Nickel-catalyzed addition of benzenethiol to alkynes: formation of carbon—sulfur and carbon—carbon bonds*

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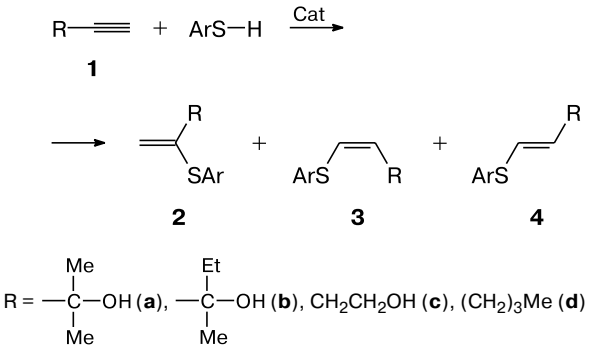
Nickel-catalyzed addition of benzenethiol to alkynes leads to alkenyl and dienyl sulfides; the direction of the process can be controlled by varying the PhSH/alkyne ratio. An advanced procedure, which ensures higher yields of 2-phenylsulfanylalkenes, includes gradual addition of alkyne to the other reactants. The structures of conjugated dienyl sulfides formed in the reaction were determined by 2D NMR spectroscopy.

Key words: nickel complexes, transition metal catalysis, alkynes, alkenyl sulfides, dienyl sulfides, green chemistry

Recently, we described[1] a new catalytic system for regioselective addition of arenethiols at the triple bond of alkynes **1** (Scheme 1). Of the three possible isomers **2—4**, only Markovnikov product **2** is formed with high selectivity. In the absence of a catalyst, the addition of arenethiols at alkynes affords anti-Markovnikov isomers **3** and **4** (see Refs 2—5).

Scheme 1



The simple and readily available $Ni(acac)_2$ was used as the catalyst precursor, which was converted *in situ* into nanostructured catalytic species $[Ni(SAr)_2]_n$ (see Ref. 1). This catalytic system was superior to the known analogs based on nickel and palladium complexes[6—9] in the activity and selectivity and provided the synthesis of Markovnikov type vinyl sulfides in preparative scale.[1] An important advantage of this strategy is the use of transition metal catalysis in combination with the atom-economic solvent-free processing.[10,11]

A disadvantage of the previously published procedure is the need to use excess arenethiol with respect to alkyne. High yields of product **2** could be attained at an ArSH : alkyne ratio of 2 : 1; lower ArSH : alkyne ratios resulted in the formation of by-products.[1]

This paper describes an improved catalytic procedure for the synthesis of product **2** in high yields at a stoichiometric reactants ratio. The structures of by-products were determined based on a detailed 2D NMR study and the mechanism of their formation was proposed.

Results and Discussion

As a model reaction, we chose the nickel-catalyzed (2 mol.% $Ni(acac)_2$) addition of benzenethiol at 2-methylbut-3-yn-2-ol (**1a**) (40 °C, 40 min) in the absence of a solvent. The variation of the reactants ratio in this reaction showed that a decrease in the PhSH : alkyne ratio from 2 : 1 to 1 : 1 entails a substantial decrease in the yield of **2a** and an increase in the yields of by-products (Table 1, runs *1* and *2*). With a PhSH : alkyne ratio of 1 : 2, the formation of by-products becomes the major reaction route (60%), while the yield of **2a** is only 40% (Table 1, run *3*).

Analysis of the ^1H NMR spectrum of the product mixture obtained with a PhSH : **1a** ratio of 1 : 2 showed

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Table 1. Effect of the PhSH : **1a** ratio on the yield of the reaction products[a]

Run	PhSH : **1a**	Yield (%)	
		2a	By-products
1	2 : 1[b]	55	35
2	1 : 1[b]	46	54
3	1 : 2[b]	40	60
4	1 : 1[c]	78	15

[a] Isolated yields.
[b] $Ni(acac)_2$ was added to the alkyne and then PhSH was added in one portion; 40 °C, 40 min.
[c] Gradual addition of alkyne at 40 °C over a period of 40 min.

that, in addition to the signals of product **2a**, the spectrum exhibits a large number of signals in the 4.9—7.0 ppm range corresponding to olefinic protons. To determine the structures of products, they were chromatographed on silica gel. The yield of product **2a** with spectral characteristics identical to reported data[8] was 40%. The by-products were mainly conjugated 1,3-dienes **5a**, **6a**, and **7a** (Scheme 2). A mixture of these compounds was isolated in an overall yield of 31%; according to ^{1}H NMR data, the yields of compounds **5a**, **6a**, and **7a** were 15, 9, and 7%, respectively. The low-field region of the ^{1}H NMR spectra of these compounds (Fig. 1) exhibits three groups of signals corresponding to the olefinic protons of each diene fragment. In the case of diene **5a**, only small spin-spin coupling constants are observed (J < 2 Hz). The spectrum of compound **6a** contains the coupling constant J(H—C=C—H_{trans}) = 16.1 Hz, and for diene **7a**, the spectrum shows the coupling constants J(H—C=C—H_{trans}) = 15.6 Hz and J(H—C—C—H) = 10.5 Hz and the far-range coupling constant ^4J = 0.7 Hz. The stereochemistry of

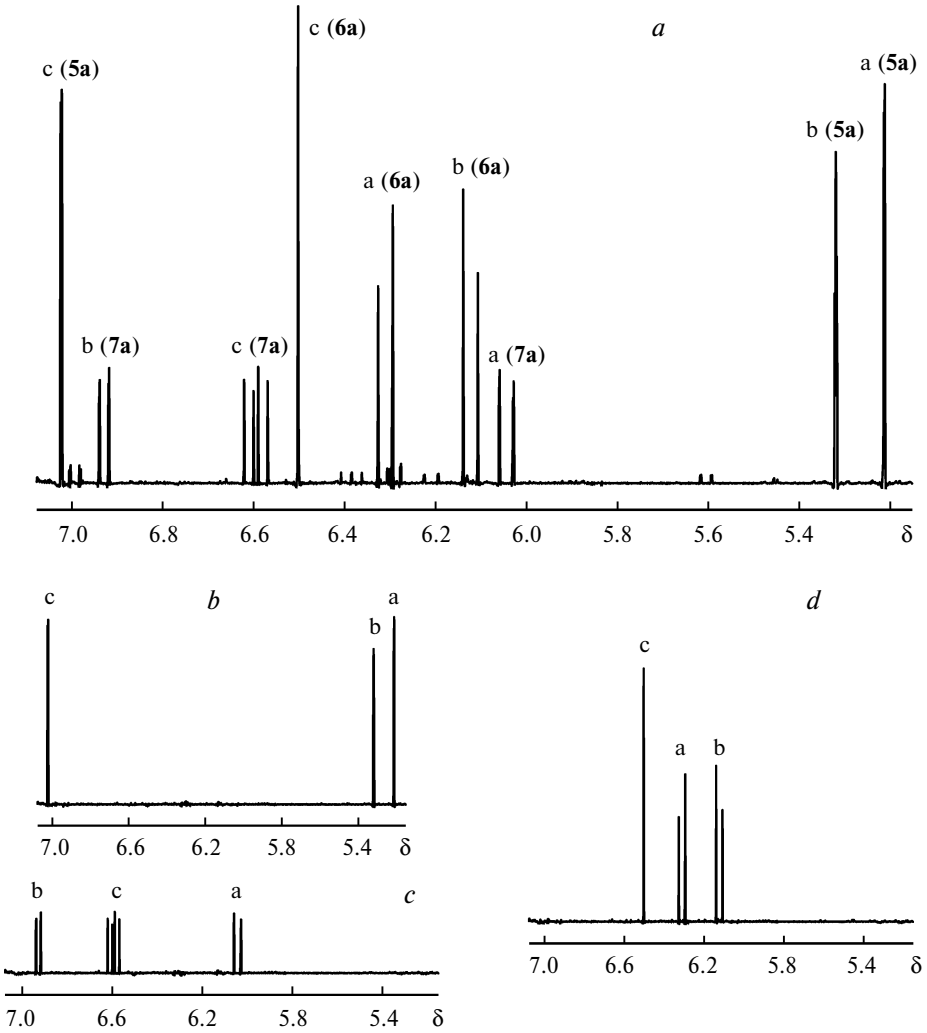


Fig. 1. Fragment of the ^{1}H NMR spectrum of the mixture of compounds **5a**, **6a**, and **7a** in the region of olefinic protons (*a*) and reconstructed fragments of the spectra of individual components of the mixture: **5a** (*b*), **7a** (*c*), **6a** (*d*). The designations are given in Fig. 2.

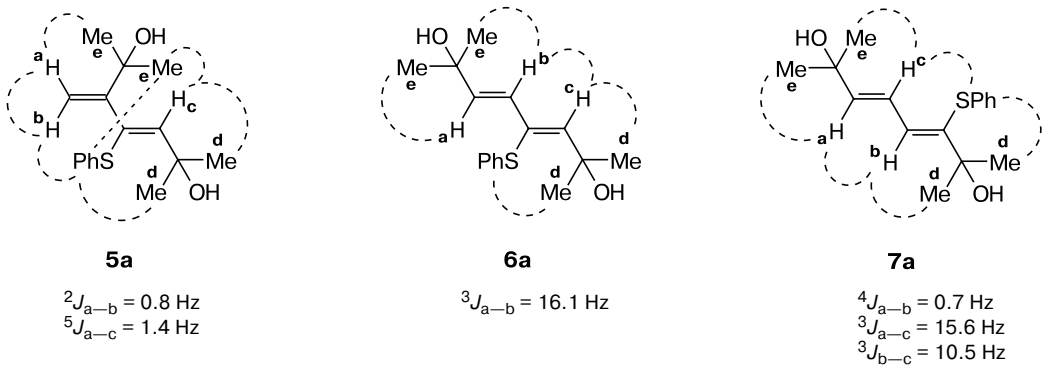
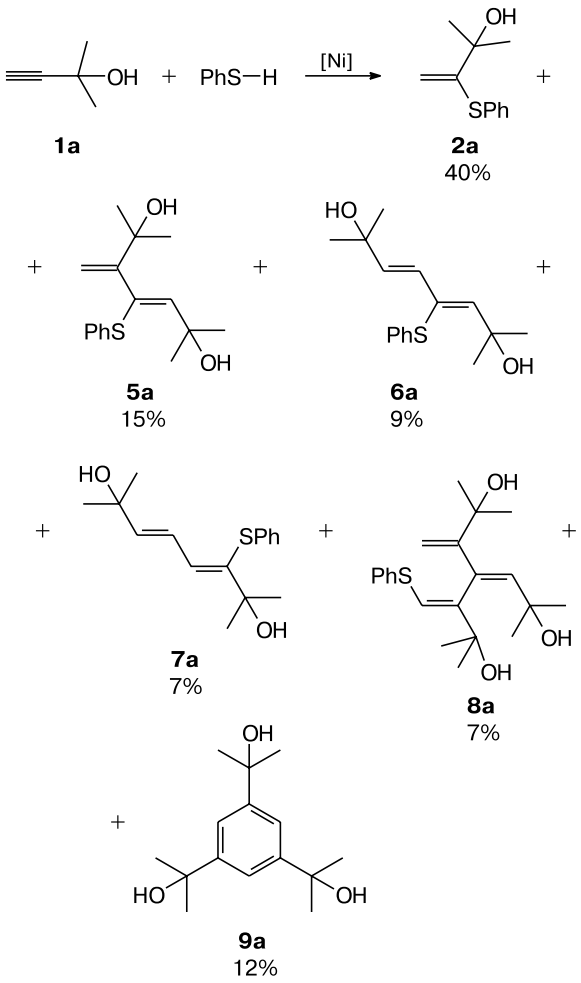


Fig. 2. NOE contacts and spin-spin coupling constants between the olefinic protons for compounds **5a—7a** observed in the NOESY spectrum.

dienes **5a—7a** was established using 2D NOESY experiments. The observed NOE contacts are schematically presented in Fig. 2. The methyl group signals in the high-field part of the spectrum were assigned using the key H^a—Me^e, H^c—Me^e, and H^c—Me^d contacts for **5a**; H^a—Me^e, H^b—Me^e, and H^c—Me^d contacts for **6a**; and H^a—Me^e, H^c—Me^e, and H^b—Me^d contacts for **7a** (for designations, see Fig. 2).

Scheme 2

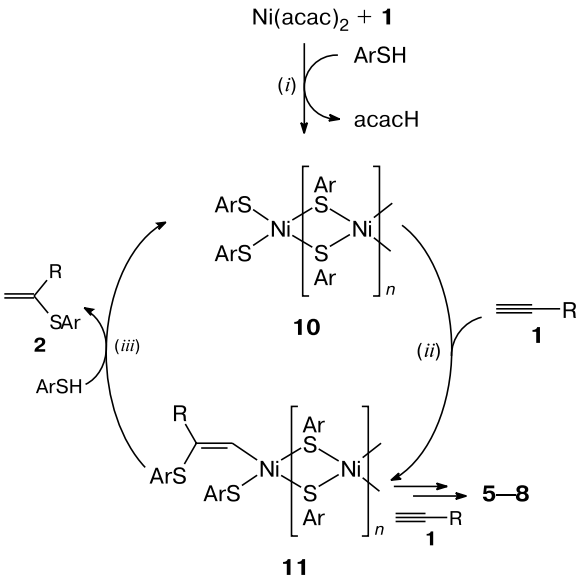


In addition, the mixture contained triene **8a** (yield 7%) and, somewhat unexpectedly, 1,3,5-tris(1-hydroxy-1-methylethyl)benzene **9a** (yield 12%). The remaining by-products fraction (~10%) could not be reliably identified, apparently, this comprised oligomers with higher molecular weights. The structure of compound **8a** was proposed based on analysis of 2D NOESY and COSY spectra (similarly to the procedure described previously). Aromatic derivative **9a** was identified based on ^1H and ^{13}C NMR and mass-spectrometry data. Previously,[12—14] the formation of symmetrical trisubstituted benzene **9a** from alkyne **1a** in a transformation catalyzed by nickel phosphine complexes has been reported; however, a catalytic activity of the sulfide nickel complexes toward trimerization is quite unusual.

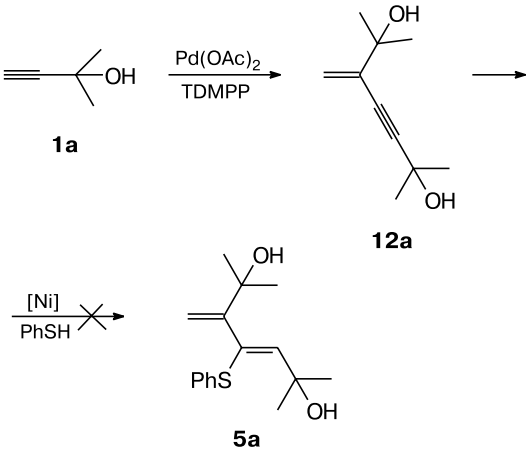
For nickel-catalyzed addition of arenethiols to alkynes (Scheme 3), a mechanism including catalyst activation (*i*), insertion of the alkyne (*ii*), and protonolysis (*iii*) has been proposed.[1] It was shown that the catalytic transformation occured under heterogeneous conditions. The insoluble polymeric complex $[Ni(SAr)_2]_n$ (**10**), resulting from replacement of the acetylacetonate ligand, was the active form of the catalyst. This reaction mechanism suggests that by-products are formed from intermediate **11** through isomerization and the reaction with other alkyne molecules.

As an alternative mechanism for the formation of dienes, one can conceive preliminary dimerization of the alkyne followed by addition of benzenethiol at the enyne triple bond. It is known from the literature that transition metal complexes,[15] in particular, nickel complexes[16—18] catalyze dimerization of alkynes. To verify this assumption, we converted alkyne **1a** into enyne **12a** (Scheme 4) and made the latter to react with benzenethiol in the presence of a catalytic amount of nickel complexes. According to NMR data, this reaction did not give diene **5a**; thus, this pathway was ruled out.

Scheme 3



Scheme 4



The involvement of intermediate **11** in the formation of by-products **5—8** is indicated by the fact that their yields increase upon a decrease in the benzenethiol concentration (see Table 1, runs *1—3*). It follows from the proposed mechanism that benzenethiol traps intermediate **11** giving rise to product **2**. Thus, the presence of excess PhSH in the reaction medium promotes an increase in the yield of product **2**.

When equimolar amounts of the reactants are used (PhSH : alkyne, 1 : 1), an excess of benzenethiol in the reaction medium can be created by using gradual addition of the alkyne. Indeed, with slow addition of the alkyne, the isolated yield of product **2a** was 78% (Table 1, run *4*), which is 32% higher than its yield obtained upon addition of the alkyne in one portion (run *2*). The synthetic procedure of choice includes stirring of the catalyst precursor $Ni(acac)_2$ (2 mol. %) with 0.25 equiv. of the alkyne (the formation of a suspension of the nickel complex in alkyne is necessary for the formation of nanostructured catalyst particles, see Ref. 1), the addition of 1 equiv. of thiol, and gradual addition of the rest alkyne (0.75 equiv.) over a period of 0.5—2 h. For a number of alkynes, it has been shown that these conditions provide high isolated yields of compound **2** (Table 2). In this case, the yield of compound **2** increased, on average, by 50% with respect to the control runs (a PhSH : alkyne ratio of 1 : 1, the addition of alkyne in one portion). Moreover, the yield of **2** obtained upon gradual addition of the alkyne is, on average, 18% higher than the published results[1] obtained at a PhSH : alkyne ratio of 2 : 1.

Table 2. Nickel-catalyzed addition of benzenethiol to alkynes under various conditions

Run	Alkyne	Yield of **2** (%) PhSH : alkyne			Conditions	
		2 : 1[a]	1 : 1[b]	1 : 1[c]	*T*/°C	*t*/h
1	**1b**	76	46	88	40	0.5
2	**1c**	70	30	81	40	2
3	**1d**	58	32	90	50	0.5

[a] Published data.[1]
[b] $Ni(acac)_2$ was added to the alkyne and then PhSH was added in one portion.
[c] The alkyne was added gradually.

In summary, we found that the yield of alkenyl sulfides **2** in the reaction with an equimolar ratio of the reactants can be essentially increased by maintaining an excess of thiol by gradual addition of the alkyne. New carbon—carbon and carbon—sulfur bonds are formed in the system with participation of intermediate σ-vinylic nickel complexes. This is an important distinction of nickel complexes from palladium-based catalytic systems studied previously in which no carbon—carbon bonds were formed in analogous transformations (the addition of arenethiols at alkynes).

Experimental

NMR spectra were recorded on a Bruker DRX-500 instrument using pulse field gradients; the solvent signals were used as internal standards. Two-dimensional spectra were recorded as described previously.[19] All measurements were carried out at room temperature. The reaction products were separated and purified by dry column flash chromatography.[20] Enyne **12a** was prepared by a known procedure[21] using 2 mol. % $Pd(OAc)_2$ and 4 mol. % tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the catalyst. The reactions with a PhSH : alkyne molar ratios of 2 : 1 and 1 : 1 and with addition of the alkyne in one portion were carried out by a previously reported procedure.[1] Prior to use,

$Ni(acac)_2$ was dried *in vacuo* (0.01—0.02 Torr, 60 °C, 30 min). The reactions were carried out under argon.

Catalytic reaction with gradual addition of alkyne. Nickel acetylacetonate $Ni(acac)_2$ (26 mg, 0.1 mmol) was transferred into a Schlenk tube, alkyne (0.25 equiv., 1.25 mmol) was added, and the mixture was magnetically stirred for 10—15 min at room temperature until a uniform suspension formed. The suspension was cooled to 5 °C (ice water), PhSH (0.55 g, 5 mmol) was added with continuous stirring, and the tube was closed with a septum sleeve stopper. The rest alkyne (0.75 equiv., 3.75 mmol) was added at a constant rate using a Cole Parmer 74900 automated syringe pump. The temperature of the thermostated bath and the time of alkyne addition are summarized in Tables 1 and 2. After completion of the reaction, the unreacted alkyne was removed on a rotary evaporator, and the residue was subjected to flash chromatography on silica gel.

Products **2a—d** were identified by comparison with published ^1H and ^{13}C NMR data (**2a**,[8] **2b**,**c**,[1] and **2d**[22]) and also by mass-spectrometry. The yields of isolated compounds are summarized in Tables 1 and 2.

(*Z*)-2,6-Dimethyl-5-methylidene-4-phenylsulfanylhept-3-ene-2,6-diol (5a). ^1H NMR ($CDCl_3$), δ: 7.20—7.40 (m, 5 H, Ph); 7.02 (d, 1 H, H^c, J = 1.4 Hz); 5.32 (dd, 1 H, H^b, J = 1.4 Hz, J = 0.8 Hz); 5.21 (d, 1 H, H^a, J = 0.8 Hz); 1.49 (s, 3 H, Me^d); 1.25 (s, 3 H, Me^e). MS, *m/z*: 278 $[M]^+$.

(3*Z*,5*E*)-2,7-Dimethyl-4-phenylsulfanylocta-3,5-diene-2,7-diol (6a). ^1H NMR ($CDCl_3$), δ: 7.20—7.40 (m, 5 H, Ph); 6.50 (s, 1 H, H^c); 6.31 (d, 1 H, H^a, J = 16.1 Hz); 6.12 (d, 1 H, H^b, J = 16.1 Hz); 1.43 (s, 3 H, Me^d); 1.41 (s, 3 H, Me^e). MS, *m/z*: 278 $[M]^+$.

(3*Z*,5*E*)-2,7-Dimethyl-3-phenylsulfanylocta-3,5-diene-2,7-diol (7a). ^1H NMR ($CDCl_3$), δ: 7.20—7.40 (m, 5 H, Ph); 6.93 (dd, 1 H, H^b, J = 10.5 Hz, J = 0.7 Hz); 6.59 (dd, 1 H, H^c, J = 15.6 Hz, J = 10.5 Hz); 6.04 (dd, 1 H, H^a, J = 15.6 Hz, J = 0.7 Hz); 1.44 (s, 3 H, Me^d); 1.23 (s, 3 H, Me^e). MS, *m/z*: 278 $[M]^+$.

(3*Z*,5*E*)-5-(1-Hydroxy-1-methylethyl)-4-(2-hydroxy-2-methyl-1-methylidenepropyl)-2-methyl-6-phenylsulfanylhexa-3,5-dien-2-ol (8a). ^1H NMR ($CDCl_3$), δ: 7.20—7.40 (m, 5 H, Ph); 6.93, 6.33 (both br.s, 1 H each); 5.15, 4.92 (both d, 1 H each, J = 0.7 Hz); 1.39, 1.38, 1.28 (all s, 3 H each). MS, *m/z*: 362 $[M]^+$.

1,3,5-Tris(1-hydroxy-1-methylethyl)benzene (9a). ^1H NMR ($CDCl_3$), δ: 7.52 (s, 3 H); 1.61 (s, 18 H). ^{13}C NMR ($CDCl_3$), δ: 149.04, 118.91, 72.86, 31.91. MS, *m/z*: 252 $[M]^+$.

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