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A NEW EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF 1,3E,5Z-UNDECATRIENE

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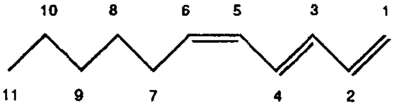
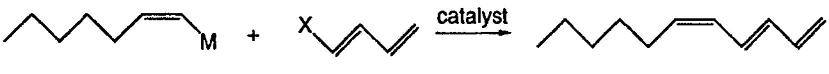
Abstract *: 1,3E,5Z-Undecatriene is synthesized by coupling of Z-heptenyl copper reagent, obtained through carbocupration of acetylene, with 1-chloro-1E,3-butadiene, in the presence of 5% $NiCl_2(PPh_3)_2$*

1,3E,5Z-Undecatriene **1** is the main odoriferant component of the essential oils of Galbanum[1] and is highly appreciated in perfumery. The E,Z structure of the triene system is very important for the olfactive properties and all other isomers are undesirable. Many syntheses of this compound have been described[2], most of which do not afford, in large amounts, material of high isomeric purity. Moreover, industrial application of these syntheses is not feasable since hazardous reagents are used or very low (or very high) temperatures are often required.



1

An attractive synthetic approach was the coupling of the Z C5-C11 fragment, with the C1-C4 E dienic fragment[3]. Such an approach was unsuccessfully attempted many years ago (for the Z,Z isomer) by Näf et al[4] with a Z dialkenyl cuprate[5] (for the C5-C11 fragment) and Z 1-bromo-1,3-butadiene. Our work on the carbocupration of acetylene[6] associated with the palladium catalyzed coupling with alkenyl halides[7] allowed us to synthesize in large quantities and excellent yields, many dienic insect sex pheromones with a very high isomeric purity[8]. This background helped us to design an efficient and economical synthesis of the desired 1,3E,5Z-undecatriene **1** according to the following scheme :



2 **3** **1**

First, the potential industrial application of this study precluded the use of palladium catalyst, being too expensive. Thus nickel derivatives were chosen. Then, for the begining of this study, the organometallic reagent **2** was the Grignard reagent (M = MgBr)[9] prepared in THF from Mg and 1-bromo-1Z-heptene[10], itself obtained from 2E-octen-1-oic acid[11] through a brominative decarboxylation which is known to occur with inversion of the stereochemistry of the double bond[10].

The choice of the butadienyl synthon **3** was also of crucial importance. The nickel catalyzed substitution of enol ethers (X = OR)[12] and thioethers (X = SR)[13] by Grignard reagents was described by Wenkert. In the case of enol ethers, alkenyl Grignard reagents were said to be inoperative due to their low reactivity[14]. Our hope was that the additional double bond in a dienic electrophile would compensate this behaviour, by an increase of the reactivity of the electrophilic partner. Unfortunately, in our hand 1-methoxy-1E,3-butadiene (X = OMe) **4** as well as 1-acetoxy-1E,3-butadiene (X = OAc) **5** were ineffective. In contrast, 1-ethythio-1E,3-butadiene (X = SEt) **6**[15] gave the desired product in moderate yield (54%)[16]. 1-Phenylthio-1E,3-butadiene (X = SPh) **7**[17] was less efficient (yield : 10%) probably because both carbons on sulfur are of the same nature : sp^2 [13b]. Attempts were also made with the organozinc reagent, without success. On the other hand, the two triphenyl phosphine ligands on the nickel catalyst were also replaced by one diphenylphosphino ethane (dppe)[18] with no improvement. Clearly, the leaving group X of **3** had to be improved.

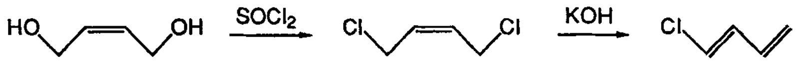
4

5

6

7

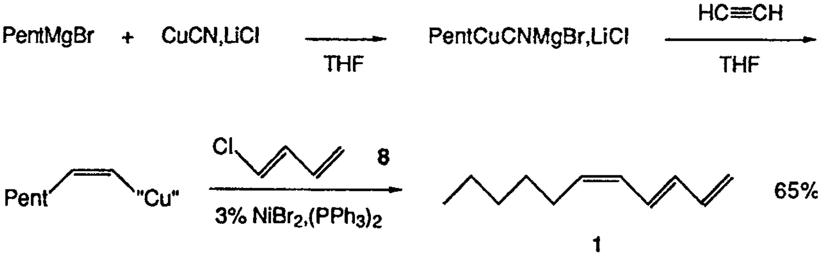
Alkenyl chlorides are known to be more reactive substrates in such reactions[19]. Our efforts were thus turned to the synthesis of 1-chloro-1E,3-butadiene **8** which was efficiently prepared from 2Z-butene-1,4-diol **9** by slight modification of a literature procedure[20]. These modifications match the recently reported procedure by L. Brandsma for 1-bromo-1E,3-butadiene[21]. Thus, **9** was transformed in 72% yield into the dichloride **10** ($SOCl_2$), which in turn was subjected to an 1-4 elimination (KOH, 180°C, hydrocarbon solvent) to give the required compound **8** in 75% yield and 95% E purity. The E purity of chlorobutadiene was not as high as we hoped, but this drawback was expected to be circumvented by the much lower reactivity of Z-alkenyl halides in such coupling reactions[22].



9 **10** **8**

The coupling of **8** with the Grignard reagent **2** (M = MgBr) occured smoothly at room temperature within a few minutes, in THF. The catalyst was 3% $NiBr_2.(PPh_3)_2$, used as a 0.1 M solution in THF. In this way, the yield of 1,3,5-undecatriene was 48%. However, the isomeric purity of this material was mediocre being the exact reflexion of the isomeric purity of the Grignard reagent **2**. Indeed, it is very difficult to have 1-bromo-1Z-heptene in a high state of isomeric purity[9,23]. The thermodynamic equilibrium is E/Z ~ 30/70 and the isomerization of 1-bromo-1Z-heptene occurs spontaneously during the distillation or by exposure to sunlight. Even more discouraging is the well known fact that alkenyl Grignard reagent are partly isomerized during their formation[24].

On the other hand, the carbocupration of acetylene affords quantitatively an alkenyl copper reagent **2**, starting from inexpensive acetylene and readily available pentyl Grignard reagent. Moreover, the isomeric purity of alkenyl copper reagent **2** is higher than 99.9%. This carbocupration of acetylene is usually performed at low temperature (-50°C) and it was necessary to modify the experimental conditions in order to allow higher reaction temperature (-20 to 20°C) and more stabilization of the organometallic species, conditions compatible with industrial requirements. The use of the soluble complex CuCN,LiCl allows such a stabilization without decreasing the reactivity of the organocopper species. The coupling step was first attempted with 1-ethythio-1E,3-butadiene (X = SEt) **6** and $NiBr_2,(PPh_3)_2$ as catalyst (3%). However, the reaction was very sluggish and raising the reaction temperature resulted only in thermal decomposition of the alkenyl copper reagent **2**. Finally, we succeeded in our synthesis by replacing **6** by the more reactive 1-chloro-1E,3-butadiene **8**. The reaction, this time, nicely gave the expected 1,3E,5Z-undecatriene **1** in 65% isolated yield :



The isomeric purity of this material was 91% and its olfactive properties were fully compatible with the perfumers' requirements. Although the chemical yield of this procedure is not excellent, its shortness (one-pot) makes it the most efficient, up to date, on both academic and industrial grounds. The carbocupration reaction has the great advantage in bringing in one operation the Z-alkenyl moiety starting from inexpensive acetylene and a simple alkyl Grignard reagent.

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EXPERIMENTAL

Copper cyanide (5.5 g ; 61.5 mmol) and lithium chloride (2.7 g ; 63.5 mmol) are dissolved in THF (70 ml) at room temperature. At -25°C, a solution of PentMgBr (27.3 ml of a 2.2M sol. in THF) is slowly added, forming a greyish precipitate. Acetylene gas (2.5 l ; 60 mmol) is bubbled at a rate such as to maintain the temperature below -15°C. After stirring at -10°C for 1h, a homogeneous dark green solution is obtained. To this solution of Z 1-heptenyl copper (60 mmol) in THF (100 ml) are added successively, at -10°C, $NiBr_2.2PPh_3$ (18 ml of a 0.1 M sol. in THF ; 1.8 mmol), then 1-chloro-1E,3-butadiene **8** (4.5 g ; 50 mmol) dissolved in THF (50 ml). The mixture is allowed to warm up to room temperature for 1h, then hydrolyzed with aq. sat. NH_4Cl (70 ml). The salts are filtered off and the organic phase concentrated *in vacuo*. The residue is taken up with Et_2O (100 ml), the aqueous phase is extracted twice with Et_2O (50 ml) and the combined organic phases are dried over $MgSO_4$. The crude product is purified by distillation. B.p. 26°C (0.01 mm Hg) ; 4.9 g (yield 65%). The isomeric purity was estimated to 91% by G.C.(OV 101, capillary column, 25m).

^{1}H NMR ($CDCl_3$, ppm) : 6.51 (dd, 1H) J =11.5 Hz and 15 Hz ; 6.39 (ddd, 1H) J = 10 Hz, 14 1 Hz and 16.8 Hz ; 6.19 (dd, 1H) J = 11 Hz and 15 Hz ; 6.02 (dd, 1H) J = 11 Hz and 11.5 Hz ; 5.47 (dt, 1H) J = 7.3 Hz and 11 Hz ; 5.19 (dd, 1H) J = 2 Hz and 16.8 Hz ; 5.06 (dd, 1H) J = 2 Hz and 10 Hz ; 2.18 (dt, 2H) J = 6.8 Hz and 7.3 Hz, 1.30 (m, 6H), 0.88 (t, 3H). **^{13}C NMR** ($CDCl_3$, ppm) : 137.3, 133.5, 133.0, 128.7, 128.4, 116.7, 31.6, 29.4, 27.9, 22.6, 14.1. **I.R.** (CCl_4) : 3100, 3020, 1625, 1580, 1000, 940, 750, 720. **M.S.** : 150 (26%), 107 (2%), 93 (22%), 91 (30%), 80 (72%), 79 (100%), 77 (41%), 67 (14%), 53 (5%), 41(25%).

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