Synthesis of some Derivatives of Imidazo[1,2-*a*]pyridine, Pyrazolo[1,5-*b*]imidazole, and 4-(3*H*)Quinazolinone from α-Ketohydrazidoyl Bromides

Ahmad S. Shawali (1), M. Sami and S. Mourad Sherif

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

and

Cyril Párkányi

Department of Chemistry, The University of Texas at El Paso, El Paso, Texas 79968

Received January 14, 1980

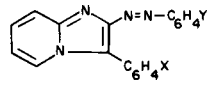
α-Aroyl-*N*-arylhydrazidoyl bromides **1** react with 2-aminopyridine in ethanol and give 2-aryl-3-arylazoimidazo[1,2-*a*]pyridines **2** in 60-75% yield. The reaction of **1** with 3-phenyl-5-aminopyrazole in ethanol leads to 2,6-diaryl-3-arylazo-1*H*-pyrazolo[1,5-*b*]imidazoles **3** in almost quantitative yield. Also, **1** react with anthranilic acid in the presence of triethylamine giving 3-arylamino-2-aroyl-4-(3*H*)quinazolinones **4** in 80-85% yield. The structures of the products were assigned and confirmed on the basis of their elemental analysis and electronic absorption, infrared and nmr spectra.

J. Heterocyclic Chem., **17**, 877 (1980).

One of the authors has shown that α-aroyl *N*-arylhydrazidoyl bromides **1** can be used in the synthesis of several types of one-ring heterocyclic compounds such as 3-aroyl derivatives of pyrazole (2), pyrazoline (3) and thiadiazoline (4), as well as of 5-arylazothiazoles (4). We now wish to report the use of **1** in the synthesis of derivatives of three types of bicyclic systems, *i.e.*, 3-arylazoimidazo[1,2-*a*]-pyridines **2**, 3-arylazo-1*H*-pyrazolo[1,5-*b*]imidazoles **3**, and 3-arylamino-4-(3*H*)quinazolinones **4** (Chart 1). Although many derivatives of imidazo[1,2-*a*]pyridine have been prepared because of their pharmaceutical and microbiological properties (5-7), the 3-arylazo derivatives **2** have not yet been obtained. Also, there are no references in the literature concerning the ring system pyrazolo[1,5-*b*]-imidazole **3**. Interest in the compounds **4** is due to their structural analogy with 3-aryl-2-alkyl-4-(3*H*)quinazolinones which are known to possess sedative activity (8-10).

Results and Discussion.

In each case, treatment of **1** with 1.2 equivalents of 2-aminopyridine in ethanol at reflux temperature gave a single product in 60-75% yield. On the basis of their spectroscopic data and elemental analysis (see Experimental), the products were assigned the structure of 2-aryl-3-arylazoimidazo[1,2-*a*]pyridines **2** (Scheme 1). The isomeric structure **6** for the obtained products was rejected because the reaction of 2-aminopyridine with α-halogenated ketones was reported to yield 2-substituted imidazo[1,2-*a*]-pyridines rather than the corresponding 3-substituted analogs (11). Furthermore, coupling of 2-phenylimidazo-[1,2-*a*]pyridine (12,13) with diazotized anilines or *N*-nitrosoacetanilides in ethanol gave products identical in all respects with **1**.



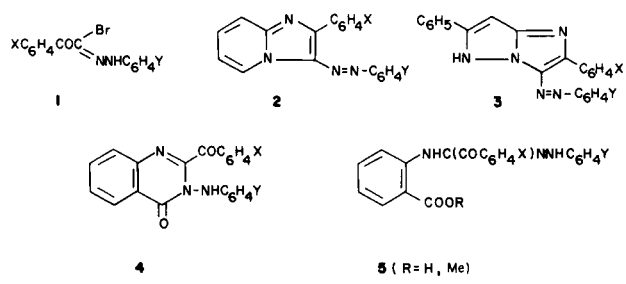
6

When **1** and 3-(5)phenyl-5-(3)aminopyrazole were refluxed in ethanol, 2,6-diaryl-3-arylazo-1*H*-pyrazolo[1,5-*b*]-imidazoles **3** were obtained in almost quantitative yield (Scheme 2). The structure of **3** was in agreement with both the elemental analysis and the spectral data. Thus, e.g., the infrared spectra of **3** exhibit a weak NH-band near 3100 cm^{-1} and no carbonyl band. The electronic absorption spectra of **3** in chloroform contain a maximum in the 400-500 nm region. This excludes the tautomeric structures **8** and **9** which are expected to show a hydrazone absorption pattern.

Reaction of **1** with anthranilic acid in ethanol in the presence of triethylamine readily afforded products identified as 3-arylamino-2-aroyl-4-(3*H*)quinazolinones **4**. The formation of **4** probably follows the sequence presented in Scheme 3. The structure of **4** is supported by their spectral data and elemental analysis. The involvement of the amidrazone (**5**, R = H) as an intermediate is substantiated by the following information. Treatment of **1** with methyl anthranilate in ethanol in the presence of triethylamine results in the formation of **5** (R = Me). The structures of the latter products follow from their method of preparation, elemental analysis and spectral data. The nmr spectra of **5** show, in each case, a singlet near δ 2.00 ppm assignable to the OMe protons. The infrared spectra of **5** reveal two CO bands near 1690 and 1640 and an NH absorption band in the 3100-3300 cm^{-1} region. Their electronic absorption spectra are typical of amidrazones

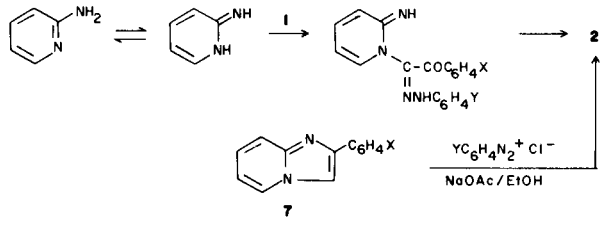
0022-152X/80/050877-04$02.25

Chart I

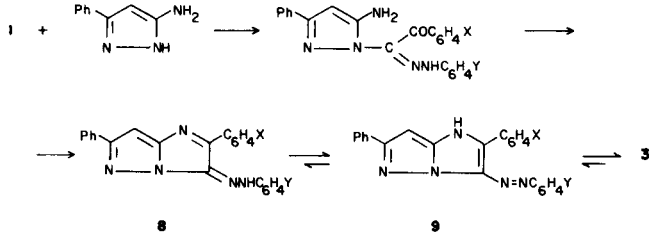


X/Y: a) H/H b) H/4-MeO c) H/4-Me
d) 4-Me/H e) 4-Br/H f) H/4-Br
g) H/4-Cl h) H/4-NO_2

Scheme 1

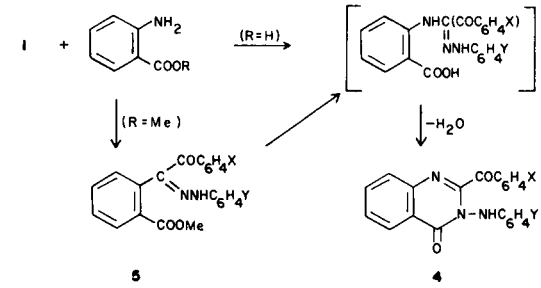


Scheme 2



(14,15) exhibiting three intense maxima (log $\epsilon > 4$) in the regions 350-420, 310-340, and 240-275 nm. Saponification of **5a** (R = Me) followed by acidification results in a product identical with **4a**. The reaction of **1** with anthranilic acid described here appears to be more efficient than that used for the synthesis of 3-aryl-4-(3*H*)quinazolinones from imidoyl chlorides and anthranilic acid (16,17).

Scheme 3



EXPERIMENTAL

Melting points are uncorrected. Electronic absorption spectra were recorded on a Unicam SP-8000 spectrophotometer. Infrared spectra were determined with a Unicam SP-1000 instrument. Nmr spectra were measured in deuteriochloroform on a Varian T-60A spectrometer using TMS as internal reference. The hydrazidoyl bromides **1** were prepared as previously described (3).

2-Aryl-3-arylazoimidazo[1,2-*a*]pyridines (**2**).

Method A.

A mixture of the appropriate hydrazidoyl bromide **1** (0.005 mole) and 2-aminopyridine (0.006 mole) in ethanol (50 ml.) was refluxed for 3-4 hours and then cooled. The precipitated solid was collected, washed with water, and crystallized from ethanol to give **2** in 60-75% yield (Table I).

Method B.

To a solution of 2-phenylimidazo[1,2-*a*]pyridine **7** (12,13) (0.01 mole) in ethanol (30 ml.) was added the appropriate *N*-nitrosoacetanilide (0.015 mole). The mixture was stirred and left overnight at room temperature. The precipitated product was collected and crystallized from ethanol.

Alternatively, 2-phenylimidazo[1,2-*a*]pyridine (0.01 mole) was coupled with diazotized aniline in ethanolic sodium acetate buffered solution at 0° in the usual way. The product obtained by either procedure was identical with the corresponding product prepared by Method A.

1*H*-Pyrazolo[1,5-*b*]imidazoles (**3**).

Equivalent amounts of 3-phenyl-5-aminopyrazole (18) and the appropriate hydrazidoyl bromide **1** were refluxed in ethanol for 3 hours

Table I

Substituted 2-Phenyl-3-phenylazoimidazo[1,2-*a*]pyridines (**2**) (a)

Compound No.	M.p., °C	Molecular Formula	Analysis Calcd. (Found) C, %	H, %	N, %
2a	175	$C_{19}H_{14}N_4$	76.49 (76.42)	4.73 (4.94)	18.78 (18.69)
2b	100	$C_{20}H_{16}N_4O$	73.15 (73.01)	4.91 (4.92)	17.06 (17.06)
2c	147	$C_{20}H_{16}N_4$	76.90 (76.76)	5.16 (5.12)	17.93 (17.85)
2d	146	$C_{20}H_{16}N_4$	76.90 (76.77)	5.16 (5.19)	17.93 (17.79)
2e	215	$C_{19}H_{13}BrN_4$	60.49 (60.37)	3.47 (3.48)	14.85 (14.76)

(a) The electronic absorption spectra of **2a-e** in ethanol reveal in each case four intense maxima (log $\epsilon > 4$) in the 402-406, 310-315, 275-280, and 248-252 nm regions.

Table II

2,6-Diphenyl-3-arylazo-1*H*-pyrazolo[1,5-*b*]imidazoles (**3**)

Compound No.	M.p., °C	Molecular Formula	Analysis Calcd. (Found) N, %
3a	215	$C_{23}H_{17}N_5$	19.27 (19.66)
3b	195	$C_{24}H_{19}N_5O$	17.80 (17.70)
3c	227	$C_{24}H_{19}N_5$ (a)	18.56 (18.62)
3f	232	$C_{23}H_{16}BrN_5$	15.83 (15.71)
3g	228	$C_{23}H_{16}ClN_5$	17.60 (17.90)
3h	240	$C_{23}H_{16}N_6O_2$	20.58 (20.85)

(a) *Anal.* Calcd. (found): C, 76.36 (76.43); H, 5.07 (5.01)%.

Table III

3-Arylamino-2-aroyl-4-(3*H*)quinazolinones (**4**)

Compound No.	M.p., °C	Molecular Formula	Analysis Calcd. (Found) C, %	H, %	N, %
4a	226	$C_{21}H_{15}N_3O_2$	73.88	4.43	12.31
			(73.95)	(4.53)	(12.13)
4c	215	$C_{22}H_{17}N_3O_2$	74.35	4.82	11.82
			(74.70)	(5.20)	(11.36)
4d	225	$C_{22}H_{17}N_3O_2$	74.35	4.82	11.82
			(74.15)	(5.13)	(11.41)

Table IV

Amidrazones (**5**) (R = Me)

Compound No.	M.p., °C	Molecular Formula	Analysis Calcd. (Found) C, %	H, %	N, %
5a	151	$C_{22}H_{19}N_3O_3$	70.76	5.13	11.25
			(70.68)	(5.23)	(11.18)
5c	146	$C_{23}H_{21}N_3O_3$	71.30	5.46	10.84
			(71.22)	(5.51)	(11.03)
5d	156	$C_{23}H_{21}N_3O_3$	71.30	5.46	10.84
			(70.98)	(5.42)	(10.91)
5e	177	$C_{22}H_{18}BrN_3O_3$	58.42	4.01	9.29
			(58.38)	(3.92)	(9.31)

and then cooled. The crude product, usually colored, was collected and crystallized from ethanol to give **3** in an almost quantitative yield (Table II).

3-Arylamino-2-aroyl-4-(3*H*)quinazolinones (**4**).

Anthranilic acid (0.001 mole) was dissolved in ethanol (50 ml.) together with the appropriate hydrazidoyl bromide **1** (0.001 mole) and triethylamine (0.001 mole) was then added. The mixture was refluxed for 4 hours and cooled. The crude product was collected and crystallized from ethanol to give **4** in 80-85% yield (Table III).

Amidrazones **5** (R = Me).

To a suspension of **1** (0.005 mole) in ethanol (50 ml.) was added methyl anthranilate (0.005 mole) and the mixture was refluxed for 2 hours and then cooled. The solid formed was collected, washed with water, and finally crystallized from methanol to afford **5** (R = Me) in 80-90% yield (Table IV).

Conversion of **5a** (R = Me) into **4a**.

Potassium hydroxide (0.5 g.) was dissolved in 95% ethanol (10 ml.), **5a** (R = Me) (0.5 g.) was added, and the mixture was stirred for 2 hours. The reaction mixture was then diluted with water (10 ml.), acidified with concentrated hydrochloric acid, heated on a water bath for 30 minutes, and cooled. The precipitate was filtered, washed with water, and crystallized from ethanol. The obtained product was identical in all respects with **4a**.

Acknowledgment.

The authors gratefully acknowledge financial support from the Robert A. Welch Foundation, Houston, Texas (Grant AH-461).

REFERENCES AND NOTES

(1) To whom inquiries should be addressed.

(2) A. S. Shawali and A. O. Abdelhamid, *Bull. Chem. Soc. Japan*, **49**, 321 (1976).

(3) A. S. Shawali and A. O. Abdelhamid, *J. Heterocyclic Chem.*, **13**, 989 (1976).

(4) A. S. Shawali and A. O. Abdelhamid, *ibid.*, **13**, 45 (1976).

(5) D. J. Pointer, J. B. Wilford and C. D. Bishop, *Nature (London)*, **239**, 332 (1972).

(6) D. J. Pointer and J. B. Wilford, *J. Chem. Soc., Perkin Trans. II*, 2259 (1972).

(7) L. Bolger, R. T. Brittain, D. Jack, M. R. Jackson, L. E. Martin, J. Mills, D. Poynter and M. B. Tyers, *Nature (London)*, **238**, 354 (1972).

(8) J. R. Boissier, C. Dumont and C. Malen, *Therapie*, **13**, 30 (1968).

(9) L. G. Zil'bermints, *Farmakol. Toksikol.*, **27**, 413 (1964).

(10) P. N. Saxena and B. K. Khanna, *Indian J. Med. Res.*, **46**, 63 (1958).

(11) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms", Interscience, New York, N. Y., 1961, Part 1, Chapter, V, p. 460.

(12) A. E. Tschitschibabin, *Ber.*, **58B**, 1704 (1925).

(13) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951).

(14) A. S. Shawali and A. Osman, *Tetrahedron*, **27**, 2517 (1971).

(15) D. G. Neilson, R. Roger, J. W. M. Heatlie and L. R. Newlands, *Chem. Rev.*, **70**, 151 (1971).

(16) O. Mumm and H. Hesse, *Ber.*, **43**, 2505 (1910).

(17) P. R. Levy and H. Stephen, *J. Chem. Soc.*, 985 (1956).

(18) A. Takamizawa and Y. Hamashima, *Yakugaku Zasshi*, **84**, 1113 (1964); *Chem. Abstr.*, **62**, 5276c (1965).