One-Pot Practical Preparation of Novel Propargylic Aryl and Heteroaryl Sulfides and Sulfones

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Abstract: A one-pot preparation of functionalized propargylic aryl and hetero aryl sulfides from primary alcohols and thiols through the formation of the corresponding iodide or tosylate compounds is presented. The corresponding sulfones are prepared by subsequent MCPBA oxidation.

Key words: thiols, sulfides, sulfones, oxidation, propargylic alcohol

Organosulfur compounds are generally useful intermediates for building highly functionalized biologically and medicinally relevant natural products.[1]

In particular, aromatic and heterocyclic sulfides and related compounds are widely used as central nervous system (CNS) agents.[2] Heteroaromatic sulfur-containing derivatives were also successfully used as antitumoral and cytotoxic compounds.[3] In the class of propargylic compounds, heteroaromatic sulfides like compounds **A** (Figure 1) were reported to possess certain memory improving and anticonvulsant activity.[2] Propargylic sulfones like compounds **B** are a simple class of compounds that cleave DNA in a pH-dependent fashion[4] and similar molecules exhibit high DNA intercalating and alkylating activity.[5]

Figure 1

Sulfides and their oxidation products, sulfoxides and sulfones, are important reagents and/or quite useful intermediates in organic synthetic applications.[6] In fact, aryl and heteroaryl sulfoxides are useful moieties in asymmetric synthesis,[7] instead their corresponding sulfones are powerful tools for double bond formation in the classical and modified Julia olefination.[8]

Because research on these sulfur compounds is widely studied, considering their important biological activities, highly selective and efficient methods are desired for the preparation of propargylic or allenylic sulfides and sulfones.

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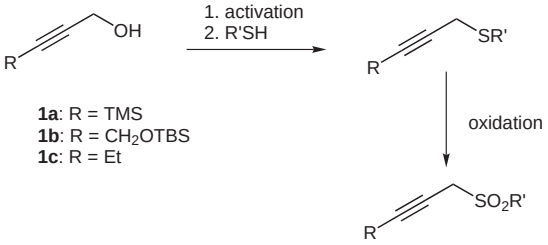
Several synthetic methods for preparing simple and not functionalized propargylic sulfides have been reported: the most utilized is the Williamson-type reaction between propargylic bromides, iodides, or mesylates with thiols in the presence of inorganic bases[9] or catalyzed by transition metal.[10]



Scheme 1 General preparation of sulfides and sulfones.

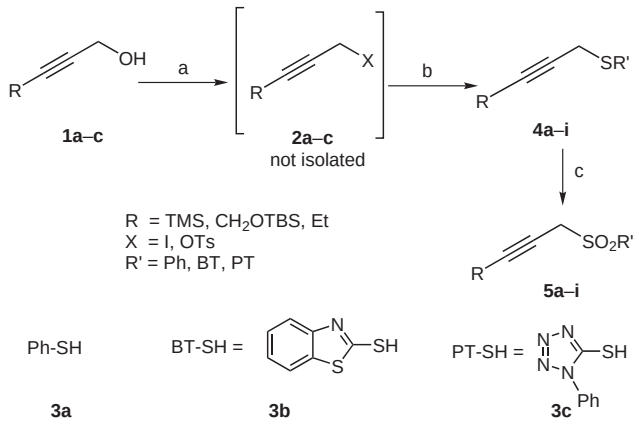
Initially, we have attempted the preparation of the corresponding tosylate of commercial alcohol **1a** and of the monoprotected 1,4-but-2-yndiol **1b**[11] under classical conditions, e.g. TsCl in pyridine (Scheme 1).[12] However, the standard protocol gave disappointing results in terms of purity and isolated yields.

A second attempt with NaOH utilization in the reaction medium afforded the desilylated product for compound **1a** and the corresponding tosylate of **1b** in good yields.

With the goal to avoid the use of NaOH for base-sensitive substrate and in general to perform the reactions in a direct one-pot synthesis procedure, we finally used and tested two different approaches to sulfides: a) via iodide formation with alcohol **1a** and **1c** (both commercial products; method **A**); b) via tosylate (method **B**) for the alcohol **1b**[13] (Scheme 2 and Table 1).

The corresponding iodides of **1a**,**c** were prepared using I_2 in the presence of imidazole and PPh_3, at reflux temperature, with complete conversion of starting materials after one hour reaction time.

In a typical procedure 1.2 equivalents of thiols **3a**–**c** were added to the organic solution (CH_2Cl_2 or toluene) of performed iodides or tosylates **2a**–**c** and the reaction was stirred at room temperature (3–4 h) until TLC indicated complete consumption of the corresponding iodide or tosylate. Under these conditions, the desired sulfides **4a**–**i** were isolated in variable yields (from 37% up to 89%), according to the type of thiol and of propargylic alcohol used (Table 1).[14,15]

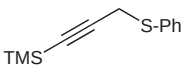
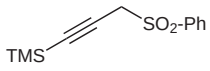
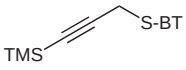
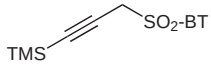
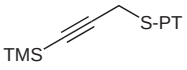
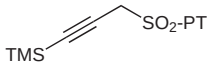
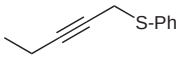
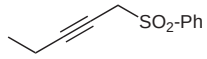
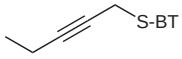
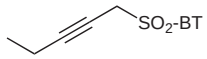
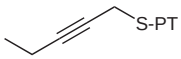
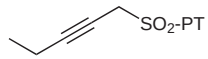


Scheme 2 *Reagents and conditions*: (a) *i*. method **A**: X = I, I_2, PPh_3, imidazole, CH_2Cl_2, reflux. *ii*. method **B**: X = OTs, TsCl, NaOH, toluene, r.t.; (b) **3a**–**c**, r.t.; (c) MCPBA, CH_2Cl_2, r.t.

The best results were obtained with heteroaromatic mercaptans. In fact, treatment of benzenethiol **3a** with **1a**–**c** gave the corresponding aryl propargyl known sulfides **4a**,[2,3,10a,16] **4d** and **4g** (entries 1, 4 and 7) in 37%, 60% and 44%, respectively (diphenyldisulfide was detected but no traces of starting material).

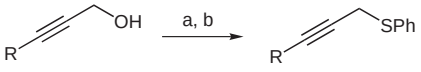
In contrast, when the 2-mercaptobenzothiazole **3b** (entries 2 and 5) was used with propargylic alcohols **1a**,**b**, sulfides **4b**[2,3] and **4e** were obtained in 72% and 82% yield, respectively. Surprisingly, this trend has not been followed in the preparation of sulfide **4h** (entry 8), which was isolated in 49% yield, although many attempts were made to increase the overall yields. In good to high isolated yields heteroaromatic propargylic sulfides were obtained (entries 3, 6 and 9) using 1-phenyl-1*H*-tetrazole-5-thiol **3c** with the alcohols **1a**–**c** (75%, 89% and 79% yield).

Table 1 Preparation of Sulfides **4** and Sulfones **5**

Entry	Propargylic alcohol **1**	Thiol **3**	Sulfide **4** (yield, %)[a]	Sulfone **5** (yield, %)[b]
1	**1a**	**3a**	 **4a** (37)[c,d]	 **5a** (100)
2	**1a**	**3b**	 **4b** (72)[c]	 **5b** (100)
3	**1a**	**3c**	 **4c** (75)[c]	 **5c** (100)[e]
4	**1b**	**3a**	 **4d** (60)[f,d]	 **5d** (100)
5	**1b**	**3b**	 **4e** (82)[f]	 **5e** (100)
6	**1b**	**3c**	 **4f** (89)[f]	 **5f** (92)[e]
7	**1c**	**3a**	 **4g** (44)[c]	 **5g** (84)
8	**1c**	**3b**	 **4h** (49)[c]	 **5h** (100)
9	**1c**	**3c**	 **4i** (79)[c]	 **5i** (95)[e]

[a] Yield of isolated sulfide.
[b] Yield of isolated sulfone.
[c] Prepared according to method **A**.
[d] Better yield was obtained according to the conditions reported below (vide infra).
[e] Unstable product.
[f] Prepared according to method **B**.

In order to improve the overall yields of the phenyl propargyl sulfides **4a**, **4d** and **4g**, benzenethiol sodium salt with 18-crown-6-ether has successively been used as a new variant in the S-propargylation. Much-improved results have been achieved (Scheme 3) for phenyl propargyl sulfides **4a** and **4d** (74% and 100%).[17] Only 2-pentyn-1-ol (**1c**) still gave the corresponding sulfide **4g** in similar 33% yield.



1a–c

4 a 74%
4 d 100%
4 g 33%

Scheme 3 *Reagents and conditions*: (a) conditions of Scheme 2; (b) PhSNa, 18-crown-6-ether, r.t.

With these novel sulfides in hand, we envisioned the opportunity to prepare the corresponding sulfones. After some attempts with different oxidants (oxone,[18] H_2O_2/catalyst,[19] or MCPBA[20]), the use of MCPBA for the oxidation of the functionalized sulfides **4a**–**i** was found to be the most efficient and practical method. Sulfones **5a**–**i** have been prepared and isolated, in the majority of cases, quantitatively and without need of purification. With respect to PT sulfones **5c**,**f**,**i**, the recovery of the crude material was also satisfactory, but a decrease in the yield was observed due to the unstable products.

In conclusion, the synthetic strategy depicted in Scheme 2 and Scheme 3 appears extremely valuable for providing, in one-pot simple procedures, new functionalized propargylic aromatic and heteroaromatic sulfides. The synthetic utility of the method is further illustrated by the transformation of sulfides to their corresponding sulfones in excellent yields, as new synthetically important intermediates in organic chemistry.

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References

(1) Metzner, P.; Thuillier, A. In *Sulfur Reagents in Organic Chemistry*; Academic Press: London U.K., **1994**.

(2) Abele, R.; Zvejniece, L.; Abele, E.; Rubina, K.; Arsenyan, P.; Vandish, M.; Pudova, O.; Dambrova, M.; Domracheva, I.; Shestakova, I.; Popelis, J.; Lukevics, E. *Appl. Organomet. Chem.* **2004**, *18*, 181.

(3) Abele, R.; Abele, E.; Rubina, K.; Dzenitis, O.; Arsenyan, P.; Shestakova, I.; Nesterova, A.; Domracheva, I.; Popelis, J.; Grinberga, S.; Lukevics, E. *Chem. Heterocycl. Compd.* **2002**, *38*, 867.

(4) (a) Nicolaou, K. C.; Skokotas, G.; Maligres, P.; Zuccarello, G.; Schweiger, E. J.; Toshima, K.; Wendeborn, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1272. (b) Nicolaou, K. C.; Wendeborn, S.; Maligres, P.; Isshiki, K.; Zein, N.; Ellestad, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 418.

(5) (a) Gupta, R.; Xie, G.; Lown, J. W. *Gene* **1994**, *149*, 81. (b) Dai, W.-M.; Fong, K. C. *Tetrahedron Lett.* **1995**, *36*, 5613. (c) Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S.-I.; Solow, M.; Mak, W. L.; Yeung, M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1093. (d) Dai, W.-M.; Chow, C. W.; Zhou, L.; Ishii, A.; Lau, C. W.; Li, Q.; Hamaguchi, W.; Nishimoto, S.-I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2789.

(6) (a) Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron Lett.* **2000**, *41*, 2675. (b) Braverman, S.; Zafrani, Y.; Gottlieb, H. *Tetrahedron* **2001**, *57*, 9177. (c) Braverman, S.; Cherkinsky, M.; Birsa, M. L.; Zafrani, Y. *Eur. J. Org. Chem.* **2002**, 3198.

(7) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651; and references therein.

(8) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Alonso, D. A.; Fuensanta, M.; Nájera, C.; Varea, M. *J. Org. Chem.* **2005**, *70*, 6404; and references therein.

(9) (a) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031. (b) Zaragoza, F. *Tetrahedron* **2001**, *57*, 5451.

(10) (a) Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 12960. (b) Tsutsumi, K.; Fujimoto, K.; Yabukami, T.; Kawase, T.; Morimoto, T.; Kakiuchi, K. *Eur. J. Org. Chem.* **2004**, 504; and references therein. (c) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(11) We have prepared **1b** using TBSCl/pyridine obtaining the monoprotected diol with 55% vs. 30% yield reported in: Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238.

(12) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, **1999**, 3rd ed.

(13) The corresponding iodide was isolated in minor yield (70% vs. 79%) with respect to the tosylate.

(14) **General Procedure for Preparation of Sulfides 4a–c, 4g–i (Method A).**
To a stirred solution of propargyl alcohol **1a**,**c** (1 equiv, 0.78 mmol) in CH_2Cl_2 (13 mL) were added PPh_3 (251 mg, 0.96 mmol), imidazole (158 mg, 2.32 mmol) and I_2 (237 mg, 0.94 mg). The reaction mixture was raised to reflux. After 1 h, a complete conversion of alcohol to the corresponding iodide was observed by TLC control. The reaction temperature was cooled to r.t. and thiol **3a**–**c** (0.94 mmol) was added. After complete conversion to sulfide (3 h), the reaction mixture was hydrolyzed with a sat. aq solution of NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel.

(15) **General Procedure for Preparation of Sulfides 4d–f (Method B).**
To a stirred solution of propargylic alcohol **1b** (202 mg, 1.01 mmol) in toluene (0.9 mL) at 0 °C Bu_4NI (39 mg, 0.10 mmol), 2 N solution of NaOH (1.5 mL), and a dropwise solution of TsCl (202 mg, 1.06 mmol) in toluene (0.4 mL) were added. The mixture was stirred for 3 h at r.t. and after the complete formation of the corresponding tosylate, thiol **3a**–**c** (1.08 mmol) was added. After additional 2 h the aqueous layer was extracted with EtOAc, while the organic layer was washed with H_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel.

(16) (a) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558. (b) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955.

(17) With our procedure the propargylic sulfides **4a** and **4b** have been prepared in higher yields than in the other older procedures reported in ref. 2, 3 and 10a.
(18) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287. (b) Webb, K. S. *Tetrahedron Lett.* **1994**, *35*, 3457.
(19) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955.
(20) (a) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784. (b) Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525.