The Reaction of α,β-Acetylenic Ketones with Aroylhydrazines†

B. Shivarama HOLLA,* K. Venkatramana UDUPA, and K. R. SRIDHAR††
Department of P. G. Studies and Research in Chemistry, Mangalore University, Mangalagangothri 574199 (DK), Mangalore, India
††Department of P. G. Studies and Research in Bio-Sciences, Mangalore University, Mangalagangothri 574199 (DK), Mangalore, India
(Received February 14, 1989)

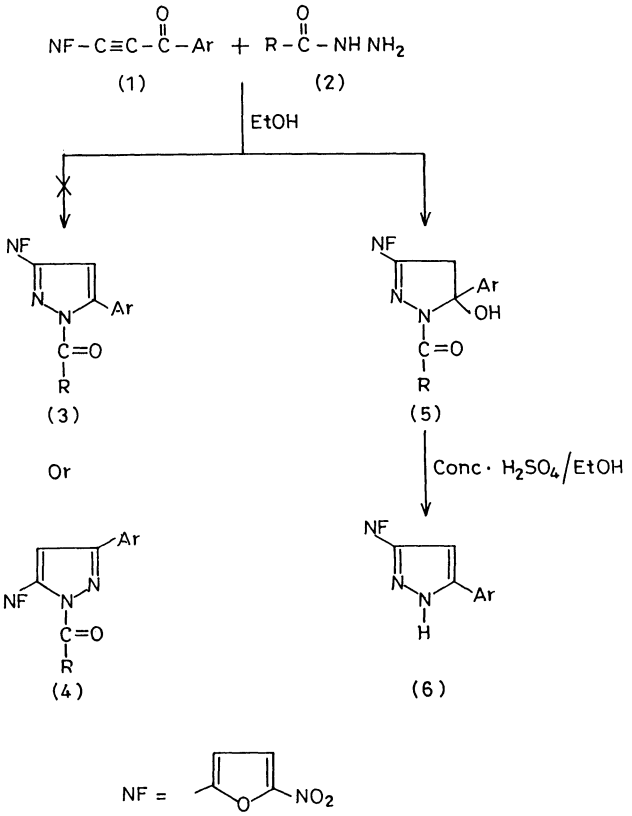
Synopsis. Reaction of 3-(5-nitro-2-furyl)-1-aryl-2-propyn-1-ones (**1**) with aroylhydrazines (**2**) furnished 1-aroyl-3-(5-nitro-2-furyl)-5-aryl-5-hydroxy-2-pyrazolines (**5**) rather than the expected pyrazoles **3** or **4**. On acid-catalyzed hydrolysis these hydroxypyrazolines are converted into the known 3-(5-nitro-2-furyl)-5-aryl-1*H*-pyrazoles (**6**). The structural elucidation of the products was carried out on the basis of analytical and spectral data. The newly synthesized nitrofuran derivatives are screened for their antibacterial properties against Gram-positive and Gram-negative bacteria. Most of them showed significant activity.

A number of pyrazole derivatives are reported to possess varied biological activities such as analgesic, antiinflammatory, antipyretic, amoebicidic, trichomonacidal, antibacterial, antimicrobial, and hypoglycemic.[1] α,β-Acetylenic ketones belong to a class of activated acetylenes.[2] Sasaki and Yoshioka[3] have prepared isoxazoles, pyrazoles, 1-carbamoylpyrazoles, and pyrimidines containing nitrofuran ring by the reaction of nitrofuryl-substituted α,β-acetylenic ketones with hydroxylamine, hydrazine, semicarbazide, and benzamidine respectively.

Prompted by the varied biological activity of pyrazoles and as a part of our general search for chemotherapeutically important nitrofuran derivatives,[4,5] a project aimed at the synthesis of 1-aroyl-3(or 5)-(5-nitro-2-furyl)-5(or 3)-aryl-1*H*-pyrazoles was undertaken employing the condensation of nitrofuryl-substituted α,β-acetylenic ketones with different aroyl- and (aryloxyacetyl)hydrazines. In all such condensations hydroxypyrazolines (**5**) are obtained rather than the expected pyrazoles **3** or **4**. Synthesis, characterization, degradation and biological activities of such hydroxypyrazolines **5** carrying nitrofuryl substituent are reported in this paper.

Results and Discussion

3-(5-Nitro-2-furyl)-1-aryl-2-propyn-1-ones (**1**) obtained by the dehydrobromination of 2,3-dibromo-1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones were condensed with the aroylhydrazines and (2-naphthyloxyacetyl)-hydrazine. The condensations were carried out using equimolar reactants in refluxing ethanol. In all the cases hydroxypyrazolines (**5**) were obtained as main products in rather good yields. The structures of the condensation products were established by IR, ^{1}H NMR, mass spectra, and elemental analysis. The hydroxypyrazolines have the structure **5** as shown in Scheme 1.



Scheme 1.

The hydroxypyrazoline structure **5** was assigned to these condensation products on the basis of analytical and spectral data and also by conversion of these hydroxypyrazolines **5** into the known pyrazoles **6** by acid hydrolysis. The IR spectra of the most condensation products **5** showed broad bands around 3400 cm^{-1} suggesting the presence of a hydrogen-bonded hydroxyl group. The amide carbonyl absorption was observed around 1650—1690 cm^{-1}. The pyrazoline structure was further confirmed by recording NMR spectra of a few selected compounds. ^{1}H NMR spectrum of the product **5a** showed a doublet of a doublet centred at δ, 8.0 integrating for two protons which is now assigned to the ortho protons of the aroyl moiety. The signals of the other aromatic protons and one β-proton of the nitrofuran ring overlapped with each other and appeared as a multiplet at δ, 7.25—7.65 integrating for nine protons. A sharp doublet (J=4 Hz) integrating for one proton appearing at δ, 7.0 is attributed to furan 3H. The OH signal of the hydroxypyrazoline appeared as a singlet integrating for one proton at δ, 5.3. The signal due to the CH_2 proton at the prochiral carbon atom of the

† Presented at the 24th Annual Convention of Chemists held at Kolhapur, November 23—26, 1987.

Table 1. Characterization Data of 1-Aroyl-3-(5-nitro-2-furyl)-5-aryl-5-hydroxy-1*H*-pyrazolines (**5**) and pyrazoles **6**

Compd. No.	Ar	R	Mp/°C	Yield	Mol. formula	Analysis Found (Calcd)		
						C	H	N
5a	Phenyl	Phenyl	168	70	$C_{20}H_{15}N_3O_5$	63.30 (63.66	4.19 3.98	11.01 11.14)
5b	Phenyl	*p*-Chlorophenyl	135	68	$C_{20}H_{14}ClN_3O_5$	58.05 (58.32	3.28 3.41	10.36 10.21)
5c	Phenyl	*o*-Hydroxyphenyl	208	65	$C_{20}H_{15}N_3O_6$	59.84 (61.07	3.75 3.82	10.48 10.69)
5d	Phenyl	2-Naphthyloxymethyl	231	64	$C_{25}H_{19}N_3O_6$	65.19 (65.65	4.02 4.16	9.33 9.19)
5e	*p*-Tolyl	Phenyl	149	69	$C_{21}H_{17}N_3O_5$	64.13 (64.45	3.99 4.35	10.52 10.74)
5f	*p*-Tolyl	*p*-Chlorophenyl	176	68	$C_{21}H_{16}ClN_3O_5$	59.51 (59.22	3.97 3.76	9.66 9.87)
5g	*p*-Tolyl	*o*-Hydroxyphenyl	164	65	$C_{21}H_{17}N_3O_6$	62.00 (61.92	4.26 4.18	10.14 10.32)
5h	*p*-Tolyl	2-Naphthyloxymethyl	124	66	$C_{26}H_{21}N_3O_6$	66.57 (66.24	4.63 4.46	8.83 8.82)
6a	Phenyl	—	216	60	$C_{13}H_9N_3O_3$	61.32 (61.18	3.68 3.53	16.33 16.47)
6b	*p*-Tolyl	—	227	63	$C_{14}H_{11}N_3O_3$	62.30 (62.45	4.25 4.09	15.39 15.61)

pyrazoline moiety appeared as two doublets centred at δ, 3.45 and 3.76 each integrating for one proton with a geminal coupling of 18 Hz. This coupling is observed in the hydroxypyrazoline due to the non-equivalence of the CH_2 protons at position 4 of the pyrazoline ring. The structure **5** is further confirmed by recording mass spectrum of **5a** which showed a molecular ion peak at m/z 377 corresponding to the molecular formula $C_{20}H_{15}N_3O_5$ thus confirming the assigned structure. A M−18 peak is also observed in the mass spectrum which indicates the loss of water molecule from the molecular ion. Two more peaks at m/z 105 and 77 are also observed in the mass spectrum of **5a** which are attributed to $C_6H_5\overset{+}{C}O$ and $\overset{+}{C_6H_5}$ respectively. The mp, yield, and analytical data of hydroxypyrazolines **5** are summarized in Table 1.

The hydroxypyrazoline structure **5** for these condensation products was further established by converting these pyrazolines to the known (nitrofuryl)pyrazoles.[6] The hydroxypyrazolines underwent smooth dehydration and debenzoylation when refluxed with ethanolic sulfuric acid. The pyrazoles thus formed were identified by their melting point and reference to literature[6] (see Table 1). Attempts to synthesize 1-aroyl-3-(5-nitro-2-furyl)-5-aryl-1*H*-pyrazoles by the dehydration of pyrazolines **5** in acetic anhydride were however unsuccessful.

Antibacterial Activity. All the hydroxypyrazolines (**5**) were screened for their antibacterial activity against S. *aureus*, A. *aerogenes*, E. *coli*, and B. *subtilis* by disc diffusion method as described earlier.[7] The results of such studies are given in Table 2.

Most of the compounds showed moderate to good antibacterial activity against all the four microorganisms tested at 5 $\mu g\,ml^{-1}$ dilution. Compound **5e** showed the highest activity among the compounds tested.

Table 2. Antibacterial Activity of Compounds **5a—h**

Compd. No.	Minimum inhibitory concentration μg/disc (diameter of inhibition in mm)			
	Bs.	*S.au*	*A.aer*	*E.coli*
5a	5 (9.6)	<5 (16.1)	<5 (10.4)	<5 (11.0)
5b	<5 (13.2)	<5 (19.6)	<5 (10.1)	<5 (9.9)
5c	<5 (11.2)	5 (9.8)	5 (9.4)	<5 (13.2)
5d	<5 (13.3)	15 (12.6)	5 (8.3)	5 (9.4)
5e	<5 (13.8)	<5 (14.8)	<5 (10.4)	<5 (10.1)
5f	<5 (12.5)	15 (10.2)	<5 (10.1)	<5 (10.9)
5g	<5 (11.4)	20 (15.1)	5 (8.6)	5 (9.0)
5h	<5 (10.9)	20 (12.1)	<5 (9.9)	5 (8.7)
Nitrofurazone (for comparison)	<5 (12.65)	<5 (14.45)	<5 (10.20)	<5 (11.15)

Experimental

All the melting points are uncorrected. The ^1H NMR spectra in $CDCl_3$ were recorded with a Bruker WH-200 200-MHz NMR spectrometer and the mass spectra with a JEOL JMS D-300 spectrometer. The IR spectra (KBr pellet) were recorded on a Perkin Elmer IR spectrophotometer.

α,β-Acetylenic ketones (**1**) were prepared by the methods reported.[3] Sustituted benzoylhydrazines were prepared from the corresponding carboxylic acids according to literature methods.[8,9]

General Procedure of Synthesizing Hydroxypyrazoline (5a—h). A mixture of appropriate nitrofuryl-substituted α,β-acetylenic ketone (**1**) (10 mmol) and suitably substituted

benzoylhydrazine (**2**) (10 mmol) in absolute ethanol (100 ml) was refluxed on a water bath for 7 h. The solvent was removed under reduced pressure and the residue was triturated with methanol. The residue was collected by filtration, dried and recrystallized from ethanol. Characterization data are given in Table 1.

General Procedure for the Conversion of Pyrazolines (5) into Pyrazoles (6): A solution of hydroxypyrazoline (**5**) (1 mmol) in ethanol (40 ml) was treated with a solution of concentrated sulfuric acid (5 ml) in ethanol (10 ml). The reaction mixture was refluxed for 3 h. The contents were cooled and diluted with water. Yellow precipitate of pyrazoles **6** were collected by filtration and recrystallized from ethanol. Treatment of **5a** as above gave pyrazole (**6a**). Similar treatment of **5g** gave pyrazole **6b**. Characterization data of **6a** and **6b** are also given in Table 1.

We are thankful to RSIC, CDRI, Lucknow for elemental analysis and mass spectra and to CSIR New Delhi for a senior research fellowship to K.V.U. We also thank Dr. K. S. Keshavamurthy, University of Alberta for 200 MHz NMR spectra of some of the samples.

References

1) J. Elguero, "Comprehensive Heterocyclic Chemistry," ed by A. R. Katrizky and C. W. Rees, Pergamon Press, New York (1984), Vol. 5, p. 291.
2) E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, **6**, 423 (1967); T. F. Rutledge, "Acetylenes and Allenes," Reinhold, New York (1969), p. 232.
3) T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, **44**, 803 (1971).
4) B. S. Holla and K. V. Udupa, *Curr. Sci.*, **57**, 79 (1988).
5) B. S. Holla and K. V. Udupa, *J. Indian Chem. Soc.*, **65**, 524 (1988).
6) R. G. Haber and E. Schoenberger, *Israel J. Chem.*, **6**, 631 (1968).
7) B. S. Holla, B. Kalluraya, and K. R. Sridhar, *Curr. Sci.*, **56**, 585 (1987).
8) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vols. 1—5, Eyre and Spottiswoode, London (1953).
9) L. Conti, *Boll. Sci. Fac. Chim. Ind. Bologna*, **22**, 13 (1964); *Chem. Abstr.*, **61**, 4253 (1964).