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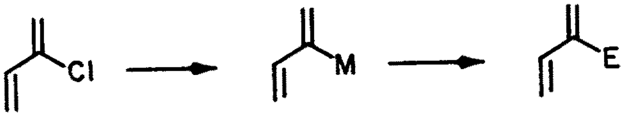
REACTIONS OF ORGANOCOPPER REAGENTS DERIVED FROM CHLOROPRENE. CONJUGATE ADDITION AND NUCLEOPHILIC SUBSTITUTION

K. J. Shea* and P. Q. Pham[1]

Department of Chemistry, University of California
Irvine, California 92717

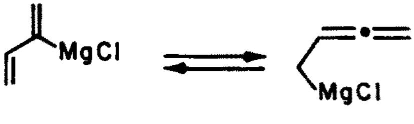
Summary: Organocopper reagents derived from 2-(1,3-butadienyl) magnesium chloride react regiospecifically with α,β-unsaturated carbonyl compounds to give 1,4-addition products of 2-substituted-1,3-butadienes.

Our program in intramolecular Diels-Alder chemistry[2] requires a wide variety of 2-substituted 1,3-butadienes. The most expeditious entry into these systems utilizes an organometallic reagent derived from chloroprene (2-chloro-1,3-butadiene), eq. 1.



(1)

Despite earlier difficulties encountered in the preparation of the organomagnesium derivative of chloroprene,[3] solutions of this reagent are now readily prepared by reaction in THF with catalytic amounts of Lewis acids such as $ZnCl_2$.[4] The resulting Grignard reagent is stable at room temperature for weeks. Several groups have reported reactions of this reagent with aldehydes,[5] ketones,[6] and epoxides.[5] Although these reactions provide a convenient entry into 2-substituted-1,3-butadienes, the product in many instances is contaminated with isomeric allenic adducts presumably resulting from the organomagnesium species 2, present in small amounts at equilibrium.



1 2

The influence of electrophiles and solvent on the dienyl-allenyl product ratio has been noted.[5,6] More recently, it has been shown that 2-lithio-1,3-butadiene, generated by the Shapiro reaction, combines with a range of aldehydes to give 2-substituted 1,3-butadienes.[7]

We report here that organocopper reagents, derived from the chloroprene Grignard reagent **1**, react regiospecifically with α,β-unsaturated carbonyl derivatives to give exclusive 1,4-addition products of 2-substituted-1,3-butadienes. We also report that chloroprene organocuprates are effective nucleophiles in substitution reactions with alkyl halides and tosylates.[8]

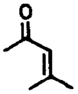
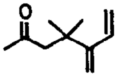
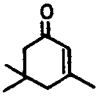
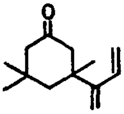
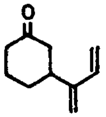
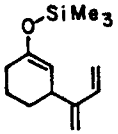
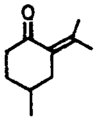
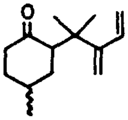
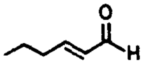
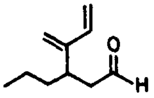
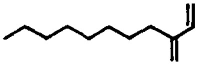
In a typical experiment 46 mL (30 mmol) of a 0.65 M solution of 2-(1,3-butadienyl) magnesium chloride is added dropwise over 0.5 hr to a stirred, cold (-40°C) solution of freshly distilled enone (25 mmol), $CuBr{\cdot}Me_2S$[9] (2.5 mmol), Me_2S (5 mL) in THF (75 mL). The temperature was adjusted to -25°C and the progress of the reaction monitored by the Gilman test. The reaction mixture was quenched by transferring to a rapidly stirred 2M HCl solution, then extracted (Et_2O), washed ($NaHCO_3$), dried ($MgSO_4$) and concentrated. Purification was accomplished by flash chromatography, Et_2O : hexanes (1:4), followed by distillation. A summary of the results is given in the Table.

In all cases, the 1,4-addition product of 2-(1,3-butadiene) was formed, inspection of the NMR of crude reaction mixtures did not reveal any allenic adducts (<5%). β-substituents retard the rate of addition but do not influence the regiochemistry at the nucleophile (entry 5). In contrast, the addition of **1** to sterically congested ketones gives exclusively the allene adduct.[5]

A further illustration of the utility of this reaction is shown in entry 4. The kinetic enolate derived from conjugate addition to cyclohexenone is trapped by chlorotrimethylsilane in good yield.

Copper catalyzed nucleophilic substitution reactions proceed at a slower rate. Thus, phenethyl bromide is recovered unchanged after treatment with two equivalents of the Grignard copper reagent at -20°C for 8 hr. At elevated temperatures, trace amounts of the substitution product is observed but decomposition of the organometallic is the principle reaction. The use of Li_2CuCl_4[10] (5 mole%) produces a reagent that exhibits greater thermal stability and results in moderate yields of the 2-(1,3-butadienyl) substitution product. This reaction is also shown in the table. In general, we have found alkyl tosylates give slightly better yields than alkyl halides.[11]

Table 1

	Reactant	Product[a]	Conditions[b]	Yield[c]
(1)			-25°, 1.5 hr	81
(2)			-60-0°C, 18 hr	52
(3)			-20°C, 3 hr	73
(4)			-20°C, 3 hr[d]	52
(5)			-20°C, 4 hr	52[e]
(6)			-25°C, 2 hr	84
(7)			X=Br, 25°C, 26 hr[f] X=OTs, 25°C, 46 hr[f]	38 55

a. All new compounds give IR, NMR (^1H, ^{13}C) and mass spectral data consistant with the assigned structures.
b. Unless otherwise stated, solvents and molar ratios of reagents are those specified in the text
c. Distilled.
d. After 3 hr at -20°C, the solution was cooled to -60°C and Me_3SiCl (75 mmol), HMPA (17.5 mL) and Et_3N (24.5 mL) were added sequentially. After stirring for 2 hr without cooling, the reaction was quenched (H_2O), extracted (hexane), washed (H_2O), dried ($MgSO_4$), then distilled
e. 47:53 mixture of isomers.
f. 1 (6 mmol), RX (5 mmol), Li_2CuCl_4 (0.5 mmol), THF.

We have also noted that 2-alkyl-1,3-butadienyl derivatives are available, albeit in very low yield, by direct coupling of chloroprene and Grignard reagents with $FeCl_3$.[12] The chloroprene substitution reaction is slow, however, and the principle reaction is reductive coupling of the Grignard reagent.

The low cost and availability of chloroprene makes this an attractive entry into a variety of 2-substituted-1,3-butadienes. Since this functional grouping serves as a starting point for many natural product syntheses,[13] we anticipate these reactions will be of particular value in this area.

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