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The work describes a convenient and highly efficient C-H butadiynylation of substituted pyrroles under mild and solvent-free conditions.
Direct Synthesis of Butadiynyl-Substituted Pyrroles under Solvent- and Transition Metal-Free Conditions

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The work describes a convenient and highly efficient C-H butadiynylation of substituted pyrroles with the use of 1-halobutadiynes. The method requires only a simple grinding of substrates in a mortar under mild, solvent- and transition metal-free conditions and constitutes the first example of pyrrole butadiynylation via cross-coupling reaction with the use of 1-halobutadiynes. The scope of this mechanochemical approach covers 4,5,6,7-tetrahydro-1H-indole, its N-substituted derivatives and 2-phenylpyrrole and on the other hand ester and phenyl end-capped 1-halobutadiynes including chlorides, bromides and iodides. Interestingly, the method has proven effective also for weak electron withdrawing aryl substituted 1-halobutadiynes what has not been yet achieved for 1-haloacetylenes. Such reactivity was unexpected in the view of the literature data and opened a gate to the plethora of substrates for organic synthesis including syntheses of pharmaceuticals. An X-ray analysis of two coupling products is also presented.

This approach is solvent-free and requires neither transition metal catalyst nor prior functionalization of a heterocycle unlike known protocols for ethynylation of arenes and heteroarenes. However, it was believed that scope of this reaction is limited only to simple 1-haloacetylenes with strongly electron withdrawing groups (ester and keton) and therefore, the applicability of this method for a direct synthesis of butadiynyl-substituted pyrroles or indoles remained unexplored.

Employed in this protocol 1-haloalkynes are considered as very useful building blocks in organic chemistry and some fundamental works in this field were published in the recent years. The use of 1-halopolyynes in organic synthesis is an important part of their chemistry. Also their solid-state crystal-to-crystal reactions are fascinating, like for instance polymerization of diiododiacetylene and dimerization of 1-bromopolyynes. Moreover 1-halopolyynes are used as substrates in the synthesis of symmetric polyynes, glycosylated polyynes, natural products, as precursors of organometallic polyynes.

In this work we describe the application of pyroles 1a-e and 1-halobutadiynes 2a-d-X (X = Cl or Br or I) as useful precursors of butadiynyl-substituted heterocycles. The scope of the known coupling reaction was extended to butadiynes that possess a great potential for further modification. As far as we know, it is the first example of such coupling with the use of halobutadiynes.

Results and discussion

In the first step, the starting 1-halobutadiynes 2a-d-X were prepared, which - despite their quite simple structures - were not known in the literature. Electron deficient 1-halobutadiynes 2a-e-X were prepared from brominated esters of propionic acid...
via Cadiot-Chodkiewicz cross-coupling with TMSA (TMSA = trimethylsilylacetylene) in the presence of Pd(PPh₃)₄Cl₂/CuI catalytic system and K₂CO₃ as a base as shown in Scheme 1. The use of disopropylamine or triethylamine, which are the most widely used bases for such reactions, did not lead to the desired products. Instead, products of hydroamination or side products of other transformations that were formed in lieu of trimethylsilyl-protected butadiynes were observed. The compound 3a was known in the literature, but it was obtained via modified synthetic pathway.²⁶

![Scheme 1. Synthesis of 1-halobutadiynes 2a-d-X (X = Cl or Br or I).](image)

Next, the reaction of 4,5,6,7-tetrahydroindole (1a) with 1-bromobutadiyne 2b-Br has been chosen as a test for the pyrrole functionalization (general reaction is shown in Scheme 2). It was first carried out under mild conditions (room temperature, 1 h) by grinding of the reactants with solid Al₂O₃ without a solvent, under aerobic conditions and with no transition metal compounds. Although the desired 1-(pyrrole-2-yl)butadiyne 4ab was obtained, the reaction under these conditions appeared non-chemoselective and other by-products (most presumably a reaction intermediate ethyl 5-bromo-5-(4,5,6,7-tetrahydro-1H-indol-2-yl)pent-4-en-2-ynoate and/or side product ethyl 5,5-bis(4,5,6,7-tetrahydro-1H-indol-2-yl)pent-4-en-2-ynoate) were detected along with the main product. Then, K₂CO₃ was used as a solid base and in this case solely 4ab was detected.²⁷ Consequently, K₂CO₃ was used for further reactions. The reaction course (conversion of reactants) was determined from the integral intensity ratio of compounds in the reaction mixture (¹H NMR data).

<table>
<thead>
<tr>
<th>Reaction time, h</th>
<th>Substrate</th>
<th>Product 4ac</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2.18</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2.28</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2.81</td>
</tr>
</tbody>
</table>

Next, the influence of halogen type on the coupling reaction was tested. In this regard, the reaction times for cross-coupling of chloride 2b-Cl, bromide 2b-Br, and iodide 2b-I with tetrahydroindole 1a were similar and the reactions were completed after 1 h in all cases. However, in case of the reaction of tetrahydroindole 1a with 1-halobutadiynes 2c-Br and 2c-I (the chloride derivative for 2c appeared unstable), the former reacted significantly faster than the iodide 2c-I (see Table 1). Moreover the reactions for benzyl derivatives (2c-Br, 2c-I) were slower than those for ethyl derivatives (2b-X). With all that in mind, we decided to test the scope of the coupling reactions with the use of bromides. The ethynylation reaction was performed for the series of 4,5,6,7-tetrahydroindoles 1a-d with the use of 1-halobutadiynes as presented in Table 2. Products were obtained with yields ranging from 43% to 80% with reaction time up to 5 h. No clear correlation between the type of R¹ and R² groups and the resulting yields was found. Purification procedure was very simple, reaction mixtures were placed at the top of the short silica gel plug and only elution by appropriate eluent was needed to obtain pure products. The coupling procedure worked well for – on the one hand unsubstituted and methyl-, benzyl- and vinyl-substituted 4,5,6,7-tetrahydroindoles and - on the other hand - for methyl, ethyl and benzyl butadiynoates. All compounds were fully characterized by ¹H and ¹³C NMR spectroscopy and HRMS (see Supporting Information) In all cases the signals of the carbon atoms from unsaturated C₄ chains could be...
unambiguously identified and were positioned at typical shifts characteristic for butadiynes.

Table 2. Products of reaction of 4,5,6,7-tetrahydroindoles 1a-d with 1-bromobutadiynes 2a-c-Br.

<table>
<thead>
<tr>
<th>R'</th>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1a</td>
<td>69%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>1b</td>
<td>77%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>1c</td>
<td>64%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1d</td>
<td>56%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1e</td>
<td>56%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1f</td>
<td>56%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1g</td>
<td>56%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1h</td>
<td>56%</td>
</tr>
</tbody>
</table>

In the next thrust, reactions of 1-bromobutadiynes 2a-c-Br with 2-phenylpyrrole (1e) were carried out. Here the reactions were significantly slower (reaction times considerably increased to 24 h) and moreover an additional portion of butadiyne (1 equiv) after ca. 7 hours was required. With this modification the reaction yields reached 46-52% range (Scheme 3). Next, we performed a test reaction between 2a-Br and 2-propyl-3-ethylpyrrole (1f) to confirm that the reaction scope is not only limited to fused tetrahydroindoles. Product 4fa was obtained with 55% yield. Moreover, we have noticed that the reaction with simple unsubstituted pyrrole does not occur (only traces of 2-substituted products were observed) and it was impossible to retrieve clean, desired products.

Next, the influence of the phenyl spacer situated between the butadiyne fragment and an ester group on the coupling reaction was explored. The cross-coupling reactions between tetrahydroindoles 1a-d and 1-halobutadiynes 2d-Cl and 2d-Br were performed as shown in Scheme 4. The reactions of 2d-Br with 1b-d gave products 4bd-dd with good 48-58% yields. We noticed that 2d-Br reacted with 1a very slowly (5 days) giving desired product with low yield (17%). Therefore reaction between chloride 2d-Cl and 1a was performed and the product 4ad was obtained with higher yield (36%). What is noteworthy, in each case the reaction time was longer (24 h) than for 1-halobutadiynes 2a-c-X proving that the phenyl spacer reduces reactivity of 1-halobutadiynes. For both 2d-Cl and 2d-Br, their reactions with 2-phenylpyrrole 1e did not occur. Nevertheless, these are the first examples of butadiynylation via pyrroles with the use of arylbutadiynes. This example is even more valuable since such coupling did not occur for substituted 1-halophenylacetylene.

A reaction mechanism for the coupling between simple 1-haloalkynes and pyrroles was previously proposed. ESR studies confirmed that the first step of the reaction is the formation of ion-radicals pair via single electron transfer. Proposed mechanism based on earlier work is shown in Scheme 5.

Single crystals suitable for X-ray analysis were obtained from compounds 4aa and 4bb by slow evaporation of their hexanes/CHCl2 solution. Each of the two compounds...
crystallize in triclinic system, \( P\ \bar{T}\) space group with \( Z = 2\) (for further details see Supporting Information). Solid-state structures were solved and refined with the use of SHELX package\(^{12}\) and molecular structures of 4aa and 4bb are shown in Figure 1.

![Molecular structures of 4aa and 4bb](image)

**Figure 1.** Molecular structures of 4aa and 4bb. Thermal ellipsoids are given at the 50% probability level.

In both cases 5-(pyrrol-2-yl)penta-2,4-diynoic moiety adopts a nearly planar geometry. The C1-C6 carbon chain adapts a geometry which is only slightly distorted from linearity. There is no significant difference between the conformation of 4aa and 4bb. The bond distances in the linear carbon chain are typical for conjugated butadiynes (for packing analysis and selected bond lengths see the Supporting Information). Interestingly, solid state structures of butadiyne-substituted pyrroles are extremely rare and only a few examples with such moiety incorporated in the macrocycle skeleton are known.

**Conclusions**

In conclusion, we have for the first time presented the successful use of 1-halobutadiynes in the cross-coupling reaction with pyrroles. Pyrroles undergo cross-coupling reaction with electron deficient butadiynes on active surface of K$_2$CO$_3$ after a simple grinding in a mortar. This versatile protocol allows to perform the reaction at room temperature under solvent-free conditions and in the presence of moisture and air. The scope of the reactions includes unsubstituted and N-substituted 4,5,6,7-tetrahydroindoles, 2-phenylpyrrole and 1-halobutadiynes with an ester and phenyl end-groups. X-ray analysis of two coupling products expanded structural information about nearly structurally unknown butadiyne-substituted pyrroles.

The resulting coupling products seem to be valuable substrates for new oligoheterocycles. We are certain that this protocol may be used for longer polyynes and it will open a gate to more complex molecules. Our present work focuses on the use of longer 1-halopolyynes in the coupling reaction. Moreover the use of compounds with less electron withdrawing groups shows that the scope of this reaction may be easily expanded in the future.

**Experimental section**

**General**

All moisture- and air-sensitive reaction were conducted under \( \text{N}_2 \) with the use of standard Schlenk techniques. Other reactions were carried out in the presence of air. Glassware was pre-dried at 120 °C. Solvents were treated as follows: THF was distilled from Na/benzophenone, CH$_3$CN (HPLC grade), hexane (HPLC grade), DCM (pure per analysis), diethyl ether (pure per analysis) were used as received.

$^1$H and $^{13}$C NMR spectra were recorded on 500 MHz spectrometer with an inverse broadband probe. For the $^1$H NMR spectra, chemical shifts in chloroform-$d$ and benzene-$d_6$ were reported in the scale relative to the solvent residual peak (7.26 ppm for CDCl$_3$ and 7.16 for C$_6$D$_6$). For the $^{13}$C NMR spectra, chemical shifts were reported in the scale relative to chloroform-$d$ (77.2 ppm) or benzene-$d_6$ (128.1 ppm). HRMS spectra were recorded using spectrometer with TOF mass analyzer and ESI ion source. Melting points are not corrected.

**Synthesis of starting 1-halobutadiynes**

**General Procedure for Cadiot-Chodkiewicz cross-coupling of propionic acid esters:**

A 3-bromopropionate (1 equivalent) was dissolved in THF (30 mL) under N$_2$ atmosphere. Next Pd(PPh$_3$)$_2$Cl$_2$ (0.02 equivalents), Cul (0.04 equivalents) and K$_2$CO$_3$ (2.5 equivalents) were added and the mixture was degassed using freeze-pump-thaw technique. Next trimethylsilylacetylene (1.5 equivalents) was added and the mixture was stirred for 1.5-24 h at room temperature. After this time precipitate was filtered off and solvent was removed under reduced pressure. Product was purified using silica gel column chromatography (hexanes/DCM, v/v, 1/2) yielding products as colorless oils.

**Methyl 5-(trimethylsilyl)penta-2,4-diynoate (3a)**

Yield: 2.855 g, (15.48 mmol), 44%. $^1$H NMR (500 MHz, CDCl$_3$): \( \delta_H 3.79\) (s, 3H), 0.23 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$): \( \delta_C\ 153.3, 94.8, 85.7, 71.3, 66.6, 53.2, -0.6 \) HRMS(ESI); $m/z$ calc for C$_9$H$_{13}$SiO$_2$: 181.0685 [M+H$^+$]; found: 181.0679.

**Ethyl 5-(trimethylsilyl)penta-2,4-diynoate (3b)**

Yield: 1.054 g (5.425 mmol), 44%. $^1$H NMR (500 MHz, CDCl$_3$): \( \delta_H 4.24\) (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 0.23 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$): \( \delta_C\ 152.9, 94.6, 85.9, 70.9, 67.0, 62.7, 14.2, -0.6 \) HRMS(ESI); $m/z$ calc for C$_{10}$H$_{14}$SiO$_2$: 217.0655 [M+Na$^+$]; found: 217.0656.

**Benzy 5-(trimethylsilyl)penta-2,4-diynoate (3c)**

Yield: 2.932 g (11.44 mmol), 61%. $^1$H NMR (500 MHz, CDCl$_3$): \( \delta_H 7.40 - 7.33\) (m, 5H), 5.21 (s, 2H), 0.22 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$): \( \delta_C\ 152.6, 134.7, 128.8, 128.3, 128.0, 95.0, 85.8, 71.5, 68.1, 66.7, -0.7 \) HRMS(ESI); $m/z$ calc for C$_{12}$H$_{16}$SiO$_2$Na: 279.0817 [M+Na$^+$]; found: 279.0819.

Please do not adjust margins
A General Procedure for Halogenation of Trimethylsilyl-Protected Butadiynes

A butadiyne (1 equivalent) was dissolved in acetonitrile (20 mL) in a Schlenk flask under N2 atmosphere. Next H2O (2 equivalents), N-halosuccinimide (1.2 equivalents) and AgNO3 (0.3 equivalents)/KFI(1.0 equivalent) or AgI (1.0 equivalent) were added. Flask was wrapped in aluminum foil and the reaction mixture was stirred for 3-24 h. Next the solvent was removed under reduced pressure and the product was purified by passing through short silica gel plug (hexanes/DCM, 1/2, v/v) yielding pure 1-halobutadiyne.

**Ethyl 5-chloropenta-2,4-diyanoate (2b-Cl)**

Yellow oil (51 mg, 0.33 mmol), yield: 20%. 1H NMR (500 MHz, CDCl3): δH = 4.25 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3): δc = 126.6, 122.6, 70.4, 64.2, 64.5, 62.8, 54.0, 14.1. HRMS(ESI): m/z calcd for 157.0051: C10H13ClO3+ [M+H]+; found: 157.0051.

**Benzy1 5-bromopenta-2,4-diyanoate (2a-Br)**

Yellow solid, yield: 489 mg (2.62 mmol) 59% 1H NMR (500 MHz, CDCl3): δH = 7.86 – 7.81 (m, 2H), 7.14 – 7.11 (m, 2H), 4.04 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 9.5 Hz, 3H). 13C NMR (126 MHz, CDCl3): δc = 158.4, 133.0, 131.5, 129.7, 125.6, 77.4, 73.8, 65.9, 61.1, 47.0, 14.2. HRMS(ESI): m/z calcd for C15H13BrO3: 276.9859 [M+H]+; found: 276.9857.

**Cross-Coupling Reactions**

**General Procedure for Cross-Coupling Reactions of 4,5,6,7-Tetrahydroindoles with Penta-2,4-diyanoates**

4,5,6,7-Tetrahydroindole (0.5 mmol) 1a-d and 1-halobutadiyne (0.55 mmol, 10% molar excess) 2a-e-X were ground at room temperature with a 10-fold amount (by weight) of K2CO3 in a mortar for 10 min. The reaction mixture within 10 min turned from yellow to orange-brown. After 5 hours the reaction mixture was placed on the column with silica gel and eluted with mixture of n-hexane and diethyl ether (5/1, v/v) to afford pure 2-(buta-1,3-diylnyl)-4,5,6,7-tetrahydro-1H-indoles 4aa-4dc.

**Methyl 5-(4,5,6,7-tetrahydro-1H-indol-2-yl)pyrano[2,3-b]pyranone (4ba)**

Brown solid, yield: 93 mg (0.39 mmol), 77%; mp 114.5 – 115.4 °C. 1H NMR (CDCl3, 500 MHz): δH = 3.80 (s, 3H), 2.64 (m, 2H), 2.48 (m, 2H), 1.78 – 1.71 (m, 2H). 13C NMR (126 MHz, CDCl3) δc = 153.9, 133.0, 119.8, 119.4, 108.0, 78.7, 76.1, 75.0, 73.2, 52.9, 23.4, 23.1, 22.9, 22.6. HRMS(ESI): m/z calcd for C15H13NO2: 228.1019 [M+H]+; found: 228.1020.

**Methyl 5-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)penta-2,4-diyanoate (4aa)**

Brown solid, yield: 93 mg (0.39 mmol), 77%; mp 114.5 – 115.4 °C. 1H NMR (CDCl3, 500 MHz): δH = 3.48 (s, 3H), 2.39 (m, 2H), 1.97 (m, 2H). 13C NMR (126 MHz, CDCl3) δc = 153.9, 134.8, 118.9, 118.6, 111.2, 78.9, 78.4, 75.9, 73.5, 52.9, 31.1, 23.2, 22.9, 22.8, 22.5. HRMS(ESI): m/z calcd for C15H13NO2: 224.1176 [M+H]+; found: 224.1169.

**Methyl 5-(1-benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)penta-2,4-diyanoate (4ca)**

Brown solid, yield: 101 mg (32 mmol), 64%; mp 114.5 – 115.4 °C. 1H NMR (CDCl3, 500 MHz): δH = 4.84 (s, 1H), 3.80 (s, 1H), 3.50 (s, 3H), 2.53 – 2.50 (m, 2H), 2.47 – 2.45 (m, 2H), 1.85 – 1.80 (m, 2H), 1.73 – 1.69 (m, 2H). 13C NMR (126 MHz, CDCl3) δc = 153.9, 134.8, 118.9, 118.6, 111.2, 78.9, 78.4, 75.9, 73.5, 52.9, 31.1, 23.2, 22.9, 22.8, 22.5. HRMS(ESI): m/z calcd for C15H13NO2: 242.1176 [M+H]+; found: 242.1169.

**Ethyl 4-(chlorobuta-1,3-diylnyl)benzoate (2d-Cl)**

Yellow crystals, yield: 78 mg (0.34 mmol), 69%; mp 115.5 – 116.2 °C. 1H NMR (CDCl3, 500 MHz): δH = 7.14 (s, 1H), 6.94 (s, 1H), 5.28 (s, 1H), 2.48 – 2.45 (m, 2H), 1.83 – 1.78 (m, 2H), 1.76 – 1.71 (m, 2H). 13C NMR (126 MHz, CDCl3) δc = 133.0, 119.4, 108.0, 78.7, 76.1, 75.0, 73.2, 52.9, 23.4, 23.1, 22.9, 22.6. HRMS(ESI): m/z calcd for C15H13BrO2: 318.1489 [M+H]+; found: 318.1491.
Benzyl 5-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)penta-2,4-diynoate (4bc)
Brown solid, yield: 98 mg (0.31 mmol), 62%; mp 83.0 – 84.3 °C. 1H NMR (CDCl3, 500 MHz): δH 7.39-7.35 (m, 5H, Ph), 6.48 (s, 1H), 5.23 (s, 2H), 3.49 (s, 3H), 2.53-2.50 (m, 2H), 2.47-2.45 (m, 2H), 1.85-1.81 (m, 2H), 1.73-1.69 (m, 2H). 13C NMR (126 MHz, CDCl3): δC 153.3, 134.9, 134.8, 128.7, 128.6, 119.0, 118.6, 111.2, 70.9, 78.0, 76.0, 73.8, 67.8, 31.1, 23.2, 22.9, 22.8, 22.5. HRMS(ESI): m/z calcd for C29H25NO2: 430.1308 [M+Na]+; found: 430.1304.

Benzyl 5-(1-benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)penta-2,4-diynoate (4ce)
Brown oil, yield: 157 mg (0.40 mmol), 80%; 1H NMR (CDCl3, 500 MHz): δH 7.38-7.37 (m, 4H), 7.32-7.30 (m, 3H), 7.27-7.25 (m, 1H), 7.03-7.02 (m, 2H), 6.56 (s, 1H), 5.21 (s, 2H), 5.08 (s, 2H), 2.49-2.47 (m, 2H), 2.41-2.39 (m, 2H), 1.78-1.73 (m, 2H), 1.70-1.66 (m, 2H). 13C NMR (126 MHz, CDCl3): δC 153.2, 137.2, 134.8, 134.7, 128.8, 128.7, 128.6, 128.5, 121.7, 120.6, 110.5, 104.2, 79.0, 78.0, 75.8, 73.2, 67.8, 48.3, 23.1, 22.9, 22.7, 22.6. HRMS(ESI): m/z calcd for C29H25NO2: 416.1621 [M+Na]+; found: 416.1629.

Benzyl 5-(1-vinyl-4,5,6,7-tetrahydro-1H-indol-2-yl)penta-2,4-diynoate (4dc)
Brown oil, yield: 71 mg (0.22 mmol), 43%; 1H NMR (CDCl3, 500 MHz): δH 7.39-7.38 (m, 5H), 6.86 (dd, J = 16.0, 9.3 Hz, 1H), 6.37 (s, 1H), 5.38 (dd, J = 16.0, 1.2 Hz, 1H), 5.24 (s, 2H), 4.94 (dd, J = 9.3, 1.2 Hz, 1H), 2.64-2.62 (m, 2H), 2.48-2.46 (m, 2H), 1.85-1.80 (m, 2H), 1.74-1.70 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3): δC 153.1, 134.8, 134.1, 129.7, 128.7, 128.6, 128.5, 121.7, 120.6, 110.5, 104.2, 79.0, 78.0, 75.8, 73.2, 67.8, 24.0, 23.0, 22.9, 22.8, 22.5. HRMS(ESI): m/z calcd for C29H25NO2: 352.1308 [M+Na]+; found: 352.1302.

General Procedure for Cross-Coupling Reactions of 2-Phenylpyrrole with Penta-2,4-diynoates
2-Phenylpyrrole (0.5 mmol) 1e and 1-halobutadiyne (0.5 mmol) 2a-c-Br were grinded at room temperature with a 10-fold amount (by weight) of K2CO3 in a mortar for 10 min. The reaction mixture within 10 min turned from yellow to brown. After 7 hours, another portion of 1-halobutadiyne (0.5 mmol) was added and the reaction mixture allowed to stay for 18 hours. Then, the reaction mixture was placed on the column with silica gel and eluted with mixture of hexanes and diethyl ether (5/1; v/v) to afford pure 5-(buta-1,3-diylnyl)-2-phenylpyroles 4ea-ec.

Methyl 5-(5-phenyl-1H-pyrrol-2-yl)penta-2,4-diynoate (4ea)
Yellow solid, yield: 57 mg (0.23 mmol), 46%; mp 111.8-112.3 °C. 1H NMR (CDCl3, 500 MHz): δH 7.51-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.32-7.29 (m, 1H), 6.81-6.79 (m, 1H), 6.50-6.49 (m, 1H), 3.82 (s, 3H). 13C NMR (126 MHz, CDCl3): δC 153.7, 136.2, 131.0, 129.1, 127.8, 124.6, 122.2, 111.1, 107.8, 77.2, 76.6, 74.9, 72.4, 53.0. HRMS(ESI): m/z calcd for C16H13NO2: 250.0863 [M+H]+; found: 250.0861.

Ethyl 5-(5-phenyl-1H-pyrrol-2-yl)penta-2,4-diynoate (4eb)
Brown oil, yield: 66 mg (0.25 mmol), 50%. 1H NMR (CDCl3, 500 MHz): δH 8.82 (br s, 1H), 7.51–7.50 (m, 2H), 7.42–7.39.
Brown solid, yield: 85 mg (0.26 mmol); mp: 135.0 °C.

C NMR (126 MHz, CDCl3): δC = 7.5 Hz, 3H), 1.68 – 1.70 (m, 3H), 6.48 (s, 1H), 5.13 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3): δC = 7.5, 76.5, 61.2, 48.2, 23.3, 22.9, 22.6, 14.3. HRMS(ESI): m/z calcd for C22H43NO2: 348.0995 [M+Na]+; found: 348.0990.

Methyl 5-[4-ethyl-5-propyl-1H-pyrrol-2-yl]penta-2,4-diynoate (4fa)

3-Propyl-2-ethylpyrrole (220 mg, 1.60 mmol) (1f) and 1-halobutadiyne 2a-Br (300 mg, 1.60 mmol) were grinded at room temperature with 5.20 g of K2CO3 in a mortar for 10 min. After 1 hour the reaction mixture was placed on the column with silica gel and eluted with mixture of n-hexane and diethyl ether (10/1; v/v) to afford pure methyl 5-[4-ethyl-5-propyl-1H-pyrrol-2-yl]penta-2,4-diynoate (4fa) as dark oily crystals (214 mg, 0.880 mmol). Yield 55%.

C NMR (126 MHz, CDCl3): δC = 7.5 Hz, 3H), 1.68 – 1.70 (m, 3H), 6.48 (s, 1H), 5.13 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3): δC = 7.5, 76.5, 61.2, 48.2, 23.3, 22.9, 22.6, 14.3. HRMS(ESI): m/z calcd for C22H43NO2: 348.0995 [M+Na]+; found: 348.0990.

General Procedure for Cross-Coupling Reactions of 4,5,6,7-Tetrahydroindoles with Ethyl 4-(halo-1,3-diyin-1-yl)benzoates

4,5,6,7-Tetrahydroindoles (0.5 mmol) la-d and 1-halobutadiyne (0.5 mmol) (2d-Cl or 2d-Br) were grinded at room temperature with a 10-fold amount (by weight) of K2CO3 in a mortar for 10 min. The reaction mixture within 10 min turned from yellow to orange. After 24 hours the reaction mixture was placed on the column with SiO2 and eluted with system hexanes/diethyl ether (v/v, 5/1) (v/v) to afford pure 2-(buta-1,3-diyinyl)-4,5,6,7-tetrahydro-1H-indoles 4ad-dd. Unless otherwise stated 2d-Br was used in synthesis.

Ethyl 4-[(4,5,6,7-tetrahydro-1H-indol-2-yl)buta-1,3-diyinyl]benzoate (4ad)

From chloride 2d-Cl, Yellow solid, yield: 39 mg (0.12 mmol) 36%; mp: 202.5 – 203.0 °C. 1H NMR (500 MHz, CDCl3): δH = 8.04 – 7.95 (m, 3H, overlapping signals of NH and 2CH=N), 7.56 – 7.50 (m, 2H), 6.41 (d, J = 2.4 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.57 (t, J = 6.2 Hz, 2H), 2.48 (t, J = 6.0 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.78 – 1.71 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3): δC = 166.1, 132.1, 131.5, 130.4, 129.6, 127.0, 119.0, 117.7, 109.4, 82.5, 77.5, 77.1, 76.1, 61.4, 23.6, 23.2, 22.8, 14.4. HRMS(ESI): m/z calcd for C21H19NO2: 318.1489 [M+H]+; found: 318.1491.

Ethyl 4-[(4-ethyl-5-propyl-1H-pyrrol-2-yl)buta-1,3-diyinyl]benzoate (4bd)

Yellow solid, yield: 86 mg (0.25 mmol), 50%; mp: 152.9 – 153.4 °C. 1H NMR (CDCl3, 500 MHz): δH = 3.18 – 3.07 (m, 2H), 2.30 – 2.19 (m, 2H), 2.05 – 2.00 (m, 2H), 1.78 – 1.50 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3): δC = 166.1, 132.1, 131.5, 130.4, 129.6, 127.0, 119.0, 117.7, 109.4, 82.5, 77.5, 77.1, 76.1, 61.4, 23.6, 23.2, 22.8, 14.4. HRMS(ESI): m/z calcd for C21H19NO2: 318.1489 [M+H]+; found: 318.1491.

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