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A HIGHLY STEREOSELECTIVE CONDENSATION PROCESS FOR THE CONVERSION OF CARBONYL COMPOUNDS TO α,β-UNSATURATED THIOL ESTERS.

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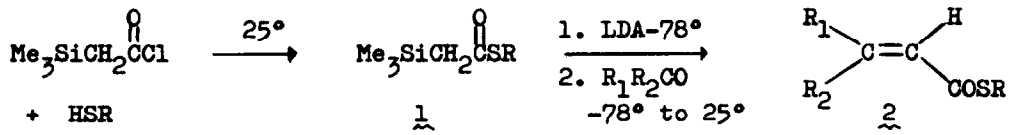
Coenzyme A thiol ester derivatives serve as important intermediates in biochemical condensation and acyl transfer reactions. Despite the biosynthetic importance of the thiol ester function, relatively little attention has been given to the laboratory preparation or synthetic utilization of this group.[1] For example, a general base induced condensation procedure for synthesis of α,β-unsaturated thiol esters has not been reported.[2] One difficulty with thiol ester condensation reactions is the high susceptibility of this group to nucleophilic attack resulting in thiol ester destruction and liberation of a reactive thiolate anion. For this reason nucleophilic bases such as the alkoxides are generally not suitable.[1] Recently we have employed nonnucleophilic bases such as lithium diisopropylamide, lithium bis[trimethylsilylamide] and sodium hydride to carry out aldol[3] and Darzens[4] condensations of thiol esters with a variety of carbonyl compounds. In developing an efficient condensation route for the conversion of carbonyl compounds to α,β-unsaturated thiol esters it would also be helpful to have a built in electrophilic site with high affinity for the β-oxy anion formed during the initial addition step. In this way we could minimize intramolecular alkoxide attack at the thiol ester function[5] and hopefully improve the yield of unsaturated thiol ester.

We report here that the reaction of α-silyl thiol ester enolates with carbonyl compounds is particularly well suited to the preparation of α,β-unsaturated thiol esters. The previously unknown α-silyl thiol esters 1 are readily

prepared in a reaction of trimethylsilylacetyl chloride with various mercaptans.[6] The condensation of the α-silyl thiol esters with carbonyl compounds takes place rapidly in THF solvent at -78° in the presence of lithium diisopropylamide or triphenylmethyl lithium. For example, S-tert-butyl trimethylsilylthiolacetate 1a (5 mmol) in THF (5 ml) was added dropwise over 2 min to lithium diisopropylamide (5 mmol) in THF (40 ml) at -78°. After 10 min benzaldehyde (5 mmol) in THF (5 ml) was added (2 min) and stirring was continued at -78° for 30 min and then at room temperature for 1 h. The solution was poured into cold 5% HCl and extracted with ether. The product was purified by column chromatography on silica gel followed by short path distillation to give pure S-tert-butyl (E)-thiolcinnamate 2d in 73% yield: mp 38-40; ir (KBr): 1655 cm^{-1}; nmr ($CDCl_3$): δ 7.56 (d, 1H, J = 16Hz), 7.42 (broad singlet, 5H), 6.58 (d, 1H, J = 16Hz), 1.55 (s, 9H). Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 71.01; H, 7.33; S, 14.35. High yields were obtained in the synthesis of S-tert-butyl, S-isopropyl as well as S-benzyl α,β-unsaturated thiol esters. Both aromatic and aliphatic aldehydes and ketones were effective.



Of particular utility is the result that this reaction is highly stereoselective. In all cases examined more than 95% of the product was found to be the trans isomer as indicated by the nmr spectra of the crude reaction mixture as well as the spectra of material obtained following purification by column chromatography on silica gel. In contrast the reaction of α-trimethylsilyl oxygen ester enolates with aldehydes and ketones gave in addition to trans product[7,8] large amounts of of the cis olefin.[8,9] The greater stereoselectivity in the thiol ester reaction may be attributed to the greater stability of the thiol ester enolates when compared to the corresponding oxygen ester enolates. This is supported by the well known high acidity of thiol esters relative to oxygen esters.[1] Also we have recently found that thiol ester enolates are substantially less reactive than oxygen ester enolates in nucleophilic substitution reactions with alkyl halides.[10]

Reaction of $Me_3SiCHLiCOSR$ with Aldehydes and Ketones in THF at -78°

Carbonyl[a] Compound	α-Silyl thiol ester	Product[b]	R	R_1	R_2	Yield[c]
cyclohexanone	1a	2a	$C(CH_3)_3$	$(CH_2)_5$		77%
cyclohexanone	1b	2b	$CH(CH_3)_2$	$(CH_2)_5$		62
cyclohexanone	1c	2c	CH_2Ph	$(CH_2)_5$		49
benzaldehyde	1a	2d	$C(CH_3)_3$	Ph	H	73
benzaldehyde	1b	2e[d]	$CH(CH_3)_2$	Ph	H	65
benzaldehyde	1c	2f	CH_2Ph	Ph	H	54
isobutyraldehyde	1b	2g	$CH(CH_3)_2$	$CH(CH_3)_2$	H	51
acetophenone	1a	2h	$C(CH_3)_3$	Ph	CH_3	52

a. In the reactions with cyclohexanone and benzaldehyde, after addition of the carbonyl compound the temperature was kept at -78° for 30 min and then at room temperature for 1 h. In the reactions with isobutyraldehyde and acetophenone, after addition of carbonyl compound the temperature was maintained at -78° for 30 min followed by 1 h at -20°.

b. Above 98% of the product was isolated as the trans isomer in the reactions of 1a, 1b, or 1c with benzaldehyde or 1b with isobutyraldehyde. In the reaction of 1a with acetophenone more than 95% of the product 2h was obtained as the trans isomer.

c. Isolated yields of pure product not corrected for recovered starting material.

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Greater stability associated with the thiol ester enolate may potentially be a factor in a number of ways including: (1)a faster rate for the thiol ester retro-aldolization reaction leading from the putative[7,11] β-hydroxy-α-trimethylsilyl ester intermediate back to starting carbonyl compound and the corresponding α-silyl ester enolate; (2)more rapid thiol ester base catalyzed epimerization at the α position in this same intermediate and/or (3)participation of a second key intermediate - i.e. a β-trimethylsiloxy ester enolate[12] produced during the formation of olefin product from either erythro or threo isomer of the β-hydroxy-α-trimethylsilyl ester intermediate. In this latter case a longer lived β-trimethylsiloxy thiol ester enolate would permit a substantial degree of rotation of the ester function away from the bulky β-substituent prior to elimination thus relieving steric interactions in the transition state leading to trans product.

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References and Notes

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6. Trimethylsilylacetyl chloride (prepared with oxalyl chloride and trimethylsilylacetic acid) was allowed to react with one equivalent of tert-butyl mercaptan in pentane at room temperature to give S-tert-butyl trimethylsilylthiolacetate: n_D^{31} 1.5469; ir (film): 1670, 1255 cm^{-1}; NMR ($CDCl_3$): δ2.17 (s,2H), 1.43 (s,9H), 0.13 (s,9H). Anal. Calcd for $C_9H_{20}OSSi$: C, 52.88; H, 9.86; S, 15.69. Found: C, 52.81; H, 9.50; S, 15.73. Trimethylsilylacetic acid was prepared according to the procedure of L.H.Sommer, J.R.Gold, G.M.Goldberg and N.S.Marans, J. Am. Chem. Soc., 71, 1509 (1949).

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9. For a direct comparison we repeated the reaction of tert-butyl trimethylsilylacetate with benzaldehyde [7] and found about 20% (Z)-tert-butyl cinnamate. In contrast less than 1% of 2d was isolated as the Z isomer.

10. We have earlier found that thiol ester enolates are substantially less nucleophilic than oxygen ester enolates in nucleophilic substitution reactions with alkyl halides: R.A.Gorski, G.Wolber and J.Wemple, Tetrahedron Letters, 2577 (1976).

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