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ALDEHYDE ENOLATES II [1]

DIRECT ALKYLATION OF ALDEHYDE ANIONS

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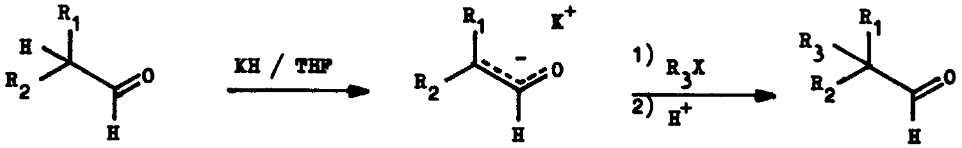
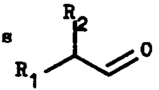
The formation of enolates from carbonyl compounds by means of strong bases of low nucleophilicity, such as lithium dialkyl amides,[2] potassium hydride,[3] and others[4] has been extensively investigated in recent years. The reactions of these anions with electrophiles are of great synthetic utility.[4,5] Aldehydes are generally considered to be unsuitable for such transformations because of their tendency towards aldol condensation.[6] To circumvent this problem several indirect methods have been devised in which a derivative of the aldehyde either is used directly[7] or is converted into a more manageable anion.[8] An obvious disadvantage of these methods is that extra reaction steps are needed. Some isolated cases have been reported in which an aldehyde with a low tendency to condensation was directly methylated via its anion.[9] Dietl and Brannock have made use of phase transfer catalysis for this purpose.[10] Also the indirect formation of lithium enolates from aldehydes via enol acetates and silyl enol ethers has been reported.[11] These lithium enolates however are rather unreactive.[12]

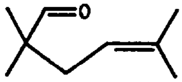
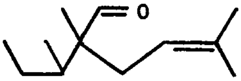
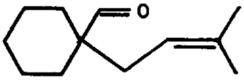
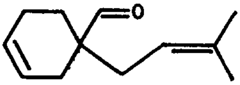
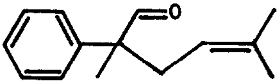
The use of potassium amide in liquid ammonia allowed Kloosterziel and co-workers to study the ^{1}H-NMR properties of some aldehyde anions.[13] We used this base-solvent combination for the direct alkylation of α,β-unsaturated aldehydes in reasonable yields.[1] Under these conditions saturated aldehydes could not be alkylated. However, if the solvent system was changed to diethyl ether-hexamethylphosphoric acid triamide (HMPA), mixtures of C- and O-alkylated products could be obtained.[14]

In this communication we report the direct C-alkylation in excellent yields of potassium enolates of aldehydes, which can be prepared by reaction of these aldehydes with potassium hydride in tetrahydrofuran (THF).[15]



In Table I the results are listed for several substrates with one α-proton when prenyl bromide (3,3-dimethylallylbromide) was used as the alkylating agent. In the NMR spectra of the reaction mixtures no traces of O-alkylated products could be detected.

TABLE I. Alkylation of aldehydes  with prenyl bromide.

aldehyde	R_1	R_2	reaction product [a]	yield (%) [b]
2-methylpropanal	CH_3	CH_3		88
2-ethylhexanal	C_2H_5	nC_4H_9		96
2,3-dimethylpentanal	CH_3	$CH_3CHC_2H_5$		89
cyclohexanecarboxaldehyde	$CH_2(CH_2)_3CH_2$			96
3-cyclohexene-1-carboxaldehyde	$CH_2CH_2CH{=}CHCH_2$			95
2-phenylpropanal	C_6H_5	CH_3		94

a. Spectral properties are in full accord with the assigned structures.

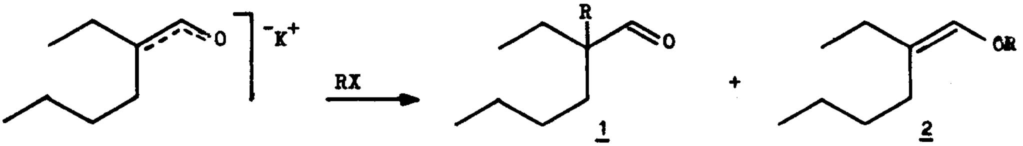
b. Yields are based on products, purified by short path distillation.

Other activated primary bromides (allyl- or benzyl) and methyl iodide also give rise to exclusive C-alkylation. With other primary alkyl iodides O-alkylation becomes apparent. Secondary alkyl iodides afford mixtures of C- and O-alkylated products, together with appreciable amounts of starting material. The general tendencies appear to be similar to those observed with ketone enolates.[16] Some results obtained by reaction of the potassium enolate of 2-ethylhexanal with several alkylating agents are shown in Table II.

Application of these reaction conditions to the previously studied[1] α,β-unsaturated aldehydes gives greatly improved results, e.g.: prenylation of the anion from 2-methyl-2-pentenal affords the Cα-alkylated product in excellent yield. No traces of Υ- or O-alkylated products were detected.

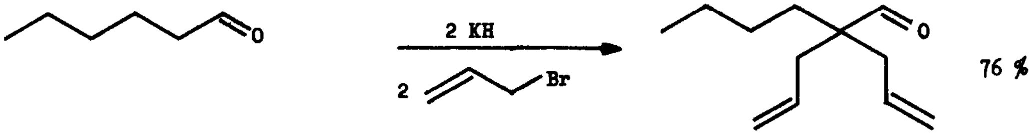
92 %

TABLE II. Alkylation of 2-ethylhexanal.



alkylating agent	starting material	products (%) 1	2	yield (%)
$C_6H_5CH_2Br$	--	100	---	90
$CH_3CH=CHCH_2Br$	--	100	---	94
$CH_2=CHCH_2Br$	--	100	---	95
CH_3I	11	89	---	75
CH_3CH_2I	3	67	30	75
$CH_3(CH_2)_3I$	4	63	33	78
CH_3CHICH_3	37	27	36	60

Aldehydes with two α-protons are also converted into their enolates by treatment with potassium hydride. In this case proton exchange between the alkylated product and the enolate is apparently rapid under the reaction conditions and mixtures of mono- and dialkylated products are isolated, together with starting material. The procedure can easily be modified to obtain good yields of α,α-dialkylated aldehydes, e.g.:



The efficient conversion of aldehydes into their potassium enolates described in this communication allows their reaction with a number of other electrophiles. Reaction with iodine provides the α-iodo aldehydes and reaction with carbon dioxide leads to C-carboxylation. These results will be reported separately.

General procedure for the alkylation of aldehydes.

A suspension of potassium hydride (11 mmol) in 25 ml of freshly distilled THF was prepared in the usual way.[3] The aldehyde (10 mmol) in 5 ml of THF was added in 5 min at room temperature in an inert gas atmosphere. After hydrogen evolution had ceased, the turbid yellowish solution was stirred for another 15 min. The alkylating agent (11 mmol) in 5 ml of THF was added and the solution was stirred for 15 more min. Water (10 ml) was added cautiously, the organic layer was separated and the water layer extracted with pentane (25 ml) and with ether (25 ml). The combined layers were dried over magnesium sulfate. After removal of solvent, the residual oil was subjected to short path distillation and analysed (GLC, NMR). Some representative results are presented in Tables I and II. To obtain dialkylation in the case of aldehydes with two α-protons, 2.05 equivalents of base and 2.2 equivalents of alkylating agent were used.

References and Notes.

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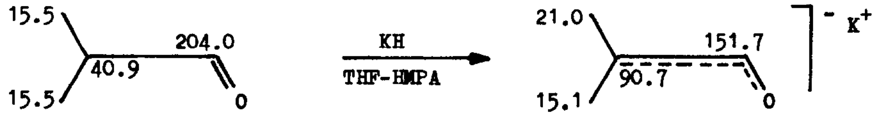
15. E.g.: Treatment of 2-methylpropanal (10 mmol) with potassium hydride (10.5 mmol) in 10 ml of THF or THF-HMPA 1/1 (v.v.) for 3 min at room temperature results in complete conversion into the enolate, as evidenced by the ^{13}C-NMR spectrum:



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