Water-promoted regioselective hydrothiolation of alkynes

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Abstract: Water promotes hydrothiolation of unactivated alkynes efficiently without any catalyst or additive. The reaction at room temperature furnishes vinyl sulfides with high regioselectivity via anti-Markovnikov addition. The terminal alkynes provide dithiolanes at 80 °C by bis-addition. The reactions are very clean and high yielding.

Key words: alkynes, hydrothiolation, vinyl sulfides, regioselectivity, water.

Résumé : L'eau favorise l'hydrothiolation des alcynes non activés d'une façon efficace, sans catalyseur ou additif. À la température ambiante, la réaction conduit à la formation de sulfures de vinyle, avec une régiosélectivité par le biais d'une addition anti-Markovnikov. Les additions à 80 °C sur des alcynes terminaux conduisent à des dithiolanes résultant d'une bis-addition. Les réactions sont très propres et les rendements sont élevés.

Mots-clés : alcynes, hydrothiolation, sulfures de vinyle, régiosélectivité, eau.

[Traduit par la Rédaction]

Introduction

The hydrothiolation of alkynes by thiols is a very interesting and challenging reaction being associated with mono- and bis-condensation, Markovnikov and (or) anti-Markovnikov addition, and stereoselectivity. This reaction is also of great importance as it provides an attractive method for the formation of vinyl sulfides, which are valuable synthetic intermediates in total synthesis[1] and serve as precursors to a wide range of functionalized molecules.[2] The conventional procedures for hydrothiolation of alkynes involves transition metal catalysts[3] or a base[4] in organic solvents. Recently, a few procedures using catalytic phenylselenyl bromide,[5a] Al_2O_3–KF,[5b] nickel[5c] under solvent-free conditions, β-cyclodextrin in water–acetone,[5d] and $NaBH_4$–alumina under solvent-free conditions[5e,5f] have been reported.

According to the basic principles of Green Chemistry the use of organic solvents should be avoided wherever possible and use of alternative green solvents such as water are encouraged.[6a] Thus, the reaction in water has attracted considerable interest in the context of Green Chemistry.[6] In addition, water often exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[7] Thus, development of an efficient procedure for an organic reaction using water as a promoter as well as reaction medium has received intense attention in the design of a chemical process. Here, we report an efficient hydrothiolation of alkynes in water without any catalysts or additives, imparting good control on regioselectivity (Scheme 1).

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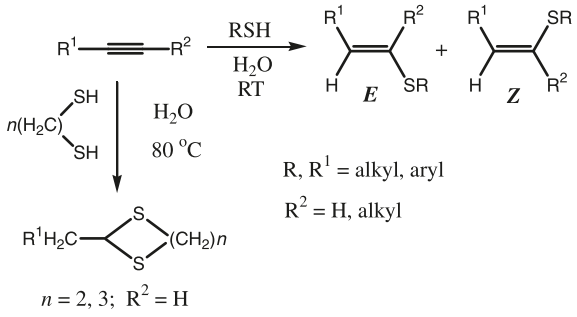
Scheme 1. Reaction of alkynes with thiols in water.

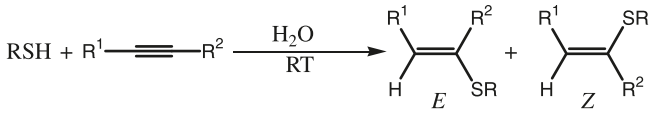


Results and discussion

The experimental procedure is very simple. A mixture of alkyne and thiol in water was stirred at room temperature (or at 80 °C) for a required period of time (TLC). Standard work-up provided the product.

A variety of terminal and internal alkynes underwent hydrothiolation with thiophenol and alkane thiols at room temperature by this procedure to provide the corresponding vinyl sulfides. The results are summarized in Table 1. Aryl- as well as alkyl-substituted alkynes and both aromatic and aliphatic thiols participated in this reaction uniformly. All reactions proceeded through anti-Markovnikov additions. Regarding the stereochemistry of the products, the reaction of terminal alkynes and thiophenols (entries 1–3, 6–8, 10, and 11 in Table 1) provided low to high selectivity with respect to *E*-isomers, whereas alkane thiols (entries 13, 14, 16, and 17 in Table 1) produced *Z*-isomers predominantly. The internal alkynes (entries 5 and 9 in Table 1) provided *Z*-isomers selectively. However, dimethyl acetylene dicarboxylate (entries 4, 12, 15, and 18 in Table 1) furnished *Z*-isomers as the sole product. As a whole, the stereoselectivity is excellent in a few of the reactions, although, in some reactions, no selectivity was observed. The steric distribution of prod-

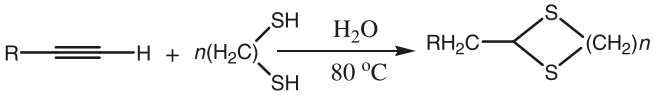
Table 1. Hydrothiolation of alkynes.



Entry	R	R^1	R^2	*Z*:*E*[a]	Time (h)	Yield (%)[b]	Reference
1	Ph	Ph	H	38:62	3	96	5d
2	Ph	C_4H_9	H	47:53	3	87	4b
3	Ph	C_6H_{13}	H	47:53	3.2	88	3c
4	Ph	CO_2Me	CO_2Me	100:0	3	94	8
5	Ph	C_2H_5	C_2H_5	75:25	3	86	9
6	Ph	*p*-ClC_6H_4	H	42:58	2.5	89	5d
7	*p*-MeC_6H_4	*p*-ClC_6H_4	H	0:100	2.5	95	10
8	*p*-ClC_6H_4	Ph	H	33:67	2.7	94	5d
9	*p*-MeC_6H_4	C_2H_5	C_2H_5	83:17	2.5	84	11
10	*p*-MeC_6H_4	*p*-MeC_6H_4	H	23:77	2	92	12
11	*p*-ClC_6H_4	*p*-$ClCC_6H_4$	H	12:88	2.8	90	13
12	$C_6H_4CH_2$	CO_2Me	CO_2Me	100:0	2	90	14
13	$C_6H_4CH_2$	Ph	H	69:31	2.5	89	3a
14	C_4H_9	Ph	H	70:30	3	93	15
15	$C_{12}H_{25}$	CO_2Me	CO_2Me	100:0	2	90	—
16	$C_{12}H_{25}$	Ph	H	85:15	3.4	85	4b
17	C_4H_9	*p*-ClC_6H_4	H	70:30	3	87	—
18	C_4H_9	CO_2Me	CO_2Me	100:0	2	86	16
19	HSC_2H_4	Ph	H	89:11	3.2	87	—

[a]*E*:*Z* ratio is based on NMR.
[b]Isolated yields.

Table 2. Bis-hydrothiolation of alkyne.



Sample No.	R	*n*	Time (h)	Yield (%)[a]	Reference
1	C_4H_9	2	4	72	11
2	C_6H_{13}	2	8	67	17a
3	Ph	2	4	81	17a
4	*p*-$MeOC_6H_4$	2	5	76	—
5	*p*-ClC_6H_4	2	5	73	—
6	*p*-ClC_6H_4	3	5	74	—
7	Ph	3	4.5	80	18

[a]Isolated yields.

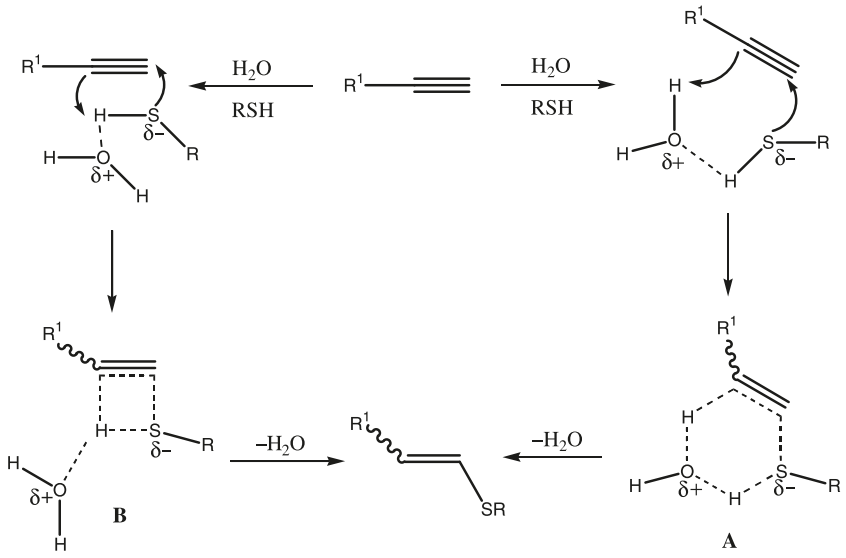
ucts is probably controlled by the steric compulsion of the bulky substituents.

The terminal alkynes produced dithiolanes or dithianes when treated with dithiols at 80 °C, based on the use of ethane or propane dithiol. It has already been mentioned that a similar reaction at room temperature produced only vinyl sulfide (entry 19 in Table 1). The results are summarized in Table 2. However, the use of 2 equiv. of monothiols in the reaction of phenyl acetylene under identical conditions produced only vinyl sulfides and no dithioacetal was obtained. On the other hand, reaction of 0.5 equiv. of ethane dithiol and phenyl acetylene at room temperature produced the corresponding vinyl sulfide associated with the starting material, whereas reaction at 80 °C provided the corresponding dithiolane together with unreacted phenyl acetylene.

The dithianes and dithiolanes are very useful compounds.[19] The standard methods[17] employ aldehydes for dithiolane–dithiane formation using an acid catalyst, whereas this procedure provides an attractive and novel alternative using alkynes through a simple operation in mild and neutral conditions.

Water plays a very significant role in this reaction. Without water the reaction in neat is very slow and low yielding. Possibly, water promotes the reaction through hydrogen bond formation with the sulfhydryl hydrogen of the thiol and thus enhances the nucleophilicity of the thiolate ion to add to the alkyne at the less-hindered carbon atom, giving anti-Markovinkov product. Although we do not have any concrete evidence regarding the exact mechanism, it may be speculated that addition of thiolate anion to the C≡C bond

Scheme 2. Speculative reaction pathway.



takes place either through a six- (**A**) or four-membered (**B**) transition state,[3f] with steric factors controlling the regioselectivity (Scheme 2).

It was found that, with the progress of reaction the product, vinyl sulfide isomerizes to the thermodynamically more stable isomer over time. For example, during the reaction of phenyl acetylene and thiophenol, the 32:68 *E*/*Z* mixture of product after 45 min of reaction ultimately gave rise to a 68:32 *E*/*Z* mixture at the end of the reaction after 3 h. This ratio for this mixture did not change even when the reaction was allowed to proceed past the 3 h time point. To check for the possibility of a radical process, the reaction was carried out in the dark. The progress of the reaction remained undisturbed. It should be mentioned that all the reactions were carried out in water that contained dissolved oxygen without an interference. Thus, a radical pathway is unlikely.

In general, the reactions were very clean. The hydrothiolations were accomplished in water at room temperature much faster (2–3.5 h) and in higher yields (84%–96%) when compared with many of the existing procedures.[3–5] All the products were obtained in high purities. The ratio of stereoisomers was determined by integration of the corresponding peaks in ^{1}H NMR spectra. Although a report[5d] using β-cyclodextrin in water stated that no reaction was observed in the absence of β-cyclodextrin, very interestingly, all the reactions listed in Tables 1 and 2 proceeded in water without any difficulty in the absence of additive. In addition, our water-mediated procedure is more general. The cyclodextrin–water mediated procedure[5d] failed to initiate reactions with alkane thiol, terminal alkyl alkynes, and internal alkynes, whereas our procedure was very successful for all these substrates. However, the stereoselectivity is better in cyclodextrin–water than in water alone by the present procedure. The reason for all these differences is not very clear to us. In general, the transition metal catalyzed reactions led to predominantly Markovnikov products,[3a,3b,3d,3e] whereas nonmetal-catalyzed reactions, including the present procedure, proceeded through anti-Markovnikov addition.[3f,4,5a,5b,5d,5e,5f] Excellent stereoselectivity was observed producing *E*-isomers in all the reactions using β-cyclodextrin,[5d] whereas attainment of high stereoselectivities providing a single isomer is not uniform in reactions using other reagents.[3,4,5a,5b,5c,5e,5f]

In conclusion, we have developed a very simple and efficient methodology for the addition of thiols to unactivated alkynes in water, producing vinyl sulfides and dithiolanes at room temperature and 80 °C, respectively. The additions exhibited high regioselectivity (exclusive anti-Markovnikov addition) and excellent stereoselectivity in several reactions (products obtained as one stereoisomer). Other significant advantages are simple operation, mild conditions (room temperature and neutral reaction media), general applicability to a variety of substituted alkynes and aromatic as well as aliphatic thiols, no catalyst or additive is required, high yields of isolated products, environment-friendly experimental conditions, and cost effectiveness. We believe, being endowed with so many attractive features, that this procedure will make an important addition to the existing methods of hydrothiolation.

Experimental

IR spectra were recorded on a Shimadzu 8300 FT IR spectrometer in neat. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker DPX-300 instrument at 300 and 75 MHz, respectively. HR-MS were taken on a Microtek Qt of a Micro YA263 spectrometer. All commercial reagents were distilled before use.

General experimental procedure for the synthesis of vinyl sulfides

Representative procedure for the reaction of phenyl acetylene with thiophenol (Table 1, entry 1)

A mixture of phenyl acetylene (102 mg, 1 mmol) and thiophenol (121 mg, 1.1 mmol) was stirred in H_2O (2 mL) at room temperature (30 °C) for 3 h (TLC). The reaction mixture was extracted with Et_2O (3 × 15 mL). The ether extract was washed with H_2O, NaOH (5%) solution, and brine and then dried over Na_2SO_4. Evaporation of solvent gave a crude product that was purified by column chromatography over silica gel (hexane) to provide (*E*)- and (*Z*)-phenyl styryl sulfane (204 mg, 96%) as a colourless liquid (*E*:*Z* = 62:38). IR (neat, cm^{-1}) ν: 3057, 3022, 1598, 1581, 1477, 1438, 1024,

945, 738, 688. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.61 (d, 1H, J = 10.8 Hz), 6.70 (d, 1H, J = 10.8 Hz), 6.85 (d, 1H, J = 15.4 Hz), 6.99 (d, 1H, J = 15.4 Hz), 7.34–7.54 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 123.4, 126.0 (2C), 126.9, 127.2, 127.6, 128.3, 128.7 (2C), 128.8, 129.2 (2C), 129.8 (2C), 130.1, 131.8, 135.3, 136.2, 136.5 (2C). These data are in good agreement with those reported.[5d] This procedure was followed for all the reactions listed in Table 1. The known compounds were identified by comparison of their spectral data with those reported earlier (see refs. in Table 1). The unknown compounds were characterized properly by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS), which are reported as follows.

2-Dodecylsulfanyl-but-2-enedioic acid dimethyl ester (Table 1, entry 15)

Pale yellow oil. IR (neat, cm^{-1}) ν: 2925, 2854, 1741, 1716, 1585, 1434, 1338, 1247, 1164, 1035, 723. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, 3H, J = 6.02 Hz), 1.25–1.39 (m, 17H), 1.61–1.69 (m, 3H), 2.79 (t, 2H J = 7.34 Hz), 3.69 (s, 3H), 3.87 (s, 3H), 5.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 22.8, 28.1, 28.9, 29.1, 29.4 (2C), 29.5, 29.6, 29.7, 31.9, 32.0, 51.9, 53.2, 112.4, 150.9, 164.2, 166.2. HRMS *m/z* [M + Na]$^+$ calcd. for $C_{18}H_{32}O_4SNa$: 367.1919; found: 367.1915.

1-(2-Butylsulfanyl-vinyl)-4-chloro-benzene (Table 1, entry 17; Z:E = 70:30)

Colourless oil. IR (neat, cm^{-1}) ν: 2957, 2928, 2871, 1558, 1520, 1489, 1397, 1091. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.69–0.76 (m, 6H), 1,17–1.29 (m, 4H), 1.41–1.50 (m, 4H), 2.55–2.60 (m, 4H), 6.06 (d, 1H, J = 10.9 Hz), 6.13–6.19 (m, 2H), 6.50 (d, 1H, J = 15.6 Hz), 6.96–7.04 (m, 2H), 7.09 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7 (2C), 21.7 (2C), 32.3 (2C), 35.7 (2C), 124.0 (2C), 125.1, 126.6, 128.6, 128.7, 128.8, 128.9, 129.8 (2C), 130.1 (2C), 132.0 (2C), 135.6 (2C). HRMS *m/z* [M + Na]$^+$ calcd. for $C_{12}H_{15}ClSNa$: 249.0481; found: 249.1879.

2-Styrylsulfanyl-ethanethiol (Table 1, entry 19; Z:E = 89:11)

Colorless oil. IR (neat, cm^{-1}) ν: 2980, 2930, 2865, 2223, 1487, 1462, 1272, 730. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.93–3.00 (m, 4H), 3.04–3.14 (m, 4H), 6.19 (d, 1H, J = 10.8 Hz), 6.48 (d, 1H, J = 10.8 Hz), 6.55 (d, 1H, J = 15.1 Hz), 6.67 (d, 1H, J = 15.1 Hz), 7.19–7.25 (m, 2H), 7.28–7.37 (m, 4H), 7.45 (d, 4H, J = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.4 (2C), 39.3 (2C), 126.3 (2C), 127.2 (2C), 127.3 (2C), 128.7 (4C), 129.0 (4C), 137.0 (2C). Anal. calcd. for $C_{10}H_{12}S_2$: C 61.18, H 6.16; found: C 61.57, H 6.28.

General procedure for the synthesis of dithiolanes–dithianes

Representative procedure for the reaction of phenyl acetylene and 1,2-ethane dithiol (Table 2, entry 2)

A mixture of phenyl acetylene (102 mg, 1 mmol) and 1,2-ethane dithiol (103 mg, 1.1 mmol) in water (2 mL) was heated at 80 °C for a required period of time (4 h) (TLC). Then the mixture was extracted with Et_2O (3 × 15 mL). The ether extract was washed with brine, dried (Na_2SO_4), and evaporated to get the crude product, which was purified by column chromatography over silica gel (hexane–ether, 95:5) to provide 2-benzyl-[1,3]-dithiolane (159 mg, 81%) as a colorless oil. IR (neat, cm^{-1}) 3060, 3026, 2930, 2894, 1604, 1498, 1453, 1427, 1270, 1240, 1172, 743, 688. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.10 (d, 2H, J = 7.08 Hz), 3.17–3.24 (m, 4H), 4.72 (t, 1H, J = 7.08 Hz), 7.20–7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.5 (2C), 45.2, 54.8, 126.7, 127.9 (2C), 129.0 (2C), 139.0. These data are in good agreement with those reported.[17a] This procedure was followed for all the reactions listed in Table 2. The known compounds were identified by comparison of their spectral data with those reported earlier (see refs. in Table 2). The unknown compounds were characterized properly by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS), which are reported as follows.

2-(3-Methoxy-benzyl)-[1,3]-dithiolane (Table 2, entry 4)

Yellowish oil. IR (neat, cm^{-1}) ν: 2999, 2922, 2833, 1598, 1583, 1488, 1454, 1434, 1259, 1153, 1049, 769, 694. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.09 (d, 2H, J = 7.2 Hz,), 3.12–3.22 (m, 4H), 3.79 (s, 3H), 4.72 (t, 1H, J = 7.2 Hz), 6.73–6.87 (m, 3H), 7.21 (t, 1H, J = 7.68 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.0 (2C), 45.1, 54.6, 55.0, 112.0, 114.6, 121.2, 129.2, 140.5, 159.4. HRMS *m/z* [M + Na]$^+$ calcd. for $C_{11}H_{14}OS_2Na$: 249.0384; found: 249.0412.

2-(4-Chloro-benzyl)-[1,3]-dithiolane (Table 2, entry 5)

Colourless oil. IR (neat, cm^{-1}) ν: 2923, 2250, 1712, 1490, 1397, 1222, 909, 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.84–2.93 (m, 4H), 2.97–3.04 (m, 2H), 4.59 (t, 1H, J = 6.9 Hz), 7.12–7.29 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 5.0, 38.2, 38.9, 54.6, 129.2 (2C), 129.9 (2C), 132.8, 135.1. HRMS *m/z* [M + H]$^+$ calcd. for $C_{10}H_{11}ClS_2H$: 231.0069; found: 231.1078.

2-(4-Chloro-benzyl)-[1,3]-dithiane (Table 2, Entry 6)

Yellowish oil. IR (neat, cm^{-1}) ν: 3060, 3026, 2898, 2825, 1602, 1494, 1452, 1421, 1274, 1242, 1178, 906, 740, 698, 663. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.98–2.06 (m, 2H), 2.70–2.81 (m, 4H), 2.91 (d, 2H, J = 7.3 Hz), 4.13 (t, 1H, J = 7.3 Hz), 7.08 (d, 2H, J = 7.4 Hz), 7.20 (d, 2H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.5, 30.4 (2C), 40.9, 48.3, 128.3 (2C), 130.5 (2C), 130.8, 135.6. HRMS calcd. for [M+Na]$^+$ $C_{11}H_{13}ClS_2Na$: 267.0045; found: 267.010.

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