# Preparation of 2-Aryl and 2-Aryloxymethyl Imidazo[1,2-*a*]pyridines and Related Compounds

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A series of substituted 2-aryl imidazo[1,2-*a*]pyridines has been prepared in which a variety of substituents are introduced on the 4′-position of the phenyl ring and on the 3, 5, 6 or 7 position of the heterocyclic ring. Most examples have acetamido, bromo, cyano, or formyl substituents at the 4′-position. Analogous imidazo-[2,1-*b*]thiazoles and imidazo[1,2-*a*]pyrimidines have also been prepared. Another series of compounds consisting of 4′-formylphenoxymethyl derivatives of imidazole, the three positional isomers of pyridine, thiazole, benzimidazole and ring-substituted imidazo[1,2-*a*]pyridines has been prepared. 2-(4′-Formylphenylethenyl) derivatives of imidazole and imidazo[1,2-*a*]pyridine were also prepared.

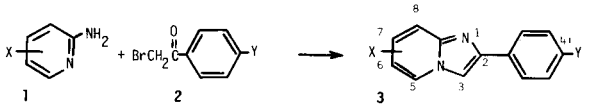
*J. Heterocyclic Chem.*, **25**, 129 (1988).

We have been engaged in the biological evaluation of 2-arylimidazo[1,2-*a*]pyridines. This has required the synthesis of a number of compounds including examples having both heterocyclic (3, 5, 6 and 7 positions) and aryl (4′-position) substitution, and the introduction of -$CH_2O$- and -CH=CH- links between the imidazo[1,2-*a*]pyridine ring and aryl substituent. A number of similar derivatives of other related heterocyclic rings including imidazole, thiazole, pyridine, benzimidazole imidazo[2,1-*b*]thiazole and imidazo[1,2-*a*]pyrimidine have also been prepared. In this paper we report the synthetic routes and physical characterization of these materials. The biological data will be reported elsewhere [1].

A. Substituents on the Aryl Ring.

The classic imidazo[1,2-*a*]pyridine synthesis from 2-aminopyridine and α-bromoacetophenones was used for preparation of the 2-aryl derivatives [2]. The direct introduction of the 4′-substituent from the acetophenone was possible in some cases. In other cases it was necessary to obtain the desired substituents by transformations following the cyclization step. The 4′-substituted 2-aryl imidazo[1,2-*a*]-pyridines derivatives which were prepared are listed in Table I. The two-letter alphabetical code designates substituents X and Y, respectively, as defined in structure **3** in Scheme I.

Scheme I



| | X | | Y |
|---|---|---|---|
| a | H | a | Br |
| b | 6-$CH_3$ | b | $NO_2$ |
| c | 7-$CH_3$ | c | $CH_3CONH$ |
| d | 6-$NO_2$ | d | $C_2H_5O_2CNH$ |
| e | 6-$CH_3CONH$ | e | $CH_3SO_2NH$ |
| f | 6-Cl | f | $C_6H_5SO_2NH$ |
| g | 6-I | g | I |
| h | 6-$CH_3O$ | h | $CH_3O$ |
| i | 6-$C_2H_5S$ | i | $(CH_3)_2CH$ |
| j | 6-$C_2H_5SO$ | j | CN |
| k | 6-$C_2H_5SO_2$ | k | CH=O |
| l | 6-$C_3H_7S$ | l | $CO_2CH_3$ |
| m | 6-$C_6H_5S$ | m | $CONH_2$ |
| n | 6-CN | n | $CSNH_2$ |
| o | 6-CH=O | o | $C(=NH_2)NH_2\ Cl^-$ |

Compounds with acetamido and related amido groups at the 4′-position were prepared from 2-(4′-nitrophenyl)-imidazo[1,2-*a*]pyridines by reduction and acylation or sulfonylation. The other major group of compounds were 2-(4′-formylphenyl)imidazo[1,2-*a*]pyridine and ring-substituted analogs. These were prepared from 2-(4′-bromophenyl)imidazo[1,2-*a*]pyridines which were converted to the corresponding nitriles [3] and then reduced to the aldehyde either with diisobutylaluminum hydride [4a] or by Raney nickel-sodium hypophosphite [4b]. The nitrile **3aj** also served as an intermediate for preparation of the 4′-carboxamide **3am** [5], thiocarboxamide **3an** [6], and amidine **3ao** [7] derivatives of 2-phenylimidazo[1,2-*a*]pyridine. The methoxycarbonyl derivative **3al** was prepared from the aldehyde **3ak** *via* generation and *in situ* methanolysis of the acyl cyanide [8]. In most cases it was possible to introduce the imidazo[1,2-*a*]pyridine ring substituents by using an appropriately substituted 2-aminopyridines in the cyclization procedure. Exceptions were the 6-acetamido compounds **3ec** and **3ae** in which the acetamido group was introduced after cyclization *via* reduction and acetylation of a nitro substituent, the sulfoxide **3jk** and the sulfone **3kk** which were prepared by oxidation of the corresponding sulfide **3ik**, and the aryl sulfide **3mc** which was prepared by phenylthiolate displacement of the iodide **3gc**. The dinitrile **3nj** was obtained by reaction of cuprous

Table 1

2-Arylimidazo[1,2-*a*]pyridines

| Structure | Ring Subst | 4'-Subst | Reactant(s) | Experimental Procedure | Yield (%) | MP°C |
|---|---|---|---|---|---|---|
| **3aa** | H | Br | **1a,2a** | A | 72 | 213-214 [a] |
| **3ab** | H | $NO_2$ | **1a,2b** | A | 76 | 268-270 [a,b,c] |
| **3ac** | H | $NHCOCH_3$ | **3ab** | B | 70 | 245-246 [c] |
| **3ad** | H | $NHCO_2C_2H_5$ | **3ab** | C | 53 | 248-250 |
| **3ae** | H | $NHSO_2CH_3$ | **3ab** | B | 55 | 252 [d] |
| **3af** | H | $NHSO_2Ph$ | **3ab** | B | 64 | 220-221 |
| **3ah** | H | $OCH_3$ | **1a,2h** | A | 71 | 142-144 [d] |
| **3ai** | H | $CH(CH_3)_2$ | **1a,2i** | A | 20 | 119-120 |
| **3aj** | H | CN | **3aa** | D | 56 | 210-211 [e] |
| **3ak** | H | CH=O | **3aj** | E or F | 89/60 | 202-203 |
| **3al** | H | $CO_2CH_3$ | **3ak** | H | 65 | 205 |
| **3am** | H | $CONH_2$ | **3aj** | I | 80 | 259-261 |
| **3an** | H | $CSNH_2$ | **3aj** | J | 95 | 201-202 |
| **3ao** | H | $C(NH_2)_2^+Cl$ | **3aj** | K | 70 | >300 |
| **3ba** | 6-$CH_3$ | Br | **1b,2a** | A | 68 | 215-216 |
| **3bb** | 6-$CH_3$ | $NO_2$ | **1b,2b** | A | 73 | 235 [f] |
| **3bc** | 6-$CH_3$ | $NHCOCH_3$ | **3bb** | B | 76 | 262 |
| **3bj** | 6-$CH_3$ | CN | **3ba** | D | 71 | 225-226 |
| **3bk** | 6-$CH_3$ | CH=O | **3bj** | E or F | 68/53 | 210-211 |
| **3ca** | 7-$CH_3$ | Br | **1c,2a** | A | 69 | 202-204 |
| **3cb** | 7-$CH_3$ | $NO_2$ | **1c,2b** | A | 81 | 215 [f,g] |
| **3cc** | 7-$CH_3$ | $NHCOCH_3$ | **3cb** | B | 11 | 233 |
| **3cj** | 7-$CH_3$ | CN | **3ca** | D | 88 | 201-203 |
| **3ck** | 7-$CH_3$ | CH=O | **3cj** | E | 68 | 191 |
| **3da** | 6-$NO_2$ | Br | **1d,2a** | A | 20 | 260 |
| **3db** | 6-$NO_2$ | $NO_2$ | **1a,2b** | A | | 305-308 |
| **3ec** | 6-$CH_3CONH$ | 6-$CH_3CONH$ | **3db** | B | | 264-270 |
| **3ea** | 6-$CH_3CONH$ | Br | **3da** | C | 62 | >300 |
| **3ej** | 6-$CH_3CONH$ | CN | **3ea** | D | 63 | >300 |
| **3ek** | 6-$CH_3CONH$ | CH=O | **3ej** | F | 36 | >300 |
| **3fa** | 6-Cl | Br | **1f,2a** | A | 71 | 221-223 |
| **3fb** | 6-Cl | $NO_2$ | **1f,2b** | A | 78 | 225 |
| **3fc** | 6-Cl | $NHCOCH_3$ | **3fb** | C | 67 | 298 |
| **3fj** | 6-Cl | CN | **3fa** | D | 65 | 217 |
| **3fk** | 6-Cl | CH=O | **3fj** | E | 60 | 197 |
| **3ga** | 6-I | Br | **1g,2a** | A | 80 | 216 |
| **3gb** | 6-I | $NO_2$ | **1g,2b** | A | 68 | 274-275 |
| **3gc** | 6-I | $NHCOCH_3$ | **3gb** | C | 60 | 286-287 |
| **3ha** | 6-$OCH_3$ | Br | **1h,2a** | A | 63 | 163 |
| **3hj** | 6-$OCH_3$ | CN | **3ha** | D | 77 | 199 |
| **3hk** | 6-$OCH_3$ | CH=O | **3hk** | E | 76 | 167 |
| **3ia** | 6-$SC_2H_5$ | Br | **1i,2a** | A | 78 | 166 |

Table 1 (continued)

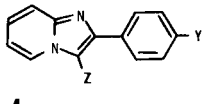
| Structure | Ring Subst | 4'-Subst | Reactant(s) | Experimental Procedure | Yield (%) | MP°C |
|---|---|---|---|---|---|---|
| **3ij** | 6-$SC_2H_5$ | CN | **3ia** | D | 72 | 174 |
| **3ik** | 6-$SC_2H_5$ | CH=O | **3ij** | E | 63 | 157 |
| **3jk** | 6-$SOC_2H_5$ | CH=O | **3ik** | L | 62 | 200 |
| **3kk** | 6-$SO_2C_2H_5$ | CH=O | **3ik** | L | 54 | 230 |
| **3la** | 6-$SC_3H_7$ | Br | **1l,2a** | A | 75 | 147-149 |
| **3lj** | 6-$SC_3H_7$ | CN | **3la** | D | 74 | 115 |
| **3lk** | 6-$SC_3H_7$ | CH=O | **3lj** | E | 71 | 120-122 |
| **3mc** | 6-$SC_6H_5$ | $NHCOCH_3$ | **3gc** | M | 65 | 192 |
| **3nj** | CN | CN | **3ga** | D | 66 | 264-266 |
| **3ok** | CH=O | CH=O | **3nj** | E | 25 | 203-205 |
| **4a** | $CH_3$ | Br | | A | 32 | 205-208 |
| **4b** | $CH_3$ | CN | **4a** | D | 64 | 185-187 |
| **4c** | $CH_3$ | CH=O | **4b** | F | 25 | 168-170 |
| **4d** | Br | CH=O | **3ak** | N | 70 | 200 dec |
| **4e** | $NO_2$ | CH=O | **3ak** | O | 70 | 230-232 |
| **5a** | 5,6,7,8-tetrahydro | $NHCOCH_3$ | **3ac** | P | 85 | 208-209 |
| **5b** | 5,6,7,8-tetrahydro | CH=O | **3ak** | P | 56 | 166 |

[a] N. Saldobols, L. L. Zeligman and S. Hillers, *Khim. Geterotsikl. Soedin.*, 860 (1971); *Chem. Abstr.*, **76**, 25167s (1972). [b]E. S. Hand and W. W. Paudler, *Tetrahedron*, **38**, 49 (1982). [c] T. Matsukawa and S. Ban, *J. Pharm. Soc. Japan*, **71**, 760 (1951); *Chem. Abstr.*, **46**, 8094 (1952). [d] N. P. Buu-Hoi, P. Jacquignon, N. D. Xuong and D. Lavit, *J. Org. Chem.*, **19**, 1370 (1954); M. H. Fisher and A. Lusi, *J. Med. Chem.*, **15**, 982 (1972). [e] M. Nakanishi, T. Muro, O. Nakatsu, T. Nakao and K. Ogawa, *German Offen.*, 2,432,410; *Chem. Abstr.*, **83**, 43367f (1975). [f] F. Mattu and E. Marongiu, *Ann. Chim.* (Rome), **54**, 496 (1964); *Chem. Abstr.*, **62**, 11801e (1965). [g] J. W. Carpenter, J. D. Mee and D. W. Heseltine, U. S. Patent 3,809,691; *Chem. Abstr.*, **81**, 51156k (1974).

cyanide with the dihalide **3ga**.

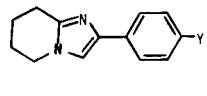
A 3-methyl substituent can be introduced directly by cyclization using α-bromopropiophenone. 2-(4'-Bromophenyl)-3-methylimidazo[1,2-*a*]pyridine (**4a**) was prepared by this method and converted to the corresponding 4'-nitrile **4b** and aldehyde **4c**. The 3-position of the imidazo[1,2-*a*]-pyridine ring is the primary site for electrophilic attack [9] and the 3-bromo **4d** and 3-nitro **4e** derivatives were prepared in this way. The 5,6,7,8-tetrahydro derivatives **5a** and **5b** were prepared by hydrogenation of **3ab** and **3ak** [10]. The yields and melting points of these products are included in Table 1 (Scheme II).

Scheme II



4

| | Y | Z |
|---|---|---|
| a | Br | $CH_3$ |
| b | CN | $CH_3$ |
| c | CH=O | $CH_3$ |
| d | CH=O | Br |
| e | CH=O | $NO_2$ |



5

| | Y |
|---|---|
| a | $CH_3CONH$ |
| b | CH=O |

In addition to the imidazo[1,2-*a*]pyridines which received primary attention, the imidazo[2,1-*b*]thiazoles **8** and imidazo[1,2-*a*]pyrimidines **9** shown in Scheme III were prepared. The imidazo[2,1-*b*]thiazoles and imidazo[1,2-*b*]-pyrimidines were prepared using procedures analogous to the imidazo[1,2-*a*]pyridines, but starting with 2-aminothia-

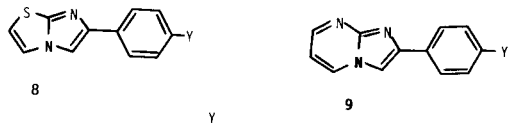
Table 2

Imidazo[2,1-*b*]thiazoles and Imidazo[1,2-*a*]pyrimidines

| Structure | 4' Subst | Reactant(s) | Method | Yield (%) | MP °C |
|---|---|---|---|---|---|
| **8a** | $NO_2$ | **6,2b** | A | 80 | 282-283 |
| **8b** | $NHCOCH_3$ | **8a** | C | 70 | 242-243 |
| **8c** | I | **6,2g** | A | 69 | 199 |
| **8d** | CN | **8c** | D | 79 | 201 |
| **8e** | CH=O | **8d** | E | 75 | 169 |
| **9a** | $NO_2$ | **7,2b** | A | 72 | >360 |
| **9b** | $NHCOCH_3$ | **9a** | B | 67 | ~325 |
| **9c** | I | **7,2g** | A | | 296-298 |
| **9d** | CN | **9c** | D | 69 | >330 |
| **9e** | CH=O | **9d** | F | 42 | ~310 dec |

zole (**6**) and 2-aminopyrimidine (**7**). The use of 4'-iodophenacyl bromide was found preferable to use of the 4'-bromo compound for these ring systems because of poor yields with the bromo compound in the reaction with cuprous cyanide. The preparation of these compounds are summarized in Table 2.

Scheme III

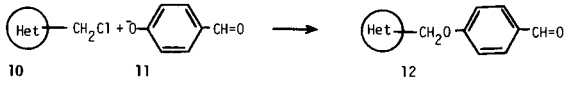


8 9

Y
- a $NO_2$
- b $CH_3CONH$
- c I
- d CN
- e CH=O

The 4'-formylphenoxymethyl compounds were prepared by substitutions of the appropriate chloromethyl heterocycle by the 4'-formylphenoxide ion. The required starting materials are commercially available in the case of the isomeric pyridines and benzimidazole. Literature methods were used for 2-(chloromethyl)-1-methylimidazole [11] and 4-(chloromethyl)thiazole [12]. The 2-(chloromethyl)imidazo[1,2-*a*]pyridines were prepared by cyclization of 2-aminopyridine, or ring-substituted analogs, with 1,3-dichloroacetone [13]. The substitution reaction was carried out in either of two ways. In method Q, 4-formylphenolate, prepared from *p*-hydroxybenzaldehyde and powdered potassium hydroxide and dimethylsulfoxide was used as the reaction medium. In method R, the phenoxide was generated by reaction of the phenol with 1.2 equivalents of sodium hydride in dimethylformamide. Method Q was the preferred one when the chloromethyl heterocycle was used as the hydrochloride salt, in which case two equivalents of 4-formylphenolate were used. The structures which were characterized are designated in Scheme IV and yields and melting points are given in Table 3.

Scheme IV



10 11 12

Heterocyclic Ring
- a 1-methylimidazol-2-yl
- b 2-pyridyl
- c 3-pyridyl
- d 4-pyridyl
- e 4-thiazolyl
- f 1-methylbenzimidazol-2-yl
- g imidazo[1,2-a]pyrid-2-yl
- h 5-methylimidazo[1,2-a]pyrid-2-yl
- i 6-methylimidazo[1,2-a]pyrid-2-yl
- j 7-methylimidazo[1,2-a]pyrid-2-yl
- k 6-trifluoromethylimidazo[1,2-a]pyrid-2-yl

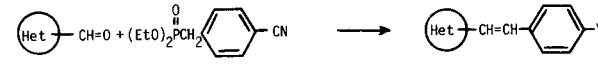
Table 3

4'-Formylphenoxymethyl Heterocycles

| Structure | Reactant | Method | Yield (%) | MP °C | MP HCl Salt °C |
|---|---|---|---|---|---|
| **12a** | **10a** | Q | 65% | 113-115 | 247-250 |
| **12b** | **10b** | Q | 70% | 93-95 | 174-176 |
| **12c** | **10c** | Q | 60% | 76-78 | 171-173 |
| **12d** | **10d** | Q | 68% | 111-115 | 201-204 |
| **12e** | **10a** | Q | 57% | 84-86 | |
| **12f** | **10a** | Q | 80% | 192-195 | 223-225 |
| **12g** | **10g** | R | 69% | 141-142 | |
| **12h** | **10h** | Q | 75% | 102-104 | |
| **12i** | **10i** | Q or R | 70%/48% | 133-134 | |
| **12j** | **10j** | Q or R | 68%/24% | 150-153 | |
| **12k** | **10k** | Q | 74% | 166-168 | |

The arylethenyl compounds shown in Scheme V were prepared starting from an appropriate heterocyclic aldehyde. 1-Methylimidazole-2-carboxaldehyde was prepared by a literature method [14]. The imidazo[1,2-*a*]pyridine-2-carboxaldehydes were prepared from the corresponding 2-carboethoxyimidazo[1,2-*a*]pyridine [15] by lithium aluminum hydride reduction to the primary alcohol followed by oxidation with manganese dioxide. Wadsworth-Emmons-Horner [16] condensation with diethyl 4-cyanobenzylphosphonate [17] gave the 4'-cyanophenylethenyl derivatives. This method is expected to give the *E*-stereoisomer and no evidence for formation of the *Z*-isomers was seen. The nitriles were reduced to the aldehyde either by reduction with diisobutylaluminum hydride (Method E) or by use of Raney nickel alloy in formic acid [4c] (Method G). The yields and melting points of the products are given in Table 4.

Scheme V



13 14 Heterocyclic Ring 15 Y = CN 16 Y = CH=O
- a 1-methylimidazol-2-yl
- b imidazo[1,2-a]pyrid-2-yl
- c 5-methylimidazo[1,2-a]pyrid-2-yl
- d 6-methylimidazo[1,2-a]pyrid-2-yl

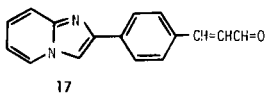
Table 4

4'-Cyanophenylethenyl and 4'-Formylphenylethenyl Heterocycles

| Nitrile | Yield | MP (°C) | Aldehyde | Method | Yield | MP (°C) |
|---|---|---|---|---|---|---|
| **15a** | 63% | 161-163 | **16a** | G | 67% | 270-275 |
| **15b** | 71% | 232-234 | **16b** | E | 73% | 207-210 |
| **15c** | 75% | 295-298 | **16c** | E | 81% | 210-212 |

We also prepared the 4'-(3-oxo-1-propenyl) derivative **17** of 2-phenylimidazo[1,2-*a*]pyridine from 2-(4'-formylphenyl)imidazo[1,2-*a*]pyridine (**3aj**) by conversion to the acrylic ester by the Wadsworth-Emmons reaction, reduction to the allylic alcohol with diisobutylaluminum hydride, and manganese dioxide oxidation. 1-(4'-Formylbenzyl)benzimidazole **18** was prepared by alkylation of benzimidazole with 4'-cyanobenzyl bromide and then reducing the nitrile with Raney nickel alloy in formic acid.

Scheme VI




17

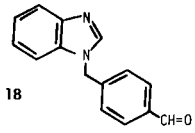



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Table 5

Elemental Analysis

| | Calcd./Found C | H | N | Other |
|---|---|---|---|---|
| **3ab** | 65.27 | 3.79 | 17.56 | |
| | 65.12 | 3.84 | 17.52 | |
| **3ad** | 68.33 | 5.34 | 14.94 | |
| | 68.15 | 5.49 | 14.88 | |
| **3ae** | 58.52 | 4.56 | 14.63 | |
| | 58.45 | 4.59 | 14.33 | |
| **3af** | 65.31 | 4.33 | 12.02 | |
| | 65.69 | 4.76 | 11.51 | |
| **3ah** | 74.98 | 5.40 | 12.49 | |
| | 75.05 | 5.42 | 12.47 | |
| **3ai** | 81.32 | 6.83 | 11.85 | |
| | 81.16 | 6.88 | 11.81 | |
| **3ak** | 75.65 | 4.54 | 12.61 | |
| | 75.59 | 4.57 | 12.61 | |
| **3al** | 71.41 | 4.38 | 11.16 | |
| | 71.23 | 4.82 | 10.91 | |
| **3am** | 70.86 | 4.67 | 17.70 | |
| | 70.74 | 4.68 | 17.67 | |
| **3an** | 66.40 | 4.35 | 16.60 | |
| | 66.24 | 4.40 | 16.52 | |
| **3ao**(1.5$H_2O$) | 50.01 | 5.08 | 16.66 | |
| | 49.61 | 4.48 | 16.30 | |
| **3bc** | 72.43 | 5.70 | 15.85 | |
| | 72.52 | 5.72 | 15.56 | |
| **3bj** | 77.23 | 4.76 | 18.01 | |
| | 77.02 | 4.81 | 17.92 | |
| **3bk** | 76.25 | 5.12 | 11.86 | |
| | 76.12 | 5.14 | 11.86 | |
| **3cj** | 77.23 | 4.76 | 18.01 | |
| | 77.23 | 4.78 | 17.95 | |
| **3ck** | 76.25 | 5.12 | 11.86 | |
| | 76.13 | 5.15 | 11.82 | |
| **3db** | 54.94 | 2.83 | 19.70 | |
| | 54.92 | 2.86 | 19.67 | |

Table 5 (continued)

| | Calcd./Found C | H | N | Other |
|---|---|---|---|---|
| **3ec**($H_2O$) | 61.13 | 5.77 | 17.82 | |
| | 61.04 | 5.82 | 17.79 | |
| **3ej** | 69.55 | 4.38 | 20.28 | |
| | 69.30 | 4.42 | 20.18 | |
| **3ek** | 68.81 | 4.69 | 15.04 | |
| | 68.58 | 4.76 | 15.24 | |
| **3fb** | 57.05 | 2.95 | 15.36 | |
| | 56.85 | 3.00 | 15.32 | |
| **3fj** | 66.30 | 3.15 | 16.56 | |
| | 66.15 | 3.21 | 16.56 | |
| **3fk** | 65.53 | 3.51 | 10.91 | |
| | 65.54 | 3.57 | 10.91 | |
| **3gc** | 47.75 | 3.18 | 11.14 | |
| | 47.71 | 3.22 | 11.11 | |
| **3hk** | 71.41 | 4.80 | 11.10 | |
| | 71.15 | 4.88 | 11.06 | |
| **3ij** | 68.79 | 4.69 | 15.04 | |
| | 68.61 | 4.75 | 15.01 | |
| **3ik** | 68.06 | 5.00 | 9.92 | |
| | 67.98 | 5.01 | 9.88 | |
| **3jk** | 64.83 | 4.76 | 9.46 | |
| | 64.33 | 4.77 | 9.31 | |
| **3kk** | 61.13 | 4.49 | 8.91 | |
| | 61.04 | 4.54 | 8.87 | |
| **3la** | 55.33 | 4.33 | 8.07 | |
| | 55.43 | 4.37 | 8.06 | |
| **3lk** | 68.92 | 5.41 | 9.46 | |
| | 68.76 | 5.46 | 9.42 | |
| **3mc**(0.5$H_2O$) | 68.45 | 4.42 | 11.40 | (S) 8.70 |
| | 68.66 | 4.93 | 11.44 | (S) 8.76 |
| **3nj** | 73.76 | 3.30 | 22.94 | |
| | 73.50 | 3.38 | 22.82 | |
| **3ok** | 71.99 | 4.03 | 11.19 | |
| | 71.53 | 4.23 | 11.66 | |
| **4c** | 76.25 | 5.12 | 11.85 | |
| | 76.32 | 5.14 | 11.86 | |
| **4d** | 55.83 | 3.01 | 9.31 | |
| | 55.79 | 3.05 | 9.29 | |
| **4e** | 62.92 | 3.39 | 15.73 | |
| | 63.06 | 3.42 | 15.67 | |
| **5a** | 70.55 | 6.72 | 16.46 | |
| | 70.34 | 6.78 | 16.40 | |
| **5b** | 74.31 | 6.24 | 12.38 | |
| | 74.31 | 6.28 | 12.35 | |
| **8a** | 53.87 | 2.88 | 17.13 | |
| | 53.65 | 3.08 | 16.88 | |
| **8d** | 63.98 | 3.13 | 18.65 | (S) 14.23 |
| | 63.93 | 3.16 | 18.60 | (S) 14.27 |
| **8e** | 63.14 | 3.53 | 12.28 | (S) 14.04 |
| | 62.90 | 3.56 | 12.21 | (S) 14.13 |
| **9b** | 66.65 | 4.80 | 22.21 | |
| | 66.71 | 4.85 | 22.17 | |

Table 5 (continued)

| | Calcd./Found C | H | N | Other |
|---|---|---|---|---|
| **9c** | 44.88 | 2.51 | 13.09 | |
| | 44.79 | 2.53 | 13.04 | |
| **9e** | 69.94 | 4.06 | 18.82 | |
| | 69.39 | 4.14 | 18.64 | |
| **12a**(HCl) | 66.68 | 5.56 | 12.95 | |
| | 66.61 | 5.61 | 12.94 | |
| **12b**(HCl) | 62.53 | 4.84 | 5.60 | |
| | 62.59 | 4.89 | 5.59 | |
| **12c**(HCl) | 62.53 | 4.84 | 5.60 | |
| | 62.43 | 4.86 | 5.56 | |
| **12d** | 73.25 | 5.16 | 6.56 | |
| | 73.16 | 5.17 | 6.52 | |
| **12d**(HCl) | 62.53 | 4.84 | 5.60 | |
| | 62.61 | 4.87 | 5.59 | |
| **12e** | 60.26 | 4.13 | 6.38 | (S) 14.62 |
| | 60.19 | 4.18 | 6.37 | (S) 14.66 |
| **12f**($HCl,H_2O$) | 61.90 | 5.19 | 9.63 | (Cl) 12.19 |
| | 61.87 | 5.22 | 9.64 | (Cl) 12.13 |
| **12g** | 71.41 | 4.80 | 11.11 | |
| | 71.19 | 4.82 | 11.07 | |
| **12h** | 72.15 | 5.30 | 10.52 | |
| | 71.86 | 5.37 | 10.43 | |
| **12i** | 72.15 | 5.30 | 10.52 | |
| | 71.91 | 5.36 | 10.29 | |
| **12j** | 72.15 | 5.30 | 10.52 | |
| | 72.04 | 5.35 | 10.50 | |
| **12k** | 60.00 | 3.46 | 8.75 | |
| | 59.94 | 3.49 | 8.74 | |
| **15a** | 74.60 | 5.30 | 20.10 | |
| | 74.51 | 5.34 | 20.03 | |
| **16a** | 62.78 | 5.26 | 11.26 | |
| | 62.54 | 5.33 | 11.18 | |
| **16b** | 77.40 | 4.87 | 11.28 | |
| | 77.82 | 5.40 | 11.04 | |
| **17** | 77.42 | 4.84 | 11.29 | |
| | 77.18 | 4.93 | 11.22 | |
| **18**($HCl,0.5H_2O$) | 63.95 | 4.97 | 9.94 | (Cl) 12.60 |
| | 63.90 | 5.05 | 9.89 | (Cl) 12.61 |

All the intermediate bromo, nitro and cyanide intermediates had spectra properties in agreement with the assigned structures. Elemental analyses were obtained for the new acetamides and aldehydes as well as for other representative intermediates. These are listed in Table 5.

## EXPERIMENTAL

Starting Materials.

The aminopyridines were either commercially available (**1a**, **1b**, **1c**, **1d**, **1f**) or prepared by published procedures: **1g** [18]; **1h** [19]; **1i** [20]. 2-Amino-5-trifluoromethylpyridine was an investigational sample provided by Ishihara Corporation. The phenacyl bromides were purchased or prepared by Friedel-Craft acylation followed by bromination [21].

Method A. General Procedure for 2-Arylimidazo[1,2-*a*]pyridines.

The 2-aminopyridine and the phenacyl bromide (equimolar quantities) were dissolved or suspended in acetone and refluxed for 3 hours or, alternatively, stirred overnight. The material which precipitated was collected and the volume of the mother liquor was reduced by rotary evaporation and a second crop was collected. Normally the initial product was the hydrate [2] of the desired product and aromatization was effected by dissolving it in methanol containing a little hydrogen bromide and refluxing for 30-60 minutes. The acidic solution was then made basic with sodium hydroxide or ammonium hydroxide. The product usually began to precipitate immediately upon neutralization and was collected by filtration.

Method B. Catalytic Reduction Followed by Acylation or Sulfonation.

The 2-(4'-nitrophenyl)imidazo[1,2-*a*]pyridine was dissolved or suspended in absolute ethanol and hydrogenated over Raney nickel at 1 atmosphere pressure of hydrogen. The hydrogen uptake was followed quantitatively and after the calculated amount had been absorbed the catalyst was removed by filtration and the ethanol removed by rotary evaporation. The residue was dissolved in chloroform and treated with a 10% excess of acylating agent and a few drops of pyridine. In cases in which acetic anhydride was used as the acylating agent, a 10-fold excess was used. After stirring 15 hours at room temperature most of the chloroform was removed by rotary evaporation. The residue was mixed with saturated sodium bicarbonate until the solution was neutral and then made strongly basic with 15% aqueous sodium hydroxide. In many cases the product precipitated from the reaction mixture and was isolated by filtration. When this did not occur the aqueous solution was extracted with chloroform and the extract was dried and evaporated. In either case the product was then recrystallized from ethanol.

Method C. Reduction by Stannous Chloride followed by Acylation or Sulfonylation.

The 2-(4'-nitrophenyl)imidazo[1,2-*a*]pyridine was added in small portions to a solution of stannous chloride dihydrate (3.0 g per g of heterocycle) in concentrated hydrochloric acid (10 ml per g of heterocycle) at 0°. After addition was complete, the mixture was allowed to warm to room temperature and stirred for one hour. The solution was then carefully made basic with 50% sodium hydroxide and cooled in an ice bath. Chloroform was added to the mixture and it was then vacuum filtered to remove the tin salts which had precipitated. The filtered salts were washed again with chloroform. The combined chloroform solution was dried over anhydrous potassium carbonate, filtered and then treated with a 10% excess of the acylating agent and a small amount of pyridine. (A ten fold excess was used in the case of acetic anhydride). The reaction mixture was stirred for 15 hours at room temperature and then mixed with saturated aqueous sodium bicarbonate solution. The mixture was then made strongly basic with 15% sodium hydroxide solution. In many cases, the product precipitated and was isolated by filtration. If precipitation was incomplete the aqueous solution was extracted with chloroform and the product isolated by evaporation.

Method D. Substitution of Aryl Bromide or Iodides by Cyanide.

The 2-(4'-halophenyl)imidazo[1,2-*a*]pyridine was mixed with dimethylformamide (5-10 ml/g) and cuprous cyanide (0.5 g/g). The mixture was refluxed for 24 hours or longer if tlc monitoring indicated incomplete reaction. The hot reaction solution was then poured into 1:4 ethylenediamine-water mixture (four times the volume of dimethylformamide used). The product was cautiously extracted from the aqueous solution using chloroform. The extract was washed with water, dried and evaporated. **CAUTION: Use appropriate precautions for cyanide toxicity!**

Method E. Reduction of Nitriles to Aldehydes Using Diisobutylaluminum Hydride.

The 2-(4'-cyanophenyl)imidazo[1,2-*a*]pyridine was dissolved in dry toluene (20 ml/g) in a reaction system under nitrogen. Diisobutylaluminum hydride (1 *M* in hexane) was added (1.2 equivalents) slowly by syringe. The solution was stirred at room temperature for one hour. Methanol was added to destroy excess hydride and the mixture was then poured into 10% sulfuric acid. The mixture was stirred for one hour and then the precipitated sulfate salt was collected by filtration. This was dissolved in a minimum amount of boiling water and basified to a *p*H of 12. The product was collected from the cooled solution. In cases where purification of the aldehyde directly was troublesome, the bisulfite adduct was prepared as described in Method F.

Method F. Reduction of Nitriles to Aldehydes Using Raney Nickel and Sodium Hypophosphite.

A mixture of 0.10 mole of the nitrile and 0.30 mole of sodium hypophosphite hydrate was placed in a flask equipped with a mechanical stirrer and reflux condenser. Raney nickel (10 g) and a solvent mixture consisting of water (100 ml), acetic acid (100 ml) and pyridine (200 ml) was added. The reaction mixture was heated to 100° for 7 hours. The solution was filtered while still hot to remove the Raney nickel and the filtrate was evaporated to an oily residue. Stirring this oily product with water (2000 ml) usually resulted in crystallization of the crude aldehyde, which was isolated by filtration. This material was purified by reaction with excess sodium bisulfite in 500 ml of 95% ethanol. The mixture was heated for 10 minutes and filtered hot. The solid bisulfite adduct crystallized and was then dissolved in boiling water, cooled to room temperature and basified with 10% sodium hydroxide solution. The precipitate was collected, washed free of base and recrystallized from 95% ethanol.

Method G. Reduciton of Nitriles to Aldehydes by Raney Nickel Alloy in Formic Acid.

The cyano compound (3.0 g) was dissolved in 50 ml of 75% formic acid and 3.0 g of Raney nickel alloy powder was added to this solution. The reaction mixture was refluxed for 1.5 hours. The nickel residue was filtered out and the filtrate was basified with sodium hydroxide solution. The mixture was extracted with ethyl acetate. The ethyl acetate layer was shaken with brine, dried over magnesium sulfate and evaporated under vacuum to give the product as a solid. When necessary, the crude product was further purified by preparation of the sodium bisulfite adduct as in Method F.

Method H. Oxidative Conversion of Aldehyde **3ak** to Methyl Ester **3al**.

A mixture of **3ak**, 500 mg, sodium cyanide, 500 mg, acetic acid, 460 mg, and active manganese dioxide (4 g) was stirred in methanol (35 ml) for 12-14 hours. The mixture was filtered, and evaporated and the residue was partitioned between water and chloroform. The chloroform layer was dried and evaporated and the residue was recrystallized from ethanol to give **3al**, mp 205°, 65% yield.

Method I. Conversion of Nitrile **3aj** to Carboxamide **3am** with Basic Hydrogen Peroxide.

A solution of **3aj** (2.2 g) in methanol (100 ml) was treated with 1.6 ml of 6*N* sodium hydroxide solution. There was then slowly added 33 ml of 30% hydrogen peroxide solution. The reaction mixture was warmed to 50° for one hour. The mixture was concentrated to about 30 ml, diluted with 10 ml of water and refrigerated overnight. Filtration gave **3am**, 1.9 g, 80%, mp 259-261°.

Method J. Conversion of Nitrile **3aj** to Thiocarboxamide **3an** by Addition of Hydrogen Sulfide.

A solution of **3aj** (2.0 g) in dimethylformamide (18 ml) containing diethylamine (2 ml) was warmed to 55° in an oil bath. A stream of hydrogen sulfide was passed through the mixture at a moderate rate for 2 hours. Excess hydrogen sulfide was removed by a vigorous nitrogen purge and the reaction mixture was poured into 100 ml of ice water. Most of the product precipitated. Additional product was obtained by extraction of the filtrate with methylene chloride. The combined yield was 3.3 g (95%), mp 201-202°.

Method K. Conversion of Nitrile **3aj** to Carboxamidine **3ao** by Pinner Reaction.

Compound **3aj**, 4.4 g, was suspended in nitrobenzene (120 ml). Absolute ethanol (10 ml) was added and hydrogen chloride gas was passed through the system. After a few minutes, crystallization occurred and the precipitate was redissolved by warming the solution for a few minutes. The solution was recooled to room temperature and a continuous stream of hydrogen chloride gas was introduced for 6 hours. Initially, precipitation occurred but by the end of the time the precipitate had redissolved. The solution was kept at room temperature for 3 days. Dry ether was then added to precipitate the imino ether hydrochloride. The salt was isolated by filtration and dried *in vacuo*. The dried salt was dissolved in 100 ml of dry ethanol which had been saturated with ammonia. The solution was stirred for 24 hours, filtered and concentrated to about one-half volume. The amidine dihydrochloride was precipitated by addition of ether. It was purified by several recrystallizations from water-acetone to give 2.7 g of product, 40% yield, mp 250° dec.

Method L. Oxidation of **3ik** to the Corresponding Sulfoxide and Sulfone.

Compound **3ik** (2.0 g) was dissolved in methylene chloride (60 ml) and treated with 1.0 equivalent of 85% *m*-chloroperoxybenzoic acid. The solution was stirred for 30 minutes, diluted with additional methylene chloride and washed with aqueous sodium bicarbonate solution. Evaporation of the dried extract left **3jk** (62%), mp 200°, after recrystallization from ethanol. When the ratio of *m*-chloroperoxybenzoic acid was increased to 2:1 the sulfone **3kk** was obtained in 54% yield, mp 230°, after recrystallization from ethanol.

Method M. Conversion of **3gc** to **3mc** by Benzenethiolate Substitution.

A solution of sodium methoxide was prepared by dissolving ~500 mg of sodium metal in dry methanol (15 ml). Thiophenol was titrated into the sodium methoxide to effect neutralization to *p*H 7. The solution was then transferred to a thick-walled pressure tube and copper powder (~150 mg) and **3gc** (2.0 g) were added. The tube was sealed and maintained at 130° for 12 hours. The tube was opened and the contents filtered to give the product, mp 192°, in 65% yield.

Method N. Compound **4e** by Bromination of **3ak**.

A stirred solution of **3ak** (2.2 g, 10 mmole) in glacial acetic acid (60 ml) was treated with bromine (2.0 g). After stirring for 2 hours, the solid precipitate was isolated and redissolved in water. The solution was made basic with ammonium hydroxide and the precipitate collected and recrystallized from ethanol to give **4d**, 2.1 g, 70% mp >200° dec.

Method O. Compound **4e** by Nitration of **3ak**.

The aldehyde **3ak**, 10 g, was stirred with 10 ml of a 1:1 mixture of concentrated sulfuric acid and concentrated nitric acid at 0-5°. After 2 hours the mixture was poured on crushed ice and the precipitate was filtered. The solid was dissolved in aqueous ethanol and the solution was made basic. The nitro derivative **4e** separated and was recrystallized from ethanol, 70% yield, mp 230-232°.

Method P. Reduction of 2-Arylimidazo[1,2-*a*]pyridines to 5,6,7,8-Tetrahydro Derivatives.

Both **3ab** and **3ak** were reduced over Raney nickel at 3-4 atmospheres for a period of 2-3 hours. After removal of catalyst by filtration and evaporation of solvent the tetrahydro derivatives were obtained as crystalline solids. Compound **5a** was isolated after acetylation. Compound **5b** was purified *via* the bisulfite addition product as described in Method F.

Method Q. Preparation of 4'-Formylphenoxymethyl Compounds Using Potassium Hydroxide as Base.

*p*-Hydroxybenzaldehyde (14 mmoles) and powdered potassium hydroxide (13 mmoles) (in the cases where the neutral chloromethyl compound was used, 7 mmoles of *p*-hydroxybenzaldehyde and 6.5 mmoles of potas-

sium hydroxide were used) were added to 25 ml of dimethyl sulfoxide and the mixture was stirred for one hour. A solution of chloromethyl compound or its hydrochloride salt (6.0 mmoles) in 4 ml of dimethyl sulfoxide was added to the alkaline solution of *p*-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature, poured into water and extracted with ethyl acetate. The extracts were combined and washed repeatedly with water and 5% aqueous sodium hydroxide solution until the washing was almost colorless. The ethyl acetate layer was shaken with brine, dried over magnesium sulfate and evaporated under vacuum to give the product, which was recrystallized from ethyl acetate/hexane.

Method R. Preparation of 4'-Formylphenoxymethyl Compounds Using Sodium Hydride as Base.

Sodium hydride (100 mmoles, 60% oil dispersion) was washed with hexane in a 250 ml three-necked round bottom flask. The flask was protected by a slow stream of nitrogen. A condenser and a 25 ml dropping funnel were fitted to the flask. Dry dimethylformamide (50 ml) was added and with stirring a solution of 80 mmole *p*-hydroxybenzaldehyde in 35 ml of dimethylformamide was added through the dropping funnel within 15 minutes. The mixture was allowed to stand for a half hour, after which 65 mmoles of the chloromethyl compound in 40 ml of dry dimethylformamide was added through the dropping funnel within 15 minutes. The flask was then heated on an oil bath at 95-100° for 24 hours. The contents of the flask were poured into 1500 ml of cold water and stirred. The product was then filtered. The crude aldehyde was recrystallized 2-3 times using ethyl acetate/hexane.

Method S. Preparation of 2-Chloromethylimidazo[1,2-*a*]pyridines.

A mixture of 50 mmoles of the 2-aminopyridine and 50 mmoles of 1,3-dichloroacetone in 150 ml of reagent grade acetone was refluxed for 6 hours. The reaction mixture was cooled and the precipitated solid was collected, redissolved in water, acidified with dilute hydrochloric acid and refluxed for an hour. The solution was cooled and neutralized with saturated sodium bicarbonate solution. The precipitated solid was collected, dried and recrystallized from ethanol.

Method T. Preparation of Imidazo[1,2-*a*]pyridine-2-carboxaldehydes.

2-Aminopyridine (0.09 mole) and ethyl bromopyruvate (0.09 mole) in 100 ml of absolute ethanol were stirred under reflux for 5 hours. The reaction mixture was cooled and evaporated. The residue was dissolved in 10% hydrochloric acid and brought to *p*H 8 with saturated sodium bicarbonate solution. The precipitated solid was filtered, dried and recrystallized from carbon tetrachloride. The ester was dissolved in a minimum amount of dry dichloromethane, 100 ml of anhydrous ether was added and the solution was kept stirring at room temperature in a nitrogen atmosphere. Lithium aluminum hydride (1.0 equivalent) was added in portions over a period of an hour, maintaining a gentle reflux. After the addition of the lithium aluminum hydride was complete, the reaction mixture was gently refluxed for an hour. The reaction mixture was cooled and treated with *n* ml of water, *n* ml of 15% sodium hydride, and 3 *n* ml of water in sequence (based on *n* = weight of lithium aluminum hydride in g) and stirred for half an hour. The precipitated lithium and aluminum salts were filtered off and thoroughly washed with hot ethyl acetate. The combined organic filtrates were evaporated and the solid obtained was recrystallized from ethyl acetate and hexane. The alcohol was dissolved in chloroform and of manganese dioxide (4 g/g of alcohol) was added. The mixture was stirred at room temperature for 3 days and filtered. The filtrate was concentrated to give the aldehyde.

Method U. 2-(4'-Cyanophenylethenyl)imidazo[1,2-*a*]pyridines.

Diethyl 4-cyanobenzylphosphonate [17] (24 mmoles), and sodium hydride (24 mmoles) were stirred in 60 ml of dry dimethoxyethane in a nitrogen atmosphere and the aldehyde (24 mmoles) in 20 ml of dimethoxyethane was added slowly using an addition funnel. The reaction mixture was gradually heated to 85° in an oil bath and maintained at that temperature for one hour. The reaction mixture was cooled and poured into excess water. The precipitated solid was filtered, dried and recrystallized from ethyl acetate.

2-[4'-(3-Oxo-1-propenyl)phenyl]imidazo[1,2-*a*]pyridine **17**.

Sodium (70 mmoles) was dissolved in 80 ml of absolute ethanol. Triethyl phosphonoacetate (70 mmoles) was added and stirred for 15 minutes. To this mixture 70 mmoles of 2-(4'-formylphenyl)imidazo[1,2-*a*]pyridine was added and the solution was heated in an oil bath at 90° for 15 minutes. The reaction mixture was poured into water and the precipitated product was recrystallized from ethanol. The ester prepared in this way (10 mmoles) was dissolved in toluene (100 ml) and reduced using an equimolar amount of diisobutylaluminum hydride. After stirring overnight a few ml (~10 ml) of methanol was added, followed by 10% sulfuric acid (100 ml). The aqueous layer was carefully neutralized and basified with 10% sodium hydroxide. The product allylic alcohol was extracted with chloroform and dried. To the chloroform solution active manganese dioxide (five times the amount of alcohol by weight) was added and the mixture was stirred for 20-24 hours. The precipitate was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in hot ethanol, heated with saturated sodium bisulfite and the bisulfite adduct was collected. It was suspended in water and basified with sodium hydroxide. The aldehyde was recrystallized from hot ethanol.

1-(4'-Formylbenzyl)benzimidazole **18**.

A solution of benzimidazole (4 g, 33.8 mmoles), in 20 ml of dry dimethylformamide was added to a suspension of 1.66 g (41.5 mmoles) of sodium hydride in 20 ml of dry dimethylformamide. The mixture was stirred for 30 minutes at room temperature under a nitrogen atmosphere at room temperature. A solution of *p*-cyanobenzyl bromide 7.4 g (37.6 mmoles) in 10 ml of dry dimethylformamide was added to the sodium benzimidazolate solution. The reaction mixture was warmed at 50° for 2 hours, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed repeatedly with water. The ethyl acetate layer was shaken with brine, dried over magnesium sulfate and evaporated under vacuum to give the product as a pale yellow oil, which solidified on standing, yield, 6.8 g (85%). The nitrile was reduced to **18** in 60% yield using Raney nickel alloy in formic acid. (Method G).

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