Lithium Iodide-promoted Aldol Condensation Reactions

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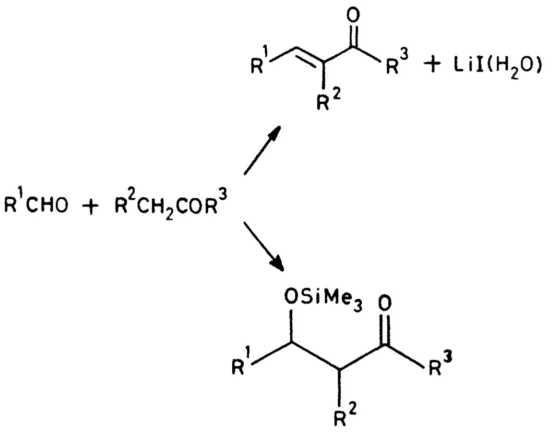
Summary Anhydrous lithium iodide in ether, tetrahydrofuran, or benzene is an effective reagent for the formation of $\alpha\beta$-unsaturated ketones by condensation of alkyl ketones with enolisable and non-enolisable aldehydes; in the presence of trimethylchlorosilane–triethylamine enone formation is suppressed and high yields of 1,3-hydroxy-

ketones are obtained as their trimethylsilyl ether derivatives.

BECAUSE of its importance in synthetic and biosynthetic chemistry the aldol condensation[1] continues to attract much attention as a method of constructing carbon–carbon single and double bonds, with recent work concentrating on the use of kinetic enolates and conditions designed to produce highly stereoselective ketol formation.[2] We report an exceedingly mild new procedure for aldol condensations between alkyl ketones and a variety of enolisable and non-enolisable aldehydes. The reaction involves the use of anhydrous lithium iodide in ether, tetrahydrofuran, or benzene under which conditions αβ-unsaturated ketones are obtained in high yields (equation 1); when the reaction is conducted in the presence of trimethylchlorosilane–triethylamine, ketols, the primary aldol products, are obtained as trimethylsilyl ethers (equation 2).



(1)

(2)

The reactions summarised in the Table were brought about by slow addition of the aldehyde (20 mmol) in dry ether to a solution of anhydrous lithium iodide (50 mmol) and the ketone (13 mmol) in the same solvent under reflux.

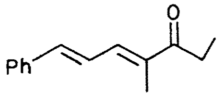
TABLE. Yields of products in the aldol condensation $R'CH{=}O + R^2CH_2C({=}O)R^3 \rightarrow$ *trans*-$R'CH{=}CR^2C({=}O)R^3$

$R^1CH{=}O$	$R^2CH_2C({=}O)R^3$		Reaction	
R^1	R^2	R^3	time/h	% Yield
Ph	H	Me	7	77
Ph	H	Et	3	74
p-$MeOC_6H_4$	H	Me	7	86
n-C_6H_{13}	H	Me	6	85
$PhCH_2CH_2$	H	Me	6	75
,,	H	Et	7	78
trans-PhCH=CH	H	Me	3	92[a]
,,	H	Et	5	80[a]
p-$MeOC_6H_4$	Me	Et	72	80
Ph	Me	Et	240	62
$Me_2C{=}CHCH_2CH_2CMe{=}CH$[b]	Me	Me	5	85[c]
,,	Me	Bu^t	5	89
p-$MeOC_6H_4$	$-[CH_2]_4-$		4	80

[a] All-*trans*-product. [b] Citral. [c] Pseudoionone.

Heating was continued for the period specified and products were isolated by addition of water and extraction; the yields, which have yet to be optimised, refer to materials judged to be pure by chromatographic and spectroscopic analysis.

The main features of this new aldol procedure are: (i) acyclic methyl ketones condense almost exclusively at the methyl carbon atom, butan-2-one producing >95% of the terminal condensation product with benzaldehyde; (ii) acyclic non-methyl ketones, *e.g.* pentan-3-one, do undergo condensation but very much more slowly than methyl ketones, a competitive experiment in which equimolar amounts of butan-2-one and pentan-3-one were allowed to react with benzaldehyde giving >90% of the product derived from butan-2-one; (iii) cyclohexanone reacts much faster than pentan-3-one, giving 89% of the condensation product with anisaldehyde after 4 h; (iv) yields of condensation products from methyl ketones and enolisable aldehydes are superior to those obtained using conventional acid or base, heptanal and acetone giving 85% of the cross-condensation product; (v) enolisable αβ-unsaturated aldehydes undergo efficient cross condensation with methyl ketones. Thus citral and acetone give pseudoionone in 85% yield, about twice that realised using sodium methoxide or barium hydroxide as base.[3]



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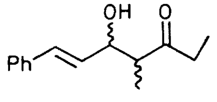

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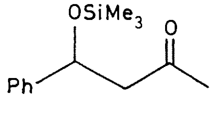

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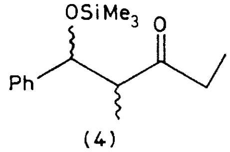

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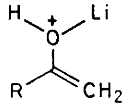

(5)

Aldol condensations involve the formation of ketols as intermediates which dehydrate to αβ-enones under appropriate conditions. Ketols were detected in some of the examples reported in the Table and in one other case a ketol was isolated. Reaction of cinnamaldehyde with pentan-3-one at room temperature gave, in addition to the dienone (**1**) (37%), 33% of the ketol (**2**) as a mixture of stereoisomers. An efficient way of suppressing enone formation was to conduct the reaction in the presence of trimethylchlorosilane–triethylamine, under which conditions ketols were trapped as their trimethylsilyl ether derivatives. Using this modification at room temperature benzaldehyde and acetone afforded the silylated ketol (**3**) in 72% yield. Similarly, benzaldehyde and pentan-3-one produced the adduct (**4**) (76%) as a 60:40 mixture of stereoisomers.

We have made additional observations which are pertinent to an understanding of the precise role played by lithium iodide in these reactions. First, preliminary inspection of various cation–anion combinations suggests that Li^+I^- is unique; neither lithium chloride or bromide nor sodium or potassium iodide was effective.[4] Secondly, the reaction is inhibited by the addition of a crown ether capable of complexing Li^+. Thirdly, Li^+ is known to complex efficiently with ketonic carbonyl groups through the oxygen atom.[5]

Furthermore, anhydrous lithium iodide promotes enolisation of ketones Thus treatment of cyclohexanone in ether with trimethylchlorosilane–triethylamine in the presence of lithium iodide at room temperature led to conversion into the corresponding silyl enol ether In these aldol reactions we suggest that lithium iodide promotes conversion of the ketone into a Li^+-complexed enol of type (**5**) which then combines with the aldehyde partner in a pericyclic process in which Li^+ is complexed to both oxygen atoms Under conditions leading to enones (which may be brought about by I^-) the reaction is not catalytic in lithium iodide because the water produced enters the co-ordination sphere of the lithium cation, but when ketols are intercepted before elimination takes place, reaction can be brought about with less than an equivalent amount of lithium iodide

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