

A Convenient Reagent For Conjugate Reduction
Of Substituted Enones, LiAlH_4 -CuI

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The reactivity of LiAlH_4 can be modified by employing this reagent in admixture with metal salts, e.g. $\text{LiAlH}_4 - \text{AlCl}_3$ ¹ has found unusual applicability in epoxide reductions, $\text{LiAlH}(\text{OCH}_3)_3$ -CuI has been recently reported to be effective in displacement of halo and mesyloxy groups² and LiAlH_4 - TiCl_3 has recently been found to be an excellent coupling reagent for carbonyl compounds³ Although conjugate reduction of enones can be effected by Pd-C hydrogenation and Na-lq NH_3 reduction, these methods are not convenient and in general reduce enones in only 50-70% yield. More recent contributions involve hydride reductions, e. g. LiCuRH ^{4,5} and $\text{KB}(\text{sec-Bu})_3\text{H}$ ⁶ however, in the former case the reagent is quite difficult to prepare whereas in the latter case only 1,2 reduction is observed when β -substituents are present. We would like to report here an excellent method for effecting conjugate reduction of enones using a reagent that is easily prepared ($\text{LiAlH}_4 - \text{CuI}$) and involving enones substituted in both the α and β -position.

The best results are obtained adding a known concentration of LiAlH_4 in THF to a stirred slurry of CuI in THF at 0°. On addition a deep black color is immediately produced with gas evolution. After 3 minutes stirring the enone is added and allowed to react for 30-60 minutes. Five representative enones were studied and TiCl_3 and FeCl_3 as well as CuI were evaluated as co-reagents with LiAlH_4 . Products were identified by nmr and yields were determined by glc.

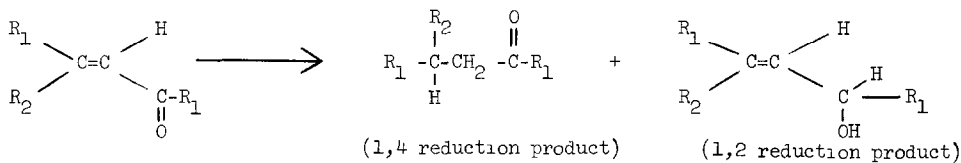


Table I shows that Enone I can be reduced in quantitative yield and excellent regioselectivity when the LiAlH_4 :CuI:Enone ratio is 1.4:1, the solvent is THF and the reaction temperature 0° . If the reagents (LiAlH_4 and CuI) are mixed at -78° , reaction does not take place readily and when the enone is added, 1,2 reduction takes place by reaction of the enone with LiAlH_4 . If the reagents are mixed at 0° and then cooled to -78° followed by enone addition, no reaction takes place. If the reagents are mixed at room temperature, decomposition of the reagent takes place and low yields are observed. Apparently the reagent forms completely within 3 minutes at 0° and subsequent reduction of the enone takes place in less than 10 minutes.

Table I. Reduction of Enones With LiAlH_4 -CuI in THF.^a

Enone ^e	Molar Ratio			Temp ($^\circ$)	Enone (%) Recovered	Products (%)	
	LiAlH_4	CuI	Enone			1,4	1,2
(I) $t\text{-BuCH}=\overset{\text{O}}{\parallel}\text{C}-\text{Bu}^t$	1.0	0	1.0	0	0	0	99
"	1.0	1.0	1.0	0	0	64	27
"	1.0	2.0	1.0	0	0	95	6
"	1.0	4.0	1.0	0	0	99	0
"	1.0	4.0	1.0 ^b	0	0	78	20
"	1.0	4.0	1.0	RT	47	34	<1
"	1.0	4.0	1.0	-78°	0	0	93
"	1.0	4.0	1.0	0° -78° ^c	101	0	0
"	1.0	4.0	1.0	0° RT ^c	29	67	~1
(II) (cis) $\text{CH}_3\text{CH}=\overset{\text{O}}{\parallel}\text{C}-\text{CH}_3$	1.0	4.0	1.0	0	33	40	0
(III) $(\text{CH}_3)_2\text{C}=\overset{\text{O}}{\parallel}\text{C}-\text{CH}_3$	1.0	4.0	1.0	0° ^d	3	66	~1
"	1.0	4.0	0.5	0	8	70	0
(IV) $\text{CH}_3\text{CH}=\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)-\text{CH}_3$	1.0	4.0	1.0	0	0	97	0
(V) $\text{CH}_3\text{CH}=\overset{\text{O}}{\parallel}\text{C}-\text{CH}_3$	1.0	4.0	1.0	0	0	78	0
(VI) $\text{PhCH}=\overset{\text{O}}{\parallel}\text{C}-\text{Ph}$	1.0	4.0	1.0	0	0	101	0

a. Reaction time for all reactions is 30-60 min. b. Diethylether used as solvent. c. Add LiAlH_4 to CuI at 0° then add enone at -78° or RT. d. Reaction time 2 hr. e. Compounds I, IV, V and VI are trans isomers.

The system LiAlH_4 - TiCl_3 has also been studied (Table II). Although excellent regioselectivity has been obtained, the yields (~60% for Enone I and 34% for Enone III) are not as good

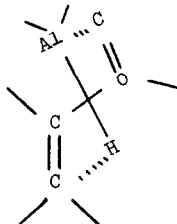
as observed for the $\text{LiAlH}_4\text{-CuI}$ system.

$\text{LiAlH}_4\text{-FeCl}_3$ was allowed to react with Enone I at different temperatures (-78° , 0° and RT) and in each case the enone was recovered unreacted.

Table II. Reduction of Enones with $\text{LiAlH}_4\text{-TiCl}_3$ in THF.

Enone	Molar Ratio			Temp ($^\circ$)	Enone (%) Recovered	Products (%)	
	LiAlH_4	TiCl_3	Enone			1,4	1,2
I (trans)	1.0	1.0	1.0	0	0	13	53
"	1.0	1.0	1.0	RT	0	58	0
"	2.0	1.0	1.0	RT	0	63	0
"	2.0	1.0	1.0	Reflux	0	60	0
"	1.0	2.0	1.0	RT	0	29	-1
"	1.0	3.0	1.0	RT	0	14	0
III	1.0	1.0	1.0	RT \rightarrow 0	-1	34	0

We have studied the reaction of LiAlH_4 and CuI in detail and have found that H_2AlI is the active reducing reagent in this mixture and not CuH or CuAlH_4 .⁷ We have also found that cyclohexenone and 3,3,5-trimethylcyclohexenone are not reduced at all by the $\text{LiAlH}_4\text{-CuI}$ reagent. These observations in addition to the considerably slower reaction rate involving cis enones or trans enones with disubstitution at the β -carbon has led us to suggest a mechanism for the reduction involving a six center transition state. Such a transition state accounts for the quantitative yield and 100% regioselectivity observed for trans enones possessing only monosubstitution at the α and β carbon whereas lower conversions are encountered with cis enones or with trans enones possessing disubstitution at the β -carbon of the enone and no reduction is observed with cyclic enones fused in the cis configuration where no rotation about the $=\text{C} \begin{matrix} \text{H} \\ \text{O} \end{matrix} \text{C}$ bond is possible in order to effect a six center transition state.



References

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