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THE REACTION OF THIOL ESTERS WITH LITHIUM DIISOPROPYLAMIDE. CONDENSATION REACTIONS OF THIOL ESTER ENOLATES.

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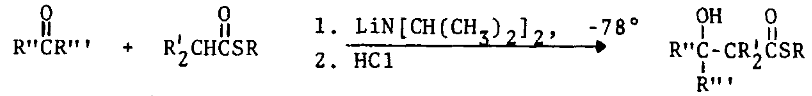
Very little attention in the literature has been given to base induced condensation reactions of thiol esters (1). This is surprising in view of extensive studies with other functional groups (2). Part of the explanation lies in the relative ease with which thiol esters undergo substitution with nucleophilic bases (3). Also it has been reported that the reaction of S-aryl as well as S-alkyl thiol esters with nonnucleophilic bases ($LiN[Si(CH_3)_3]_2$, KOtBu, $LiC(Ph)_3$ in ether, glyme or dimethylformamide results in elimination of the thiolate anion giving rise to ketene derivatives (4).

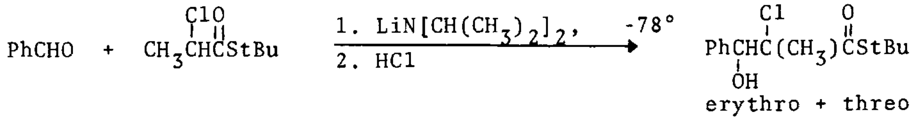
We have found that the treatment of thiol esters with lithium diisopropylamide at -78° in THF-hexane results in the formation of the corresponding thiol ester enolates. These may then be used at -78° in condensation reactions with aldehydes and ketones to give β-hydroxy thiol esters in high yield. At present this is the only general, base condensation method that is available for the synthesis of S-aryl and S-alkyl β-hydroxy thiol esters:



$$\mathrm{R''\overset{O}{\overset{\|}{C}}R''' + R'_2CH\overset{O}{\overset{\|}{C}}SR \xrightarrow[2.\ HCl]{1.\ LiN[CH(CH_3)_2]_2,\ -78^\circ} R''\overset{OH}{\underset{R'''}{C}}-CR'_2\overset{O}{\overset{\|}{C}}SR}$$

S-*tert*-Butyl thiolacetate (5) (10mmol) in THF (5 ml) was added over a 5 minute period to lithium diisopropylamide (10 mmol, prepared from diisopropylamine in THF (25ml) and 2.2 M n-butyl lithium in hexane) at -78°. This was followed by the addition over a 5 min. period of benzophenone (10mmol) in THF (5 ml). The solution was stirred for 1 hr at -78° and then quenched by pouring into ice cold 2% HCl (100 ml). Ether extraction followed by recrystallization from benzene-hexane gave 80% pure S-tert-butyl 3,3-diphenyl-3-hydroxypropanethioate (mp 127-129). A second recrystallization provided the analytical sample: mp 128-129; nmr ($CDCl_3$): δ1.35 (s,9H), 3.41 (s,2H), 4.97 (broad singlet,1H), 7.15 - 7.65 (m,10H); ir (KBr): 3410, 1655cm^{-1}; Calcd. for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05; S, 10.20. Found: C, 72.79; H, 7.23; S, 9.96.

A similar procedure was used to prepare the other thiol esters listed in the table. Aromatic aldehydes and aliphatic and aromatic ketones were acceptable substrates. S-Benzyl as well as S-tert-butyl β-hydroxy thiol esters were prepared, but of particular interest is the formation of S-phenyl derivatives. S-Phenyl thiolacetate would be expected to be the least stable with respect to ketene formation or a competing Claisen condensation process. It is well known that S-phenyl thiolacetate is a reactive acylating agent (3). However, apparently no appreciable acylation of lithium diisopropylamide occurred probably due to steric factors. Also with this procedure we have been able to prepare α-chloro β-hydroxy thiol esters such as S-tert-butyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropanethioate:



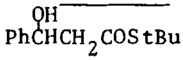
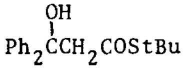
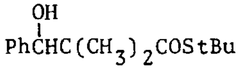
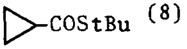
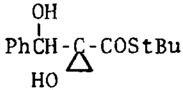
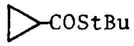
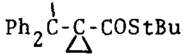
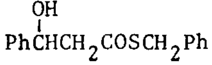
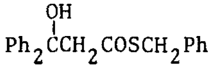
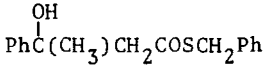
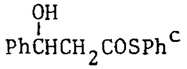
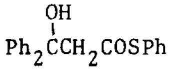
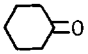
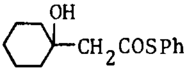
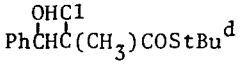
$$\mathrm{PhCHO} + \mathrm{CH_3\overset{Cl}{C}H\overset{O}{\overset{\|}{C}}StBu} \xrightarrow[2.\ \mathrm{HCl}]{1.\ \mathrm{LiN[CH(CH_3)_2]_2},\ -78^\circ} \mathrm{Ph\underset{OH}{C}H\overset{Cl}{C}(CH_3)\overset{O}{\overset{\|}{C}}StBu}$$

erythro + threo

It has been reported that oxygen ester enolates are relatively stable when prepared with lithium isopropylcyclohexylamide or lithium diisopropylamide. Self condensation of ethyl or tert-butyl ester enolates occurs only slowly at room temperature (6). In preliminary studies with thiol esters we found that lithio S-tert-butyl thiolacetate could be formed at 0° and used successfully in condensation reactions with carbonyl compounds (also at 0°) to produce the corresponding β-hydroxy thiol esters in high yield. Thus the yield of S-tert-butyl 3,3-diphenyl-3-hydroxypropanethioate was essentially unchanged when the above procedure was carried out at 0° rather than at -78°. We were not, however, successful in preparing S-phenyl or S-benzyl 3,3-diphenyl-3-hydroxypropanethioate at 0° using benzophenone and S-phenyl or S-benzyl thiolacetate. Apparently competing Claisen condensation and/or ketene formation is more prevalent in these cases.

Table

Synthesis of β-hydroxy thiol esters in THF-hexane from carbonyl compounds and thiol ester enolates at -78°.

Thiol Ester	Aldehyde or Ketone	Product[a]	Yield[b]	Melting Point Refractive Index
$CH_3COStBu$	PhCHO	 $Ph\overset{OH}{C}HCH_2COStBu$	68%	n_D^{28} 1.5324
$CH_3COStBu$	Ph_2CO	 $Ph_2\overset{OH}{C}CH_2COStBu$	80	128-129
$(CH_3)_2CHCOStBu$ (7)	PhCHO	 $Ph\overset{OH}{C}HC(CH_3)_2COStBu$	67	67-69
 -COStBu (8)	PhCHO	 $Ph\overset{OH}{C}H\text{-}\underset{\triangle}{C}\text{-}COStBu$	76	37-39
 COStBu	Ph_2CO	 $Ph_2\overset{HO}{C}\text{-}\underset{\triangle}{C}\text{-}COStBu$	40	98-100
CH_3COSCH_2Ph (9)	PhCHO	 $Ph\overset{OH}{C}HCH_2COSCH_2Ph$	64	n_D^{26} 1.5963
CH_3COSCH_2Ph	Ph_2CO	 $Ph_2\overset{OH}{C}CH_2COSCH_2Ph$	66	117-119
CH_3COSCH_2Ph	$PhCOCH_3$	 $Ph\overset{OH}{C}(CH_3)CH_2COSCH_2Ph$	66	n_D^{28} 1.5836
CH_3COSPh (10)	PhCHO	 $Ph\overset{OH}{C}HCH_2COSPh^c$	50	85-86
CH_3COSPh	Ph_2CO	 $Ph_2\overset{OH}{C}CH_2COSPh$	58	116-118
CH_3COSPh			85	n_D^{27} 1.5646
$CH_3CHClCOStBu$ (11)	PhCHO	 $Ph\overset{OH}{C}H\overset{Cl}{C}(CH_3)COStBu^d$	56	75-76; 92-93

(a) All hydroxy thiol esters were characterized by nmr, ir and elemental analysis The oils were purified by column chromatography on silica gel. The analytical sample was obtained by short path distillation under vacuum. Melting points are uncorrected.

(b) In the case of oils the yields are reported on purified material obtained after column chromatography. The yields of solids are given for compounds obtained after one recrystallization. These yields have not been optimized. Most of the reactions were carried out on 10 mmol scale.

(c) Mp 84.5-85.5: T. Mukaiyama, K. Inomata, M. Muraki, J. Amer. Chem. Soc., 95, 967 (1973); Bull. Chem. Soc. Japan, 46, 1807 (1973).

(d) This reaction gave a 1:1 mixture of the two diastereomers. The calculated yield is based on the purified mixture of isomers obtained after column chromatography on silica gel eluting with benzene-petroleum ether. The two isomers were separated by fractional crystallization using benzene-hexane.

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(8) Prepared from cyclopropanecarboxylic acid chloride (Aldrich Chemical Co.) and tert-butyl mercaptan: bp 74-75° at 3mm, n_D^{27} 1.4809.

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(10) Aldrich Chemical Co.

(11) Prepared from 2-chloropropionyl chloride (Aldrich Chemical Co.) and tert-butyl mercaptan: bp 105° at 35mm, n_D^{29} 1.4734.