

Reactions of α -Ketohydrazidoyl Halides with Some Heterocyclic Amines.
Facile Synthesis of Arylazo Derivatives of Fused Heterocycles with
a Bridgehead Nitrogen Atom (1)

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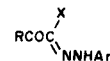
Received October 22, 1982

Arylazo derivatives of imidazo[2,1-*b*]thiazoles, imidazo[1,2-*b*]pyrazoles, imidazo[1,2-*b*]-*s*-triazoles, imidazo[1,2-*a*]pyrimidines, and imidazo[1,2-*a*]pyridines were obtained in good yields from α -keto hydrazidoyl halides and 2-aminothiazole, 5-aminopyrazole, 5-aminotriazole, 2-aminopyrimidine, and 2-aminopyridine, respectively (*cf.* Tables I and II). The structures of the products were assigned and confirmed on the basis of their elemental analyses, spectra, and alternate synthesis wherever possible.

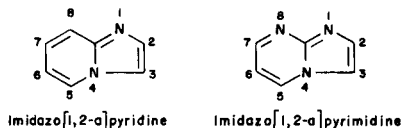
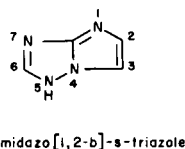
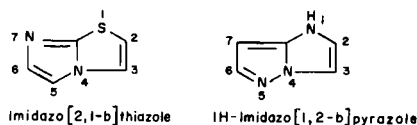
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Introduction.

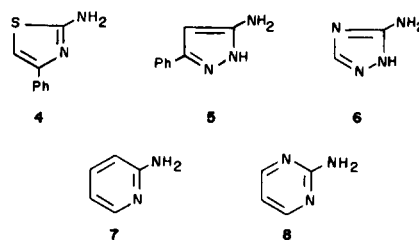
The reaction of several hydrazidoyl halides with benzamidines has been investigated by several groups of authors (4-7). They reported that this reaction leads to the



- 1, R = YC_6H_4 , X = Br
2, R = Me, X = Cl
3, R = OEt, X = Cl



Parent Heterocycles

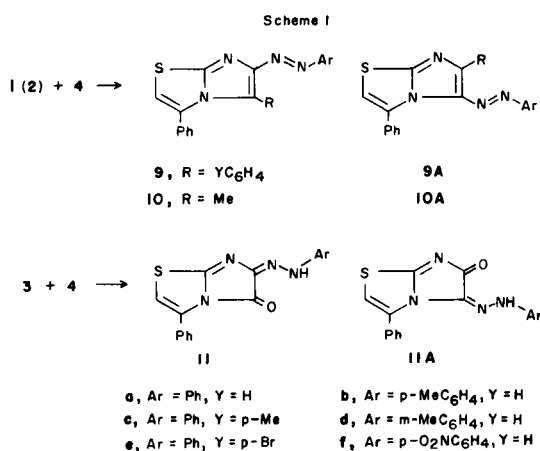


formation of *s*-triazole or imidazolin-2-one derivatives depending on the nature of the hydrazidoyl halide employed. In connection with our research concerning the use of hydrazidoyl halides in the synthesis of fused heterocyclic systems and some of their arylazo derivatives, it was of interest to examine the reaction of α -ketohydrazidoyl hal-

Table I
Imidazo[2,1-*b*]thiazoles, 9-11

Compound No.	Mp, °C (Solvent) (a)	Molecular Formula	C, %	Analysis	
				Calcd.	(Found)
				H, %	S, %
9a	208 (A)	C ₂₃ H ₁₆ N ₄ S	72.60 (72.7)	4.23 (4.2)	8.42 (8.5)
9b	224 (A)	C ₂₄ H ₁₈ N ₄ S	73.07 (73.1)	4.60 (4.5)	8.12 (8.2)
9c	220 (A)	C ₂₄ H ₁₈ N ₄ S	73.07 (73.0)	4.60 (4.4)	8.12 (8.1)
9d	230 (A)	C ₂₄ H ₁₈ N ₄ S	73.07 (73.2)	4.60 (4.6)	8.12 (8.2)
9e	252 (D)	C ₂₃ H ₁₅ BrN ₄ S	59.87 (60.0)	3.27 (3.3)	6.95 (6.9)
10f	198 (A)	C ₁₈ H ₁₃ N ₅ O ₂ S	59.49 (59.5)	3.60 (3.5)	8.82 (8.8)
11f	220 (A)	C ₁₇ H ₁₁ N ₅ O ₃	55.88 (55.9)	3.03 (3.0)	8.77 (8.8)

(a) A, acetic acid; D, dimethylformamide.



ides with some heterocyclic amines which have the amide residue in their structures. In this paper, the results obtained with the reactions of the halides **1-3** with the amines **4-8** are described. The products of the reactions studied are expected to be of commercial and biological interest. For example, the search undertaken in recent years for biologically active imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*] and imidazo[1,2-*c*]pyrimidines, and imidazo[1,2-*b*]pyrazoles has led to the discovery that some of them possess a broad spectrum of biological activity (8-13). Also, the arylazo derivatives of imidazo[2,1-*b*]thiazole have found use as dyes for hydrophobic fibers (14).

Results and Discussion.

When **1a** was refluxed in ethanol with two equivalents of 4-phenyl-2-aminothiazole **4**, three products were isolated. These were identified as the hydrobromide salt of **4**, 3,6-dibenzoyl-1,4-diphenyl-1,4-dihydro-tetrazine (60%),

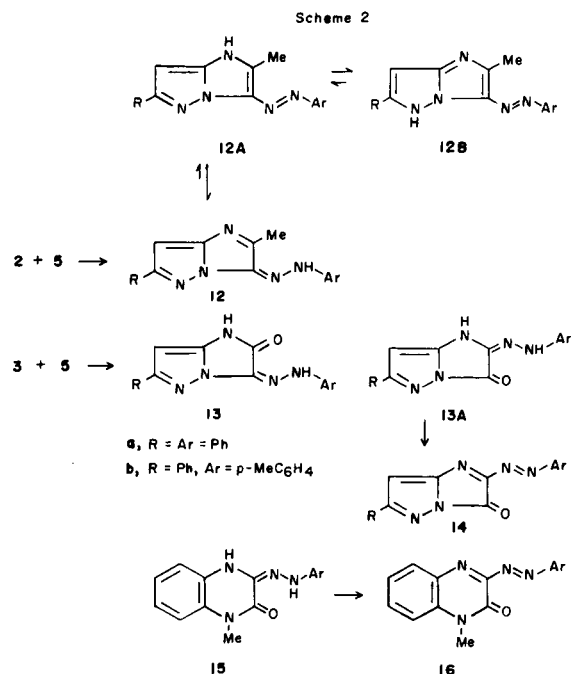


Table II

Synthesized Heterocycles

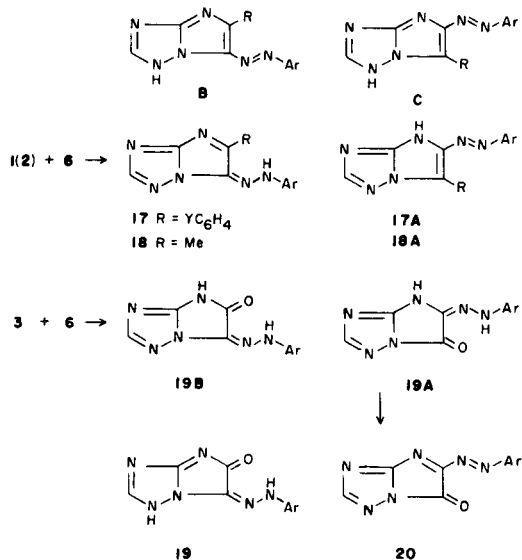
Compound No.	Mp, °C (Solvent) (a)	Molecular Formula	C, %	Analysis	
				Calcd.	(Found)
Imidazo[1,2- <i>b</i>]pyrazoles, 12-13					
12a	172 (E)	C ₁₈ H ₁₇ N ₅	71.26 (71.2)	5.64 (5.5)	28.08 (23.0)
13b	182 (E)	C ₁₈ H ₁₅ N ₅	68.12 (67.9)	4.76 (4.7)	22.07 (22.1)
Imidazo[1,2- <i>b</i>]triazoles, 17-19					
17a	242 (D)	C ₁₆ H ₁₂ N ₆	66.65 (66.5)	4.19 (4.2)	29.15 (29.1)
17b	233 (D)	C ₁₇ H ₁₄ N ₆	67.53 (67.4)	4.66 (4.6)	27.79 (27.9)
17c	237 (D)	C ₁₇ H ₁₄ N ₆	67.53 (67.3)	4.66 (4.7)	27.79 (27.7)
18a	252 (D)	C ₁₁ H ₁₀ N ₆	58.39 (58.2)	4.45 (4.5)	37.15 (37.2)
19a	236 (D)	C ₁₀ H ₈ N ₆ O	52.62 (52.5)	3.53 (3.5)	36.82 (36.7)
Imidazo[1,2- <i>a</i>]pyridines, 24 and 27					
24a	226 (D)	C ₁₄ H ₁₁ N ₅ O ₂	59.78 (60.0)	3.94 (3.9)	24.89 (24.8)
27a	343 (D)	C ₁₃ H ₉ N ₅ O ₃	55.12 (54.8)	3.20 (3.1)	24.73 (24.6)
Imidazo[1,2- <i>a</i>]pyrimidines, 25-26					
25b	188 (E)	C ₁₈ H ₁₃ N ₅	72.22 (72.0)	4.38 (4.5)	23.39 (23.3)
26b	182 (B)	C ₁₃ H ₁₁ N ₅	65.81 (65.6)	4.67 (4.9)	29.52 (29.4)

(a) B, benzene; D, dimethylformamide; E, ethanol.

and 6-phenylazo-3,5-diphenylimidazo[2,1-*b*]thiazole **9a** (20%). However, when equivalent amounts of **1a** and **4** were refluxed in ethanol in the presence of triethylamine, the product **9a** was obtained in a good yield (80%). Similar reactions of the chlorides **2** and **3** with **4** yielded the products **10** and **11**, respectively (Scheme 1 and Table I). The analytical and spectroscopic (ir and pmr) data of the products **9-11** are consistent with their structural assignments. Thus, the ir spectra of the compounds in the series **9** and **10** revealed the absence of CO and NH bands. In the case of **11**, the ir spectra showed a CO band near 1710 cm^{-1} and an NH band near 3360 cm^{-1} (*cf.* Table III). Their pmr spectra revealed the absence of the characteristic signals of the ethoxy group protons. Although these data cannot distinguish between the isomeric structures **11** and **11A**, the latter structure and the structures **9a** and **10a** were rejected on the basis that 2-aminothiazole reacts with α -halo ketones and α -halo esters to give 5-substituted and 5-oxo derivatives of imidazo[2,1-*b*]thiazole (14). Furthermore, coupling of 3,5-diphenylimidazo[2,1-*b*]thiazole with diazotized aniline or *N*-nitrosoacetanilide in ethanol gave a product identical in all respects with **9a**.

The reaction of 3-phenyl-5-aminopyrazole **5** with hydrazidoyl chlorides **2** and **3** in ethanol yielded the corresponding imidazo[1,2-*b*]pyrazole derivatives **12** and **13**, respectively (Scheme 2 and Table II). The structures of the latter products can be assigned on the basis of their elemental analyses and the spectral data. For example, their ir spectra exhibit a weak NH band near 3250 cm^{-1} and, in the case of **13**, a carbonyl band near 1685 cm^{-1} (Table III). The electronic absorption spectra of **12** in chloroform exhibit a maximum in the 400-500 nm region (*cf.* Table IV).

Scheme 3



a, Ar = Ph, Y = H
 b, Ar = *p*-MeC₆H₄, Y = H
 c, Ar = Ph, Y = *p*-Me

This finding seems to be more compatible with the azo structures **12A** and **12B** than with the hydrazone form **12**. The isomeric structure **13A** was discarded since the product obtained from **3** and **5** was recovered unchanged after being subjected to oxidation treatments. Structures of the type **13A** are expected to be oxidized to give **14** by analogy with 1-methyl-3-phenylhydrazono-1,4-dihydroquinoxalin-2-one **16** upon oxidation (15).

Treatment of **1-3** with aminotriazole **6** in ethanol yielded the corresponding imidazo[1,2-*b*]triazole derivatives **17-19** in an almost quantitative yield, respectively (Scheme 3 and Table II). The structures of these products were in agreement with their analytical and spectral data. Thus, the pmr spectrum of **19** indicates the absence of the characteristic signals of the ethyl carboxylate protons. Its ir spectrum showed the carbonyl and NH bands near 1670 and 3280 cm^{-1} , respectively (Table III). By analogy with **13A**, the isomeric structure **19A** was excluded, since all the attempts to oxidize the isolated product by air or hydrogen peroxide (**19A** would give the product **20**) were unsuccessful.

Table III

The Infrared Spectral Data for Selected Compounds (a)

Compound No.	$\tilde{\nu}$ CO (cm^{-1})	$\tilde{\nu}$ NH (cm^{-1})
11f	1710	3360
13b	1685	3250
19a	1670	3280
27a	1680	3200

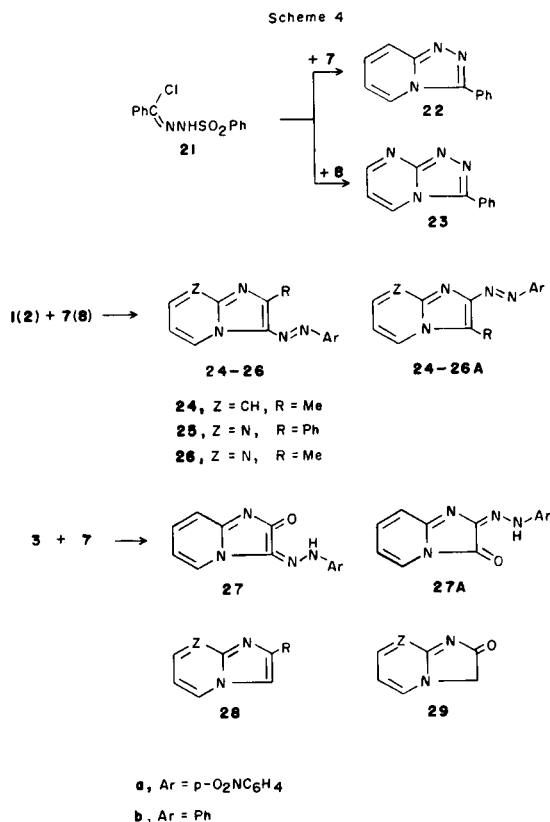
(a) In potassium bromide disc.

Table IV

The Electronic Absorption Spectral Data of Compounds Under Study (a)

Compound No.	λ max, nm (log ϵ) (b)
9a	361 (4.43), 256 sh (4.17)
9b	372 (4.20), 258 sh (3.88)
9c	370 (4.19), 258 sh (3.90)
9d	364 (4.06), 268 (3.91)
9e	365 (4.12), 266 (4.16)
10f	395 (4.30), 358 sh (3.88)
11f	380 (4.23)
12a	426 (4.38), 370 sh (3.92), 246 (4.19)
13b	370 (4.42), 255 (4.55)
17a	350 (4.27), 275 sh (3.55)
17b	360 (4.44), 285 sh (3.41)
17c	350 (4.04), 270 (3.55)
18a	334 (3.71), 274 (3.14)
19a	325 (4.09), 285 sh (3.50)
24a	420 (4.12), 264 (4.56)
27a	410 (3.72), 264 (4.76)
25b	387 (4.51), 280 (4.38), 244 (4.31)
26b	420 (3.78), 360 (3.86), 263 (4.30)

(a) In ethanol. (b) Sh indicates a shoulder.



The behavior of **1-3** towards 2-aminopyridine **7** and 2-aminopyrimidine **8** is different from that of **21** with the same reagents. It was reported that **21** reacts with **7** and **8** and gives 3-phenyl-*s*-triazolo[4,3-*a*]pyridine **22** and 3-phenyl-*s*-triazolo[4,3-*a*]pyrimidine **23**, respectively (7). In the present work, the reaction of **2** and **3** with 1.2 equivalents of 2-aminopyridine in ethanol at reflux temperature gave, in both cases, a single product (as evidenced by thin-layer chromatography) in 70-75% yield. On the basis of their spectral and elemental analyses, the products from **2** were assigned the structure of 2-methyl-3-arylazoimidazo[1,2-*a*]pyridine **24** and those from **3** the structure of 2-oxo-3-arylhydrazonoimidazo[1,2-*a*]pyridine **27** (Table II). A similar reaction of 2-aminopyrimidine with **1** and **2** yielded the corresponding imidazo[1,2-*a*]pyrimidines **25** and **26**, respectively (Scheme 4 and Table II). The isomeric structures **24A** and **27A** were rejected because 2-aminopyridine was reported to react with α -halo ketones and esters to give **28** (Z = CH) and **29** (Z = CH), respectively (16-17). Furthermore, coupling of 2-methylimidazo[1,2-*a*]pyridine **28** (Z = CH, R = Me) with *N*-nitrosoacetanilide or diazotized aniline in ethanol yielded a product identical in all respects with **24** (Ar = Ph). Also, 2-aminopyrimidine reacts similarly with α -halo ketones and α -halo esters and yields **28** (Z = N) and **29** (Z = N), respectively. However, all attempts to couple the latter with the diazotized aniline or *N*-nitrosoacetanilide failed. This failure indicates that

the reactivity of imidazo[1,2-*a*]pyrimidines with electrophiles is lower than that of imidazo[2,2-*a*]pyridines (19).

In conclusion, the results described here indicate that the reaction of α -ketoimidoyl halides with heterocyclic amines appears to be an efficient method for the synthesis of arylazo derivatives of fused heterocycles which requires only readily available starting materials.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide disc) were recorded on Beckman Acculab and Perkin-Elmer 580B spectrophotometers and the electronic absorption spectra were obtained in ethanol using Cary 17 and Cary 118 spectrophotometers. The ir spectral data for several selected compounds under study are shown in Table III, the electronic absorption spectra are summarized in Table IV. The pmr spectra in deuterated chloroform were recorded on a Varian T60-A spectrometer using tetramethylsilane as the internal reference. Elemental analyses were performed by the Microanalytical Laboratory, University of Cairo, Giza, Egypt. The hydrazidoyl halides **1-3** were prepared as previously described (20-23).

Preparation of **9-19**.

Method A.

A mixture of the appropriate hydrazidoyl halide (0.005 mole) and a heterocyclic amine (0.006 mole) in ethanol (50 ml) was refluxed for 3-4 hours and then cooled. The solid that precipitated was collected and crystallized from the appropriate solvent. The compounds prepared by this method are listed in Tables I and II together with their physical constants.

In the case of the reaction of **4** with **1-3**, the precipitates from the reaction mixture were bicyclic products **9-11** obtained in low yields (10-20%). 4-Phenyl-2-aminothiazole hydrobromide was isolated from the filtrates after addition of diethyl ether. Its melting point and mixed melting point with an authentic sample were 180-181° (ethanol-ether).

Method B.

Equivalent amounts of a hydrazidoyl halide (0.005 mole), **4** (0.005 mole), and triethylamine (0.006 mole) in ethanol (50 ml) were refluxed for 3 hours and then cooled. The solid formed was collected and washed with water. The products **9-19** were obtained in this case in almost quantitative yields. The results are summarized in Table I.

Preparation of **24-27**.

A mixture of the appropriate hydrazidoyl chloride (0.005 mole) and 2-aminopyrimidine **8** (0.01 mole) in ethanol (40 ml) was stirred at room temperature for 12 hours. During this period, the material went into solution and a new solid precipitated. It was collected and crystallized from the proper solvent. The results are summarized in Table II.

Preparation of an Authentic Sample of **24b**.

To a solution of 2-methylimidazo[1,2-*a*]pyridine **28** (Z = CH, R = Me) (24) (0.01 mole) in ethanol (30 ml), *N*-nitrosoacetanilide (0.015 mole) was added. The mixture was stirred and left overnight at room temperature. The precipitated solid was collected and crystallized from ethanol. The product obtained was identical in all respects with **24b** prepared from **2** and **7**.

Acknowledgement.

The financial support of this work by the Robert A. Welch Foundation, Houston, Texas, through Grant AH-461 is gratefully acknowledged.

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