Synthesis of Imidazo[1,2-*a*]pyridines from Pyridines and *p*-Bromophenacyl Bromide *O*-Methyloxime

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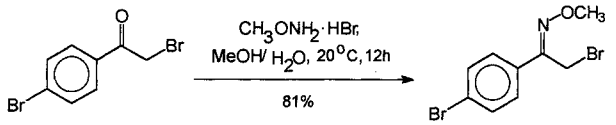
Received 24 November 1995; revised 8 March 1996

p-Bromophenacyl bromide *O*-methyloxime reacts with pyridines in acetone to form the corresponding pyridinium salts which, when heated in methanol in the presence of Et_3N, undergo cyclization followed by elimination of MeOH to give imidazo[1,2-*a*]pyridines.

The imidazo[1,2-*a*]pyridine unit is found in drugs and pesticides and shows a wide spectrum of biological activity.[1] The most common method for the synthesis of imidazo[1,2-*a*]pyridines is the reaction of an α-halocarbonyl compound with an α-aminopyridine (Chichibabin reaction).[2] These α-aminopyridines are obtained by the amination of pyridines.[3] However, the direct amination of pyridines does not always result in the substituted α-aminopyridines, which are not easily accessible. The methods for synthesis of imidazo[1,2-*a*]pyridines based on the cyclization of 2-halo-1-phenacyl pyridinium bromides by treatment with NH_3[4] or NH_2OH[5] were also reported. However, the yields of target products are rather low in these cases due to side reactions. Degradation of 2-hydroxyethylcobaloximes[6] leading to imidazo[1,2-*a*]pyridines proceeds with yields of only about 30%. Elaboration of a synthetic method, which leads to imidazo[1,2-*a*]pyridines without the use of substituted α-aminopyridines with high yields will provide an easy access to this class of compounds. We now report such a new method for the regioselective synthesis of imidazo[1,2-*a*]pyridines using *p*-bromophenacyl bromide *O*-methyloxime **(1)** and pyridines. The oxime ether **1** was prepared from *p*-bromophenacyl bromide and *O*-methylhydroxylamine hydrobromide according to Scheme 1:

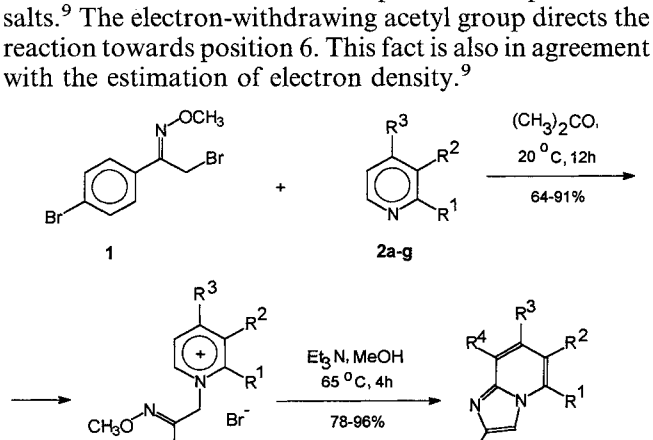


Scheme 1

As was shown previously,[7] the *O*-unsubstituted oxime obtained using these conditions is exclusively the *Z*-isomer. The *Z*-configuration of the oxime ether **1** was confirmed by comparison of its ^1H and ^{13}C NMR spectra with the *O*-unsubstituted[7] compounds.

p-Bromophenacyl bromide *O*-methyloxime **(1)** reacts with pyridines **2a–g** in acetone to form the pyridinium salts **3a–g** (Scheme 2). The *E*-configuration of the oxime group in **3** was established by comparison of their spectra with those of *O*-unsubstituted salts.[8]

We have previously shown[8] that such *anti*-isomers exist in the fixed configuration, which stipulates the proximity of the nucleophilic *N*-atom of the oxime group to the electron-deficient pyridinium moiety. The *Z* to *E* isomerization of the oxime group during quaternization is most likely due to the greater stability of the *anti*-isomer. Such a configuration favors the nucleophilic attack by the *N*-oxime atom on the pyridinium ring. Indeed compounds **3a–g**, when heated in methanol in the presence of Et_3N, undergo cyclization and elimination of MeOH leading to imidazo[1,2-*a*]pyridines **4a–g** (Scheme 2). The cyclization reaction proceeds regioselectively at the most electron-deficient position. In the case of β-picolinium salt **3c**, nucleophilic attack is directed at position 2. This is in agreement with the estimation of the electron density made on the basis of ^{13}C NMR spectra of the picolinium salts.[9] The electron-withdrawing acetyl group directs the reaction towards position 6. This fact is also in agreement with the estimation of electron density.[9]



2,3	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me
e	H	COMe	H
f	$-(CH=CH)_2-$		H
g	H	$-(CH=CH)_2-$	

4	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Me	H	H	H
c	H	H	H	Me
d	H	H	Me	H
e	H	COMe	H	H
f	$-(CH=CH)_2-$		H	H
g	H	H	$-(CH=CH)_2-$	

Scheme 2

Yields and characterization of compounds **3a–g** and **4a–g** are presented in Tables 1 and 2.

In summary, we have elaborated a novel yet simple method for the regioselective synthesis of imidazo[1,2-*a*]pyridines, which is not based on α-aminopyridines.

IR Spectra were recorded on Specord-M80, ^{1}H NMR on Bruker WM 250 (250 MHz), ^{13}C NMR on Bruker WM 300 (300 MHz) and mass spectra on Varian Mat CH-6 (70 eV) spectrometers. Elemental analyses were obtained on a Perkin-Elmer C, H, N-analyzer.

***p*-Bromophenacyl Bromide *O*-Methyloxime (1):**
To a hot solution of *p*-bromophenacyl bromide (2.00 g, 7.2 mmol) in MeOH (30 mL) was added dropwise water until a slight turbidity was observed. Then *O*-methylhydroxylamine hydrobromide (2.75 g, 21.6 mmol) was added and the resulting mixture was heated to boiling and allowed to stand for 12 h at r. t. The precipitated product was filtered, washed with water (2 × 20 mL) and dried in the air; yield: 1.80 g (81%); mp 57–58 °C.

$C_9H_9Br_2NO$	calc.	C 35.21	H 2.96	N 4.56
(307.2)	found	35.43	2.88	4.64

Table 1. Pyridinium Salts **3** Prepared

Product[a]	Yield (%)	mp (°C)[b]	IR (KBr_3) ν (cm^{-1})	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)
3a	64	187–188	3024, 2920 (CH), 1628 (C=N azine), 1588 (C=N oxime), 1500, 1482, 1450	3.98 (s, 3H, OCH_3), 6.03 (s, 2H, CH_2), 7.63, 7.67 (AA'BB', 4H, Ar), 8.10 (dd, J = 6, 8, 2H, 3- and 5-H Py), 8.59 (t, J = 8, 1H, 4H-Py), 9.00 (d, J = 6, 2H, 2- and 6-H Py)
3b	90	232–234	3020, 2984, 2936 (CH), 1634 (C=N azine), 1596, 1576 (C=N oxime), 1520	2.74 (s, 3H, 2-CH_3), 3.96 (s, 3H, OCH_3), 5.96 (s, 2H, CH_2), 7.54–7.66 (m, 4H, Ar), 7.90 (dd, J = 6, 8, 1H, H5), 8.00 (d, 1H, H3), 8.45 (t, J = 8, 1H, H4), 8.92 (d, J = 6, 1H, H6)
3c	90	200–202	3028, 2940 (CH), 1632 (C=N azine), 1592 (C=N oxime), 1504, 1474, 1448	2.46 (s, 3H, 3-CH_3), 3.99 (s, 3H, OCH_3), 5.95 (s, 2H, CH_2), 7.64, 7.66 (AA'BB', 4H, Ar), 7.98 (dd, J = 6, 8, 1H, H-5), 8.42 (d, J = 8, 1H, H4), 8.77 (d, J = 6, 1H, H6), 8.87 (s, 1H, H2)
3d	75	206–207	3018, 2935, 2900 (CH), 1637 (C=N azine), 1590 (C=N oxime), 1525, 1473	2.56 (s, 3H, 4-CH_3), 3.98 (s, 3H, OCH_3), 5.90 (s, 2H, CH_2), 7.60–7.70 (m, 4H, Ar), 7.91 (d, J = 6.5, 2H, H3, H5), 8.77 (d, J = 6.5, 2H, H2, H6)
3e	91	176–177	3060, 3007, 2984 (CH), 1698 (C=O), 1628 (C=N azine), 1592 (C=N oxime)	2.69 (s, 3H, $COCH_3$), 3.97 (s, 3H, OCH_3), 6.07 (s, 2H, CH_2), 7.60–7.70 (AA'BB', 4H, Ar), 8.20 (dd, J = 6, 8, 1H, H5), 8.99 (d, J = 8, 1H, H4), 9.03 (d, J = 6, 1H, H6), 9.50 (s, 1H, H2)
3f	83	207–208	3018, 2997, 2932 (CH), 1624 (C=N azine), 1584 (C=N oxime), 1528, 1480	4.05 (s, 3H, OCH_3), 6.42 (s, 2H, CH_2), 7.39–7.49 (AA'BB', 4H, Ar), 8.03 (t, J = 7.5, 1H, H6), 8.13 (dd, J = 6, 8, 1H, H3), 8.19 (d, J = 7.5, 1H, H5), 8.29 (t, J = 7.5, 1H, H7), 8.42 (d, J = 7.5, 1H, H8), 9.26 (d, J = 8, 1H, H4), 9.59 (d, J = 6, 1H, H2)
3g	80	228–229	3025, 2997, 2940 (CH), 1640 (C=N azine), 1590 (C=N oxime), 1508, 1490	3.99 (s, 3H, OCH_3), 6.09 (s, 2H, CH_2), 7.63, 7.72 (AA'BB', 4H, Ar), 8.06 (t, J = 7.5, 1H, H6), 8.26 (t, J = 7.5, 1H, H7), 8.32 (d, J = 8, 1H, H4), 8.48–8.60 (m, 3H, H3, 5, 8), 10.02 (s, 1H, H2)

[a] Satisfactory microanalyses obtained: C ± 0.17, H ± 0.15, N ± 0.21.
[b] All products were purified by washing with acetone.

Table 2. Imidazo[1,2-*a*]pyridines **4** Prepared

Product[a]	Yield (%)	mp (°C) (heptane)	IR ($CHCl_3$) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	96	215–216	2928, 2856 (CH), 1480, 1470, 1455	6.80 (t, J = 6.5, 1H, H6), 7.20 (dd, J = 6.5, 9, 1H, H7), 7.57, 7.83 (AA'BB', 4H, Ar), 7.64 (d, J = 9, 1H, H8), 7.86 (s, 1H, H3), 8.12 (d, J = 6.5, 1H, H5)
4b	89	95–96	2932, 2856 (CH), 1588, 1548, 1512, 1476, 1412	2.62 (s, 3H, CH_3), 6.64 (d, J = 7, 1H, H6), 7.18 (dd, J = 7, 9, 1H, H7), 7.50–7.60 (m, 3H, H8 and Ar), 7.74 (s, 1H, H3), 7.83–7.90 (m, 2H, Ar)
4c	78	129–130	2988, 2928, 2856 (CH), 1588, 1542, 1476, 1432, 1402	2.65 (s, 3H, CH_3), 6.67 (t, J = 7, 1H, H6), 6.95 (d,. J = 7, 1H, H7), 7.53, 7.82 (AA'XX', 4H, Ar), 7.79 (s, 1H, H3), 7.95 (d, J = 7, 1H, H5)
4d	83	204–205	2932, 2856 (CH), 1588, 1542, 1476, 1430, 1410	2.60 (s, 3H, CH_3), 6.61 (d, J = 7, 1H, H6), 7.55, 7.80 (AA'XX', 4H, Ar), 7.60 (s, 1H, H8), 7.82 (s, 1H, H3), 8.04 (d, J = 7, 1H, H5)
4e	83	217–218	2965, 2845 (CH), 1680 (CO), 1622, 1476, 1430	2.64 (s, 3H, CH_3), 7.57, 7.82 (AA'XX', 4H, Ar), 7.64 (d, J = 9.5, 1H, H8), 7.73 (dd, J = 9.5, 1.5, 1H, H7), 7.94 (s, 1H, H3), 8.80 (s, 1H, H5)
4f	88	174–175	2980 (CH), 1602, 1478, 1448, 1416	7.50 (t, J = 7.5, 1H, H7), 7.54–7.65 (m, 4H, H8, H10 and Ar), 7.68 (t, J = 8, 1H, H6), 7.84 (d, J = 8, 1H, H5), 7.88 (m, 2H, Ar), 7.96 (d, J = 8.5, 1H, H9), 8.33 (s, 1H, H3)
4g	87	203–204	2930 (CH), 1630, 1478, 1446, 1420	7.05 (d, J = 8, 1H, H6), 7.52–7.73 (m, 5H, H7, H8, H9 and Ar), 7.81 (s, 1H, H3), 7.85–7.95 (m, 3H, H10 and Ar), 8.72 (d, J = 8, 1H, H5)

[a] Satisfactory microanalyses obtained: C ± 0.22, H ± 0.16, N ± 0.20.

^{1}H NMR ($CDCl_3$/TMS): δ = 4.10 (s, 3 H, CH_3), 4.33 (s, 2 H, CH_2), 7.54 and 7.58 (AA'BB', 4 H, Ar).

^{13}C NMR ($CDCl_3$/TMS): δ = 34.5 (CH_2), 63.6 (CH_3), 123.3 (C4-Ar), 127.6 (C2-Ar), 131.7 (C3-Ar), 134.9 (C1-Ar), 161.2 (C=N).

IR (KBr): ν = 3055 (CH-Ar), 2980 (CH_2), 2898, 2823, 1592 (C=N), 1488, 1463, 1447 cm^{-1}.

MS: m/z = 309, 307, 305 (M^+), 228, 226 ($M^+ - Br$).

_O_-Methyl _p_-Bromophenacyloximepyridinium Bromides 3a–g; General Procedure:

To a solution of **1** (3 mmol) in anhyd acetone (15 mL) was added the corresponding pyridine **2** (3 mmol) and the mixture was allowed to stand for 12 h at r.t. Precipitated salt was filtered, washed with acetone, and dried in the air (Table 1).

Imidazo[1,2-_a_]pyridines 4a–g; Typical Procedure:

To a solution or a suspension of pyridinium salt **3** (2 mmol) in MeOH (20 mL) was added Et_3N (253 mg, 2.5 mmol) and the mixture was refluxed for 4 h. The resulting mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ phase was dried ($MgSO_4$), and passed through a layer of silica gel (5 g) for the removal of gummy products. Removal of solvent afforded practically pure products. Analytical samples were obtained by recrystallization from heptane (Table 2).

This work was supported by International Science Foundation, Grant No. MEN 300.

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