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Synthesis of new unsaturated enynes, catalysed by copper (I) complexes.

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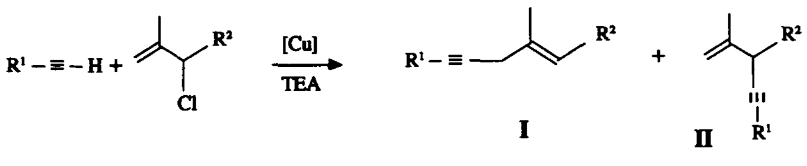
Summary : The copper (I) catalysed substitution of allylic chlorides by alk-1-ynes leads to the synthesis of new terpene derivatives. An efficient synthesis of phytone is described.

Enynes, allenynes and diynes can be prepared by a direct substitution of halides ; for example propargylic, allylic, olefinic and aromatic halides (or their homologs) can be substituted by terminal alkynes under the catalytic effect of a copper (I) complex. This method is described in detail in the literature for the synthesis of organic intermediates [1].

We wish to report the preparation of new unsaturated enynes catalysed by copper (I) complexes under basic conditions [2]. Some of these new unsaturated enynes can be used in the synthesis of phytone which is an important intermediate in the synthesis of vitamin E [3].
The key step in this reaction is the direct substitution of allylic halides by terminal alkynes in the presence of the catalytic system (CuI / TEA) with formation of a carbon-carbon bond with a high stereoselectivity. Important for the terpene synthesis are molecules of the general structure I.

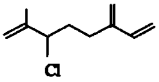
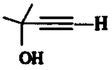
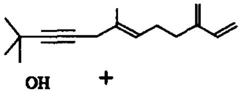
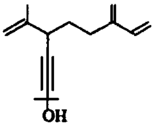
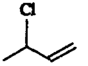
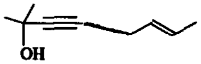
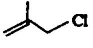
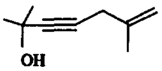
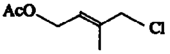
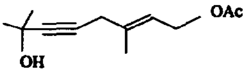
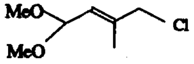
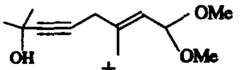
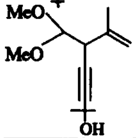
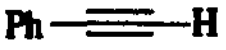
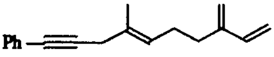
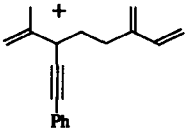
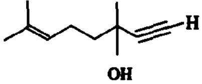
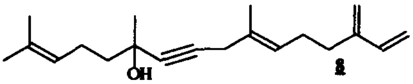
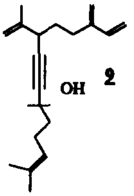


The results are summarized in the table below. Good yields and high stereoselectivities were obtained in many cases.

This general procedure has the following advantages :

- High tolerance for the functional groups present.
- Possibility to recover the catalytic system from the final organic mixture by several extractions with ether (6 times, 90% yield). The non-etheral solution can be used for a new catalytic process.

Table : Reaction of allylic chlorides with acetylenes (a)

entry	allylic compounds (b)	acetylenes	Products	Yield % (c)	Selectivity % (d)
a	 1	 (excess : 4.6 eq.)	 2 +  3	83	2/2+3 = 91
b		″ (excess : 2.5 eq.)		85	100
c		″ (excess : 2.5 eq.)		~ 100	
d		″ (excess : 3.0 eq.)		98	
e		″ (excess : 6.5 eq.)	 4 +  5	60	4/4+5 = 95
f	1	 (excess : 3.0 eq.)	 6 +  7	72	6/6+7 = 87
g	1	 (excess : 2.0 eq.)	 8 +  9	31	8/8+9 = 85

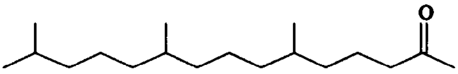
(a) All reactions were carried out using CuI catalyst (5% mol.) in dry TEA at 50-60°C under argon. An excess of the acetylene compounds was applied.

(b) The allylic chloride 1 was prepared by direct chlorination of myrcene [4].

(c) Isolated yield. Satisfactory analytical and spectroscopical data were obtained for all new derivatives.

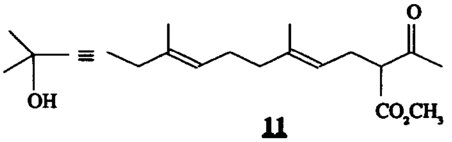
(d) Selectivity deduced from GC analysis.

It seems that the steric effect of the terpene chain results in a high selectivity for a terminal attack. This result was used for the synthesis of phytone **10**.

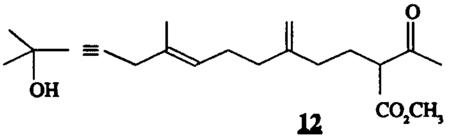


10

When a mixture of **2** and **3** was reacted with methyl acetoacetate in the presence of a water soluble rhodium complex in a biphasic system, [(RhCl (COD)$_2$ / tris (rodium-3-sulfophenyl) phosphine, TPPTS) ; H_2O ; CH_3OH ; Na_2CO_3], a very high selectivity was obtained. Products **11** and **12** were isolated in a 90% yield.



11

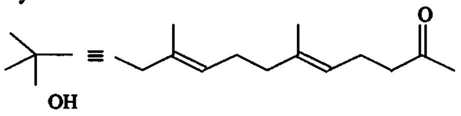


12

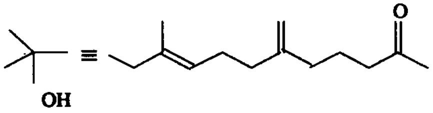
11 / **12** = 55 / 45, GC analysis

The water-soluble system (Rh(I) / TPPTS) selectively catalyses numerous condensations ; for example the condensation of isoprene with barbituric acid to yield isofeprazone [5] ; the condensation of amines [6], phenols [7] and active methylenes [8] with dienes to give terpenoid intermediates.

The alcaline hydrolysis of **11** and **12** (NaOH / H_2O / 16h, 25°C) gave the ketones **13** and **14** quantitatively.



13



14

The mixture of **13** and **14** was dehydrated (toluene/H_2SO_4/30mn - reflux / $NaHCO_3$/16h - room temperature) and the resulting solution hydrogenated (Pd/C : 10% / toluene / hydrogen pressure 3 bar, 8h, 50°C) to give phytone **10** (96.5% yield, purity 98%-GC).

General procedure : (entry a)

A solution of 2g (10.5 mmol) CuI, 200 ml TEA, 73.77g (0.877 mol) 2-methyl-3-butyn-2-ol and 32.05g (0.188 mol) **1** was stirred at 50°C for 28h. After cooling, the resulting mixture was filtered off and the salt washed with TEA. The solvent was evaporated under reduced pressure. Distillative purification under reduced pressure resulted in compounds **2** and **3** (34g, 83% yield).bp / 0.2 = 90-92°C.

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