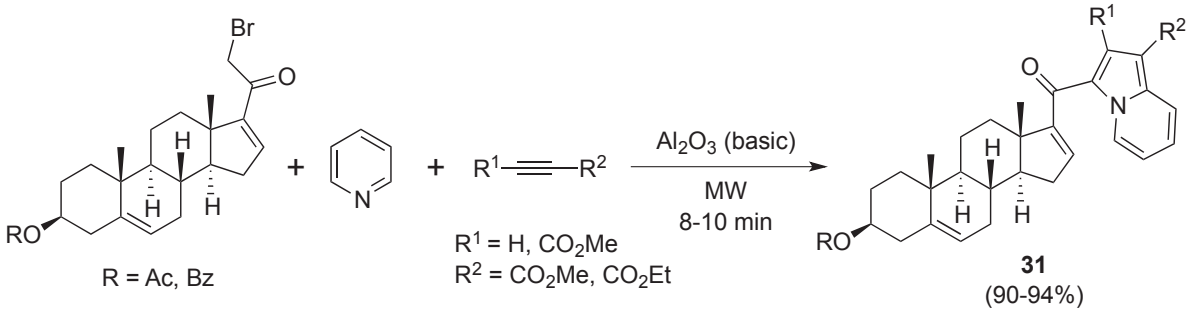
Ketones can be subjected to thionation under simple toluene-reflux condition in the presence of P_4S_{10}; however, attempts of direct thionation of α,β-unsaturated ketone using P_4S_{10} to its corresponding thione were futile.[70] In continuation of our studies on steroidal conjugated enones, we took upon the task of synthesizing thiopyrans from α,β-unsaturated ketone by carrying out [4+2] cycloaddition reaction. The preliminary investigation proved to be a failure effort as instead of the expected dimer thione, a novel 16-DPA-P_2S_5 adduct (**29**) was achieved.[71] The adduct was subsequently utilized as a reactive masked enone for preparing steroidal (17,16-*c*)pyrans (**30**) *via* [4+2] cycloaddition with alkyne dienophiles (Scheme 18).



Scheme 18. Synthesis of pyrans from conjugated enones

3.05. Indolizines from conjugated enones

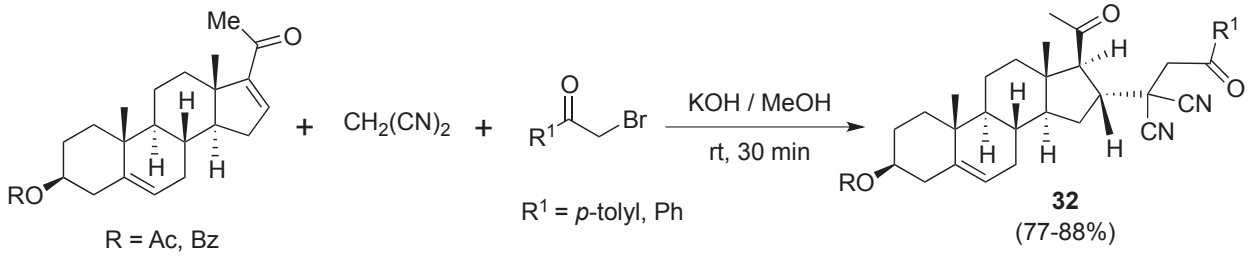
The core structure of several naturally occurring alkaloids are made up of indolizines *viz.* indalozin 167B, (-)-dendroprimine, coniceine, (-)-slaframine. Indolizines are commonly synthesized by the cycloaddition reaction of *N*-acyl/alkylpyridinium salts or by sequential *N*-quarternization and intramolecular cyclocondensation reactions.[72] Tanimori *et al.* reported the synthesis of chiral indolizines from proline *via* the Pauson-Khand reaction.[73] Steroidal indolizines (**31**) were prepared by Bora and coworkers[74] using a three-component microwave assisted protocol. Here, mono-bromo substituted 16-DPA was subjected to microwave irradiation in the presence of pyridine, substituted alkynes and basic alumina to afford steroidal indolizines (Scheme 19).



Scheme 19. Synthesis of indolizines from conjugated enones

3.06. 1,6-Diketones from conjugated enones

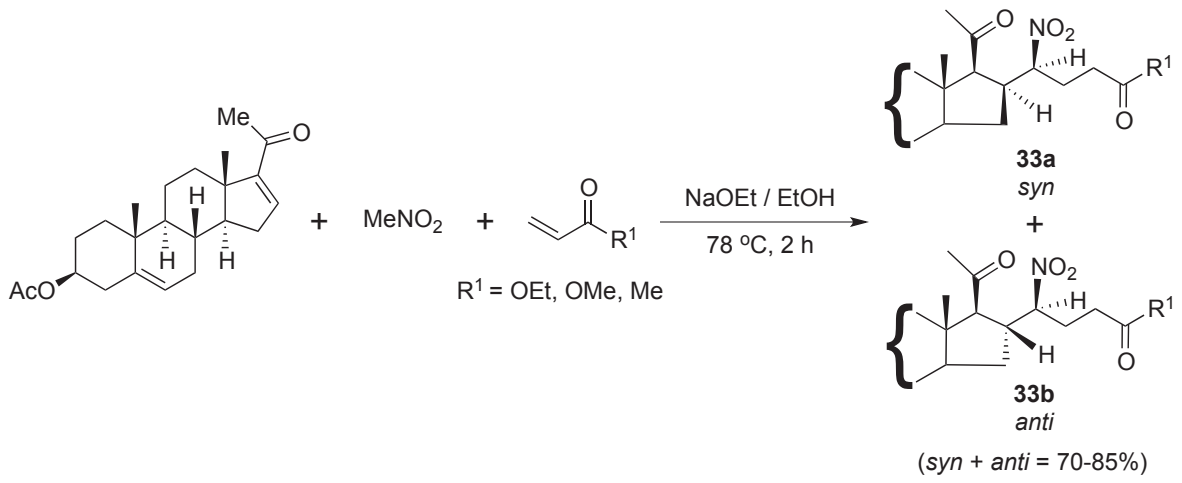
1,6-Diketones are widely employed for the synthesis of strategic five and six membered heterocycles.[75] There are numerous reports on cyclization reactions of 1,6-diketo compounds but less emphasis have been given on its synthesis protocols. Some of the known protocols are carbonylation of trialkylboranes,[76] oxone® mediated oxidative cleavage of cyclohexanone,[77] decomposition of *t*-butylperoxy cycloalkanol[78] and siloxycyclopropanes.[79] Most of these reported methods involve multistep synthesis or harsh conditions. Saikia and coworkers designed a simple three-component Michael reaction involving conjugated enones, malononitrile and α-bromoketones for preparing 1,6-diketones (**32**).[80] A methanolic potassium hydroxide solution efficiently aided in promoting this reaction under room temperature stirring condition (Scheme 20).



Scheme 20. Synthesis of 1,6-diketones from conjugated enones

3.07. 1,7-Dicarbonyl compounds from conjugated enones

1,7-Dicarbonyl containing compounds have been extensively exploited in the chemistry of natural products for the synthesis of enantiomerically pure alcohols.[81] Michael addition of α,β-unsaturated ketones to afford 1,5-diketones[82] is an efficient strategy; however, not much is known about preparation of 1,7-dicarbonyl compounds from α,β-unsaturated ketones. Chetia and co-workers accomplished in synthesizing

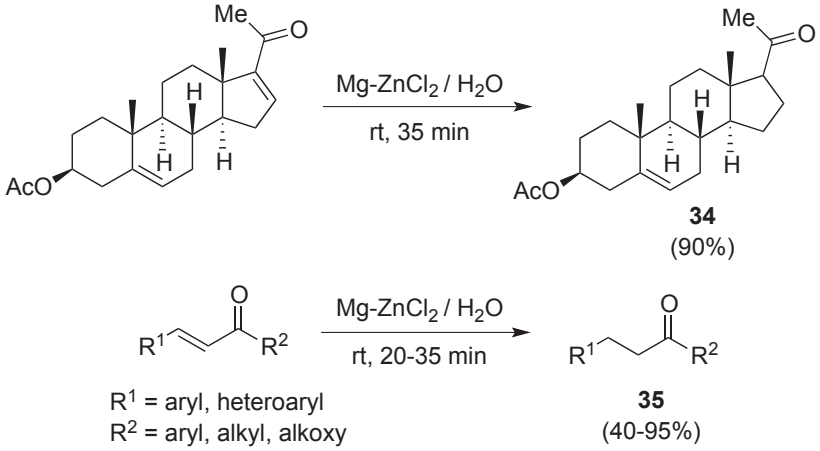


Scheme 21. Synthesis of 1,7-dicarbonyl compounds from conjugated enones

1,7-dicarbonyl compounds *via* a three component base-catalyzed process (**33a** and **33b**).[83] Here, two unsymmetrical α,β-unsaturated carbonyl compounds were reacted with nitromethane using Michael addition strategy (Scheme 21).

3.08. Selective reduction of conjugated enones

The selective reduction of the carbon-carbon double bond of conjugated enones has been of utmost importance when it comes to synthesis of steroidal molecules. The presence or absence of a double bond can strongly influence the characteristics and properties of an organic compound. Some of the known reagents for the selective reduction of α,β-unsaturated carbonyl compounds are NaTeH, NaSeH, Zn-AcOH, LiSeH, Zn-Cu, PhSeH, Zn-$NiCl_2CuH$, In, and $PhSiH_3$. Organozinc reagents have several applications but sometimes inaccessibility under normal condition poses as a hindrance. Normally the zinc is activated by treatment with either catalytic iodine or 1,2-dibromoethane-TMSCl[84] or aqueous ammonium chloride.[85] Another alternative to obtain activated zinc (Reike powder) is by reduction of zinc salts with monovalent alkali metals, but it is a strenuous process due to the requirement of stringent anhydrous condition.[86] Considering these setbacks, Saikia and co-workers prepared a highly reactive form of zinc by treating magnesium turnings with zinc chloride in aqueous medium.[87] This strategy was then utilized for selective reduction of carbon-carbon double bond of both steroidal as well as non-steroidal conjugated enones to afford corresponding adducts (**34** and **35**) (Scheme 22).

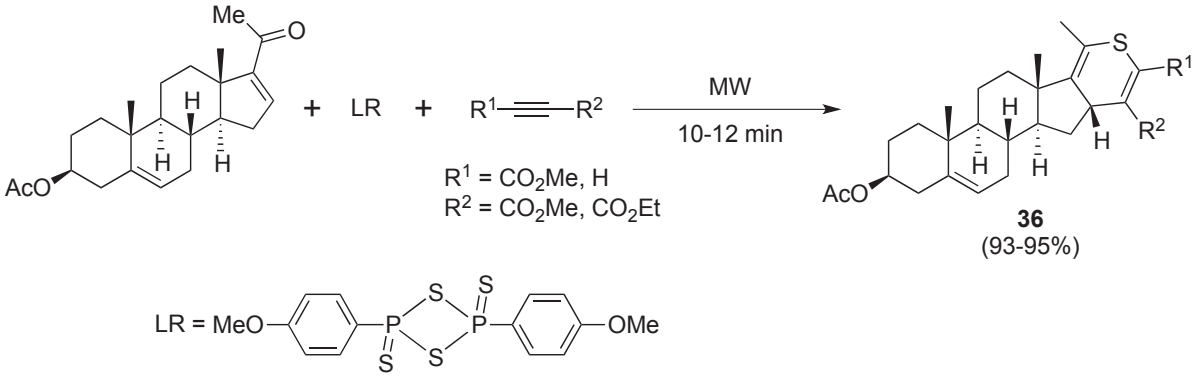


Scheme 22. Selective reduction of conjugated enones

3.09. 4*H*-Thiopyrans from conjugated enones

The hetero Diels-Alder reaction is an important strategy for the preparation of 4*H*-thiopyran from α,β-unsaturated thioketones and activated dienophiles.[88] However, the high dimerization tendency of α,β-unsaturated aliphatic thioketones posed as a setback in the accessibility of the monomeric form of

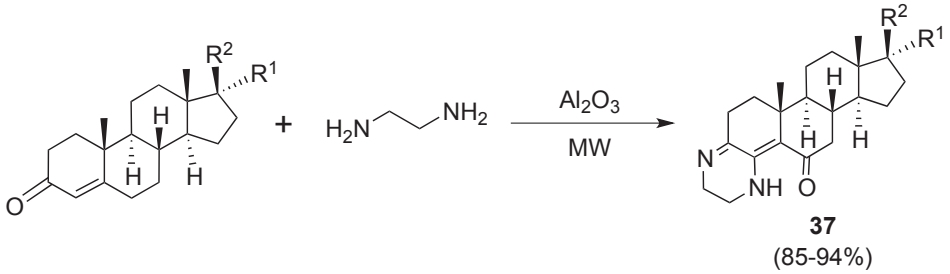
α,β-unsaturated aliphatic thioketones.[89] In order to prepare a monomeric thioketone, a stable thione dimer precursor is required[90] which is a tedious process. Barthakur *et al.* worked on the one-pot synthesis of thiopyrans from α,β-unsaturated ketones and alkynes using Lawesson's reagent as a facilitating reagent to afford 4*H*-thiopyran annulated steroid (**36**).[91] The reaction was carried out under microwave irradiation (Scheme 23).



Scheme 23. Synthesis of 4*H*-thiopyrans from conjugated enones

3.10. Dehydropiperazines from conjugated enones

Piperazines exhibit a wide range of biological activities[92] and it has been found that steroidal pyrazine derivatives possess inhibition activities against cancerous cells.[93] The initiative taken by Christiansen and Clinton for the preparation of 2,3-position fused steroidal piperazine molecules[94] have been well documented. They followed a two-step synthetic protocol *viz* (a) preparation of steroidal pyrazine from androsta-2,3-dione and ethylenediamine, (b) hydrogenation of the steroidal pyrazine ring to its corresponding steroidal piperazine analogue. Barthakur and co-workers employed microwave energy to carry out a facile one-pot reaction of 3-keto-4-ene steroids with ethylenediamine to afford steroidal dehydropiperazine (**37**).[95] Basic alumina was used as a facilitator for the aforesaid conversion (Scheme 24).

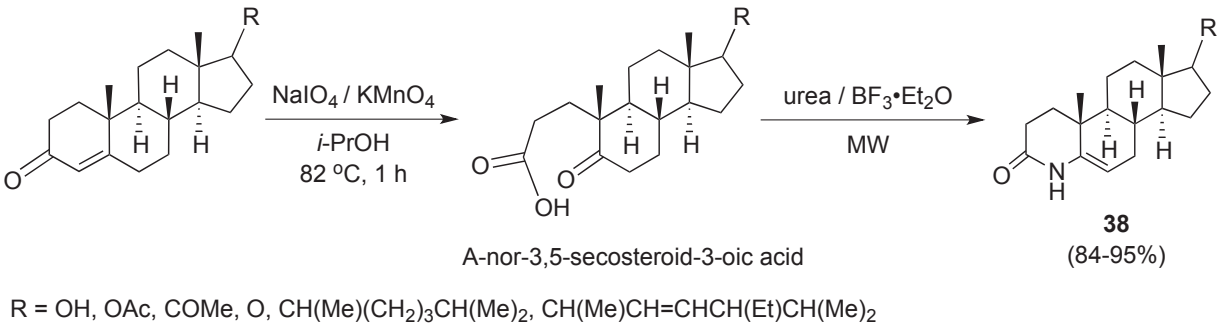


R^1 = H
R^2 = OH, OCOMe, COMe, $CH(Me)(CH_2)_3CH(Me)_2$, $CH(Me)CH{=}CHCH(Et)CH(Me)_2$
R^1R^2 = O

Scheme 24. Synthesis of dehydropiperazines from conjugated enones

3.11. 4-Azasteroids from conjugated enones

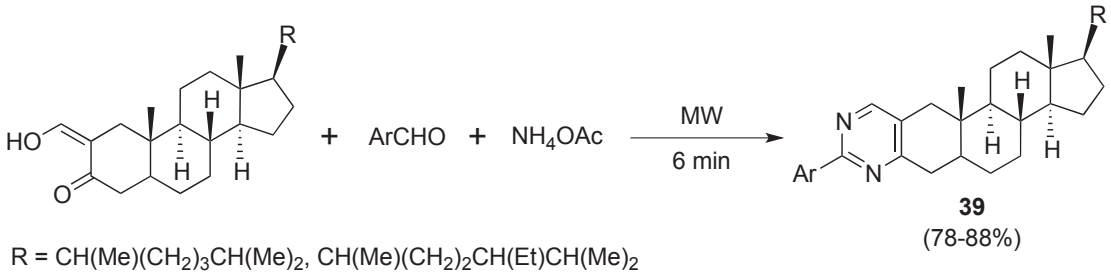
The biological activities of a steroidal molecule can be greatly enhanced by replacing one or more carbon atoms in a steroidal molecule by a nitrogen atom. Azasteroids have attracted great attention because of their pharmaceutical importance and amongst them 4-aza-lactams have risen as a prominent 5α-reductase inhibitor (finasteride). It plays a major role in the conversion of androgen testosterone to 5α-dihydrotestosterone as well as for the treatment of benign prostatic hyperplasia, prostate cancer and baldness.[96] As per documented articles, finasteride has been prepared from 3β-hydroxy-5-pregnen-20-one (pregnenolone) or 4-androstene-3,17-dione *via* multi-step synthesis.[97] However, due to the stringent conditions employed, there has been continuous demand for the development of more sustainable synthetic methods. Borthakur *et al.* developed a two-step procedure for the conversion of steroidal conjugated enone into aza-lactam (**38**) *via* oxidative ring cleavage followed by cyclisation (Scheme 25).[98]



Scheme 25. Synthesis of 4-azasteroids from conjugated enones

3.12. Pyrimidines from conjugated enones

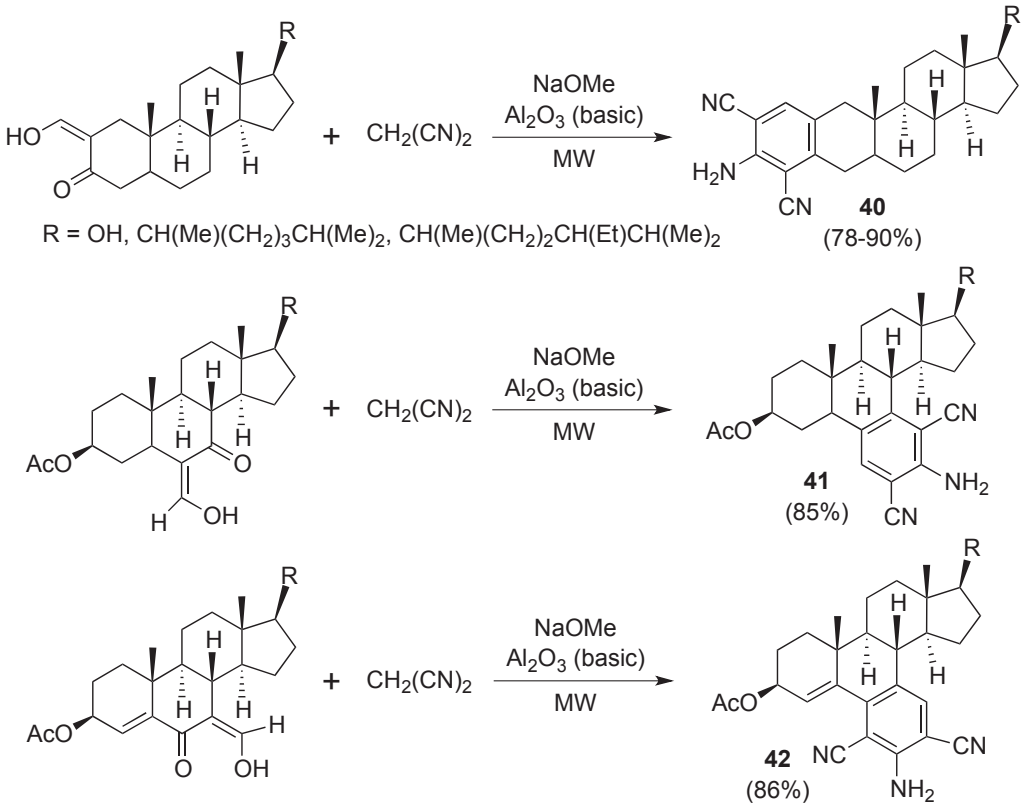
A-Ring heterosteroids possess inherent biological properties,[14] and annelation of the A-ring with heterocyclic moieties is of great importance. Efforts are being made towards developing newer strategies for preparation of A-ring annelated steroidal pyrimidines. For instance, steroidal[3,2-*b*]pyrimidines were prepared from 2-hydroxymethylene-3-ketosteroids and acetamidine hydrochloride by Clinton and his co-workers.[99] Similarly, Laitonjam *et al.* synthesized A-ring fused steroidal pyrimidine from 2-bis(methylthio)methylene-3-ketosteroid and guanidine nitrate.[100] In our previous discussions on the applications of β-formylenamides, we have demonstrated the preparation of A- and D-ring annelated pyrimidines from steroidal β-formylenamides.[56] Barthakur *et al.* carried out explorations pertaining to the scope of pyrimidine synthesis from conjugated enones as well.[101] Here, steroidal conjugated enones was reacted with aryl-aldehyde and ammonium acetate under microwave irradiation to afford steroidal pyrimidines (**39**) (Scheme 26).



Scheme 26. Synthesis of pyrimidines from conjugated enones

3.13. Annulation of A/B-ring of conjugated enones

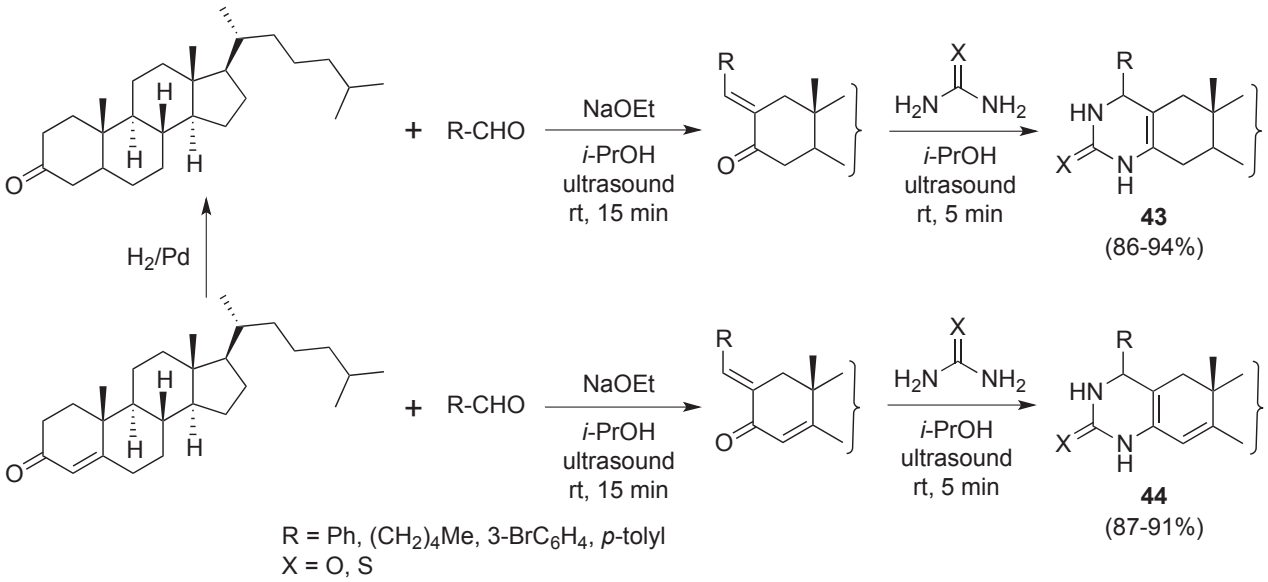
Benzene scaffolds bearing amino group flanked by two nitrile substituents display anti-leishmanial activities and they also act as important synthetic intermediates.[102] 2,6-Dicyanoanilines are commonly synthesized from acyclic substrates.[103] Earlier, we have discussed on usage of microwave for the synthesis of steroidal A-ring fused pyrimidines from 2-hydroxymethylene-3-ketosteroid. Barthakur and co-workers successfully attempted annulation of 2,6-dicyanoaniline to steroidal A/B-ring (**40**, **41** and **42**) under base catalyzed condition.[104] The process constitutes a one-pot reaction of malononitrile with 2-keto-hydroxymethylenes in the presence of basic alumina and sodium methoxide under microwave irradiation for 8-10 min (Scheme 27).



Scheme 27. Annulation of A/B-ring of conjugated enones

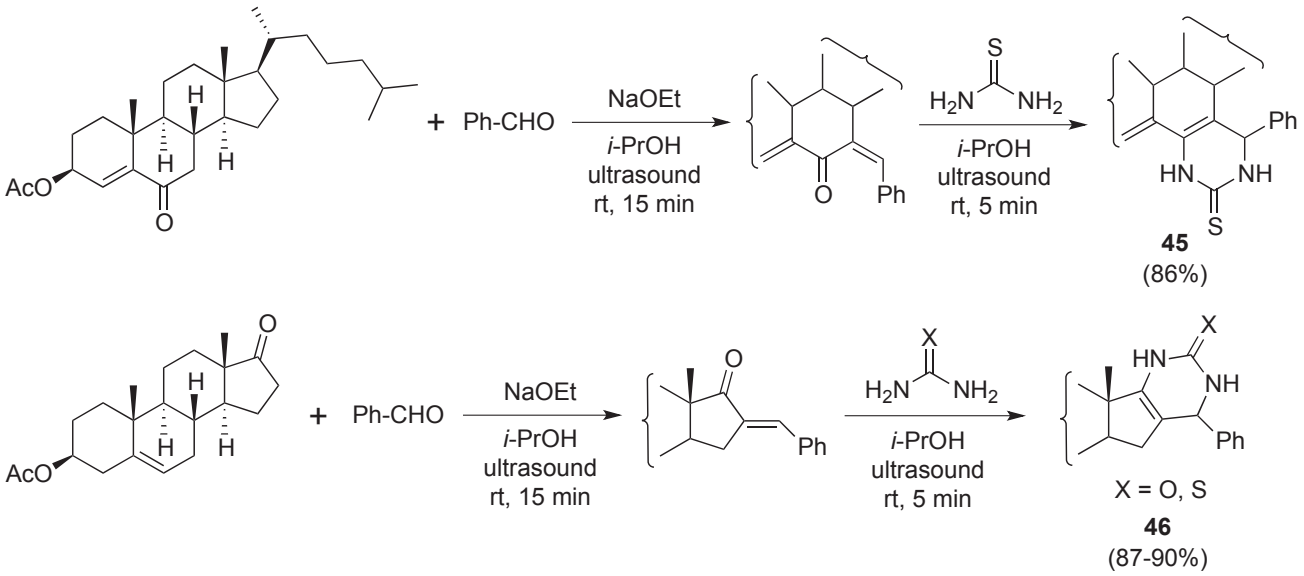
3.14. 3,4-Dihydropyrimidinone/thione from conjugated enones

Dihydropyrimidinones and dihydropyrimidinethiones constitute an important class of bioactive molecules exhibiting a broad spectrum of activities including anti-bacterial, anti-inflammatory, anti-viral and anti-tumorproperties.[105] In addition, they also possess properties such as anti-hypertensives, α_{1a} adrenergic antagonists, anti-cancer agents, neuropeptide Y antagonists and calcium-channel blockers.[106] The first known reported method for the synthesis of dihydropyrimidinones/thione was in 1893 by Biginelli.[107] Since then, numerous Biginelli-like scaffolds have been developed for the synthesis of these compounds. However, due to the several shortcomings accompanying these new strategies, search for better alternative continues. Dutta and co-workers implemented ultrasound energy for the synthesis of dihydropyrimidinone/thione fused steroids (**43** and **44**) and nonsteroids from conjugated enones and urea/thiourea.[108] Here, firstly a conjugated enone was generated by reaction of an isolated ketone with an aldehyde in the presence of a base. This adduct was then reacted with urea/thiourea (Scheme 28).



Scheme 28. Synthesis of A-ring fused 3,4-dihydropyrimidinone/thione from conjugated enones

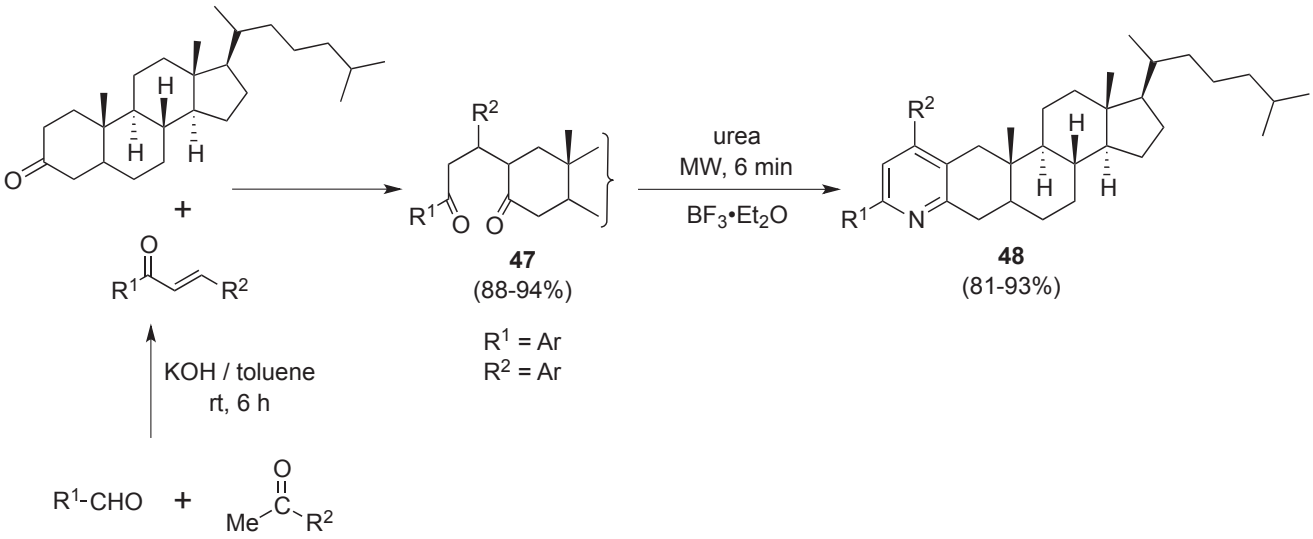
The same protocol was further extended to the synthesis of B- and D-ring annulated steroids (**45** and **46**) by utilizing conjugated keto group on either the B- or D-ring (Scheme 29).



Scheme 29. Synthesis of D-ring fused 3,4-dihydropyrimidinone/thione from conjugated enones

3.15. 4,6-Diarylpyridines from conjugated enones

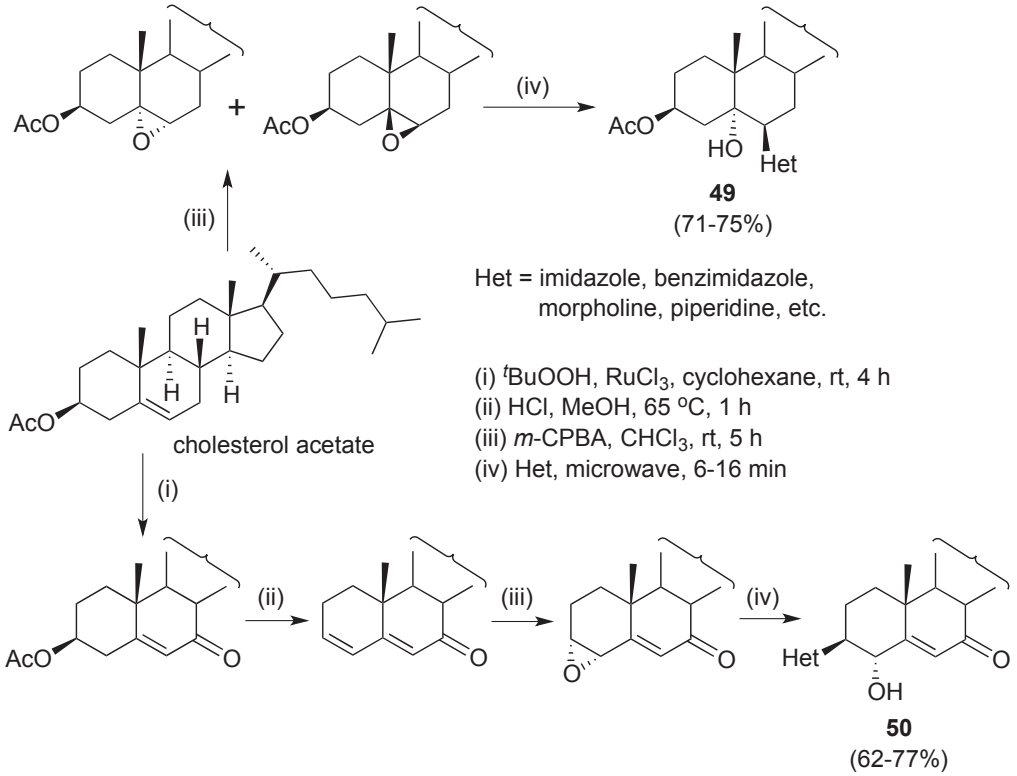
In order to explore facile synthetic strategies for differently substituted pyridosteroids, we stressed on the preparation of steroidal pyridines from steroidal 1,5-dicarbonyl and urea under microwave irradiation condition.[109] This entire process involves two steps where the starting steroidal molecule reacts with a conjugated enone moiety to generate a 1,5-dicarbonyl steroidal adduct (**47**) which then reacts further with urea to afford steroidal pyridine product (**48**). The conjugated enone system was prepared by condensation of aryl aldehyde with acetophenone derivatives (Scheme 30).



Scheme 30. Synthesis of 4,6-diarylpyridines from conjugated enones

3.16. Vicinal heterocyclic alcohols from conjugated enones

Non-steroidal vicinal imidazolyl alcohols such as metronidazole, ornidazole, secnidazole are well known anti-protozoal drugs. Steroidal compounds having vicinal hydroxyl group are also found to display biological activities like its non-steroidal counterparts. There are documented reports on steroidal compounds demonstrating anti-proliferative potency and cytotoxic activity.[110] Our group has developed a strategy for the steroidal and nonsteroidal epoxide ring opening by employing heterocycles such as imidazole, benzimidazole, piperidine, morpholine as nucleophiles to result B- and A-ring annelated products (**49** and **50**).[111] Heterocyclic substitution on the A-ring of steroidal molecule was done by carrying out oxidation followed by epoxidation of cholesterol acetate (Scheme 31). The anti-microbial screening of few synthesized compounds exhibited moderate inhibition activity against *Bacillus subtilis* (ATCC 6633), *Proteus vulgaris* (MTCC 426), *Escherichia coli* (ATCC 8739), *Staphylococcus aureus* (ATCC 29213) and *Pseudomonas syringae* (MTCC 673) species.

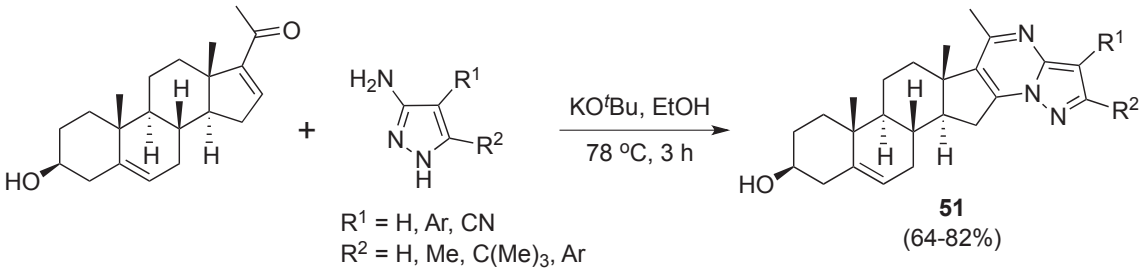


Scheme 31. Synthesis of vicinal heterocyclic alcohols from conjugated enones

3.17. Pyrazolo[1,5-*a*]pyrimidines from conjugated enones

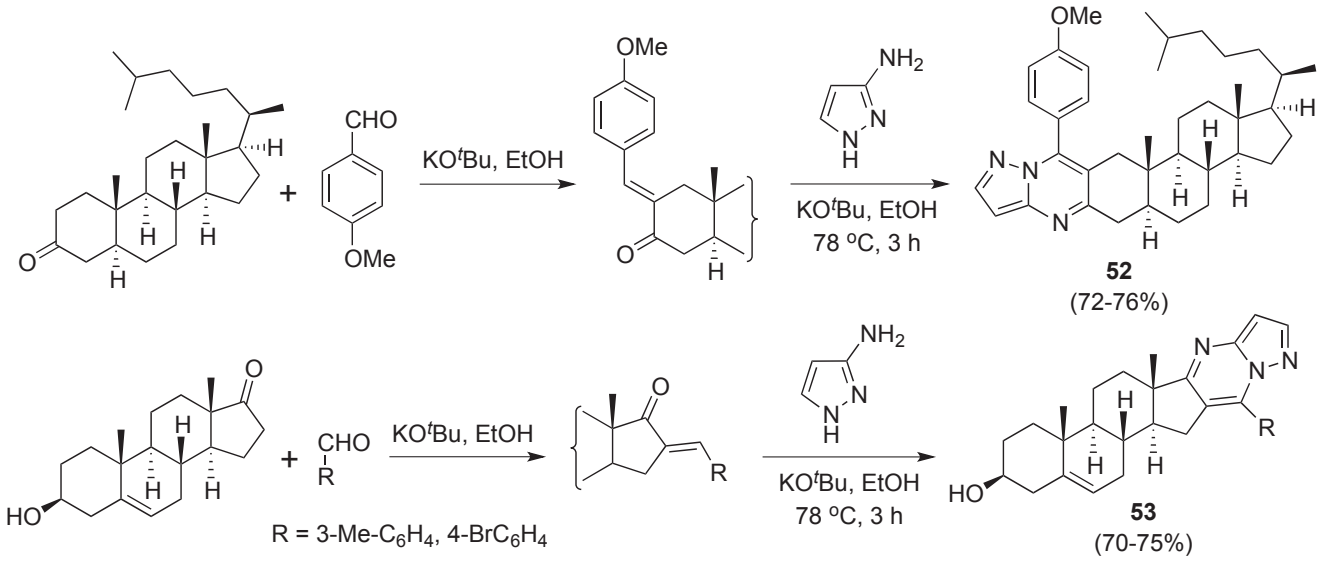
Pyrazolo[1,5-*a*]pyrimidine derivatives are another class of aza-heterocycles which show anti-schistosomal, anti-trypanosomal, COX-2 selective inhibitor activity, HMG-CoA reductase inhibitor activity and CK-2 kinase inhibitor activities.[112] The reported synthetic methods for

pyrazolo[1,5-*a*]pyrimidine compounds employed 5-aminopyrazoles and 1,3-bis-electrophilic compounds as the starting materials.[113] Bajwa and Sykes prepared steroidal pyrazolo[1,5-*a*]pyrimidines by reacting 3-aminopyrazole with 2-hydroxymethylene-5α-androstan-3-one derivatives and 16-hydroxymethylene-5α-androstan-17-one.[114] Kaishap *et al.* prepared pyrazolo[1,5-*a*]pyrimidines (**51**) by condensation reaction of steroidal as well as non-steroidal conjugated enones with substituted 3-amino-1*H*-pyrazoles.[115] Several D-ring annulated steroidal pyrazolo[1,5-*a*]pyrimidines derivatives were prepared from 16-dehydropregnenolone and substituted 3-amino-1*H*-pyrazoles by following this procedure (Scheme 32).



Scheme 32. Synthesis of D-ring fused pyrazolo[1,5-*a*]pyrimidines from conjugated enones

The method was further extended to preparation of some additional A/D-ring annulated pyrazolo[1,5-*a*]pyrimidines (**52** and **53**); however, in this case the conjugated enone system was first generated by reacting a steroidal molecule with aryl aldehyde followed by condensation with the 3-amino-1*H*-pyrazole moiety (Scheme 33).[116]



Scheme 33. Synthesis of A/D-ring fused pyrazolo[1,5-*a*]pyrimidines from conjugated enones

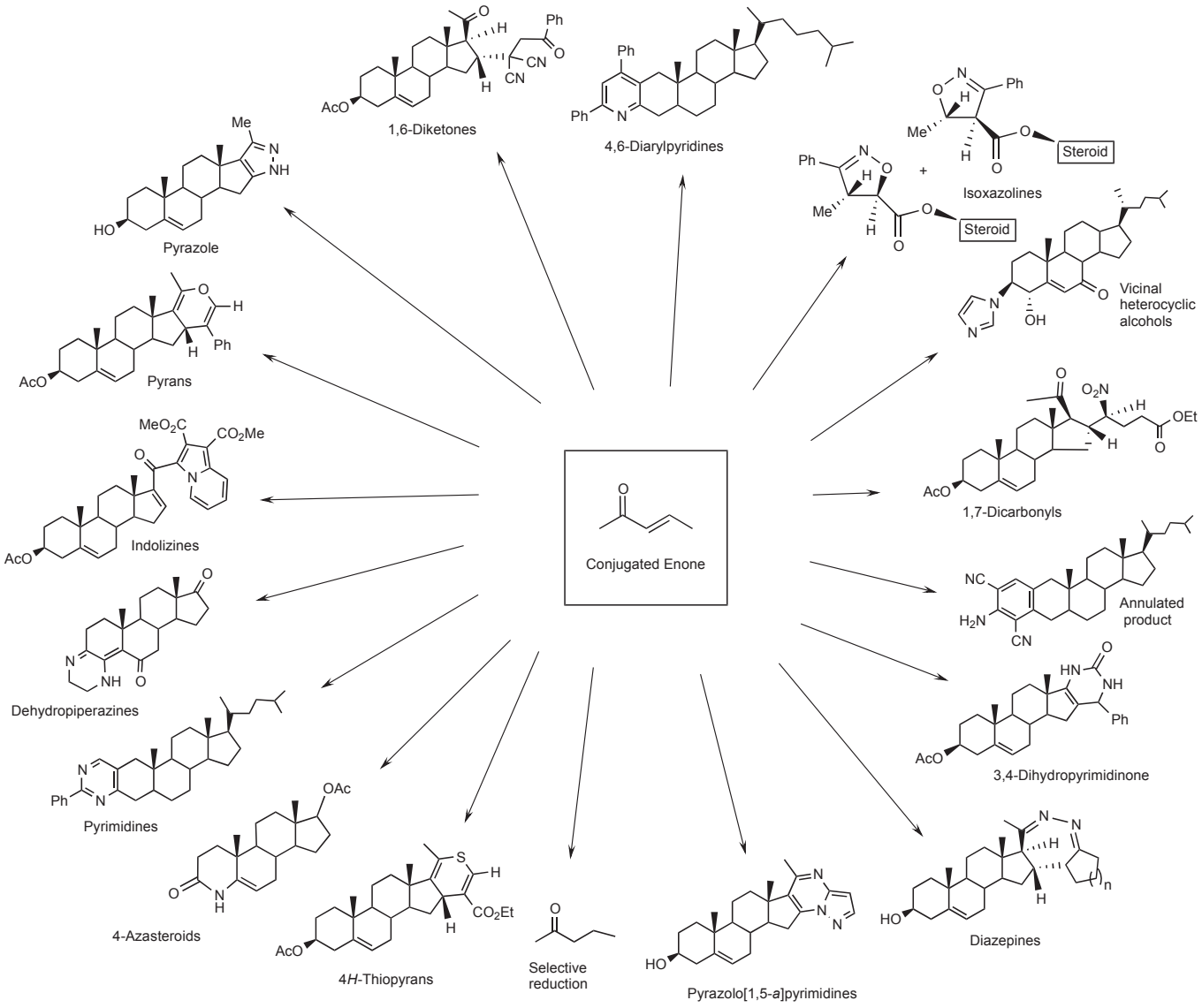


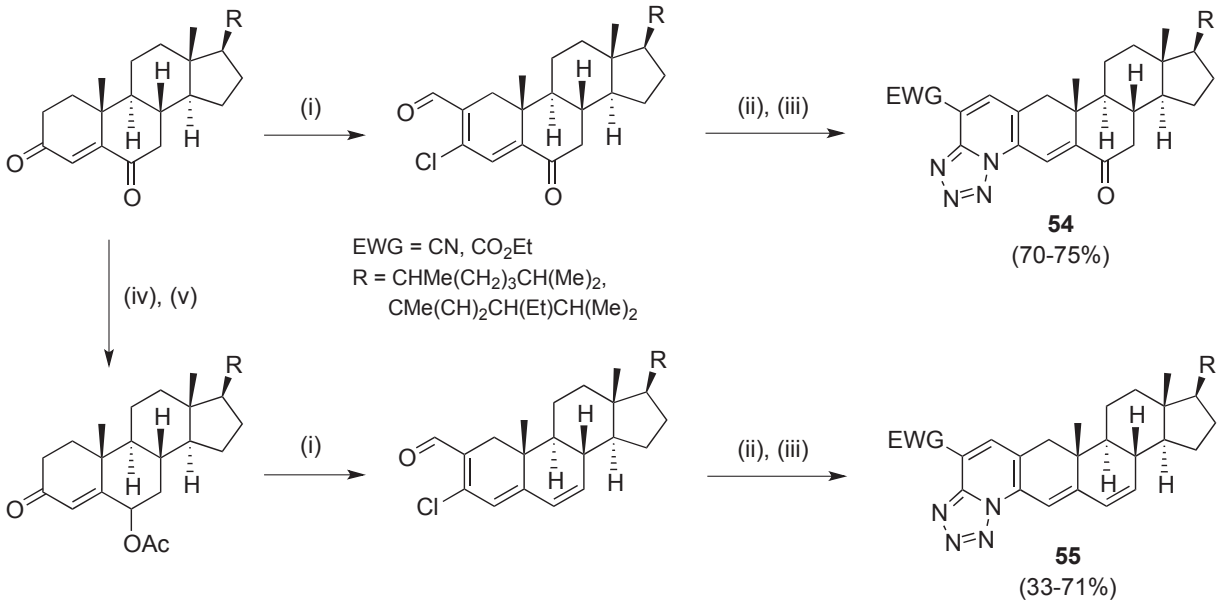
Figure 4. A summary of diverse steroidal molecules derived from conjugated enone

4. STEROIDAL β-FORMYLVINYL HALIDES

4.01. Tetrazolo[1,5-*a*]pyridines from β-formylvinyl halides

The significance of tetrazoles is mainly attributed to its nitrogen rich ring systems which are responsible for exhibiting diverse biological properties.[117] Fused tetrazolo[1,5-*a*]pyridine systems have been exploited as azide surrogate for the synthesis of 1,2,3-triazoles *via* click reaction.[118] They are also employed as precursors of pyridylnitrenes thereby becoming a convenient source of 1,3-diazepines/diazepinones, pyrroles, iminophosphoranes, and pyrazoles.[119] A typical preparative method for tetrazolopyridines is achieved by heating a mixture of 2-halopyridine and NaN_3/$TMSN_3$ in the presence of TBAF.[120] It is also prepared by reacting pyridine *N*-oxides with sulfonyl or phosphoryl azides.[121] Amongst steroidal tetrazolopyridines, literature reports on the synthesis of androst-2-eno[2,3-*g*](tetrazolo[1,5-*a*]-

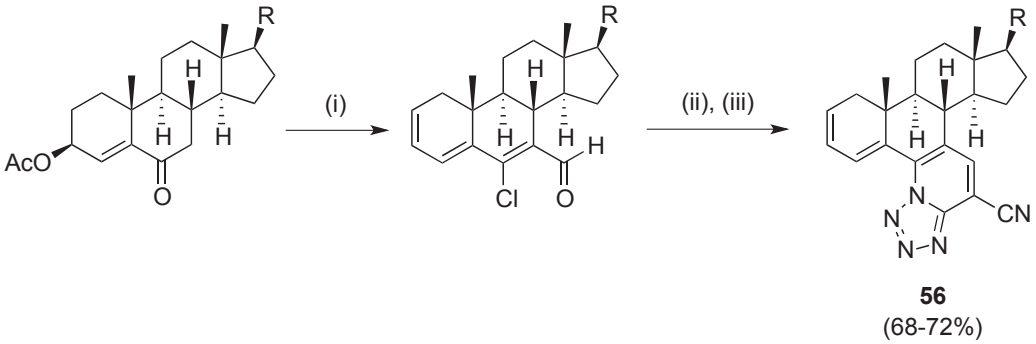
pyrimidines) from (hydroxymethylene)oxosteroids is available.[114] Gogoi and co-workers developed a reaction scheme for the synthesis of steroidal tetrazolo[1,5-*a*]pyridines from β-formylvinyl halides.[122] Here, A- and B-ring annulated steroidal tetrazolo[1,5-*a*]pyridines (**54**, **55** and **56**) were successfully prepared from chloroformyl-steroidal trienes (Schemes 34 and 35).



Reagents: (i) $POCl_3$, DMF, $CHCl_3$ (ii) $CH_2(CN)(EWG)$, Et_3N, DCM (iii) NaN_3, DMF, 50-60 °C (iv) $NaBH_4$/MeOH (v) Ac_2O/pyridine

Scheme 34. Synthesis of A-ring fused tetrazolo[1,5-*a*]pyridines from β-formylvinyl halides

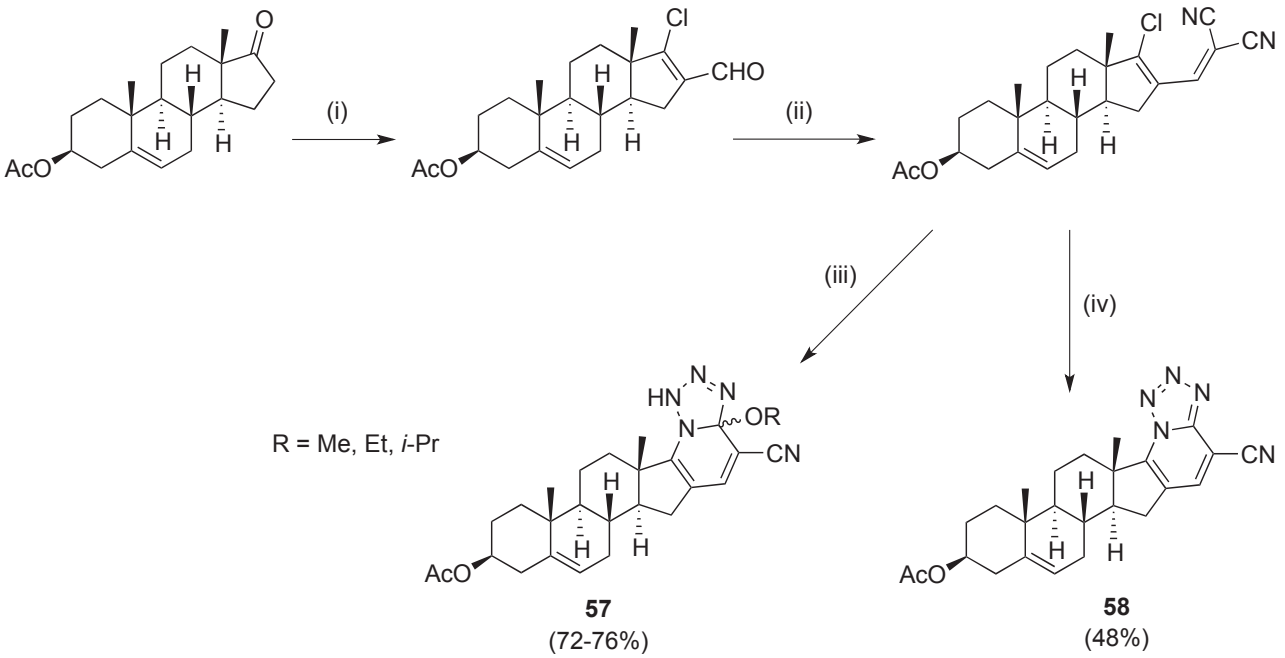
The reaction steps involved intramolecular 1,3-dipolar cycloaddition reaction of azide with nitrile group in appropriate solvents.



Reagents: (i) $POCl_3$, DMF, $CHCl_3$ (ii) $CH_2(CN)(EWG)$, Et_3N, DCM (iii) NaN_3, DMF, 50-60 °C

Scheme 35. Synthesis of B-ring fused tetrazolo[1,5-*a*]pyridines from β-formylvinyl halides

D-Ring annulated steroidal tetrazolo[1,5-*a*]pyridines (**57** and **58**) were also prepared using the same protocol of intramolecular azide-nitrile cycloaddition reaction. The β-formylvinyl chloride moiety on the D-ring was accomplished from the Vilsmeier reaction of 3β-acetoxy-androst-5-en-17-one (Scheme 36).

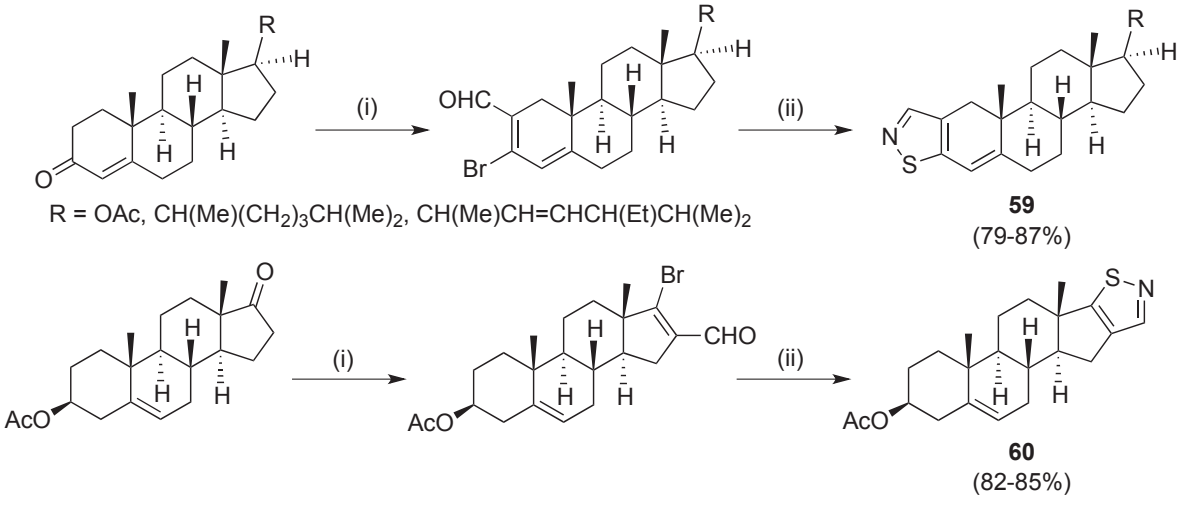


Reagents: (i) $POCl_3$, DMF, $CHCl_3$ (ii) $CH_2(CN)_2$, Et_3N, DCM (iii) NaN_3, ROH, 50-60 ^oC (iv) NaN_3, DMF, 50-60 ^oC

Scheme 36. Synthesis of D-ring fused tetrazolo[1,5-*a*]pyridines from β-formylvinyl halides

4.02. Isothiazoles from β-formylvinyl halides

The isothiazole moiety is present in the core structure of several pharmaceuticals. The significance of this class of compounds has led to the development of synthetic strategies of their analogs.[123] Steroidal isothiazoles have also attracted the interest of the synthetic medicinal community. A-ring fused steroidal isothiazole was reportedly synthesized by Seldes *et al.*[124] from 5α-cholestan-3-one *via* a tedious multi-step reaction. Barton *et al.*[125] also reported the synthesize 3β-acetoxycholest-4-eno[6,5,4-*c*,*d*]-



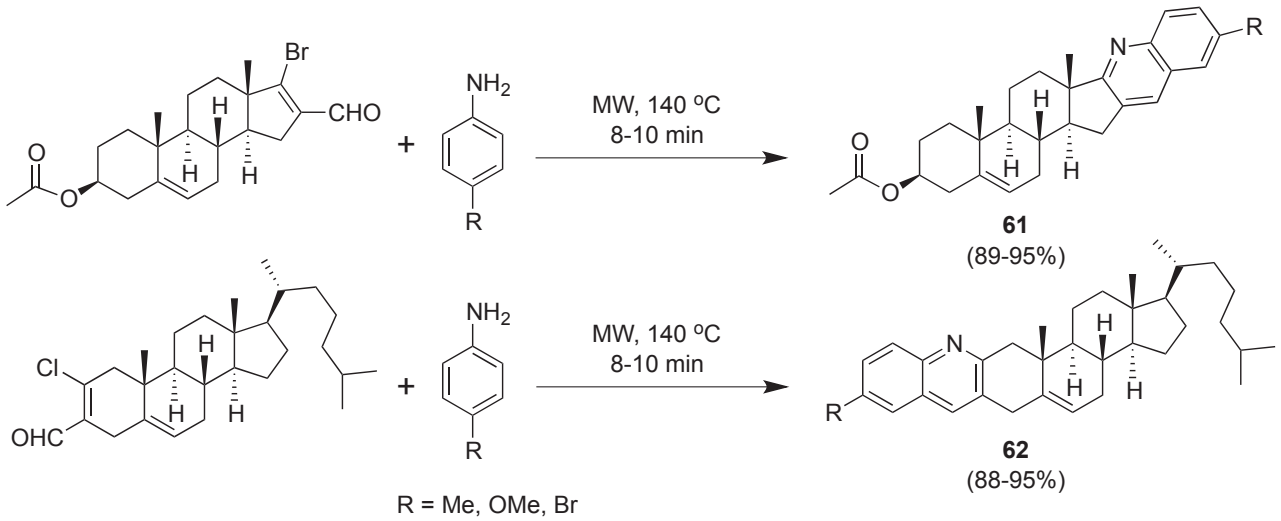
Reagents: (i) PBr_3/DMF/$CHCl_3$ (ii) NaSCN/urea/DMF, MW 360 W

Scheme 37. Synthesis of isothiazoles from β-formylvinyl halides

isothiazole from thiazyl chloride and cholesteryl acetate; however, the yield obtained was very poor (15%). Bezbaruah and co-workers synthesized A- and D-ring annulated isothiazoles (**59** and **60**) from β-bromo-α,β-unsaturated aldehydes, sodium thiocyanate and urea under microwave irradiation in high yields (Scheme 37).[126]

4.03. Quinolines from β-formylvinyl halides

The derivatives of quinoline possess anti-asthmatic, anti-inflammatory, anti-malarial (for example, quinine or chloroquine), anti-hypertensive, anti-bacterial activities.[127] Several natural products[128] are made up of quinoline core structure and as a result, they have profound applications as synthetic building blocks.[129] In 1962, Hassner *et al.* carried out annulation of quinoline to steroidal core *via* Friedlander reaction and succeeded in preparing A- and D-ring fused quinolines.[130] Non-steroidal quinoline derivatives have been prepared from β-halo-vinylaldehydes using Pd catalyst[131] or *via* multi-step synthesis;[132] however, no reports were available on the synthesis of steroidal quinolines from β-halo-vinylaldehydes. In 2012, Gogoi *et al.* developed a one-pot synthetic method for the preparation of D- and A-ring fused steroidal quinolones (**61** and **62**) from steroidal β-bromo-vinylaldehydes and arylamines under microwave condition (Scheme 38).[133] Furthermore, *in vitro* anti-fungal screening of the synthesized steroidal quinoline derivatives against *C. albicans* and *A. niger* exhibited very promising activities comparable to nystatin.

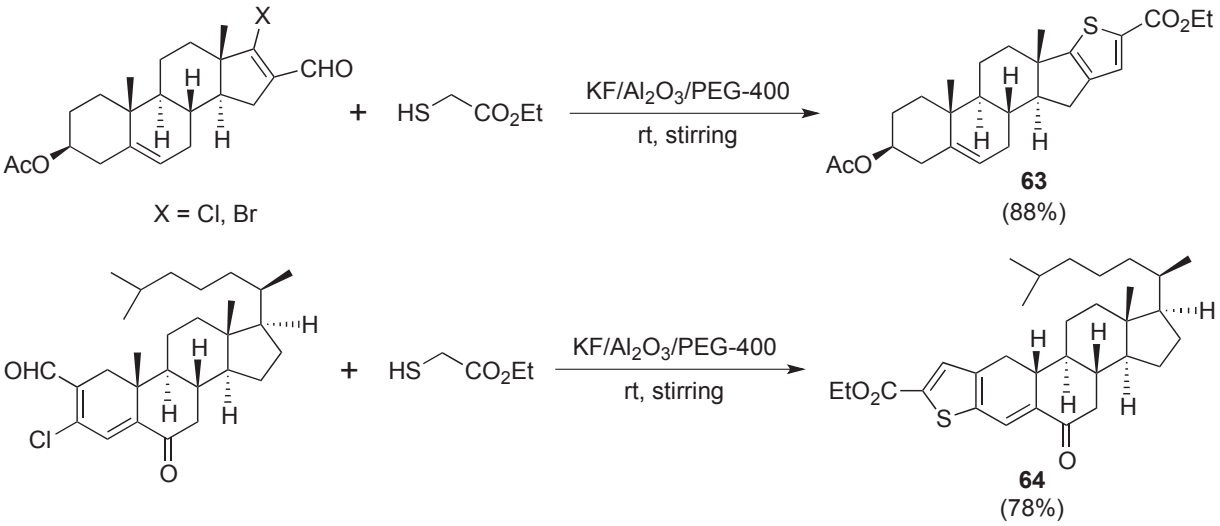


Scheme 38. Synthesis of quinolines from β-formylvinyl halides

4.04. Thiophene from β-formylvinyl halides

Sulphur heterocyclic thiophene is an important class of compound which constitutes the building block of many natural products[134] and pharmaceutically active agents.[135] Even in material chemistry, the presence

of thiophene core units are found to influence the physical parameters related to increased dielectric anisotropy and dielectric biaxiality.[136] The mechanism involved in the synthesis of thiophene is normally Michael addition, followed by Knoevenagel reaction. Steroidal thiophene derivatives were first prepared by Kumar *et al.*[137] in 1991 from 3-chloro-2-aldehyde and ethyl thioglycolate using pyridine/ trimethylamine and sodium hydride. Later in 2013, Bezboruah and co-workers employed KF/Al_2O_3/PEG-400 (Scheme 39) as a catalyst for the Fiesselmann-type synthesis of steroidal (**63** and **64**) as well as nonsteroidal thiophenes derivatives from β-formylvinyl halides.[138]

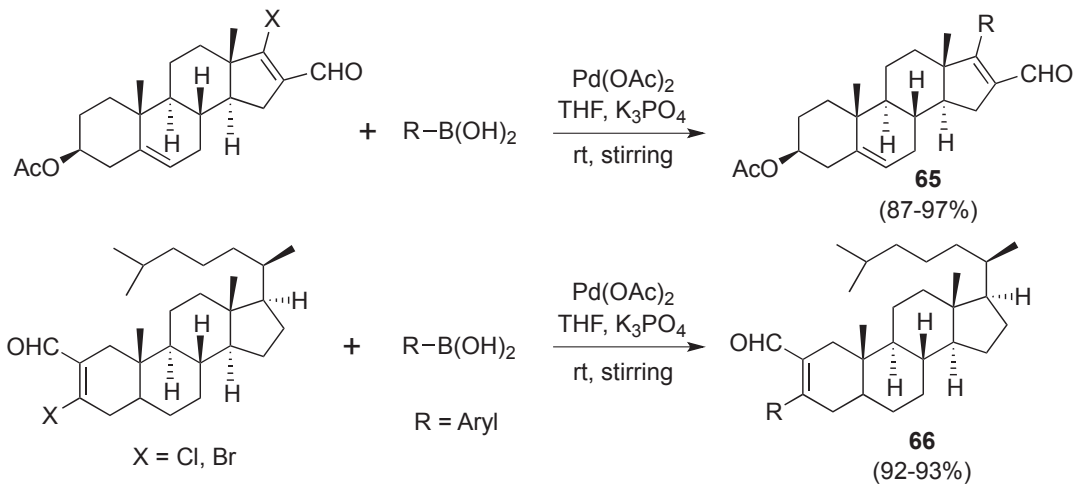


Scheme 39. Synthesis of thiophene from β-formylvinyl halides

4.05. Suzuki cross coupling of β-formylvinyl halides

Suzuki-Miyaura cross coupling reactions are mainly employed for selective construction of carbon-carbon bonds.[139] This cross coupling reaction has earned tremendous interests from the synthetic community due to the use of appreciably stable and less toxic organoboron compounds.[140] The efficiency of this reaction has been further enhanced by the presence of additives or ligands and precatalysts such as Pd(0) and Pd(II).[141] The most common ligand which is usually employed in Suzuki-Miyaura cross coupling is phosphane ligand; however, due to their sensitivity to air and moisture, their use becomes a setback.[142] There are few reports on the use of β-formylvinyl halides for Suzuki cross coupling reactions but these methods are known to employ phosphane ligands and high reaction temperatures.[143] Hesse *et al.* first reported a ligand-free method for the aforementioned cross coupling reaction and it was carried out in the presence of $Pd(OAc)_2$ with a stoichiometric amount of Bu_4NBr.[144] Gogoi *et al.* worked on developing a ligand-free Suzuki-Miyaura cross coupling reaction and successfully exploited the catalytic prowess of $Pd(OAc)_2/K_2CO_3$/THF for the following conversion.[145] This method was tested on steroidal β-formylvinyl halides and several steroidal analogs (**65** and **66**) were synthesized using different

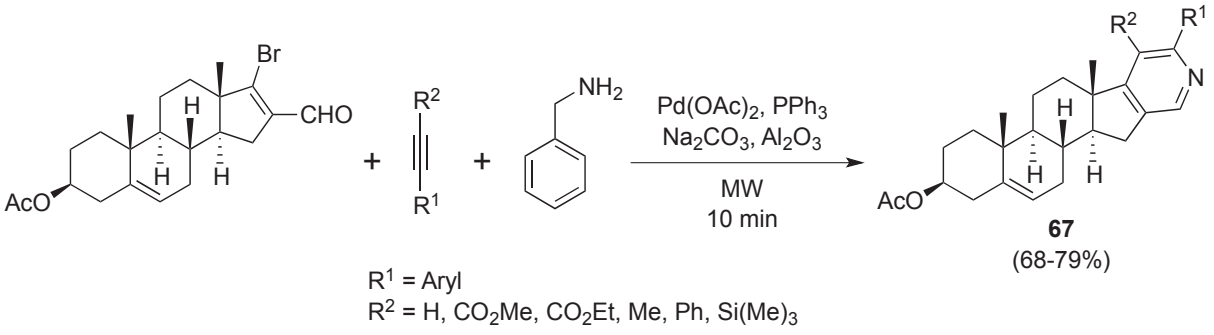
arylorganoboron compounds (Scheme 40).



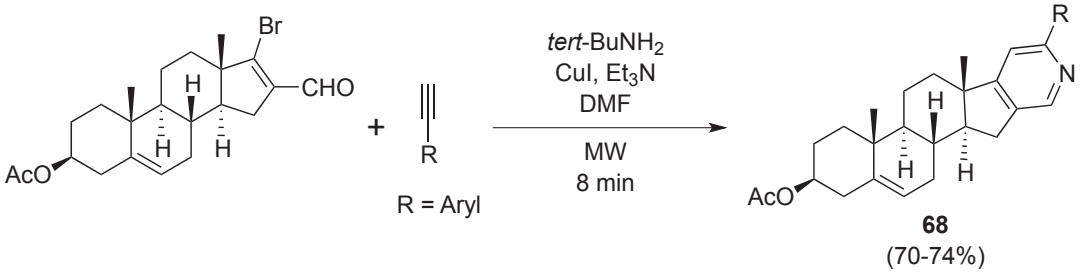
Scheme 40. Suzuki cross coupling of β-formylvinyl halides

4.06. Pyridines from β-formylvinyl halides

The importance of pyridine derivatives in medicinal chemistry is evident from our earlier discussions and so our group further investigated the synthetic viability of 5,6-disubstituted steroidal pyridines from steroidal β-formylvinyl halides. Two approaches were adopted for the synthesis of D-ring fused steroidal pyridines.[146,147] Firstly, 5,6-disubstituted pyridines (**67**) were targeted by reacting β-formylvinyl bromide



Scheme 41. Three component synthesis of pyridines from β-formylvinyl halides

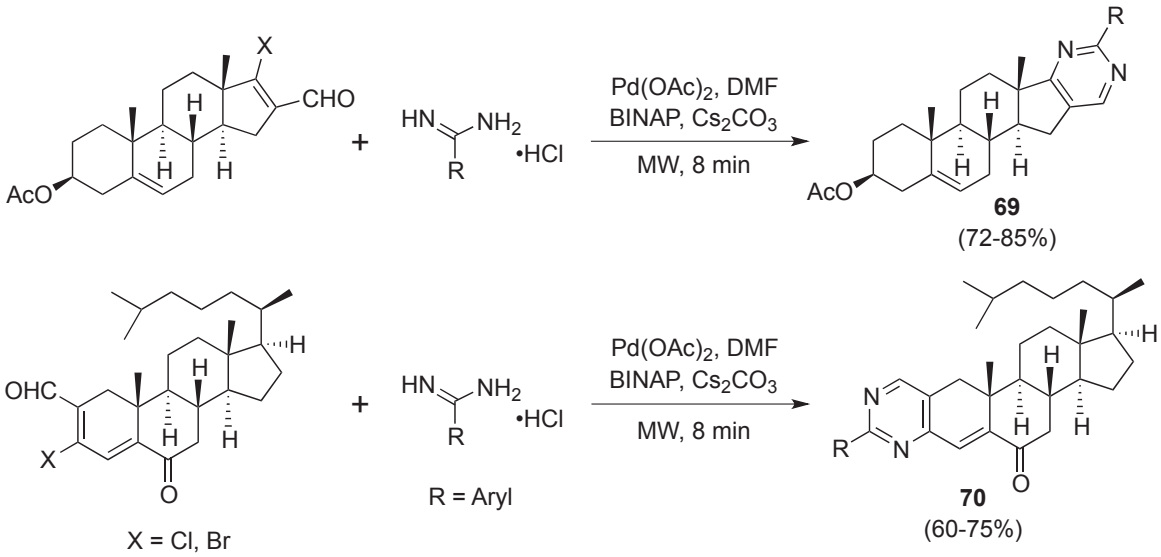


Scheme 42. Alternative synthesis of pyridines from β-formylvinyl halides

with substituted alkynes and benzylamine in the presence of $Pd(OAc)_2/PPh_3/Na_2CO_3/Al_2O_3$ under microwave condition (Scheme 41). In second attempt, monosubstituted steroidal pyridines (**68**) were prepared from β-formylvinyl bromide, alkynes and triethylamine under CuI catalyzed microwave condition (Scheme 42).

4.07. Pyrimidines from β-formylvinyl halides

Gogoi and co-workers developed a process to prepare steroidal pyrimidines from β-formylvinyl halides and benzamidine hydrochloride using $Pd(OAc)_2/BINAP/Cs_2CO_3/DMF$.[148] The reaction was carried out under microwave irradiation for 8 minutes. Several D- and A-ring annulated steroidal pyrimidines (**69** and **70**) were synthesized from steroidal molecules bearing β-formylvinyl halides moieties on A- and D-rings respectively (Scheme 43).

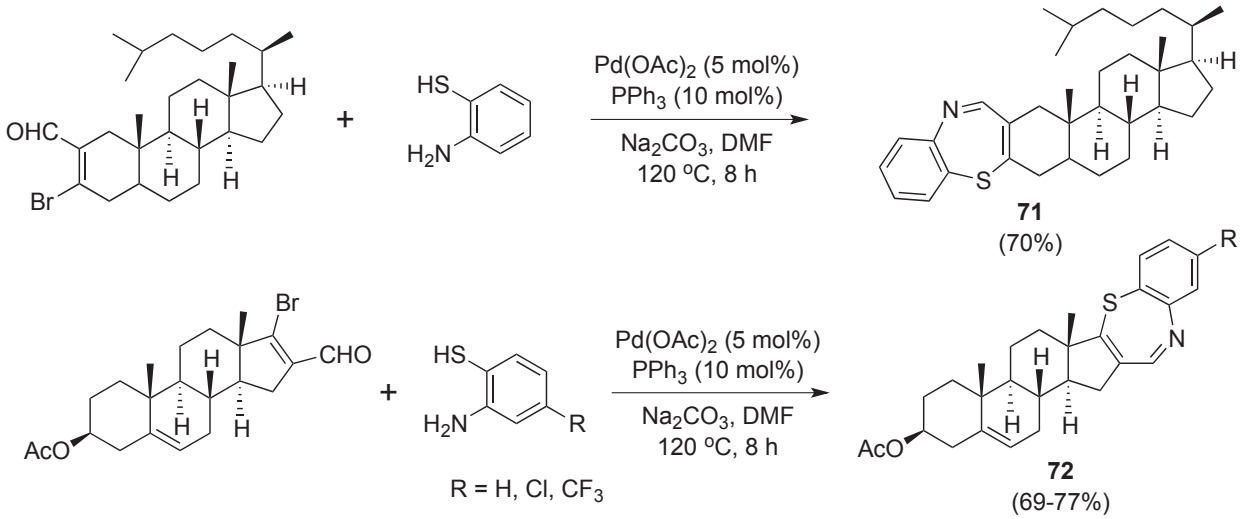


Scheme 43. Synthesis of pyrimidines from β-formylvinyl halides

4.08. Benzo[*b*][1,4]thiazepine from β-formylvinyl halides

Compounds bearing benzo[*b*][1,4]thiazepine moiety have been found to possess anti-HIV, anti-cancer, anti-convulsant, anti-anginal, anti-microbial, anti-fungal activities. Some of the well-known benzo[*b*][1,4]thiazepine drugs are diltiazem (an anti-hypertensive drug), clentiazem (cardiovascular drug), quetiapine (anti-psychotic agent), thiazesim (anti-depressant). Because of their medicinal importance, their synthesis has been received much attentions from many research groups. For instance, Willy and Müller carried out the synthesis of 2,4-disubstituted benzo[*b*][1,4]thiazepine *via* a coupling-addition-cyclocondensation sequence.[149] Nigam and Joshi also reported its synthesis from 1-(benzo[*d*][1,3]dioxol-5-yl)-3-phenylpropane-1,3-diones and *o*-aminothiophenol in pyridine.[150] In addition, several other procedures are reported, however, synthesis of 2-substituted benzo[*b*][1,4]thiazepine as well as steroidal

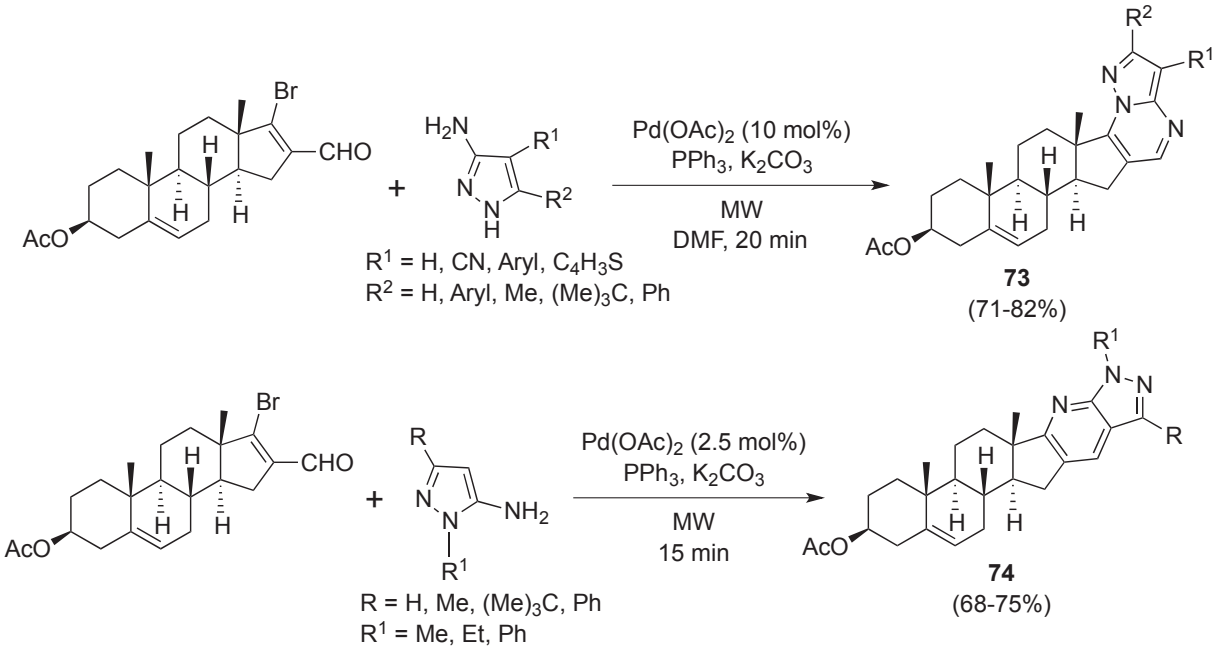
benzo[*b*][1,4]thiazepines are still obscure in the literature. Kaishap *et al.* reported the syntheses of steroidal as well as nonsteroidal fused benzo[*b*][1,4]thiazepine (**71**) and 2-substituted benzo[*b*][1,4]thiazepine derivatives (**72**) from β-bromovinylaldehydes and 2-aminothiophenol.[151] The reaction was catalyzed by palladium acetate under heating condition in DMF (Scheme 44).



Scheme 44. Synthesis of benzo[*b*][1,4]thiazepine from β-formylvinyl halides

4.09. Pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidines from β-formylvinyl halides

Microwave assisted synthesis of pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]quinolines and pyrazolo[1,5-*a*]pyrimidines in the presence of an acid is well documented.[152] In order to replace the acid

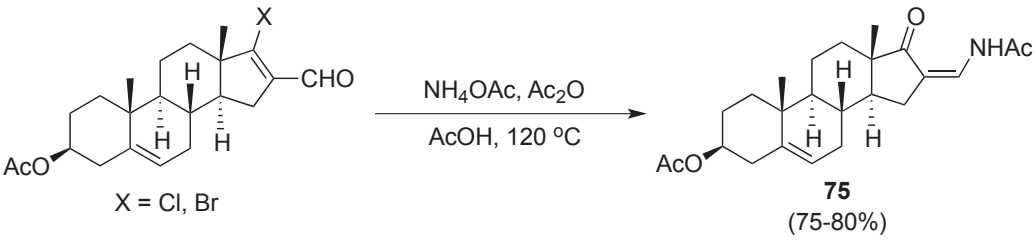


Scheme 45. Synthesis of pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidines from β-formylvinyl halides

catalyst with milder reagents, Shekarrao *et al.* developed a synthetic protocol involving palladium acetate as catalyst in the presence of PPh_3 and K_2CO_3.[153,154] Several derivatives of pyrazolo[1,5-*a*]pyrimidines (**73**) and pyrazolo[3,4-*b*]pyridines (**74**) were prepared from steroidal β-bromovinylaldehyde by varying the substituents on the 3-aminopyrazole/5-aminopyrazole ring (Scheme 45). The reactions were carried out under microwave irradiation for 15-20 minutes and the yields were satisfactory.

4.10. (*Z*)-β-Ketoenamides from β-formylvinyl halides

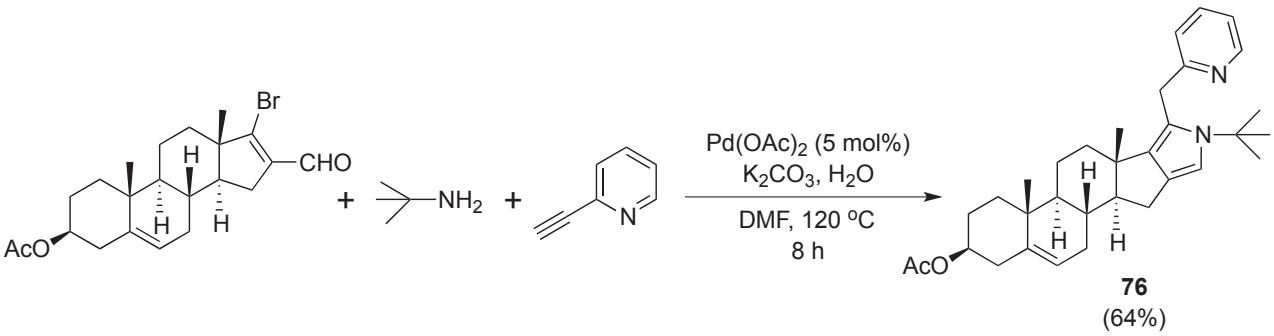
The stereoselective synthesis of *Z*-enamides remains a challenge due to difficulties arising from its thermodynamically less favourable factors and hence has been rarely explored. There are a few known methods for its synthesis *via* Pd/Cu-catalyzed oxidative amidation of conjugated olefins,[155] Curtius rearrangement,[156] Pd-catalyzed hydroamidation of electron-deficient terminal alkynes,[157] Peterson reaction,[158] Pd- and/or Cu-catalyzed cross coupling of vinyl derivatives with amides.[159] However, owing to the involvement of harsh reaction conditions, explorations for better method are still being sought. Gogoi and co-workers exploited the applicability of β-halo-α,β-unsaturated aldehydes as synthons for the synthesis of D-ring annelated β-ketoenamides (**75**) using ammonium acetate/acetic anhydride in acetic acid medium.[160] The reaction was carried out under thermal condition for 2 hours at 120 °C (Scheme 46).



Scheme 46. Synthesis of (*Z*)-β-ketoenamides from β-formylvinyl halides

4.11. Pyridine substituted pyrroles from β-formylvinyl halides

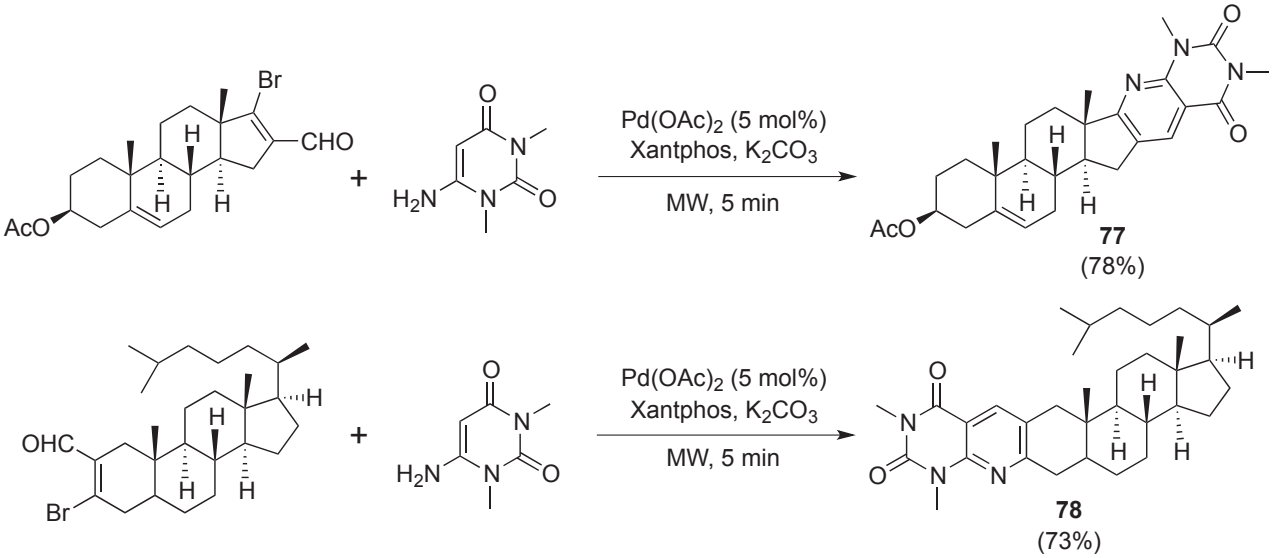
Substituted pyridine derivatives hold an important position amongst drugs and functional materials. Some of these systems include 2-alkylated pyridines,[161] pyridine-substituted 3,4-dihydrocoumarins[162] and pyridine substituted 3-hydroxy-2-oxindoles.[163] 2-Alkylated pyridine substituted pyrrole derivative such as peldesine, has been found to be potent purine nucleoside phosphorylase (PNP) inhibitor which has the viability to treat T-cell leukemia. Furthermore, they exhibit analgesic, insecticidal and anti-inflammatory activities.[164] Shekarrao *et al.* designed a synthetic pathway involving a three-component reaction of β-bromovinylaldehyde, aliphatic amines and 2-ethynylpyridine catalyzed by $Pd(OAc)_2$ under ligand free condition to afford pyridine substituted pyrroles (**76**) (Scheme 47).[165]



Scheme 47. Synthesis of pyridine substituted pyrroles from β-formylvinyl halides

4.12. Pyrido[2,3-*d*]pyrimidines from β-formylvinyl halides

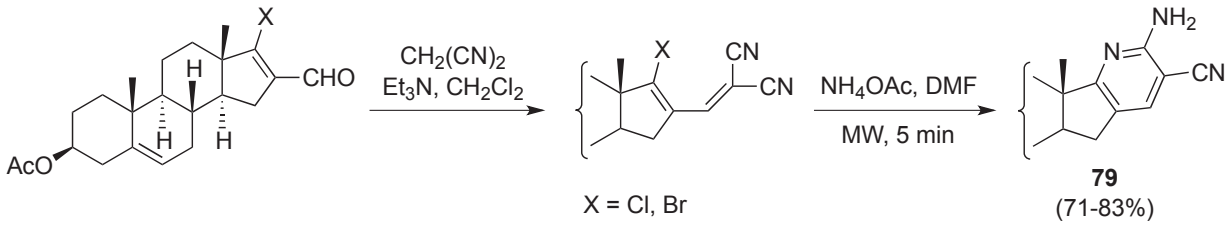
Pyrido[2,3-*d*]pyrimidine derivatives have exhibited considerable biological activities and hence they belong to another class of nitrogen heterocycle which has received substantial attentions. They are reportedly synthesized by treating 6-aminouracils with either electron-rich enamines[166] or α,β-unsaturated carbonyl compounds[167] or Meldrum's acid derivatives.[168] Kolos *et al.* prepared pyrido[2,3-*d*]pyrimidines by reacting 3-(hetero)aroylacrylic acids or their methyl esters with 6-amino-1,3-dimethyluracil.[169] Saikia *et al.* also developed a method for the synthesis of D- and A-ring annulated steroidal pyrido[2,3-*d*]pyrimidine derivatives (**77** and **78**) using β-bromovinylaldehyde and 6-amino-1,3-dialkyluracils under microwave irradiation in the presence of palladium acetate[170] (Scheme 48).



Scheme 48. Synthesis of pyrido[2,3-*d*]pyrimidines from β-formylvinyl halides

4.13. 2-Aminopyridines from β-formylvinyl halides

In our earlier discussion we have mentioned the synthesis of 2-aminopyridines from β-formylenamides and active methylene groups under microwave irradiation.[35] In furtherance of our interest in



Scheme 49. Synthesis of 2-aminopyridines from β-formylvinyl halides

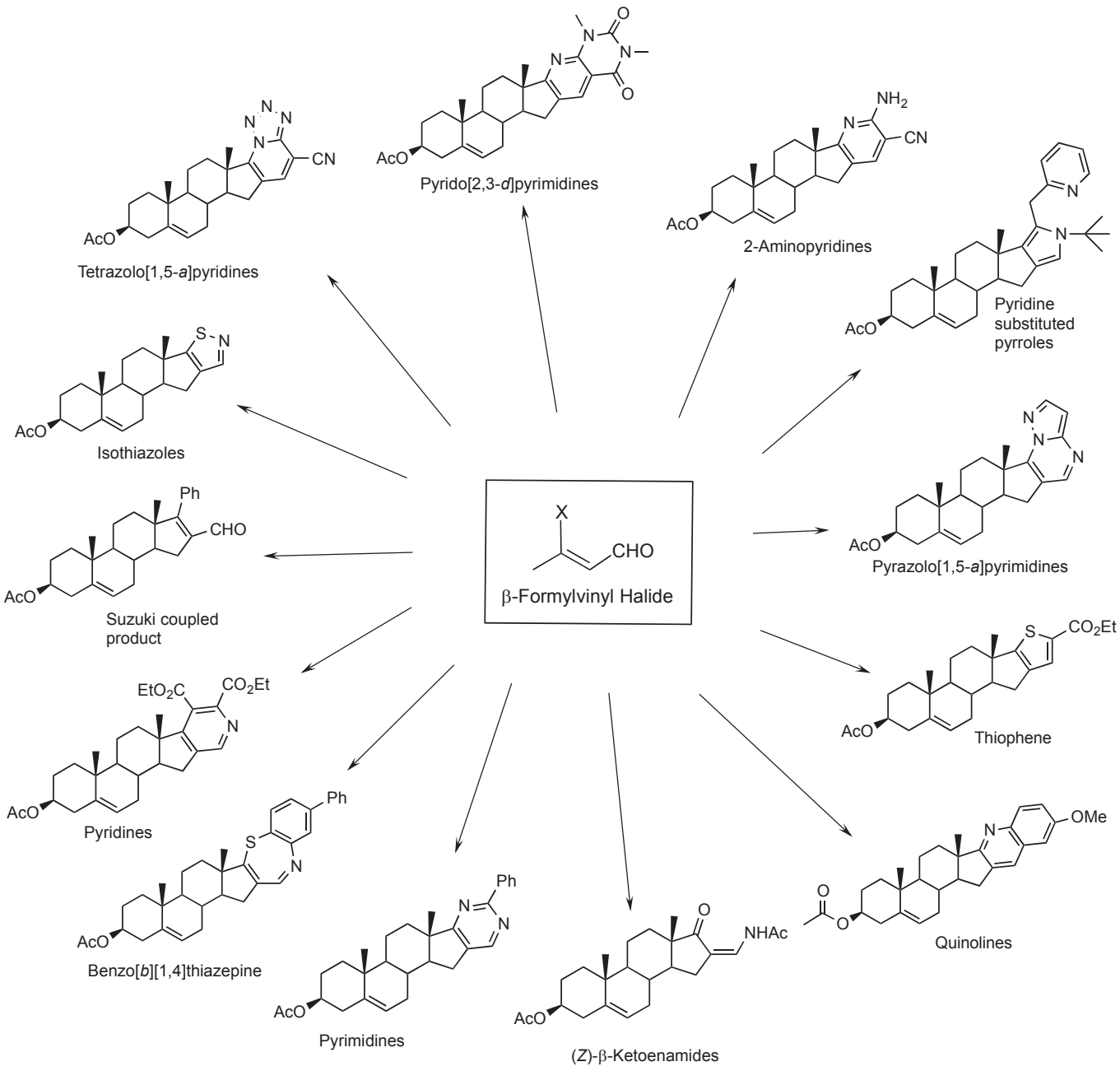


Figure 5. A summary of diverse steroidal molecules derived from β-formylvinyl halide

β-formylvinyl halides as versatile synthons for various azasteroids, the task for the synthesis of 2-aminopyridines was taken up by our group. Several steroidal as well as non-steroidal β-formylvinyl halides were first converted to their corresponding Knoevenagel products using active methylene compounds and trimethylamine followed by microwave assisted construction of 2-aminopyridines (**79**) in the presence of ammonium acetate[171] (Scheme 49).

5. CONCLUSION

In this review, we have focused on the synthesis of A-, B- and D-ring annulated heterosteroids utilizing three functional groups, β-formylenamide, conjugated enone and β-formylvinyl halide generated on the steroidal core. The endeavor afforded a library of novel N-, O- and S-heterosteroids adopting efficient synthetic strategies for synthesis of annulated heterocycles such as pyridines, pyrimidines, pyrazoles, pyrole, indolizine, 1,4-oxazepine, diazepine, pyrazolopyrimidine, tetrazolopyrimidine, isothiazoline, isoxazolidine, benzothiazepine, dihydrothiopyran, oxetene, pyran, thiopyran, *etc*. Most of the reactions developed have been extended to non-steroidal cyclic and alicyclic β-formylenamide, conjugated enone and β-formylvinyl halide. Considering the fact that several azasteroids play important role as enzyme inhibitors and proven clinical drugs, we believe that the synthetic strategies documented in this review will facilitate in understanding and developing new azasteroids as potential drug in future. Moreover, the three functional groups, β-formylenamide, conjugated enone and β-formylvinyl halide could contribute immensely to the advancement of new strategies for preparation of complicated non-steroidal heterocycles.

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