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# Synthesis of vinyl sulfides via hydrothiolation of alkynes using $Al_2O_3$/KF under solvent-free conditions

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## Abstract

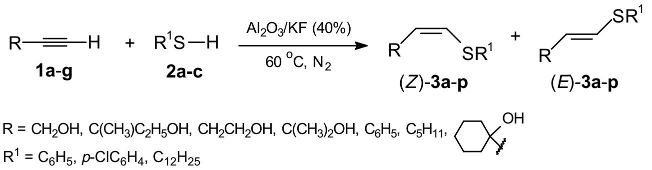
We present here a clean, solvent-free hydrothiolation of alkynes using solid supported catalyst ($Al_2O_3$/KF). This efficient and improved method selectively furnishes the corresponding anti-Markovnikov vinyl sulfides in good to excellent yields. The method is applicable for aliphatic and aromatic thiols and the catalytic system can be re-used up to two times without previous treatment and with comparable activity.

*Keywords:* Solvent-free reaction; Hydrothiolation; Vinyl sulfide

Vinyl sulfides have been found to be a very useful tool in organic synthesis, since sulfur-containing groups serve as important auxiliary function in synthetic sequences.[1] In this way, various methods are mentioned for the preparation of vinyl sulfides and the most common protocols involve the addition of thiol, or the respective anions, to terminal or internal alkynes.[2,3] Most of the described methods make use of toxic organic solvents and are catalyzed by transition-metals[2a,b] or promoted by base.[2c–e] More recently, some improvements on selective preparation of vinyl sulfides have been described.[3] These comprise the use of catalytic phenylselenenyl bromide[3a] or nickel[3b] under solvent-free conditions, β-cyclodextrin in the presence of water and acetone[3c] or under catalyst-free conditions.[3d] In recent years, the use of potassium fluoride supported on alumina ($Al_2O_3$/KF) as a green catalytic system for a number of transformations has been increased.[4] By using $Al_2O_3$/KF, the products can be easily isolated by filtration and the generation of large amounts of salts at the end of the synthesis, as well as the use of stoichiometric strong bases, can be avoided.

Our major research goal has been the development of new and cleaner protocols for the preparation and synthetic applications of organochalcogenium compounds.[5] More recently, we have described several efficient approaches using $Al_2O_3$/KF.[6] In continuation to these studies, we describe here the results of the hydrothiolation of alkynes **1** using $Al_2O_3$/KF without any solvent (Scheme 1).[7,8]

Initially, we chose propargyl alcohol (**1a)** and phenylthiol (**2a**) as standard starting materials. We examined the temperature, amount of $Al_2O_3$/KF (40%) and the use of $N_2$ atmosphere. It was found that stirring a mixture of



Scheme 1.

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**1a** (2 mmol) and **2a** (1 mmol) in the presence of 0.08 g (51 mol %) of $Al_2O_3$/KF (40%) at room temperature, the products of hydrothiolation (**3a**) were obtained in an overall yield of 25% after 3.5 h, together with a great amount of diphenyldisulfide. On the other hand, when the same protocol was performed at gentle heating (60 °C) and under $N_2$ atmosphere, the yield increased to 63% yield (Table 1, entry 1). Using 0.120 g (77 mol %) of the catalyst or prolonged time (24 h) did not significantly increase the vinyl sulfides yields. It was also observed that the catalytic system can be re-used for 2 cycles, just by washing it with ethyl acetate and drying under vacuum.

Using the optimized conditions, the protocol was extended to other alkynyl alcohols and thiols (Table 1, entries 2–12).[8] Concerning the stereochemistry of products, for all the studied examples, the anti-Markovnikov adduct **3** was obtained in higher amount than the Markovnikov one. The formation of a *Z* and *E* mixture of **3** was also observed (determined by $^1$H NMR) and the selectivity was influenced by the substituent at alkynes (see Table 1). Thus, for example, *Z*-**3a** was obtained preferentially from the reaction of propargyl alcohol (**1a**) with **2a** (63% yield, *Z*:*E* ratio = 86:14, entry 1), while *E*-**3h** was the major obtained isomer for the reaction of 1-ethynylcyclohexanol

Table 1
Hydrothiolation of alkynes using $Al_2O_3$/KF under solvent-free condition

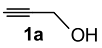
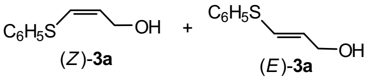
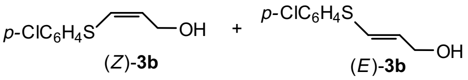
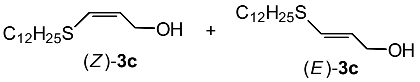
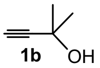
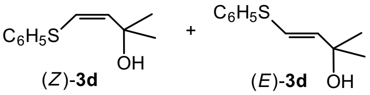
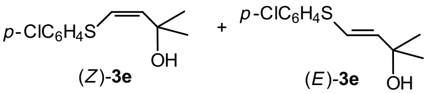
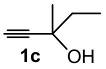
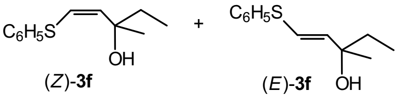
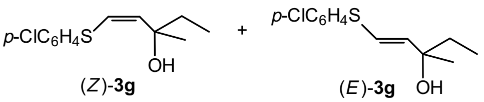
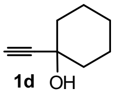
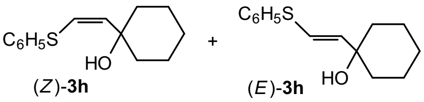
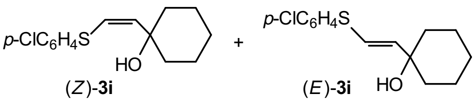
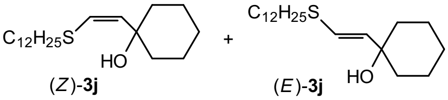
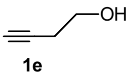
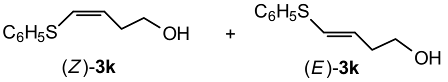
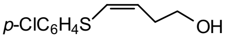
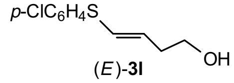
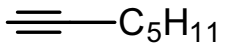
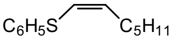
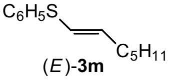
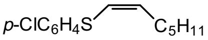
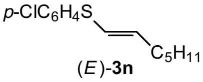
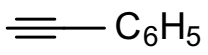
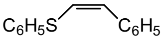
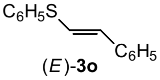
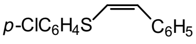
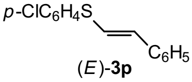
| Entry | Alkyne **1** | Thiol **2** | Product **3** | Time (h) | Ratio$^a$ (*Z*):(*E*) | Yield$^b$ (%) |
|---|---|---|---|---|---|---|
| 1 |  **1a** | $C_6H_5SH$ **2a** |  (*Z*)-**3a**<br>(*E*)-**3a** | 3.5 | 86:14 | 63 (64:36)$^c$ |
| 2 | **1a** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3b**<br>(*E*)-**3b** | 1 | 75:25 | 57 (51:49)$^c$ |
| 3 | **1a** | $CH_3(CH_2)_{11}SH$ **2c** |  (*Z*)-**3c**<br>(*E*)-**3c** | 4 | 55:45 | 65 (92:8)$^c$ |
| 4 |  **1b** | $C_6H_5SH$ **2a** |  (*Z*)-**3d**<br>(*E*)-**3d** | 4 | 31:69 | 90 (93:7)$^c$ |
| 5 | **1b** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3e**<br>(*E*)-**3e** | 3 | 23:77 | 88 (96:4)$^c$ |
| 6 |  **1c** | $C_6H_5SH$ **2a** |  (*Z*)-**3f**<br>(*E*)-**3f** | 2.5 | 60:40 | 70 (86:14)$^c$ |
| 7 | **1c** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3g**<br>(*E*)-**3g** | 3 | 29:71 | 74 (96:4)$^c$ |
| 8 |  **1d** | $C_6H_5SH$ **2a** |  (*Z*)-**3h**<br>(*E*)-**3h** | 3 | 13:87 | 56 (94:6)$^c$ |
| 9 | **1d** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3i**<br>(*E*)-**3i** | 5 | 20:80 | 63 (93:7)$^c$ |
| 10 | **1d** | $CH_3(CH_2)_{11}SH$ **2c** |  (*Z*)-**3j**<br>(*E*)-**3j** | 6.5 | 2:98 | 86 (92:8)$^c$ |
| 11 |  **1e** | $C_6H_5SH$ **2a** |  (*Z*)-**3k**<br>(*E*)-**3k** | 2 | 53:47 | 62 (92:8)$^c$ |

Table 1 (*continued*)

| Entry | Alkyne **1** | Thiol **2** | Product **3** | Time (h) | Ratio[a] (*Z*):(*E*) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 12 | **1e** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3l** +  (*E*)-**3l** | 2 | 50:50 | 55 (54:46)[c] |
| 13 |  **1f** | $C_6H_5SH$ **2a** |  (*Z*)-**3m** +  (*E*)-**3m** | 5.5 | 48:52 | 52 (100:00)[c] |
| 14 | **1f** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3n** +  (*E*)-**3n** | 7 | 45:55 | 53 (100:00)[c] |
| 15 |  **1g** | $C_6H_5SH$ **2a** |  (*Z*)-**3o** +  (*E*)-**3o** | 1 | 80:20 | 90 (100:00)[c] |
| 16 | **1g** | *p*-$ClC_6H_4SH$ **2b** |  (*Z*)-**3p** +  (*E*)-**3p** | 1 | 63:37 | 95 (100:00)[c] |

[a] Determined by $^1H$ NMR of the crude reaction mixture and confirmed after isolation of pure products.

[b] Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by mass spectrometry, $^1H$ and $^{13}C$ NMR.[2,3]

[c] The regioselectivity of the hydrothiolation (the ratio of anti-Markovnikov: Markovnikov product).

(**1d**) with **2a** (56% yield, *Z*:*E* ratio = 13:87, entry 8). The scope of our methodology was successfully expanded to aromatic and aliphatic alkynes (Table 1, entries 13–16). We observed that for these alkynes the reaction afforded exclusively the respective anti-Markovnikov adducts **3m–p** in good yields (52%–95%). Besides, the possible interference of the light in the stereoselectivity of the reaction was also studied. Thus, when **1a** and **2a** reacted in the dark, we observed the same results described above for the preparation of **3a** (Table 1, entry 1).

We also observed that, for some alkynes, the hydrothiolation with phenylthiol took place even in the absence of a catalyst. Thus, for example, when a mixture of thiol **2b** and alkynols **1c** or **1d** was stirred at 60 °C for 3.5 h, the respective vinyl sulfides **3f** and **3h** were obtained in good yields (68% and 55%). For the reaction of propargyl alcohol (**1a**), however, the respective vinyl sulfide **3b** was obtained only in 23% yield. The hydrothiolation without $Al_2O_3$/KF did not proceed satisfactorily for the reaction of 1-heptyne (**1f**) with thiols. Similar result was observed for the reactions with dodecanethiol (**2c**).

In conclusion, several vinyl sulfides could be prepared directly under solvent-free conditions using $Al_2O_3$/KF, which can be re-used up to two times. The method is general for the reaction of several alkynes with aromatic and aliphatic thiols. This method consists in low consumption of solvent in the overall protocol, short reaction time, mild reaction conditions, good yields and simplicity, with non-aqueous workup.

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7. *Preparation of alumina supported potassium fluoride:*[9] Alumina (6.0 g of $Al_2O_3$ 90, 0.063–0.200 mm, Merck), $KF{\cdot}2H_2O$ (5.2 g) and water (10 mL) were mixed in a 50 mL beaker and the suspension stirred at

65 °C for 1 h. The resulting solid was dried at 80 °C for 1 h and subsequently for 4 h at 300 °C in an oven and finally cooled to room temperature in a desiccator. The content of KF is about 40% (m/m).

8. *General procedure for the synthesis of vinyl sulfides*: To a mixture of phenyl acetylene (**1g**; 0.424 g; 2 mmol) and phenylthiol (**2a**; 0.110 g; 1 mmol) under $N_2$ atmosphere, $Al_2O_3$/KF (0.08 g, obtained as described above) was added at room temperature. Then, the temperature was slowly raised to 60 °C. The reaction progress was followed by TLC, and after 1 h (see Table 1) ethyl acetate (10 mL) was added and the organic solution was separated of the aluminum oxide by filtration. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel eluting with hexanes, yielding a mixture of *Z*- and *E*-**3o** (0.191 g, 90%, *Z*:*E* ratio = 80:20). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ (ppm) ($Z$+$E$) 7.20–7.56 (m, 10H); *E* isomer: 6.88 (d, $J = 15.4$ Hz, 1H); 6.72 (d, $J = 15.4$ Hz, 1H); *Z* isomer: 6.59 (d, $J = 10.6$ Hz, 1H); 6.48 (d, $J = 10.6$ Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ (ppm) *E* isomer: 123.2, 125.9, 126.7, 127.4, 128.5, 129.0, 129.6, 131.6, 135.1, 136.3; *Z* isomer: 125.9, 127.0, 127.1, 127.2, 128.2, 128.7, 129.1, 130.0, 136.1, 136.4.[3a]

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