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Synthesis of Thiolactones using Benzyltriethylammonium Tetrathiomolybdate as Sulfur Transfer Reagent.

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Abstract: *An interesting sulfur transfer reaction mediated by benzyltriethylammonium tetrathiomolybdate [$(PhCH_2NEt_3)_2MoS_4$] converts ω-halo acid chlorides to the corresponding thiolactones in moderate to good yields in one step.* © 1997 Elsevier Science Ltd.

Introduction

Small ring heterocycles play an important role in the field of organic synthesis and thiolactones are one such class of compounds. β-thiolactones have been shown to participate in crucial carbon-carbon bond forming alkylation reactions. [1, 2] The remarkable differences in properties of ascorbic acid and its thio analogue have been attributed to their different molecular geometries.[3]

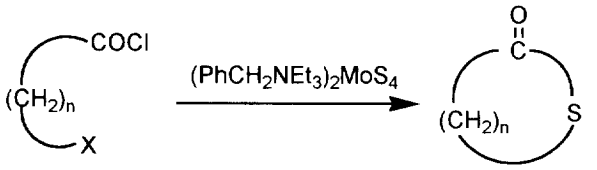
In general, small ring thiolactones can be prepared by the addition of thioacetic acid to β, γ or γ, δ unsaturated straight chain acids.[4] The action of sulfur and hydrogen on levulinic acid at 200 °C in the presence of a cobalt polysulfide catalyst, yields the thiovalerolactone in 44% yield,[5] whereas the same thiolactone was obtained in 9% yield by the action of phosphorous pentasulfide on valerolactone at 60-80 °C.[6] Synthesis of γ-thiobutyrolactone was carried out conveniently by pyrolysis of γ-mercaptobutyric acid in 78% yield.[7,8]

Compared to small ring thiolactones, protein bound macrocyclic thiolactones are a special class of macrolide family due to their important biochemical properties which is currently under intensive investigation.[9-11] In contrast to the many new macrolide forming methods that have recently been developed, very few procedures are available in chemical literature for the preparation of macrocyclic thiolactones.[12-14] Cyclic stannadithianes can be used as activated dithiols for the preparation of macrocyclic thiolactones, both dithiolactones and tetrathiolactones.[14] These macrocyclic thiolactones can be used as potential diacylating agents.

Oxidative cleavage of bicyclic enol ethers to the 12-oxo-pentadeconolide and its sulfur analogue, is one of the approaches towards the synthesis of macrocyclic lactones.[10] Steliou *et al.*[15] have reported a group 14 metal assisted method for carbon-sulfur bond formation that is applicable to the synthesis of macrocyclic thiolactones from ω-bromo carboxylic acid chlorides.

Results and Discussion

Previously we have shown that benzyltriethylammonium tetrathiomolybdate (**1**) converts a number of alkyl and acyl halides to the corresponding disulfides in high yields.[16, 17] It was therefore of interest to study the reactivity of tetrathiomolybdate **1** on substrates containing both the functional groups in the same molecule. It was anticipated that if an intramolecular reaction can be mediated by tetrathiomolybdate **1** it would be useful for the synthesis of a variety of thiolactones.



Accordingly, a number of ω-halo acid chlorides were prepared according to the literature procedure[18, 19] and they were allowed to react with benzyltriethylammonium tetrathiomolybdate (**1**) in dry chloroform or acetonitrile under argon atmosphere. The reactions were carried out under mild conditions (-10 - 0 °C, 2 - 7 h). In a few cases reacions were carried out at RT (25 °C) for longer period of time (24 h). The results of this sulfur transfer reaction are summarized in **Table-1**.

3-Iodopropionyl chloride **2** when treated with tetrathiomolybdate **1** at 0 °C the β-thiolactone **3** [20,21] was obtained in poor yield (30%). The reason for this poor yield is probably due to the fact that β-thiolactones readily react with various nucleophilic reagents present in the reaction mixture and the β-thiolactone ring gets ruptured at the S-acyl bond.

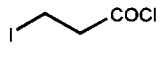
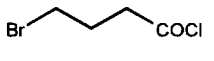
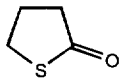
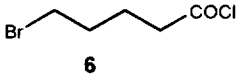
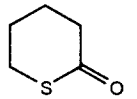
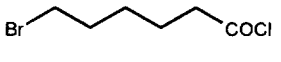
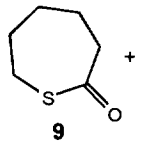
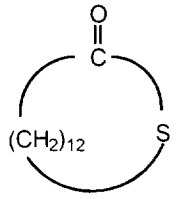
4-Bromobutyryl chloride **4**[22] and 5-bromovaleryl chloride **6**[23] on treatment with tetrathiomolybdate **1** yielded the corresponding 5-membered thiolactone **5**[24] and 6-membered thiolactone **7**[15, 24] respectively as the only products in moderate to good yield.

In the case of 6-bromohexanoyl chloride **8**,[26] the reaction was carried out at RT for 24 h and the solvent was changed from chloroform to acetonitrile. In this case the products obtained were monothiolactone **9**[15] (13%) and the dimer **10** (16%)

In the reaction of 11-bromoundecanoyl chloride **11** with tetrathiomolybdate **1** (1.5 eq., 0 °C, 24 h, CH_3CN) the monothiolactone **12**[15] was obtained in 31% yield. High dilution reaction did not improve the yield of the product. When the same reaction was carried out at RT in CH_3CN (24 h),

Table 1

Reaction of ω-halo acid chlorides with Tetrathiomolybdate in solution

Entry	Substrate	Product	Temp(°C)	Time(h)	Yield(%)
1	 **2**	 **3**	0	4.0	30[a]
2	 **4**	 **5**	0	5.0	65[a]
3	 **6**	 **7**	0	7.0	77[a]
4		 + **9** Dimer **10**	25	24.0	13[b] 16[b]
5	$BrCH_2(CH_2)_9COCl$ **11**	 **12**	0	24	31[b]
6	$BrCH_2(CH_2)_9COCl$ **11**	**12** + Dimer **13**	25	24.0	11[b] 24[b]

[a] Solvent: $CHCl_3$; [b] Solvent: CH_3CN

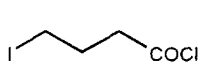
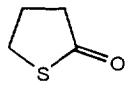
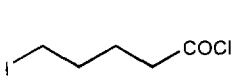
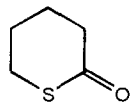
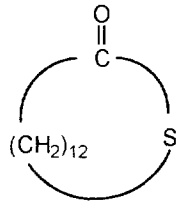
the monothiolactone **12**[15] and the dimer **13**[15] were formed in approximately 1:2 ratio in 11% and 24% yields respectively.

During our earlier studies on sulfur transfer reactions we found that tetrathiomolybdate **1** reacts readily (5-30 min) in the solid state with benzyl halides, alkyl iodides and acyl halides to afford the corresponding disulfides in good yields.[26]

Since the solid state sulfur reactions were very specific for iodo and acylhalide systems we decided to explore this solid state reaction for the formation of small and medium ring thiolactones. Accordingly a number of ω-iodoacid chlorides were prepared from the corresponding bromo acids.[27] The results of this investigation on the sulfur transfer reaction are summarized in **Table-2**. Thus, 4-iodobutyryl chloride **14** and 5-iodovaleryl chloride **15** were allowed to react with tetrathiomolybdate **1** in the solid state (15 min, RT) and the corresponding thiolactones **5** and **7** respectively were obtained as the only products in reasonable yields. When 11-iodoundecanoyl chloride **16** was treated with tetrathiomolybdate **1** in the solid state (15 min, RT), thiolactone **12** was obtained in poor yield.

Table 2

Reaction of ω-iodo acid chlorides with Tetrathiomolybdate in the solid state

Entry	Substrate	Intra:Inter	Time(h)	yield(%)
1	 **14**	 **5**	0.25	52
2	 **15**	 **7**	0.25	70
3	$ICH_2(CH_2)_9COCl$ **16**	 **12**	0.25	3

Although a number of procedures are available for the preparation of thiolactones, especially small ring lactones, most of them involve the intermediacy of mercapto-acids. In those cases the preparation of mercapto-acid itself, requires a number of steps. Moreover, lactonisation of mercapto-acid requires harsh conditions, generally accelerated in the presence of acid or by heating. Although our original objective was to develop a general methodology using tetrathiomolybdate **1** for the synthesis of medium and large ring thiolactones, it turns out that the methodology works well for small and medium ring compounds and it is not that useful for macrocyclic thiolactones. The failure of these reactions for macrocyclic systems is probably due to the large difference in reactivity of the two functional groups namely halo and the acid chloride with tetrathiomolybdate **1**.

Experimental

All the reactions were carried out under argon atmosphere. Chloroform and acetonotrile were kept over phosphorous pentoxide, distilled and stored over molecular sieves (4Å). TLC was performed on 0.25 mm precoated silica plates (60F-254); the plates were initially examined under UV light and spots were then visualised with iodine and 10% solution of phosphomolybdic acid in ethanol. Evaporations were carried out using Büchi rotary evaporator under suction. The mp's reported are uncorrected. IR spectra were recorded on a Perkin Elmer model 781 and the frequencies are reported in wave number (cm^{-1}). ^1H NMR spectra were run using $SiMe_4$ as internal standard; spectra were measured at 60 MHz using Hitachi R-1500 FT and at 90 MHz using Jeol 90FXQ spectrophotometer. Gas chromatography was done using SHIMADZHU GC14A. Mass spectra were determined using Jeol JMS-DX 303 instrument. Benzyl triethylammonium tetrathiomolybdate **1** was prepared as described earlier.[16] ω-bromocarboxylic acid chlorides were prepared according to the literature procedure.[18, 19] In the case of ω-iodoacid chlorides the method was as described for the preparation of ω-bromocarboxylic acid chlorides.[19] But in these cases excess of thionyl chloride was removed under reduced pressure and the acid chloride was used as such without any further purification (during distillation iodoacid chlorides undergo decomposition).

General Procedures:

Reaction of 5-bromovaleryl chloride 6 with tetrathiomolybdate 1 at low temperature:- To a solution of tetrathiomolybdate **1** (1.56g, 2.6 mmol) in dry chloroform (15 ml) was added the acid chloride **6**[23] (0.49 g, 2.4 mmol) dropwise at -10 °C with stirring under argon atmosphere. After 7h, most of the solvent was removed under reduced pressure and the black material was slurried with dichloromethane (5 ml) and ether (25 ml). It was filtered through a pad of Celite and washed with ether (6 x 25 ml). The combined filtrate on removal of solvent yielded the crude product. GC

of the crude product shows only one peak (77% yield, column: HR-1 megabore capillary, 0.53 mm dia, 15 M long, Temperature 80 °C, carrier gas: H_2, pressure maintained 0.4 kg/cm^2). Column chromatography of the crude material on silica gel (95:5 petroleum ether-EtOAc as eluent) gave the thiolactone **7**[24] (0.18g, 61%). IR (neat) 2914, 1659, 1437, 1407, 1293, 1188, 1068, 972, 930, 846, 786 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.80-2.31 (m, 4H), 2.48-2.85 (m, 2H), 2.99-3.36 (m, 2H); MS (m/z) 116 (100, M^+), 88 (25), 83 (26), 60 (73), 55 (34), 41 (35); HRMS Found M^+, 116.0294. Calc. For C_5H_8OS: 116.0296.

β-Propiothiolactone(3)[20, 21]**:-** Acid chloride **2** (0.226, 1.04 mmol) was added dropwise to a solution of tetrathiomolybdate **1** (0.78g, 1.3 mmol) in $CHCl_3$ at 0 °C, allowed to come to room temperature and stirred for 4h. After usual workup the thiolactone **3** was obtained as a liquid (0.026g, 30%). bp 48-50 °C/12 mm Hg (lit[21] 50-53 °C/12 mm Hg). MS (m/z) 89 (15, M^++1), 71 (20), 57 (47), 40 (67).

γ-Butyrothiolactone (5)[24]**:-**Acid chloride **4** (0.37g, 0.23 ml, 2.0 mmol) was added dropwise to a solution of tetrathiomolybdate **1** (1.34g, 2.2 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 5h. After usual work up the thiolactone **5** was isolated as a liquid (0.133g, 65%). b.p 38-39 °/1mm Hg (lit[24]: 39-40 °C). IR (neat) 2940, 1690, 1440, 1410 and 1280 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.85-2.72 (m, 4H), 3.39 (t, J= 9.6 Hz, 2H); MS (m/z) 102 (100, M^+), 55 (90), 42 (85).

Reaction of acid chloride 8 with tetrathiomolybdate 1 at RT:- Tetrathiomolybdate **1** (1.83g, 3 mmol) was dissolved in dry acetonitrile (5 ml). 6-bromohexanoyl chloride **8**[25] (0.427g, 0.31 ml, 2 mmol) was added to that and the reaction mixture was stirred at RT for 22 h. After usual work-up the product was purified by flash column chromatography on silica gel using neat petroleum ether to 1% EtOAc in petroleum ether as eluent to isolate monothiolactone **9**[15] and the dimer **10**.

Monothiolactone (9)[15] : Yield: 0.033 g, 13%; IR (nujol): 2900, 2840, 1660, 1440, 1210 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.68-2.27 (m, 6H), 2.78-3.03 (m, 4H); MS (m/z): 130 (100, [M^+]), 102 (54), 87 (46), 68 (55), 60 (42), 55 (53).

Dimeric thiolactone (10): Yield: 0.040g, 16%; mp: 150 °C; IR (nujol): 2900, 2840, 2680, 1450, 1370 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.04-1.93 (m, 12H), 2.59 (br t, 4H), 3.03 (br t, 4H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 25.1, 25.9, 28.3, 29.1, 43.3, 199.7; MS (m/z): 260(1.2, [M^+]), 131 (100), 130 (75), 102 (78), 87 (44), 69 (42), 55 (36); HRMS Found M^+, 260.0919. Calc. For $C_{12}H_{20}O_2S_2$: M^+, 260.0905.

Thioundecanolide (12)[15]: The product **12** was isolated as an oil. IR ($CHCl_3$): 1670 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.30-1.89 (m, 16H), 2.54 (t, J= 6 Hz, 2H), 3.01 (t, J= 6 Hz, 2H); MS (m/z): 201 (46, [M^+ + 1]), 98 (64), 83 (50), 69 (72), 55 (100), 39 (70).

Dimeric thiolactone (13)[15]: ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.28-1.85 (m, 32H), 2.55 (t, J= 7 Hz, 4H), 2.91 (t, J= 7 Hz, 4H); MS (m/z): 400 (24, [M^+]), 201 (100), 167 (28), 112 (25), 98 (82), 87 (62), 69 (47), 55 (90), 39 (59).

Reaction of 4-iodo-butyryl chloride 14 with tetrathiomolybdate 1 in the solid state: A general procedure. 4-iodo-butyryl chloride **14** (0.49g, 2.09 mmol) was added dropwise to tetrathiomolybdate **1** (1.34g, 2.20 mmol) in an agate mortar and the mixture was ground continuously for 5 min. The color the mixture changed immediately from dark red to black and the initially viscous product became powdery within minutes. The mixture was ground occasionally for 15 min and then extracted with dichloromethane or diethyl ether; flash column chromatography of the crude product on silica gel gave the thiolactone **5**[24] as a liquid (0.11g, 52%). B.p 38-39 °C at 1mm Hg (Lit[24] b.p 39-40 °C at 1mm Hg). Compound **5** exhibited identical spectroscopic data to the one described earlier.

Reaction of acid chloride 15 with tetrathiomolybdate 1 in the solid state:- Acid chloride **15** (0.492g, 2mmol) was added dropwise to tetrathiomolybdate **1** (1.34g, 2.2 mmol) and the mixture was ground for 15 min. The thiolactone **7** (0.162g, 70%) isolated from this reaction exhibited spectral data identical to the one already described.

Reaction of acid chloride 16 with tetrathiomolybdate 1 in the solid state:- Acid chloride **16** (0.66g, 2 mmol) was added dropwise to tetrathiomolybdate **1** (1.34g, 2.2 mmol) and the mixture was ground for 15 min. The thiolactone **12** (0.012g, 3%) isolated after purification by chromatography over silica gel showed spectral data identical to the one described earlier.

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