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One Pot Conversion of Alcohols to Disulfides Mediated by Benzyltriethylammonium Tetrathiomolybdate

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Abstract: A one pot conversion of alcohols to disulfides in good yields via the activation of a hydroxyl group with DCC or $P(NMe_2)_3$ / CCl_4 followed by treatment with benzyltriethylammonium tetrathiomolybdate is reported.

Keywords: alcohols; amino acids; disulfides; macrocycles

Disulfides are a very important class of compounds in chemistry as well as biology.[1] Because of their importance, their synthesis assumes significance and several methods are known for this purpose. Most of the methods involve the conversion of alkyl halides or sulfonates into the corresponding thiols followed by oxidation.[2] Since halides and sulfonates are made from alcohols and sometimes the conversion of alcohols to halides or sulfonates are troublesome, direct conversion of an alcohol to the corresponding disulfide will be a significantly useful methodology

We have previously shown that alkyl halides and tosylates react with benzyltriethylammonium tetrathiomolybdate $[(PhCH_2NEt_3)_2MoS_4]$, **1** to give alkyl disulfides in good yield.[3] We wanted to extend this methodology for the conversion of alcohols to disulfides (ROH → RSSR). In order to apply the sulfur transfer reaction mediated by tetrathiomolybdate, **1** for this transformation we decided to adopt the *in situ* activation of alcohols using either DCC[4] or $P(NMe_2)_3/CCl_4$[5] which can be further treated with tetrathiomolybdate, **1** to yield the corresponding disulfides (Scheme 1 & 2).

Benzyl alcohol, **2** was chosen as the model substrate and was treated with dicyclohexyl carbodi-

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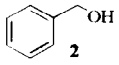
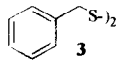
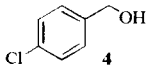
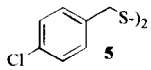
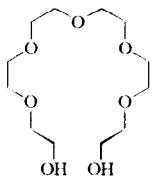
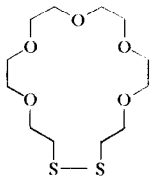
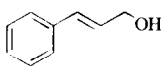
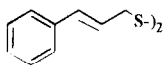
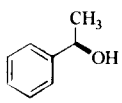
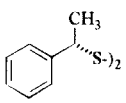
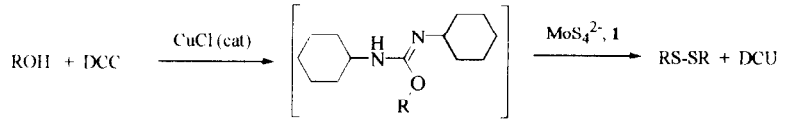
Table 1.

$$RCH_2OH \xrightarrow[2.\ MoS_4^{2-},\ \mathbf{1}]{1.\ DCC\ /\ CuCl} RCH_2SSCH_2R$$

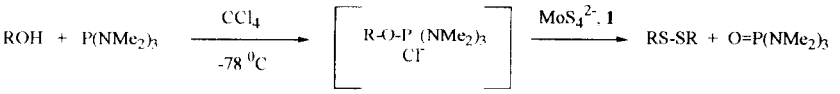
Substrate	Product	Time(h)	Yield(%)
 **2**	 **3**	11	88
 **4**	 **5**	14	70
 **6**	 **7**	27	70
 **8**	 **9**	27	77
 **10**	 **11**	30	40
 **12**	 **13**	17	79
 **14**	 **15**	49	80
 **16**	 **17**	8	47[a]
Z-Ser-OMe **18**	Di-Z-Cyst-di-OMe **19**	29	45
t-Butanol	-------	51	-----

[a] conversion = 75%, (*R,R*) : *meso* = 90 : 10.

imide and CuCl (5 mol%, neat reaction) to form the isourea which on further treatment with tetrathiomolybdate, **1** (1.2 eq) in CH_3CN (25 ^{0}C, 11 h) yielded dibenzyl disulfide **3** as the only product in 88% yield. Encouraged by the initial success, this methodology was then extended to a number of other alcohols and the results are summarised in Table 1.



Scheme 1.

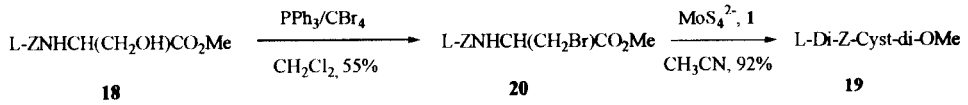


Scheme 2.

Following the same protocol it was found that aliphatic primary alcohols like *n*-butanol, **6** and *n*-octanol, **8** reacted much more slowly (25 ^{0}C, 27 h) compared to the benzylic alcohol but the corresponding disulfides **7** and **9**, respectively were isolated in good yields. Since we had previously shown that tetrathiomolybdate can mediate the sulfur transfer reaction of α,ω dihalides to form cyclic disulfides of various ring sizes[6] it was of interest to find out whether a similar reaction can be performed on α,ω diols. For this purpose hexaethylene glycol, **10** was subjected to the same reaction conditions with DCC/CuCl followed by treatment with tetrathiomolybdate (25 ^{0}C, 30 h). In this case macrocyclic disulfide **11** was isolated in 40% yield. The reaction of cinnamyl alcohol, **12** was reasonably fast to give the disulfide **13** in 79% yield. Reaction of a secondary alcohol like isopropanol, **14** was extremely slow (49 h) but the disulfide **15** was isolated in 80% yield. As expected *t*-butanol under the reaction conditions did not yield any of the corresponding disulfide. Although the formation of a disulfide from a secondary alcohol was extremely slow it was of interest to study the reaction of a secondary alcohol positioned at a chiral centre. Accordingly (S)-(-)-1-phenylethanol, **16** was reacted with DCC/CuCl (50 ^{0}C, 5 h) followed by treatment with tetrathiomolybdate **1** in CH_2Cl_2 as a slurry under sonochemical conditions (ultrasonic cleaning bath, 20 KHz, 25 ^{0}C, 3 h) and the disulfide **17** was obtained in 47% isolated yield. From ^{1}H NMR and optical rotation data available on **17**[7] it turns out that the major product is the (*R,R*)-isomer with inversion of configurations at the chiral centre.[8]

Covalent linkages between amino acid side chains stabilise proteins by reducing the conformational entropy of the unfolded state. This is principally achieved mainly by the formation of disulfide bond between two cysteine residues. In this connection, it was decided to investigate whether a one pot of conversion of

L-Serine to L-Cystine can be achieved using the present methodology. When Z-Ser-OMe, **18** was subjected to activation with DCC followed by treatment with **1**, the product di-Z-Cyst-di-OMe **19** was obtained in 45% isolated yield. The same conversion was also achieved by another route via the formation of bromide **20** which on further treatment with tetrathiomolybdate, **1** yielded disulfide **19** in high yield (Scheme 3).

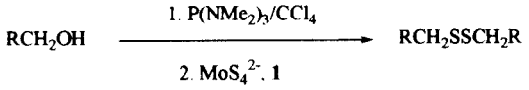


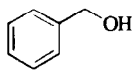
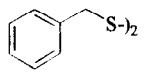
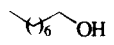
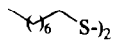
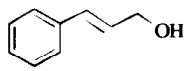
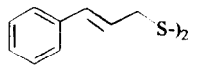
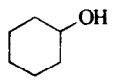
18 **20** **19**

Scheme 3.

The one pot conversion of alcohol to disulfide was also studied using hexamethyl phosphorous amide as the activating agent. The results achieved using this procedure are summarised in Table 2. Thus when benzyl alcohol was treated with hexamethyl phosphorous triamide/CCl_4 (-78 °C, CH_2Cl_2) followed by treatment with tetrathiomolybdate **1** (3 h) the disulfide **3** was isolated in 70% yield. It is interesting to note that although the

Table 2.



Substrate	Product	Time (h)	Yield (%)
 **2**	 **3**	3	70
 **8**	 **9**	8	69
 **12**	 **13**	7	60
	---	48	---

conditions (7-8 h) and gave the corresponding disulfides in moderate yield. The isolated yields of the disulfides in this procedure were consistently lower than the method that was described earlier. Cyclohexanol failed to give any of the corresponding disulfide using this procedure.

In conclusion we have shown that simple benzylic and primary alcohols can be activated *in situ* by using DCC or $P(NMe_2)_3/CCl_4$ and on further treatment with tetrathiomolybdate **1** can be converted in one pot to the corresponding disulfides in good yields.

Experimental Section:

General. All the reactions were performed in oven dried glassware. ^1H NMR spectra were recorded on Jeol 90 FXQ at 90 MHz and Jeol Lambda 300 at 300 MHz in $CDCl_3$. IR were recorded on Perkin-Elmer model - 781 spectrometer. Mass spectra were recorded on a Jeol MSD 300 mass spectrometer. TLC were performed on 0.25 mm E. Merck precoated silica plates (60F-254). Silica gel (60-120 mesh) was used for normal column chromatography and TLC grade silica gel (200-400 mesh) was used for flash column chromatography. Bulb to bulb distillation was carried out on a Buchi-GKR-50 distillation unit. Optical rotation was measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and is reported as follows: $[\alpha]$ $t(^0C)$ λ, [c (g/100 mL), solvent]. The melting points and boiling points are uncorrected. CH_3CN and CH_2Cl_2 were dried over P_2O_5.

Preparation of benzyltriethylammonium tetrathiomolybdate $[(BnNEt_3)_2MoS_4]$, 1:

The present procedure is a modification of that described previously.[3]

Ammonium molybdate (10 g) was dissolved in a mixture of ammonium hydroxide (60 mL, sp.gr. 0.91) and water (20 mL) and the solution was filtered. Hydrogen sulfide was bubbled *rapidly* at room temperature (25^0C) for 10 min with constant stirring and at 60 ^0C for 1 h. Then the mixture was cooled to 0 ^0C for 15 min and the product was isolated by filtration. It was washed with isopropyl alcohol (25 mL) and ether (25 mL). The brick red crystals of ammonium tetrathiomolybdate (13.5 g) were dried under vacuum.

A solution of ammonium tetrathiomolybdate (13 g, 50 mmol) in water (60 mL) was added to a rapidly stirred solution of benzyltriethylammoniumchloride (23.31 g, 102.5 mmol) in distilled water (60 mL) over 5 min. The reaction mixture was stirred vigorously for 2 more hours. The solid that separated was filtered, washed with cold water (20 mL), isopropyl alcohol (40 mL) and ether (40 mL) and dried under vacuum. The dark red powder of benzyltriethylammonium tetrathiomolybdate $[(BnNEt_3)_2MoS_4]$, **1** (24 g, 80%) was stored in dessicator. mp: 130 ^0C, Elemental Analysis: Calcd for $[(BnNEt_3)_2MoS_4]$ C 51.29, H 7.28, N 4.60; Found C 50.93, H 7.31, N 4.31.

Typical experimental procedure for the synthesis of disulfides directly from alcohols using DCC and CuCl for activation (Procedure A):

Benzyl alcohol, **2** (1 mmol) was added by syringe to a stirred mixture of copper(I) chloride (5 mg, 5 mol%) and DCC (0.226 g, 1.1 mmol) at 0 ^0C. The reaction mixture was stirred for 3 h at 25 ^0C. After completion of the

reaction, tetrathiomolybdate, **1** (0.727 g, 1.2 mmol) and CH_3CN (3 mL) were added and the reaction mixture was stirred at room temperature for 8 h. The solvent was removed in vacuum and the product was extracted with ether/CH_2Cl_2 5:1 (25 mL × 4) and filtered through a pad of Celite. The residue obtained after evaporation of solvent followed by chromatographic purification over silicagel using 2% EtOAc in hexanes yielded the pure product, dibenzyl disulfide **3**[9] as a white solid (0.108 g, 88%). mp: 71-72 ^{0}C (lit.[7] 71-72 ^{0}C); IR (neat): 3095, 3030, 2930, 1600, 1495, 1455 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.60 (s, 4H), 7.28 (s, 10H).

Typical experimental procedure for the synthesis of disulfides directly from alcohols using $P(NMe_2)_3/CCl_4$ for activation (Procedure B):

To a stirred and cooled (-78 ^{0}C) solution of benzyl alcohol, **2** (1 mmol) and CCl_4 (0.2 mL) in CH_2Cl_2 (2 mL), a solution of $P(NMe_2)_3$ (0.179 g, 1.1 mmol) in CH_2Cl_2 (2 mL) was added over a period of 0.5 h under argon. The mixture was allowed to come to room temperature and was stirred for 2 h. After the disapperance of the starting material, tetrathiomolybdate, **1** (0.668 g, 1.1 mmol) was added and stirred for 0.5 h. The solvent was evaporated at reduced pressure and the residue was extracted with ether/CH_2Cl_2 5:1 (25 mL × 4) and was filtered through a pad of Celite. Removal of solvent and chromatographic purification over silicagel yielded the pure disulfide **3**[9] as a white solid (0.086 g, 70 %).

p-Chloro dibenzyl disulfide (5)[10]**:** Purified by column chromatography on silica gel using 5% EtOAc/hexanes as eluent to give **5** as a white solid. Yield: 0.109 g (70%); mp: 58 ^{0}C (lit.[8] 59 ^{0}C); IR (neat): 1600, 1490, 1370, 1090, 1010 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.60 (s, 4H), 7.20-7.32 (m, 8H).

Di *n*-butyl disulfide (7)[11]**:** Purified by column chromatography on silica gel using hexanes as eluent to yield **7** as a colourless oil. Yield: 0.062 g (70%); bp: 96-99 ^{0}C/6mm (lit.[9] 93-99 ^{0}C/6mm); IR (neat): 2690, 2860, 1465, 1450, 1375 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.93 (t, *J* 6.9 *Hz*, 6H), 1.28-1.68 (m, 8H), 2.83 (t, *J*=6.7 *Hz*, 4H).

Di *n*-octyl disulfide (9)[12]**:** After purification by column chromatography on silica gel using hexanes as eluent the compound **9** was isolated as colourless oil. Yield: 0.107 g (77%); bp: 174-176 ^{0}C/1mm (lit.[10] 175-176 ^{0}C/1mm); ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.88 (t, *J* 6.9 *Hz*, 6H), 1.12-1.84 (m, 24H), 2.64 (t, *J*=6.7 *Hz*, 4H).

Dithio-18-crown-6 (11)[13]**:** Purified by column chromatography using 10 % MeOH in $CHCl_3$ as eluent to give **11** as a white solid. Yield: 0.125 g (40%); mp: 32-33 ^{0}C (lit.[11] 34 ^{0}C); IR (neat): 2820, 1460, 1360, 1285, 1100 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.92 (t, *J* 6.92 *Hz*, 4H), 3.68 (br s, 20H). Ms (70 ev): *m z* 312 (M^+), 257, 181, 168, 136, 103, 93, 61.

Dicinnamyl disulfide (13)[14]**:** Purified by column chromatography on silica gel using 4% EtOAc/hexanes as eluent to yield **13** as a white solid. Yield: 0.118 g (79%); mp: 88-89 ^{0}C (lit.[12] 89 ^{0}C); IR (neat): 1600, 1360, 1200, 940 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (d, *J* 6.6 *Hz*, 4H), 6.20 (dt, J_1=15.8, J_2=6.4 *Hz*, 2H), 6.64

(d, *J* 15.9 *Hz*, 2H), 7.26-7.38 (m, 10H).

Diisopropyl disulfide (15)[15]: It was purified by column chromatography on silica gel using hexanes as eluent the compound **15** was obtained as a colourless oil.

Yield: 0.107 g (80%); bp: 95 ^{0}C/56mm (lit.[13] 95 ^{0}C/56mm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, *J* = *6.0 Hz*, 12H), 2.95 (m, 2H).

Preparation of *(R,R)*-(+)-Bis(1-phenylethyl) Disulfide (17)[7]: A mixture of (S)-(-)-1-phenylethanol, **16** (0.050 g, 0.40 mmol), copper(I) chloride (5 mol%) and DCC (0.090 g, 0.44 mmol) were stirred for 5 h at 50 ^{0}C under argon. A solution of tetrathiomolybdate, **1** (0.292 g, 1.2 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction mixture was sonicated in an ultrasonic cleanning bath (20 KHz, 25 ^{0}C, 3 h). The crude reaction mixture was loaded on a silica gel column and was elueted with petroleum ether (60-120 ^{0}C) to yield **17** as a colourless oil (0.026 g, 47%). $[\alpha]^{25}_D$ +203^0 (*c* 0.7, absolute EtOH) [lit.[7] $[\alpha]_D$ +271.9^0 (*c* 1, EtOH)]; IR (neat): 1590, 1490, 1465 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (*meso*) 1.54 (d, *J* *6.9 Hz*, 3H), 3.60 (q, *J* *6.9 Hz*, 1H); (*R,R*)-isomer 1.56 (d, *J* *6.9 Hz*, 3H), 3.52 (q, *J* *6.9 Hz*, 1H), 7.30 (m, 5H).

L-ZNHCH(CH_2Br)CO_2Me(20)[17]: L-Z-Ser OH was prepared according to the literature[16] procedure and then it was esterified with diazomethane.

Triphenylphosphine (0.352 g, 1.61 mmol) in dry dichloromethane (5 mL) was added dropwise by syringe over 10-15 min to a well stirred solution of *N*-benzyloxycarbonyl-L-serine methyl ester, **18** (0.340 g, 1.346 mmol) and CBr_4 (0.670 g, 2.02 mmol) in dry dichloromethane (10 mL) at 0 ^{0}C. It was stirred at room temperature for 9-10 h and was treated with pentane (60 mL) and the resulting precipitate was removed by filtration and washed several times with pentane. The combined pentane solution was washed with 5% $NaHCO_3$ (50 × 2 mL), H_2O (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated and the oil was purified by flash chromatography over silica gel using hexanes:EtOAc (4:1) to give bromide, **20** as viscous liquid (0.234g, 55%). IR (neat): 3320, 1700 (br s), 1500 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.80 (s, 5H), 4.82 (m, 1H), 5.18 (s, 2H), 5.65 (br s, NH), 7.40 (s, 5H).

Preparation of *N*-di-benzyloxycarbonyl-L-cystine-di-methyl ester 19[18] from bromide 20:

To a solution of **18** (0.128 g, 0.405 mmol) in dry CH_3CN (3 mL) was added benzyltriethylammonium tetrathiomolybdate, **1** (0.250 g, 0.405 mmol) and the reaction mixture was stirred for 7-8 h at r.t. The solvent was removed under vacuum, extracted with ether/CH_2Cl_2 5:1 (25 mL × 4) and filtered through a pad of Celite. Removal of solvent and chromatographic purification over silicagel using 30 % EtOAc in hexanes yielded the pure product **19** (0.100 g, 92%). IR (neat): 3320, 1700 (br s), 1500, 1050 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.10 (d, *J* *5.5 Hz*, 4H), 3.70 (s, 6H), 4.60 (m, 2H), 5.10 (s, 4H), 5.70 (br s, 2H, NH), 7.30 (s, 10H); ^{13}C NMR (22.2 MHz, $CDCl_3$): δ 40.55, 52.39, 53.04, 66.82, 127.82, 128.21, 135.88, 155.52, 170.61; MS (EI 70 eV): *m/z*

536 (M$^+$), 385, 301, 268, 236, 208, 92.

Direct Conversion of Z-Ser-OMe 18 to di-Z-Cyst-di-OMe 19: A mixture of Z-Ser-OMe, **18** (0.253 g, 1 mmol), copper(I) chloride (5 mol%) and DCC (0.226 g, 1.1 mmol) were stirred for 4 h at 28 ^{0}C under argon. A solution of tetrathiomolybdate, **1** (0.727 g, 1.2 mmol) in CH_3CN (3 mL) was added and the reaction mixture was stirred at room temperature for 25 h. The reaction mixture was worked up and purified as described above to give di-Z-Cyst-di-OMe **19** as viscous liquid (0.121 g, 45 %).

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