Synthesis and Stereochemistry of 2-Benzylidene-4-carbethoxy-5-methyl-3-(2*H*)-furanones

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The title products were obtained by Knoevenagel condensation between 4-carbethoxy-5-methyl-3-(2*H*)furanone and substituted benzaldehydes (or 4-chloroacetophenone). The configuration of the resulting compounds was investigated by ^{1}H nmr using the lanthanide shift reagent.

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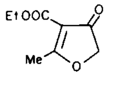
Furanones are a class of compounds interesting because of their conformational aspects. They are precursors of alkaloid and steroid synthesis. Carbethoxy 5-methyl-3(2*H*)-furanones were prepared by Becker (3) and Richter (4). Recently, syntheses of 4-carbethoxy-3-(2*H*)furanones were also described by Gelin (5,7). These compounds were obtained by acylation of an α-ketoester using halogenated acid chlorides. Cyclization was spontaneous with acid chlorides. Rosenkranz (8) showed by chemical and spectroscopic investigation that furanone (**1**) exists ony in its keto form. The possible enol form, stabilized by intramolecular hydrogen bonding was not present in the reaction products.



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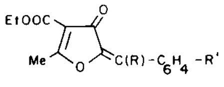


2a (R=H)
2b (R=Me)

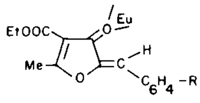
The condensation between furanone (**1**) and appropriate carbonyl compounds in acid solution gave benzylidenes (**2**). In the absence of any data in the literature, the configuration of the benzylidene furanones has been investigated.

Results and Discussion.

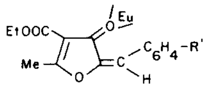
Elemental analysis, nmr spectra and melting point constitute physical characteristics of the fifteen furanones in Table I. The ir spectra agreed with these structures.

E and *Z* isomerism was possible with benzylidene furanones (**2**). As a rule, in α,β-unsaturated carbonyl compounds, the anisotropic, deshielding of the carbonyl group causes the olefinic proton *cis* to the carbonyl to give an absorption at a lower field (*ca.*, 1 ppm) than in the *trans* arrangement, so that assignment of configuration can be made on the basis of the chemical shift of the olefinic proton. However, the ASIS effect (aromatic solvant interaction shift) of the olefinic proton is not significant in our experiments.

The configuration of *E* and *Z* isomers has been resolved by ^{1}H nmr spectrometry using the Siever's reagent, an Aldrich shift product. The region of best fit is also the region of minimum steric interaction, and the Siever's reagent fixed preferentially to the ketone group. Willcott and Davis (9) have discussed complexity of lanthanide shift reagents at the carbonyl group and reached a similar conclusion about xanthones. Sequential addition of Siever's reagent to a deuteriochloroform solution of **2a** shifted the olefinic proton to a lower field, when **2a** was in the *Z* configuration (see Table II). The shift reagent bonded to the ketone group gave a Carbone-Oxygen-Europium colinear description for the furanone. The europium shift reagent was in proximity to the olefinic proton. It gave an absorption at a lower field with this arrangement. Experimental chemical shifts were subordinate to the shift reagent concentration (10).



2a Z

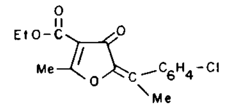


2a E

Compounds **2a** were found in the *Z* configuration exclusively.

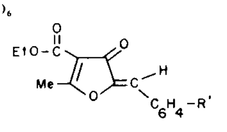
When R = methyl group (compound **2b**) experimental shifts of this methyl are not significant with an addition of Siever's reagent. However, the ASIS effect (11) on the 5-methyl and the ethylenic methyl were both positive (△δ = 12 Hz and 27 Hz, respectively). This is conceivably due to the fact that they are on the opposite sides of the carbonyl groups, and **2b** must have the *E* arrangement.

$\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$



(Δδ = 12 Hz) (Δδ = 27 Hz)

2b z



(Δδ = 16 Hz)

2a

The assignment of △δ is based on the ASIS effect of **2a** (R = H): the chemical shift of the methyl group has a value of △δ = 16 Hz.

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Table I

Physical Data for Compounds **2**

Compound	R	R′	Isomer	Yield %	M.p. °C	Analyses Calcd. Found C	H	Halogen	^{1}H nmr (ppm) R	R′	5-Me
2a1	H	4-Cl	Z	60	150	61.55	4.48		6.71		2.70
						61.36	4.50				
2a2	H	3,4 Cl_2	Z	17	164	55.07	3.70	21.68	6.67		2.77
						54.96	3.71	21.40			
2a3	H	4-Br	Z	31		53.43	3.88	23.70	6.65		2.72
						53.04	3.92	23.46			
2a4	H	4-F	Z	29	171	65.21	4.74	6.88	6.77		2.24
						65.07	4.65	6.71			
2a5	H	3,4,5-OMe	Z	10	169	62.06	5.79		6.69	3.87	2.71
						62.29	5.73				
2a6	H	3-OH	E	5	221	65.68	5.14		8.23	10.14	2.71
						65.57	5.09				
2a7	H	4-OMe	Z	30	146	66.65	5.59		6.67	3.73	2.62
						66.46	6.07				
2a8	H	2,4-Cl_2	Z	73	149	55.07	3.70	21.68	7.24		2.74
						55.10	3.52	21.71			
2a9	H	2,4-Me	Z	59	136	71.28	6.33		6.95	2.42	2.71
						71.10	6.00			2.32	
2a10	H	2,6 Cl_2	Z	5	184	55.07	3.70		6.86		2.62
						54.92	3.51				
2a11	H	4-NO_2	Z	63	236	59.40	4.32		6.80		2.78
						59.27	4.42				
2a12	H	2,4-NO_2	Z	76	143	51.73	3.47		7.19		2.74
						51.26	3.60		7.27		2.53
2a13	H	2-F	Z 85%	8	104	65.21	4.74	6.88	7.08		2.74
			E 15%			65.10	4.79	6.91			2.45
2a14	H	4-Me	Z	35	129	70.57	5.92		6.75	2.36	2.72
						70.35	6.09				
2b	Me	4-Cl	E	15	126	62.65	4.93	11.56	2.59		2.62
						62.69	4.72	11.79			

Table II

^{1}H Nmr Parameters of Compounds **2a**

Compound		Ethylenic proton (ppm) Deuteriochloroform	Deuteriochloroform + Resolve Eu(FOD)^{Tm}
2a2		6.67	7.24
2a4		6.77	7.30
2a6		8.23	8.22
2a7		6.67	7.54
2a8		7.24	7.70
2a9		6.95	7.91
2a11		6.80	7.95
2a12	*Z*	7.19	7.42
	E	7.27	7.25
2a13		7.08	7.23
2a14	*Z*	6.75	7.33
	E	7.00	

EXPERIMENTAL

The nmr spectra were measured using TMS as the internal standard with a Hitachi Perkin Elmer R. 24 A 60 Hz spectrometer. Elementary analysis were performed by the Microanalysis Laboratory, C.N.R.S., Villeurbanne, France.

Preparation of 4-Carbethoxy-3-(2*H*)furanone (**1**).

The preparation of furanone (**1**) was previously described by Gelin, *et al.*, (6) in a good yield (70%). We obtained only 20% yield as was indicated by Mulholland (12).

Preparation of 2-Benzilydene-4-carbethoxy-5-ethyl-3-(2*H*)furanones (**2**).

Carbethoxyfuranone (**1**) (2.5 g.) and an equimolar amount of a carbonyl compound were dissolved in 100 ml. of anhydrous benzene. Toluolsulfonic acid (50 mg.) was added as a catalytic reagent. The mixture was then heated in a Claisen flask provided with a Dean and Stark separator. The reaction was carried out very quickly (5 mn to 15 mn). An excessive heating time gave a mixture of by-products. Benzene was then removed and the residue was purified by column chromatography with chloroform as the eluent.

Configuration Determination:

To 1 ml. of a deuteriochloroform solution of benzylidenefuranone (**2**) (50 mg.), tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (or Siever's reagent) (20 to 50 mg.) were added by 10 mg. amounts. The nmr spectra of the clear solution was determined and it was compared to a spectra without the shift reagent.

REFERENCES AND NOTES

(1) On leave from the Federal University of Pernambuco, Brasil, on a grant from the Ministère des Affaires Etrangères, France.

(2) To whom correspondence should be addressed.

(3) A. Becker, *Helv. Chim. Acta*, 1114 (1949).

(4) R. Richter, *ibid.*, 115 (1952).

(5) S. Gelin and A. Galinaud, *C. R. Acad. Sci.*, **275 C**, 897 (1972).

(6) R. Gelin, A. Galinaud, B. Chantegrel and S. Gelin, *Bull. Soc. Chim. France*, 1043 (1974).

(7) S. Gelin and D. Hartmann, *J. Heterocyclic Chem.*, **13**, 521 (1976).

(8) R. E. Rosenkranz, K. Allner, R. Good, W. Philipsborn and C. H. Eugster, *Helv. Chim. Acta*, 1259 (1963).

(9) M. R. Willcott III and R. E. Davis, in "Nuclear Magnetic Resonance Shift Reagents", R. E. Sievers, Ed., Academic Press, New York, N. Y., 1973 p. 159.

(10) D. Baudry and M. Charpentier-Morize, *Nouveau J. Chim.*, **2**, 257 (1978).

(11) C. J. Timmons, *Chem. Commun.*, 576 (1965); J. E. Baldwin, *J. Org. Chem.*, **30**, 2423 (1965); J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 153 (1962).

(12) T. P. C. Mulholland, *J. Chem. Soc.*, 1225 (1972).