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1,6-ADDITION OF ORGANOCOPPER REAGENTS TO 3-ETHYNYL-2-METHYL-2-CYCLOPENTENONE

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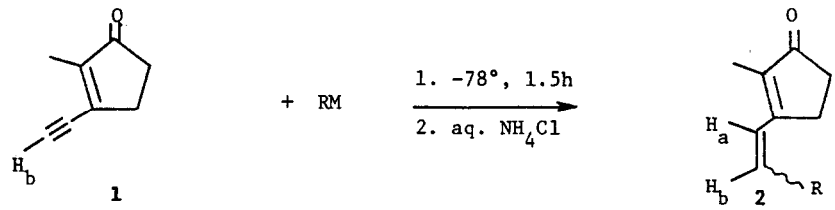
Abstract. Enynone **1** undergoes facile 1,6-addition of organocopper reagents to yield allenyl enols **5** which stereoselectively isomerize to Z-dienones **2.**

Conjugate, 1,4- or Michael-type addition reactions of organometallic nucleophiles to α,β-unsaturated carbonyl substrates in aprotic solvents are powerful synthetic tools.[1-3] In contrast, 1,6-additions to α,β, ,δ-unsaturated carbonyl substrates have received comparatively little attention.[1c,4] Reported examples using 2,4-dienones as substrates indicate that the preponderance of 1,2-, 1,4- or 1,6-addition is dependent upon a number of factors,[4c,5] including nucleophile identity, relative steric environments of the electrophilic carbons of the dienone and substrate planarity. Although 1,6-additions to 2-en-4-ynones are unexplored, the relative steric congestion of the electrophilic carbons of such substrates suggest that organocopper nucleophiles would react with high regioselectivity[1c] in a 1,6-fashion.

To test this hypothesis as well as to investigate the possibility of preparing allenes by a conjugate addition process, 3-ethynyl-2-methyl-2-cyclopentenone (**1**, mp 61-63°C) was prepared from 3-isobutoxy-2-methyl-2-cyclopentenone[6] by addition of lithium acetylide and subsequent workup using 1 N acid.[7] When an ether solution of **1** was added dropwise to dialkylcoppermetal reagents formed in ether and held at -78°C, a rapid reaction occurred wherein all of **1** was consumed as monitored by TLC. Subsequent workup by quenching at -78°C using aqueous saturated NH_4Cl and isolation of the reaction products by chromatography indicated very good conversions to dienones **2** (Eq. 1 and TABLE). "Higher-order" organocuprates[8] formed from two equivalents of a Grignard reagent or (better still) an organolithium reagent and one equivalent of CuCN are clear reagents of choice for the transformation; "lower-order" Gilman-type reagents react more slowly and yields of **2** are quite variable. Additionally, products **2** are formed stereoselectively. In each case using an organocopper nucleophile, the less thermodynamically stable Z-geometry of the 3-alkenyl



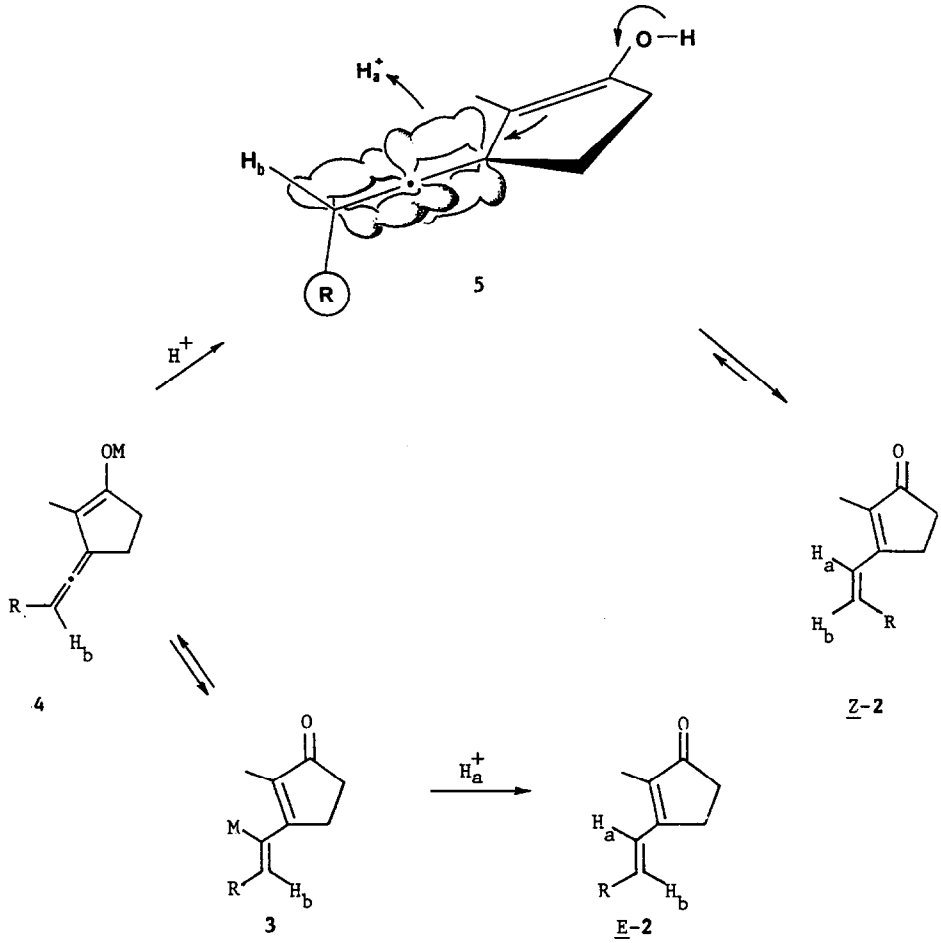
TABLE

Addition Reactions to Enynone 1

RM	Product 2,R=	Yield,%[a,d]	^{1}H-NMR,H_a	Ratio Z-2:E-2
$(CH_3)_2CuLi$	CH_3	44-82	Z: δ 6.34,d,J_{AB}=12.8Hz E: δ 6.65,d,J_{AB}=14.9Hz	2:1
$CH_3Cu(CN)Li$	CH_3	95[c]		2:1
$(CH_3)_2Cu(CN)Li_2$	CH_3	91,99[c]		2.5:1
$(C_2H_5)_2Cu(CN)(MgBr)_2$	C_2H_5	77,87[c]	Z: δ 6.36,d,J_{AB}=11.9Hz E: δ 6.72,d,J_{AB}=15.8Hz	3:1
$(i\text{-}C_3H_7)_2Cu(CN)(MgCl)_2$	$i\text{-}C_3H_7$	87	Z: δ 6.17,d,J_{AB}=12.0Hz E: δ 6.53,d,J_{AB}=15.8Hz	4:1
$(t\text{-}C_4H_9)_2Cu(CN)Li_2$	$t\text{-}C_4H_9$	93	Z: δ 5.77,d,J_{AB}=13.2Hz E: δ 6.50,d,J_{AB}=16.1Hz	34:1
$(C_6H_5)_2Cu(CN)(MgBr)_2$	C_6H_5	57	Z: δ 6.86,d,J_{AB}=12.2Hz E: δ 7.30,d,J_{AB}=15.8Hz	6:1
$(C_6H_5)_2Cu(CN)Li_2$	C_6H_5	88		6:1
C_6H_5SLi	C_6H_5S	52	Z: δ 6.78,d,J_{AB}=10.5Hz E: δ 7.02,d,J_{AB}=15.6Hz	1:17

a. Isolated yield using preparative thin layer chromatography. b. Determined by ^{1}H-NMR and GC or HPLC. c. GC or HPLC yield using an internal standard. d. All products 2 gave satisfactory C,H elemental analyses.

substituent in the product predominates. Moreover, this stereoselectivity is a function of the steric bulk of the R group added: the ratio Z-2:E-2 increases from 2.5:1 to 34:1 when R is varied from methyl to t-butyl. Such Z-stereoselectivity in the formation of 2 can be rationalized by examining the consequences of a predominant 1,6-addition mode for substrate 1: addition of R initially gives rise to vinylmetallic species 3, which isomerizes to a resonance-stabilized allenyl enolate, 4, that upon workup forms a transient allenyl enol 5. As suggested in equilibrations of β-allenyl esters[9] and analogous addition reactions to α,β-acetylenic carbonyl substrates,[10] enol 5 isomerizes to its thermodynamically more stable, fully conjugated isomer 2 by preferential protonation from the less hindered face of the sp-hydridzed carbon of the allene moiety, resulting in the predominant Z-geometry of the 3-alkenyl substituent of 2.



In contrast to this 1,6-addition mode and its stereochemical consequences, addition of a heteroatom nucleophile that favors formation of localized vinyl anion[11] **3** and stabilizes it so that isomerization to enolate **4** is inhibited should result in a complementary, distinct mode of syn 1,2-addition across the ethynyl group of **1**[12] and in a preferential formation of E-**2**. Indeed, addition of phenylthiolithium to **1** favors the formation of E-**2** (R=SC_6H_5, Z:E = 1:17), suggesting that this complimentary 1,2-addition pathway through a β-thio-stabilized vinyllithium intermediate, rather than the 1,6-addition pathway via a resonance-stabilized enolate intermediate, is operative.

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