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ALDEHYDE ENOLATES III [1]

DIRECT SULFENYLATION AND IODINATION OF ALDEHYDE ANIONS.

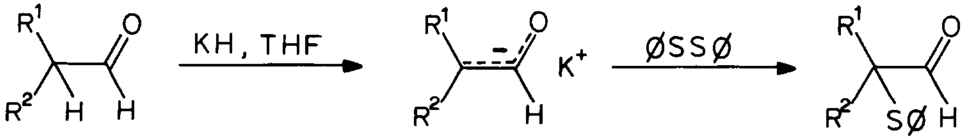
P. Groenewegen, H. Kallenberg and A. van der Gen[x]
Gorlaeus Laboratories, Department of Organic Chemistry,
University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands.

Summary: Directly generated potassium enolates of aldehydes react with diphenyldisulfide to give the α-sulfenylated aldehydes. Reaction with iodine likewise provides the α-iodo aldehydes.

In a previous paper the direct alkylation of aldehydes via their potassium enolates was reported.[1] The present communication describes the reactions of aldehyde enolates with diphenyldisulfide and with iodine. Both reactions give access to useful products that are not readily available by other routes.[2]

The application of α-sulfenylated carbonyl compounds as intermediates in organic synthesis has been the object of much recent interest.[3] Among the methods used for the synthesis of these species the sulfenylation of enolates from esters,[4a] ketones,[4a] carboxylic acids,[4b] amides [4b] and aldehydes,[4b] with disulfides, sulfenyl chlorides or other sulfenylating agents is the most widely applied. In the case of aldehydes the requisite enolates were prepared by reaction of the corresponding silyl enol ethers with methyl lithium. Other methods that have been applied for the synthesis of α-sulfenylated aldehydes include the use of metallated enamines[5] and the bromination and hydrolysis of vinylthioethers.[6] All these methods involve multistep preparations and, in the case of the indirectly generated lithium enolates, the use of reactive sulfenylating agents like sulfenyl chlorides is necessary.

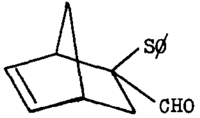
A number of α-phenylthioaldehydes have now been prepared by the following reaction sequence:



The results are presented in Table I. The reaction products were generally obtained in good yields after purification by column chromatography. The yields did not improve when diphenyldisulfide was replaced by a more reactive sulfenylating agent.

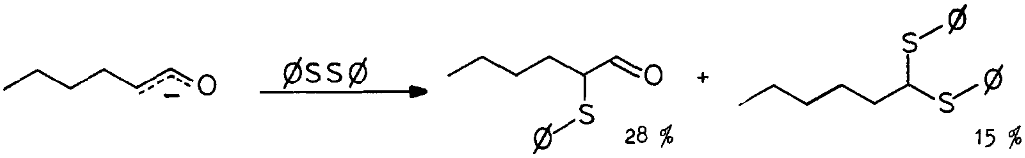
The enolate of 2-ethylhexanal gave yields of 66% and 68% with phenylsulfenylchloride and diphenylthiosulfonate, respectively.

TABLE I. α-Phenylsulfenylation of aldehydes with diphenyldisulfide.

	Starting aldehyde	Product R^1	 R^2	Yield [a] (%)	NMR δ-C$\underline{H}$O (ppm)
1.	isobutyraldehyde	CH_3	CH_3	42	9.24
2.	2-ethylbutyraldehyde	C_2H_5	C_2H_5	82	9.30
3.	2-ethylhexanal	C_2H_5	C_4H_9	67	9.21
4.	2,3-dimethylvaleraldehyde	CH_3	$CH(CH_3)C_2H_5$	81	9.16
5.	cyclohexane carboxaldehyde	$-(CH_2)_5-$		75	9.28
6.	3-cyclohexene carboxaldehyde	$-CH_2CH{=}CH(CH_2)_2-$		58	9.12
7.	2-phenylpropionaldehyde	C_6H_5	CH_3	83	9.59
8.	1-methylundecanal	CH_3	C_9H_{19}	60	9.44
9.	cyclooctane carboxaldehyde	$-(CH_2)_7-$		48	9.28
10.	norbornene carboxaldehyde			48	9.36

a. Yields are based on products, isolated by column chromatography (ether/hexane). Purity (NMR/VPC) better than 96%.

When the starting aldehyde contains two α-protons, the yields of mono-sulfenylated products are much lower and diphenyldithioacetals are formed as major side-products, e.g.:

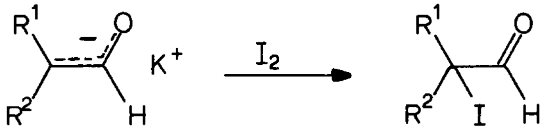


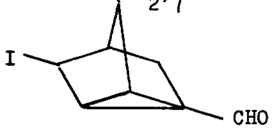
This product composition is suggestive of a rapid proton exchange between the aldehyde anion and the mono sulfenylated product.[7] The aldehyde thus formed will react with the phenylthiolate ions, generated during the sulfenylation step, ultimately leading to formation of the diphenyldithioacetal. The situation could not be improved by the use of excess KH, because this hydride reacts rapidly with diphenyldisulfide.

Although many classes of α-halocarbonyl compounds are readily available and frequently used as intermediates in organic synthesis, this does not hold for α-iodoaldehydes. Few methods are reported for their preparation and purification of the reaction products is cumbersome. The first α-iodoaldehyde was prepared as early as 1904 by Nef,[8] by treatment of the corresponding α-bromoaldehyde with potassium iodide. Riehl[9] provided three additional examples by a similar exchange reaction of α-chloroaldehydes. Another α-iodoaldehyde was prepared by reaction of an enamine with iodine.[10] The method recently published by Cardillo and Shimizu[11] for the preparation of α-iodoketones by oxidation-iodination of olefins is not applicable to the synthesis of α-iodoaldehydes.

Iodination of the aldehyde anions was performed in a way, similar to the one described by Rathke and Lindert[12] for esters, namely by addition of the enolate solution in THF to a solution of iodine in THF kept at -78°C. The reactions proceeded smoothly and the α-iodinated products were isolated in excellent yields. No impurities were detectable by NMR and IR analysis. The α-iodoaldehydes are colourless liquids that decompose slowly upon standing at room temperature. Distillation results in appreciable loss of product. The results are presented in Table II.

TABLE II. Direct iodination of aldehyde enolates



Starting aldehyde	Product R^1	R^2	Yield (%)	NMR δ-C$\underline{\text{H}}$O (ppm)
1. 2-ethylbutyraldehyde	C_2H_5	C_2H_5	83	9.32
2. 2-ethylhexanal	C_2H_5	C_4H_9	91	9.20
3. 2,3-dimethylvaleraldehyde	CH_3	$CH(CH_3)C_2H_5$	86	9.24
4. cyclohexane carboxaldehyde	$-(CH_2)_5-$		88	9.21
5. 3-cyclohexene carboxaldehyde	$-CH_2CH{=}CH(CH_2)_2-$		93	9.24
6. cyclooctane carboxaldehyde	$-(CH_2)_7-$		76	9.24
7. norbornene carboxaldehyde	 I CHO		65	9.20

Iodination of norbornene carboxaldehyde did not yield the α-iodoaldehyde. Instead, the interesting 2-formyl-5-*exo*-iodo $2,2,1,0^{2,6}$ tricycloheptane was obtained in 65% yield. As was the case with alkylation[1] and sulfenylation (*vide infra*), the successful iodination of aldehyde anions is limited to substrates with only one α-proton.

General Procedures

Sulfenylation: A solution of the potassium enolate of the aldehyde was prepared by adding dropwise a solution of the aldehyde (20 mmol) in 5 ml of THF to a stirred suspension of potassium hydride (21 mmol) in 25 ml of THF at room temperature. After additional stirring for 25 min, 4.4 g of diphenyldisulfide (20 mmol) in 20 ml of THF was added in one portion. Stirring was continued for 30 min. 25 Ml of saturated brine was added to the reaction mixture. The layers were separated and the organic layers were dried ($MgSO_4$) and the solvents were removed at reduced pressure. The residue was purified by column chromatography. Diphenyldisulfide was removed by hexane; the α-phenylthioaldehydes were eluted with hexane/ether (9:1).

Iodination: To a solution of the aldehyde enolate, prepared as described above, and kept at -78°C, a solution of iodine (5 g, 20 mmol) in 100 ml of THF was added in 20 min. After stirring for an additional 10 min the dry-ice bath was removed and the reaction mixture was allowed to warm to room temperature. A saturated solution of sodium thiosulfate was added dropwise until the brown colour had disappeared. Then 25 ml of water and 100 ml of ether were added. The layers were separated and the organic layer was dried in the dark ($MgSO_4$). The solvent was removed under reduced pressure to afford the α-iodoaldehydes in the yields, indicated in Table II.

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