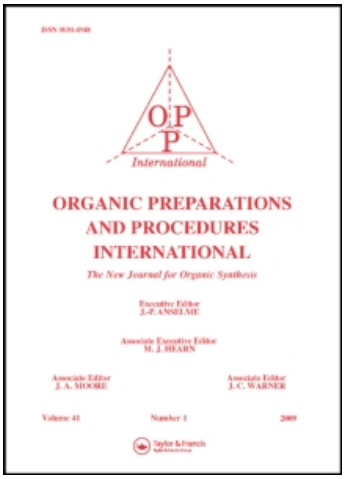

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SYNTHESIS OF IMIDAZOQUINOLINES AND IMIDAZOISOQUINOLINES FROM AZANAPHTHALENE CARBOXYLIC ACIDS

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SYNTHESIS OF IMIDAZOQUINOLINES AND IMIDAZOISOQUINOLINES FROM AZANAPHTHALENE CARBOXYLIC ACIDS

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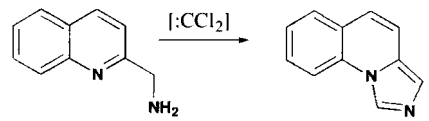
The carbene-induced cyclization of α-(aminomethyl)quinoline analogs leads to the intensely fluorescent imidazoquinoline and imidazoisoquinoline systems.[1] Our objective was to use this carbene-promoted cyclization reaction in a fluorescence-based personal dosimeter to monitor human exposure to chloroform and other haloforms. However, we needed to synthesize the starting aminomethyl compounds and the corresponding imidazo reaction products to adequately evaluate the chemistry of the carbene-induced cyclization reaction. We report an improved synthetic approach to form imidazoquinolines and imidazoisoquinolines from azanaphthyl carboxylic acids. In this approach, the α-carboxylic acids are converted into the corresponding α-aminomethyl derivatives. Subsequent formylation of the amines facilitates cyclization to the imidazoazanaphthalenes with phosphorous oxychloride. This reaction sequence provides products rapidly and in high yield and does not involve the cyanide-dependent formation of Reissert intermediates.



Our approach to this synthesis is outlined in Scheme 1 for the conversion of **1-6** and the results are shown in Table 1.

Scheme 1

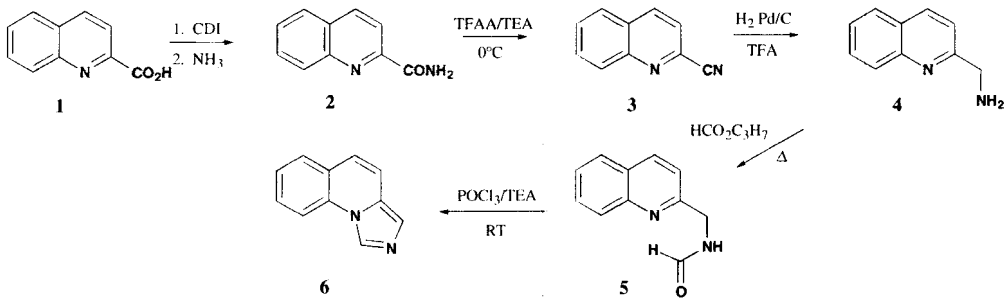
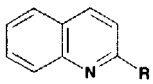
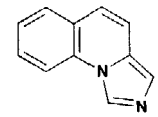
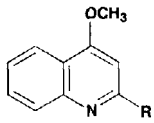
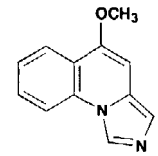
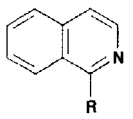
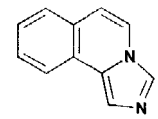
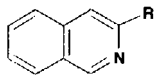
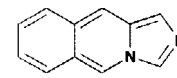


TABLE 1. Yields of Quinoline and Isoquinoline Derivatives.

R =	CO_2H	$CONH_2$	CN	CH_2NH_2 2HCl	CH_2NHCHO	Imidazo
	**1**	**2** (96)	**3** (89)	**4** (92)	**5** (83)	 **6** (80)
	**7**	**8** (92)	**9** (96)	**10** (89)	**11** (74)	 **12** (73)
	**13**	**14** (91)	**15** (90)	**16** (84)	**17** (89)	 **18** (86)
	**19**	**20** (98)[a]	**21** (92)	**22** (65)	**23** (75)	 **24** (0)

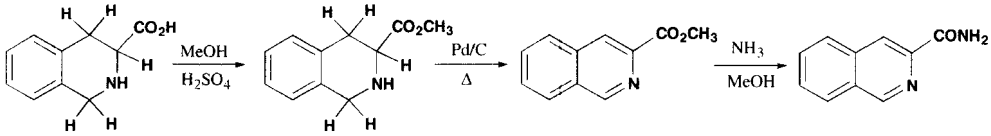
a) Amide **20** was prepared from 3-methoxycarbonylisoquinoline (**27**)(see Scheme **2**).

The reaction sequence involves reduction of the cyano group of α-azanaphthylcarbonitriles to the corresponding -CH_2NH_2 derivatives. The 1-cyanoisoquinolines and 2-cyanoquinolines can be prepared from Reissert intermediates by dehydroclimination with base (e. g., N,N-diisopropylethylamine or *t*-BuOK).[2] However, Reissert-type chemistry does not provide 3-cyanoisoquinolines[3] and formation of Reissert intermediates on a large scale can be hazardous because of the quantity of cyanide (KCN, NaCN, or Me_3SiCN) required. To circumvent these problems, the cyano groups were introduced by way of the α-carboxylic acids. The acids (**1**, **7**, **13**) were converted to their amides [**2**, **8**, **14**; carbonyldiimidazole (CDI)/NH_3] which were then dehydrated under mild conditions with trifluoroacetic anhydride (TFAA) and triethylamine (TEA)[4] to nitriles **3**, **9**, and **15** instantaneously and free of quinoline-based impurities. The use of thionyl chloride to prepare the amides *via* the acid chloride led to formation of impurities that were difficult to remove. In the case of **7**, the major impurity was 4-chloroquinaldamide, apparently formed by replacement of the 4-OCH_3 group by Cl. The 4-chloroquinolines exhibited chromatographic mobility similar to the 4-OMe compounds making detection and separation of the impurities difficult.

Since isoquinoline-3-carboxylic acid (**19**) is not commercially available, 3-isoquinaldamide (**20**) was prepared as shown in Scheme 2.[5] 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (**25**) was

esterified in MeOH with 3% H_2SO_4. Ester **26** was then dehydrogenated with Pd/C in refluxing xylene.[6] Isoquinoline ester **27** was converted quantitatively into amide **20** by treatment with NH_3-saturated methanol at ambient temperature and pressure.[7] Dehydration of the amide to form the nitrile **21** was accomplished as above with TFAA.

Scheme 2



25 **26** **27** **20**

The azanaphthylcarbonitriles (**3**, **9**, **15**, **21**) were reduced to the corresponding aminomethyl compounds by catalytic hydrogenation (10% Pd/C, 30 psi H_2) in acidic methanol to yield the air-stable ammonium salts of **4**, **10**, **16**, and **22**. Reduction of the nitriles in HCl-ethanol solution produced insoluble amine hydrochloride salts that were difficult to separate from the catalyst.[8] By substituting trifluoroacetic acid (5% v/v TFA/MeOH) for HCl, the reduction proceeded smoothly and rapidly forming the alcohol-soluble trifluoroacetate salts. The catalyst was easily removed by filtration and, when necessary, the filtrate decolorized with activated carbon. The amine hydrochlorides were prepared and crystallized in good yields by removing the TFA *in vacuo* and treating the resulting viscous oil with ethanolic HCl (5% v/v HCl/EtOH). However, since attempted reduction of 3-isoquinolinecarbonitrile (**21**) in MeOH/TFA generated a red solution and low yields of the amine, so **22** was prepared in HCl/MeOH.

The difficulty encountered in the hydrogenation of the nitrile of **21** may be related to the ease of reduction of the azanaphthyl ring in TFA. Eliel[9] reported that quinoline could be reduced with 5% Pd/C at 50 psi H_2 to a mixture of tetrahydropyridine and piperidine compounds and that isoquinoline is reduced at atmospheric pressure in acetic acid with PtO_2. Nevertheless, except for problems with nitrile **21**, no ring-reduced compounds using MeOH/TFA over Pd/C at 30 psi H_2 could be detected. 1-Isoquinolinecarbonitrile (**15**) has been converted to **16** with Raney Ni, but this reduction requires high pressures (1200-1500 psi) at elevated temperatures and uses a mixture of H_2 and NH_3.[10]

With the α-(aminomethyl)azanaphthalenes in hand, we were able to compare the carbene-induced cyclization with other reactions that proceed through analogous intermediates. The reaction of dichlorocarbone (:CCl_2) with primary amines is postulated to involve formation of imidoyl chlorides;[1,11] then, the reaction of $POCl_3$ with formamide groups represented a suitable model because it too generates the imidoyl group.[12] Consequently, the amines were formylated by reflux in formic acid to give moderate yields of formamides **5**, **11**, **17**, and **23**. However, with these conditions 1-aminomethylisoquinoline (**16**) produced a mixture of 1-formamidomethylisoquinoline (**17**) and imidazoisoquinoline **18**. Subsequently, a non-acidic method was developed whereby the free amines, or

their HCl-salts with excess TEA, were refluxed in propyl formate to generate the corresponding formamides in good yields and without the side-chain-cyclized compounds.

Finally, the imidazoazanaphthalenes were prepared in minutes at ambient temperature by treating the formamidomethyl compounds (**5**, **11**, **17**, **23**) with $POCl_3$ in a solution of CH_2Cl_2 that contained excess equivalents of TEA. In the absence of base, protonation of the ring nitrogen inhibits the reaction and elevated temperatures are required to force the cyclization.[13] The imidazo compounds (**6**, **12**, **18**) were purified on silica. As was noted earlier, the formation of imidazo[1,2-*b*]isoquinoline (**24**) using the $POCl_3$/TEA method does not appear to be energetically favorable compared to formation of the isocyanide derivative.[1] Even at low temperatures (-78°) the imidazole could not be induced to form.

In summary, the sequence of reactions described herein to form α-(aminomethyl)quinoline analogs and their corresponding imidazoquinoline derivatives, is initiated with commercially available carboxylic acid derivatives. The methods reported provide improved yields over more established procedures and employ milder and faster reactions to generate the desired products. In addition, these procedures provide the target compounds in reaction media that are easily worked-up and that facilitate product purification.

EXPERIMENTAL SECTION

Melting points were determined from samples in open capillary tubes and are uncorrected. IR spectra were obtained on an FTIR spectrometer at 4 cm^{-1} resolution. NMR spectra were recorded at 200 or 300 MHz with $CHCl_3$ as an internal standard. Low-resolution electron-impact mass spectra were obtained at 70 eV with direct sample insertion or by GC separation on a 0.32-mm x 30-m DB1 capillary column. High-resolution mass spectra were recorded at the Facility for Advanced Instrumentation at the University of California, Davis on a VG ZAB-2H. All TLC was performed on Analtech (Newark, DE) precoated glass plates of silica gel GF. Analytical TLC to monitor reactions was accomplished with 0.25-mm-thick silica gel plates briefly exposed to anhydrous NH_3. Preparative TLC was performed on 20-cm x 20-cm plates coated to a thickness of either 0.50 mm or 1.0 mm of silica gel. The quinoline carboxylic acids, phosphorous oxychloride, $SOCl_2$, 1,1'-carbonyldiimidazole (CDI), trifluoroacetic anhydride, 10% Pd/C, and CH_2Cl_2 were obtained from Aldrich Chemical Co. and were not purified unless otherwise noted. Hydrogen, anhydrous NH_3, and technical grade hydrogen chloride gas were obtained from Matheson Gas Products, Inc., and were not purified further.

Formation of Amides from Carboxylic Acids. 2-Quinaldamide (2).- To 2-quinolinecarboxylic acid (**1**) (2.54 g, 14.67 mmol) and CDI (4.68g, 28.87 mmol) stirred in a 250 mL flask was added 50 mL of CH_2Cl_2. The reaction was monitored by analytical TLC (silica: 5% MeOH-CH_2Cl_2) which showed that formation of the imidazolide was complete in 30 min. The amide was then formed by rapidly bubbling anhydrous NH_3 into the reaction mixture. The amidation of the imidazolide was complete within three minutes. The reaction mixture was poured into water (75 mL) and the NH_3 neutralized by the addition of 1.0 N aqueous HCl. The pH of the aqueous phase was adjusted to approximately 7, and the organic layer was separated, collected, and the aqueous phase extracted with 3 x 50 mL portions

of CH_2Cl_2. The organic phases were combined, dried and the solvent concentrated *in vacuo*; analytical chromatography (TLC, GC) indicated that the sample was pure. The amide was crystallized from ethanol-heptane, to give 2.41 g (96%) of long flat white plates (3 crops), mp. 123-124°, lit.[14] 133°. IR (KBr): 3442, 3230, 1692, 1665, 1592, 1561, 1504, 1391, 1169, 854, 772 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.66-7.74 (m, 1H), 7.80-7.89 (m, 1H), 8.05 (dm, J = 8.6 Hz, 1H), 8.12 (dm, J = 8.6 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 8.52 (dm, J = 8.6 Hz, 1H). EIMS *m/z* (%): 172 (39), 129 (100), 102 (22), 77(9).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.67; H, 4.78; N, 16.33

4-Methoxy-2-quinaldamide (**8**) from 4-methoxy-2-quinaldic acid (**7**) (2.03 g, 10.0 mmol), CDI (4.0 g, 24.69 mmol), CH_2Cl_2 (50 mL); yield 1.85 g, 92%, mp. 177-178°. IR (KBr): 3459, 3196, 1694, 1593, 1566, 1509, 1399, 1316, 1116, 993, 859, 853, 754 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 4.20 (s, 3H), 7.60-7.68 (m, 1H), 7.69 (s, 1H), 7.78-7.85 (m, 1H), 8.05 (dm, 1H, J = 8.2 Hz), 8.25 (dm, 1H, J = 8.2 Hz). EIMS *m/z* (%): 202 (56), 159 (100), 143 (12), 130 (14), 115 (17), 102 (28), 89 (18).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.15; H, 4.99; N, 13.81

1-Isoquinaldamide (**14**) from 1-isoquinaldic acid (**13**) (2.50 g, 14.44 mmol), CDI (4.68 g, 28.88 mmol), CH_2Cl_2 (50 mL); yield 2.25 g, 91%, mp. 165-166°, lit.[15] 167-168°. IR (KBr): 3431, 3176, 1686, 1586, 1551, 1370, 1316, 1259, 1188, 1154, 830 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.68-7.84 (m, 2H), 7.97-8.04 (m, 2H), 8.12 (b, 2H), 8.52 (d, 5.6 Hz, 1H), 9.48 (dm, J = 8.4 Hz, 1H). EIMS *m/z* (%): 172 (75), 154 (11), 129 (100), 102 (35), 75 (20).

Anal. Calcd. for: $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.64; H, 4.74; N, 16.35

3-Isoquinaldamide (**20**): A solution of 3-methoxycarbonylisoquinoline (**19**) (3.40 g, 18.18 mmol) in 70 mL of dry MeOH was chilled in an ice bath as the solution was saturated with anhydrous NH_3. After overnight standing without stirring, the long white needles of amide which formed were collected and the filtrate treated with NH_3 as before to provide a second batch of crystalline amide. The combined two crops were recrystallized from MeOH to give 3.05 g (98% yield), mp. 205-206°, lit.[7] 206-207°. IR (KBr): 3434, 3407, 3383, 3167, 1697, 1678, 1599, 1495, 1464, 1402, 1337, 957, 906, 802, 765, 736 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.76-7.92 (m, 2H), 8.16-8.23 (m, 2H), 8.59 (s, 1H), 9.32 (s, 1H). EIMS *m/z* (%): 172 (75), 129 (100), 102 (21), 77 (12).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.71; H, 4.46; N, 16.42

Conversion of Amides to Nitriles. 2-Cyano-4-methoxyquinoline (**9**).- To the partially dissolved 4-methoxy-2-quinolinecarboxamide (**8**) (1.646 g, 8.15 mmol) stirred in a solution of CH_2Cl_2 (50 mL) at 0° and that contained 3.0 equivalents of TEA (3.4 mL, 24.44 mmol.) was added in one portion 1.5 mL of TFAA (1.3 equivalents, 10.62 mmol). The solution subsequently became homogeneous, and after 2 min the reaction was determined to be complete by TLC (silica plate eluted with CH_2Cl_2). The reaction mixture was poured into water and extracted. The organic layer was separated, washed with water twice, and the combined aqueous fractions back-extracted with two 50 mL portions of CH_2Cl_2. The organic fractions were combined, dried over Na_2SO_4, and column chromatographed on silica gel eluted with CH_2Cl_2 from the crude solid. Crystallization from heptane afforded 1.44 g (96%) of 2-

cyano-4-methoxyquinoline (**9**) as white flakes, mp. 121-122°. IR (KBr): 3069, 3027, 2992, 2945, 2234, 1581, 1556, 1509, 1461, 1414, 1356, 1331, 1129, 1114, 986 946, 838, 771 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 4.23 (s, 3H), 7.45 (s, 1H), 7.69-7.77 (m, 1H), 7.84-7.93 (m, 1H), 8.04 (dm, J = 8.4 Hz, 1H), 8.25 (dm, J = 8.4 Hz, 1H). EIMS *m/z* (%): 184 (100), 154 (19), 141 (29), 127 (10), 114 (24), 102 (9), 89 (9), 75(9).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.20. Found: C, 71.58; H, 4.32; N, 15.37

2-Cyanoquinoline (**3**) from 2-quinaldamide (**2**) (1.855 g, 10.78 mmol), TFAA (1.83 mL, 12.96 mmol), TEA (4.5 mL, 32.35 mmol), CH_2Cl_2 (50 mL); yield 1.484 g, 89%, mp. 93-94°, lit.[2b] 94-95°. IR (KBr): 3075, 3060, 2234, 1588, 1499, 1379, 1336, 1304, 1122, 957, 827 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 8.22-8.30 (m, 1H), 8.35-8.44 (m, 2H), 8.55-8.62 (m, 1H), 9.08 (dm, J = 8.5 Hz, 1H). EIMS *m/z* (%): 154 (100), 127 (20), 102 (6), 76 (11).

Anal. Calcd. for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.18. Found: C, 78.14; H, 4.00; N, 18.09

1-Cyanoisoquinoline (**14**) from 1-isoquinaldamide (**13**) (2.50g, 14.53 mmol), TFAA (2.15 mL, 15.22 mmol), TEA (6.0 mL, 43.13 mmol), CH_2Cl_2 (50 mL); yield 2.024 g, 90%, mp. 88-89°, lit.[2b] 89-90°. IR (KBr): 3059, 2228, 1622, 1581, 1557, 1495, 1455, 1391, 1345, 878, 839, 789, 746, 662 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.92-8.05(m, 2H), 8.14-8.22 (m, 2H), 8.28-8.35 (m, 1H), 8.69 (d, J = 5.6 Hz, 1H). EIMS *m/z* (%): 154 (100), 127 (44), 100 (10), 76 (11).

Anal. Calcd. for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.18. Found: C, 77.86; H, 3.76; N, 18.18

3-Cyanoisoquinoline (**21**) from 3-isoquinaldamide (**20**) (1.532 g, 8.91 mmol), TFAA (1.50 mL, 10.61 mmol), TEA (4.0 mL, 28.75 mmol), CH_2Cl_2 (50 mL); yield 1.264 g, 92%, mp. 124-125°, lit.[16] 127.5-128°. IR (KBr): 3057, 2227, 1622, 1577, 1491, 1437, 1275, 966, 938, 903, 764, 748 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.97-8.02 (m, 2H), 8.12-8.17 (m, 1H), 8.25-8.32 (m, 1H), 8.48 (s, 1H), 9.34 (s, 1H). EIMS *m/z* (%): 154 (100), 127 (40), 103 (6), 100 (9), 77 (11).

Anal. Calcd. for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.18. Found: C, 77.80; H, 3.64; N, 17.91

Catalytic Hydrogenation of the Nitrile. 2-(Aminomethyl)-4-methoxyquinoline (**10**).- To a 500 mL Parr hydrogenation flask containing 2-cyano-4-methoxyquinoline (**9**) (1.130 g, 6.14 mmol) and 10% palladium-on-carbon catalyst (200 mg) was added a 100 mL solution of methanol containing 5% (v/v) trifluoroacetic acid. The flask was purged of air and pressurized with H_2 (30 psi) and then the reaction mixture was stirred at room temperature for 2 hrs. The catalyst was then removed from the yellowish solution by filtering the mixture through a fine-porosity sintered glass funnel. The filtrate was concentrated *in vacuo* to about 5 mL and then 15 mL of a 10% (w/w) solution of anhydrous HCl in ethanol was added, causing the amine hydrochloride to crystallize slowly from solution. The white crystals were collected and rinsed with ethanol giving the 2-(aminomethyl)-4-methoxyquinoline dihydrochloride monohydrate in 89% yield (1.425 g), mp. 186-187°. IR (KBr): 2801, 2711, 2625,1643, 1622, 1601, 1501, 1485, 1456, 1424, 1392, 1347, 1221, 1109, 943 cm^{-1}. ^1H NMR (300 MHz, dmso-d_6): 4.11 (s, 3H), 4.40 (br, 2H), 7.36 (s, 1H), 7.61-7.69 (m, 1H), 7.82-7.91 (m, 1H), 8.04 (d, 1H, J = 8.2 Hz), 8.19 (d, 1H, J = 8.2 Hz), 8.62 (br, 2H). EIMS *m/z* (%): 188 (100), 173 (23), 159 (70), 145 (17), 130 (21).

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.32; H, 5.78; N, 10.04. Found: C, 47.30; H, 5.88; N, 10.03

2-(Aminomethyl)quinoline Dihydrochloride (**4**) from 2-cyanoquinoline (**3**) (1.001 g, 6.50 mmol), 10% palladium-on-carbon catalyst (200 mg), 5% (v/v) trifluoroacetic acid in methanol (100 mL), H_2 (30 psi); yield 1.375 g, 92%, mp. 230-232°, lit.[17] dec. 199-201°. IR (KBr): 2778, 2576, 1653, 1604, 1550, 1470, 1440, 1420, 1130, 1030, 932, 875, 775, 763 cm^{-1}. ^1H NMR (300 MHz, dmso-d_6): 4.41 (m, 2H), 7.60 (d, 1H, J = 8.4 Hz), 7.61-7.68 (m, 1H), 7.80-7.85 (m, 1H), 8.02-8.06 (m, 2H), 8.45 (d, 1H, J = 8.4 Hz), 8.53 (br, 3H). EIMS *m/z* (%): 158 (100), 130 (96), 102 (20), 77 (15).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 51.96; H, 5.23; N, 12.12. Found: C, 51.71; H, 5.17; N, 11.96

1-(Aminomethyl)isoquinoline Dihydrochloride Monohydrate (**16**) from 1-cyanoisoquinoline (**15**) (1.054, 6.84 mmol), 10% Pd/C (200 mg), 5% (v/v) trifluoroacetic acid in methanol (100 mL), H_2 (30 psi); yield 1.428 g, 84%, mp. 216-218°, lit.[17] 211-212°. IR (KBr): 3481, 3430, 2827, 2598, 1643, 1616, 1532, 1487, 1383, 1366, 1146, 895, 833 cm^{-1}. ^1H NMR (300 MHz, dmso-d_6): 4.79 (m, 2H), 7.77 (m, 1H), 7.84-7.92 (m, 2H), 8.07 (d, 1H, J = 8.2 Hz), 8.23 (d, 1H, J = 8.2 Hz), 8.52 (d, 1H,), 8.57 (br, 2H). EIMS *m/z* (%): 158 (44), 130 (100), 102 (32), 77 (36).

Anal. Calcd. for: $C_{10}H_{14}Cl_2N_2O$: C, 48.21; H, 5.66; N, 11.25. Found: C, 48.31; H, 5.58; N, 11.35

3-(Aminomethyl)isoquinoline Dihydrochloride Monohydrate (**22**) from 3-cyanoisoquinoline (**21**) (1.143 g, 7.42 mmol), 5% (w/w) HCl in methanol (100 mL), 10% palladium-on-carbon catalyst (200 mg); yield 1.209 g, 65%, mp. 231-233°. IR (KBr): 3304, 2773, 2612, 1667, 1622, 1522, 1491, 1387, 1358, 1127, 924, 779 cm^{-1}. ^1H NMR (300 MHz, dmso-d_6): 4.30 (m, 2H), 7.73 (m, 1H), 7.84 (m, 1H), 7.93 (s, 1H), 7.99 (d, 1H, J = 7.9 Hz), 8.19 (d, 1H, J = 7.9 Hz), 8.41 (br, 2H), 9.41 (s, 1H). EIMS *m/z* (%): 158 (48), 130 (100), 102 (13), 77 (10).

Anal. Calcd. for $C_{10}H_{14}Cl_2N_2O$: C, 48.21; H, 5.66; N, 11.25. Found: C, 48.49; H, 5.39; N, 11.41

Formylation of the Amine. 2-Formamidomethylquinoline (**5**).- To 10 mL of propyl formate containing 1.5 mL of ethanol was added 2-(aminomethyl)quinoline dihydrochloride (**4**) (340 mg, 1.472 mmol). The solution was brought to reflux and, after 2 min, 0.5 mL of TEA was added to dissolve the salt completely. The reaction mixture was refluxed for 2 h after which time an analytical TLC (NH_3-sprayed silica, eluted with 5% MeOH-CH_2Cl_2) indicated that the formylation was complete. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with water. The aqueous phase was back-extracted with 20 mL portions of CH_2Cl_2 until no formamide remained. The organic fractions were combined, dried over Na_2SO_4, and chromatographed on a thick-layer preparative silica plate eluted with 5% MeOH in CH_2Cl_2. The major band was collected and crystallized from CH_2Cl_2/mixed hexanes to give white needles of 2-(formamidomethyl)quinoline (228 mg) in 83% yield; mp. 98-99°. IR (KBr): 3293, 2874, 1653, 1541, 1509, 1421, 1380, 977, 825, 766 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 4.71-4.75 (m, 2H), 7.52 (dm, J = 8.6 Hz, 1H), 7.53-7.61 (m, 1H), 7.91-8.02 (m, 2H), 8.30 (dm, J = 8.6 Hz, 1H), 8.37 (s, 1H). EIMS *m/z* (%): 186 (68), 157 (100), 143 (62), 129 (46).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.91; H, 5.47; N, 14.99

2-Formamidomethyl-4-methoxyquinoline (**11**) from 2-(aminomethyl)-4-methoxyquinoline 2HCl

monohydrate (**10**) (1.39 g, 4.98 mmol), propyl formate (20 mL), ethanol (10 mL), TEA (2 mL); yield 800 mg, 74%, mp. 147-148°. IR (KBr): 3295, 3059, 2878, 1657, 1595, 1570, 1546, 1511, 1420, 1386, 1362, 1112, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 4.06 (s, 3H), 4.72 (d, J = 4.6 Hz, 2H), 6.66 (s, 1H), 7.34 (b, 1H), 7.48-7.53 (m, 1H), 7.68-7.73 (m, 1H), 7.96 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.41 (s, 1H). EIMS *m/z* (%): 216 (24), 187 (58), 173 (100), 159 (28), 144 (11), 130 (20).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.73; H, 5.82; N, 12.81

1-Formamidomethylisoquinoline (**17**): 1-(Aminomethyl)isoquinoline 2HCl monohydrate (**16**) (300 mg, 1.20 mmol), propyl formate (5 mL), ethanol (2 mL), TEA (1 mL); yield 200 mg, 89%, mp. 64-65°, lit.[10] 88°. IR (KBr): 3300, 3057, 2876, 1655, 1547, 1385, 1234, 750 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): 5.05 (m, 2H), 7.69-7.75 (m, 2H), 7.77-7.82 (m, 1H), 7.98 (d, 1H, J = 8.1 Hz), 8.28 (d, 1H, J = 8.1 Hz), 8.35 (s, 1H), 8.43 (d, 1H, 5.5 Hz). EIMS *m/z* (%):186 (62), 157 (100), 143 (43), 130 (35), 115 (18). HRMS: calcd for $C_{11}H_{11}N_2O$ (M+1) *m/e* 187.0871, found 187.0869.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.95; H, 5.43; N, 15.02

3-Formamidomethylisoquinoline (**23**) from 3-(aminomethyl)isoquinoline 2HCl monohydrate (**22**) (321 mg, 1.29 mmol), propyl formate (15 mL), ethanol (2 mL), TEA (1 mL); yield 181 mg, 75%, mp. 96-97°. IR (KBr): 3279, 3055, 2901, 1655, 1630, 1548, 1427, 1382, 1231, 978 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 4.65-4.70 (m, 2H), 7.60-7.68 (m, 1H), 7.71-7.93 (m, 2H), 7.92 (dm, J = 8.2 Hz, 1H), 8.09 (dm, J = 8.2 Hz, 1H), 8.35 (s, 1H), 9.26 (s, 1H) . EIMS *m/z* (%):186 (34), 157 (100), 143 (30), 130 (46), 115 (15), 102 (17).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.94; H, 5.41; N, 15.06

Pendent Group Cyclization. Imidazo[1,5-*a*]quinoline (**6**).- To a solution of 2-formamidomethylquinoline (**5**) (200 mg, 1.08 mmol) in 16 mL of CH_2Cl_2 was added TEA (0.96 mL, 6.90 mmol) followed by $POCl_3$ (260µL, 2.8 mmol). The reaction was allowed to progress at room temperature. Analytical TLC (silica, 3% EtOH/EtOAc) indicated that the reaction was complete after 4 min. The reaction mixture was then neutralized by the addition of 25 mL of 0.28 M Na_2CO_3. After vigorous stirring for several minutes, the organic fraction was separated and the aqueous phase extracted with CH_2Cl_2. The organic fractions were combined, dried over Na_2SO_4, and chromatographed on two thick-layer preparative silica gel plates eluted with 3% EtOH/EtOAc. The major band (R_f 0.5) was collected and crystallized from heptane giving flat white crystals of **6** (145 mg) in 80% yield; mp. 75-76°, lit.[18] 73-75°. IR (KBr): 3100, 1610, 1485, 1463, 1454, 1405, 1332, 1263, 1219, 1118, 926, 810, 758, 655 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 7.13-7.18 (d, 1H), 7.42-7.51 (m, 3H), 7.58-7.68 (m, 1H), 7.77-7.83 (dd, 1H), 8.27-8.33 (dm, 1H), 8.91 (s, 1H). EIMS *m/z* (%): 168 (100), 140 (30), 128 (21).

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.47; H, 4.86; N, 16.56

5-Methoxyimidazo[1,5-*a*]quinoline (**12**) from 2-formamidomethyl-4-methoxyquinoline (**11**) (200 mg 0.93 mmol), $POCl_3$ (220 µL, 2.37 mmol), TEA (865 µL, 6.21 mmol) in 16 mL CH_2Cl_2; yield 133 mg, 73%, mp. 131.5-132.5°. IR (KBr): 3098, 2967, 1631, 1565, 1486, 1460, 1400, 1359, 1277, 1211, 1139, 1103, 926, 820, 761, 652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 4.01 (s, 3H), 6.80 (s, 1H), 7.18 (s,

1H), 7.44-7.54 (m, 1H), 7.62-7.72 (m, 1H), 8.08-8.08 (dd, 1H), 8.24-8.30 (dm, 1H), 8.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 149.43, 131.17, 129.07, 128.71, 126.52, 124.91, 123.71, 120.11, 119.75, 114.17, 91.03, 55.29. EIMS *m/z* (%): 198 (100), 183 (43), 155 (68).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.77; H, 5.27; N, 13.81

Imidazo[5,1-*a*]isoquinoline (18) from 1-formamidomethylisoquinoline (**17**) (400 mg, 2.15 mmol), $POCl_3$ (480 µL, 5.16 mmol), TEA (1.92 mL, 13.8 mmol), in 32 mL CH_2Cl_2; yield 311 mg, 86%, mp. 115-116°, lit.[10,13a] 116°. IR (KBr): 3122, 3107, 3072, 1490, 1459, 1446, 1364, 1239, 1114, 912, 821, 793, 762, 656 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): 6.92-6.96 (d, 1H), 7.41-7.60 (m, 12 lines, 2H), 7.68-7.73 (dm, 1H), 7.86 (s, 1H), 8.11-8.17 (dm, 2H), 8.25 (s, 1H). EIMS *m/z* (%): 168 (100), 140(33), 128 (8).

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.55; H, 4.76; N, 16.52

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