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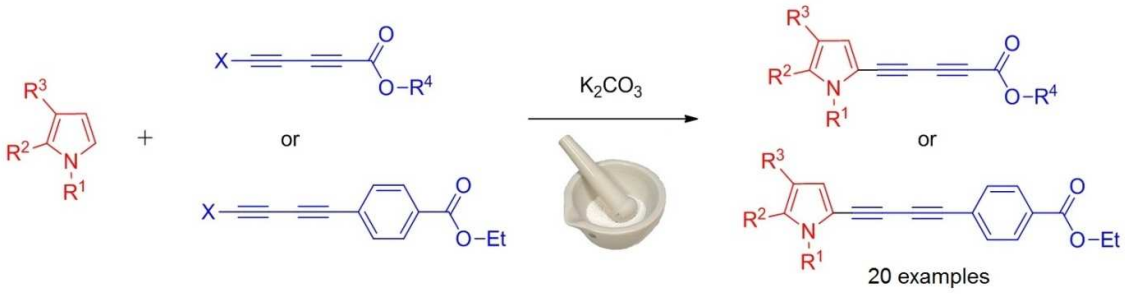

Journal Name

ARTICLE

Direct Synthesis of Butadiynyl-Substituted Pyrroles under Solvent- and Transition Metal-Free Conditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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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-1*H*-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.

Introduction

Substituted pyrroles play a very important role in the chemistry of drugs,[1] organic electronics,[2] and photoluminescence materials.[3] Butadiynyl and, in general, polyyne substituted pyrroles are additionally interesting in the context of a construction of linear polypyrroles which - as tetrapyrroles - form and important class of pigments like phycocyanobilin.[4,5] Such compounds are also important building blocks, which are used in the syntheses of furans,[6] thiophenes,[6c,6e,7] pyrroles,[6a,6e,8] naphthalenes,[9] and other cyclic compounds[10] makes them very useful substrates for novel oligoheterocycles with high application potential.[11] Moreover, butadiynes with pyrrole substituent are used in the synthesis of intriguing class of porphirynoids with C_4 fragment incorporated into a macrocycle skeleton[12] or are present in the modified bilirubins.[4,13] To the best of our knowledge, there are only a few publications concerning effective pathways for the synthesis of butadiynyl-substituted pyrroles and indoles.[14] Among them, there are Sonogashira cross-coupling,[15] acetylene oxidative homocoupling,[12b,16] and elimination of tosyl group.[5] About a decade ago, C-H ethynylation of pyrroles and indoles with the use of 1-haloalkynes and solid Al_2O_3 has been developed.[17] 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 hetero-arenes.[18] 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.[19] 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[20] and dimerization of 1-bromopolyynes.[21] Moreover 1-halopolyynes are used as substrates in the synthesis of symmetric polyynes,[22] glycosylated polyynes,[23] natural products,[24] and as precursors of organometallic polyynes.[25]

In this work we describe the application of pyrroles **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 1-halopolyynes.

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-c**-X were prepared from brominated esters of propiolic acid

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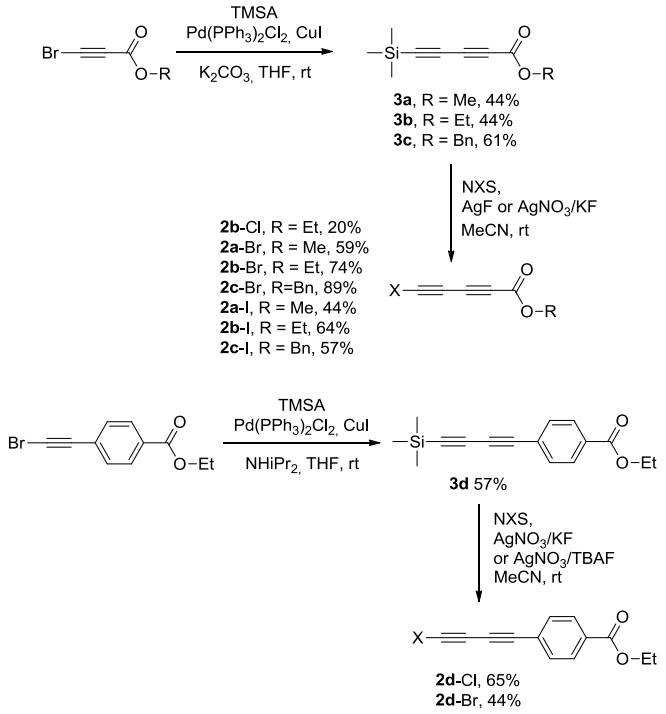
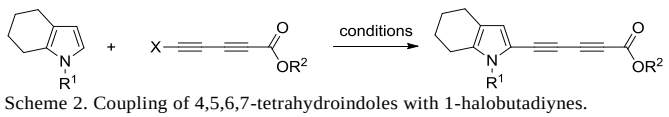
Electronic Supplementary Information (ESI) available: . See DOI: 10.1039/x0xx00000x CCDC 1037921 (**4aa**) and CCDC 1037920 (**4bb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

via Cadiot-Chodkiewicz cross-coupling with TMSA (TMSA = trimethylsilylacetylene) in the presence of $Pd(PPh_3)_2Cl_2$/CuI catalytic system and K_2CO_3 as a base as shown in Scheme 1. The use of diisopropylamine 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).

Next, bromination and iodination reactions were carried out according to the known procedures[27] to give corresponding 1-bromo and 1-iodobutadiynes in good yields. Chlorination presented a greater challenge. The known procedure with the use of NCS (NCS = *N*-chlorosuccinimide), $AgNO_3$ and TBAF (TBAF = tetrabutyloammonium fluoride)[28] led to dichloroenynes instead of 1-chlorobutadiynes. Surprisingly, the use of NCS, $AgNO_3$ and KF gave the desired product **2b**-Cl, whereas previously these conditions were found useless for less active acetylenes. Synthesis of 1-halobutadiynes **2d**-X with phenyl end-group was routine and both Cadiot-Chodkiewicz coupling[29] with the use of diisopropylamine and chlorination with the use of NCS/$AgNO_3$/TBAF system worked well.



Scheme 2. Coupling of 4,5,6,7-tetrahydroindoles with 1-halobutadiynes.

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 Al_2O_3 without any 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 not 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)[17] were detected along with the main product. Then, K_2CO_3 was used as a solid base and in this case solely **4ab** was detected.[30] Consequently, K_2CO_3 was used for further reactions. The reaction course (conversion of reactants) was determined from the ^{1}H NMR spectra of $CDCl_3$ extracts.

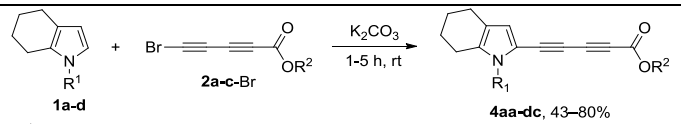
Table 1. The influence of halogen type on reaction rate for benzyl 4-(4-halobuta-1,3-diynyl)benzoate.

Reaction time, h	Integral intensity ratio of compounds in the reaction mixture (^{1}H NMR data)		
	Substrate	Product **4ac**	
	1a	For **2c**-I	For **2c**-Br
1	1	2.18	3.98
2	1	2.28	4.28
3	1	2.81	5.87

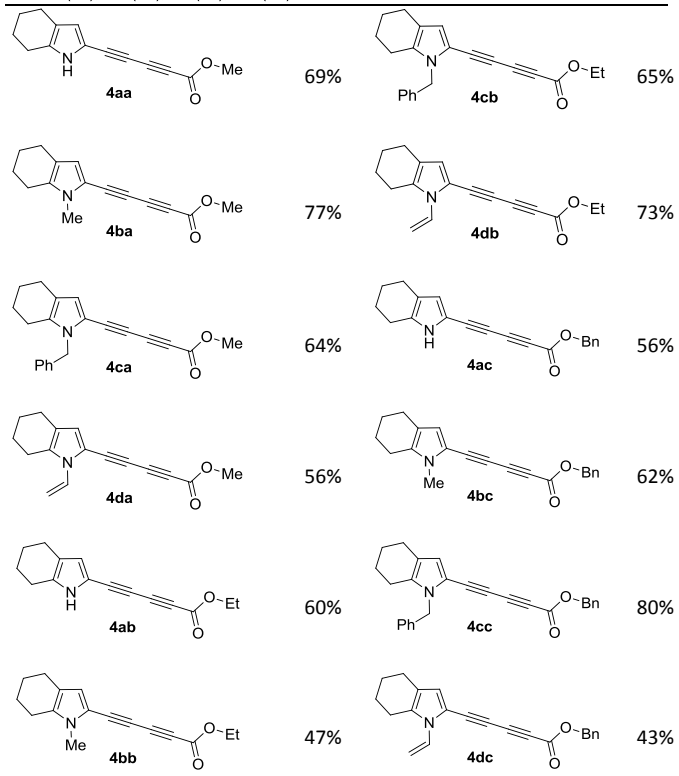
Next, the influence of halogen type on the coupling reaction was tested. In this regard, the reaction times for cross-coupling of chloride **2b**-Cl, bromide **2b**-Br, and iodide **2b**-I with tetrahydroindole **1a** were similar and the reactions were completed after 1 h in all cases. However, in case 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, 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-bromobutadiynes 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 R^1 and R^2 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 ^{1}H and ^{13}C NMR spectroscopy and HRMS (see Supporting Information). In all cases the signals of the carbon atoms from unsaturated C_4 chains could be

unambiguously identified and were positioned at typical shifts characteristic for butadiynes.

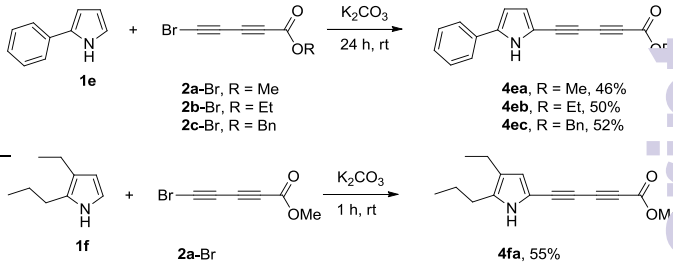
Table 2. Products of reaction of 4,5,6,7-tetrahydroindoles 1a-d with 1-bromobutadiynes 2a-c-Br.



R^1 = H (**1a**), Me (**1b**), Bn (**1c**), Vin (**1d**)

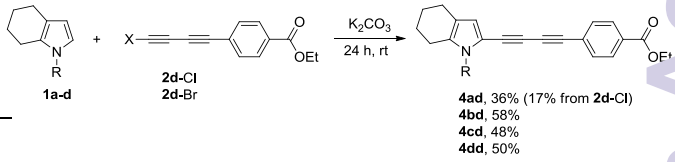


In the next thrust, reactions of 1-bromobutadiynes **2a-c**-Br with 2-phenylpyrrole (**1e**) were carried out. Here the reactions were significantly slower (reaction times considerably increased to 24 h) and moreover an additional portion of butadiyne (1 eqiv) after ca. 7 hours was required. With this 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 occurs (only traces of 2-substituted products were observed) and it was impossible to retrieve clean, desired products.



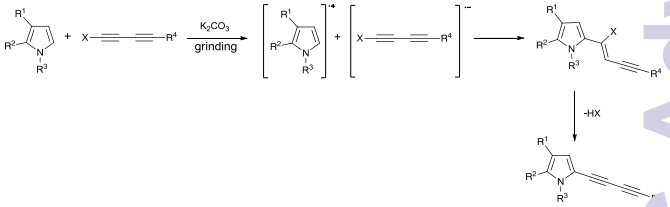
Scheme 3. Coupling reaction between 2-phenylpyrrole (**1e**) and 1-bromobutadiynes **2a-c**-Br and reaction between **1f** and **2a**-Br.

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.



Scheme 4. Cross-coupling reactions of 4,5,6,7-tetrahydroindoles (**1a-d**) with 1-halobutadiynes **2d**-Cl, Br.

A reaction mechanism for the coupling between simple 1-haloalkynes and pyrroles was previously proposed.[31] 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.



Scheme 5. Proposed mechanism for butadiynylation reaction.

Single crystals suitable for X-ray analysis were obtained for compounds **4aa** and **4bb** by slow evaporation of their hexanes/CH_2Cl_2 solution. Each of the two compound

crystallize in triclinic system, P $\bar{1}$ space group with Z = 2 (for further details see Supporting Information). Solid-state structures were solved and refined with the use of SHELX package[32] and molecular structures of **4aa** and **4bb** are shown in Figure 1.

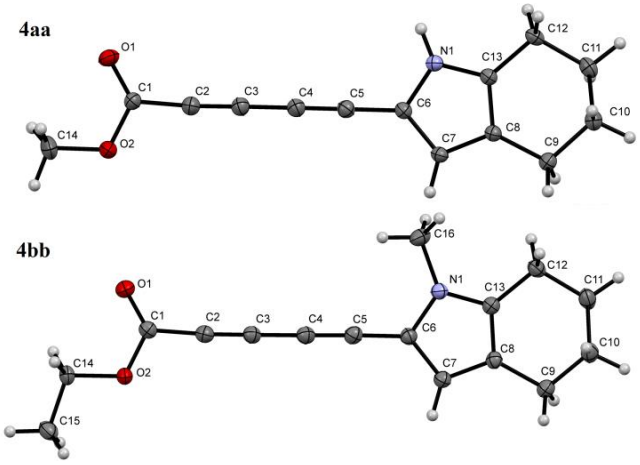


Figure 1. Molecular structures of **4aa** and **4bb**. Thermal ellipsoids are given at the 50% probability level.

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 form 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.[12b,12c]

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_2CO_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 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 ^oC. Solvents were treated as follows: THF was distilled from Na/benzophenone, CH_3CN (HPLC grade), hexane (HPLC grade), DCM (pure per analysis), diethyl ether (pure per analysis) were used as received.

^1H and ^{13}C NMR spectra were recorded on 500 MHz spectrometer with an inverse broadband probe. For the ^1H NMR spectra, chemical shifts in chloroform-*d* and benzene-d_6 were reported in the scale relative to the solvent residual pe (7.26 ppm for $CDCl_3$ and 7.16 for C_6D_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 propiolic acid esters:

A 3-bromopropiolate (1 equivalent) was dissolved in THF (30 mL) under N_2 atmosphere. Next $Pd(PPh_3)_2Cl_2$ (0.02 equivalents), CuI (0.04 equivalents) and K_2CO_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 o 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[26] (3a)

Yield: 2.855 g, (15.48 mmol), 44%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 3.79 (s, 3H), 0.23 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.3, 94.8, 85.7, 71.3, 66.6, 53.2, -0.6. HRMS(ESI): *m/z* calcd for $C_9H_{13}SiO_2$: 181.0685 $[M+H^+]$; found: 181.0679.

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

Yield: 1.054 g (5.425 mmol), 44%. ^1H NMR (500 MHz, $CDCl_3$): δ_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, $CDCl_3$): δ_C 152.9, 94.6, 85.9, 70.9, 67.0, 62.7, 14.2, -0.6. HRMS(ESI): *m/z* calcd for $C_{10}H_{14}SiO_2Na$: 217.0655 $[M+Na^+]$; found: 217.0656.

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

Yield: 2.932 g (11.44 mmol), 61%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.40 – 7.33 (m, 5H), 5.21 (s, 2H), 0.22 (s, 9H). ^{13} NMR (126 MHz, $CDCl_3$): δ_C 152.6, 134.7, 128.8, 128.8, 128. 95.0, 85.8, 71.5, 68.1, 66.7, -0.7. HRMS(ESI): *m/z* calcd fo $C_{15}H_{16}SiO_2Na$: 279.0817 $[M+Na^+]$; found: 279.0819.

A General Pocedure for Halogenation of Trimethylsilyl-Protected Butadiynes

A butadiyne (1 equivalent) was dissolved in acetonitrile (20 mL) in a Schlenk flask under N_2 atmosphere. Next H_2O (2 eqivalents), *N*-halosuccinimide (1.2 equivalents) and $AgNO_3$ (0.3 equivalents)/KF(1.0 equivalent) or AgF (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-diynoate (2b-Cl)

Yellow oil (51 mg, 0.33 mmol), yield: 20%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.25 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.6, 70.4, 64.8, 64.5, 62.8, 54.0, 14.1. HRMS(ESI): *m/z* calcd for 157.0051; $C_7H_6ClO_2$: [M+H$^+$]; found: 157.0051.

Methyl 5-bromopenta-2,4-diynoate (2a-Br)

Yellow solid, yield: 489 mg (2.62 mmol) 59% ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.9, 71.3, 64.1, 64.0, 53.3, 48.8. HRMS(ESI): *m/z* calcd for 186.9389; $C_6H_4BrO_2$: [M+H$^+$]; found: 186.9389.

Ethyl 5-bromopenta-2,4-diynoate (2b-Br)

Yellow oil, yield: 374 mg (1.86 mmol) 74% ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.25 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.6, 70.9, 64.5, 64.1, 62.8, 48.6, 14.1. HRMS(ESI): *m/z* calcd for 200.9546; $C_7H_6BrO_2$: [M+H$^+$]; found: 200.9547.

Benzyl 5-bromopenta-2,4-diynoate (2c-Br)

Yellow solid, yield: 592 mg (2.25 mmol), 89%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.43 – 7.34 (m, 5H), 5.21 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.3, 134.6, 128.9, 128.9, 128.7, 71.5, 68.3, 64.1, 64.0, 48.9. HRMS(ESI): *m/z* calcd for $C_{12}H_7O_2BrNa$: 284.9527 [M+Na$^+$]; found: 284.9514.

Methyl 5-iodopenta-2,4-diynoate (2a-I)

Yellow solid, yield: 119 mg (0.258 mmol), 44%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.8, 77.0, 71.6, 63.6, 53.3, 9.1. HRMS(ESI): *m/z* calcd for $C_6H_4O_2I$: 234.9256 [M+H$^+$]; found: 234.9251.

Ethyl 5-iodopenta-2,4-diynoate (2b-I)

Brown solid, yield: 342 mg (1.38 mmol), 64%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.24 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.4, 77.1, 71.3, 64.0, 62.8, 14.1, 8.9. HRMS(ESI): *m/z* calcd for $C_7H_6O_2I$: 248.9412 [M+H$^+$]; found: 248.9416.

Benzyl 5-iodopenta-2,4-diynoate (2c-I)

Yellow solid, yield: 125 mg (0.272 mmol), 57%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.41 – 7.31 (m, 5H), 5.21 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 152.2, 134.6, 128.9, 128.8, 128.7, 77.0, 71.9, 68.3, 63.6, 9.3. HRMS(ESI): *m/z* calcd for $C_{12}H_7O_2INa$: 332.9389 [M+Na$^+$]; found: 332.9388.

Ethyl 4-(chlorobuta-1,3-diyn-1-yl)benzoate (2d-Cl)

Ethyl 4-(chlorobuta-1,3-diyn-1-yl)benzoate was obtained according to the known procedure.[29] White solid, yield: 157 mg (0.661 mmol), 65%. ^{1}H NMR (500 MHz, C_6D_6): δ_H 7.76 – 7.73 (m, 2H), 7.05 – 7.03 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6): δ_C 165.3, 133.0, 131.5, 129.8, 125.6, 76.6, 74.1, 63.4, 61.1, 55.8, 14.2. HRMS(ESI): *m/z* calcd for $C_{13}H_9ClO_2$: 255. 0183 [M+Na$^+$]; found: 255.0188.

Ethyl 4-(bromobuta-1,3-diyn-1-yl)benzoate (2d-Br)

Yellow solid (210 mg, 0.757 mmol), yield: 44%. ^{1}H NMR (500 MHz, C_6D_6): δ_H 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). ^{13}C NMR (126 MHz, C_6D_6): δ_C 165.4, 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 $C_{13}H_9BrO_2$: 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-diynoates

4,5,6,7-Tetrahydroindole (0.5 mmol) **1a-d** and 1-halobutadiyne (0.55 mmol, 10% molar excess) **2a-c**-X were grinded at room temperature with a 10-fold amount (by weight) of K_2CO_3 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-diynyl)-4,5,6,7-tetrahydro-1*H*-indoles **4aa-dc**.

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

Yellow crystals, yield: 78 mg (0.34 mmol), 69%; mp 115.5 – 116.2 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.08 (br s, 1H), 6.49 (s, 1H), 3.80 (s, 3H), 2.58–2.56 (m, 2H), 2.48–2.45 (m, 2H), 1.83–1.78 (m, 2H), 1.76–1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 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 $C_{14}H_{13}NO_2$: 228.1019 [M+H$^+$]; found: 228.1020.

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

Brown solid, yield: 93 mg (0.39 mmol), 77%; mp 114.5 – 115.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 6.48 (s, 1H), 3.80 (s, 3H), 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 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 $C_{15}H_{15}NO_2$: 242.1176 [M+H$^+$]; found: 242.1169.

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

Brown oil, yield: 101 mg (32 mmol), 64%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.33–7.30 (m, 2H), 7.27–7.24 (m, 1H), 7.04–7.03 (m, 2H), 6.57 (s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 2.49–2.47 (m, 2H), 2.41–2.39 (m, 2H), 1.78–1.74 (m, 2H), 1.71–1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 153.8, 137.3, 134.7, 128.8, 127.5, 126.6, 119.6, 119.2, 111.3, 78.9, 78.3, 75.8, 73.4, 52.8, 48.3, 23.2, 22.9, 22.7, 22.6. HRMS(ESI): *m/z* calcd for $C_{21}H_{19}NO_2$: 318.1489 [M+H$^+$]; found: 318.1489.

Methyl 5-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4da)

Yellow crystals, yield: 71 mg (0.28 mmol), 56%; mp 69.2 – 71.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 6.86 (dd, *J* = 16.0, 9.3 Hz, 1H), 6.57 (s, 1H), 5.38 (dd, *J* = 16.0, 1.2 Hz, 1H), 4.94 (dd, *J* = 9.3, 1.2 Hz, 1H), 3.80 (s, 3H), 2.64–2.62 (m, 2H), 2.48–2.45

(m, 2H), 1.85–1.80 (m, 2H), 1.74–1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 152.7, 133.0, 128.7, 120.6, 119.5, 109.5, 103.1, 77.9, 76.8, 74.6, 71.9, 51.9, 22.9, 21.9, 21.8, 21.78. HRMS(ESI): *m/z* calcd for $C_{16}H_{15}NO_2$: 254.1176 [M+H$^+$]; found: 254.1174.

Ethyl 5-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4ab)

Light yellow crystals, yield: 72 mg (0.30 mmol), 60%; mp 113.7 – 115.1. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.10 (br s, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.58–2.56 (m, 2H), 2.48–2.46 (m, 2H), 1.83–1.79 (m, 2H), 1.76–1.71 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 153.5, 132.9, 119.7, 119.4, 108.1, 78.5, 76.1, 75.3, 72.7, 62.2, 23.4, 23.1, 22.9, 22.6, 14.1. HRMS(ESI): *m/z* calcd for $C_{15}H_{15}NO_2$: 242.1176 [M+H$^+$]; found: 242.1177.

Ethyl 5-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4bb)

Yellow crystals, yield: 60 mg (0.24 mmol), 47%, mp 115.1 - 115.9 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 6.47 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.50 (s, 3H), 2.53–2.50 (m, 2H), 2.47–2.44 (m, 2H), 1.85–1.80 (m, 2H), 1.73–1.68 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.5, 134.7, 118.9, 118.5, 111.2, 78.9, 78.2, 76.2, 73.0, 62.2, 31.1, 23.2, 22.9, 22.8, 22.5, 14.1. HRMS(ESI): *m/z* calcd for $C_{16}H_{17}NO_2$: 256.1332 [M+H$^+$]; found: 256.1336.

Ethyl 5-(1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4cb)

Brown solid, yield: 108 mg (0.33 mmol), 65%; mp 75.9 – 76.5 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.33–7.30 (m, 2H), 7.27–7.24 (m, 1H), 7.04–7.02 (m, 2H), 6.56 (s, 1H), 5.09 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.49–2.47 (m, 2H), 2.41–2.39 (m, 2H), 1.77–1.73 (m, 2H), 1.71–1.66 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 153.4, 137.2, 134.6, 128.8, 127.5, 126.5, 119.5, 119.2, 119.0, 111.4, 78.9, 78.1, 76.1, 72.9, 62.2, 48.3, 23.1, 22.9, 22.7, 22.6, 14.1. HRMS(ESI): *m/z* calcd for $C_{22}H_{21}NO_2$: 332.1645 [M+H$^+$]; found: 332.1645.

Ethyl 5-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4db)

Brown solid, yield: 97 mg (0.34 mmol), 73%; mp 69.9 – 70.6 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 6.86 (dd, *J* = 16.0, 9.3 Hz, 1H), 6.56 (s, 1H), 5.38 (dd, *J* = 16.0, 1.2 Hz, 1H), 4.93 (dd, *J* = 9.3, 1.2 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.64–2.62 (m, 2H), 2.48–2.45 (m, 2H), 1.84–1.80 (m, 2H), 1.74–1.70 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.3, 133.9, 129.7, 121.5, 120.5, 110.6, 104.1, 78.9, 77.6, 75.9, 62.3, 24.0, 23.0, 22.9, 22.8, 14.1. HRMS(ESI): *m/z* calcd for $C_{17}H_{17}NO_2$: 268.1332 [M+H$^+$]; found: 268.1332.

Benzyl 5-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4ac)

Brown solid, yield: 85 mg (0.28 mmol), 56%; 133.9 – 134.7 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.08 (br s, 1H), 7.38–7.34 (m, 5H), 6.49 (d, *J* = 2.4 Hz, 1H), 5.22 (s, 2H, CH_2), 2.58–2.55 (m, 2H), 2.48–2.45 (m, 2H), 1.83–1.79 (m, 2H), 1.75–1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.2, 134.9, 133.1, 128.7, 128.6, 128.5, 119.9, 119.5, 108.0, 78.9, 76.2, 75.1, 73.5, 67.8, 23.4, 23.1, 22.9, 22.6. HRMS(ESI): *m/z* calcd for $C_{20}H_{17}NO_2$: 326.1152 [M+Na$^+$]; found: 326.1154.

Benzyl 5-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4bc)

Brown solid, yield: 98 mg (0.31 mmol), 62%; mp 83.0 – 84.3 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.3, 134.9, 134.8, 128.7, 128.6, 128.5, 119.0, 118.6, 111.2, 79.0, 78.6, 76.0, 73.8, 67.8, 31.1, 23.2, 22.9, 22.8, 22.5. HRMS(ESI): *m/z* calcd for $C_{21}H_{19}NO_2$: 340.1308 [M+Na$^+$]; found: 340.1304.

Benzyl 5-(1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4cc)

Brown oil, yield: 157 mg (0.40 mmol), 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.2, 137.2, 134.8, 134.7, 128.8, 128.7, 128.6, 128.5, 126.5, 119.6, 119.3, 111.3, 79.0, 78.5, 76.0, 73.6, 67.8, 48.3, 23.1, 22.9, 22.7, 22.6. HRMS(ESI): *m/z* calcd for $C_{27}H_{23}NO_2$: 416.1621 [M+Na$^+$]; found: 416.1629.

Benzyl 5-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)penta-2,4-diynoate (4dc)

Brown oil, yield: 71 mg (0.22 mmol), 43%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.39–7.38 (m, 5H), 6.86 (dd, *J* = 16.0, 9.3 Hz, 1H), 6.57 (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), 1.75–1.60 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 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. HRMS(ESI): *m/z* calcd for $C_{22}H_{19}NO_2$: 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 K_2CO_3 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-diynyl)-2-phenylpyrroles **4ea-ec**.

Methyl 5-(5-phenyl-1*H*-pyrrol-2-yl)penta-2,4-diynoate (4ea)

Yellow solid, yield: 57 mg (0.23 mmol), 46%; mp 111.8 – 112.3 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.76 (br s, 1H), 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 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 $C_{16}H_{12}NO_2$: 250.0863 [M+H$^+$]; found: 250.0861.

Ethyl 5-(5-phenyl-1*H*-pyrrol-2-yl)penta-2,4-diynoate (4eb)

Brown oil, yield: 66 mg (0.25 mmol), 50%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.82 (br s, 1H), 7.51–7.50 (m, 2H), 7.42–7.39

(m, 2H), 7.31–7.28 (m, 1H), 6.80–6.79 (m, 1H), 6.50–6.49 (1H, m), 4.28 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.3, 136.2, 131.0, 129.1, 127.8, 124.6, 122.2, 111.1, 107.7, 77.2, 76.6, 75.2, 72.1, 62.5, 14.1. HRMS(ESI): *m/z* calcd for $C_{17}H_{13}NO_2$: 264.1019 [M+H$^+$]; found: 264.1013.

Benzyl 5-(5-phenyl-1*H*-pyrrol-2-yl)penta-2,4-diynoate (4ec)

Brown solid, yield: 85 mg (0.26 mmol), 52%; mp 135.0 – 136.1 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.75 (br s, 1H), 7.50–7.49 (m, 2H), 7.42–7.35 (m, 7H), 7.31–7.28 (m, 1H), 6.80–6.79 (m, 1H), 6.50–6.49 (m, 1H), 5.24 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 153.1, 136.3, 134.7, 131.0, 129.1, 128.7, 128.6, 127.8, 124.6, 122.3, 111.1, 107.8, 77.5, 76.7, 75.0, 72.7, 67.0. HRMS(ESI): *m/z* calcd for $C_{22}H_{15}NO_2$: 348.0995 [M+Na$^+$]; found: 348.0990.

Methyl 5-(4-ethyl-5-propyl-1*H*-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 K_2CO_3 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-1*H*-pyrrol-2-yl)penta-2,4-diynoate **4fa** as dark oily crystals (214 mg, 0.880 mmol). Yield 55%. ^{1}H NMR ($CDCl_3$. 400 MHz) δ_H 8.17 (s, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.68 – 1.49 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.0, 134.1, 124.1, 120.9, 107.6, 78.8, 76.2, 75.2, 73.4, 52.9, 28.2, 22.9, 18.9, 15.4, 13.9.

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

4,5,6,7-Tetrahydroindoles (0.5 mmol) **1a-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 K_2CO_3 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 SiO_2 and eluted with system hexanes/diethyl ether (v/v, 5/1) to afford pure 2-(buta-1,3-diynyl)-4,5,6,7-tetrahydro-1*H*-indoles **4ad-dd**. Unless otherwise stated **2d**-Br was used in synthesis.

Ethyl 4-((4,5,6,7-tetrahydro-1*H*-indol-2-yl)buta-1,3-diynyl)benzoate (4ad)

From chloride **2d**-Cl, Yellow solid, yield: 39 mg (0.12 mmol) 36%; mp 202.5 – 203.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.04 – 7.95 (m, 3H, overlapping signals of N*H* and 2xCH_{Ar}), 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 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, 23.1, 22.8, 14.4. HRMS(ESI): *m/z* calcd for $C_{21}H_{19}NO_2$: 318.1489 [M+H$^+$]; found: 318.1491.

Ethyl 4-((1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)buta-1,3-diynyl)benzoate (4bd)

Yellow crystals, yield: 96 mg (0.29 mmol), 58%; mp 148.4 – 149.0 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.00–7.99 (m, 2H), 7.55–7.53 (m, 2H), 6.40 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.53 (s, 3H), 2.54–2.51 (m, 2H), 2.48–2.46 (m, 2H), 1.86–1.81 (m, 2H), 1.74–1.70 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 159.9, 132.0, 131.9, 130.2, 129.5, 126.9, 118.3, 116.4, 112.3, 83.0, 78.7, 77.6, 76.5, 61.2, 31.0, 23.4, 22.9, 22.9 (coincided), 22.4, 14.3. HRMS(ESI): *m/z* calcd for $C_{22}H_{22}NO_2$: 332.1645 [M+Na$^+$]; found: 332.1641.

Ethyl 4-((1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)buta-1,3-diynyl)benzoate (4cd)

Yellow crystals, yield: 98 mg (0.24 mmol), 48%; mp 74.7 – 75.7 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.99–7.97 (m, 2H), 7.52–7.51 (m, 2H), 7.34–7.32 (m, 2H), 7.27–7.24 (m, 1H), 7.09–7.08 (m, 2H), 6.48 (s, 1H), 5.13 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.50–2.48 (m, 2H), 2.40–2.37 (m, 2H), 1.78–1.73 (m, 2H), 1.71–1.66 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 165.9, 137.8, 132.9, 131.9, 130.2, 129.0, 128.7, 127.4, 126.9, 126.7, 119.0, 116.9, 112.5, 83.0, 78.7, 77.5, 76.5, 61.2, 48.2, 23.3, 23.0, 22.9, 22.6, 14.3. HRMS(ESI): *m/z* calcd for $C_{28}H_{26}NO_2$: 408.1958 [M+Na$^+$]; found: 408.1949.

Ethyl 4-((1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)buta-1,3-diynyl)benzoate (4dd)

Yellow solid, yield: 86 mg (0.25 mmol), 50%; mp 152.9 – 153.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.01–7.99 (m, 2H), 7.56–7.54 (m, 2H), 6.95 (dd, *J* = 16.0, 9.4 Hz, 1H), 6.48 (s, 1H), 5.40 (dd, *J* = 16.0, 1.1 Hz, 1H), 4.91 (dd, *J* = 9.3, 1.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.66–2.64 (m, 2H), 2.49–2.46 (m, 2H), 1.85–1.80 (m, 2H), 1.75–1.70 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 165.9, 132.3, 132.0, 130.3, 130.1, 129.5, 126.7, 120.2, 119.3, 111.8, 103.0, 83.2, 79.1, 77.3, 76.1, 61.2, 24.1, 23.1, 23.0, 22.9, 14.3. HRMS(ESI): *m/z* calcd for $C_{23}H_{22}NO_2$: 344.1645 [M+Na$^+$]; found: 344.1627.

ACKNOWLEDGMENTS

The work was supported by the National Science Centre Poland (Grant numbers: UMO-2012/05/N/ST5/00665 and UMO-2013/08/M/ST5/00942) and Russian Foundation of Basic Research (Project No 14-03-32042).

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