

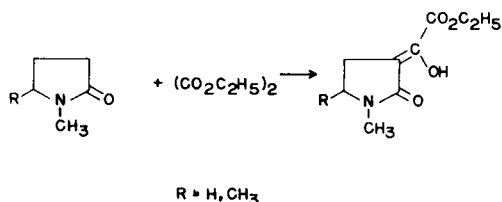
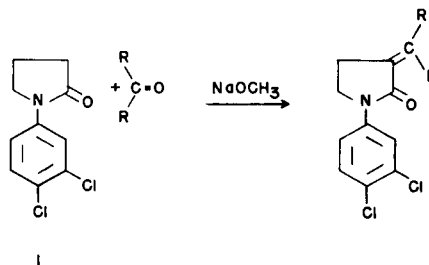
Rohm and Haas Company

Aldol and Claisen Condensations with 1-(3,4-Dichlorophenyl)-2-pyrrolidinone

Michael C. Seidel and Richard S. Cook

1-(3,4-Dichlorophenyl)-2-pyrrolidinone (I) has been condensed at the 3-position with a series of aldehydes, ketones and esters.

The α -hydrogen atoms of lactams are not very acidic and few condensations have been carried out involving them. Reactive esters, such as quinolinic and nicotinic esters, have been condensed (1,2) with 1-methyl-2-pyrrolidinone and ethyl oxalate has been condensed with 1-methyl-2-pyrrolidinone (3) and with 1,5-dimethyl-2-pyrrolidinone (4). Korte (3)

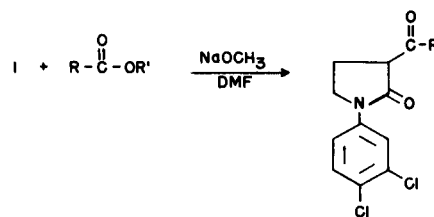


used sodium hydride or potassium powder as catalyst and Celmer (4) used sodium ethoxide but yields were low in the last case. It is surprising, in this context, to find that 1-(3,4-dichlorophenyl)-2-pyrrolidinone (I) can be condensed with a variety of aldehydes, ketones, and esters almost as easily as butyrolactone (5). The reason for this unusual behavior might be found in the electron withdrawing power of the 3,4-dichlorophenyl group which makes the electron pair on the nitrogen less available for an amide-type resonance and thus brings about a reactivity at the 3-position more like that of butyrolactone. Recently Zimmer, Armbruster, and Trauth (6) succeeded in preparing 3-arylidene-2-pyrrolidinones by condensing aromatic aldehydes with 1-acetyl-2-pyrrolidinone. Here, too, the electron withdrawing character of the substituent on the nitrogen facilitates condensation at the 3-position.

Aldol condensations of I were successful using benzaldehyde, *isobutyraldehyde*, cyclohexanone, and acetone (see Table I).

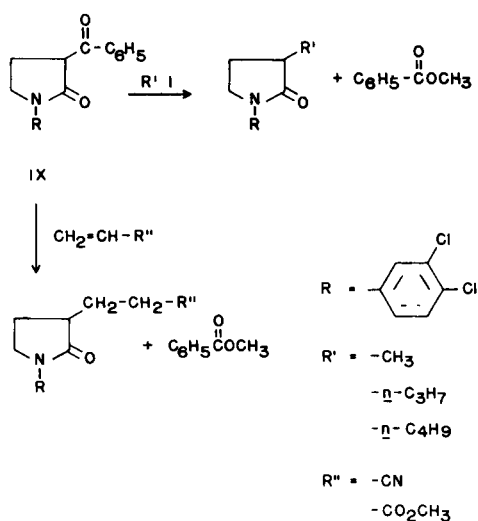
The reactions were carried out in DMF/benzene mixtures. The reaction with benzaldehyde yielding II could be carried out in benzene alone. In the other cases some DMF was required in the reaction mixture. Hydrogen atoms in the α -position of the aldehydes had to be absent or somewhat hindered as it was impossible to isolate a product from the reaction of I with acetaldehyde or butyraldehyde. Formaldehyde did not react with I directly; the expected product (XVII), however, could be obtained by reaction of formaldehyde with VI (see below).

A variety of esters could be made to condense with I under the same conditions employed in the aldol condensations (see Table II).

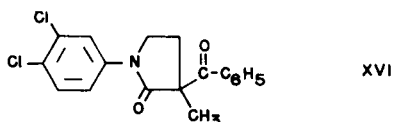


The yields were quite good except in the case of $R = \text{CH}_3$ (VIII), where self-condensation of the ester interfered, and in the case of X. The intermediate ester ($R = \text{OR}'$) was not isolated in this case, but the product hydrolyzed to X with methanolic potassium hydroxide. Both tautomeric forms of IX were isolated; the keto form (m.p. 121-122°) by recrystallization from glacial acetic acid, the enol form by recrystallization from methanol (m.p. 107-108°). (See also discussion of the IR spectra below.)

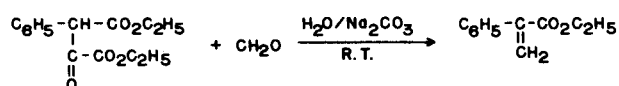
The benzoyl derivative (IX) was used for a number of alkylations (see Table III) using excess sodium methoxide in DMF:



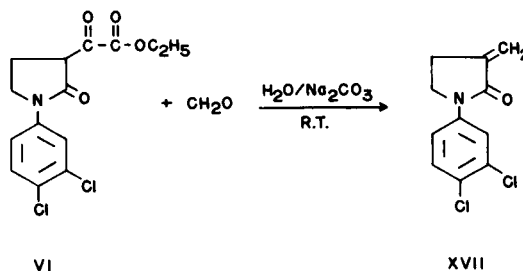
The use of only one equivalent of base in the reaction of methyl iodide with IX led to the formation of XVI, which could be converted to XI and methyl benzoate on treatment with excess sodium methoxide.



Since the direct reaction of I with formaldehyde had failed it was attempted to obtain the desired aldol product (XVII) in the same way that Schinz and Hinder (7) used in their preparation of ethyl α -phenyl acrylate:

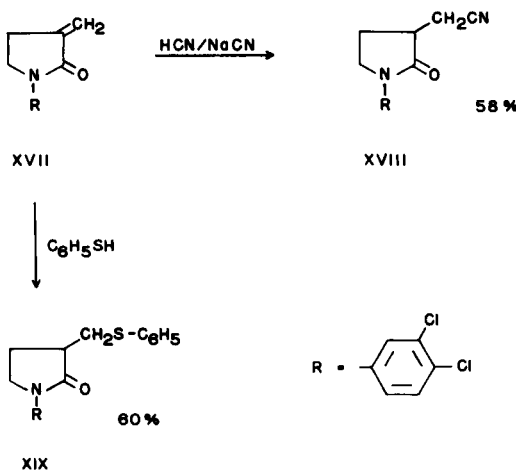


Using this method, a 14% yield of XVII could be obtained:



An even better yield (50%) of XVII was obtained in an unsuccessful attempt to prepare a Mannich base by substituting dimethylamine for the sodium carbonate in the reaction.

Even though dimethylamine did not appear to add irreversibly to XVII, Michael addition was possible with other nucleophiles:

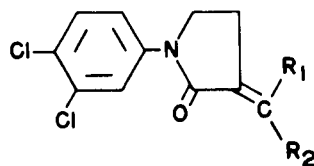


These reactions were run at room temperature.

The IR spectra of the aldol products (II to V and XVII) have a carbonyl band at 5.95 μ (the same band is found in the spectrum of I) and a C=C stretching band at 6.10 μ . Of the ester condensation products, VI seemed to be almost completely in the enolic form. Its IR spectrum exhibited a band at 5.85 μ , attributed to the carboxy group, and a band at 6.15 μ , attributed to the enolic β -dicarbonyl system. This assignment was strengthened by the IR spectra of the two tautomeric forms of IX that could be isolated. One form, isolated by recrystallization from glacial acetic acid (m.p. 121-122°), had bands at 5.95 μ and 6.05 μ and was considered to be the keto form; the other, obtained by recrystallization from methanol (m.p. 107-108°), showed only one band, at 6.18 μ , and was considered to be the enolic form. The spectrum of XVI, a compound that cannot enolize, has the same carbonyl bands (5.95 μ and 6.05 μ) as the spectrum of the keto form of IX.

TABLE I

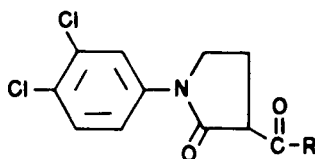
Aldol Condensation Products of I



Compound	R ₁	R ₂	m. p.	Yield %	Formula	Analysis (calcd. over found)		
						C	H	N
II	H	C ₆ H ₅	195-197°	72	C ₁₇ H ₁₃ Cl ₂ NO	64.17 64.47	4.12 4.29	4.40 4.30
III	H	CH(CH ₃) ₂	146-148°	42	C ₁₄ H ₁₅ Cl ₂ NO	59.17 59.30	5.20 5.44	4.93 4.91
IV	CH ₃	CH ₃	182-184°	11	C ₁₃ H ₁₃ Cl ₂ NO	57.79 58.03	4.85 5.04	5.19 5.02
V	-(CH ₂) ₅ -		155-157°	26	C ₁₈ H ₁₇ Cl ₂ NO	61.94 62.20	5.53 5.76	4.52 4.46

TABLE II

Ester Condensation Products of I



Compound	R	m. p.	Yield %	Formula	Analysis (Calcd. over found)		
					C	H	N
VI	-CO ₂ C ₂ H ₅	160-162°	72	C ₁₄ H ₁₃ Cl ₂ NO ₄	50.90 50.90	3.97 3.83	4.24 4.14
VII	-H	71° (decomp.)	64	C ₁₁ H ₉ Cl ₂ NO ₂	Cl 27.4 Cl 27.4		5.43 5.32
VIII	-CH ₃	108-110°	31	C ₁₂ H ₁₁ Cl ₂ NO ₂	52.96 52.71	4.08 4.12	5.15 5.08
IX	-C ₆ H ₅	107-108° & 121-122°	85	C ₁₇ H ₁₃ Cl ₂ NO ₂	61.10 60.53	3.92 4.04	4.19 4.03
X	-OH	159-161°	10	C ₁₁ H ₉ Cl ₂ NO ₃	48.20 48.31	3.31 3.45	5.11 5.12

EXPERIMENTAL

All melting points are uncorrected. The microanalyses (see also Tables I, II and III) were carried out by Mr. C. W. Nash and his associates, Rohm and Haas Company, Bristol, Pa. The IR spectra were taken in Nujol mulls using a Perkin Elmer Infracord.

1-(3,4-Dichlorophenyl)-2-pyrrolidinone (I).

A method analogous to the one used by Pernot and Willemart (8) for the preparation of 1,5-diphenyl-2-pyrrolidinone was used. 3,4-Dichloroaniline was heated to 180-190° with butyrolactone and a catalytic amount of 3,4-dichloroaniline hydrochloride. After 8 hours yields of

90-95% of crude product, m.p. 101-108°, could be realized. After one recrystallization from methanol, the material melted at 110-111°.

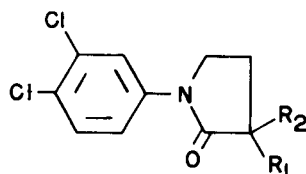
Anal. Calcd. for C₁₀H₉Cl₂NO: C, 52.22; H, 3.94; N, 6.09. Found: C, 52.34; H, 4.10; N, 5.95.

General Procedure for the Aldol Condensations.

A solution of 11.5 g. (0.05 moles) I and 0.1 mole of aldehyde or ketone in 20 ml. of DMF and 30 ml. of benzene was prepared in a 100 ml. three-necked flask equipped with a magnetic stirrer, a thermometer and an ice bath. Sodium methoxide (6.0 g., 0.11 mole) was dropped in quickly. The temperature rose to 35-40°. When the exothermic reaction had subsided, the ice bath was removed and

TABLE III

Alkylation Products of IX



Compound	R ₁	R ₂	m. p.	Yield %	Formula	Analysis (calcd. over found)		
						C	H	N
XI	-CH ₃	H	91-92°	81	C ₁₁ H ₁₁ Cl ₂ NO	54.12 54.25	4.54 4.71	5.74 5.48
XII	-n-C ₃ H ₇	H	76-78°	29	C ₁₃ H ₁₅ Cl ₂ NO	57.37 57.43	5.56 5.29	5.15 5.11
XIII	-n-C ₄ H ₉	H	63-64°	22	C ₁₄ H ₁₇ Cl ₂ NO	58.75 58.90	5.99 6.25	4.90 4.97
XIV	-CH ₂ -CH ₂ -CN	H	78-80°	34	C ₁₃ H ₁₂ Cl ₂ N ₂ O	55.94 56.04	4.27 4.42	
XV	-CH ₂ -CH ₂ -CO ₂ CH ₃	H	86-88°	46	C ₁₄ H ₁₅ Cl ₂ NO ₃	53.18 53.17	4.78 5.07	4.43 4.26
XVI	$\begin{array}{c} \text{O} \\ \\ -\text{CC}_6\text{H}_5 \end{array}$	-CH ₃	133-135°	25	C ₁₈ H ₁₅ Cl ₂ NO ₂	62.08 62.33	4.34 4.48	4.02 4.00

stirring was continued for 2 hours. After that the mixture was washed with excess water, the benzene was stripped off and the residue was recrystallized from methanol.

General Procedure for the Ester Condensations.

To a solution of 11.5 g. (0.05 mole) of I and 0.1 mole of the ester in 50 ml. of DMF was added 6.0 g. (0.11 mole) of sodium methoxide. After one hour at room temperature the mixture was heated to 70-80° for 3 hours. Then the mixture was poured into an excess of 2 N hydrochloric acid, filtered and the residue was recrystallized from methanol or glacial acetic acid.

In the case of X the oily product was boiled for one hour in 5% potassium hydroxide in methanol. After adding excess 2 N hydrochloric acid and filtering, the product (X) was recrystallized from methanol.

Compound VII had to be prepared at a temperature of -10° to -5° to avoid poor yields and excessive foaming.

Alkylations of 1-(3,4-Dichlorophenyl)-3-benzoyl-2-pyrrolidinone (IX).

The alkylations were carried out in methanol using a two-fold excess of the alkyl iodide and sodium methoxide. After 4 hours of reflux, the methanol was evaporated and the residue was taken up in benzene and filtered. The benzene solutions were chromatographed on neutral silicic acid and the products were recrystallized from hexane.

The reactions with acrylonitrile and methyl acrylate were carried out analogously using a two-fold excess of the unsaturated compound. Work-up included acidification, evaporation of the methanol and the methyl benzoate formed in the reaction, and recrystallization of the products from methanol.

1-(3,4-Dichlorophenyl)-3-methylidene-2-pyrrolidinone (XVII).

To 10.0 g. (0.03 mole) of VI suspended in 50 ml. of water, 10 ml. of aqueous dimethylamine (48%) and 10 ml. of aqueous formaldehyde (38%) were added. The mixture was stirred overnight, the product was filtered off and recrystallized from methanol, yield, 3.6 g. (50%), m.p. 124-126°.

Anal. Calcd. for C₁₁H₉Cl₂NO: C, 54.47; H, 3.75; N, 5.79; Cl, 29.30. Found: C, 54.49; H, 3.88; N, 5.64; Cl, 29.02.

1-(3,4-Dichlorophenyl)-3-(thiophenyl)methyl-2-pyrrolidinone (XIX).

To a solution of 4.0 g. (0.0165 mole) of XVII in 20 ml. of pyridine, 5 ml. of thiophenol was added. The mixture was left standing for 72 hours and then poured into water, the product was filtered off and recrystallized from methanol, yield, 3.5 g. (60%), m.p. 93-94°. Anal. Calcd. for C₁₇H₁₅Cl₂NOS: C, 57.96; H, 4.29; N, 3.98. Found: C, 57.85; H, 4.44; N, 3.95.

1-(3,4-Dichlorophenyl)-3-cyanomethyl-2-pyrrolidinone (XVIII).

To an ice-cooled suspension of 25 g. (0.5 mole) of sodium cyanide in 100 ml. of DMF, 25 ml. of concentrated hydrochloric acid was added drop-wise. Five grams (0.02 mole) of XVII was added. After standing for 24 hours excess water was added and the solid product was filtered off and recrystallized from methanol, 3.2 g. (58%); m.p. 111-112°.

Anal. Calcd. for C₁₂H₁₀Cl₂N₂O: C, 53.55; H, 3.75; N, 10.41. Found: C, 53.82; H, 3.98; N, 10.29.

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