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BISMETALATED DERIVATIVES OF THIOACIDS. SYNTHONS FOR GENERATION OF β-HYDROXY THIOACIDS. A NOVEL, CONVENIENT ROUTE TO γ AND δ THIOLACTONES.

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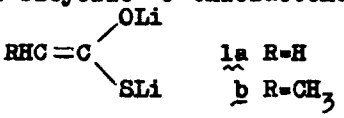
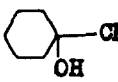
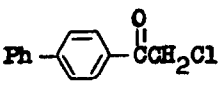
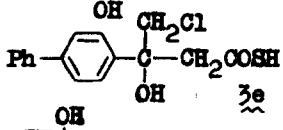
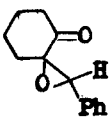
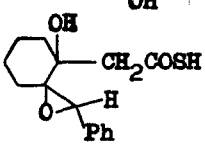
In connection with our continuing interest in thiol ester and thiolactone chemistry [1] and as a result of recent reports concerning antitumor activity associated with certain γ-thiolactone derivatives, [2] we have pursued new general methods for the preparation of this system. We now report the first synthesis of bismetalated derivatives of thioacids (1) [3,4] and their utility as reagents in the formation of a variety of new or little known structural types including β-hydroxy thioacids, γ-chloro β-hydroxy thioacids and γ-epoxy β-hydroxy thioacids. A simple, general approach to γ and δ thiolactones including α,β or γ substituted derivatives, α,β-unsaturated γ-thiolactones and bicyclic γ-thiolactones has been developed. [5]



1a R=H
b R=CH$_3$

Addition (2-3 min) of thioacetic acid (2a, 10 mmol) in THF (5 ml) to two equivalents of lithium diisopropylamide in tetrahydrofuran (25 ml)-hexane (15 ml) at -78° followed by stirring at -78° for another 15 min cleanly gave the bis lithium salt (1a). Dropwise addition (~5 min) of the carbonyl compound (10 mmol) in THF (5 ml) to this anion solution at -78° followed by stirring for an hour at -78° and then quenching by addition to ice cold 5% HCl, ether extraction and finally concentration of the dried ether extract gave the corresponding β-hydroxy thioacid condensation products (3) in yields ranging from 80-95% (table I). This provides the only general method available for the synthesis of the β-hydroxy thioacid system. The proce-

Table I Synthesis of β-hydroxy thioacids by reaction of aldehydes and ketones with the bis lithium salts of thioacetic acid or thiopropionic acid.

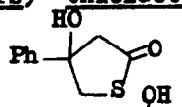
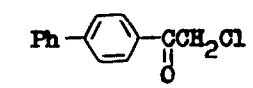
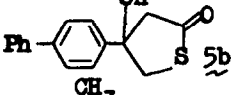
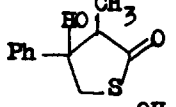
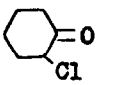
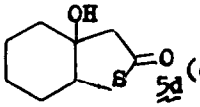
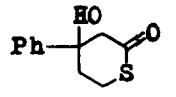
entry	thioacid	carbonyl compound	β-hydroxy thioacid (3) (a)(b)		yield (%)(c)	mp
1	CH_3COSH (2a)	PhCHO	$PhCHCH_2COSH$ (OH)	3a	80	oil
2	2a			3b	90	oil
3	2a	Ph_2CO	Ph_2CCH_2COSH (OH)	3c	92 (82)	131-132
4	2a	PhCH=CHCHO	$PhCH{=}CHCHCH_2COSH$ (OH)	3d	85	oil
5	2a			3e	95 (45)	84
6	2a			3f	85 (65)	107-108
7	CH_3CH_2COSH (2b)	Ph_2CO	$Ph_2C(OH)CHCOSH$ (CH_3)	3g	89 (54)	125-126

(a)All of the solids gave C, H and S analytical data within 0.30 percent of the theoretical values.
(b)The nmr and ir spectra are in agreement with the structures assigned to products 3a through 3g. Thus in the case of 3f the following data were obtained: NMR ($CDCl_3$, TMS): δ 7.32 (s, 5H); 4.49 (s, 1H), 4.35-3.20 (2H), 3.10 and 3.05 (AB quartet, J=15Hz, 2H), 2.30-1.00 (m, 8H); ir (KBr): 3440, 1675 cm^{-1}.
(c)The yield of product which is greater than 95% pure by nmr analysis is listed initially. This is followed by the yield of pure solids obtained after two or three recrystallizations.

dure has been applied to aromatic as well as aliphatic aldehydes and ketones. It can be extended to the preparation of thiopropionic acid bisanion (1b) which has been used in a reaction with benzophenone to give 2-methyl-3-hydroxy-3,3-diphenyl-thiopropionic acid (3g) in 89% yield.

We have found that this condensation process may be carried out on carbonyl derivatives that contain other labile functional groups thus providing a convenient route to several new systems. For example, the previously unknown γ-chloro β-hydroxy thioacid structural unit (3e, table I) as well as the γ-epoxy β-hydroxy thioacid (3f) are obtained in high yield starting from the corresponding γ-chloro or γ-epoxy ketones. The ready availability of γ-chloro β-hydroxy thioacid derivatives has permitted the development of a method for the synthesis of thiolactones. This involves a twostep procedure beginning with thioacid bisanions (1) and α or β-chloro ketones

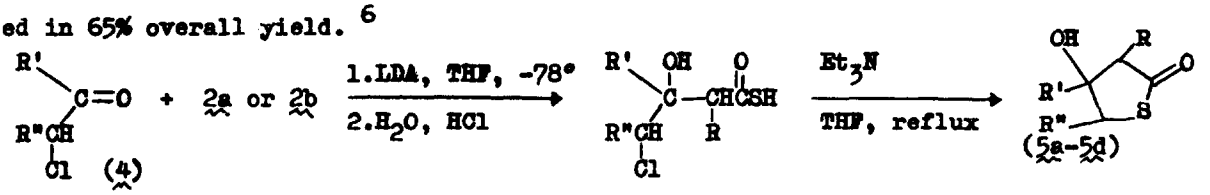
Table II Synthesis of thiolactones by reaction of α or β-chloro ketones with the bis lithium salts of thioacetic acid or thiopropionic acid followed by refluxing in THF in the presence of one equivalent of triethylamine.

entry	thioacid	chloro ketone	reflux (hrs)	thiolactone (a)	Yield (%)(b)	mp
1	2a	PhCCH$_2$Cl (O)	1.5	 5a	90 (57)	94
2	2a		1.5	 5b	90 (52)	163-165
3	2b	PhCCH$_2$Cl (O)	1.5	 5c (c)	70 (50)	87-91
4	2a		6.5	 5d (d)	33	oil
5	2a	PhCCH$_2$CH$_2$Cl (O)	7	 6	70 (65)	128-129

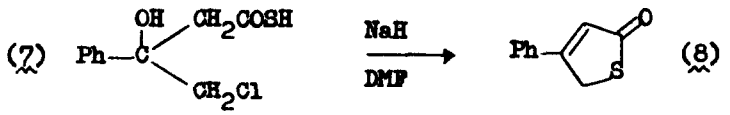
(a)All of the solids gave C, H and S analytical data within 0.30 percent of the theoretical values.
(b)These are the overall yields for both steps. The yield of product which is greater than 95% pure by nmr analysis is listed initially. This is followed by the yield of pure solid obtained after two or three recrystallizations.
(c)A 4:6 mixture of diastereomers was obtained in the initial nucleophilic addition step. Recrystallization from chloroform-hexane gave a 3:1 ratio of diastereomers (mp 87-91°) which was used for the analytical sample.
(d)This product was purified by preparative thin layer chromatography on silica gel eluting with hexane-ethyl acetate (2:1). The product obtained was stereoisomerically pure. NMR ($CDCl_3$, TMS): δ 3.90-3.55 (m,1H), 3.11 (s,1H), 2.87 and 2.50 (AB quartet, J=17Hz) partially superimposed on a multiplet, 2.55-1.20 (10H); ir (film): 3410, 1700 cm^{-1}; M.S. m/e (rel. intensity %): 174 (1.6), 173 (2.4), 172 (M$^{\oplus}$,22.4), 154 (20), 139 (5), 138 (7), 130 (15), 126 (14), 98 (12), 97 (13), 88 (18), 86 (100), 84 (98), 49 (26), 47 (46). A higher yield (51%) of product (5d) was obtained when the reaction was carried out in toluene with a total reflux time of 2 hrs.

(table II). Thus γ-chloro β-hydroxy thioacids prepared as described above from 5 mmol of α-chloro ketone were dissolved (without purification) in anhydrous THF (25 ml) and the solution was then added dropwise (30 min) to triethylamine (5 mmol) in refluxing THF (75 ml). This was refluxed an additional 1.5-7 hrs (table II) before work up by addition to cold 5% HCl followed by ether extraction to give the desired γ-thiolactones (5a-5c) in yields ranging from 50-57% following purification by recrystallization. The bicyclic γ-thiolactone (5d) was prepared from the adduct of (1a) with 2-chlorocyclohexanone in 33% yield. It is interesting that β-chloropropiophenone reacts with (1a) at -78° to give a high yield of the carbonyl addition product. Products resulting from HCl elimination were not observed. The adduct

undergoes cyclization with triethylamine to give γ-thiolactone (6) which was isolated in 65% overall yield.[6]



On the other hand unsaturated thiolactones have been obtained by the following procedure. γ-Chloro β-hydroxy thioacid condensation product (7) (18.5 mmol) in DMF (25 ml) was added dropwise to a suspension of sodium hydride (20 mmol) in DMF (20 ml) at 25° at such a rate that the temperature rose to 60°. This addition period required 10-15 min after which the reaction was allowed to stir another 10 min before addition to cold 5% HCl. Work up gave the 5H-thiophen-2-one product (8) in 59% yield after recrystallization from chloroform-hexane:[7]



Thus it appears that a large variety of structural types may be synthesized using (1) in reactions with various aldehydes and ketones. We are presently investigating other possibilities including the formation of thiolactone derivatives from γ-epoxy β-hydroxy thioacid addition products.

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References and Notes:

1. See (a) D.H.Lucast, J.Wemple, Tetrahedron Letters, 1103 (1977); (b)D.H.Lucast, J.Wemple, Synthesis, 724 (1976) and references therein.
2. K.S.McCully, P.Clopath, Chemotherapy, 23, 44 (1977); K.S.McCully, Cancer Res., 36, 3198 (1976).
3. For reviews of dialkalimetal derivatives of organic compounds and their preparation using lithium dialkylamide or related bases see: E.M.Kaiser, J.D. Petty and P.L.A.Knutson, Synthesis, 509 (1977); D.Ivanov, G.Vassilev and I. Panayotov, ibid, 83 (1975) and references therein.
4. Dithioic acid dianions are known: see F.E.Ziegler and C.M.Chan, J. Org. Chem., 43, 3065 (1978); M.Augustin, R.Schmidt, W.D.Rudorf, Z. Chem., 17, 289 (1977) and references therein.
5. Very few methods have been developed for the construction of the γ-thiolactone ring system: K.Fries, H.Mengel, Chem. Ber., 45, 3409 (1912); E.Schjanberg, ibid, 75, 468 (1942); H.R.Snyder, W.Alexander, J.Am.Chem.Soc., 70, 217 (1948); J.Brunet, D.Paquer, P.Rioult, Phosphorous Sulfur, 3, 377 (1977).
6. A multistep procedure has been used in the synthesis of a β-hydroxy δ-thiolactone, namely β-hydroxy-β-methyl-δ-valerothiolactone, starting with methyl vinyl ketone and thioacetic acid and employing a Reformatsky reaction: H.U.Daeniker, J.Druey, Helv. Chim. Acta., 43, 983 (1960).
7. The analytical sample was obtained by vacuum sublimation of the recrystallized product: mp 134-36°, NMR ($CDCl_3$, TMS): δ 7.70-7.30 (m, 5H), 6.65 (t, 1H, J= 1.5Hz), 4.40 (d, 2H, J=1.5Hz); ir (KBr) 1655 cm^{-1} (strong) 1605 cm^{-1}.

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