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STEREO- AND REGIOSPECIFIC SYNTHESIS OF UNBRANCHED ALKENES AND 1,4-ALKADIENES BY MEANS OF STABILISED ORGANOCUPRATES

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Total synthesis of polyunsaturated compounds, particularly fatty acids, with methylene-interrupted *cis* double bonds (1,4-diene structure) is frequently accomplished by synthesis of the corresponding polyacetylenic compounds, followed by partial catalytic hydrogenation[1]. Methylene-interrupted polyene compounds having *cis* and *trans* double bonds, however, cannot be constructed in this way and the availability of a method that enables synthesis directly from enoic fragments would be a useful complement.

One of the possible approaches to the synthesis of compounds with a 1,4-diene system is cross-coupling of an organometallic vinylic reagent with an allylic substrate:

$$R^1CH{=}CHCH_2X \;+\; MCH{=}CHR^2 \longrightarrow R^1CH{=}CHCH_2CH{=}CHR^2 \;+\; MX$$

In general, substitution of allylic substrates without (or with) complete allylic rearrangement is still a precarious process[2,3]. Several literature sources refer to propenyl halides, cyclo-allylic halides or branched allylic compounds[4] in which cases the problem of partial rearrangement either does not exist or is overshadowed by attendant factors. Concerning reactions with unbranched, noncyclic 2-alkenyl halides, $CH_3(CH_2)_nCH{=}CHCH_2Hal$ (n=0,1,2 etc), difficulties are reported on the points of allylic transposition, geometric isomerisation and cyclisation, as in the case of reaction of Grignard and lithium compounds with crotyl chloride[5-9]. Allylic substrates containing oxygen in the leaving group would be attractive to use[2]; cross-couplings of these substrates with organometallics incidentally give promising results[10-13], although isomerisation, rearrangement and formation of side-products in many cases is reported[10,14,15].

Organocopper chemistry was chosen out of the methods considered, because of the reported high nucleophilicity combined with low basicity of these organometallics[16]. The first experiments were done with lithiumbutyl cuprate and 1-chloro-2-butene; after some unsatisfactory experiments we decided to use dimethylsulfide as a complexant because of its ease of removal after reaction[17]:

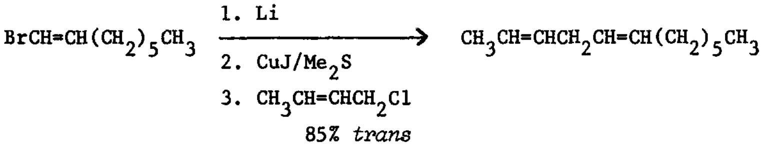
$$CH_3(CH_2)_3Li \xrightarrow[\substack{2.\ CH_3CH=CHCH_2Cl \\ 85\%\ \textit{trans}}]{1.\ CuJ/Me_2S} CH_3CH{=}CH(CH_2)_4CH_3$$

In THF as solvent at a reaction temperature of -40° or -70°, after cuprate formation at -40°, total conversion of butenyl chloride was observed, accompanied, however, by 25-30% formation of branched product, $CH_3CH(CH{=}CH_2)C_4H_9$, as a result of allylic rearrangement. Reaction in diethyl ether with excess cuprate at -76° shows almost negligible allylic rearrangement, as is shown in Table I; *cis-trans* ratios of 2-octene in these cases were identical with

Table I

R_2CuLi : RCl	Reaction temperature (°C)	Branched isomer in product (GLC analysis) (%)
5	-76	1-2
2½	-76	1-2
1½	-76	1-2
1	-76	20
3/4	-76	34
1½	-90	1-2

that of the substrate. Use of commercial copper(I) iodide (ex Riedel-de Häehn, dried over P_2O_5) or purified cuprous salt after reprecipitation[18] gave similar results. At cuprate/substrate ratios below 1½, the coupling reaction was no longer instantaneous but took several hours, while allylic rearrangement increased drastically; in all cases isolated yields of octene were above 90%. As a comparison, cross-coupling experiments between stoechiometric amounts of n-butyllithium and crotyl chloride were carried out in ether under the same conditions, but here, as with pentane as solvent[6], a minimum of 5% branched product was found. For the synthesis of a 1,4-diene system where the use of vinylic metallic compounds can cause difficulties, 1-bromo-1-octene, after lithiation and cuprate formation, was reacted with 1-chloro-2-butene. When the coupling was carried out analogously to the



$$BrCH{=}CH(CH_2)_5CH_3 \xrightarrow[\substack{2.\ CuJ/Me_2S \\ 3.\ CH_3CH{=}CHCH_2Cl \\ 85\%\ \textit{trans}}]{1.\ Li} CH_3CH{=}CHCH_2CH{=}CH(CH_2)_5CH_3$$

alkylcuprate experiments, viz. cuprate formation at -30° to -40° and coupling at -76° in ether with, for certainty, a cuprate/substrate ratio 3:1, slow and incomplete conversion was observed. Moreover, a notable amount of hexadecadiene was present in the mixture probably due to thermal cuprate decomposition. Lowering of the cuprate formation temperature to -76° resulted in a fast and complete reaction giving the cross-coupling product in the expected stereochemical composition (stereospecific conversion). The reaction mixture, however, contained, besides 1-2% branched compound, still appreciable amounts of hexadecadiene. Therefore, efficient synthesis of a diene system by this route requires removal of the dimer, as demonstrated in the synthesis of 2,5-undecadiene, in which hexadiene is evaporated after reaction.

$$BrCH=CHCH_3 \xrightarrow[\substack{2.\ CuJ/Me_2S \\ 3.\ CH_3(CH_2)_4CH=CHCH_2Cl}]{1.\ Li} CH_3(CH_2)_4CH=CHCH_2CH=CHCH_3$$

0.52 ml 1-Bromopropene (6.2 mmol; 75% *cis*, 25% *trans*) in 90 ml diethyl ether (freshly distilled from $LiAlH_4$; all operations under argon) was metalated with 85 mg lithium (12.3 mmol; ex Metallgesellschaft, "natriumreich", cut in small pieces) at -10° within 1½ h (monitored by GLC). After siphoning over glass wool, the turbid white solution was added to 0.59 g CuJ (3.1 mmol; ex Riedel-de Häehn, dried in vacuo over P_2O_5 after reprecipitation[18,19]), and 0.9 ml Me_2S (12.4 mmol) in 100 ml ether within ½ h; the temperature was kept between -70° and -76°, colour changed from dark red to orange. Subsequently 0.18 ml 1-chloro-2-octene (1.1 mmol, 98% *trans*) in 15 ml ether was added in 5 minutes, colour turning to dark red. After 5 minutes at -76° the mixture was hydrolysed by addition of saturated NH_4Cl solution, filtered over Celite, washed neutral, dried on Na_2SO_4, concentrated by evaporation, filtered ($CuJ.Me_2S$) after adding pentane, and again concentrated, leaving 0.16 g yellow liquid (yield 95% based on 1-chloro-1-octene), GLC purity (OV 101) about 96%. IR: 3010, 1650 and 700 cm^{-1} (*cis*, isolated); 965 cm^{-1} (*trans*, isolated); 1400 cm^{-1} ($-CH_2-$ between *cis* and *trans* and/or *cis* and *cis*). PMR (300 Mhz): about 75 mol % 2-*cis*-5-*trans* and 25 mol % 2-*trans*-5-*trans*.

Preliminary experiments with stereochemically almost pure vinylic reactants that contain an extra functionality in the 3-position, e.g. $HalCH=CHCH_2OR$ (Hal=Cl,Br; $R=C_2H_5$) showed that these compounds are more sensitive to decomposition, after metallation, than comparable branched compounds of the type $HalCH=CHCHR(OR^1)$[20]. We are currently investigating how cross-coupling reactions of the former reactants with allylic and vinylic compounds can be effected.

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