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Carbocyclisation of ω-Ethylenic Propargylic Zinc Reagents

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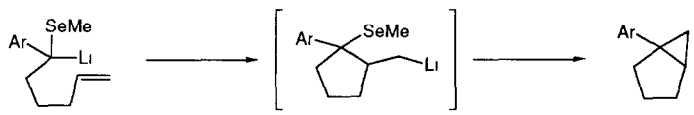
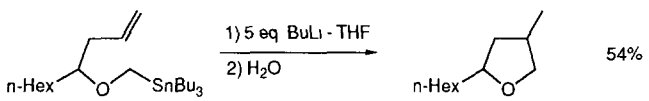
Abstract. *ω-ethylenic propargylic zinc reagents undergo cyclisation Particularly efficient are the reagents derived from propargylic ethers*

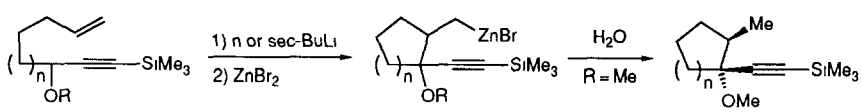
The intramolecular carbon-carbon bond formation to produce five membered rings via anionic cyclisation of ω-alkenyl main metals is well documented[1], and has been particularly demonstrated by Bailey[2] in the case of primary lithium derivatives. Vinyl lithium reagents cyclise also[3] to give exomethylenecyclopentanes. In the case of allylic reagents, ω-ethylenic allylic Grignards are generally preferred, and the reaction mechanism is considered to be a metallo-ene reaction[4,5] although "direct" addition may occur[6]. In most instances the substrate is a metallated hydrocarbon, however a few heteroatom-substituted metallated alkenes have been successfully tackled[6,7]. Particularly relevant are the work of Krief *et al*, who could cyclise ω-ethylenic benzyllithiums bearing a methyl or methylselenyl[8] (but not a methylsulfinyl[9]) moiety in benzylic position :



and that of Broka *et al*[10] who obtained tetrahydrofuranyl methyllithiums via :



During a study of the propargyl-allenyl metallatropy of zinc reagents we observed that some ω-ethylenic metallated propargylic ethers undergo an easy cyclisation .



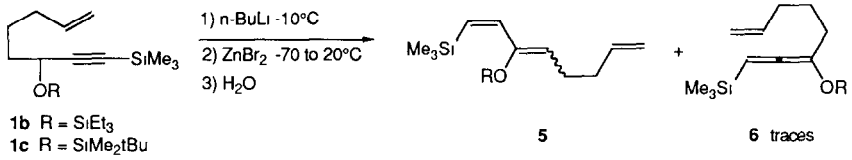
1a R = Me
1d R = $SiMe_2Thex$

2

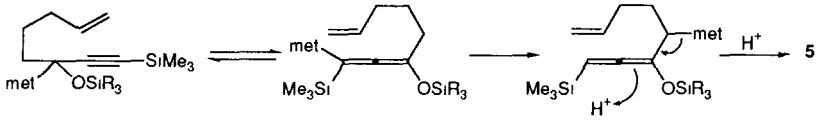
n = 1 yield 80% **3a**
n = 2 yield 0%

Worthy of note is the fact that, even at room temperature, the lithium derivative of **1a** (n = 1) proved totally unable to cyclise (and, by standing 2h at 20°C, led to heavy side products), whereas its zinc equivalent cyclised smoothly. The stereochemistry of the single isomer thus obtained in 80% yield was difficult to surmise since, according to what is generally accepted for the cyclisation of the corresponding C_{sp3}-Li derivatives[2c], the suprafacial addition of C - met on C = C would bring into competition two groups of low steric requirements (MeO and C ≡ C - $SiMe_3$). For **1a** (n = 2) no cyclisation to a six membered ring occured.

In order to prepare the free alcohol corresponding to **3**, we devised the preparation of other ethers, known to cleave easily The benzyl ether **1** (n = 1, R = benzyl), was not satisfactory since its metallation led instantaneously to a Wittig rearrangement[11]. Various silyl ethers were then tested. For **1b** and **1c** (n = 1), lithiation followed by addition of zinc bromide, gave none of the cyclic product but instead a triene **5** as an almost pure isomer (contaminated with traces of its other three isomers, and a trace of allene **6**) :

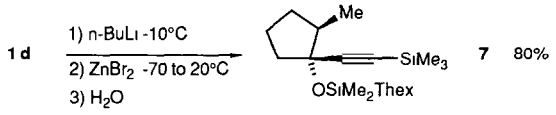


we suppose that a transmetallation occurs, according to :

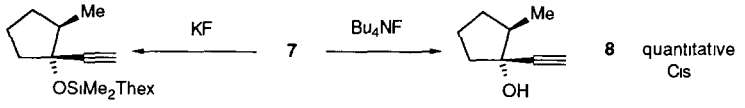


and that the protonolysis of the so-formed allenyl metal is highly stereoselective.

Fortunately the thexyldimethylsilyl reagent **1d** does not lead to such side reactions, and undergoes cyclisation to give also a single isomer **7**.



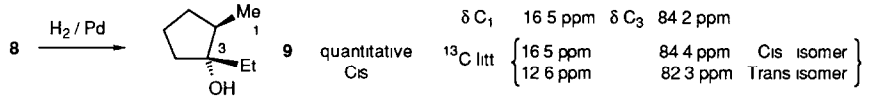
7 can be selectively, or totally desilylated, according to the fluoride used (respectively potassium or tetrabutylammonium fluoride).



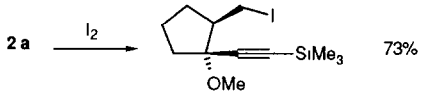
Protection by a MEM ether is also suitable and leads to **3** (n = 1, R = MEM) in 81% yield.

The stereochemistry of **8** has been assigned from previous work of Chodkiewicz *et al*[12] who prepared both isomers of **8** and established their structures The ^1H NMR singlet of C ≡ CH from **8** at δ = 2.45 ppm correlates

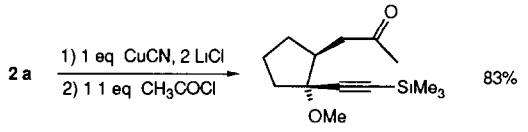
with that of the cis isomer of these authors (δ = 2.41 ppm) whereas the trans isomer gives a signal at 2.25 ppm. A second proof derives from the work of Cannone *et al*[13] who prepared both isomers of the saturated analog of **8** and described their ^{13}C NMR spectra. Compound **9** is indeed similar to their cis isomer.



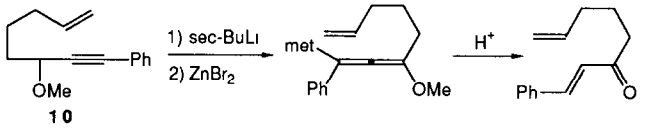
The presence of a metal in **2a** (n = 1, R = Me) is shown by iodinolysis :



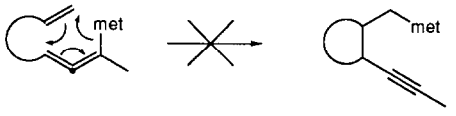
Whereby no traces of **3a** are found · this fact confirms the stability of **2a** towards adventitious protonation Transmetallation to copper enhances its reactivity towards various electrophiles[14], for example, acetyl chloride leads to the corresponding methyl ketone ·



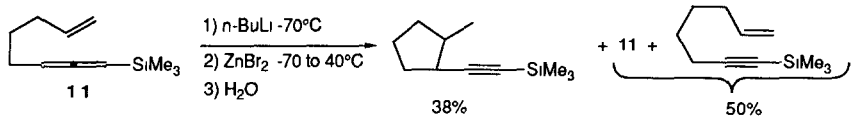
In order to delineate the scope of this cyclisation, we considered the case where the starting enyne **1** bears a phenylacetylenic moiety :



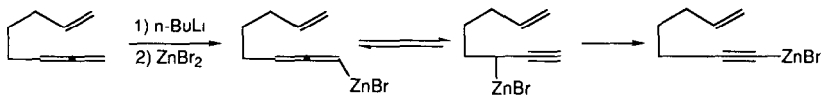
10 is easily metallated, but behaves as if its allenic zinc derivative were not in equilibrium with its propargylic counterpart. This behaviour is an argument for considering that the cyclisation reaction is not relevant of a metallo-ene process ·



If substrate **1** is devoid of an alkoxy function, cyclisation still occurs, but to a much lower extent . 1-trimethylsilylocta-1,2,7-triene leads to only 38% of cyclised product (single isomer), admixed with 50% of the protonated non cyclised intermediate organometallics in the form of a 1/1 mixture of alkyne and allene :



Finallyl 1,2,7-octatriene itself does not give any cyclisation, since transmetallation of the intermediate terminal alkyne takes place before the cyclisation process occurs :



In summary, α-alkynylcyclopentylmethylzinc derivatives can be obtained from δ-ethylenic propargylic zinc reagents. The cyclisation is synthetically useful when the alkynyl moiety is silylated, and when a propargylic ether (OMe, $OSiMe_2Thex$, OMEM) is used. In this case, only one stereoisomer of the cyclised product is formed in good yield. The application for the construction of angularly hydroxylated bicyclic compounds is currently underway.

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