

ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS I.  
MECHANISTIC ASPECTS OF THE CONJUGATE ADDITION  
REACTIONS OF ORGANOCOPPER REAGENTS TO  $\alpha\beta$   
UNSATURATED KETONES

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Organocuprate reagents (e.g.  $R_2CuLi$ ) have been utilised extensively in the conjugate addition of alkyl and aryl groups (i.e. R) to  $\alpha\beta$  unsaturated carbonyl compounds<sup>1</sup>. However the mechanism of this reaction does not appear to have been conclusively elucidated.

It has been established that the mechanism of conjugate addition does not involve a carbanionic ( $R^-$ )<sup>2</sup> nor a radical ( $R^\cdot$ )<sup>3</sup> migratory group. In agreement with previous reports<sup>4</sup> we have not observed any radical anion or Cu(II) species during these reactions. Thus an ethereal solution of excess lithium dimethylcopper [ $(CH_3)_2CuLi$ ] and cholest-4-en-3-one gave an orange solution at  $-100^\circ C$ . Protonation at  $-100^\circ$  gave only unreacted cholest-4-en-3-one. If this solution is allowed to warm to ca.  $-80^\circ$  rapid reaction occurs and 5 $\beta$ -methylcholestan-3-one<sup>5</sup> is obtained in 67% yield. Repetition of this sequence in the probe of an e.s.r. spectrometer did not produce any signal

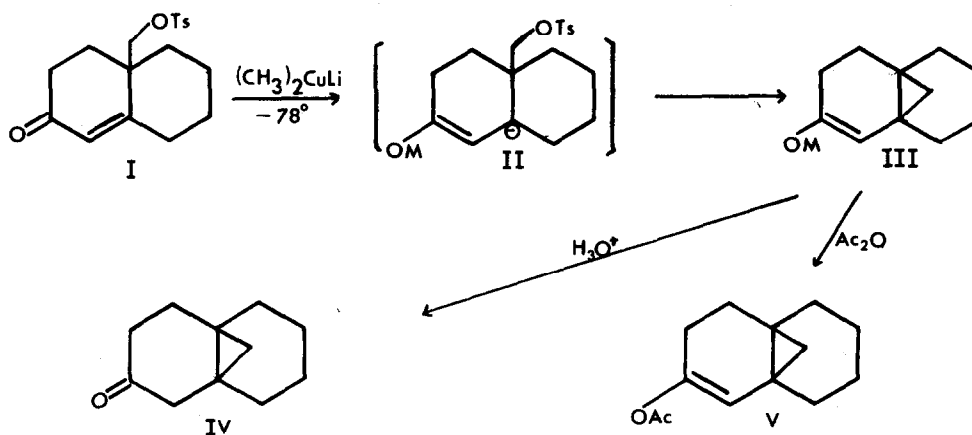
attributable to an unpaired electron.

Reaction of (I)<sup>6</sup> with excess ethereal  $(\text{CH}_3)_2\text{CuLi}$  followed by hydrolytic work-up gave (IV)<sup>6,7</sup> in 96% yield. Treatment of the reaction mixture with acetic anhydride prior to hydrolytic work-up gave enol acetate (V)<sup>8</sup>. It is well established that the initially formed products of organocopper conjugate addition reactions prior to hydrolysis are anionic<sup>2</sup>, although the exact nature of these species i.e. (III) has not been elucidated<sup>10</sup>. The products (IV) and (V) can be envisaged as arising from a species possessing considerable electron density at the  $\beta$  carbon (i.e. (II)), which intramolecularly displaces the neighbouring tosylate to give (III) (Scheme). Reaction of (I) with  $(\text{CH}_3)_2\text{CuLi}$  (1 equivalent) gave (IV) (95%)<sup>11</sup> together with methyl iodide (86%)<sup>11,12</sup>. The formation of methyl iodide can be rationalised as arising from reaction of an organocopper (III) species with iodide ion which is produced during the preparation of the organocuprate reagent:-



These results indicate the conjugate addition reaction proceeds by a transfer of two electrons from the reagent to the  $\alpha\beta$  unsaturated ketone giving a (presumably) complexed dianion and an organocopper (III) species, followed by electrophilic attack at the  $\beta$  carbon by the Cu(III) species.

In concert with this postulate, organocopper reagents have been found to react with other good electron acceptors: i.e. reaction of benzophenone with  $(\text{CH}_3)_2\text{CuLi}$  gives 1,1-diphenylethanol (72%)<sup>11,15</sup>.



SCHEME

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 (b) i.r. (nujol),  $\nu_{\text{max}}$   $1710\text{cm}^{-1}$ ; n.m.r. (60MHz) ( $\text{CDCl}_3$ ), 2H AB system  $J_{\text{AB}}$  6Hz,  $H_{\text{A}}$  6.042,  $H_{\text{B}}$  0.53; 2.52 (2H, singlet).  
 (c) Treatment<sup>6</sup> of IV with aqueous acid gave 10-methyl- $\Delta^1(9)$ -octal-2-one.

8. i.r. (nujol),  $\nu_{\max}$  1750, 1675 $\text{cm}^{-1}$ ; n.m.r. ( $\text{CDCl}_3$ ),  $\delta$  0.49 (2H, broad unresolved doublet,  $W_{1/2} = 3.4\text{Hz}$ ), 2.06 (3H, singlet), 5.48 (1H, doublet,  $J = 1.5\text{ Hz}$ ). Mass spectrum,  $m/e$  206 ( $\text{M}^+$ ). Found: C, 75.24; H, 8.94. Calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}_2$ : C, 75.60; H, 8.80.
9. Direct displacement of the tosylate group to produce 10-ethyl- $\Delta^{1(9)}$ -octal-2-one was not observed, in accord with the report that neopentyl tosylates react very slowly with  $(\text{CH}_3)_2\text{CuLi}$  under these conditions, cf. C.R. Johnson and G.A. Dutra, J. Amer. Chem. Soc., **95**, 7777, (1973).
10. These intermediates do not react as lithium enolates, although enolate-type reactions have been observed; R.K. Boeckman, Jr., J. Amer. Chem. Soc., **95**, 6867, (1973); R.M. Coates and L.O. Sandefur, J. Org. Chem., **39**, 275, (1974); R.K. Boeckman, Jr., ibid., **38**, 4450, (1973); K.K. Heng, R.W. Morris and R.A.J. Smith, unpublished results.
11. Yield is based on amount of starting material reacted.
12. Methyl iodide in the reaction mixture was determined by a modified Zeisel's method. The reaction mixtures resulting from the conjugate addition of  $(\text{CH}_3)_2\text{CuLi}$  and 10-methyl- $\Delta^{1(9)}$ -octal-2-one and from the hydrolysis of unreacted  $(\text{CH}_3)_2\text{CuLi}$  reagent did not contain any detectable quantities of methyl iodide.
13. For simplicity this reagent is shown in its simplest monomeric form. The exact form of this reagent in ether solution has not yet been established.
14. The proposal that organocopper reactions involve Cu(III) species has been presented previously: (a) cf. reference 3a; (b) G.M. Whitesides, W.F. Fischer, Jr., J. San Filippo, Jr., R.W. Bashe and H.O. House, J. Amer. Chem. Soc., **91**, 4871, (1969); (c) C.R. Johnson and G.A. Dutra, ibid., **95**, 7783, (1973); (d) G.H. Posner and J-S Ting, Tetrahedron Letters, 683, (1974).
15. Reaction of  $(\text{CH}_3)_2\text{CuLi}$  with flourenone has been reported to give the corresponding methylated product together with a dimeric pinacol.<sup>2</sup> We did not detect any benzopinacol in the reaction products.