

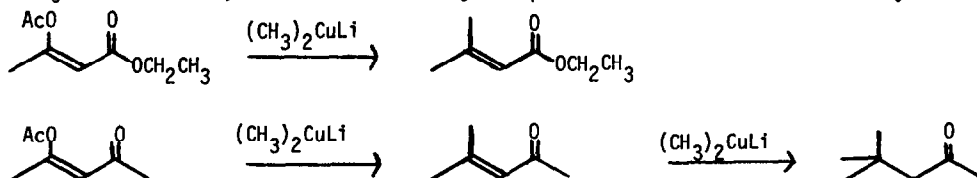
REACTION OF LITHIUM DIALKYL-CUPRATES WITH β -ACETOXY α,β -UNSATURATED CARBONYL COMPOUNDS--A NEW SYNTHESIS OF SUBSTITUTED α,β -UNSATURATED CARBONYL COMPOUNDS.

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Lithium diorganocuprates are now widely used in conjugate additions to α,β -unsaturated carbonyl compounds¹ and in coupling reactions with alkyl halides², allylic acetates³, and other compounds possessing good leaving groups. Here we report a new reaction of lithium dialkylcuprates which is formally related to both the conjugate addition and coupling reactions. Lithium dialkylcuprates react with the enol acetates of β -dicarbonyl compounds to give the corresponding substituted α,β -unsaturated carbonyl compounds in moderate to excellent yields. In

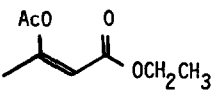
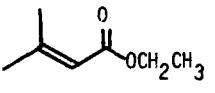
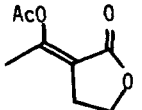
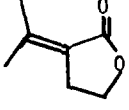
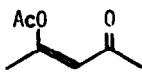
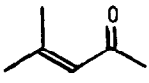
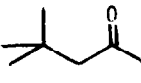
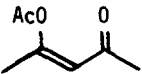
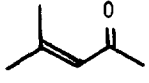
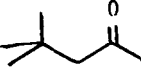
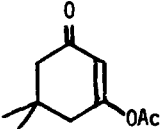
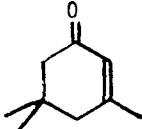
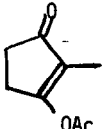
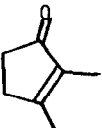


the case of the enol acetates of β -diketones, reaction with one equivalent of cuprate gives the α,β -unsaturated ketone while reaction with two equivalents of cuprate gives the saturated dialkylated ketone.⁴ The ready availability of the β -diketones and β -keto esters from which the required enol acetates are prepared enhances the synthetic potential of these new reactions.

The reactions of lithium dialkylcuprates with several β -acetoxy α,β -unsaturated ketones, esters and lactones are summarized in Table I.

The experimental procedure is illustrated for the reaction of ethyl (Z)-3-acetoxy-2-butenate with lithium dimethylcuprate to give ethyl 3-methyl-2-butenate. Ethyl (Z)-3-acetoxy-2-butenate (10.0 g, 58 mmol) was added to $(\text{CH}_3)_2\text{CuLi}^2$ (70 mmol in 270 ml ether) at -78° . The reaction mixture was quenched at -20° by the successive addition of 50 ml 3 N HCl in ether and of 100 ml water. The ether layer was separated, dried (MgSO_4), and distilled to give ethyl 3-methyl-2-butenate (7.04 g, 95%) which was shown to be 97% pure by gas chromatography.

Table I. Reaction of Lithium Dimethylcuprate with β -Acetoxy α,β -Unsaturated Carbonyl Compounds

Substrate ^a	$(\text{CH}_3)_2\text{CuLi}$ (equiv)	Products ^a (% Yield) ^b
	1.1	 (91) ^c
	1.1	 (88)
	1.0	 (76)  (2)
	2.7	 (2)  (81)
	1.0	 (91)
	1.0	 (99)

(a) Satisfactory infrared, nuclear magnetic resonance, and high resolution mass spectral data were obtained for all compounds using chromatographically homogeneous samples.

(b) Yield determined by gas chromatography.

(c) Yield of isolated product.

To achieve the monoalkylation of the enol acetates of β -diketones, slow inverse addition of lithium dialkylcuprate to a rapidly stirred -78° ether solution of the enol acetate was employed.

The stereochemistry of the coupling reaction was determined by investigating the reactions of $(\text{CH}_3\text{CH}_2)_2\text{CuLi}$ with methyl (Z)-3-acetoxy-2-butenolate 1 and of $(\text{CH}_3)_2\text{CuLi}$ with methyl (Z)-3-acetoxy-2-pentenoate 2. The differences in the ratio of methyl (Z)-, 3, and (E)-3-methyl-2-pentenoate, 4, obtained in the two reactions (Table II) indicate a stereoselective replacement of acetoxy by alkyl with retention of configuration. The partial loss of stereochemistry observed in these reactions can be explained by the intervention of an intermediate such as 5 ($X = \text{alkyl}$ or copper) which can undergo expulsion of acetate at a rate competitive with rotation about the $\text{C}_2\text{-C}_3$ bond.

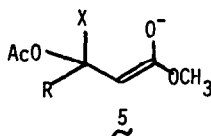
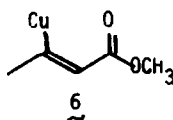


Table II. Stereochemistry of Reaction of R_2CuLi with β -Acetoxy α,β -Unsaturated Esters.

Substrate	Cuprate	Products	3 + 4 % Yield	
 (<u>1</u>)	$(\text{CH}_3\text{CH}_2)_2\text{CuLi}$	 <u>3</u>	 <u>4</u>	1:1 52
 (<u>2</u>)	$(\text{CH}_3)_2\text{CuLi}$			1:10.8 92

The reaction of $(\text{CH}_3\text{CH}_2)_2\text{CuLi}$ with 1 gave a 19% yield of methyl (E)-2-butenolate in addition to the normal products 3 and 4.⁵ When the reaction mixture was quenched with DCl in ether, methyl (E)-2-butenolate-3- d_1 (88% d_1 , by mass spectrometry) was formed. This deuteration experiment implicates an organometallic species such as 6 which could possibly be formed by displacement of acetate by copper. The ability of the copper atom of lithium

dialkylcuprates to act as a nucleophile has been suggested previously.^{2b,6}



Acknowledgement. We wish to thank the Eli Lilly Company for support of this work.

References

- (1) For a recent review see G. H. Posner, Org. Reaction, 19, 1 (1972).
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- (4) A similar reaction involving the addition of lithium dimethylcuprate to 2-n-butylthio-methylenecyclohexanone to give 2-isopropylcyclohexanone in 95% yield has been reported. R. M. Coates and R. L. Sowerby, J. Amer. Chem. Soc., 93, 1027 (1971).
- (5) In addition, a low yield (5%) of methyl 3-methylpentanoate is also obtained. Quenching the reaction mixture with DCl gave methyl 3-methylpentanoate-2,3-d₂. The significance of these results will be discussed in subsequent reports.
- (6) E. J. Corey and I. Kuwajima, J. Amer. Chem. Soc., 92, 395 (1970); J. Klein and R. Levene, ibid., 94, 2520 (1972).