INFLUENCE OF THE LEWIS ACID ON THE NUCLEOPHILIC ADDITION TO $\$ BB-DISUBSTITUTED α -ENONES.

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<u>Summary</u>: Lewis acids as BF_3 , Et_2O , $Ti(OiPr)_4$, $ZnCl_2$ allow the Michael addition of lithiated aminonitrile <u>1</u> to β_4 -disubstituted α -enones leading thus after carbonyl unmasking to the corresponding diketones.

In recent years the 1,4-addition of organometallic reagents to sterically crowded α -enones has been extensively studied. It appeared to us that in this field the acyl equivalents play an important role.

We have recently shown that the reaction of benzoyl equivalent <u>I</u> towards α -enones was very sensitive to their degree of substitution : without Lewis acids, no reaction took place with

 $\beta\beta$ -disubstituted $\alpha\text{-enones}$ while 1,4-addition was exclusively observed in the case of unsubstituted ones ^{1}a .

We now report the results concerning the reaction of <u>1</u> with 3-methyl cyclohexenone <u>2</u>, isophorone <u>3</u>, mesityl oxide <u>4</u> and $\Delta^{1(9)}$ 2-octalone <u>5</u> in the presence of various Lewis acids such as BF₃·Et₂O, Ti(OiPr)₄, ZnCl₂ and LiBr. All the reactions were performed in tetrahydrofuran and the Lewis acid was introduced after the α -enone addition to <u>1</u>, a different order of addition lowering the yiclds.



The most significant results are reported in the table I.

Table I

Effects of various reaction conditions on the reaction of <u>1</u> with <u>2</u> - <u>5</u>

Entry α -enone Lewis acid Temp. Time 1,2+1,4 yield %^{a)} 1,4/1,2 ratio^{b)} Diketone yield %^{c)}

1		BF3.Et20	-60°	5 mn	90-95	80/20	70
2		я	-30°	l hr	90-95	91/9	80
3	2	Ti(OiPr) ₄	-50°C	l h	90-95	82/18	70
4		ZnCl ₂	-50°C	30 mn	75	65/35	
5		LiBr	-30°C	30 mn	25	98/2	
6	3	BF3.Et20	-30°C	l h	65-70	90/10	55
7	_	(1 or 2 eq)	-30°C				
7		BF3.Et20	-30°C	l h	55-60	83/17	40
8	<u>4</u>	Ti(OiPr) ₄	-78°C	5 mn	45	33/67	15
9			-30°C	l h	65	65/35	40
10	<u>5</u>	BF ₃ .Et ₂ O	-78°C	30°C	d)	3 h	

a) Yields determined by ¹H NMR on the crude product. Next to adducts, starting materials were only observed.

b) 1,4/1,2 ratio determined by ^{l}H NMR on the crude products.

c) Yields in isolated diketones.

d) Only starting materials were recovered.

From table I it appears that 1,4-addition strongly predominates next to 1,2-addition in the case of the α -enones 2, 3 and 4 (entries 1-7, 9). In these cases the 1,2/1,4 ratios varied according to the Lewis acid nature, the α -enone structure ^{1b} and the experimental conditions (Θ , t). On the other hand, only starting materials were recovered with $\Delta^{1(9)}$ 2-octalone (entry IO). Carbonyl unmasking² of the 1,4-adducts leads to the pure known diketones <u>6</u>, <u>7</u> and <u>8</u> ³ after simple thick layer chromatography while the keto alcools arising from the 1,2-adducts were proved unstable on silicagel.



With Lewis acids both 1,2- and 1,4-additions were accelerated with enones 2-4: 1,2-addition took place under kinetic control while 1,4-addition was thermodynamically controlled (entries 1 and 2, 7 and 8).

The l,2-addition can easily be explained in terms of a carbonyl-Lewis acid complexation decreasing the repulsive interactions due to the carbonyl lone pairs ⁴. The strongly favoured l,4-addition can be interpreted either by stabilization of the enolate species ⁵ or/and by structural modification of the nucleophilic reagent and/or by lowering the l,4-activation energy.

The spectacular increase of 1,4-addition observed with $BF_3.Et_2O$ was in line with those reported recently in the organocuprate ⁶ and organocopper ⁷ field. Moreover, we have shown that in our case $BF_3.Et_2O$ is not the only Lewis acid that catalyzes the 1,4-addition ; in effect $Ti(OiPr)_4$ and $ZnCl_2$ work in the same way. The literature data related to zinc salts show opposite regioselectivity according to the reagent and α -enone structures and the experimental conditions as to say the kinetic or thermodynamic control of the reactions ^{8,9,1O}. Finally the quasi-ineffectiveness of LiBr was in accordance with previous results concerning other aminonitriles ¹¹.

In conclusion, the synthetic potentiality of the benzoyl equivalent <u>1</u> was strongly increased in the presence of Lewis acids as $BF_3 \cdot Et_2O$, $Ti(OiPr)_4$, $ZnCl_2$, allowing Michael addition in the case of sterically crowded α -enones <u>2-4</u> except <u>5</u>.

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