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A One-pot Stereoselective Synthesis of Hydroxy-ketenedithioacetals from Aldehydes

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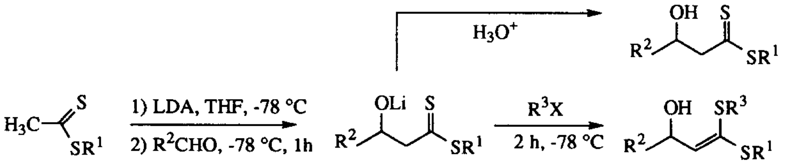
Abstract: The reaction of aldehydes with dithioacetate enethiolates followed by alkylation of the intermediate aldolate gives hydroxy-ketenedithioacetals with high stereoselectivity.

Ketene dithioacetals have proved to be interesting reagents in organic synthesis.[1,2] They can be obtained by various methods including Wittig or Peterson olefination[1,2] and S-alkylation of dithioester enethiolates.[3] Of special interest are their reactions with organolithium compounds leading by addition[4] or allylic proton abstraction[5] to umpoled carbanions.

In this communication, we present a one-pot synthesis of hydroxy-ketenedithioacetals[6,7] from aldehydes and dithioacetates. The reaction of dithioester enethiolates with aldehydes is known to give β-hydroxy-dithioesters in good yields and, in certain cases, with high diastereoselectivity.[8] We have now found that treatment of the aldolates resulting from the condensation of dithioacetates with aldehydes, with alkylating reagents (methyl iodide or benzyl bromide) leads to S-alkylated products.



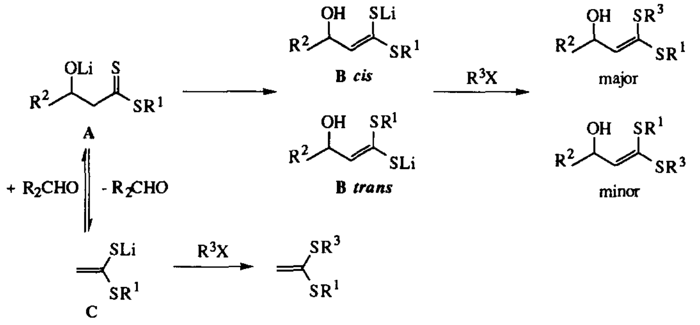
In a typical experiment, methyl dithioacetate was deprotonated by LDA in THF. The resulting lithium enethiolate was treated with ethanal (1 eq.) at -78 °C for 1 h. Methyl iodide (1.5 eq.) was added and the obtained mixture was stirred for another 2 h at -78 °C. After quenching with NH_4Cl/H_2O, extraction with ether and liquid chromatography (silica, pentane / ethyl acetate : 4 / 1), 4,4-dimethylthiobut-3-en-2-ol **1** was isolated in 61 % yield. Other examples of this S-alkylation are presented in the Table.[9]

The S-alkylation clearly results from the transformation of the alcoolate form **A** into the enethiolate **B**.[10] As the thiolate anion is much more nucleophilic than the alcoolate, the S-alkylation is favored. Eventhough we have not firmly established the geometry of the obtained ketene dithioacetals, the high tendancy of dithioesters to give *cis* enethiolates[8] and the possible O-H···S^- hydrogen bond and S-Li···O chelation strongly suggest a favored *cis* geometry for the enethiolate **B**. Attribution of the ketene dithioacetals geometries were made on this basis.[11] As seen from the Table the *Z*/*E* selectivities are high. Depending of the choice of the starting dithioester and alkylating agent, either of the two isomers can be obtained nearly pure.[9]

Table

Product	R^1	R^2	R^3X	Z/E^a	yield^b	Product	R^1	R^2	R^3X	Z/E^a	yield^b
1	Me	Me	MeI		61%	**6**	Bn	Et	MeI	3/97	70%
2	Me	Me	BnBr	99/1	67%	**7**	*n*-Bu	Et	BnBr	1/99	57%
2	Bn	Me	MeI	4/96	58%	**8**	*n*-Bu	Et	MeI	1/99	69%
3	*n*-Bu	Me	MeI	4/96	51%	**9**	Me	*i*-Pr	MeI		65%
4	*n*-Bu	Me	BnBr	3/97	50%	**10**	Me	*i*-Pr	BnBr	98/2	60%
5	Me	Et	MeI		65%	**11**	Bn	*i*-Pr	BnBr		64%
6	Me	Et	BnBr	96/4	72%	**12**	*n*-Bu	*i*-Pr	MeI	1/99	52%

^{a} Determined by ^{1}H NMR (200 or 300 MHz). ^{b} After liquid chromatography.



Yields ranged from 50 to 72 %, the major by-product being the non-hydroxylated ketene dithioacetals derived from the starting dithioester. The formation of this product can be explained by the aldol ⇔ retro-aldol equilibrium giving back the enethiolate C from the aldolate A. Such equilibrium has been noticed previously.[8]

References and notes

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4. Seebach, D.; Kolb, M. *Liebigs Ann.*, **1977**, 811-829.
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6. Hydroxy-ketenedithioacetals were previously obtained from the corresponding oxo derivative by reduction or reaction with Grignard reagents.[1,2] Concerning sugar derived hydroxy-ketenedithioacetals, see : Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.*, **1978**, *100*, 3548-3553.
7. *S*-allyl hydroxy-ketenedithioacetals have been obtained by allylation of β-hydroxy-dithioesters after double-deprotonation. They underwent a Claisen rearrangement : Beslin, P.; Perrio, S. *Tetrahedron*, **1991**, *47*, 6275-6286. The synthesis of the *S*-benzyl hydroxy-ketenedithioacetals **2** by this double-deprotonation procedure was reported in the same paper.
8. Beslin, P.; Vallée, Y. *Tetrahedron*, **1985**, *41*, 2691-2705. Meyers, A. I.; Walkup, R. D. *Tetrahedron*, **1985**, *41*, 5089-5106.
9. The obtained dithioacetals gave ^{1}H and ^{13}C NMR and MS data in agreement with their structure. For instance, **1**, ^{1}H NMR : 1.29 (d, J = 6.5Hz, CH_3), 2.29 and 2.34 (2s, 2 SCH_3), 4.94 (m, CH-O), 5.77 (d, J = 8, HC=); ^{13}C NMR : 17.02, 16.37, 23.11, 66.89, 134.9. **6***E* , ^{1}H NMR : 0.79 (t, J = 7.5, CH_3), 1.4-1.65 (m, CH_2), 2.30 (s, SCH_3), 3.8-4.2 (AB system, J = 12, SCH_2), 4.59 (m, CH-O), 5.85 (d, J = 8, HC=), 7.27 (narrow m, Ph); ^{13}C NMR : 9.55, 16.51, 29.05, 37.92, 70.73, 127.14, 128.41, 128.89, 133.09, 137.64, 138.47; **6***Z* : 0.76 (t, J = 7.5, CH_3), 1.13-1.54 (m, CH_2), 2.32 (s, SCH_3), 3.8-4.1 (AB system, J = 13, SCH_2), 4.28 (m, CH-O), 5.85 (d, J = 8, HC=), 7.27 (narrow m, Ph); ^{13}C NMR : 9.44, 16.66, 29.79, 37.58, 70.94, 127.03, 128.33, 128.90, 133.50, 137.71, 140.38 ppm.
10. A similar proton transfer has been noticed after the [1,4]-addition of enethiolates to enones : Berrada, S.; Desert, S.; Metzner, P. *Tetrahedron*, **1988**, *44*, 3575-3586.
11. The proposed *Z-E* configurations for compound **2** are in agreement with those reported in ref.[7].

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