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One-pot synthesis of unsymmetrical 1,3-butadiyne derivatives and their application in the synthesis of unsymmetrical 2,5-diarylthiophenes

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Abstract: A novel one-pot protocol was developed for the synthesis of unsymmetrical 1,3-butadiynes. The procedure is based on two sequential reactions: deprotection of R–C≡C–C≡C–C(Me)$_2$OH derivatives in a retro-Favorskii reaction to furnish a terminal 1,3-butadiyne compound, which reacted with aryl iodides in a Sonogashira-type cross-coupling reaction catalyzed by Pd(PPh$_3$)$_4$ and CuI, using TBAOH as activator and toluene as solvent under reflux for 10 min. We also studied *in situ* thiocyclization of 1,3-butadiynes, leading to unsymmetrical 2,5-diarylthiophenes. The principal features of this method are operational simplicity, good substrate scope, very fast reaction, and high yields.

Introduction

1,3-diynes are important building blocks in organic synthesis, used as starting materials to synthesize natural products[1] and new electronic[2] and optical materials (Figure 1).[3]

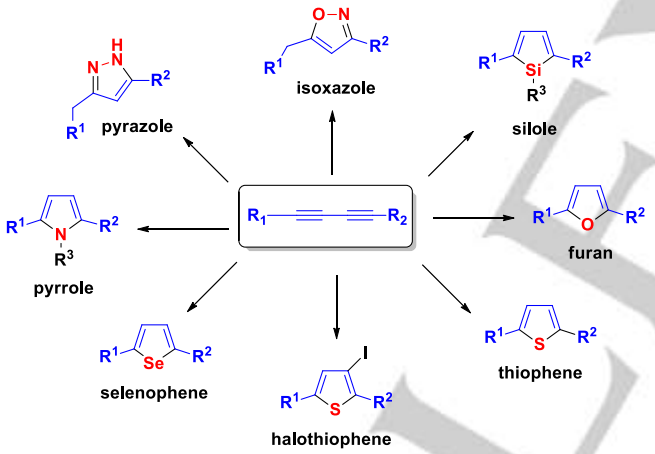

Figure 1. Synthesis of heterocycles from 1,3-butadiynes.

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Also, 1,3-butadiynes are important intermediates for the preparation of heterocyclic compounds such as pyrroles,[4] pyrazoles,[5] isoxazoles,[6] siloles,[7] furans,[8] thiophenes,[4d,9] 3-halothiophenes,[10] and selenophenes,[11] among others (Figure 1).

The classical method for the synthesis of symmetrical 1,3-butadiynes, oxidative coupling of terminal acetylenes in copper-catalyzed reactions, established decades ago, uses Glaser's homocoupling[12] and its variations, such as the Eglinton[13], Hay reactions,[14a-b] and one-pot sequential Sonogashira-Glaser reactions approach.[14c] This method has been used to synthesize unsymmetrical 1,3-butadyines, but it requires the use of an excess of one of the terminal alkynes, and the resulting mixture of unsymmetrical and symmetrical 1,3-butadiynes is a drawback of this reaction.[15]

On the other hand, Cadiot-Chodkiewicz coupling has been widely used to synthesize unsymmetrical 1,3-butadyines.[16] This consists of a cross-coupling reaction of terminal acetylenes with 1-haloalkynes, using copper and suitable amines. The advantages of this reaction are good yields, a variety of substrates, mild conditions, and the low cost of the catalysts. However, the electronic properties of terminal acetylenes and haloalkyne substituents can affect the selectivity of the reaction, with the formation of homocoupling by-products that complicate the purification of the unsymmetrical 1,3-butadyines, leading to a decrease in yields.[1,16] Variations of the Cadiot-Chodkiewicz reaction were described by Wang *et al.*,[17] employing CuI (10 mol%)/P(o-Tol)$_3$/K$_2$CO$_3$ and EtOH as a solvent. This protocol gave good results with high selectivity. However, bromoacetylene derivatives are toxic, lachrymators, volatile, and air- and photosensitive.[18]

Rao *et al.* circumvented this drawback by generating bromoacetylene *in situ* from the reaction of 1,1-dibromo alkenes and terminal acetylenes, using the CuI/K$_3$PO$_4$/TBAA and DMF catalytic system at 90 °C in 4 h of reaction.[19] However, the preparation of 1,1-dibromo alkenes is problematic due to use of the air sensitive Schwartz's reagent, or because of the tedious and laborious extractions and purifications of phosphorus by-products in the Wittig-type protocol.[20]

Recently, Li *et al.*[21] developed an attractive alternative method for the synthesis of unsymmetrical 1,3-butadiynes, based on gold-catalyzed Cadiot-Chodkiewics-type cross-coupling, using terminal alkynes and alkynyl hypervalent iodine reagents. The main drawback is the difficulty of preparing hypervalent iodine.

In another strategy, Fiandanese *et al.*[22] employed 1,4-bis(trimethylsilyl)-1,3-bytadiyne as the starting material. Monodesilylation with MeLi-LiBr, followed by the Sonogashira cross-coupling reaction of buta-1,3-diyn-1-yl-trimethylsilane with aryl iodides, provided unsymmetrical 1,3-butadiynes. However, the handling of moisture-sensitive reagents and the volatility of buta-1,3-diyn-1-yl-trimethylsilane, which hinders its isolation, are disadvantages of this method.

As an alternative, terminal 1,3-butadiynes can be generated from suitable starting materials and react with aryl halides via

acetylene zipper-Sonogashira reactions to provide unsymmetrical 1,3-butadiynes.[23]

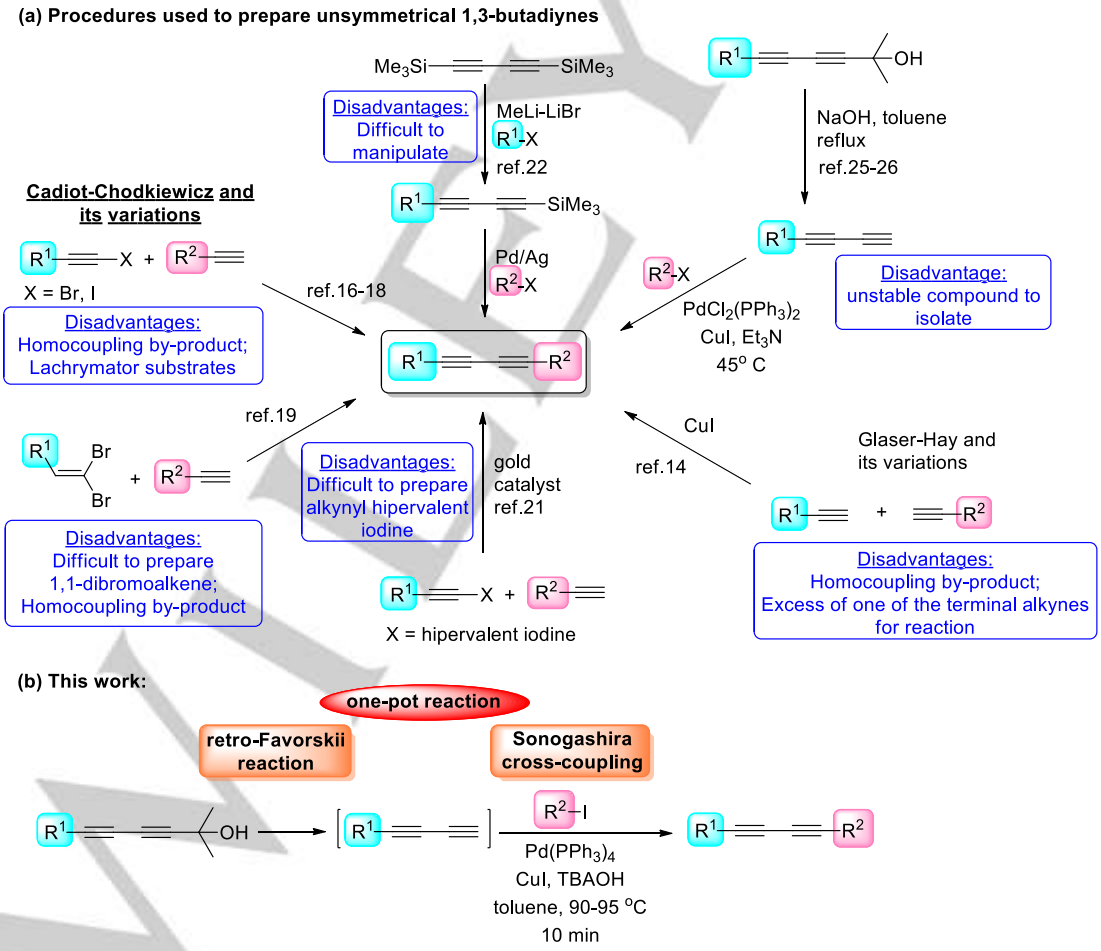
In addition, a suitable starting material for obtaining unsymmetrical 1,3-butadiynes is the Ar–C≡C–C≡C–C(Me)$_2$OH derivatives, which react with strong bases such as NaOH or KOH under reflux in solvents such as toluene or benzene in retro-Favorskii conditions to eliminate the acetone compound, furnishing the terminal 1,3-butadiynes, which could be employed in cross-coupling reactions. The high polarity of Ar–C≡C–C≡C–C(Me)$_2$OH derivatives compared to the terminal butadiynes lead to easy separation and purification of unreacted precursor. Ar–C≡C–C≡C–C(Me)$_2$OH derivatives can be prepared by the use of different terminal acetylenes and 4-bromo-2-methyl-3-butyn-2-ol, in the same Cadiot-Chodkiewicz cross-coupling strategy.[24a] Therefore, this approach shows to be more suitable because is simple, furnish excellent yields, product is easy to purify, 4-bromo-2-methyl-3-butyn-2-ol is non lachrymator, stable in low temperatures, and its use avoids the synthesis of several other bromoacetylene derivatives, which have disadvantages as described prior.[18] 2-methyl-3-butyn-2-ol used to prepare 4-bromo-2-methyl-3-butyn-2-ol is abundant, inexpensive, demonstrating great advantage over other starting materials.

Further, this strategy has also been used for construction more complex triynes, or high oligoynes.[24b]

Bryce *et al.*[25] employed this approach to synthesize terminal 1,3-butadiynes from 2-methyl-6-phenyl-hexa-3,5-diyn-2-ol derivatives, and isolated eight compounds with the aim of showing their relative stability and applicability in the Sonogashira cross-coupling reaction. However, Bryce and co-workers obtained only one coupling product after 18 h of reaction, in 75% yield.

Balova *et al.*[26] used the same strategy for the synthesis of several unsymmetrical diaryldiacetylenes. However, Ar—C≡C—C≡CH was filtered to remove NaOH and held in toluene solution before the Sonogashira-type cross-coupling reaction. Unless a bulky terminal aryl group is attached to terminal 1,3-butadiynes,[27a-b] the instability of these compounds remains a drawback for the use of these two methods.[27c-d]

Considering the instability of the terminal 1,3-butadiynes, we explored the possibility of performing this reaction using Ar—C≡C—C≡C—C(Me)$_2$OH as the starting material in a one-pot reaction, avoiding the manipulation of the unstable terminal 1,3-butadiyne outside of an inert atmosphere (Scheme 1).



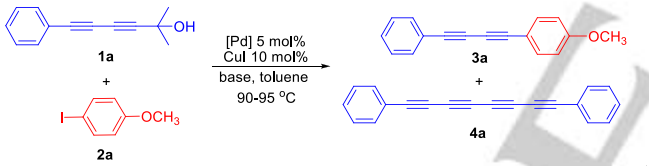
Scheme 1. Procedures used for the synthesis of unsymmetrical 1,3-butadiynes.

A one-pot method via deprotection and cross-coupling sequential reactions for the synthesis of diarylethynes from Ph—C≡C—C(Me)$_2$OH is known,[28] but to the best of our knowledge, this approach has not yet been used for the synthesis of unsymmetrical 1,3-butadiynes. We also decided to explore the synthesis of 2,5-diarylthiophene through *in situ* thiocyclization of 1,3-butadiynes generated in a one-pot procedure.

Results and Discussion

In order to optimize the protocol conditions, the reaction of 2-methyl-6-phenyl-hexa-3,5-diyn-2-ol **1a** with 4-iodoanisole **2a** was performed, in the presence of the catalyst system $PdCl_2(PPh_3)_2$ 5% / CuI 10% and NaOH (4.5 equiv.) as a base at 110 °C. First, a retro-Favorskii reaction occurs between Ar—C≡C—C≡C—C(Me)$_2$OH and NaOH. Next, the Ar—C≡C—C≡CH formed *in situ* reacts with 4-iodoanisole in a Sonogashira cross-coupling reaction (Scheme 1). Thus, the NaOH acts as a base in these two sequential reactions. Although NaOH is not a usual base in Sonogashira cross-coupling reactions, it was observed after 30 min of reaction, and the terminal 1,3-butadiyne **3a** was obtained in 40% yield, with the formation of a small amount of homocoupling product **4a**. Furthermore, 4-iodoanisole **2a** was not fully consumed in these reaction conditions (Table 1, entry 1).

Table 1. Optimization of coupling reaction of 1,3-butadiyne **1a** with 4-iodoanisole **2a**.



Entry	Reaction conditions[a]	Catalyst	Time	Yield **3a** (%)[b]	Yield **4a** (%)[b]
1	A	$PdCl_2(PPh_3)_2$	30	40	10
2	A	$Pd(PPh_3)_4$	30	53	10
3	B	$Pd(PPh_3)_4$	30	80	5
4	C	$Pd(PPh_3)_4$	5	51	10
5	D	$Pd(PPh_3)_4$	5	73	5
6	E	$Pd(PPh_3)_4$	10	95	0

[a] Reaction conditions – A: **1a** (2.0 mmol), **2a** (1.0 mmol), NaOH (4.0 equiv.), toluene (5 mL), 110 °C. B: **1a** (2.0 mmol), **2a** (1 mmol), NaOH (3.0 equiv.), toluene (5 mL), 110 °C. C: **1a** (2.0 mmol), **2a** (1 mmol), TBAOH 40% in H_2O (3.0 equiv.), toluene (5 mL), 90–95 °C. D: **1a** (1.5 mmol), **2a** (1 mmol), TBAOH (2.0 mmol), toluene (5 mL), 90–95 °C. E: **1a** (1.5 mmol), solubilized in toluene (15 mL) was added dropwise in a solution of **2a** (1 mmol), TBAOH (2.0 mmol) in toluene (5 mL), 90–95 °C. [b] Yields after purification by chromatographic column.

In order to improve the reaction yields, the catalytic system $Pd(PPh_3)_4$ / CuI 10% was tested, using NaOH (4.5 equiv.) as a base, and the product was obtained in 53% yield, contaminated with homocoupling by-product **4a** (Table 1, entry 2) and other by-products. Considering that the amount of base can affect the reaction yields,[29] we used NaOH (3 equiv.) in order to determine the appropriate proportion of base to promote the retro-Favorski reaction and at the same time promote the cross-coupling reaction with efficiency and with the formation of fewer by-products (Table 1, entry 3). Product **3a** was obtained in 80% yield after 30 min of reaction, with a small amount of homocoupling by-product **4a** (5%). Also, purification of 1,3-butadiyne of this reaction is very difficult in the chromatographic column, due to contamination with unknown impurities.

In recent years, TBAOH has been used by our research group and others as an activator in Sonogashira cross-coupling reactions[30] and as a base in the synthesis of symmetrical and unsymmetrical (Z)-thiobutenynes.[31] Recently, TBAOH was used in deprotection of alkynyl carbinols.[32] Thus, tetrabutylammonium hydroxide appears to be a more suitable alternative to synthesize unsymmetrical 1,3-butadiynes in a one-pot procedure from Ar—C≡C—C≡C—C(Me)$_2$OH derivatives. Therefore, we decided to use TBAOH as a base to substitute the NaOH in this reaction.

In the first attempt, we used the catalyst system $Pd(PPh_3)_4$ 5% / CuI 10% in TBAOH 40% in H_2O (3.0 equiv.) under reflux (90–95 °C). The reaction was monitored by thin-layer chromatography, and work-up occurred after 5 min. The product was obtained in 51% yield, and homocoupling product **4a** was isolated in 10% yield (Table 1, entry 4), with no observation of the formation of other by-products. Although the yield was not good, the reaction was cleaner than that using NaOH.

When we reduced the amount of 2-methyl-6-phenyl-hexa-3,5-diyn-2-ol **1a** to 1.5 equiv. and the amount of TBAOH to 2.0 equiv., the product was obtained in 73% yield, and homocoupling compound **4a** in 5% yield (Table 1, entry 5).

The analysis of the results showed that the use of NaOH 4.5 equiv. (Table 1, entries 1 and 2) caused the deprotection of **1a** to Ar—C≡C—C≡C—H in only 5 min (TLC monitoring), while the use of NaOH 3 equiv. caused total deprotection in 15 min (monitored by TLC). However, for the coupling reaction to occur efficiently, an additional 15 min reaction time was necessary (Table 1, entry 3). On the other hand, all reaction conditions mediated by TBAOH were much faster, and the overall reaction occurred in only 5 min to furnish product **3a** (Table 1, entries 4–5).

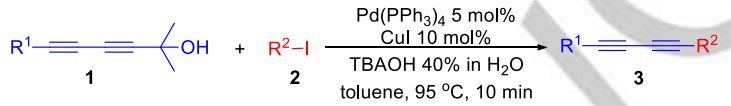
The smaller amounts of NaOH (Table 1, entry 3) and TBAOH (Table 1, entry 6) gave the best yields of the desired product, with less formation of the homocoupling by-product **4a**. We speculate that the rapid formation of the intermediate in the reaction medium promoted the homocoupling reaction (Table 1, entries 1–5); while the decrease in the rate of formation of Ar—C≡C—C≡C—H, favoring cross-coupling with 4-iodoanisole **2a**, which is in a proportionately higher concentration in the reaction medium, promoted the formation of unsymmetrical 1,3-butadiyne. Therefore, we decided to modify the experimental procedure adopted. Initially, for the reactions performed up to then, all the

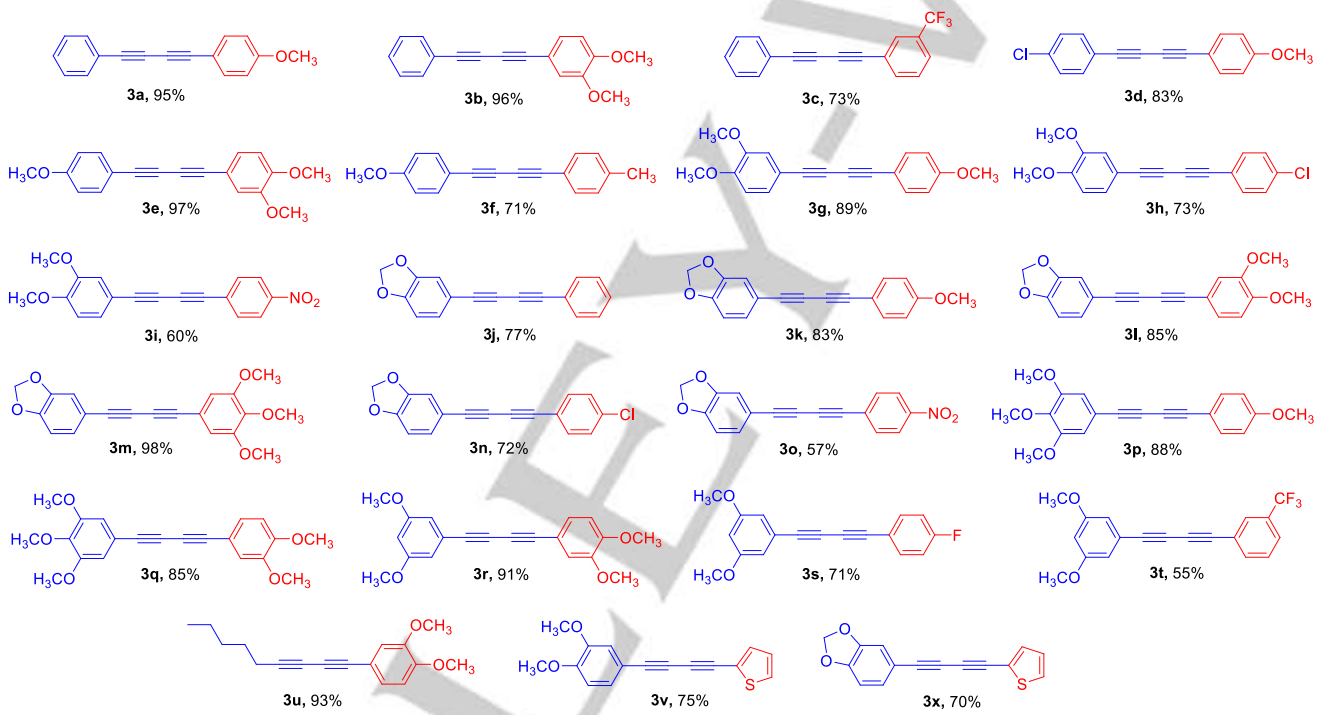
reagents were added to the reaction flask, and then TBAOH in H_2O 40% was added rapidly, and the reaction mixture was refluxed at 90 °C (Table 1, entries 4–5). In the new procedure, Ar—C≡C—C≡C—C(Me)$_2$OH **1a** in toluene (15 mL) was added dropwise (5 min) to a solution of 4-iodoanisole **2a**, Pd(PPh$_3$)$_4$ 5%, CuI 10% and 40% TBAOH in H_2O, in toluene (5 mL) at 90–95 °C. A further 5 min was required to finalize the Sonogashira cross-coupling, affording **3a** in 95% yield, and the homocoupling by-product was not detected (Table 1, entry 6).

Different palladium catalysts ($PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$, a decrease in the amount of Ar—C≡C—C≡C—C(Me)$_2$OH **1a** to 1.2 equiv., as well as reduction of the temperature to 75 °C were also tested. However, none of these conditions increased the efficiency of the Sonogashira cross-coupling reaction.

In view of this result (Table 1, entry 6), we decided to investigate the scope of the reaction, and aryl iodides **2** with different substituents were reacted with 2-methyl-6-aryl-hexa-3,5-diyn-2-ol **1** to provide unsymmetrical 1,3-butadiynes **3a-x**.

Table 2. Synthesis of unsymmetrical 1,3-butadiynes.[a][b]





[a] Reagents and reaction conditions: Pd(PPh$_3$)$_4$ 5 mol%, CuI 10 mol%, aryl iodide **2** (1 mmol, 1.0 equiv.), TBAOH 40% in H_2O (2 mmol, 2.0 equiv.) and toluene (5.0 mL). Then, the reaction mixture was heated to 95 °C, and **1** (1.5 mmol, 1.5 equiv.) solubilized in toluene (15 mL) was added dropwise. Heating was maintained for 5 min. [b] Yields isolated after column chromatography.

Due to the high interest of our research group in the synthesis of bioactive derivatives of tetrahydrofuran neoligans such as Veraguensin, Grandisin, and Machilin G,[33] we gave priority to the preparation of unsymmetrical 1,3-butadiynes containing methoxy, and methylenedioxy substituent patterns (compounds **3e-r**).

The reaction tolerated a variety of functional groups present in 2-methyl-6-phenyl-hexa-3,5-diyn-2-ol. Electron-acceptor or electron-donor groups attached to the aromatic ring affected the reaction yield (compounds **3a-d**). An aliphatic carbinol diyne as starting material was also used, and product **3u** was obtained in good yield. Concerning the substituent attached to the aryl iodide, electronic effects influenced the reaction to some degree. Electron-donor groups attached to the aryl halide provided better yields (Table 2, compounds **3a-b**, **3d-g**, **3k-m**, **3p-r,** and **3u**) than those with an electron-acceptor substituent (Table 2, compounds **3c**, **3h-i**, **3n-o**, **3s-t**).

For instance, product **3g** with the electron-donor group -OCH$_3$ was obtained in 89% yield, while the derivative with the electron-acceptor group -Cl **3h** was obtained in 73% yield (Table 2).

Similarly, the methylenedioxy and 3,5-dimethoxy derivatives with electron-donor groups (Table 2, compounds **3k-m** and **3r** respectively) were obtained in higher yields than derivatives with

electron-acceptor patterns (Table 2, compounds **3n-o** and **3s-t** respectively).

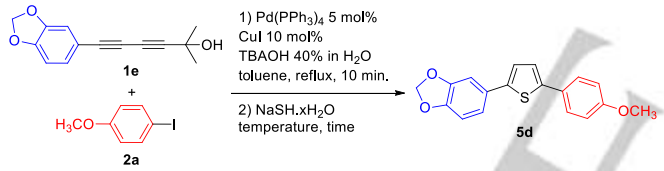
1,3-butadiynes functionalized with only methylenedioxy substituents were obtained in very good yields, which is highly important in organic synthesis since these compounds have not been described previously (Table 2, compounds **3k-m**).

On the other hand, the strength of the electron-acceptor group also affected the reaction yield. Methylenedioxy 1,3-butadyine **3o** synthesized using 1-iodo-4-nitrobenzene was obtained in 57% yield, while the derivative with the chlorine substituent **3n** (a weaker electron acceptor than the nitro group) was obtained in 72% yield.

The scope of this reaction was extended to 1,3-butadiynes substituted with thiophene ring, and compounds **3v-x** were obtained in good yields (Table 2).

Encouraged by the success of this protocol, we explored the applicability of 1,3-butadiynes to the synthesis of more complex substances. Based on the literature reports,[4d,9,19a,34] we reasoned that *in situ* thiocyclisation of unsymmetrical 1,3-butadiynes would provide a straightforward approach to prepare unsymmetrical 2,5-diarylthiophenes. For this purpose, we performed a series of experiments to optimize the thiocyclization reaction after the formation of 1,3-butadiynes, using only sodium hydrosulfide in different amounts under different temperatures and times (Table 3).

Table 3. Optimization of *in situ* thiocyclization of 1,3-butadiynes.[a]



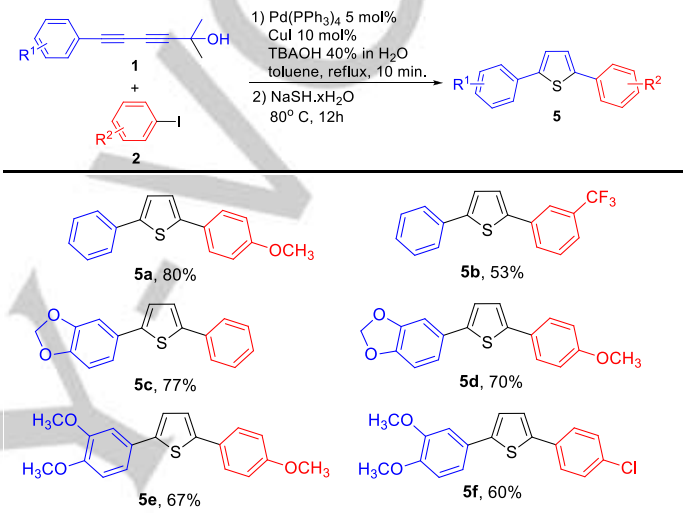
Entry	Amount of NaSH.×H_2O (equiv.)	Temperature (°C)	Time (h)	Yield (%)[b]
1	5	95	12	30
2	5	80	12	55
3	5	80	24	58
4	10	80	12	70

[a] Reagents and reaction condition: step 1: $Pd(PPh_3)_4$ 5 mol%, CuI 10 mol%, **2a** (1 mmol, 1.0 equiv.), TBAOH 40% in H_2O and toluene (5.0 mL). Then **1e** (1.5 mmol, 1.5 equiv.) solubilized in toluene (15 mL) was added dropwise and the mixture heated to reflux for 10 min. Step 2: Reaction mixture was cooled to 60 °C, and then NaSH.×H_2O was added in portions. [b] Yields isolated after chromatography column and recrystallization with hexane.

Initially, the use of 5.0 equiv. of NaSH.×H_2O at 95 °C for 12 h furnished the product in only 30% yield, and the degradation of 1,3-butadiyne was observed (Table 3, entry 1). When the temperature was decreased to 80 °C, the product was isolated in 55% yield (Table 3, entry 2).

Thus, we decided to extend the reaction time to 24 h. However, 2,5-diarylthiophene was obtained in 58% yield (Table 3, entry 3). Then, we increased the amount of NaSH.×H_2O to 10.0 equiv., and the yield of product was 70% (Table 3, entry 4). After determining the optimal conditions for *in situ* thiocyclization, we expanded the scope of this one-pot protocol (Table 4). Our procedure proved to be general, furnishing different unsymmetrical 2,5-diarylthiophenes **5a-f** in moderate to good yields.

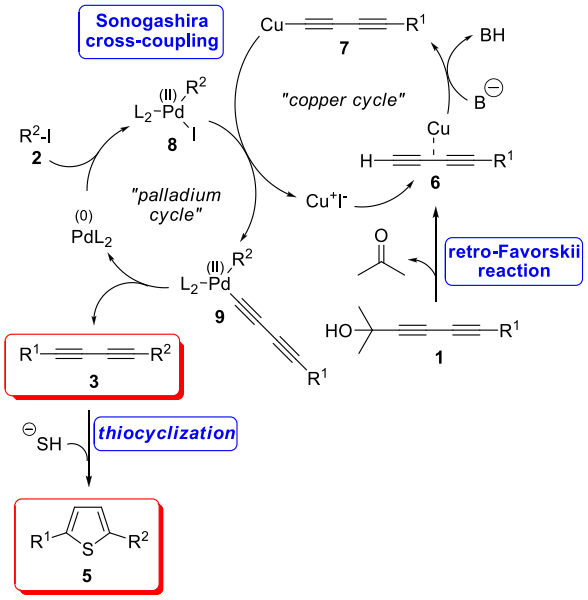
Table 4. Synthesis of unsymmetrical 2,5-diaryl-thiophenes.



[a] Step 1: $Pd(PPh_3)_4$ 5 mol%, CuI 10 mol%, **2** (1 mmol, 1.0 equiv.), TBAOH 40% in H_2O and toluene (5.0 mL). Then **1** (1.5 mmol, 1.5 equiv.) solubilized in toluene (15 mL) was added dropwise and the mixture heated to reflux for 10 min. Step 2: Reaction mixture was cooled to 60 °C, and then NaSH.xH_2O (10 mmol, 10 equiv.), 80 °C, 12 h. [b] Yields isolated after column chromatography and recrystallization with hexane.

Based on literature reports,[35] the overall mechanism proposed is depicted in Scheme 2. Ar—C≡C—C≡C—$C(Me)_2OH$ **1** is deprotected by a base in a retro-Favorskii reaction to furnish terminal 1,3-butadiyne **6**, which reacts with copper iodide to form copper acetylide **7**.

In the "palladium cycle", aryl iodide **2** is added to palladium catalyst in an oxidative addition, and the intermediate **8** is transformed to **9** after transmetallation with copper acetylide. The *cis/trans* isomerization followed by reductive elimination generates the unsymmetrical 1,3-butadiyne **3**, which reacts with sodium hydrosulfide in the thiocyclization reaction to deliver the unsymmetrical 2,5-diaryl thiophene **5**.



Scheme 2. Proposed mechanism for the one-pot synthesis of unsymmetrical 1,3-butadiynes and 2,5-diarylthiophenes.

Conclusions

In conclusion, we have developed a synthetic protocol to synthesize unsymmetrical 1,3-butadiynes through the deprotection of 2-methyl-6-phenyl-hexa-3,5-diyn-2-ol, followed by a Sonogashira cross-coupling reaction with Ar-I derivatives, using TBAOH as a base. The protocol developed in this study has the following advantages: (i) operational simplicity, since it is a one-pot reaction that generates terminal 1,3-butadiyne *in situ* and employs stable and easily manipulable starting materials; (ii) good substrate scope; (iii) very fast reaction; (iv) products obtained in good yields; and (v) easy purification of the desired products because there is no formation of the homocoupling by-product. Additionally, this method proved to be very useful for the straightforward synthesis of unsymmetrical 2,5-diarylthiophenes.

Experimental Section

General

Reactions were carried out under a nitrogen atmosphere and monitored by TLC using prepared plates (silica gel 60 F254 on aluminum). The chromatograms were examined under both 254 and 360 nm UV light or with the developing agent ethanolic vanillin and heat. Flash column chromatography was performed on silica gel 60 (particle size 200–400 mesh ASTM, purchased from Aldrich, USA). Melting points were determined using Fisatom 430D equipment. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using a Brucker 75 MHz or 300 MHz spectrometer, as noted. Chemical shifts (δ) are expressed as parts per million (ppm) downfield from tetramethylsilane or deuterated solvent ($CDCl_3$ ^{1}H δ 7.27, ^{13}C δ 77.0) as the internal standard. HR-ESI-MS measurements were carried out on a quadrupole time-of-flight instrument (UltrOTOF-Q, BrukerDaltonics, Billerica, MA). Details of the synthesis of diacetylenic alcohol **1** and NMR data are shown in the Supporting Information.

One-pot protocol for the preparation of unsymmetrical 1,3-butadiynes 3a-x

A solution of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.25 mol) and toluene (5 mL) was stirred for 15 min at room temperature. Aryl iodide **2** (1.0 mmol, 1.0 equiv.), CuI (0.1 mmol) and TBAOH 40% aqueous solution (2.0 mmol, 2.0 equiv.) were added and the resulting mixture was heated to 95 °C. Then, a solution of diacetylenic alcohol **1** (1.5 mmol, 1.5 equiv.) in toluene (15 mL) was added dropwise for 10 min. After the addition of diacetylenic alcohol solution was completed, the reaction mixture was kept heated for 5 min. The crude mixture was extracted with ethyl acetate (3 x 60 mL), and the organic phase washed with saturated aqueous solution NH_4Cl (3 × 60 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford the unsymmetrical 1,3-butadiynes **3a-x**.

1-methoxy-4-(phenylbuta-1,3-diynyl)benzene (3a)[36]: The product was obtained as yellow solid in 95% yield. Mp: 92 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.86 (d, *J* 8.4 Hz, 2H), 7.33-7.35 (m, 3H), 7.47 (d, *J* 8.4 Hz, 2H), 7.50-7.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 72.7, 74.2, 81.0, 81.8, 113.7, 114.2, 122.0, 128.4, 129.0, 132.4, 134.1, 160.4. HRMS (ESI+) m/z calcd. for $C_{17}H_{12}O$ [M + H] 233.0966; found 233.0970.

1,2-dimethoxy-4-(phenylbuta-1,3-diynyl)benzene (3b)[36]**:** The product was obtained as brown solid in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.90 (s, 3H), 6.82 (d, *J* 6Hz, 1H), 7.02 (d, *J* 3 Hz, 1H), 7.16 (dd, *J* 3 Hz and *J* 6Hz, 1H), 7.33-7.35 (m, 3H), 7.52 (dd, *J* 6Hz and *J* 3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 72.6, 74.0, 81.1, 81.9, 111.0, 113.8, 115.0, 122.0, 126.2, 128.4, 129.0, 132.4, 148.7, 150.4. HRMS (ESI+) m/z calcd. for $C_{18}H_{14}O_2$ [M + H] 263.1072; found 263.1072.

1-(phenylbuta-1,3-diynyl)-3-(trifluoromethyl)benzene (3c)[37]**:** The product was obtained as white solid in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.38 (m, 3H), 7.45 (t, *J* 7.8 Hz, 1H), 7.51-7.54 (m, 2H), 7.59 (d, *J* 7.8 Hz, 1H), 7.67 (d, *J* 7.8 Hz, 1H), 7.76 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.4, 75.4, 79.6, 82.5, 121.4, 122.9, 123.5 (q, J_F 270.7 Hz), 125.6 (q, J_F 3.1 Hz), 128.4, 129.0, 129.2 (q, J_F 3.8 Hz), 129.5, 131.1 (q, J_F 32.5 Hz), 132.6, 135.4.

1-chloro-4-(4-methoxyphenyl)buta-1,3-diynyl)benzene (3d)[36]**:** The product was obtained as pale yellow crystal in 83% yield. Mp: 155-157 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.84 (d, *J* 9Hz, 2H), 7.28 (d, *J* 8.7 Hz, 2H), 7.40-7.47 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 72.6, 75.2, 79.8, 82.4, 113.5, 114.2, 120.5, 128.8, 133.6, 134.1, 135.1, 160.5. HRMS (ESI+) m/z calcd. for $C_{17}H_{11}ClO$ [M + H] 267.0577; found 267.0561.

1,2-dimethoxy-4-(4-methoxyphenyl)buta-1,3-diynyl)benzene (3e): The product was obtained as yellow crystal in 97% yield. Mp: 106 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 6.78 (d, J 8.3 Hz, 1H), 6.82 (d, J 8.7 Hz, 2H), 6.98 (d, J 1.6 Hz, 1H), 7.11 (dd, J 1.6 Hz and 8.3 Hz, 1H), 7.43 (d, J 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.9, 72.9, 81.3, 81.4, 111.0, 113.8, 113.9, 114.1, 114.8, 126.1, 134.0, 148.6, 150.2, 160.3. HRMS (ESI+) m/z calcd. for $C_{19}H_{16}O_3$ [M + H] 293.1178; found 293.1184.

1-methoxy-4-(p-tolylbuta-1,3-diynyl)benzene (3f)[36]: The product was obtained as pale yellow solid in 71% yield. Mp: 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.81 (s, 3H), 6.85 (d, *J* 8.2 Hz, 2H), 7.11 (d, *J* 7.6 Hz, 2H), 7.39 (d, *J* 8.2 Hz, 2H), 7.44 (d, *J* 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 55.3, 72.8, 73.5, 81.0, 81.8, 113.8, 114.1, 118.8, 129.2, 132.3, 134.1, 139.4, 160.3. HRMS (ESI+) m/z calcd. for $C_{18}H_{14}O$ [M + H] 247.1123; found 247.1135.

1,2-dimethoxy-4-(4-methoxyphenyl)buta-1,3-diynyl)benzene (3g): The product was obtained as a yellow crystal in 89% yield. Mp: 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.79 (d, *J* 8.4 Hz, 1 H), 6.83 (d, *J* 8.7 Hz, 2H), 6.99 (d, *J* 1.5 Hz, 1H), 7.12 (dd, *J* 1.5 Hz and 8.4 Hz, 1H), 7.44 (d, *J* 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.8, 72.9, 81.4, 81.41, 111.0, 113.7, 113.9, 114.1, 114.7, 126.1, 134.0, 148.6, 150.2, 160.3. HRMS (ESI+) m/z calcd. for $C_{19}H_{16}O_3$ [M + H] 293.1178; found 293.1159.

4-(4-chlorophenyl)buta-1,3-diynyl)-1,2-dimethoxybenzene (3h): The product was obtained as pale yellow solid in 73% yield. Mp: 132-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 3H), 6.79 (*d, J* 8.4 Hz, 1H), 6.98 (s, 1H), 7.13 (d, *J* 8.4 Hz, 1H), 7.28 (d, *J* 8.1 Hz, 2H), 7.41 (d, *J* 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 72.4, 75.1, 79.9, 82.5, 111.1, 113.5, 114.8, 120.5, 126.3, 128.8, 133.6, 135.2, 148.7, 150.5. HRMS (ESI+) m/z calcd. for $C_{18}H_{13}ClO_2$ [M + H] 297.0682; found 297.0699.

1,2-dimethoxy-4-(4-nitrophenyl)buta-1,3-diynyl)benzene (3i): The product was obtained as a tan solid in 60% yield. Mp: 137-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), 3.89 (s, 3H), 6.60 (d, *J* 9Hz, 2H), 6.80 (d, J 9 Hz, 1H), 7.00 (d, *J* 3Hz, 1H), 7.14 (dd, *J* 3Hz and *J* 9Hz, 1H), 7.32 (d, *J* 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 81.0, 81.8, 113.7, 114.2, 122.0, 128.4, 129.0, 132.4, 134.1, 160.3. HRMS (ESI+) m/z calcd. for $C_{18}H_{13}NO_4$ [M + H] – NO = 278.0943; found 278.1164.

5-(phenylbuta-1,3-diynyl)benzo[d][1,3]dioxole (3j): The product was obtained as pale yellow solid in 77% yield. Mp: 105-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H), 6,76 (d, *J* 9Hz, 1H), 6.94 (d, *J* 3Hz, 1H), 7.06 (dd, *J* 9 Hz and *J* 3 Hz, 1H), 7.31-7.33 (m, 3H), 7.48-7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.5, 74.1, 81.2, 81.7, 101.5, 108.7, 112.1, 114.9, 121.9, 127.9, 128.4, 129.1, 132.5, 147.5, 148.8. HRMS (ESI+) m/z calcd. for $C_{17}H_{10}O_2$ [M + H] 247.0759; found 247.0777.

5-(4-methoxyphenyl)buta-1,3-diynyl)benzo[d][1,3]dioxole (3k): The product was obtained as pale yellow solid in 83% yield. Mp: 129-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.74 (d, *J* 9 Hz, 1H), 6.84 (d, *J* 9 Hz, 2H), 6.92 (s, 1H), 7.04 (d, *J* 9Hz, 1H), 7.44 (d, *J* 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 72.7, 72.8, 81.1, 81.4, 101.5, 108.6, 112.1, 113,7, 114.1, 115.1, 127.6, 134.1, 147.4, 148.7, 160.3. HRMS (ESI+) m/z calcd. for $C_{18}H_{12}O_3$ [M + H] 277.0865; found 277.0856.

5-(3,4-dimethoxyphenyl)buta-1,3-diynyl)benzo[d][1,3]dioxole (3l): The product was obtained as yellow solid in 85% yield. Mp: 149-151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 5.97 (s, 2H), 6.74 (d, *J* 9 Hz, 1H), 6.80 (d, *J* 9 Hz, 1H), 6.92 (d, *J* 3Hz, 1H), 6.99 (d, *J* 1.5Hz, 1H), 7.04 (dd, *J* 9 Hz and *J* 3.0 Hz), 7.12 (dd, *J* 1.5Hz and *J* 9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 72.6, 72.7, 81.2, 81.5, 101.5, 108.6, 111.0, 112.1; 113.8, 115.0, 126.2, 127.6, 148.6, 147.4, 148.7, 150.2. HRMS (ESI+) m/z calcd. for $C_{19}H_{14}O_4$ [M + H] 307.0970; found 307.0965.

5-(3,4,5-trimethoxyphenyl)buta-1,3-diynyl)benzo[d][1,3]dioxole (3m): The product was obtained as dark yellow solid in 98% yield. Mp: 175-177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 9H), 5.98 (s, 2H), 6.74-6.77 (m, 3H), 6.93 (d, *J* 3Hz, 1H), 7.05 (dd, *J* 9 Hz and *J* 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 61.0, 72.6, 73.2, 81.2, 101.5, 108.6, 109.7, 112.1, 114.6, 116.7, 127.7, 147.5, 149.5, 153.1. HRMS (ESI+) m/z calcd. for $C_{20}H_{16}O_5$ [M + H] 337.1076; found 337.1064.

5-(4-chlorophenyl)buta-1,3-diynyl)benzo[d][1,3]dioxole (3n): The product was obtained as a yellow solid in 72% yield. Mp: 184-186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H), 6.75 (d, *J* 9 Hz, 1H), 6.93 (d, *J* 3 Hz, 1H), 7.06 (dd, *J* 9 Hz and *J* 3 Hz, 1H), 7.28 (d, *J* 9 Hz, 2H), 7.42 (d, *J* 9Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3, 75.0, 79.9, 82.2, 101.5, 108.7, 112.1, 114.7, 120.4, 127.8, 128.8, 133.6, 135.2, 147.5, 148.9. **HRMS** (ESI+) m/z calcd. for $C_{17}H_9ClO_2$ [M + H] 281.0369; found 281.0386.

5-(4-nitrophenyl)buta-1,3-diynyl)benzo[d][1,3]dioxole (3o): The product was obtained as red solid in 57% yield. Mp: 147-148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H), 6.58 (d, *J* 9 Hz, 2H), 6.74 (d, *J* 9H, 1H), 6.91 (d, *J* 3 Hz, 1H), 7.03 (dd, *J* 3 Hz and 9 Hz, 1 H), 7.30 (d, *J* 9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.1, 73.0, 80.8, 82.4, 101.4, 108.6, 110.8, 112.0, 114.6, 115.4, 127.5, 134.2, 147.4, 147.5, 148.5. HRMS (ESI+) m/z calcd. for $C_{17}H_9NO_4$ [M + H] – NO = 262.0630; found 262.0889.

1,2,3-trimethoxy-5-(4-methoxyphenyl)buta-1,3-diynyl)benzene (3p): The product was obtained as pale yellow crystal in 88% yield. Mp: 122-123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.82 (s, 3H), 3.84 (s, 6H), 6.73 (s, 2H), 6.83 (d, *J* 8.4 Hz, 2H), 7.43 (d, *J* 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.1, 61.0, 72.7, 73.4, 81.1, 81.8, 109.6, 113.7, 114.2, 116.8, 134.1, 139.7, 153.1, 160.4. HRMS (ESI+) m/z calcd. for $C_{20}H_{18}O_4$ [M + H] 323.1283; found 323.1289.

5-(3,4-dimethoxyphenyl)buta-1,3-diynyl)-1,2,3-trimethoxybenzene (3q): The product was obtained as pale yellow crystal in 88% yield. Mp: 114-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 6.74 (*s*, 2H), 6.86 (d, *J* 9Hz, 1H), 6.99 (s, 1H), 7.13 (d, *J* 9Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.2, 61.0, 72.6, 73.3, 81.3, 81.9, 109.7, 111.1, 113.9, 114.9, 116.8, 126.2, 139.8, 148.7, 150.0, 153.1. HRMS (ESI+) m/z calcd. for $C_{21}H_{20}O_5$ [M + H] 353.1389; found 353.1379.

4-(3,5-dimethoxyphenyl)buta-1,3-diynyl)-1,2-dimethoxybenzene (3r): The product was obtained as pale yellow crystal in 91% yield. Mp: 101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H), 3.84 (s, 3H), 3.86 (*s*, 3H), 6.45 (s, 1H), 6.64 (s, 2H), 6.78 (d, *J* 8.2 Hz, 1H), 6.98 (s, 1H), 7.12 (d, *J* 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.9, 72.6, 73.6, 81.2, 82.0, 102.7, 110.1, 111.0, 113.7, 114.8, 123.1, 126.3, 148.7, 150.5, 160.5. HRMS (ESI+) m/z calcd. for $C_{20}H_{18}O_4$ [M + H] 323.1283; found 323.1285.

1-(4-fluorophenyl)buta-1,3-diynyl)-3,5-dimethoxybenzene (3s): The product was obtained as yellow solid in 71% yield. Mp: 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47-6.48 (m, 1H), 6.65-6.66 (m, 2H), 6.99-7.04 (m, 2H), 7.47-7.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 73.3, 73.6, 80.4, 81.5, 102.9, 110.1, 115.9 (d, J_F 22.1 Hz), 117.8 (d, J_F 3.6 Hz), 122.9, 134.5 (d, J_F 8.5 Hz), 160.5, 163.0 (d, J_F 250 Hz). HRMS (ESI+) m/z calcd. for $C_{18}H_{13}FO_2$ [M + H] 281.0978; found 281.0970.

1,3-dimethoxy-5-(3-(trifluoromethyl)phenyl)buta-1,3-diynyl)benzene (3t): The product was obtained as yellow solid in 71% yield. Mp: 36 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 6H), 6.49 (s, 1H), 6.66 (s, 2H), (m, 2H), 7,44 (t, *J* 7.8 Hz, 1H), 7.59 (d, *J* 7.7 Hz, 1H), 7.65 (d, *J* 7.7 Hz, 1H), 7,75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 55.2, 72.9, 75.4, 79.6, 82.5, 103.1, 110.2, 122.6, 122.8, 123.4 (q, J_F 270.9 Hz), 125.8 (q, J_F 3.9 Hz),

129.0, 129.2 (q, J_F 3.8 Hz), 131.1 (q, J_F 32.6 Hz), 135.5, 160.6. HRMS (ESI+) m/z calcd. for $C_{19}H_{13}F_3O2$ [M + H] 331.0946; found 331.0941.

1,2-dimethoxy-4-(octa-1,3-diynyl)benzene (3u): The product was obtained as yellow solid in 93% yield. Mp: 47-49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, *J* 7.1 Hz, 3H), 1.29-1.46 (m, 4H), 2.24 (t, *J* 6.7 Hz, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 6.65 (d, *J* 8.3 Hz, 1H), 6.83 (s, 1H), 6.95 (d, *J* 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 19.2, 21.9, 30.3, 55.7, 65.2, 73.1, 74.8, 84.2, 110.9, 113.9, 114.7, 125.9, 148.5, 149.9. HRMS (ESI+) m/z calcd. for $C_{16}H_{18}O_2$ [M + H] 243.1385; found 243.1385.

2-(3,4-dimethoxyphenyl)buta-1,3-diynyl)thiophene (3v): The product was obtained as yellow viscous liquid in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.79 (d, *J* 8.4 Hz, 1H), 6.95-6.98 (m, 2H), 7.13 (dd, *J* 8.4 Hz and *J* 1.8 Hz, 1H), 7.27-7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 72.5, 74.2, 78.1, 84.0, 111.0, 113.6, 122.2, 126.2, 127.2, 128.5, 134.1, 148.6, 150.5. HRMS (ESI+) m/z calcd. for $C_{16}H_{12}O_2S$ [M + H] 269.0636; found 269.0647.

5-(thiophen-2-ylbuta-1,3-diynyl)benzo[d][1,3]dioxole (3x): The product was obtained as yellow solid in 70% yield. Mp: 94-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H), 6.76 (d, *J* 9Hz, 1H), 6.92 (d, *J* 3Hz, 1H), 6.97 (t, *J* 6Hz, 1H), 7.05 (dd, *J* 9 Hz and *J* 3 Hz, 1H), 7.28-7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3, 74.2, 78.2, 83.7, 101.5, 108.7, 112.1, 114.8, 112.2, 127.1, 127.7, 128.5, 134.1, 147.5, 148.9. HRMS (ESI+) m/z calcd. for $C_{15}H_8O_2S$ [M + H] 253.0323; found 253.0353.

One-pot protocol for the preparation of unsymmetrical 2,5-disubstituted thiophene 5a-f

The one-pot protocol to the synthesis of unsymmetrical 1,3-butadiynes given above was followed in the first step. After the formation of 1,3-butadiyne, the reaction mixture was cooled to 60 °C, and $NaSH.\times H_2O$ was added in portions. Then, the reaction mixture was heated at 80 °C for 12 h. The crude mixture was extracted with ethyl acetate (3 x 60 mL), and the organic phase washed with saturated aqueous solution NH_4Cl (3 x 60 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography followed by recrystallization using hexane, to afford the unsymmetrical 2,5-disubstituted thiophene **5a-f**.

2-(4-methoxyphenyl)-5-phenylthiophene (5a)[38]**:** The product was obtained as yellow solid in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.92 (d, *J* 8.7Hz, 2H), 7.16 (d, *J* 3.6 Hz, 1H), 7.24-7.27 (m, 2H), 7.39 (t, *J* 7.5 Hz, 2H), 7.56 (d, *J* 8.7Hz, 2H), 7.61 (d, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 114.3, 122.9, 123.9, 125.5, 126.9, 127.2, 127.3, 128.9, 134.4, 142.6, 143.6, 159.3. HRMS (ESI+) m/z calcd. for $C_{17}H_{14}OS$ [M + H] 267.0844; found 267.0854.

2-phenyl-5-(3-(trifluoromethyl)phenyl)thiophene (5b): The product was obtained as pale yellow solid in 53% yield. Mp: 129-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.34 (m, 3H), 7.40 (t, *J* 6 Hz, 2H), 7.46-7.54 (m, 2 H), 7.63 (d, *J* 6 Hz, 2 H), 7.77 (d, *J* 6 Hz, 1 H), 7.85 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.2 (q, J_F 3.6 Hz), 123.9 (q, J_F 3.7 Hz), 124.1, 125.0, 125.7, 127.9, 128.7, 129.0, 129.4, 131.1 (q, J_F 32.1 Hz), 133.9, 135.1, 141.6, 144.8 HRMS (ESI+) m/z calcd. for $C_{17}H_{11}F_3S$ [M + H] 305.0612; found 305.0661.

5-(5-phenylthiophen-2-yl)benzo[d][1,3]dioxole (5c): The product was obtained as white solid in 77% yield. Mp: 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H), 7,10-7.14 (m, 3H), 7.23-7.29 (m, 2H), 7.35-7.40 (m, 2H), 7.59-7.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.3, 106.3, 108.7, 119.5, 123.3, 123.9, 125.5, 127.4, 128.7, 128.9, 134.3, 142.8, 143.5, 147.2, 148.2. HRMS (ESI+) m/z calcd. for $C_{17}H_{12}O_2S$ [M + H] 281.0636; found 281.0638.

5-(5-(4-methoxyphenyl)thiophen-2-yl)benzo[d][1,3]dioxole (5d): The product was obtained as white solid in 70% yield. Mp: 169-170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.97 (s, 2H), 6.81 (d, *J* 8.6 Hz, 2H), 6.90 (d, *J* 8.8 Hz, 2H), 7.12-7.07 (m, 4H), 7.52 (d, *J* 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 55.4, 101.2, 106.2, 108.6, 114.3, 119.3, 122.8, 123.3, 126.8, 127.2, 128.8, 142.5, 142.8, 147,1, 148.1, 159.2. HRMS (ESI+) m/z calcd. for $C_{18}H_{14}O_3S$ [M^+] 310.0664; found 310.0659.

2-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)thiophene (5e): The product was obtained as white solid in 67% yield. Mp: 151-153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.84-6.91 (m, 3 H), 7.10-7.17 (m, 4 H), 7.53 (d, J 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 55.94, 55.98, 109.0, 111.5, 114.3, 118.2, 122.9, 123.1, 126.8, 127.2, 127.6, 142.6, 142.7, 148.7, 149.1, 159.1. HRMS (ESI+) m/z calcd. for $C_{19}H_{18}O_3S$ [M + H] 327.1055; found 327.1054.

2-(4-chlorophenyl)-5-(3,4-dimethoxyphenyl)thiophene (5f): The product was obtained as pale yellow solid in 60% yield. Mp: 153-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 3H), 6.86 (d, *J* 9 Hz, 1H), 7.09-7.20 (m, 4 H), 7.31 (d, *J* 9 Hz, 2H), 7.51 (d, *J* 9 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.96, 55.99, 109.1, 111.5, 118.3, 123.2, 124.3, 126.6, 127.2, 129.0, 132.9, 133.0, 141.3,144.1, 148.9, 149.2. HRMS (ESI+) m/z calcd. for $C_{18}H_{15}ClO_2S$ [M + H] 331.0560; found 331.0603.

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Keywords: cross-coupling • unsymmetrical 1,3-butadiynes • one-pot • cyclization • sulfur heterocycles

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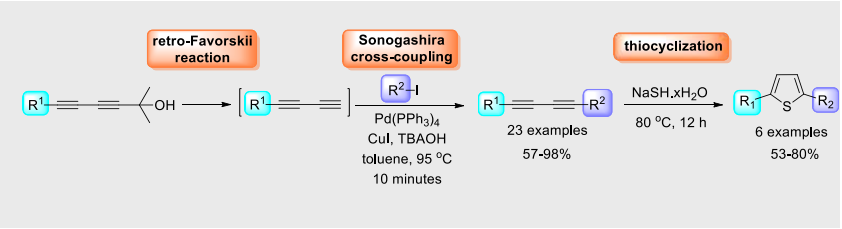

Novel one-pot, fast and efficient protocol was developed to synthesize unsymmetrical 1,3-diynes. The procedure involved two sequential reactions: a retro-Favorskii reaction to furnish terminal diacetylenic compound, and its coupling with organic iodide in a Sonogashira under reflux in toluene for ten minutes. In addition, the described protocol was also extended to the synthesis of 2,5-diarylthiophenes through *in situ* thiocyclization of 1,3-butadiynes.

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Page No. – Page No.

One-pot synthesis of unsymmetrical 1,3-butadiyne derivatives and their application in the synthesis of unsymmetrical 2,5-diarylthiophenes

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