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ALKYLATION OF DIENE ALLYLIC TERTIARY AMINES WITH GRIGNARD REAGENTS. IN SITU ACTIVATION WITH ALKYL CHLOROFORMATES.

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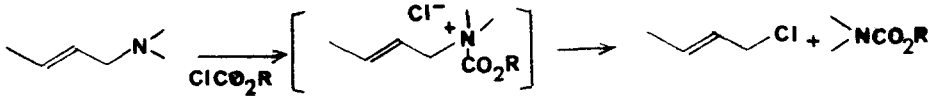
Summary : Diene allylic tertiary amines were substituted with Grignard reagents in the presence of lithium tetrachlorocuprate and alkyl chloroformates. According to the experimental condition employed, this reaction afforded exclusively γ-alkylation products.

Carbon-carbon bond formation by alkylation of allylic substrates with organometallic derivatives has been the subject of a considerable amount of work [1,2]. This type of reaction is of interest from both mechanistic and synthetic point of view.

Among the various allylic substrates which have been used in the past, there are very few examples of substitution reactions using allylic ammonium salts [3,4]. We have applied this methodology for the synthesis of Z,E, E,E and E,Z 1,3 [5,6] and 1,4 [7] dienic pheromones of Lepidoptera.

However, partial isomerisation of Z double bond (10-15%) has been observed during the coupling reaction of Z,E diene ammonium salts. This drawback could potentially be overcome by using a more reactive allylic derivative.

It is well known [8-10] that allylic or benzylic acyl ammonium salts, which are the reactive intermediates obtained by acylation of benzylic or allylic tertiary amines with alkyl chloroformates, are readily substituted with the counterion present in the reaction medium to afford the corresponding benzylic or allylic halides (Scheme I).



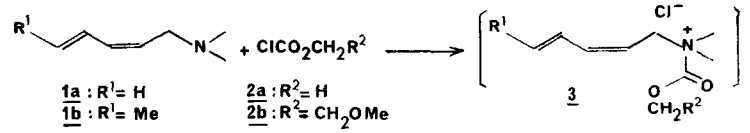
Scheme I

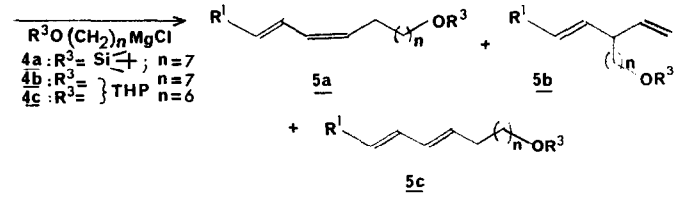
We wish to report now the use of these allylic acyl ammonium salt intermediates in the substitution reactions with Grignard reagents.

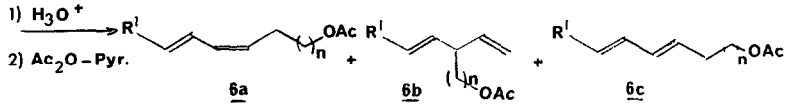
Acyl ammonium salt intermediates 3 were readily obtained by treatment of diene amines 1a or 1b with one equivalent of alkyl chloroformate 2a or 2b in THF or in ether at -30°C. The resulting salt 3 partially insoluble was treated without isolation with 1.1 equivalent of Grignard reagent 4 in the presence of a catalytic amount (5%) of lithium tetrachlorocuprate [11]. As anticipated the reaction was much faster than in the case of diene

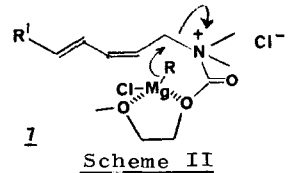
ammonium salts (24h, -30°C) and was generally complete within 1 hour at -30°C and afforded dienes 5a, 5b and/or 5c. These compounds led to the corresponding acetates 6 after deprotection and acetylation. (Scheme II).

A systematic study of the reaction revealed that the regio as well as the stereoselectivity is highly dependent on several factors : substitution pattern of the diene amine (entries 3 and 4) (Table), nature of the solvent (entries 4 and 5), temperature (entries 4, 6 and 7). On the other hand, the regioselectivity is partially affected by the nature of the Grignard reagent (entries 2 and 3 and 4 and 9). A clean γ-substitution can be performed either at -30°C in ether or at -75°C in THF (entries 5 and 6). It was noted that, at -30°C, 1-dimethylamino 2,4-hexadiene 1b did not afford 1-chloro 2,4 hexadiene and was recovered in more than 90% yield (entry 10). This observation implied that the diene allylic acyl ammonium salt 3 was the reactive intermediate [12] involved during the alkylation step.







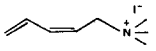
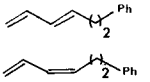
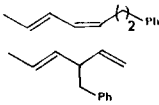


Scheme II

In order to change the regioselectivity of the reaction, 2-methoxy ethyl chloroformate 2b was used with the hope that this reagent could be able to chelate the Grignard reagent as depicted in 7 and to induce α-substitution via a cyclic transition state. This hypothesis was only partially verified (entry 11), in as much as the diene 6a (R=Me) resulting from the α-substitution was obtained in rather low yield.

The present method demonstrated that allylic tertiary amines can be directly substituted with a Grignard reagent after activation with alkyl chloroformate. γ-alkylation was generally the major pathway of this

substitution. Further scope of this reaction is under investigation in our laboratory.

Entry n°	Amine deriv. + Alkyl chlorof.	Grignard Reag. + 5% Li_2CuCl_4	Solv.	Temp.	Products Ratio		Yield %
1		4a	THF	-30°	6c	(R^1=H)	10
2	1a + 2a	4a	THF	-30°	6b+6c 43/57	(R^1=H)	73
3	1a + 2a	4b	THF	-30°	6b+6c 88/12	(R^1=H)	94
4	1a + 2a	4c	THF	-30°	6a+6b 41/59	(R^1=Me)	66
5	1b + 2a	4c	Ether	-30°	6b	(R^1=Me)	75
6	1b + 2a	4c	THF	-70°	6b	(R^1=Me)	82
7	1b + 2a	4c	THF	+20°	6a+6b 30/70		27
8	1a + 2a	$PhCH_2MgCl$	THF	-30°		28/72	47
9	1b + 2a	$PhCH_2MgCl$	THF	-30°		58/42	96
10	1b + 2a	none	THF	-30°	1b		90
11	1b + 2b	4c	Ether	-30°	6a	(R^1=Me)	22

Table

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