

RECENT STRATEGIES IN STEROIDAL D-RING MODIFICATION

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THE CHEMISTRY OF STEROID IS ALWAYS IMPORTANT,

BECAUSE

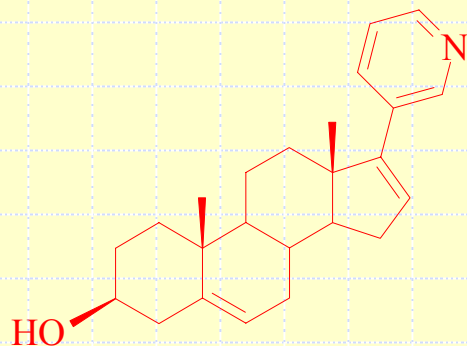
They comprise a group of compounds that are widely distributed in animals and plants

...AND EXCITING,

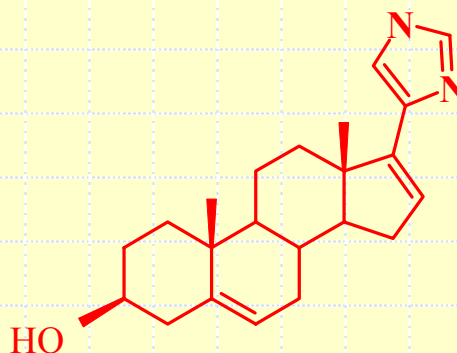
BECAUSE

They are "Biological Regulators" which show dramatic physiological effects when administered to living organism

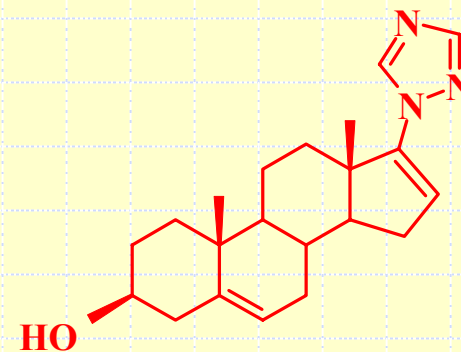
HETEROSTEROIDS AS ANTICANCER AGENTS



Abiraterone
(Prostate cancer)



17-Imidazolyl-Steroid

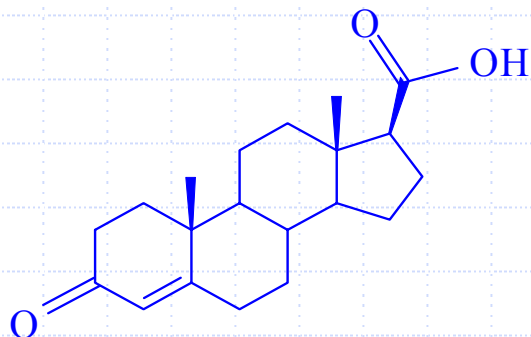


17-Triazolyl-steroid

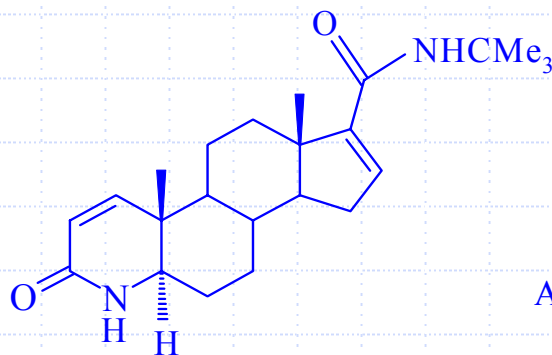
- o The excessive accumulation of androgens is the main cause of PC.
- o The enzymes $P450_{17\alpha}$ and 5α -reductase are responsible for the biosynthesis of these androgens.
- o D-ring substituted azasteroids are inhibitor of 17α -lyase enzymes.

BACKGROUND

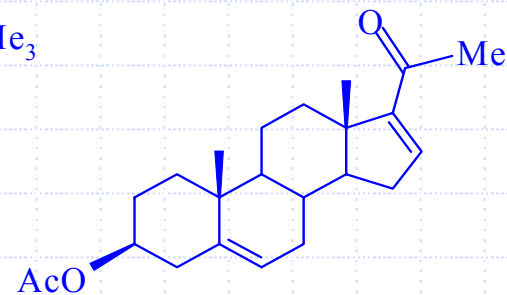
(ORIGIN OF THE IDEA)



3-Keto-4-androsten-17-carboxylic acid (3-KACA)



FINASTERIDE

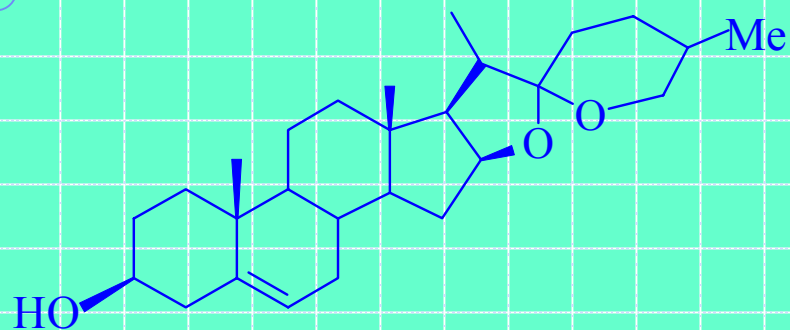


16-Dehydro-pregnenolone-3-acetate (16-DPA)

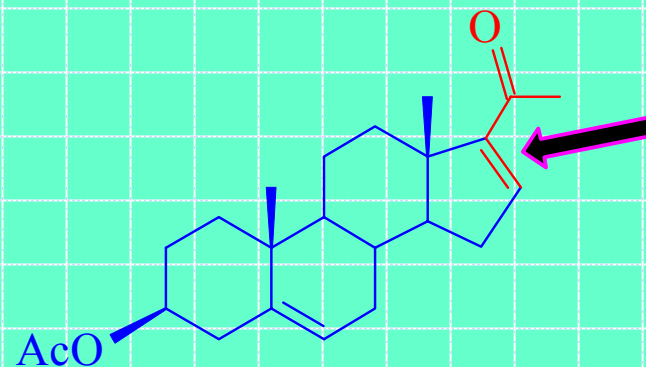
- o 3-KACA is recognized as potential 5 α -reductase inhibitor
- o 3-KACA is key intermediate for steroidal drug such as Finasteride, Epristeride and Turosteride used as chemotherapeutic agent for BPH and prostate cancer
- o 3-KACA can be prepared from 16-DPA

16-DPA FROM DIOSGENIN

(NATURAL SOURCE)



DIOSGENIN

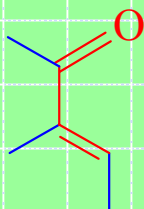


16-DPA

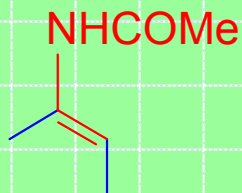
- o 16-DPA is a semisynthetic product of diosgenin.
- o 16-DPA comprises a conjugated enone system at D-ring.
- o It provides a great scope for ring-D modification of steroids.

OUR ACHIEVEMENT

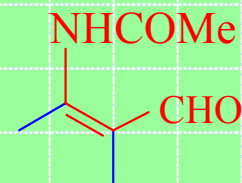
- DISCOVERY OF A NOVEL CLASS OF FORMYL ENAMIDE
- USE OF BETA FORMYL ENAMIDE AS ORGANIC SYNTHON
- USE OF CONJUGATED ENONE IN ORGANIC SYNTHESIS



Conjugated enone



Enamide



β -Formyl enamide

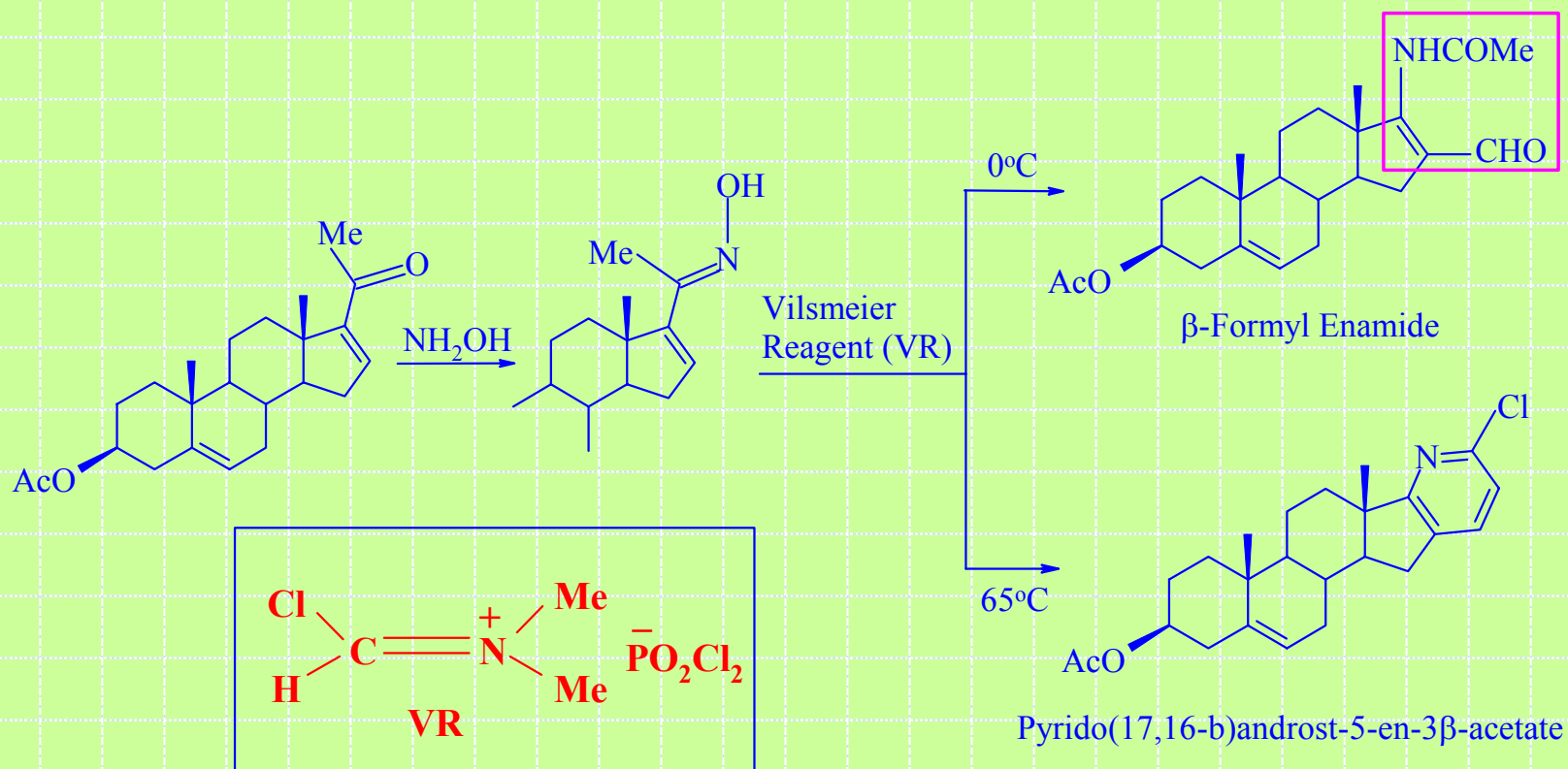
REACTION STRATEGIES EMPLOYED FOR STEROIDAL RING-D MODIFICATION

Vilsmeier reaction

- Knoevenagel condensation
- Inverse electron demand Diels-Alder reaction
- [4+2] and [2+2] Cycloaddition reactions
- 1,3-Dipolar cycloaddition reaction
- Henry reaction
- Michael reaction
- Transfer reaction
- Three-component reaction
- Microwave mediated solid phase reaction

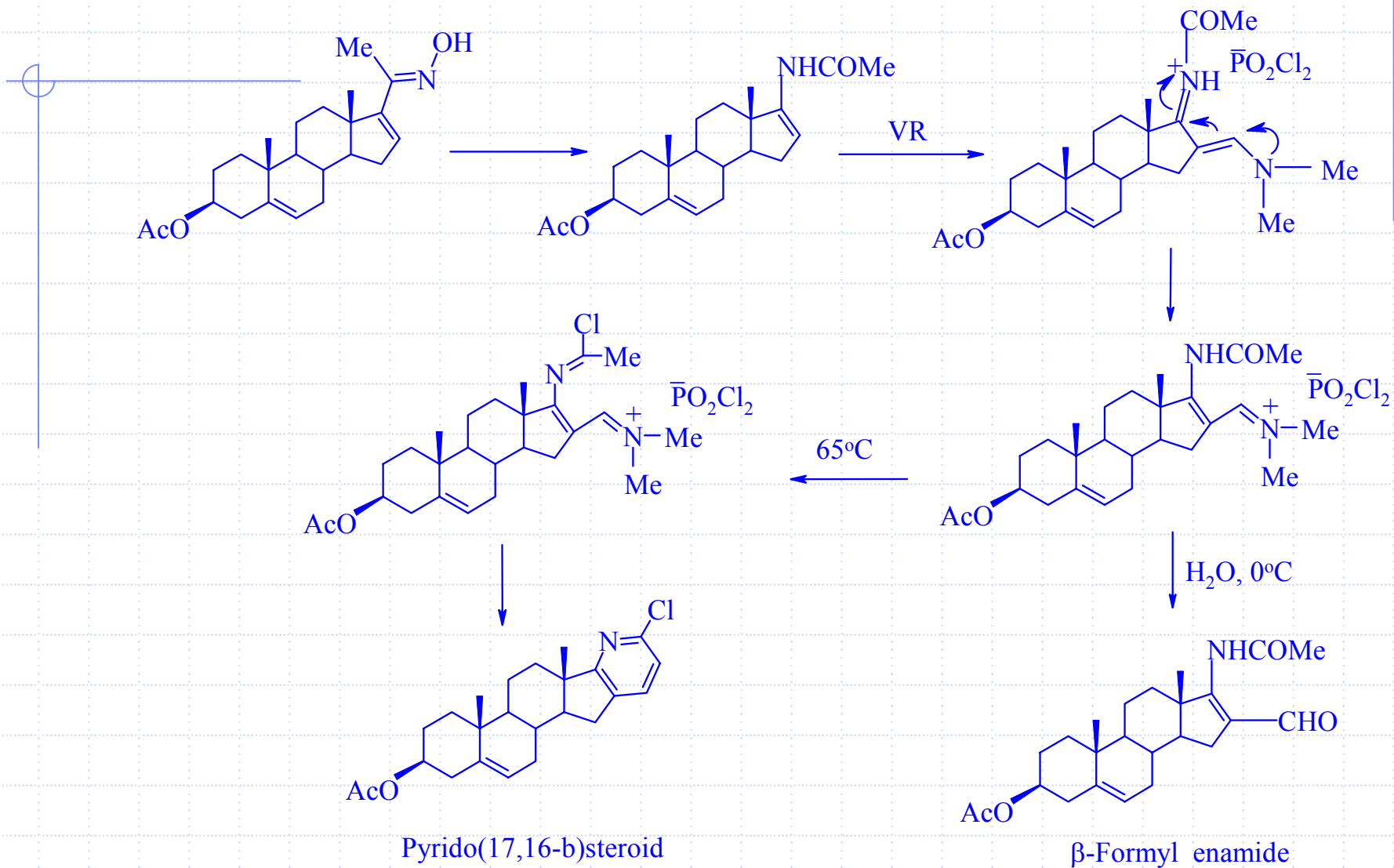
Synthesis of β -formyl enamide.

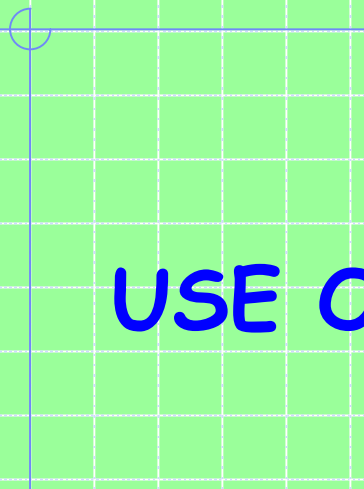
Vilsmeier Reaction on conjugated oxime



Tetrahedron Lett, 1996, 37, 8231

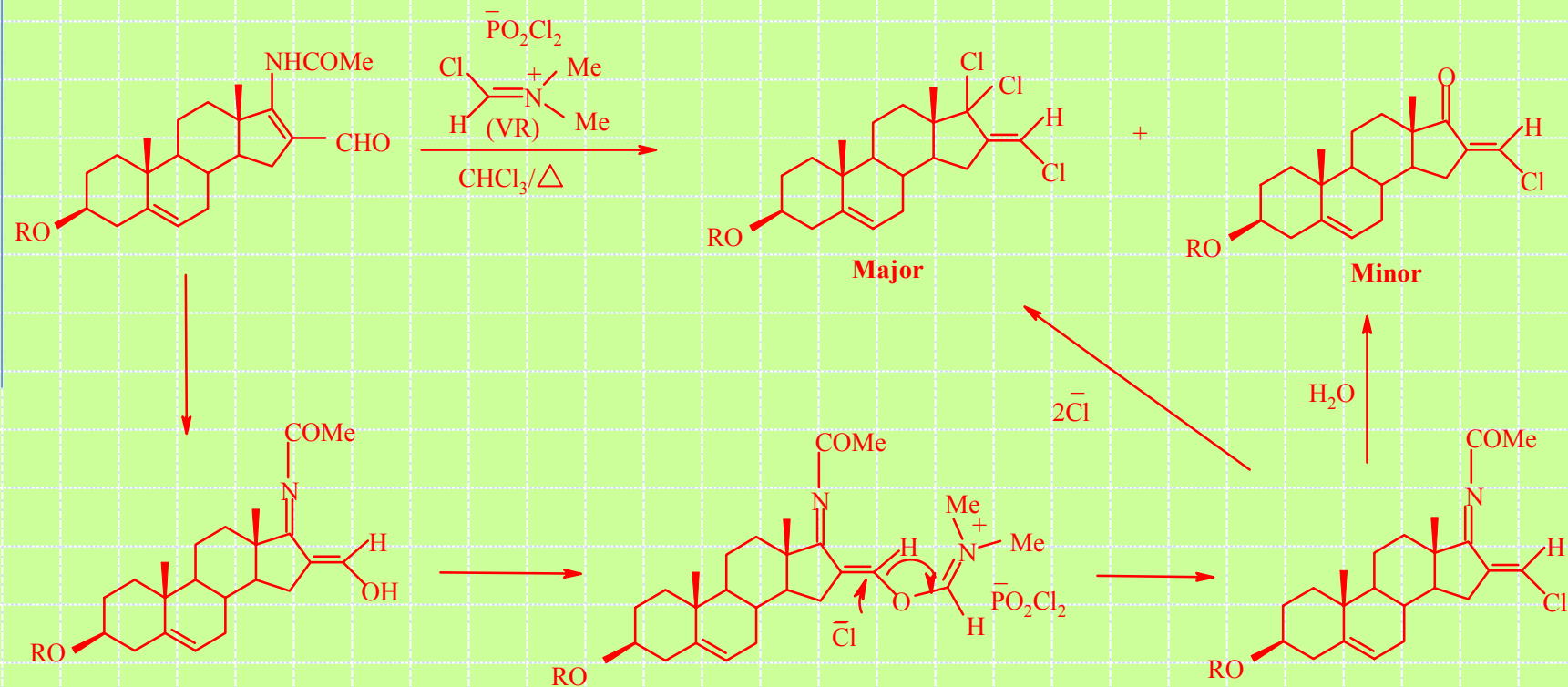
Mechanism





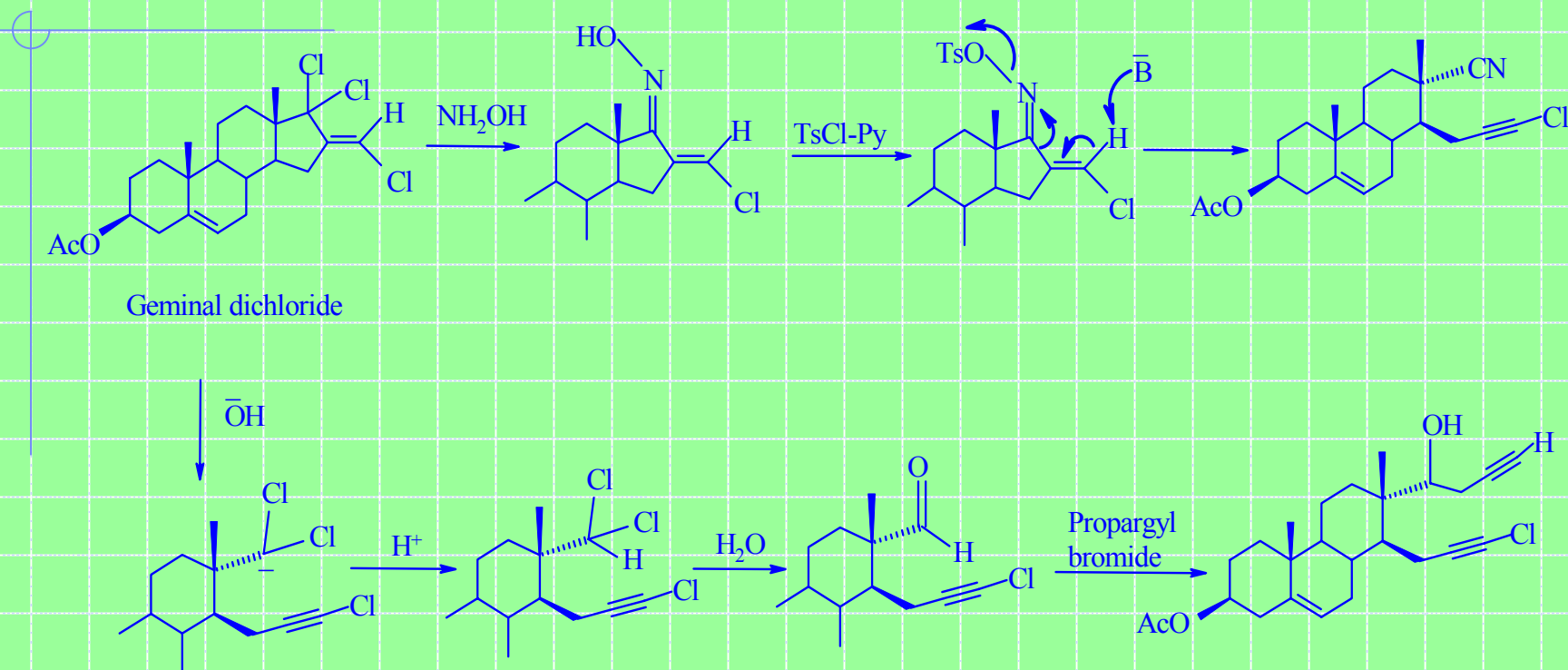
USE OF BETA-FORMYL ENAMIDE AS ORGANIC SYNTHON

PREPARATION OF GEMINAL DICHLORIDES



Tetrahedron Lett, 1997, 38, 1845

D-Ring Cleavage Reaction



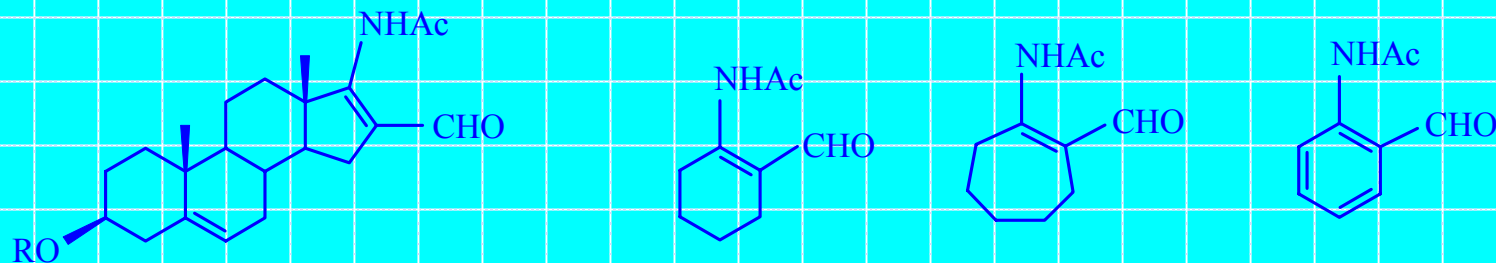
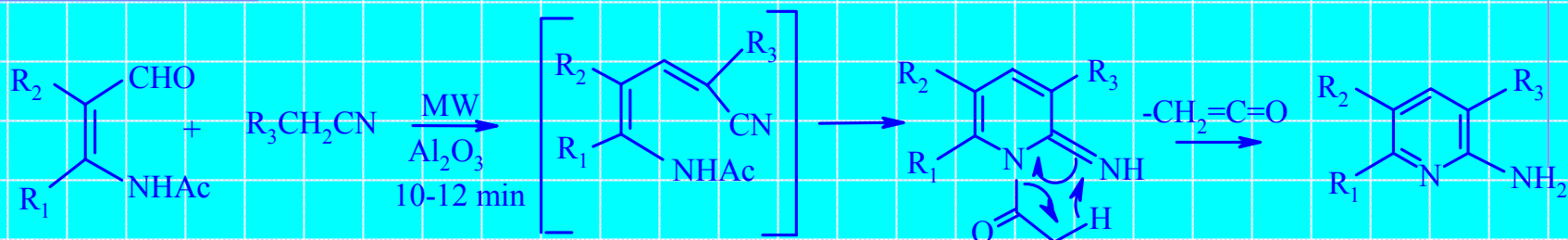
- o Trans stereochemistry of 16-chloromethylene group
- o TsOH elimination facilitated cleavage of C16-C17 bond
- o Strong base abstracts olefinic proton with concomitant ring cleavage to form dichloro carbanion intermediate via an inverse Reimer-Tiemann mechanism

PYRIDINE SYNTHESIS

EMPLOYING FORMYL ENAMIDE

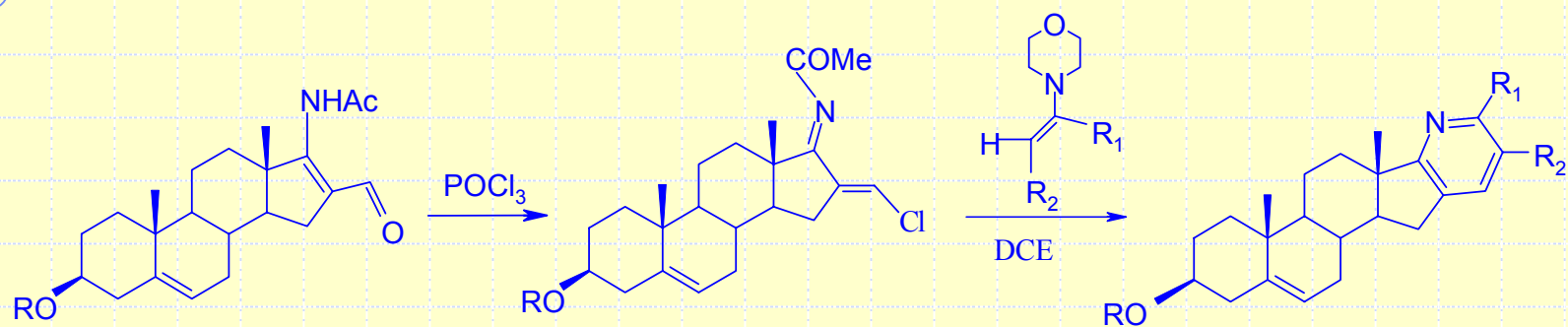
- KNOEVENAGEL CONDENSATION
- IEDDA REACTION
- HENRY REACTION

Knoevenagel condensation



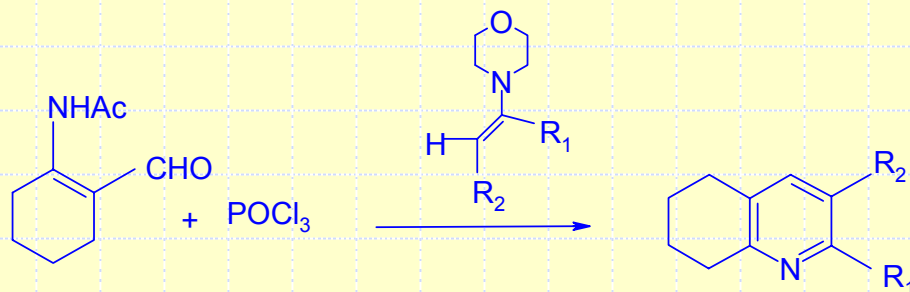
- o Basic alumina catalysed intramolecular cyclisation
- o Intramolecular hydride shift from N-acetyl to imino group
- o Loss of ketene involving a six-membered transition state

Inverse electron demand Diels-Alder reaction



51-57%

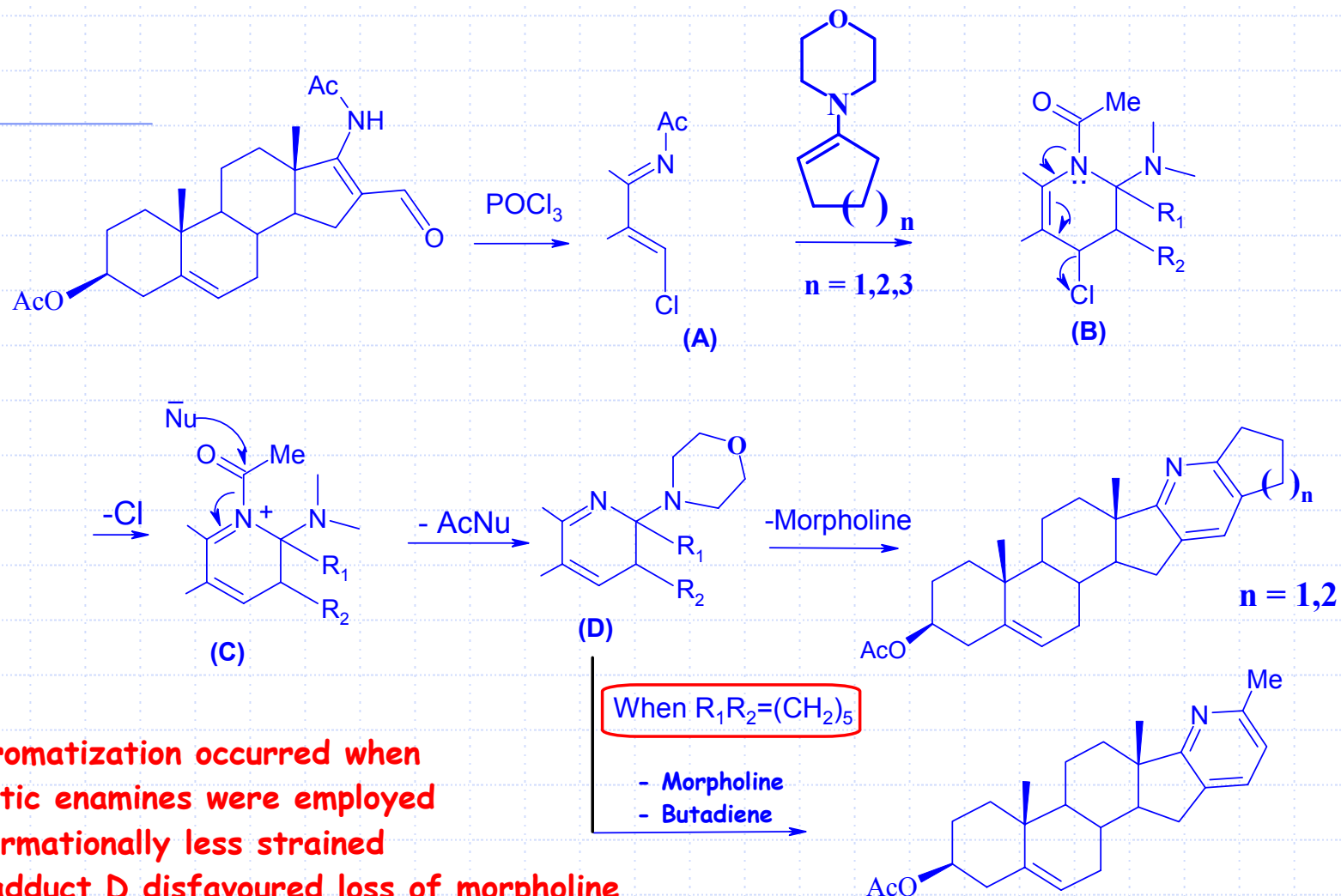
82-88% ($\text{BF}_3 \cdot \text{OEt}_2$, TiCl_4)



- o Conversion of β -formyl enamide to electron deficient 1-aza-1,3-diene
- o Enamine behaved as electron rich dienophile
- o IEDDA reaction is catalysed by Lewis acid

J. Org. Chem., 2000, 65, 922

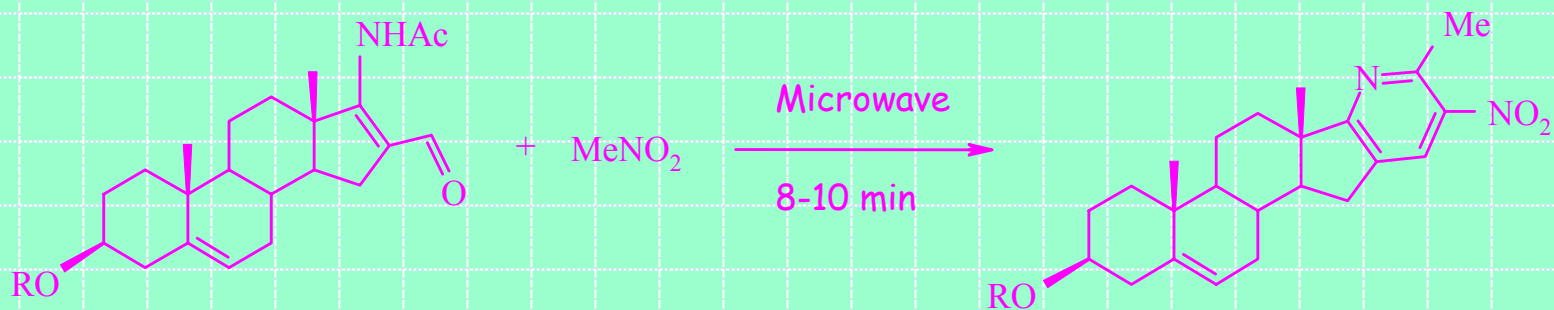
MECHANISM



- o No aromatization occurred when aliphatic enamines were employed
- o Conformationally less strained cycloadduct D disfavoured loss of morpholine
- o Cycloheptanone enamine facilitated loss of butadiene

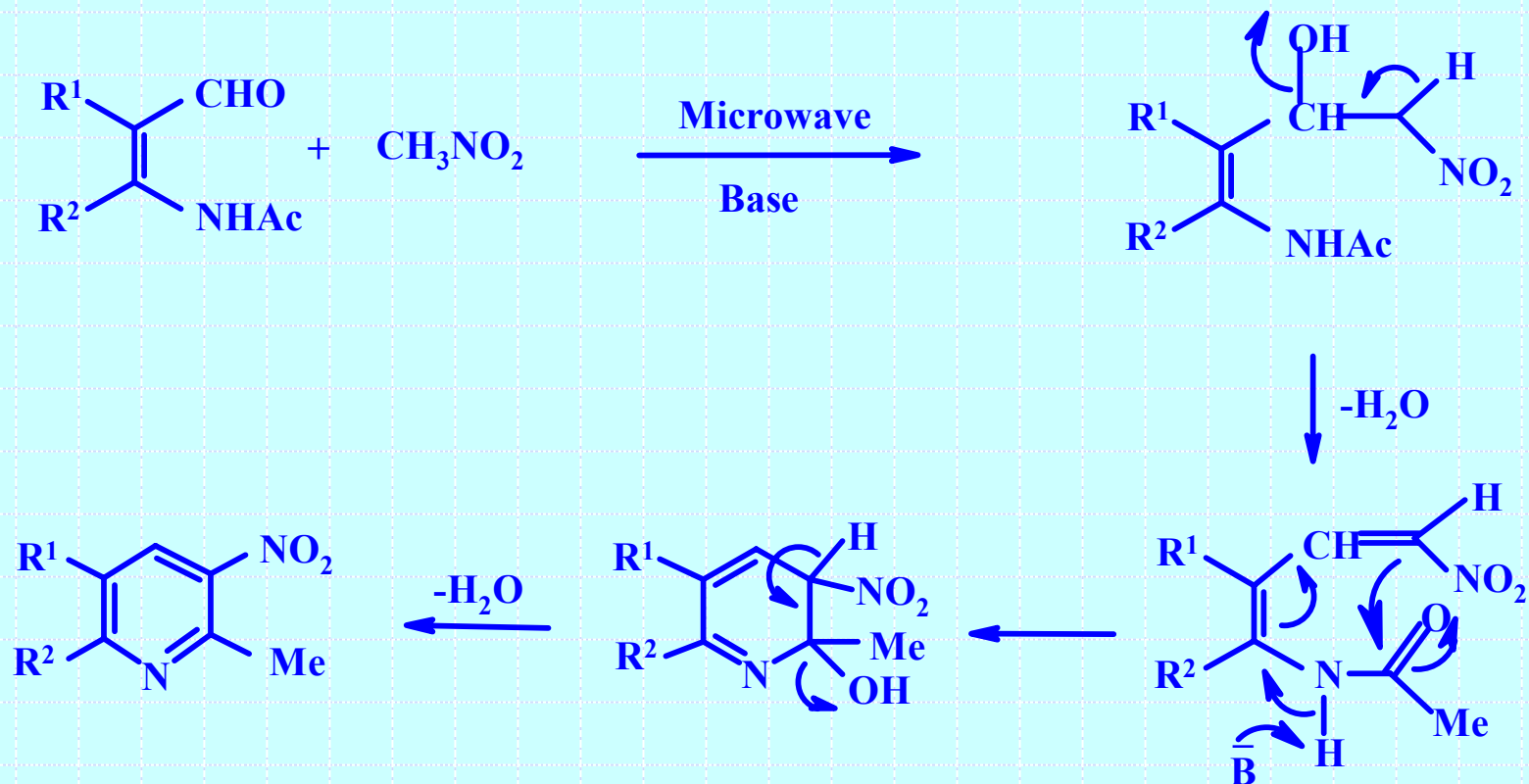
Henry reaction

- o Valuable fundamental synthetic strategies for construction of C-C bond
- o Provides great potential for newly formed β -nitro alcohol or nitroalkene for further transformation
- o Under microwave β -formyl enamide provides a facile synthesis of fused pyridine via a novel nitroaldol or Henry reaction



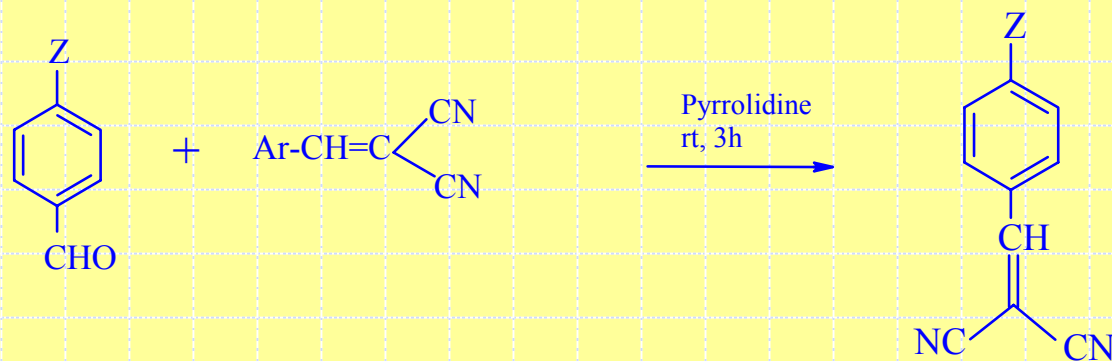
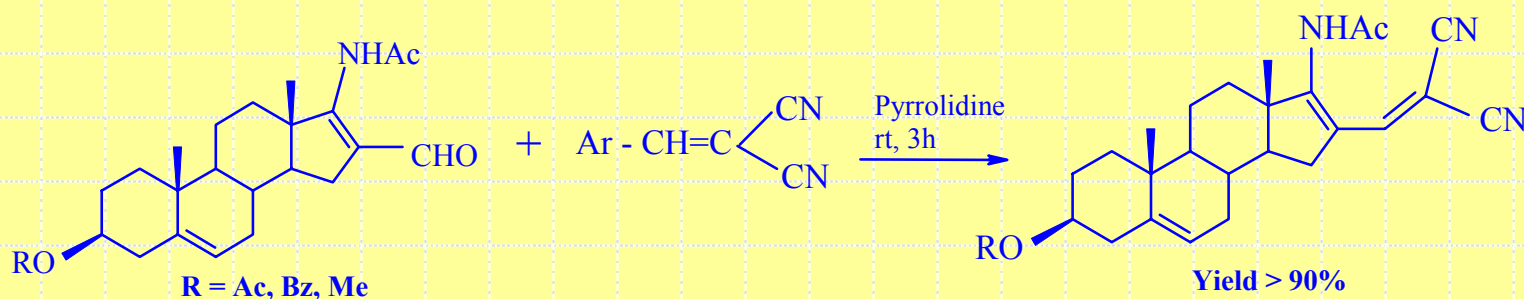
Synlett, 2004 , 1309

MECHANISM



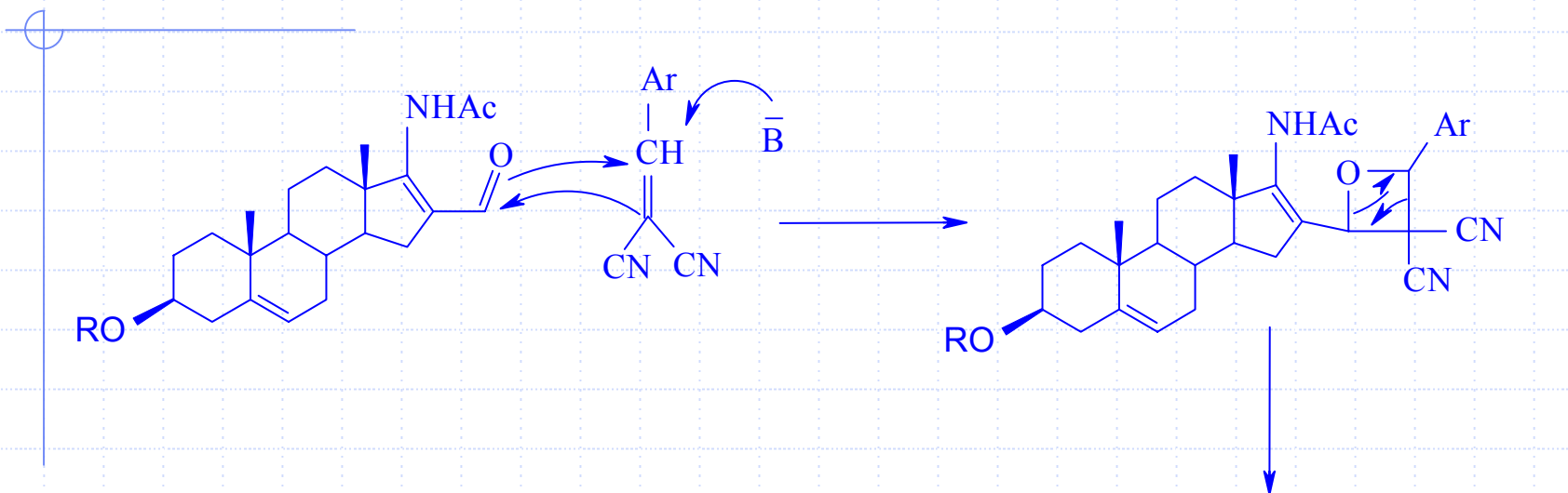
Transfer Reaction

- o Valuable tool in synthesis due to mild reaction conditions
- o More advantageous in transhydrogenation, transalkylation, transacetylation, transesterification, transamidation etc
- o Arylidene malonitriles undergo facile exchange of dicyano methylene group with β -formyl enamides



Synthetic Commun, 2000, 30, 771

MECHANISM



Ar

Yield (%)

Ph

95

p-Cl-C₆H₄

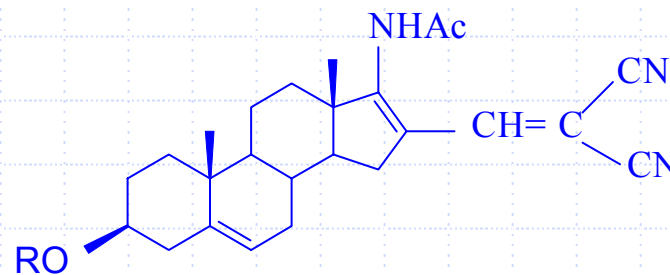
80

p-Me-C₆H₄

60

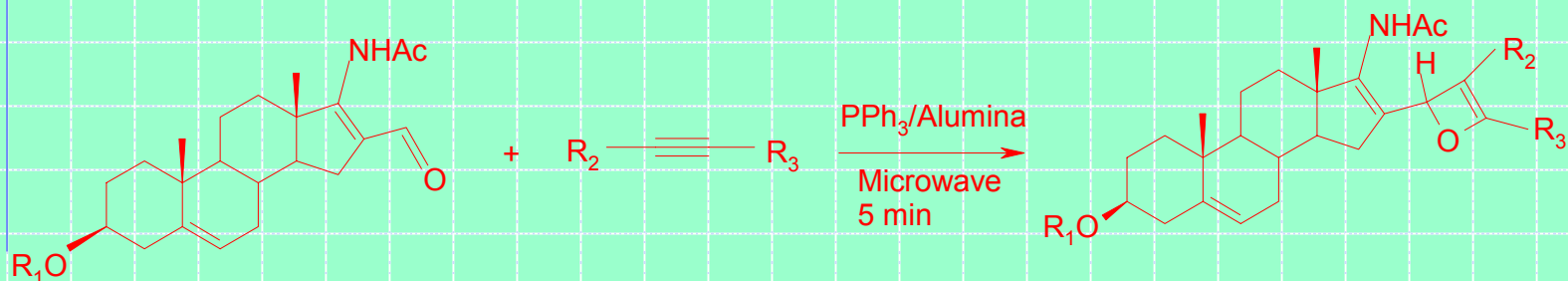
p-NMe₂-C₆H₄

Nil



SYNTHESIS OF OXETEN VIA [2+2] CYCLOADDITION REACTION

Oxetan constitutes the core structure of Taxol (anticancer), obafluorin (antibiotic) and lipstatin (cholesterol lowering agent)



1a, $R_1 = Ac$
1b, $R_1 = Bz$

2a, $R_2 = R_3 = COOMe$
2b, $R_2 = H, R_3 = COOEt$
2c, $R_2 = Ph, R_3 = COOEt$

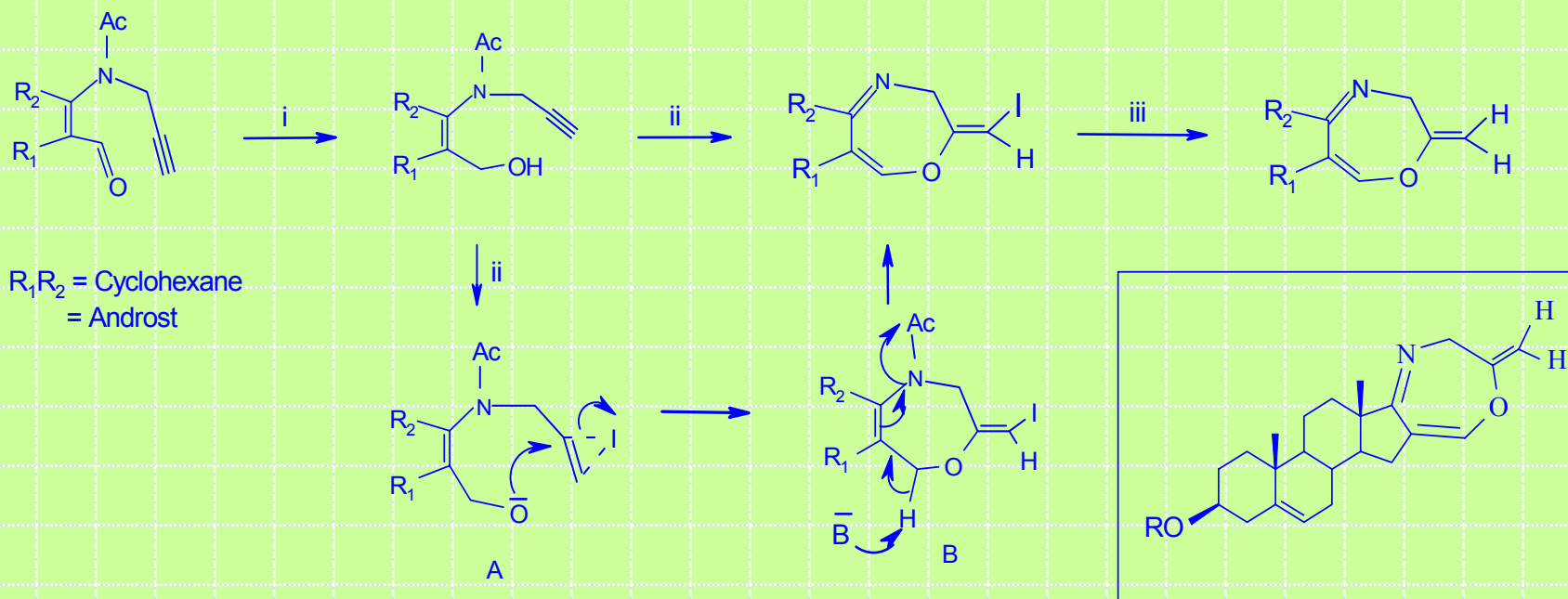
3a, $R_1=Ac, R_2=R_3=COOMe$
3b, $R_1=Ac, R_2=H, R_3=COOEt$
3c, $R_1=Ac, R_2=Ph, R_3=COOEt$
3d, $R_1=Ph, R_2=R_3=COOMe$
3e, $R_1=Ph, R_2=H, R_3=COOEt$
3f, $R_1=Ph, R_2=Ph, R_3=COOEt$

	Yield	Time
Microwave	70-80 %	5-7 min
Thermal	15-23%	60-72 h

Synthetic Commun, 2000, 32, 3611

D-Ring Heterosteroid: 1,4-oxazepine

1,4-oxazepine constitutes the parent core of loxapine, nitroxapine hydrochloride and linadryl-H. Also it finds application in asymmetric synthesis of monoterpene alkaloids and secoiridoids

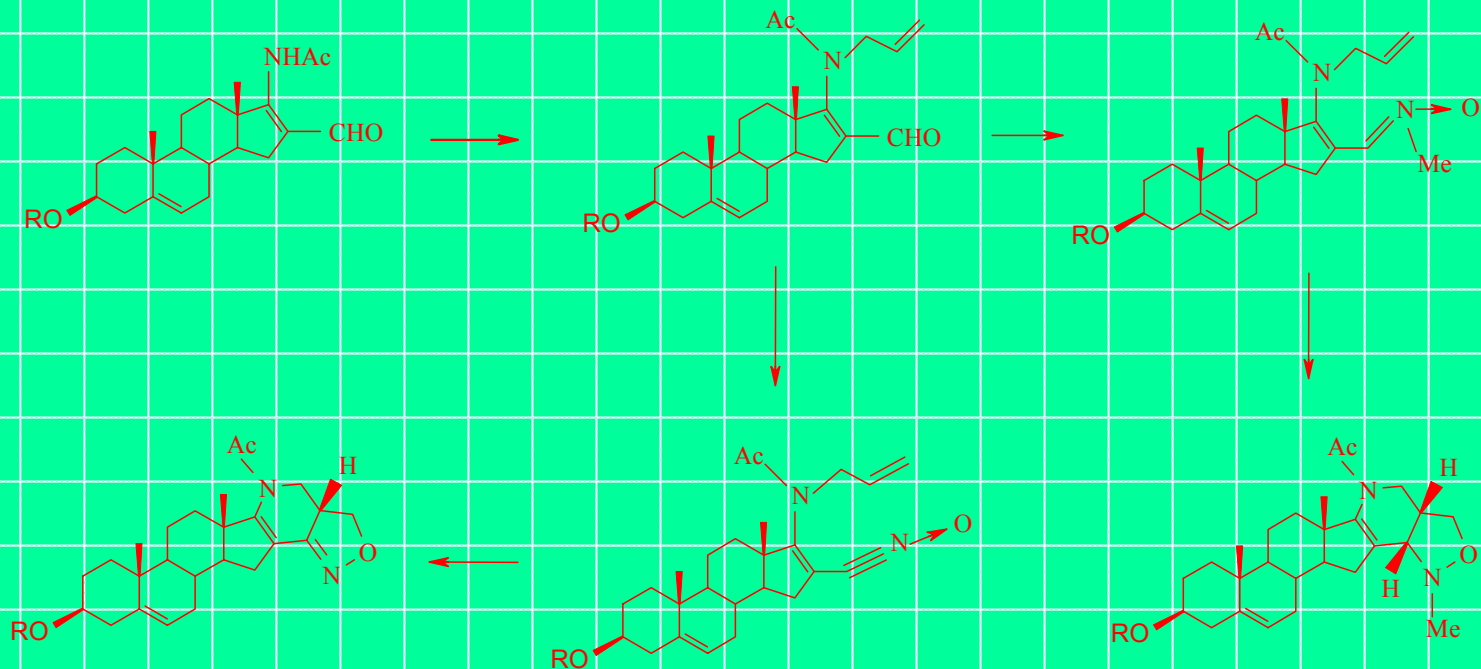


Reagents i) $\text{NaBH}_4/\text{MeOH}/0-10^\circ\text{C}$; ii) $\text{I}_2\text{-NaHCO}_3/\text{Et}_2\text{O-H}_2\text{O}/\text{r.t.}$; iii) $\text{Na}_2\text{SO}_3\text{-H}_2\text{O}$

Synthetic Commun, 2001, 31, 3281

1,3-DIPOLAR CYCLOADDITION REACTION

- o An indispensable methodology for isoxazolidine synthesis
- o Isoxazolidines are important intermediates for synthesis of natural products including alkaloids, amino acids, penem and carbepenem antibiotics
- o Steroidal β -formyl enamide provided *endo/cis*-isoxazolidine and isoxazoline via 1,3-dipolar nitron and nitrile oxide cycloaddition reactions



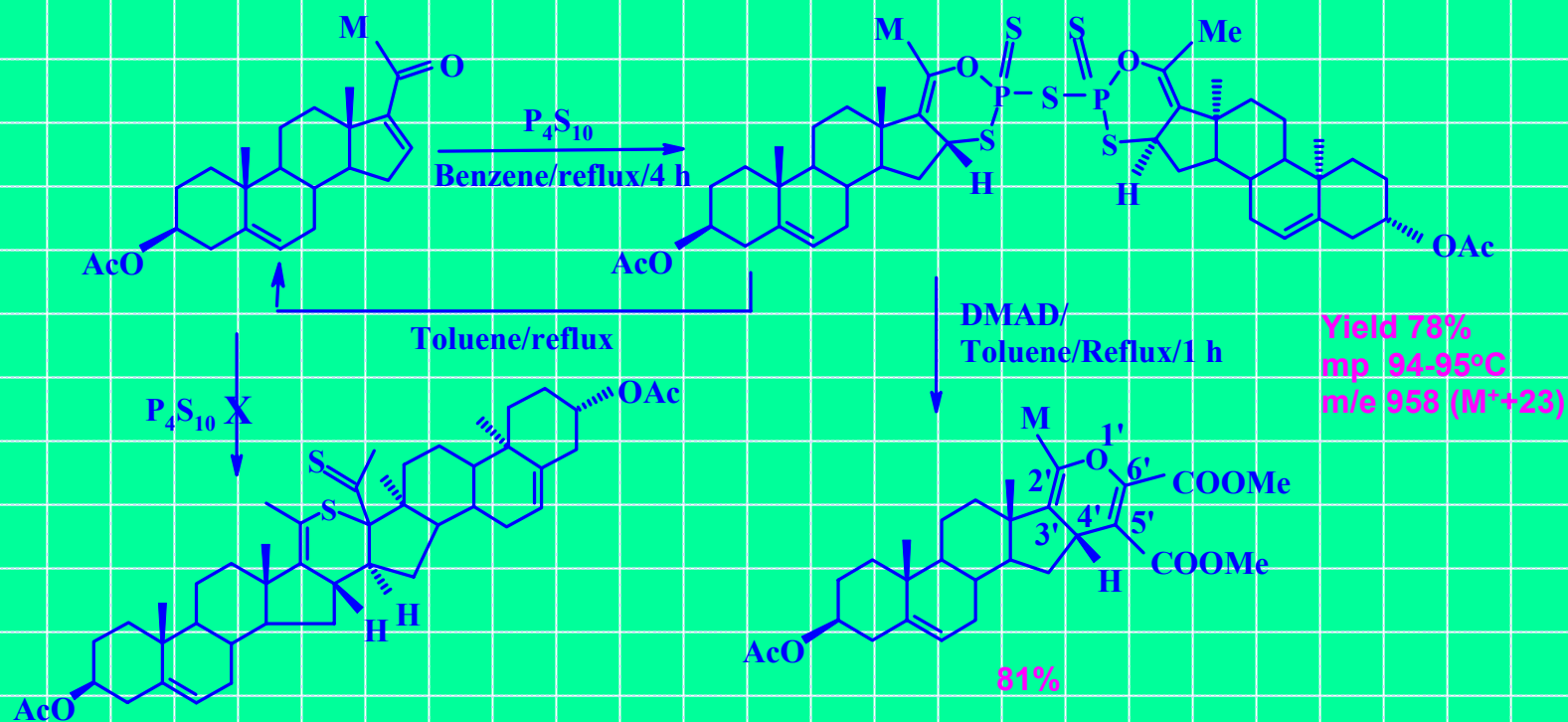


CONJUGATED ENONES

16-DPA- P_2S_5 ADDUCT AS MASKED ENONE

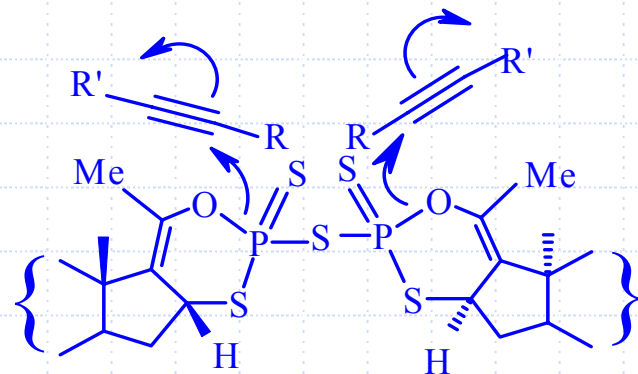
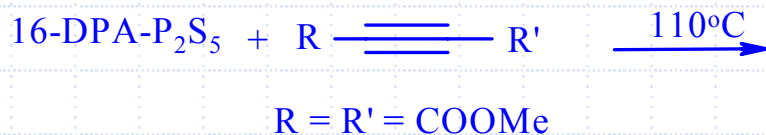
[4+2]Cycloaddition reaction

- o α,β -Unsaturated thiones are unstable in their monomeric form
- o Thionation of α,β -unsaturated ketone led to thione dimer
- o However, thionation of 16-DPA afforded a novel 16-DPA- P_2S_5 adduct
- o The 16-DPA- P_2S_5 adduct could be employed as a masked conjugated enone

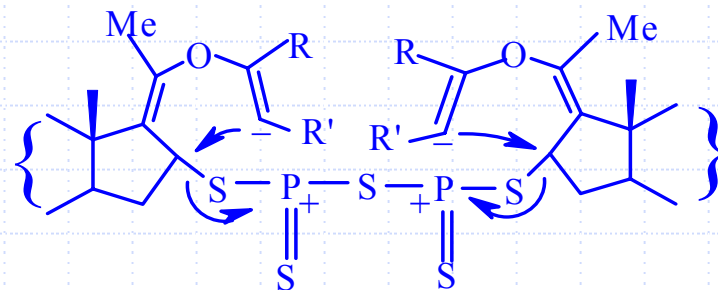
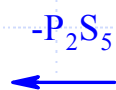
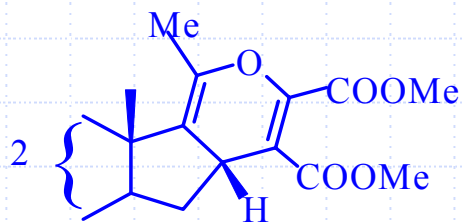


Tetrahedron Lett, 2003, 44, 2741

MECHANISM



16-DPA-P₂S₅ adduct

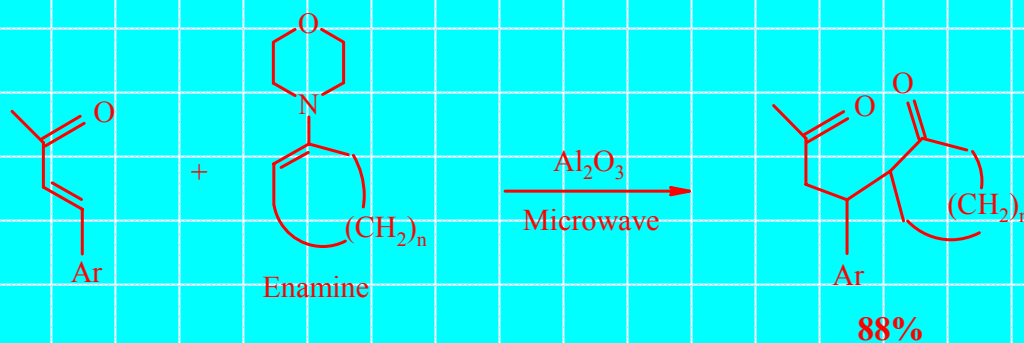
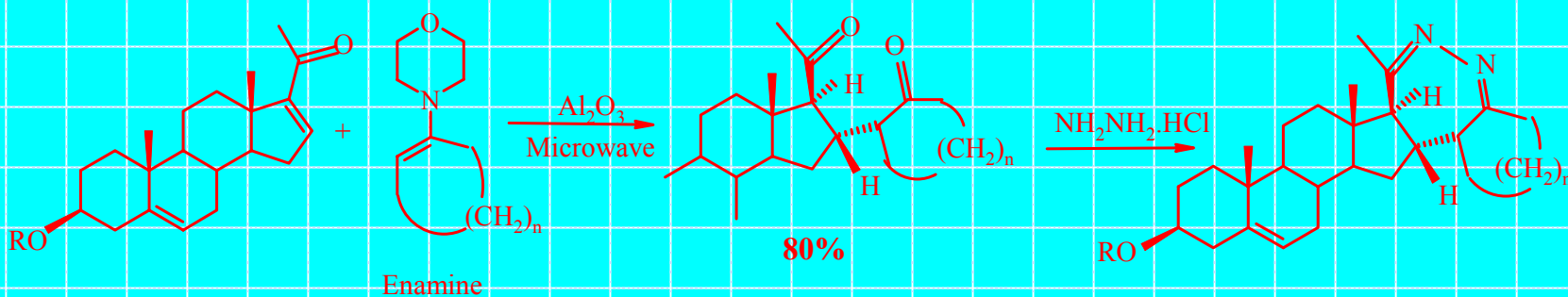


- o The reaction initiates due to cleavage of P-O bond via a diion intermediate
- o Conversion of 16-DPA-P₂S₅ adduct to 16-DPA supported the mechanism

Michael Addition Reaction

Preparation of 1,5-diketone

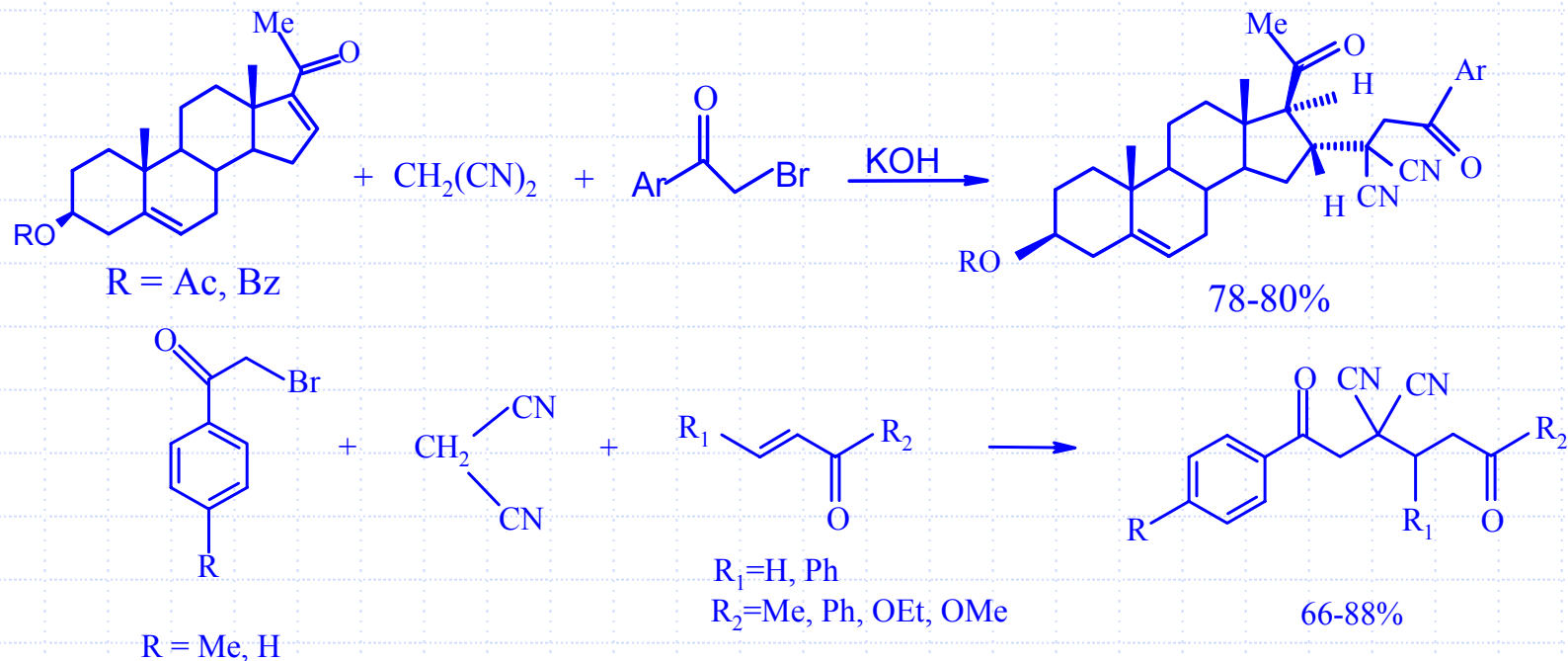
- o Michael addition of conjugated carbonyl compounds are generally carried in strong basic condition, however, such condition is detrimental to base sensitive functionalities and leads to auto-oxidation or retro-Michael type decomposition
- o Michael reaction of enamine with steroidal enones provides high yield of 1,5-diketones by a solid phase alumina promoted reaction under microwave irradiation



THREE-COMPONENT REACTION SYNTHESIS OF 1,6-DIKETONE

1,6-Diketones are useful precursors of biologically potential five- and six-membered carbocycles and heterocycles

The reaction proceeded via initial condensation of α -bromoketone with malonitrile followed by Michael addition with conjugated enone

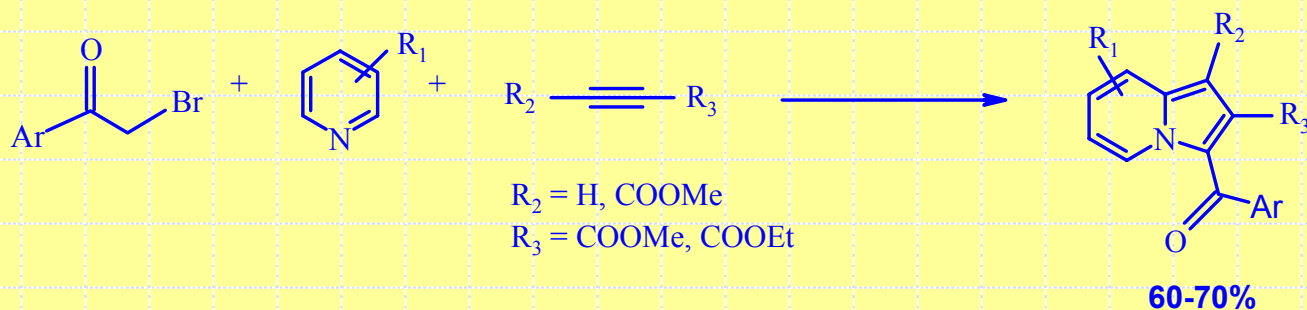
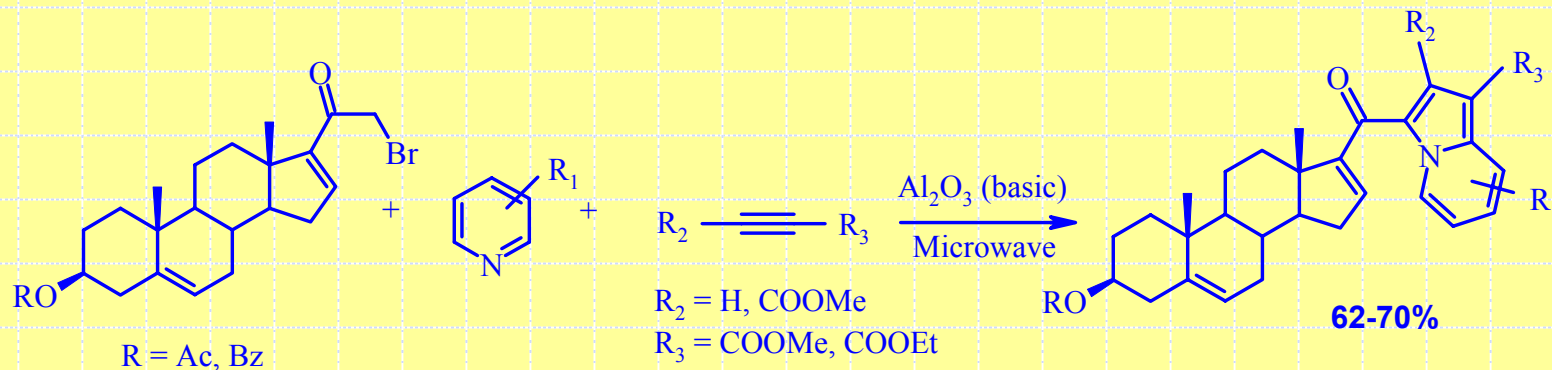


Synlett, 2003, 1506

THREE-COMPONENT REACTION

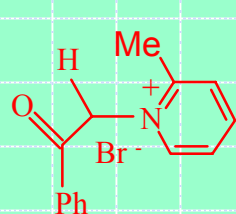
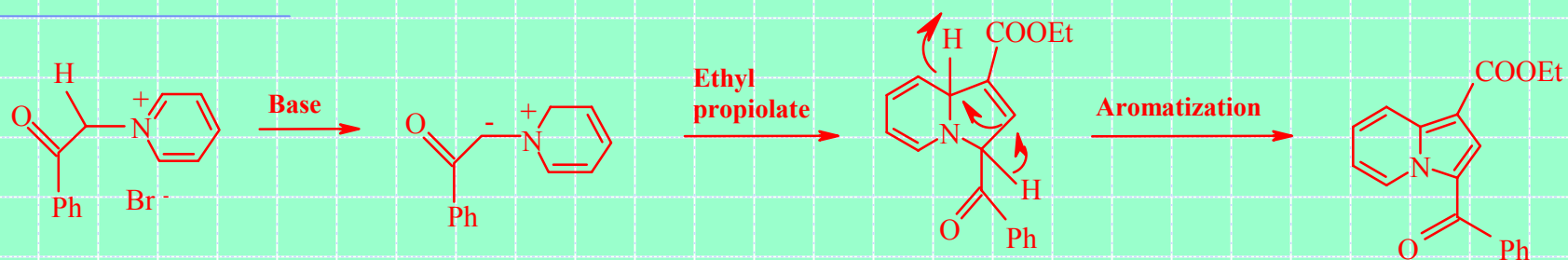
Synthesis indolizines

- o Indolizines constitutes the core structure of alkaloids (-)-slaframine, (-)-dendoprimine and coniceine
- o Multicomponent reaction is important due to combinatorial synthesis, one-pot reaction, good yields of the product
- o Three component reaction of acyl bromide, pyridine and acetylene under the influence of basic alumina as catalyst afforded corresponding indolizines in excellent yield in a one-pot reaction

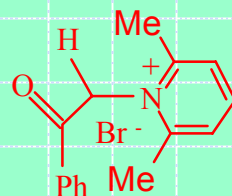


Organic Lett, 2003, 4, 435

MECHANISM



2-Picoline



2,6-Lutidine

- o N-Alkylpyrimidium salt is generated in situ from condensation of phenacyl bromide and pyridine
- o It is converted into a 1,3-dipolar species under the influence of base
- o 1,3-Dipolar cycloaddition followed by aromatization to 10- π electron system
- o 2,6-Lutidine failed to react while 2-picoline afforded excellent yield

CONCLUSION

OUR ENDEAVOUR
ON THE STEROIDAL D-RING MODIFICATION
USING CONJUGATED ENONE SYSTEM
LED TO THE DISCOVERY OF A NOVEL
STEROIDAL BETA FORMYL ENAMIDE SYSTEM,
WHICH EXHIBITED ENORMOUS POTENTIAL
AS ORGANIC SYNTHON

FURTHER STUDIES ARE BEING PURSUED

ACKNOWLEDGEMENT

- DST, NEW DELHI
- DIRECTOR, RRL-JORHAT

..... and to my coworkers & students

- Dr Shahadat Ahmed
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- Dr Moanochet Longchar
- Mr Utpal Bora
- Mr Apurba Chetia
- Mr Anil Saikia
- Mr Chandan J Saikia
- Mr M G Barthakur
- Miss M Borthakur

Thank you