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A METHOD FOR ALKYLATION OF THIOL ESTERS AND γ-THIOLBUTYROLACTONE

Robert A. Gorski, Gregory J. Wolber and James Wemple*

Department of Chemistry, University of Detroit, Detroit, Michigan 48221

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Biochemically the thiol ester group is the ester function of choice for carrying out aldol and Claisen condensation reactions.[1] We have been interested in the synthetic potential of this group in the laboratory including recently aldol condensation reactions of thiol ester enolate anions with aldehydes and ketones.[2] Here we report on alkylation and Claisen condensation reactions of thiol esters and thiol lactones. In the past little success has been obtained in attempts to alkylate thiol esters. Thus in a recent report on the chemistry of thiol ester α-anions,[3] the reaction of S-ethyl thiolacetate or S-tert-butyl thiolacetate with non-nucleophilic bases (KOtBu, $LiCPh_3$, $LiN[SiMe_3]_2$) in aprotic solvents (ether, DMF, glyme) followed by addition of an alkyl halide (methyl iodide, allyl bromide) led to formation of thioethers instead of the alkylated thiol esters. This approach has provided a useful synthesis of thioethers.[3] Decomposition of the thiol ester enolate anion leading to ketenes and ketene polymers was proposed to explain this result.[3] In contrast, we have now found that lithium thiol ester enolates may be alkylated in aprotic solvents if enolate formation and alkylation steps are carried out at -78°:

$$CH_3\overset{O}{\overset{\|}{C}}SR'' + LiNR_2 \xrightarrow[-78°]{THF} CH_2{=}\overset{OLi}{\overset{|}{C}}SR'' \xrightarrow[-78° \text{ to } 25°]{R'X} R'CH_2\overset{O}{\overset{\|}{C}}SR''$$

S-Benzyl thiolacetate (10 mmol) in THF (2 ml) was added over a two minute period to lithium diisopropylamide (10 mmol, prepared from diisopropylamine and 2.2 M n-butyl lithium in hexane) in THF (35-40 ml) at -78°. The reaction was allowed to stir at -78° for 10 min prior to the addition over a one minute period

of bromomethyl methyl ether (20 mmol). Stirring was continued for 30 min at -78° and then for another 90 min following removal of the dry ice-acetone bath when the reaction was allowed to warm to room temperature. The reaction mixture was poured into cold, 2% hydrochloric acid and the thiol ester was extracted with ether. The product was purified by column chromatography on silica gel eluting with benzene to give a 70% yield of S-benzyl 3-methoxypropanethioate: nmr ($CDCl_3$): δ2.79 (t,2H,J=6Hz), 3.31(s,3H), 3.67(t,2H,J=6Hz), 4.12(s,2H), 7.27(s,5H); ir(thin film): 1690cm^{-1}. The analytical sample was obtained by short path distillation under reduced pressure: n_D^{20} 1.5454; Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.25. Found: C, 63.06; H, 6.78; S, 15.12. In a similar way other thiol esters have been alkylated using a variety of reactive alkylating agents (c.f. table). Improved yields were obtained in many cases by adding hexamethylphosphoric triamide following addition of the alkyl halide.[4]

The thiol ester enolates appear to be substantially less nucleophilic than the corresponding oxygen ester enolates. Thus treatment of the lithium enolate of S-tert-butyl thiolacetate with 1.3 equivalents of benzyl bromide followed by 0.5 equivalents of HMPTA at -78° for 2 hrs did not give any appreciable amount of alkylation product. Most of the S-tert-butyl thiolacetate was recovered unchanged. In contrast the lithium enolate of tert-butyl acetate was completely alkylated by benzyl bromide under the same conditions (81% isolated yield). Direct comparison of the nucleophilicities of thiol ester and oxygen ester enolates is of interest in connection with developing an understanding of the mechanisms of enzyme catalyzed thiol ester condensation reactions.[5]

We have also been successful in alkylating γ-thiobutyrolactone. Thus a 74% isolated yield of α-methyl-γ-thiobutyrolactone was obtained using methyl iodide (5 equiv) and HMPTA (0.5 equiv) at -78° for 2 hrs. It is noteworthy that in the absence of HMPTA the yield of α-methyl-γ-thiobutyrolactone was only slightly less than that observed when HMPTA was present.[6]

When these reactions were carried out at higher temperatures with less reactive alkylating agents such as n-butyl iodide or benzyl bromide, Claisen condensation products were isolated. The reaction of S-tert-butyl thiolacetate with n-butyl iodide (5 equiv) in the presence of HMPTA (1.0 equiv) initially at -78° for 30

Table

Alkylation of lithium thiol ester enolate anions in THF-hexane

Thiol Ester	Alkylating Agent	Temperature	HMPTA	Yield[a]
CH_3CSCH_2Ph	$MeOCH_2Br$ (2 eq)	-78° (1/2 hr) to 25° (1 1/2 hr)	none	70 %
CH_3CSCH_2Ph	MeI (5 eq)	-78° (1/2 hr) to 25° (1 1/2 hr)	none	75
CH_3CSCH_2Ph	MeI (5 eq)	-78° (2 hr)	0.5 eq[b]	81
CH_3CStBu	MeI (5 eq)	-78° (2 hr)	0.5 eq[b]	64[c]
CH_3CStBu	$CH_2=CHCH_2Br$ (5 eq)	-78° (6 hr)	1.0 eq	71[d]
	$MeOCH_2Br$ (2 eq)	-78° (2 hr)	none	75
	MeI (5 eq)	-78° (2 hr)	0.5 eq	74
	$CH_2=CHCH_2Br$ (5 eq)	-78° (2 hr)	0.5 eq	61
	$CH_3(CH_2)_3I$ (5 eq)	-78° (1/2 hr) to 25° (1 1/2 hr)	0.5 eq	35

(a) All new compounds gave nmr, ir and analytical data in agreement with the assigned structures. Except in one case (see below) the yields are reported on material obtained after purification by column chromatography on silica gel. The analytical sample was prepared by short path distillation of the chromatographed product.

(b) Substantial amounts of starting material were reisolated when these reactions were carried out in the absence of HMPTA at -78° for 2 hrs.

(c) It was not necessary to purify this product by column chromatography. The yield is that obtained for material isolated after short path distillation. It is low primarily because of the volatility of the S-tert-butyl propanethioate product (bp760 155°). The refractive index of distilled material (n_D^{26} 1.4526) is close to the value (n_D^{24} 1.4528) found for S-tert-butyl propanethioate synthesized by refluxing propionyl chloride with tert-butyl mercaptan. The literature value is n_D^{25} 1.4495.[9]

(d) A small amount of bisalkylation product was obtained when 2.5 equiv of HMPTA was used at -78° for 2 hr.

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min and then at room temperature for another 1 1/2 hr gave among other products S-tert-butyl 3-ketooctanethioate[7] (22 %) and S-tert-butyl acetothiolacetate (17%). The isolation of S-tert-butyl 3-ketooctanethioate suggests initial alkylation of the enolate followed by Claisen condensation which apparently competes effectively with alkylation when n-butyl iodide is employed:

$$CH_3\overset{O}{\overset{\|}{C}}StBu \xrightarrow{LiNR_2} CH_2=\overset{OLi}{\overset{|}{C}}StBu \xrightarrow[HMPTA]{nBuI} CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}StBu + CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}StBu$$

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(4) HMPTA has previously been shown to be useful in raising yields in the alkylation of lithium (oxygen) ester enolates (R.J. Cregge, J.L. Herrmann, C.S. Lee, J.F. Richman and R.H. Schlessinger, Tetrahedron Letters, 2425 (1973)), α-anions of n-carboxylate salts (P.E. Pfeffer and L.S. Silbert, J. Org. Chem., 35, 262 (1970)) as well as other compounds (H. Normant, Angew. Chemie Int. Ed., 6, 1046 (1967)).

(5) Either the thiol ester enolate anion or the corresponding enol would be involved in the citrate synthase reaction and related enzyme catalyzed condensation processes. See S.W. Weidman, G.R. Drysdale and A.S. Mildvan, Biochemistry, 12, 1874 (1973) and references cited therein. Many enzyme catalyzed thiol ester condensation reactions are now known.[1b] See also A. Mahlen, Eur. J. Biochem., 22, 104 (1971); 38, 32 (1973). The question of the relative acidity of protons at the α position in thiol esters and oxygen esters has already received considerable attention in this connection (c.f. reference 1).

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