New Crossed Aldol Reaction. Reaction of Enamines with Aldehydes Activated by Lewis Acids

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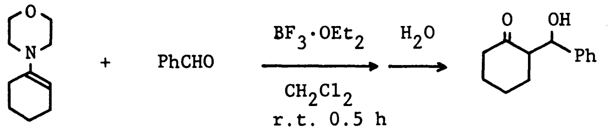
Synopsis. Enamines react with aldehydes in the presence of Lewis acids such as $BF_3 \cdot OEt_2$ to give the corresponding crossed aldol products in good yields. Reaction of dienamines with aldehydes gives the corresponding β,γ-unsaturated α-(1-hydroxyalkyl) carbonyl compounds.

The aldol reaction is one of the most versatile methods in organic synthesis.[1] In recent years, various useful direct aldol reactions have been reported, most of them being carried out under basic conditions;[2] Mukaiyama and coworkers[3] reported that enol silyl ethers, enol ethers, or enol esters react with carbonyl compounds in the presence of $TiCl_4$ under acidic conditions to give crossed aldol products.

Generally, it is known that the reaction of enamines with aldehydes gives α,β-unsaturated ketones, but that aldols cannot be obtained in this reaction except for some special substances such as chloral.[4] In contrast, we found that a use of Lewis acids allows enamines to react smoothly with aldehydes to give the corresponding aldols in good yields under acidic conditions, as with enol silyl ethers.

In our preceding papers,[5] we reported that enamines react with acetals or trialkyl orthoformates activated by Lewis acids to give the corresponding β-alkoxy or α-dialkoxymethyl carbonyl compounds, respectively. We considered that enamines also would react with aldehydes to afford the corresponding aldols. The reaction of 1-morpholino-1-cyclohexene (**1**) with benzaldehyde (**2**) was first tried. To a dichloromethane solution of a 1.2 molar amount of **2** was added a 1.3 molar amount of $BF_3 \cdot OEt_2$ at −40 °C. Then **1** was added and the reaction mixture was stirred for 0.5 h at room temperature. The aldol product, 2-(α-hydroxybenzyl)-1-cyclohexanone (**3**), was obtained in 92% yield.



1 **2** **3** 92%
(threo/erythro=78/22)

Scheme

The effect of the amount of $BF_3 \cdot OEt_2$ upon the yield of **3** was investigated by using the reaction between **1** and **2** under similar conditions as described above. It was found that the product **3** was obtained in the highest yield when a 1.3 molar amount of $BF_3 \cdot OEt_2$ was applied (Table 1).

Table 1. Effect of the amount of $BF_3 \cdot OEt_2$ on the yield

Molar ratio of $BF_3 \cdot OEt_2$	0.1	0.5	1.0	1.3	2.0
Yield[a)] of **3**/%	12	32	78	92	87
threo/erythro	100/0	82/18	73/27	78/22	68/32

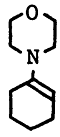
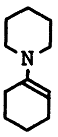
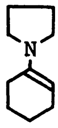
a) Isolated yield.

Table 2. Reaction of the enamine **1** with benzaldehyde **2** in the presence of various Lewis acids

Lewis acid	Reaction conditions Temp/°C	Time/h	Yield[a)] of **3** %	threo/erythro
$BF_3 \cdot OEt_2$	r.t.	0.5	92	78/22
$TiCl_4$	r.t.	0.5	83	70/30
$AlCl_3$	r.t.	1	75	92/8
$SnCl_4$	r.t.	0.5	68	75/25
$FeCl_3$	r.t.	5	35	94/6
$ZnCl_2$	r.t.	5	19	100/0
$MgCl_2$	r.t.	5	0	—
LiCl	r.t.	5	0	—

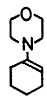
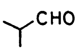
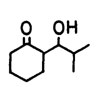
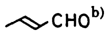
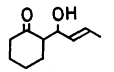
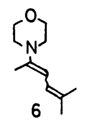
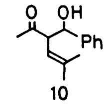
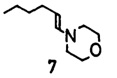
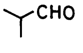
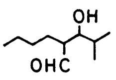
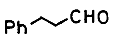
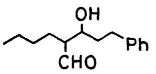
a) Isolated yield.

Table 3. Effect of the structure of the amine moiety in the enamines

Enamine	 **1**	 **4**	 **5**
Yield[a)] of **3**/%	92	17	0
threo/erythro	78/22	93/7	—

a) Isolated yield.

Table 4. Synthesis of aldols from enamines and aldehydes in the presence of $BF_3 \cdot OEt_2$

Enamine	Aldehyde	Product	Yield[a)] %	(threo/erythro)
 1		 8	85	
		 9	63	(78/22)
 6	PhCHO	 10	60	(33/67)
 7		 11	72	
		 12	70	

a) Isolated yield. b) $BF_3 \cdot OEt_2$ was added to a mixture of **1** and crotonaldehyde.

In order to investigate the effect of Lewis acids, reactions of **1** with **2** in the presence of various Lewis acids were then tried according to the procedure

TABLE 5. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF THE ALDOLS

Product	IR	NMR	Found (Calcd)/%	
	cm^{-1}	$\delta(CDCl_3)$ J/Hz	C	H
3, threo	3520	1.1—2.9 (9H, m), 3.95 (1H, s), 4.75 (1H, d, J=9.0),		
	1698	7.26 (5H, s).		
erythro	3550	1.1—2.7 (9H, m), 3.05 (1H, s), 5.37 (1H, d, J=2.5),		
	1698	7.26 (5H, s).		
8	3550	0.88 (3H, d, J=6.0), 1.00 (3H, d, J=6.0),		
	1700	1.2—2.7 (10H, m), 3.30 (1H, s), 3.50 (1H, m).		
9, threo	3450	1.2—2.6 (9H, m), 1.68 (3H, d, J=5.5), 3.55 (1H, s),	71.22	9.68
	1710	4.17 (1H, t, J=7.0), 5.17—6.0 (2H, m).	(71.39)	(9.59)
	965			
erythro	3470	1.2—2.7 (9H, m), 1.68 (3H, d, J=5.5), 3.05 (1H, s),	71.18	9.65
	1705	4.45 (1H, m), 5.25—6.0 (2H, m).	(71.39)	(9.59)
	970			
10, threo	3430	1.32 (3H, d, J=1.5), 1.58 (3H, d, J=1.5), 2.13 (3H, s),	76.91	8.28
	1710	3.28 (1H, broad s), 3.63 (1H, dd, J=10.0 and 8.6),	(77.03)	(8.31)
		4.85 (2H, m), 7.23 (5H, s).		
erythro	3470	1.42 (3H, d, J=1.5), 1.71 (3H, s), 1.98 (3H, s),	76.82	8.25
	1705	3.32 (1H, broad s), 3.58 (1H, dd, J=10.0 and 5.0),	(77.03)	(8.31)
		5.05 (1H, d, J=5.0), 5.27 (1H, d, J=10.0), 7.23 (5H, s).		
11	3430	0.7—2.1 (16H, m), 2.47 (1H, m), 3.07 (1H, broad s),	69.97	11.81
	1720	3.62 (1H, m), 9.73 (1H, m).	(69.72)	(11.70)
12	3320	0.90 (3H, t, J=5.5), 1.1—2.1 (8H, m), 2.33 (2H, m),	76.95	9.41
	1720	2.80 (2H, m), 3.92 (1H, m), 7.22 (5H, s), 9.75 (1H, m).	(76.88)	(9.46)

mentioned above (Table 2). The results described in Table 2 demonstrate that, of the Lewis acids examined, $BF_3\cdot OEt_2$ exhibits a remarkable effect as compared with the others in respect of the yield of **3**. It is noteworthy that the reaction gave predominantly the *threo*-isomer when $AlCl_3$, $FeCl_3$, or $ZnCl_2$ was used.

Furthermore, the effect of the structure of the amine moiety in the enamines was studied by treating enamines with **2** and $BF_3\cdot OEt_2$. It was found that **1** realizes an excellent yield (Table 3).

Since it was noted that the combination of morpholine enamine (**1**) and $BF_3\cdot OEt_2$ is significantly better than other possible combinations (Tables 2 and 3), reactions of morpholine enamines, such as **1**, 2-methyl-5-morpholino-2,4-hexadiene (**6**), or 1-morpholino-1-hexene (**7**), with various aldehydes were tried in the presence of $BF_3\cdot OEt_2$, and the corresponding aldols were obtained in good yields as shown in Table 4.

In the present reaction, the reverse reaction or the dehydration of aldol would be impossible because of the formation of a stable iminium salt as an intermediate. Furthermore, the acidic reaction medium makes the method useful for compounds that have base-sensitive functional groups. On the other hand, it is known that the reaction of dienoxysilanes with aldehydes in the presence of $TiCl_4$ gives α,β-unsaturated γ-(1-hydroxyalkyl) carbonyl compounds.[3g,6] In contrast to this reaction, the present reaction of a dienamine **6** with **2** in the presence of $BF_3\cdot OEt_2$ regioselectively afforded β,γ-unsaturated α-(1-hydroxyalkyl) carbonyl compound **10**.

Experimental

Reaction of 1-Morpholino-1-cyclohexene (1) with Benzaldehyde (2) in the Presence of $BF_3\cdot OEt_2$. To a dichloromethane (20 ml) solution of 1.27 g (12 mmol) of **2** was added 1.85 g (13 mmol) of $BF_3\cdot OEt_2$ at −40 °C under an argon atmosphere. Then 1.67 g (10 mmol) of **1** was added immediately and the reaction mixture was stirred for 0.5 h at room temperature. The mixture was quenched with water and stirred for 1 h at room temperature. After hydrolysis, the organic layer was separated, washed with a saturated solution of $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica-gel column chromatography. Elution with hexane–ether afforded 0.418 g (20%) of *erythro*-2-(α-hydroxybenzyl)-1-cyclohexanone (**3**) and 1.46 g (72%) of *threo*-**3**.

Reactions of a variety of enamines with various aldehydes in the presence of Lewis acids were carried out according to the same procedure, and the yields of the corresponding aldols are listed in Tables 1, 2, 3, and 4. The physical properties and analytical data of the products are shown in Table 5.

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