A Synthesis of 2-Arylimidazo[1,2-*a*]pyridin-3-ols

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Substituted 2-aminopyridine 1-oxides condense with phenacyl bromides to form the title compounds.

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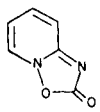
2-Aminopyridine 1-oxide and related compounds are potential binucleophiles in ring synthesis reactions but have not received much study in this area. Reaction with ethyl chloroformate followed by pyrolysis has been shown (1) to yield pyridino[1,2-*b*]oxadiazolones, **1**.



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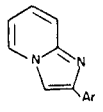
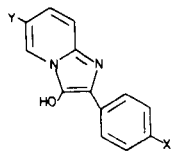


2

Reaction of 2-aminopyridine with phenacyl halides is the standard method (2) for preparing 2-arylimidazo-[1,2-*a*]pyridines, **2**. We wish to report here that this reaction, when carried out with the aminopyridine 1-oxide, is a convenient synthesis of 2-arylimidazo-[1,2-*a*]pyridin-3-ols, **3**.

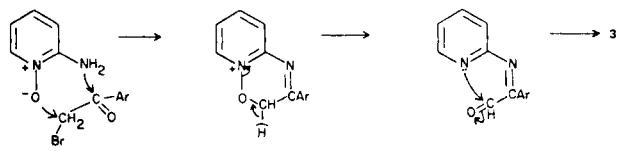


3

a. X = H; Y = H
b. X = Br; Y = H
c. X = NO_2; Y = H
d. X = Br; Y = Br
e. X = H; Y = NO_2

This series of compounds is less well known than is the isomeric 2-hydroxy-3-phenyl series, and the synthesis of **3a** was incorrectly claimed twice (3,4) before being obtained in 1969 by reaction of 2-aminopyridine with phenylglyoxal (5). The novel 1-oxide synthesis probably proceeds by *in situ* generation of the aldehyde function (Scheme 1), since it is known that 2-picoline 1-oxide will convert phenacyl bromide to phenylglyoxal (6). The synthesis reported here is therefore an alternative to the phenylglyoxal one.

Scheme 1



The reaction is simply carried out by refluxing an ethanol solution of the phenacyl bromide and the readily obtainable (7,8) aminopyridine 1-oxide. The product, as the hydrobromide salt, separates from the hot solution, or on cooling. Though readily handled and recrystallized, these salts did not give satisfactory elemental analyses. In some cases the free base could be isolated by treatment with carbonate or triethylamine, but for compounds where the hydroxy group is appreciably acidic, water soluble salt formation occurred under these conditions. The compounds **3** are not very soluble in common organic solvents, give poorly resolved nmr spectra, and decompose prior to melting. The ms at *ca.*, 180°, are characterized by strong M-29 and weak M-16 peaks (the relative intensities are reversed for **3c**). We found that *O*-acylation was the best means of characterizing these compounds. The acyl derivatives gave satisfactory analyses and well resolved nmr spectra.

The compounds **3** (and salts) are brightly colored and generally fluorescent. The red nitro compound, **3c**, forms an intense violet color in weakly basic solution, due no doubt to the extended conjugation that is possible.

We have not investigated in detail the chemistry of this class of compounds. An attempted preparation of **3c** by nitration of **3a** was unsuccessful. Much oxidation occurred with the standard nitrating mixture. Nitrous acid also caused the molecule to break down in a rapid reaction. In this case, 4-bromophenylglyoxylic acid and 2-pyridone were identified from reaction of **3b**.

EXPERIMENTAL

Nmr spectra were recorded, in deuteriochloroform solution, on a Perkin-Elmer R-32 90 MHz spectrometer, and ms on a Jeol D-100 mass spectrometer operating at 70eV.

2-Phenylimidazo[1,2-*a*]pyridin-3-ol (**3a**).

A mixture of 2-aminopyridine 1-oxide (**7**) (2 g.) and phenacyl-bromide (3.6 g.) in ethanol (25 ml.) was refluxed for 0.75 hour. The solution was cooled to give **3a** as the hydrobromide salt, m.p. 192-194° (from ethanol). The filtrate was poured onto ice and basified with triethylamine. More **3a** was obtained. This was combined with the hydrobromide salt and recrystallized from aqueous ethanol containing triethylamine to give **3a** (1.5 g., 39%) as a yellow powder, m.p. > 200° dec.; ms: m/e 210 (M^+), 181, 79,78.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.8; N, 13.3. Found: C, 74.5; H, 4.9; N, 13.5.

The acetyl derivative was prepared by adding a slight excess of acetic anhydride to a slurry of **3a** in acetone containing an eqimolar amount of triethylamine. The mixture was stirred for 0.25 hour, during which time the **3a** dissolved, and then poured onto ice. The white acetyl derivative was recrystallized from aqueous ethanol and had m.p. 134-135°; nmr: δ 2.6 ($COCH_3$),

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6.9 (t, 1H), 7.1-8.2 (m, 8H).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.8; N, 11.1. Found: C, 71.0; H, 4.9; N, 11.0.

The same acetyl derivative was prepared from the product of the reaction of 2-aminopyridine with phenylglyoxal.

2-(4′-Bromophenyl)imidazo[1,2-*a*]pyridin-3-ol (**3b**).

This compound was prepared (34%) in the same was as **3a**. The hydrobromide salt had m.p. 212-213° (from methanol) and the yellow-orange free base had m.p. *ca.* 250° dec.; ms: m/e 290 and 288 (M^+), 284, 282, 271, 269, 181.

Anal. Calcd. for $C_{13}H_9BrN_2O$: C, 54.0; H, 3.1; N, 9.7. Found: C, 54.25; H, 3.5; N, 9.6.

The acetyl derivative, m.p. 134-135° (from ethanol) was unstable but the benzoyl derivative, m.p. 208-210° (from light petroleum-acetone) was prepared under Schotten-Baumann conditions; ms: m/e 394 and 392 (M^+), 261, 259, 180, 158.

Anal. Calcd. for $C_{20}H_{13}BrN_2O_2$: C, 61.0; H, 3.3; N, 7.1. Found: C, 61.15; H, 3.65; N, 7.3.

2-(4′-Nitrophenyl)imidazo[1,2-*a*]pyridin-3-ol (**3c**).

The red hydrobromide salt (36%), m.p. 214° dec., separated during the reflux period. The free base was obtained by dissolving the salt in aqueous potassium carbonate solution (an intense violet solution was obtained) and then neutralizing with acetic acid. The red **3c** had m.p. 228-230° dec. (from aqueous acetic acid); ms: m/e 255 (M^+), 239, 193.

Anal. Calcd. for $C_{13}H_9N_3O_3$: C, 61.1; H, 3.5; N, 16.5. Found: C, 61.3; H, 3.7; N, 16.4.

The acetyl derivative had m.p. 195-197° (from aqueous ethanol); nmr δ 2.4 ($COCH_3$), 6.8 (t, 1H), 7.1 (t, 1H), 7.6 (t, 2H), 8.1 (2d, 4H, ArH).

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.6; H, 3.7; N, 14.1. Found: C, 60.3; H, 3.8; N, 14.1.

6-Bromo-2-(4′-bromophenyl)imidazo[1,2-*a*]pyridin-3-ol (**3d**).

The yellow hydrobromide salt (37%), m.p. 285-286° (from acetic acid) separated during the reflux period. The free base, m.p. 248-250° dec. (from aqueous acetic acid) was obtained as a yellow powder, as for **3c**; ms: m/e 380, 378 and 376 (M^+), 351, 349, 347, 262, 260.

Anal. Calcd. for $C_{13}H_8Br_2N_2O$: C, 42.4; H, 2.2; N, 7.6. Found: C, 42.5; H, 2.5; N, 7.6.

The acetyl derivative had m.p. 204-206° dec. (from ethanol); nmr: δ 2.6 ($COCH_3$), 7.3 (d, J = 9 Hz, 1H, H_7), 7.6 (d, 1H, H_8), 7.8 (2d, 4H, ArH), 7.9 (s, 1H, H_5).

Anal. Calcd. for $C_{15}H_{10}Br_2N_2O_2$: C, 43.9; H, 2.4; N, 6.8. Found: C, 44.0; H, 2.8; N, 6.6.

6-Nitro-2-phenylimidazo[1,2-*a*]pyridin-3-ol (**3e**).

The red hydrobromide salt (22%) separated during the reflux period and had m.p. *ca.* 240° dec. after being washed with ethanol; ms: m/e 255 (M^+-HBr), 226, 180, 124, 104, 103. The free base was not isolated but was characterized directly as the acetyl derivative, m.p. 210-212° (from aqueous ethanol); nmr: δ 2.5 ($COCH_3$), 7.1-8.0 (m, 7H), 8.8 (s, 1H, H_5).

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.6; H, 3.7; N, 14.1. Found: C, 60.2; H, 3.9; N, 14.05.

Reaction with Nitrous Acid.

A sample of **3b** was dissolved in aqueous acetic acid and sodium nitrite was added to the dark solution until the color disappeared. The solution was evaporated to dryness and the residue extracted with hot acetone.

The acetone extract was evaporated and the residual oil was treated with sodium bicarbonate solution until neutral. The solution was evaporated, the residue extracted with chloroform and 2-pyridone, m.p. 107° (from benzene) [lit., (9) 107°] was obtained.

The acetone insoluble solid was dissolved in water and acidified with concentrated hydrochloric acid. The solid which separated was *p*-bromophenylglyoxylic acid, m.p. 103-105° (ligroin) [lit., (9) 108°]; ms: m/e 230 and 228 (M^+), 185, 183, 157, 155.

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