Synthesis of allylic sulfides *via* cleavage of S–S bonds promoted by zinc metal in DMF

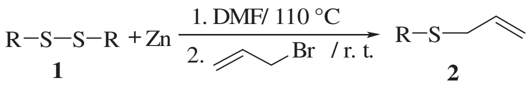
Jingxing Du*, Renwei Zheng and Xinsheng Li

College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua, Zhejiang, 321004, P.R. China

Cleavage of S–S bonds was achieved without any activation or catalysis, with a Zn/DMF system and subsequent treatment with allylic bromide afforded allylic sulfides in good to excellent yields.

Keywords: allyic sulfides, S–S bonds, Zn/DMF

Allylic sulfides are a class of useful synthetic intermediates.[1] A number of synthetic methods have been reported for their preparation, including the allylation of thiols,[2] the reaction of an allylic halide with sodium sulfide,[3] the addition of thiophenol to an alkene,[4] the reductive deoxygenation of sulfoxides with titanium(II) chloride, triphenylphosphine/iodide/sodium iodide[5] or samarium metal/ammonium chloride in methanol under sonication.[6] Allylic sulfides can also be synthesised by the reaction of disulfides with allylsamarium bromide[7] or allylytterbium bromide.[8] Reductive cleavage of disulfides with zinc metal has seemed to be a focus of interest for the synthesis of organic sulfides in recent years. Zinc/cobalt (II) chloride/acetonitrile,[9] in the presence of allylic halide, was reported for the synthesis of allylic sulfides; Zinc/aluminum chloride in DMF/H_2O media was used for the formation of aryl benzyl sulfides from benzyl bromide and aryl disulfides.[10] Zinc/zirconium(IV) chloride inTHF was reported for the synthesis of dibenzyl sulfide.[11] Very recently, Taniguchi reported the alkyl- and arylthiolation of aryl iodides by the cleavage of the S–S bond of disulfides by a zinc reduction-nickel catalysis method.[12] Generally, it is considered that the disulfide alone cannot be activated by zinc metal,[9] or that the presence of a Lewis acid such as aluminum chloride is essential.[10b,13] However, we have recently found that the cleavage of disulfides could be successfully realised with zinc in DMF in the absence of any other activating agents or catalysts, and that subsequent treatment with allylic bromides afforded allylic sulfides in good to excellent yields (Scheme 1).



Scheme 1

Experiments were first carried out to optimise the reaction conditions (Table 1). When the molar ratio of zinc to diphenyl disulfide was 1:1, the anticipated allylic sulfide was obtained in 67% yield, with the disulfide recovered in 26 % yield. Extension of the reaction time to 24 hours at 110 °C did not improve the results obviously (Table 1, entry 1). However, when we changed the ratio of zinc to disulfide to 2:1, only 5.5 % of the starting disulfide remained unreacted and the yield of the allylic sulfide could be increased to 84% (Table 1, entry 2). Since the close polarity of the disulfides and the products makes it difficult to separate them by preparative TLC, it is crucial to ensure the complete disappearance of disulfides at the first stage so that the pure target compound could be obtained. We finally increased the ratio of zinc and disulfide to 3:1, and it could be detected by TLC that under these conditions the disulfide disappeared completely at 110 °C within 11 hours. It should be noted that the extra amount of zinc present in the system has no obvious influence on the yields of the allylic sulfides. The results are shown in Table 2.

Table 1 The effect of the molar ratio of Zn and disulfide on the yield of **2a**

Entry	Zn / $(PhS)_2$	Yield of **2a**/%[a]	Recovered $(PhS)_2]$/%
1	1:1	67	26
2	2:1	84	5.5
3	3:1	93	0

[a]Yield of isolated products based on the disulfide.

Table 2 Synthesis of allylic sulfides from disulfides and allylic bromide in Zn/DMF

Entry	R in **1** and **2**	Product	Yield/%[a]
1	Ph	**2a**	93
2	4-ClPh	**2b**	96
3	$4\text{-}CH_3Ph$	**2c**	91
4	$PhCH_2$	**2d**	82
5	$4\text{-}CH_3C_6H_4CH_2$	**2e**	63
6	$4\text{-}ClC_6H_4CH_2$	**2f**	87
7	$4\text{-}BrC_6H_4CH_2$	**2g**	72
8	$4\text{-}CH_3OC_6H_4CH_2$	**2h**	56
9	$n\text{-}C_8H_{17}$	**2i**	81

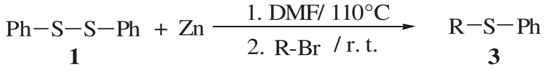
[a]Yield of isolated products based on the disulfide.

A relatively longer time was required for the reductive cleavage of the dibenzyl disulfides (usually 30 hours. Di (*p*-methoxybenzyl)disulfide, especially, required 48 hours) than for the diaryl disulfides. Electron-withdrawing groups attached to the aromatic rings facilitate the reaction and result in better yields than these from compounds with electron-donating groups for both dibenzyl and diaryl disulfides. Dialkyl disulfides can also undergo reductive cleavage and the subsequent substitution reaction, affording the allylic sulfide smoothly and in good yield (Table 2, entry 9).

3-Bromocyclohexene and benzyl bromide could also undergo the substitution reaction to give the corresponding sulfides in good yield.

In conclusion, we have demonstrated that the cleavage of S–S bond of the disulfides can be realised with a zinc/DMF system without any other auxiliary reagents. This is in contrast with the reports hitherto concerning the synthesis of organic disulfides from the cleavage of disulfides with zinc and Lewis acids or by transition metal catalysis. The principal advantages of this method are (a) absence of any other Lewis acid, (b) inexpensive reagents, (c) high yields and (d) a facile workup procedure.

Mechanistic studies are underway in our laboratory so as to clarify the activating species resulting from the reductive cleavage of the S–S bond by the zinc metal in these reactions.

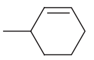


Scheme 2

---

* Correspondent. E-mail: sky29@zjnu.cn

Table 3 Synthesis of sulfides from disulfides in Zn/DMF

Entry	R in **3**	Product	Yield/%[a]
1		**3a**	92
2	$PhCH_2$	**3b**	86

[a]Yield of isolated products based on the disulfide.

Experimental

General

Melting points are uncorrected. IR spectra were recorded on an IR-408 spectrometer in their films. ^1H NMR and ^{13}C NMR spectra were determined in a Bruker AC–400 spectrometer as $CDCl_3$ solutions. J values are in Hertz. Chemical shifts are expressed in ppm downfield from internal TMS. Microanalysis was carried out on a EA 1110 instrument. DMF was redistilled and dried by molecular sieve before use. The reaction was monitored by TLC, and the products were isolated by silica gel column chromatography using ethyl acetate and cyclohexane (0.5:9.5) as eluant. The disulfides were prepared according to literature.[14]

Typical procedure for the synthesis allylic sulfides: Zinc powder (98 mg, 1.50 mmol) and diphenyl disulfide (109 mg, 0.5 mmol) in freshly distilled DMF (3 ml) were mixed at room temperature with magnetic stirring under a nitrogen atmosphere. The mixture was stirred at 110 °C for 11 h and then cooled to room temperature. Allyl bromide(151 mg, 1.25 mmol) was introduced by a syringe. The mixture was stirred at room temperature for 2–3 h and monitored by TLC. Then the HCl solution (5%, 20 ml) was added, the mixture was extracted with ethyl acetate and the products were isolated by silica gel column chromatography using ethyl acetate and cyclohexane (0.5 : 9.5) as eluant. The solvents were removed under reduced pressure to give a light yellow liquid product (140 mg) in 93 % yield.

For AA'XX' systems below $J^* = J_{23} + J_{25}$

Allyl phenyl sulfide (**2a**)[7]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3077, 3059, 2923, 2853, 1636, 1583, 1480, 1438, 987, 917, 736, 690. $\delta_H(CDCl_3)$: 7.14–7.34 (5H, m), 5.82–5.92 (1H, m), 5.04–5.14 (2H, m), 3.53 (2H, d, J = 6.8). $\delta_C(CDCl_3)$: 37.21 (C H_2), 117.7 (C H_2=), 133.6 (CH=), 126.2, 128.8, 129.9, 136.5 (*Ar*-C).

Allyl 4-chlorophenyl sulfide (**2b**)[7]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3082, 3010, 2979, 2916, 2854, 1636, 1573, 1476, 1228, 1095, 920, 812, 731. $\delta_H(CDCl_3)$: 7.25 (2H, m, J^*=8.2), 7.24 (2H, m, J^*=8.2), 5.81–5.87 (1H, m), 5.05–5.13 (2H,m), 3.51 (2H, d, J=6.8). $\delta_C(CDCl_3)$: 37.4 (CH_2), 117.9 (CH_2=), 133.3 (CH=), 128.9, 131.4, 132.3, 134.4(Ar-C).

Allyl 4-methylphenyl sulfide (**2c**)[7]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3080, 3018, 2978, 2919, 2865, 1636, 1492, 1425, 1092, 987, 917, 804. $\delta_H(CDCl_3)$: 7.27 (2H, m, J^*=7.8), 7.10 (2H, m, J^*=7.8), 5.85–5.91 (1H, m), 5.05–5.13 (2H, m), 3.51 (2H, d, J=7.0), 3.33 (3H, s). $\delta_C(CDCl_3)$: 21.1 (CH_3), 37.9 (CH_2), 117.4 (CH_2=), 133.9 (CH=), 129.6, 130.7, 132.3, 136.7 (Ar-C).

Allyl benzyl sulfide (**2d**)[7]: Light yellow oil. ν_{max}(film)/cm^{-1}: 3080, 3028, 2976, 2848, 1634, 1600, 1493, 1452, 989, 916, 741, 699. $\delta_H(CDCl_3)$: 7.22–7.32 (5H, m), 5.76–5.84 (1H, m), 5.08–5.15 (2H, m), 3.66 (2H, s), 3.04 (2H, d, J=6.8). $\delta_C(CDCl_3)$: 34.1 (CH_2S), 34.9 (CH_2Ph), 117.3 (CH_2=), 134.2 (CH=), 126.9, 128.4, 129.0, 138.3 (Ph-C).

Allyl 4-methylbenzyl sulfide (**2e**)[7]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3080, 3020, 2921, 2854, 1634, 1513, 1460, 1423, 989, 916, 816. $\delta_H(CDCl_3)$: 7.20 (2H, m, J^*=8.0), 7.10 (2H, m, J^*=8.0), 5.74–5.82 (1H, m), 5.02–5.12 (2H, m), 3.61 (2H, s), 3.01 (2H, d, J=7.2), 2.32 (3H, s). $\delta_C(CDCl_3)$: 21.1 (CH_3), 34.1 (CH_2S), 34.7 (CH_2Ph), 117.2 (CH_2=),134.3 (CH=), 128.9, 129.2, 135.2, 136.5 (*Ar*-C).

Allyl 4-chlorobenzyl sulfide (**2f**)[7]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3080, 3042, 2976, 2917, 2851, 1634, 1596, 1486, 1423, 1226, 989, 918, 831. $\delta_H(CDCl_3)$: 7.24 (2H, m, J^*=8.4), 7.20 (2H, m, J^*=8.4), 5.72–5.79 (1H, m), 5.02–5.11 (2H, m), 3.56 (2H, s) 2.98 (2H, d, J =7.5). $\delta_C(CDCl_3)$: 34.1 (CH_2S), 34.2 (CH_2Ar), 117.5 (CH_2=), 134.1 (CH=), 128.6, 130.4, 132.6, 136.8 (Ar-C).

Allyl 4-bromobenzyl sulfide (**2g**): Light yellow oil. ν_{max}(film)/cm^{-1}: 3078, 2976, 2850, 1633, 1486, 1070, 989, 918, 823. $\delta_H(CDCl_3)$: 7.41 (2H, m, J^*=8.0), 7.17(2H, m, J^*= 8.0), 5.72–5.82 (1H, m), 5.04–5.14 (2H, m), 3.59 (2H, s), 3.01 (2H, d, J=4). $\delta_C(CDCl_3)$: 34.1 (CH_2C=), 34.3 (CH_2Ar), 117.5 (CH_2=), 134.0 (CH=), 120.8, 130.7,131.5, 137.3 (Ar-C). Anal. $C_{10}H_{11}BrS$. Calcd: C, 49.4; H, 4.6; Br, 32.9; S, 13.2. Found: C, 49.3; H, 4.6, S, 13.2.

Allyl 4-methoxylbenzyl sulfide (**2h**): Light yellow oil. ν_{max}(film)/cm^{-1}: 3078, 2948, 2912, 2834, 1609, 1508, 1463, 1248, 990, 917. $\delta_H(CDCl_3)$: 7.21 (2H, m, J^*=9.2), 6.83 (2H, m, J^*=9.2), 5.76–5.85 (1H, m), 5.06–5.13 (2H, m), 3.78 (3H, s), 3.62 (2H, s), 3.01 (2H, d, J=7.2). $\delta_C(CDCl_3)$: 34.0 (CH_2C=), 34.3 (CH_2Ar), 55.3 (CH_3O), 117.2 (CH_2=), 134.3 (CH=), 113.8, 130.1, 130.3, 158.7 (Ar-C). Anal. $C_{11}H_{14}OS$. Calcd: C, 68.0; H, 7.3; S, 16.5. Found C, 67.9; H, 7.3, S, 16.5.

Allyl n-octyl sulfide (**2i**)[7]: Light yellow oil. ν_{max}(film)/cm^{-1}: 3080, 2925, 2854, 1635, 1464, 1426, 1225, 988, 913, 734. $\delta_H(CDCl_3)$: 5.73–5.83 (1H, m), 5.05–5.09 (2H, m), 3.10 (2H, d, J=7.1), 2.43 (2H, t, J=7.4), 1.26–1.61 (12H, m), 0.87 (3H, t, J=6.8). $\delta_C(CDCl_3)$: 14.1, 22.7, 28.9, 29.1, 29.2, 29.3, 30.7, 31.8 (C_8H_{17}), 34.8 (CH_2), 116.6 (CH_2=), 134.6 (CH=).

Cyclohex-2-enyl phenyl sulfide (**3a**)[15]: Light yellow liquid. ν_{max}(film)/cm^{-1}: 3057, 3024, 2928, 2833, 1644, 1584, 1478, 1438, 1255, 1203, 1024, 870, 737, 691. $\delta_H(CDCl_3)$: 7.16–7.41 (5H, m), 5.75–5.84 (2H, m), 3.85 (1H, m), 1.26–2.10 (6H, m). $\delta_C(CDCl_3)$: 19.5, 25.0, 28.8, 43.9, 126.6, 130.5 (cyclohexene-C), 127.0, 128.9, 131.3, 136.0 (Ar-C).

Phenyl benzyl sulfide (**3b**): White solid, m.p. 42–44 °C(lit.[16] 40–42 °C). ν_{max}(film)/cm^{-1}: 3061, 3029, 2923, 2851, 1601, 1584, 1479, 1453, 1025, 787, 762, 691. $\delta_H(CDCl_3)$: 7.17–7.32 (10H, m), 4.15 (2H, S). $\delta_C(CDCl_3)$: 39.1 (CH_2), 126.3, 127.2, 128.5, 128.8, 129.8 (Ar-C).

The authors are thankful to Dr Xiaoxia Wang for support and to Weidong Liu for obtaining elements analysis and IR spectra.

Received 9 November 2004; accepted 6 January 2005
Paper 04/2863

References

1 (a) J.F. Biellmann and J.B. Ducep, *Org. React.,* 1982, **27**, 1; (b) S. Choppin, P. Gros and Y. Fort, *Synth. Commun.,* 2000, **30**, 795; (c) J.F. Biellmann and J.B. Dueep, *Tetrahedron Lett.,* 1969, 3707; (d) L. Stotter and R.E. Nornish, *J. Am. Chem. Soc.,* 1973, **95**, 444; (e) K-I. Fujita and T. Kamakaki, *Drug. Metab. Dispos.,* 2001, **29**, 983.

2 S.B. Tsay, L.C. Lin and P.A. Furth, *Synthesis,* 1993, **3**, 329.

3 (a) E.M. Faber and G.E. Miller, *Org. Synth.,* 1943, **Coll. 2**, 576; (b) J.K. Lawson, W.K. Easley and W.S. Wagner, *Org. Synth.,* 1963, **4**, 892.

4 H.J. Vamder, P.J. Knotnerus and A.F. Bicked, *Rect. Trav. Chim.,* 1962, 81.

5 C.G. Moori and B.R. Trego, *Tetrahedron,* 1963, **8**, 1251.

6 J.S. Yadav, B.V.S. Reddy, C. Srinivas and P. Srihari, *Synlett,* 2001, **6**, 854.

7 M.X. Yu and Y.M. Zhang, *Synth. Commun.,* 1997, **27**, 2743.

8 W.K. Su, Y.S. Li, Y.M. Zhang and J.H. Li, *J. Indian Chem. Soc.,* 2001, **78**, 263.

9 S. Chowdbury and S. Roy, *Tetrahedron Lett.,* 1997, **38**, 2149.

10 (a) B. Movassagh, M.M. Lakouraj and Z. Fadaei, *J. Chem. Res.*(S), 2000, 350; (b) M.M. Lakouraj, B. Movassagh and Z. Fadaei, *Synth. Commun.,* **32**(8),1237, 2002.

11 F.S. Tian, Y.M. Zhu, S.L. Zhang and Y.L. Wang, *J. Chem. Res.*(S), 2002, 582.

12 N. Taniguchi, *J. Org. Chem.*, 2004, **69**, 6904.

13 B. Movassagh, M.M. Lakouraj and Z. Fadael, *J. Chem. Res.*(S), 2001, 22.

14 C.N. Yiannios and J.V. Karabions, *J. Org. Chem.,* 1963, **28,** 3234.

15 R.W. Saville, *J. Chem. Soc.,* 1958, 2880.

16 L. Lu and Y.M. Zang, *Synth. Commun.,* 1998, **28**, 4479.