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A GENERAL ESTER SYNTHESIS *VIA* 2-LITHIO-2-METHYLTHIO-1,3-DITHIANE

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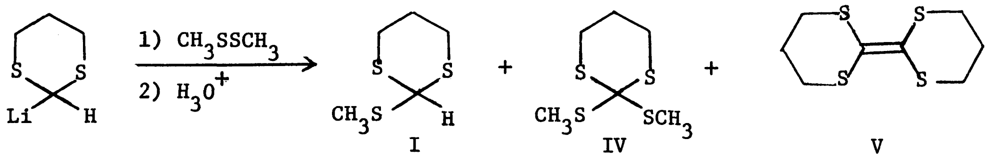
A facile synthesis of esters *via* nucleophilic reaction of the lithiated orthothioester (I) with halides, aldehydes, and ketones is described. The resultant substituted orthothioesters (III) are hydrolyzed to esters with mercuric salts in the presence of aqueous alcohol in high yield.

Although lithiated 1,3-dithianes are well-known synthetic reagents, only a few reports have appeared suggesting the utility of metalated orthothioformates as ester synthons.[1] A single experiment (Example a, Table I) performed during our investigation of the oxidation of aldehydes to esters *via* orthothioesters indicated that pre-formed, lithiated orthothioformates might function as nucleophilic masked ester synthons ($\ominus CO_2R$). Manas and Smith recently reported the conjugate addition of *tris*(phenylthio)methyllithium to α,β-unsaturated ketones. Hydrolysis effected an efficient synthesis of γ-ketoesters.[1c] Seebach has reported the hydrolysis of orthothiomandelic acid triphenyl ester to mandelic acid in 60% yield.[2] This communication describes further ester preparations *via* 2-lithio-2-methylthio-1,3-dithiane (I).

Use of the reagent I permits the formal oxidation of relatively inaccesible α-hydroxyaldehydes and γ-ketoaldehydes to the corresponding esters. Reagent I is stable at room temperature and easily prepared. Its use obviates the conversion of the substrate aldehydes to dithianes and thence to orthothioesters *via* the 2-lithio-2-substituted-1,3-dithiane.

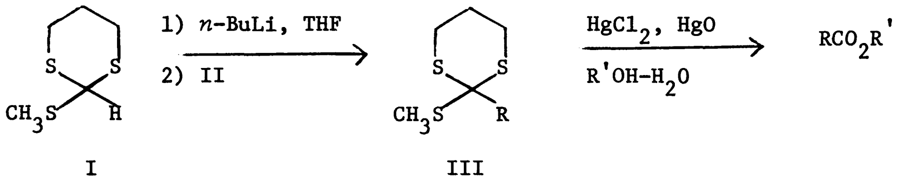
The preparation of I by reaction of 2-lithio-1,3-dithiane and dimethyl disulfide has been previously reported (eq.I).[1b] We found that yields of subsequent reactions were improved if crude I was purified by column chromatography (85:15 silicic acid-Celite, cyclohexane). The purification removed the minor impurities IV and V.[2,3]

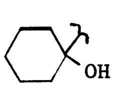
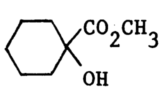
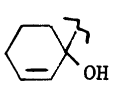
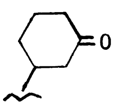
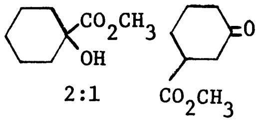


(eq. I)

Orthothioformate I was lithiated in THF by the addition of one equivalent of *n*-butyllithium in hexane at -20 to -35°C. After 3-4 min, the unstable lithio-anion was allowed to react with a halide or carbonyl compound II to yield the desired substituted orthothioformate (III) in high yield. The desired methyl of ethyl ester was obtained by mercuric ion catalyzed alcoholysis of crude III. Table I outlines the experimental results.

Table I. Synthesis of Substituted Orthothioformates and Esters.



II	III, R(% yield)^a	RCO_2R' (% yield)^a
a) *n*-butyl iodide	*n*-butyl (78)^b	ethyl pentanoate^c (97)
b) benzyl chloride	benzyl (92)	methyl *α*-phenylacetate (86.5)
c) hexanal	1-hydroxyhexyl (94.5)	methyl *α*-hydroxyheptanoate (71.8)
d) cyclohexanone	 (92.8)	 (61.4)
e) 2-cyclohexen-1-one	 and  (96.5)	 (62.3)^d

[a] Crude yield. New compounds were characterized by nmr, infrared and/or mass spectra.

[b] Crude I employed. [c] Alcoholysis with 95% ethanol. [d] Ratio determined by nmr analysis of relative intensity of $CO_2C\underline{H}_3$ signals and relative positions before and after $NaBH_4$ reduction of the carbonyl.

The following experimental procedure is representative:

2-Benzyl-2-methylthio-1,3-dithiane (IIIb).

A solution of 166 mg (1.0 mmol) of I in 5.0 ml of THF was cooled to -35°C with stirring under argon. *n*-Butyllithium (0.41 ml of a 1.63M solution in hexane) was injected. After 3.5 min at -35°C, 0.115 ml (1.0 mmol) of benzyl chloride was injected. The reaction mixture was stirred for 3 hr at -35°C, stored for 16 hr at 0°C, then stirred at 25°C for 2.5 hr. An equal volume of water was added and the mixture reduced to one-half volume *in vacuo*. The mixture was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous sodium hydrogencarbonate and brine, then dried (Na_2SO_4), filtered and solvents evaporated *in vacuo* to afford 239 mg IIIb as a clear oil (92%):nmr($CDCl_3$) δ1.92(s, $SC\underline{H}_3$), 3.26(s, 2, $C\underline{H}_2Ar$), 7.35(s, 5, Ar-$\underline{H}$); ir($CHCl_3$) 3.83, 3.93, 6.67, 6.85, 6.97, 7.04, 7.06, 7.83, 10.98μ;[5] *m/e* (70 eV, 60°), 209 (M^+-SCH_3), 165(M^+-CH_2Ar), 134, 91.

Methyl α-phenylacetate.

A solution of 234 mg of IIIb in 21.0 ml of 12:1 methanol-water was refluxed with 1.0 g $HgCl_2$ and 330 mg of HgO for 6 hr under argon. The reaction mixture was cooled and filtered through Celite. The residue was washed with two 5 ml portions of CH_2Cl_2. The combined filtrates were diluted with water and the aqueous layer extracted with CH_2Cl_2. The combined extracts were washed with 75% aqueous NH_4OAc, saturated aqueous NH_4Cl, then dried, filtered, and evaporated *in vacuo* to afford 111 mg methyl α-phenylacetate as a light yellow oil (86.5%). The characterization by nmr and infrared spectroscopy indicated no significant impurities: nmr($CDCl_3$) δ3.62(s, 2, $C\underline{H}_2Ar$), 3.70(s, 3, $CO_2C\underline{H}_3$), 7.46(s, 5, Ar-$\underline{H}$); ir ($CHCl_3$) 5.78μ.

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References

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