A new procedure for the synthesis of aryl- or hetaryl-substituted conjugated diynes

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On treatment with two equivalents of $NaNH_2$ in liquid ammonia the enyne sulfides $RC\equiv C-CH=CHSEt$ (*cis*-isomers, where R is an aryl or a hetaryl) afford sodium salts of 1,3-diynes. The latter react with ethyl bromide to produce disubstituted diynes $RC\equiv C-C\equiv CEt$ in high yields.

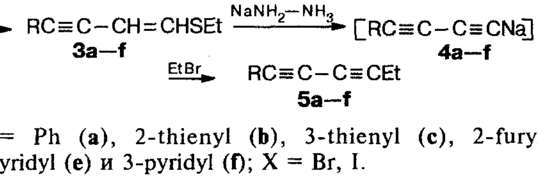
Key words: 1-alkylthio-1-buten-3-ynes; 1,3-diynes, mono- and disubstituted.

Monosubstituted 1,3-diynes are convenient synthones for the preparation of various dienes, enynes and polyynes.

The synthesis of monosubstituted 1,3-diynes by functionalizing one of the two methyne groups of butadiyne is often accompanied by the formation of a mixture of mono- and disubstituted diacetylenes that are difficult to separate.[1] In addition, the explosive nature of butadiyne makes it impossible to perform the reactions on a large scale.

We have chosen the ethylsulfide group as the protective group for butadiyne. On the one hand, this group stabilizes the 1,3-butadiyne system. On the other hand, due to the blocking of one of the ethynyl fragments, the remaining terminal $HC\equiv C$ group can be functionalized unambiguously; subsequent removal of the sulfide protection makes it possible to repeat the substitution at the other terminus.

The procedure that we have elaborated includes the condensation of aryl- or hetarylbromides and -iodides (**1**) with 1-ethylthio-1-buten-3-yne (**2**) in the $PdCl_2(PPh_3)_2$—Cu(I)—amine catalytic system,[2–4] followed by treatment of the coupling product (**3**) with 2 equiv. of $NaNH_2$ in liquid ammonia, and subsequent alkylation of the sodium diacetylenides thus obtained (**4**) with ethyl bromide.



$$\underset{\mathbf{1a-f}}{RX} + \underset{\mathbf{2}}{HC\equiv C-CH=CHSEt} \xrightarrow[50-80\,^{\circ}C]{PdCl_2(PPh_3)_2-CuBr-Et_3N} \underset{\mathbf{3a-f}}{RC\equiv C-CH=CHSEt} \xrightarrow{NaNH_2-NH_3} \underset{\mathbf{4a-f}}{[RC\equiv C-C\equiv CNa]} \xrightarrow{EtBr} \underset{\mathbf{5a-f}}{RC\equiv C-C\equiv CEt}$$

R = Ph (**a**), 2-thienyl (**b**), 3-thienyl (**c**), 2-furyl (**d**), 2-pyridyl (**e**) и 3-pyridyl (**f**); X = Br, I.

The condensation of aryl- and hetaryl halides **1a—f** with **2** was carried out in the $PdCl_2(PPh_3)_2$—CuBr—Et_3N system at 50—80°C (Table 1). Compounds **3a—f** are rather stable and withstand vacuum distillation. According to the ^1H NMR spectral data, they retain the initial *cis*-configuration. As could be anticipated, the halopyridines were more reactive than the corresponding halo derivatives of five-membered heterocycles.

The elimination of ethylthiol from **3a** was carried out by the action of $NaNH_2$ in liquid ammonia; however, we could not isolate the individual 1-phenylbutadiyne. The low stability of terminal diynes prompted us to carry out the substitution at the second methyne group without isolating the intermediate monosubstituted 1,3-diyne.

Synthesis of aryl- (hetaryl-) ethylbutadiynes was carried out by treating **3** with 2 equiv. of $NaNH_2$ in liquid ammonia followed by the action of an excess of ethyl bromide (1 mol of EtBr is necessary to bind the EtSNa formed). Phenyl-, 2-furyl-, 2- and 3-thienyl-, and 3-pyridylenynes react smoothly to give the corresponding disubstituted butadiynes **5** in 60—90 % overall yields (Table 2). In the case of the 2-substituted pyridine derivative **3e** the final product contained an admixture (~30 %) of a product resulting from the further transformations, 6-(2-pyridyl)-2,4-octadiyne (**6**). Its formation is assumed to be caused by rapid deprotonation of butadiyne **5e** followed by attack on the anion formed by ethyl bromide.[5] In order to verify this assumption, compound **5e**, prepared from 2-ethynylpyridine and 1-bromo-1-butyne, was treated with an equimolar amount of $NaNH_2$ in NH_3 in the presence of excess EtBr, which in fact led to the formation of diyne **6** (70 %); in addition, 25 % of the starting **5e** was returned.

The structure of **6** was confirmed by means of mass-spectrometry and by the ^1H NMR and IR spectroscopy data (see Table 2).

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Table 1. 4-Aryl(hetaryl)-1-ethylthio-1-buten-3-ynes (**3**)

Compound	Time (*T*)	Yield (%)	Bp (°C) at 0.05 Torr	n_D^{20}	Molecular formula	Found / Calculated (%) C	H	N	^{1}H NMR (CCl_4), δ, *J* (Hz)
3a	1.5 (80°C)	93.0	118—120	1.6410	$C_{12}H_{12}S$	76.23 76.55	6.59 6.42	17.20 17.03	1.25 (t, 3 H, Me, *J* = 6); 2.75 (q, 2 H, CH_2, *J* = 6); 5.55 (d, 1 H, =CH, *J* =10); 6.40 (d, 1 H, =CH, *J* =10); 7.1—7.4 (m, 5 H, Ph)
3b	3 (80°C)	87.9	122—125	1.6740	$C_{10}H_{10}S_2$	61.85 61.80	5.12 5.18	33.00 33.02	1.30 (t, 3 H, Me, *J* = 6); 2.76 (q, 2 H, CH_2, *J* = 6); 5.62 (d, 1 H, =CH, *J* = 10); 6.8—7.2 (m, H arom.)
3c	2 (80°C)	77.3	125—126	1.6640	$C_{10}H_{10}S_2$	61.72 61.80	5.19 5.18	33.13 33.02	1.23 (t, 3 H, Me, *J* = 6); 2.65 (q, 2 H, CH_2, *J* = 6); 5.55 (d, 1 H, =CH, *J* = 10); 6.35 (d, 1 H, =CH, *J* = 10); 6.9—7.4 (m, H arom.)
3d	3.5 (80°C)	74.0	110—112	1.6325	$C_{10}H_{10}SO$	67.50 67.38	5.42 5.65	17.80 17.99	1.25 (t, 3 H, Me, *J* = 6); 2.68 (q, 2 H, CH_2, *J* = 6); 5.55 (d, 1 H, =CH, *J* = 9); 6.2—6.5 (m, 4 H, =CH, H arom.), 7.22 (d, 1 H, α-H furyl)
3e	1.5 (50°C)	92.3	140—145	1.6490	$C_{11}H_{11}NS$	69.51 69.80	5.92 5.85	17.09 16.94	1.30 (t, 3 H, Me, *J* = 6); 2.81 (q, 2 H, CH_2, *J* = 6); 5.68 (d, 1 H, =CH, *J* = 9); 6.98 (d, 1 H, =CH, *J* = 9); 7.3—7.4 (m, 3 H, β,β',γ-H pyridyl); 8.45 (d, 1 H, α-H pyridyl)
3f	2.5 (50°C)	79.1	135—140	1.6490	$C_{11}H_{11}NS$	70.01 69.80	5.71 5.85	17.10 16.94	1.40 (t, 3 H, Me, *J* = 6); 2.82 (q, 2 H, CH_2, *J* = 6); 5.67 (d, 1 H, =CH, *J* = 10); 6.60 (d, 1 H, =CH, *J* = 10); 7.0—7.8 (m, 2 H, β,γ-H pyridyl); 8.3—8.8 (m, 2 H, α,α'-H pyridyl)

Table 2. Products obtained on treatment of sulfides **3** with $NaNH_2$ and EtBr

Compound	Yield (%)	Bp (°C) at 0.05 Torr	n_D^{20}	Molecular formula	Found / Calculated (%) C	H	N	S	^{1}H NMR (CCl_4), δ, *J* (Hz)
5a	90.2	85—90	1.6140	$C_{12}H_{10}$	93.71 93.46	6.28 6.54			1.22 (т, 3 H, Me, *J* = 6); 2.35 (q, 2 H, CH_2, *J* = 6); 7.1—7.5 (5 H, Ph)
5b	62.5	90—95	1.6475	$C_{10}H_8S$	75.09 74.96	4.85 5.03		20.09 20.01	1.28 (т, 3 H, Me, *J* = 6); 2.46 (q, 2 H, CH_2, *J* = 6); 6.8—7.4 (m, 3 H, α,β,β'-H tienyl)
5c	94.5	93—97	1.6380	$C_{10}H_8S$	74.70 74.96	5.23 5.03		20.00 20.01	1.20 (т, 3 H, Me, *J* = 6); 2.32 (q, 2 H, CH_2, *J* = 6); 6.9—7.5 (m, 3 H, α,α',β-H tienyl)
5d	70.0	75—80	1.5930	$C_{10}H_8O$	83.65 83.30	5.40 5.59			1.20 (т, 3 H, Me, *J* = 6); 2.36 (2 H, CH_2, *J* = 6); 6.2—6.6 (m, 3 H, α,β,β′-H furyl)
5e	60.0	100—105	1.6185	$C_{11}H_9N$	85.40 85.13	5.61 5.84	8.92 9.03		1.20 (т, 3 H, Me, *J* = 6); 2.38 (q, 2 H, CH_2, *J* = 6); 7.0—7.7 (m, 3 H, β,β',γ-H pyridyl); 8.45 (1H, α-H pyridyl)
5f	61.0	90—95	1.6135	$C_{11}H_9N$	84.91 85.13	5.98 5.84	9.21 9.03		1.28 (т, 3 H, Me, *J* = 6); 2.35 (q, 2 H, CH_2, *J* = 6); 6.9—7.5 (m, 2 H, β,γ-H pyridyl); 8.3—8.7 (m, 2H, α,α'-H pyridyl)
6*	30.0	112—115	1.5930	$C_{13}H_{13}N$	84.98 85.21	7.30 7.15	7.81 7.64		0.75 (т, 3 H, Me, *J* = 6); 1.95 (с, 3 H, $CH_3C{\equiv}C$); 2.38 (m, 3 H, CH_2 и CH); 7.0—7.6 (m, 3 H, β,β',γ-H pyridyl); 8.46 (1 H, α-H pyridyl)

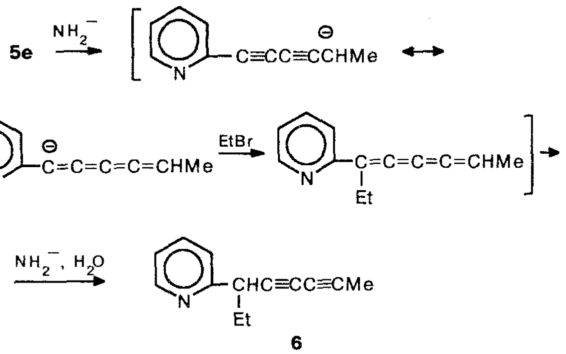
* Mass spectrum, *m/z*: 183 [M^+]; IR, ν (cm^{-1}): 2220, 2235 ($C{\equiv}C$).

In a similar way, the products of deeper alkylation were found when even a minor excess of $NaNH_2$ (2.1 *M*) and EtBr were allowed to interact with the 2-thienyl- and 2-furyl derivatives (**3b**, **3d**). The side process can be avoided if exactly two equivalents of $NaNH_2$ are used.

Experimental

The ^{1}H NMR spectra were recorded with a Varian EM 360 spectrometer in CCl_4.

The starting sulfide **2** was prepared in 82 % yield using a modified[6] Shostakovski procedure.[7]



The condensation of aryl- (hetaryl-) halides (1) with 1-ethylthio-1-buten-3-yne (2) (general procedure). A mixture containing 0.1 mol of a bromo- (**1d—1f**) or iodo-derivative (**1a—1c**), a terminal acetylene **2** (0.13 mol), 0.3 g of $PdCl_2(PPh_3)_2$, 0.5 g of PPh_3, and 0.2 g of CuBr in Et_3N (50 mL) was heated under a N_2 atmosphere at 50—80°C (Table 1) until the reaction was completed. After cooling, the reaction mixture was twice diluted with pentane and decanted. The combined organic extract (*ca.* 400 mL) was washed with water (2×100 mL), the organic layer was separated, dried with $MgSO_4$, and purified by distillation (see Table 1).

The following compounds were prepared according to this procedure: 4-phenyl-1-ethylthio-1-buten-3-yne (**3a**); 4-(2-thienyl)-1-ethylthio-1-buten-3-yne (**3b**); 4-(3-thienyl)-1-ethylthio-1-buten-3-yne (**3c**); 4-(2-furyl)-1-ethylthio-1-buten-3-yne (**3d**); 4-(2-pyridyl)-1-ethylthio-1-buten-3-yne (**3e**); 4-(3-pyridyl)-1-ethylthio-1-buten-3-yne (**3f**).

The combined elimination-ethylation step (general procedure). Sulfide **3** (0.05 mol) in 50 mL of dry ether was added dropwise to a stirred suspension of sodium amide (0.1 mol) in liquid NH_3 cooled to −40÷−45°C in a flow of N_2. The mixture was kept for 40 min, then EtBr (1.5 mol) was added dropwise. The reaction mixture was stirred for a further 40 min, and ammonia was evaporated. Then ether and water were added, the product was extracted with ether, dried with $MgSO_4$, and distilled *in vacuo*. The yields and constants of the compounds obtained are given in Table 2.

The following compounds were prepared according to this procedure: 1-phenyl-1,3-hexadiyne (**5a**), 1-(2-thienyl)-1,3-hexadiyne (**5b**), 1-(3-thienyl)-1,3-hexadiyne (**5c**), 1-(2-furyl)-1,3-hexadiyne (**5d**), and 1-(2-pyridyl)-1,3-hexadiyne (**5e**), along with 6-(2-pyridyl)-2,4-hexadiyne (**6**) as a by-product, and 1-(3-pyridyl)-1,3-hexadiyne (**5f**).

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