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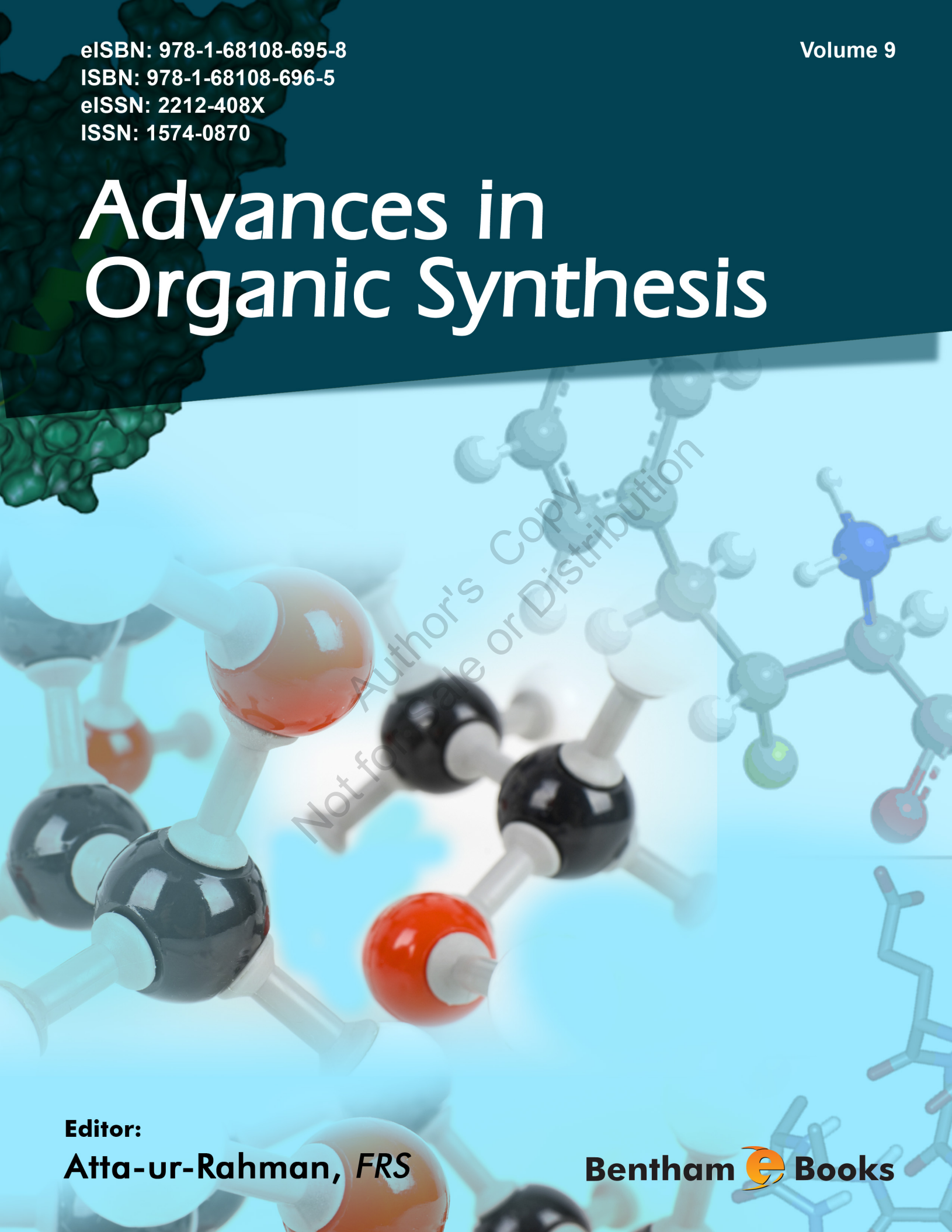
Advances in Organic Synthesis



Editor:
Atta-ur-Rahman, *FRS*

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Advances in Organic Synthesis

(Volume 9)

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PREFACE

This volume of ***Advances in Organic Synthesis*** presents some recent exciting developments in synthetic organic chemistry. It covers a range of topics including important researches on novel approaches to the construction of complex organic compounds. The chapters are written by authorities in the field and are mainly focused on asymmetric hydrogenation of tetrasubstituted olefins, catalytic organic synthesis, applications of covalently supported ionic liquids, intramolecular cyclization reactions *via* carbon-heteroatom (C-X) bond formation, quinazoline analogues and their biological importance, and synthesis of N,O,S-heterocycles by one-pot reactions of epoxides, aziridines and oxaziridines.

The book should prove to be a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information about synthetic organic chemistry. I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new developments in the field.

I am thankful to the efficient team of Bentham Science Publishers especially Dr. Faryal Sami (Assistant Manager), Mr. Shehzad Naqvi (Senior Manager) and Mr. Mahmood Alam (Director Publications).

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CHAPTER 3

Recent Developments in Intramolecular Cyclization Reactions *via* Carbon-heteroatom (C-X) Bond Formation

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Abstract: The overwhelming potential of heterocyclic compounds in pharmaceutical sector continuously demands the development of new synthetic approaches. The beginning of 19th century witnessed an era of development of various condensation reactions for the development of new heterocyclic scaffolds. Most of the developed classical reactions still hold great value while the field is inundated in 21st century with the advent of catalysis. The activation of unsaturated functionalities of acyclic compounds to undergo intramolecular cyclization *via* metal catalyzed approaches or the transformation of azetidin-2-ones to functionally enriched compounds have occupied a prominent place in heterocyclic synthesis.

Keywords: Aza-Michael Addition, Biological Activities, *β*-Amino Ester, *β*-Lactam-Synthon Protocol, Cross-Dehydrogenative-Coupling, Cyclo-Isomerisation, Cycloaddition, Diastereoselective, Enatioselective, Enatiomeric Excess, Fries Rearrangement, Heterocycles, Intramolecular Amidolysis, Intermolecular Amidolysis, Intramolecular Cyclization, Intramolecular Ullmann, Metal-Catalyzed Reactions, Photocatalyst.

INTRODUCTION

Heterocyclic compounds have received the attention of synthetic chemists worldwide because of their enormous potential in medicinal chemistry and pharmaceutical applications [1]. In particular, natural products, drugs, and renewable resources having heterocyclic moieties are essential because of their manifold properties [2]. The commercially available drugs such as Penicillin (antibiotic), cyclosporine (immunosuppressant), azidothymidine (HIV), and

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Atta-ur-Rahman (Ed.)

sofusbuvir (hepatitis C) have overwhelming prevalence of heterocyclic motif which changed the world for the better, and it is estimated that these antibiotics alone have increased the life expectancy up to 10 years [3]. The major advances in synthetic medicinal chemistry is focused on the development of new strategies for the affording heterocyclic compounds with biological relevance.

Over the years, enormous efforts have been devoted in developing synthetic methodologies for the preparation of highly functionalized heterocycles. Metal-catalyzed intramolecular addition of oxygen, nitrogen and sulphur nucleophile across unsaturated carbon-carbon bond constitutes one such important synthetic protocol [4]. Direct C-H bond activation with subsequent carbon-carbon (C-C) as well as carbon-heteroatom (C-X) bond formation is considered of primary significance in organic synthesis [5]. Among the many C-H bond activation approaches, catalytic cross-dehydrogenative-coupling (CDC) reactions are considered important primarily because of their step-economical property [6]. Selective functionalization of C-H bonds next to a nitrogen atom using the CDC approach has been explored for the synthesis of functionalized heterocycles [7].

Another important protocol for the construction of functionalized hetrocycles *via* intramolecular C-N, C-O and C-S bond formation is termed as "*β* lactam synthon" [8]. *β*-lactam (azetidin-2-one) ring is the central core of one of the most known classes of antibiotics [9] and also an important pharmacophore for a range of other bioactive compounds. Apart from their significant pharmacological effects, *β*-lactams also serve as useful intermediates in organic synthesis because of the strain energy associated with the four-membered ring making it susceptible for nucleophilic ring cleavage. The selective bond cleavage of the strained ring coupled with interesting transformations renders this fascinating molecule as a powerful building block for the synthesis of *α* and *β*-aminoacids, natural products (taxoids), alkaloids, peptidomimetics and other heterocyclic rings [10]. The purpose of present chapter is to focus on various intramolecular (C-X) bonds forming methodologies reported recently (2011-2017) for the synthesis of functionalized heterocycles with particular emphasis on *β*-lactam-synthon protocol and metal-catalyzed reactions. For convenience, the present chapter is divided into two sections *viz.* five and six membered heterocyclic scaffolds and fused heterocyclic scaffolds with subsequent sub-sections.

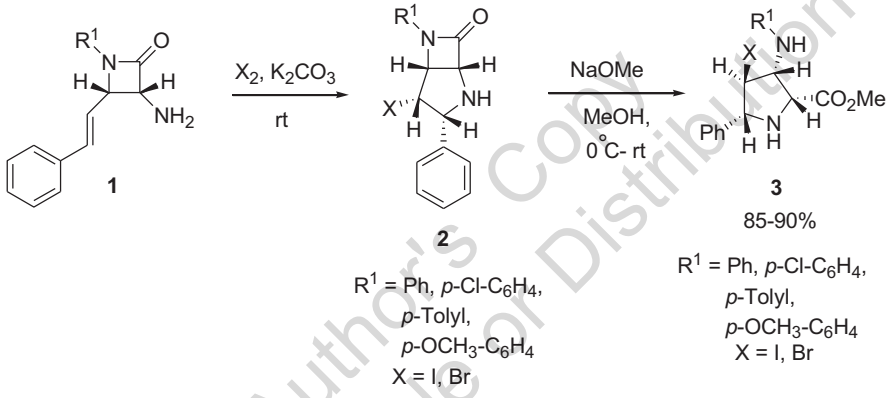
FIVE AND SIX MEMBERED HETEROCYCLIC SCAFFOLDS

Five Membered Ring with One Hetero Atom

Pyrrolidine, Pyrole and Furan-based Scaffolds

Functionalized pyrrolidine esters are essential building blocks for various natural

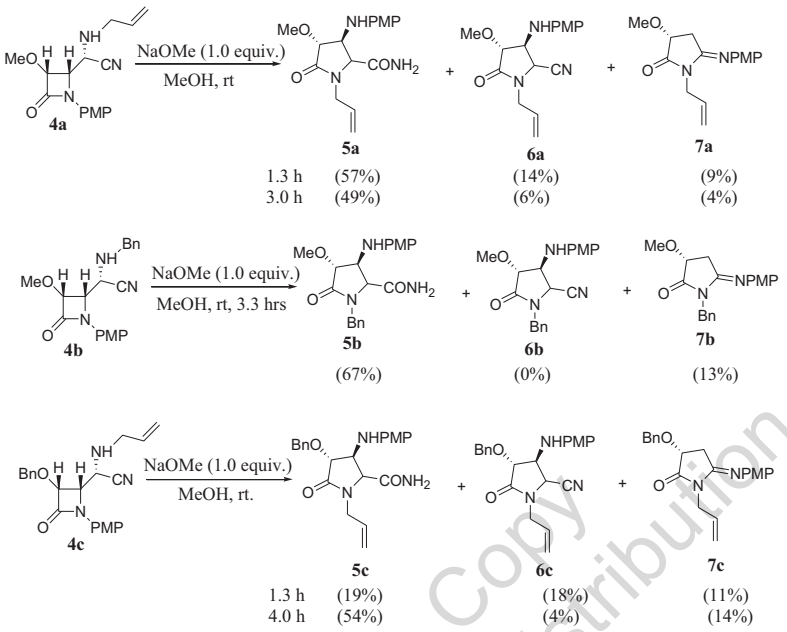
products and important pharmacophores due to their diverse biological activities [11]. Enantiopure functionalized pyrrolidines also serve as organocatalysts, chiral ligands, as well as chiral auxiliaries. Bhargava *et al*. [12] have utilized the *β*-lactam synthon protocol for the synthesis of functionalized pyrrolidine-2-carboxylic acid methyl esters from C-3 functionalized azetidin-2-one. The key step in the synthesis involved the treatment of 3-amino-azetidin-2-one **1** with iodine/bromine in the presence of potassium carbonate resulting in intramolecular ring cyclization yielding 4-halo-3-phenyl-6-aryl-2,6-diaza-bicyclo[3.2.0]heptan-7-one **2**. The amidolytic ring opening reaction of **2** with sodium methoxide in methanol at 0°C to room temperature afforded the desired 4-halo-5-phenyl-3-arylamino-pyrrolidine-2-carboxylic acid methyl ester (**3**) as depicted in (Scheme **1**).



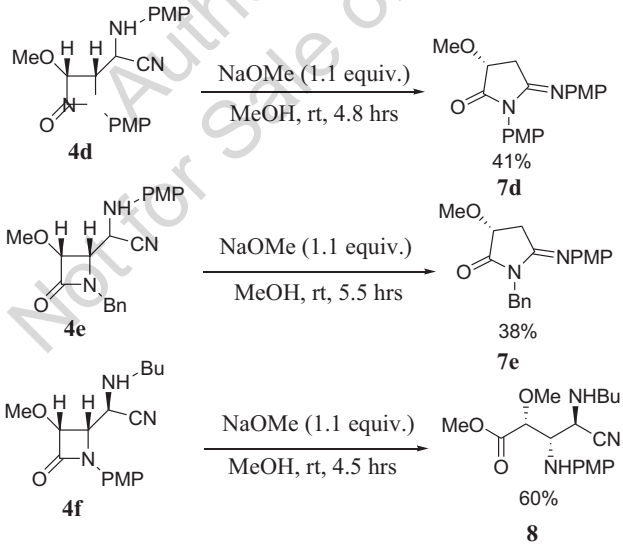
Scheme 1. Synthesis of pyrrolidine-2-carboxylic acid methyl ester **3**.

Functionalized *γ*-lactams and in particular, succinimide and pyroglutamic acid cores have emerged as scaffolds of considerable importance because of their biological relevance [13]. Alcaide and co-workers [14] have recently disclosed the utilization of *β*-lactam-*α*-aminonitriles for the stereocontrolled synthesis of *γ*-lactams and succinimide derivatives. The use of sodium methoxide to affect these transformations in case of **4a-c** resulted in the isolation of corresponding amides in good yields as depicted in (Scheme **2**).

However, 5-(arylimino) pyrrolidin-2-ones (**7d**) and (**7e**) were formed as sole products when **4d** and **4e** were employed as starting material. By contrast, the use of (*tert*-butylamino) nitrile **4f** as starting material afforded the acyclic *γ*-cyano-*β*-aminoester (**8**) *via N*1-*C*2 bond cleavage. Probably, the steric hindrance of *tert*-butyl group inhibited the intramolecular cyclization and explained the observed behavior (Scheme **3**).

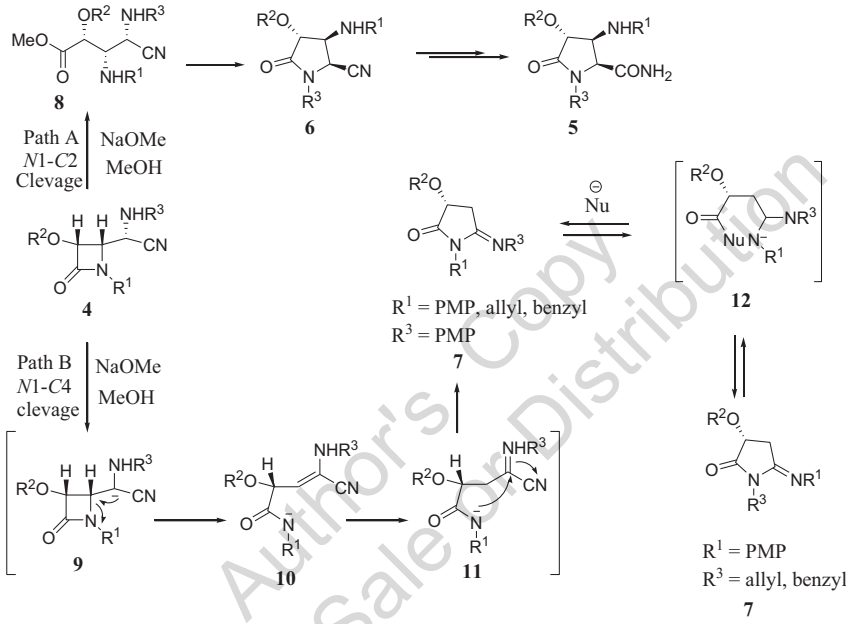


Scheme 2. Synthesis of γ-lactams and succinimide derivatives **5**, **6** and **7**.



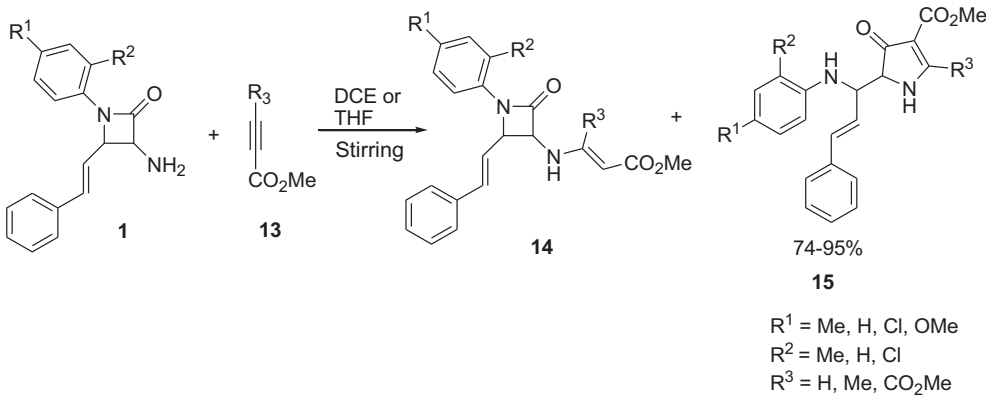
Scheme 3. Synthesis of 5-(arylimino) pyrrolidin-2-ones **7d**, **7e** and γ-cyano-β-aminoester **8**.

The isolation of different products in methoxide mediate transformation of *β*-lactam aminonitriles has shown to depend upon the nature of R^3 substituent. The presence of R^3 as aliphatic substituent facilitated the reaction *via* **Path-A** *i.e. N*1-*C*2 bond cleavage resulting in the formation of pyroglutamic acid derivatives. The introduction of R^3 as aromatic substituent suppressed the rearrangement resulting in the formation of 5-(arylimino) pyrrolidin-2-ones (**7**) *via* **Path-B** invoking *N1-C*4 bond cleavage (Scheme **4**).



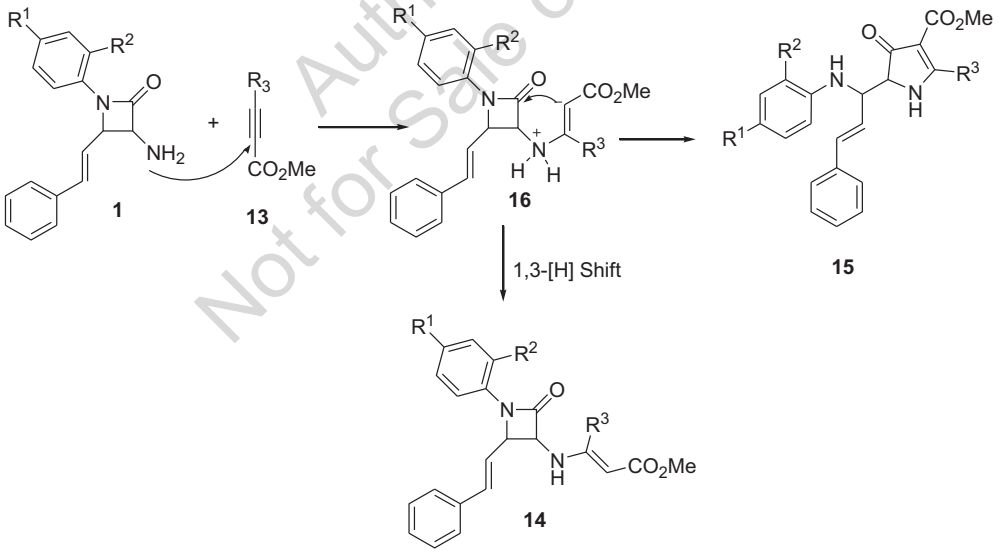
Scheme 4. Mechanistic pathway for the formation of **5**, **6**, **7** and **8**.

Pyrroles are key heterocycles having wide array of biological activities. Storniamide A for examples has been evaluated against multidrug resistance (MDR) TB whereas Nakamuric acid and marinopyrrole A and B have shown inhibitory activity against *Staphylococcus aureus* [15]. Numerous pyrrole-based drugs are present in market which increases the significance of functionalized pyrroles in heterocyclic synthesis [16]. Recently, Bhargava and co-workers [17] described a facile route for the synthesis of 4-oxo-dihydro-1*H*-pyrrole *via* tandem aza-Michael addition reactions of 3-amino-azetidin-2-ones **1** with different acetylenic esters with subsequent intramolecular amidolysis. The synthetic approach involved the treatment of variedly substituted 3-amino-azetidin-2-ones **1** with substituted acetylenic esters **13** in polar aprotic solvent such as (DCE and THF) resulting in the formation of 4-oxo-4,5-dihydro-1*H*-pyrrole ester (**15**) along with its aza Michael adduct (**14**) as depicted in (Scheme **5**).



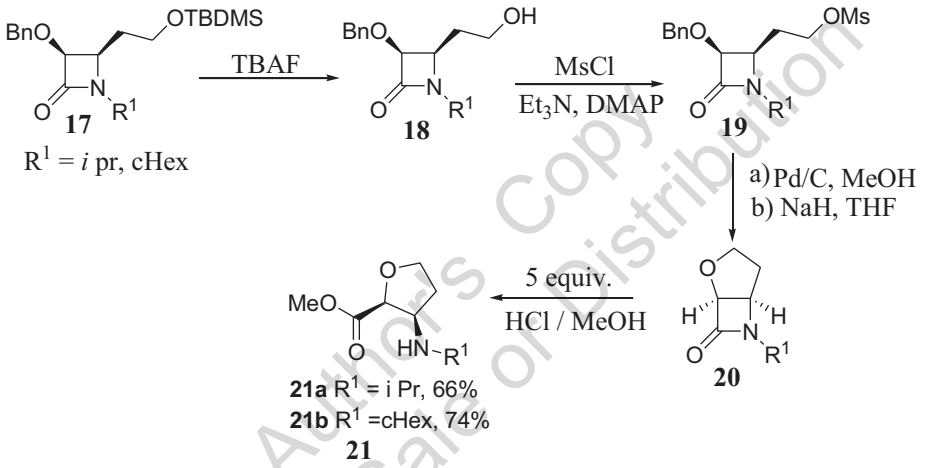
Scheme 5. Synthesis of 4-oxo-4,5-dihydro-1*H*-pyrrole ester **15**.

Mechanistically, the reaction involves an initial nucleophilic attack of the amino substituent of **1** at one of the acetylenic carbons of **13** results in intermediate **16**, which undergoes 1,3-sigmatropic shift to afford the aza-Michael adducts (**14**). 4-oxo-5-(3-aryl-1-arylamino-allyl)-4,5-dihydro-1*H*-pyrrole ester (**15**) is probably formed by nucleophilic attack of the carbanion, at the carbonyl carbon of the azetidin-2-ones as depicted in (Scheme **6**).



Scheme 6. Mechanistic pathway for the formation of **14 and 15**.

A convenient protocol for the diastereoselective synthesis of methyl *cis*-3-amino tetrahydro furan-2-carboxylates [18] has been developed *via* acid-promoted amidolysis of tetrahydrofuran-*β*-lactams **20**. An initial deprotection of **17** with *tert*-butyl ammonium fluoride (TBAF) yielded *β*-lactams **18** which were mesylated to result in *cis*-3-benzyloxy-4-(2-mesyloxyethyl)azetidin-2-ones **19**. The treatment of **19** with 20% (W/W) palladium on activated carbon afforded the corresponding *cis*-3-hydroxy-*β*-lactams which upon NaH-promoted intramolecular cyclization resulted in the desired *cis*-2-oxa-6-azabicyclo[3.2.0] heptan-7-ones **20** in good yields. The *N*1-*C*2 ring cleavage of **20** under acidic conditions yielded the corresponding methyl *cis*-3-aminotetrahydrofura--2-carboxylates (**21**) as shown in (Scheme **7**).



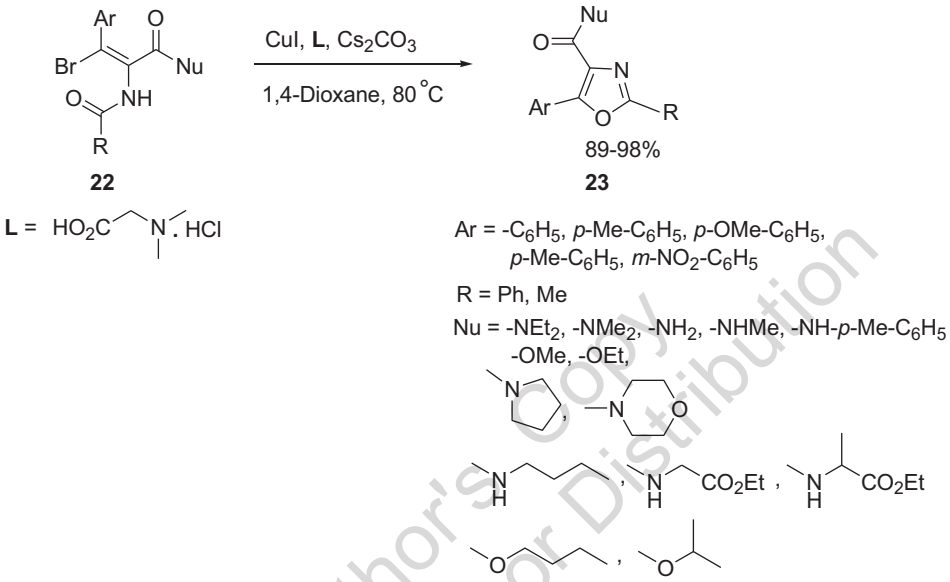
Scheme 7. Synthesis of furan-2-carboxylates **21**.

Five Membered Ring with Two Hetero Atoms

Azole-based Scaffolds

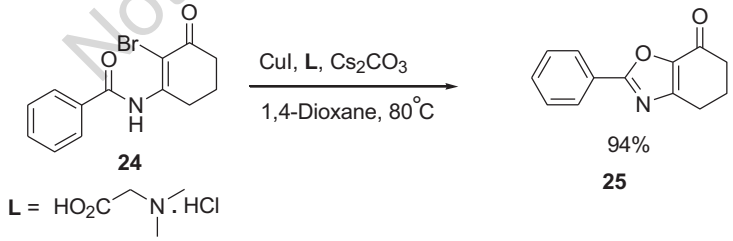
Oxazoles represent one of the most important pharmacophores due to their diverse biological activities [19]. Chang *et al*. [20] have developed a facile route for the synthesis of oxazole derivatives *via* copper(I)/amino acid catalyzed intramolecular Ullmann-type C-O coupling reaction. The synthetic approach involved the treatment of **22** with cesium carbonate (Cs_2CO_3) in 1,4-dioxane without any catalyst or ligand to result in the formation of oxazoles derivatives (**23**) in moderate yields. Further the inclusion of copper(I) iodide (CuI, 10 mol%) as a catalyst and a temperature of 90 °C significantly improved in the yield of product. It has been found that the addition of *N*,*N*-dimethyl-glycine hydrochloride as the ligand in copper-catalyzed Ullman-type reactions, at a relatively lower

temperature (80 °C) afforded the desired oxazole **23** in good yield. (Scheme **8**) The effect of substituents on the aryl ring of the substrate was also studied. It has been found that both electron-donating and electron-withdrawing groups on the aryl ring smoothly gave the corresponding oxazoles derivatives (**23**) in good to excellent yields.



Scheme 8. Synthesis of oxazoles derivatives **23**.

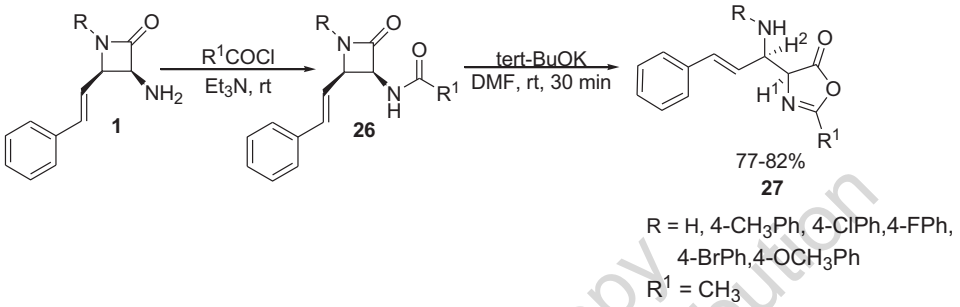
To further examine the feasibility of above method, *N*-(2-bromo-3-oxocyclohex-1-en-1-yl) benzamide **24** was subjected to the intramolecular cyclization which afforded the synthesis of 2-Phenyl-5,6-dihydro-4H-benzooxazol-7-one (**25**) in good yield (Scheme **9**).



Scheme 9. Synthesis of fused oxazoles **25**.

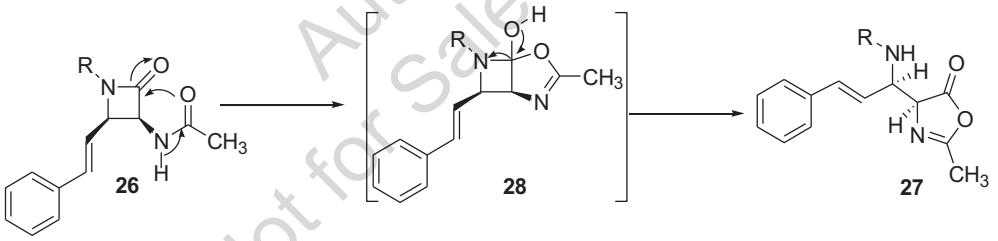
Oxazolones possess a myriad of biological activities such as anti-microbial, anti-diabetic, anti-viral, antifungal, anti-cancer, cardioprotective, anti-inflammatory,

anti-depressant, anti-HIV, anti-angiogenic, anti-convulsant, sedative, tyrosinase inhibition, fungicidal and herbicidal properties [21]. Thus, Kumar and co-workers [22] recently developed the route for the synthesis of functionally decorated oxazol-5-ones *via* β-lactam synthon protocol. The synthetic protocol involved the treatment of C-3 functionalized *N*-acylated-azetidin-2-ones **26** with potassium *tert*-butoxide in dry DMF resulting in the synthesis of corresponding oxazolones (**27**) as shown in (Scheme **10**).



Scheme 10. Synthesis of oxazolones **27**.

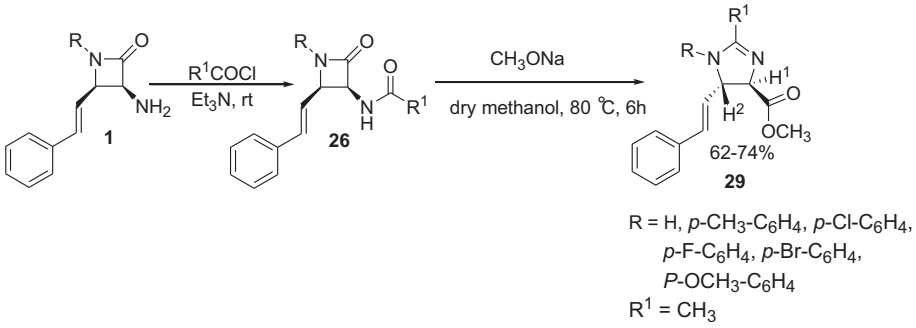
The mechanism of the reaction is thought the base-promoted generation of alkoxide ion which underwent intramolecular nucleophilic addition to produce an intermediate **28**, which upon ring opening resulting into desired 2,5-disubstituted oxazol-5-ones (**27**) as depicted in (Scheme **11**).



Scheme 11. Mechanistic pathway for the formation of **27**.

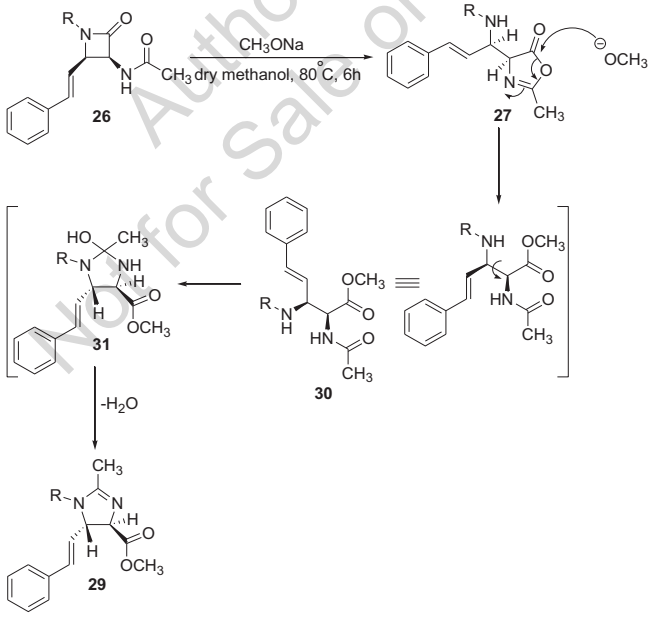
Imidazole represents a significant core fragment found in varied pharmaceuticals having unique physical and biological properties [23]. This heterocyclic motif, has fascinated the synthetic chemists because of its reactivity and relevance in diverse areas such as agrochemicals, artificial acceptors, supramolecular ligands and biomimetic catalysts. Many marketed drugs such as Candesartan, Omeprazole, Pimobendan, Losartan, Eprosartan, and Trifenagrel possess functionalized imidazoles. Kumar *et al*. [22] have recently explored the β-lactam synthon protocol for the synthesis of 1,2,4,5-substituted dihydroimidazoles. The synthetic methodology involved the heating of *N*-acetyl-azetidin-2-ones **26** with

sodium methoxide at 80 °C for 6h to afford the corresponding 1,2,4,5-substituted dihydroimidazoles (**29**) as shown in (Scheme **12**).



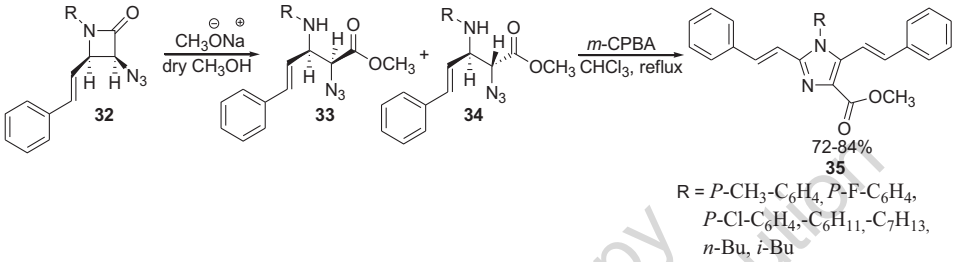
Scheme 12. Synthesis of 1,2,4,5-substituted dihydroimidazoles **29**.

Mechanistically, the reaction involved an initial intramolecular amidolysis of **26** to result in the formation of corresponding oxazol-5-ones **29** which upon methoxide-promoted ring opening afforded the corresponding ester **30**. The aminoester **30** *via* C-C bond rotation resulted in another intermediate **31** with subsequent loss of water to form 1,2,4,5-dihydroimidazole (**29**) as shown in (Scheme **13**).



Scheme 13. Mechanistic pathway for the formation of **29**.

Kumar *et al*. [24] have described the utility of *β*-lactam synthon protocol for the synthesis of 1,2,4,5-tetra-substituted imidazoles *via m*-chloro-perbenzoic acid (*m*-CPBA) promoted tandem Michael addition-intramolecular cyclization of functionalized 2-azido-*β*-amino esters. Thus refluxing of *β*-aminoesters **33** and **34** in dry chloroform in the presence of *m*-CPBA yielded the corresponding 1-aryl/alkyl-2,5-distyryl-1*H*-imidazole-4-carboxylic acid methyl ester (**35**) as shown in (Scheme **14**).



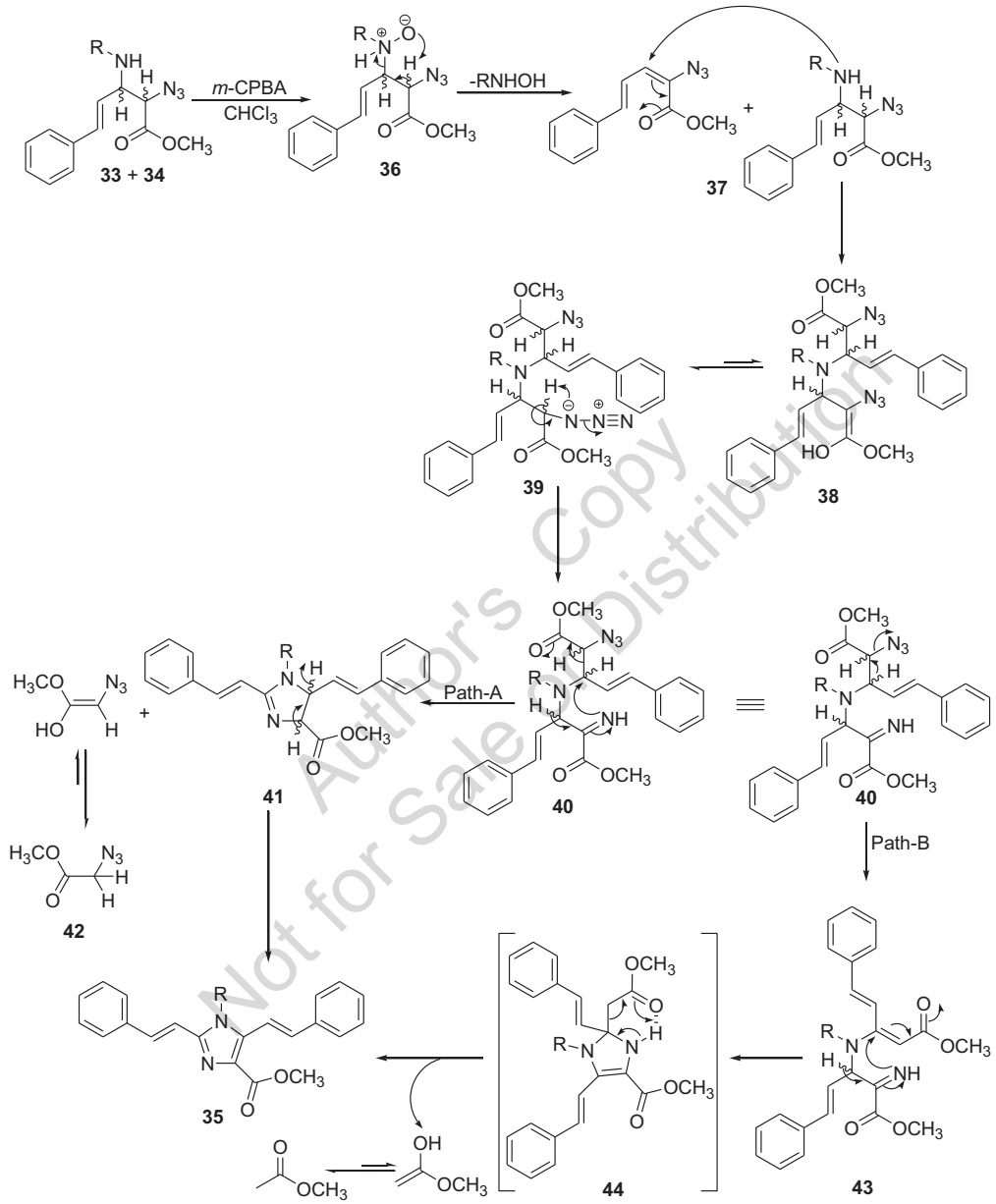
Scheme 14. Synthesis of Imidazole-4-carboxylic acid methyl ester **35**.

Mechanistically, the reaction is thought to proceed with an initial formation of *N*-oxide **36** with subsequent Cope-elimination to yield the corresponding 2-azido-*α*,*β*-unsaturared ester **37**. This upon Michael-addition with second molecule of *β*-amino-ester resulted in an intermediate **39** which undergoes enolization and subsequent loss of a nitrogen molecule leading to the formation of another imine-ester-intermediate **40** which may follow either **Path-A** or **Path-B** as depicted in (Scheme **15**) resulting in the formation of corresponding 1-aryl/alkyl-2,5-distyryl-1*H*-imidazole-4-carboxylic acid methyl ester (**35**).

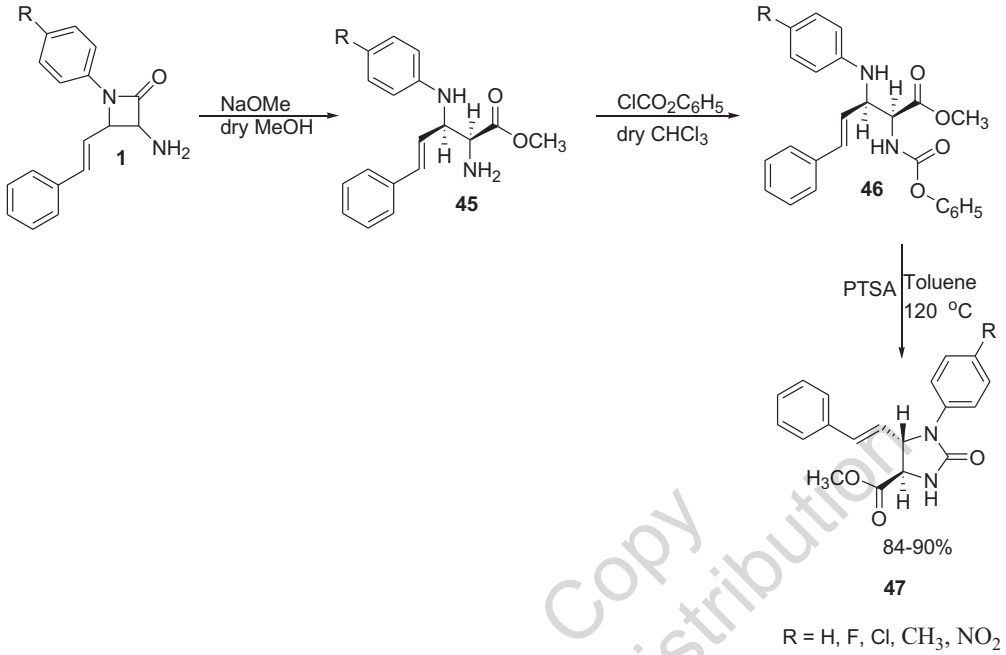
Kumar and co-workers [25] have used *β*-lactam-synthon protocol for the synthesis of imidazolidin-2-ones **47**. The synthetic methodology involved base promoted ring amidolysis of racemic *cis*-3-amino-azetidin-2-ones **1** resulting in corresponding *cis*-*α*-aminoesters **45** in a diastereoselective manner which were then reacted with phenyl chloroformate with subsequent heating in toluene in the presence of *p*-toluene sulfonic acid affording diastereoselective access to 1,4,5-trisubstituted *trans*-imidazolidin-2-ones (**47**) as shown in (Scheme **16**).

Thiohydantoin based heterocycles represent an interesting class of compounds in medicinal and agricultural chemistry with wide array of biological properties. Kumar *et al*. [26] have developed the route for the synthesis of thiohydantoin *via* *β*-lactam synthon protocol. Thus, the room temperature stirring of azetidin-2-one **48** with sodium methoxide in dry methanol for 50-55 min interestingly led to the formation of 3-alkyl/aryl-5-(3-phenyl-allylidene)-2-thioxo-imidazolidin-4-ones

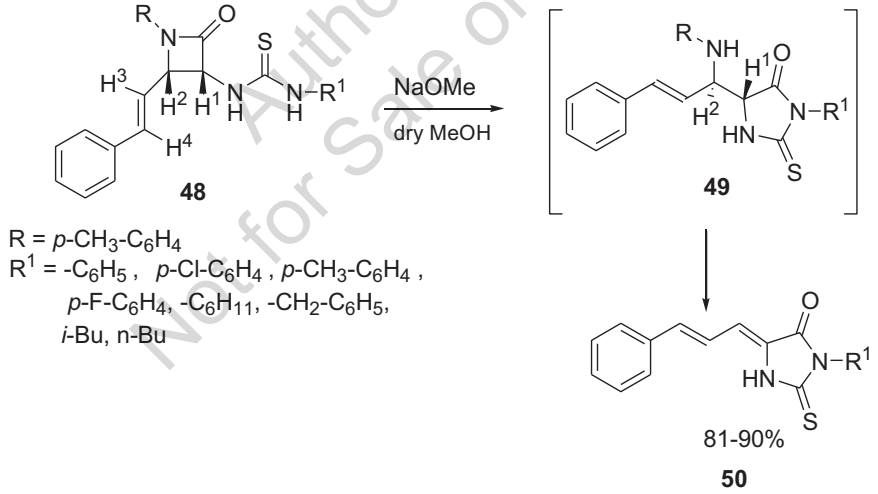
(**50**) in good to excellent yields (Scheme **17**).



Scheme 15. Mechanistic pathway for the formation of **35**.



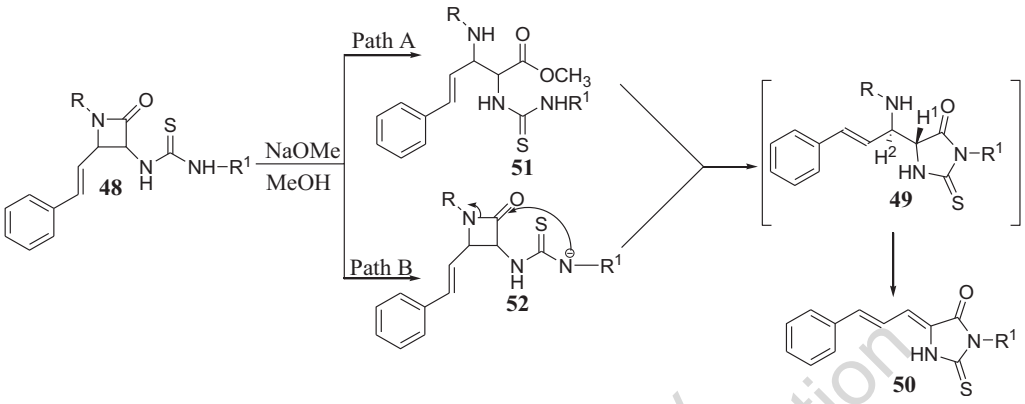
Scheme 16. Synthesis of imidazolidin-2-ones **47**.



Scheme 17. Synthesis of 3-alkyl/aryl-5-(3-phenyl-allylidene)-2-thioxo-imidazolidin-4-ones **50**.

Mechanistically, it has been found that the reaction may involve either methoxide-assisted tandem intermolecular amidolysis-intramolecular cyclization (**Path-A**) or the generation of thiouriedo anion (**Path-B**), leading to the

intermediate **49** with subsequent *β*-elimination resulting in formation of 3-alkyl/aryl-5-(3-phenyl-allylidene)-2-thioxo-imidazolidin-4-ones (**50**) (Scheme **18**).



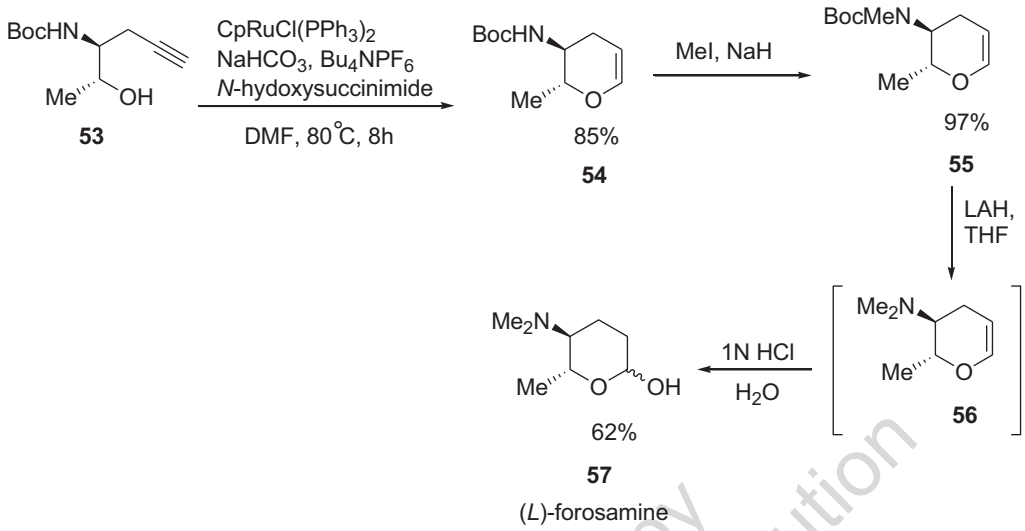
Scheme 18. Mechanistic pathway for the formation of **50**.

Six Membered Ring with One Hetero Atom

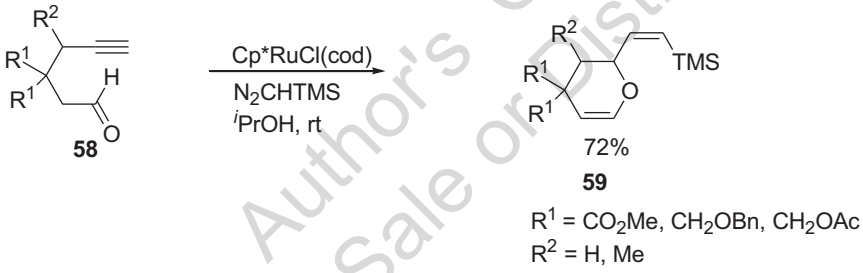
Pyran-based Scaffolds

Pyrans are privileged heterocyclic structures found in numerous simple and sophisticated bioactive natural products [27]. 3,4-Dihydropyrans (3,4-DHP), for example, are useful precursors for tetrahydropyrans, glycals, and typical building blocks in carbohydrate chemistry [28]. Over the years, a great deal of effort has been done to synthesize these relevant structures. Metal-catalyzed intramolecular addition of oxygenated nucleophiles to unsaturated carbon-carbon bonds is one of the most innovative approaches for the synthesis of such heterocycles. Zacuto *et al*. [29] have developed the protocol for the synthesis of 3,4-dihydropyrans *via* Ru-catalyzed cycloisomerization of 2-amino-4-alkyn-1-ol. Ru-catalyzed cycloisomerization reaction of amino alcohol **53** *via* treatment with $CpRu(PPh_3)_2Cl$, $NaHCO_3$, *N*-hydroxysuccinimide, and Bu_4NPF_6 in DMF at 80 °C for 8h resulting in the synthesis of desired 3,4-dihydropyran (**54**) which was further utilized in the total synthesis of *L*-forosamine (**57**) as depicted in (Scheme **19**).

Saa and co-workers [30] have recently explored the synthesis of 2-vinyl-3-4-dihydropyrans through Ru(II)-catalyzed cyclization. The treatment of alkynals **58** with [Cp*RuCl(cod)] in presence of tri(methylsilyl)diazomethane ($TMSCHN_2$) yielded the desired 2-vinyl-3,4-dihydropyrans (**59**) as shown in (Scheme **20**).



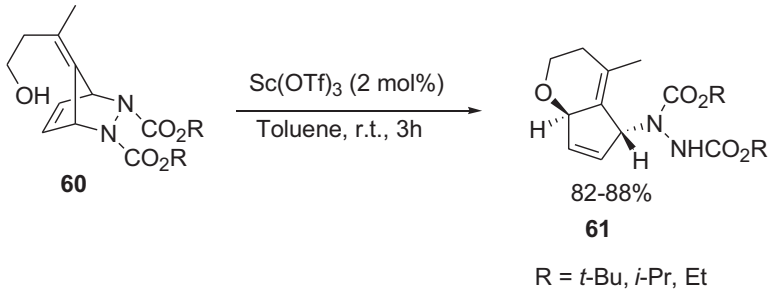
Scheme 19. Synthesis of dihydropyran and *L*-forosamine **54** and **57**.



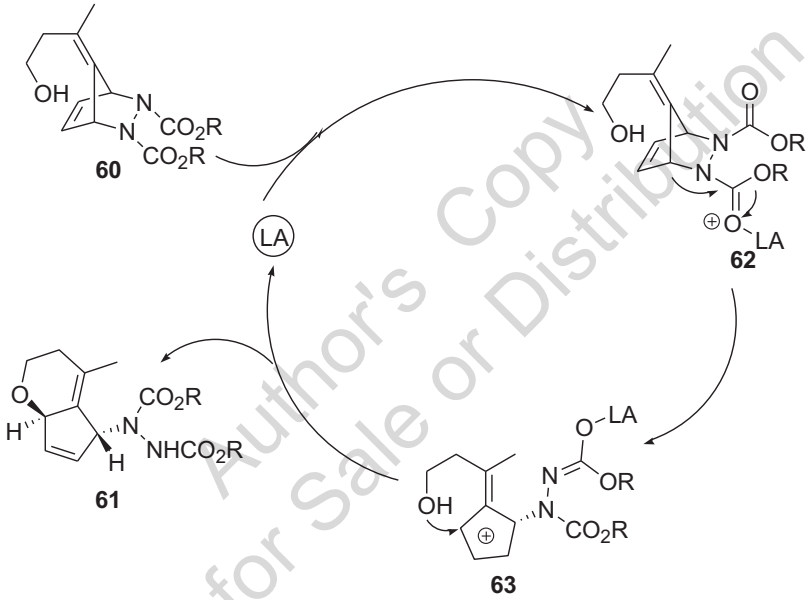
Scheme 20. Synthesis of dihydropyran **59**.

Radhakrishnan *et al*. [31] have utilized diazanorbornene systems bearing a flexible hydroxy group in Lewis acid-catalyzed intramolecular rearrangement giving cyclopentannulated dihydro-2*H*-pyrans. The synthetic methodology involved the treatment of diazabicyclic alkene **60** with $Sc(OTf)_3$ in toluene to yield the desired tetrahydrocyclopenta[b]pyrans (**61**) in good yields *via* intramolecular cyclization (Scheme **21**).

Mechanistically, it was found that the Lewis acid intially coordinated to an ester carbonyl group of the diazabicyclic alkene **60** to generate the intermediate **62** with subsequent cleavage of the adjacent C-N bond to yield a transient allylic cationic species **63**. Intramolecular cyclization *via* nucleophilic attack by the hydroxyl group gave the fused tetrahydrocyclopenta[b]pyran (**61**) as depicted in (Scheme **22**).



Scheme 21. Synthesis of tetrahydrocyclopenta[b]pyrans **61**.



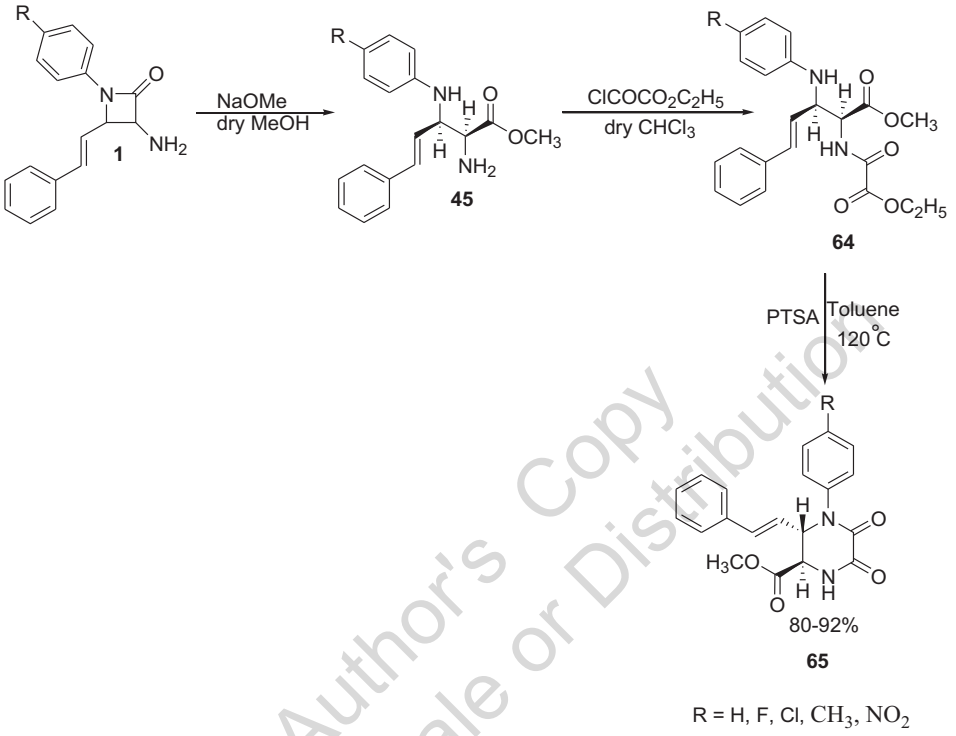
Scheme 22. Mechanistic pathway for the formation of **61**.

Six Membered Ring with Two Hetero Atoms

Piperazine-based Scaffolds

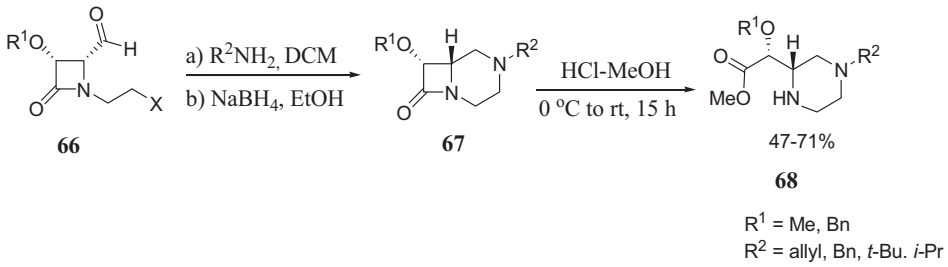
Kumar *et al*. [25] have reported the synthesis of functionally decorated piperazine-5,6-diones *via* methoxide-promoted amidolysis of azetidin-2-one **1**. Base-promoted ring amidolysis of racemic *cis*-3-amino-azetidin-2-ones **1** resulting in corresponding *cis*-*α*-aminoesters **45** in a diastereoselective manner which then reacted with ethyl oxalylchloride with subsequent heating in toluene in the presence of *p*-toluene sulfonic acid resulting in the diastereoselective

formation of 1,2,3-trisubstituted *trans*-piperazine-5,6-diones (**65**) in good to excellent yields as shown in (Scheme **23**).



Scheme 23. Synthesis of piperazine-5,6-diones **65**.

De Kimpe *et al*. [32] have also described the potential of acid-promoted amidolysis of azetidin-2-one **66** for the synthesis of chiral piperazines **68**. The reaction involved an initial imination of azetidin-2-ones **66** with primary amines with subsequent reduction using $NaBH_4$ in ethanol to afford the bicyclic *β*-lactams **67**. The acid-promoted amidolysis of *β*-lactam ring was done by using HCl gas in MeOH to yield methyl (*R*)-[(*S*)-piperazin-2-yl]acetates (**68**) as depicted in (Scheme **24**).



Scheme 24. Synthesis of chiral piperazines **68**.

FUSED HETEROCYCLIC SCAFFOLDS

Fused Heterocycles with One Hetero Atom

Indole, Indoline, Quinolone, Isoquinolone, Isoquinoline and Cyclic nitrone-based scaffolds

3-Acylindoles constitute important core structures in scaffolds with biological and pharmaceutical importance [33]. For example, Pravadoline (Fig. **1, I**) marketed as an anti-inflammatory and analgesic drug. Ramosetron (Fig. **1, II**) has been used as a serotonin 5-HT3 receptor antagonist for the treatment of nausea and vomiting. 3-Aroylindole compound BPR0L075 (Fig. **1, III**) exhibits potent *in vitro* activity against a variety of human tumor cell lines. Consequently, the development of an efficient method for the synthesis of 3-acylindoles has become a subject of great interest [34].

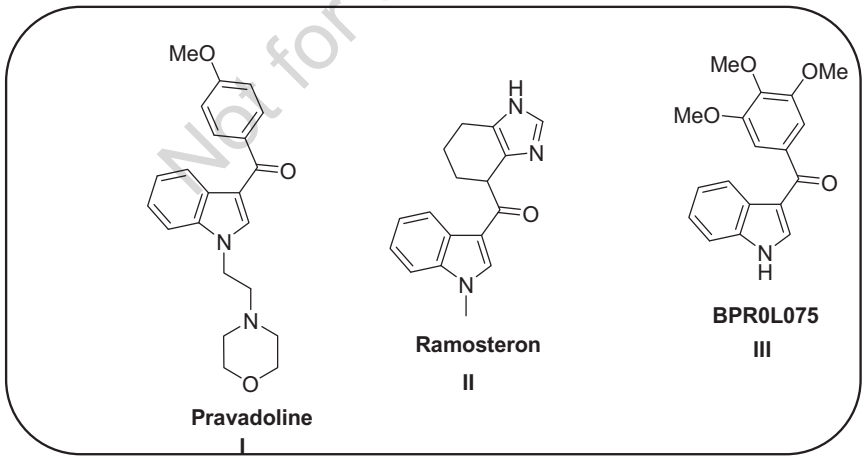
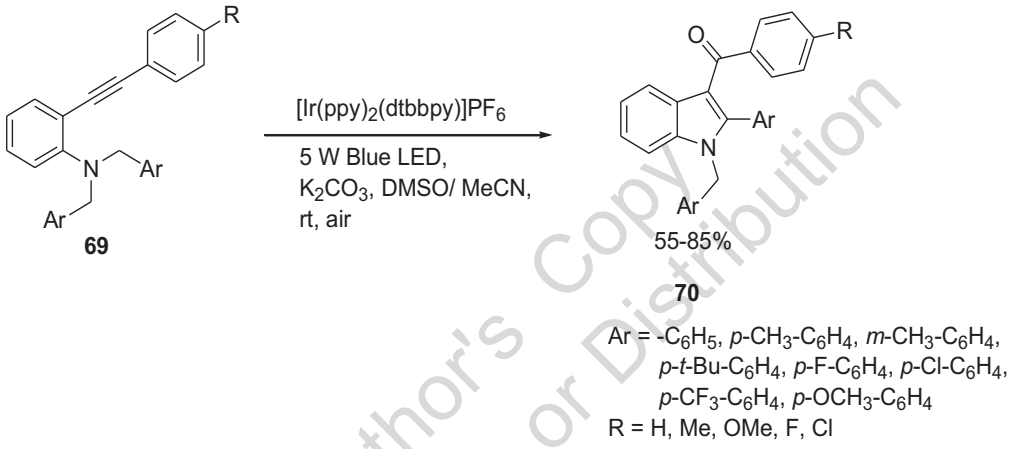


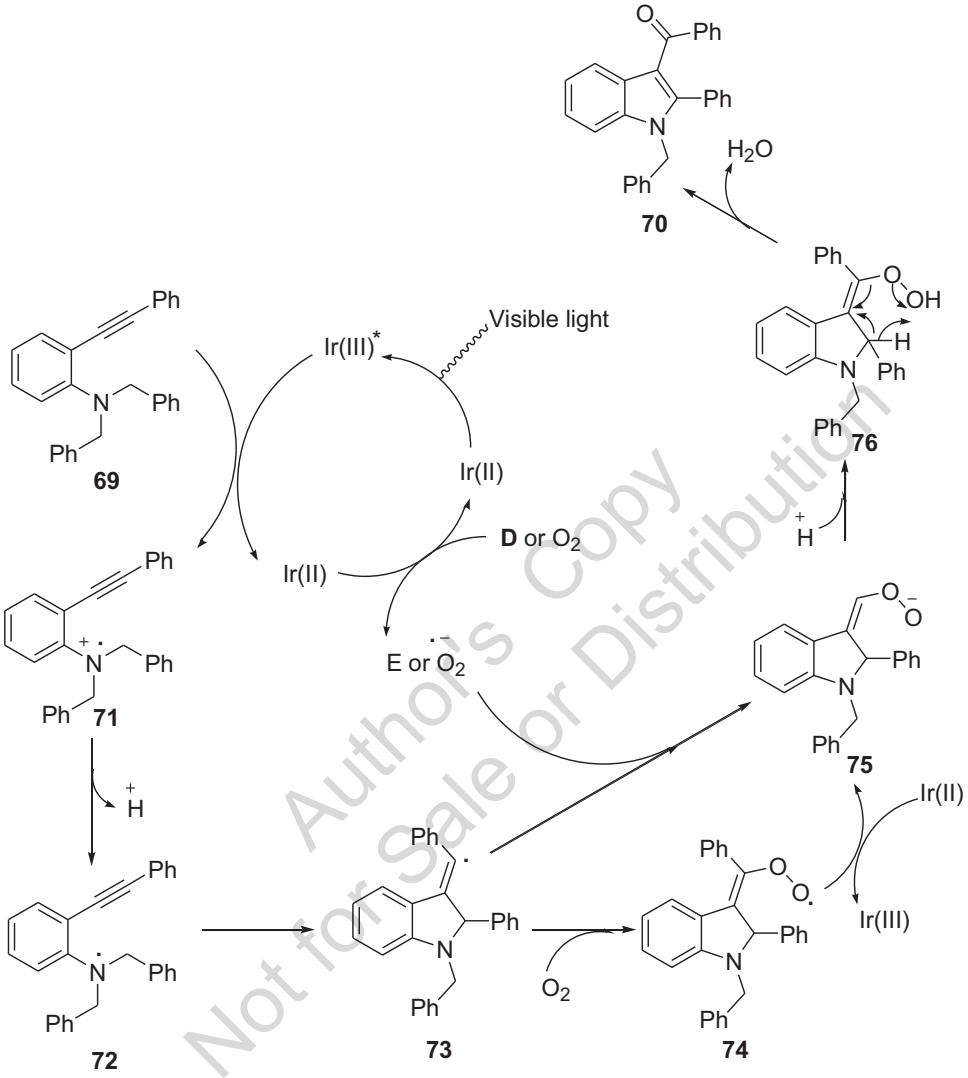
Fig. (1). Compounds having 3-acylindoles.

Zhou *et al*. [35] have recently developed the protocol for the simultaneous formation of C-C and C-O bonds through an intramolecular oxidation of *O*-alkynylated *N,N*-dialkylamines to result in the synthesis of 3-acylindoles. The synthetic approach involved the irradiation of *N,N*-dibenzyl substituted substrates **69** in DMSO with 5W blue LED in the presence of photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ resulting in the synthesis of 3-acylindoles (**70**). It has been found that when the reaction was carried out in the 1:1 mixture of MeCN and DMSO, the transformation proceeded quite smoothly in 16h, with reduced amount of catalyst (Scheme **25**).



Scheme 25. Synthesis of 3-acylindoles **70**.

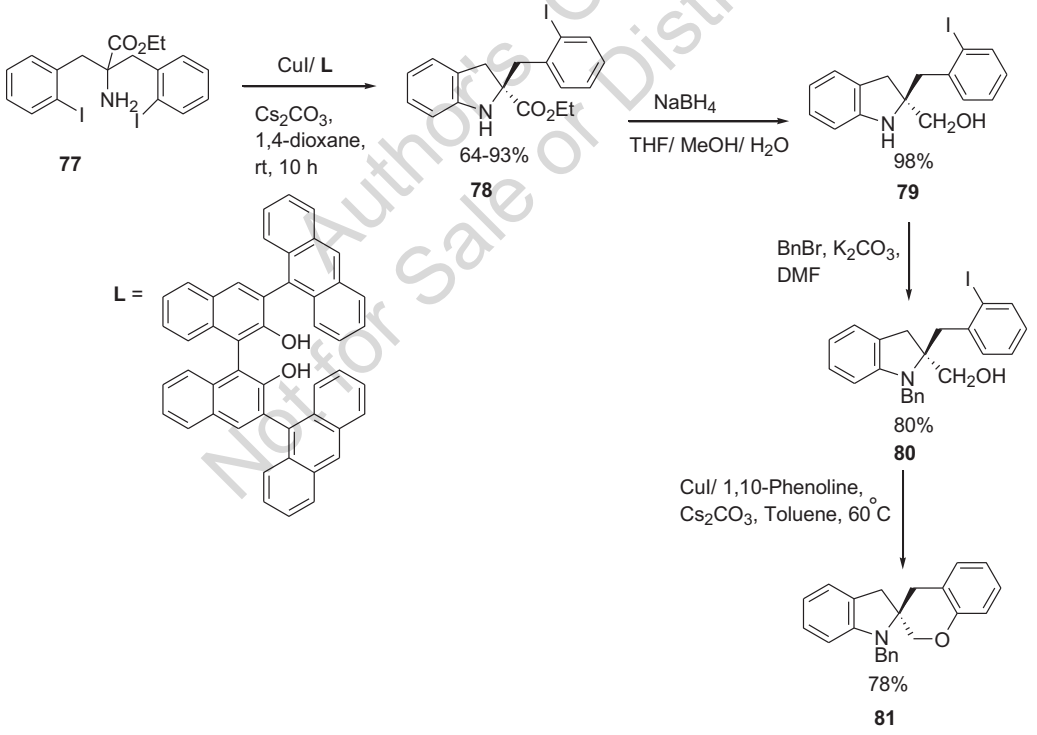
Mechanistically, it has been found that the photoexcitation of Ir(III) by visible-light generated excited Ir(III)*. Further, single-electron transfer (SET) took place from substrate **69** to Ir(III)* generating Ir(II) and radical cation **71**, which underwent facile deprotonation to give α-amino alkyl radical **72**. Intramolecular addition of radical **72** to C-C triple bonds occurred to produce vinyl radical **73**. Intermediate **73** was captured by oxygen, leading to the formation of superoxide radical **74** which was reduced by Ir(II), regenerating the Ir(III) catalyst along with concomitant formation of intermediate **75**. Another possible route to access **75** was the regeneration of Ir(III) *via* aerobic oxidation, followed by addition of superoxide radical anion $O_2^{\bullet-}$ to vinyl radicals **73**. Finally, the protonation of **75** gave vinyl hydrogen peroxide **76** where intramolecular abstraction of the hydrogen atom afforded the 3-acylindoles (**70**) as depicted in (Scheme **26**).



Scheme 26. Mechanistic pathway for the formation of **70**.

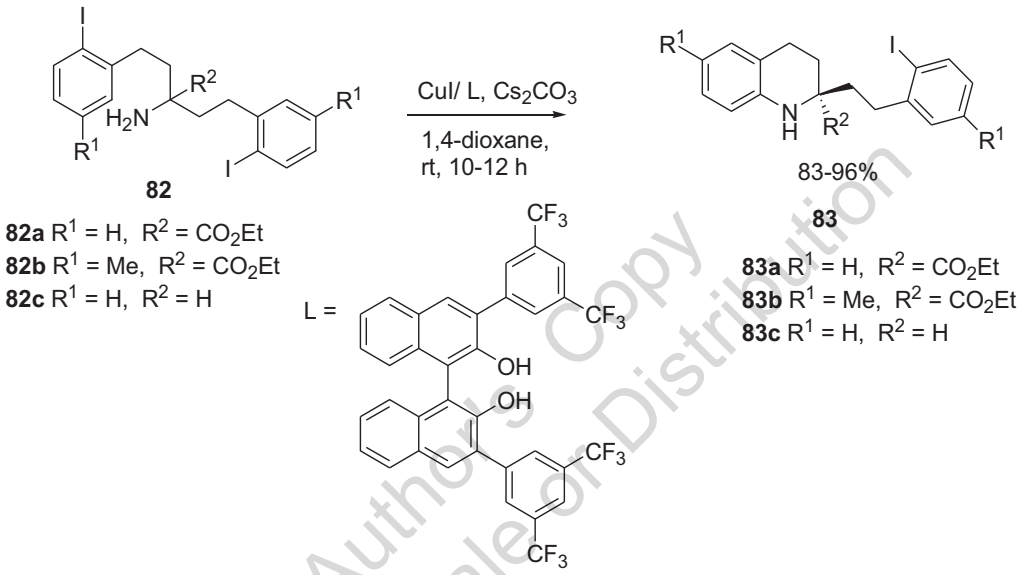
Yu and co-workers [36] have envisioned the copper-catalyzed intramolecular Ullmann C-N coupling reaction of 1,3-bis(2-iodoaryl)propan-2-amines with (*R*)-BINOL-derived ligands leading to the enantioselective formation of indolines and 1,2,3,4-tetrahydroquinolines. Thus, the reaction of ethyl 2-(2-iodobenzyl--2-amino-3-(2-iodophenyl)propanoate **77** with 10 mol% CuI in presence of (*R*)-

BINOL-derived ligand in 1,4-dioxane at room temperature, yielded the desired product indoline (**78**) in 54% yield with 40% ee. The reactions were repeated under the same conditions by utilizing ligands having bulky aryl substituents in the 3,3-positions of the BINOL, which however did not improve the conversion ratio. It was observed that the ligands which bearing electron-withdrawing trifluoromethyl groups in the aryl rings, accelerated the reaction rate and afforded the desired product **78** in relatively higher yields due to enhancement of the acidity of the ligand which facilitates deprotonation and coordination with CuI. Based on these observations, two ligands bearing bulkier substituents at 3,3′-positions than previous ligands were utilized for the reaction. It has been found that the CuI-L-catalyzed reaction proceeded very smoothly and afforded the desired product in both high yields and with good enantioselectivity. A range of solvents such as MeCN, THF, and toluene were explored with the best result in terms of enantioselectivity was observed using 1,4-dioxane. Cs_2CO_3 was proved to be the best base to accelerate the reaction rate. Further, the synthesized indoline was utilized in the synthesis of spirocyclic compound (**81**) as shown in (Scheme **27**).



Scheme 27. Synthesis of indoline **81**.

Encouraged by the success of enantioselective synthesis of chiral indolines, the above methodology was further explored for the enantioselective synthesis of 1,2,3,4-tetrahydroquinoline derivatives as depicted in (Scheme **28**). It has been found that **82a** and **82b** could undergo desymmetrization easily with 20 mol% CuI as catalyst and 40 mol% **L**, to afford the corresponding 1,2,3,4-tetrahydroquinolines **83a** and **83b** bearing quaternary chiral centers with high yields and excellent enantioselectivity.



Scheme 28. Synthesis of tetrahydroquinoline **83**.

4-Aryltetrahydroisoquinolines have been found to exhibit important biological properties [37], for example, Nomifensine (Fig. **2, IV**) and Dichlorofensine (Fig. **2, V**) are effective inhibitors of reuptake of central neurotransmitters such as Serotonin, Norepinephrine, and dopamine at postsynaptic receptors.

Tummanapalli and co-workers [38] have recently explored the protocol for the synthesis of 4-substituted tetrahydroisoquinolone *via* scandium(III) triflate-promoted intramolecular ring expansion of aziridines. The synthetic approach involved the treatment of *N*-benzyl azridines **84** with 1.2 equiv of $Sc(OTf)_3$ in 1,2-dichloroethane at 90 °C for 1h resulting in synthesis of corresponding 4-substituted tetrahydroisoquinolones (**85**) as shown in (Scheme **29**).

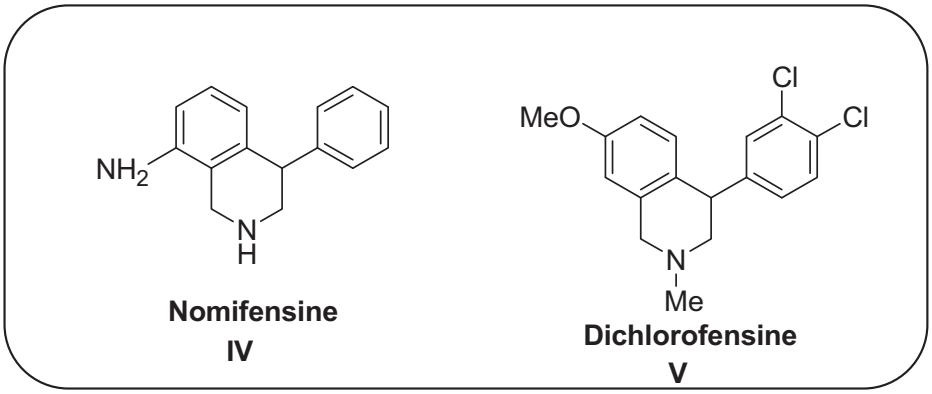
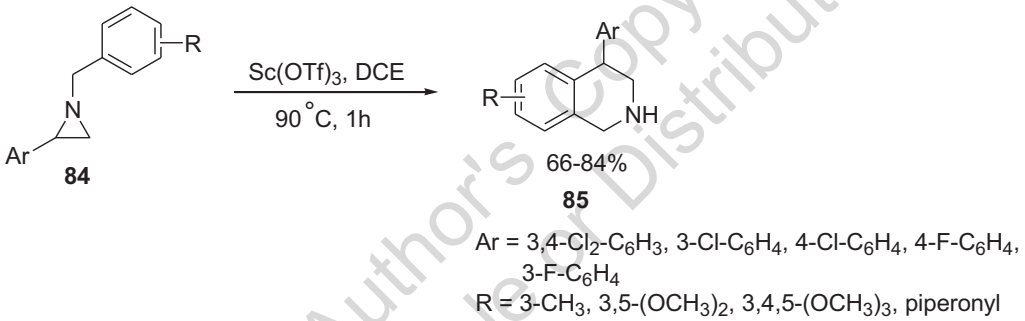
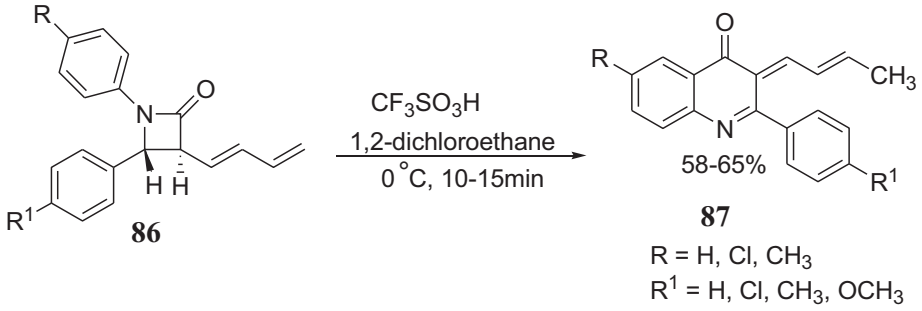


Fig. (2). Nomifensine and Dichlorofensine having 4-aryltetrahydroisoquinolines moiety.



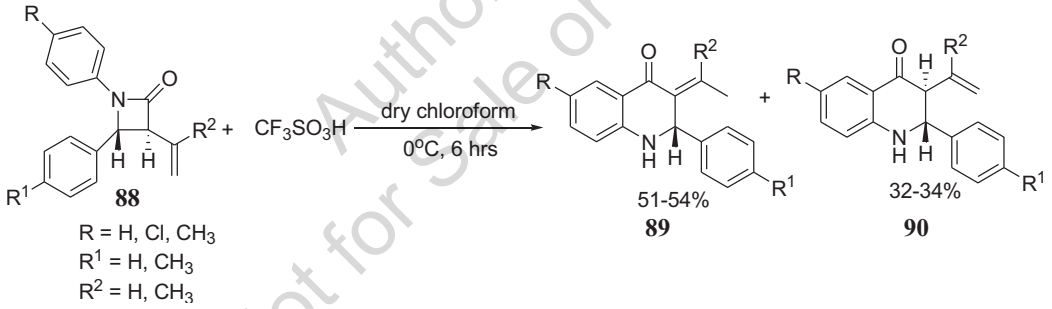
Scheme 29. Synthesis of tetrahydroisoquinolones **85**.

Quinoline-4-ones, because of their synthetic accessibility and possibility of functionalization at different positions of the molecule, exemplify an attractive platform for the design of combinatorial libraries of functionally enriched scaffolds with a range of pharmacological profiles. Kumar *et al*. [39] utilized *β*-lactam synthon protocol for single-pot synthesis of quinolin-4(3*H*)-ones. The synthetic methodology involved the treatment of *trans* 3-butadienyl-azetidin-2-ones **86** with 1.0 mmol of triflоromethanesulphonic acid (triflic acid) in dry 1,2-dichloroethane at 0°C for 10-15 min affording 3-(but-2-enylidene)-2-arylquinolin-4(3*H*)-one (**87**) as depicted in (Scheme **30**).



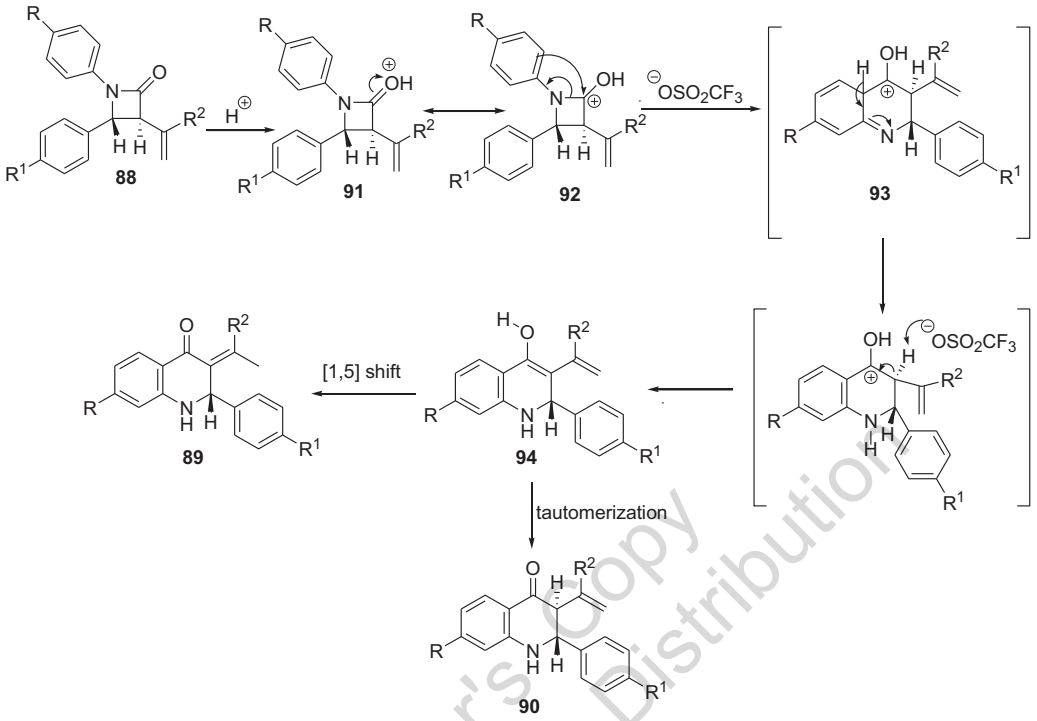
Scheme 30. Synthesis of quinolin-4(3*H*)-ones **87**.

The above methodology has been further extended to 3-vinyl/isopropenyl-1, 4-diaryl-azetidin-2-ones **88** as substrate and resulted in the formation of C-3 functionalized quinolin-4(1*H*)-ones (**89**) and (**90**). The treatment of C-3 vinyl/isopropenyl-*β*-lactams **88** with 1.0 mmol of trifluoromethanesulphonic acid (triflic acid) in dry chloroform at 0°C for 6h resulted in the formation of a mixture of 3-ethylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones (**89**) and 3-vinyl-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones (**90**) [40] as depicted in (Scheme **31**).



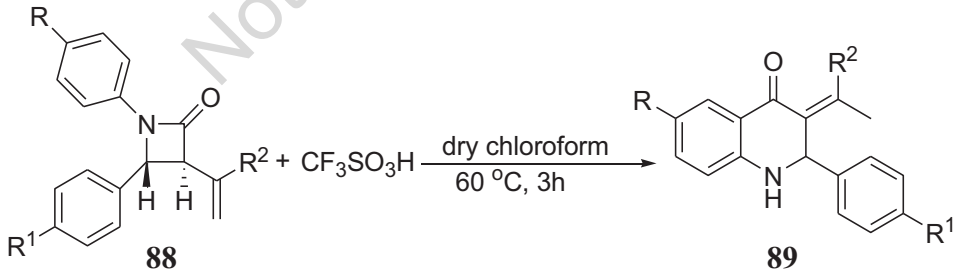
Scheme 31. Synthesis of quinolin-4(3*H*)-ones **89** and **90**.

Mechanistically, the initially protonation of 3-vinyl/isopropenyl-*β*-lactam **88** generated the carbenium ion intermediate **92** which underwent Fries rearrangement *via* an *ortho* attack of the aromatic substituent on the nitrogen atom, resulting in a ring expanded intermediate **93**. The aromatization of **93** accompanied by proton abstraction generated the intermediate **94** which underwent [1, 5] sigmatropic shift or tautomerization yielding a mixture of 3-ethylidene/isopropylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones (**89**) and 3-vinyl/isopropenyl-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones (**90**) respectively, as shown in (Scheme **32**).



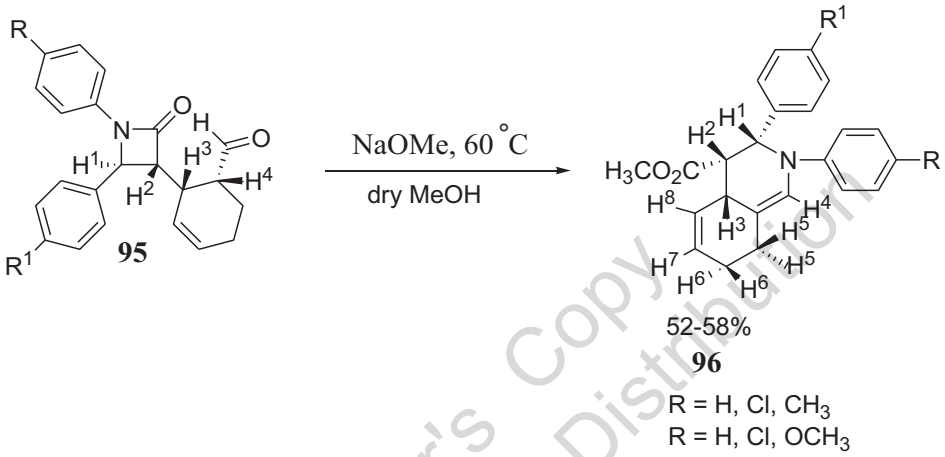
Scheme 32. Mechanistic pathway for the formation of **89** and **90**.

Interestingly, the similar reactions when carried out under reflux in dry chloroform led to the exclusive formation of **89** in excellent yields without the formation of **90** even in traces due to the higher thermodynamic stability of **89** as compared to **90** at higher temperature because of the presence of conjugation in **89** (Scheme **33**).



Scheme 33. Exclusive formation of **89** as compared to **90**.

A convenient protocol for the diastereoselective synthesis of substituted hexahydroisoquinolines and hexahydroisoquinolones *via* inter/intramolecular amidolysis of C-3 functionalized *β*-lactam ring was reported by Kumar and co-workers [41]. The treatment of *β* -lactam synthon precursor **95** with sodium methoxide at 60 °C for 1 h resulted in the isolation of corresponding hexahydro-isoquinoline-4-carboxylic acid methyl esters (**96**) as depicted in (Scheme **34**).

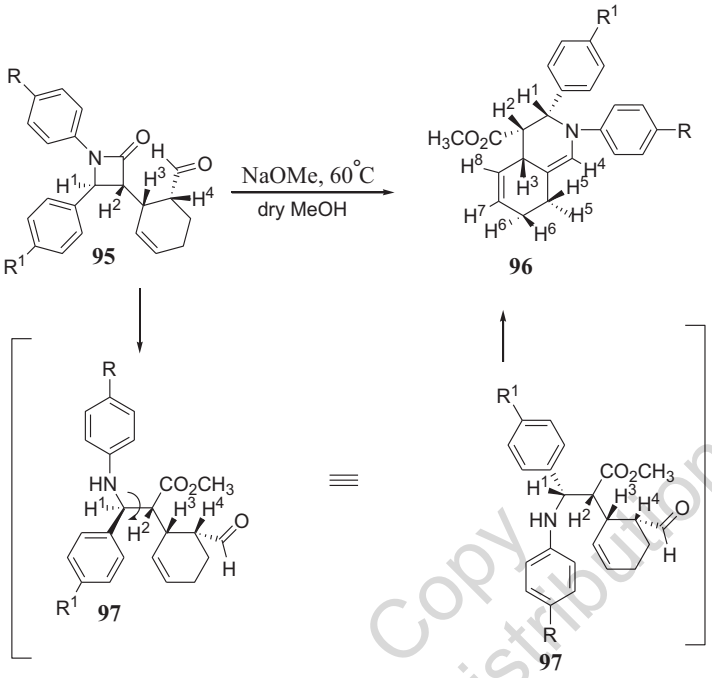


Scheme 34. Synthesis of hexahydroisoquinolines **96**.

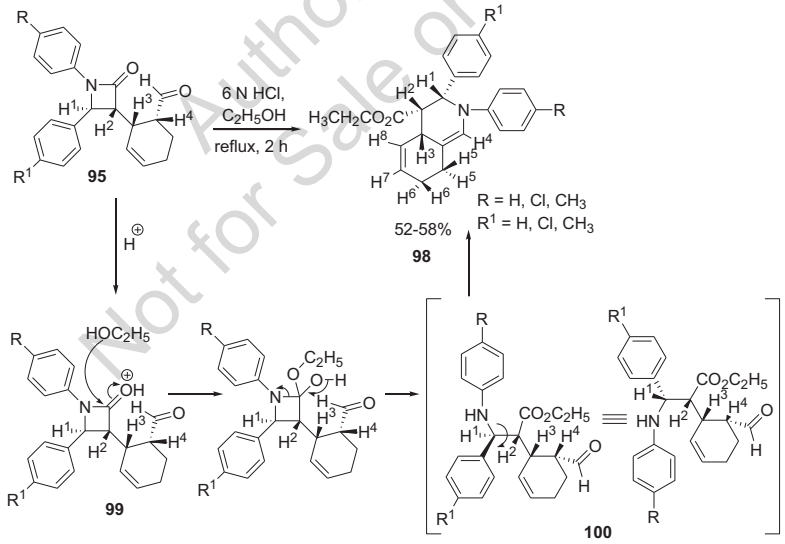
Mechanistically, the reaction proceeded *via* methoxide-promoted *β*-lactam ring amidolysis to result in the corresponding *β*-aminoesters **97** *in situ*, which underwent intramolecular nucleophilic addition with the aldehydic carbonyl followed by dehydration to afford the corresponding hexahydro-isoquinoline-4-carboxylic acid methyl esters (**96**) as shown in (Scheme **35**).

Further, acid promoted *β*-lactam ring amidolysis was also carried out affording hexahydro-isoquinoline-4-carboxylic acid ethyl esters (**98**) as shown in (Scheme **36**).

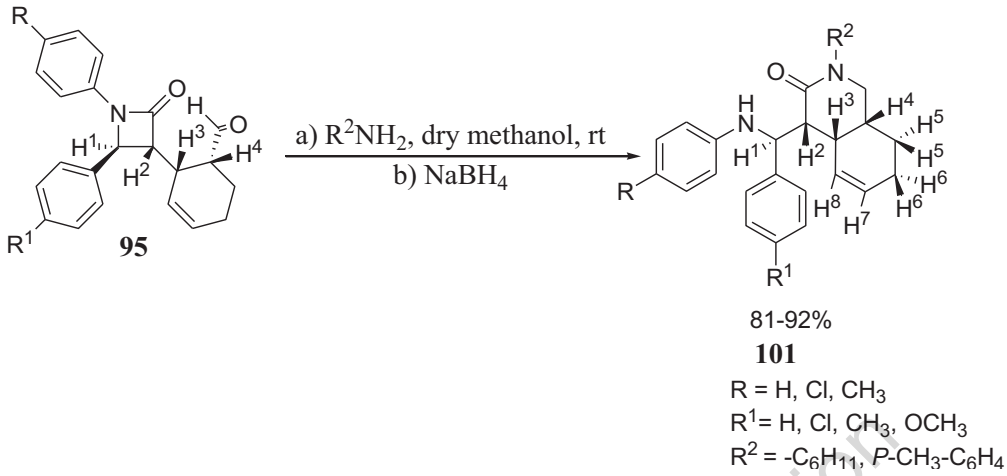
The diastereoselective synthesis of functionalized hexahydro-2*H*-isoquinoline-3-ones (**101**) was developed by Kumar and co-workers *via* $NaBH_4$-promoted intramolecular ring amidolysis of **95**. The synthetic protocol involved an initial condensation reaction of **95** with primary amines *via p*-toluidine/cyclohexylamine to generate the corresponding imine which was reduced *in situ* by the addition of sodium borohydride ($NaBH_4$) leading to the formation of desired hexahydro-2*H*-isoquinoline-3-ones (**101**) without the isolation of corresponding amines. (Scheme **37**)



Scheme 35. Mechanistic pathway for the formation of **96**.



Scheme 36. Synthesis of hexahydroisoquinoline **98**.

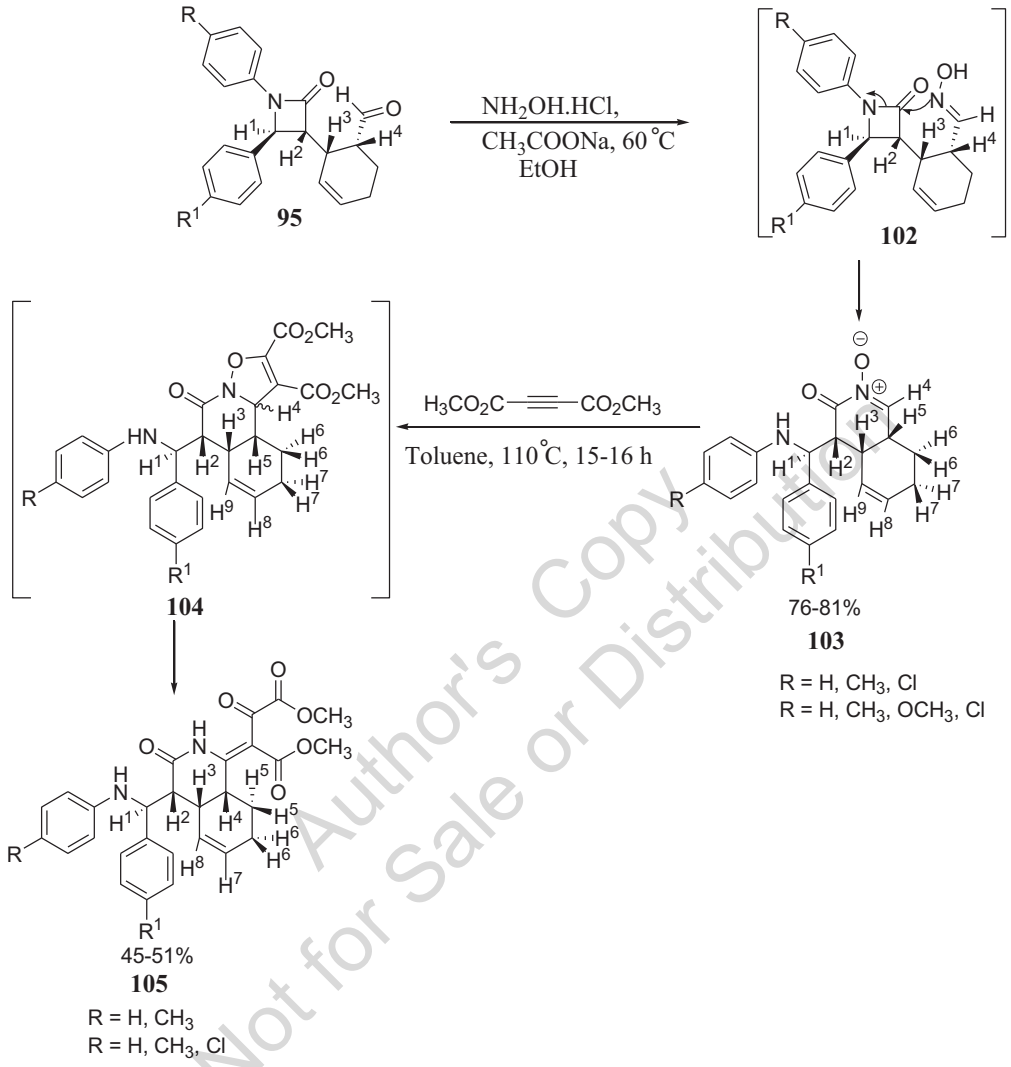


Scheme 37. Synthesis of hexahydroisoquionolones **101**.

Apart from its well established potential to undergo 1,3-dipolar cycloaddition, cyclic nitrones constitute an important class of heterocyclic scaffolds with myriad of biological and therapeutic activities including antitumor, neuroprotective, anti-stroke, suppression of age-associated degeneration and as spin trapping reagents in the identification of transient radicals. Thus, *β*-lactam synthon precursor **95** was utilized for the synthesis of six membered cyclic (*E*)-endo-aldonitrones (**103**) [42]. The key step in the synthesis involved the refluxing of C-3 functionalized *β*-lactam **95** with a solution of hydroxyl amine hydrochloride and sodium acetate resulting in the isolation of diastereoselective six membered cyclic (*E*)-endo-aldonitrones (**103**) *via* intermediate **102**, which was further explored in 1,3-dipolar cycloaddition reactions with dimethylacetylene dicarboxylate (DMAD) leading to the isolation of corresponding 2-oxo-3-[3-oxo-4-(aryl-arylamino-methyl)-3,4,4a,7,8,8a-hexahydro-2*H*-isoquinolin-1-ylidene]-succinic acid dimethyl ester (**105**) as shown in (Scheme **38**).

Carbazole-based Scaffolds

Carbazole motif has drawn the attention of chemists due to its various applications such as bioactive alkaloids [43, 44] (Fig. **3**) and electronic materials [45]. Therefore new synthetic methods are highly desirable for the preparation of carbazoles. Chang *et al*. [46] have reported the synthesis of carbazoles *via* intramolecular oxidative C-N bond formation of *N*-substituted amidobiphenyls under Cu-catalyzed conditions using hypervalent iodine(III) as an oxidant.



Scheme 38. Synthesis of (*E*)-endo-aldonitrones **103**.

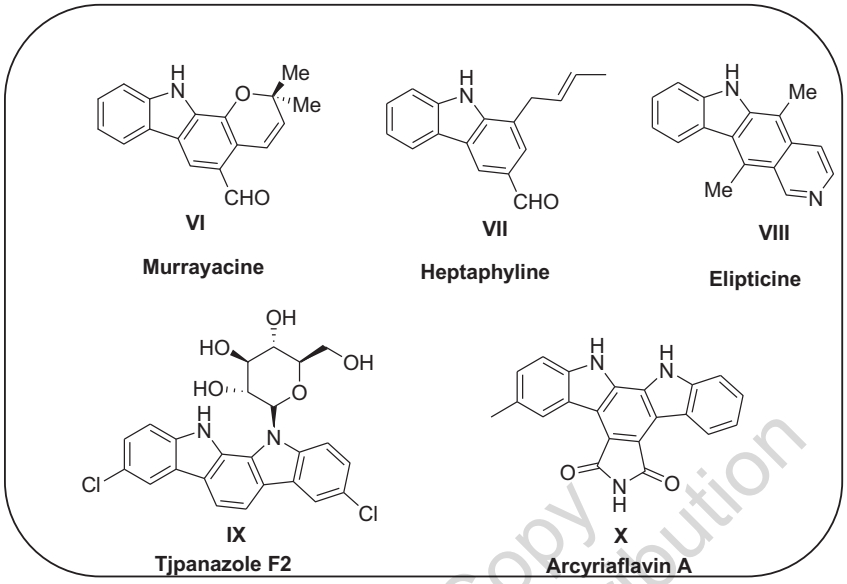
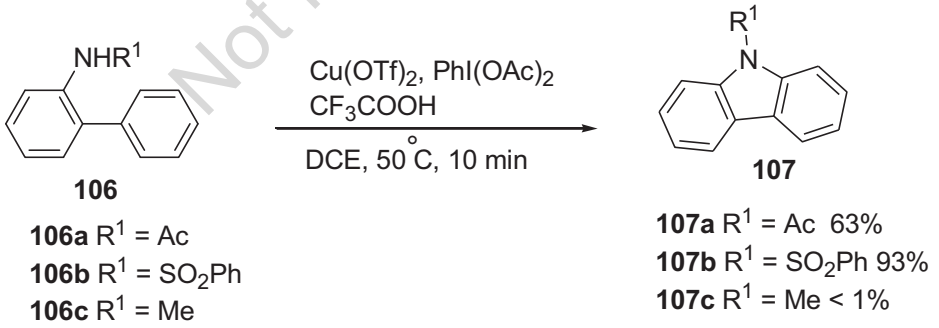


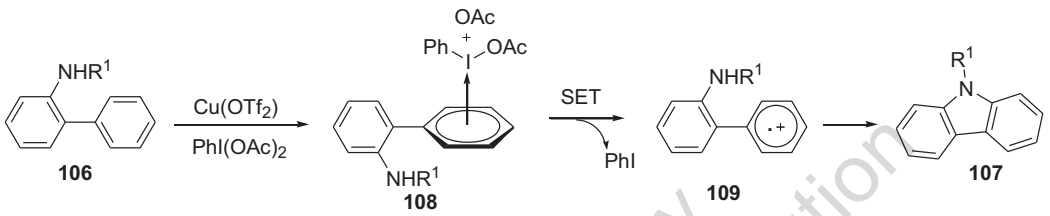
Fig. (3). Biologically active alkaloids having carbazole moiety.

A range of catalysts as well as oxidants were employed to optimize the reaction conditions. Thus, the reaction of 2-acetamidobiphenyl **106a** with copper(II) triflate as catalyst and $PhI(OAc)_2$ as an oxidant gave the desired *N*-acetylcarbazole (**107a**). An improvement in the yields was observed by replacing *N*-acetyl with *N*-sulphonyl group along with addition of trifluoroacetic acid. However best result in term of yield was obtained using $Cu(OTf)_2$ as catalyst and $PhI(OAc)_2$ as an oxidant. Furthermore, the introduction of electron-donating substituent at *N*-1 (e.g.**106c**) deteriorated the reaction yield as depicted in (Scheme **39**).



Scheme 39. Synthesis of *N*-acetylcarbazole **107**.

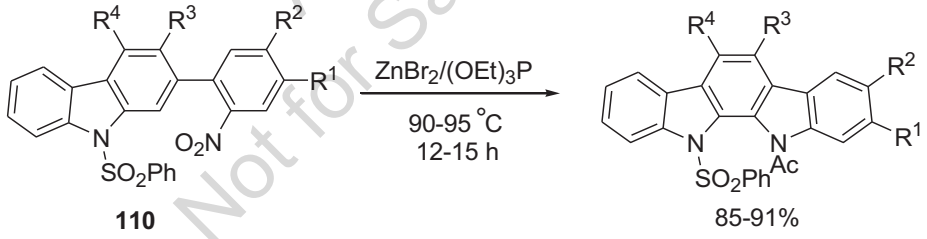
Mechanistically, it has been found an aromatic cation radical **109** was generated by a single electron transfer, through a charge-transfer π-complex **108**. It was demonstrated that aromatic cation radicals can be introduced when hypervalent iodine(III) reagents react with electron-rich arenes such as *para*-substituted phenol, ethers and thiophenes derivatives where subsequent trapping of the aromatic cation radicals has been done with certain nucleophiles such as $TMSN_3$ or mesitylene to yield the corresponding carbazoles (**107**) as depicted in (Scheme **40**).



106 108 109 107

Scheme 40. Mechanistic pathway for the formation of **107**.

Mohanakrishnan and co-workers [47] have developed the synthetic route for indolocarbazole analogs *via* nitrene insertion and thermal electrocyclization reactions. The synthetic protocol involved the triethylphosphite-mediated nitrene insertion to carbazole **110** in the presence of 1 equiv of $ZnBr_2$ at 90-95°C for 12-15 h resulting in the formation of the corresponding indolocarbazoles (**111**) as depicted in (Scheme **41**).

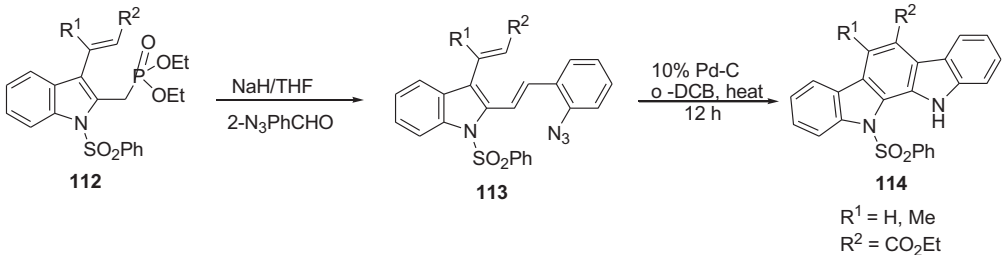


110 85-91%

111

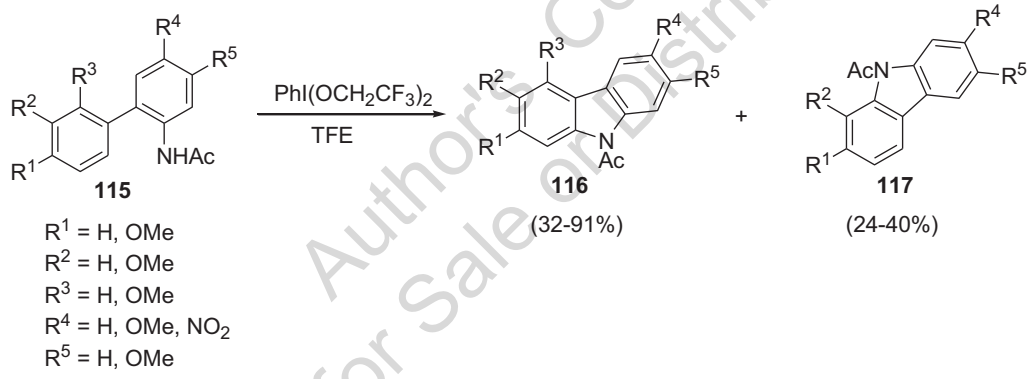
Scheme 41. Synthesis of indolocarbazole **111**.

Further, consecutive electrocyclization and nitrene insertion reaction has been carried out with 2-azidophenylvinylindole **113** in o-DCB in the presence of 10% Pd-C affording the desired indolocarbazole (**114**) as show in (Scheme **42**).



Scheme 42. Synthesis of indolocarbazole **114**.

Nishiyama *et al*. [48] have explored new synthetic route for carbazoles *via* oxidative cyclization of diaryl derivatives with electrochemically generated hypervalent iodine oxidant. The key step in the synthesis involved the reaction of corresponding diaryl derivatives **115** with $PhI(OCH_2CF_3)_2$ in TFE resulting in the formation of mixture of carbazoles (**116**) and (**117**), the ratio being dependent upon the substituents attached to aromatic rings (Scheme **43**).



Scheme 43. Synthesis of carbazole **116** and **117**.

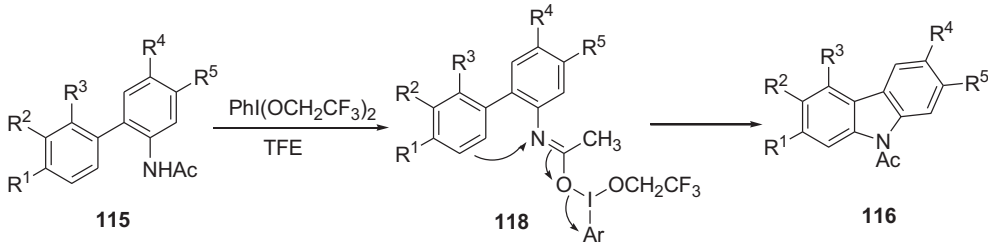
Mechanistically, the SN^2 attack of the amide oxygen to the oxidant gave the imidate-type intermediate **118**, with subsequent intramolecular nucleophilic attack from the adjacent aromatic ring to achieve the desired cyclized product (**116**) as shown in (Scheme **44**).

Fused Heterocycles with Two Hetero Atom

Benzoxazinone, Benzothiazine, Benzothiazepines and Benzodiazepinones Scaffolds

4*H*-3,1-benzoxazin-4-one skeleton is found in a numerous pharmaceutically

active natural products [49]. 2-Substituted 4*H*- 3,1-benzoxazin-4-ones have been reported to act as chymotrypsin inactivators, inhibitors of human leukocyte elastase and serine proteases as shown in (Fig. **4**). In this regard, their syntheses have attracted much interest from both organic and pharmaceutical chemists.



Scheme 44. Mechanistic pathway for the formation of **116**.

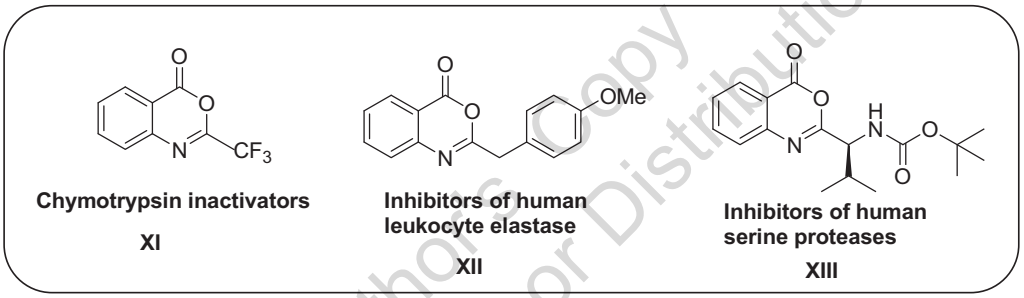
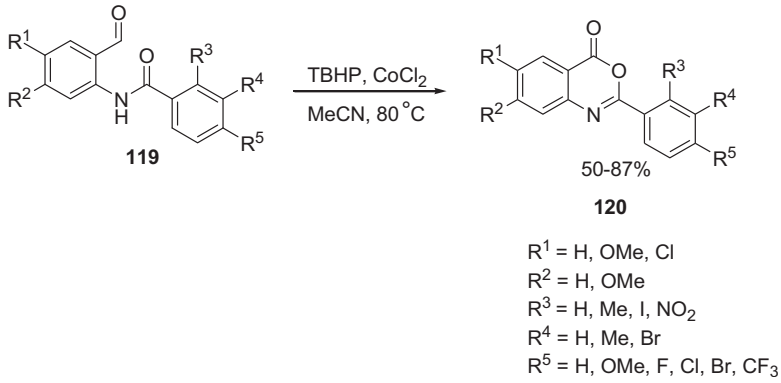


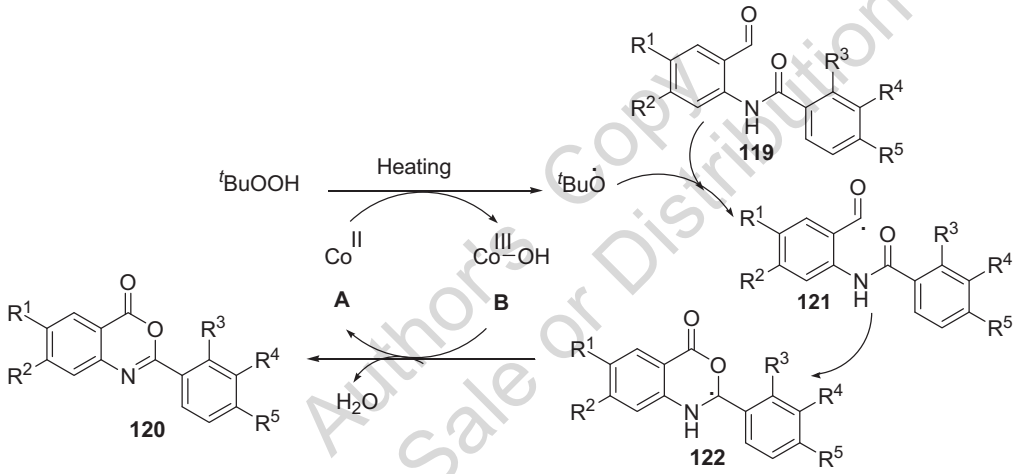
Fig. (4). Bioactive compounds containing 4*H*-3,1-benzoxazin-4-one moiety.

Du and co-workers [50] have developed a new approach for the construction of 4*H*-3,1-benzoxazin-4-ones *via* TBHP/$CoCl_2$-mediated intramolecular oxidative C-O bond forming reaction. The synthetic methodology involved the treatment of substituted *N*-(2-formylphenyl)benzamide **119** with $CoCl_2$ (0.1 equiv) as the catalyst and TBHP (5.0 equiv) as oxidant in MeCN under refluxing conditions affording substituted 4*H*-3,1-benzoxazin-4-one (**120**) in good yield as shown in (Scheme **45**).

Mechanistically, it was observed that the bond dissociation of TBHP gave the *tert*-butoxy and hydroxy radicals, which upon treatment with **A**, generating intermediate **B**. Further, the abstraction of hydrogen from aldehyde **119** by the *tert*-butoxy radical resulting in formation of acyl radical **121**, which underwent a carbon-oxygen bond forming reaction to result in another radical **122**. A second hydrogen abstraction from **122** by the hydroxy radical, which was released when **B** was converted back into **A**, led to the desired product **120** along with the generation of Co^{II} and one molecule of H_2O (Scheme **46**).



Scheme 45. Synthesis of benzoxazin-4-one **120**.



Scheme 46. Mechanistic pathway for the formation of **120**.

Benzothiazine, an important heterocyclic scaffolds having benzene ring attached to the six-membered heterocyclic thiazine has attracted the attention of organic medicinal chemists due to their various pharmacological activities. Various benzothiazine-based compounds have been reported to act as potent anti-inflammatory agents. For example, well known anti-inflammatory drugs such as meloxicam (Fig. **5, XIV**) and piroxicam (Fig. **5, XV**) belong to this category of compounds.

Pal *et al*. [51] recently explored the $AgNO_3$-promoted the intramolecular ring closure of *o*-(1-alkynyl)benzenesulfonamides *via* a regioselective C-N bond forming reaction leading to the formation of 3-substituted benzothiazine derivatives. The synthetic investigation involved the intramolecular cyclization of *o*-(1-alkynyl)benzenesulfonamides **123** with $AgNO_3$ in DMF at 80 °C resulting in

the synthesis of corresponding 3-substituted benzothiazines (**124**) as depicted in (Scheme **47**).

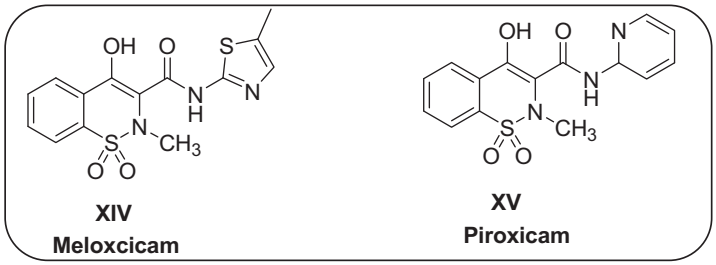
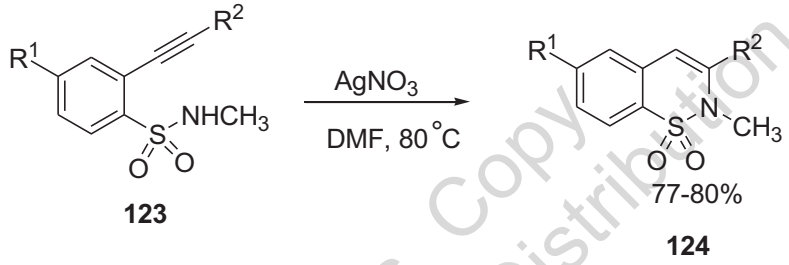


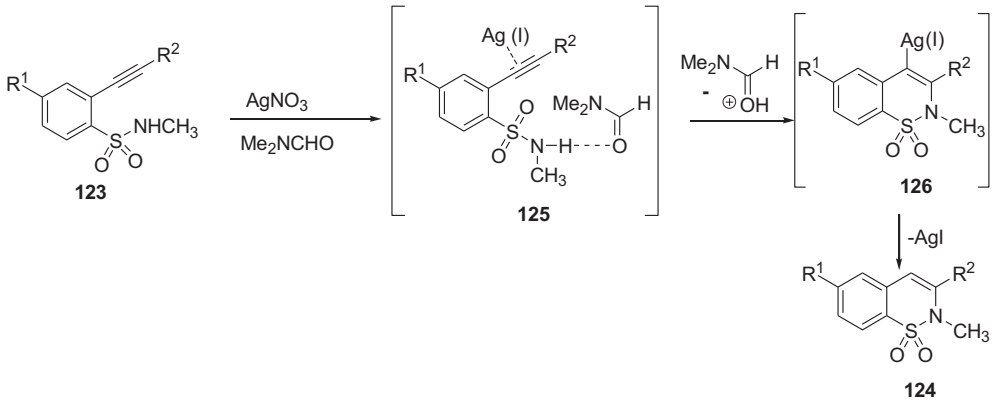
Fig. (5). Anti inflammatory drugs containing benzothiazine moiety.



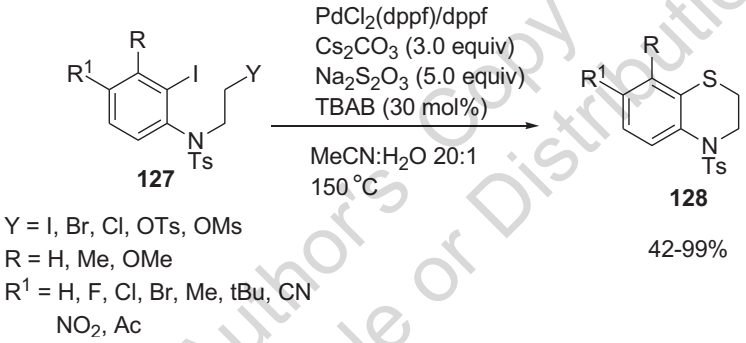
Scheme 47. Synthesis of benzothiazines **124**.

Mechanistically, it was proposed that Ag-salt activated the triple bond of **123** forming σ complex **125**. The intereaction of σ complex with DMF *via* the formation of S–N–H---O=C hydrogen bond which enhanced the nucleophilicity of the sulfonamide nitrogen. Further, regioselective intramolecular nucleophilic attack of the sulfonamide group to the Ag-coordinated triple bond in a '6-endo dig' fashion provided the Ag-vinyl species **126** which underwent subsequent protonation regenerating the catalyst and afforded the desired product (**124**) as depicted in (Scheme **48**).

Jiang and co-workers [52] have recently developed a protocol for the synthesis of substituted 1,4-benzothiazine derivates *via* Pd-catalyzed coupling reaction. The important feature of this method was the use of $Na_2S_2O_3.5H_2O$ (Sodium thiosulfate pentahydrate) as sulfurating reagent which made it free from foul-smelling thiols. The synthetic methodology involved the reaction of **127** with $PdCl_2$(dppf) in the presence of $Na_2S_2O_3.5H_2O$ yielding benzothiazine (**128**). Best results in term of yields was obtained when additional 5 mol% dppf was used with $PdCl_2$(dppf) in presence of $Na_2S_2O_3$ in a MeCN:H_2O (20:1) mixture as show in (Scheme **49**).

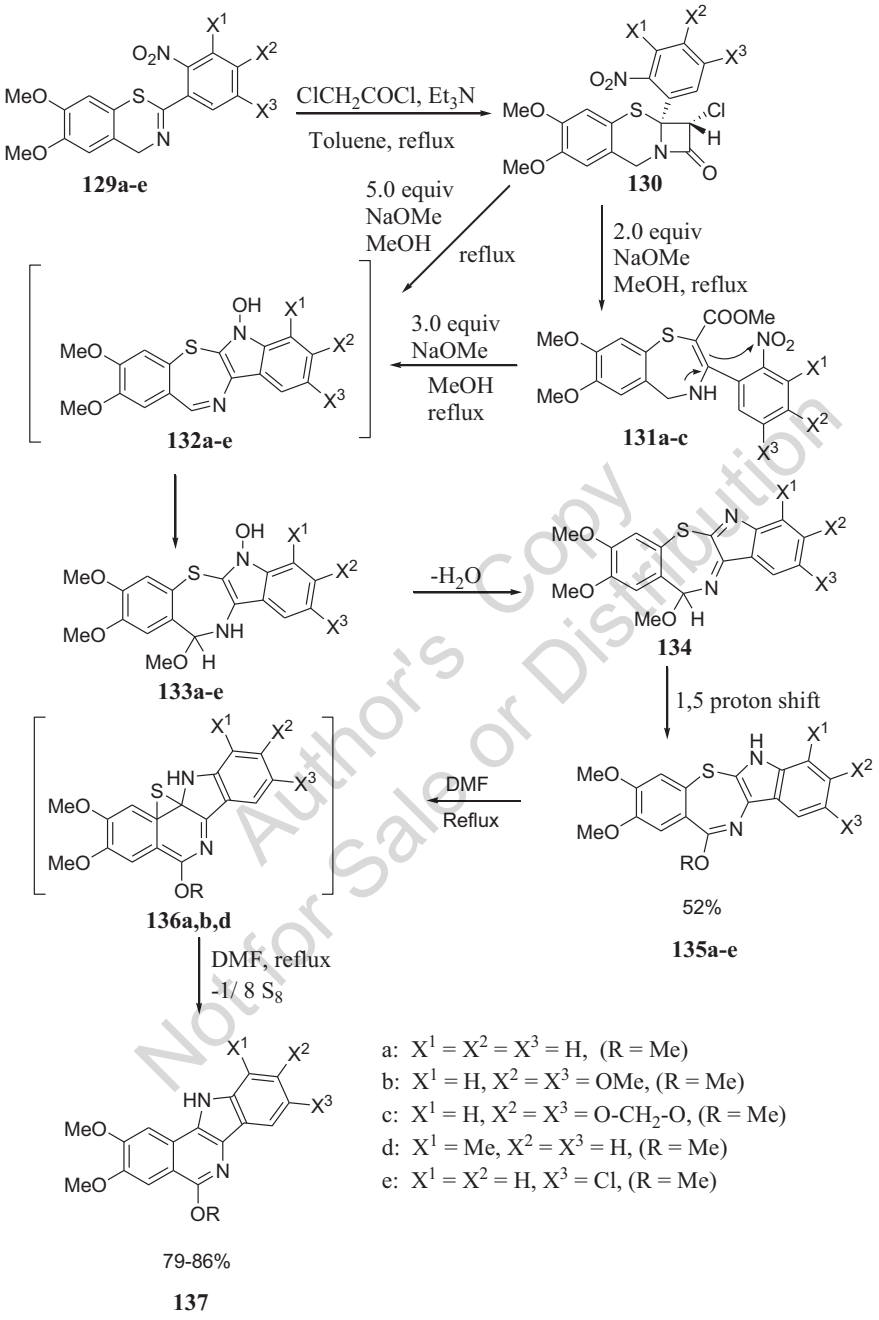


Scheme 48. Mechanistic pathway for the formation of **124**.



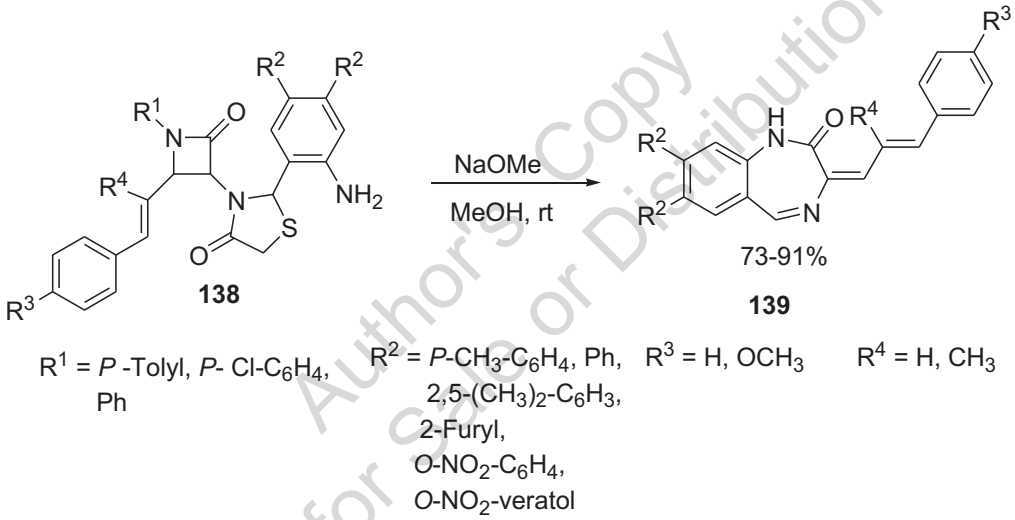
Scheme 49. Synthesis of 1,4-benzothiazine **128**.

Fodor and co-workers [53] have reported the synthesis of substituted 4,5-dihydro-1,4-benzothiazepines (**131a-c**) and indolo-1,4-benzothiazepines (**135a-e**) from mono-chloro-*β*-lactams **130** as synthetic precursor. The reaction of **130a-e** with 2 equiv of sodium methoxide in dry methanol afforded the 4,5-dihydro-1-4-benzothiazepines (**131a-c**) while the treatment with 5 equiv of sodium methoxide led to the formation of indolo-1,4-benzothiazepines (**135a-e)**. Mechanistically, the formation of **135a-e** is thought to proceed *via* an initial alcholysis of *β*-lactam ring to yield the corresponding *α*-chloro ester with subsequent tandem dehydration [1, 5] sigmatropic shift as depicted in (Scheme **50**). Sulphur extrusion in refluxing DMF of **135a-e** finally resulted in the isolation of alkaloid type indolo [3,2-c] isoquinolines (**137a,b,d**) in good yields.



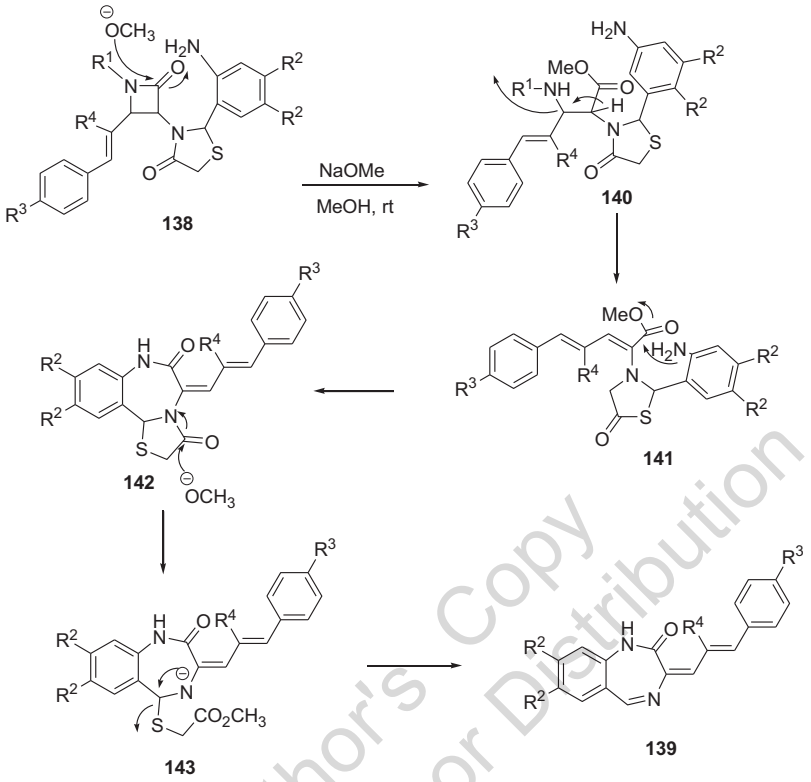
Scheme 50. Synthesis of benzothiazepines **137**.

1,4-Benzodiazepin-2-ones (BZD) are a very successful class of drugs and extensively employed in the context of their wide range of biological activities. There have been significant revelations in the synthesis of C-3 functionalized BZD [54] due to their significant potency at C-3 position. Benzodiazepines having latent functionalities at C-3 position have shown potential in medicinal chemistry and thus attracted the urgency of synthetic chemists for the development of new preparatory routes. Bhargava and co-workers [55] developed *β*-lactam synthon mediated strategy for facile and chemoselective synthesis of new 1,4-benzodiazepin-2-ones. The synthetic methodology involved the treatment of 2-(2-aminoaryl)-3-(azetidin-3-yl)thiazolidin-4-ones (**138**) having 2-aminoaryl at the C-2 position of the thiazolidinone with sodium methoxide in methanol to afford 1*H*-benzo[e] [1, 4]diazepin-2(3H)-ones (**139**) as show in (Scheme **51**).



Scheme 51. Synthesis of benzodiazepin-2-ones **139**.

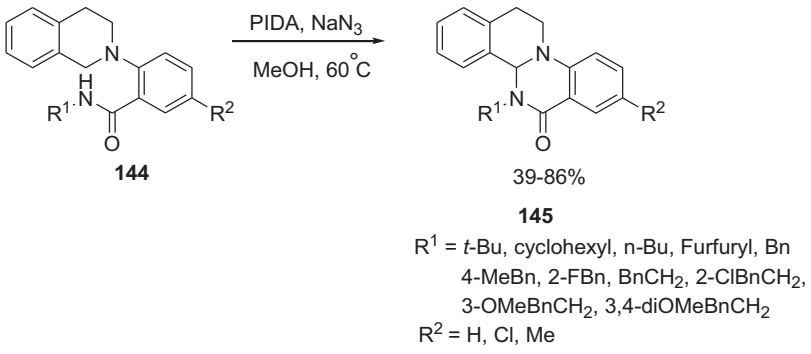
Mechanistically, the reaction involved an initial alkoxide-promoted cleavage of the *N*1-*C*2 bond of the *β*-lactam ring to yield unstable intermediate **140** which underwent a quick deamination reaction under basic condition to form the corresponding dienyl thiazolidin-4-ones **141**. Further, intramolecular nucleophilic addition of the aryl amino group of **141** to the carbonyl carbon of the ester moiety afforded intermediate **142**. Methoxide-promoted ring opening of thiazolidinone of **142** with the removal of the thioglycolic acid resulted in desired benzo[e] [1, 4]diazepin-2(3H)-one **140** as shown in (Scheme **52**).



Scheme 52. Mechanistic pathway for the formation of **139**.

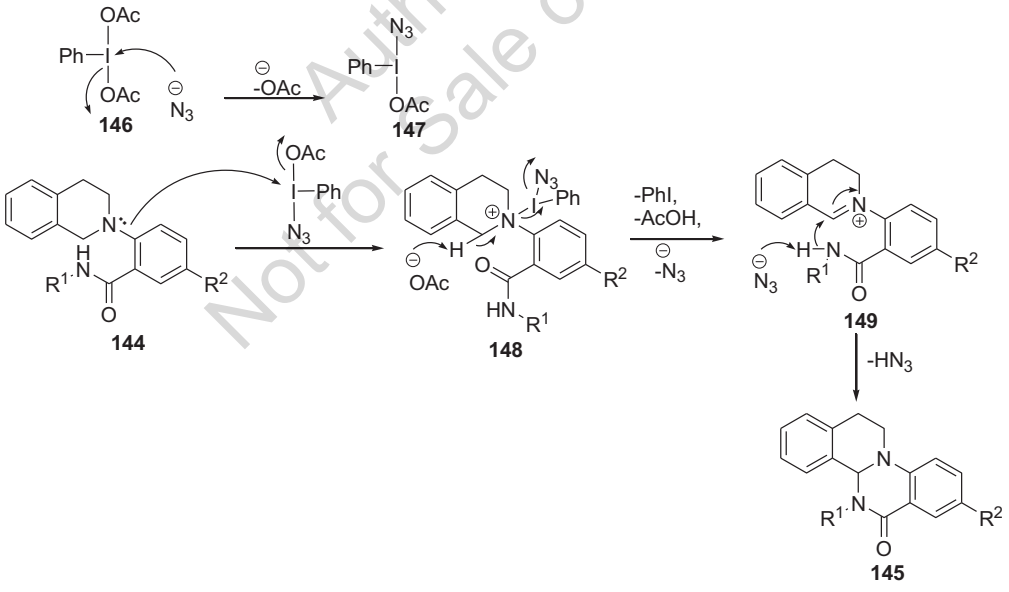
Quinazolinone-based Scaffold

Quinazolinone represent one of the most important pharmacophores exhibiting central nervous system, cardiovascular and anti-inflammatory activities and also act as a psychotropic, hypnotic, cardiotonic, or antihistamine agent [56]. Although the significance of these compounds is obvious, only a few synthetic strategies have been developed for the construction of this skeleton. Thus, Du *et al*. [57] have explored the synthesis of *N*-aryltetrahydroisoquinoline compounds through intramolecular cross-dehydrogenative coupling reactions. The synthetic approach involved the treatment of *N*-aryltetrahydroisoquinoline **144** with an appropriate hypervalent iodine reagent phenyl iodine(III) diacetate (PIDA) in methanol at room temperature yielding the corresponding cyclized product quinazolinones (**145**) in a satisfactory yields. It has been found that additives have pronounced effect on the yield of the reaction. When $BF_3 \cdot Et_2O$ or TMSOTf was used as additive, the yield of **145** remain unchanged while1.2 equiv of NaN_3 resulted in satisfactory yield (Scheme **53**).



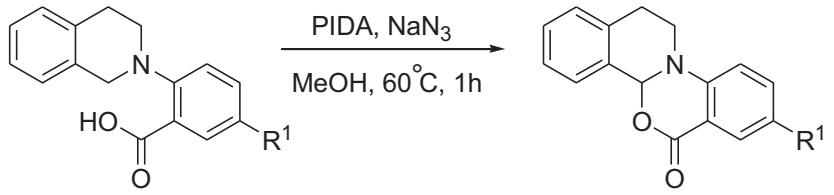
Scheme 53. Synthesis of quinazolinones **145**.

Mechanistically, it was found that highly reactive azidoiodinane, $PhI(N_3)OAc$, was formed *via.* SN^2 reaction of phenyl iodine(III) diacetate (PIDA) with azide anion. Further, reaction of **144** with $PhI(N_3)OAc$ resulted in the formation of the ammonium ion intermediate **148** which underwent an E^2 reaction in the presence of acetate anion furnishing the iminium ion intermediate **149**, along with the generation of one molecule of iodobenzene and acetic acid. Intramolecular nucleophilic cyclization on iminium intermediate **149** with the abstract of hydrazoic acid, resulted in the desired product **145** as depicted in (Scheme **54**).



Scheme 54. Mechanistic pathway for the formation of **145**.

The above protocol when tested with tetrahydroisoquinoline-*N*-benzoic acid derivatives **150**, afforded the desired lactones (**151**) in good yield through the formation of a new C-O bond (Scheme **55**).



150

151

151a R^1 = H 61%

151b R^1 = Cl 74%

Scheme 55. Synthesis of lactones **151**.

Fused Heterocycles with Three Hetero Atom

Benzotriazole-based Scaffold

Benzotriazole is another fused heterocyclic compound having three vicinal nitrogen atoms in its five-member ring. These nitrogen-containing heterocycles are extensively found in pharmaceuticals and are structural components of many UV stabilizers and organic electronic materials [58]. Especially, 2-aryl-2*H* benzotriazole core is present in various scaffolds such as seratonine/dopamine receptor ligand (**XVI**), human PPAR-*α*activator (**XVII**), Tinuvin-P (**XVIII**) an ultraviolet light absorber, PCDTPBt (**XIX**) an electron acceptor in organic solar cell, an ultraviolet light stabilizer (**XX**), and antiviral agent (**XXI**) against ssRNA positive viruses as shown in (Fig. **6**).

Patel and co-workers [59] have recently developed an efficient and regioselective route for the synthesis of 2-aryl-2*H*-benzotriazoles *via* Pd(II)-catalyzed ortho sp^2 C-H activation of azoarenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant. The key step in the synthesis is the treatment of azoarenes **152** with $TMSN_3$ and TBHP (oxidant) in DMSO at 100 °C to result in corresponding 2*H*-benzotriazoles (**153**) in good yields as depicted in (Scheme **56**).

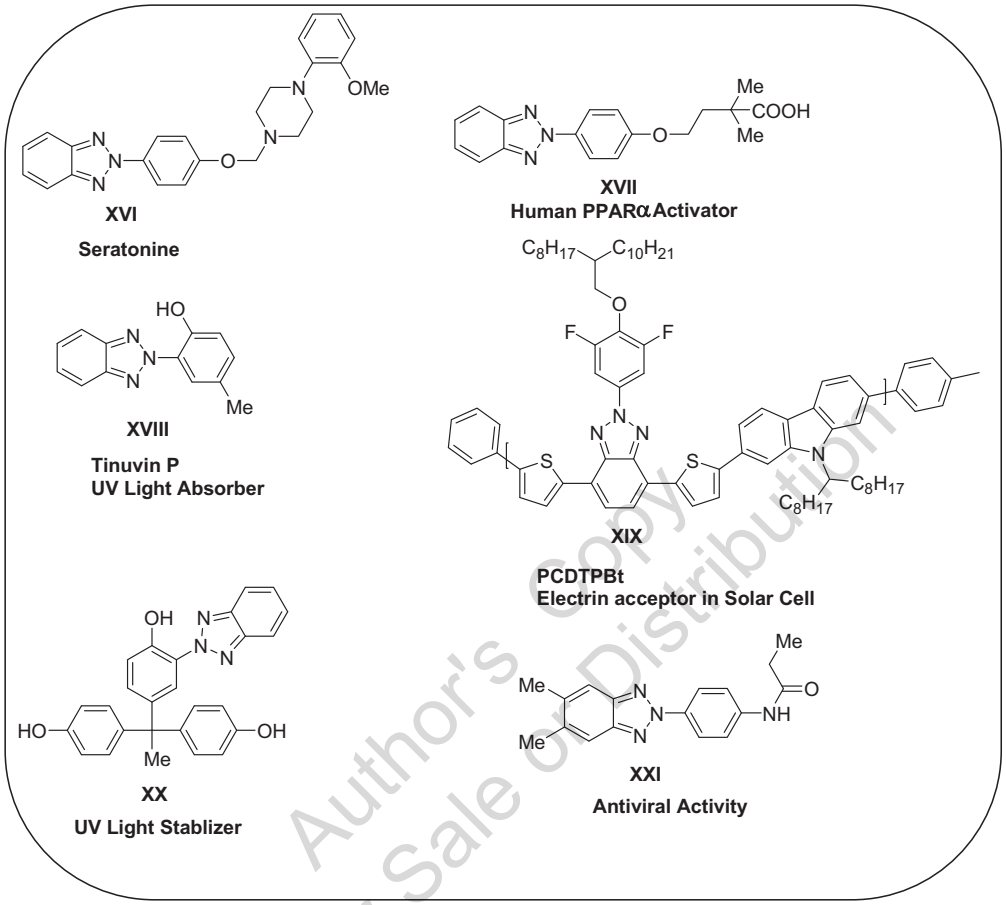
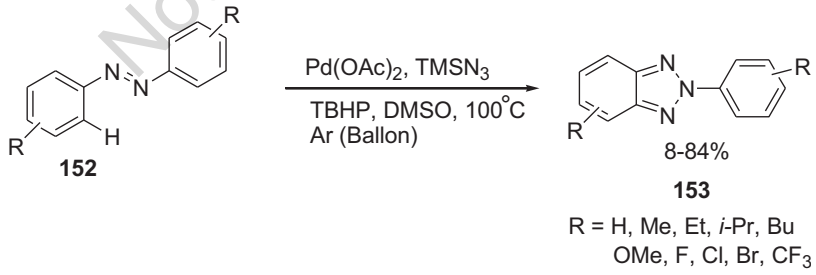
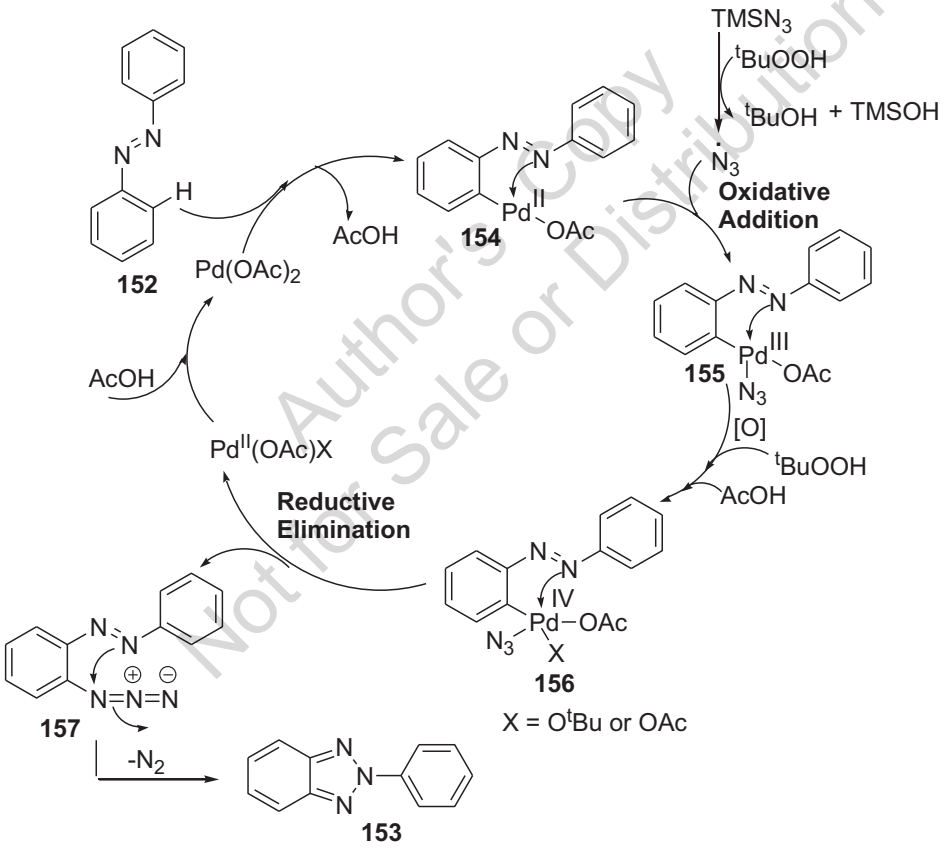


Fig. (6). Compounds having 2-aryl-2*H*-benzotriazoles core with its importance.



Scheme 56. Synthesis of benzotriazole **153**.

Mechanistically, the cyclopalladation reaction between "azo moiety" of azobenzene and Pd(II) catalyst led to the generation of intermediate complex **154**. Azide radical, obtained by the reaction of $TMSN_3$ and TBHP *in situ* reacted with Pd-complex **156** and oxidized it to give Pd(III) intermediate **155** which on oxidation with TBHP leading to the formation of a Pd(IV) intermediate **156**. Thus, TBHP was playing the dual role of an oxidant as well as a radical generator. The reductive elimination of intermediate **156** led to the generation of an *o*-azido azobenzene **157**, regenerating palladium(II) catalyst for the next cycle. In the final stage, attack of one of the azo nitrogen onto the *o*-azide nitrogen *in situ* generated *ortho* azido substrate **157** and resulted in the desired cyclization product **153**, with the expulsion of a molecule of N_2 as depicted in (Scheme **57**).



Scheme 57. Mechanistic pathway for the formation of **153**.

CONCLUDING REMARKS

Metal catalyzed intramolecular cyclization and *β*-lactam-synthon protocol are two diverse synthetic approaches with one common goal of constructing diverse heterocycles with latent functionalities. A number of examples explicating their potential in the intramolecular construction of C-X (X = N, O, S) bond has been included in the present chapter which will help the readers to appreciate their role in modern day organic synthesis. We believe that more variants of the above protocols will be reported in future which will facilitate the synthesis of structurally arduous heterocycles of biological and medicinal interest.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author confirms that he has no conflict of interest to declare for this publication.

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Declared None

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