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Transition metal free functionalization of nitrogen heterocycles, triggered and driven by electrophilic acetylenes

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ABSTRACT

The review covers the advances reached during the last five years in transition metal free functionalization and modification of nitrogen heterocycles with electrophilic acetylenes. The reactions are triggered and further driven by the initially formed 1,3(4)-dipole complexes (zwitterions), adducts of the nucleophilic attack of nitrogen heterocycles at the triple electrophilic carbon-carbon bond of the acetylenes. The carbanionic sites of these zwitterions are usually captured by electrophiles such as second molecule of the acetylenes or other electrophilic C═C and C═O unsaturated compounds, as well as various CH—, OH—, NH—, PH— acids thereby raising molecular complexity (in the course of diverse cascade transformations) to a new higher level. The rich energy potential of the activated carbon-carbon triple bond warrants mild reaction conditions and allows the functionalization to be performed without transition metal catalysts.

Introduction

Functionalization of nitrogen heterocycles is old and traditional, but dynamically developing area of heterocyclic chemistry. Today in this area, the transition metal catalyzed functionalizations almost exclusively dominate. At the same time, there is a transition metal free approach to the functionalization of nitrogen heterocycles using electrophilic acetylenes, which though is also progressing, but still stays somewhat in a shadow of the transition metal based mainstream. Meanwhile, the electrophilic acetylene approach owns a number of advantageous features, which make it attractive for the chemical community. Among these advantages is the absence of heavy metal contaminations in the reaction products that is important for pharmaceutically oriented applications, as well as a high, still not yet unfolded synthetic potential allowing the diverse functionalization of nitrogen heterocycles to be realized.

The essence of the nitrogen heterocycles activation by electrophilic acetylenes is known [1] to be the formation of the 1,3(4)-dipolar complexes (zwitteriones), the products of nucleophilic attack of nitrogen atom at the triple bond. These complexes essentially function as intramolecular ion pairs, featuring a vinyl carbanionic site and a positive charge localized within the heterocycles. Thus, the nucleophilic nitrogen heterocycles become electrophilic, whereas the acetylenic moiety turns nucleophilic, i.e. a kind of “umpolung” here occurs. The above zwitteriones are able to trigger a great diversity of transformations involving the “mother” heterocycle and a multitude of external electrophiles, and therefore, often make possible such functionalizations, which are improbable for transition metal catalyzed transformations. The growing interest in transition metal free functionalization of nitrogen heterocycles with a help of electrophilic acetylenes is reflected in frequent appearance of reviews covering various aspects of this field. Indeed, after publication in 2020 of our overlook on application of electrophilic acetylenes for reaching diversity and complexity of nitrogen heterocycles [1], five more reviews saw the light highlighting hitherto unknown facets of nitrogen heterocycle functionalization via the above zwitterionic intermediates such as exploitation of cyanoacetylenic alcohols, a group of highly electrophilic acetylenes [2], S_N^HAr reactions with phosphorus nucleophiles [3], cyclative multicomponent reactions of azines and azinium salts [4]; utilizing sulfur- and nitrogen-based pyridinium and quinolinium 1,4-zwitterions for the synthesis of three- to eight-membered cyclic compounds [5], functionalization and annulation reactions with pyrrolylacetylenic ketones [6]. However, the publication of reviews fails to keep pace with synthetic advances in this area. Since the above reviews became a public domain more than 40 experimental papers concerning novel aspects of electrophilic acetylenes application for the functionalization of nitrogen heterocycles have been issued. Among these works were those referring to the following topics: (i) synthesis of pyrroloimidazoles via the (3+2) cyclization of

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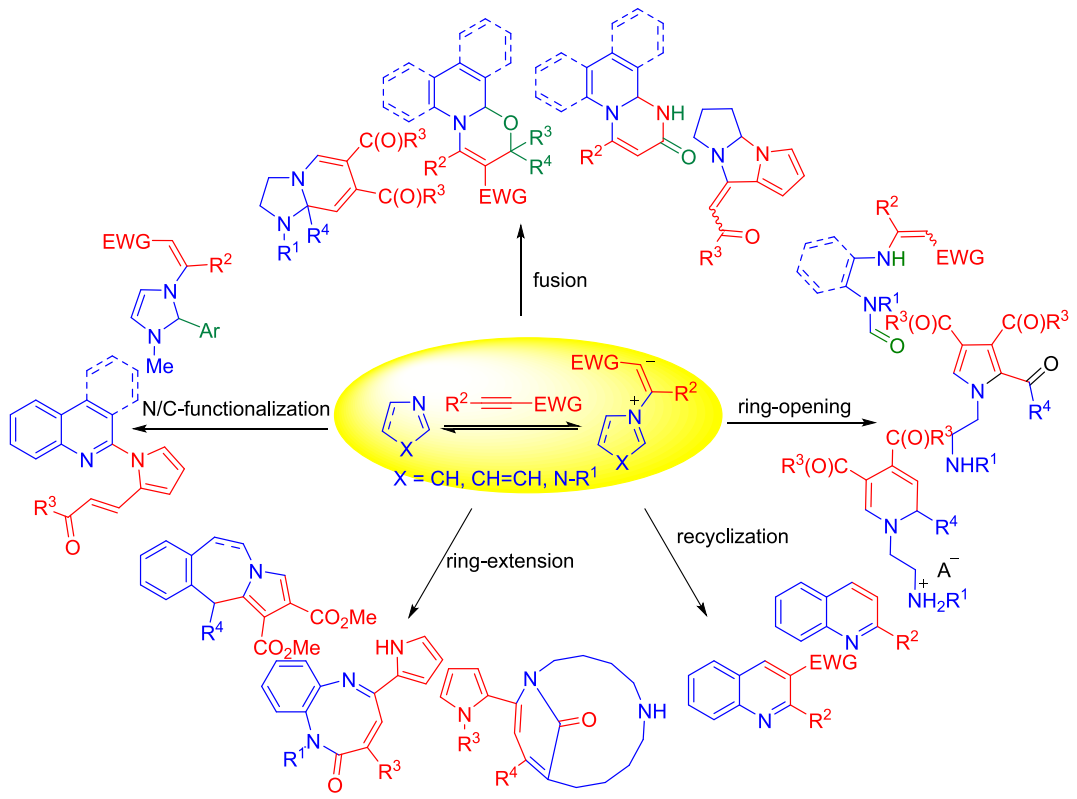
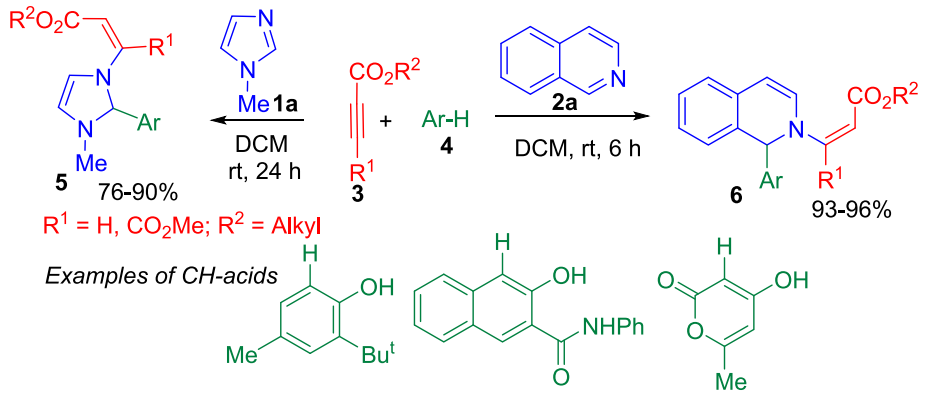


Fig. 1. The main directions of nitrogen heterocycles functionalization by electrophilic acetylenes (selected examples).

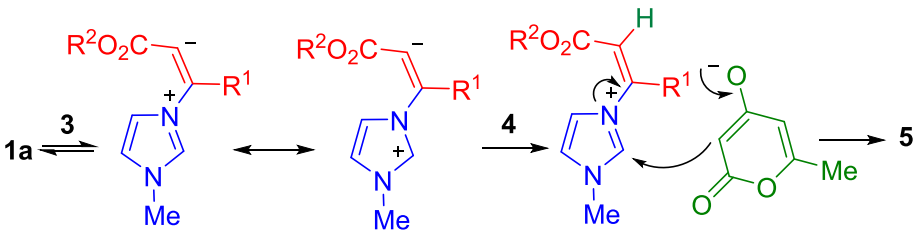
pyrrolylacetylenic ketones with the C═N bond of nitrogen heterocycles [7,8]; (ii) or (3+3)-cyclodimerization of pyrrolylacetylenic ketones to dipyrrolopyrazines via zwitterionic intermadiates [9]; (iii) the unprecedented zwitterion-promoted ring expansion of DBU to afford macrocyclic bridgehead 14-membered diazaheterocycles, a new class of fluorophores with giant Stokes shift [10]; (iv) synthesis of densely functionalized fused heterocyclic systems using oxalylacetylenic esters as source of zwitterions [11]; (v) activation of C—H bond of methyl substituents, adjacent to nitrogen atom, in 1,3(4)-zwitterionic intermediates, adducts of isoquinolines with acetylenic ketones: synthesis of functionalized terphenyl derivatives of isoquinolines [12]; (vi) nucleophilic substitution of hydrogen in the phenanthridine ring by polyfluorinated phosphanes triggered and driven by the complexing with acetylenic ketones [13]; (vii) *N*-ethenylation/*C*-ethynylation of (dihydro)isoquinolines by electrophilic acetylenes and their further transformation to dihydropyrido-, dihydropyrrolo[2,1-*a*]isoquinolines or pyrrolo[2,1-*b*][3]benzazepines [14]; (viii) synthesis of indolizines via (3+2)-cycloaddition of 2-ethynylpyridines with electrophilic acetylenes and their further carbene-triggered functionalizations [15]; (ix) annulation of 1-aroylisoquinolines with terminal acylacetylenes, malononitrile and other CH-acids [16]. These issues are discussed in detail in the corresponding section of this article. The major part of the papers included in this survey was not covered in any other reviews and those if there mentioned, here are discussed under other aspects.

The compounds obtained using the zwitterions generated in situ from nitrogen-containing heterocycles and electron-deficient acetylenes exhibit valuable photophysical properties, biological activity and high potential as useful building blocks.

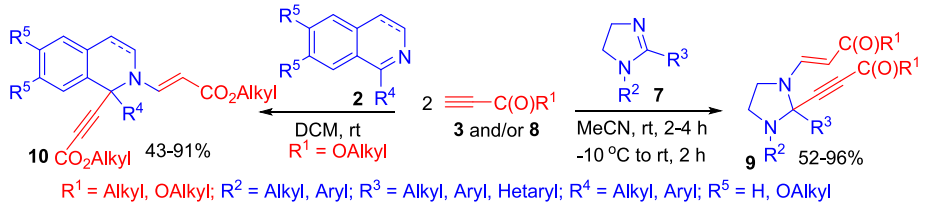
The material is considered according to the types of nitrogen heterocycle transformations: *N*- (and/or *C*)-functionalization, annulation (fusion), ring-opening, recyclization, and ring-extension (Fig. 1).



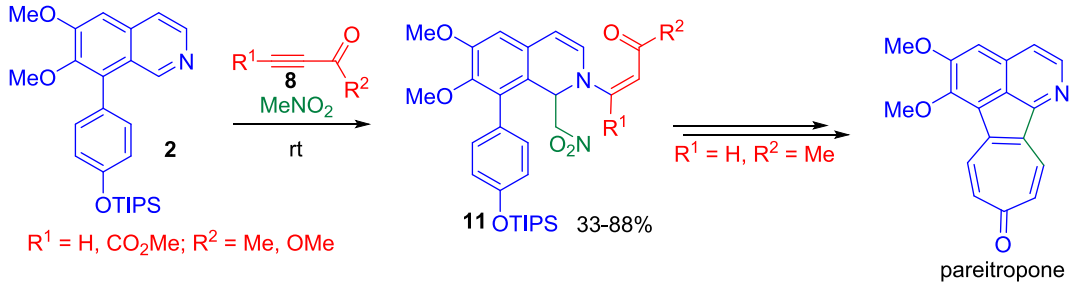
Scheme 1. *N*-Ethenylation/*C*-arylation of nitrogen heterocycles **1** and **2** by electrophilic acetylenes **3** and aromatic compounds **4**.



Scheme 2. The mechanism of the reaction.



Scheme 3. *N*-Ethenylation/*C*-ethynylation of nitrogen heterocycles **2** and **7** by electrophilic acetylenes **3** or **8**.



Scheme 4. *N*-Ethenylation/*C*-nitromethylation of isoquinoline derivative **2** by acylacetylene **8** and nitromethane and the usage of product **11** in total synthesis of pareitropone.

N- and/or *C*-functionalization of nitrogen heterocycles

Three-component reaction between *N*-methylimidazole **1a** or isoquinoline **2a,** alkyl esters of acetylenecarboxylic acids **3** and 4-hydroxy-6-methyl-2*H*-pyran-2-one or *N*-phenyl-3-hydroxynaphthalene-2-carboxamide as CH-acids **4** afforded *N*-alkenyl-*C*-arylheterocycles **5** or **6**, correspondingly (Scheme 1) [17,18].

As it is exemplified for 1-methylimidazole **1a**, in this cascade process the pyridine nitrogen attacks the triple bond of acetylene **3** to form a zwitterionic intermediate, the vinyl carbanion center of which is neutralized by the proton of CH-acid **4**, and the generated carbanion is added to the positively charged α-position of the heterocycle (Scheme 2).

The reaction between 1-alkyl-2-imidazolines **7** [19,20] or (dihydro) isoquinolines **2** [14] with two molecules of alkyl propiolates **3** or acylacetylenes **8** delivered *N*-ethenyl-*C*-propargyl imidazolidines **9** or –(dihydro)isoquinolines **10**, products of heterocycle/propiolate zwitterion interception by the second molecule of alkynes **3** or **8** (Scheme 3).

Products **9** and **10** are suitable for the further functionalization and modification, which provide the annulated, ring-opened or ring-extended adducts. These transformations are described in the relevant sections of this review (see below Schemes 27, 28, 43, 44, 49 and 50).

N-Alkenyl-1-nitromethylisoquinoline **11**, product of the three-component reaction between substituted isoquinoline **2**, butynone **8a** and nitromethane, was applied in the total synthesis of pareitropone (Scheme 4) [21].

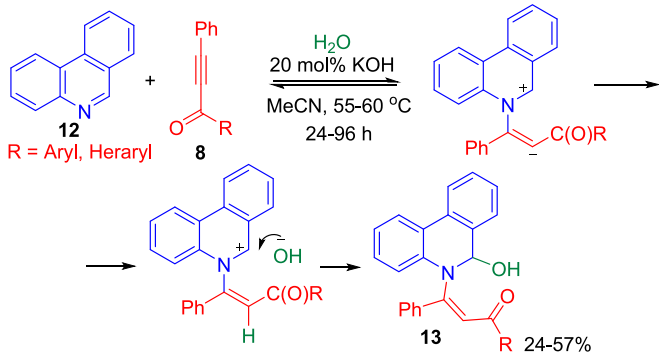
The interception of the primary zwitterion, generated from the phenanthridine **12** and acylacetylenes **8**, by water as OH-acid led to the stereoselective formation of *N*-(*Z*)-acylethenyl-6-hydroxydihydrophenanthridines **13** (Scheme 5) [22].

This reductive functionalization of phenanthridine scaffold contrasts to the reaction of quinolines with the same reagents wherein double functionalization of the azine ring occurs (see Scheme 45).

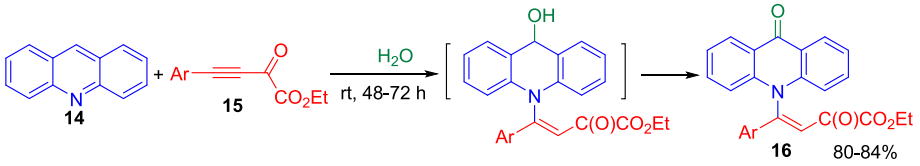
Acridine **14** underwent simultaneous *N*(10)- and *C*(9)-functionalization under the action of a relatively new family of strong electrophilic acetylenes, oxalylacetylenic esters **15** and water. In this case, the hydroxyl group was easily oxidized (by ambient oxygen) to a carbonyl group and the reaction furnished pharmacologically promising previously unknown *N*-alkenylacrid-9-ones **16** (Scheme 6) [23].

NH-Pyrroles **17** were added as electrophiles to zwitterionic adducts of Δ^1-pyrrolines **18** and benzoylphenylacetylene **8b** or cyanophenylacetylene **19a** to form 2-(pyrrol-1-yl)pyrrolidin-1-ylacrylonitriles and 2-(pyrrol-1-yl)-pyrrolidin-1-ylenones **20** (Scheme 7) [24].

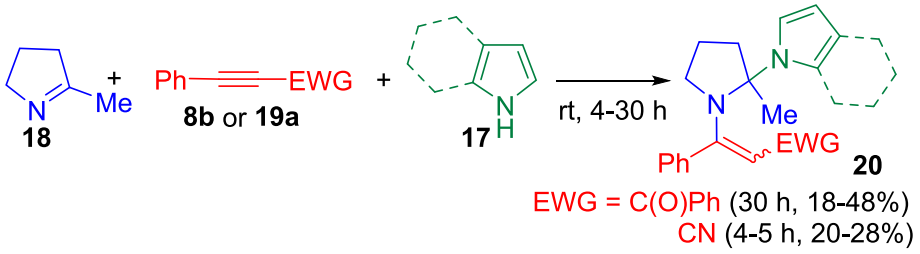
The reaction of electrophilic pyrrolylacetylenic ketones **21**,



Scheme 5. *N*-Ethenylation/*C*-hydroxylation of phenanthridine **12** by acylacetylenes **8** and water.



Scheme 6. The synthesis of *N*-alkenylacrid-9-ones **16** via functionalization of acridine **14** by oxalylacetylenic esters **15** and water.



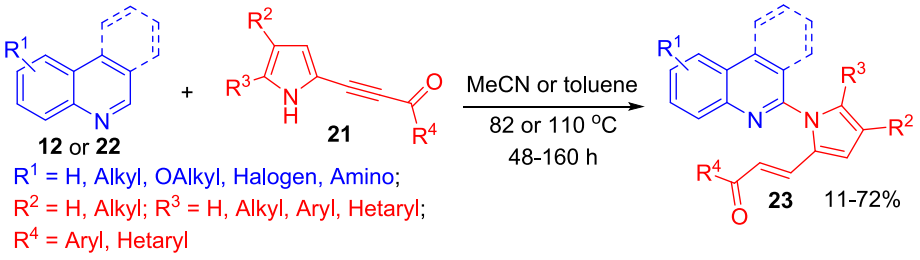
Scheme 7. *N*-Ethenylation/*C*-amination of Δ^1-pyrrolines **18** by electrophilic acetylenes **8b** or **19a** and NH-pyrroles **17**.

combining NH-pyrrole, triple C≡C bond and carbonyl group in their structure, with quinolines **22** or phenanthridine **12** proceeded as unprecedented *C*-2 functionalization of the azine ring to stereoselectively produce 2-(*E*-2-acylethenylpyrrolyl)quinolines (or -phenanthridines) **23** (Scheme 8) [25].

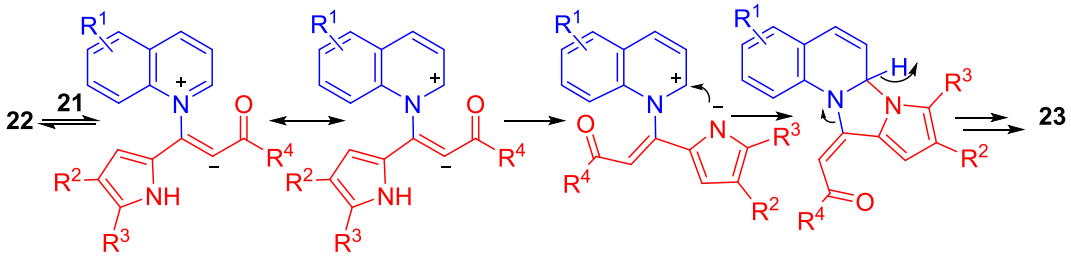
The reaction involves the formation of zwitteriones and (3+2)-cycloaddition adducts, which undergo deeper rearrangements with the *N*(1)-*C* bond cleavage to restore the quinoline aromaticity (Scheme 9, on the example of qiunolines **22**).

The reactions between azines (pyridines **24**, quinolines **22**, isoquinolines **2**, phenanthridine **12**), electron-deficient acetylenes (acylacetylenes **8**, propiolates **3**, cyanophenylacetylene **19a**) and secondary phosphine oxides, sulfides or selenides **25** or bis(polyfluoroalkyl)-*H*-phosphonates **26** proceeded as *N*-ethenylation/*C*-phosphorylation (Scheme 10). These reactions were highlighted in a recent review [3] and now keep actively studied [13,26].

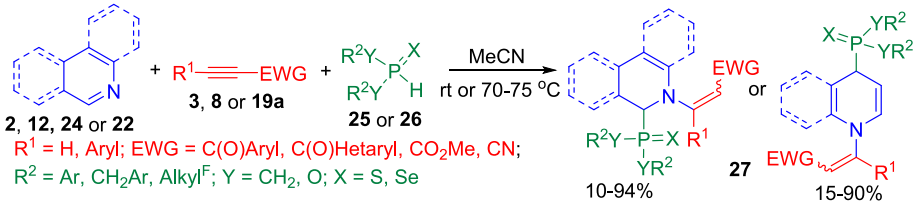
This chemistry, extended over substituted pyridines **24**, is unique since under certain conditions, a nucleophilic aromatic substitution of a hydrogen atom in the azine core ($S_N^H Ar$) by a phosphoryl substituent occurs, and electrophilic acetylenes **3**, **8** or **19a** play the role of the



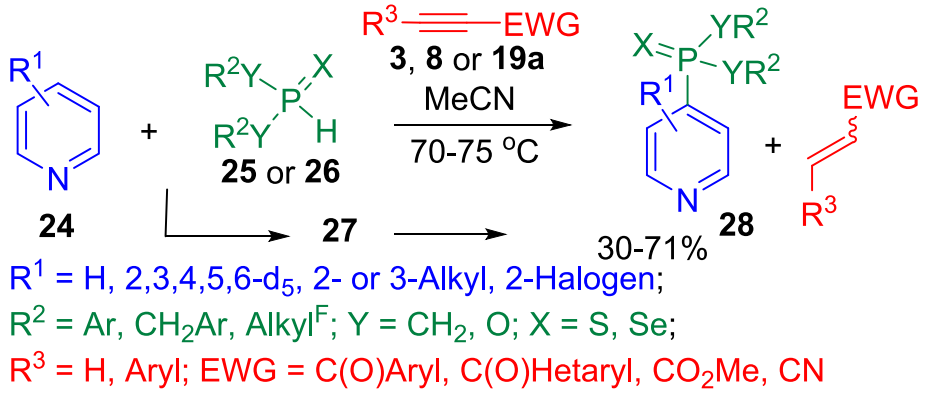
Scheme 8. *C*-Amination of quinolines **22** or phenanthridine **12** by pyrrolylacetylenic ketones **21**.



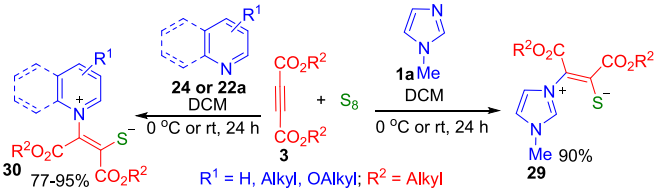
Scheme 9. The mechanism of *C*-2 functionalization of quinolines **22** or phenanthridine **12** by pyrrolylacetylenic ketones **21**.



Scheme 10. *N*-Ethenylation/*C*-phosphorylation of azines **2**, **12**, **22** or **24** by electrophilic acetylenes **3**, **8** or **19a** and secondary phosphine chalcogeniges **25** or phosphonates **26**.



Scheme 11. S_N^HAr reaction between pyridines **24** and secondary phosphine chalcogeniges **25** or phosphonates **26**, triggered by electrophilic acetylenes **3**,**8** or **19a**.



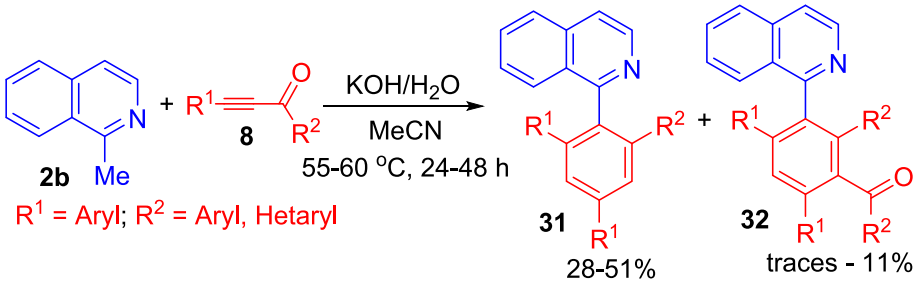
Scheme 12. *N*-Functionalization of nitrogen heterocycles **1**, **22** or **24** by acetylenedicarboxylates **3** and elemental sulfur.

reaction trigger and are reduced to the corresponding alkenes [3,26a,c,27] (Scheme 11).

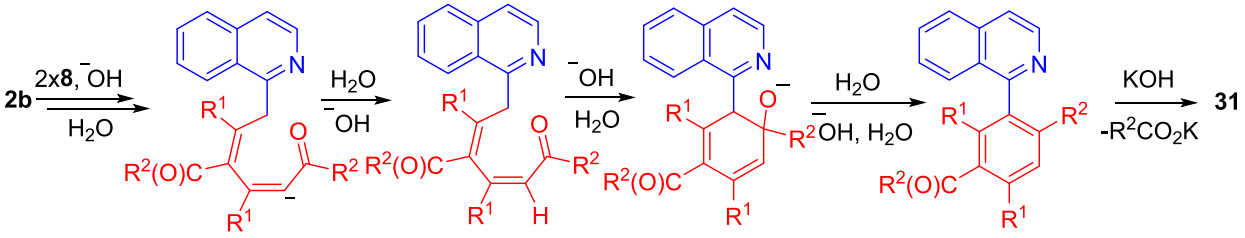
The functionalized *N*-imidazolium- or *N*-aziniumbytenetiolates **29** or **30**, generated via interception of the corresponding imidazole **1a** or azines **22a**, **24**/acetylenedicarboxylates **3** zwitteriones by elemental sulfur (Scheme 12), have proven to be valuable building blocks in organic synthesis [5].

Acylarylacetylenes **8** reacted with 1-methylisoquinoline **2b** in 2:1 M ratio in the presence of KOH/H_2O to give 1-(5-arylterphenyl)isoquinolines **31** and 1-(4-acyl-5-arylterphenyl)isoquinolines **32**, products of the methyl group transformation to polyaryl substituent (Scheme 13) [12].

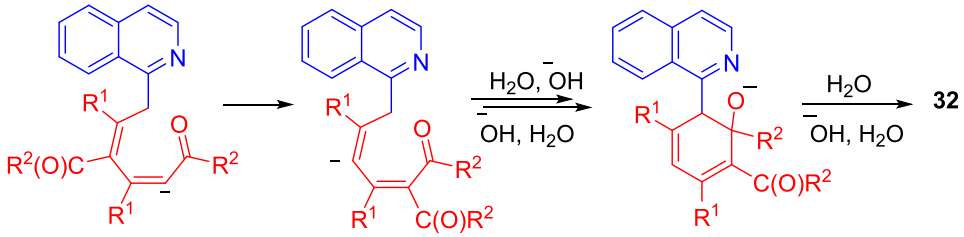
Presumably, the formation of functionalized terphenyl-substituted isoquinolines **31** (Scheme 14) involves the hydroxide-mediated deprotonation of the methyl group and thus formed carbanion consequently adds to the triple bond of two molecules of acetylene **8** and is neutralized by a proton of water to the open-chained diene intermediate. The latter



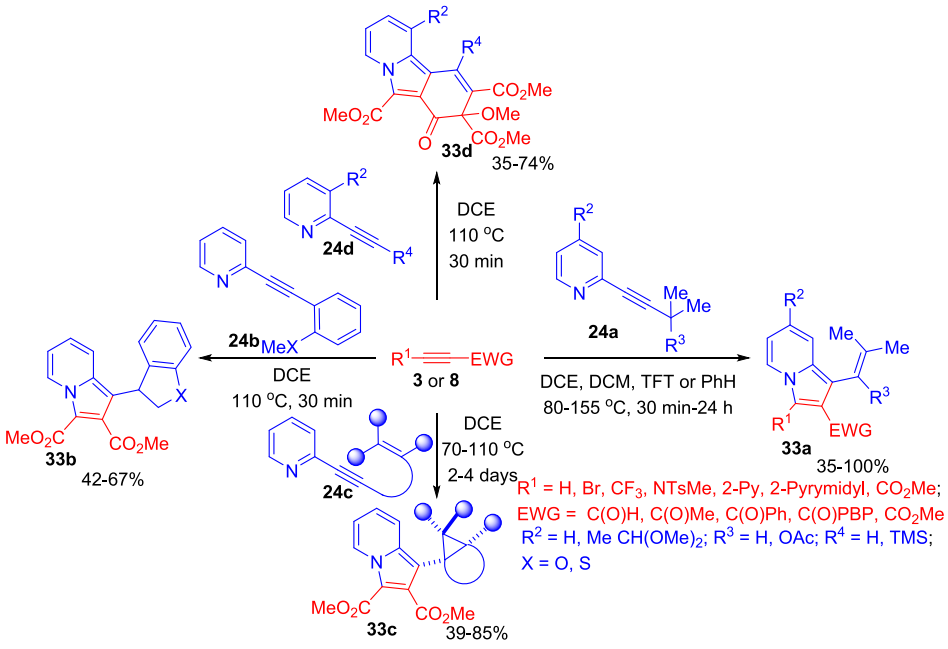
Scheme 13. Synthesis of 1-arylisoquinolines **31** and **32** from 1-methylisoquinoline **2b** and acylacetylenes **8**.



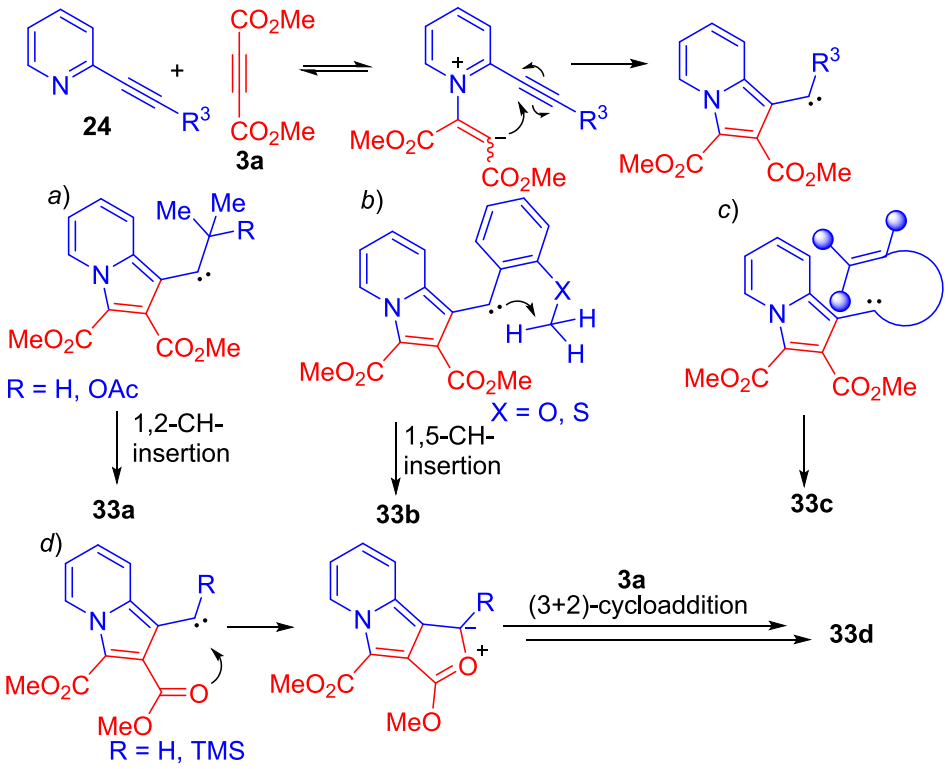
Scheme 14. Pathway for synthesis of 1-arylisoquinolines **31** from 1-methylisoquinoline **2b** and acylacetylenes **8**.



Scheme 15. Pathway for synthesis of 1-arylisoquinolines **32** from 1-methylisoquinoline **2b** and acylacetylenes **8**.



Scheme 16. Synthesis of indolizines **33** from 2-ethynylpyridines **24** and electrophilic acetylenes **3** or **8**.



Scheme 17. Pathway for fusion of 2-ethynylpyridines **24** with pyrrole cycle and routes for the synthesis of indolizine **33** derivatives via carbenic intermediates.

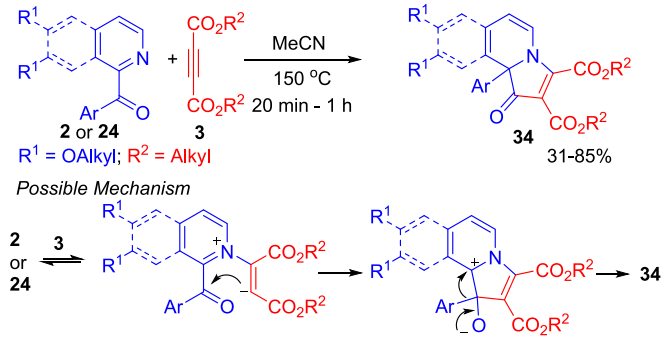
undergoes the ring closure with participation of the deprotonated CH_2 group and the carbonyl function of the acyl group. Following dehydration provides substituted triarylphenyl derivative, which would eliminate potassium carboxylate under the action of KOH, leading to product **31**.

Acylarylterphenylisoquinolines **32** are resulted from 1,3-acyl transfer in open-chain intermediate followed by quenching of the emerging carbanion with a proton of water, ring-closure and dehydration (Scheme 15). The driving force of this process is a lower proton concentration due to the higher medium basicity. In such a case, the transferring acyl cation would partially replace the medium proton.

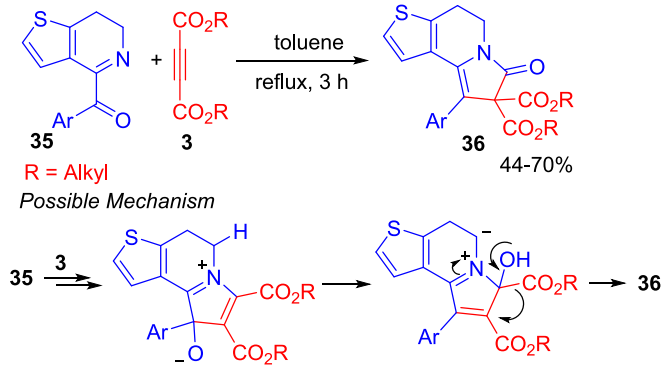
Synthesis of fused nitrogen heterocycles

Fusion with pyrrole scaffold

Annulation of 2-ethynylpyridine derivatives **24** with electrophilic acetylenes **3** or **8** proceeded through a formal (3+2)-cycloaddition to



Scheme 18. Annulation of aroylpyridines **24** or -isoquinolines **2** with electrophilic acetylenes **3**.



Scheme 19. Synthesis of dihydrothieno[2,3-*g*]indolizine-7(8*H*)-ones **36**.

give pyrrole-fused products, indolizines **33** in good to quantitative yields (Scheme 16) [15].

Twelve different ethynyl-substituted nitrogen-containing heterocycles were also involved in the reaction thus demonstrating its general character.

Cyclization of the key zwitterionic intermediate leads to the formation of a pyrrole ring and the appearance of a carbene center in further intermediate (Scheme 17). The latter, depending on the substituent in ethynylpyridine **24**, triggers either a 1,2- or 1,5-CH-insertions [routes *a*), *b*) in Scheme 17] or cyclopropanations [route *c*) in Scheme 17] to products **33a** or **33b** or **33c**. Carbene center can also be attacked by the adjacent carbonyl oxygen atom of the ester group to form a 1,2-zwitterion, capable of (3+2)-cycloaddition with the second molecule of dimethyl acetylenedicarboxylate (DMAD) **3a**, followed by the rearrangement into product **33d** [route *d*) in Scheme 17].

An efficient approach to the synthesis of indolizines and pyrrolo[2,1-*a*]isoquinolines **34** via the domino reaction between aroylpyridines **24** or -isoquinolines **2** and electrophilic acetylenes **3** (Scheme 18) was developed [28]. The vinyl carbanionic center of the zwitterion intramolecular attacks the carbonyl group to close the pyrrole cycle of the next intermediate, the rearrangements of which give product **34**.

The reaction between aroylsubstituted thienopyridines **35** and acetylenedicarboxylates **3** lead to 7-oxo-thienoindolizinedicarboxylates **36** with a geminal arrangement of ester groups (Scheme 19) [29]. The possible mechanism includes generation of zwitterions (similar those in Scheme 18). The formation of the target products **36** is accompanied by nucleophilic migration of the alkoxycarbonyl group.

The three-component domino reaction of 1-aroyl-3,4-dihydroisoquinolines **2** with electrophilic alkynes **3** or **8**, and CH- or NH-acids **37** or **38** afforded 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **39** substituted at the position 3 by dicyanomethylene, different propyl-2-diones-1,3 or *N*-azolyl moieties (Scheme 20) [30,31].

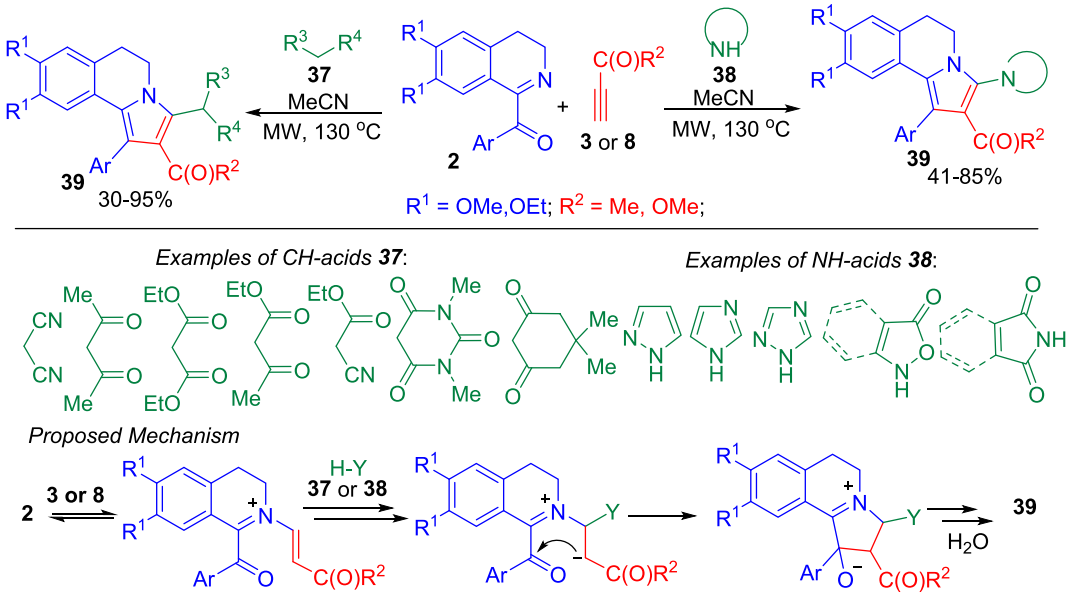
The possible mechanism of the reaction involves the generation of zwitterions, the anionic center of which deprotonates CH- or NH-acids **37** or **38**, facilitating their attachment to the enamine fragment. Next, intramolecular nucleophilic addition of carbanion to the aroyl group closes the five-membered ring intermediate. The subsequent protonation and dehydration complete the synthesis of pyrroloisoquinolines **39** (Scheme 20).

The reaction between 1-aroyl-3,4-dihydroisoquinolines **2**, terminal acylacetylenes **8**, malononitrile **37a** and other CH-acids **37** produced new highly functionalized 5,6-dihydroindolo[2,1-*a*]isoquinolines **40** and pyrido[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinolines **41** (Scheme 21) [16].

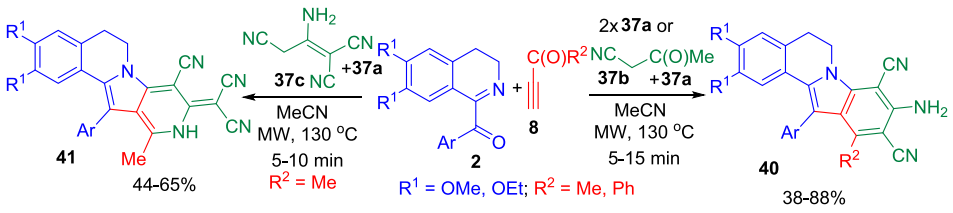
It was found that 5,6-dihydroindolo[2,1-*a*]isoquinolines **40** exhibited attractive luminescent characteristics.

Fusion with imidazole scaffold

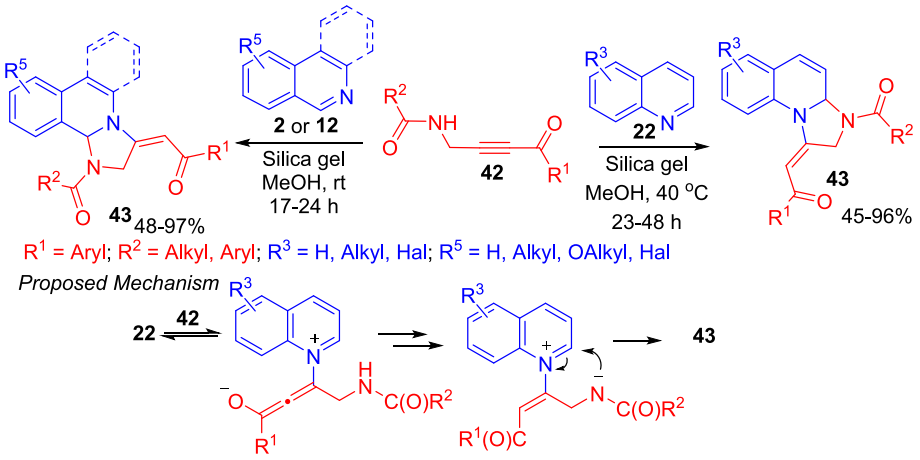
A mild cascade annulation of quinolines **22** (isoquinolines **2** or phenanthridine **12**) with acyl(aminomethylene)acetylenes **42** was



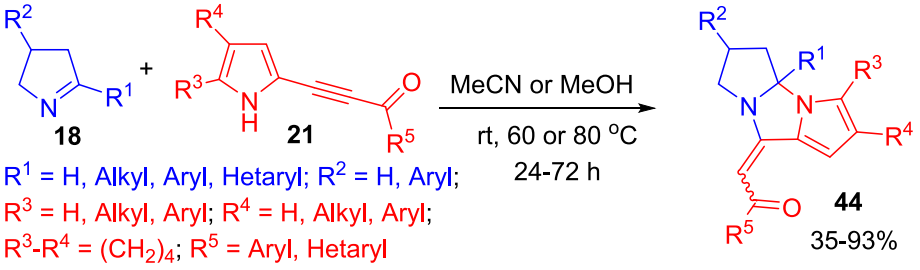
Scheme 20. Synthesis of 3-substituted dihydropyrrolo[2,1-*a*]isoquinolines **39**.



Scheme 21. Synthesis of 5,6-dihydroindolo[2,1-*a*]isoquinolines **40** and pyrido[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinolines **41**.

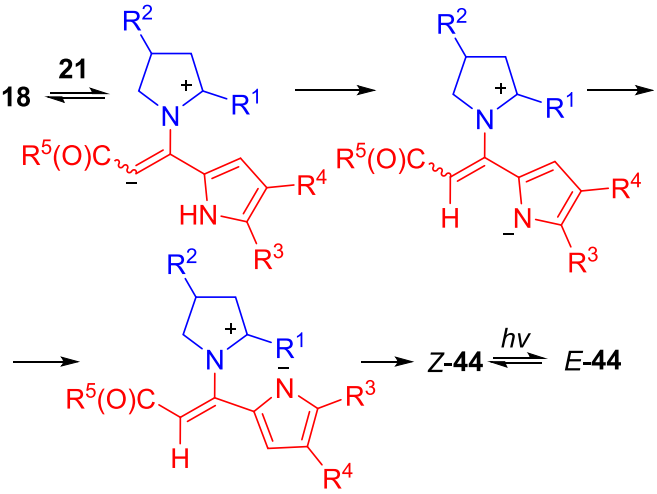


Scheme 22. Synthesis of imidazo[2,3-*a*](iso)quinolines **43**.

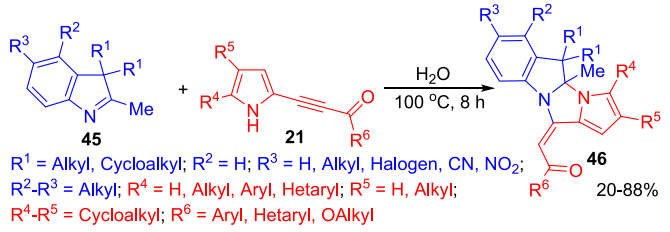


Scheme 23. Synthesis of dipyrrolo[1,2-*a*:1′,2′-*c*]imidazoles **44**.

developed (Scheme 22). Highly functionalized imidazo[2,3-*a*]quinoline or imidazo[3,2-*a*]isoquinoline derivatives **43** were prepared directly in moderate to excellent yields [32]. The proposed mechanism (on the example of quinolines **22**) involves intramolecular proton transfer in allenyl zwitterion intermediate from the amino group and subsequent annulation via an intramolecular *aza*-Mannich reaction to form imidazo



Scheme 24. The mechanism of reaction between Δ^1-pyrrolines **18** and pyrrolylacetylenic ketones **21**.



Scheme 25. Synthesis of pyrrolo[1′,2′:3,4]imidazo[1,2-*a*]indoles **46**.

[2,3-*a*](iso)quinolines **43**.

Pyrrolylacetylenic ketones **21** underwent a facile [3+2]-cycloaddition to Δ^1-pyrrolines **18** to afford acylmethylenetetrahydrodipyrrolo[1,2-*a*:1′,2′-*c*]imidazoles **44** in up to 93 % yield and 90 % *E*-stereoselectivity of the olefin moiety (Scheme 23) [33].

To gain a better understanding of the reaction progress, its mechanisms was examined using a DFT B2PLYP-D3/6-311++G**//B3LYP/6-31+G* approach (on the pair of 2-methylpyrroline and phenylpyrrolylacetylenic ketone in MeOH) (Scheme 24) [34]. In the thermodynamically and kinetically favorable *Z*-isomer of the intermediate zwitterion ($\Delta G^{\neq}$ = 19.72 kcal/mol, ΔG = 8.39 kcal/mol) a mobile proton of the pyrrole ring migrates towards the carbanion center of the vinyl group via participation of MeOH molecule ($\Delta G^{\neq}$ = 0.57 kcal/mol, ΔG = −20.47 kcal/mol). Then pyrrole ring rotation is occurred ($\Delta G^{\neq}$ = 14.24 kcal/mol, ΔG = −1.03 kcal/mol), thereby providing favorable conditions for the subsequent attack of the pyrrolidine C2 atom, which consequently results in the formation of a dipyrroloimidazole structure ($\Delta G^{\neq}$ = 11.36 kcal/mol, ΔG = −13.87 kcal/mol). The overall Gibbs free energy decrease in the course ot this reaction is ΔG = −26.97 kcal/mol. The photochemical isomerization process of the end product was also studied.

Green, in water, catalyst-free of stereoselective 3*H*-indoles **45**/pyrrolylacetylenic ketones **21** (2+3)-cyclization to afford dihydropyrrolo[1′,2′:3,4]imidazo[1,2-*a*]indoles **46** functionalized by acylethenyl groups of the *E*-configuration in up to 88 % yield was implemented (Scheme 25) [35]. Mechanistically, this reaction is assumed to represent a kind of micellar catalysis, when cross-aggregates of the starting compounds behave as surfactants and self-organized micro-reactors, wherein a favorable (relative to charge and electron density distribution) mutual orientation of the reactants is realized. The DFT calculations are in agreement with (2+3)-cycloaddition, particularly underlying the crucial role of water in the studied cascade process.

The strategy for the imidazole ring fusion under the action of pyrrolylacetylenic ketones **21** with a cyclic C=N bond was successfully extended over six- and seven-membered cyclic imines [8,36] and 1-methylisoquinoline [7].

Fusion with pyridine and naphthyridine scaffolds

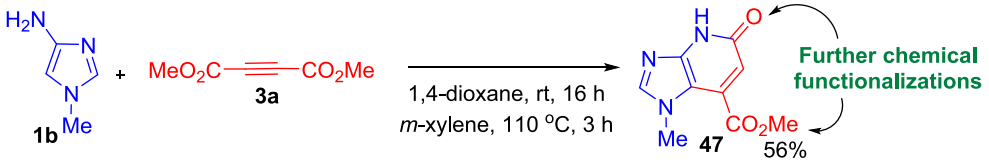
Michael addition of 4-amino-1-methylimidazole **1b** to DMAD **3a**, followed by intramolecular cyclization via nucleophilic addition of the amino group to ester moiety, provided novel imidazo[4,5-*b*]pyridine **47** (Scheme 26) [37]. The synthesized product **47** was successfully used for further functionalization at the pyridine ring to afford pharmaceutically prospective purine bioisosteres.

The products of *N*-ethenylation/*C*-ethynylation **9**, obtained from imidazolines **7** and acetylenes **3** according to Scheme 2, were easily transformed into tetrahydroimidazo[1,2-*a*]pyridines **48** by the action of TFA with subsequent treatment with base solution (Scheme 27) [20].

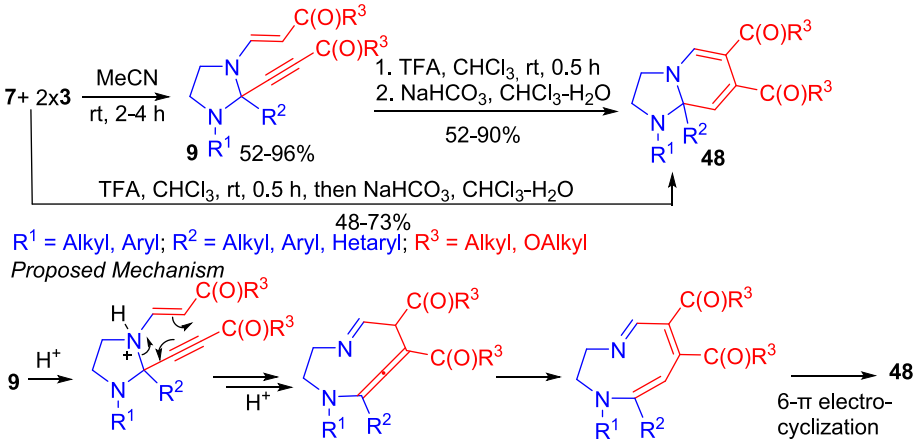
The formation of a small amount of less stable cation by the protonation of imidazolidine **9** triggers the [3,3]-sigmatropic *aza*-Claisen rearrangement. The nine-membered allene resulting from the loss of proton is converted into a more stable conjugate azatriene. This azatriene undergoes 6π-electrocyclization to form partially saturated imidazo[1,2-*a*]pyridine system **48** (Scheme 27).

N-Ethenylation/*C*-ethynylation adducts **10** bearing a tetrahydroisoquinoline scaffold were transformed to dihydropyrido[2,1-*a*]isoquinolines **49** (PPh_3, MeCN, MWI, 22–50 %), when Me or Ph substituent was in the position 1 (Scheme 28) [14]. If hydrogen atom is located in this position, the transformation of adduct **10** delivered dihydropyrrolo[2,1-*a*]isoquinolines **50**.

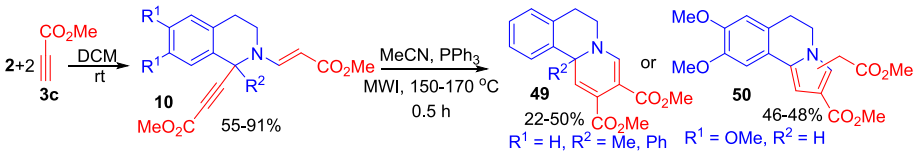
The process commences with the polarization of enamine moiety under the action of acetonitrile or activation with PPh_3 (Scheme 29). The negative charge has two ways for attacking the propargyl moiety leading to either six-membered cycle or five-membered one. This



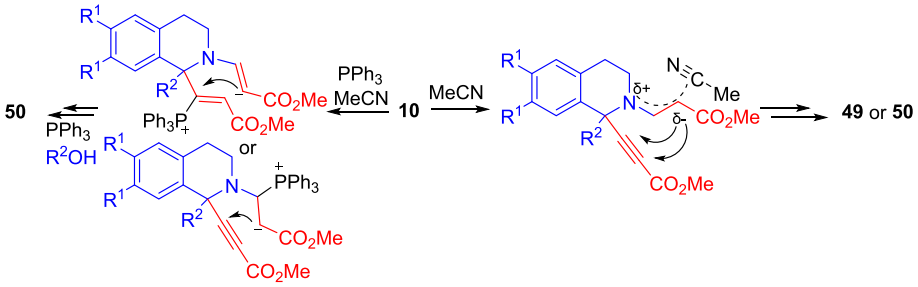
Scheme 26. Synthesis of imidazo[4,5-*b*]pyridine **47**.



Scheme 27. Synthesis of tetrahydroimidazo[1,2-*a*]pyridines **48**.



Scheme 28. Synthesis of dihydropyrido[2,1-*a*]isoquinolines **49** or dihydropyrrolo[2,1-*a*]isoquinolines **50** from *N*-ethenyl-*C*-propargyldihydroisoquinolines **10**.

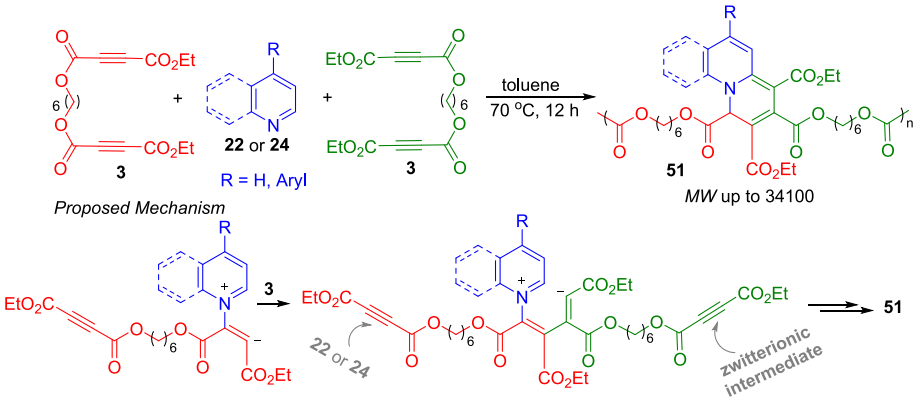


Scheme 29. Routes of *N*-ethenyl-*C*-propargyldihydroisoquinolines **10** transformation to dihydropyrido[2,1-*a*]isoquinolines **49** or dihydropyrrolo[2,1-*a*]isoquinolines **50**.

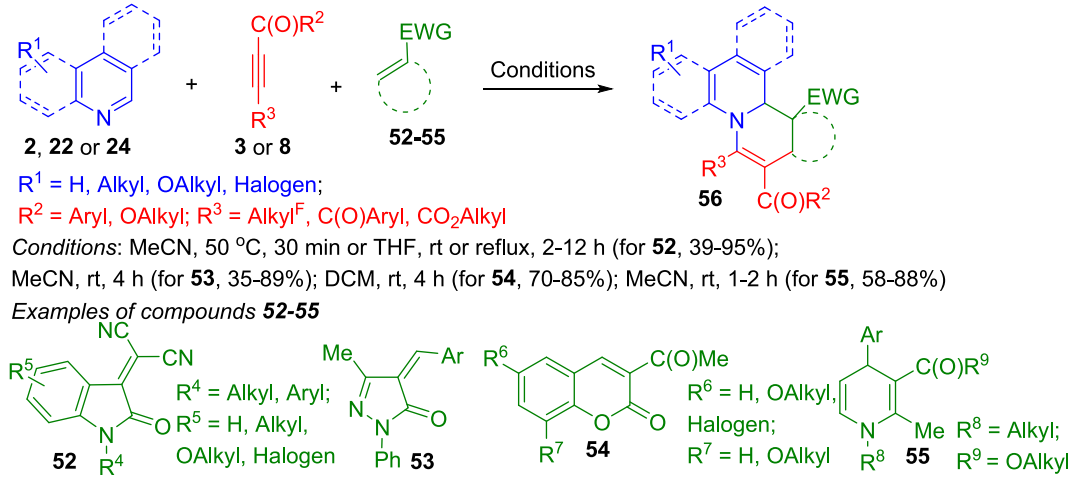
transformation might be caused by the *cis*-position (or close to it) of the abovementioned groups and the ease of formation of a flat five- or six-membered cycle rather than a ten-membered one (this transformation will be discussed below, Scheme 50). The subsequent [1,3]-H shifts and/or aromatization give compound **49** and **50**.

A new annulation of pyridine **24** (or quinoline **22**) ring with esters of dimeric acetylenedicarboxylic acid **3**, known since Achenson's works, was implemented in a "polymeric" version with the formation of poly(quinolizine)s **51** (Scheme 30) [38]. The resulting polymers show strong red emission, exhibit low cytotoxicity and can selectively label lysosomes in living cells.

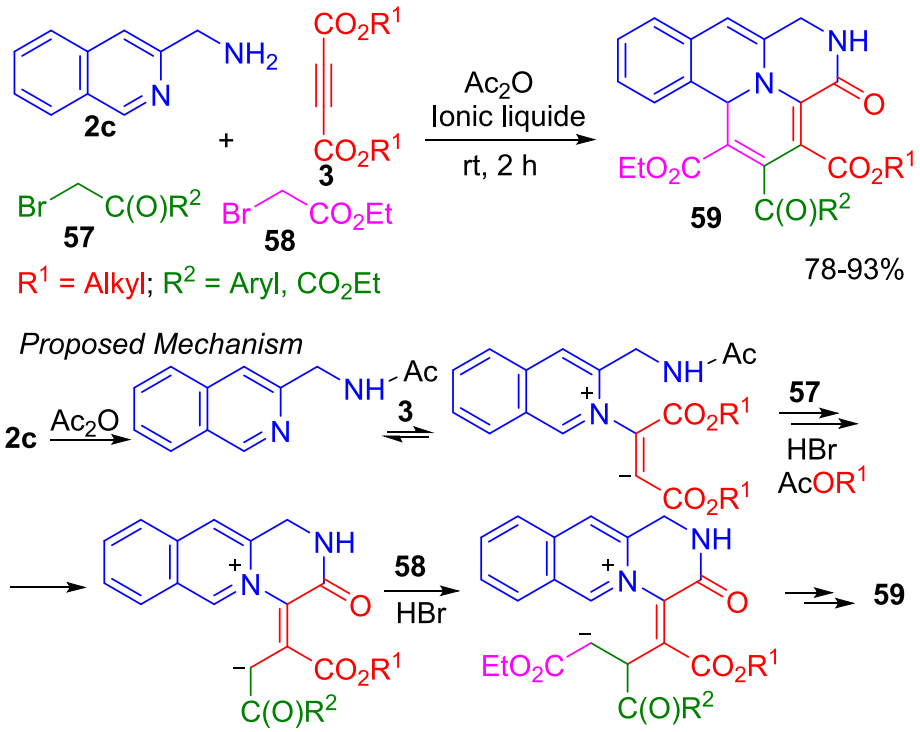
In this case, the zwitterionic intermediate is captured by the



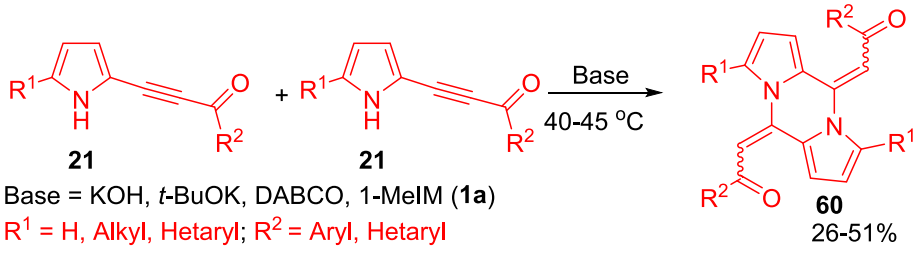
Scheme 30. Synthesis of poly(quinolizine)s **51**.



Scheme 31. Synthesis of pyridoazines **56** from azines **2**, **22** or **24**, electrophilic acetylenes **3** or **8** and electrophilic unsaturated compounds **52–55**.



Scheme 32. Synthesis of pyrazinoquinazolines **59**.



Scheme 33. Synthesis of dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazines **60**.

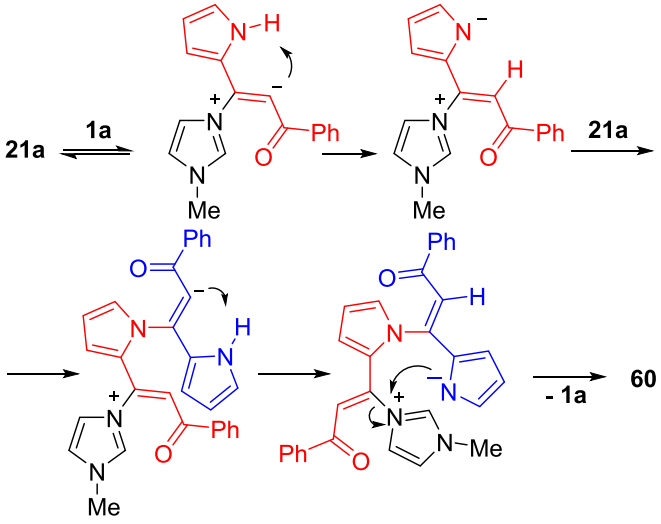
electrophilic C≡C bond of the second diacetylene molecule **3**.

The zwitterionic intermediates of pyridines **24**, quinolines **22** or isoquinolines **2** and electrophilic acetylenes **3** or **8** could be intercepted by the electrophilic C=C bond of derivatives **52** of isatines with malonitrile [39], 2-arylidene substituted cyclic compounds **53** [40], 3-acetyl coumarins **54** [41] or by dienophilic 5,6-unsubstituted 1,4-dihydropyridines **55** [42] to provide the functionalized pyrido[1,2-*a*]pyridines, -[1,2-*a*]quinolines or -[2,1-*a*]isoquinolines or isoquinolino[1,2-*f*][1,6]naphthyridines **56** (Scheme 31).

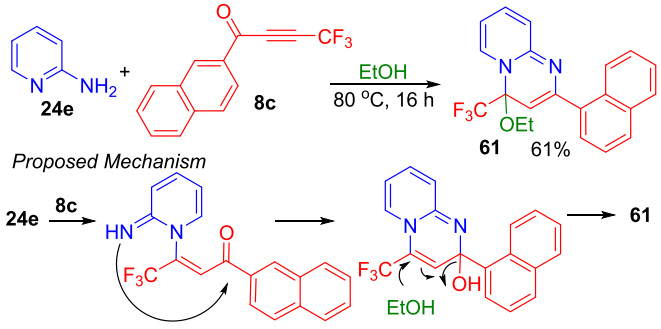
Fusion with pyrazine scaffold

The four-component reaction between 3-aminomethylisoquinoline **2c**, DMAD **3a** or DEAD **3b**, α-bromoketones **57** and ethyl bromoacetate **58** in ionic liquid as a green media delivered the functionalized pyrazinoquinazolines **59**, products of fusion of the isoquinoline core with both pyridine and pyrazine cycles (Scheme 32) [43].The formation of the former cycle is triggered by sequential interception of vinyl carbanionic center of zwitterion by α-haloketones **57** and ethyl bromoacetate **58**, while the second process is carried out as an intramolecular addition of the amino group to alkoxycarbonyl fragment of the activated acetylene.

The high synthetic potential of pyrrolylacetylenic ketones **21** was revealed in their original (3+3)-cyclodimerization under the action of 1-



Scheme 34. Pathway of (3+3)-cyclodimerization of pyrrolylacetylenic ketones **21**.



Scheme 35. Synthesis of pyrido[1,2-*a*]pyrimidine **61**.

methylimidazole (**1a**) or other bases, thus opening access to functionalized dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazines **60** (Scheme 33) [9].

Among several possible mechanisms, quantum-chemical calculations [44] favor self-assembly via zwitterionic intermediates of pyrrolylacetylenic ketones **21** and 1-methylimidazole (**1a**), in which, after intramolecular neutralization of the vinyl carbanionic center with a proton of the pyrrole moiety, 1,4-zwitteriones with a pyrrole nitrogen-centered anion were formed. The nucleophilic attack of the latter at the electron-deficient triple bond of the second molecule of acetylenes **21** leads to the next zwitterionic intermediate with other vinyl carbanionic center. Undergoing a similar transformation, pyrrole-centered zwitterion is generated, which attacks the carbon of imidazolium site in a nucleophilic mode to release neutral imidazole, thereby completing the formation of pyrazine **60** (Scheme 34).

Fusion with pyrimidine scaffold

The reaction between 2-aminopyridine **24e** and 2-naphthoyltrifluoromethylacetylene **8c** afforded the unexpected pyrido[1,2-*a*]pyrimidine **61** (Scheme 35) [45]. The pyridine nitrogen first seemingly attacks the *sp*-hybridized carbon of the triple bond at the CF_3 group of acetylene **8c**, after which the resulting imine acts as a nucleophile, attacking the carbonyl and closing the hydropyrimidine ring. On the next step, ethanol adds via a second Michael reaction to the electron-poor pyridopyrimidine intermediate before losing water to form product **61**.

3-Arylcyanoacetylenes **19** were readily fused with quinolines **22**, isoquinoline **2** [46] or phenanthridine **12** [47] in the KOH/H_2O/MeCN system at room temperature to afford aryldihydropyrimidoazin-2-ones **62** in 12–92 % yields (Scheme 36). The water proton neutralizes the carbanion center of zwitterion, and the released hydroxide ion is added to the cyano group. The resulting intermediate is then added intramolecularly by its anionic imine center at the carbocationic α-position to close the pyrimidine cycle.

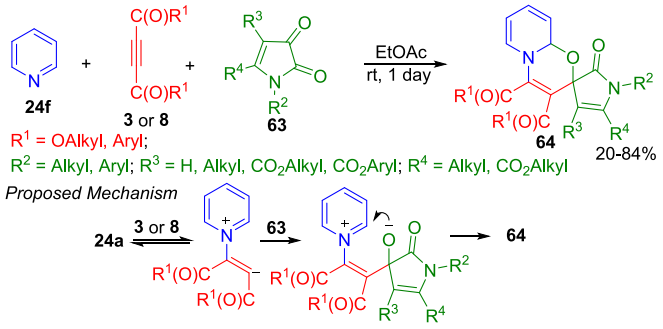
Fusion with 1,3-oxazine scaffold

The (4 + 2)-cycloaddition of 1*H*-pyrrole-2,3-diones **63** as new dipolarophiles to zwitteriones generated from pyridine **24f** and electrophilic acetylenes **3** or **8** was found to proceed regioselectively at the C═O group of pyrroledione position 3 affording spiropyrrolo substituted 1,3-oxazinopyridines **64** as diastereomeric mixtures, which exist in rapid equilibrium in a solution (Scheme 37) [39c].

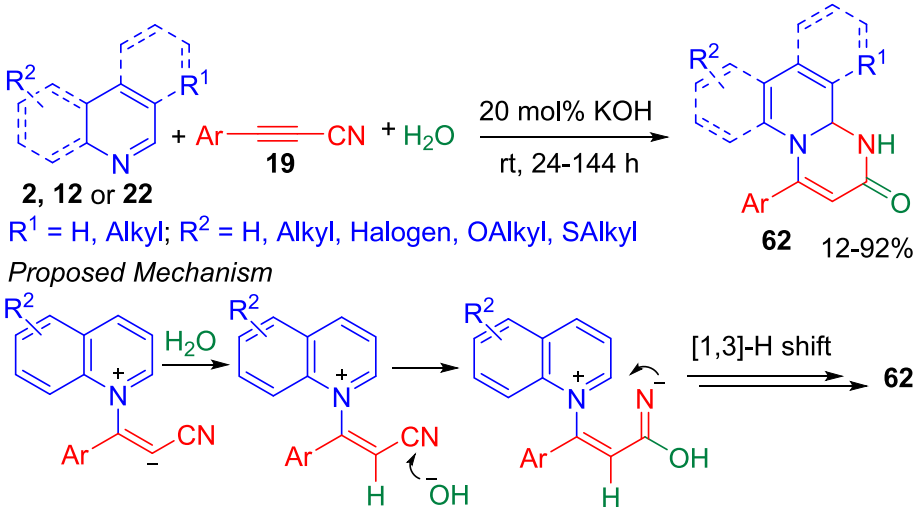
1,3-Oxazinopyridines (-quinoline, -isoquinoline, -1,8-naphtiridine, -benzo[*f*]quinoline), synthesized similarly to compound **64** via three-component coupling of azines **2**, **22**, **24** with DMAD **3a** and methyl pyruvate **65**, were used as effective precursors for the preparation of 3- or 3,4-substituted pyridine derivatives [48,49] or multisubstituted benzenes [50] (Scheme 38).

One-pot assembly of pyridines **24** [51], quinolines **22** [52], isoquinolines **2** [11] or phenanthridine **12** with oxalylacetylenic ester **15**, proceeding in 1:2 manner (without catalysts and solvent at room temperature), opened an efficient facile and straightforward route to a novel family of uniquely functionalized ethynyl substituted 1,3-oxazinoazines **66** in up to 88 % yield (Scheme 39). Pyridooxazines were assembled mainly (90 %) as 2*S**,9a*S**-diastereomers.

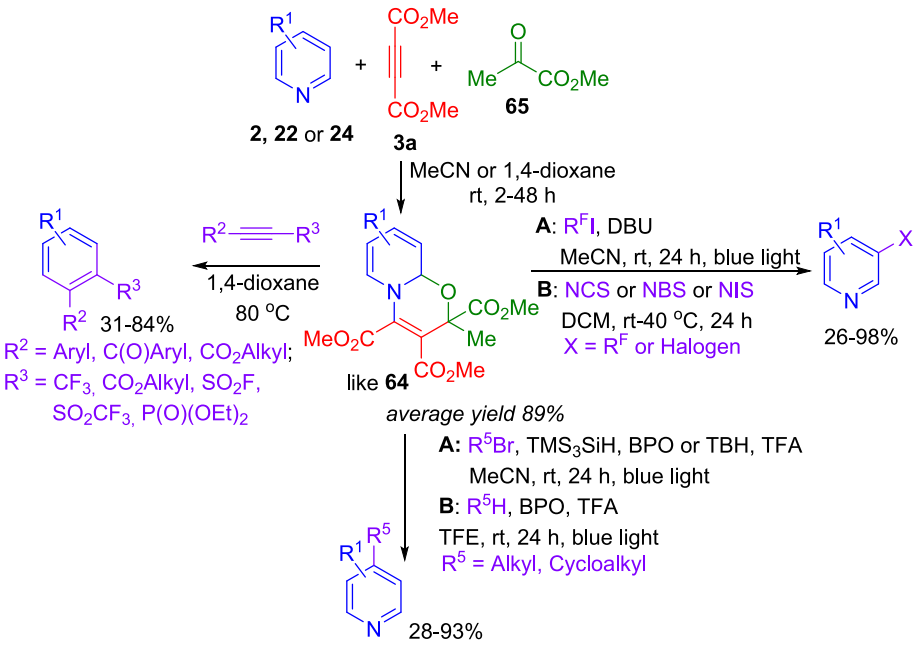
A novel point of the reaction mechanism is the involvement of the second molecule of acetylene **15** as C═O electrophile into the annulation, while the first molecule of the same acetylene **15** behaves as C≡C electrophile.



Scheme 37. Synthesis of 1,3-oxazinopyridines **64**.



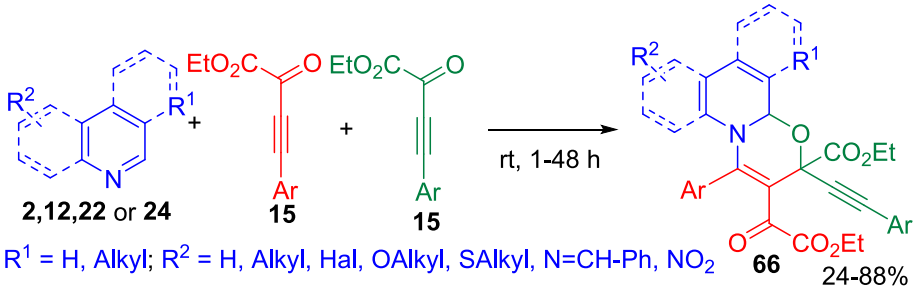
Scheme 36. Synthesis of pyrimidoazin-2-ones **62**.



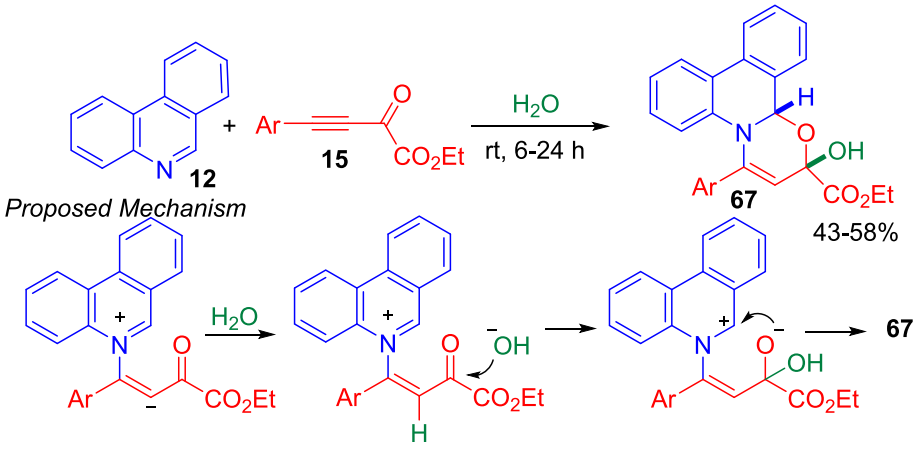
Scheme 38. Synthetic potential of 1,3-oxazinoazines **64**.

Analogously, the reaction between 1-methylquinoline **22b** and 1,4-diphenylbut-3-yne-1,2-dione (MeCN, 5 °C, 24 h) gave benzoyl(carbonylbenzoyl)ethynyloxazino[2,3-*a*]isoquinoline in 41 % yield. It was shown that the nucleophilic C═N bond exclusively participated in the cyclization, while the CH_3 group remained intact (in contrast with Scheme 13) [12].

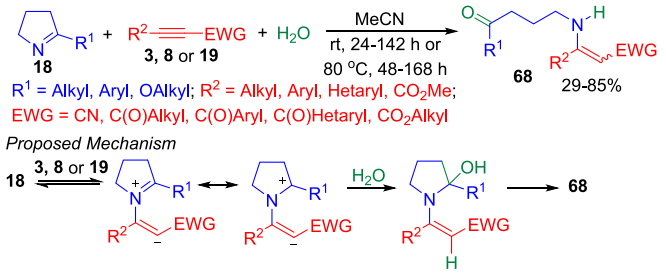
Another type of 1,3-oxazine ring building up on the pyridine cycle was demonstrated by the three-component reaction of phenanthridine **12** with oxalylacetylenic ester **15** and water diastereoselectively leading to (*R**,*R**)-2-hydroxy-4-aryl-2*H*,13b*H*-[1,3]oxazino[3,2-*f*]phenanthridines **67** in up to 58 % yields [53] (Scheme 40). According to quantum-chemical calculations, among the possible transformations of the 1,3(4)-zwitterionic phenanthridine/oxalylacetylene intermediate protonated with water, the preferred route leading to the target product involves the attack of the hydroxyl anion at the carbonyl moiety, followed by closing of the oxazine ring.



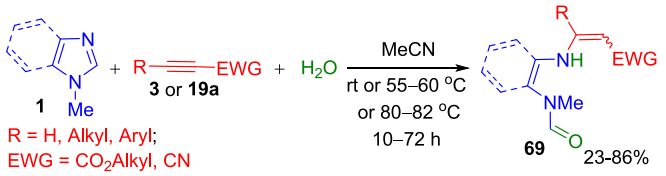
Scheme 39. Synthesis of ethynyl substituted 1,3-oxazinoazines **66**.



Scheme 40. Synthesis of hydroxyl-[1,3]oxazino[3,2-*f*]phenanthridines **67**.



Scheme 41. Synthesis of δ-keto aminoenones or aminoacrylonitriles **68**.



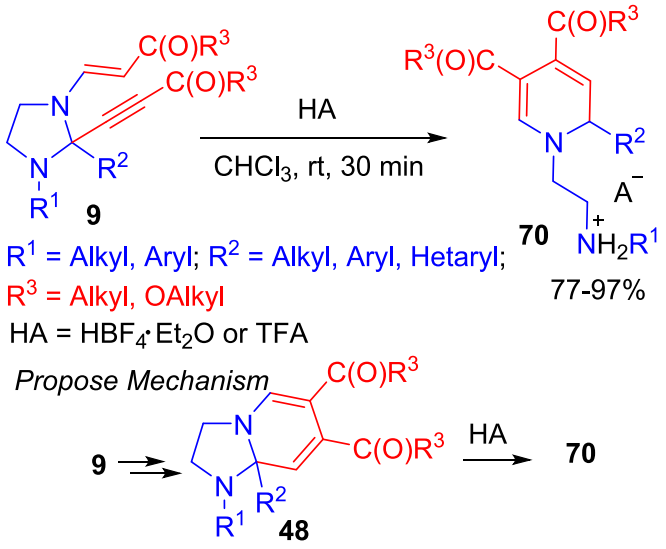
Scheme 42. (Benz)imidazole **1** ring-opening by the action of electrophilic acetylenes **3** or **19a** and water.

Ring-opening of nitrogen heterocycles

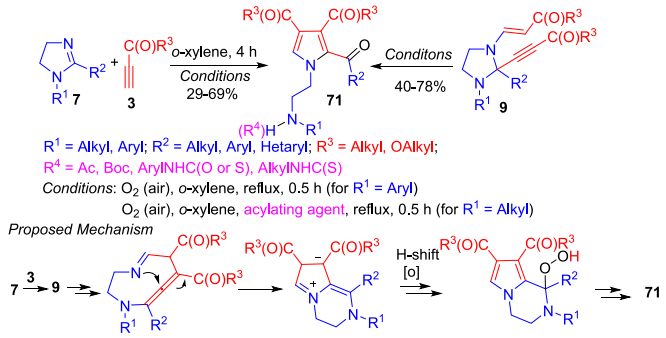
The ring-opening of Δ^1-pyrrolines **18** by electrophilic acetylenes **3**, **8** or **19** (20–80 °C, MeCN, H_2O) afforded δ-keto aminoenones or aminoacrylonitriles **68**, mostly as *Z*-isomers, in up to 85 % yield (Scheme 41) [54]. The synthesis involves the *C*(2)-*N* bond cleavage in the intermediate hemiaminal resulting from the 1,3(4)-zwitterionic 1-pyrroline/acetylene complexes and water.

One-pot, regioselective synthesis of 3-[2-formamidovinyl(phenyl) amino]acrylic acid derivatives **69** in up to 86 % yield was developed. The process comprises imidazole or benzimidazole **1** ring-opening under the action of esters of acetylene carboxylic acids **3** or cyanophenylacetylene **19a** and water (Scheme 42) [55].

The divergent character of the acid-catalyzed transformation of *N*-ethenyl-*C*-ethynylimidazolidines **9** was demonstrated under conditions of their treatment with $HBF_4{\cdot}Et_2O$ or TFA, leading to the opening of the azole cycle and the production of pyridinium salts with β-(alkylammonio)ethyl group **70** (Scheme 43) [20]. The synthesis of product **70** occurs via the formation of tetrahydroimidazo[1,2-*a*]pyridines **48** (Scheme 27)



Scheme 43. Transformation of *N*-ethenyl-*C*-ethynylimidazolidines **9** into pyridinium salts with β-(alkylammonio)ethyl group **70**.



Scheme 44. Transformation of *N*-ethenyl-*C*-ethynylimidazolidines **9** into polysubstituted pyrroles **71**.

with further opening of the imidazolidine ring.

When *N*-ethenyl-*C*-ethynylimidazolidines **9** or starting imidazolines **7** and acetylenes **3** were refluxed in *o*-xylene in the air with or without acylation agents, another products of azole ring cleavage, polysubstituted pyrroles **71**, were obtained (Scheme 44) [19].

The domino transformation of adduct **9** into pyrrole **71** involves the formation of labile nine-membered allene (from Scheme 27), which immediately undergoes a transannular nucleophilic addition of the nitrogen atom to the central atom of the allene system generating bicyclic zwitterion (Scheme 44). Then proton transfer and autoxidation delivers the intermediate, which undergoes a ring opening reaction to give either pyrrole **71** or (in the presence of an acylating reagent) its acylated derivative.

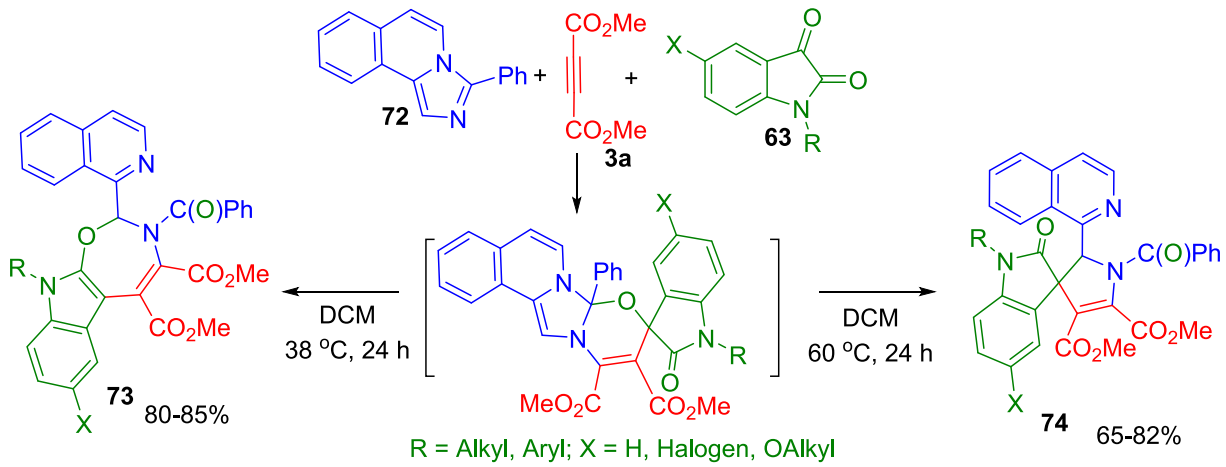
Three-component reaction between 3-phenylimidazo[5,1-*a*]isoquinoline **72**, DMAD **3a** and *N*-alkyl-1*H*-indole-2,3-diones **63** proceeded via in situ generated imidazo[5,1-*a*]isoquinolinooxazines, which further underwent the imidazole ring cleavage (due to the strain in the structure) and rearrangements to kinetic products, 2-isoquinolinyl-dihydro-2*H*-[1,3]oxazepino[7,6-*b*]indoles **73** or thermodynamic products, 2′-isoquinolinyl-1-methyl-2-oxo-dihydrospiroindoline-3,3′-pyrroles **74** (Scheme 45) [56].

Ring-opening/ring-closing of nitrogen heterocycles

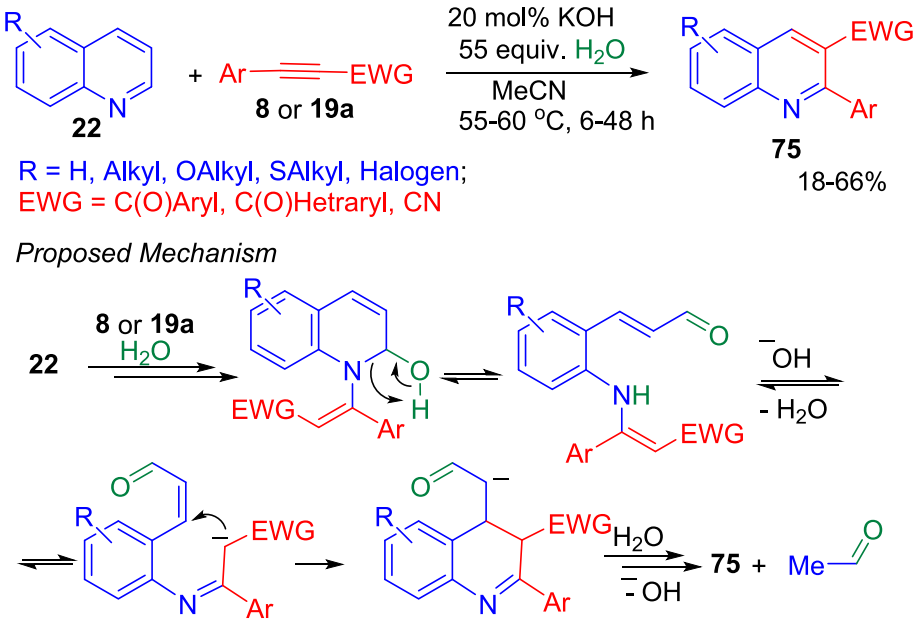
One-pot C—H difunctionalization of quinolines **22** with electrophilic acetylenes **8** or **19** occurred in the presence of water and potassium hydroxide to form 3-acyl- or 3-cyano-2-aryl-quinolines **75** in up to 66 % yield (Scheme 46) [57]. The process proceeds through the formation of heminal (analogously to Scheme 5), pyridine ring opening (on the example of pyridines **24** with acylacetylenes **8** and water similar adducts were isolated [58]). Here generated in situ derivatives of cinnamic aldehyde undergo further transformations via ring closure, aldehyde elimination and aromatization.

Further development of 2,3-difunctionalization of quinolines **22** under the action of electron-deficient acetals of cyanoacetylenic alcohol **19** (KOH/H_2O/MeCN, 55–60 °C) via hydrolysis of the corresponding 2-(1-ethoxyalkoxy)-3-cyanoquinolines **75** (7 % aqueous HCl, acetone, rt) paved a route to furo[3,4-*b*]iminoquinolines **76** and furo[3,4-*b*]quinolinones **77** (up to 98 %) (Scheme 47) [59].

The treatment of the reaction mixture consisting of quinolines **22**, trifluoroacetylacetylenes **8** and water with a base initiated deep structural transformation of primary products, 1,3-oxazinoquinolines of type **67** into 2-aryl-3-trifluoroacetylquinolines **78** (under the action of organic bases) and 2-arylquinolines **79** (under the action of inorganic bases, Scheme 48) [60]. Presumably, the process starts with the opening of the 1,3-oxazine ring to give hemiaminal like **13**, which undergoes similar transformations as shown in Scheme 46. In the case of usage NaOH as a base, C(*O*)CF_3 group was transformed to CO_2H, which was easily eliminated under the reaction conditions.



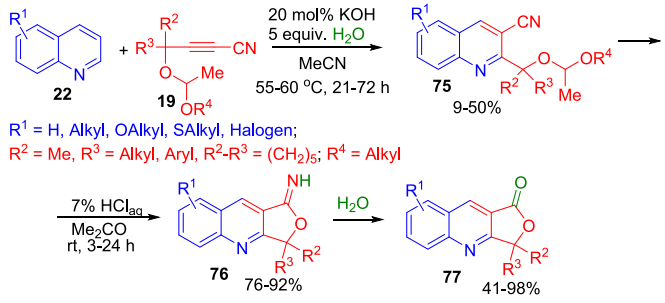
Scheme 45. Synthesis of oxazepino- or pyrrolo- substituted isoquinolines **73** or **74** via imidazole ring opening in 3-phenylimidazo[5,1-*a*]isoquinoline **72** under the action of DMAD **3a** and *N*-alkyl-1*H*-indole-2,3-diones **63**.



Scheme 46. 2,3-Difunctionalization of quinolines **22** under the action of electrophilic acetylenes **8** or **19a** and water.

Ring-extensions of nitrogen heterocycles

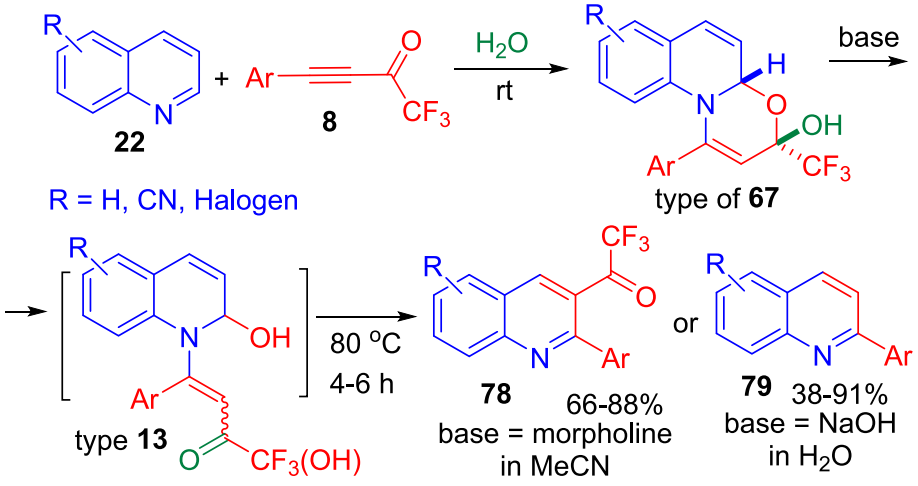
Another transformation of *N*-ethenyl-*C*-ethynylimidazolidines **9** is the azole ring extension under the action of Cs_2CO_3/MeCN, MW irradiation at 130–150 °C or CsF/DMSO, 135 °C into 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **80** in 43–90 % (Scheme 49) [61]. Products **80** (28–86 %) were synthesized in one-pot manner directly from imidazolines **7** and acetylenes **3** or **8**. The process proceeds via the formation of anionic form of nine-membered allene, which undergoes transannular cyclization to give, after protonation of the anion, the final 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **80**.



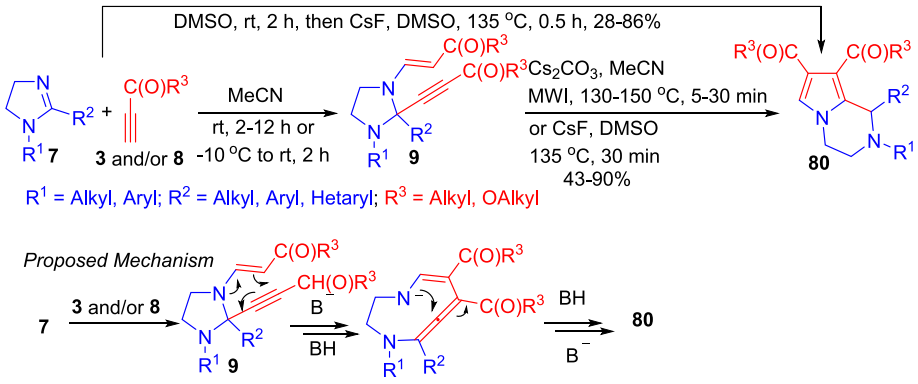
Scheme 47. Synthesis of furo[3,4-*b*]iminoquinolines **76** and furo[3,4-*b*]quinolinones **77**.

N-Ethenylation/*C*-ethynylation products **10** of isoquinoline or dihydroisoquinoline **2** with methyl propiolate **3c** were involved the pyridine ring extension (PPh_3, toluene, MWI, 150 °C) to furnish pyrrolo[2,1-*b*][3]benzazepines **81** in 35–97 % yields (Scheme 50) [14]. The triphenylposphine activates the triple bond of **10** and triggers [3,3]-sigmatropic rearrangement accompanied by elimination of the nucleophile delivering allene-containing benzazecine. Attack of the nitrogen atom at the allene system leads to the formation of benzazepine. Migration of the proton and subsequent [1,3]-H-shift completes the process, yielding the final products **81**.

The imidazole ring of 1-substituted benzimidazoles **1** was extended under the action of pyrrolylacetylenic ketones **21** (MeCN, 80–82 °C) to eight-membered ones with the formation of pyrrolyl-substituted benzo[1,4]diazocinones **82** in up to 93 % yield (Scheme 51) [62]. The proposed mechanism of the reaction involves the generation of zwitterion



Scheme 48. Synthesis of 2-aryl- or 2-aryl-3-trifluoroacetylquinolines **79** or **78**.



Scheme 49. Extending of *N*-ethenyl-*C*-ethynylimidazolidines **9** to 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **80**.

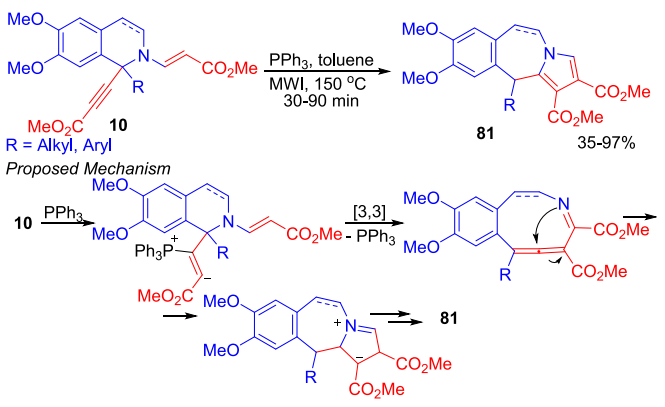
and ylide intermediates. The latter intramolecularly attack the carbonyl group, triggering further cascade transformations with sequential closing of the five and three-membered cycles, and cleavage of the imidazole and oxirane rings.

Indolyl substituted acetylenic ketones were also active in above described reaction [63].

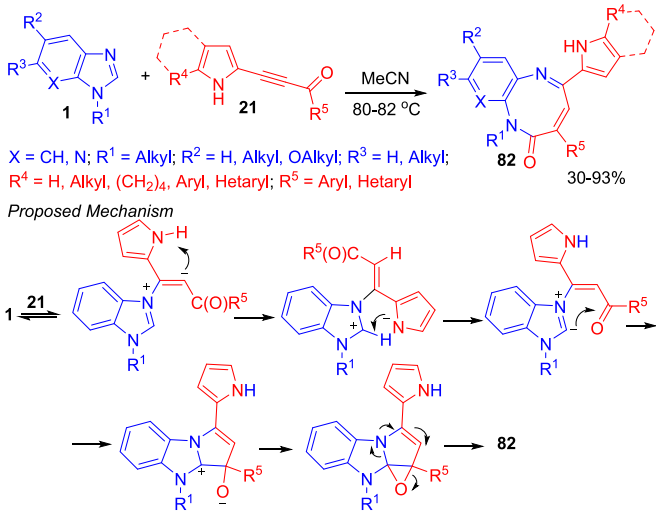
The data on biological activities, molecular docking, dynamics simulations, and ADME predictions highlight the potential of 3-(furan-2-yl)-1-methyl-5-(1*H*-pyrrol-2-yl)benzo[*b*][1,4]diazocin-2(1*H*)-one **82** as a candidate for acetylcholinesterase inhibitor ($Ki = 6.01 \pm 0.15$ nM) [64].

Cascade reactions of the addition of DMAD **3a** to imidazo[1,2-*a*]pyridine **72**, proceeding through annulation and 1,5-alkyl shift, expansion of the imidazole ring to a pyrazine ring, gave a new cross-conjugated mesomeric betaine with the hydropyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine scaffold **83** (Scheme 52) [65].

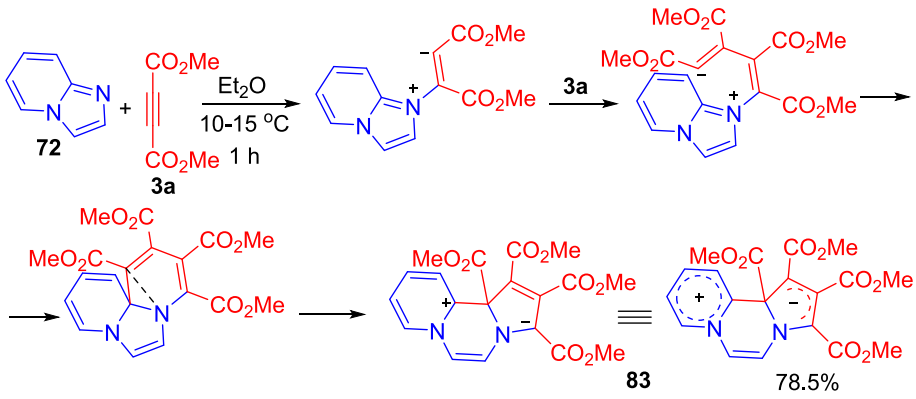
Ring-extension of DBU **84** by N-substituted pyrrolylacetylenic ketones **21** proceeded in a one-pot manner (MeCN, 80 °C, 3 h) through the formal [3+3]-annulation followed by the C—N bond opening to pyrrolyl-diazabicyclo[8.3.1]-tetradecadienones **85** (PY-14-ONE) in



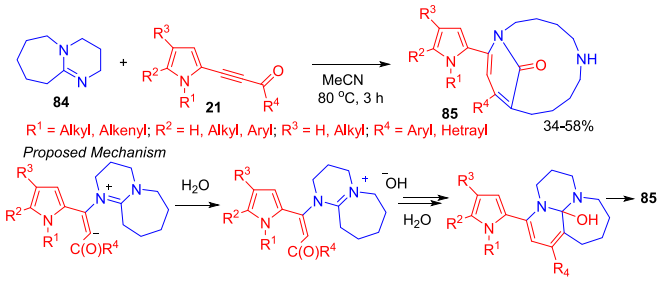
Scheme 50. Extending of *N*-ethenyl-*C*-ethynyl(dihydro)isoquinolines **10** into pyrrolo[2,1-*b*][3]benzazepines **81**.



Scheme 51. Extending of benzimidazoles **1** into benzo[1,4]diazocinones **82**.



Scheme 52. Extending of imidazo[1,2-*a*]pyridine **72** into hydropyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine **83**.



Scheme 53. Extending of DBU **84** into pyrrolyl-diazabicyclo[8.3.1]-tetradecadienones **85**.

34–58 % yields (Scheme 53) [10]. PY-14-ONEs, a new class of fluorescent bridgehead macrocycles, are characterized by giant Stokes shifts of ~8000–10,250 cm^{-1} and virtually zero overlap of the absorption and emission bands.

In a similar way but less effective, nonpyrrole aromatic and heteroaromatic macrocyclic bridgehead ketones can be synthesized from the corresponding acylacetylenic ketones **8**.

Conclusion

The review highlights the rich potential of transition metal-free functionalization of nitrogen heterocycles under the action of electrophilic acetylenes, which is triggered and driven by 1,3(4)-dipolar complexes (zwitterions), the products of nucleophilic addition of nitrogen to activated triple bond. Such complexes undergo various transformations due to intra- or intermolecular interception of their carbanionic site by electrophilic functional groups, thus launching deep cascading rearrangements to ultimately afford the functionalized and modified nitrogen heterocyclic systems.

In the context of organic synthesis, the main advantages of activation and functionalization of nitrogen heterocycles by electrophilic acetylenes are absence of transition metal catalysts, mild conditions (room or slightly elevated temperature), no harmful waste, often chemo-, regio- and stereoselectivity, and one-pot implementation of the reactions. The new functionalized heterocycles often exhibit biological activity (drug precursors), possess valuable photophysical properties, and can be employed as powerful synthetic building blocks. The research in this field continues to develop rapidly, unfolding the versatility and generality of this chemistry.

As follows from the review, the synthetic potential of the approach covered is far from being exhausted and keeps rapidly and fruitfully developing. However, there is still a room for extending the number of nitrogen heterocycle transformations triggered and driven by electron-deficient acetylenes. These transformations were shown to significantly depend on the nature of electron-deficient acetylenes, especially their electrophilicity and functionality. Consequently, it may be expected that the involvement of electron-deficient acetylenes of new types as activators of nitrogen heterocycles will reward the researchers by novel chemical surprises of high synthetic value. Besides, almost unexplored part of this general approach remain multicomponent synthesis, in particular with bifunctional (electrophilic and nucleophilic) components capable of interacting both with carbanionic and cationic sides of the primary 1,3(4)-dipolar intermediates. Especially intriguing and appealing line of further possible investigation is simultaneous double functionalization of the pyridinoid rings allowing diverse functional groups to be readily introduced into a heterocyclic scaffold. Along this line, novel practically useful and theoretically important achievements are highly likely awaited the researchers. A special attention deserves the cases of electrophilic acetylenes-promoted nucleophilic substitution of hydrogen in a heterocyclic ring proceeding without transition metal catalysts under mild conditions, which at the moment is just slightly experimentally touched. In the framework of the above approach, cardinally new opportunities are now opening for the synthesis of larger size functional nitrogen heterocycles (pyrrolobenzazepines, benzodiazocinones, pyrrolyldiazabicyclotetradecadienones) via the ring extension with inclusion of the alkyne moiety. Due to the novelty and developing nature of the general approach here highlighted, certain challenges and concerns are expectedly met in the course of investigations such as modest yields and narrow substrate scope, which can be overcome during systematic optimization of the reaction.

CRediT authorship contribution statement

Boris A. Trofimov: Methodology, Conceptualization. **Kseniya V. Belyaeva:** Writing – review & editing.

Declaration of competing 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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Data availability

No data was used for the research described in the article.

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