Convenient Synthesis of Fused Heterocycles from α-Ketohydroximoyl Chlorides and Heterocyclic Amines [1]

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Nitroso derivatives of imidazo[1,2-*a*]pyridine (**11, 13, 14**), imidazo[1,2-*a*]pyrimidine (**15**), imidazo[1,2-*a*]pyrazine (**16**), imidazo[1,2-*b*]pyrazole (**17**), and imidazo[1,2-*b*]-1,2,4-triazole (**19**) were obtained in good yields from α-ketohydroximoyl chlorides **3** and 2-aminopyridines (**4-6**), 2-aminopyrimidine (**7**), 2-aminopyrazine (**8**), 5-amino-3-phenylpyrazole (**9**), and 3-amino-2*H*-1,2,4-triazole (**10**), respectively. Under different conditions, the reaction of **3** with 3-amino-2*H*-1,2,4-triazole (**10**) and 2-aminopyrazine (**8**) afforded the noncyclized substitution products **18** and **22**, respectively. The structures of the products were assigned and confirmed on the basis of their elemental analyses, spectral data, and alternate synthesis wherever possible.

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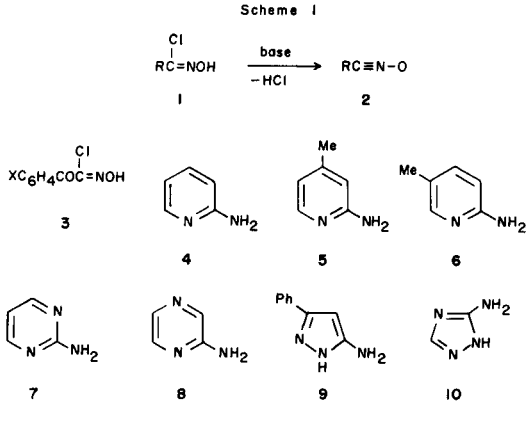
Introduction.

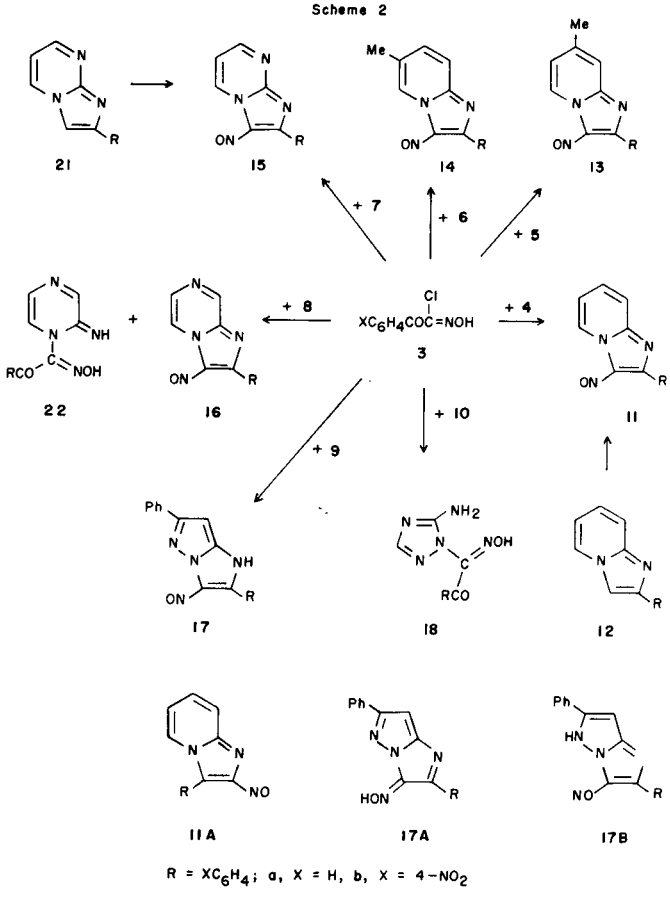
Hydroximic acid chlorides **1** have been extensively studied since 1894. They are versatile intermediates for the synthesis of nitrile oxides **2** which undergo various dipolar 1,3-cycloaddition and 1,3-addition reactions leading to cyclic and open chain products, respectively [4-8]. However, until recently, the use of such compounds in the preparation of fused heterocycles has been relatively little explored. Thus, it seemed of interest to examine the reaction of α-ketohydroximoyl chlorides with some heterocyclic amines as a convenient procedure for the synthesis of some fused heterocycles. In the present work we have investigated the reaction of the hydroximoyl chlorides **3a-3b** with

Scheme 1



the amines **4-10** (Scheme 1). The products of these reactions (Schemes 2 and 3) are expected to be biologically active. For example, some derivatives of 2-arylimidazo-[1,2-*a*]pyrimidine have been reported to possess analgesic, anti-inflammatory, antimicrobial, and antiviral properties [9-12].

Scheme 2



R = XC_6H_4; a, X = H, b, X = 4-NO_2

Results and Discussion.

Treatment of arylglyoxylhydroximoyl chlorides **3a-3b** with two equivalents of 2-aminopyridine (**4**) in ethanol gave products identified as 3-nitroso-2-arylimidazo[1,2-*a*]-pyridines **11a** and **11b**, respectively (Scheme 2 and Table

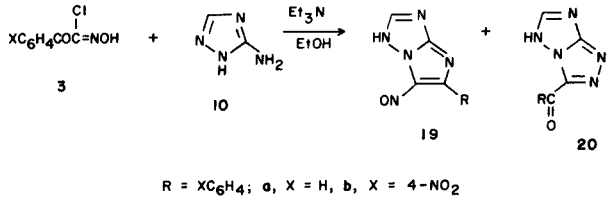
Table I

Synthesized Heterocycles

Compound No.	Mp, °C [a]	Yield %	Molecular Formula	Analysis Calcd. (Found) C, %		H, %		N, %	
11a	162-164 [b]	80	$C_{13}H_9N_3O$	—		—		—	
11b	217-219	75	$C_{13}H_8N_4O_3$	58.12	(57.97)	3.01	(2.97)	20.89	(20.66)
13a	188	80	$C_{14}H_{11}N_3O$	70.87	(70.58)	4.67	(4.69)	17.71	(17.72)
13b	211-213	80	$C_{14}H_{10}N_4O_3$	59.57	(59.67)	3.57	(3.76)	19.85	(19.76)
14a	180-182	75	$C_{14}H_{11}N_3O$	70.87	(70.82)	4.67	(4.68)	17.71	(17.81)
14b	253-255	80	$C_{14}H_{10}N_4O_3$	59.57	(59.55)	3.57	(3.52)	19.85	(19.90)
15a	219-220 [c]	70	$C_{12}H_8N_4O$	—		—		—	
15b	217-219	75	$C_{12}H_7N_5O_3$	53.54	(53.25)	2.62	(2.65)	26.01	(26.11)
16a	194-196	55	$C_{12}H_8N_4O$	64.28	(64.10)	3.60	(3.57)	24.99	(25.03)
16b	182-184	60	$C_{12}H_7N_5O_3$	53.53	(53.27)	2.62	(2.60)	26.01	(25.83)
17a	263-265	75	$C_{17}H_{12}N_4O$	70.82	(70.66)	4.20	(4.22)	19.43	(19.49)
17b	262-264	70	$C_{17}H_{11}N_5O_3$	61.26	(60.99)	3.33	(3.21)	21.01	(20.94)
18a	153-155	60	$C_{10}H_9N_5O_2$	51.95	(51.73)	3.92	(3.80)	30.29	(30.28)
18b	164	75	$C_{10}H_8N_6O_4$	43.48	(43.34)	2.92	(3.08)	30.43	(30.36)
19a	234	50	$C_{10}H_7N_5O$	56.33	(56.12)	3.30	(3.20)	32.84	(32.75)
19b	288	65	$C_{10}H_6N_6O_3$	46.51	(46.15)	2.34	(2.43)	32.54	(32.45)
20a	255	25	$C_{10}H_7N_5O$	56.33	(56.12)	3.30	(3.10)	32.84	(32.80)
20b	334	20	$C_{10}H_6N_6O_3$	46.51	(46.42)	2.34	(2.32)	32.54	(32.20)
21a	200	30	$C_{12}H_{10}N_4O_2$	59.49	(59.62)	4.16	(4.01)	23.12	(23.31)

[a] All compounds were crystallized from ethanol with the exception of **19b** and **20b** which were crystallized from dimethylformamide. [b] Lit mp 164-165° [20]. [c] Lit mp 223° [16].

Scheme 3



I). The isomeric structure **11A** possible for these compounds was excluded because of reaction of 2-aminopyridine with α-halogenated ketones was reported to yield 2-substituted imidazo[1,2-*a*]pyridines **12** [13]. Furthermore, nitrosation of 2-phenylimidazo[1,2-*a*]pyridine (**12a**) with sodium nitrite and acetic acid gave **11a** identical in all respects (mp, mixed mp, spectra) with the product obtained from **3a** and 2-aminopyridine (**4**).

Similarly, the reaction of **3a-3b** with aminopicolines **5** and **6** in ethanol at room temperature afforded the corresponding 3-nitroso-2-arylimidazo[1,2-*a*]pyridines **13** and **14**, respectively, in an approximately 80% yield. The structures of the latter products were deduced from their spectra and elemental analyses (Tables I-III). For example, the nmr spectrum of **13a** in chloroform-d shows a singlet at δ 2.5 ppm (3H, Me), and a multiplet at δ 7.0-8.0 ppm (9H, ArH). The ir spectra of **13** and **14** reveal the absence of bands in the regions 1650-1800 and 3100-3300 cm^{-1} due to the CO and NH groups, respectively (Table II). The electronic spectral data for **13** and **14** are given in Table III.

Table II

The Infrared Spectra of the Compounds under Study [a]

Compound No.	ν CO	ν CN	ν C-N=O	ν NH
11a	—	1620	1540	—
11b	—	1630	1520	—
13a	—	1630	1520	—
13b	—	1630	1520	—
14a	—	1620	1530	—
14b	—	1625	1540	—
15a	—	1620	1540	—
15b	—	1640	1540	—
16a	—	1610	1530	—
16b	—	1610	1530	—
17a	—	1640	1560	3300
17b	—	1640	1560	3300
18a	1660	1630	—	3150, 3300, 3400
18b	1660	1630	—	3150, 3300, 3400
19a	—	1620	1580	3150
19b	—	1620	1580	3150
20a	1680	1630	—	3200
20b	1680	1640	—	3200
22a	1700	1630	—	3150, 3300, 3400

[a] In nujol.

The reaction of **3a-3b** with 2-aminopyrimidine (**7**) in ethanol at room temperature produced 3-nitroso-2-arylimidazo[1,2-*a*]pyrimidines **15a** and **15b**, respectively, in 70-75% yields. The proposed sructures of **15a** and **15b** are in accord with the elemental analyses and spectral data (Tables I-III). The ir spectra of these compounds exhibit a moderately strong band at 1530 cm^{-1} due to the nitroso group [14] and no bands in the carbonyl region (Table II). The nmr spectra show three typical 1:1:1:1 quadruplet patterns with J > 2.0 Hz. The chemical shifts were 9.9, 7.5, and 7.6-8.8 ppm, and the coupling constants ($J_{5,6}$, $J_{5,7}$, and $J_{6,7}$) were 6.9, 2.1, and 4.3 Hz, respectively. An alternate synthesis of **15a** by nitrosation of 2-phenylimidazo-[1,2-*a*]pyrimidine [15] provided additional support for the proposed structures.

Table III

The Electronic Absorption Spectra of the Compounds under Study

Compound No.	λ max (ethanol) nm (log ε)
11a	650 (2.22), 356 (3.73), 282 (3.74), 260 (3.84), 227 (3.74)
11b	664 (1.81), 380 (3.39), 342 (3.44), 252 (3.80), 223 (3.93)
13a	635 (2.00), 364 (4.67), 291 (4.54), 258 (4.62), 229 (4.76)
13b	645 (2.06), 384 (3.50), 340 (3.47), 253 (3.83), 227 (3.86)
14a	641 (2.42), 356 (4.85), 256 (4.91), 229 (4.81)
14b	680 (2.42), 345 (3.76), 257 (4.39), 221 (4.34)
15a	674 (2.06), 315 (4.68), 298 (4.58), 278 (4.62), 229 (4.24)
15b	684 (2.19), 350 (4.26), 298 (4.29), 263 (4.52), 213 (4.93)
16a	704 (2.14), 353 (4.57), 274 (4.69), 229 (4.25)
16b	714 (2.05), 345 (4.55), 258 (4.97), 227 (4.59)
17a	421 (2.43), 349 (3.32), 264 (3.67), 222 (4.50)
17b	367 (3.20), 353 (3.24), 256 (3.70), 217 (4.30)
18a	407 (2.67), 371 (2.53), 330 (2.80), 242 (3.20)
18b	410 (2.69), 291 (3.22), 235 (4.39)
19a	407 (2.39), 353 (3.24), 230 (3.09)
19b	352 (3.38), 263 sh (3.31), 224 (4.38)
20a	331 (0.87), 243 (3.10)
20b	224 (4.35)
22a	440 (2.74), 421 (2.80), 345 (2.49), 274 (3.23)

3-Nitroso-2-arylimidazo[1,2-*a*]pyrazines **16a-16b** were obtained the 55-60% yields by condensation of **3a-3b** with 2-aminopyrazine (**8**) in ethanol [16]. The structures **16a-16b** were consistent with the elemental analyses and spectral data (Tables I-III).

Also, the chlorides **3a-3b** react with 5-amino-3-phenylpyrazole (**9**) in ethanol at room temperature to give 3-nitroso-2-aryl-6-phenyl-1*H*-imidazo[1,2-*a*]pyrazoles **17a** and **17b** in 60-75% yields, respectively. The possibility of formation of other products was excluded on the basis of tlc analysis of the reaction mixture in each case. Both the spectral and elemental analysis data were compatible with the assigned structures **17a-17b**. For example, the ir spectra displayed bands near 1640 cm^{-1} (conjugated C=N) and 1560 cm^{-1} (-N=O) and they contained no carbonyl bands (Table II). The presence of bands due to the nitroso group excludes the oxime tautomeric structure **17A**. However, the available data cannot distinguish between the tautomeric structures **17** and **17B**.

Treatment of **3a-3b** with 3-amino-2*H*-1,2,4-triazole (**10**) in ethanol at room temperature gave, after 5 days, the noncyclized substitution products **18a-18b** in 60-75% yields. The structures of **18a-18b** are in accord with their analytical and spectral data (Tables I-III). The ir spectra of **18** possess bands at 3100-3300 (NH), 1660 (C=O), and 1620 cm^{-1} (conjugated C=N).

When the reaction of **3** with **10** was carried out in the presence of triethylamine and the mixture was refluxed for 4 hours, the cyclic products **19a-19b** and **20a-20b** were obtained. The structures of **19a-19b** were consistent with the elemental analyses of the compounds and with their spectral data (Tables I-III). For example, the ir spectra for **19a-19b** possess no bands at 1600-1800 cm^{-1} (no carbonyl band), however, they contain a band at 1580 cm^{-1} (N=O) and a weak band at 3150 cm^{-1} (NH). The ir spectra of compounds **20a-20b** possess bands at 3200 cm^{-1} (NH) and 1680 cm^{-1} (C=O).

The results demonstrate that the reaction of α-ketohydroximoyl chlorides **3** with heterocyclic amines provides a convenient procedure for the synthesis of fused imidazoheterocycles.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. The nmr spectra were obtained in chloroform-d, trifluoroacetic acid, pyridine-d_5, and dimethyl sulfoxide-d_6 on a Varian EM-360 spectrophotometer (60 MHz), with tetramethylsilane as the internal reference. The ir spectra were taken in nujol using a Perkin-Elmer 580B spectrophotometer with a Model 3600 Data Station (Table II). The electronic absorption spectra were measured in ethanol on a Perkin-Elmer 552 spectrophotometer (Table III). Elemental analyses were carried out by MicAnal, Tucson, Arizona. The hydroximoyl chlorides **3a** and **3b** were prepared as previously described [17,18]. 5-Amino-3-phenylpyrazole (**9**) was prepared from ω-cyanoacetophenone and hydrazine hydrate according to the literature [19]. Other heterocyclic amines used in this work were obtained from Aldrich Chemical Co., Milwaukee, Wisconsin.

Synthesis of the Nitroso Derivatives **11** and **13-17**. Method A.

A mixture of the appropriate hydroximoyl chloride **3a** or **3b** (0.003 mole) and the heterocyclic amine (0.006 mole) in ethanol (50 ml) was stirred at room temperature for 30 minutes and then left for 2 hours. The green precipitate was collected and crystallized from ethanol. The compounds prepared by this method are listed in Table I.

Method B.

Equivalent amounts of the hydroximoyl chloride **3a** or **3b** (0.005 mole), heterocyclic amine (0.005 mole), and triethylamine (0.006 mole) in ethanol were refluxed for 30 minutes and then left at room temperature for 2 hours. The crude product was collected and crystallized from ethanol. The compounds prepared by this method were identical in all respects with those prepared by Method A.

Preparation of **18**.

A mixture of **3a** or **3b** (0.003 mole) and 3-amino-2*H*-1,2,4-triazole (**10**, 0.5 g, 0.006 mole) in ethanol (30 ml) was stirred for 5 days at room tempe-

rature. The yellow precipitated solid was collected and crystallized from ethanol. The obtained products **18a** and **18b**, respectively, are listed in Table I along with their mp and the results of the elemental analysis. Their spectral data are given in Tables II and III.

Preparation of **19** and **20**.

A mixture of **3a** or **3b** (0.005 mole), 3-amino-2*H*-1,2,4-triazole (**10**, 0.5 g, 0.005 mole), and triethylamine (0.5 g, 0.005 mole) in ethanol (30 ml) was refluxed for 4 hours. The yellow precipitated solid was collected and washed with water several times. Then it was boiled with ethanol (20 ml), filtered, and allowed to cool. The solid was collected and crystallized from ethanol to give the nitroso derivatives **19a** or **19b** (50 and 65% yield), respectively. The remaining solid which did not dissolve in boiling ethanol was crystallized from dimethylformamide to afford **20a** or **20b** (20 and 25% yield), respectively.

Preparation of Authentic Samples of **11a** and **15a**. Synthesis of **15a**.

2-Phenylimidazo[1,2-*a*]pyrimidine (**21a**, 1.54 g, 0.0075 mole) [15] was heated with glacial acetic acid (6 ml) until it dissolved. Distilled water (9 ml) was added, the solution was quickly cooled to about 5°, and sodium nitrite (0.75 g, 0.19 mole) was added in small portions with cooling and stirring. The formation of green coloration and subsequent rapid precipitation of a green solid were observed. After 24 hours of periodic stirring, the crude green product (1.6 g, 93% yield) was obtained by filtration. Recrystallization from 2-propanol gave **15a** as fine emerald-green needles (1.25 g, 74%) melting at 223-225°. The ir and nmr spectra were identical in every regard with those obtained for the 3-nitroso derivative **15a** prepared by the reaction of phenylglyoxylohydroximoyl chloride with 2-aminopyrimidine (**7**).

Synthesis of **11a**.

Nitrosation of 2-phenylimidazo[1,2-*a*]pyridine (**12a**) [13] using the above-described procedure gave the nitroso derivative **11a** in a 70% yield, with the physical constants matching those of **11a** obtained from the appropriate hydroximoyl chloride and amine.

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[16] In addition to **16a**, the reaction of **3a** with 2-aminopyrazine (**8**) yielded the noncyclized product **22a** (analogous to **18a**). The ir spectrum of **22a** possessed bands at 3400, 3300, 3150 (NH, NH_2), 1700 (C=O), and 1630 cm^{-1} (conjugated C=N).

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