Recent Strides in the Transition Metal-Free Cross-Coupling of Haloacetylenes with Electron-Rich Heterocycles in Solid Media

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Abstract: The publications covering new, transition metal-free cross-coupling reactions of pyrroles with electrophilic haloacetylenes in solid medium of metal oxides and salts to regioselectively afford 2-ethynylpyrroles are discussed. The reactions proceed at room temperature without catalyst and base under solvent-free conditions. These ethynylation reactions seem to be particularly important, since the common Sonogashira coupling does not allow ethynylpyrroles with strong electron-withdrawing substituents at the acetylenic fragments to be synthesized. The results on the behavior of furans, thiophenes, and pyrazoles under the conditions of these reactions are also provided. The reactivity and structural peculiarities of nucleophilic addition to the activated acetylene moiety of the novel C-ethynylpyrroles are considered.

Keywords: electrophilic haloacetylenes; pyrroles; ethynylpyrroles; furans; thiophenes; pyrazoles; Al₂O₃

1. Introduction

Functionalized five-membered aromatic heterocycles represent a frequent structural motif of bioactive natural products and pharmaceuticals [1–12]. Among them, of particular interest are the compounds bearing acetylenic moieties [13–15]. The combination of the electron-rich, five-membered aromatic heterocyclic nucleus with highly reactive carbon-carbon triple bond in one molecule allows using these compounds for the targeted synthesis of various complex heterocyclic systems. Commonly, ethynylation of heterocycles is implemented via Sonogashira reaction employing the halogenated heterocycles and terminal alkynes [16–19]. In 2004, as a complementation to the existing cross-coupling protocols, the direct palladium- and copper-free ethynylation of the pyrrole ring with haloacetylenes in the Al₂O₃ medium (room temperature, no solvent) was discovered [20]. Later, haloacetylenes were involved in ethynylation of diverse heterocycles using palladium [21,22], nickel [23,24], copper [25], or gold [26] catalysts. In parallel, the Al₂O₃-mediated ethynylation of pyrroles and indoles kept being steadily developed [27–43]. A number of pyrroles with alkyl, cycloalkyl, aryl, and hetaryl substituents were successfully ethynylated with acylhaloacetylenes and halopropynoates within a framework of this cross-coupling procedure. It was shown that some other metal oxides (MgO, CaO, BaO) [33] and salts (K₂CO₃) [35] can also be beneficially applied instead of Al₂O₃. On the basis of the experimental facts, it was concluded that this cross-coupling includes the nucleophilic attack of pyrroles at the electron-deficient triple bond of haloacetylenes followed by the elimination of hydrogen halide from the zwitterionic intermediates.
As far as the relationship between the reactivity of the heterocycle and the solid salt used is concerned, a broad screening of various metal oxides and salts as mediators for the cross-coupling has shown that some of them are rather active (i.e., BaO). However, due to availability and convenience of the work-up of the reaction mixtures, Al₂O₃ and K₂CO₃ were taken as the agents of choice. A selection of specific metal oxides (Al₂O₃ or K₂CO₃) for a particular reaction is determined experimentally because the results significantly depend on the structure of both the pyrrole and haloacetylene employed.

This methodology was already partially documented in recent reviews [44–52]. This survey covers the recent publications (since 2014) concerning this reaction and the related chemistry which have not been yet summarized in a review.

2. Cross-Coupling of Haloacetylenes with Electron-Rich Heterocycles

2.1. Cross-Coupling of Haloacetylenes with Pyrroles

2.1.1. Cross-Coupling of Bromo- and Iodopropiolaldehydes with Pyrroles

A series of substituted pyroles 1 were ethynylated by iodopropiolaldehyde in solid K₂CO₃ (a 10-fold excess) under mild conditions without solvent to afford highly reactive functionalized pyrrole compounds, 3-(pyrrol-2-yl)propiolaldehydes 2, in up to 40% yield (Scheme 1) [53]. The reagents were ground intensively for 5–10 min and allowed to stand at room temperature for 4 h. Iodopropiolaldehyde was more preferable over explosive bromopropiolaldehyde.

\[ R^1 = H, Bn, CH=CH_2; R^2 = Ph, 3-F, 4-CHO; R^3 = H, Et, n-C_8H_17, n-C_6H_13 \]

**Scheme 1.** Synthesis of 3-(pyrrol-2-yl)propiolaldehydes 2.

In this case, the use of Al₂O₃ proved to be inappropriate, since the above ethynylation, albeit accelerated (the reaction time was 1 h), proceeded non-selectively to form, along with the target 3-(pyrrol-2-yl)propiolaldehydes 2, 3-bis(pyrrol-2-yl)acrylaldehydes 3, with the molar ratio being 1:1 (Scheme 2).

\[ R^1 = H, R^2 = Ph, R^3 = H \]

**Scheme 2.** Reaction of pyroles 1 with iodopropiolaldehyde in solid Al₂O₃.

It was found that 2-phenylpyrrole (1, R¹ = H, R² = Ph, R³ = H) gave the lowest yield (25%) of the ethynylated product that is likely associated with side reactions of the NH-function, e.g., nucleophilic addition across the triple bond or condensation with the aldehyde moiety.

The mechanism of the cross-coupling involves the single-electron transfer (SET) from pyrrole to iodopropiolaldehyde to generate the radical-ion pair A and/or the formation of the zwitterion B followed by elimination of hydrogen iodide (Scheme 3). Apparently, the role of K₂CO₃ is to stabilize the intermediate ion pairs by dipole-dipole interaction inside the ionic crystalline lattice of the medium, thus somewhat resembling ionic liquids.
The generation of radical-ions during this process was evidenced from ESR signals observed in the reaction of 1-vinyl-2-phenyl-3-amylpyrrole (1, \(R^1 = \text{CH}=\text{CH}_2, R^2 = \text{Ph}, R^3 = \text{C}_6\text{H}_{11}\)) with iodopropionaldehyde in solid \(\text{K}_2\text{CO}_3\).

2.1.2. Cross-Coupling of Acylbromoacetylenes with Pyrroles

With 2-(Furan-2-yl)- and 2-(2-thiophen-2-yl)pyrroles

The reaction of 2-(furan-2-yl)- (4) and 2-(thiophen-2-yl)pyrroles 5 with acylbromoacetylenes 6a-c was carried out according to the similar procedure: the reactants (1:1 molar ratio) were ground with a 10-fold excess of \(\text{Al}_2\text{O}_3\) at room temperature for 1 h [54]. The major direction of this ethynylation of 2-(furan-2-yl)pyrroles 4 was the formation of 2-acylethynyl-5-(furan-2-yl)pyrroles 7 (Scheme 4), while the alternative 2-acylethynyl-5-(pyrrol-2-yl)furans 8 were minor products (7:8 \(\approx\) 5–7: 1). This result was key to understanding the ethynylation of five-membered aromatic heterocycles with haloacetylenes. In fact, this was the first observation of a relative reactivity of the furan ring in this reaction.

![Scheme 4. Reaction of 2-(furan-2-yl)pyrroles 4 with acylbromoacetylenes 6a-c in the solid \(\text{Al}_2\text{O}_3\).](image)

Double ethynylation, i.e., ethynylation of each ring, was not observed in any cases. In other words, the reaction occurs either with the pyrrole or furan ring. This points to a strong deactivating effect of the acyl substituent that is transmitted from one ring to another through the system of ten bonds involving conjugated one triple, four double, and five ordinary bonds. The ratio of products 7:8 \(\approx\) 5–7: 1 can be considered as an approximate measure of relative reactivity of the pyrrole and the furan ring towards the acylhaloacetylenes. The reaction of pyrroles with electrophilic acetylenes is commonly regarded as a nucleophilic addition of electron-rich pyrrole moiety (often as the pyrrolate anion) to the electron-deficient triple bond which occurs as N- and C-vinylation [55]. As mentioned above (see Section 2.1.1.) this reaction is likely initiated by the single-electron transfer to generate the radical-ion pairs as key intermediates, further forming C-C covalent bond with a final elimination of hydrogen halide [33]. Such a mechanism and the experimental isomer ratios are in agreement with a lower ionization potential of the pyrrole ring (8.09 eV) compared to that of furan ring (8.69 eV) [56].

In accordance with this rationale, 2-(thiophen-2-yl)pyrroles 5 reacted with acylbromoacetylenes 6a–c under the above conditions to give only products of the pyrrole ring ethynylation, ethynylypyrroles 9 (Scheme 5) that also agrees with a higher ionization potentials of the thiophene ring (8.72 eV) [56].
thiophene ring by the reaction studied. (Scheme 8). The formation of dipyrromethane 16 by the condensation of trifluoropyrrolylethanols with pyrrole.

In cases of NH-pyrroles (4, 5, R¹ = H), 3-bromo-1-(pyrrol-2-yl)prop-2-en-1-ones 10 were isolated as the E-isomers stabilized by a strong intramolecular hydrogen bond between NH-proton and oxygen atom of the carbonyl group (Scheme 6).

The similar propanones were not observed among the products of ethynylation of N-vinylpyrroles (4, 5, R¹ = CH=CH₂) because they are not able to form the above stabilizing intramolecular hydrogen bonding.

With Dipyrromethanes

The solid-phase (Al₂O₃) ethynylation of dipyrromethane 11 with acylbromoacetylenes 6a–c afforded 5-acylethynyl dipyrromethanes 12 in 38%–53% yields (Scheme 7) [57]. In contrast to the ethynylation of pyrrole giving 2-acylethynylpyrroles in the yield of 55%–70% for 1 h [20], the cross-coupling of dipyrromethane 11 with acylbromoacetylenes 6a–c required a much longer time and portion-wise addition of acetylene 6a–c to the reaction mixture.

The low reaction rate in this case is likely resulted from the strong electron-withdrawing effect of the CF₃-group, deactivating the pyrrole ring that acts as a nucleophile.

A general synthesis of such non-symmetrical dipyrrromethanes was previously developed [58] by the condensation of trifluoropyrrolylethanols with pyrrole.

In the solid K₂CO₃, effective in the ethynylation of pyrroles with haloacetylenes [35], the above reaction did not take place at all.

In the solid alumina (room temperature, 96 h), dipyrromethane 13 reacted with benzoylethynylacetylene 6a to give insignificant amounts of products. From the reaction mixture, apart from the target dipyrromethane 14, 5-(1-bromo-2-benzoylethynyl)dipyrromethane 15, and the double ethynylation product, (dibenzoylethynyl)dipyrromethane 16, were isolated in low yields (Scheme 8). The formation of dipyrromethane 16 was the first example of ethynylation of the thiophene ring by the reaction studied.
61% yield.

Upon treatment of the aqueous solution of salt 11. This prevented the salt formation with the NH moiety. With the ethynylation of dipyrromethane 13 in the solid Al₂O₃.

To increase the nucleophilicity of the pyrrole ring, trimethylsilyl group was introduced to nitrogen atom of the pyrrole ring (Scheme 9). The ethynylation (K₂CO₃, room temperature, 168 h) of a mixture of dipyrromethanes 17 and 18 with acylbromoacetylenes 6a–c gave acylethynyldipyrromethanes 14, 19 in 39%–44% yields (Scheme 9). Thus, the yields of ethynylated product were increased due to the introduction of trimethylsilyl groups in the pyrrole ring to enhance their nucleophilicity.

With Tetrahydropyrrolo[3,2-c]pyridines

The cross-coupling of pyrrolo[3,2-c]pyridines 20 with acylbromoacetylenes 6a,b in solid K₂CO₃ was strictly chemo- and regioselective: exclusively propynones 21 were isolated (Scheme 10) [59].

In this case, the use of K₂CO₃ appeared to be essential, since it allowed the released HBr to be effectively fixed. This prevented the salt formation with the NH-function of the tetrahydropyrroline moiety.

Indeed, when Al₂O₃ (instead of K₂CO₃) served as an active medium, the reaction of pyrrole 20 (R¹ = C₆H₅) with benzoyl bromoacetylene 6a afforded salt of propynone, hydrobromide 22 (Scheme 11). Upon treatment of the aqueous solution of salt 22 with NH₄OH propynone 21 was obtained in 61% yield.

Scheme 8. Ethynylation of the dipyrromethane 13 in the solid Al₂O₃.

Scheme 9. Synthesis and ethynylation of dipyrromethanes 17, 18.

Scheme 10. Cross-coupling of tetrahydropyrrolo[3,2-c]pyridines 20 with acylbromoacetylenes 6a,b in the solid K₂CO₃.

Scheme 11. Cross-coupling of pyrrolo[3,2-c]pyridine 20 with benzoyl bromoacetylene 6a in the solid Al₂O₃.
With Pyrrole-2-carbaldehydes

Pyrrole-2-carbaldehydes 23 proved to be inactive under usual conditions of the cross-coupling of pyrroles with acylhaloacetylenes in alumina medium (room temperature, 1 h). The reason is likely strong electron-withdrawing effect of the aldehyde group which decreases the pyrrole ring nucleophilicity. This fundamental hurdle was overcome by the acetal protection of the aldehyde function thereby decreasing its electron-withdrawing power [60,61]. The acetals 24 were treated with acetylbromoacetylenes 6a–c in the alumina medium (room temperature, 6 h) to obtain the expected ethynylated acetals 25. After the deprotection (aqueous acetone, HCl, room temperature, 1 h), the target ethynylated pyrrole-2-carbaldehydes 26 were isolated in 75%–89% yields (Scheme 12).

![Scheme 12](https://example.com/scheme12.png)

**Scheme 12.** Synthesis of pyrrole-2-carbaldehydes with the electron-deficient acetylenic substituents.

2.1.3. Cross-Coupling of Bromotrifluoroacetylacetylene with Pyrroles

Pyrroles 27, when reacted with bromotrifluoroacetylacetylene 28 in the solid Al₂O₃ (room temperature, 2 h), gave only 4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones 29 in 12%–21% yields [62,63], while the cross-coupling of acetylbromoacetylene 30 with the same pyrroles under the same conditions afforded the expected acetylenylpyrroles 31 (Scheme 13) [62].

![Scheme 13](https://example.com/scheme13.png)

**Scheme 13.** The cross-coupling of NH-pyrroles 27 with acetylbromoacetylenes 28 and 30 in the solid Al₂O₃.

Interestingly, N-vinylpyrroles 32 underwent normal cross-coupling with bromotrifluoroacetylacetylene 28 (Al₂O₃, rt, 2 h) to deliver ethynylpyrroles 33 in 42%–58% yields (Scheme 14).

![Scheme 14](https://example.com/scheme14.png)

**Scheme 14.** The cross-coupling of N-vinylpyrroles 32 with bromotrifluoroacetylacetylene 28 in the solid Al₂O₃.
This implies that the cause of abnormal reaction (Scheme 13) is the interaction between NH and trifluoroacetyl groups that stabilizes 4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones 29 in their E-configuration.

This is evidenced from the extraordinary downfield shift of the NH group proton signal (13 – 14 ppm) in the 1H NMR spectra of pyrroles 29.

The intramolecular H-O-bonding of such a type is likely realized already in the E-form of the intermediate zwitterion A (Scheme 15). This hydrogen bonding prevents the E→Z isomerization and hence elimination of HBr, which usually occurs as a trans-process. Notably, in most cases of ethynylation of pyrroles under similar conditions [20], bromopyrrolylethenylketones of the type 29 are formed just as minor contaminants, if any (0%-10% yields), that may also be a result of easier elimination of hydrogen halides (HBr in this case) from their Z-configuration. As the elimination of HBr does not occur at a stage of the zwitterion A formation, the proton in the 2 position of the pyrrole ring is transferred to the carbanionic center. This should be facilitated by a strong electron-withdrawing effect of trifluoroacetyl substituent. Consequently, the target product 29 is formed stereoselectively (as the E-isomer).

Scheme 15. Proposed mechanism of formation of E-isomers of the hydrogen-bonded compounds 29.

In the reaction of N-vinylpyrroles 32 with the bromotrifluoroacetylacetylene 28, the formation of an intramolecular hydrogen bond in the products is impossible (Scheme 16). Moreover, the formation of the E-isomer of 4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones B would be sterically hindered (due to the repulsion between N-vinyl group and trifluoroacetyl substituent).

Scheme 16. Formation of products 33 from N-vinylpyrroles 32 and bromotrifluoroacetylacetylene 28.

Probably, the effect of steric strain destabilizes the E-form at the stage of formation of the intermediate zwitterion B (Scheme 16), for which the Z-form turns out to be energetically favorable. At the final stage, the zwitter-ion B is transformed to trifluoroacetylethenylpyrroles 33 via elimination of the bromine anion accompanied by releasing of proton from the position 2 of the pyrroline ring (Scheme 16).

Pyrrole 33a, after 7 days contact with Al2O3, lost the trifluoroacetyl group to give 2-ethynylypyrrole 34 in 24% yield (Scheme 17). The partial detrifluoroacylation of pyrroles 33 also occurred during their passing through Al2O3-packed chromatographic column.

Scheme 17. Detrifluoroacylation of compound 33a after 7 days contact with Al2O3.
2.1.4. Cross-Coupling of Chloroethynylphosphonates with Pyrroles

Pyrroles 35 were cross-coupled with chloroethynylphosphonates 36 in solid alumina (room temperature, 24–48 h) to give 2-(pyrrol-2-yl)ethynylphosphonates 37 in 40%–58% yields (Scheme 18) [64].

\[
\text{R}^1 = \text{H, Me, Br, CH=CH}_2; \text{R}^2 = \text{n-Pr, n-Bu, R}^3 = \text{Et, n-Pr, R}^2\cdot \text{R}^3 = \text{(CH}_2)_3; \text{R}^4 = \text{Me, Et}
\]

Scheme 18. Synthesis of 2-(pyrrol-2-yl)ethynylphosphonates 37.

In the absence of AlCl₃ (both in a solvent and under solvent-free conditions), the ethynylation did not take place. At room temperature, the complete conversion of the reactants was reached after 24 h. The exception was N-vinyl-4,5,6,7-tetrahydroindole 35a (R¹ = H; R²-R³ = (CH₂)₃), the ethynylation of which lasted twice as long (48 h).

As minor products (2%–10%), 2,2-bis(pyrrol-2-yl)vinylphosphonates 38 were detected in the reaction (Figure 1). Also, in the case of 1-vinyl-4,5,6,7-tetrahydroindole [35, R¹ = CH=CH₂; R²-R³ = (CH₂)₃], dialkyl 2,2-dichlorovinylphosphonates 39 (2%–9%) were present in the reaction mixture (Figure 1).

Figure 1. Side products of cross-coupling of pyrroles 35 with chloroethynylphosphonates 36.

The formation of the product 39 required [64] a longer reaction time (48 vs. 24 h) that allowed hydrogen chloride to be competitively added to the starting chloroethynylphosphonates according to [65]. A longer reaction rate is also due to the electron-withdrawing effect of the vinyl group, which reduces nucleophilicity of the pyrrole moiety.

In the solid K₂CO₃ medium (other conditions being the same), the cross-coupling of pyrroles with chloroethynylphosphonates produced only pyrrolylethynylphosphonates 37 in 38%–43% yields.

It is suggested [64] that the reaction mechanism in this case represents the direct nucleophilic substitution of chlorine atom by the pyrrole moiety. This is supported by known data [66,67] that the reactions of chloroethynylphosphonates with nucleophiles including the neutral ones proceed mainly as a nucleophilic substitution of chlorine atom at the Cₛₚ carbon.

2.1.5. Cross-Coupling of Halopolyyynes with Pyrroles

The above transition metal-free solid-phase mediated cross-coupling of haloacetylenes with pyrroles turns out to be efficient also for halopolyyynes (di-, tri-, and tetrapolyyynes) [68,69], allowing the pyrroles functionalized with polyynes chains to be synthesized. Such rare, highly reactive pyrrole compounds represent exclusively promising building blocks and precursors for the design of biologically and technically valuable heterocyclic molecules of exceptional complexity and structural diversity, including porphyrinoids with the polyyne substituents [70], modified bilirubins [71], and various ensembles of pyrroles with furans [72,73], thiophenes [72,73], pyroles [72,73], naphthalenes [73], and other cyclic counterparts [73].
Thus, ester end-capped 1-halobutadiynes were successfully cross-coupled with pyrroles 40 in the solid K_2CO_3 to afford the expected butadiynyl-substituted pyrroles 41 in 43%-80% yields (Scheme 19) [68].

\[
\begin{align*}
\text{R}^1 & = \text{H, Me, Br, CH=CH}_2; \text{R}^2 = \text{Ph, R}^3 = \text{H; R}^2 - \text{R}^3 = \text{(CH}_2)_2; \text{R}^4 = \text{Me, Et, Bn}
\end{align*}
\]

Scheme 19. Cross-coupling of electron-deficient halobutadiynes with pyrroles 40.

The scope of reactions covers 2-phenylpyrrole, NH-4,5,6,7-tetrahydroindole, N-substituted 4,5,6,7-tetrahydroindoles, and chloro-, bromo-, and iodobutadiynes. The most suitable butadiynyl agents proved to be 1-bromobutadiynes.

The reaction rate depends on the pyrrole structure, with tetrahydroindole derivatives being the most reactive. For them, the cross-coupling with one equivalent of various halobutadiynes did not exceed 5 h, whereas for 2-phenylpyrrole, to reach 46%-52% yield of the target product it required 2 equivalents of halobutadiynes and much longer reaction time (24 h).

This study was further extended over the longer chain aryl-capped 1-halopolyynes (up to tetratetraynes) [69]. As pyrrole substrates, 4,5,6,7-tetrahydroindole and its N-substituted derivatives were employed.

For the interaction of 41-N-methyl-4,5,6,7-tetrahydroindole with 1-bromo-2-(4-cyanophenyl)acetylene 42a, 1-bromo-2-(4-cyanophenyl)butadiyne 42b, 1-bromo-2-(4-cyanophenyl)hexatriyne 42c, the expected cross-coupling was observed only for triyne 42c (K_2CO_3, room temperature, 3 h, 82% yield of hexatriynyl substituted N-methyl-4,5,6,7-tetrahydroindole 43c), while with acetylene 42a no target product was detected (^1H-NMR), and in the case of diyne 42b a slow reaction (several days) took place (Scheme 20).

\[
\begin{align*}
\text{Scheme 20. The reaction of polyyynes 42a-c with N-methyl-4,5,6,7-tetrahydroindole.}
\end{align*}
\]

Since longer bromopolyyynes were less stable than the corresponding iodine derivatives, 1-bromotetra- and -hexatriyne were used for the synthesis of tetradiynyl- and hexatriynyl-substituted tetrahydroindoles (Scheme 21), while 1-iodotetraynes were employed to produce octatetraynyltetrahydroindoles (Scheme 22).

\[
\begin{align*}
\text{R}^1 & = \text{H, Me, Br, CH=CH}_2; \text{R}^2 = \text{CN, NO}_2; \text{MeCO}_3, \text{CO}_2\text{Me, CO}_2\text{Et}; n = 2, 3
\end{align*}
\]

Scheme 21. Synthesis of tetradiynyl- and hexatriynyl-substituted tetrahydroindoles.

\[
\begin{align*}
\text{R}^1 & = \text{Me, CH=CH}_2; \text{R}^2 = \text{CN, NO}_2
\end{align*}
\]

Scheme 22. Synthesis of octatetraynyltetrahydroindoles.
Like in the work of Trofimov B.A. [33] (see also Section 2.1.1.), it is assumed that the reaction mechanism involves radical-ion pairs generated by the SET process (Scheme 23). According to experimental results longer polyyne chains secure a better stabilization of radical-ion pairs that provide higher yields of polyyynyl substituted tetrahydroindoles and a shorter reaction time.

\[
\text{R}^3\text{R}^2\text{N}^+\text{R}^1 + \text{Hal} \equiv = \equiv \text{R}^4 \xrightarrow{\text{K}_2\text{CO}_3, \text{mechanocalcination}} \rightarrow \left[ \text{R}^2\text{R}^1\text{N}^+\text{R}^1 \right]^+ + \left[ \text{Hal} \equiv = \equiv \text{R}^4 \right]^- \\
\left[ \text{R}^2\text{R}^1\text{N}^+\text{R}^1 \right]^+ + \left[ \text{Hal} \equiv = \equiv \text{R}^4 \right]^- \rightarrow \left[ \text{R}^3\text{H}^\bullet + \text{N}^+\text{R}^1\text{H}^\bullet + \text{Hal} \equiv = \equiv \text{R}^4 \right]^{-} \\
\left[ \text{R}^3\text{H}^\bullet + \text{N}^+\text{R}^1\text{H}^\bullet + \text{Hal} \equiv = \equiv \text{R}^4 \right]^{-} \rightarrow \text{R}^3\text{R}^2\text{N}^+\text{R}^1 + \text{Hal} \equiv = \equiv \text{R}^4 + \text{HHal} \\
\]

**Scheme 23.** Proposed mechanism of long-chain stabilization of a radical intermediate product.

3. Reaction of Acylhaloacetylenes with Furans

A logical development of ethynylation of pyrroles with haloacetylenes [20] was the translation of this methodology to the furan compounds. In this line, on the example of menthofuran (3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran 44), first synthetically appropriate results on the transition metal-free cross-coupling of the furan ring with haloacetylenes 6a–f initiated by their grinding with solid Al\(_3\)O\(_3\) (room temperature, 1–72 h) were attained [74].

As it was found by Trofimov B.A. [74], after 1 h the reaction of menthofuran 44 with benzoylbromoacetylene 6a in solid Al\(_3\)O\(_3\) resulted in the formation of ethynylfuran 45 along with the pair of diastereomeric cycloaducts of oxanorbornadiene structure 46 in 44:56 ratio (Scheme 24). The reaction is regioselective: the bromine atom is neighboring the position 2 of the furan ring exclusively.

\[
\text{44} + \text{PhCO} \xrightarrow{\text{Al}_2\text{O}_3, \text{rt}, 1 \text{~h}} \text{45} + \text{46} \\
\text{(mixture of diastereoisomers, ratio 44:56)} \\
\]

**Scheme 24.** Reaction of benzoylbromoacetylene 6a with menthofuran 44 in the solid Al\(_3\)O\(_3\).

Upon standing the reaction mixture for 72 h, the content of ethynylfuran 45 was increased up to 88%, while amount of cycloaduct 46 was reduced. These results indicate that cycloaduct 46 converts to ethynylfuran 45, i.e., the cycloaduct 46 is a kinetic intermediate of the ethynylation (this transformation is accompanied by elimination of hydrogen bromide).
The reaction of menthofuran 44 with chloro- and iodobenzoylecetylones proceeded analogously leading for 1 h to a mixture of ethynylfuran 45 and cycloadduct 46, the latter disappearing completely after 72 h.

Thus, in contrast to cross-coupling of pyrroles with acylhaloacetylones under similar conditions, ethynylation of the furan ring with acylhaloacetylones occurred through [$4+2$]-cycloaddition followed by the elimination of HX during the ring-opening of the cycloadducts.

This reaction was proved to be applicable to bromoacetylones with formyl (6d), acetyl (6e), furoyl (6b), thenoyl (6c), and ethoxy (6f) groups at the triple bond, which reacted with menthofuran 44 in the solid Al₂O₃ to afford the acetylenic derivatives 45a–f in 40%–88% yields (Scheme 25).

```
R = Ph (a), 2-furyl (b), 2-thienyl (c), H (d), Me (e), OEt (f)
```

Scheme 25. Reaction of haloacetylones 6a-f with menthofuran 44 in the solid Al₂O₃.

Following the experimental results, the oxanorbornadiene intermediates such as 46, reversibly generated on the first reaction step, are transformed to the ethynyl derivatives of menthofuran 45 via a zwitterion with the positive charge distributed over the whole furan ring. The latter eliminates hydrogen bromide in the concerted process (hydrogen is released from the position 2 of the furan moiety, Scheme 26).

```
\[
\begin{align*}
44 + 6a & \rightarrow 45a, \\
\text{via} & \\
46 & \rightarrow 45a.
\end{align*}
\]
```

Scheme 26. Possible reaction pathway.

An experimental evidence for the proposed mechanism is the observation that cycloadducts 46 are gradually transformed to ethynylated products 45 in the solid Al₂O₃.

4. Reaction of Acylhaloacetylones with Pyrazoles

The reaction of benzoyl bromoacetylene 6a with pyrazole under conditions similar for the ethynylation of pyrroles (10-fold excess of Al₂O₃, room temperature, the molar ratio 1:1, 24 h), instead of the expected 2-benzoylethynylpyrazole 47, led to dipyrarazolylenone 48a in 18% isolated yield (Scheme 27) [75]. The yield of enone 48a increased to 32%, when 2 equivalents of pyrazole was taken and reached 43% for the reaction with a 3-molar excess of the starting heterocycle.

The reaction proceeded via the intermediate (Z)-2-bromo-2-[(pyrazol-1-yl)enone 49a and was accompanied by the formation of 2,2-dibromoenoone 50a (Scheme 27).

Modest yields (22%–35%) of dipyrarazolylenones 48a–c were observed using a two-fold molar excess of pyrazole relative to acylhaloacetylones 6a–c, with the yields of bromopyrazolylenones 49a–c and dibromoenoones 50a–c being 10%–18% and 8%–14%, respectively (Scheme 27).
Acylethynylpyrroles and their analogs are considered below. Important functionalized heterocyclic systems, some selected synthetically attractive reactions of acylethynylpyrroles and their analogs are considered below.

Scheme 27. Reaction of pyrazole with acylbromoacetylenes 6a-c.

Surprisingly, no traces of ethynylpyrazoles 47 were detectable in the reaction mixture, implying that dipyrazolylenones 48a–c are not adducts of the reaction of pyrazole with the intermediate ethynylated pyrazoles 47.

3,5-Dimethylpyrazole reacted with acylbromoacetylenes 6a–c,e in a 2:1 molar ratio to form dipyrazolylenones 51a–c, e in 42%–55% yields (Scheme 28). Bromopyrazolylenone of the type 49 in this case, was not discernible in the reaction mixture.

Scheme 28. Reaction of 3,5-dimethylpyrazole with acylbromoacetylenes 6a–c, e.

On the basis of the results obtained and previous mechanistic rationalizations concerning the reactions of pyrroles with haloacetylenes [20], it may be suggested that the synthesis of dipyrazolylenones 48 is triggered by the nucleophilic addition of pyrazole to the triple bond of acylbromoacetylenes 6a–c to form the intermediate zwitterion (Scheme 29), which converts via proton transfer from the pyrazole moiety to its carbanionic center to give isolable intermediate 49. Subsequent nucleophilic substitution of the bromine atom by a second molecule of pyrazole affords dipyrazolylenone 48.

Scheme 29. Proposed mechanism of dipyrazolylenones 48 formation.

Unlike the ethynylation of pyrroles, where the initial zwitterion releases a halogen anion to restore the triple bond, for pyrazole, rapid intramolecular neutralization of the carbanionic site of the intermediate Zwittrion occurs, which precludes formation of the ethynyl derivatives. Such a change of the reaction mechanism is likely due to the higher acidity of pyrazoles compared with pyrroles (pKₐ of pyrazole is 14.2 whereas pKₐ of pyrrole is 17.5).

5. Selected Reactions of Acylethynylpyrroles and Their Analogs

To demonstrate the possibilities of the cross-coupling developed for the construction of important functionalized heterocyclic systems, some selected synthetically attractive reactions of acylethynylpyrroles and their analogs are considered below.
5.1. Cyclizations with Propargylamine

5.1.1. Synthesis of pyrrolo[1,2-α]pyrazines

Acylethynylpyrroles 52 were used for the synthesis of pyrrolo[1,2-α]pyrazines 53a,b according to the strategy which includes the following steps: (i) the non-catalyzed chemo- and regioselective nucleophilic addition of propargylamine to the triple bond of acylethynylpyrroles 52 to afford N-propargyl(pyrrolyl)aminoenones 54 and (ii) base-catalysed intramolecular cyclization of N-propargyl(pyrrolyl)aminoenones 54 to pyrrolo[1,2-α]pyrazines 53a,b (Scheme 30) [76].

![Scheme 30. Synthesis of pyrrolo[1,2-α]pyrazines 53a,b from acylethynylpyrroles 52 and propargylamine.](image)

Nucleophilic addition of propargylamine to the triple bond of acylethynylpyrroles 52 was carried out under reflux of reactants (52: propargylamine ratio being 1:2) in methanol for 5 h to deliver N-propargyl(pyrrolyl)aminoenones 54 (Scheme 30). The latter were formed as a mixture of E/Z isomers stabilized by intramolecular H-bonds between carbonyl group and NH-function of the amino moiety (the Z-isomer) or NH-function of the pyrrole ring (the E-isomer) with predominance of the Z-isomer.

The electronic nature of the substituents attached to the pyrrole ring determines the isomers ratio. Thus, for aminoenone 54 with unsubstituted pyrrole ring, the Z/E ratio is ~9:1. When a donor cyclohexane moiety is attached to the pyrrole ring \([R^1-R^2= (CH_2)_4]\), this ratio becomes 15:1, probably owing to a lower NH-acidity of the pyrrole counterpart and hence a weaker stabilization of the E-isomer by the intramolecular H-bonding. Consequently, for pyrroles with electron-withdrawing aryl substituents, having more acidic pyrrole NH-proton, the content of the E-isomer increases, Z/E ratio being ~4:1.

The cyclization of N-propargyl(pyrrolyl)aminoenones 54 was implemented by heating (60 °C, 15–30 min) in the system Cs₂CO₃/DMSO to afford pyrazines 53a with exocyclic double bond and their thermodynamically more stable endocyclic isomers 53b. Pyrrolopyrazines 53b with the endocyclic double bond were formed selectively only from aminoenones 54 with unsubstituted pyrrole ring or with tetrahydroindole derivatives. In the case of enamines with phenyl or fluorophenyl substituents, the major products were pyrrolopyrazines having the exocyclic double bond 53a (their content in the reaction mixture was spanned 70–90%), while pyrrolopyrazines 53b were minor products. The total yield of both isomers remained almost quantitative (90–96%).

Later, pyrrolopyrazines 53a,b were obtained (90–95% yields) via a one-pot procedure from ethynylpyrroles 52 and propargylamine when the reactants were heated (60–65 °C) in DMSO [77].

5.1.2. Synthesis of Pyrrolyl Pyridines

The one-pot reaction of N-substituted acylethynylpyrroles 55 with propargylamine in the presence of Cul selectively afforded 2-(pyrrol-2-yl)-3-acylpyridines 56 (Scheme 31) [78].
Evidently, the cause of this difference compared to the previous cyclization [78] was the in

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The MS spectra of the reaction mixtures showed that the oxidation of intermediate 58 did not take place under the action of DMSO (no MeS was detected). The air oxygen also did not participate in this process: the same results were obtained both under argon blanket and on air. Therefore, the Cu+ cation was considered [78] as a likely oxidant.

Latter [79] from the reaction of NH-acylethynylpyrroles 59 with propargylamine in the presence of CuX (X = Cl, Br, I), 3-acyl-2-(pyrrol-2-yl)-5-halopyridines 60 were unexpectedly isolated in 4%–14% yields along with 3-acyl-2-(pyrrol-2-yl)pyridines 61 (28%–61% yields) (Scheme 33). Evidently, the cause of this difference compared to the previous cyclization [78] was the NH-functionality of the starting acylethynylpyrroles.

Scheme 31. The formation of pyrrolyl pyridines 56 from acylethynylpyrroles and propargylamine.

Catalyst-free heating of the reactants led to N-propargyl(pyrrolyl)aminoenones 57 which, upon keeping with CuI (equimolar amount) for 2.5 h at the same temperature, underwent the dihydrogenative ring closure to give pyrrolyl pyridines 56 (Scheme 31).

The duration of non-catalytic step strongly depended on the pyrrole structure: the acceptor substituents in the pyrrole ring facilitated the reaction (the reaction time was 6 h), while the donor ones slowed down the process (the reaction time was 16 h). A peculiar feature of this dehydrogenative cyclization is that the intermediate dihydropyridines 58 were aromatized rapidly (they are not usually detectable in the reaction mixture). Only in the case of acylethynyltetrahydroindole dihydropyridine 58 was isolated in 4% yield. Notably, the catalytic ring closure was almost insensitive to the structure of the initial acylethynylpyrroles 55 (the reaction time was about 2.5 h for all the cases).

A less predictable step of the synthesis is the intramolecular nucleophilic addition of the CH-bond adjacent to carbonyl group across the acetylenic moiety (Scheme 32). This CH-bond can be deprotonated under the action of amino group, either intramolecularly (autodeprotonation) to generate intermediate A or intermolecularly. Upon the complexing of Cu+ cation with the triple bond, the latter should be polarized to increase sensitivity towards the nucleophilic attack. This attack is completed by the addition of the carbanionic site to the terminal acetylenic atom to give the intermediate dihydropyridine 58.

Scheme 32. Formation of pyrrolyl pyridines 56 from aminoenones 57.

The MS spectra of the reaction mixtures showed that the oxidation of intermediate 58 did not take place under the action of DMSO (no MeS was detected). The air oxygen also did not participate in this process: the same results were obtained both under argon blanket and on air. Therefore, the Cu+ cation was considered [78] as a likely oxidant.

Latter [79] from the reaction of NH-acylethynylpyrroles 59 with propargylamine in the presence of CuX (X = Cl, Br, I), 3-acyl-2-(pyrrol-2-yl)-5-halopyridines 60 were unexpectedly isolated in 4%–14% yields along with 3-acyl-2-(pyrrol-2-yl)pyridines 61 (28%–61% yields) (Scheme 33). Evidently, the cause of this difference compared to the previous cyclization [78] was the NH-functionality of the starting acylethynylpyrroles.

Scheme 33. Synthesis of pyrrolyl pyridines 60 and 61 from NH-2-acylethynylpyrroles and propargylamine.
Under the above conditions, pyrrolyl pyridines 61 were not halogenated with CuX, thus indicating that construction of the halogenated pyridine ring occurred before its closure. It is supposed (Scheme 34) [79] that hydrogen halides, reversibly generated by the interaction of the NH pyrrole moiety of the intermediate N-propargyl(pyrrrolyl)aminoenone 57 with CuX, add to the triple bond activated by π-complexing with other CuX molecules to give haloallyl intermediate B (Scheme 34). Afterwards, the intramolecular addition of the CH bond to the allyl moiety takes place to form the intermediate 5-halotetrahydropyridyl intermediate C. Aromatization of the latter is finalized via the reaction with CuX and further oxidation by Cu⁺ cations as previously described for a similar process [78].

![Scheme 34. Proposed scheme of halopyridines 60 formation.](image)

5.2. Synthesis of Pyrrolizines via Three-Component Cyclization with Benzylamine and Acetylenes.

On the platform of acetylenylpyrroles 52, a new general strategy for the synthesis of functionalized pyrrolizines was developed [80]. It consisted of the two steps: (i) the base-catalyzed addition of a benzylamine to 2-acetylenylpyrroles 52 to give pyrrolylaminoenones 62; (ii) non-catalyzed addition of N-benzyl(pyrrrolyl)aminoenones 62 to the triple bond of acetylenes 63 followed by the intramolecular cyclization of the intermediate pentadienones 64 thus formed to 1-benzylamino-2-acyl-3-methylenoacylpyrrolizines 65 (Scheme 35).

![Scheme 35. Synthesis of 1-benzylamino-2-acyl-3-methylenoacylpyrrolizines 65.](image)
The nucleophilic addition of benzylamine to the triple bond of 2-acylethanlypyrroles 52 was realized in the presence K2PO4/DMSO catalytic system to smoothly deliver N-benzyl(aryl)aminoenones 62 in up to 97% yield (Scheme 35). The latter were formed as a mixture of the E/Z isomers, the E-isomer being obviously stabilized by intramolecular H-bonds between the carbonyl group and NH-function of the pyrrole ring. As in the case of the addition of propargylamine to acylethanlypyrrole (see Section 5.1.), the structure of the substituents of the pyrrole ring strongly influences the isomer ratio of the adducts: the donor substituents increase the content of the Z-isomers.

Further, the aminoenones 62 chemo- and regioselectively reacted with acylacetylenes 63 to afford the intermediate pentadiendiones 64, which then cyclized to 1-benzamino-2-acyl-3-methyleneacetylpyrrolyazines 65 in up to 80% yield (Scheme 35).

5.3. Reactions with Ethylenediamine

The reaction of 2-benzoylthanolpyrroles 55a,b with ethylenediamine was realized upon reflux of their equimolar mixture in dioxane (40 h) [81]. Expectedly, first the addition of diamine gave monoadduct 66a,b, which, in the case of acylethanlypyrrole 55a, underwent intramolecular cyclization/fragmentation to afford tetrahydrodindolyl imidazoline 67a and acetophenone (Scheme 36).

![Scheme 36. Reaction of 2-benzoylthanolpyrroles 55a,b with ethylenediamine.](image)

In this reaction, in the case of acylethanlypyrrole 55b, the formation of dihydrodiazepine 68 takes place. This is a result of the intramolecular cyclization of monoadduct 66b with the participation of the carbonyl group followed by dehydration (Scheme 37).

![Scheme 37. The formation of tetrahydrodindolyl dihydrodiazepine 68b.](image)

5.4. Cyclization with Hydrazine: Synthesis of Pyrrolyl Pyrazoles

The building up of the pyrazole ring over acetylenic moiety of pyrrolopyridine propynones 21 via its ring closure with hydrazine gave 4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine-pyrazole ensembles 69 in 92%-98% yields (Scheme 38) [59].

![Scheme 38. Synthesis of 4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine-pyrazole ensembles 69.](image)
According to the above procedure, a new extended dipyrrmethane system conjugated with pyrazole cycle 70 was obtained in almost quantitative yield (Scheme 39) [57].

![Scheme 39. Synthesis of dipyrrmethane-pyrazole ensemble 70.](image)

5.5. Cyclization with Hydroxylamine: Synthesis of Pyrrolyl Isoxazoles

Acylethynyltetrahydroindoles 71 readily cyclized with hydroxylamine to give regioselectively either 3-(4,5,6,7-tetrahydroindol-2-yl)-4,5-dihydrisoaxazol-5-ols 72 or 5-(4,5,6,7-tetrahydroindol-2-yl)isoxazoles 73 (Scheme 40) [82]. The cyclization can be easily switched from the direction leading exclusively to isoxazoles 72 to the formation of isoxazoles 73 by simple changing of the proton concentration in the reaction mixture. When the reaction was carried out in the presence of acetic acid (NH₂OH-HCl/NaOAc, 1:1 system), only isoxazoles 72 were formed, whereas under neutral or basic conditions (NH₂OH-HCl/NaOH (1:1 or 1:1.5 system), the cyclization took another pathway to produce preferably (94%–97% or entirely) isoxazoles 73.

![Scheme 40. Reaction of acylethynyltetrahydroindoles 71 with hydroxylamine.](image)

Apparenty, in the presence of acetic acid, the attack of the NH₂OH nucleophile at the β-acetylenic carbon of tetrahydroindoles 71 is electrophilically assisted by the simultaneous protonation of the carbonyl group (and finally 1,4-addition takes place to deliver isoxazoles 72), as shown in Scheme 41.

![Scheme 41. The formation of 3-(4,5,6,7-tetrahydroindol-2-yl)-4,5-dihydrisoaxazol-5-ols 72.](image)

In the presence of the NH₂OH-HCl/NaOH system, which is unable to exert the electrophilic assistance, the common oximation of the carbonyl group prevailed.

Moreover, 4,5-dihydrisoaxazol-5-ols 72 underwent easy aromatization when refluxing (benzene, 1 h) in the presence of TsOH-H₂O to isoxazoles 74 in 73%–91% yields (Scheme 42) [82].
Scheme 42. Dehydration of 3-(4,5,6,7-tetrahydroindol-2-yl)-4,5-dihydroisoxazol-5-ols 72.

On the basis of the above cycloaddition, two approaches to the synthesis of meso-CF$_3$ substituted dipyrrromethanes 75–77 bearing isoxazole moieties were developed [83].

The key stages of these approaches are the cycloaddition of hydroxylamine to the triple bond of ethynylidipyrromethanes 12a, 78 (Schemes 43 and 44), or the synthesis of pyrrolyl isoxazoles 75, 77 from ethynylpyrole 79 (accessible from pyrrole and benzoylebromoacetylene), and its further condensation with 2,2,2-trifluoro-1-(pyrrol-2-yl)-1-ethanols 80, as described in Section 2.1.2. (Scheme 45).

Scheme 43. Synthesis of (3-phenylisoxazol-5-yl)dipyrromethanes 75a,b from ethynylidipyrromethanes 12, 78.

Scheme 44. Synthesis of (3-phenylisoxazol-3-yl)dipyrromethanes 77a,b from ethynylidipyrromethanes 12, 78.

Scheme 45. Alternative synthesis of (3- or 5-phenylisoxazolyl)dipyrromethanes 75 and 77 by condensation of pyrrolylisoxazoles 81 or 82 and with 2,2,2-trifluoro-1-(pyrrol-2-yl)-1-ethanols 80.

5.6. Cyclization with Methylene Active Esters: Synthesis of Pyrrolyl Pyrones

The [4+2]-cycloaddition between 2-acyethylpyrroles 83 and methylene active esters (Scheme 46), offering a short-cut to pyrrolyl pyrones 84 in good to high yields, was described [84].
The reaction was carried out in acetonitrile in the presence of 1.5 molar excess of KOH. As methylene active esters, diethylmalonate, ethyl acetoacetate and ethyl cyanoacetate were used.

The cyclization is triggered by the proton abstraction from the active CH₂ group of methylene active esters followed by the nucleophilic attack of the carbanion A, thus generated at the triple bond of acylethynylpyrroles 83 to afford intermediate B. The subsequent intramolecular nucleophilic substitution of the ethoxy group in the ester function by the oxygen-centered anion (the resonance form of the intermediate B) furnishes the target products (Scheme 47).

Scheme 47. Scheme of pyrrolyl pyrones 84 formation.

5.7. Unprecedented Four-Proton Migration in Acylethynylmenthofurans: “a Proton Pump”

When benzoylethynylmenthofuran 45a was heated at reflux in CHCl₃ in the presence of HBr, the formation of benzoylethylbenzofuran 85a in 95% yield was observed (Scheme 48) [85]. Thus, the transfer of four hydrogen atoms from the cyclohexane ring to the triple bond took place.

Scheme 48. Rearrangement of acylethynylmenthofurans 45 to acethylbenzofurans 85.

This rearrangement was found to be general for other acylethynyl derivatives (furoyl, thenoyl, alkoxyacarbonyl) of menthofuran to give their acetylbenzofuran derivatives in the yield of 44%, 48%, and 24% respectively (Scheme 48).

Basing on these experimental results, it can be postulated that the rearrangement starts with protonation of acylethynyltetrahydrobenzofuran moiety with HBr to give carocation A, which in its more stable mesomeric form B abstracts a hydride-ion from the adjacent position (C-7) with positive charge transfer to form carbocation C. Then, two hydride shifts in the cyclohexane ring transform carbocation C into carbocation D with the positive charge at C-5. Proton abstraction from the C-4 position of this carbocation leads to the cyclohexene moiety and regenerates HBr. Simultaneously, after two 1,3-hydrogen shifts in the furan counterpart, it is transformed into vinyl intermediate E. Next, protonation of the double bond with HBr results in the formation of carbocation F which in its stable endocyclic form accepts the hydride ion from the cyclohexene ring to give cyclohexene carbocation G. The release of a proton from the latter gives the cyclohexadiene ring and HBr. Two 1,3-hydrogen shifts in the furan moiety completes the four-hydrogen transfer to the side chain giving 3,6-dimethylbenzofuran 87 with a saturated side chain, i.e., an exhaustively hydrogenated acetylene moiety (Scheme 49).

The driving force of this spectacular “hydrogen pump” is the energy gain due to the formation of the aromatic benzofuran system.
Scheme 49. Proposed mechanism for the transfer of four hydrogens.

6. Concluding Remarks and Outlook

This review evidences that the cross-coupling reactions between electrophilic haloacetylenes and electron-rich heterocycles assisted by Al₂O₃ or K₂CO₃ or similar solid oxides and salts continue to be expanded, occupying more and more areas of heterocyclic chemistry. These endeavors are stimulated by such competitive beneficial features of this methodology as transition metal-free, no-solvent, mild conditions, availability of the starting materials, very simple synthetic operations, and possibility to introduce acetylenic substituents with electron-withdrawing groups into a heterocyclic core. Now, these reactions pave a short way to previously inaccessible or unknown, highly reactive heterocyclic building blocks and precursors to create novel heterocyclic systems of greater diversity and complexity.

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