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TANDEM GEMINAL DIALKYLATION: NUCLEOPHILIC DOUBLE ADDITION OF ORGANOCOPPER REAGENTS TO 3-ETHYNYL-2-CYCLOALKENONES

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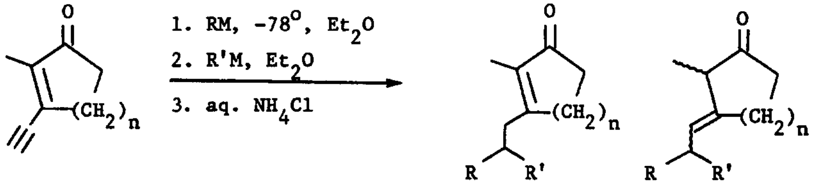
Abstract. Enynones 1 undergo regiospecific double addition of organocopper reagents at their terminal sp-hybridized carbons to yield enones 2 or 3.

One-flask, multiple bond-forming reactions are powerful synthetic tools widely used in the convergent total synthesis of complex molecules. Most common among these reactions are vicinal dialkylation reactions, which form two new carbon-carbon bonds on adjacent atoms of a substrate molecule. Examples include the Diels-Alder reaction and sequential processes such as radical cyclization-trapping and conjugate addition-trapping. Geminal dialkylation reactions, which form two new carbon-carbon bonds on the same carbon of a substrate molecule, are less common. Typical successful nucleophilic geminal dialkylation strategies exploit an sp^2-to-sp^3 conversion via sequential nucleophilic addition-nucleophilic substitution,[1] the prototype of which can be considered to be the double addition of Grignard reagents to esters, resulting in tertiary alcohols. Other examples include the gem-dimethylation of ketones[2] and the β,β-dialkylation of β-halo-α,β-unsaturated esters.[3] Less commonly, double nucleophilic substitution[4] has been used to effect gem-dialkylation.[5] Geminal double nucleophilic addition reactions to alkynes are extremely rare: those examples that have been reported proceed by means of double syn-carbometallation and almost invariably require that one of the two organometallic nucleophiles used be an allylic organozinc reagent.[6-8] We report here a new, general tandem geminal dialkylation (TGD) reaction exploiting an sp-to-sp^3 conversion via sequential 1,6 addition-5,6 addition of organocopper reagents to enynones 1.

When 3-ethynyl-2-cycloalkenones 1 are reacted with higher-order[9] organocopper reagents, a net 1,6 addition reaction ensues[10] to produce an allenyl enolate[11] (5, Scheme). Realizing that 5 contains two orthogonal π systems and assuming that a significant portion of the negative charge delocalized over the dienolate moiety of 5 resides at the enolate oxygen, we wondered if the terminal sp^2-hybridized carbon of the allene group might retain sufficient electrophilicity to react with a second equivalent of an organocopper reagent.[12] Such an addition would produce a dianion (6), the charges of which would be in a favorable, orthogonal orientation; protic quenching would result in geminally dialkylated



1 2 3

(1)

TABLE

Tandem Geminal Additions to Enynones 1

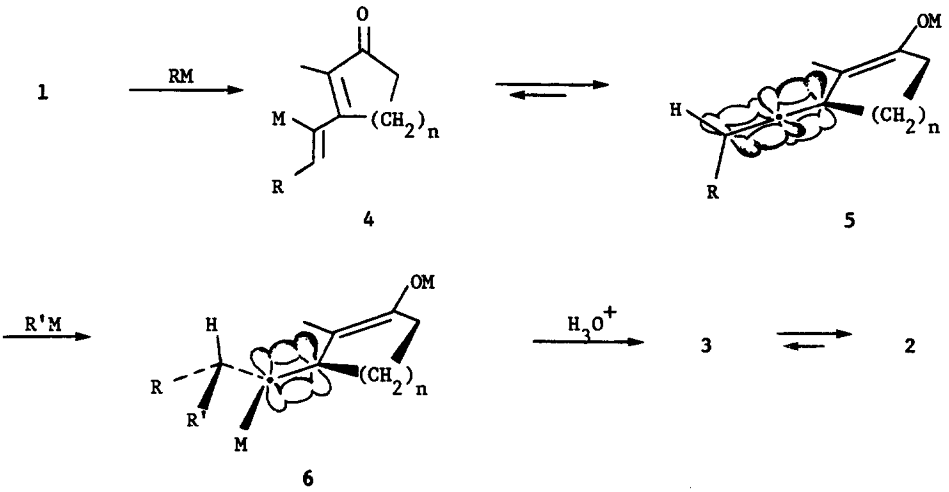
RM	R'M	Products R=	R'=	n=	Yield,%[a,b] 2	3
$Me_2Cu(CN)Li_2$	$Me_2Cu(CN)Li_2$	Me	Me	1	50[c]	
$Me_2Cu(CN)Li_2$	$(PhMe_2Si)_2Cu(CN)Li_2$	Me	$PhMe_2Si$	1	60	
$PhCu(CN)MeLi_2$		Me	Ph	1	53	
$Ph_2Cu(CN)Li_2$	MeLi	Ph	Me	1	20[d]	
$Me_2Cu(CN)Li_2$	$(PhMe_2Si)_2Cu(CN)Li_2$	Me	$PhMe_2Si$	2		37

a. Isolated yield. b. Products identified by ^1H NMR, ^{13}C NMR, IR and MS. c. GC or HPLC yield. d. Not optimized.

ketones 2 or 3. When a solution of 3-ethynyl-2-methyl-2-cyclopentenone (1, n=1; Eq 1) was added dropwise to 3 equivalents of $Me_2Cu(CN)Li_2$ formed in ether and held at -78°C, 1,6 addition proceeded rapidly as monitored by TLC. No subsequent reaction was noted until the reaction temperature was warmed to approximately -30°C, when a new product appeared in the reaction mixture. Workup by recooling to -78°C and quenching with aqueous saturated NH_4Cl gave a crude product, the components of which were isolated by preparative TLC. In addition to the 1,6 adduct, an approximate 40% yield of *gem*-dimethylated 2 (R,R'=CH_3; n=1) was isolated. Unambiguous identification of the dialkylated adduct was made by GC/MS ($M^{\dagger}$ 152), IR (1690 cm^{-1}), combustion analysis, ^1H NMR and ^{13}C NMR.

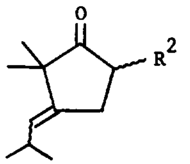
The reaction was explored; results are recorded in the Table. The double addition reaction appears general and different geminal substituents can be added to 1 either by utilizing sequential addition of two nonidentical organocopper nucleophiles or by use of a mixed homocuprate reagent[13] capable of transferring both[14] of its alkyl ligands to the electrophilic substrate. Although the sequence must be initiated using an organocopper reagent, the identity of the second organometallic nucleophile appears to be more flexible. Addition of $Ph_2Cu(CN)Li_2$ to 1 (n=1) at -78°C, followed by warming to 0°C and susequent addition of MeLi, gives dialkylated product 2 (R=Ph, R'=Me; n=1) in relatively low yield after workup (presumably via the intermediacy of the mixed homocuprate $PhCu(CN)MeLi_2$, formed

SCHEME



in situ during the course of the reaction). Double addition is not restricted to carbon nucleophiles, as illustrated by use of the nucleophilic organosilicon reagent $(PhMe_2Si)_2Cu(CN)Li_2$.[12a,15] The reaction also is regiospecific: no dialkylated products other than those from formal 1,6 + 5,6 double addition to the terminal carbon of the alkynyl moiety of 1 are detected. Typically, the thermodynamically more stable α,β-unsaturated cycloalkenones are isolated; however, when 3-ethynyl-2-methyl-2-cyclohexenone (1, n=2) is used as substrate, β,γ-unsaturated exocyclic enones (3, n=2), initially formed upon protic quenching of the dianion under kinetic conditions, are isolated instead of their equilibrated, conjugated isomers (2, n=2). An initial trapping experiment (Eq 2) with MeI indicates a similar course of reaction for cyclopentenone products.

$$1\ (n=1) + 1.5\ CH_3CuCNLi \xrightarrow[\text{2. 5 eq MeI, }-78^\circ\text{ to rt}]{\text{1. Et}_2\text{O, }-78^\circ\text{ to }0^\circ} \qquad (2)$$



12%, R^2=H
16%, R^2=Me

Finally, although yields of the dialkylated adducts are modest, the chemical yields per carbon-nucleophile bond formed are reasonable (60-80%) and the reaction particularly noteworthy given the ease of this one-flask, three-component, tandem geminal dialkylation.

We are actively investigating the use of this new method in cycloannulation strategies[16] and quaternary carbon synthesis.[17]

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