New Routes to Aroylthiadiazolines and Arylazothiazoles from Phenylglyoxalyl Bromide Arylhydrazones and Phenacyl Thiocyanate

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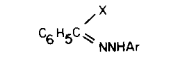
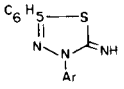
Reaction of phenylglyoxalyl bromide arylhydrazones (III) with thiourea in ethanol produces 2-amino-4-phenyl-5-arylazothiazoles (XI) instead of the expected 2-benzoyl-4-aryl-5-imino-Δ^2-1,3,4-thiadiazolines (V) obtained from III and potassium thiocyanate. Phenacyl thiocyanate (IV) couples with diazotized anilines to give V. The mechanisms of formation of V and XI from VI and III, respectively, are postulated. Nitrosation of V gives the corresponding *N*-nitroso derivatives (VII), which decompose upon refluxing in xylene to give 2,4-disubstituted Δ^2-1,3,4-thiadiazolin-5-ones (VIII). The thiadiazolines V give the respective *N*-acyl derivatives IX and X with acetic anhydride and benzoyl chloride in pyridine.

Earlier studies have shown that hydrazonyl halides I produce the corresponding 2,4-diaryl-5-imino-Δ^2-1,3,4-thiadiazolines (II) upon treatment with either thiourea or potassium thiocyanate (3). In an attempt to examine the effect of the presence of a carbonyl conjugated with the hydrazone group on the course of such reactions, we have investigated the reactions of phenylglyoxalyl bromide arylhydrazones (III) with potassium thiocyanate and thiourea. In the course of this investigation, we studied also the azo coupling of phenacyl thiocyanate (IV). To date there has been no data published regarding the azo coupling of active methylene thiocyanate compounds other than that given in our preliminary recent communication (4). The results of the reactions studied are summarized in Scheme 1.



I

Ar = C_6H_5; X = Cl
Ar = 2,4-$Br_2C_6H_3$; X = Br



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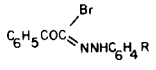
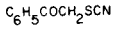


III

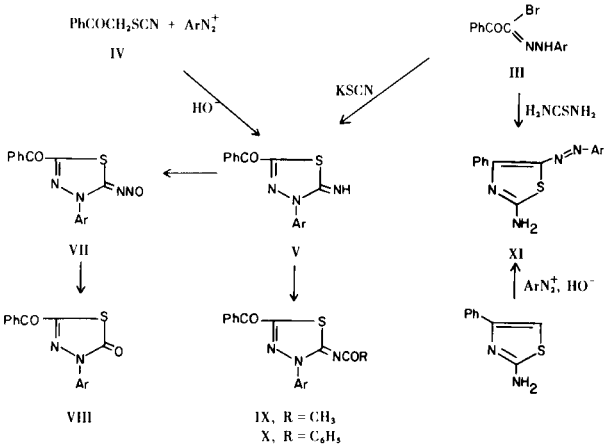


IV

Results and Discussion

Phenacyl thiocyanate couples with aryldiazonium salts in a sodium acetate buffered solution of ethanol to give 2-imino-3-aryl-5-benzoylthiadiazolines (V). The structures

Scheme 1

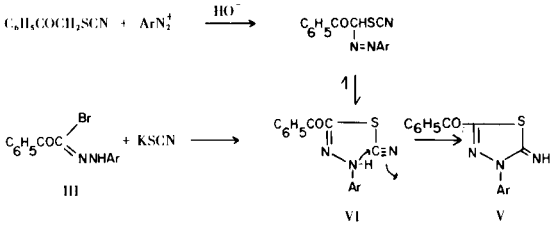


a, Ar = C_6H_5; b, Ar = *p*-MeC_6H_4; c, Ar = *p*-ClC_6H_4; d, Ar = *p*-$O_2NC_6H_4$; e, Ar = *p*-$MeOC_6H_4$

of the latter were deduced from their spectra and from their chemical reactions described below. Ir spectra of V revealed no bands in the 2000-2200 cm^{-1} region due to a free -SCN group. The spectra contained, however, bands at 3320 cm^{-1} (imino NH); 1650 cm^{-1} (C=O) and at 1610 cm^{-1} (C=N). The absorption pattern of V in the uv region was, in each case, characterized by three maxima in the 380-360, 280-250 and 230-210 nm regions (Table I). As an example of the series, the nmr spectrum of V (Ar = *p*-$CH_3C_6H_4$) in deuterated chloroform showed a multiplet at δ 7.0-8.5 (10H, aromatic and imino NH) and a singlet at

δ 2.36 (3H, CH_3Ar) ppm. Upon shaking with deuterium oxide a new singlet appeared at δ 4.50 ppm assignable to DOH proton and the multiplet at δ 7.0-8.5 ppm corresponds to nine protons only. The structures of V were further indicated by independent synthesis. Thus treatment of III with excess potassium thiocyanate in ethanol at room temperature produced products that proved to be identical in all respects with those of V prepared above. These results indicate that both the azo coupling of IV and the reaction of III with potassium thiocyanate proceed through one common intermediate. The latter is, undoubtedly, the hydrazone VI, which cyclizes readily to give V (Scheme 2).

Scheme 2



Nitrosation of V gave the nitroso derivatives VII. The electronic absorption spectra of the latter in ethanol (Table II) showed two common maxima in the 510-470 (log e < 2) and 340-365 (log e > 4) nm regions. These are assigned to the n-π^* and π-π^* transitions of the nitrosoimino group (5). These assignments are supported by the fact that the former maximum shifts towards the shorter wavelength side by changing solvents from non-polar to polar ones, whereas the latter absorption (*i.e.*, that near 358 nm) is unaffected by the polarity of the solvent. Ir spectra of VII showed no NH band, but contained a common band at 1650 cm^{-1} (C=O). The nmr spectrum of VII (Ar = *p*-$CH_3C_6H_4$) exhibits a multiplet at δ 7.0-8.4 (9H, aromatic) and a singlet at δ 2.40 (3H, *p*-CH_3Ar) ppm.

All compounds VII decomposed to the corresponding thiadiazolones VIII (Table II) upon refluxing in xylene. The products VIII in ethanol showed no absorption in the visible region. The uv spectra showed however, three maxima in the 340-300, 290-250, and 240-200 nm regions. Ir spectra (potassium bromide) of VIII revealed in each case two CO absorption bands near 1650 and 1705 cm^{-1}. The nmr spectrum of VIII (Ar = *p*-$CH_3C_6H_4$) in deuterated chloroform showed a singlet at δ 2.40 (3H, *p*-$CH_3C_6H_4$-) and a multiplet in the aromatic region of δ 7.0-8.5 (9H, aromatic) ppm.

Acylation of V with acetic anhydride (and with benzoyl chloride in pyridine) yielded the corresponding *N*-acetyl (and *N*-benzoyl) derivatives, IX and X, respectively. Both elemental and spectral data were consistent with the assigned structures of the products IX and X. The nmr spectrum of IX (Ar = *p*-$CH_3C_6H_4$-) in deuterated chloroform revealed the presence of two singlets at δ 2.34 (3H, CH_3CON-) and δ 2.41 (3H, *p*-CH_3Ar-) and a multiplet at δ 7.0-8.5 (9H, aromatic) ppm. Ir spectra of IX contained bands at 1650 (benzoyl CO) and 1630 (CH_3CON=) cm^{-1}. The uv data are summarized in Table III.

Treatment of III with excess thiourea in ethanol yielded products which were identified as 5-arylazo-4-phenyl-2-aminothiazoles (XI). The structures of the latter were inferred from their spectral and elemental analyses. The nmr spectrum of XI in deuterated chloroform showed, in each case, an NH_2 singlet at δ 5.98 ppm. Upon addition of deuterium oxide, the latter singlet disappeared and a new singlet appeared at δ 4.50 ppm. The electronic absorption spectra of these products, XI, (ethanol) were different from those of V. As shown in Table IV, each compound exhibits two intense maxima (log e > 4) in the 470-420 and 280-260 nm regions. The structures of XI were confirmed further by comparison with authentic samples prepared from 2-amino-4-phenylthiazole and diazotized anilines.

Scheme III shows two possible pathways that account for the formation of XI from III and thiourea. It is assumed that the first stage involves formation of a carbon-sulfur link by elimination of a molecule of hydrogen bromide to give XII, by analogy to the reaction of thioamides with α-halo carbonyl compounds (9). In the second stage, ring closure occurs through direct attack by either the imino- (pathway A) or the amino nitrogen atom (pathway B) on the carbonyl carbon, and a molecule of water is then eliminated.

Scheme 3

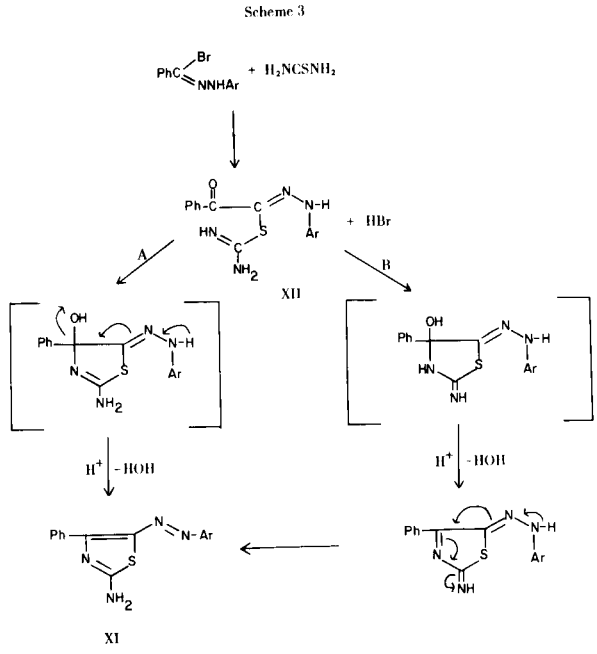


Table I

2-Benzoyl-4-aryl-5-imino-Δ^2-1,3,4-thiadiazolines (V)

No.	4-Ar	M.p., °C	Method	Molecular Formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	λ max (Ethanol) (log ε)
Va	C_6H_5	89-90	A,B	$C_{15}H_{11}N_3OS$ (a)	14.93	14.78	11.39	11.23	368 (3.823); 265 (4.035); 215 (4.003)
Vb	*p*-MeC_6H_4	110	A,B	$C_{16}H_{13}N_3OS$	14.22	14.24	10.85	10.76	370 (3.989); 265 (4.151); 219 (4.130)
Vc	*p*-ClC_6H_4	127	A,B	$C_{15}H_{10}ClN_3OS$	13.30	13.13	10.15	9.96	366 (4.047); 268 (4.272); 220 (4.259)
Vd	*p*-$NO_2C_6H_4$	191	A	$C_{15}H_{10}N_4O_3S$	17.16	16.92	9.82	9.93	372 (4.219); 267 (4.240); 230 (4.240)
Ve	*p*-$MeOC_6H_4$	128	A,B	$C_{16}H_{13}N_3O_2S$	13.49	13.33	10.29	10.16	370 (3.947); 265 (4.144); 225 (4.248)
Vf	*p*-BrC_6H_4	138	A	$C_{15}H_{10}BrN_3OS$	11.66	11.69	8.90	8.91	370 (4.023); 268 (4.255); 220 (4.284)
Vg	*m*-ClC_6H_4	106	A	$C_{15}H_{10}ClN_3OS$	13.30	13.14	10.15	10.17	368 (4.033); 265 (4.245); 217 (4.267)
Vh	*m*-BrC_6H_4	112	A	$C_{15}H_{10}BrN_3OS$	11.66	11.50	8.90	8.66	366 (3.956); 265 (4.174); 223 (4.404)
Vi	*p*-$HO_2CC_6H_4$	204	A	$C_{16}H_{11}N_3O_3S$	12.91	12.84	9.85	9.70	370 (4.028); 273 (4.261); 217 (4.147)
Vj	*m*-$NO_2C_6H_4$	177	A	$C_{15}H_{10}N_4O_3S$	17.16	17.00	9.82	9.90	360 (3.960); 262 (4.315); 214 (4.186)
Vk	*m*-MeC_6H_4	80-81	A	$C_{16}H_{13}N_3OS$	14.22	14.13	10.85	10.81	368 (4.033); 265 (4.214); 216 (4.245)

(a) *Anal.* Calcd.: C, 64.04; H, 3.94. Found: C, 64.28; H, 3.88.

Table II

Compound No.	4-Ar,	M.p., °C	Molecular Formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	λ max (Ethanol) (a) (log ε)
			2-Benzoyl-4-aryl-5-nitrosoimino-Δ^2-1,3,4-thiadiazolines (VII)					
VIIa	C_6H_5	135	$C_{15}H_{10}N_4O_2S$	18.05	17.94	10.33	10.35	480 (1.74); 360 (4.293); 277 (4.362)
VIIb	*p*-MeC_6H_4	134	$C_{16}H_{12}N_4O_2S$	17.27	17.04	9.88	9.72	480 (1.754); 358 (3.966); 275 (3.966)
VIIc	*p*-ClC_6H_4	115	$C_{15}H_9ClN_4O_2S$	16.25	16.30	9.30	9.16	480 (1.842); 360 (4.366); 280 (4.478)
VIId	*p*-$NO_2C_6H_4$	137	$C_{15}H_9N_5O_4S$	19.71	19.56	9.02	9.00	480 (1.856); 360 (4.270); 276 (4.399)
VIIe	*p*-$MeOC_6H_4$	132	$C_{16}H_{12}N_4O_3S$	16.46	16.27	9.42	9.50	480 (1.802); 358 (3.723); 288 (3.794)
			2-Benzoyl-4-aryl-Δ^2-1,3,4-thiadiazolin-5-ones (VIII)					
VIIIa	C_6H_5	112	$C_{15}H_{10}N_2O_2S$	9.92	10.00	11.35	11.24	322 (3.989); 270 (3.926)sh; 246 (4.028)
VIIIb	*p*-MeC_6H_4	112	$C_{16}H_{12}N_2O_2S$	9.45	9.69	10.82	10.80	328 (3.994); 272 (3.964)sh; 248 (4.126)
VIIIc	*p*-ClC_6H_4	100	$C_{15}H_9ClN_2O_2S$	8.84	8.70	10.12	9.98	322 (4.049); 250 (4.213)sh
VIIId	*p*-$NO_2C_6H_4$	148	$C_{15}H_9N_3O_4S$	12.84	12.68	9.79	9.80	322 (4.299); 262 (4.605)
VIIIe	*p*-$MeOC_6H_4$	94	$C_{16}H_{12}N_2O_3S$	8.97	9.03	10.26	10.34	335 (3.902); 270 (4.065)sh; 252 (4.203)

(a) VIIa (chloroform), λ max (log ε): 500 (1.739); 368 (4.386); 280 (4.395) nm. VIIa (acetic acid), λ max (log ε): 475 (1.79); 358 (4.123); 277 (4.165) nm. VIIb (chloroform), λ max (log ε): 490 (1.770); 367 (4.140); 281 (4.204) nm. VIIb (acetic acid), λ max (log ε): 475 (1.790); 358 (4.137); 280 (4.174) nm. sh, shoulder.

Table III

Compound No.	4-Ar	M.p., °C	Molecular Formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	λ max (Ethanol) (log ε)
			2-Benzoyl-4-aryl-5-*N*-acetylimino-Δ^2-1,3,4-thiadiazolines (IX)					
IXa	C_6H_5	165	$C_{17}H_{13}N_3O_2S$	13.00	13.03	9.91	9.79	333 (4.081); 275 (4.228)
IXb	*p*-MeC_6H_4	131	$C_{18}H_{15}N_3O_2S$	12.45	12.60	9.50	9.32	335 (4.074); 275 (4.267)
IXc	*p*-ClC_6H_4	150	$C_{17}H_{12}ClN_3O_2S$	11.74	11.71	8.96	8.88	323 (4.581); 260 (4.323)
IXd	*p*-$O_2NC_6H_4$	142	$C_{16}H_{12}N_4O_4S$	15.21	15.15	8.70	8.65	320 (4.402); 265 (4.261)
IXe	*p*-$MeOC_6H_4$	137	$C_{18}H_{15}N_3O_3S$	11.89	12.00	9.07	9.10	335 (3.966); 272 (4.249)
			2-Benzoyl-4-aryl-5-*N*-benzoylimino-Δ^2-1,3,4-thiadiazolines (X)					
Xa	C_6H_5	198	$C_{22}H_{15}N_3O_2S$	10.90	10.77	8.32	8.27	342 (4.409); 280 (4.298)sh
Xb	*p*-MeC_6H_4	226	$C_{23}H_{17}N_3O_2S$	10.52	10.35	8.02	8.12	345 (4.301); 275 (4.267)br
Xc	*p*-ClC_6H_4	204	$C_{22}H_{14}ClN_3O_2S$	10.00	9.89	7.63	7.70	340 (4.335); 275 (4.235)sh
Xd	*p*-$O_2NC_6H_4$	226	$C_{22}H_{14}N_4O_4S$	13.01	13.06	7.45	7.30	335 (4.388); 265 (4.301)br
Xe	*p*-$MeOC_6H_4$	206	$C_{23}H_{17}N_3O_3S$	10.11	10.01	7.72	7.67	340 (4.174); 265 (4.235)

sh = shoulder. br = broad band

Table IV

2-Amino-4-phenyl-5-arylazothiazoles

Compound No.	5-Ar	M.p., °C	Molecular Formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	Method of Preparation	Lit. (8) M.p., °C	λ max (Ethanol) (log ε)
XIa	C_6H_5	195	$C_{15}H_{12}N_4S$	19.98	19.74	11.43	11.32	A,B	195	426 (4.457); 263 (4.312)
XIb	*p*-MeC_6H_4	199	$C_{16}H_{14}N_4S$	19.03	18.84	10.89	10.90	A,B	200	430 (4.395); 270 (4.298)
XI	*p*-ClC_6H_4	245	$C_{15}H_{11}ClN_4S$	17.79	17.70	10.18	9.98	A,B	----	444 (4.180); 268 (4.324)
XId	*p*-$NO_2C_6H_4$	254	$C_{15}H_{11}N_5O_2S$	21.52	21.70	9.85	9.79	A,B	254	440 (4.301); 272 (4.301)
XIe	*p*-$MeOC_6H_4$	208	$C_{16}H_{14}N_4OS$	18.05	17.92	10.33	10.34	A,B	----	446 (4.452); 270 (4.362)

The present work establishes that α-keto hydrazonyl bromides, unlike benzhydrazidic halides, give different products in their reactions with potassium thiocyanate and thiourea. Furthermore, the azo coupling of active methylene thiocyanates provides a useful route to substituted thiadiazolines. It is a rapid and efficient procedure that reuqires only readily available starting materials.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra (potassium bromide) were recorded on a Pye-Unicam SP1000 spectrophotometer. Uv spectra were determined on a Pye-Unicam SP8000 spectrophotometer. Nmr spectra (deuterated chloroform) were determined with a Varian T-60A spectrometer using TMS as an internal standard. Phenacyl thiocyanate (IV) (6) and phenylglyoxalyl bromide arylhydrazones (III) (7) were prepared as previously described. Analyses were by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

2-Aroyl-4-aryl-5-imino-Δ^2-1,3,4-thiadiazolines (V).

Method A.

A cold solution (0-5°) of IV (1.7 g., 0.01 mole) and sodium acetate (1.3 g.) in ethanol (50 ml.) was treated, while stirring, with the appropriate diazonium salt (0.01 mole) and left in the ice chest for 8 hours. The solid which formed was collected, washed with water, and then recrystallized from ethanol. Compounds V were obtained in 70-85% yield. The compounds prepared and their physical properties are listed in Table I.

Method B.

To a suspension of the appropriate III (0.005 mole) in ethanol (50 ml.), a solution of potassium thiocyanate (0.01 mole) in water (10 ml.) was added, and the mixture was stirred for 4 hours at room temperature. During this period, the material went into solution and a new solid was formed. The latter was collected, washed with water, and purified by recrystallization from ethanol. By this method, compounds V were obtained in 75-80% yields. The spectra (uv, ir, nmr) and melting points of these products were identical with those of the products obtained by Method A (Table I).

Nitrosation of VII. General Procedure.

A solution of V in acetic acid (30 ml.) was treated with a saturated aqueous solution of sodium nitrite while stirring (30 minutes). The reddish product which precipitated was collected and recrystallized from ethanol. 2-Aroyl-4-aryl-5-nitrosoimino-Δ^2-1,3,4-thiadiazolines (VII) were obtained in almost quantitative yield (Table II).

2-Aroyl-4-aryl-Δ^2-1,3,4-thiadiazolin-5-ones. General.

The appropriate nitroso derivative (VII) (1 g.) was refluxed in xylene (40 ml.) for 30 minutes and left overnight at room temperature. The solvent was removed under reduced pressure and a small amount of ethanol was added to the residue. The solid which formed was collected and recrystallized from ethanol. The products VIII (Table II) were obtained in 80-93% yields.

Acylation of V.

Compound V (1 g.) was refluxed in acetic anhydride (20 ml.) for 15 minutes, cooled and poured on crushed ice. The crude solid which precipitated was collected and recrystallized from ethanol. The benzoylation of V was effected by refluxing equimolecular amounts of V and benzoyl chloride in pyridine (6 ml./mmole) for 20 minutes, cooled and poured on ice. Recrystallization form acetic acid gave X in 65-78% yields (Table III).

2-Amino-4-aryl-5-arylazothiazoles (XI).

Method A.

A mixture of the appropriate phenylglyoxalyl bromide arylhydrazone (III) (0.005 mole) and thiourea (0.01 mole) in ethanol (40 ml.) was refluxed for 4 hours, then poured on ice, and two drops of ammonium hydroxide were added. The solid which formed was collected, washed with water, and recrystallized from ethanol, except XIc and XId (Table II) recrystallized from acetic acid. The products XI were obtained in 65-87% yields.

Method B.

A diazonium salt solution, prepared from 0.011 mole of the appropriate aniline and buffered with sodium acetate, was added at 0° to 2-amino-4-phenylthiazole giving 75-88% of XI. The isolated products proved to be identical (m.p., m. m.p., uv, nmr) with those prepared above by method A.

Acknowledgment.

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NOTES AND REFERENCES

(1) To whom all inquiries should be addressed.

(2) Abstracted in part from the Ph.D. Thesis of Mr. Abdou. O. Abdelhamid, University of Cairo, 1975.

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