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Conjugated pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles: new motives in heterocyclic chemistry

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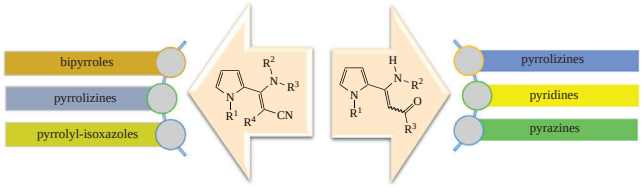
Methods for the preparation of two highly flexible synthetic building blocks, namely pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles, on the basis of available starting materials such as 2-acylethynylpyrroles or pyrrole-2-carbodithioates, are summarized. The presence of several reactive centers in their molecules (pyrrole ring, enamine and carbonyl or nitrile moieties) ensures their multiple reactivity and application as versatile intermediates in the synthesis of heterocyclic ensembles such as pyrrolyl-pyridines, bipyrroles, pyrrolyl-isoxazoles and condensed compounds, such as pyrrolo[3,2-*a*]pyrazines, pyrrolizines, which have high potential for use in medical chemistry and materials science.



Keywords: pyrrole, acylethynylpyrrole, aminoenone, aminoacrylonitrile, pyridine, pyrrolo[1,2-*a*]pyrazine, pyrrolizine, bipyrrole, pyrrolyl-isoxazole, cyclization.

Introduction

Conjugated pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles represent extremely reactive multifunctional building blocks with special synthetic potential (as yet underestimated) for drug design and preparation of heterocyclic systems of higher complexity and diversity. Their diverse reactions with different nucleophiles warrant one-pot, atom, and step-economic (in compliance with PASE paradigm[1]) formation of various heterocyclic architectures incorporating the pyrrole ring in both linked ensembles and fused polyfunctional structures. In essence, pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles can be rated as very reactive carriers of the pyrrole ring, capable of integrating into a multitude of polyfunctional compounds including natural bioactive products and other life-sustaining substances thereby expanding the frontiers of the pyrrole chemistry.

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Enamines as important counterpart of the above ensembles are a popular class of organic compounds that attract a steady attention of researchers.[2] They serve as versatile intermediates in the synthesis of heterocyclic ensembles, which are widely used in medicinal chemistry and materials science.

The most commonly used representatives of these compounds are conjugated aminoenones[3] and aminoacrylonitriles.[4]

In recent years, they were employed for the synthesis of azirines,[5] pyrroles,[6] indoles,[7] pyrazoles,[8] imidazoles,[9] oxazoles,[4(a)] pyridines,[10] dihydropyridines,[11] pyrimidines,[12] pyridazines,[13] quinolines,[14] and diverse condensed heterocyclic systems.[15]

Commonly, these compounds have a considerable potential for design of medicines or their precursors.[15(d),16] However, both aminoenones and aminoacrylonitriles conjugated with pyrrole substituents remain outside the focus of the current studies. Meanwhile, the conjugation of the pyrrole ring with aminoenone or aminoacrylonitrile moieties in one molecule may promise synergetic amplification of pharmaceutical value of these two biologically important structural units.

Note that the literature on the synthesis and transformations of pyrrolylaminoenones and pyrrolylaminoacrylonitriles is represented almost exclusively by our publications, which are here systematized and concisely reviewed.

As to parallel research related to close heterocyclic analogs, in 1997, Stille *et al*. reported on the synthesis of enamino esters conjugated with aryl, thiophene, and indole moieties from the corresponding ethyl amines *via* isothiocyanate and acid-catalyzed ring closure, the indolyl derivatives being converted to indoloquinolizinone and -quinolone carboxylates.[17] Indolo[2,3-*a*]quinolizidine carboxylates were obtained from the corresponding β-enamino esters and α,β-unsaturated aldehydes in the presence of prolines as assymetric catalysts.[18] The same approach (only with other catalyst) based on annulation of cyclic β-enamino esters with enals was applied for the synthesis of functionalized indolo[2,3-*a*]quinolizinone carboxylates.[19] Later, functionalized pyrrolo[1,2-*a*]indoles were synthesized *via* the reaction of enamino esters with sodium ethoxide in DMSO (120 °C) followed by migration of pyrimidin-2-yl group from the indolyl ring.[20] Likewise, 3*H*-pyrrolo[1,2-*a*]indol-3-ones incorporating indolyl/enaminone structural units were prepared from enamino esters with 6-(indol-1-yl)purine substituents in the presence of $NaHCO_3$.[21] Different heterocyclic compounds, containing enaminoketone[2,3,22] and enaminonitrile fragments in the cycle,[2,4,23] were also synthesized and employed in the synthesis of more complex heterocyclic system.

It is worthwhile to underline that all the structures disclosed in the above-cited parallel works just remotely resemble the conjugated pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles, which are integrated in more complex molecular architectures with specific chemical properties, non-typical for the conjugated pyrrole, enamine carbonyl (nitrile) systems.

Pyrrolylaminoenone ensembles become easily available owing to the development of the transition metal-free cross-coupling of pyrroles with acylhaloacetylenes in the solid alumina or potassium carbonate.[24]

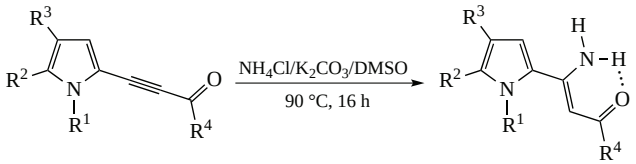
The unfolding of the chemistry of pyrrolyl-aminoacrylonitrile began since their easy synthesis from the pyrrole-2-carbodithioates and methylene-active nitriles followed by the reaction with primary and secondary amines.[25]

In this focus article, the works (mainly of the last decades) on the synthesis of conjugated pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles and their applications in the design of pharmaceutically related heterocycles are analyzed and highlighted.

1. Conjugated pyrrole/aminoenone ensembles

1.1. Synthesis of pyrrolyl-aminoenones

Nucleophilic addition of ammonia to the triple bond of 2-acylethynylpyrroles **1**, **2** (Scheme 1) stereoselectively afforded 1-(pyrrol-2-yl)-1-aminoenones **3a–j** of the *Z*-configuration in up to 95% yield.[26]



1, **2** → **3a–j**, 78–95%

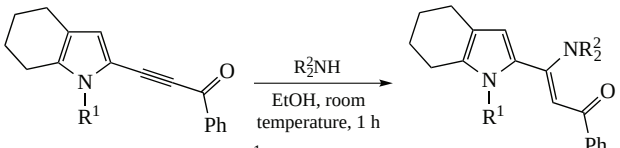
R^1 = H, Me, $CH=CH_2$
R^2 = H, Me, Bu, Ph, 2-FC_6H_4
R^3 = H, Pr
$R^2 + R^3 = (CH_2)_4$
R^4 = Ph (**1**), OEt (**2**)

Scheme 1

The stability of the *Z*-isomers is due to strong hydrogen bonding between amino and carbonyl groups. Even in cases when alternative bonding between the carbonyl group and the pyrrole NH-proton is possible (R^1 = H), the *E*-isomers were not detected even in trace amounts.

With ethyl 3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-propynoate **2** [R^1 = Me, $R^2 + R^3 = (CH_2)_4$, R^4 = OEt], the reaction greatly slowed down: under the standard conditions only 15% conversion of the starting pyrrolylpropynoate **2** was achieved, whereas the complete conversion required 48 h, the yield of corresponding *Z*-aminoacrylate **3** [R^1 = Me, $R^2 + R^3 = (CH_2)_4$, R^4 = OEt] being 78%.[26] This reduced reactivity of the acetylenic bond is associated with a lesser electron-accepting power of the ester function as compared to the keto group.

3-(Dimethyl- and -diethylamino)-3-(4,5,6,7-tetrahydroindol-2-yl)propenones **4a–f** were obtained by the nucleophilic addition of secondary amines to 2-(benzoylethynyl)-4,5,6,7-tetrahydro-indoles **1**. The adducts **4a–f** were formed as the *E*-isomers, either exclusively (for pyrrole **4** with R^1 = H) or predominantly (for pyrroles **4** with R^1 = Me, Bn), Scheme 2.[27]



1 → **4a–f**, 64–88%

R^1 = H, Me, Bn
R^2 = Me, Et

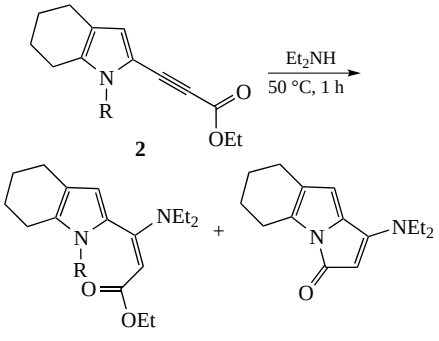
Scheme 2

Diethylamine reacted with propynoates **2** (aqueous ethanol, 50 °C, 1 h) to stereoselectively produce the *E*-isomers of adducts **5a–c** in up to 85% yield (Scheme 3).[27]

The reaction of propynoate **2** (R = H) with diethylamine was accompanied by intramolecular cyclization of primary adduct **5** to pyrroloindole **6**, the ratio of **5**:**6** being 1:1. Upon chromatography (Al_2O_3) this mixture completely cyclized to pyrroloindole **6**.[27]

Addition of benzylamine to 2-acylethynylpyrroles **1** in the K_3PO_4/DMSO catalytic system gave *N*-benzylamino(pyrrolyl)-enones **7a–i** in good to excellent yields (Scheme 4).[28] The latter were formed as a mixture of *E*- and *Z*-isomers, the former being stabilized by intramolecular H-bonds between the carbonyl group and NH-moiety of the pyrrole (see Scheme 4). In the case of NMe pyrrole, only the *Z*-isomer was expectedly formed.

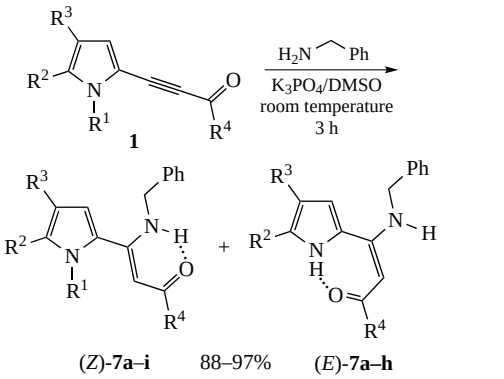
The electronic nature of the substituents in the pyrrole ring determines the isomer ratio. If *E*/*Z* ratio for enaminones **7** with



5a–c, 37–85%

R = H, Me, Bn

Scheme 3



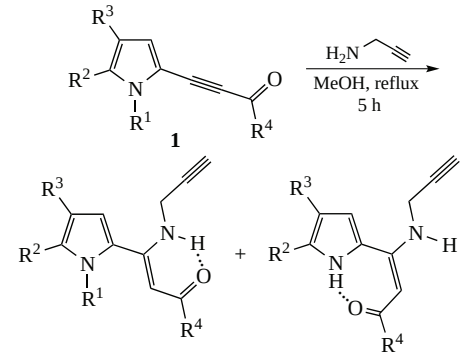
(*Z*)-**7a–i** 88–97% (*E*)-**7a–h**

R^1 = H, Me
R^2 = H, Ph, 3-FC_6H_4, 4-FC_6H_4
R^3 = H
$R^2 + R^3 = (CH_2)_4$
R^4 = Ph, 2-furyl, 2-thienyl

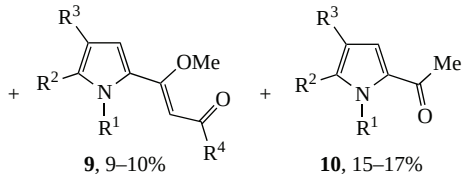
Scheme 4

an unsubstituted pyrrole ring or with a donor cyclohexane moiety is ~1 : 9–10, then for enaminones **7** with an electron-withdrawing aryl substituents, this ratio changes to 1 : 2–3 due to the higher NH-acidity of the pyrrole counterpart and, hence, a stronger stabilization of the *E*-isomer by intramolecular H-bonding.[28]

Propargylamine reacted with acylethynylpyrroles **1** in methanol without catalyst to form *N*-propargylamino(pyrrolyl)-enones **8a–n** in 42–85% yields (Scheme 5) along with side 3-(pyrrol-2-yl)-3-methoxypropenones **9** and 2-acetylpyrroles **10** in 9–10 and 15–17% yields, respectively.[29]



(*Z*)-**8a–n** 42–85% (*E*)-**8a–k**



R^1 = H, Me
R^2 = H, Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4
R^3 = H
$R^2 + R^3 = (CH_2)_4$
R^4 = Ph, 2-furyl, 2-thienyl

Scheme 5

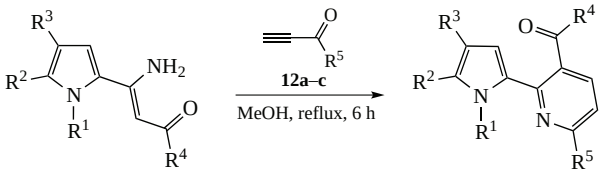
As seen from Scheme 5, aminoenones **8a–k** were isolated as the mixtures of *E*- and *Z*-isomers, their ratio, as above, being dependent on the product structure.

N-Propargylamino(pyrrolyl)enones **8** were selectively synthesized in DMSO (60–65 °C) without catalysts in 90–97% yields.[30] The reaction time was determined by the substituents nature in the pyrrole ring: in accordance with the character of the process, the acceptor substituents facilitated the reaction (the reaction time was 6–7 h), while the donor substituents slowed down the process (the reaction time was 16 h). *N*-Propargyl-amino(pyrrolyl)enones **8a–k**, as in methanol, were formed as the mixtures of *E*/*Z* isomers.

1.2. Reactions of pyrrolyl-aminoenones

1.2.1. Cyclizations of pyrrolyl-aminoenones with acylacetylenes

Functionalized pyrrolyl-pyridines **11a–n** were obtained by the reflux of the pyrrolylaminoenones **3a–j** with acylacetylenes **12a–c** without catalyst in methanol (Scheme 6).[26]

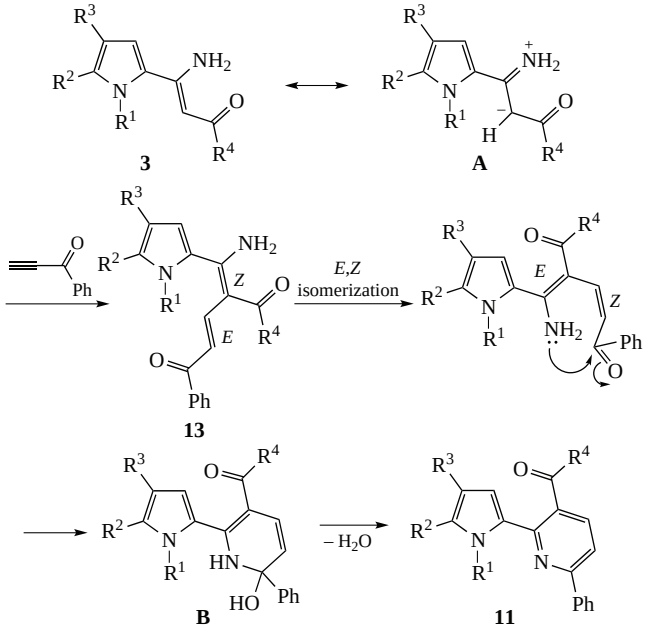


R^1 = H, Me, CH=CH_2
R^2 = H, Me, Bu, Ph, 2-FC_6H_4
R^3 = H, Pr
$R^2 + R^3 = (CH_2)_4$
R^4 = Ph, OEt
R^5 = Ph, 2-furyl, 2-thienyl

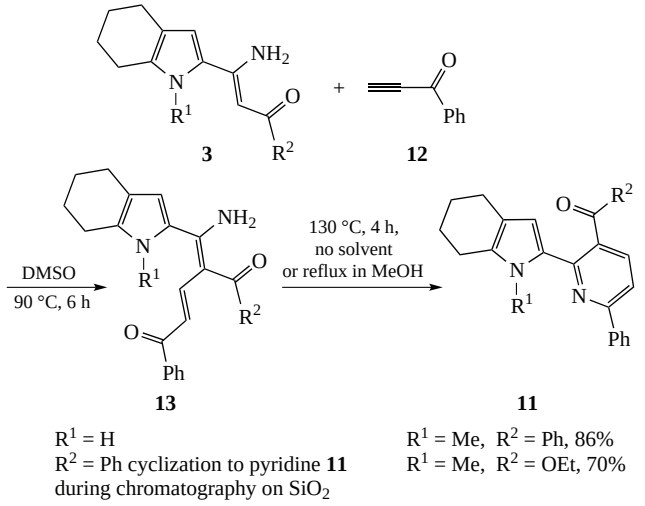
Scheme 6

The assembly of pyrrolyl-pyridines represents a nucleophilic addition of the intermediate carbanion **A** to the triple bond of acylacetylene producing intermediate diene **13**, which further cyclizes to the pyridine by the addition of amino group to the carbonyl function *via* dihydropyridine intermediate **B** and its dehydration (Scheme 7).

When the reaction was carried out in DMSO, the isolation of intermediate diene **13** became possible (Scheme 8).



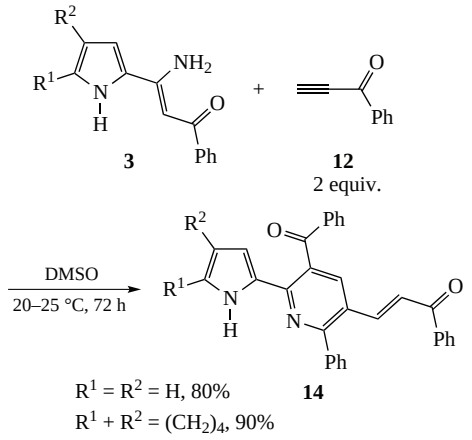
Scheme 7



Scheme 8

Dienes **13** were transformed to the corresponding pyrrole-pyridine ensembles **11** by heating (130 °C, 4 h) without solvent or upon reflux in methanol. Diene **13** [R^1 = H, $R^2+R^3=(CH_2)_4$, R^4 = Ph] was converted to pyrrolyl-pyridine **11** already during chromatography on silica gel (see Scheme 8). However, the complete conversion of diene **13** [R^1 = Me, $R^2+R^3=(CH_2)_4$, R^4 = OEt] in pyridine was achieved in the presence of CuI or CuCl (0.5 equiv., MeOH, reflux, 3 h, 67% of pyridine **11**).[26]

The cyclization of aminoenones **3**, prepared from N-unsubstituted pyrroles (R^1 = H), was accompanied by stereoselective formation of *C*-vinylated pyridines, (*E*)-3-[5-acyl-2-aryl-6-(pyrrol-2-yl)pyridin-3-yl]-1-(aryl)prop-2-en-1-ones **14**. This new synthetically attractive reaction was realized in a one-pot manner to afford *C*-vinylated pyridines **14** in high yields when these aminoenones reacted with a twofold excess of acylacetylene **12** in DMSO at room temperature (Scheme 9).

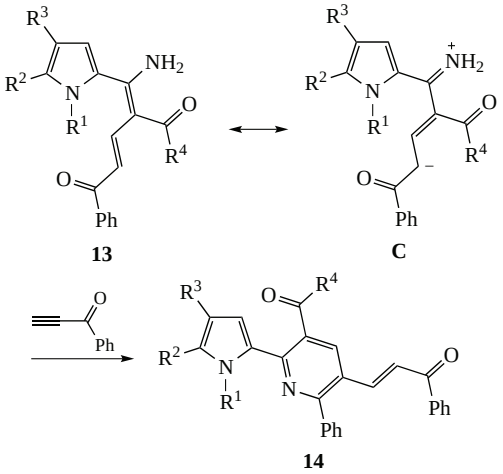


Scheme 9

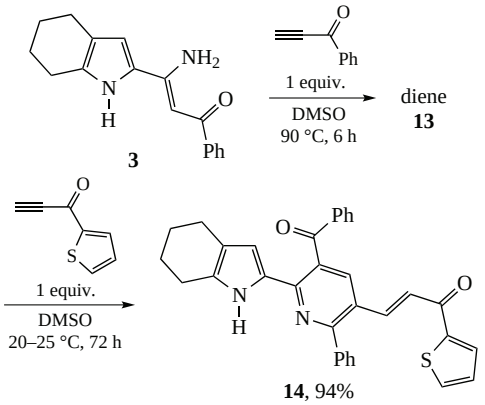
The formation of vinyl pyridines was rationalized as an attack of the intermediate carbanion **C** at the triple bond of a second molecule of acylacetylene. From this it follows, why this reaction became a major one in a proton-free medium (DMSO) (Scheme 10).

These reactions pave the simple way to unique functionalized pyridines **14** with desirable acyl and acylvinyl substituents *via* the combination of pyrrolyl-aminoenones **3** with different acylacetylenes, particularly using two-step strategy (Scheme 11).

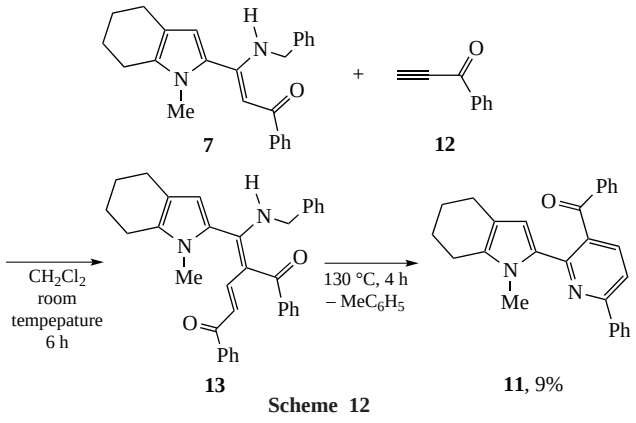
In contrast to the above reactions under the conditions of Scheme 8 (130 °C, 4 h) without solvent diene **13** prepared from *N*-benzylamino(pyrrolyl)enone **7** and benzoylacetylene lost



Scheme 10



Scheme 11

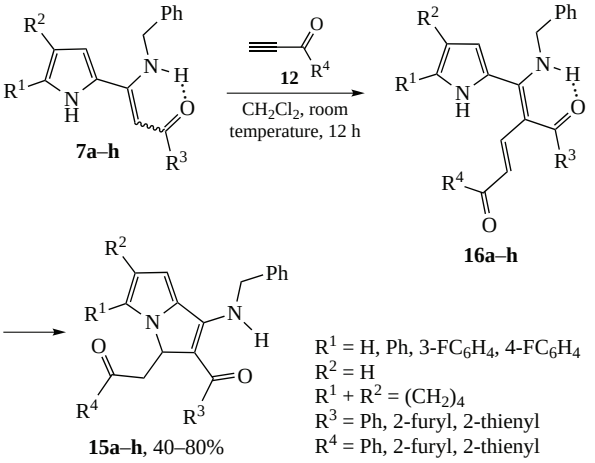


Scheme 12

benzyl group likely as toluene to give pyridine **11** in 9% only (Scheme 12).[26]

Thus, the cyclization of pyrrolyl-aminoenones with acylacetylenes paves an expedient route to previously hardly accessible functionalized pyrrolyl-pyridines, which are privileged rewarding objects for drug design[31] and advanced materials science.[32] Among them, there are effective anti-tubercular agents,[33] antioxidants,[34] inhibitors of prolyl 4-hydroxylase efficient against fibrotic diseases,[35] and P38 kinase as anti-inflammatory agents.[36] The spectrum of biological activity of these compounds includes also blocking of glucagon action as well as TNF (Tumor Necrosis Factor) and IL1 (Interleukin-1) inhibition that is prospective for curing diabetes and cytokine-mediated diseases.[37]

The non-catalyzed cyclization of *N*-benzylamino(pyrrolyl)-enones **7a**–**h**, having no substituents at the pyrrole nitrogen, with acylacetylenes **12** under mild conditions produced richly



Scheme 13

functionalized pyrrolizines **15a**–**h** in good yields.[28] The reaction starts with a nucleophilic addition of the CH-bond of aminoenones to the triple bond of acylacetylenes to stereoselectively generate the intermediate 2*E*,4*Z*-dienes **16**, which further chemo- and regioselectively cyclize to pyrrolizines **15a**–**h** (Scheme 13).

It is relevant to note that pyrrolizines are promising scaffolds for anticancer drugs.[38] They also show antiviral,[39] antiproliferative,[40] analgesic,[41] anti-inflammatory,[42] antimalarial,[43] and antibacterial[44] activities, exhibit the property of inhibiting aromatase,[45] cyclo-oxygenase and 5-lipoxygenase,[46] microsomal prostaglandin E2 synthase-1, mPGES-1 and 5-lipoxygenase.[47]

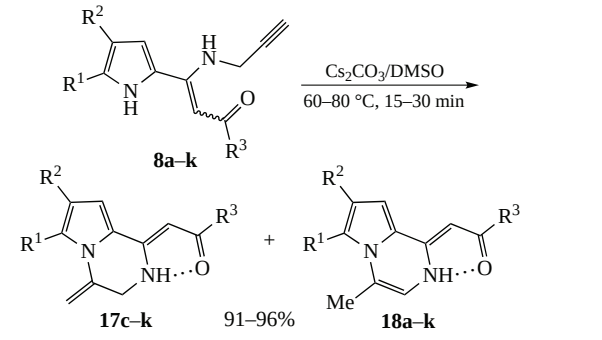
Thus, the developed strategy of pyrrolizines synthesis should become a new useful tool for drug design.

1.2.2. Intramolecular cyclization of *N*-propargylamino(pyrrolyl)enones

The base-catalyzed (Cs_2CO_3/DMSO) intramolecular cyclization of *N*-propargylamino(pyrrolyl)enones **8a**–**k** led to pyrrolo[1,2-*a*]pyrazines with exocyclic (**17c**–**k**) and endocyclic (**18a**–**k**) double bonds in the total yield of both isomers of 91–96% (Scheme 14).[29]

The process was strictly stereoselective: only *Z*-isomers of pyrazines **17**,**18** were formed apparently due to a strong intramolecular H-bonding between pyrazine *N*H- and carbonyl groups.

Pyrrolopyrazines **18** having the endocyclic double bond were formed selectively only from aminoenones **8a**,**b** [$R^1 = R^2 = H$, R^3 = 2-furyl (**8a**) and $R^1 + R^2 = (CH_2)_4$, R^3 = Ph (**8b**)]. In the case of derivatives with aryl substituents, the major products were pyrrolopyrazines **17c**–**k** with the exocyclic double bond.



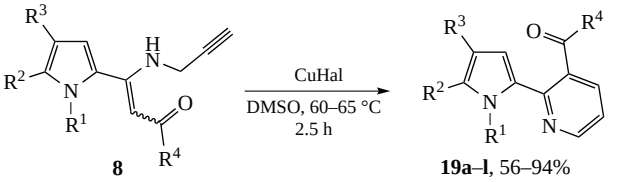
Scheme 14

The initial isomer ratios **17**:**18** have a kinetic nature since their further heating under the reaction conditions resulted in predominance of isomers **18** with the endocyclic double bonds. This shift of the double bond of isomers **17** inside the pyrazine cycle is mainly due to gain a better conjugation, *i.e*. to reach more thermodynamic stability of the heterocycle formed.

Pyrrolopyrazines **17**,**18** were also synthesized (80–95% yields) directly from 2-acylethynylpyrroles **1** and propargylamine [without isolation of intermediate *N*-propargylamino(pyrrolyl)-enones **8**] upon heating (60–80 °C) the reactants in DMSO.[30]

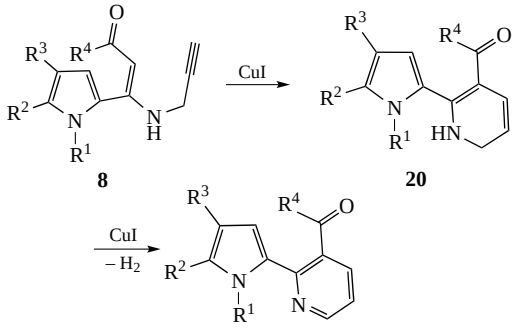
According to numerous literature data, functionalized pyrrolopyrazines possess pharmaceutically prospective properties, including anticancer,[48] tuberculostatic,[49] anti-inflammatory,[50] antimalarial,[51] antibacterial,[52] anticonvulsive,[53] and anxiolytic activities.[54] They also inhibit HIV-1 integrase,[55] topoisomerase II,[56] vasopressin 1b,[57] ERK2,[58] alpha-V integrin,[59] and aldose reductase,[60] act as mGluR5 antagonists,[61] cb1 modulators,[62] and 5-agonists of HT_3 receptor.[63] Therefore, the above new expedient synthesis of highly functionalized pyrrolopyrazines opens additional possibilities for drug design.

Pyrrolyl-pyridines **19a**–**l** were assembled in a one-pot procedure from *N*-propargylamino(pyrrolyl)enones **8**, formed *in situ* from N-substituted 2-acylethynylpyrroles **1** and propargylamine, in the presence of 1 equiv. of Cu^I halide in DMSO (Scheme 15).[64]



Scheme 15

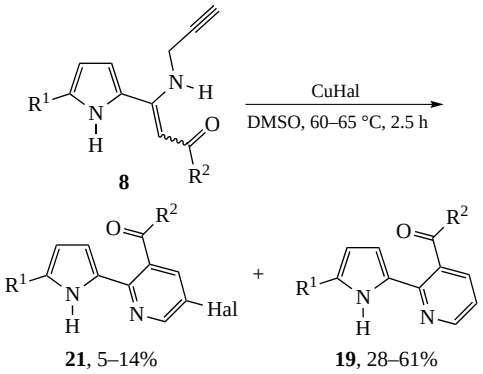
The assembly of pyrrolyl-pyridines **19a**–**l** involves the copper-catalyzed formation of intermediate dihydropyridine **20** which is oxidized to final product **19** likely by Cu cations (the oxidation by DMSO was excluded since no Me_2S was detected in the reaction mixture), Scheme 16.



Scheme 16

In the case of N-unsubstituted pyrrolylaminoenones **8** also generated *in situ* from propargylamine and corresponding 2-acylethynylpyrroles **1** under the above conditions (1 equiv. of CuHal, DMSO, 60–65 °C, 2.5 h), pyrrolyl-halopyridines **21** along with the expected pyrrolyl-pyridines **19** were formed in 5–14 and 28–61% yields, respectively (Scheme 17).[65]

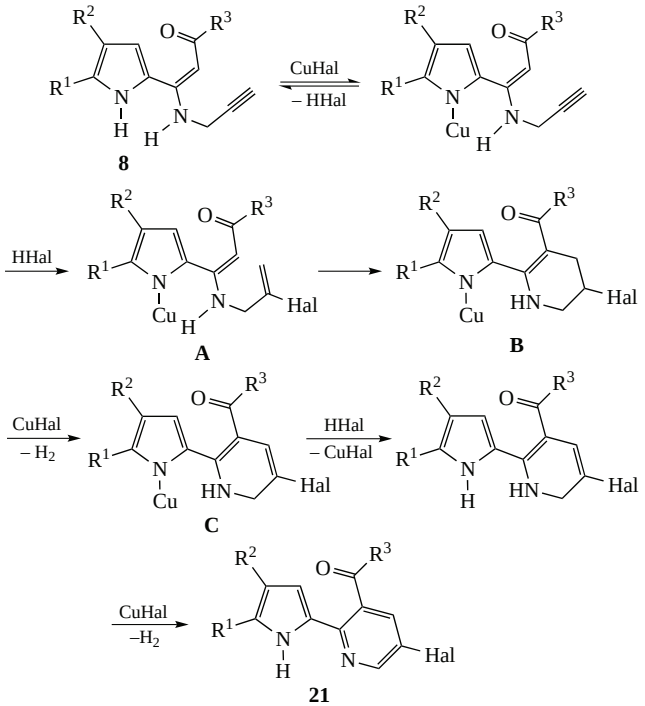
This unexpected halogenation of the pyridine ring is evidently associated with the presence of unsubstituted pyrrole function (NH) in the molecules of the starting compounds **8**.



R^1 = H, Ph, 4-FC_6H_4, 4-ClC_6H_4
R^2 = Ph, 2-furyl
Hal = Cl, Br, I

Scheme 17

The halogenation was proved to occur before the pyridine ring closure as the pure pyrrolyl-pyridines are not halogenated under the reaction conditions.[65] Apparently, the haloallyl intermediate **A** produced by addition of hydrogen halide to the propargyl group of *N*-propargylamino(pyrrolyl)enones **8** undergoes intramolecular cyclization to tetrahydropyridine **B** which is further transformed to the halopyridine **21** *via* the reaction with CuX and subsequent oxidation by Cu^+ cations. The process is preceded by the reversible reaction between NH function of the pyrrole moieties and CuHal to give copper-containing pyrroles and hydrogen halides (Scheme 18).



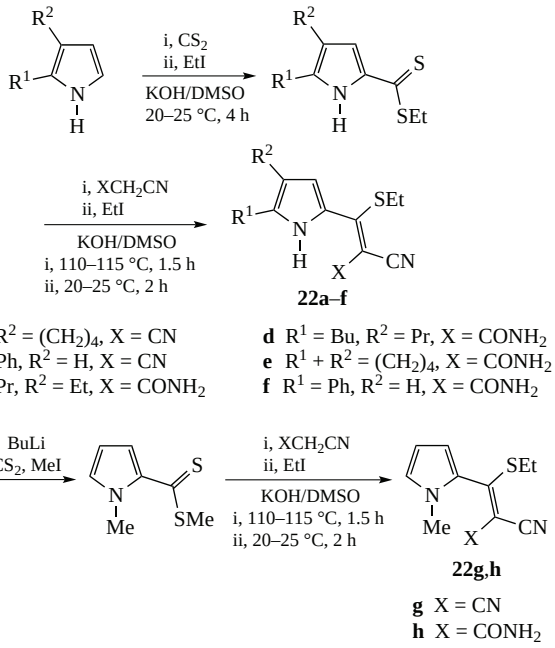
Scheme 18

2. Conjugated pyrrole/aminoacrylonitrile ensembles

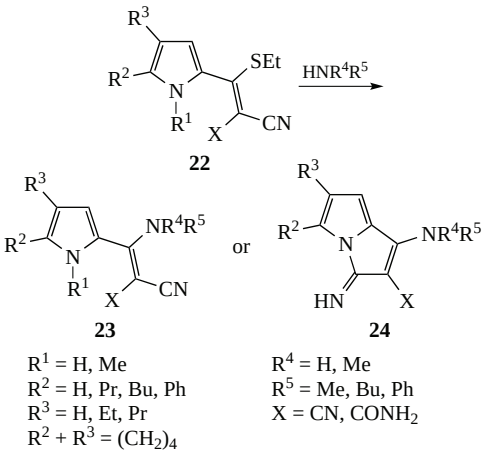
2.1. Synthesis of pyrrolyl-aminoacrylonitriles

The precursors of conjugated pyrrolyl-aminoacrylonitriles, pyrrolyl-ethylthioacrylonitriles **22a**–**h**, are synthesized by the reaction of pyrrole-2-carbodithioates with methylene active nitriles in superbase system KOH/DMSO (Scheme 19) according to the methodology as described in reviews.[25]

Based on these precursors, a general approach to the synthesis of pyrrolyl-aminoacrylonitriles **23** or their cyclic isomers, aminopyrrolizinecarbonitriles **24**, *via* the reaction



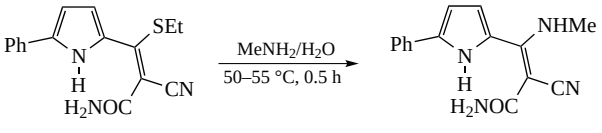
Scheme 19



Scheme 20

with primary or secondary amines was developed (Scheme 20).[66]

In this line, pyrrolyl-ethylthioacrylonitrile **22f** when treated with aqueous methylamine gave pyrrolyl-aminoacrylonitrile **23f** in good yield (Scheme 21).

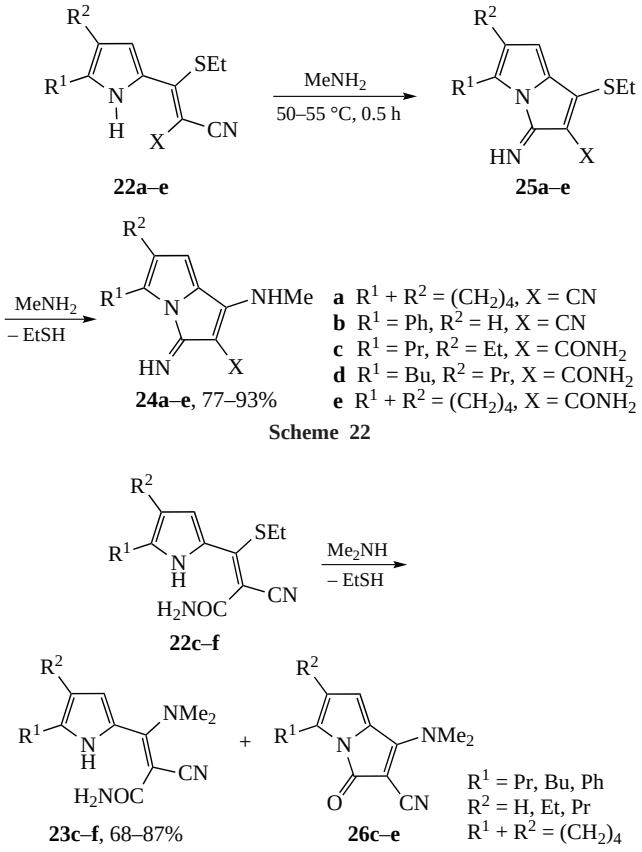


Scheme 21

A similar reaction of pyrrolyl-ethylthioacrylonitriles **22a**,**b** with aqueous methylamine produced methylaminopyrrolizine-carbonitriles **24a**,**b** (Scheme 22). First, the cyclization of pyrroles **22a**,**b** to their isomers, ethylthiopyrrolizinecarbonitriles **25a**,**b**, occurs. Then the latter exchanges the ethylthio group for the methylamine substituent.

This pathway was confirmed by the reaction of 1-ethylthiopyrrolizines **25a**–**e** with methylamine under the same conditions which led to the expected aminopyrrolizines **24a**–**e** in 77–93% yields (see Scheme 22).

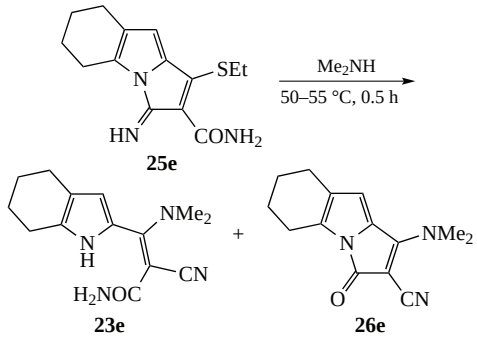
The major or exclusive (in the case of pyrrole **22f**) products of the reaction of pyrrolyl-ethylthioacrylonitriles **22c**–**f** with



Scheme 23

dimethylamine were pyrrolyl-aminoacrylonitiriles **23c**–**f** with minor amount of products of intramolecular cyclization of the latter, aminopyrrolizinones **26c**–**e** (~5%) (Scheme 23).

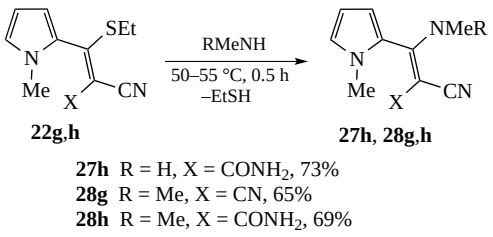
Cyclic isomer of pyrrolyl-ethylthioacrylonitrile **22e**, ethylthiopyrrolizine **25e**, when reacted with dimethylamine, underwent ring-opening affording pyrrolyl-aminoacrylonitrile **23e** and aminopyrrolizinone **26e** (7 : 1) (Scheme 24).



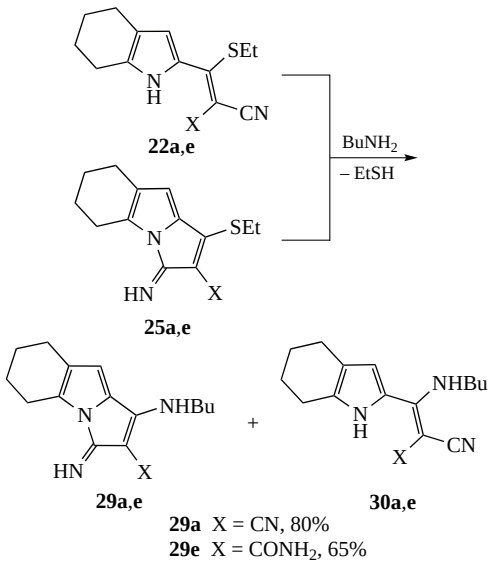
Scheme 24

N-Methyl substituted pyrrolyl-ethylthioacrylonitriles **22g**,**h** with aqueous methyl- and dimethylamines gave pyrrolylaminoacrylonitriles **27h**,**28g**,**h** (Scheme 25) Pyrrolyl-aminoacrylonitrile **27h** was formed owing to the hydrolysis of one nitrile group.

The reaction of pyrrolyl-ethylthioacrylonitriles **22a**,**e** or its cyclic isomers, pyrrolizines **25a**,**e**, with *n*-butylamine in aqueous ethanol (70 °C, 4 h) proceeded slower and less selectively than that with methylamine producing mainly 1-*n*-butylamino-pyrrolizines **29a**,**e** with a minor admixture (5–20%) of pyrrolyl-*n*-butylaminoacrylonitriles **30a**,**e**. When the reaction was carried out in pure ethanol, *n*-butylaminopyrrolizine **29a** was formed exclusively (80% yield) (Scheme 26).[66]



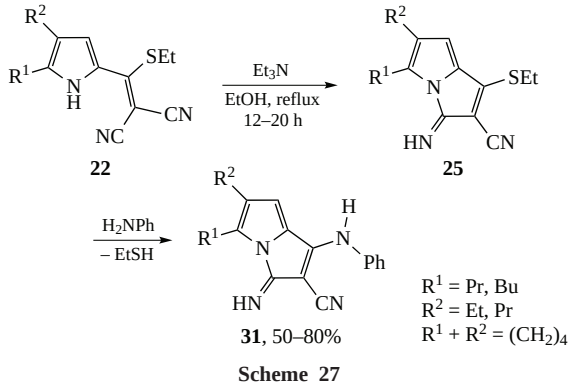
Scheme 25



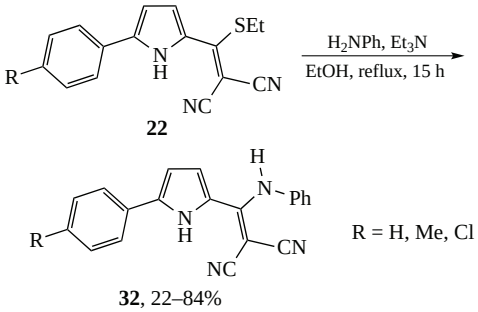
Scheme 26

Unlike these results, the reaction of pyrrolyl-ethylthio-acrylonitriles **22** with aniline took place only in the presence of triethylamine (an equimolar amount of triethylamine, ethanol, reflux, 12–20 h) providing selectively 1-anilino-3-imino-3*H*-pyrrolizine-2-carbonitriles **31** (Scheme 27).[67]

If pyrrolyl-aminoacrylonitrile precursors **22** contained aryl substituents in the pyrrole ring, the only products of these reactions with aniline were pyrrolyl-aminoacrylonitriles **32** (Scheme 28).



Scheme 27



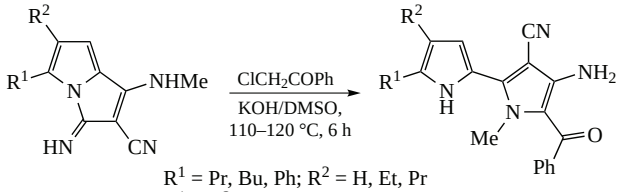
Scheme 28

2.2. Reactions of pyrrolyl-aminoacrylonitriles

2.2.1. Reactions with 1-chloroacetophenone: synthesis of 2,2′- and 2,3′-bipyrroles

Cyclic pyrrolyl-aminoacrylonitriles (pyrrolizines) **24** were used as the starting materials for the synthesis of the functionalized 2,2′- and 2,3′-bipyrroles with neighboring amino and cyano substituents.[68]

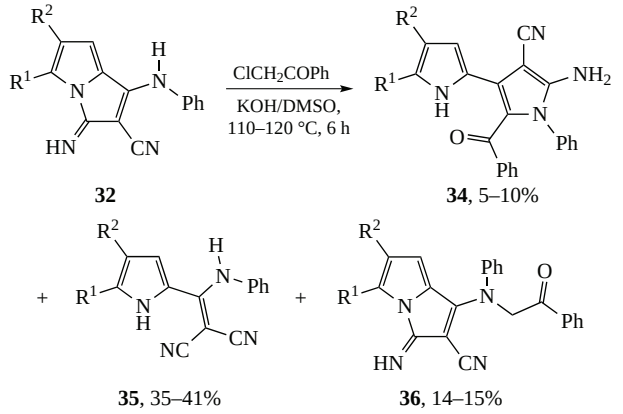
When they were treated with 1-chloroacetophenone in the KOH/DMSO system, 2,2′-bipyrroles **33** were formed in 20–54% yields (Scheme 29).



24 **33**, 20–54%

Scheme 29

However, if methylamino substituent in the pyrrolizine ring was replaced by the phenylamino group, 2,3′-bipyrroles **34** (instead of the expected 2,2′-bipyrroles) were formed (Scheme 30). In this case, along with 2,3′-bipyrroles **34**, pyrrolylenaminonitriles **35** and **36** were also formed.



32 **34**, 5–10%

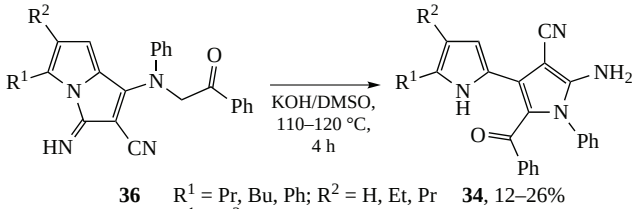
35, 35–41% **36**, 14–15%

Scheme 30

Cyclic pyrrolyl-aminoacrylonitriles **36** were proved to be intermediates in the synthesis of 2,3′-bipyrroles: their heating in the KOH/DMSO system resulted in the formation of 2,3′-bipyrroles **34** (12–26% yields) (Scheme 31).

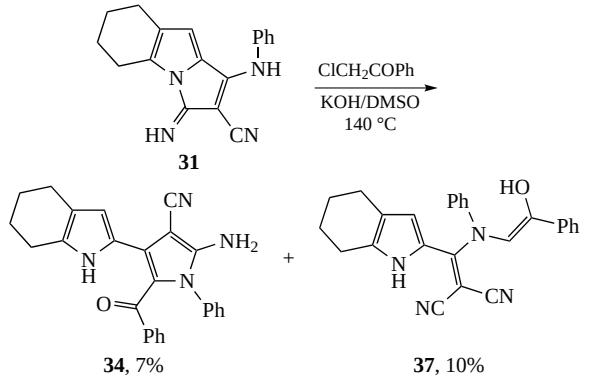
Pyrrolyl-aminoacrylonitriles **35** did not react with 1-chloroacetophenone under the above conditions, indicating that they are not intermediates of the bipyrrole synthesis.

At a higher temperature (140 °C, other conditions being the same) from pyrrolizine **31** and 1-chloroacetophenone, along with bipyrrole **34**, enol **37**, the tautomer of ketone **36**, was isolated in 10% yield (Scheme 32).



36 **34**, 12–26%

Scheme 31

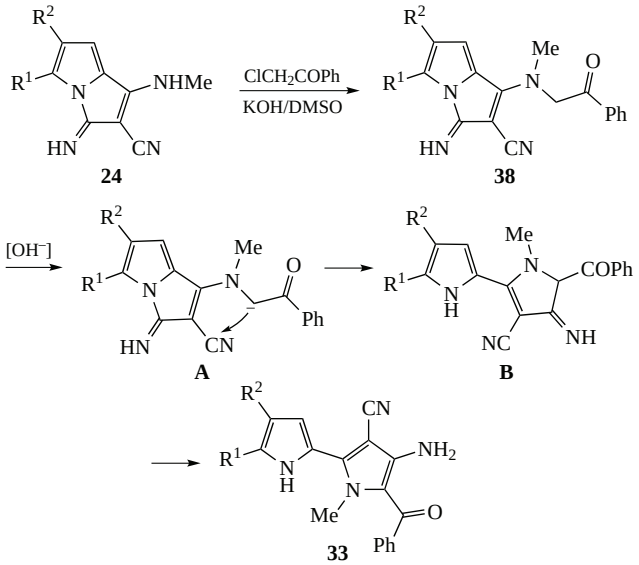


31

34, 7% **37**, 10%

Scheme 32

Mechanistically, the formation of 2,2′-bipyrroles starts with alkylation of 1-methylaminopyrrolizines **24** by 1-chloroacetophenone to give intermediate ketones **38**, which are deprotonated to carbanions **A**. The latter add to the cyano group with simultaneous pyrrolizine ring-opening to provide, after reprotonation, pyrrolyliminopyrrolines **B**, further aromatizing to 2,2′-bipyrroles **33** (Scheme 33).



24 **38**

A **B**

33

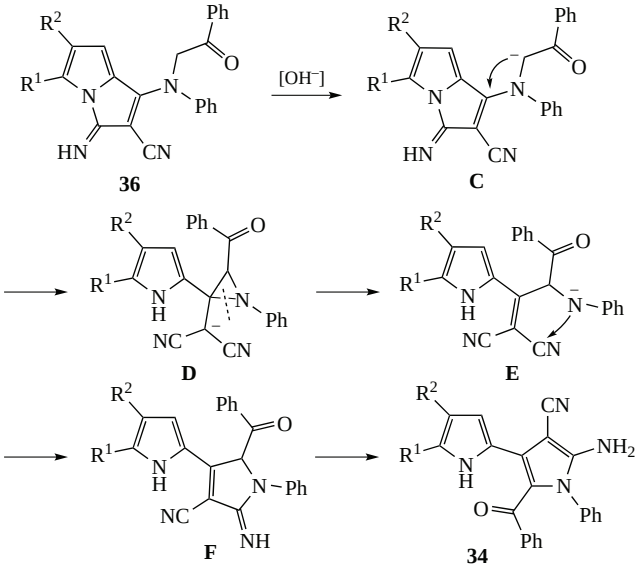
Scheme 33

A plausible mechanism of the rearrangement leading to 2,3′-bipyrroles **34** consists of the following reaction sequences (Scheme 34): (i) carbanionic form **C** of ketones **36** intramolecularly attacks the C–C double bond with simultaneous pyrrolizine ring-opening to give the intermediate carbanionic aziridines **D**; (ii) these intermediates transform to aniline-anions **E**; (iii) the nitrogen-centered anions **E** add to the cyano group to afford pyrrolyliminopyrrolines **F** with are finally prototropically isomerized to 2,3′-bipyrroles **34**.

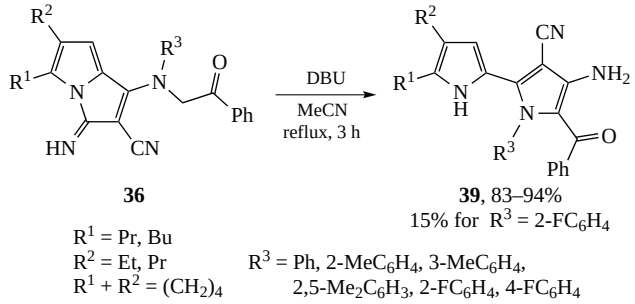
The thermodynamic reason of the alternative recyclization in the case of aniline derivatives **36** is probably the formation of more stable *N*-phenyl anionic intermediates relative to the corresponding *N*-methyl anionic moieties **38**.

In the presence of the organic superbase, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the recyclization mode of pyrrolyl-aminoacrylonitriles **36** was completely changed: instead of 2,3′-bipyrroles only 2,2′-bipyrroles **39** were formed in high yields (Scheme 35).[69]

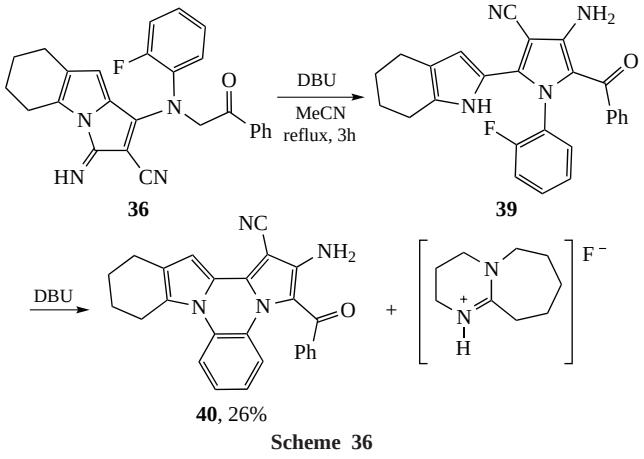
The reduced yield of bipyrrole **39** with $R^3 = 2\text{-}FC_6H_4$ was resulted from the side cyclization with participation of the pyrrole NH-group and the fluorine atom to provide a highly condensed 2,2′-bipyrrole system **40** in 26% yield (Scheme 36).



Scheme 34



Scheme 35



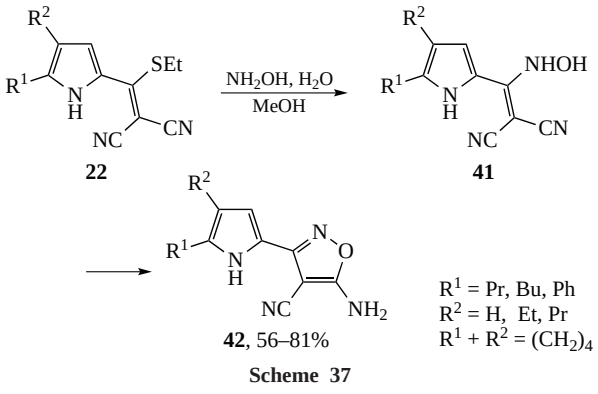
Scheme 36

The resolute effect of DBU on the selective switch from the 2,3′- to 2,2′-junction is likely owing to spatial screening of the position 1 from the attack of the carbanionic center in intermediate **C** (see Scheme 34). The latter is accompanied by the bulky DBU counteraction.

Thus, reaction of cyclic pyrrolyl-aminoacrylonitriles with 1-chloroacetophenone paves an expedient route to previously inaccessible functionalized by neighboring amino and cyano substituents 2,2′- and 2,3′-bipyrroles, precursors of pyrrolic purine analogs.[70]

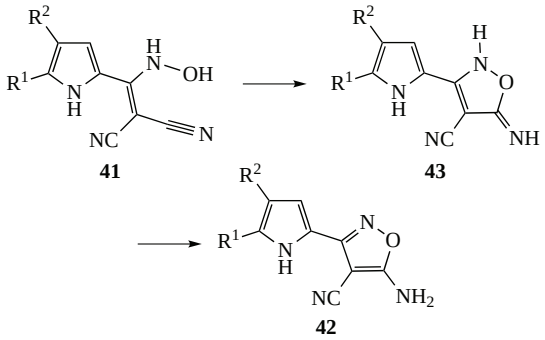
2.2.2. Reaction with hydroxylamine

Pyrrolyl-aminoacrylonitriles **41**, formed on heating (40–45 °C, 30 min) of pyrrolyl-ethylthioacrylonitriles **22** with aqueous hydroxylamine in methanol, selectively cyclized to 5-amino-3-(pyrrol-2-yl)isoxazoles **42** (Scheme 37).[71]



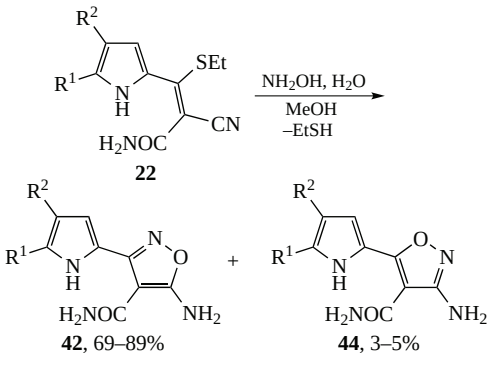
Scheme 37

The pyrrolyl-aminoisoxazoles **42** obviously resulted from addition of hydrohylamino group to a one of nitrile functions with formation of intermediate pyrrolyl-iminoisoxazolines **43** which are expectedly finally prototropically aromatized to aminoisoxazoles (Scheme 38).



Scheme 38

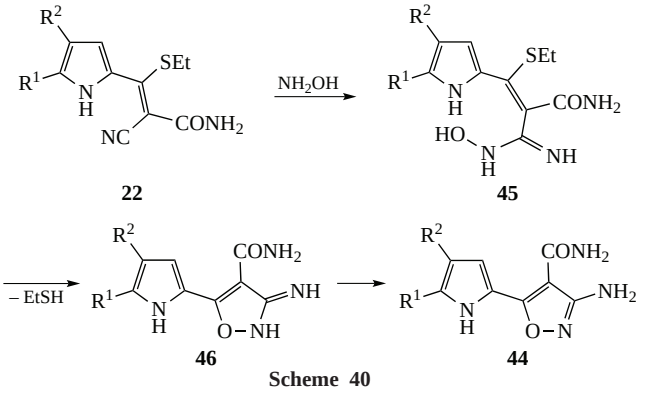
Under analogous conditions, from pyrrolyl-ethilthio-acrylonitriles **22** with carbamoyl substituent and hydroxylamine, along with 5-amino-4-carbamoyl-3-(pyrrol-2-yl)isoxazoles **42**, their minor isomers, 3-amino-4-carbamoyl-5-(pyrrol-2-yl)-isoxazoles **44**, were formed (Scheme 39).



Scheme 39

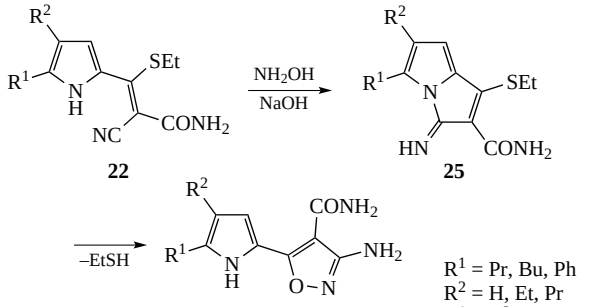
Apparently, the minor isomers **44** are assembled when hydroxylamine adds by its amino group to the nitrile function of pyrrolyl-ethylthioacrylonitriles **22** (to their *E*-isomers) and the intermediate imines **45** cyclized (with elimination of ethane thiol) to isoxazolines **46**, which rearranged into 3-amino-isoxazoles **44** (Scheme 40).

In the presence of NaOH, pyrrolyl-aminoacrylonitriles **22** with carbamoyl substituent reacted with hydroxylamine to give exclusively 3-aminoisoxazoles **44** (Scheme 41). Under these conditions, the reaction probably proceeded through intermediate formation of 3-iminopyrrolizines **25** that was confirmed by the



22 **45** **46** **44**

Scheme 40



22 **25** **44**, 12–48%

Scheme 41

reaction of the latter with hydroxylamine affording under analogous conditions mainly 3-aminoisoxazoles **44** (Scheme 41).

Thus, this reaction may become a useful tool for synthesis of new isoxazole derivatives, key intermediates for design of medicines and materials for advanced technology. In fact, the pyrrole-isoxazole ensembles exhibit high pharmacological activity: they are inhibitors of HIV-1 integrase,[72] antimicrobial,[73] and antibacterial[74] agents, used to treatments for autoimmune diseases,[75] depression.[76] On the basis of pyrrolyl-isoxazoles, sensors for fluorine ions and advanced material science were created.[77]

Conclusions

This focus article is an attempt to draw attention of synthetic professionals, drug designers and material scientists to two broad classes of two highly flexible synthetic building blocks, namely pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles, which are easily accessible from available starting materials *via* transition metal-free reliable reactions such as cross-coupling of pyrroles with haloacetylenes and sequential condensation of pyrrolecarbodithioates with methylene-active nitriles and amines. The through conjugation of three basic entities (pyrrole ring, enamine and carbonyl or nitrile moieties) secures the easy electronic communication between the functional groups thereby rendering excellent mutual influence and fine response during chemical reactions. The reactions considered in this article represent just few examples illustrating possible but still far from being unfolded synthetic potential of pyrrole/aminoenone and pyrrole/aminoacrylonitrile ensembles. It is understood that modification of such important chemical objects as amino acids, nucleic bases, nucleosides, sugars, and oligopeptides with the above ensembles promises the development of novel easy one-step approaches and strategies for drug design and creation of high-tech materials.

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