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A NEW PREPARATION OF β AND γ-ALKYL ALDEHYDES OR ACIDS BY USING ACTIVATING CYANO GROUP ; THE SYNTHESIS OF NORPHYTENE

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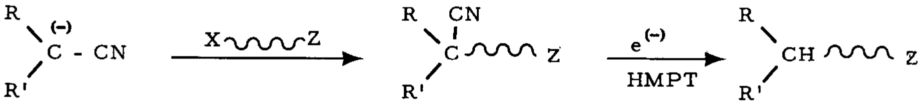
Various procedures have been developed to introduce alkyl substituents α to carbonyl group (1). But at the present time there is no method which allows to alkylate a molecule in any of its parts (β, γ ... ω).

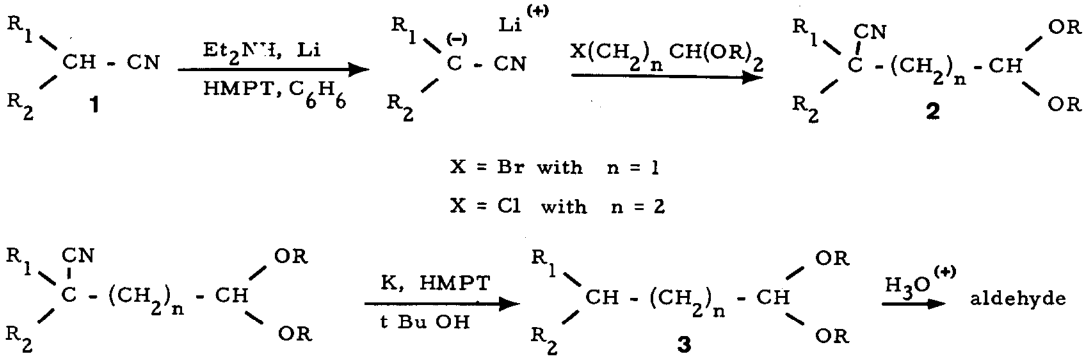
Such a reaction may involve the introduction of an activating electro-attractive group A on the desired carbon to favour the proton removal by a suitable base, the anion being then reacted with an electrophile. But this method is only interesting if the further breaking of the C-A bond is obtained with a good yield.

Last years, carbanions α to sulfone group have been frequently used (2). As far as we are concerned, we have employed another activating group : the cyano function.



This function is attractive in two ways : on one hand, alkylation reaction of aliphatic nitriles is now quite perfected (3), besides we have shown that it was possible to break a C - CN bond with excellent yields by reduction in HMPT (4).

There are not many methods to prepare β and γ-alkyl aldehydes (5) and we describe in this paper a synthesis of these compounds by the previously illustrated way. In this case, the function Z is an acetal.



The acetal nitrile **2** is obtained by reaction of "activated dialkylamides" on the nitrile **1** followed by condensation of bromo-acetaldehyde acetal or β-chloro propionaldehyde acetal (6). When n = 1, dialkylamide is added on the mixture nitrile -halogen compound, at - 65° (7), while it is necessary if n = 2 to prepare carbanion before adding the acetal to prevent a dehydrohalogenation of the latter. The further elimination of the cyano group is carried out with a solution of sodium or potassium in HMPT in presence of tertiobutanol as protic cosolvent.

Results are summarized in table I.

Table I : Synthesis of β and γ -alkyl aldehydes

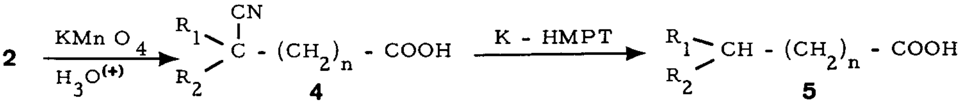
	1		R	n	**2** % *	**3** % *
	R_1	R_2				
1	$(CH_3)_2$ CH	H	C_2H_5	2	80	92
2	$(CH_3)_2$ CH-CH_2	H	- CH_2 -	1	78	96
3	CH_3	CH_3	C_2H_5	1	82	94
4	CH_2- $(CH_2)_3$ - CH_2		- CH_2 -	1	67	88
5	CH_2 - $(CH_2)_3$ - CH_2		C_2H_5	2	75	94
6	CH_2 - CH = CH - CH_2 - CH_2		C_2H_5	1	84	90
7	n C_4H_9	C_2H_5	C_2H_5	1	73	95
8	n C_4H_9	C_2H_5	C_2H_5	2	79	95

* yields of distilled products

acetals give aldehydes after hydrolysis with H_2SO_4 n(35°) (yields : 80-100 %)

It will be noted that intramolecular double bonds are not reduced during the reaction (experiment 6).

It is possible to prepare substituted acids from the corresponding aldehydes, but one can also obtain these compounds by oxidating nitriles **2** in acidic medium. They give cyano acids **4** which are cleaved in acids **5** (Table II).



$$\mathbf{2} \xrightarrow[H_3O^{(+)}]{KMnO_4} \underset{\mathbf{4}}{R_1R_2C(CN) - (CH_2)_n - COOH} \xrightarrow{K - HMPT} \underset{\mathbf{5}}{R_1R_2CH - (CH_2)_n - COOH}$$

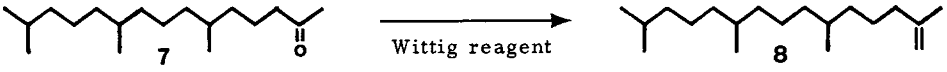
This method is better than direct alkylation of cyano acids **6** . Indeed, these really afford a mono carbanion α to the nitrile function (8) but, even in HMPT, these anions are difficult to alkylate.

$CN - (CH_2)_n - COOH$ **6**

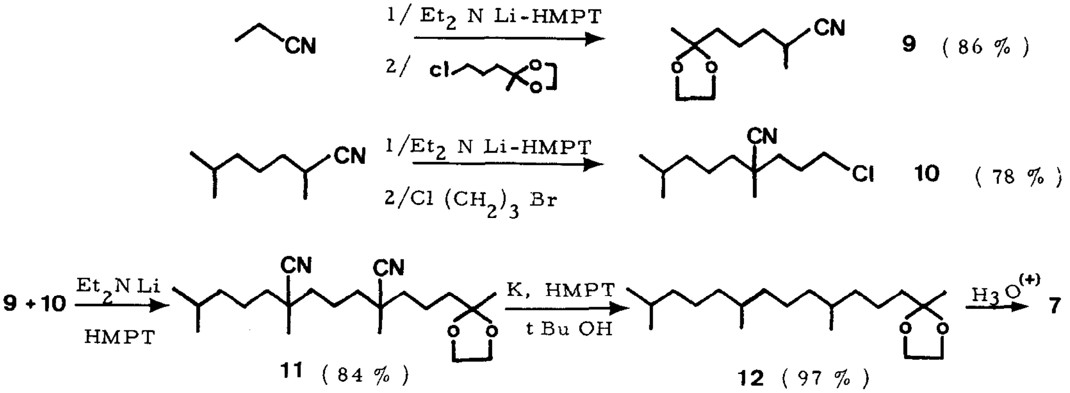
Table II : Synthesis of substituted acids

2		n	**4** %	**5** %
R_1	R_2			
$(CH_3)_2CH$	H	2	85	85
$CH_2 - (CH_2)_3 - CH_2$		2	88	87
nC_4H_9	C_2H_5	2	82	80

To illustrate our method, we have prepared norphytene **8** , a natural compound which was isolated from cigarette smoke (9) and from marine zooplankton (10). The synthesis requires the preparation of phytone **7** . Moreover this ketone also allows to obtain phytol and pristane (11). The anionic coupling between the nitriles **9** and **10** which are prepared by two distinct ways leads to the nitrile **11** . This one is then reduced by a solution of potassium in HMPT to give the dioxolanne **12** which affords the ketone **7** after acid hydrolysis. Lastly, conversion to the required isopropenyl group by Wittig reaction gives norphytene **8** .



This attractive and efficient route outlines the interest provided in organic synthesis by the use of cyano function as activating group.



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