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The Aldol Condensation of Aromatic Aldehydes With *N*-Acetyl-2-pyrrolidinone: Part II. Formation of Cinnamic Acids in the Synthesis of 3-Arylidene-2-pyrrolidinones

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In an earlier paper (3), it was reported that the aldol condensation between aromatic aldehydes possessing electron-releasing (or neutral) substutients and *N*-acetyl-2-pyrrolidinone I resulted in the formation of *trans*-3-arylidene-2-pyrrolidinones (II). In the present paper we wish to communicate that when aromatic aldehydes possessing electron-withdrawing substituents (and some possessing *ortho*-electron-releasing substituents) are utilized in this condensation reaction with *N*-acetyl-2-pyrrolidinone, that simultaneous formation of the *trans*-cinnamic acids (III) occurred along with the *trans*-3-arylidene-2-pyrrolidinones (II). (See Scheme I.)

The results with a variety of aldehydes are summarized in Table I. In some cases, both products were obtained while in others only one of the products could be isolated. Since recognition of the occurrence of this formation of cinnamic acids was not realized until much of this work was completed and furthermore feasible separation of the cinnamic acid from the 3-arylidene-2-pyrrolidinone by sodium bicarbonate extraction was complicated by the low solubility of the crude reaction products in appropriate solvents, quantitative yield data was not obtained. (Possible contamination of the 3-arylidene-2-pyrrolidinones reported earlier (3) by the corresponding cinnamic acids is recognized but would be expected to be insignificant since purification of these compounds by single or duplicate recrystallization was accomplished.)

These results can readily be understood in terms of the participation of the two different carbanions Ia and Ib which can form from *N*-acetyl-2-pyrrolidinone. (See Scheme I). Aldol condensation of these carbanions with the aldehyde, followed by facile deacylation and dehydration, results in the formation of *trans*-3-arylidene-2-pyrrolidinone (II) and *trans*-cinnamic acid (III). (Possible formation of these products from bis-condensation of dicarbanion IV followed by deacylation and dehydration cannot be eliminated from consideration.) It can be observed from Table I that some *ortho*-substituted aldehydes seem to have preference for reaction with the sterically less hindered carbanion Ib which results in the formation of cinnamic acids. These results have some analogy in the work of Korte (4) in the Claisen condensation of ethyl isonicotinate with *N*-acetyl-2-pyrrolidinone in which a product analogous to the cinnamic acid was formed. However, recognition of the possible intermediacy of carbanion Ib was not made. Efforts to circumvent the complications introduced through the intermediacy of the competing carbanion Ib by utilization of *N*-benzoyl-2-pyrrolidinone (4) (*i.e.*, without additional α-hydrogens) were generally unsuccessful.

The structures of the products were proven by elemental analysis and infrared spectra. All the cinnamic acids were soluble in dilute sodium bicarbonate solution. The infrared spectra showed the following characteristics: 3-arylidene-2-pyrrolidinones II (R=H sharp NH ~ 3.10μ, C=O (lactam) ~ 5.95μ, C=C ~ 6.10μ; *N*-acetyl-3-arylidene-2-pyrrolidinones II (R=Ac) no NH absorption, two C=O absorption bands ~ 5.8μ and ~ 5.95μ, C=C ~ 6.10μ; *trans*-cinnamic acids broad OH ~ 3.25μ, C=O ~ 5.9μ, and C=C ~ 6.15μ.

The generality of the base-catalyzed aldol condensation of aromatic aldehydes with *N*-acetyl-2-pyrrolidinone for the synthesis of *trans*-3-arylidene-2-pyrrolidinones II had thus been found to possess some limitations (3).

SCHEME I

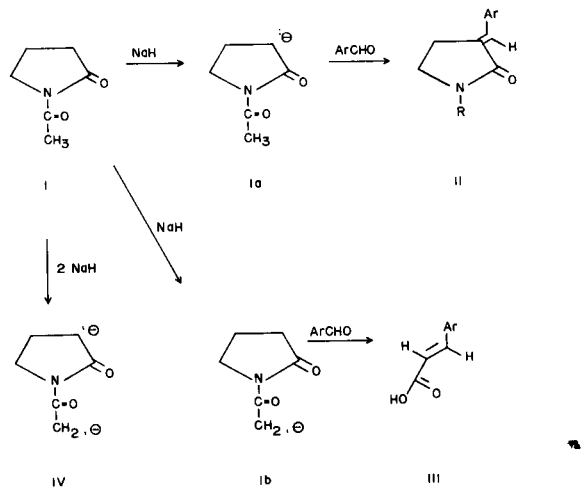
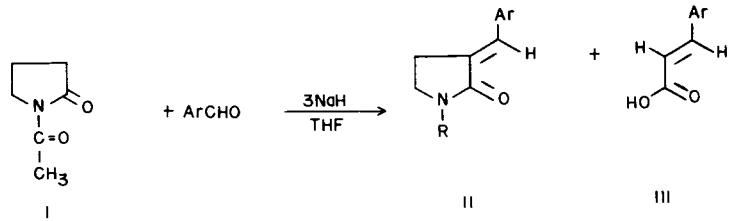


TABLE I

trans-3-Arylidene-2-Pyrrolidinones (II) and/or *trans*-Cinnamic Acids (III)



I II III

Compound No.	Ar	R	Product	Yield	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found	M.P., °C	Recry. Solvent
1	3,4-dichlorophenyl	Ac	II	76 (a)	$C_{13}H_{11}Cl_2NO_2$	54.92	55.04	3.90	3.98	4.93	4.87	24.95	24.97	204-205	EtOAc
2	3,4-dichlorophenyl	--	III	--	$C_9H_6Cl_2O_2$	49.81	49.91	2.79	2.82	--	--	32.67	32.66	222-223 (c)	MeOH
3	4-chlorophenyl	Ac	II	92 (a)	$C_{13}H_{12}ClNO_2$	62.53	62.38	4.85	5.04	5.61	5.57	14.21	14.31	226-228	EtOAc
4	4-chlorophenyl	--	III	low	$C_9H_7ClO_2$	---	---	--	--	--	--	---	---	245-247 (d)	EtOAc
5	4-bromophenyl	Ac	II	63 (a)	$C_{13}H_{12}BrNO_2$	53.08	52.76	4.11	4.33	4.76	4.64	27.17	27.27	251-252	EtOAc
6	4-fluorophenyl	H	II	48 (a)	$C_{11}H_{10}FNO$	69.10	69.08	5.27	5.44	7.33	7.00	---	---	204-205	EtOAc
7	2-chlorophenyl	--	III	65 (b)	$C_9H_7ClO_2$	59.19	59.39	3.86	3.88	--	--	19.42	19.46	208-210 (e)	EtOAc
8	2-bromophenyl	--	III	58 (b)	$C_9H_7BrO_2$	47.60	47.24	3.11	3.42	--	--	35.20	35.38	223-224 (f)	CH_2Cl_2
9	2-hydroxyphenyl	H	II (g)	5 (a)	$C_{11}H_{11}NO_2$	69.82	69.80	5.86	6.00	7.40	7.32	---	---	269-271	MeOH-EtOAc
10	β-phenylvinyl	H	II	low	$C_{13}H_{13}NO$	78.36	77.84	6.58	6.63	7.03	7.23	---	---	178-179	EtOAc
11	2,3-dimethoxyphenyl	H	II	low	$C_{13}H_{15}NO_3$	66.93	66.77	6.48	7.02	6.01	5.88	---	---	145-146	EtOAc
12	2,3-dimethoxyphenyl	--	III (h)	46 (b)	$C_{11}H_{12}O_4$	63.45	63.05	5.81	5.17	--	--	---	---	182-183 (h)	EtOAc
13	2-methylphenyl	--	III	high	$C_{10}H_{10}O_2$	74.05	74.05	6.22	6.02	--	--	---	---	175-176 (i)	C_6H_6
14	3-nitrophenyl	H	II	low	$C_{11}H_{10}N_2O_3$	60.54	60.21	4.62	4.72	12.84	12.81			230-231	EtOAc

(a) Yield was calculated on the basis of the deacetylated compound (R = H) and on the basis that this was the only product, although it is recognized that these compounds were contaminated with an undetermined amount of the *trans*-cinnamic acids. This was necessitated since a quantitative separation was not feasible. (b) Yield was based on cinnamic acid although it also was contaminated with *trans*-3-arylidene-2-pyrrolidinone. (c) Literature m.p. 217-218°; C. Walling and K. B. Wolfstirn, *J. Am. Chem. Soc.*, 69, 852 (1947). (d) Literature m.p. 240-242°; S. Gabriel and M. Herzberg, *Ber.*, 16, 2036 (1883). (e) Literature m.p. 210-211°; G. Lasch, *Monatsh. Chem.*, 34, 1653 (1913). (f) Literature m.p. 215-216°; S. Reich and P. Chaskelis, *Bull. Soc. Chim. France*, [4] 19, 287 (1916). (g) Structure fully confirmed by the similarity of the ultraviolet spectrum with that for the corresponding *trans*-3-(2-hydroxybenzylidene)-γ-butyrolactone. The infrared spectrum had a broad absorption at ~ 3.05 μ due to overlap of OH and NH absorption bands. (h) Unequivocal proof of the structural assignment as the cinnamic acid was obtained by comparison of the infrared and ultraviolet spectra of this material with those for authentic *trans*-2,3-dimethoxycinnamic acid (Aldrich Chemical Co.) and by the observation of no depression in the mixture melting point. Literature m.p. 180-181°; H. Kranichfeldt, *Ber.*, 46, 4016 (1913). (i) Literature m.p. 174-175°; K. V. Auwers, *Ann.*, 413, 253 (1917).

EXPERIMENTAL

Melting points are uncorrected. Microanalysis by A. Bernhardt, Microanalytisches Laboratorium in Max-Planck Institut, Mülheim/Ruhr, Germany, and Galbraith Laboratories, Knoxville 21, Tennessee. The infrared spectra were taken on potassium bromide discs on a Baird double beam spectrophotometer.

Procedure.

The general condensation procedure for reaction of aromatic aldehydes with *N*-acetyl-2-pyrrolidinone using sodium hydride as base in tetrahydrofuran solvent was described earlier (3). The crude products obtained were then treated in the following manner: (a) recrystallization of the product to constant melting point from the appropriate solvent (compounds 6-9, 11, and 13); (b) formation of the *N*-acetyl derivative of the 3-arylidene-2-pyrrolidinone with acetic anhydride (3), which fortuitously effected a separation from cinnamic acid (compounds 1, 3, and 5); (c) extraction of a chloroform solution with dilute sodium bicarbonate solution followed by acidification to give the cinnamic acid (compounds 2, 7, and 8); (d) column chromatography on neutral alumina (compounds 10 and 14). Compound 12 was obtained in very low yield from reaction of *N*-benzoyl-2-pyrrolidinone with 2,3-dimethoxybenzaldehyde.

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REFERENCES

(1) This is paper XXI of the series: Substituted γ-Lactones; paper XX, *J. Heterocyclic Chem.*, 2, 477 (1965).

(2) Taken in part from Ph.D. Thesis, D. C. Armbruster, University of Cincinnati, 1965.

(3) H. Zimmer, D. C. Armbruster, and L. J. Trauth, *J. Heterocyclic Chem.*, 2, 171 (1965).

(4) F. Korte and H. J. S. Steinen, *Chem. Ber.*, 95, 2444 (1962).

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