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An Easy Lewis Acid-Mediated Isomerization from (E)- to (Z)-Oxoindolin-3-Ylidene Ketones.

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Abstract - (*E*)-2-Oxoindolin-3-ylidene ketones can be easily isomerized to their (*Z*)-isomers by $AlCl_3$ at room temperature in CH_2Cl_2. The behaviour of the unsaturated dicarbonyl framework in the (*Z*)-configuration as a bidentate ligand can be the key-step of the isomerization. The limits of a reaction that allows to prepare several yet-unknown products is discussed.

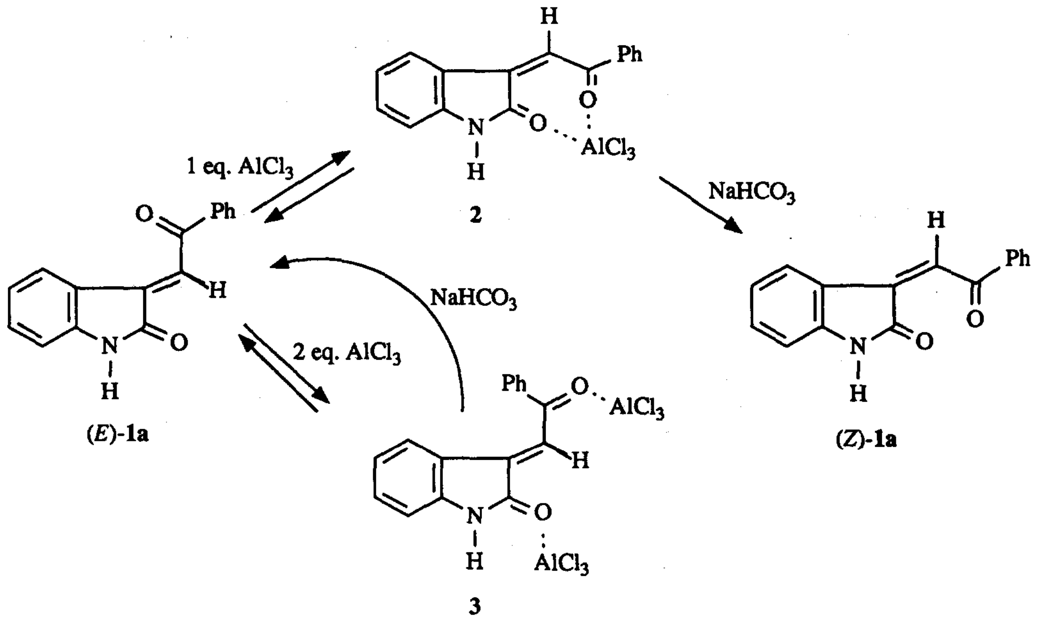
Whereas 2-oxoindolin-3-ylidene derivatives carrying in the β-position an alkyl[1] or an aryl group[2,3] are easily obtained in both (*Z*)- and (*E*)-configurations by thermal equilibration, those with aroyl[4,5] or alkanoyl[6] groups in the same position are known to exist exclusively in the (*E*)-configuration. Sometimes, erroneus attributions of the (*Z*)-configuration to some 2-oxoindolin-3-ylidene acetophenones on the basis of their reactivity with NH_2NH_2 were reported in the literature.[7,8] Only 1-benzyl-2-oxoindolin-3-ylidene acetaldehyde[6] was obtained as an admixture of the (*E*)- and (*Z*)-isomers and the authors assumed that only the small sized formyl group can be accomodated in the (*Z*)-configuration without severe "compression and angle strain".

A route to (*Z*)-isomers could involve the behaviour of both carbonylic oxygen atoms of 2-oxoindolin-3-ylidene ketones as donor ligands with an appropriate acceptor. The reaction of (*E*)-2-oxoindolin-3-ylidene acetophenone [(*E*)-**1a**] in the presence of differing amounts of $AlCl_3$ was therefore investigated.

RESULTS AND DISCUSSION.

When (*E*)-**1a** was treated with 1.1 equivalents of $AlCl_3$ at room temperature in CH_2Cl_2, a dark solid separated, that was filtered out and analyzed (Scheme 1). The i.r. spectrum had absorptions in the low frequency range of the carbonyl groups at 1650 cm^{-1} assigned to both C=O groups coordinated by the Lewis acid. If the spectrum is recorded after about 1 hour standing at air, the carbonyl absorptions at 1705 and 1658 cm^{-1} of (*Z*)-**1a** appeared. The elemental analysis of the crude product is reasonably in accordance with a 1:1 ratio of oxoindolin derivative and $AlCl_3$,[9] hence both carbonyl groups coordinated a single Lewis acid molecule to give **2**.

Scheme 1



When the dark solid was quenched in an aqueous solution of saturated $NaHCO_3$ and extracted with CH_2Cl_2, (*Z*)-**1a** was obtained as a single product in 86% yield. A further 5% of (*Z*)-**1a**, together with only a 5% of starting (*E*)-**1a** was obtained by the chromatographic separation of the filtered mother liquor.

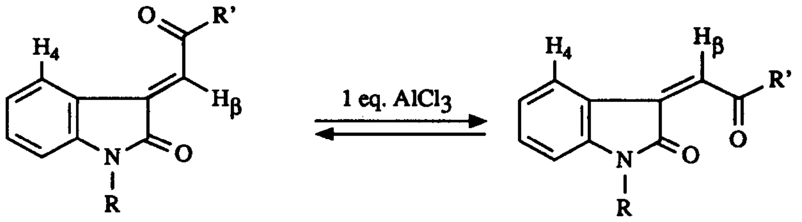
If the same reaction is performed in the presence of 2.2 eq. of $AlCl_3$, an orange solid separated that was filtered out and analyzed. The i.r. spectrum had carbonyl absorptions at low frequency (1660 and 1640 cm^{-1}) and since the elemental analysis was in accordance with a 1:2 ratio of oxoindolin derivative and $AlCl_3$,[9] the above data are consistent with the coordination of one $AlCl_3$ onto each single carbonyl group to give **3**. After exposition to air of this solid, its i.r. spectrum was superimposable to that of the starting (*E*)-**1a**.

When this solid was quenched in saturated $NaHCO_3$, only the starting (*E*)-**1a** was obtained (69% yield). From the mother liquor, a further 24% of (*E*)-**1a** was recovered after chromatographic separation, together with a 4% only of the isomerized product (*Z*)-**1a**.

The same behaviour was observed for compounds (*E*)-**1b,c** (Scheme 2) and the relative *Z*/*E* ratios are reported in Table 1.

The (*Z*)-configuration for the new compounds was assigned on the basis of ^1H-NMR spectroscopy: Table 1 shows that both the "diagnostic" protons H_4 and H_β (see Scheme 2) are always less deshielded in the (*Z*)-**1** isomers that in the (*E*)-**1** corresponding ones.

Scheme 2



(*E*)-**1**: R = H
-**4**: R = Me
-**5**: R = Ac

a: R' = Ph
b: R' = *p*.Br-C_6H_4
c: R' =*p*.MeO-C_6H_4
d: R' = *p*.NO_2-C_6H_4
e: R' = Me
f: R' = *ter*.But

(*Z*)-**1,4,5**

Table 1. Isomer ratio, H_β and H_4 chemical shifts of compounds **1a-c,e,f**, **4a-f**, and **5a-c**.

Compd.	Z : E	H_β		H_4	
		E	Z	E	Z
1a	96: 4	7.87	7.18	8.32	7.50
1b	92: 8	7.80	7.12	8.35	7.50
1c	96: 4	7.84	7.17	8.24	7.49
1e	32:68	7.16	6.82	8.50	7.40
1f	53:47	7.46	7.10	8.36	7.40
4a	72:28	7.90	7.19	8.32	7.52
4b	84:16	7.82	7.12	8.38	7.52
4c	90:10	7.85	7.17	8.23	7.50
4d	42:58	7.86	7.13	8.47	7.52
4e	42:58	7.17	6.79	8.49	7.41
4f	54:46	7.47	7.08	8.34	7.40
5a	29:71	7.88	7.32	8.32	7.62
5b	36:64	7.81	7.24	8.36	7.61
5c	33:67	7.85	7.31	8.22	7.61

The isomerization procedure (1.1 eq. of $AlCl_3$, CH_2Cl_2 room temperature) was further applied to N-methyl and N-acetyl substituted oxoindolin derivatives (*E*)-**4** and (*E*)-**5** (Scheme 2). Their 1:1 complexes did not separated for solubility reasons, hence the reaction mixtures were quenched in saturated $NaHCO_3$, extracted with CH_2Cl_2, and column chromatographed to give both isomers as crystalline stable compounds. The relative *Z/E* ratios are reported in Table 1.

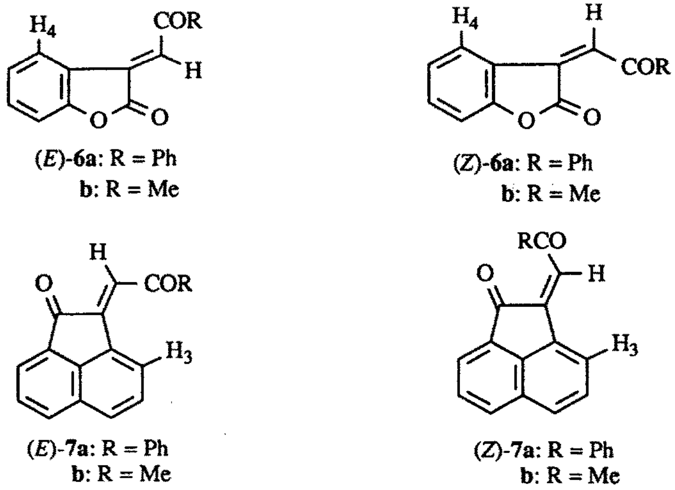
The *Z/E* ratios for **4,5** allow one to derive some considerations about factors affecting the isomerization. When R' has electron-releasing groups, the increased donor character of the ketonic carbonyl gives higher yields of the (*Z*)-isomer, while electron-attracting groups have the opposite effect. When R is acetyl, the low yields of isomerization are due to the competitive chelation of the Lewis acid by the amidic and lactamic carbonyls. A route to obtain good yields of (*Z*)-**5a-c** is the acylation at low temperature of (*Z*)-**1a-c**. *E.g.*: (*Z*)-**5c** was obtained from (*Z*)-**1c** in about 60% yield.

There are some limits in this method. Whereas aroylidene groups are widely compatible with the isomerization condition, alkanoylidene ones are sensitive to the Lewis acid and reasonable yields of (*Z*)-isomer can be obtained for R' = Me, *ter*.But and R = Me, H only. For R = Ac, an excess of $AlCl_3$ does not improve the yields, but only increases the formation of tarry materials.

The presence of protic acid (HCl from hydrolysis of $AlCl_3$ in non-anhydrous environment) reverses the equilibrium towards the (*E*)-isomer. This again strongly suggests that bicoordination to a Lewis acid is the crucial factor determing the isomerization.

This method can be applied to other similar structures such as 2-(3*H*)-benzofuranon-3-ylidene ketones (**6a,b**) and acenaphthenon-2-ylidene ketones (**7a,b**), with good results for R = Ph and poor yield for R = Me. The relevant ^1H-NMR signals of (*E*)- and (*Z*)-**6,7a,b** are reported in the experimental part, and these data allow identification of the unknown configuration of compounds **6,7**[10,11] (Scheme 3).

Scheme 3



(*E*)-**6a**: R = Ph
b: R = Me

(*Z*)-**6a**: R = Ph
b: R = Me

(*E*)-**7a**: R = Ph
b: R = Me

(*Z*)-**7a**: R = Ph
b: R = Me

In conclusion, (*E*)-2-oxoindolin-3-ylidene ketones can be easily isomerized to the corresponding (*Z*)-isomers by one equivalent of $AlCl_3$ coordinating both the carbonylic oxygen atoms. *Z*-complexes of **1a-c** separated out and these precipitates give pure *Z*-isomers only. When complexes are soluble, an equilibrium between *Z* and *E* ones is established, mainly depending on substituents, and the *Z*/*E* largely reflects this since pure (*Z*)-**4a**, submitted to the isomerization condition, gives the same isomer ratio obtained from pure (*E*)-**4a**.

EXPERIMENTAL

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were made on C. Erba CHN analyzer mod. 1106. ^{1}H-NMR spectra ($CDCl_3$, TMS as standard) were recorded on a Bruker AC 300 spectrometer, i.r. spectra (nujol mulls) on a Perkin Elmer 983 spectrophotometer.

Materials. The following starting products were prepared as reported in the literature: (*E*)-**1-4,5a,c,d**;[12] **-4b**;[13] **-1,5b**;[14] **-1e,f**;[15] **-6a,b**;[10] **-7a,b**.[11] (*E*)-**4e** was prepared in 65% yield from equimolar amounts of 1-methylisatin and 1-triphenylphosphoranylidene-2-propanone in ethyl acetate at r.t. (12 h): bright red crystals, m.p. 121-122 °C (EtOH); $\nu_{C=O}$: 1710 (lactam) and 1680 cm^{-1} (ketone). Elem. anal.: found C, 71.85; H, 5.78; N, 6.73. $C_{12}H_{11}NO_2$ requires C, 71.62; H, 5.51; N, 6.96%. (*E*)-**4f** was prepared in 40% yield, following the reported method,[15] by condensation of 1-methylisatin and pinacolone and dehydration of the intermediate aldol: orange crystals, m.p. 61-62° C (H_2O/EtOH:1/1); $\nu_{C=O}$: 1715 (lactam) and 1675 cm^{-1} (ketone). Elem. anal.: found C, 74.32; H, 7.18; N, 5.77. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%.

Isomerization: general method - To a solution of (*E*)-**1,4,5a-f** (1 mmol) in dry CH_2Cl_2 (10 ml) a slight excess of $AlCl_3$ (1.1 mmol) was added under stirring at room temperature. At the reported time (Table 2) the dark mixture was quenched with cold sat. $NaHCO_3$ solution and worked up. After evaporation of the solvent the residue was column chromatographed over flash silica gel, eluting with CH_2Cl_2 (cyclohexane/EtOAc : 8/2 for **4d**), the (*Z*)-isomers being recovered always after the (*E*) derivative as second fraction. (*E*)-**1d** failed to isomerize, owing to its high insolubility, and was recovered quantitatively after a week.

The reaction mixture of (*E*)-**5a-c** contained a 10-15% of the corresponding N-deacetylated compounds (*E*)-**1a-c** which could be recovered by column chromatography as third fraction. (*E*)-**5d-f** gave a complex mixture from which only small amounts of starting products and of the corresponding N-deacetylated compounds (*E*)-**1d-f** were recovered by column chromatography.

By the same method the following isomerizations were performed:

(*E*)-**6a** (δH_β; 7.93; δH_4: 8.48) to (*Z*)-**6a** (δH_β: 7.39; δH_4: 7.59)
(*E*)-**7a** (δH_β: 7.96; δH_3: 8.68) to (*Z*)-**7a** (δH_β: 7.25; δH_3: 7.89)
(*E*)-**7b** (δH_β: 7.24; δH_3: 8.85) to (*Z*)-**7b** (δH_β: 6.88; δH_3: 7.10).

In Table 2 are reported the chemico-physical characteristics of all new compounds.

Table 2. Chemico-physical characteristics of compounds (*Z*)-**1a-c,e,f**, -**4a-f**, -**5a-c**, -**6a**, and -**7a,b**.

Compd.	Reaction time (h)	Yield[a] *Z/E* (%)	M.p.°C (solvent)	I.R., cm^{-1} $\nu_{C=O}$	Formula		Elemental Analysis		
							%C	%H	%N
(*Z*)-**1a**	120	91/5	163-4	1705 - 1658	$C_{16}H_{11}NO_2$	calcd.	77.09	4.45	5.62
			(EtOH)			found	77.12	4.38	5.54
1b	120	90/8	192-3	1715 - 1635	$C_{16}H_{10}BrNO_2$	calcd.	58.55	3.07	4.26
			(EtOH)			found	58.38	3.18	4.35
1c	120	95/3	168-9	1702 - 1658	$C_{17}H_{13}NO_3$	calcd.	73.11	4.69	5.02
			(EtOH)			found	73.21	4.72	5.11
1e	12	23/50	150-2	1710 - 1700	$C_{11}H_9NO_2$	calcd.	70.58	4.85	7.48
			(EtOH)			found	70.31	5.01	7.50
1f	24	50/45	138-9	1710 - 1690	$C_{14}H_{15}NO_2$	calcd.	73.34	6.59	6.11
			(EtOH/H_2O)			found	73.50	6.52	6.09
(*Z*)-**4a**	24	65/25	156-8	1698 - 1650	$C_{17}H_{13}NO_2$	calcd.	77.55	4.98	5.32
			(EtOH)			found	77.51	5.03	5.30
4b	48	80/15	191-2	1698 - 1660	$C_{17}H_{12}BrNO_2$	calcd.	59.66	3.53	4.09
			(EtOH-Diox.)			found	59.61	3.30	4.20
4c	60	85/10	171-2	1703 - 1648	$C_{18}H_{15}NO_3$	calcd.	73.70	5.15	4.78
			(EtOH)			found	73.61	5.00	4.65
4d	72	40/55	[b]	1703 - 1675	$C_{17}H_{12}N_2O_4$	calcd.	66.23	3.92	9.09
			(Diox.)			found	66.45	3.71	9.15
4e	12	18/25	90-1	1710 - 1680	$C_{12}H_{11}NO_2$	calcd.	71.63	5.51	6.96
			(EtOH)			found	71.38	5.64	7.17
4f	48	52/45	114-6	1707 - 1688	$C_{15}H_{17}NO_2$	calcd.	74.05	7.04	5.76
			(EtOH)			found	73.80	7.15	5.92
(*Z*)-**5a**	2	10/15	173-5	1742 - 1710	$C_{18}H_{13}NO_3$	calcd.	74.22	4.50	4.81
			(EtOAc)	1665		found	74.13	4.57	4.72
5b	2	18/32	157-9	1742 - 1702	$C_{18}H_{12}BrNO_3$	calcd.	58.40	3.27	3.78
			(EtOAc)	1670		found	58.54	3.22	3.73
5c	2	15/30	150-1	1752 - 1705	$C_{19}H_{15}NO_4$	calcd.	71.02	4.71	4.36
			(EtOH)	1650		found	70.91	4.65	4.42
(*Z*)-**6a**	48	60/25	133-4	1785 - 1665	$C_{16}H_{10}O_3$	calcd.	76.69	4.03	
			(EtOAc)			found	76.58	4.07	
(*Z*)-**7a**	24	75/22	154-5	1710 - 1660	$C_{20}H_{12}O_2$	calcd.	84.49	4.25	
			(EtOAc)			found	84.69	4.29	
7b	6	35/30	124-5	1705 - 1673	$C_{15}H_{10}O_2$	calcd.	81.07	4.54	
			(Isp_2O)			found	80.85	4.50	

[a] isolated yield after chromatographic separation; [b] isomerization to (*E*)-**4d** occurred prior to fusion.

Isolation and analysis of complex 2 and 3. 2 mmol of (*E*)-**1a** were suspended in 20 ml of dry CH_2Cl_2 and, under stirring, 2.2 mmol of $AlCl_3$ were added. A fast solubilization was observed in few minutes and then the solution assumed a strong dark color and a solid separated out. After 5 days the mixture was cooled and filtered. The dark solid was washed with 10 ml of anhydrous CH_2Cl_2, dried 8 hours at 80 °C/0.1 mbar and analyzed by i.r. and elemental analyses (Table 3). It was then quenched in cool saturated $NaHCO_3$, extracted with CH_2Cl_2, and evaporated to give 0.430 g of (*Z*)-**1a** (86% yield).

2 mmol of (*E*)-**1a** were suspended in 20 ml of dry CH_2Cl_2 and added, under stirring, with 4.4 mmol of $AlCl_3$. In few minutes the suspension became a solution and after 1 hour an orange solid began to separate out. After a day, the mixture was cooled and filtered, the orange solid was washed with 10 ml of anhydrous CH_2Cl_2, dried as above reported for **2** and analyzed by i.r. and elemental analyses (Table 3). It was then treated as previously described, and 0.345 g of (*E*)-**1a** were obtained (69% yield). A further amount of this product (24%) was recovered by column chromatography of the mother liquor as described in the general procedure.

Table 3. I.r. data and elemental analyses[9] of the complexes **2** and **3**.

Complex	i.r., cm^{-1} ($\nu_{C=O}$)	Formula		Elem. Anal. %C	%H	%N	%Al
2	1650	$C_{16}H_{11}NO_2AlCl_3$	calcd.	50.23	2.90	3.66	7.05
			found	50.85	3.41	3.67	7.5
3	1660 - 1640	$C_{16}H_{11}NO_2Al_2Cl_6$	calcd.	37.25	2.15	2.71	10.46
			found	36.6	2.71	2.46	11.3

*Acylation of (Z)-***1c**. - (*Z*)-**1c** (0.280 g - 1 mmol) was dissolved in 20 ml of dry THF and cooled to -80 °C. 0.7 ml of a solution 1.6 M of BuLi in hexane were added; CH_3COCl (0.087 g - 1.1 mmol) were then added to the solution in few minutes. After 1 hour, the cooling was stopped and the reaction was quenched in 150 g of ice and then extracted with CH_2Cl_2 (3 x 30 ml). The organic phase was dried and evaporated to give an oil that was column chromatographed (CH_2Cl_2 as eluant). The first fraction corresponds to (*E*)-**5c** (0.05 g - 16%), while the second one is (*Z*)-**5c** (0.19 g - 60%).

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