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ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS II[1]. ALDOL CONDENSATION OF ORGANOCOPPER ENOLATES.

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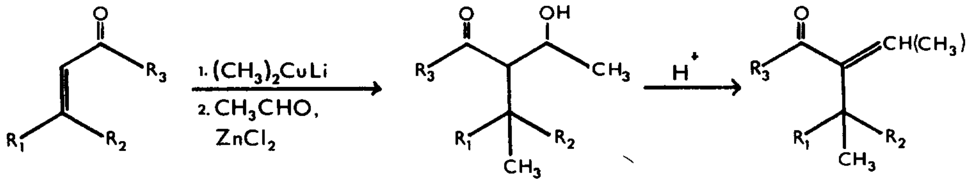
The utility of organocuprate reagents [R_2CuLi] in the 1,4 addition of alkyl and aryl groups to α,β-unsaturated carbonyl compounds is well established.[2] Extensions of this reaction by subsequent carbon alkylation of the initially formed anionic copper species producing α,β-dialkylated products have been reported[3] although in some instances, particularly with β,β-disubstituted enones, the reaction results in low yields and poor regioselectivity. Reports of the reaction of the anionic copper intermediate with electrophiles other than alkylating agents have also appeared.[4] We report that the solution produced from the reaction of α,β-unsaturated ketones with $(CH_3)_2CuLi$ undergoes aldol condensation with acetaldehyde in the presence of zinc chloride[5] producing the corresponding β-methyl-α-(1-hydroxyethyl)-ketones in acceptable yields (Scheme).

As previously reported,[6] mesityl oxide (I) reacts readily with organocuprate reagents. Reaction of (I) with $(CH_3)_2CuLi$ followed by treatment with zinc chloride[7] and excess acetaldehyde prior to protonation gives a product whose spectral properties are consistent with (II)[8] i.r.(film) ν_{max} 3400, 1700 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.02 (9H,singlet), 1.20(3H, doublet, J = 7Hz), 2.18 (3H,singlet), 2.58 (1H, doublet, J = 7 Hz), 4.13 (1H, quintet,J = 7 Hz).

The results from using this sequence with other α,β-unsaturated ketones are listed in the Table. It is noteworthy that the reaction product formed using 1-phenyl-3-penten-2-one[9] as substrate (followed by dehydration) was (III)[8] n.m.r. ($CDCl_3$) δ 1.11 (6H,doublet, J = 7Hz), 1.83 (3H, doublet, J = 7Hz), 3.87 (2H,singlet), 6.56(1H, quartet, J = 7Hz), 7.18 (5H, broad singlet) and not the isomeric compound (IV). This result indicates that the initially formed anionic copper intermediate has considerable stability in that it does not isomerize into conjugation with the adjacent phenyl ring.

Studies, using this procedure,with electrophiles other than acetaldehyde[10] (viz. benzaldehyde, acetone, methyl iodide[11]) have, to date, given only the corresponding saturated β-methyl ketone.

Typical experiment: The α,β-unsaturated ketone (1 mmole) is added to a solution of $(CH_3)_2CuLi$ (2 mmole) in ether (20 ml) at 0° under N_2 atmosphere. After stirring 30 min at 0° a saturated ethereal solution of anhydrous zinc chloride[5] (2 mmole) is added followed by acetaldehyde (10 mmole). Stirring is continued for 5 min then the mixture is poured[5] into 10% aqueous ammonium chloride (100 ml) and the product isolated by extraction with ether. Because of the labile nature of the initial β-hydroxy carbonyl products they were generally dehydrated to the corresponding α,β-unsaturated ketone by refluxing in benzene with a catalytic amount of p-toluene sulphonic acid.



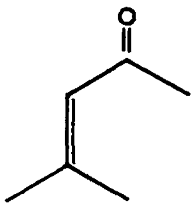
SCHEME

TABLE

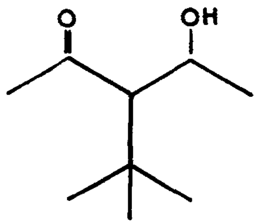
Substrate	Yield[a,b] of β-methyl-α-(1-hydroxyethyl)-ketone (%)	Yield[a,b] of β-methyl-α-ethylidene-ketone (%)
mesityl oxide (I)	96	–[c]
cyclohexenone	97	87
2-methylcyclohexenone	32	–[c]
3-methylcyclohexenone	98	> 95
4,4-dimethylcyclohexenone	87	89
3,5,5-trimethylcyclohexenone	82	> 95
1-phenyl-3-penten-2-one	91	50[d]
10-methyl-$\Delta^{1(9)}$-octal-2-one	76	24[d]

[a] based on n.m.r. and v.p.c. analysis. [b] stereochemistry not determined

[c] dehydration not observed. [d] considerable amounts of β-alkyl ketone were identified resulting from reverse aldol reaction.



(I)



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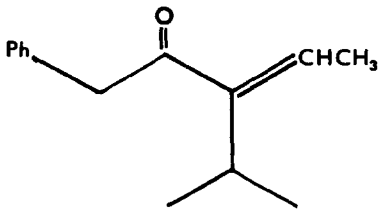

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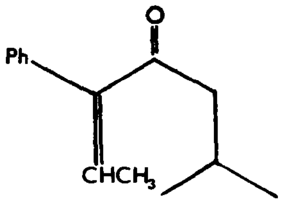

(IV)

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