Reaction of α-Keto Hydrazonyl Bromide with Carbanions of some Active Methylene Compounds

A. Sami Shawali (1)

Department of Chemistry, Faculty of Science, University of Kuwait, State of Kuwait

and

A. Osman Abdelhamid (2)

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt.

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Treatment of 1-phenyl-2-bromo-2-arylhydrazonoethanone (VII) with sodium enolates of 2,4-pentanedione, 1-phenyl-1,3-butanedione, dibenzoylmethane, ethyl benzoylacetate, acetoacetanilide, and of benzoylacetanilide in ethanol afforded the substituted pyrazoles, VIII-XIII, respectively. The results show that VII, unlike 1-phenyl-2-bromo-2-hydroximinoethanone (V), is not easily deprotonated by carbanions; and that its reactions with β-diketones, β-keto esters, and β-keto amides follow one and the same mechanism. The structures of the products (VIII-XIII) were inferred from their elemental analyses and spectral data.

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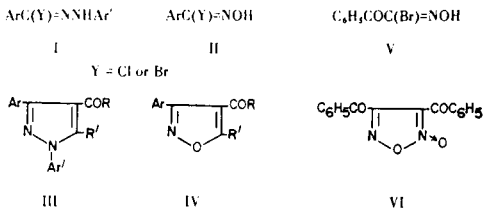
Hydrazonyl halides of type I and α-halogeno-oximes (II) have been known to react with the sodium enolates of β-diketones and give respectively the 4-acyl derivatives of pyrazoles (III) (3,4) and of oxazoles (IV)(5). A similar reaction takes place with β-keto esters (3-5). Mukaiyama and coworkers (6) have recently reported, however, that treatment of 1-phenyl-2-bromo-2-hydroximinoethanone (V) with sodium enolate of dibenzoylmethane afforded dibenzoylfuroxane (VI), *via* the dimerization of benzoylcyanide *N*-oxide intermediate. This finding prompted the investigation of the reaction of the related 1-phenyl-2-bromo-2-phenylhydrazonoethanone (VII) with carbanions. Our object was, on one hand, to examine the extent to which the presence of a carbonyl conjugated with the hydrazone group can modify the reactions of VII with carbanions; and on the other, to prepare pyrazole derivatives that are useful in the formation of 5-5, 5-6, and 5-6-6 heterocycles. To our knowledge, there have been no reports on the use of VII in such reactions, although the parent halide VIIa (Ar = Ar′ = C_6H_5) has been known for over twenty years (7).

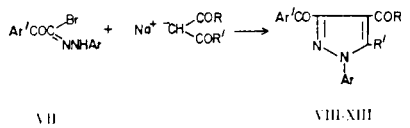


We now wish to report the results of the reactions of a series of 1-phenyl-2-bromo-2-arylhydrazonoethanones (VIIa-h) with sodium enolates of 1,4-pentanedione, 1-phenyl-1,3-butanedione, dibenzoylmethane, ethyl benzoylacetate, acetoacetanilide, and of benzoylacetanilide. The results are formulated in Scheme 1 and the products obtained are given in Tables I-III.

Results and Discussion.

Addition of VII to an ethanolic solution of sodium enolate of 2,4-pentanedione yielded 1-phenyl-3-benzoyl-4-acetyl-5-methylpyrazoles (VIII) in 78-84% yield. Reactions of VII with sodium enolates of 1-phenyl-1,3-butanedione and dibenzoylmethane proceeded similarly and gave the corresponding 1-aryl-3-aroyl-4-acetyl-5-phenylpyrazoles (IX) and 1-aryl-3-aroyl-4-benzoyl-5-phenylpyrazoles (X), respectively. The structures of the products VIII-X were established by elemental analyses and by study of their spectra. Thus, the ir spectra of VIII and IX (KBr) revealed, in each case, the existence of acetyl CO (1685 cm^{-1}), benzoyl CO (1660 cm^{-1}), and C=N (1620 cm^{-1}) bands. The nmr spectra of VIII in deuteriochloroform showed, in addition to an aromatic proton multiplet at 7.0-8.5 ppm, two common singlets at δ 2.65 (3H, CH_3CO) and δ 2.41 (3H, 5-CH_3) ppm. The nmr spectra of IX in deuteriochloroform showed a characteristic singlet at δ 2.22 (3H, CH_3CO), and an aromatic multiplet at δ 7.2-8.6

Scheme I



VII VIII-XIII

VIII, R = R' = Me XI, R = OEt; R' = C_6H_5
IX, R = Me; R' = C_6H_5 XII, R = NHAr''; R' = Me
X, R = R' = C_6H_5 XIII, R = NHAr''; R' = C_6H_5

a, Ar = Ar' = Ar'' = C_6H_5
b, Ar = 4-ClC_6H_4; Ar' = Ar'' = C_6H_5
c, Ar = 4-$NO_2C_6H_4$; Ar' = Ar'' = C_6H_5
d, Ar = 4-MeC_6H_4; Ar' = Ar'' = C_6H_5
e, Ar = 4-$MeOC_6H_4$; Ar' = Ar'' = C_6H_5
f, Ar = C_6H_5; Ar' = 4-$NO_2C_6H_4$
g, Ar = C_6H_5; Ar' = 4-MeC_6H_4
h, Ar = C_6H_5; Ar' = 4-BrC_6H_4
i, Ar = C_6H_5; Ar' = 4-BrC_6H_4; Ar'' = 4-MeC_6H_4
j, Ar = 4-ClC_6H_4 Ar' = C_6H_5; Ar'' = 4-MeC_6H_4

ppm. Compound Xd, taken as a typical example of series X shows in its nmr spectrum a singlet at δ 2.50 (3H, 1-*p*-CH_3Ar) and a multiplet at δ 7.0-8.4 (19H, aromatic) ppm. The electronic spectra of compounds VIII-X in ethanol showed in each case a characteristic pyrazole absorption maximum in the region 250-260 nm (9).

Treatment of VII with sodium enolates of ethyl benzoylacetate, acetoacetanilide, and benzoylacetanilide in ethanol produced the corresponding 1-aryl-3-aroyl-4-carbethoxy-5-phenylpyrazoles (XI); 1-aryl-3-aroyl-4-carbanilino-5-methylpyrazoles (XII); and 1-aryl-3-aroyl-4-carbanilino-5-phenylpyrazoles (XIII), respectively. The structures of these products were derived from their elemental and spectral data. The electronic spectra were similar to those of typical pyrazole derivatives (9); each compound exhibits a maximum in the 300-250 nm region (log ε 4.20-4.97) (Tables II-III). Their ir spectra were also consistent with the assigned structures XI-XIII. For example, compound XIf exhibits an ester CO (1735 cm^{-1}) and a benzoyl CO (1660 cm^{-1}), and C=N (1615 cm^{-1}) in its ir spectrum. The spectra of all XII-XIII exhibit an anilide CO (1670 cm^{-1}) and a benzoyl CO (1650 cm^{-1}) bands. The structures of the products so formed were finally established by their nmr spectra. Thus, the spectra of XI prepared showed the following signals: an aromatic proton multiplet at δ 7.0-8.4, a quartet at δ 4.10 (2H, J = 7 Hz, -OC*H*$_2$CH$_3$) and a triplet at δ 1.0 (3H, J = 7 Hz, -OCH$_2$-C*H*$_3$) ppm. The spectra of XII all show a singlet at δ 2.75 (3H, 5-CH_3) ppm. Compounds of series XIII exhibit a rather simple pattern. For example, XIIId in deuteriochloroform shows a singlet at δ 2.26 (3H, 1-*p*-CH_3Ar), and a multiplet at δ 7.0-8.5 (20H, aromatic and anilide NH) ppm. These data together with the fact that none of the products give color with ethanolic ferric chloride solution and couple with diazotized aniline, indicate that the assigned structures XI-XIII are correct.

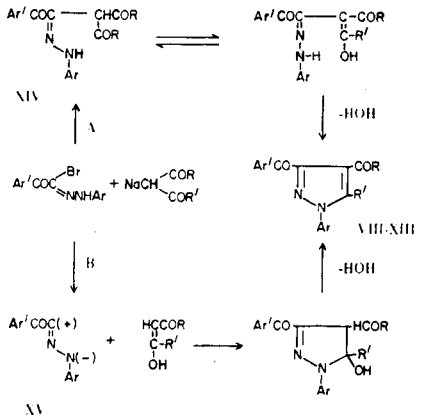
The foregoing results may be considered in terms of two alternative mechanisms illustrated in Scheme 2. In the substitution sequence (A), it is assumed that the carbanion attacks the hydrazonyl halide VII to give the open chain intermediate hydrazone (XIV) (10); which then undergoes cyclization through the loss of the elements of water. Alternatively, dehydrobromination of VII by the carabion may occur to give the nitrilimine intermediate (XV) (11). Addition of the latter to the enol double bond, followed by dehydration, would lead to the products (VIII-XIII) (sequence B). Although no attempt was made to isolate or identify the reaction intermediate, the substitution sequence seems to be much more plausible for the reaction studied than sequence B. This is because, if XV were involved, it might dimerize to yield the tetrazine XVI (8).

Table I

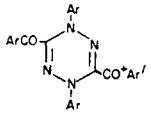
Compound No.	M.p., °C	Molecular Formula	Nitrogen, % Calcd.	Found	λ max (Ethanol) (log ε)
		1-Aryl-3-aroyl-4-acetyl-5-methylpyrazoles (VIII):			
VIIIb	86-87	$C_{19}H_{15}ClN_2O_2$ (a)	8.26	8.49	250 (4.393)
VIIIc	158	$C_{19}H_{15}N_3O_4$	12.03	12.29	260 (4.467)
VIIIf	132-133	$C_{19}H_{15}N_3O_4$	12.03	12.08	250 (4.368)
VIIIg	93-94	$C_{20}H_{18}N_2O_2$	8.80	9.01	265 (4.329)
		1-Aryl-3-aroyl-4-acetyl-5-phenylpyrazoles (IX):			
IXa	120-121	$C_{24}H_{18}N_2O_2$	7.64	7.46	255 (4.498)
IXb	162	$C_{24}H_{17}ClN_2O_2$	6.99	7.13	251 (4.498)
IXc	140	$C_{24}H_{17}N_3O_4$ (b)	10.21	10.36	263 (4.505)
IXd	162-163	$C_{25}H_{20}N_2O_2$	7.36	7.19	258 (4.548)
IXe	130	$C_{25}H_{20}N_2O_3$	7.06	7.04	258 (4.541)
IXg	152	$C_{25}H_{20}N_2O_2$	7.36	7.60	262 (4.407)

(a) *Anal.* Calcd.: C, 67.35; H, 4.46. Found: C, 67.58; H, 4.51. (b) *Anal.* Calcd.: C, 70.06; H, 4.16. Found: C, 70.25; H, 4.17.

Scheme 2



The lack of formation of the latter seems to favor sequence A. The finding that V undergoes dehydrobromination whereas VII does not, might be rationalized in terms of the difference in acidity of the oxime OH and the hydrazone NH protons. The former proton, being more acidic than the hydrazone one, can be easily eliminated by bases, such as carbanions, to give an anion that loses, in turn, the bromine atom forming the corresponding nitrile oxide, which may dimerize readily.



XVI

The present work suggests that VII, unlike V, is not easily dehydrohalogenated by carbanions, and that VII is an eminently suitable intermediate for synthesis of 3-aroyl-3,4-diacyl-, and 3-aroyl-4-carethoxypyrazole derivatives. Work in progress shows that the latter products are useful intermediates in the formation of new 5-5, 5-6, and 5-6-6 fused heterocycles. The results will be described in a future report.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured as potassium bromide pressings on a Pye-Unicam SP1000 spectrophotometer. The nmr spectra were recorded in deuteriochloroform on a Varian T60-A spectrometer with TMS as internal reference. The uv spectra were run on a Pye-Unicam SP8000 spectrophotometer. Elemental analyses were carried out by Alfred Bernhardt, Mikro-analytisches Laboratorium, West Germany. 1-Phenyl-2-bromo-2-arylhydrazonoethanone and its substituted derivatives were synthesized as previously described (8). Acetoacetanilide and benzoylacetanilide were prepared by literature methods (12). 2,4-Pentanedione, 1-phenyl-1,3-butanedione, dibenzoylmethane, and ethyl benzoylacetate were of commerical origin.

Substituted Pyrazoles (VIII-XIII). General Procedure.

The appropriate active methylene compound (0.01 mole) was added to an ethanolic sodium ethoxide solution (prepared from sodium metal (0.23 g., 0.01 g.-atom) and 50 ml. of absolute ethanol). After stirring for 10 minutes, VII (0.01 mole) was added and stirring was continued for a further 30 minutes. The reaction mixture was then left overnight at room temperature. The product was collected by (a) filtration or (b) dilution of the reaction mixture with water followed by filtration; then washed, dried and purified by recrystallization from ethanol. The compounds prepared and their physical properties are listed in Tables I-III.

Table II

Compound No.	M.p., °C	Molecular Formula	Nitrogen, % Calcd.	Found	λ max (Ethanol) (log ε)
		1-Aryl-3-aroyl-4-benzoyl-5-phenylpyrazoles (X).			
Xa	179	$C_{29}H_{20}N_2O_2$ (a)	6.54	6.55	
Xb	168	$C_{29}H_{19}ClN_2O_2$	6.05	6.24	257 (4.658)
Xc	182	$C_{29}H_{19}N_3O_4$	8.87	9.09	262 (4.518)
Xd	178	$C_{30}H_{22}N_2O_2$	6.33	6.18	256 (4.624)
Xg	191	$C_{30}H_{22}N_2O_2$	6.33	6.30	259 (4.558)
		1-Aryl-3-aroyl-4-carbethoxy-5-phenylpyrazoles (XI).			
XIc	153	$C_{25}H_{19}N_3O_5$ (b)	9.52	9.78	258 (4.160)
XId	105	$C_{26}H_{21}N_2O_3$	6.84	6.90	253 (4.200)
XIf	155	$C_{25}H_{19}N_3O_5$	9.52	9.29	260 (4.463)
XIh	122	$C_{25}H_{19}BrN_2O_3$	5.89	5.58	263 (4.475)

(a) *Anal.* Calcd.: C, 81.29; H, 4.70. Found: C, 80.88; H, 4.95. (b) *Anal.* Calcd.: C, 68.02; H, 4.34. Found: C, 68.47; H, 4.36.

Table III

Compound No.	M.p., °C	Molecular Formula	Nitrogen, % Calcd.	Found	λ max (Ethanol) (log ε)
		1-Aryl-3-aroyl-4-carbanilino-5-methylpyrazoles (XII).			
XIIa	162	$C_{24}H_{19}N_3O_2$ (a)	11.01	11.17	256 (4.558)
XIIb	157	$C_{24}H_{18}ClN_3O_2$	10.10	10.34	257 (4.624)
XIId	154	$C_{25}H_{21}N_3O_2$	10.63	10.52	256 (4.340)
XIIe	162	$C_{25}H_{21}N_3O_3$	10.21	10.14	258 (4.615)
XIIi	163	$C_{25}H_{20}BrN_3O_2$	8.86	9.04	265 (4.586)
XIIj	181	$C_{25}H_{20}ClN_3O_2$	9.77	10.09	260 (4.674)
		1-Aryl-3-Aroyl-4-carbanilino-5-phenylpyrazoles (XIII).			
XIIIa	170	$C_{29}H_{21}N_3O_2$	9.47	9.32	252 (4.451)
XIIIb	200	$C_{29}H_{20}ClN_3O_2$	8.79	8.68	255 (4.645)
XIIId	191	$C_{30}H_{23}N_3O_2$	9.18	9.20	255 (4.678)
XIIIh	193	$C_{29}H_{20}BrN_3O_2$	8.04	7.89	260 (4.614)

(a) *Anal.* Calcd.: C, 75.57; H, 5.02. Found: C, 75.32; H, 4.89.

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(1) To whom all inquiries should be addressed.

(2) Taken in part from the Ph.D. Thesis of Mr. Abdou Osman Abdelhamid, University of Cairo.

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