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Improvement in the synthesis of (*Z*)-organylthioenynes via hydrothiolation of buta-1,3-diynes: a comparative study using NaOH or TBAOH as base

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ABSTRACT

Hydrothiolation of symmetrical and unsymmetrical buta-1,3-diynes with sodium organylthiolate anions in reflux, generated in situ by reacting C_4H_9SH with NaOH, afforded (*Z*)-organylthioenynes in low to good yields (25–80%). By using tetrabutylammonium hydroxide (TBAOH) as base instead of NaOH, the hydrothiolation of buta-1,3-diynes was more rapid and efficient, providing (*Z*)-organylthioenynes in good to excellent yields (70–95%).

Vinyl sulfides are versatile intermediates that have been intensively applied in organic synthesis[1–12] and identified in biologically active molecules such as Griseoviridin, a type A streptogramin antibiotic, first isolated from *Streptomyces graminofaciens*;[13a,b] and benzylthiocrellidone, a yellow pigment isolated from the bright-red sponge *Crella spinulata*. Aromatic vinyl-sulfide derivatives are found in several drugs with pharmaceutical activity against important diseases such as Alzheimer's, Parkinson's, diabetes, AIDS, and cancer.[14]

The methodologies most widely used to obtain vinyl sulfides involve the addition of organothiols or organylthiolate anions into 1-alkynes.[15–18] However, hydrothiolation using organothiols can lead to an undesired regio- and stereoisomeric mixture of vinyl sulfides.[15,16] Anti-Markovnikov or Markovnikov addition of thiol to 1-alkynes depends on the reaction conditions used, such as: type of catalyst (radical catalyzed reactions, metal-catalyzed reactions), organothiol, or functional group bound to the terminal alkyne.[15,16]

Moreover, the regio- and stereoselective addition of organylthiolate anions to 1-alkynes (nucleophilic addition) only occurs when a coordinating active moiety is located in close proximity to a triple bond.[17,18]

To solve these problems, our group recently studied the hydroalumination of thioacetylenes, using the inexpensive and commercially available DIBAL-H (diisobutyl-aluminum hydride) and the 'ate complex' lithium di(isobutyl)-*n*-butyl aluminate hydride (Zweifeĺs reagent) as reducing agent, allowing high regio- and stereoselective synthesis of (*Z*) and (*E*)-vinyl sulfides, respectively.[19] Stereocontrolled S-vinylation of thiols using vinyl halides under copper-catalyst is an excellent alternative to obtain vinyl sulfide.[20]

Conjugated (*Z*)-organylthioenynes type **2** have emerged recently as powerful intermediates, which can be used as precursors to construct an enediyne system and substituted thiophenes.

Few methods to prepare (*Z*)-organylthioenynes with high regio- and stereoselectivity have been published.[17d,e,18] Perin and co-workers[21] studied the green-hydrothiolation of 1,4-diorganylbuta-1,3-diynes type **1** using thiols in a solid-catalyst system containing KF/Al_2O_3 and PEG-400 or glycerol as recyclable solvents. However, a mixture of (*E*) and (*Z*)-organylthioenynes was detected, which limits the use of this protocol.

We became interested in the synthesis of (*Z*)-1-butylthio-1,4-di-(4-methoxyphenyl)-but-1-en-3-yne **2a**, which can be used as a precursor to synthesize 2,5-di-(4-methoxyphenyl)-3-iodo thiophene **3a**, a new prototype to construct efficacious drugs against neglected diseases (Scheme 1).[22]

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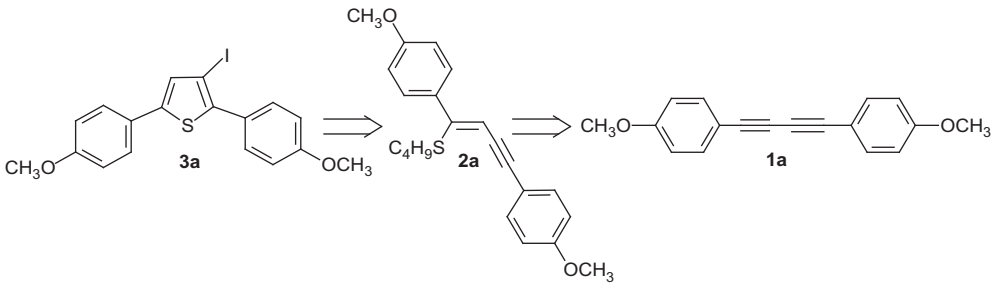
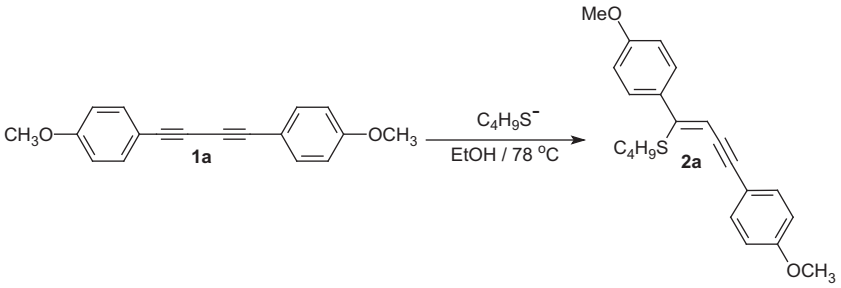


Scheme 1.



Scheme 2.

Table 1
Hydrothiolation of buta-1,3-diyne **1a**

Entry	Buthylthiolate anion formation	Reaction condition[a]	Time	Yield (%)
1	$C_4H_9SSC_4H_9/NaBH_4$	A	24 h	15
2	$C_4H_9SH/NaOH$	B	48 h	25
3	$C_4H_9SH/NaOH$	C	24 h	56
4	C_4H_9SH/TBAOH	D	15 min	95
5	$C_4H_9SH/NaOH$	E	4 h	80

[a] A—See reference[17e]; B—Addition of C_4H_9SH (1.0 equiv)/NaOH (1.0 equiv) to **1a** (1.0 equiv) at room temperature, and after 5 min, heated to 78 °C for the desired time; C—Addition of C_4H_9SH (1.4 equiv)/NaOH (1.4 equiv) to **1a** (1.0 equiv) at room temperature, and after 5 min, heated to 78 °C for the desired time; D—Addition of C_4H_9SH (1.4 equiv)/TBAOH (1.4 equiv) to **1a** (1.0 equiv) at 78 °C and left for the desired time; E—Addition of C_4H_9SH (1.4 equiv)/NaOH (1.4 equiv) to **1a** (1.0 equiv) at 78 °C and left for the desired time.

Our first attempt to synthesize compound **2a** was by applying the protocol that we recently reported, which involves the regio- and stereospecific hydrothiolation of 1,4-di-(4-methoxyphenyl)-buta-1,3-diynes (1.0 equiv)[17e] **1a** employing the reductive system $C_4H_9SSC_4H_9/NaBH_4$ (1.0 equiv) in EtOH. However, the result was unsatisfactory, since the reaction time was long (24 h under reflux), a large amount of starting material was recovered intact, and the desired product **2a** was obtained in only 15% yield (Scheme 2, Table 1, entry 1).

This prompted us to investigate the use of a classical reaction[1f,17a–d] such as S-Csp^2 bond formation via the addition of C_4H_9SH (1.0 equiv)/NaOH (1.0 equiv) to the 1,4-di-(4-methoxyphenyl)-buta-1,3-diynes **1a**. To our surprise, (***Z***)-thiobutenyne **2a** was obtained in low yield (25%), using a long reaction time and reflux (Scheme 2, Table 1, entry 2).

In order to increase the yield of this reaction, we further investigated the hydrothiolation of 1,4-diorganyl-but-1,3-diynes. First, we modified the ratio of the reactant system $C_4H_9SH/NaOH$ (1.4 equiv) with respect to buta-1,3-diyne **1a** (1.0 equiv). We obtained a small increase in the formation of (***Z***)-thiobutenyne **2a** (56% yield) after 24 h of reaction under reflux. A small amount of starting material was recovered intact (Scheme 2, Table 1, entry 3).

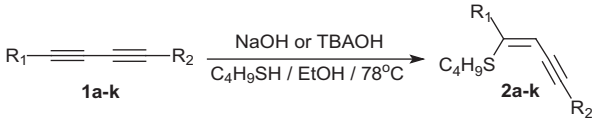
In an attempt to increase the yield and speed of the reaction, we decided to use tetrabutylammonium hydroxide (TBAOH) as the basis for the synthesis of (***Z***)-thiobutenyne **2a**. TBAOH has been used as a strong base in titrations,[23] and as a phase-transfer catalyst (PTC)[24,25] to accelerate transesterifications,[26] etherifications,[27] alkylations,[28] eliminations,[29] and aldol-type reactions.[30,31]

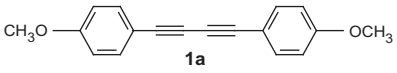
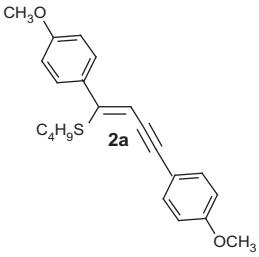
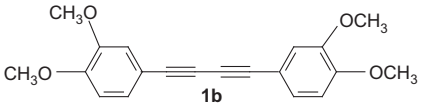
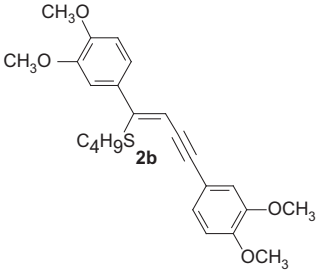
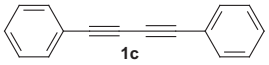
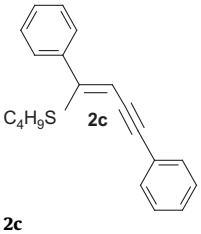
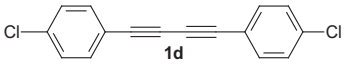
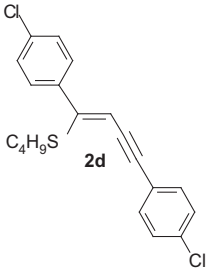
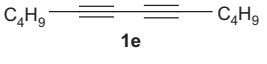
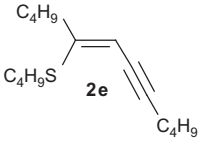
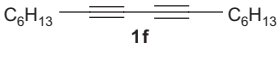
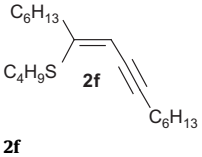
More recently, our group and others demonstrated that TBAOH is a very efficient activator for accelerating Sonogashira cross-coupling reactions.[32–36] While the cross-coupling reaction between (*E*)-1-iodovinyl-1-tributylstannanes and 1-heptyne for the synthesis of (*Z*)-tributylstannyl enynes occurred in 2.5 h using $Pd(PPh_3)_4$, CuI, pyrrolidine, the same reaction occurred in only 10 min when pyrrolidine was replaced by TBAOH as a base.[32]

Therefore, a mixture of C_4H_9SH/TBAOH (1.4 equiv) in 95% ethanol was added dropwise to a solution containing 1,4-di(4-methoxyphenyl)-buta-1,3-diyne **1a** (1.0 equiv) at 78 °C (Table 1, entry 4), because the yields were only moderate when the addition of $C_4H_9SH/NaOH$ (1.4 equiv) to **1a** was carried out at room temperature (Table 1, entry 3). Compound **1a** was consumed very smoothly (15 min), furnishing (***Z***)-1-butylthio-1,4-di-(4-methoxyphenyl)-but-1-en-3-ynes **2a** in 95% yield (Table 1, entry 4).

This excellent result inspired us to perform a wide systematic study involving the highly stereoselective hydrothiolation of symmetrical and unsymmetrical buta-1,3-dyines **1a–k** employing the addition of butylthiolate anions at 78 °C, generated in situ by the reaction of inexpensive and commercially available C_4H_9SH with

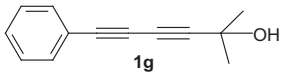
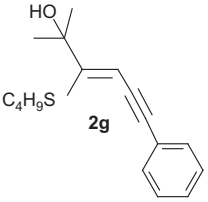
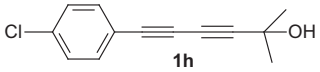
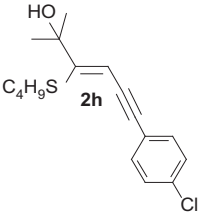
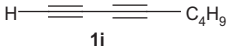
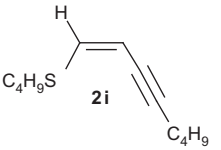
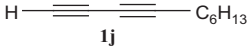
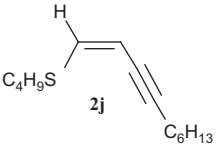
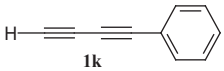
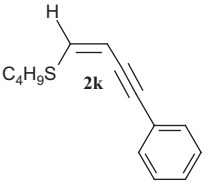
Table 2
Hydrothiolation of buta-1,3-diynes using C_4H_9SH/TBAOH or C_4H_9SH/NaOH[41–45]



Entry	Buta-1,3-diynes	Reaction conditions	Base	Time	Product	Yield (%)
1	 **1a**	D	TBAOH	15 min	 **2a**	95
2	**1a**	E	NaOH	4 h	**2a**	80
3	 **1b**	D	TBAOH	15 min	 **2b**	94
4	**1b**	E	NaOH	4 h	**2b**	79
5	 **1c**	D	TBAOH	5 min	 **2c**	93
6	**1c**	E	NaOH	4 h	**2c**	78
7	 **1d**	D	TBAOH	5 min	 **2d**	79
8	**1d**	E	NaOH	15 min	**2d**	52
9	 **1e**	D	TBAOH	9 h	 **2e**	87
10	**1e**	E	NaOH	24 h	**2e**	72
11	 **1f**	D	TBAOH	9 h	 **2f**	85
12	**1f**	E	NaOH	24 h	**2f**	66

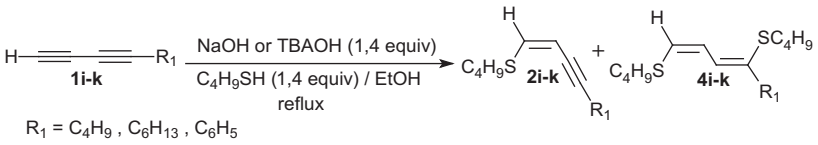
(*continued on next page*)

Table 2 (*continued*)

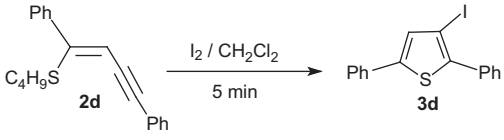
Entry	Buta-1,3-diynes	Reaction conditions	Base	Time	Product	Yield (%)
13	 **1g**	D	TBAOH	5 min	 **2g**	91
14	**1g**	E	NaOH	1 h	**2g**	75
15	 **1h**	D	TBAOH	5 min	 **2h**	92
16	**1h**	E	NaOH	1 h	**2h**	77
17	 **1i**	F	TBAOH	5 min	 **2i**	70[a]
18	**1i**	G	NaOH	1 h	**2i**	62[a]
19	 **1j**	F	TBAOH	5 min	 **2j**	72[a]
20	**1j**	G	NaOH	1 h	**2k**	71[a]
21	 **1k**	F	TBAOH	5 min	 **2k**	74[a]
22	**1k**	G	NaOH	1 h	**2k**	73[a]

Reaction conditions: D—Addition of C_4H_9SH (1.4 equiv)/TBAOH (1.4 equiv) to **1** (1.0 equiv) at 78 °C and left for the desired time; E—Addition of C_4H_9SH (1.4 equiv)/NaOH (1.4 equiv) to **1** (1.0 equiv) at 78 °C and left for the desired time. F—Addition of C_4H_9SH (1.0 equiv)/TBAOH (1.0 equiv) to **1** (1.0 equiv) at 78 °C and left for the desired time; G—Addition of C_4H_9SH (1.0 equiv)/NaOH (1.0 equiv) to **1** (1.0 equiv) at 78 °C and left for the desired time.

[a] Excess of C_4H_9SH (1.4 equiv)/NaOH or TBAOH (1.4 equiv) produced a mixture of (***Z***)-thiobutenynes **2i–k** and divinyl disulfides **4i–k**.



Scheme 3.



Scheme 4.

TBAOH, in order to make a comparison with C_4H_9SH/NaOH in the synthesis of several (***Z***)-thiobutenynes **2a–k** (Table 2).

We observed that hydrothiolation involving several symmetrical and unsymmetrical disubstituted buta-1,3-diynes type **1a–h** (1.0 equiv) with C_4H_9SH/TBAOH (1.4 equiv) afforded (***Z***)-thiobutenynes **2a–h** in shorter reaction times (5–15 min) and in good to excellent yields (79–95%), than using C_4H_9SH/NaOH (1.4 equiv).

Hydrothiolation using C_4H_9SH/TBAOH is more efficient because TBAOH is a strong base and also a phase-transfer catalyst (PTC),[23–36] increasing the solubility of reagents in the organic phase. We also believe that TBAOH increases the reactivity of the butylthiolate anion ($C_4H_9S^-$), accelerating the hydrothiolation of 1,3-dyines to afford (***Z***)-thiobutenyne type **2** in excellent yields.

All hydrothiolation reactions of 1,3-butadiynes with TBAOH or NaOH were monitored by thin-layer chromatography. Also, the GC analysis showed that the addition of C_4H_9SH/NaOH to 1,3-buta-

dyine **1a** which occurred in 4 h (Table 1, entry 5) furnished (*Z*)-thiobutenynes **2a** in 80% yield, showing that using NaOH, the hydrothiolation always occurred more slowly and in lower yields.

Concerning the chemoselectivity of the hydrothiolation of monosubstituted unsymmetrical buta-1,3-diynes types **1i–k**, we observed that the terminal triple bond was more reactive than the substituted triple bond, because of the lower steric hindrance to the addition of C_4H_9SH/NaOH (1.0 equiv) or C_4H_9SH/TBAOH (1.0 equiv), furnishing in only 5 min (*Z*)-thiobutenoynes **2i–k** (Table 1, entries 17, 19 and 21). On the other hand, we believe that an excess of C_4H_9SH and NaOH or TBAOH (1.4 equiv) is responsible for the formation of small amounts of divinyl disulfides **4i–k** (Scheme 3).

Analysis of compounds **1g–h** indicated that the propargylic triple bond underwent an addition of the butylthiolate anion, which was generated more quickly than triple bonds bearing the substituted phenyl and *p*-chlorophenyl (Table 1, entries 15 and 17). This probably occurred due to the formation of a stable cyclic five-member transition state, similar to that which we recently described, involving the addition of phenylthiolate anions (generated by the reduction of phenyl disulfide) to propargyl substituted buta-1,3-dyines.[17e]

Based on these results, we envision the possibility of applying (*Z*)-organylthioenynes **2** in the synthesis of 3-halothiophenes **3**. Thiophene molecules can be used as the starting material to construct useful molecules in medicinal chemistry[37,38] and electronic materials.[39,40]

We describe herein a novel application involving the electrophilic cyclization of (*Z*)-organylthioenynes to synthesize 3-iodothiophenes type **3**. We examined the reaction of (*Z*)-1-phenylthio-1,4-diphenyl-but-1-en-3-yne **2d** (1.0 equiv) and I_2 (1.1 equiv) in CH_2Cl_2, which provided 2,5-diphenyl-3-iodo thiophene **3d** in 82% yield (Scheme 4).

In conclusion, we made improvements in the methodology to synthesize (*Z*)-thiobutenynes, using the reducing system C_4H_9SH/TBAOH rather than C_4H_9SH/NaOH. Applying this methodology, we were able to prepare the desired compounds **2a–k** rapidly and in good to excellent yields. The efficiency of these compounds for obtaining 3-iodothiophenes was demonstrated. The synthesis of (*Z*)-enedyines using substrate (*Z*)-organylthioenynes in metal-catalyzed Kumada cross-coupling reaction will also be examined.

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41. Typical procedure for the synthesis of (*Z*)-1-buthylthio-1,4-diorganyl-1-buten-3-ynes with C_4H_9SH/TBAOH. To a solution of 1,4-methoxyphenyl-butadiyne 1a (5.0 mmol) in ethanol (35 ml) at 78 °C, we added dropwise a solution of C_4H_9SH (7.0 mmol) and 40% TBAOH in H_2O (7.0 mmol) in 95% ethanol (35 mL) under a nitrogen atmosphere and vigorous stirring. The reaction mixture was stirred at 78 °C for 15 min, allowed to reach room temperature, diluted with

ethyl acetate (3 × 20 mL) and washed with a saturated solution of NH_4Cl (3 × 30 mL) and brine (3 × 30 mL). After the organic phase was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel using hexane: ethyl acetate 9.5:0.5 as mobile phase, to give pure (Z)-butylthio-1,4-bis(4-methoxyphenyl)but-1-en-3-yne 2a as a yellow solid, mp = 38–40 °C; Yield: 95%. GC/MS *m*/*z* 352 (M^+), 309 (100%), 281, 253, 207, 151, 121, 96, 73, 56; ^1H NMR (300 MHz, δ in $CDCl_3$): 0.81 (t, J 7.2 Hz, 3H); 1.35 (sex, *J* 7.2 Hz, 2H); 1.48 (quint, *J* 7.3 Hz, 2H); 2.63 (t, *J* 7.2 Hz, 2H); 3.80 (s, 3H); 3.81 (s, 3H); 5.98 (s, 1H); 6.84 (d, J 8.7 Hz, 2H); 6.88 (d, J 8.7 Hz, 2H); 7.43 (d, J 8.7 Hz, 2H); 7.46 (d, J 8.7 Hz, 2H). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 13.6; 21.6; 31.9; 32.5; 55.3; 86.8; 96.9; 108.8; 113.8; 114.0; 116.0; 129.2; 131.5; 132.8; 148.3; 159.3; 160.0.

42. (***Z***)-1,4-bis(4-chlorophenyl)-1-(*n*-thiobutyl)-but-1-en-3-ynyl 2d as a yellow solid. Yield: 79%. Mp = 63–65 °C. GC/MS *m*/*z* 362 (M^+), 341, 317, 304, 268, 236, 207, 189, 155 (100%), 135, 113, 96, 73, 55; 1H NMR (300 MHz, δ in $CDCl_3$): 0.81 (t, J 7.2 Hz, 3H); 1.33 (sex, J 7.2 Hz, 2H); 1.45 (quint, J 7.2 Hz, 2H); 2.58 (t, J 7.2 Hz, 2H); 5.99 (s, 1H); 7.29 (d, J 8.6 Hz, 2H); 7.33 (d, J 8.6 Hz; 2H); 7.44 (d, J 8.6 Hz, 2H). 13C NMR (75 MHz, δ in $CDCl_3$): 13.5; 21.5; 31.8; 32.5; 88.4; 96.4; 110.0; 122.0; 128.7; 128.7; 129.1; 132.6; 134.2; 134.7; 137.2; 149.1.
43. (***Z***)-7-(*n*-thiobutyl)-hexadec-7-en-9-yne **2f** as a yellow oil. Yield: 85%. GC/MS *m*/*z* 308 (M^+), 265, 251, 207, 181 (100%), 167, 147, 111, 91, 55; 1H NMR (300 MHz, δ in CDCl3): 0.84–0.92 (m, 9H); 1.23–1.60 (m, 20H); 2.35 (td, J 7.3 and 1.9 Hz, 2H); 2.22 (t, J 7.4 Hz, 2H); 2.79 (t, J 7.4 Hz, 2H); 5.47 (s, 1H). 13C NMR (75 MHz, δ in CDCl3): 13.7; 14.0; 19.8; 21.9; 22.6; 28.5; 28.6; 28.7; 28.8; 30.5; 31.4; 31.6; 31.9; 36.3; 77.7; 96.9; 106.0; 148.5.
44. Typical procedure for the synthesis of (*Z*)-1-buthylthio-1,4-diorganyl-1-buten-3-ynes with C_4H_9SH/NaOH. To a solution of 1,4-bis(3,4-dimethoxyphenyl)buta-1,3-diyne **1b** (5.0 mmol) in ethanol (35 ml) at 78 °C, we added dropwise a solution of C4H9SH (7.0 mmol) and NaOH (7.0 mmol) in 95% ethanol (35 mL) under a nitrogen atmosphere and vigorous stirring. The reaction mixture was stirred at 78 °C for 4 h, allowed to reach room temperature, diluted with ethyl acetate (3 × 20 mL) and washed with a saturated solution of NH4Cl (3 × 30 mL) and brine (3 × 30 mL). After the organic phase was dried over anhydrous MgSO4, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel using hexane: ethyl acetate 9:1 as mobile phase, to give pure (*Z*)-butylthio-1,4-bis(3,4-dimethoxyphenyl)but-1-en-3-yne **2b** as a yellow solid, mp = 58–60 °C; Yield: 79%. GC/MS *m*/*z* 412 (M^+), 369, 341, 281, 253, 207 (100%), 191, 135, 96, 73, 45; 1H NMR (300 MHz, δ in CDCl3): 0.80 (t, J 7.2 Hz, 3H); 1.34 (sex, J 7.3 Hz, 2H); 1.47 (quint, J 7.3 Hz, 2H); 2.62 (t, J 7.2 Hz, 2H); 3.86 (s, 6H); 3.87 (s, 3H); 5.99 (s, 1H); 3.88 (s, 3H); 6.79 (d, J 8.3 Hz, 1H); 6.83 (d, J 8.3 Hz, 1H); 6.97 (d, J 1.76 Hz, 1H); 7.04–7.10 (m, 3H). 13C NMR (75 MHz, δ in CDCl3): 13.6; 21.6; 31.9; 32.5; 55.8; 86.5; 97.0; 108.7; 110.8; 110.9; 110.9; 113.9; 115.9; 120.4; 124.7; 131.7; 148.5; 148.6; 148.7; 149.3; 149.4.
45. Typical procedure for the synthesis of 3-iodo-2,5-diphenylthiophene **4d**. To a solution of (*Z*)-1-buthylthio-1,4-diorganyl-1-buten-3-yne **2d** (2.0 mmol) in CH_2Cl_2 (12 ml), we added dropwise a solution of I2 (2.2 mmol) in CH_2Cl_2 (28 mL) under vigorous stirring. The reaction mixture was stirred for 5 min, diluted with CH_2Cl_2 (20 mL) and washed with a 10% solution of $Na_2S_2O_3$ (3 × 30 mL) and brine (3 × 30 mL). After the organic phase was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel using hexane as mobile phase, to give pure 3-iodo-2,5-diphenylthiophene 4d as a yellow solid, mp = 42–44 °C; Yield: 82%. GC/MS *m*/*z* 362 (M^+) [100], 234, 202, 191, 165, 121, 77; 1H NMR (300 MHz, δ in $CDCl_3$): 7.28–7.66 (m, 11H). ^{13}C NMR (75 MHz, δ in $CDCl_3$): 78.7; 125.6; 128.1; 128.4; 128.5; 129.0; 129.2; 132.3; 133.1; 134.2; 141.5; 145.1.