

Reactions of Acetylenic β -Keto Cyanides and β -Keto Esters with Different Ammonia Derivatives

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Received January 15, 1975 - Revised December 10, 1975

Different aryl substituted acetylenic β -keto cyanides (IAa-o) and β -keto esters (IBa-o) reacted with each of hydrazine hydrate, phenylhydrazine, hydroxylamine hydrochloride and semicarbazide hydrochloride in boiling alcohol to give the same heterocyclic nucleus for each type of ammonia derivative. In certain cases, intermediate acetylenic hydrazides were isolated at room or zero temperatures and cyclized to give the appropriate pyrazol-5-one compounds when heated above their melting points. It is concluded that Michael addition is favoured at elevated temperatures and Claisen addition is favoured at lower temperatures.

J. Heterocyclic Chem., **13**, 455 (1976).

Recently, we reported that the type of pyrazolone obtained from the reaction between phenylpropionic acid or its ethyl ester and hydrazine hydrate or phenylhydrazine depends mainly on the experimental reaction conditions (2). The extension of this work to cover the condensation of these and other ammonia derivatives with the recently

(3,4,5) prepared acetylenic β -keto cyanides and β -keto esters are reported here.

The reaction between equimolar quantities of hydrazine hydrate and acetylenic β -keto cyanides (IAa-o) or β -keto esters (IBa-o) were carried out under different experimental conditions. In boiling ethanol or at room temperature and

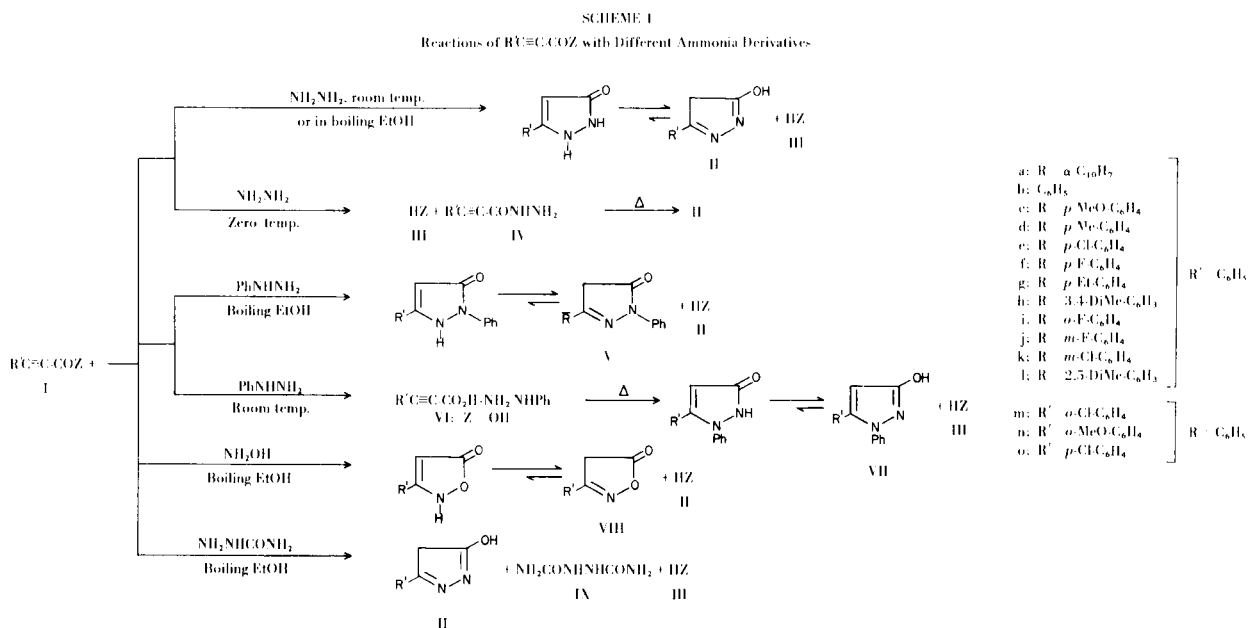


Table I

Arylpyrazole-5-ones

Compound	R	R'	M.p. °C	Formula	C	Analyses (%)				
						Calcd.	Found			
					H	N	C	H	N	
II	--	Ph (a)	242 (16)	C ₉ H ₈ N ₂ O	67.50	5.00	17.50	67.30	5.08	17.49
II	--	<i>o</i> -Cl-C ₆ H ₄ (a)	168-170	C ₉ H ₇ ClN ₂ O	55.54	3.60	14.40	55.85	3.83	14.47
II	--	<i>p</i> -Cl-C ₆ H ₄ (a)	240-242 (10)	C ₉ H ₇ ClN ₂ O	55.54	3.60	14.40	55.63	3.78	14.39
VIIb	Ph	Ph (b)	254-256 (19)	C ₁₅ H ₁₂ N ₂ O	76.27	5.08	11.86	76.29	5.14	11.76
VIIm	Ph	<i>o</i> -Cl-C ₆ H ₄ (b)	224-226	C ₁₅ H ₁₁ ClN ₂ O	66.56	4.07	10.35	66.51	4.03	10.24
VIIo	Ph	<i>p</i> -Cl-C ₆ H ₄ (c)	283 (10)	C ₁₅ H ₁₁ ClN ₂ O	66.56	4.07	10.35	66.20	4.07	10.23

(a) Recrystallized from methanol. (b) From 1-butanol. (c) From dioxan.

Table II

Aryl Acid Hydrazides (RCONHNH₂)

R	M.p. °C (a)	Formula	C	Analyses (%)				
				Calcd.	Found			
				H	N	C	H	N
α -C ₁₀ H ₇	134	C ₁₂ H ₁₂ N ₂ O	71.99	6.03	14.02	72.19	5.59	14.16
<i>p</i> -MeO-C ₆ H ₄	136	C ₉ H ₁₂ N ₂ O ₂	59.99	6.71	15.54	59.84	6.46	16.04
<i>p</i> -Me-C ₆ H ₄	146	C ₉ H ₁₂ N ₂ O	65.82	7.36	17.06	65.99	7.26	17.07
<i>p</i> -Cl-C ₆ H ₄	170	C ₈ H ₉ ClN ₂ O	52.04	4.91	15.17	51.92	5.02	15.24

(a) The melting points of other substituted aryl hydrazides are as follow: *o*-F, 128°; *m*-F, 92°; *m*-Cl, 110°; 2,5-diMe, 120°. Recrystallized from chloroform.

Table III

Acetylenic Acid Hydrazides

Compound	R	M.p. °C (a)	Formula	C	Analyses (%)				
					Calcd.	Found			
					H	N	C	H	N
IV	Ph	114-115	C ₉ H ₈ N ₂ O	67.50	5.00	17.50	67.81	5.18	17.47
IV	<i>o</i> -Cl-C ₆ H ₄	82	C ₉ H ₇ ClN ₂ O	55.54	3.60	14.40	55.98	3.74	14.25
IV	<i>p</i> -Cl-C ₆ H ₄	120	C ₉ H ₇ ClN ₂ O	55.54	3.60	14.40	55.65	3.62	14.36

Table IV
Phenyl Hydrazonium Salts of Arylpropionic Acids

Compound	R	R'	M.p. °C (a)	Formula	C	Analyses (%)				
						Caled.		Found		
						H	N	C	H	N
VIb	Ph	Ph	137	C ₁₅ H ₁₄ N ₂ O ₂	70.87	5.51	11.02	70.46	5.69	10.98
VIIm	Ph	<i>o</i> -Cl-C ₆ H ₄	120-122							
VIo	Ph	<i>p</i> -Cl-C ₆ H ₄	152-154	C ₁₅ H ₁₃ ClN ₂ O ₂	62.40	4.51	9.71	62.44	4.79	9.50

(a) Recrystallized from chloroform.

in the absence of solvent, 3-arylpyrazol-5-one (II) and arylacetonitriles (IIIA) or ethyl arylacetates (IIIB) were obtained from compounds (IAa-o) and (IBa-o) respectively. The pyrazol-5-ones (II) were identified and their ir spectra indicated that they are predominantly present in their enol forms (6).

Repetition of the above reaction at zero temperature afforded the intermediate acetylenic hydrazide (IV) (2,7) in case of IBa-o while no reaction occurred when compounds IAa-o were used. The acetylenic hydrazides (IV) were identified on the basis of their ir and nmr spectra. The ir spectrum for compound (IV, R' = Ph) showed the following absorption bands: 1663, 1510 and 1300 attributed to the amide system, 1627 (bending NH₂), 2220 (C≡C stretching), 3370 and 3470 cm⁻¹ (NH and NH₂ stretching vibrations) (8). The nmr spectrum of this compound (IV, R' = Ph) showed a broad signal at 4.05 (due to NH₂ protons), and a multiplet between 8.0-6.98 (6H) due to 5 aromatic and CONH protons. The uv spectrum in ethanol showed two maxima at 212 ($\epsilon = 4,100$) and 255 nm ($\epsilon = 9,400$).

Heating of the intermediate hydrazides (IV) over their melting points afforded 3-arylpyrazol-5-ones (II) identical with authentic samples obtained from the reaction between hydrazine hydrate and arylpropionic acids or their ethyl esters (9). Furthermore, when excess of hydrazine hydrate was used in the case of IBa-o, arylhydrazides were separated instead of ethyl arylacetates (IIIB). The latter hydrazides were identified from their ir and nmr spectra beside the m.p. based on authentic samples obtained from ethyl arylacetate. The ir spectra of these hydrazides showed similar absorption pattern to those reported earlier by Mashima (8). A typical nmr spectrum for phenylacetylhydrazide showed the following signals: 3.52 (singlet, PhCH₂), 3.8 (broad, NH₂) and a signal at 7.25 δ due to the aromatic and NH protons. The isolation of the above acetylenic

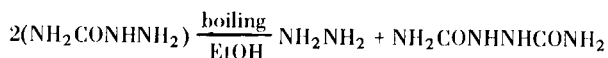
hydrazides contradicts the view given by Baddar (10) that the reaction between hydrazine and propionic acid initially involve protonation of the hydrazine followed by addition at the triple bond. It is clear that such protonation is not possible when ethyl arylpropionate or compounds IBa-o were used and the reaction mainly proceeds by Claisen condensation of hydrazine to the acetylenic compounds (Scheme 1).

Moreover, the above reactions were repeated using phenylhydrazine under various experimental conditions. In boiling ethanol, the products obtained from compounds IAa-o and IBa-o were identified as 1-phenyl-3-arylpyrazol-5-ones (V) (11). The ir spectrum of the latter compound showed carbonyl absorption band at 1713 cm⁻¹. When the same reactions were repeated at room or zero temperature, starting materials were recovered in the case of IAa-o, while unidentified semisolid compounds which were difficult to purify were obtained from compounds IBa-o.

Furthermore, when arylpropionic acids (II) were reacted with phenyl hydrazine at room temperature the corresponding phenyl hydrazonium salts (VI) of the acids were isolated. When the latter compounds (VI) were heated over their melting points, compounds VII were isolated and identified.

Moreover, the reactions between different acetylenic β -keto esters or β -keto cyanides and each of hydroxylamine hydrochloride or semicarbazide hydrochloride were also carried out. 3-Phenylisoxazol-5-one (VIII) (12) and 3-phenylpyrazol-5-one (II) were isolated in addition to arylacetonitriles or ethyl arylacetates, respectively. The ir spectrum of compound VIII showed the stretching bands at 1802 (C=O), 1564 (C=N) and 1160 cm⁻¹ (13). The formation of compound II in this case could be explained by the initial formation of hydrazine which reacted similarly with compounds IAa-o and IBa-o and as mentioned above. In addition, biurea (IX) was isolated according to

the following equation:



Repetition of this reaction and using phenylpropionic acid or its ethyl ester afforded the same reaction products (II & IX) mentioned above. Similar observations for the formation of hydrazine from semicarbazide hydrochloride has been reported for the reaction between semicarbazide and each of tri and tetra unsaturated ethyl esters (14).

From the above discussion it can be generalized that at elevated temperatures, the reaction between the acetylenic carbonyl compounds ($\text{RC}\equiv\text{C}\cdot\text{COZ}$, where $\text{Z} = \text{OH}$, OEt , CHRCN or CHRCO_2Et) and ammonia derivatives (NH_2X , where $\text{X} = \text{NH}_2$, NlPh , NHCONH_2 or OH) involve cleavage of the Z group with the formation of HZ and the appropriate heterocyclic nuclei. In certain cases the isolation of the intermediate acetylenic hydrazide at room or zero temperatures indicates that as Claisen condensation is favoured at the latter temperatures, Michael addition is favoured at higher temperatures.

EXPERIMENTAL

Unless otherwise stated, ir spectra were carried out using Unicam SP 200 spectrophotometer with chloroform as a solvent. NMR spectra were for deuteriochloroform solutions with TMS as internal reference on a Varian A60 D spectrometer. Analyses were performed by Microanalysis Unit, NRI, Atomic Energy Commission, Tuwaitha, Baghdad, and using HP-185B CHN analyzer.

The acetylenic β -keto cyanides (IAa-o) and β -keto esters (IBa-o) were prepared according to the recently published procedures (3,4,5). A typical procedure in each section mentioned below is given for the condensation of unsubstituted acetylenic carbonyl compounds. The procedures for the various substituted carbonyl compounds were similarly carried out and the products were obtained in comparatively similar yields. The various cleavage reaction products mentioned below were identified by comparison of their melting points and ir spectra with authentic samples obtained similarly from the reaction between ethyl phenylpropiolate or the corresponding acid and ammonia derivatives.

Reaction of Hydrazine Hydrate with α -(Phenylpropioloyl)phenylacetonitrile (IAb) and Ethyl α -(Phenyl)phenylpropiolylacetate (IBb).

Hydrazine hydrate (99% w/w, 5 ml.) was added to the solution of compound IAb or IBb (1.0 g.) in ethanol (20 ml.) and the mixture was kept under reflux for 3 hours. Distillation of the solvent followed by filtration resulted in a colourless solid (0.8 g.) identified as 3-phenylpyrazol-5-one (II, $\text{R}' = \text{Ph}$). Similarly the other pyrazolones (II, $\text{R}' = o\text{-Cl}$ or $p\text{-Cl-C}_6\text{H}_4$) were isolated and recrystallized from methanol (16) (Table I). The filtrate was extracted with chloroform and worked up in the usual manner to give benzyl cyanide or the acid hydrazide of IIIB from compounds IAb and IBb, respectively. Similar results were obtained by mixing the reactants without any solvent and keeping the reaction mixture at room temperature. The arylhydrazides of IIIB which were separated are tabulated in Table II.

and the acetylenic β -keto ester (IB) was mixed and kept at zero temperature for one hour, the solid obtained was filtered off, recrystallized from ether and identified as arylpropioloylhydrazide (IV) (Table III). When compounds IV were heated for five minutes above their melting points, cyclization took place and the above 3-arylpyrazol-5-ones (II) were obtained in quantitative yields. The filtrate, after extraction with chloroform and drying (magnesium sulfate), was identified as ethyl phenylacetate on the basis of ir spectra. Moreover, when compound IA was treated with equimolar amount of hydrazine hydrate at zero temperature, no reaction occurred and the starting material was isolated.

Reaction of Phenylhydrazine with α -(Phenylpropioloyl)phenylacetonitrile (IAb) or Ethyl α -(Phenyl)phenylpropiolylacetate (IBb).

Phenylhydrazine (0.5 g.) was added to a solution of compound IAb or IBb (1.0 g.) in ethanol (20 ml.) and the mixture was refluxed for 12 hours. After distillation of the alcohol the remaining residue, which solidified on treatment with petroleum ether (30-40°), was recrystallized from methanol (0.7 g.), m.p. 137° lit. (17), m.p. 136°. This product was identified as 1,3-diphenylpyrazol-5-one (V). Similarly, compound V, ($\text{R}' = o\text{-chlorophenyl}$) m.p. 152° lit. (18), m.p. 152°, was isolated from compounds IAm and IBm and recrystallized from methanol. The mother liquor was worked up, and as in the case of hydrazine hydrate, to give benzyl cyanide or ethyl phenylacetate in case of compounds IAb and IBb, respectively. Furthermore, no reaction occurred at room or zero temperature in the case of the cyanide IAb, and an unidentified semisolid product was obtained from compound IBb. The case is different when phenylpropionic acid or its benzene solution was treated at the latter experimental conditions with phenylhydrazine where the product was identified as phenylhydrazonium salt of phenylpropionic acid (VI). Other salts (VI, $\text{R}' = o\text{-Cl}$ or $p\text{-Cl-C}_6\text{H}_4$) were isolated and their results are tabulated (Table IV). Heating of the latter salt (VI) for five minutes over its melting point resulted in another solid material which proved to be 2,3-diphenylpyrazol-5-one (VII, $\text{R}' = \text{Ph}$). Similarly other pyrazol-5-ones (VII, $\text{R}' = o\text{-Cl}$ or $p\text{-Cl-C}_6\text{H}_4$) were isolated and identified (11,19) (Table I).

Reaction of Semicarbazide Hydrochloride with α -(Phenylpropioloyl)phenylacetonitrile (IAb) and Ethyl α -(Phenyl)phenylpropiolylacetate (IBb).

A solution of sodium acetate (0.5 g.) and semicarbazide hydrochloride (0.5 g.) in water (5 ml.) was added to a solution of compound IAb or IBb in ethanol (100 ml.). The reaction mixture was kept under reflux for 5 hours and then filtered. The solid compound (0.2 g.) thus obtained was proven to be biurea by m.p. and mixed m.p., 247-250° dec., (15). The filtrate was extracted with chloroform and the latter was worked up in the usual manner to give benzyl cyanide or the acid hydrazide of IIIB respectively. The mother liquor was acidified with dilute hydrochloric acid and then filtered to give a solid compound (0.2 g.), m.p. 242° (from methanol) which was identical in all respects with 3-phenylpyrazol-5-one (II).

Reaction of Hydroxylamine Hydrochloride with α -(Phenylpropioloyl)phenylacetonitrile (IAb) and Ethyl α -(Phenyl)phenylpropiolylacetate (IBb).

A mixture of anhydrous sodium acetate (0.5 g.) and hydroxylamine hydrochloride (0.5 g.) in water (6 ml.) was added to a solution of compound (IAb) or compound (IBb) in ethanol (50 ml.). The reaction mixture was kept under reflux for 4 hours and

the crude residue was diluted with water and then filtered. The solid obtained (0.5 g.) was identified as 3-phenylisoxazol-5-one (VIII), m.p. 150-151° (from carbon tetrachloride), lit. (12), m.p. 152°. The mother liquor was worked up as above to give benzyl cyanide or the acid hydrazide of IIIB from compounds IAb and IBb, respectively.

Notes:

The acetylenic β -keto cyanide (IA) and β -keto ester (IB) mentioned below were condensed with the following ammonia derivatives:

a. Hydrazine Hydrate: Compounds IA include a-o except g-i. Compounds IB include a-o except g,i,l and o.

b. Phenylhydrazine: Compounds IA include a-o except h,m and n. Compounds IB include a-o except l-n.

c. Semicarbazide and Hydroxylamine Hydrochlorides: Compounds IA include a-o except g-i and o. Compounds IB include a-o except g-i, l and o.

Acknowledgment.

We wish to thank Mr. Faris Ibrahim for determination of the elemental analysis and to Mrs. Fatin Al-Azawi for her technical assistance.

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