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Arylsulfonylmethyl isocyanides: α-acidity in the structure of isocyanides

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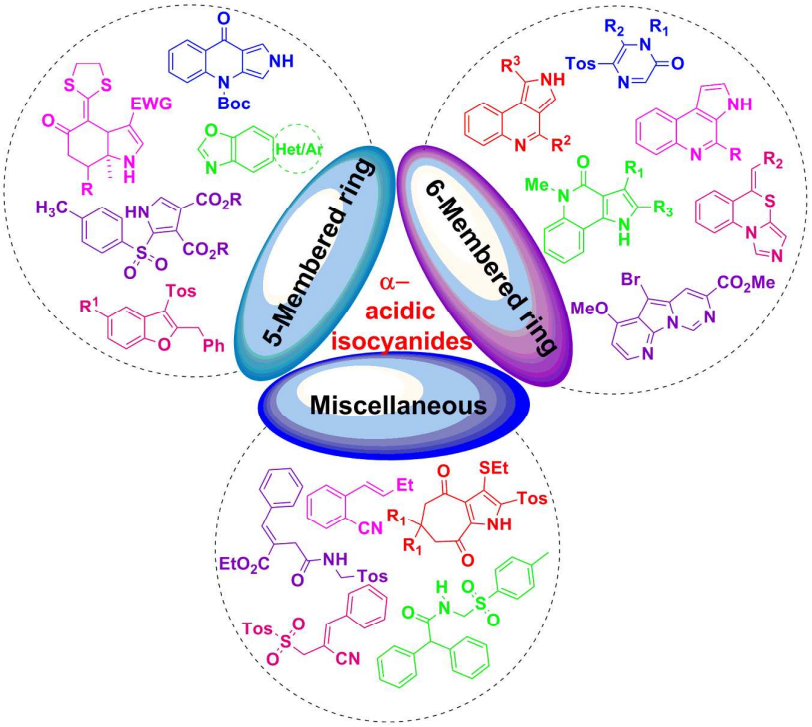
Abstract:

p-Tosylmethyl isocyanide (TosMIC), an α-acidic isocyanide has emerged as a privileged reagent to access biologically relevant scaffolds. The present review highlights the significant advancements of TosMIC in the construction of fused heterocycles *viz.* pyrroles, benzimidazoles, imidazopyridines, quinolones, quinolines and some natural products like (-)-Ushikulide A, Variolin B, Porphobilinogen and mansouramycin B. The review article encompasses literature from the period starting from 2010 onwards and covers novel synthetic methodologies involving TosMIC. A wide range of reaction strategies have been reported involving TosMIC during this period such as Michael additions, cycloadditions and many cascade/tandem/multicomponent reactions.

Graphical Abstract:



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Arylsulfonylmethyl isocyanides: A Novel Paradigm in Organic Synthesis

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p-Tosylmethyl isocyanide (TosMIC), an α-acidic isocyanide has emerged as a privileged reagent to access biologically relevant scaffolds. The present review highlights the significant advancements of TosMIC in the construction of fused heterocycles *viz.* pyrroles, benzimidazoles, imidazopyridines, quinolones, quinolines and some natural products like (-)-Ushikulide A, Variolin B, Porphobilinogen and Mansouramycin B. The review article encompasses literature from the period starting from 2010 onwards and covers novel synthetic methodologies involving TosMIC. A wide range of reaction strategies have been reported involving TosMIC during this period such as Michael additions, cycloadditions and many cascade/tandem/multicomponent reactions.

Introduction

In recent time where premium is put on speed, diversity and efficiency in drug discovery process, multicomponent reactions (MCRs) represent one of the most powerful tools owing to easy accessibility of molecules in terms of both skeletal and decorational diversity.[1] Amongst various MCRs, quite prolific are isocyanide-based multicomponent reactions (IMCRs) due to isocyanide's peculiar reactivity, its tendency to act both as nucleophile and electrophile and has thus rendered a prominent role in various chemical transformations in past.[2] Last couple of decades have witnessed a renaissance in the chemistry of IMCRs *via* several twists and turns in the classical age old Passerini (P-3CC) and Ugi (U-4CC) IMCRs thereby insinuating several new methodologies.[2] IMCR chemistry is a significant contributor to the contemporary organic synthetic tools such as diversity-oriented synthesis (DOS), high throughput screening and combinatorial chemistry.[3] Due to a tremendous growth in this field, IMCRs has been the subject of different reviews.[2-4] Of late, incorporation of additional functionalities into the isocyanide moiety has gained significant development that would naturally increase the versatility of these synthons and indeed many new functionalized isocyanides have also been successfully synthesized.[5] A number of isocyanides bearing additional functionalities are known such as sulfonylmethyl isocyanides, vinyl isocyanides, isocyanoacetates, isocyanophosphonoacetates *etc.*[5,6] Among them α-acidic isocyanides, in particular, have gained a considerable attention, due to their 1, 3-dipolar character, thus interacting with a wide range of dipolarophiles in cycloaddition reactions.[7] Typically, these reaction sequences utilize nucleophilic addition of the α-carbanion, rather than the divalent carbon of the isocyanide as in the P-3CR and U-4CR, onto the respective electrophiles.[5] The names of Schöllkopf and Van Leusen stand for many pioneering developments in this field of α-acidic isocyanides. From all that pertinent chemistry, three primary α-acidic isocyanide templates have emerged to the mainstream of organic synthesis: 1) arylsulfonylmethyl isocyanides (**I**) 2) α-isocyano esters (**II**) and 3) α-isocyanamides (**III**) (Fig. 1).

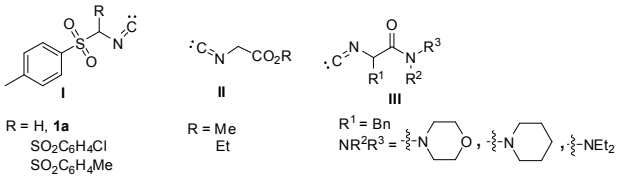

Fig. 1 Structures of diverse α-acidic isocyanides.

Amongst these three types, TosMIC reagents (template I), originally introduced by Van Leusen, are most versatile and valuable synthons in organic chemistry.[7,8] TosMIC reagents are densely functionalized moieties with three groups that can engage in a multitude of reactions: the isocyano functionality can undergo α-addition reactions whereas the acidic α-carbon atom and the sulfonyl group in the α-position can act as a leaving group thereby further enhancing the acidity of α-carbon.[7] TosMIC due to its remarkable properties in synthesis, such as ease of preparation, tolerance to various functionalities and effortless removal of the tosyl group if so desired, has facilitated a wide range of chemical

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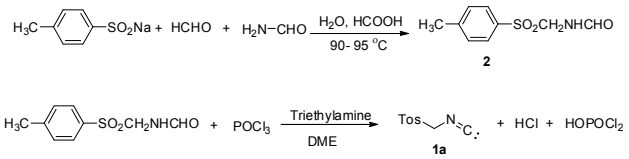
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

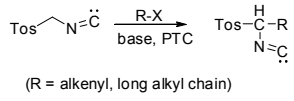
transformations, both in the chemical and biological sphere through synthesis of molecules such as oxazolidinones, oxazoles, thiazoles, imidazoles, indoles, triazoles, pyrroles, benzofuranes, quinoxalines, and pyrrolopyrimidines.[6-8] Moreover, they also have been implied in the synthesis of natural products such as Variolin B, porphobilinogen and mansouramycin B.[9-11] In view of its widespread role in synthesis, TosMIC has been documented in the form of elegant reviews so far which have largely accounted for the reactions of TosMIC reagents till the year 2010.[6,12] Therefore, the present review article summarizes progress in the chemistry of TosMIC reagents reported after 2010 till 2015. Moreover, the emphasis in writing this manuscript has been on the method development from a pure synthesis perspective and hence use of TosMIC in the preparation of biologically/medicinally active compounds appearing in the medicinal chemistry and other application based journals was not considered.

The pioneering and revolutionary work on the synthesis of TosMIC reagents was carried out by Van Leusen either by irradiating the solution of corresponding *p*-tosyl diazomethane in liquid hydrogen cyanide[13] or by treating *p*-tosylfluoride with isocyanomethyl lithium.[14] These methods do have several disadvantages for instance, use of poisonous HCN gas, fluorides, harsh reaction conditions and lesser yields. Later on, these shortcomings were overcome by a more facile two-step three component approach involving sulfinates, aldehydes and formamides.[15] This modified protocol was started with Mannich condensation to synthesize *N*-(*p*-tosylmethyl)formamide **2**, and followed by its dehydration with phosphoryl chloride to furnish TosMIC **1a** (Scheme 1). This method was further modified by Sisko to improve the scope of aldehyde input in the same approach.[16]



Scheme 1 Preparation of *p*-tosylmethyl isocyanide **1a**.

Owning to TosMIC's reactivity, its various synthetic analogues were prepared. One such protocol to access the functional mono-substituted TosMIC's was exploited by Van Leusen, it utilized deprotonation and alkylation of α-acidic isocyanides using phase transfer catalyst (PTC) conditions (Scheme 2).[17]



Scheme 2 Synthesis of TosMIC reagents via phase transfer catalyst (PTC) approach.

As TosMIC reagents have propound applications towards the construction of *N*-heterocycles (Fig. 2). Therefore, based upon the types of heterocycles that they synthesized, this review has been subdivided into (i) Synthesis of five membered heterocycles; (ii) Synthesis of six membered heterocycles; and (iii) Miscellaneous.

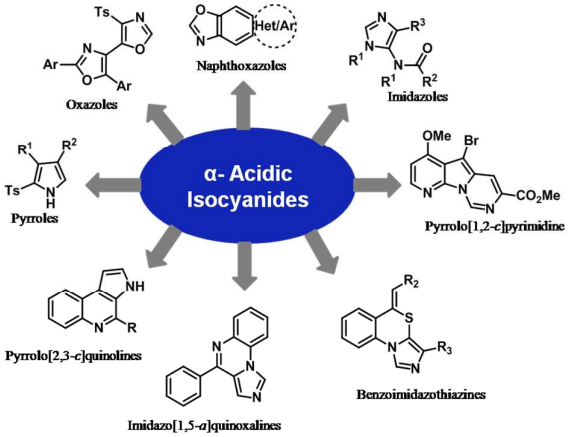
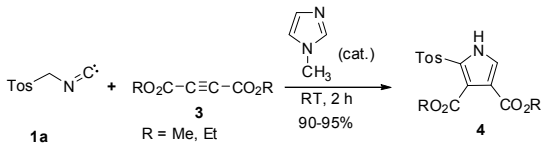


Figure 2 Access of biologically active scaffolds through α-acidic isocyanides.

2.1 Synthesis of Five Membered Heterocycles

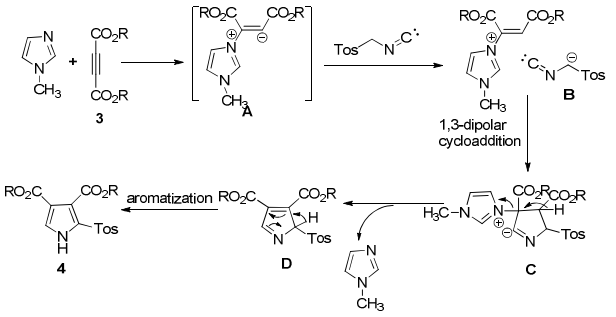
2.1.1 Pyrroles

Pyrroles are privileged scaffold exhibiting an array of pharmacophoric activities *viz.* antitumor, antibacterial, antifungal, anti-inflammatory *etc*.[18] Moreover, they are useful building blocks not only in the field of natural product synthesis but also in the area of heterocyclic chemistry.[19] To access this bio-dynamic core, several syntheses for instance, Knorr, Paul-Knorr, Hantzsch and Van Leusen *etc.* have been reported.[20,21] Later approach involves base mediated 1,3-dipolar cycloaddition of TosMIC with various Michael acceptors *e.g.* electron deficient alkenes, alkynes, ketene dithioacetals *etc*.[22-24] However, the need for improving Van Leusen's pyrrole synthesis is evident. Subsequently, Adib and coworkers described an efficient and novel synthesis of dialkyl 2-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates **4** by the reaction of dialkylacetylene dicarboxylates **3** with TosMIC **1a** using 1-methylimidazole as a catalyst.[23] Interestingly, the cycloaddition reaction was performed at room temperature under mild conditions and in excellent yields (Scheme 3).



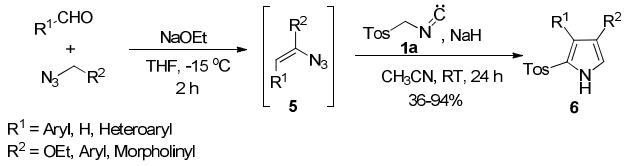
Scheme 3 Synthesis of dialkyl 2-[(4-methylphenyl) sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates.

A detailed mechanistic rationalization for the reaction is provided in Scheme 4. First the nucleophilic addition of 1-methylimidazole on the acetylenic ester generated the zwitterion **A**, which deprotonated the TosMIC to form intermediate **B**. This species **B** underwent 1, 3-cycloaddition followed by removal of the catalyst and subsequent aromatization to yield the desired product **4**.



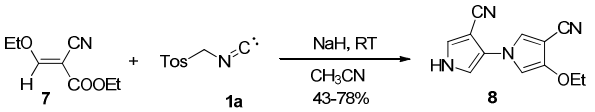
Scheme 4 Proposed mechanism for the substituted pyrrole-3,4-dicarboxylates.

Similarly, Yu and co-workers also reported synthesis of multi-functionalized pyrroles **6** from TosMIC **1a** and vinyl azides **5**.[22] The synthesis protocol proceeded via *in situ* generation of vinyl azides from the respective aldehydes and alkyl azides under mild basic conditions and its subsequent 1,3-dipolar cycloaddition on TosMIC to afford the desired product **6** in 36-94% yield (Scheme 5).



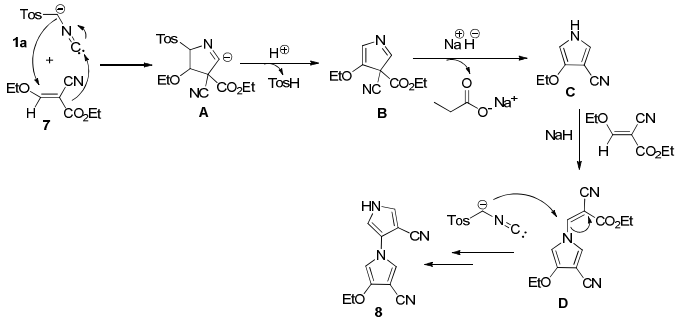
Scheme 5 Synthesis of substituted pyrrole analogues.

In a similar way, 1,3'-bipyrrole motifs, a basic constituent of a number of polypyrrole pigments, have relevance in medicinal chemistry and various marine natural products *e.g.*, antibacterial bipyrrole Marinopyrroles A and B *etc.*[25] Owning to its importance in medicinal chemistry, Wu and coworkers attempted its synthesis by treating multisubstituted olefins with TosMIC **1a** *via* classical Van Leusen's methodology.[26] The reaction mixture was stirred at room temperature under basic conditions to afford the respective 1,3'-bipyrroles **8** in 43-78% yield (Scheme 6).



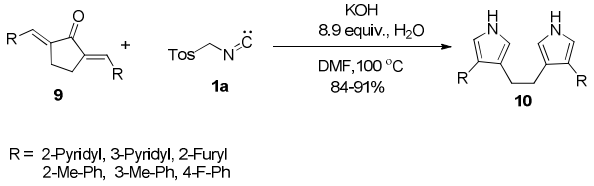
Scheme 6 Synthesis of substituted 1,3'-bipyrroles.

A plausible reaction mechanism of the reaction has been described in Scheme 7. Possibly, the reaction proceeded through the iterative process of cascade 1,3-dipolar cycloaddition through the intermediates (**A-D**) as discussed in Scheme 4.



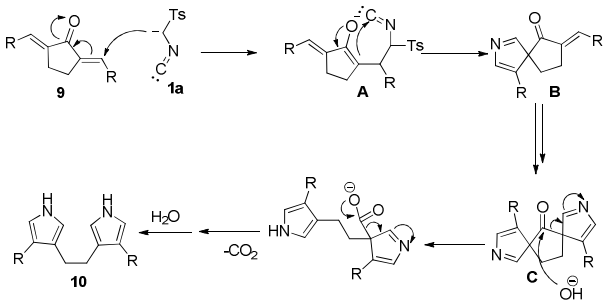
Scheme 7 Mechanism for the synthesis of substituted 1,3'-bipyrrole analogues.

On a similar line, Wang and coworkers also reported the methodology for the synthesis of 3, 3'- bipyrroles **10** using dienones **9** and TosMIC **1a**.[27] This reaction involved C-C bond cleavage promoted by water. Moreover, the reaction tolerated a broad range of functional groups and conformationally restricted dienones (Scheme 8).



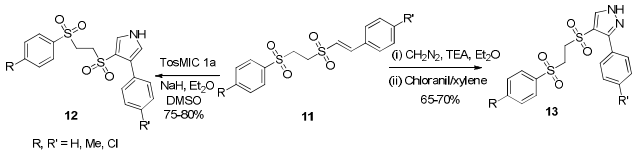
Scheme 8 Synthesis of *bis*-pyrrole derivatives.

A plausible mechanism for the reaction has been depicted in Scheme 9. The first step involved the Michael addition of **1a** to dienone **9** in the presence of KOH furnished enolate intermediate **A**, which subsequently underwent intramolecular cyclization to yield a spirocyclic intermediate **B**. Further, the same iterative step occurred again and generated the *bis*-spirocyclic intermediate **C**. The intermediate **C** underwent cascade reaction involving ring-opening, decarboxylation and protonation in the presence of aqueous KOH and to furnish the desired product **10**.



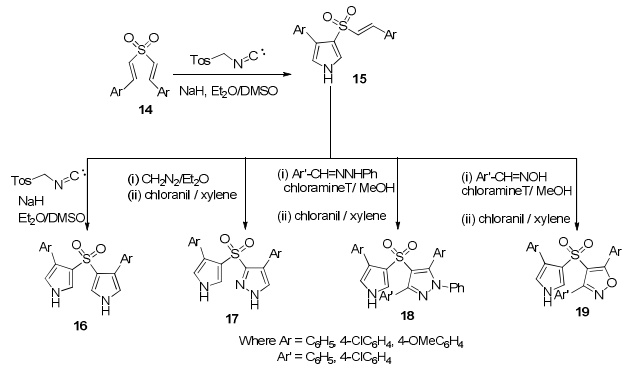
Scheme 9 Mechanistic route towards the synthesis of *bis*-pyrrole derivatives.

Afterwards, Padmaja *et al.* utilized *E*-1-(arylsulfonylethylsulfonyl)-2-arylethene **11** as Michael acceptor to synthesize pyrroles **12** and pyrazoles **13** *via* 1,3-dipolar cycloaddition of TosMIC **1a** and diazomethane, respectively (Scheme 10).[28]



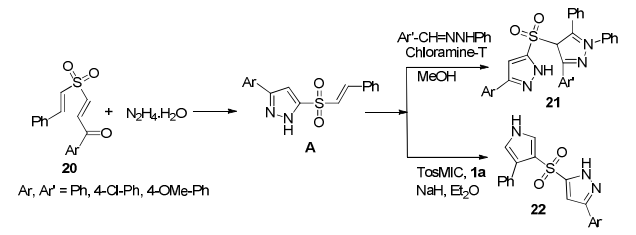
Scheme 10 Synthesis of pyrrole and pyrazole analogues.

Similarly, Padmavathi and co-workers also synthesized sulfone-linked *bis*-heterocycles (**16-19**) containing either similar or different pendant heterocyclic rings such as *bis*-pyrroles **16**, *bis*-pyrrolyl pyrazoles (**17-18**), or *bis*-pyrrolyl isoxazole **19**. The reaction involved 1,3- dipolar cycloaddition of dipolarphile *bis*(styryl)sulfone **14** with TosMIC **1a**, diazomethane, nitrile imines and nitrile oxides.[29] The reaction is highly regiospecific yielding the desired products in 65-82% yield (Scheme 11).



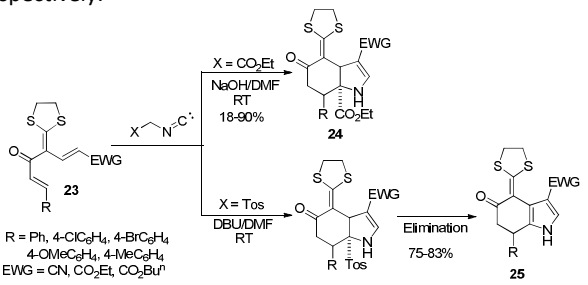
Scheme 11 Synthesis of *bis*-heterocycle derivatives.

Moreover, the same group further exploited the reaction of 1-aroyl-2-styrylsulfonylethenes **20** with TosMIC **1a** and synthesized the sulfone-linked *bis*-heterocycles **21-22**. The reaction proceeded *via* the common intermediate **A**, which was readily accessed by the reaction of 1-aroyl-2-styryl sulfonylethenes **20** and hydrazine hydrate (Scheme 12).[30]



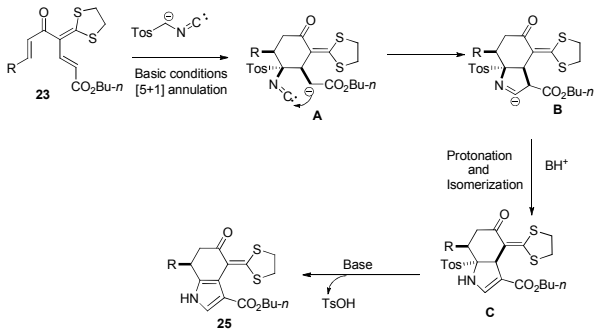
Scheme 12 Synthesis of *bis*-heterocycle derivatives.

Ketene dithioacetals are important intermediates in organic synthesis.[24] Liu and coworkers expanded the synthesis of polysubstituted fused bicyclic pyrrole systems **25** *via* the domino reaction of 1,5-dielectrophilic substrates such as α-alkenoyl ketene dithioacetals **23** with α-acidic isocyanides **1a** using mild conditions in 18-90% yield (Scheme 13). It was observed that isocyanoacetate in the presence of NaOH and TosMIC under DBU conditions gave excellent yields respectively.[31]



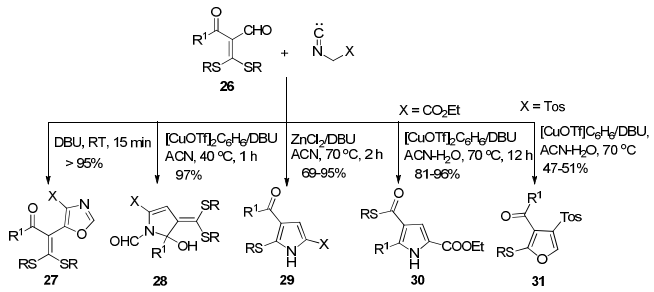
Scheme 13 Synthesis of bicyclic pyrroles.

The reaction mechanism involved [5+1] annulation of TosMIC (or ethyl isocyanoacetate) with 1,5-dielectrophile under basic conditions which initially provided anion intermediate **A**. The intermediate **A** underwent intramolecular cyclization followed by further protonation, isomerization and elimination (in case of TosMIC) to furnish the desired product **25** (Scheme 14).



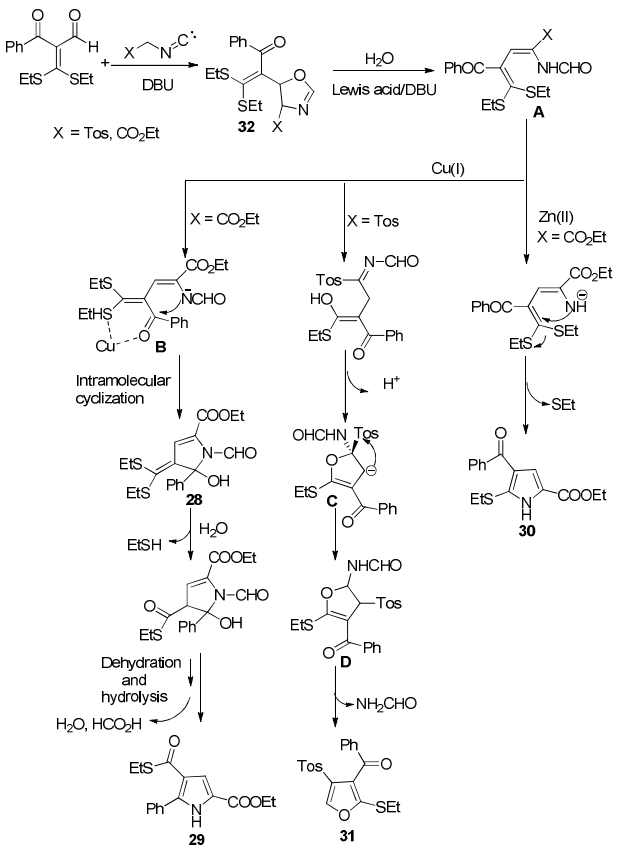
Scheme 14 Proposed mechanism for the synthesis of bicyclic pyrroles.

Similarly, Pan *et al.* also employed α-formyl ketene dithioacetals **26** as a common precursor for the synthesis of oxazoles **27**, 5-alkylthio-pyrroles **28-29**, 4-alkylthiocarbonyl-pyrroles **30** and 2-alkylthio-4-tosyl-furans **31** through their regiodivergent cyclization with α-acidic isocyanides by changing catalysts and promoters under mild reaction conditions and in good to excellent yields (Scheme 15).[32]



Scheme 15 Synthesis of various annulated pyrroles by Pan and co-workers.

Based on the above results, a probable mechanism has been depicted in Scheme 16. Initially, compound **32** was formed presumably *via* DBU mediated 1,3-cycloaddition. Next, in the presence of Lewis acid and water, **32** underwent hydrolysis to afford intermediate **A**, which served as a common intermediate for the formation of various derivatives **27-31**. Under the presence of $Zn(II)/H_2O$, sequential hydrolysis followed by cyclization and elimination afforded **30**. On the other hand, Cu(I) facilitated the formation of complex **B**, thereby affording derivative **28** which was further hydrolyzed to pyrrole derivative **29** in water. Moreover, in the case of TosMIC, hydrolysis of carbonyl group took place first to afford **C** which subsequently underwent intramolecular cyclization to produce intermediate **D**. Finally, 1,2-sulfonyl migration and subsequent elimination afforded furan derivative **31**.



Scheme 16 Proposed mechanism for the synthesis of various annulated pyrroles.

In continuation, Ila and co-workers disclosed a domino process for the diversity oriented synthesis of annulated pyrroles involving a base-induced reaction of cyclic α-oxoketene dithioacetals with activated methylene isocyanides.[33] The generality and scope of this method is described in Fig. 3. This methodology facilitated synthesis of biologically relevant and structurally diverse pyrroles for instance, pyrrolonapthoquinones, pyrroloquinolones, tetracyclic fused indoles, pyrrole annulated dibenzooxocinone and dibenzothiocinone *etc.*

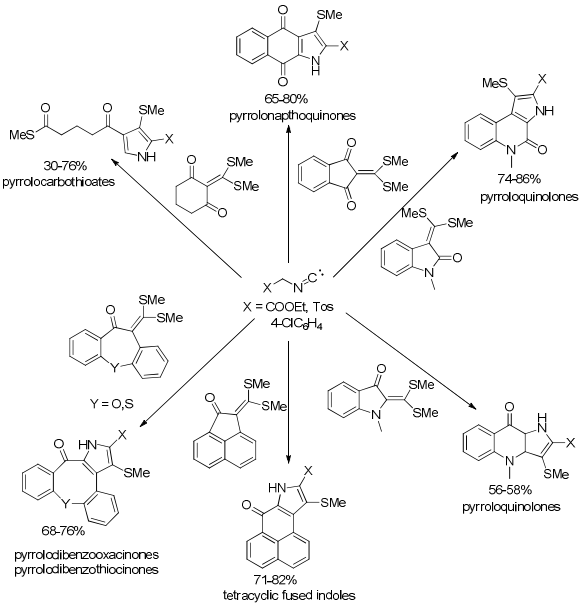
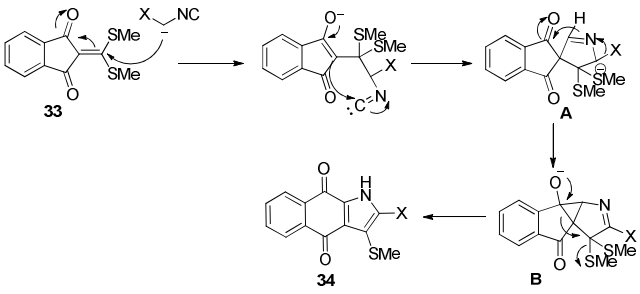


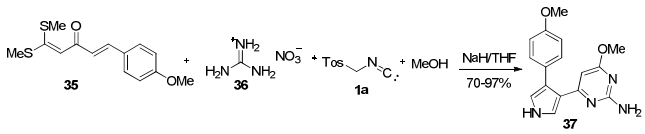
Fig. 3 Synthesis of various annulated pyrroles.

Mechanistically, it was suggested that initial Michael addition of α-acidic isocyanide on substrate **33** was facilitated by intramolecular cyclization to yield *spiro*-aza-allyl intermediate **A**. Further nucleophilic attack on the carbonyl group resulted the strained tricyclic alkoxide intermediate **B**. Next, subsequent ring expansion followed by elimination and aromatization afforded the desired product **34** (Scheme 17).



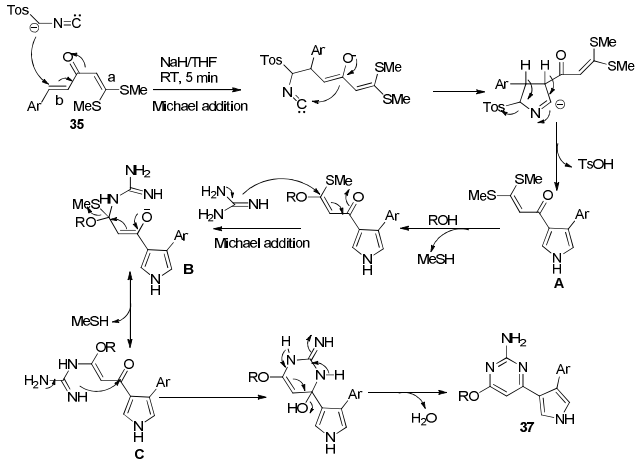
Scheme 17 Postulated mechanism for the synthesis of annulated pyrroles.

In a recent example, Shanmugam and co-workers reported a multicomponent route towards construction of 6-pyrrolyl pyrimidin-2-amine analogues **37** in good to excellent yields.[34] The reaction proceeded *via* cycloaddition reaction of α-aroylidine ketene dithioacetals **35**, guanidine nitrate **36**, alcohols and TosMIC **1a** in the presence of NaH/THF in a highly chemo- and regioselective manner (Scheme 18).



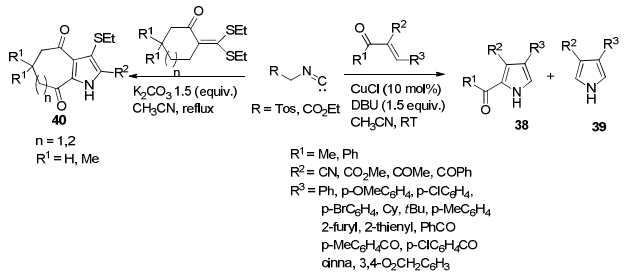
Scheme 18 Multicomponent cascade for the synthesis of substituted 6-pyrrolyl pyrimidin-2-amines.

A plausible mechanistic pathway is depicted in Scheme 19. The reaction was proceeded *via* the 1, 3-dipolar cycloaddition of TosMIC selectively on the α-aroylidene ketenedithioacetals **35**. It is postulated that attack of nucleophile is favored at the side **b** of the double bond rather than the side **a**, because later double bond is more electron rich due to presence of two electron donating methyl sulfonyl groups. Subsequently, tosylic acid was eliminated to yield intermediate **A**, which followed the nucleophilic substitution of alcohol and iterative Michael addition and intramolecular cyclization to afford the desired product **37**.



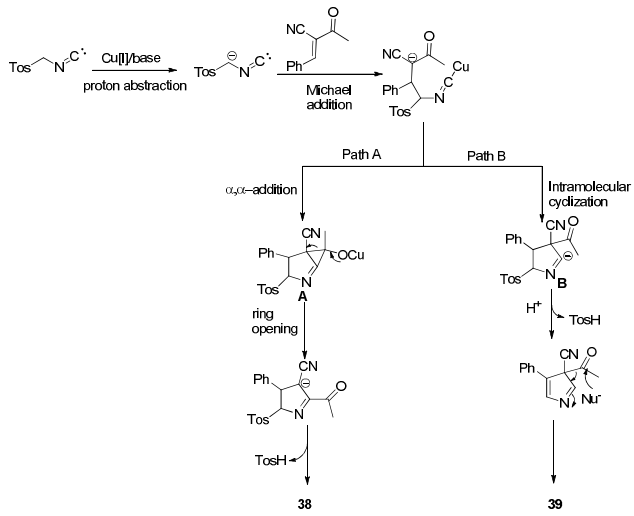
Scheme 19 Proposed mechanism for the synthesis of substituted 6-pyrrolyl pyrimidin-2-amines.

Similarly, Liu and co-workers described a tandem Michael addition/isocyanide insertion protocol on acyl C-C bond allowing an access to polyfunctionalized 2-acylpyrroles and seven-/eight-membered ring fused pyrroles from the reaction of α-acidic isocyanides with enones.[35] As depicted in Scheme 20, reaction of acyclic enones with isocyanide furnished two products **38** and **39**. The formation of product **39** was favored in the presence of NaOH/DMF, while product **38** was formed exclusively under the presence of CuCl, DBU/ACN conditions. On the other hand, cyclic enedione exclusively afforded the desired product **40** in good yields.



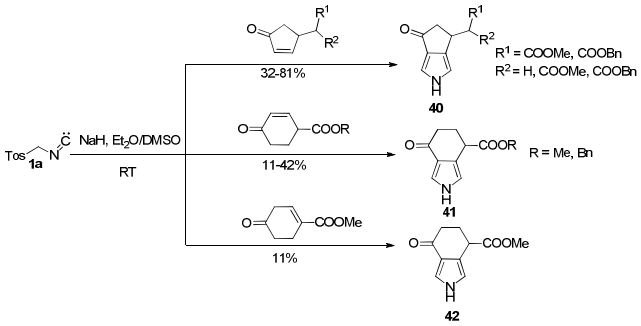
Scheme 20 Synthesis of substituted 2-acylpyrroles and bicyclic pyrroles.

The mechanistic pathway for the formation of acetyl pyrroles **A** and deacetyl pyrroles **B** is depicted in Scheme 21. First, TosMIC was co-ordinated with CuCl under the basic conditions, which generated carbanion by Michael addition, Afterwards it followed two different pathways to form either **38** or **39**. The formation of product **38** (path A) involved intramolecular α, α-addition through the cyclopropane intermediate **A**, its subsequent ring opening followed by elimination furnished the desired product **38**. However, the formation of **39** was rendered by the intramolecular cyclization of the intermediate **B**, elimination of the tosylic acid and hydrolysis of the acetyl group (path B) (Scheme 21).



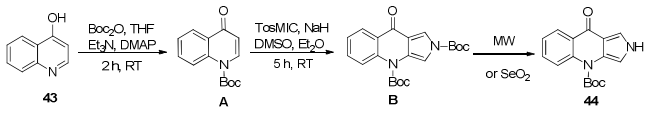
Scheme 21 Mechanistic route for the synthesis of fused 2-acylpyrroles.

In order to diversify annulated pyrrole scaffolds, Kelly and Leeper synthesized cycloalkano[*c*]-pyrroles **40-42** using 1, 3-dipolar cycloaddition of Michael acceptor cycloalkenones and α-acidic isocyanides.[10] This method is highly compatible to a variety of Michael acceptors as shown in Scheme 22. Moreover, this method has been utilized for the synthesis of conformationally constrained analogues of porphobilinogen, which is an important precursor of natural tetrapyrroles.



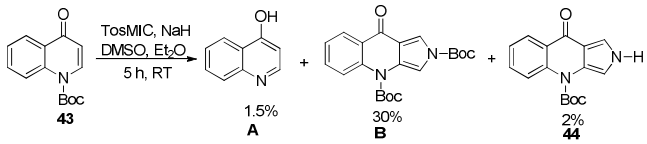
Scheme 22. Synthesis of cycloalkano[*c*]-pyrroles.

In continuation, Costi *et al.* utilized quinolinones **43** for the synthesis of annulated pyrroles. However, it involved subsequent steps of protection and deprotection. In order to further improve the yield and selectivity, a variety of protecting groups such as acetyl, mesyl, and *Boc* were used.[36] Amongst, *Boc* gave best results under microwave irradiation and funished the desired 2*H*-pyrrolo[3,4-b]quinolin-9(4*H*)-ones **44** with a yield of 55% (Scheme 23).



Scheme 23 Synthesis of 2*H*-pyrrolo[3,4-*b*]quinolin-9(4*H*)-ones.

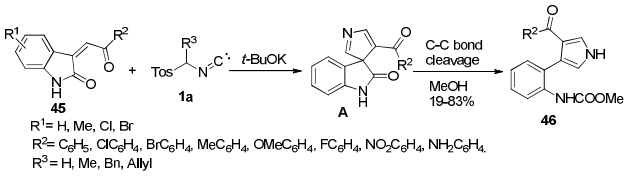
Initially, authors were attempting to synthesize 2*H*-pyrrolo[3,4-*b*]quinolin-9(4*H*)-one **44**, in one step by the reaction of *N*-alkyl derivative **A** and TosMIC **1a**. Unfortunately the reaction yielded multiple products **43** (1.5%), **B** (30%) and **44** (2%), respectively. Out of these, formation of product **B** could be rationalized on the basis of cleavage of the *Boc* group from the starting material and sequentially shifting it to the pyrrole ring (Scheme 24).



Scheme 24 Optimized conditions for the synthesis of 2*H*-pyrrolo[3,4-*b*]quinolin-9(4*H*)-one.

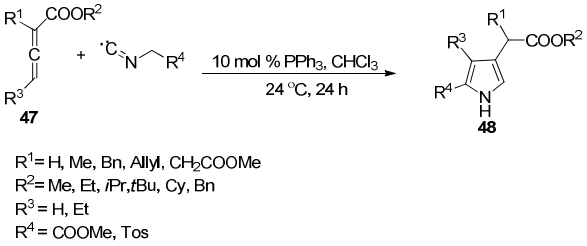
Besides, Wang and co-workers utilized C-C bond cleavage strategy for the construction of 2*H*-pyrrolo[3,4-*c*]quinoline derivatives **45** in 19-83% yields.[37] The present protocol demonstrated a non-classical Van Leusen's pyrrole synthesis where C-C bond cleavage occurred during the final aromatization step. Initially, 1, 3-dipolar cycloaddition of 3-phenacylideneoxindoles **45** with TosMIC **1a** furnished highly strained *spiro* intermediate **A**, which subsequently underwent

C-C bond cleavage, followed by aromatization and its reaction with MeOH, to afford the desired product **36**. Here, *t*-BuOK functioned both as base and additive. The methodology was tolerant to a variety of functional groups present on the phenacylideneoxindole moiety. However, substituted TosMIC derivatives failed to give the desired product probably due to steric hindrance (Scheme 25).



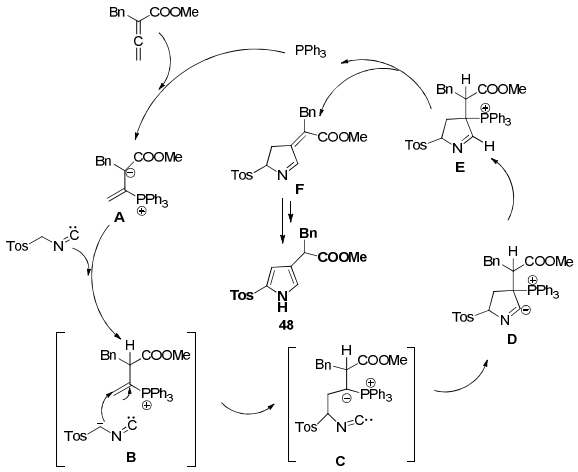
Scheme 25 Synthesis of 2*H*-pyrrolo[3,4-*c*]quinoline derivatives.

Next, Zhao *et al.* utilized allenoates to access 3*H* and 1*H* pyrroles scaffolds, catalyzed by phosphine conditions.[38] It is an attractive method due to its significant advantages for instance, highly efficient, use of cheap PPh_3, easy to handle, reactions under air *etc.* Different substituents on allenoates **47**, isocyanoacetates as well as TosMIC are well tolerated and product **48** was formed in highly chemo- and regio-selective fashion with comparable yields (Scheme 26).



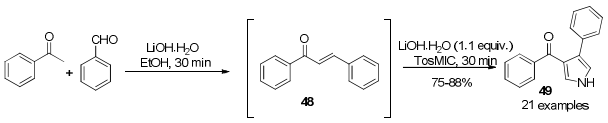
Scheme 26 Synthesis of 3*H* and 1*H* pyrroles described by Zhao and co-workers.

Mechanistically, intermediate ylide **A** was initially formed by the addition of PPh_3 to allenoate, which consequently deprotonated. Subsequently the generated ylide **A** followed by intramolecular cyclization, protonation and elimination to furnished intermediate **F**, which eventually transformed to the final product **48** (Scheme 27).



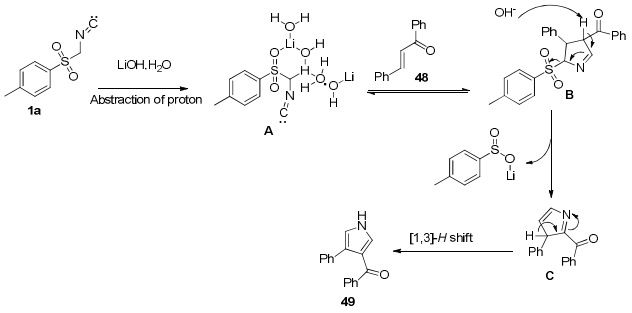
Scheme 27 Postulated mechanism for the synthesis of 3*H* and 1*H* pyrroles.

Further, Nair and co-workers studied range of effective bases in Van Leusen's pyrrole synthesis, and found that $LiOH.H_2O$/EtOH can act as an effective base and also with cinnamaldehyde and thiophene-2-carboxaldehyde derivatives. Under optimized conditions, enolisable ketone and aromatic aldehydes *in-situ* generated chalcones **48**, which subsequently underwent 1,3-dipolar cycloaddition with TosMIC to afford the pyrrole derivatives **49** in 75-88% yield (Scheme 28).[39]



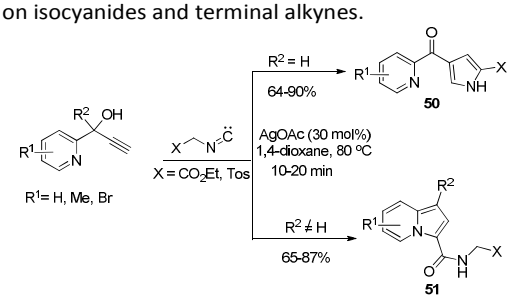
Scheme 28 LiOH mediated cyclization for synthesis of substituted pyrroles.

A plausible mechanism is depicted in Scheme 29. The first step involved abstraction of proton, followed by its stabilization by $LiOH.H_2O$, which underwent [3+2] cycloaddition and afforded cycloadduct **B**. It was observed that polar solvents accelerated the equilibrium step by stabilizing the ionized species, and facilitated the reaction rate (Scheme 29).



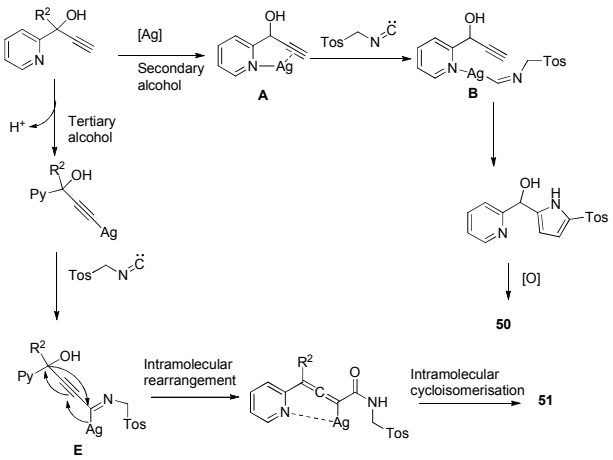
Scheme 29 Proposed mechanism as described by Nair and co-workers.

Similarly Bi *et al.* also reported silver-catalyzed cyclization reactions between tertiary or secondary 2-pyridyl alkynyl carbinols and isocyanides, which divergently afforded 2,4-disubstituted pyrroles **50** and indolizines **51**, respectively in good to excellent yields.[40] Herein, the reaction involved regioselective [3+2] cycloaddition of terminal alkynes with isocyanides to afford the 2, 4-disubstituted pyrroles (Scheme 30). The present method showed wide substrate tolerance both on isocyanides and terminal alkynes.



Scheme 30 Synthesis of indolizines and 2,4-disubstituted pyrroles.

The authors hypothesized that the coordination effect of pyridyl and alkynyl units facilitated the formation of complex **A**, which afforded complex **B** through further coordination with isocyanide (Scheme 31), it was further followed by the [3+2] cycloaddition of the alkynyl unit with isocyanide, to afford 2,4-disubstituted pyrroles **C** regioselectively, which oxidizes to furnish the desired product **50**. On the other hand, desired indolizines **51** were generated from tertiary 2-pyridyl alkynyl carbinols *via* their silver acetylide intermediate. Next, 1,1'-insertion of the isocyanide into the Ag–C bond catalyzed to afford the acetylenic imido complex **E**, which subsequently underwent intramolecular rearrangement to produce 2,3-allenamides **F** followed by intramolecular cycloisomerization to afford the indolizines **51**. The different reactivities of tertiary and secondary alkynyl carbinols can be attributed to the steric hindrance and easy cleavage of hydroxyl group in case of tertiary alkynyl carbinols.

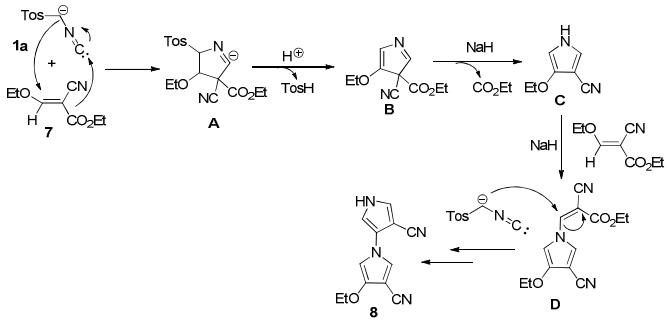


Scheme 31 Plausible reaction mechanism to synthesize indolizines and 2,4-disubstituted pyrroles.

2.1.2 Oxazoles

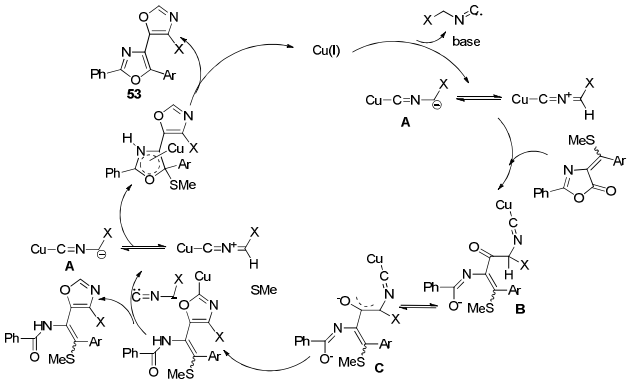
Oxazoles have gained attraction due to their presence in various biologically active natural products and also their utility as valuable precursors in many useful synthetic transformations.[41] Basically, this core can be synthesized from Hantzsch reaction,[42] Schmidt rearrangements,[43] intramolecular alkyne additions,[44] the use of isocyanides as toluenesulfonylmethyl isocyanide (TosMIC) *etc*.[45] Due to their potential in diverse areas, still there is need for more diversity oriented synthesis for these heterocycles.

Moreover, Ila and co-workers in 2013 demonstrated Cu(I)-catalyzed domino process for diversity-oriented synthesis of 2,5,4′-trisubstituted-4,5′-bisoxazoles **44**.[46] The reaction displayed broad substrate scope and excellent functional group compatibility by employing a variety of heteroaryl and aryl-substituted oxazolones and activated methylene isocyanides (Scheme 32).



Scheme 32 Cu-mediated cyclization for the synthesis of bisoxazoles.

On the basis of preliminary results, the authors postulated a plausible mechanism for the above reaction, depicted in Scheme 33. Initially, α-cuprioisocyanide species **A** or its tautomer was generated *in situ* by the reaction of isocyanide with Cu catalyst. Next, intermediate **A**, catalyzed the nucleophilic ring opening of oxazolone which in turn generated acyclic α-acylisonitrile intermediate **B**, which exists in equilibrium with its enolate counter **C**. Subsequently, intramolecular cyclization of intermediate **C** followed by protonation furnished oxazole. After the generation of oxazole, the same iterative process was repeated to give bisoxazoles **53.**

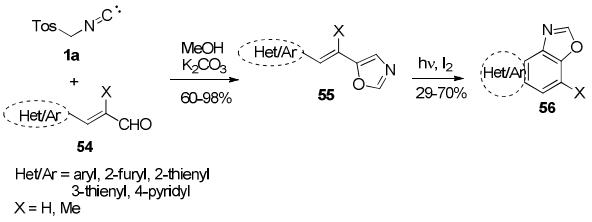


Scheme 33 Proposed mechanism for the synthesis of 2,4,5-substituted-4,5-bisoxazoles.

2.1.3 Naphthoxazoles

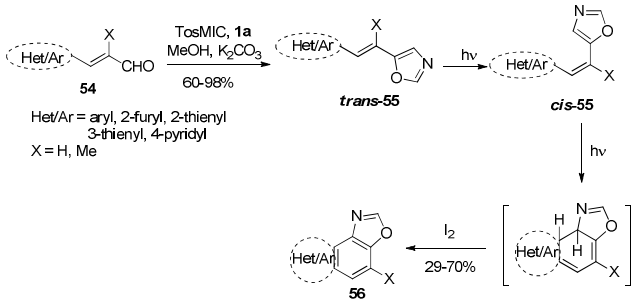
Naphthoxazole derivatives occupy a large domain of biologically significant activities exhibiting anti-trypanosidal, bacteriostatic, cysteine protease inhibitor *etc*.[47]

Kulyk and co-workers explored the synthesis of 5-(aryl/furyl/thienyl/pyridylethenyl)oxazoles, **55** *via* the reaction of α, β-unsaturated aldehydes **54** with TosMIC **1a** (Scheme 34) in refluxing under basic conditions. Furthermore, the synthesized oxazoles **55**, underwent photo-irradiation in the presence of iodine to afford fused heterobenzoxazoles **56**. The present method not only provided access to naphthoxazoles, but also to furyl, thienyl, pyridyl substituted oxazoles in good yields.[48]



Scheme 34 Synthesis of functionalized naphthoxazoles.

A plausible mechanism for the synthesis of naphthoxazoles is depicted in Scheme 35. Initially, the Ar/Het-ethenyloxazole derivatives **55** in *trans*-conformation was generated by the reaction of α, β-unsaturated aldehydes **54** with TosMIC **1a**, which upon photochemical irradiation in a Rayonet reactor having 300 nm lamp afforded the *cis*-**55** derivative. The generated dihydro-intermediate aromatizes in the presence of iodine to afford the title 5-(aryl/furyl/thienyl/pyridylethenyl)oxazoles **56**.

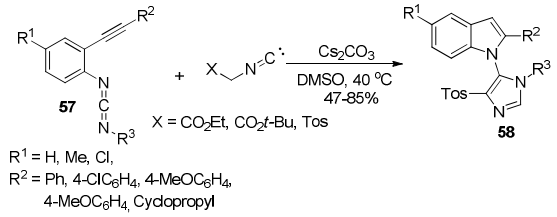


Scheme 35 Synthetic route towards the synthesis of naphthoxazole derivatives.

2.1.4 Imidazoles

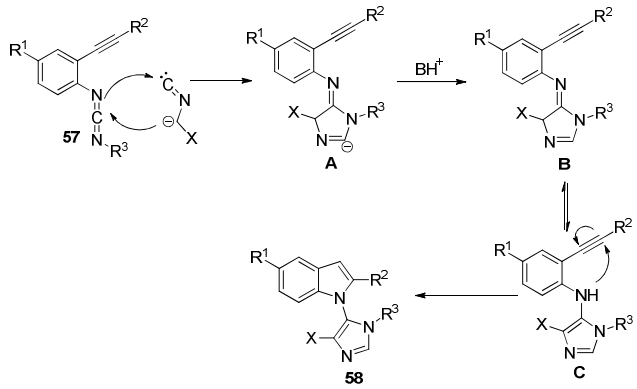
Imidazoles and its derivatives play an important role in the synthesis of natural products and exhibit biologically significant activities, for instance anti-flammatory, antiallergic, analgesic, antitumor agents and glucagon receptor antagonists.[49] This class of compounds has wide application in biology, material science, catalysis etc. This core is presumably present in number of enzymes and metallo-enzymes in the biological systems and is valuable drug candidate.[50]

Moving further, Cai *et al.* described an efficient *en route* towards the construction of indolyl imidazole derivatives **58** *via* base catalyzed reaction of *N*-[2-(1-alkynyl)phenyl]carbodiimides **57** with isocyanides. This reaction involved [3+2] cycloaddition of isocyanide to carbodiimide and its intramolecular cyclization to afford the desired products in good yields (Scheme 36).[51]



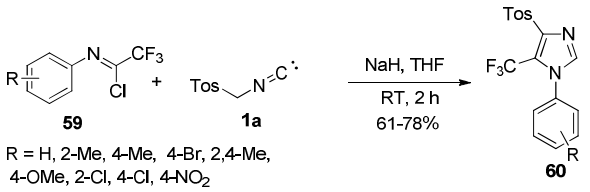
Scheme 36 Synthesis of imidazole derivatives.

A possible pathway for the above transformation is depicted in Scheme 37. Initially, the reaction involved a base catalyzed reaction of isocyanides with the carbodiimide **57**, which first generated the anion **A**, followed by its proton abstraction to form **B** and subsequently isomerized to 2-amino substituted imidazoyl derivative **C**, followed by its intramolecular cyclization to afford the indolyl imidazole derivative **58**.



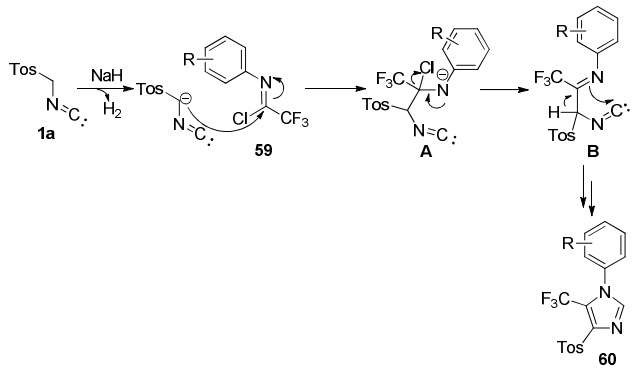
Scheme 37 Proposed route towards the synthesis of indoyl-imidazole derivatives.

Bunev and co-workers also exploited the Van Leusen reaction for the construction of multisubstituted imidazoles **60**. The reaction involves condensation reaction between substituted trifluoroacetimidoyl chlorides **59** and TosMIC **1a**. This protocol provided a quick access to trifluoromethyl substituted 1,4,5-trisubstituted imidazoles **60** in good yields (Scheme 38) and tolerant to both electron-donating as well as electron-withdrawing groups.[52]



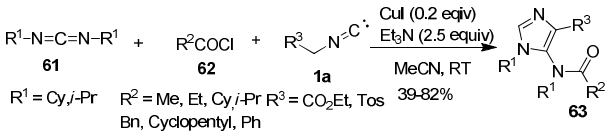
Scheme 38 Synthesis of imidazole derivatives.

A possible mechanistic route is displayed in Scheme 39. It is presumed that TosMIC molecule generated stable carbanion under basic conditions, which attacked on the substituted trifluoroacetaimidoyl chlorides **59**, resulted in the iminium intermediate **B** and its subsequent cyclization afforded the imidazoles **60**.



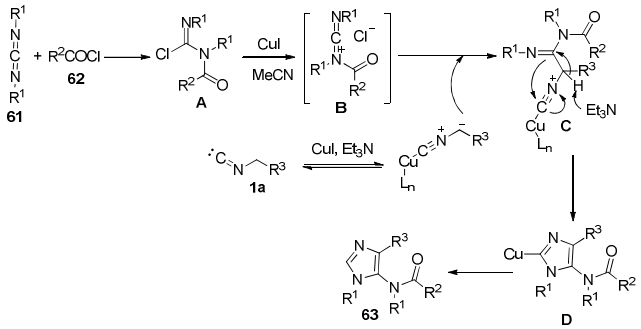
Scheme 39 Tentative mechanism for the synthesis of imidazole derivatives.

Very recently, Zhu and co-workers attempted an efficient CuI catalysed synthesis of unique heterocyclic core of 5-acetamidoimidazoles **63** by reacting isocyanides **1a**, carbodiimide **61** and acyl chlorides **62** (Scheme 40) in 39-82% yield.[53]



Scheme 40 Synthesis of 5-substituted imidazole derivatives.

The mechanism towards construction of the 5-substituted imidazoles is depicted in Scheme 41. Initial mixing of carbodiimide **61** and acyl chloride **62** generated *N*-acyl chloroformamidine intermediate **A** which upon addition of copper iodide formed the hypothetical *N*-acyliminium intermediate **B**. On the other hand, copper (I)-coordinated isocyanide yielded the enolate anion. The later derivative attacked on the intermediate **B** and initiated a cascade of reactions for instance, proton abstraction led by the intramolecular cyclization to furnish the desired derivative **63**.

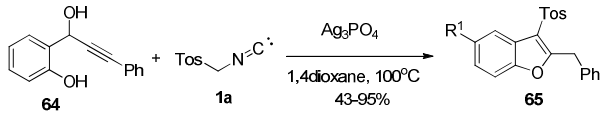


Scheme 41 A plausible reaction pathway for the synthesis of 5-substituted imidazole derivatives.

2.1.5 Benzofurans

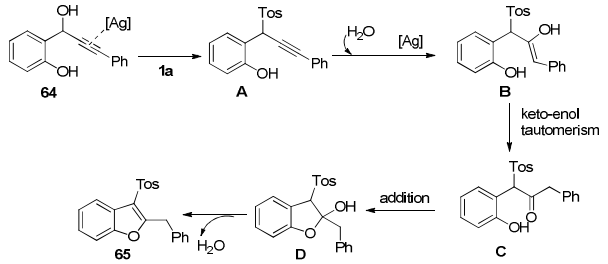
Benzofurans are known as potent biodynamic class of molecules which not only exhibits antiparasitic, antibiotic, antitumor, fluorescent molecules, antihyperglycemic, analgesic activities but also gained importance as privileged synthon in organic synthesis.[54]

Bi and co-workers again attempted [3+2] cycloaddition reaction of α-acidic isocyanides and propargyl alcohols. They observed the dual role of TosMIC **1a** both as a sulfonyl source and as a ligand in heteroaromatization of propargylic alcohols **64**. The reaction went through the remarkable deoxysulfonylation/hydration/condensation cascade pathway for the formation of the sulfonyl benzofurans **65** (Scheme 42).[55]



Scheme 42 Synthesis of benzofuran derivatives.

A probable mechanistic pathway for the synthesis of benzofurans is outlined in Scheme 43. The first step involved the nucleophilic replacement of hydroxyl compound **64** by TosMIC **1a** to generate intermediate **A**, which further reacted with water to form derivative **B**. It was found that conversion of **64** to **65** needed both TosMIC as well as water molecule, where TosMIC acts as a ligand in silver catalyzed reaction. The derivative **C** followed keto-enol tautomerisation to generate intermediate **D**, which again through sequential addition/elimination cascade to afford the desired product **65**.

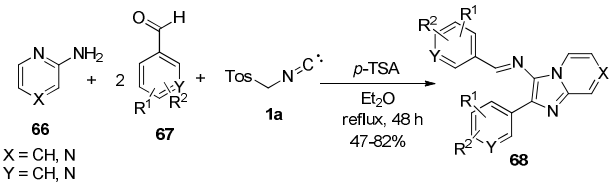


Scheme 43 Mechanistic pathway for the synthesis of benzofuran derivatives.

2.1.6 Imidazo[1,2-a]pyridines

Imidazo[1,2-*a*]azines are drug prejudice scaffolds which demonstrate a wide spectrum of biological activities such as antifungal, antiinflammatory, antitumor, analgesic, antibacterial, antiviral, hypnoselective, and antipyretic *etc*.[56] There are many drugs such as zolpidem for insomnia, alpidem, necopidem and saripidem as anxiolytic agent, minodronic acid to control osteoporosis *etc.* in the market which contain the imidazo[1,2-*a*]pyridine moiety. Due to the pharmaceutical importance of imidazo[1,2-*a*]azines, there is continuous effort to develop new methods for their synthesis.

In continuation, Rahmati and co-workers developed a novel and efficient one-pot, four-component synthetic route of *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines/*N*-arylidene-2-arylimidazo[1,2-*a*]pyrazin-3-amines **68** from readily and cheaply available 2-aminopyridine **66**, aldehydes **67**, and TosMIC **1a** (Scheme 44)[57]



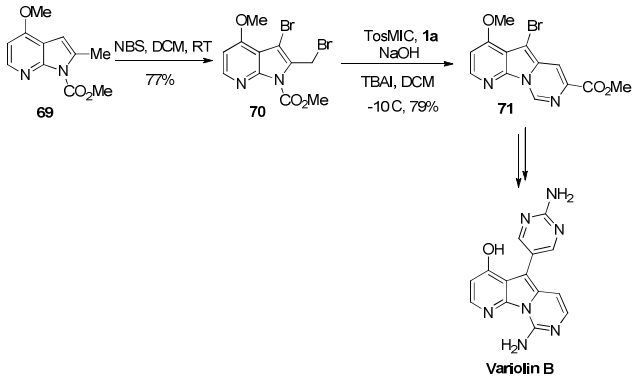
Scheme 44 Synthesis of *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines.

2.2 Synthesis of Six Membered Heterocycles

2.2.1 Pyrrolo[1,2-c]pyrimidine

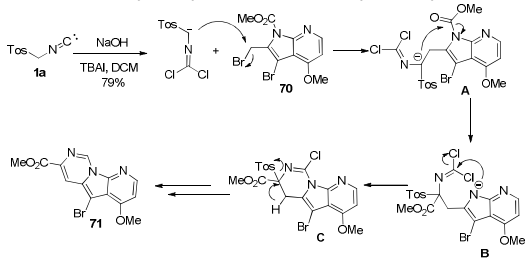
Similar to other nitrogenated heterocycles, the pyrrolo [2,3-*d*] pyrimidine or 7-deazapurine, is an important scaffold, which exists in a vast number of biologically active natural compounds and synthetic drugs [58]. In comparison to purine alkaloids, only scarce literature reports have been published for their synthesis.

To fill this gap, Vaquero and co-workers reported a formal synthesis of anti-proliferative natural alkaloid Variolin B. The synthetic approach was started by treating analogue 69 with *N*-bromo succinimide (NBS) to form derivative 3-bromo-2-(bromomethyl)-4-methoxypyrrolo[2,3-*b*]pyridine **70.** The later derivative **70** was reacted with TosMIC **1a** under basic conditions which resulted in the synthesis of 7-carboxylated pyrido[3',2',4,5]pyrrolo[1,2-*c*]pyrimidine derivative **71** (Scheme 45) [9]



Scheme 45 Synthesis of Variolin B utilizing TosMIC.

The mechanistic pathway for the synthesis of derivative **71** is demonstrated in Scheme 46. Initially, TosMIC was allowed to react under basic and phase-transfer conditions to form the *N*-tosylmethyl dichloroformimide. The formation of **71** was started with the treatment of bromomethyl pyrrole **70** on the *N*-tosylmethyl dichloroformimide, followed by intramolecular transfer of methoxycarbonyl protecting group to form **B**. Further, removal of the chloride from the intermediate **B** and 1,2-elimination of *p*-tosylic acid led the cyclized product **71**.

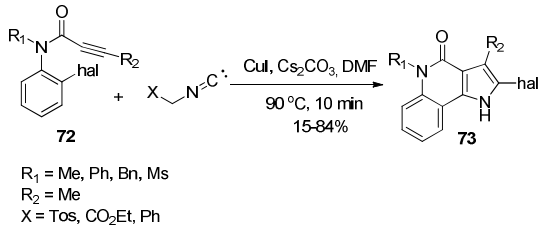


Scheme 46 Synthesis of Variolin B utilizing TosMIC.

2.2.2 Quinolinones

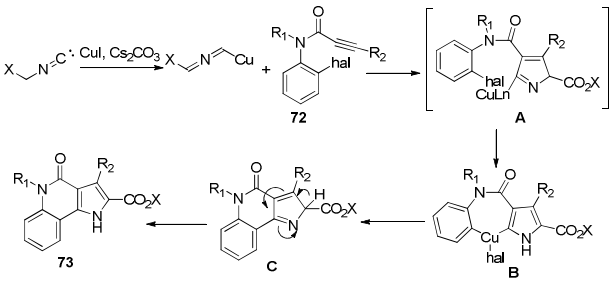
Many alkaloids exhibit potent biological activities invariably due to the presence of quinolinone moiety. These analogues possess antioxidant, anti-inflammatory, enzyme-inhibitor activities *etc.*[59]

Captivated by the promising activities of this biologically elegant core, Cai and co-workers attempted its synthesis. The synthesis of functionalized quinolinones **73** was carried out by reacting *N*-(2-haloaryl)propiolamide **72** with isocyanides efficiently through copper-catalyzed tandem cycloaddition reaction (Scheme 47).[60]



Scheme 47 Synthesis of quinolinones utilizing TosMIC.

Mechanistically, initially Cu-isocyanide was generated by the reaction of isocyanide with copper iodide, which attacked on *N*-(2-haloaryl)propiolamide **72** to form cyclic organocopper intermediates **A-B** through the formal [3+2] cycloaddition and generated C-C bond. Finally, tautomerism of the intermediate afforded the desired product **73** (Scheme 48).

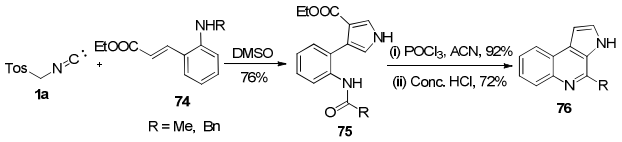


Scheme 48 Mechanistic pathway for the synthesis of quinolinones.

2.2.3 Pyrrolo[2,3-c]quinoline

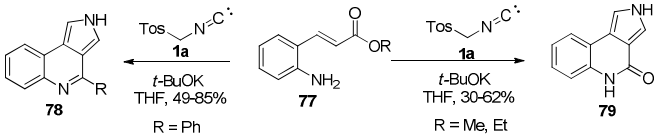
Pyrrolo[2,3-*c*]quinoline derivatives are yet another interesting class of biologically active heterocyclic natural products comprising of antibacterial, antimalarial activities *etc.*[61]

To attempt the first concise total synthesis of pyrroloquinoline natural product marinoquinoline **76**, Yao and co-workers employed the key reaction between TosMIC **1a** and α,β-unsaturated ester **74** under basic conditions. Initially, the reaction resulted in the formation of intermediate **75** and its subsequent cyclization to furnish the natural product marinoquinoline **76** by Morgen-Walls reaction (Scheme 49).[62]



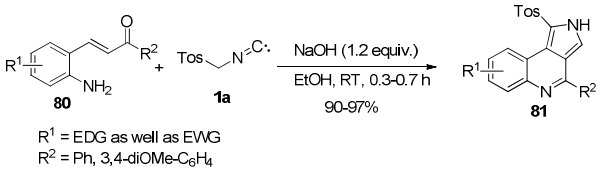
Scheme 49 Synthesis of antimalarial Marinoquinolines A-C.

Ji and co-workers developed an efficient and regioselective approach arising from 2-aminoarylacrylates/2-aminochalcones **77** and TosMIC **1a** *via* Van Leusen reaction under basic conditions. In this regioselective transformation, 2-aminoarylacrylates and 2-aminochalcones resulted in the generation of 2*H*-pyrrolo[3,4-*c*]quinolines **78** and 2*H*-pyrrolo[3,4-*c*]quinolone **79** derivatives, respectively (Scheme 50)[63]



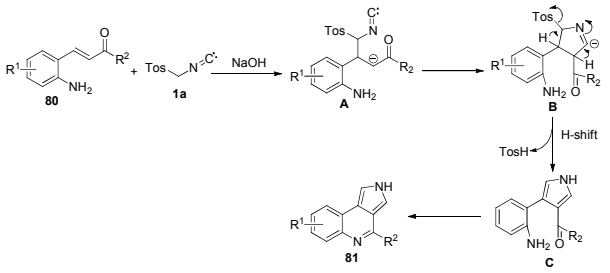
Scheme 50. Synthesis of 2*H*-pyrrolo[3,4-*c*]quinolines.

Going further, Xu and co-workers developed tandem [3+2] cycloaddition followed by cyclization reaction of aminochalcones **80** with TosMIC **1a** derivatives to furnish the diverse tricyclic pyrrolo[3,4-*c*]quinolones **81** (Scheme 51) in 90-97% yield under basic conditions.[64]



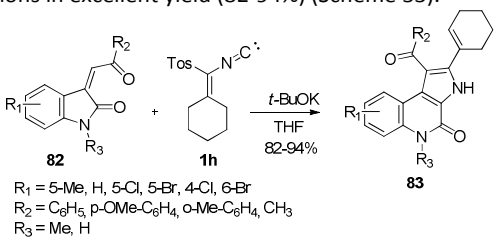
Scheme 51 Synthesis of tricyclic-pyrrolo[3,4-*c*]quinolone derivatives.

Mechanistically, the pathway involved Michael addition of TosMIC to aminochalcones **80** under the basic conditions providing carbanion intermediate **A**, followed by its intramolecular cyclization to generate the imidazoyl anion intermediate **B** and further elimination of tosylic acid provided the intermediate **C** and afterwards intramolecular condensation of ketone with amine furnished the desired product **81** (Scheme 52).



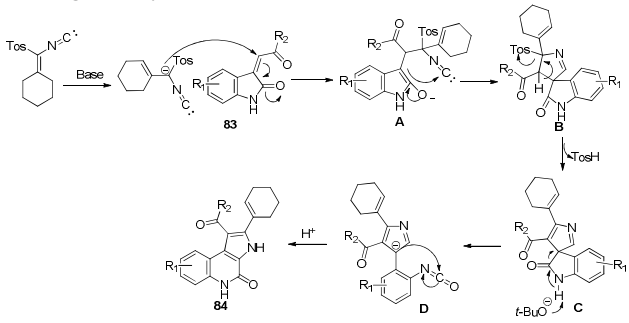
Scheme 52 Mechanistic route towards the synthesis of tricyclic-pyrrolo-*A*-[3,4-*c*]quinolone derivatives.

Another method to synthesize fused pyrrolo[2,3-*c*]quinolinones **83** was described by Wang and co-workers wherein (*Z*)-3-(2-oxo-2-ethylidene)indolin-2-one derivatives **82** were allowed to react with functionalized TosMIC under basic conditions in excellent yield (82-94%) (Scheme 53).[65]



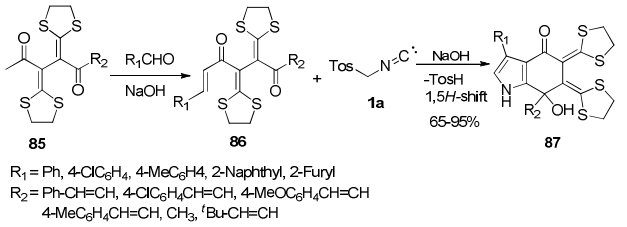
Scheme 53 Synthesis of 3*H*-pyrrolo[3,2-*c*]quinolinones.

The mechanism for the synthesis of 3*H*-pyrrolo[3,2-*c*]quinolinones **84** involved generation of anion from 1-((cyclohexylidene(isocyano)methyl)sulfonyl)-4-methylbenzene, which attacked on the indoline derivative **A**, followed by elimination of tosylic acid which resulted in the generation of *spiro* derivative **C**. The later derivative **C** induced base mediated ring opening and its subsequent cyclization to yield the target compound **84** (Scheme 54).



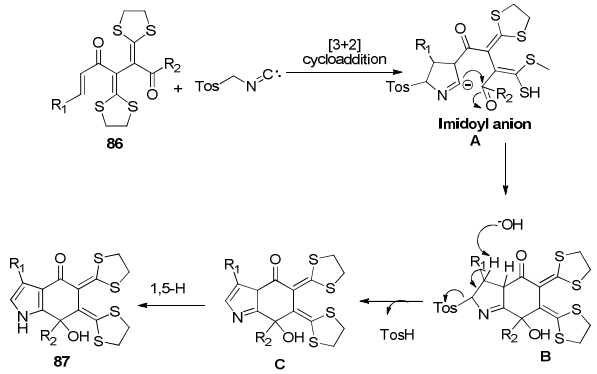
Scheme 54 Mechanism for the synthesis of 3*H*-pyrrolo[3,2-*c*]quinolinones.

Liu and co-workers successfully implemented the tandem [3+2] cycloaddition/intramolecular imidoyl anion trapping strategy for the synthesis of 6,7-dihydro-1*H*-indol-4(5*H*)-ones **87** from alkenoyl-*bis*-(ketene dithioacetals) **86** and TosMIC **1a**. These alkenoyl-*bis*-(ketene dithioacetals) **86** was isolated from the corresponding ketones **85** *via* the basic Knoevenagel condensation (Scheme 55).[66]



Scheme 55 Synthesis of indol-4(5*H*)-ones.

Mechanistically, first alkenoyl-*bis*-(ketene dithioacetals) **86** were allowed to react with TosMIC **1a** under the basic conditions, which underwent [3+2] cycloaddition to generate imidoyl anion **A**. This was further trapped by intramolecularly tethered terminal carbonyl group, eliminated tosylic acid to yield **B** and spontaneous 1,5-*H* shift led to indol-4(5*H*)-ones **87** (Scheme 56).

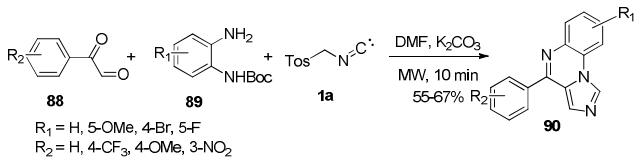


Scheme 56 Mechanistic route towards synthesis of indol-4(5*H*)-ones.

2.2.4 Imidazo[1,5-a]quinoxalines

Imidazo[1,5-*a*]quinoxalines derivatives constitute biologically important class and exhibits a wide variety of biological activities *viz*. antibacterial, antianxiolytic, anticancer etc.[67]

Hulme and coworkers adopted a modified Van Leusen protocol by employing arylglyoxaldehydes **88**, masked amino nucleophile **89**, and TosMIC **1a** using deprotection-cyclisation strategy. The method provided a diversity oriented synthesis of biologically appealing imidazo[1,5-*a*]quinoxalines **90** (Scheme 57).[68]

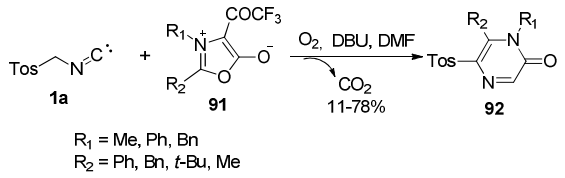


Scheme 57 Synthesis of imidazo[1,5-*a*]quinoxalines.

2.2.5 Pyrazinones

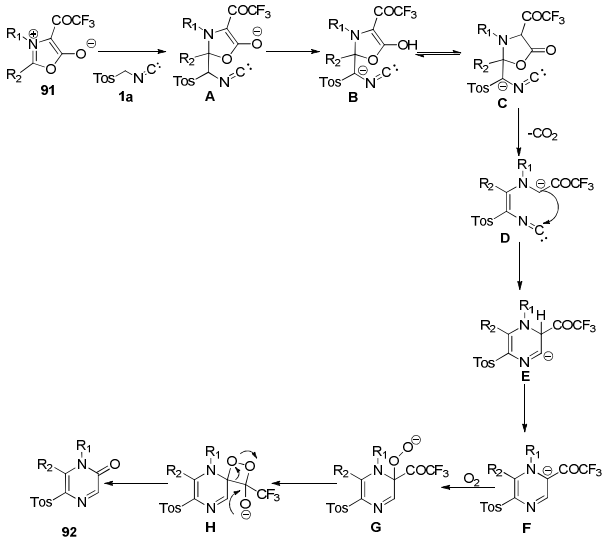
Pyrazinones are important scaffolds from the therapeutic point of view and have been reported for applications in the areas of organic and medicinal chemistry.[69] Similarly, mesoionic compounds have always fascinated chemists due to their masked 1,3-dipolar character.[70]

In order to synthesize 2-(1*H*)-pyrazinones **92**, Kawase and coworkers, transformed mesoionic 1,3-oxazolium-5-olates **91** or münchnones with TosMIC **1a** under oxygen atmosphere (Scheme 58).[71]



Scheme 58 Synthesis of 2(1*H*)-pyrazinones.

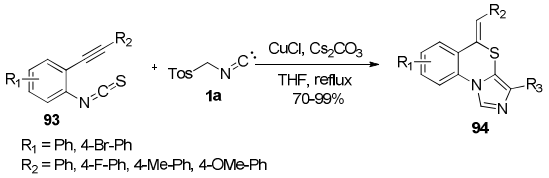
The mechanistic pathway is postulated in Scheme 59. Initially, attack of TosMIC anion on the C-2 position of the oxazole ring **91**, followed by decarboxylation which is due to the electron withdrawing effect of trifluoro group, furthermore addition of oxygen generated superoxide anion, followed by hydro peroxide anion **G** and finally extrusion of trifluoroacetate anion **H** to afford 2-(1*H*)-pyrazinones **92**.



Scheme 59 Synthesis of 2(1*H*)-pyrazinones.

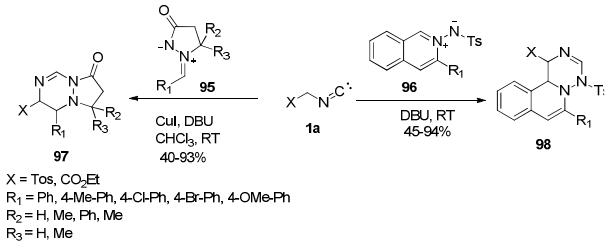
2.2.6 Benzoimidazothiazines

Benzoimidazothiazines core of many bioactive molecules have potential as valuable synthetic intermediates in the organic chemistry.[72] Cai and co-workers explored an efficient route for the synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines **94** using the copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates **93** with isocyanides **1a** with Cs_2CO_3 as a base. The reaction is based on [3+2] cycloaddition of the acidic isocyano group with the isothiocyanate and followed by the ring formation with the intervention of copper (Scheme 60).[73]



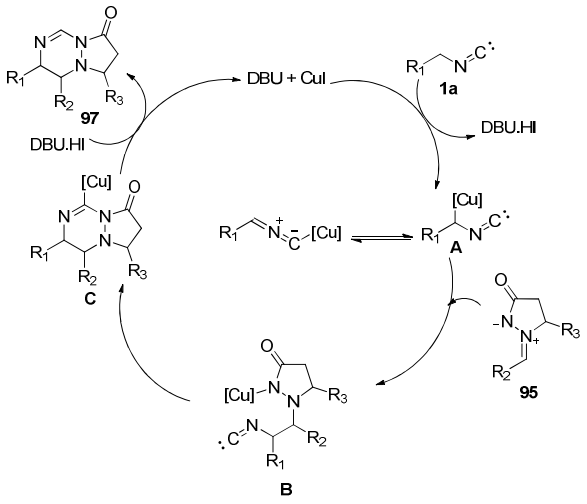
Scheme 60 Synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines.

Herein we have discussed several examples of [3+2] cycloaddition of isocyanides, but the first example of [3+3] cycloaddition reactions of isocyanide was attempted by Liu and co-workers. In this reaction, α-metalated isocyanides[74] were allowed to react with azomethine imine **95** and 1,3-dipoles **96**, which in turn provided regio- and diastereoselectivity to a variety of 1,2,4-triazine **97** & **98** derivatives, respectively in good yields (Scheme 61).[75]



Scheme 61 Synthesis of 1,2,4-triazines.

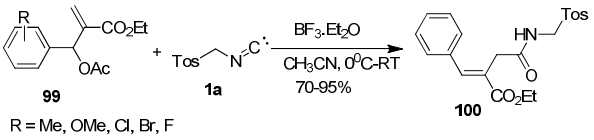
Mechanistic details derived from experimental results are depicted in Scheme 62. The reaction was started with the initial formation of α-cuprioisocyanide and it tautomerized to **A**, which underwent [3+3] cycloaddition on the imine and generated intermediate **B**. This intermediate **B** showed *N*-isocyanide insertion and formed imidoyl-copper complex **C**, which protonated to yield the 1,2,4-triazines, **97**.



Scheme 62 Mechanism for the synthesis of 1,2,4-triazines.

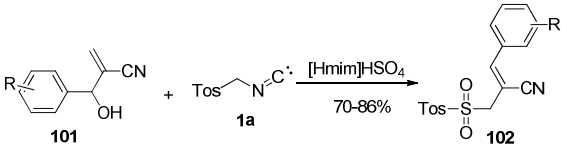
2.3 Miscellaneous Reactions

To check the reactivity of TosMIC on Baylis–Hillman acetates, Yadav and co-workers reported an efficient synthesis of *E*-trisubstituted olefins **100** by allylic nucleophilic substitution of Baylis-Hillman acetates **99** with TosMIC **1a** in the presence of $BF_3.OEt_2$ in good yields (Scheme 63). The present protocol worked well with both electron donating as well as electron withdrawing groups.[76]



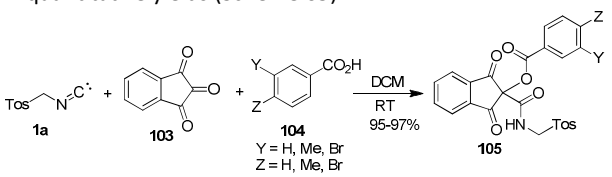
Scheme 63 Synthesis of trisubstituted olefins derivatives.

Also, Garima and co-workers observed an unexpected reaction of Baylis–Hillman alcohols **101** and TosMIC **1a** catalyzed by Brønsted acidic ionic liquid-[Hmim]HSO_4 resulting in the formation of corresponding sulfone derivatives **102** through nucleophilic attack of *p*-toluene-sulfinate anion (Scheme 64).[77]



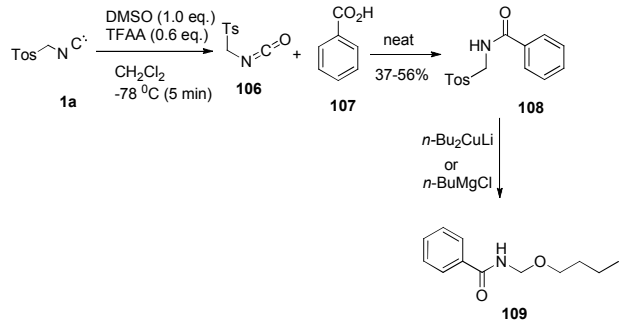
Scheme 64 Synthesis of sulfone derivatives *via* TosMIC mediated Michael addition.

To study the reaction of TosMIC towards Passerini reaction, Ramazani and co-workers synthesized highly substituted 2,2-disubstituted indane-1,3-dione derivatives **105**. The reaction followed Passerini reaction of indane-1,2,3-trione **103**, TosMIC **1a** and substituted benzoic acids **104** at room temperature and in quantitative yields (Scheme 65).[78]



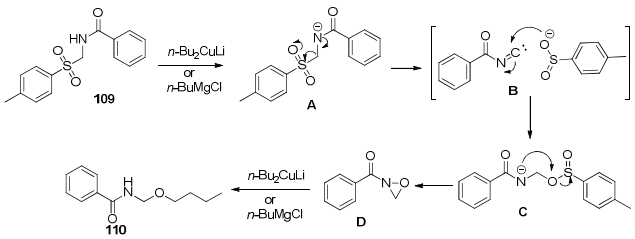
Scheme 65 Synthesis of 2,2-disubstituted indane-1,3-dione derivatives using TosMIC.

Going ahead, Ganem and co-workers reported an efficient method for the synthesis of alkoxymethylamides. The synthetic oxidation protocol started from TosMIC **1a** which generated tosylmethylisocyanate **106**. The later derivative **106** involved in nucleophilic addition reactions with alcohols, amines, and thiols, as well as with benzoic acid **107** to form *N*-tosylmethylbenzamides **108**. The generated *N*-tosylmethylbenzamides **108** underwent an unusual substitution reaction in the presence of organocopper and organo-magnesium reagents to furnish *N*-(alkoxymethyl)benzamides **109** (Scheme 66).[79]



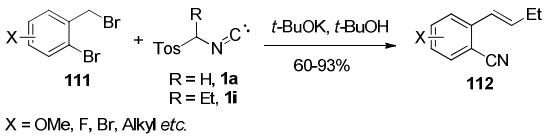
Scheme 66 Synthesis of *N*-(alkoxymethyl)benzamides.

Mechanistically, *N*-tosylmethylbenzamides **109** generated anion **A** in the presence of organometallic reagent and eliminated tosylsulfinate anion **B** which attacked the imine and cyclized to generate acyloxaziridine intermediate **D**. Further the attack of organometallic reagent at the oxaziridine oxygen furnished *N*-(alkoxymethyl)benzamides **110** (Scheme 67).



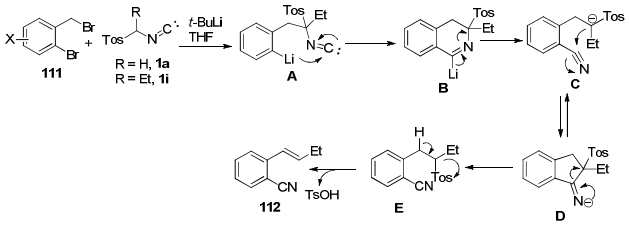
Scheme 67 Synthesis of *N*-(alkoxymethyl)benzamides.

Vaquero and co-workers reacted 2-bromo-benzylbromide **111** with alkylated TosMIC derivatives **1i** in the presence of organolithium and observed an unexpected cascade processes for the synthesis of aryl-(or heteroaryl)cyano derivatives **112** (Scheme 68) in good yields.[80]



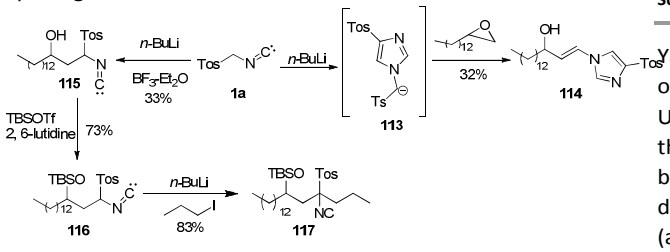
Scheme 68 Synthesis of aryl (or heteroaryl)cyano derivatives.

The reaction involved isocyanide-cyanide rearrangement. It initiated with the treatment of isocyanides with *t*-BuLi yielded 2,3-dihydro-1*H*-indenimines **D**, followed by further treatment with *t*-BuOK in *t*-BuOH to afford the *E*-vinylnitriles **112** (Scheme 69).



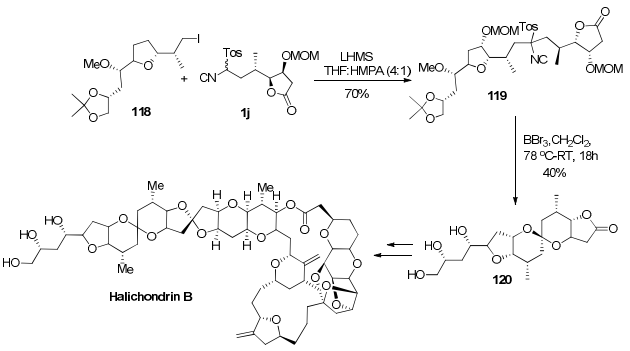
Scheme 69 Proposed mechanism for the isocyanide-cyanide rearrangement.

Williams and co-workers studied the reactivity of acyl anion equivalents (umpolung) *en route* towards the 1,3-hydroxy keto compounds. In short, they treated TosMIC **1a** with butyl lithium to generate the imidazolyl anion **113** which further attacked on the epoxide ring to generate the enols **114**. On the other hand in the presence of $BF_3.Et_2O$, monoalkylated TosMIC derivative **115** were formed, which was subsequently dialkylated **117** under basic conditions (Scheme 70). So, their investigation evaluated computationally and experimentally the reactivity of acyl anion equivalents in the epoxide ring opening[81]



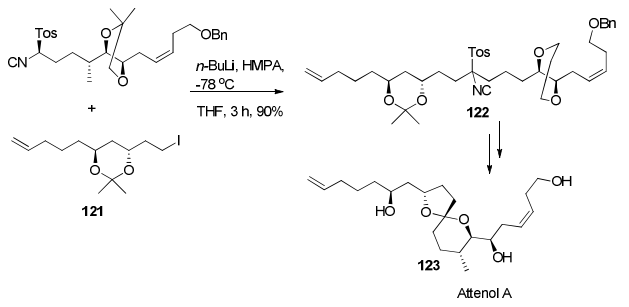
Scheme 70 Synthesis of hydroxyl derivatives *via* TosMIC mediated epoxide ring opening.

Yadav and co-workers reported the stereoselective synthesis of the segment C_{38}-C_{54} of a marine metabolite Halichondrin B. The key feature of the synthesis involved reaction of iodo derivative **118** with mono-alkylated TosMIC **1j** which resulted in the formation of double alkylated derivative **119**. The later derivative **119** was treated with boron tribromide to remove the acidic protecting groups and its subsequent cyclization to yield the product **120**, which upon further functional group transformations to yield the Halichondrin B (Scheme 71)[82].



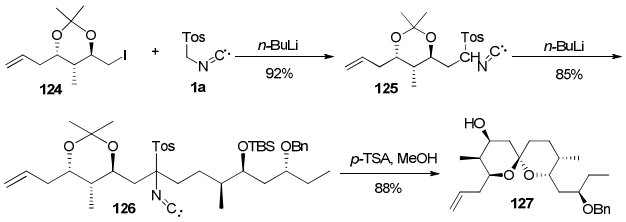
Scheme 71 Synthesis of C_{38}-C_{54} fragment of marine metabolite halichondrin B derivatives.

Same group undertook and developed a highly stereoselective total synthesis of Attenols A and B. The key feature of the synthesis involved double alkylation of TosMIC derivative **1k** to construct the spiroacetal segment **122**. This spiroacetalization strategy is one-pot, simple and efficient in contrast to dithiane mediated spiroacetalization protocol. The generated spiroacetal **188** after functional group transformations gave Attenol A, **123** (Scheme 72).[83]



Scheme 72 Synthesis of Attenol A.

Yadav and co-workers discussed the stereoselective synthesis of the spiroketal fragment of the immune suppressant (-)-Ushikulide A, **127**. The key feature of this synthesis involved the construction of the spiroketal moiety, which was formed by the subsequent hydrolysis of a dialkylated TosMIC **126** derivative which is generated from monoalkylated TosMIC **125** (alkylation of TosMIC **1a**) with suitably substituted iodohydrin derivatives **124** (Scheme 73).[84]



Scheme 73 Synthesis of (-)-Ushikulide A.

Conclusions

The present survey has clearly reflected that activated isocyanides has become part and parcel in the synthesis of diversified heterocyclic systems. Although tremendous advances have been achieved in this field, it is firmly believed that the applications of the TosMIC and its analogues to deliver novel scaffolds will continue to grow. These synthetically viable reagents possess high synthetic utility in modern organic, combinatorial and medicinal chemistry. There are many opportunities to tame the potential of this synthetically viable reagent. Among other isocyanides, these acidic isocyanides occupy an important place due to their exciting chemistry and for opening new avenues for other class of molecules. They do help in advancing new cascade reactions/domino reactions in order to synthesize complex acyclic and cyclic systems *viz* peptides, peptide molecules, nitrogen heterocycles *etc*. These complexes not only have useful potential in the synthetic organic chemistry, but also in the areas of inorganic, coordination and polymer chemistry. In a nut shell, they are perspective monomers with diverse functional groups and have unique qualities of isocyanide and carboxylic group. Therefore, the exploration of α-acidic isocyanides will open new paradigms of synthetically challenging molecules.

Acknowledgements

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