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REVIEW

Cyanomethyl pyridinium and isoquinolinium salts: a versatile chemical reagent for the synthesis of annulated heterocycles

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Abstract

Over the years, numerous advancements have been in synthesizing various heterocyclic compounds using pyridinium ylides. Imidazo pyridine derivatives are highly valued heterocyclic motifs that are commonly present in various natural and pharmaceutical compounds. These can be conveniently synthesized using cyanomethyl salts of pyridine and analogous isoquinolines. In this mini-review, we will discuss the latest developments regarding the use of these salts in the creation of annulated heterocycles. Various annulated heterocycles such as chromeno-imidazo pyridines, isoquinolines, imidazothiazine, chromenoimidazocarbolines, imidazo pyridines, chromeno azepines, pyrido indolizine carbonitriles, pyridoindolizines, cyanoindolizinyl acetamides, tetrahydroindolizines, indolizinoindol amines, pyridobenzimidazoles, cyclo azines, pyrroloisoquinolines have been synthesized under mild reaction conditions. These salts are also used for the synthesis of spirocyclic isoxazolo pyrrole isoquinolines and optically active pyrroloisoquinolines, pyrrolophthalazine, and tetrahydropyrrolophthalazinyl pentadienoate derivatives.

Keywords Cyanomethyl pyridinium · Ylides · Cycloaddition · Annulated heterocycles · Imidazo[1,2-a] pyridine

Introduction

Pyridinium and its similar salts have proven to be highly useful frameworks in natural products and pharmaceuticals due to their structural diversity (Sowmiah et al. 2018). Many organic transformations employ these salts as acylating agents, phase transfer agents, and ionic liquids (He et al. 2019). Salts like pyridinium ylides are important in industrial applications, as they serve as high-ranking building blocks for creating various heterocycles. Pyridinium ylides are nitrogen ylides that have a pyridinium N as a cationic component. They are created from pyridinium salts. It exhibits exceptional stability due to the delocalization of charge in the heteroaromatic system (Fig. 1). The first stable pyridinium ylide was generated by Kröhnke in 1935 (Kröhnke 1935). A widely used technique for creating pyridinium/isoquinolinium ylide involves reacting pyridine/isoquinolinium (1) with cyanomethyl halides. This creates 1-(cyanomethyl) pyridinium and isoquinilinium halides (3), which can then be treated with a base to form the desired ylide (4) (Fig. 1). Pyridinium ylides are also used in the synthesis of many significantly important heterocyclic intermediates such as indolizines, cyclopropanes, 2,3-dihydrofurans, substituted pyridines, nitrones, and azepines (Funt et al. 2020). The reactivity of pyridinium ylides is influenced by the characteristics of the reactants employed. In general, it undergoes a reaction with different nucleophiles, specifically an addition reaction with a Michael acceptor through [3 + 2] cycloaddition, at room temperature, when a base is present.

Applications of 1-(cyanomethyl)pyridinium and isoquinilinium salts

The pyridinium ylides generated in situ have been widely used in the synthesis of annulated heterocycles based on chromeno framework such as chromeno-imidazo pyridines and isoquinolines, imidazo-thiazines, imidazo-carbolines, azepines, etc. It has also been used in the construction of pyrido-based scaffolds like indolizine-10-carbonitriles, indolizines, cyanoindolizinyl-acetamides, tetrahydroindolizines, indolizino-indolamines, benzimidazoles,

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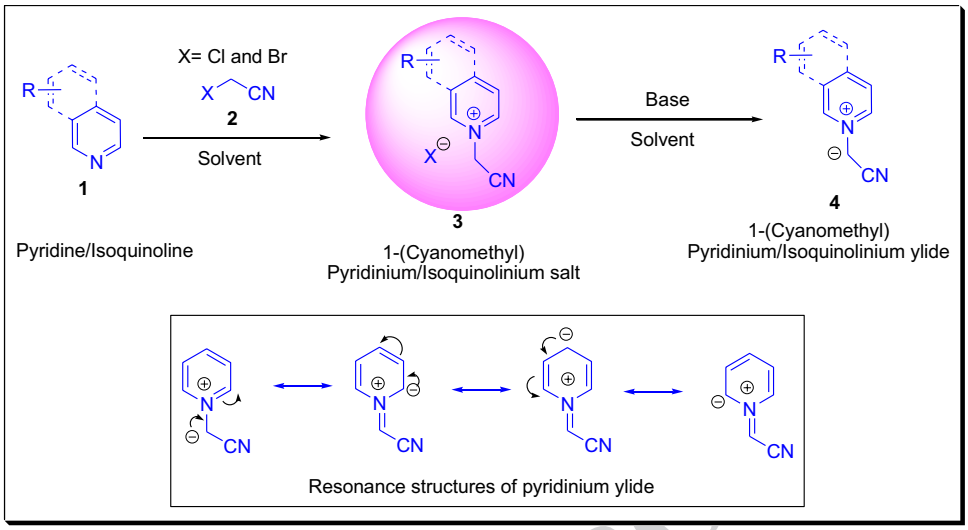

Fig. 1 Generation of 1-(cyanomethyl)pyridinium and isoquinilinium ylides

cyclazines, and pyrrolo-isoquinolines (Fig. 2). It can also be used for the synthesis of spirocyclic isoxazole derivatives and optically active pyrroloisoquinolines, pyrrolophthalazine, and tetrahydropyrrolo[2,1-a]phthalazin-1-yl)penta-2,4-dienoate derivatives (Fig. 2).

Synthesis of chromene imidazo derivatives

Chromene derivatives are an important class of heterocyclic compounds found in many biological active (Kostova 2006; Nayyar and Jain 2005) as well as therapeutic compounds (Fylaktakidou et al. 2004; Asres et al. 2005). The substituent at three positions of the chromene ring is crucial for good biological activity (Chimenti et al. 2009). Consequently, the substituted imidazo[1,2-a]pyridines are very significant heterocyclic scaffolds (Ismail et al. 2008) found in many bioactive compounds.

In this regard, Proença and Costa (2010) reported the synthesis of imidazo[1,2-a]pyridines containing chromene units (**7**) by one-pot condensation-cyclization reactions of salicylaldehydes (**5**) and 1-(cyanomethyl)pyridinium chloride (**3**) in an aqueous Na_2CO_3 solution at room temperature (Scheme 1). The various mono-substituted cyanomethyl pyridinium chloride salts were synthesized and reacted with mono-substituted salicylaldehydes under optimized reaction conditions. The yields of the novel compounds were moderate (47–71%) due to the various side reactions. The products were isolated in high purity by simple filtration from the aqueous solution. It was observed that the 4-amino substituted pyridinium salt didn't get desired product due to the formation of imino-chromene intermediate (**8**). The reaction of 3-amido-1-(cyanomethyl) pyridinium chloride with 3-methoxy salicylaldehyde gave a mixture of two isomeric tetracyclic products (**9a** and **9b**). The mechanism of the reaction involves the first formation of Knoevenagel product (**I**) from 1-(cyanomethyl)pyridinium chlorides and aromatic aldehyde. In the presence of a base, the product (**I**) undergoes intramolecular cyclization to form **II**. Intermediate **II** gets converted into intermediate **III** via an intramolecular nucleophilic attack of imine nitrogen onto C-2 of the activated pyridinium ring, which rapidly tautomerizes into the desired product.

Voskressensky and co-workers synthesized various chromeno[2',3':4,5]imidazo[2,1-a]isoquinolines (**10**) via novel domino reactions of isoquinoline-derived immonium salts (**3**) and various salicylaldehydes (**5**) in the presence K_2CO_3 as a base in DMF:H_2O mixture at room temperature(Voskressensky et al. 2012) (Scheme 2). They applied the same methodology for the synthesis of substituted chromeno-isoquinoline derivatives (**11**) via domino reactions of corresponding isoquinolinium salts (**3**) and aldehydes (**5**) using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a base in a MeOH:H_2O mixture at room temperature(Voskressensky et al. 2016). It was observed that DBU is a superior base as compared to Na_2CO_3. Similarly, a novel domino condensation–intramolecular nucleophilic cyclization approach was developed for the synthesis of annulated thiochromenes (**12**) under similar reaction conditions (Voskressensky et al. 2013b).

They also obtained benzosilanochromenoimidazopyridines (**13**) by a domino reaction of 5,5-dimethyl-10-oxo- and 10-hydroxy-10-allyldihydrobenzosilanopyridinium *N*-cyanomethyl salts (**3a**) with salicylaldehydes (**5**) in a MeOH:H_2O mixture at room temperature (Scheme 3). In the case of the

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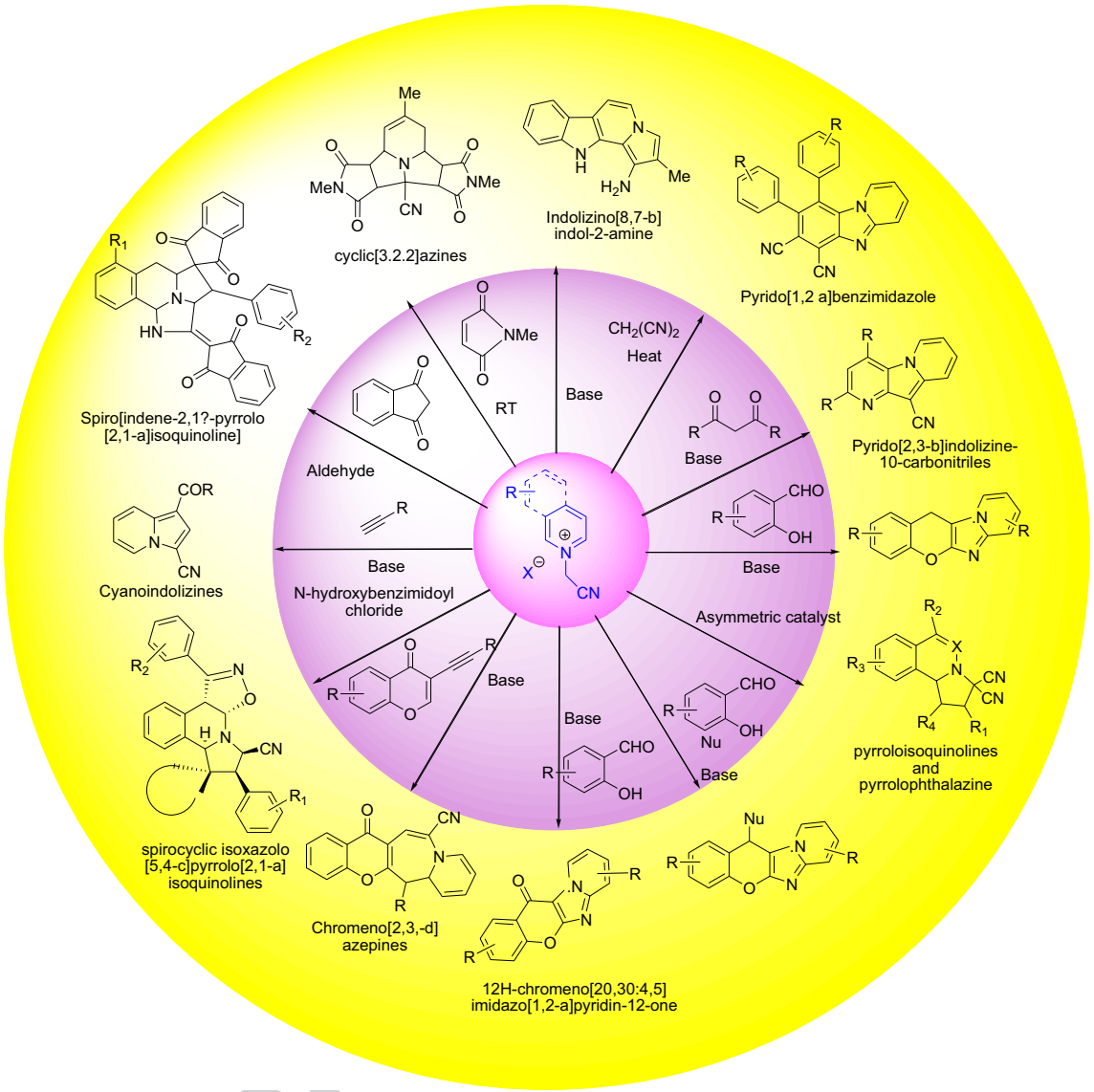

Fig. 2 Various heterocyclic scaffolds obtained from cyanomethyl pyridinium and isoquinolinium salts

10-allyl-10-hydroxy-dihydrobenzosilanopyridinium salts (**3b**), the reaction occurred at both positions of the pyridine fragment to form a mixture of the isomeric benzosilano and benzosilano-chromeno imidazopyridines (**14**) (Voskressensky et al. 2013a). Unfortunately, the yields of the reactions are very less.

A new route toward the synthesis of chromenes, annulated with an imidazo[5,1-c][1,4]thiazine core (**15**), was also reported by Voskressensky et al. (2015a). The yield of *N*-(cyanomethyl)-1,3-azolium salts significantly increased under microwave (MW) irradiation. The reaction involves a base-promoted ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) domino reaction of cyanomethyl-azolium quaternary salts (**3**) with salicylaldehydes (**5**) in MeOH:H_2O using different bases at RT to reflux (Scheme 4). A few of them showed high cytotoxic activity against human tumor cells. It has been shown that cyanomethyl imidazolium chloride reacts with salicylic aldehydes differently, forming coumarin-substituted imidazolium salts. It has also been reported that the 1,3-oxazole failed to give

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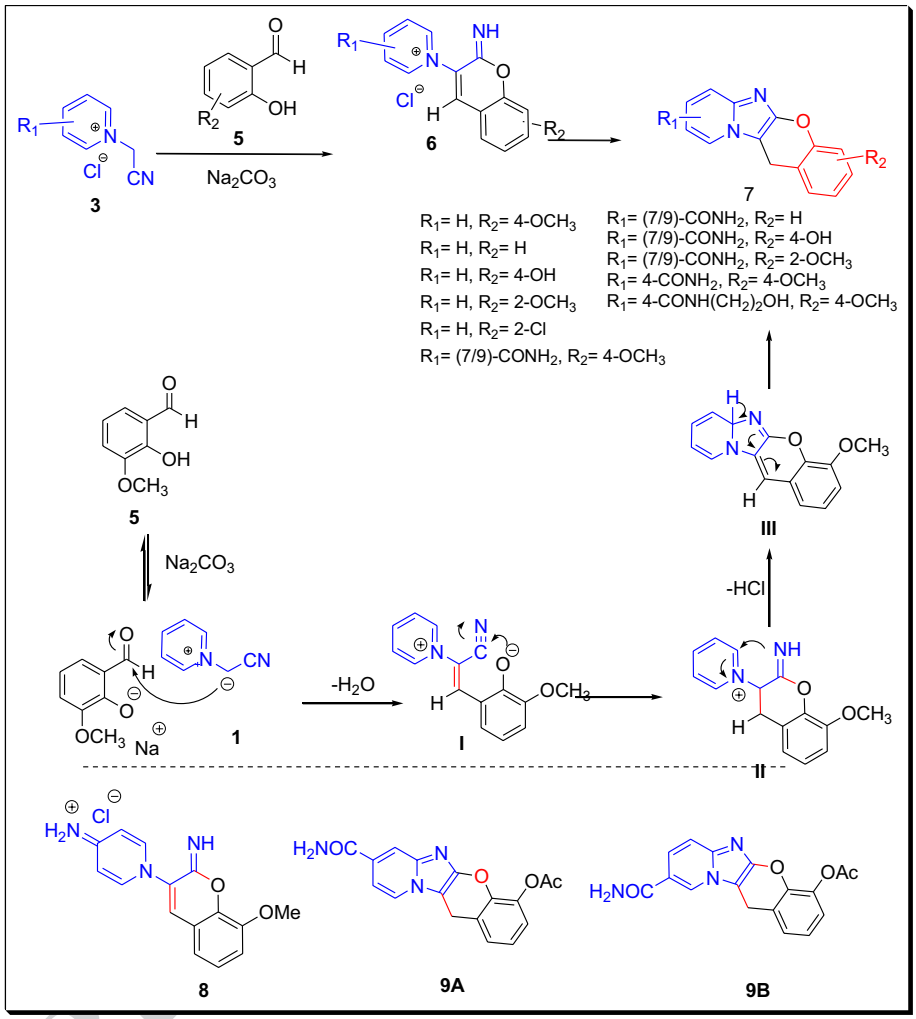
Scheme 1 Synthesis of chromeno-imidazo[1,2-*a*]pyridines via one-pot condensation-cyclization



the *N*-cyano methyl quaternary salt. The mechanism involves the reaction of thiazolium salts (**3**) with salicylaldehyde (**5**) under a base-encouraged domino process, involving an ANRORC step through intermediate **I**, **II**, and **III**.

Similarly, they reported a novel domino condensation-intramolecular nucleophilic cyclization approach toward the synthesis of an annulated imidazo-pyrrolo-pyridine core (Scheme 5). The reactions proceeded through a base-promoted domino reaction of azaindole quaternary salts. In the first report, they synthesized chromenes annulated with an imidazo[1,2-a]pyrrolo[2,3-c]pyridine core (**16**) by refluxing 6-azaindole quaternary salts (**3a**) with salicylaldehydes (**5**) in ethanol in the presence of NH_4OAc (200 mol%) for 3 h. The precipitated products were collected by filtration in 25–57% yields(Voskressensky et al. 2015b). In continuation with this, *N*-(cyanomethyl)azaindolium salt (**3b**) reacts with salicylic aldehydes (**5**) under similar conditions giving coumaryl-substituted 7H-7-azaindoles (**17**). However, performing the reaction under MW irradiation led to the formation of the desired product **18** in absolute EtOH, molecular sieves, and anhydrous K_2CO_3 with 27–42% yields (Voskressensky et al. 2017b). Under similar reaction conditions, 5-azaindolium salt (**3c**) gave annulated pyrrolopyridines (**19**) in 70–87% yield. While 4-(cyanomethyl)-4-azaindolium salt (**3d**) in the domino process gave isomeric chromenoimidazo-pyrrolopyridines (**20**) under similar reaction conditions.

Similarly, they reported the reaction of N^2-(cyanomethyl)-*β*-carbolinium bromide (**3**) with different salicylaldehydes (**5**) in the presence of NH_4OAc in refluxing EtOH(Voskressensky et al. 2017a). The reaction proceeded as a domino reaction that led to the formation of chromeno-imidazocarbolines (**21**) in 38–54% yields (Scheme 6).

A similar approach was reported, which involves the intramolecular cyclization of 1-(2-imino-2H-chromen-3-yl)

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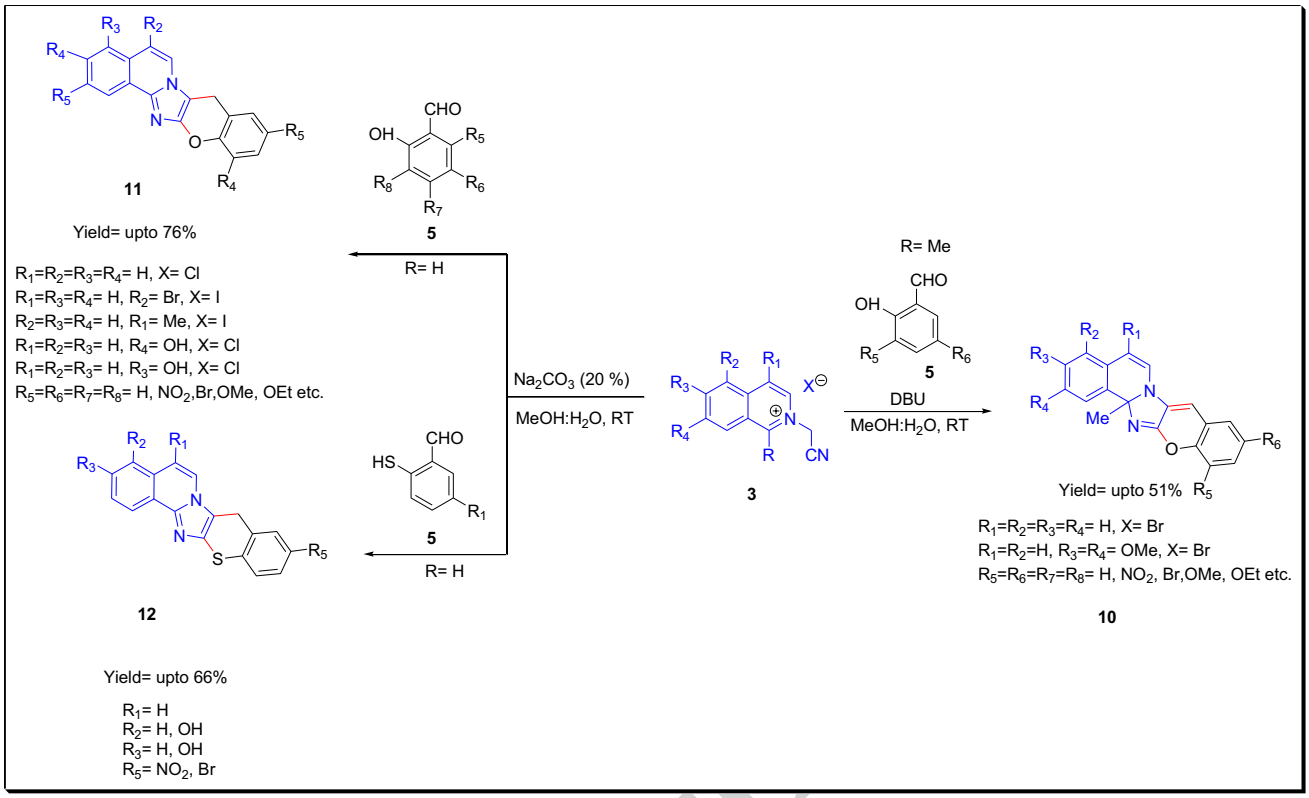
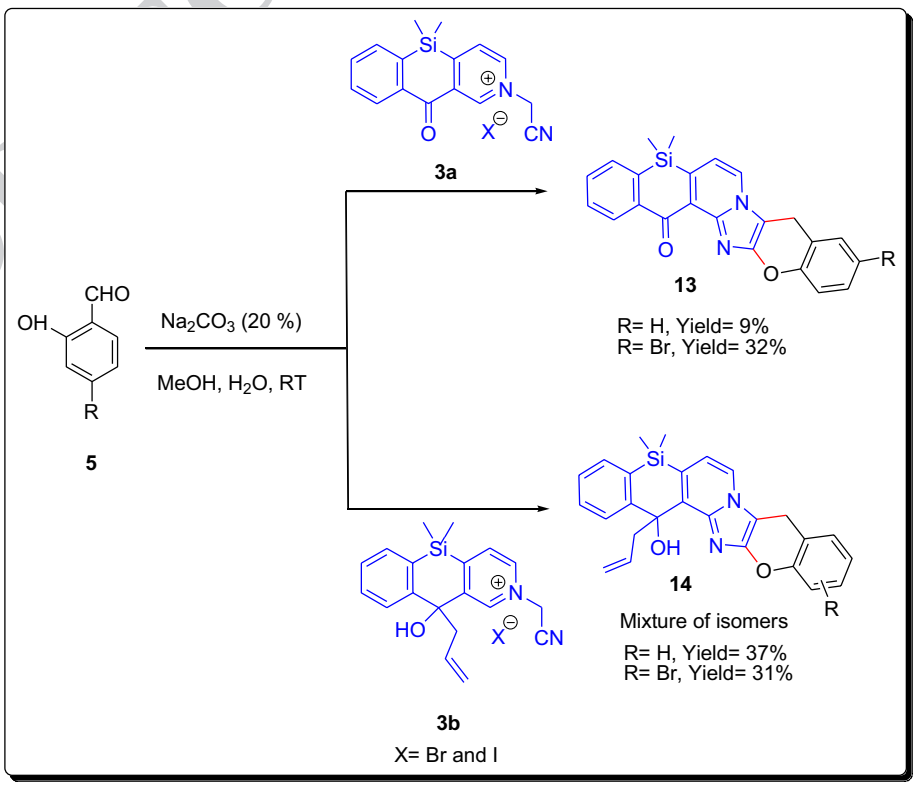


Scheme 2 Synthesis of chromeno-isoquinolines via a domino reaction

Scheme 3 Synthesis of chromeno-isoquinolines via a domino reaction



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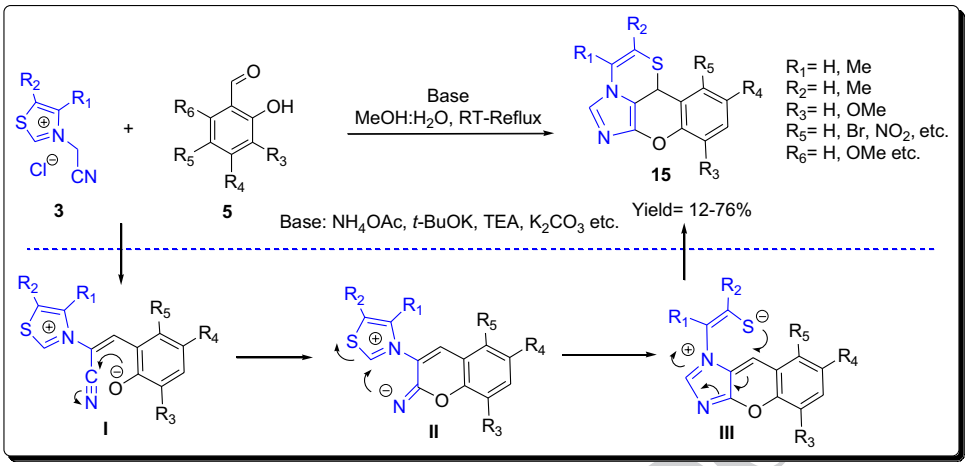
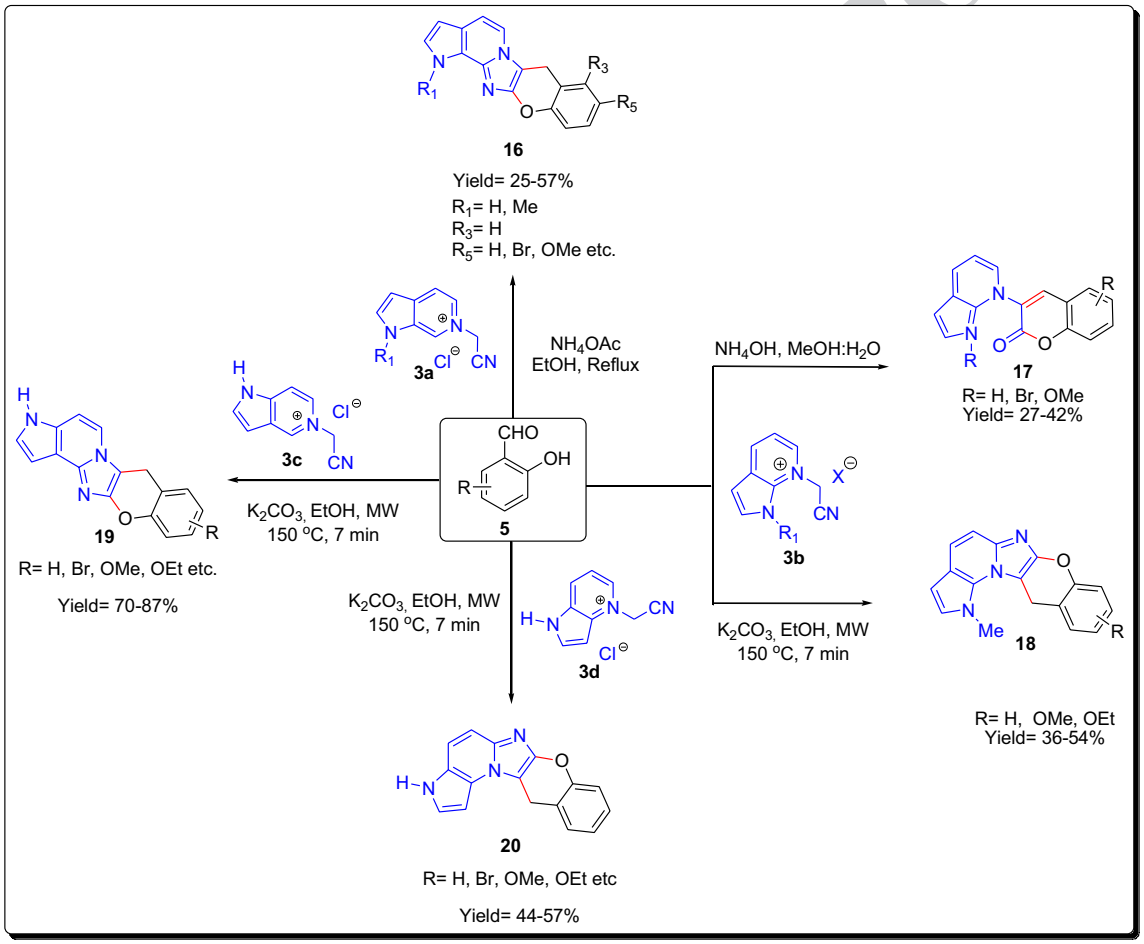
Scheme 4 Synthesis of the imidazo-thiazine core via base-promoted ANRORC domino reaction





Scheme 5 Synthesis of chromeno-imidazo-carbolines by domino reaction

pyridinium chloride (**6**) in the presence of various organic bases such as DABCO, *N*-methyl piperazine, and quinuclidine in ethanol to form compound **22**(Costa and Proena 2011)(Lima et al. 2015). The method is a simple

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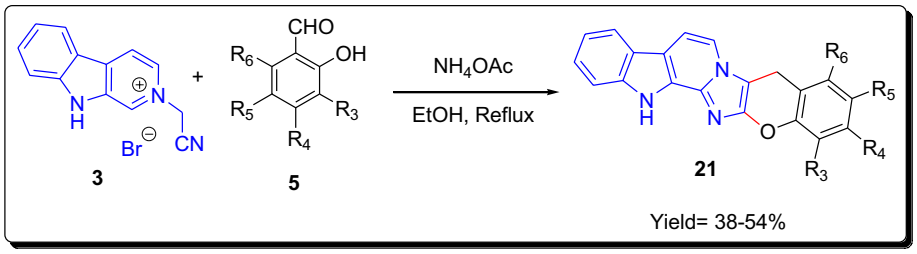
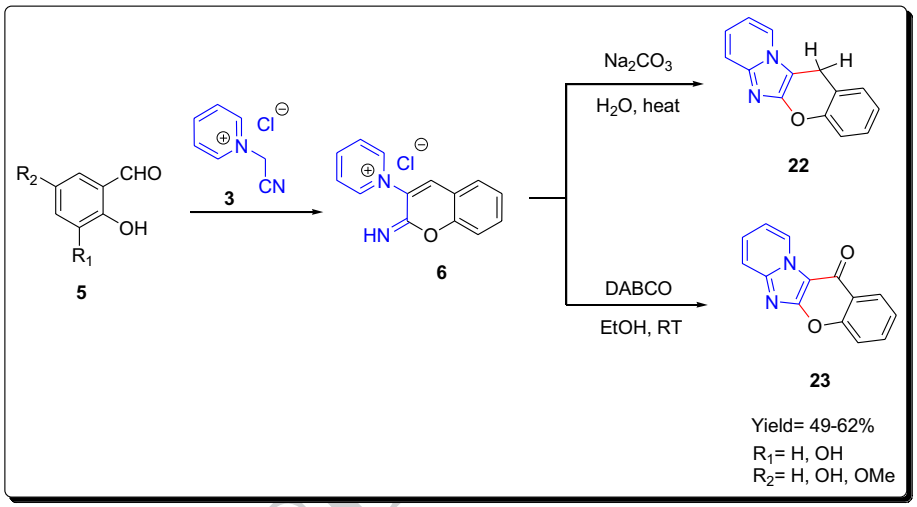
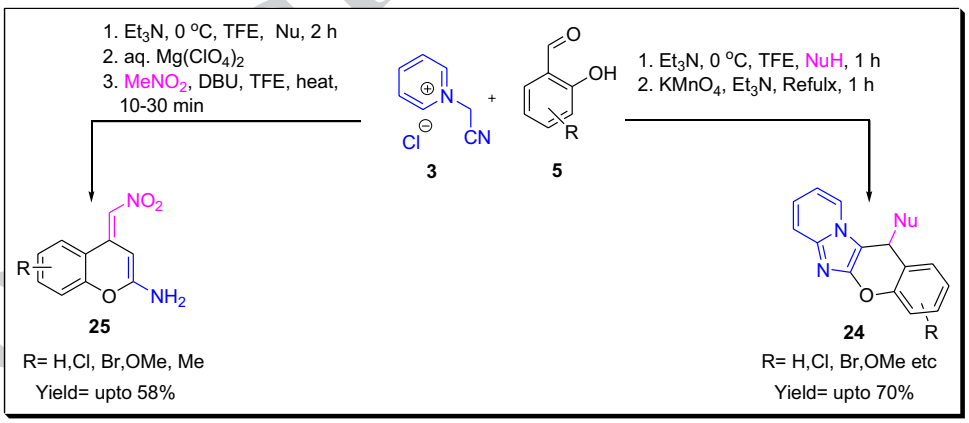
Scheme 6 Synthesis of chromenoimidazocarbolines



Scheme 7 One-pot synthesis of chromeno-imidazo-pyridin-one



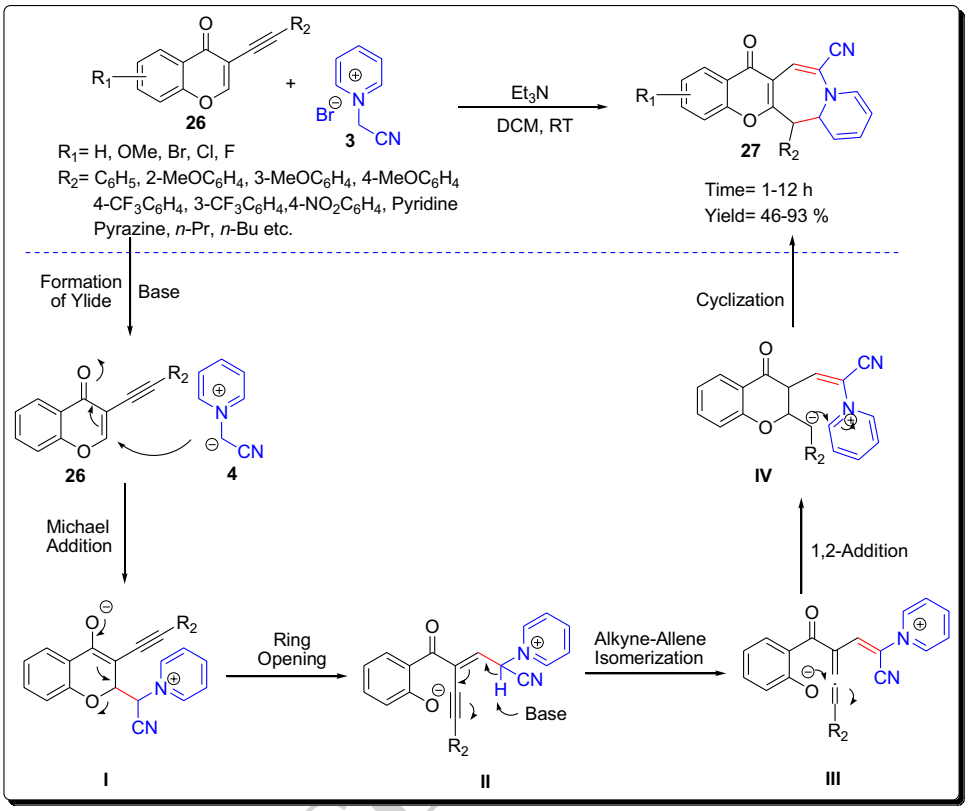
Scheme 8 Mn-mediated sequential three-component domino reactions for the synthesis of annulated imidazopyridines

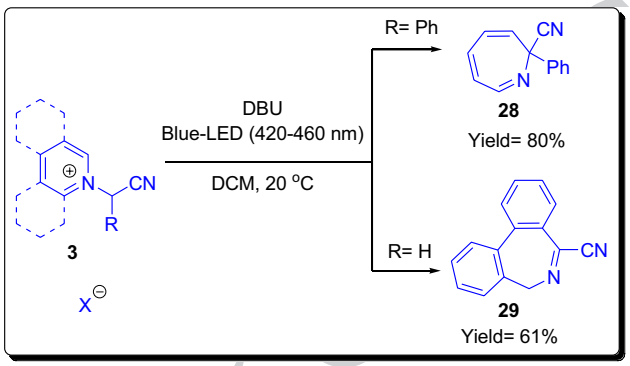


one-pot synthesis of chromeno-imidazo-pyridinone (**23**) in the presence of DABCO in ethanol at room temperature (Scheme 7). The method also contributed to forming other interesting side products. A detailed study of the experimental conditions allowed a clear understanding of the reaction pathways.

Recently, Voskressensky and co-workers (Storozhenko et al. 2018) reported Mn-mediated sequential three-component domino Knoevenagel/cyclization/Michael addition/oxidative cyclization reactions for the synthesis of annulated imidazopyridines (**24**) (Scheme 8). The various nucleophiles, such as nitromethane, indoles, pyrroles, phenols, pyrazole, indazole, diethyl malonate, etc., were successfully reacted using $Mn(OAc)_3{\cdot}2H_2O$ or $KMnO_4$ as stoichiometric oxidants in the presence of TEA in trifluoroethanol (TFE) at reflux. The protocol offers a broad substrate scope and tolerates a wide range of functional groups. The reaction produces a library of

Scheme 9 Synthesis of chromeno azepines via base-promoted cascade reactions of 3-(1-alkynyl)chromones





Scheme 10 Synthesis of monocyclic and polycyclic azepines by dearomative photochemical rearrangement of aromatic *N*-ylides

chromenoimidazoles with complex substitution and annulation patterns. The mechanism involves the Knoevenagel condensation of salicylaldehyde (**5**) and *N*-(cyanomethyl) pyridinium salt (**3**) to form styryl derivative, which suffers intramolecular cyclization to form 2-imino-chromene salt. The consequent reaction of with nucleophiles followed by cyclization, deprotonation, and oxidation, leads to the final product. In continuation with this, they (Storozhenko et al. 2020) synthesized a novel 2-amino-4-(nitromethylidene) chromenes (**25**) from the reaction of 1-(2-imino-2H-chromen-3-yl)pyridinium perchlorates and nitromethane in the presence of DBU at reflux in TFE (Scheme 8).

Synthesis of azepines

Recently, Hu et al. (Zhang et al. 2019) developed a new approach for the synthesis of chromeno[2,3-d]azepine derivatives (**27**) through base-promoted cascade reactions of 3-(1-alkynyl)chromones (**26**) with pyridinium ylides (Scheme 9). The tandem process contains a Michael addition/deprotonation/alkyne–allene isomerization/cyclization followed by the subsequent 1,2-addition. The reaction provided novel access to a new class of polycyclic heterocycles. This ring system can also be expanded to the xanthone skeleton. The screening of various reaction parameters for the reaction of 3-(1-alkynyl)-chromone (R = Ph) with cyanomethyl pyridinium bromide showed that up to 93% yield was obtained using TEA as a base in DCM at room temperature. The optimized reaction conditions

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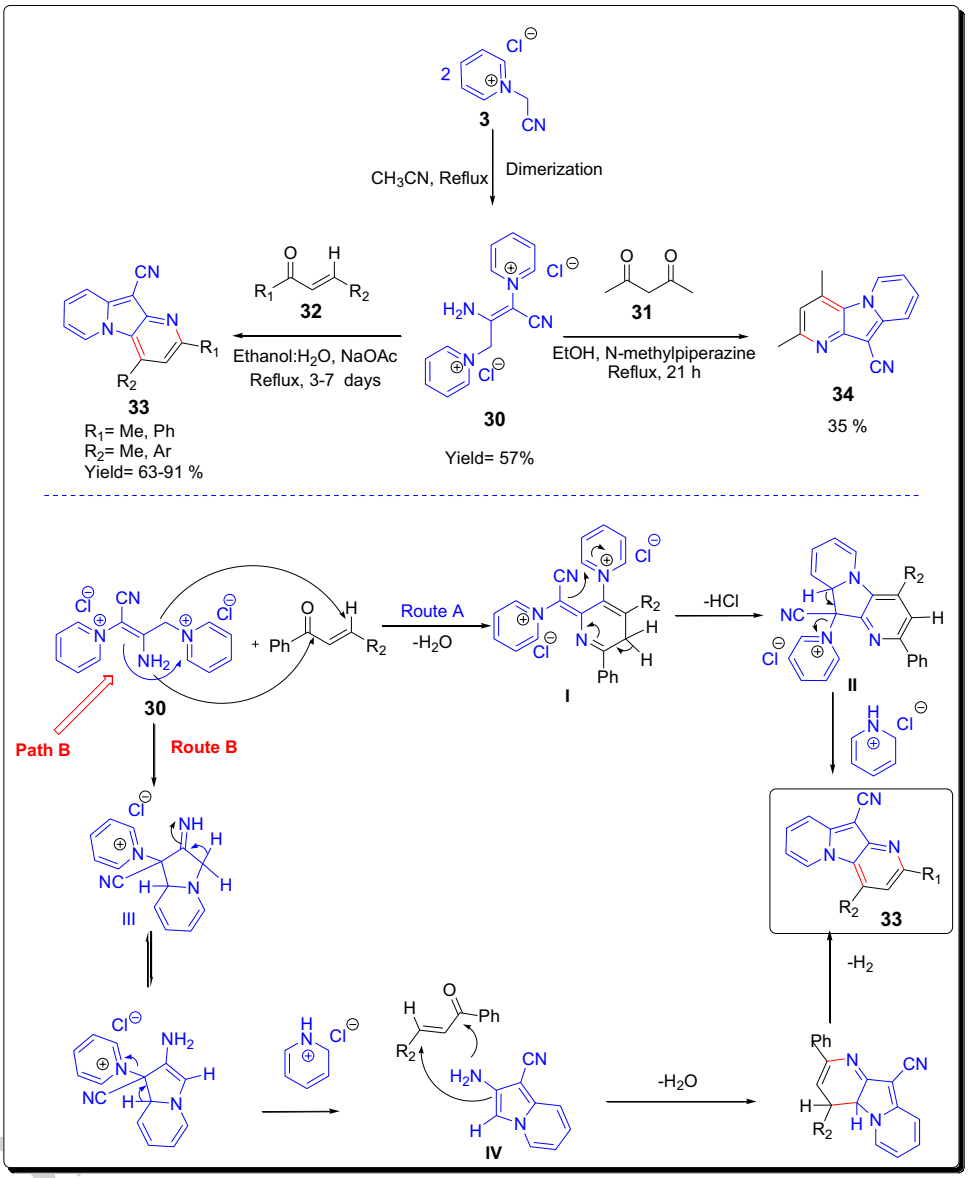

Scheme 11 Synthesis of pyrido-indolizine-carbonitriles using dipyridinium dichloride

were applied for the reaction of various 3-(1-alkynyl)chromones to get desired products with moderate to excellent yields (36–93%). The plausible mechanism involves the first formation of intermediate **I** via Micahel addition. The intermediate **I** undergo ring opening to form **I**, which undergoes alkyne-alkene isomerization for form **III**. The carbanion intermediate **IV,** which is formed from the cyclization of **III,** undergoes a 1,2-addition reaction and generates the desired chromeno azepine skeleton.

Recently, Beeler and coworkers (Mailloux et al. 2021) developed a unified method for the synthesis of monocyclic (**28**) and polycyclic (**29**) azepines by dearomative photochemical rearrangement of aromatic *N*-ylides (Scheme 10). The protocol involves deprotonation of salts with DBU/TMG under visible light (420–460 nm) with good yields. This ring-expansion method opened a new mode for the synthesis of functionalized azepines from *N*-heteroarenes using simple starting materials. The preliminary mechanistic studies strongly suggest the photochemical excitation of the ylide followed by diradical recombination by 6π-electrocyclic ring opening.

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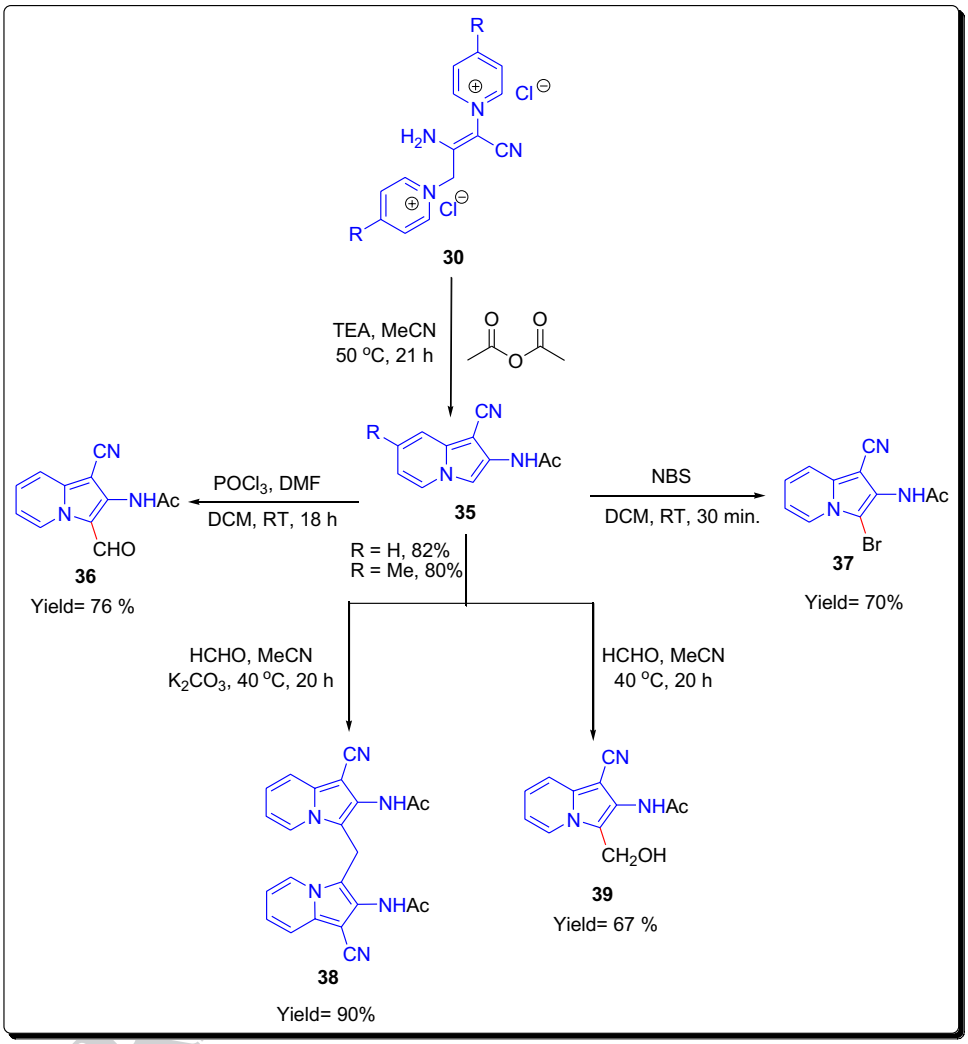

Scheme 12 Synthesis of cyanoindolizin-acetamide derivatives

Synthesis of substituted pyrido[2,3-b]indolizine derivatives

The indolizine scaffolds are present in many biologically active compounds and have been used for the preparation of different pharmaceuticals. These derivatives have been identified as anticancer, antiviral, anti-inflammatory, anti-tuberculosis, analgesic, and antioxidant agents (de Fatima Pereira et al. 2015; Dawood and Abbas 2020).

As a result, different approaches have been reported in the literature for their synthesis. Proenc¸ and Costa (Proença and Costa 2011) reported that the reaction of cyanomethyl pyridinium chlorides (**3**) undergoes competitive dimerization in the refluxing acetonitrile to form the dipyridinium salt (**30**). This dipyridinium salt was formed by a nucleophilic attack of the methylene carbon atom of a pyridinium salt to the cyano group of another molecule, followed by tautomerization (Scheme 10). As an extension, this dipyridinium dichloride was used for the synthesis of various substituted pyrido[2,3-b]indolizine-10-carbonitriles (**33** and **34**) using 1,3 diketone (**31**) in EtOH in the presence of *N*-methyl piperazine under reflux and various enones (**32**) in EtOH:H_2O mixture in the presence of NaOAc under reflux (Scheme 11). The approach is eco-friendly and regioselective for the construction of pyridoindolizine cores. This one-pot procedure gave various substituted pyrido-indolizine-carbonitriles from *β*-unsaturated carbonyl compounds with a yield ranging from 63 to 91%.

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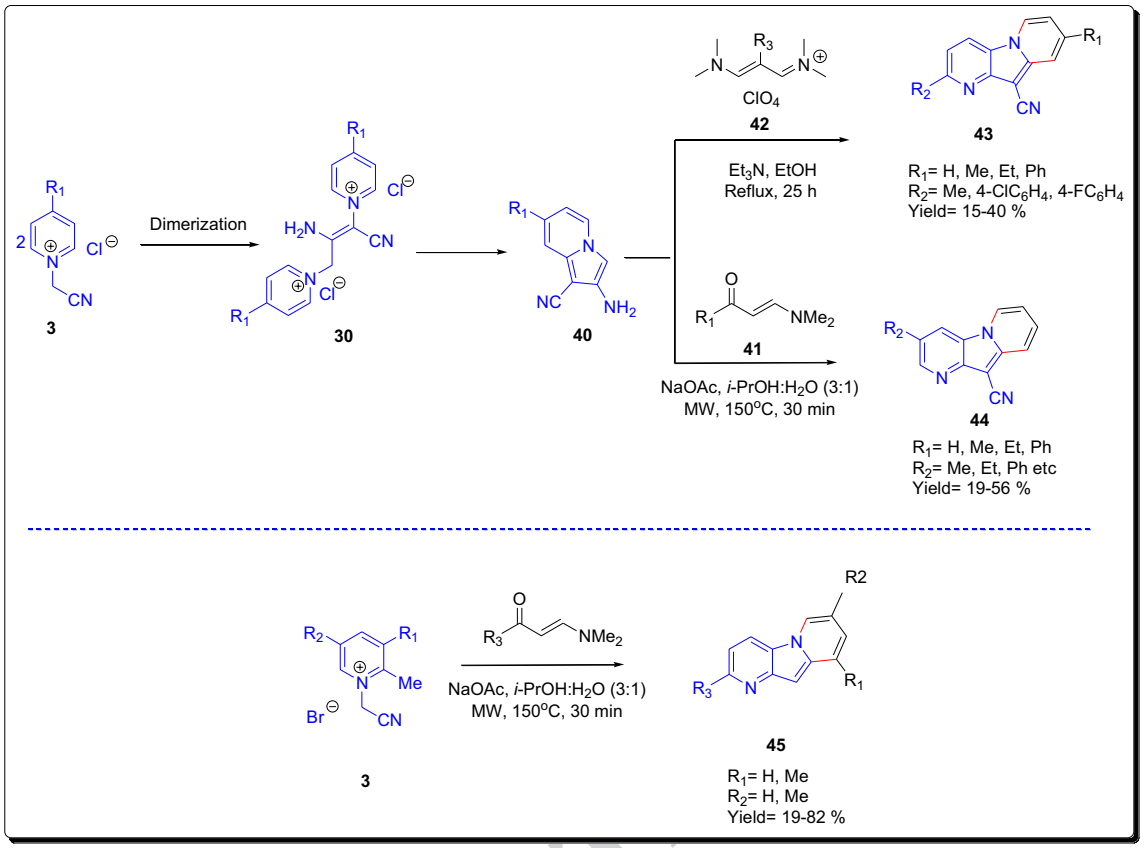

Scheme 13 Synthesis of pyridoindolizine derivatives

The plausible mechanism involves two pathways. Route **A** involves a nucleophilic attack of the active methylene group of dimers (**30**) on the β carbon as well as the amino group of **I** to the carbonyl carbon of unsaturated carbonyl compounds to give intermediate **32** which leads to **I**. Intramolecular cyclization of the intermediate species **II** which on the elimination of HCl and pyridinium chloride leads to the desired compound **33**. According to route **B**, dimer **30** undergoes intramolecular cyclization and generates intermediate **III,** which subsequently undergoes tautomerization and elimination of pyridinium chloride, giving indolizine **IV**. The reaction of **IV** with the unsaturated carbonyl compound through nucleophilic attack by the enamine moiety after dehydration followed by oxidation leads to the final product (**33**).

They extended this protocol for cyclization of the dipyridinium salts (**30**) in the presence of acetic anhydride that generates an indolizine derivative in 80–82% yields (Costa et al. 2013) (Scheme 12). The *N*-(1-cyanoindolizin-2-yl) acetamides (**35**) formed initially can be converted into the amino group that allowed the successful formation of 2-aminoindolizine-1-carbonitrile. The C3 ring carbon of the indolizine derivative allowed the 76% yield of indolizine aldehyde (**36**) under standard Vilsmeier-Haack reaction conditions. In addition, 2-aminoindolizine-1-carbonitrile on bromination using NBS, gave indolizine bromide (**37**), while hydroxymethylation using formaldehyde, and dimerization reactions give corresponding products (**38** and **39**) with good yields (67 and 90%). All the products were isolated in pure form by simple filtration.

In 2019, Voskressensky et al.(Sokolova et al. 2019) prepared a highly fluorescent pyrido[2,3-b]indolizine-10-carbonitriles (**43–44**) through pseudo-three-component reactions of cyanomethyl pyridinium salts (**3**) (Scheme 13). The compounds **40** obtained from dipyridinium salts (**30**) were reacted with enaminones (**41**) or vinamidinium salts (**42**) were converted into desired carbonitriles (**43–44**) using different bases and solvents, varying the reaction time as well as performing the reactions under MW conditions (Scheme 13). Under similar reaction conditions, the

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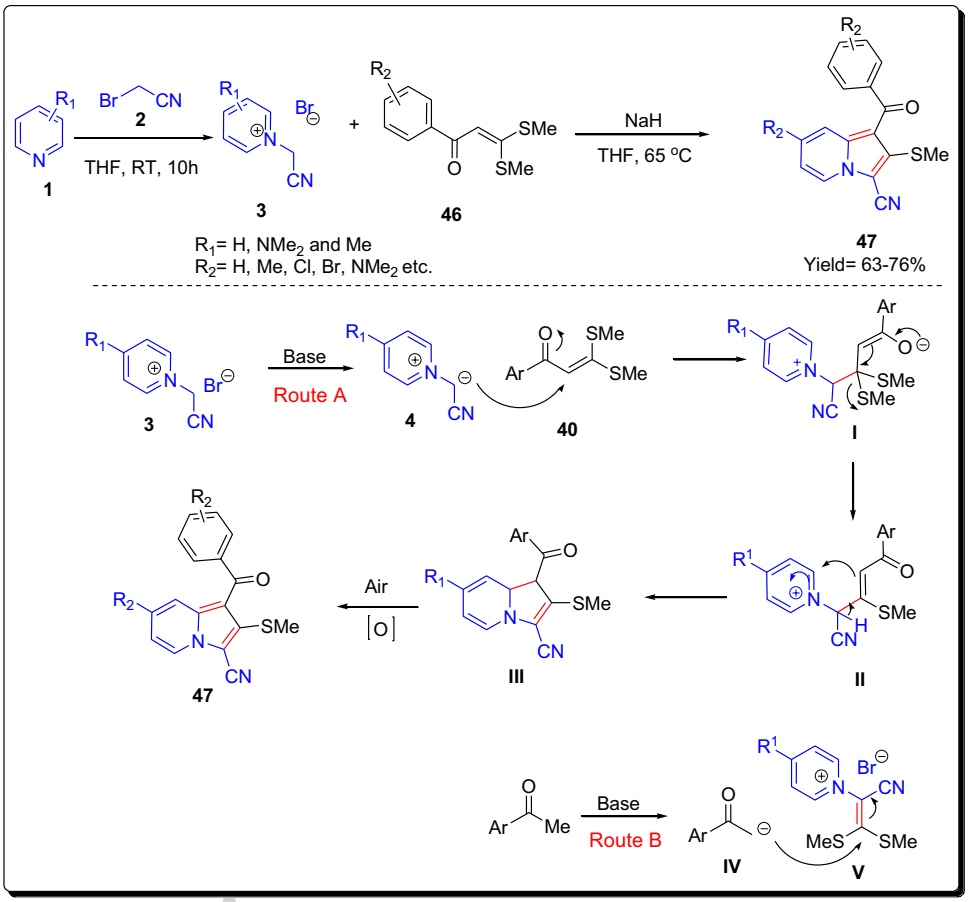
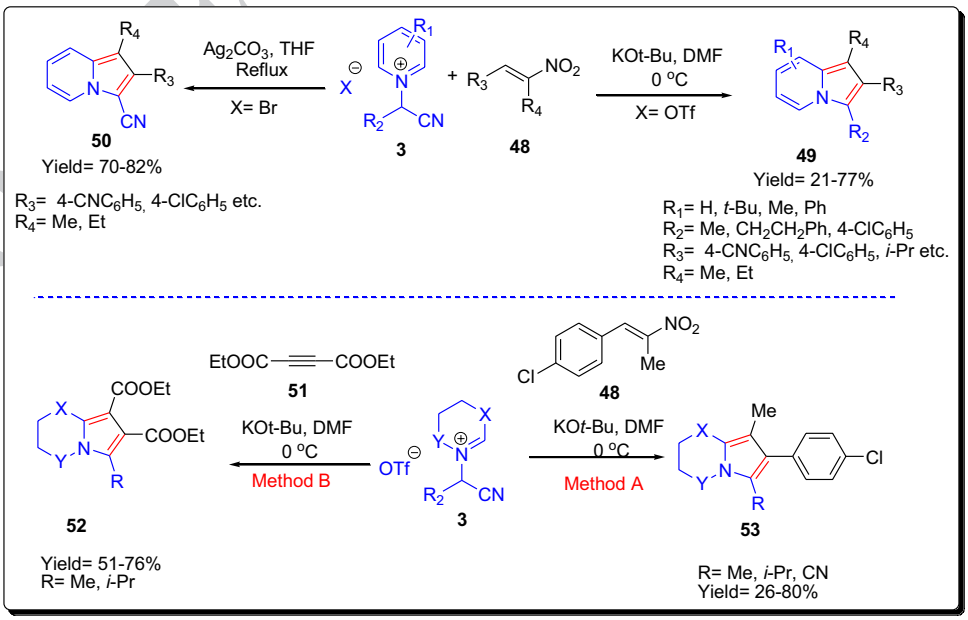
Scheme 14 NaH promoted one-pot three-component domino synthesis of indolizines



Scheme 15 Synthesis of poly-substituted indolizines



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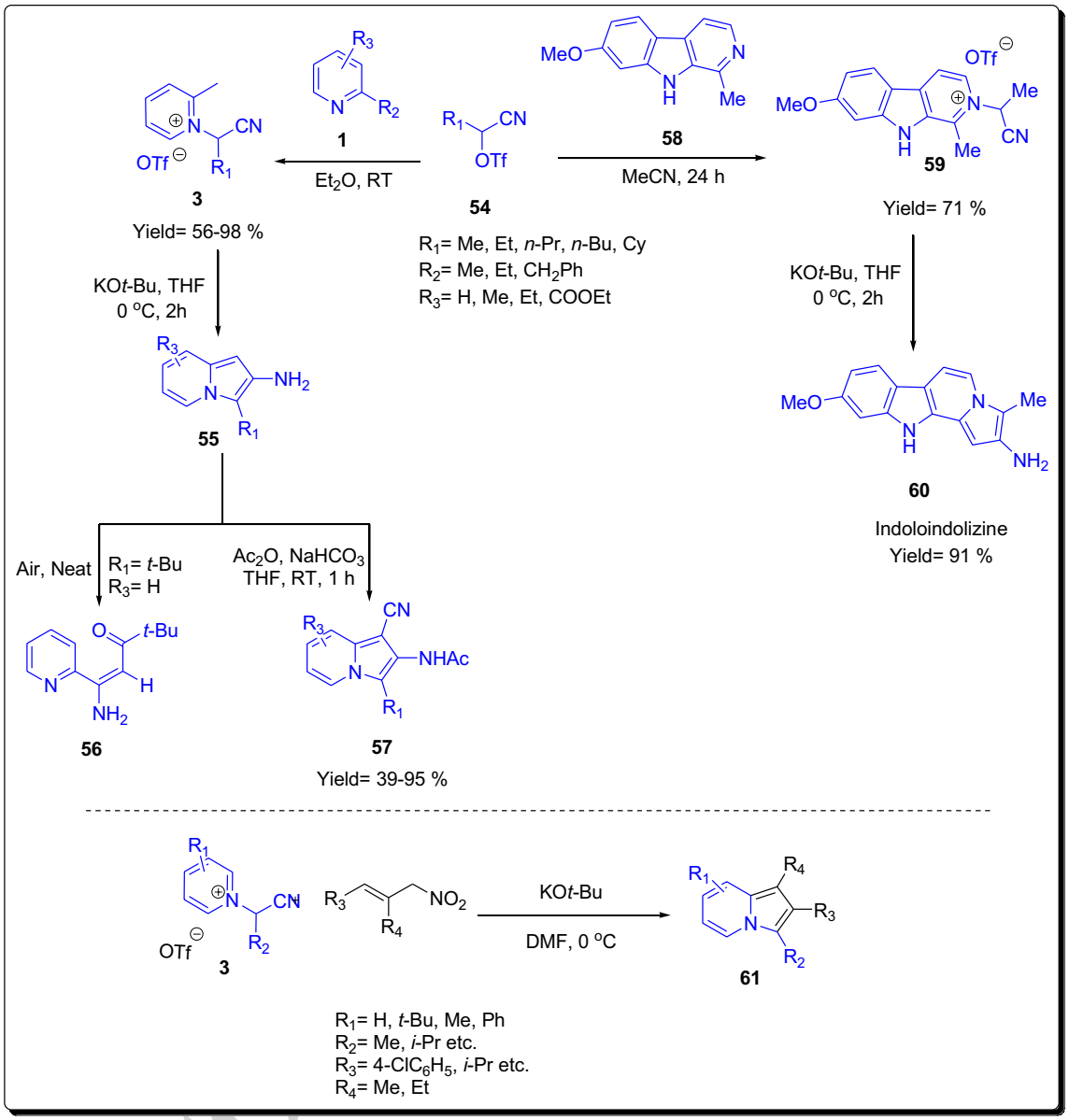

Scheme 16 Synthesis of acetylated 2-aminoindolizines and indolizinoindol amines

pyrido[2,3-b]indolizines (**45**) also obtained with moderate to good yields by the reactions of *N*-(cyanomethyl)-2-alkyl pyridinium salts (**3**) with enaminones (**41**) in the presence of NaOAc as a base in *i*-PrOH: water (1:3) mixture at 150 °C (Sokolova et al. 2020). The reaction unexpectedly proceeded as a domino sequence of cycloisomerization and cyclo condensation reactions instead of a 1,3-dipolar cycloaddition. The resulting pyrido[2,3-b]indolizines (**45**) showed green light emission with high fluorescence quantum yields. The reaction of various *N*-cyanomethyl-2,3-dimethylpyridinium salts with different enaminones has proceeded with low to good isolated yields (19–82%). The synthesized compounds are effective fluorophores, emitting green light with FQYs up to 82%.

Shanmugam et al. (Ramesh et al. 2019) reported a NaH-promoted one-pot three-component domino synthesis of

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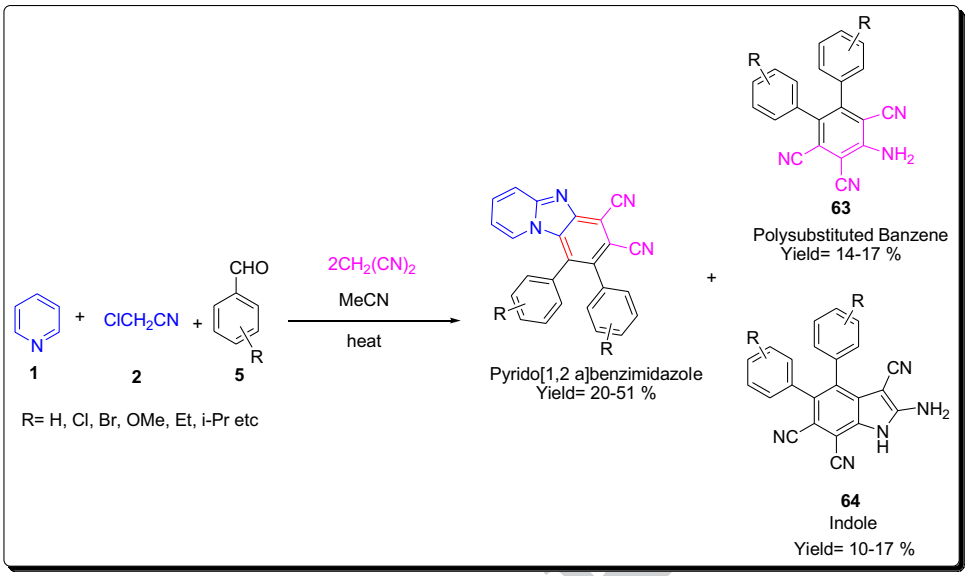

Scheme 17 A one-pot, four-component synthesis of pyrido-benzimidazole derivatives

indolizine derivatives (**47**) through in situ generated pyridinium ylides with α-oxoketene dithioacetals (AKDTAs) (**46**) (Scheme 14). The reaction protocol involves the use of NaH in THF at 65 °C, and the desired products were obtained with 63–76% yield. The formation of desired product was explained by two different routes (**A** and **B**). Route **A** involves the first formation of pyridinium ylide **4,** which is attacked by AKDTA with the formation of intermediate **I**. The intermediate **I** on the intramolecular nucleophilic attack at ortho-position of pyridine followed by air oxidation to give the desired indolizines (**47**). Route **B** involves the nucleophilic attack of enolate (**IV**) on **V,** followed by the elimination of a methylthio group leading to the formation of an intermediate **II**, which is converted into desired products via intermediate **III**.

Kucukdisli and Opatz also reported a modular synthesis of polysubstituted indolizines (Kucukdisli and Opatz 2012) (Scheme 15). The reaction of pyridinium salts (**3**) with various nitroolefins (**48**) leads to 2,3-disubstituted indolizines (**49**) in good yields in DMF and KO*t*-Bu at 0 °C. In addition, the 1-(cyanomethyl)pyridinium bromide exclusively yielded indolizine-3-carbonitriles (**50**) with 70–82% yields instead of 3-unsubstituted indolizines in the presence of silver (I) carbonate in THF at reflux. The applicability of the protocol was extended for the synthesis of various indolizines (**52** and **53**) using different *N*-heterocyclic cyanohydrin triflates, such as isoquinoline, benzothiazole, phthalazine etc., and 1-chloro-4-[(1*E*)-2-nitroprop-1-en-1-yl]benzene (**48**) (**Method A**) or diethyl azodicarboxylate (DEAD) (**51**) (**Method B**) in presence of KO*t*-Bu in DMF at 0 °C.

They (Kucukdisli and Opatz 2014) also developed a simple two-step method for the synthesis of 2-aminoindolizines (**55**) by a 5-exo-dig cyclization of 2-alkyl-1-(1-cyanoalkyl) pyridinium triflates (**3**) in presence of KO*t*-Bu in THF which can be converted into compounds **56** and **57** (Scheme 16). The protocol was also applied to the two-step synthesis of tetracyclic indolizinoindol amine (**60**) from the *β*-carboline alkaloid harmine salt (**59**) obtained from the corresponding *β*-carboline alkaloid harmine (**58**) and reagent **54**. The synthesis involves the intramolecular cyclization of 2-(1-cyanoethyl) triflate (**59**) to give the tetracyclic indolizinoindol amine (**60**) in 91% yield. In most cases, the products are obtained without any chromatographic purification. This method allows the formation of 2-aminoindolizines (**61**) with different substituents at the 1, 3, 7, and 8 positions.

Yan et al. (Wang et al. 2009) developed a new one-pot, four-component (pseudo-six-component) synthesis of polysubstituted pyrido[1,2-a]benzimidazole derivatives (**62**) from pyridines (**1**), aromatic aldehydes (**5**), malononitrile, and chloroacetonitrile (**2**). The yield of the products is moderate in refluxing acetonitrile, due to the formation of side products such as polysubstituted benzene (**63**) and indole (**64**). The short reaction time and easy-to-use feature make this reaction applicable to synthesizing different polysubstituted pyridobenzimidazole derivatives (Scheme 17).

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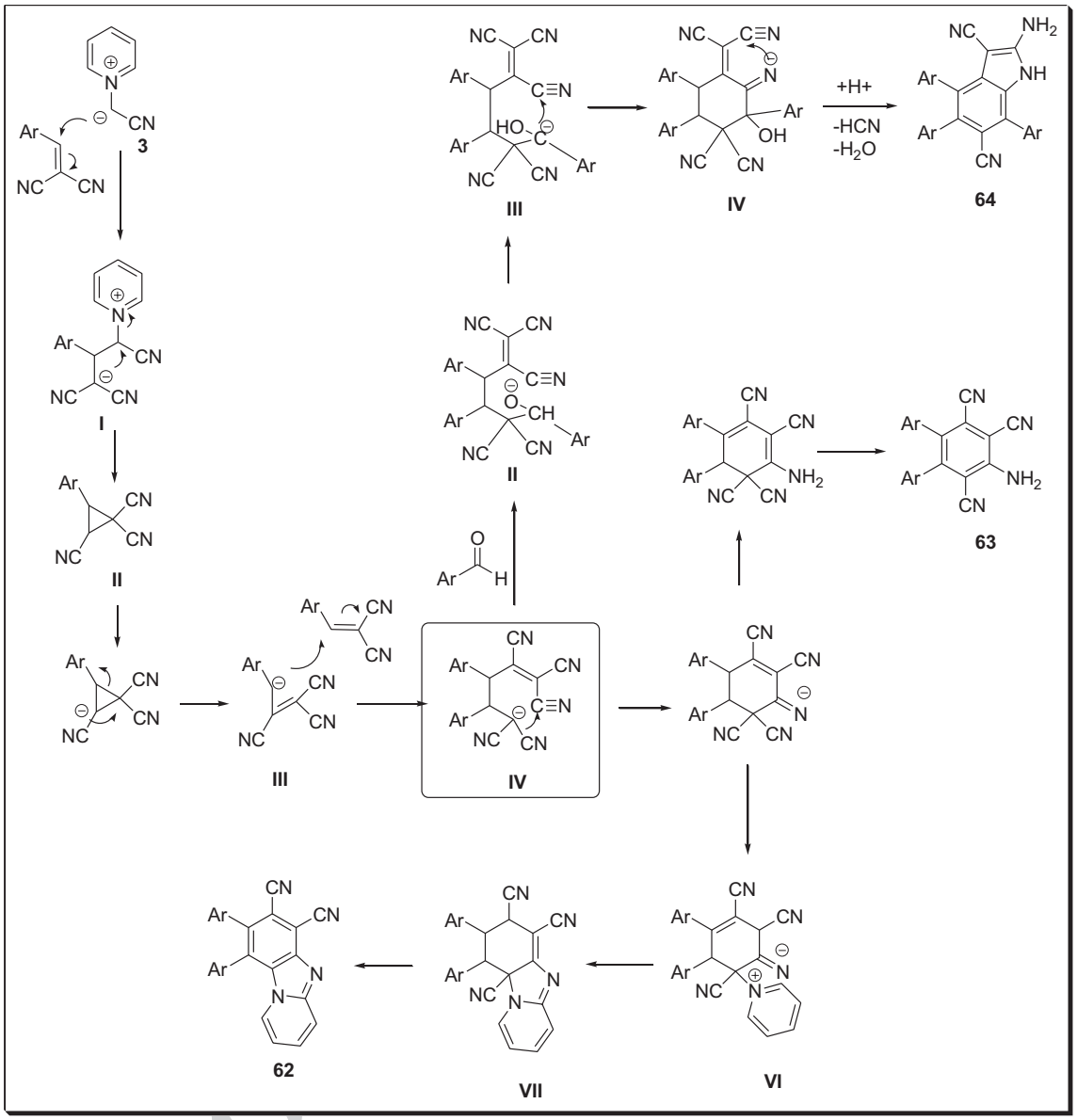

Scheme 18 Plausible mechanism of formation of pyrido[1,2 a]benzimidazoles, polysubstituted benzene, and polysubstituted indoles

The plausible mechanism of the one-pot multi-component tandem reaction is illustrated in Scheme 18. In the first step, Michael addition of a pyridinium ylide with the arylidenemalononitrile gives anion intermediate **I**. This intermediate eliminates one pyridine molecule to afford a cyclopropane derivative **II**, which on deprotonation followed by ring-opening, affords an allylic carbanionic intermediate **III**. In turn, this reacts with a second molecule of arylidenemalononitrile to form a new cyano-stabilized carbanionic intermediate **IV**, which concomitantly adds to one of the cyano groups to give a six-membered carbon ring (**V**). The intermediate **V** reacts further in two different ways to give two different products. The tautomerization of **V,** followed by the elimination of HCN and aromatization, yields the polysubstituted benzene derivative (**63**). On the other hand, the substitution of one cyano group in intermediate **V** forms a new pyridinium ion **VI**, which undergoes intramolecular cyclization to yield intermediate **VII**. This intermediate eliminates HCN and two hydrogen atoms to form pyrido[1,2-a]benzimidazole (**64**). The carbanionic intermediate (**I**) reacts with an aromatic aldehyde to form an adduct **II,** which forms carbanion **III** by proton

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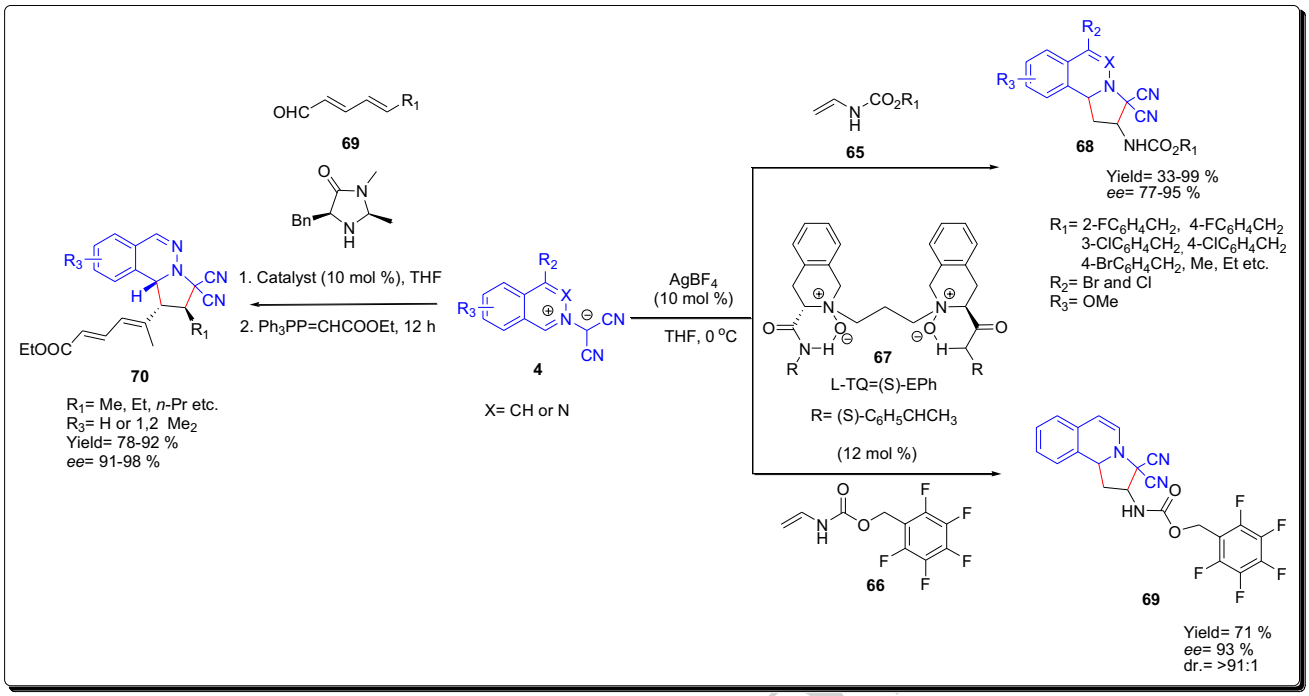
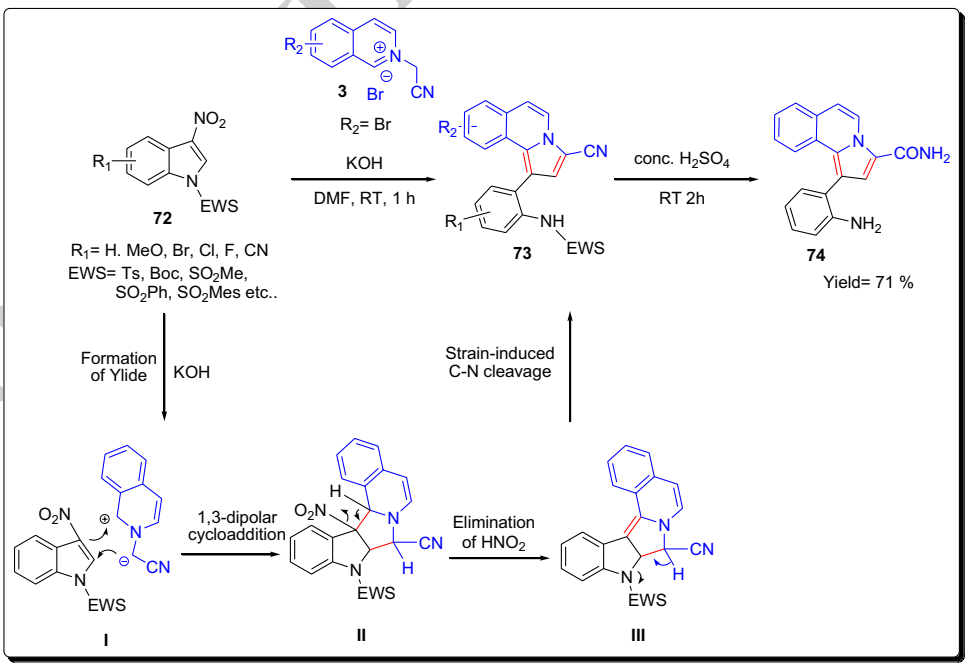


Scheme 19 Synthesis of optically active pyrroloisoquinolines, pyrrolophthalazine, and tetrahydropyrrolo phthalazinyl pentadienoate derivatives

Scheme 20 Synthesis of pyrrolo isoquinolines by the domino reaction of isoquinolinium ylides and electrophilic indoles



immigration from carbon to an oxygen atom. The **III** on intramolecular addition forms a cyclohexyl imine intermediate **IV**, which gives the desired polysubstituted indole by the elimination of water and HCN.

Feng and co-workers (Xu et al. 2016) carried out catalytic asymmetric inverse-electron demand (IED)1,3-dipolar cycloaddition of isoquinolinium methylides (**4**) with enecarbamates (**65**) by using a chiral N, N'-dioxide/Ag(I)

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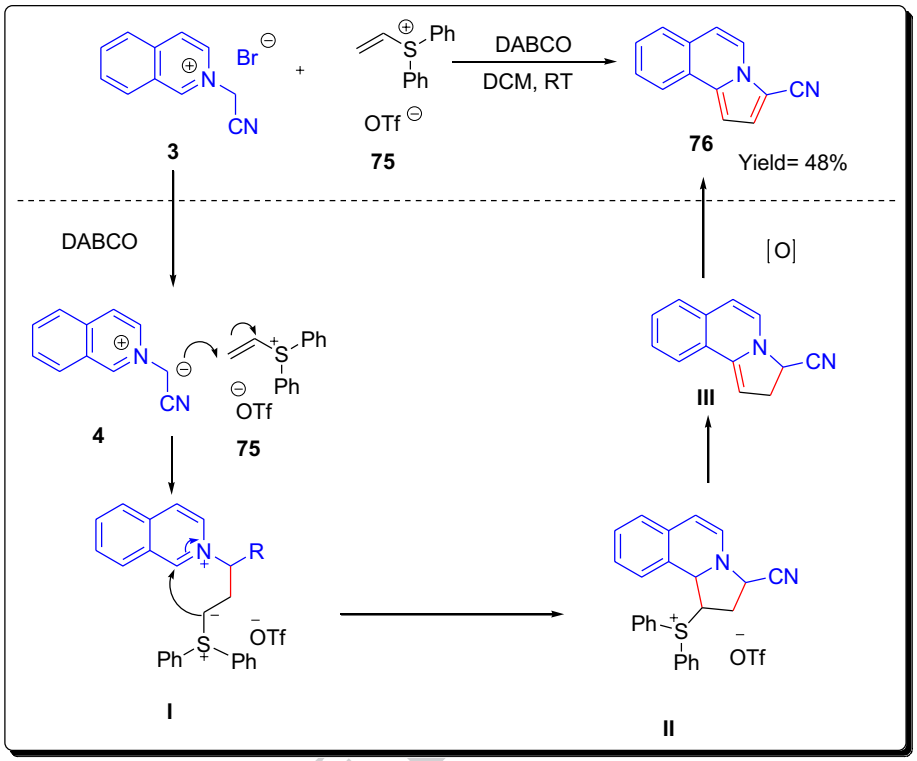
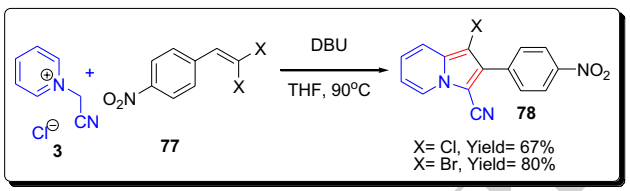


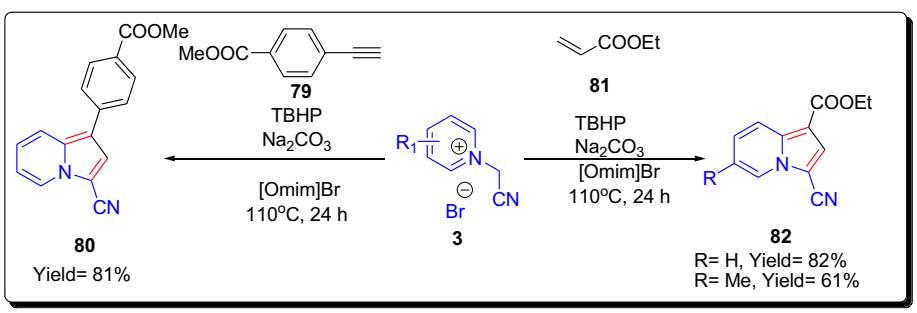
Scheme 21 Direct synthesis of pyrrolo[2,1-a]isoquinolines by 1,3-dipolar cycloaddition of isoquinolinium *N*-ylides with vinyl sulfonium salts



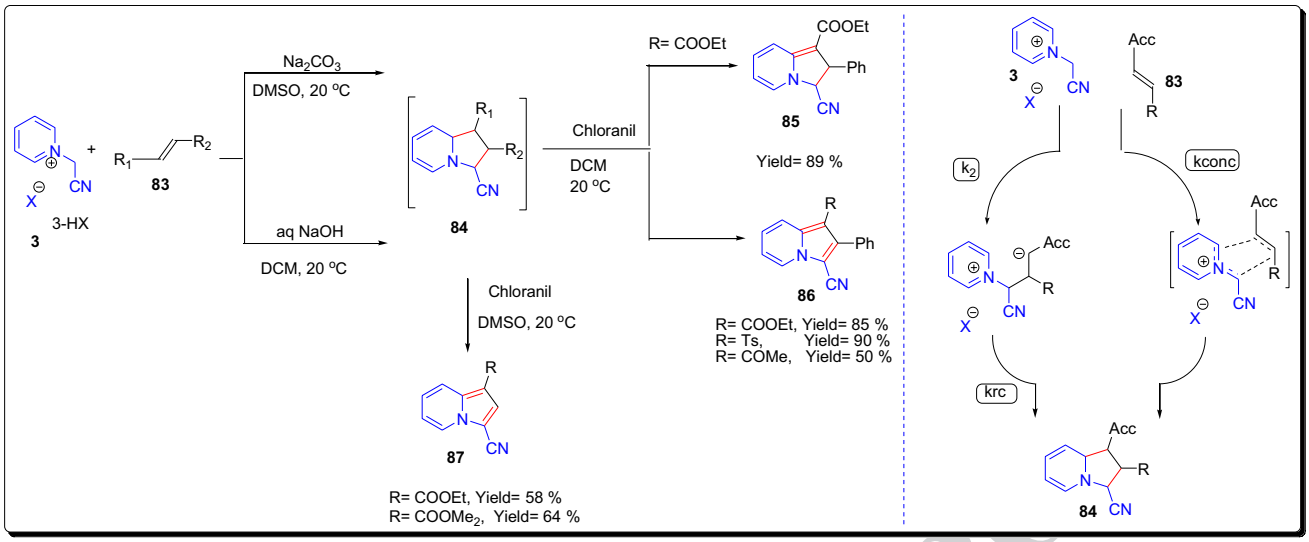
Scheme 22 Synthesis of 2-aryl-1-haloindolizines through the 1,3-dipolar cycloaddition

catalytic system (Scheme 19). The present catalytic system was more efficient than $Sc(OTf)_3$, $Cu(OTf)_2$, and $Ni(OTf)_2$ showed excellent enantioselectivities in THF at 0 °C. The yield of the optically active pyrroloisoquinolines and pyrrolophthalazine (**68**) were up to 99% with d.r. > 19:1 and 95% ee. The $AgBF_4$/L-TQ-(S)-Eph (**67**) (10 mol %) catalytic system also showed good utility for a gram-scale synthesis of **69** using isoquinolinium dicyanomethylide (**4**) and (perfluorophenyl)methyl vinyl carbamate (**66**). The yield of the gm scale synthesis was 71% with 93% ee and > 19:1 d.r. The proposed transition state of the reaction was supported by fluorescence, ESI–MS, and X-ray structure analysis.

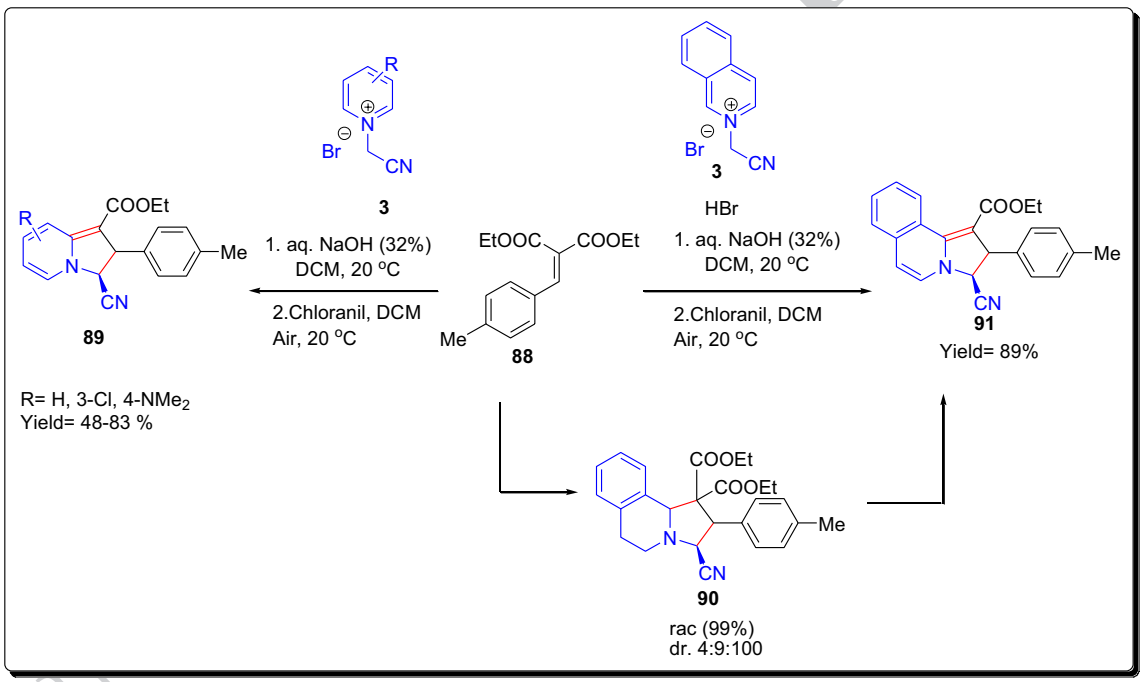
Similarly, Guo et al. (Jiang et al. 2020) reported a regio and stereoselective [3 + 2] cycloaddition of phthalazinium dicyanomethanides (**4**) with 2,4-dienals (**70**) using a commercially available MacMillan's catalyst. This catalyst afforded chiral tetrahydro pyrrolophthalazinyl pentadienoate derivatives (**71**) in high yields with excellent diastereoselectivity and enantioselectivity. Moreover, the synthetic utility of this protocol was developed for gram scale asymmetric reaction of phthalazinium dicyanomethanide with (*2E,4E*)-hexa-2,4-dienal in the presence of 20 mol % of catalyst.



Scheme 23 Synthesis of indolizines using recyclable [Omim]Br ionic salt



Scheme 24 Mechanistic study of the formation of tetrahydro indolizines



Scheme 25 Tandem one-pot two-step [3 + 2] cycloaddition reaction for the synthesis of indolizines

The desired chiral product was obtained in 72% yield with 90% *ee*. As enal cycloadducts were found to be unstable, the treatment of the cycloadduct with $TiCl_4$, the aldehyde group was transformed into the dimethyl acetal group (68% yield) with excellent d.r. in methanol at room temperature in 12 h (Scheme 22).

John et al. (Babu et al. 2021) reported unprecedented access for functionalized pyrrole isoquinolines (**73**) from the domino reaction of isoquinolinium ylides (**3**) and indoles as electrophilic benzannulated heterocycles (Scheme 20). The reaction of isoquinolinium bromide and *N*-tosyl-3-nitro indoles (**72**) was carried out in the presence of KOH in

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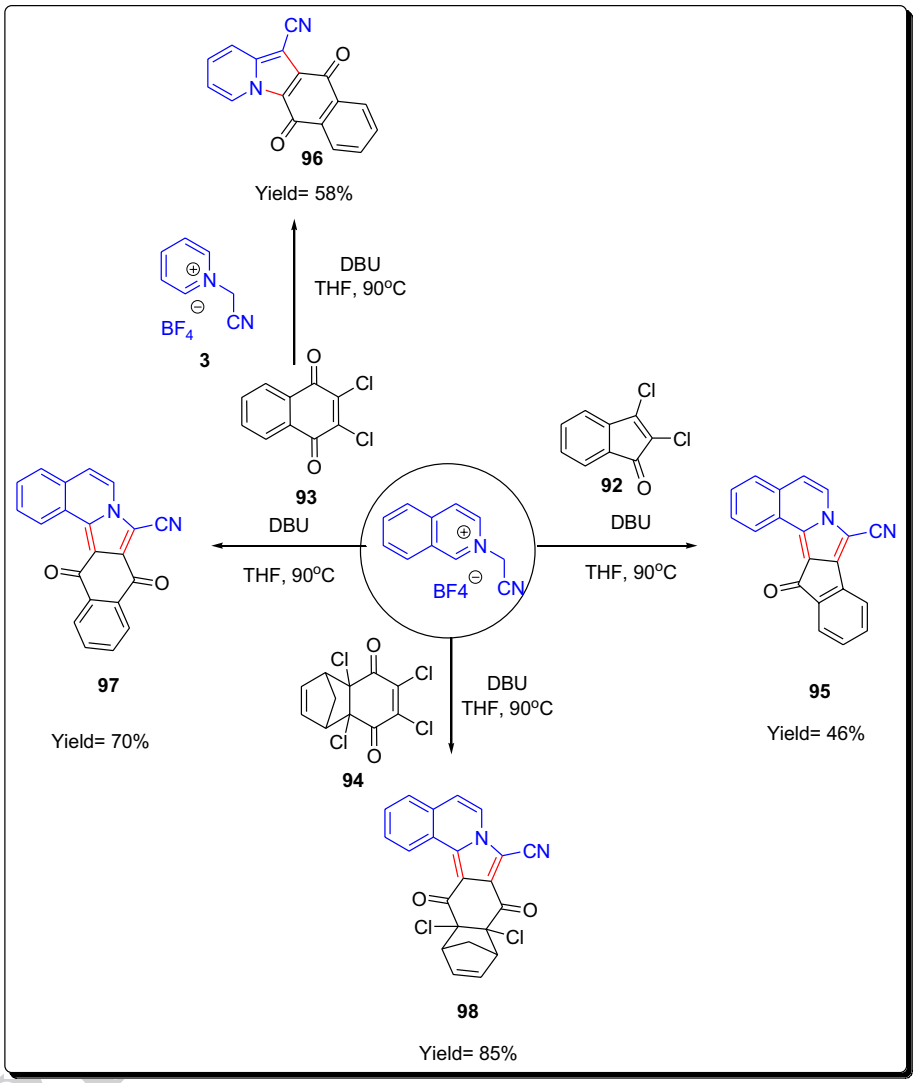
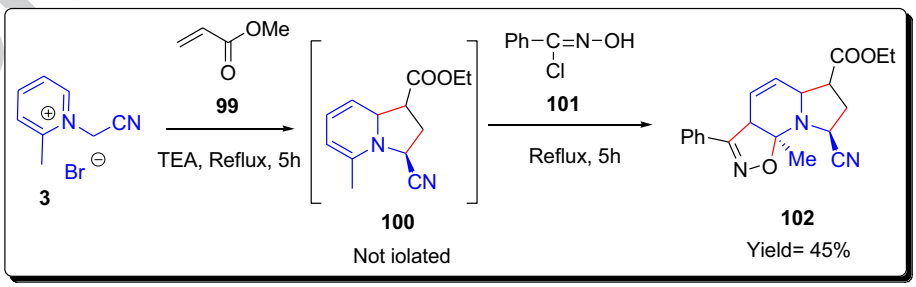
Scheme 26 Synthesis of polycyclic annulated indolizines via one-pot tandem reactions



Scheme 27 Synthesis of isoxazole fused tetrahydroindolazine



DMF at room temperature. All the products were obtained in moderate to good yields (40–91%) in 1 h. This protocol also attempted a gram-scale synthesis of pyrrolo-isoquinoline (**74**) by treating the CN compound with concentrated H_2SO_4 for two h with a 72% yield. A plausible mechanism is depicted in Scheme 20. Initially, the deprotonation of the activated methylene group of the isoquinolinium generates the corresponding *N*-ylide (**I**), which undergoes a 1,3-dipolar cycloaddition with the dipolarophile (*N*-tosyl-3-nitro indole) and generate the cycloadduct **II**. The adduct **II** subsequently eliminates HNO_2 and generates intermediate **III**, which undergoes a strain-induced cleavage of the C–N bond to furnish the pyrrolo[2,1-a]isoquinoline compound.

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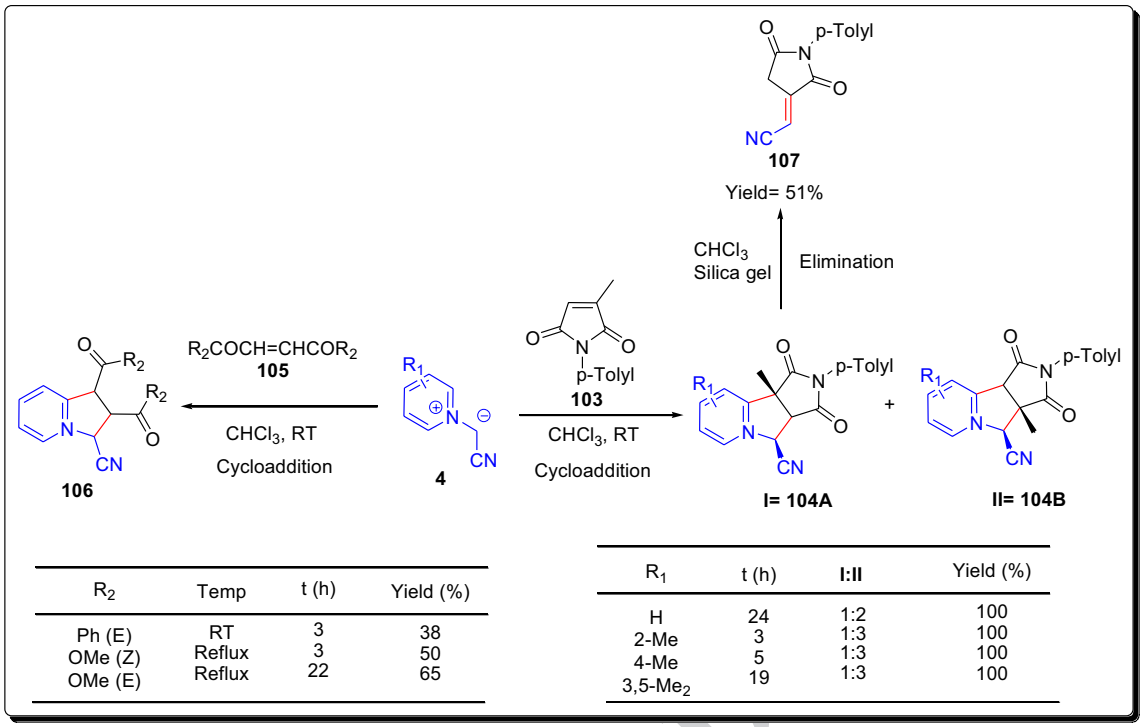
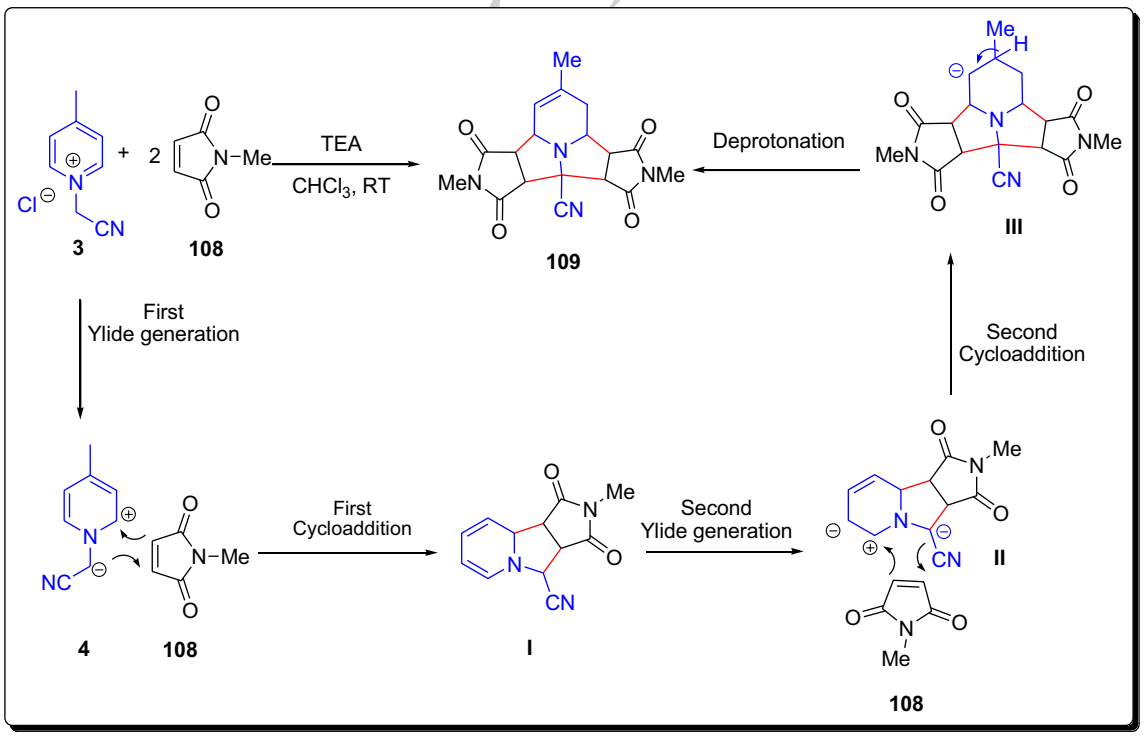


R_2	Temp	t (h)	Yield (%)
Ph (E)	RT	3	38
OMe (Z)	Reflux	3	50
OMe (E)	Reflux	22	65

R_1	t (h)	I:II	Yield (%)
H	24	1:2	100
2-Me	3	1:3	100
4-Me	5	1:3	100
3,5-Me_2	19	1:3	100

Scheme 28 Sequential method of alkylation or hydroalkylidenation of olefins



Scheme 29 Tandem 1,3-dipolar cycloadditions for the synthesis of azines

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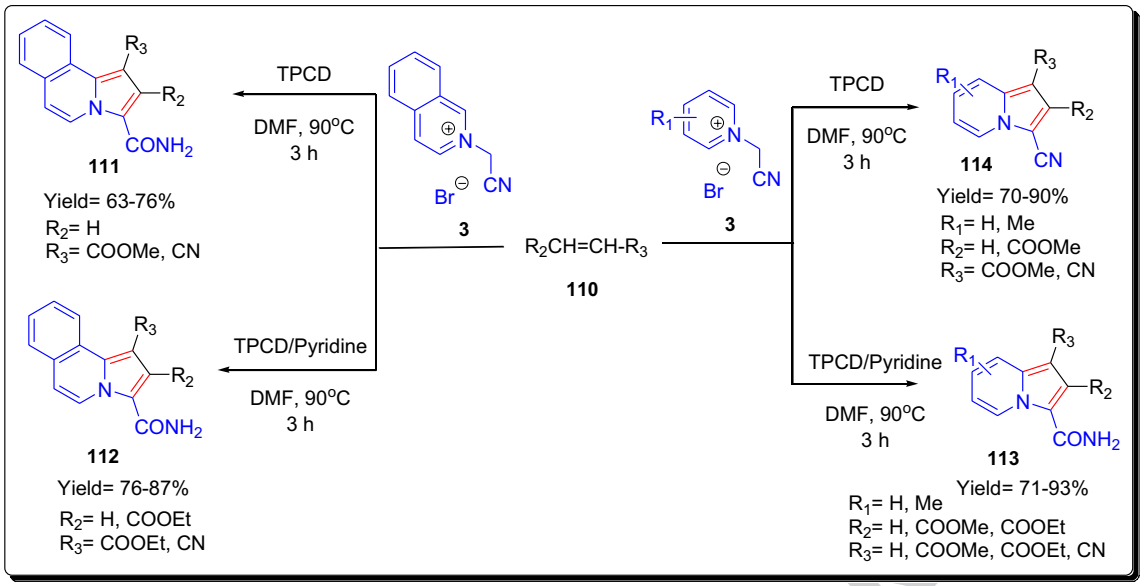


Scheme 30 Synthesis of indolizine-3-carboxamides and indolizine-3-carbonitriles

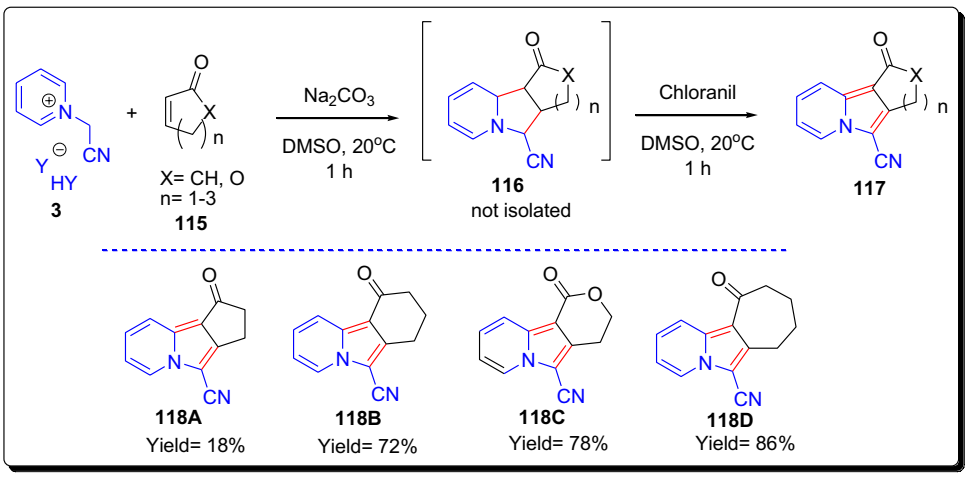
Direct synthesis of pyrrolo[2,1-a]isoquinolines (**76**) was carried out by 1,3-dipolar cycloaddition of stabilized isoquinolinium *N*-ylides with vinyl sulfonium salts (**75**) (An et al. 2013). The yield of the product was 48% in the presence of DABCO in acetonitrile at RT (Scheme 21). The reported method can be used for the preparation of biologically relevant compounds with a simple workup under mild reaction conditions.

Yang and coworkers (Yang et al. 2011) synthesized 2-aryl-1-haloindolizines (**78**) from pyridinium salts (**3**) and 2-aryl-1,1-dihaloalk-1-enes (**77**) using a DBU as a base in THF at 90 °C with good yields. The reaction proceeds through the 1,3-dipolar cycloaddition (Scheme 22).

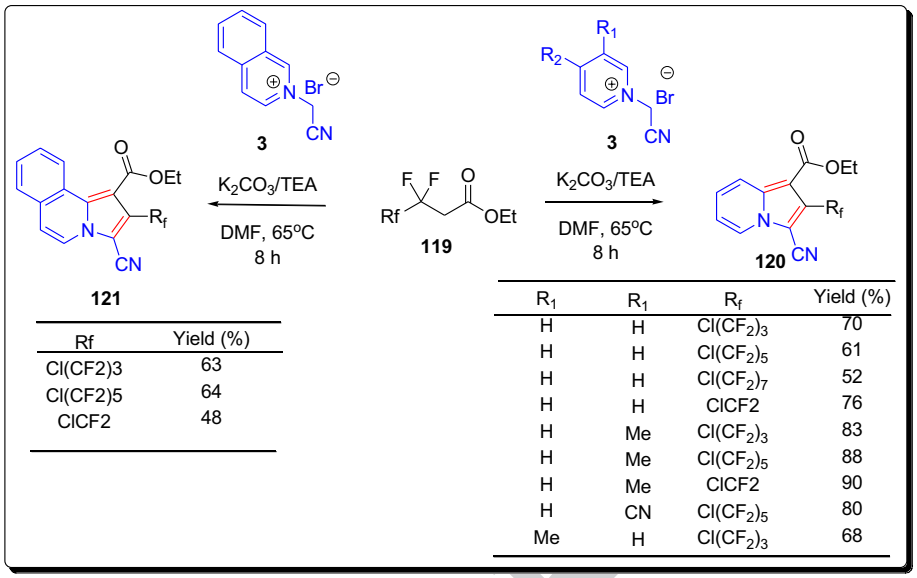
Lu et al. (Zhang et al. 2017) synthesized various indolizines through one-pot, two-step 1,3-dipolar cycloadditions in recyclable 1,2-dimethyl-3-octyl-1H-imidazolium bromide ([Omim]Br) with high yields (Scheme 23). Using NMR experiments they studied the non-covalent interactions such as hydrogen bonding, π–π^+, and electrostatic interactions between [Omim]Br and substrates or intermediates in the reaction. The protocol involves 1,3-polar cycloadditions of alkene (**81**) with pyridinium ylide to give indolizine (**82**) with 82% yield in [Omim]Br Na_2CO_3 and TBHP at 110°C. In addition, the 1,3-polar cycloadditions of alkynes (**79**) with pyridines and organic bromides gave 81% indolizine (**80**) in [Omim]Br at 50°C in the presence of Cs_2CO_3 as the base.

Meyer and coworkers (Allgäuer et al. 2013) carried out kinetic studies of the reactions of pyridinium, isoquinolinium, and quinolinium ylides with diaryl carbenium ions, quinone methides, and arylidene malonates in DMSO by

Scheme 31 Diastereomeric synthesis of tetrahydroindolizines and indolizines

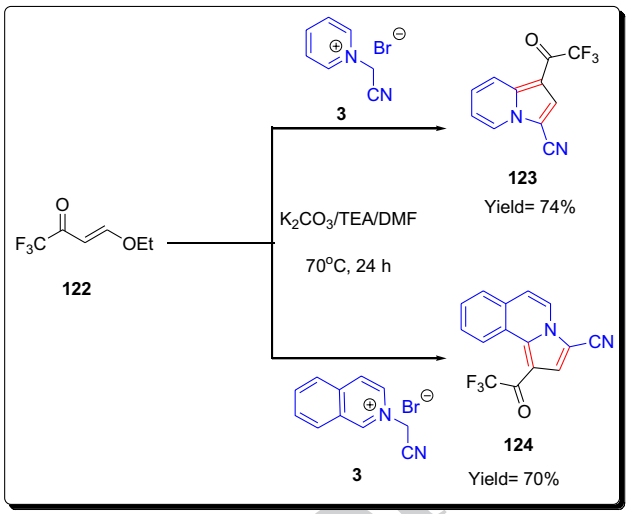


Scheme 32 Synthesis of fluroalylated indolizine derivatives



Rf	Yield (%)
Cl(CF2)3	63
Cl(CF2)5	64
ClCF2	48

R_1	R_1	R_f	Yield (%)
H	H	$Cl(CF_2)_3$	70
H	H	$Cl(CF_2)_5$	61
H	H	$Cl(CF_2)_7$	52
H	H	ClCF2	76
H	Me	$Cl(CF_2)_3$	83
H	Me	$Cl(CF_2)_5$	88
H	Me	ClCF2	90
H	CN	$Cl(CF_2)_5$	80
Me	H	$Cl(CF_2)_3$	68



Scheme 33 Synthesis of 1-trifluoroacetyl indolizine derivatives

UV–vis spectroscopy. In connection with this, they studied quantification and theoretical analysis of the electrophilic reactivities of common Michael acceptors (Allgäuer et al. 2017) (Scheme 24), the study involves reactions of substituted olefins (**83**) and pyridinium salts (**3**) in the presence of a base in DMSO/DCM at 20 °C, followed by oxidation by Chloranil to form indolizines (**85–86**). All the reactions proceed via a common rate-determining step. The (3 + 2)-cycloadditions (Huisgen reactions) of Michael acceptors with pyridinium ylides involve six electrons [4π + 2π], concerted (k_{conc}) or stepwise (k_2) proceed via a common rate-determining step. In stepwise processes, the formed (k_2) betaines intermediate cyclizes (k_{rc}) to give tetrahydroindolizines (**84**).

As pyrrolo[2,1-a]isoquinoline scaffolds have been found as a good candidate in drug discovery, these derivatives were synthesized by tandem reaction of isoquinoline, α-halogenated methylene compounds, aromatic aldehydes, and cyanoacetamide in the presence of TEA in EtOH at RT. The obtained tetrahydropyrrolo[2,1-a]isoquinolines on oxidation with DDQ give the corresponding pyrrolo[2,1-a] isoquinolines and dihydropyrrolo[2,1-a]isoquinolines with good yields at RT (Han et al. 2011).

In connection with this, Allgäuer and H. Mayr reported a one-pot, two-step synthesis of indolizines (**89** and **91**) via pyridinium/isoquinolinium ylides (Scheme 25) (Allgäuer and Mayr 2013). The reaction proceeds at 20 °C in the presence of NaOH to give cycloadducts by stepwise [3 + 2]-cycloaddition of the ylides in DCM. The obtained tetrahydro products (**90**) on oxidation with chloranil give the corresponding indolizines with good yields (48–89%) in DCM at 20 °C.

Xu et al. (Liu et al. 2007) synthesized polycyclic 1,2-annulated, and 1,2-, 5,6- and 1,2-, 7,8-bis annulated indolizines via one-pot tandem reactions of *N*-ylides with dichloro substituted α, β-unsaturated carbonyl compounds (**95–98**) (Scheme 26). These polycyclic indolizines are interesting target compounds for screening biological activity. In addition, they also show strong fluorescence in the visible region. The protocol reaction of corresponding salts with 2,3-dichloroindenone (**92**), 2,3-dichloro-1,4-naphthoquinone (**93**), and 4a,6,7,8a-tetrachloro-1,4-methanonaphthalene-5,8-dione (**94**) in presence of DBU in THF at 90 °C. Most of the products were obtained via a [2 + 3] cycloaddition followed by the elimination of two hydrogen chloride molecules with good yields.

Tsuge et al. (Tsuge 1986) reported the synthesis of isoxazole fused tetrahydroindolazine (**102**) (Scheme 27). The

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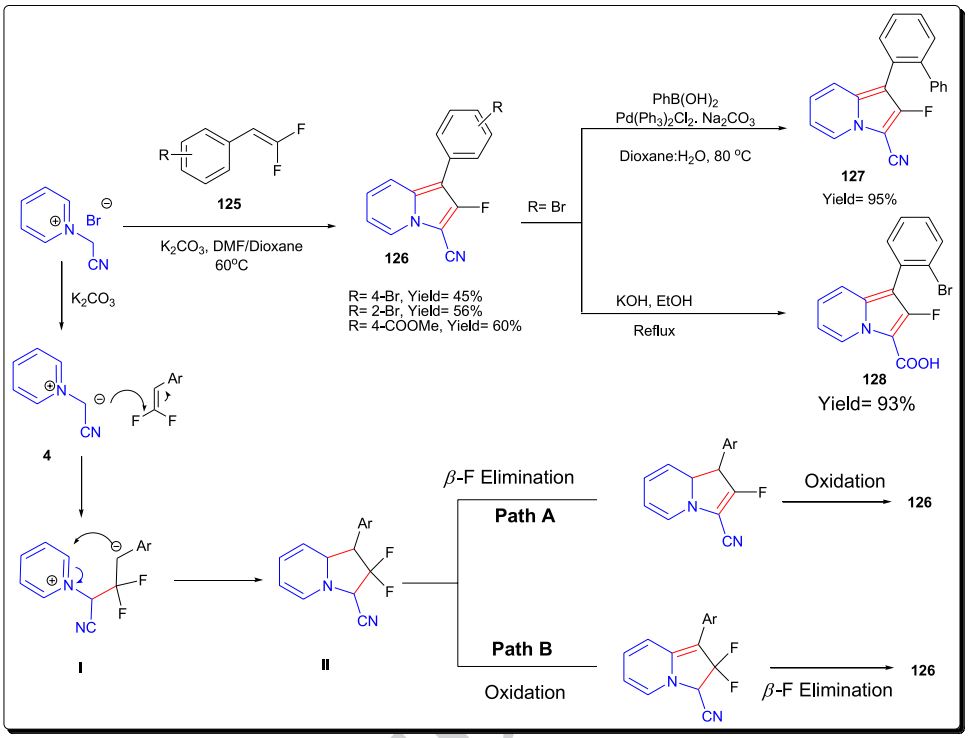
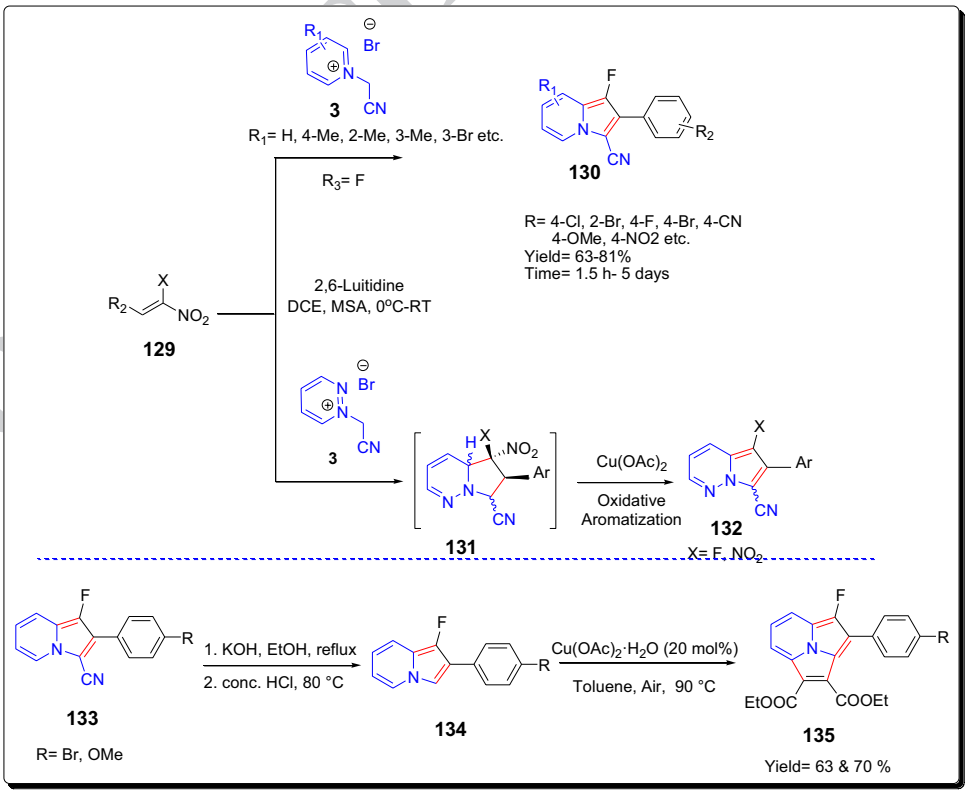
Scheme 34 Functionalized 2-fluoroindolizines by base mediated [3 + 2]-annulation of gem-difluoro alkenes and pyridinium ylides



Scheme 35 Oxidative [3 + 2]-annulation of nitroalkenes and pyridinium ylides for functionalized indolizines

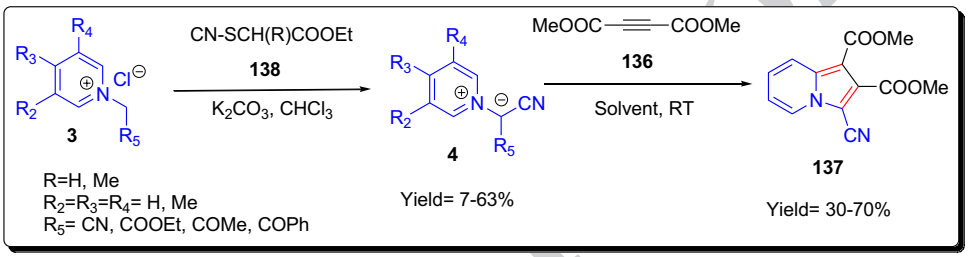


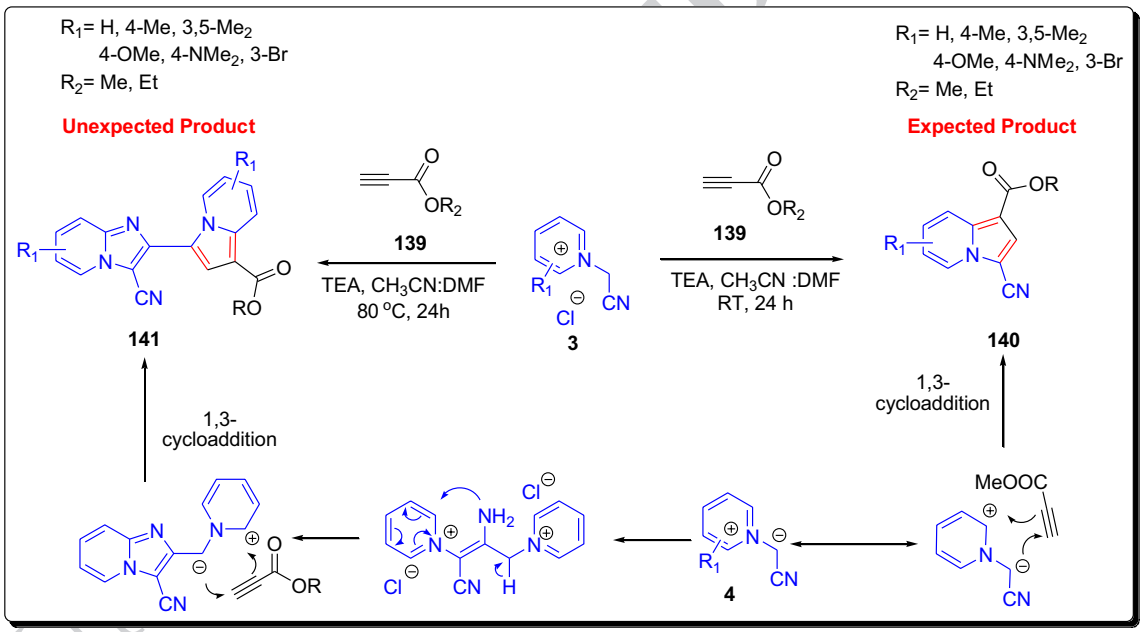
protocol involves stereoselective and regioselective cycloaddition reactions of in situ-*generated* pyridinium ylide with olefinic dipolarophile (**101**) in the presence of TEA to form tetrahydroindolazine (**100**). This tetrahydroindolazine subsequently undergoes cycloaddition with nitrile oxide to form the desired product with a 45% yield.

They (Tsuge et al. 1987) developed a new sequential method of alkylation or hydroalkylidenation of olefins (Scheme 28). The method involves reactions of pyridinium salts (**3**) with a variety of olefins (**103** and **105**) carrying two electron-withdrawing groups at both carbons such as *N*-substituted maleimides, citraconimide, dimethyl maleate, dimethyl fumarate, and 1,2-dibenzoyl ethene and *N*-(*p*-tolyl)citraconimide to give mixtures of two regioisomeric cycloadducts (**104**). Major regioisomers carry the methyl moiety at the 3a-exo position. The stereoselectively formed cycloadducts readily undergo the elimination of pyridines by passing with silica gel in a glass column to form itaconimide derivatives (**107**).

Kanemasa and Tsuge reported that either pyridinium or isoquinolinium methylides could participate in tandem 1,3-dipolar double cycloadditions to form cycle[2,2,3]azines (**109**) (Scheme 29) (Tsuge and Kanemasa 1989)(Kanemasa et al. 1989). The protocol involves the reaction of pyridinium methylides (**4**) with two molecules of *N*-methyl maleimide (**108**). The cyclic[3.2.2]azines were obtained in a highly

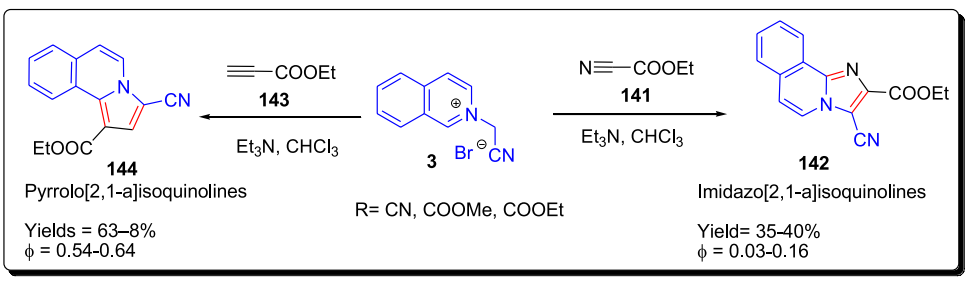
Scheme 36 Synthesis of dimethyl 3-cyanoindolizine-l,2-dicarboxylate





Scheme 37 Cyanoindolizines or cyanoazaindolizinyl-indolizines via 1,3-cycloaddition with alkyl propiolates

Scheme 38 Synthesis of pyrrolo[2,1-a]isoquinolines and imidazo[2,1-a]isoquinolines



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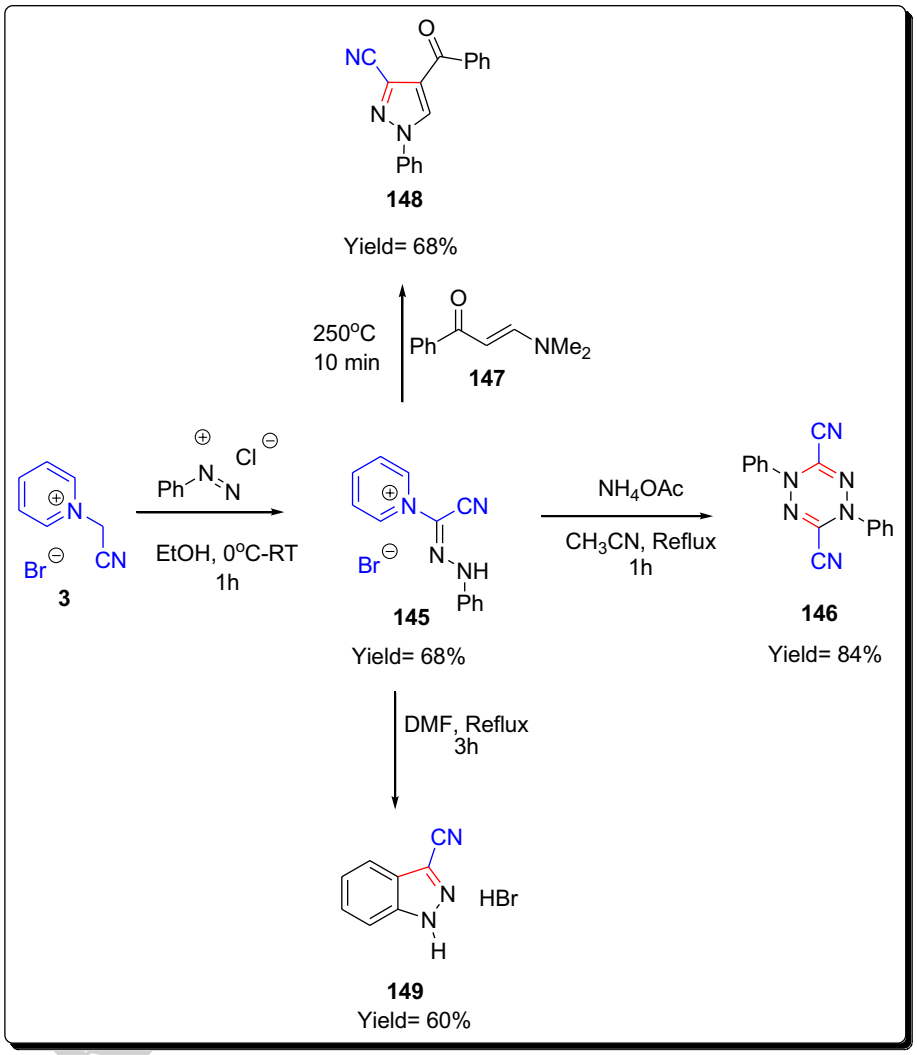
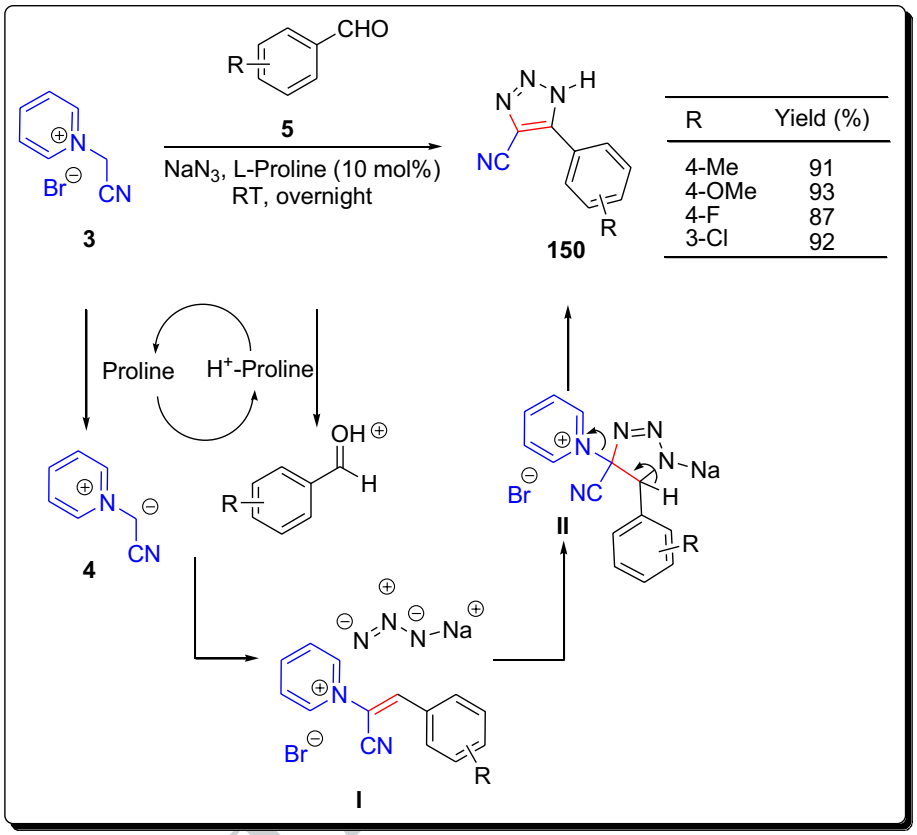


Scheme 39 Synthesis of various compounds using cyno-methylpyridinium salt

regioselective, stereoselective, and face-selective manner. The yield of the reaction was 30% in chloroform at room temperature. The various dipolarophiles were successfully utilized for this reaction with good yields. The reaction sequence involves first the cycloaddition of ylide (**4**) with the first molecule of *N*-methyl maleimide (**108**) to form intermediate **I**. The intermediate **I** was converted into ylide **II**, which further undergoes cycloaddition with the second molecule of *N*-methyl maleimide (**108**) yielding the intermediate **III**, which on deprotonation gave the desired cyclic[3.2.2]azines (**109**).

Hu et al. (Wang et al. 1999) synthesized indolizine-3-carboxamides (**111–113**) and indolizine-3-carbonitriles (**114**) by reaction of pyridinium ylides to alkenes (**110**) in the presence of tetrakis-pyridine cobalt (II) dichromate (TPCD) or manganese(IV) oxide (Scheme 30). The reaction proceeds via 1,3-dipolar cycloaddition of *N*-(cyanomethyl)pyridinium ylides to alkenes followed by aromatization and hydration reactions. When the reaction was carried by using TPCD the reaction proceeded via 1,3-dipolar cycloaddition followed by aromatization reaction, but without hydration of nitrile gave indolizine-3-carbonitriles (**114**).

Recently, Ofial et al. (Mayer et al. 2021) synthesized diastereomeric tetrahydroindolizines (**116**) by the treatment of a 1:1-mixture of the pyridinium ylides with cyclic Michael acceptors such as 5–7 membered cycloenones and α,β-unsaturated lactones (**115**). The yield of the products was good in with a DMSO solution at 20 °C (Scheme 31). The reaction occurs via a (3 + 2)-cycloaddition. As tetrahydroindolizines are highly sensitive toward oxidation, oxidation with chloranil gave aromatic indolizine (**117** and **118**) 72–86% isolated yields. A combination of the electrophilicity parameters E with tabulated nucleophilicity descriptors *N* was used to predict the rate constants for the reactions of cyclic Michael acceptors with various C-nucleophiles. This work nurtures the development of medicinal and pharmaceutical drug discovery.



Scheme 40 Synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles

Zhang and Huang (Zhang and Huang 1998) synthesized fluroalylated indolizine derivatives (**120** and **121**) by cycloaddition reactions of *N*-(cyanomethyl)pyridinium ylides with 2,2-dihydropolyfluoroalkanoates ($RFCF_2CH_2CO_2Et$) (**119**) in presence of K_2CO_3/TEA in DMF at 65 °C (Scheme 32). The products' yields ranged from 20 to 90% depending on the polyflouroalkyl groups. The indolizine derivatives based on isoquinolinium were obtained with 48–64% isolated in yields.

Similarly, Zhu et al. (1999) synthesized 1-trifluoroacetyl indolizine derivatives (**123** and **124**) via the cycloaddition of pyridinium *N*-ylides with 4–4-ethoxy1-1,1,1-trifluorobut-3-en-one (**122**) (Scheme 33). The protocol involves the reactions of 4-ethoxyl-1,1,1-trifluorobut-3-en-2-one (**122**) with the corresponding salt in DMF at 70 °C.

Recently, Ren et al. (Zhang et al. 2021) accessed various functionalized 2-fluoroindolizines (**127** and **128**) by base mediated [3 + 2]-annulation of gem-difluoro alkenes (**125**) and pyridinium ylides using ambient air as the sole oxidant (Scheme 34). The protocol involves the reaction of pyridinium salt with fluoro alkenes in the presence of K_2CO_3 in DMF:Dioxane (1:1) mixture at 60 °C. The 3-cyano-2-fluoroindolizine-3-carbonitrile (**126**) can be further functionalized into different derivatives. The reaction of 2-fluoroindolizines in refluxing alcoholic KOH gave the corresponding 2-fluoroindolizine-3-carboxylic acid (**128**) with 93% yield, while Pd catalyzed coupling with phenylboronic acid gave the corresponding biaryl compounds (**127**) with 95% yield. The stepwise anionic mechanism involves the first formation of pyridinium ylide **4**, which attacks the gem-difluoro alkene **125** to form an intermediate **I**. Subsequently, **I** undergoes an intramolecular ring-closure process to form tetrahydro indolizine **II** which undergoes β-F elimination delivering intermediate **127**. Lastly, the 2-fluoroindolizine is formed through spontaneous oxidation process via path **A**. Alternatively, path **B** involves the formation of the product via sequential oxidation and β-F elimination process.

The 1-fluoroindolizines (**130** and **131**) were obtained with good yields by reacting various fluoronitroalkenes (**129**) and pyridinium ylides in the presence of 2,6 lutidine in DCE at 0 °C to RT (Motornov et al. 2019). The 3-cyano-substituted derivatives (**134**) were converted into 3-unsubstituted indolizines (**133**) using KOH, EtOH, and reflux, followed by treatment with conc. HCl, 80 °C. The resultant compounds on treatment with $EtO_2CC{=}CCO_2Et$, $Cu(OAc)_2{\cdot}H_2O$ (20 mol.%) in toluene and air at 90 °C gave fluorinated cyclizine (**134**). In continuation with this, they used copper acetate (Scheme 35) for the synthesis of functionalized pyrrolo[1,2-b]pyridazines and pyrrolo[1,2-a]phthalazines (**135**) by oxidative [3 + 2]-annulation reactions of nitroalkenes and pyridazinium ylides (Motornov et al. 2021).

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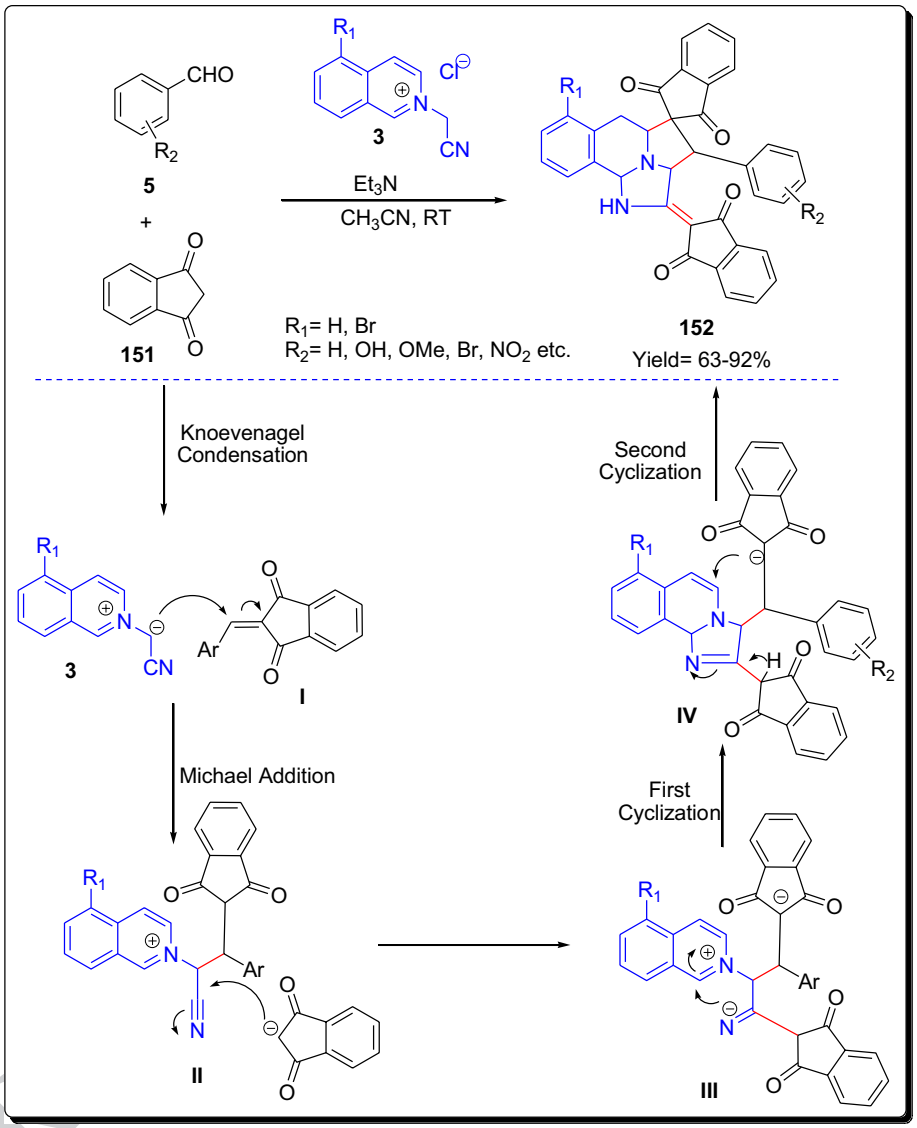
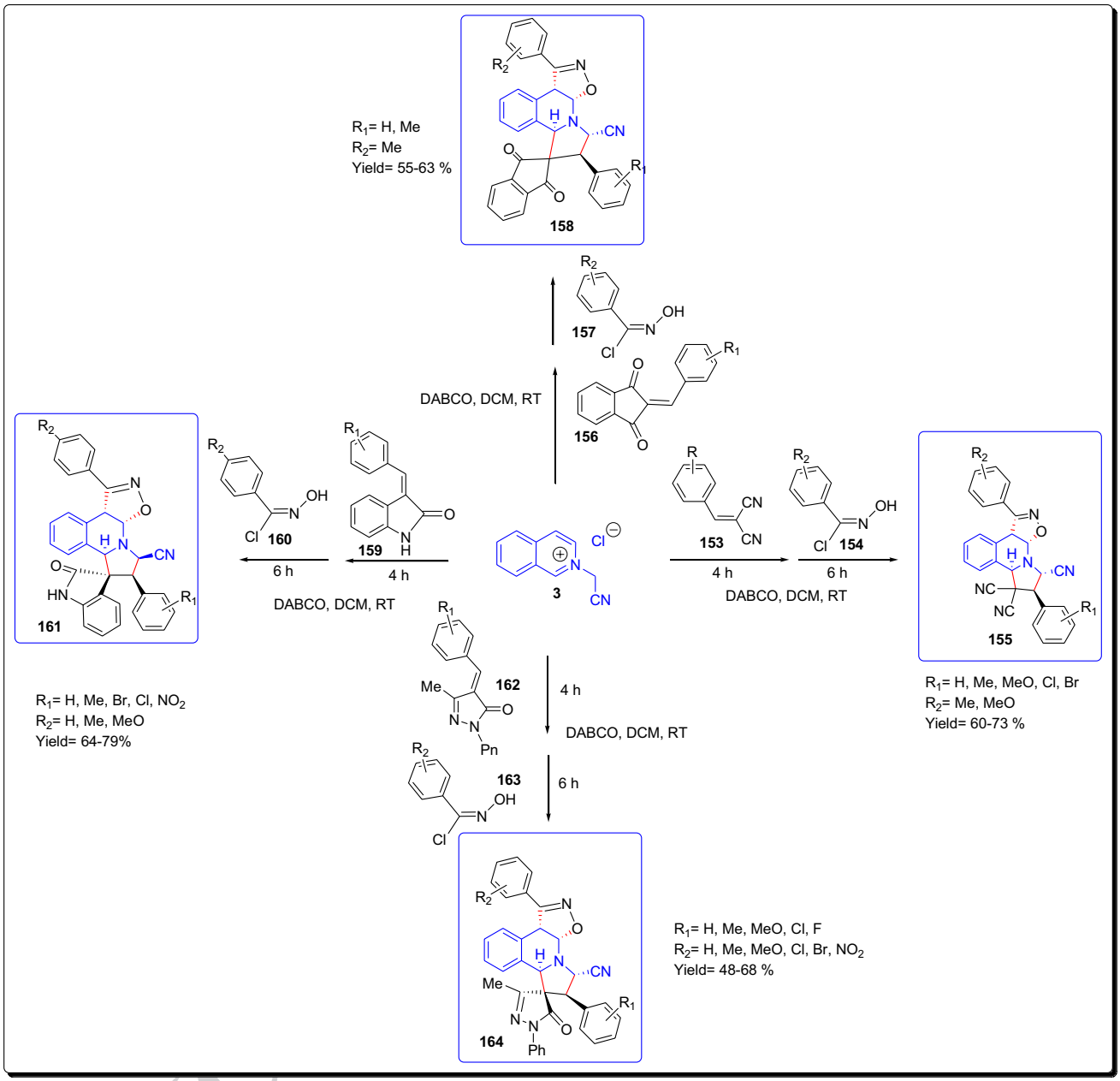


Scheme 41 Tandem double [3 + 2] reported a three-component cycloaddition reaction

Various pyridinium monosubstituted methylides were smoothly converted into pyridinium substituted cyanomethylide (**4**) in low-moderate yields by the attacked of cyano group from ethyl thiocyanatoacetate or ethyl 2-thiocyanatopropionate (**138**) in presence of K_2CO_3 in $CHCl_3$ (Kakehi et al. 1996). Subsequently, these substituted cyanomethylide (**4**) undergo the 1,3-dipolar cycloadditions with dimethyl acetylenedicarboxylate (DMAD) (**136**) in various solvents delivering only dimethyl 3-cyanoindolizine-l,2-dicarboxylate (**137**) in moderate yields at RT (Scheme 36).

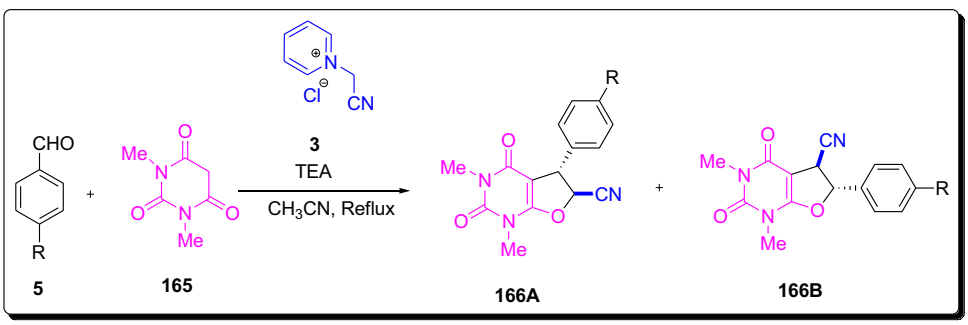
Iodine was also used as a promoter for the synthesis of acylindolizine derivatives from acetylene carboxylates and pyridinium ylides in DMSO at room temperature via 1,3-dipolar addition (Liu et al. 2014). Bicu and coworkers (Moise et al. 2020) synthesized cyanoindolizines or cyanoazaindolizinyl-indolizines from cyanomethyl pyridinium salts through the 1,3-cycloaddition conditions with alkyl propiolates (**139**). It was observed that the cycloadducts (**140**) were obtained at room temperature, while ethyl or methyl 3-(3-cyanoimidazo[1,2-a]pyridin-2-yl) indolizine-1-carboxylates (**141**) was obtained in refluxing CH_3CN in the presence of TEA (Scheme 37). Thus, the reactions at room temperature favor the classical reactivity to form cyanoindolizines (**140**) while the formed bis pyridinium salts formed at heating tempted the formation of cyanoazaindolizine-indolizine by tandem 1,3-cyclization to form (**141**).

Similarly, Airinei et al. (Gherasim et al. 2020) synthesized compounds with pyrrole-isoquinoline (**144**) and imidazo-isoquinoline (**143**) skeleton using the [3 + 2] cycloaddition of the several in situ generated cycloimmonium ylides and ethyl propiolate (**142A**) or ethyl cyanoformate (**142B**)



Scheme 42 Diastereoselective synthesis of spirocycles via cascade double [3 + 2]cycloadditions reactions

Scheme 43 One-pot three-component diastereoselective synthesis of novel regioisomers of furo[2,3-d]pyrimidines



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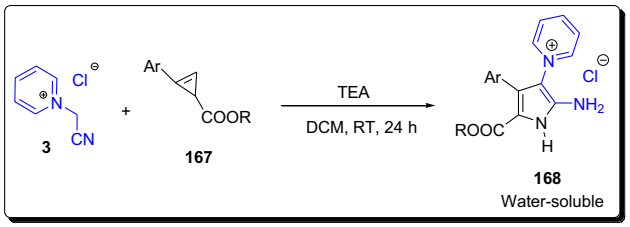


Scheme 44 Synthesis of water-soluble α-amino pyrroles from alkyl 3-aryl-2H-azirine-2-carboxylates

(Scheme 38). Both the compounds were studied by UV–VIS absorption as well as steady and time-resolved fluorescence methods. These derivatives displayed an intense emission between 360 and 420 nm. In addition, the emission quantum yields (Φ) of pyrroloisoquinoline derivatives were 0.54–0.64 in dimethylsulfoxide (DMSO), which are significantly higher than those of imidazoquinolines (Φ = 0.03–0.16).

Cynomethylpyridinium salt (**3**) can readily be coupled with benzenediazonium chloride to yield the phenylhydrazonylpyridinium bromides (**145**) in good yields, which were further converted into the 1,4-di-hydro-1,2,4,5-tetrazines (**146**) in the presence of ammonium acetate in refluxing acetonitrile. The resultant compound **145** was converted into the cyano indazole (**149**) when refluxed into DMF (Abdel-Khalik et al. 2000). The fusion reaction of **145** with the enaminone (**147**) afforded the pyrazole (**148**) at 250 °C with a 68% yield (Scheme 39).

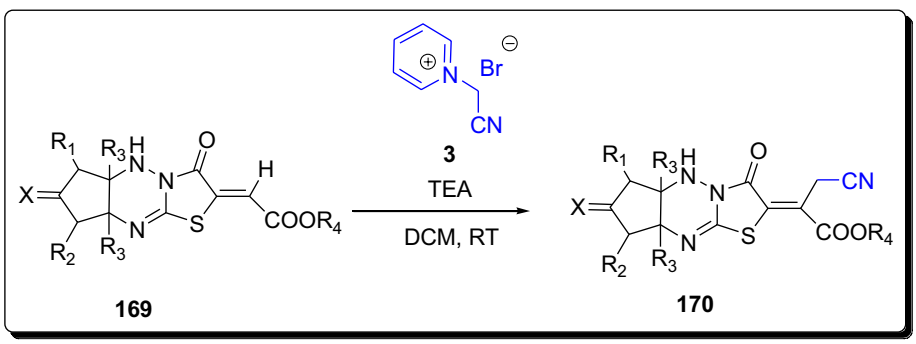
Wu et al. (Wu and Wu 2018) carried out a synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles (**150**) by the sequential reaction of pyridinium salts (**3**) with aldehydes (**5**) and sodium azide in presence of L-Proline (10 mol %) (Scheme 40). All the products were obtained in 87–93%. The proposed reaction mechanism involves coupling pyridinium ylide **I**, with aldehyde/protonated aldehyde to form *β*-hydroxypyridinium salt **II**. This salt is transformed into the key intermediate **III** via dehydration. Intermediate **III** on [3 + 2] cycloaddition with azide ion followed by elimination of pyridine produce the 4,5-disubstituted 1,2,3-triazole (**150**).

Other reactions

Yan et al. (Shi et al. 2017) developed a tandem double [3 + 2] three-component cycloaddition reaction of cyanomethyl isoquinolinium chloride (**3**) with 2-arylidene-1,3-indane diones (**151**) and different aldehydes (**5**). The reaction produces the spiro indene pyrrole isoquinoline derivatives (**152**) in the presence of TEA in acetonitrile at room temperature in 63–92% yields (Scheme 41). The reaction occurs both at C-1 and C-3 atoms of cyanomethyl isoquinolinium chloride. The plausible mechanism based on the experimental results is depicted in Scheme 41. Initially, isoquinolinium ylide reacts with 2-arylidene-1,3-indanedione formed by the Knoevenagel condensation of the aldehyde and indanedione in the presence of TEA. Next, Michael addition of a ylide on 2-arylidene-1,3-indanedione (**I**) afforded an intermediate **II**. Next, intermediate **II** reacted with the second molecule of 1,3-indanedione and afforded zwitterionic intermediate (**III**), which on the intermolecular cyclization, delivered the desired spiro compound.

Similarly, Yan et al. (Liu et al. 2019) reported the diastereoselective synthesis of spirocyclic isoxazolopyrrolo isoquinolines via cascade double [3 + 2] cycloaddition reactions of cyanomethylisoquinolinium chloride (**3**) with (*E*)-3-arylideneindolin-2-ones and (*E*)-*N*-hydroxybenzimidoyl chloride. All the reactions were carried out using DABCO in DCM at room temperature (Scheme 42). A novel polycyclic spiro indoline-isoxazolopyrrolo isoquinolines (**161**) were obtained in good yields with high diastereoselectivity *N*-ethoxycarbonylmethyl isoquinolinium bromide under the same reaction conditions gave a mixture of two diastereoisomers. Similarly, 4-arylidene-5-methyl-2-phenylpyrazol-3-ones (**162**) gave corresponding spiro compounds (**164**) in 48–68% yields. In addition, the reaction of 2-arylidene-1,3-indane diones (**156**) gave the corresponding spiro derivatives (**158**) in 55–63% yield, while arylidene malononitriles (**153**) were converted into corresponding spiro compounds (**155**) with 60–73% yields under similar reaction conditions.

Scheme 45 Annulated 4-oxothiazolidin-5-ylides via a cascade of Michael addition/elimination reactions



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The stereochemistry of the spiro compounds was elucidated by single-crystal analysis.

Bhuyan et al. (Dutta et al. 2016) reported the one-pot three-component diastereoselective synthesis of novel regioisomers of furo[2,3-d]pyrimidines (**166**) using barbituric acids (**165**), aryl aldehydes (**5**), and pyridinium bromides (**3**) in the presence of TEA in refluxing acetonitrile (Scheme 43). The reaction occurred via Knoevenagel condensed Michael addition route. There is involvement of nitrogen ylides in [4 + 1] annulations as well as [2 + 1] annulation followed by intramolecular ring transformation in the presence of a base to afford two isomeric products.

Khlebnikov and co-workers (Galenko et al. 2021) reported the synthesis of water-soluble α-amino pyrroles (1-(2-amino-1H-pyrrol-3-yl)pyridinium chlorides) (**168**) by the reaction of 1-(cyanomethyl)pyridinium chloride (**3**) with alkyl 3-aryl-2H-azirine-2-carboxylates (**167**) in the presence of TEA in DCM at RT (Scheme 44).

Recently, Chen and co-workers (Tang et al. 2023) synthesized a novel reactivity annulated 4-oxothiazolidin-5-ylidenes (**170**) via a cascade of Michael addition/elimination reactions. The method gives an excellent yield of the desired products using TEA as a base in DCM at RT (Scheme 45).

Conclusion

In this account, we have highlighted the feasibility of cyanomethyl pyridinium, isoquinolinium, and related salts as useful reagents to synthesize many important annulated heterocycles. Although this reagent has witnessed several advances, its application in organic synthesis is yet to be seen in a broader range. The presented analysis shows that the application of cyanomethyl pyridinium salts and their related derivatives is less. In addition, the ready access of these salts from easily available reagents will certainly make them an appealing class of promoters for the development in the synthesis of many other classes of heterocycles.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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