A General Synthesis of Substituted Fluorenones and Azafluorenones

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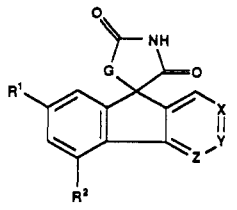
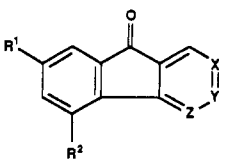
Twenty-one variously substituted fluorenones and azafluorenones have been synthesized via photochemical Pschorr cyclizations of 2-diazoniodiaryl ketones as the key ring-forming step. Direct, $(bipy)_3Ru^{II}$-, or $(bipy)_3Ru^{II}/Cu^{II}$-photosensitized conditions were used, depending on the system to be cyclized. Where selectivities were possible in the ring closure, the isomer ratios obtained were in accord with an aryl radical as the reactive intermediate. The precursor aminodiaryl ketones were obtained from the sequence ortho lithiation of an arylpivalamide, reaction with an aryl aldehyde to give a 2-pivalamidodiarylcarbinol, oxidation to give a 2-pivalamidodiaryl ketone, and hydrolysis to give the 2-aminodiaryl ketone.

It has been known for some time that several hydantoins (**a**) and succinimides (**b**) derived from substituted fluorenes (1; X, Y, Z ≠ N) and azafluorenes (1; X, Y, or = N) are physiologically active, in particular, as aldose reductase inhibitors (ARI).[1] As part of a program of evaluating novel ARI it was necessary to have a reasonably flexible and general approach to the fluorenones and azafluorenones (**2**), which would serve as precursors to **1**. A survey of the



1

a; G = NH, hydantoin
b; G = CH_2, succinimide
X, Y, Z = CH, CR, or N
R^2,R^1, R = H, alkyl, halogen, alkoxy, or thioalkoxy



2

R^2,R^1, R, X, Y, Z as in **1**

methods available for the preparation of **2** indicated two major routes, one in which the key C–C bond formation is the aryl to carbonyl,[2] i.e., intramolecular Friedel–Crafts acylation, and the other, the aryl to aryl.[3] Other, rather specific methods involve oxidative ring contractions of benzo(iso)quinolines,[4] cyclodehydrogenations of 2-methylbiaryls using an interesting but apparently unavailable catalyst known as K-16,[5] and cyclization of 2-arylphenylcarbenes generated by the FVP technique to give the fluorene congeners of **2**.[6] Also, the elaboration of the 6-membered ring from indanones or indandiones has been reported.[7]

Recently, we have recently developed a flexible and quite general approach to **2**, which allows the generation of desired substitution patterns in each of the aromatic rings.

Results and Discussion

The general approach that we have taken is outlined in Scheme I. The pivalamides were obtained from the corresponding anilines and pivaloyl chloride in yields in excess of 90%. Lithiation of **3** according to the procedure of Fuhrer and Gschwend[8] proceeded well except where R^1 and R^2 were fluorine. In this case competitive lithiation between the two fluorine atoms occurred. This type of problem had been noted earlier with the methoxy derivative **3a** (R^1 = OMe, R^2 = H), which gave substantial amounts of lithiation ortho to the MeO.[8] It was necessary to use the bromide (**3b**: $R^1 = R^2$ = F), to conduct the lithiation at −100 °C, and to add the aldehyde **5** to **4** without warming, in order to obtain **6** ($R^1 = R^2$ = F) exclusively. If **4** ($R^1 = R^2$ = F) is allowed to warm to 0 °C before adding an electrophile, e.g., 5-methylnicotinaldehyde, the major product becomes alcohol **10**, which is the result of an intramolecular aromatic nucleophilic displacement followed by addition to the aldehyde. In general, alcohols **6** were isolated in yields of 45–55% although several were in the 20–30% range. Oxidation of **6** to **7** using pyridinium chlorochromate or chromium trioxide in pyridine generally proceeded in yields greater than 80%. In most cases, the acid-catalyzed hydrolysis of the keto amides **7** gave the keto amines **8** in yields in excess of 85%, but in certain instances it was necessary to modify the workup to obtain high yields. It appeared that when the aryl ring bearing the amino group in **8** was electron-deficient, e.g., R^1 = Cl or $R^1 = R^2$ = F, the addition of aqueous sodium hydroxide resulted in the precipitation of substantial quantities of insoluble polymeric material and a lowering of the yields of the desired keto amines to 15–30%. Presumably, these substances were polyimines, although no effort was made to identify them. This side reaction could be avoided if an inverse base quench were used wherein the acidic hydrolysis solution was poured into concentrated aqueous sodium hydroxide maintained at 0–5 °C.

With the keto amines **8** in hand, we investigated various methods of effecting a Pschorr cyclization to obtain the fluorenones **2**. Our results paralleled those of Abramovitch,[3a-c] in which the Gattermann copper-catalyzed decomposition of the diazonium ion derived from **8** gave appreciable (even equivalent) amounts of the deaminated species **9**. In some cases, **2** and **9** had quite similar chromatographic properties, which led to significant problems in purifying the desired product. Thus we focused on the photochemical method[9] of decomposition of the diazonium ion. In most cases, direct photolysis, using Pyrex optics

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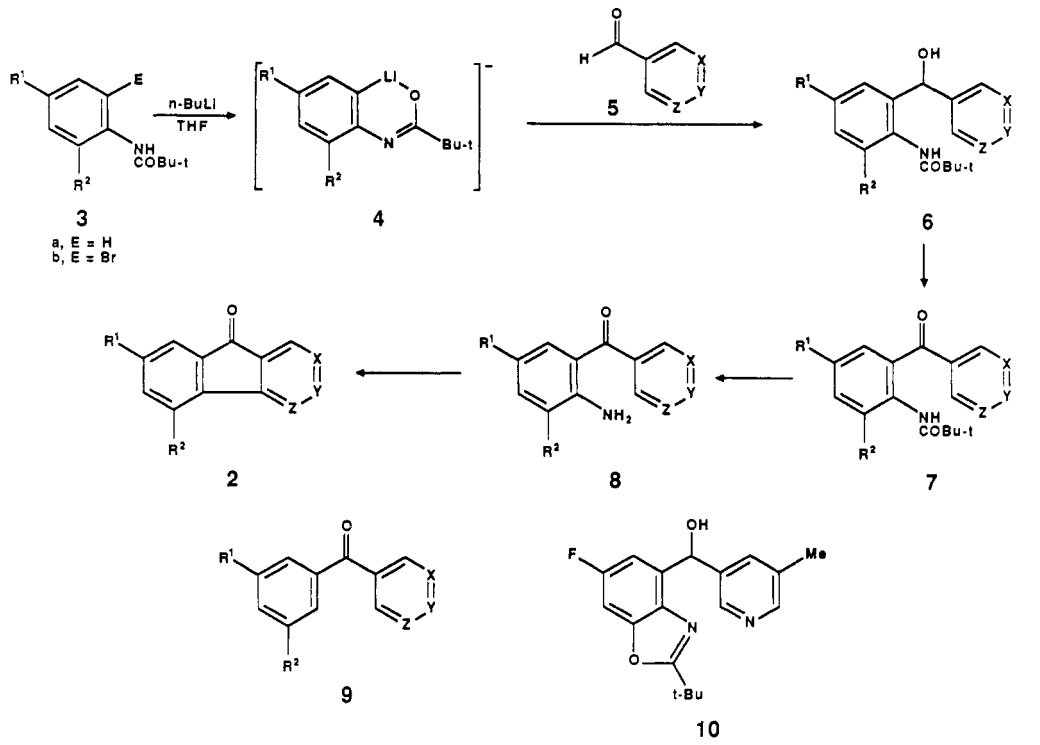
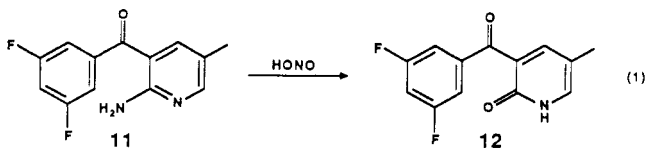
Scheme I



and a medium-pressure mercury vapor lamp, of the aqueous solution of the diazonium ion gave **2** without concomitant formation of **9**. The yields of **2** could be improved considerably if tris(2,2′-bipyridyl)ruthenium(II) dichloride were used as a photosensitizer.[9] When one of the substituents on the aromatic ring in **8** was a methyl group, the reductive deamination side reaction was difficult to avoid. For example, with **8** (R^1 = Me; R^2 = H; X, Z = CH; and Y = N) the $(bipy)_3Ru^{II}$-photosensitized reaction gave a ratio of **2**/**9** = 2.5/1. Upon addition of copper(II) acetate (ratio Cu/Ru = 15), this ratio increased to 5/1. Since presumably the source of the hydrogen atom is the methyl group, via an intermolecular transfer, conducting the reaction at low concentrations was also useful, although there was a practical limit in terms of the amount of material to be reacted in a run. Although we did not investigate this rigorously, we did note a fall-off in yield of **2** (Y = CH, R^1 = R^2 = F; X = CMe, Z = N and X = N, Z = CMe) and an increase in the amount of the corresponding **9**, as a function of increase in concentration of the corresponding diazonium ion.

The only instance that led to failure in the ring-closing step was one in which the diazonium ion was too unstable to survive the time necessary to effect the photochemical step. Thus, the diazotization and attempted photolysis of **11** led to high yields of the pyridone **12** (eq 1). It has

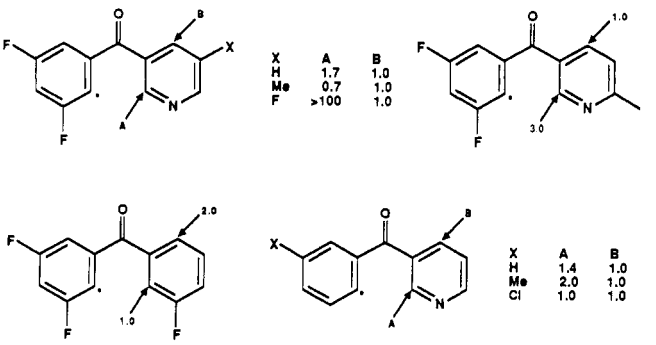


(1)

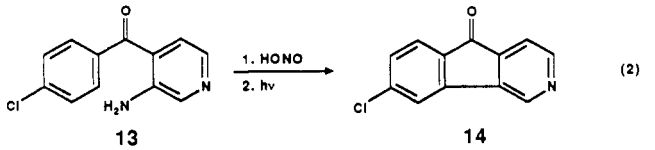
11 12

been noted that the 2-pyridinediazonium ion is particularly unstable.[10] A variety of conditions were investigated in which mixtures of water and methanol or ethylene glycol and temperatures below −15 °C were employed in order to increase the lifetime of the diazonium ion. None of these led to any cyclized product. The desired material was thus obtained via diazonium ion on the benzene moiety (Scheme I) rather than the pyridine (**11**). The

Scheme II



disadvantage to this alternate approach was that two isomers (7-methyl-2 and -4-azafluorenone) were obtained in a ratio of 1/2, respectively, although the yield was reasonable (67%). Generating and photolyzing a diazonium group in the 3-position of a pyridine ring (**13**) did not prove to be as troublesome, although the cyclization yield to give **14** was only 25% (eq 2).



(2)

13 14

In seven cases in this work and one due to Abramovitch and Tertzakian,[3b] the photochemical Pschorr cyclization gave the opportunity to observe any selectivity there might be due to the dissymmetry in aromatic ring to be attacked by the radical[9] generated by photolysis of the diazonium ion. Scheme II summarizes these selectivies. With one exception, only low selectivities were observed, in accord with multitudinous studies[11] on free-radical aromatic

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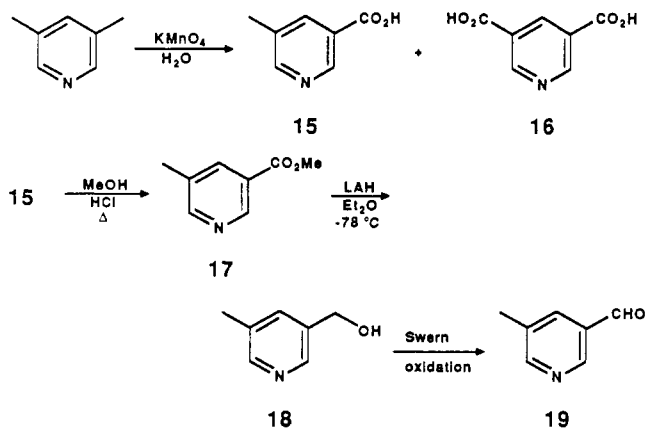
Scheme III



substitution. The selectivity on the pyridine ring is about what might be expected, based on the free-radical phenylation of pyridine, in which a statistically corrected $\alpha/\beta/\gamma$ distribution of 2/1/1 was observed.[12] The increase in selectivity for the γ-position with the introduction of a β-methyl group and magnitude and direction of the effect of an α-methyl group is also precedented.[13] The only surprising result was the very high selectivity for attack at the α-position on the 3-acyl-5-fluoropyridyl moiety to give, within the limits of our detection, the 4-azafluorenone **2** (X = CF, Y = CH, Z = N, $R^1 = R^2$ = F) exclusively. To our knowledge, there is no work extant on the free radical directing effects of a fluoro substituent on a pyridine or related ring.

In most cases, aldehyde **5** or the corresponding carboxylic acid was commercially available. This was not so with 5-methylnicotinaldehyde (**19**) and 5-fluoronicotinaldehyde (**26**), where several methods were investigated before those shown in Schemes III and IV, respectively, were developed. Oxidation of the inexpensive 3,5-lutidine with sufficient aqueous $KMnO_4$ to convert one methyl group to a carboxyl gave a mixture of starting material, monocarboxylic (**14**) and dicarboxylic (**15**) acids, which could be separated readily on the basis of volatility and solubility properties. Acid **14**, isolated in about 30% yield, was esterified with methanol and dry hydrochloric acid to give **16** in about 75% yield, which was then reduced to the alcohol **17** with LAH. It was important to carry out the reduction at −78 °C and to quench the reaction mixture at this temperature in order to obtain good yields (ca. 80%) of **17**. Literature reports on analogous systems to the contrary not withstanding,[14] at higher temperatures, hydride attack on the pyridine nucleus became important and lowered the yield of **18** drastically. The desired aldehyde was then obtained in about 90% yield from the alcohol via a Swern oxidation.

Although aldehyde **26** is known,[15] in our hands, the literature procedures[15,16] were extremely difficult to scale up to the point that reasonable quantities of **26** could be obtained. Since the 3,5-substitution patterns with differentiated functional groups was available in **15**, we used that to obtain the desired aldehyde as outlined in Scheme IV. Although the preparation of amide **20** might appear simple, it was necessary to react the corresponding acid chloride with anhydrous ammonia in 1,2-dichloroethane at −30 °C in order to obtain a 67% yield. The Hofmann rearrangement of **20** to **21** proceeded in 67% yield. Transformation of amine **21** to the fluoride **22** in 71% yield was effected via a Schiemann reaction. This was followed by oxidation of the methyl to a carboxyl group (**23**, 66%), esterification (**24**, 99%), reduction to a hydroxymethyl (**25**, 70%) as described above for **18**, and finally, Swern oxidation gave **26** in 91% yield.

In summary, we have described a flexible synthesis of variously substituted fluorenones and azafluorenones via a photochemical Pschorr cyclization, and have demonstrated the scope of the reaction by synthesizing 21 of these species.

Experimental Section

General Information. Melting points were obtained by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Analytical HPLC determinations were carried out on a Waters ALC 204 instrument, equipped with a varible-wavelength detector. Most analyses were done at 280 nm on a Waters μ-Porasil 10 μM, 3.9 mm i.d. × 30 cm column. Quantitative analyses were performed on a Hewlett-Packard 3390A reporting integrator. Response factors were obtained with pure samples. Preparative HPLC was carried out on a Waters Prep 500 instrument.

Infrared spectra were recorded on a Perkin-Elmer 1320 grating spectrophotometer on $CHCl_3$ solutions, unless otherwise stated.

Proton magnetic resonance spectra were obtained in $CDCl_3$ solutions (unless otherwise stated) on a Varian EM-390 or GE 360 spectrometer. Proton-decoupled carbon-13 NMR spectra were determined on a Varian FT-80 or GE 360 spectrometer. Chemical shifts are given in parts per million relative to Me_4Si. Fluorine-19 NMR spectra were run on a Varian EM-390 or GE 360 spectrometer and chemical shifts are given relative to $CFCl_3$.

Melting points, the CO stretching frequencies, and proton and fluorine-19 NMR spectra for fluorenones **2** are reported only in Table I.

Mass spectra (HRMS or MS) were determined on a CEC-21-100 high-resolution instrument or a Du Pont 21-491 instrument at 70 eV.

Photolyses were carried out in a 1- or 3-L reactor with a cooled source insert. Either a 450-W or a 550-W Hanovia medium-pressure mercury vapor lamp was used with a Pyrex filter. Occasionally a uranium filter was used as noted.

Unless otherwise noted, all air-sensitive reactions were conducted under an atmosphere of dry nitrogen. All solutions were dried over anhydrous sodium sulfate. All concentrations of solutions were carried out on a rotary evaporator under water aspirator pressures unless otherwise noted. The concentration of *n*-butyllithium was determined by titration with standard *tert*-butyl alcohol in benzene solution with 9,10-phenanthroline as an indicator.

Starting Materials. The following compounds were commercially available: aniline, *p*-toluidine, *p*-anisidine, *p*-chloro- and *p*-fluoroaniline, 2,4-difluoroaniline, 2- and 3-aminopyridine, benzaldehyde, *p*-chlorobenzaldehyde, 3-fluorobenzaldehyde, 3,5-difluorobenzaldehyde, 3- and 4-pyridinecarboxaldehyde, 6-methylnicotinic acid, methyl 6-methylnicotinate and 3,5-lutidine. The following compounds were prepared to literature procedures: 2,4-difluoro-6-bromoaniline,[17] *N*-pivaloyl-4-chloroaniline,[18] *N*-pivaloyl-*p*-anisidine,[18] *N*-pivaloyl-*p*-toluidine,[18] *N*-pivaloylaniline.[18]

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Table I. Yields and Physical and Spectroscopic Data for Fluorenones 2[a]

fluorenone (2)	yield, %	mp, °C	ν_{CO}[c] cm^{-1}	^1H NMR,[d] ppm	^{19}F NMR,[d] ppm
X, Z = CH; Y = N; R^2 = H					
R^1 = H[e]	49	124–125	1720	8.7–7.6 (m, 3 H), 7.2–6.4 (m, 5 H)	
R^1 = Me	29	103–104	1725	9.00 (s, 1 H), 8.80 (d, J = 6 Hz, 1 H), 7.73–7.38	
R^1 = MeO	44	148–149	1725	8.20 (s, 1 H), 8.64 (d, J = 6 Hz, 1 H), 7.54 (d, J = 7 Hz, 1 H), 7.46 (d, J = 6 Hz, 1 H), 7.30 (s, 1 H), 7.08 (m, 1 H), 3.80 (s, 3 H)	
R^1 = Cl	31	157–158	1730	8.9–8.5 (m, 2 H), 7.7–7.3 (m, 4 H)	
R^1 = F	51	169–171	1730	8.77 (s, 1 H), 8.60 (d, J = 5 Hz, 1 H), 7.63–7.02 (m, 4 H)	110.8 (m)
X, Y = CH; Z = N; R^2 = H					
R^1 = H[f]	37				
R^1 = Me[g]	40	151–152	1725	8.63 (dd, J = 5, 2 Hz, 1 H), 7.9–7.1 (m, 5 H), 2.41 (s, 3 H)	
R^1 = Cl[h]	37	144–146	1725	8.7 (dd, J = 6, 2 Hz, 1 H), 7.9–7.4 (m, 4 H), 7.16 (dd, J = 8, 6 Hz, 1 H)	
Y, Z = CH; X = N; R^2 = H					
R^1 = H[f]	26				
R^1 = Me[g]	21	120–122	1725	8.89 (s, 1 H), 8.79 (d, J = 4 Hz, 1 H), 7.6–7.3 (m, 3 H), 2.43 (s, 3 H)	
R^1 = Cl[h]	37	150–152	1725	8.92 (s, 1 H), 8.82 (d, J = 5 Hz, 1 H), 7.8–7.6 (m, 2 H), 7.55 (d, J = 5 Hz, 1 H)	
Y = CH; R^1, R^2 = F					
X, Z = CH	46	135–136	1725	7.8–7.1 (m, 5 H), 6.90 (td, J = 9, 2 Hz, 1 H)	115.9 (t, J = 8.4 Hz, 1 Hz), 107.5 (m, 1 F)
X = CF; Z = CH[i]	38	158–160	1725	7.6 (m, 1 H), 7.5–7.1 (m, 3 H), 6.95 (td, J = 9, 2, 1 H)	116.5 t, J = 7.8 Hz), 112.0 (m, 1 F), 108.3 (m, 1 F)
X = CH; Z = CF[i]	13	185–186	1725	7.8–7.2 (m, 4 H), 6.95 (td, J = 9, 2 Hz, 1 H)	111.5 (dm, J = 62 Hz, 1 H), 106.5 (dt, J = 62, 6 Hz, 1 F), 106.3 (m, 1 F)
X, Z = CF[j]	55	168–171	1730	7.8–7.2 (m, 2 H), 7.1–6.7 (m, 2 H)	107.4 (m, 2 F), 106.7 (m, 2 F)
X = CH; Z = N[k]	37	188–189	1730	8.63 (dd, J = 5, 2 Hz, 1 H), 7.83 (dd, J = 7, 2 Hz, 1 H), 7.23–6.83 (m, 3 H)	111.7 (t, J = 9 Hz, 1 F), 103.9 (q, J = 8 Hz, 1 F)
X = N; Z = CH[k]	26	193–194	1730	8.92 (s, 1 H), 8.81 (d, J = 5 Hz, 1 H), 7.63 (d, J = 5 Hz, 1 H), 7.33 (dd, J = 6, 2 Hz, 1 H), 7.07 (dt, J = 9, 2 Hz, 1 H)	
X = CMe; Z = N[l]	27	174–175	1720	8.56 (d, J = 2 Hz, 1 H), 7.76 (d, J = 2 Hz, 1 H), 7.26 (dd, J = 7, 2 Hz, 1 H), 7.00 (dt, J = 10, 2 Hz, 1 H), 2.40 (s, 1 H)	112.6 (m, 1 F), 105.3 (m, 1 F)
X = N; Z = CMe[l]	38	171–172	1720	8.76 (s, 1 H), 8.61 (s, 1 H), 7.33 (dd, J = 7, 2 Hz, 1 H), 7.03 (dt, J = 9, 2 Hz, 1 H), 2.63 (d, J = 8 Hz, 3 H)	103.8 (m, 1 F), 101.7 (m, 1 F)
X = Cf; Z = N	46	189–190	1730	8.59 (m, 1 H), 7.68 (dd, J = 7, 2 Hz, 1 H), 7.33 (dd, J = 7, 2 Hz, 1 H), 7.08 (dt, J = 9, 2 Hz, 1 H)	127.2 (d, J = 8 Hz, 1 F), 112.6 (t, J = 8 Hz, 1 F), 105.0 (m, 1 F)
Y = CMe; R^1, R^2 = F					
X = CH; Z = N[m]	34	144–145	1720	7.83 (d, J = 8 Hz, 1 H), 7.28 (dd, J = 8, 2 Hz, 1 H), 7.16–6.92 (m, 2 H), 2.66 (s, 3 H)	111.0 (t, J = 8 Hz, 1 F), 104.0 (m, 1 F)
X = N; Z = CH[m]	11	190–191	1720	8.81 (s, 1 H), 7.50 (s, 1 H), 7.30 (dd, J = 7, 2 Hz, 1 H), 7.04 (dt, J = 10, 2 Hz, 1 H), 2.66 (s, 3 H)	113.5 (t, J = 9 Hz, 1 F), 104.0 (m, 1 F)

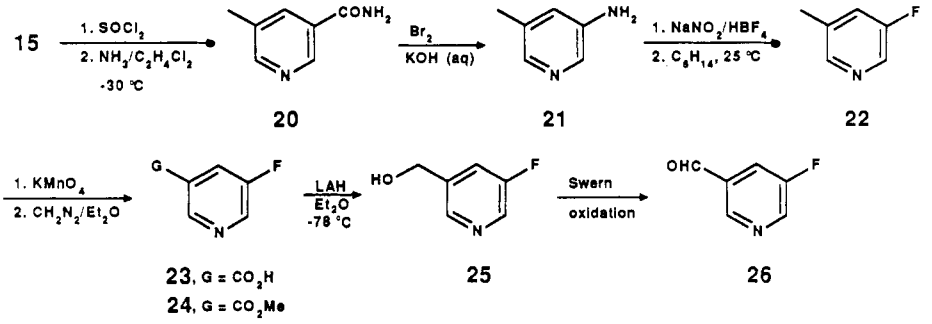
[a] Satisfactory analytical data (±0.40% for C and H) are reported in the Experimental Section for all new compounds listed in this table. See Scheme I for the general formula. [b] All the yields reported are for isolated, purified materials. [c] IR specra were determined on ca. 5% (w/v) CH_2Cl_2 solutions. [d] NMR spectra were determined on ca. 5% (w/v) $CDCl_3$ solutions. [e] Known compound; see ref 4 and 6. [f] Compounds **2** (R^1 = R^2 = H, Y = CH and X = CH, Z = N or X = N, Z = CH) were prepared by Abramovitch and Tertzakian (ref 3b), and their yields are reported. [g] Isomers **2** (R^1 = Me, R^2 = H, Y = CH and X = CH, Z = N or X = N, Z = CH) produced in the same cyclization for a total yield of 61%. [h] Isomers **2** (R^1 = Cl, R^2 = H, Y = CH and X = CH, Z = N or X = N, Z = CH) were produced in the same cyclization for a total yield of 74%. [i] Isomers **2** (R^1 = R^2 = F, Y = CH and X = CF, Z = CH or X = CH, Z = CF) produced in the same reaction for a total yield of 51%. [j] Known compound; see ref 1 b. [k] Isomers **2** (R^1 = R^2 = F, Y = CH and X = CH, Z = N or X = N, Z = CH) produced in the same reaction for a total yield of 63%. [l] Isomers **2** (R^1 = R^2 = H, Y = CH and X = CMe, Z = N or X = N, Z = CMe) produced in the same reaction for a total yield of 65%. [m] Isomers **2** (R^1 = R^2 = H, Y = CMe and X = CH, Z = N or X = N, Z = CH) produced in the same reaction, total yield 45%.

***N*-Pivaloyl-2,4-difluoro-6-bromoaniline (3b: R^1 = R^2 = F).** 2,4-Difluoro-6-bromoaniline (100 g, 0.48 mol) was dissolved in chloroform (1.5 L), and pivaloyl chloride (53.5 mL, 0.433 mol) was added dropwise to the mechanically stirred solution. The mixture was stirred at room temperature for 15 min, boiled under reflux for 3 h, cooled to room temperature, and stirred overnight. A solution of sodium hydroxide (22 g, 0.55 mol) in water (550 mL) was added and stirred for 3 h. The pH of the aqueous layer was alkaline. The layers were separated, and the organic phase was washed with water (4 × 400 mL) followed by brine and dried. Upon removal of the solvent, a purple solid (143 g) was obtained. Recrystallization from ethyl acetate/hexane yielded the title compound as a colorless solid (125 g, 99%) in several crops, mp 139.5–141 °C; ^1H NMR δ 7.3–6.7 (m, 3 H), 1.34 (s, 9 H); ^{19}F NMR δ 111.11 (m, 1 F), 111.15 (m, 1 F); IR 3470, 1690 cm^{-1}; HRMS, m/e 291.0076 (calcd 291.0070).

***N*-Pivaloyl-4-fluoroaniline.** This was prepared as described above for **3b** (R^1 = R^2 = F) in 92% yield, mp 121–123 °C; ^1H NMR δ 7.6–7.4 (m, 3 H), 7.1–6.9 (m, 2 H), 1.30 (s, 9 H); IR (CH_2Cl_2) 3450 (m), 1678 (s) cm^{-1}; HRMS, m/e 195.106 26 (calcd 195.105 94).

(2-Pivalamido-3,5-difluorophenyl)phenylcarbinol (6a). The bromoanilide **3b** (R^1 = R^2 = F) (20 g, 0.0685 mol) was dissolved in dry THF (175 mL) and cooled to −100 °C (pentane/liquid nitrogen). A 3.40 M solution of *n*-butyllithium (44.3 mL, 0.151 mol) was added dropwise over 1 h. The solution was stirred at −100 °C for 45 min, and freshly distilled benzaldehyde (20.9

Scheme IV



mL, 0.206 mol) was added dropwise. The solution was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was poured into a mixture of water (500 mL) and ether (500 mL) and stirred. The layers were separated, and the organic layer was washed with water (3 × 300 mL) followed by brine. The aqueous layers were extracted separately with ether (2 × 150 mL). A few drops of dilute hydrochloric acid were added to facilitate separation of the layers. The combined organic solution was dried and concentrated to give a red liquid, which was subjected to high vacuum at 50–55 °C for 2 h. A mixture of ethyl acetate (20 mL) and hexane (65 mL) was added to the residue and cooled to 0 °C for 4 h whereupon white crystals were obtained. The crystalline solid was filtered and washed with a small portion of ice-cold hexanes. Solvents were removed from the filtrate, and 35 mL of hexanes was added and cooled to 0 °C to obtain a second crop of crystals. The combined yield of **6a** was 12.5 g (58%). The solid was suitable for oxidation and was used as such without further purification. A small amount of the solid was recrystallized from ethyl acetate/hexanes: mp 141–142 °C; ^{1}H NMR δ 7.5–6.8 (m, 8 H), 5.75 (d, J = 4 Hz, 1 H), 4.13 (d, J = 4 Hz, 1 H), 1.18 (s, 9 H); ^{19}F NMR δ 111.0 (m, 1 F), 116.3 (m, 1 F); IR 3400 (br m), 1675 (s) cm^{-1}; HRMS, m/e 319.1391 (calcd 319.1384).

2-Pivalamido-5-fluorophenyl-4′-pyridylcarbinol (6b). A 3.2 M hexane solution of n-butyllithium (100 mL, 320 mmol) was added slowly to a solution of N-pivaloyl-4-fluoroaniline (24.2 g, 124 mmol) in THF (500 mL) at 0 °C and then stirred at this temperature for 2 h. A solution of 4-pyridincarboxaldehyde (33.0 g, 308 mmol) in THF (30 mL) was slowly added at 0 °C and the resulting solution was allowed to warm to room temperature. After 4 h, water (150 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (2 × 120 mL). The combined organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ethyl acetate (70 mL), which upon standing overnight at 5 °C, gave **6b** as a white crystalline solid (17.2 g). The mother liquor was chromatographed on alumina (70 g) with 10% ethyl acetate in hexanes and then ethyl acetate to give an additional 2.3 g of the alcohol for a total yield of 19.5 g (52%): mp 179–180 °C; ^{1}H NMR δ 8.9–8.8 (m, 2 H), 8.49 (s, 1 H), 8.0–7.8 (m, 2 H), 7.3–6.6 (m, 4 H), 5.67 (s, 1 H), 1.00 (s, 9 H); ^{19}F NMR δ 117.8 (m); IR (CH_2Cl_2) 3340 (m), 1670 (s) cm^{-1}; HRMS, m/e 302.142 55 (calcd 302.143 05).

6-Fluoro-2-*tert*-butyl-4-benzo[*c*]oxazolyl-5′-methyl-3′-pyridylcarbinol (10). A solution of bromoanilide **3b** ($R^1 = R^2$ = F) (21.3 g, 0.073 mol) in dry THF (150 mL) was cooled to −100 °C and a 2.4 M solution of n-butyllithium (61 mL, 0.146 mol) was added dropwise over a period of 30 min. The resulting yellow-colored suspension was stirred at this temperature for 15 min and warmed to −78 °C and then to 0 °C. After it was stirred for a few seconds, the color of the suspension changed to brown. Immediately the temperature was lowered to −78 °C and a solution of 5-methylnicotinaldehyde (8.0 g, 0.066 mol) in THF (25 mL) was added dropwise. After stirring at −78 °C for 30 min, the suspension was allowed to warm to room temperature slowly and stirred overnight. Ether (150 mL) and water (100 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 75 mL), and the combined organic solution was washed with brine, dried, and concentrated to give a dark brown liquid. Purification by preparative HPLC (ethyl acetate/hexanes 70/30) gave carbinol **6** (X = CH, Y = CH, Z = N, $R^1 = R^2$ = F) in only 10% yield along with a major, chromatographically more mobile component. The major product was further purified by passing it through a short column of alumina (ethyl acetate/hexanes, 3/1) followed by recrystallization from ethyl acetate/hexanes to yield **10** as a pale yellow crystalline solid (5.7 g, 25%): mp 143–144 °C; ^{1}H NMR (DMSO-d_6) δ 8.49 (d, J = 1 Hz, 1 H), 8.30 (d, J = 1 Hz, 1 H), 7.75 (s, 1 H), 7.62 (dd, J = 9, 5 Hz, 1 H), 7.22 (dd, J = 11, 9 Hz, 1 H), 6.38 (d, J = 4 Hz, 1 H), 6.27 (d, J = 4 Hz, 1 H), 2.29 (s, 3 H), 1.35 (s, 9 H); ^{19}F NMR (DMSO-d_6) δ 122.5 (m); ^{13}C NMR δ 174.1 (s), 157.0 (d, J = 244 Hz), 148.4 (s), 144.5 (s), 138.0 (d, J = 9 Hz), 134.5 (s), 132.7 (s), 119.2 (d, J = 11 Hz), 115.2 (d, J = 20 Hz), 111.9 (d, J = 26 Hz), 65.1 (s), 34.1 (s), 28.2 (s), 18.2 (s); IR 3610 (m), 3150 (br), 1640 (w), 1620 (m) cm^{-1}; HRMS, m/e 314.14208 (calcd 314.14306).

2-Pivalamido-3,5-difluorobenzophenone (7a). A solution of 2-pivalamido-3,5-difluorophenyl-3′-fluorophenylcarbinol (10 g, 0.0315 mol) in dry methylene chloride was added to a suspension of pyridinium chlorochromate (10.2 g, 0.0473 mol) in dry methylene chloride (200 mL) and stirred overnight. The mixture was diluted with ether (400 mL) and filtered successively through two short columns of Florisil and alumina, each time eluting the last portion of reaction mixture from the column with 50 mL of a 1:2 mixture of methylene chloride and ether. Removal of solvents yielded a white solid with a slight greenish tint, 9.5 g (100%). The solid was suitable for hydrolysis and was used as such in the next step without further purification. A small amount of the solid was purified further by filtration through a short column of alumina and eluted with 30% ethyl acetate in hexanes. Concentration yielded **7a** as a white solid, which was recrystallized from ethyl acetate/hexanes: mp 143–145 °C; ^{1}H NMR δ 8.2 (br s, 1 H), 8.0–6.8 (m, 7 H), 1.16 (s, 9 H); ^{19}F NMR δ 112.9 (m, 1 F), 113.3 (m, 1 F); IR 3350 (br m) 1680 (m), 1650 (m) cm^{-1}; HRMS, m/e 317.1220 (calcd 317.1227).

2-Pivalamido-5-fluorophenyl 4-Pyridyl Ketone (7b). A solution of alcohol **6b** (12.0 g, 39.7 mmol) in pyridine (80 mL) was added to a stirred suspension of chromium trioxide (9.0 g, 90 mmol) in pyridine (80 mL) and the resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was poured into water (1 L) and extracted with ether (5 × 200 mL). The ether extracts were washed with brine, dried, and concentrated. The residue was chromatographed on silica with hexane/ethyl acetate (1/1). The resulting solid was recrystallized from ethyl acetate to give **7b** as a light yellow solid (11.0 g, 92%): mp 118–119 °C; ^{1}H NMR δ 9.0–8.7 (m, 3 H), 7.5–7.1 (m, 4 H), 1.40 (s, 9 H); ^{19}F NMR δ 118.9 (m); IR 3310 (br m), 1682 (s), 1645 (m) cm^{-1}; HRMS, m/e 300.12712 (calcd 300.12740).

2-Pivalamido-3,3′,5,5′-tetrafluorobenzophenone (7c). The bromoanilide **3b** ($R^1 = R^2$ = F) (25 g, 0.0856 mol) was dissolved in dry THF (220 mL) and cooled to −130 °C (pentane/liquid nitrogen). A 2.46 M solution of n-butyllithium in hexane (76.4 mL, 0.188 mol) was added dropwise over 75 min. The solution was stirred at −130 °C for 45 min, 3,5-difluorobenzaldehyde (16 g, 0.113 mol) was added dropwise, and the stirring was continued for 30 min at −130 °C. The pentane/liquid nitrogen bath was replaced by dry ice/acetone bath and stirred at −78 °C for 1 h. It then was further stirred at 0 °C for 2 h and finally at room temperature overnight. The reaction mixture was poured into a mixture of water (400 mL) and ether (300 mL) and stirred for 10 min. The layers were separated, and the aqueous phase was further extracted with ether (2 × 100 mL). The organic phase was washed with water (4 × 300 mL) followed by brine and dried. Upon removal of solvents, a dark red oil was obtained, which was

subjected to high vacuum at 50–60 °C for 2 h and used directly in the following reaction without further purification. The dark red oil, dissolved in dry methylene chloride (500 mL), was added to a suspension of pyridinium chlorochromate (27.7 g, 0.128 mol) in dry methylene chloride (500 mL), and the suspension was stirred overnight at room temperature. The reaction mixture was diluted with ether (1 L) and filtered through Celite. The solid chromium residue was rinsed with ether, and the rinsings were added to the filtrate, which was then passed through a short column of Florisil (50 g). The solution was concentrated to give a dark red oil and chromatographed on alumina with 30% ethyl acetate in hexanes to give a red oil, which was triturated with a few milliliters of pentane and cooled to 0 °C. The precipitated solid was filtered and washed with ice-cold pentane to give a pale yellow solid (6 g). Additional solid (3 g) was obtained as a second crop from the mother liquor kept at 0 °C for several days. The combined yield was 30%. The crude solid was suitable for hydrolysis and used as such without further purification. A small amount of the crude product was filtered through a short column of alumina with 30% ethyl acetate in hexanes and recrystallized from ethyl acetate/hexanes to give **7c** as a light yellow solid: mp 146–149 °C; ^{1}H NMR δ 7.95 (br s, 1 H), 7.6–6.8 (m, 5 H), 1.18 (s, 9 H); ^{19}F NMR δ 108.9 (t, J = 7.6 Hz, 1 F), 112.8 (m, 2 F), 116.3 (t, J = 7.6 Hz, 1 F); IR 3440 (m), 1680 (s) cm^{-1}; HRMS, m/e 353.1049 (calcd 353.1039).

2-Amino-3,3′,5,5′-tetrafluorobenzophenone (8c). The amide **7c** (17.5 g, 0.0496 mol) was suspended in 70% sulfuric acid (100 mL) and stirred overnight at 95–100 °C. The brown solution was cooled to room temperature, diluted with water (1 L), and cooled to 0 °C. Ice-cold concentrated sodium hydroxide was added dropwise until the pH was alkaline. Methylene chloride (300 mL) was added and stirred until all the precipitated solid dissolved. The layers were separated, and the aqueous layer was extracted with additional methylene chloride (3 × 150 mL). The combined organic solution was washed with water to neutrality (4 × 300 mL) followed by brine and dried. It was then concentrated, transferred to a short column of alumina (60 g), and eluted with methylene chloride to give **8c** as a yellow solid (13 g, 100%), which was suitable for the following reaction without further purification. A small amount was recrystallized from methanol: mp 82–84 °C; ^{1}H NMR δ 7.7–6.8 (m, 5 H), 5.97 (br s, 2 H); ^{19}F NMR δ 132.0 (d, J = 8.4 Hz, 1 F), 126.9 (t, J = 8.4 Hz, 1 F), 108.5 (t, J = 7.6 Hz, 2 F); IR 3500 (m), 3375 (m), 1640 (m) cm^{-1}; HRMS, m/e 269.0459 (calcd 269.0464).

2-Amino-5-fluorophenyl 4-Pyridyl Ketone (8b). This was prepared as above for **8c**, except that 6 M hydrochloric acid was used, in 87% yield as a yellow crystalline solid: mp 173–174 °C; ^{1}H NMR δ 8.9 (br d, J = 5 Hz, 2 H), 7.50 (m, 2 H), 7.3–7.0 (m, 2 H), 6.73 (dd, J = 10, 5 Hz, 1 H), 6.2 (br s, 2 H); ^{1}H NMR δ 128.6 (m); IR 3490 (m), 3360 (m), 1640 (s) cm^{-1}; HRMS, m/e 216.0709 (calcd 216.0699).

2-Amino-5-chlorophenyl 3-Pyridyl Ketone (8d). A stirred suspension of 2-pivalamido-5-chlorophenyl 3-pyridyl ketone (2.30 g, 7.26 mmol) in 70% sulfuric acid (20 mL) was heated to 95–100 °C overnight. The resulting solution was cooled to 0 °C and added dropwise to stirred, ice-cold, concentrated sodium hydroxide solution. A bright yellow solid precipitated. As soon as a small amount of a red solid began to persist for a few seconds, the acid solution was added to another fresh batch of ice-cold, concentrated sodium hydroxide. After the addition was complete, the contents of both the flasks were combined, diluted with water 10 times the volume of the aqueous suspension, and extracted with methylene chloride (3 × 75 mL). The organic phase was washed with water (4 × 100 mL). The aqueous washings were then extracted with one portion of methylene chloride (50 mL). The combined organic extracts were washed with brine and dried. The solution was concentrated, passed through a short column of alumina (15 g), and eluted with methylene chloride to yield **8d** as a bright yellow solid (1.2 g, 71%), which was recrystallized from methanol: mp 110.5–112 °C; ^{1}H NMR δ 9.0–8.8 (m, 2 H), 8.0 (dt, J = 8.0, 2 Hz, 1 H), 7.6–7.2 (m, 3 H), 6.75 (d, J = 9 Hz, 1 H), 6.13 (br s, 2 H); IR 3500 (m), 3350 (m), 1630 (s) cm^{-1}; HRMS, m/e 232.040 79 (calcd for ^{35}Cl isotope 232.040 43).

2,4,5,7-Tetrafluorofluorenone (2c). Finely powdered amine **8c** (2.60 g, 9.67 mmol) was dissolved in 50% sulfuric acid (240 mL) and diluted with water (120 mL). The solution was warmed 50 °C, stirred at that temperature for 30 min, and then cooled to 0 °C. A solution of sodium nitrite (0.700 g, 10.2 mmol) in water (4 mL) was added dropwise, and the stirring was continued at 0 °C for 45 min. It was diluted with deaerated ice-cold water (2.2 L) and the excess nitrous acid decomposed by the addition of solid urea. The resulting solution was transferred under nitrogen to a photochemical reactor charged with tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (200 mg, 0.27 mmol) and photolyzed, with vigorous stirring, at −5 to 0 °C through a uranium filter for 20 min. The heterogeneous mixture was then transferred to a separate flask and diluted with methylene chloride (200 mL). The layers were separated, and the aqueous phase was further extracted with methylene chloride (3 × 75 mL). The combined organic extracts were washed with 10% sodium hydroxide (3 × 150 mL), water (4 × 200 mL), and brine (100 mL). The organic solution was dried and concentrated. Alumina (12 g) was added to the concentrated solution, the mixture shaken for a few minutes, and the solvent removed completely in vacuo. The residue was transferred to an alumina column (60 g) and chromatographed with 30% methylene chloride in hexane until all of the yellow band was collected. Ketone **2c** was obtained as a crystalline, bright yellow solid (1.33 g, 55%), which was recrystallized from ethyl acetate/hexanes (3/17). An analytical sample was obtained by sublimation of the recrystallized solid, at 70 °C (0.25 mm): ^{13}C NMR δ 188.6 (s), 163.7 (dm, J = 255 Hz), 156.5 (dm, J = 275 Hz), 137.3 (m), 122.8 (s), 110.9 (m), 109.0 (d, J = 23.9 Hz); MS, m/e 252 (M$^+$). Anal. Calcd for $C_{13}H_4F_4O$: C, 61.92; H, 1.60. Found: 62.03; H, 1.39.

2,4-Difluorofluorenone. This was prepared as for **2c** in 46% yield to give a bright yellow solid: ^{13}C NMR δ 191.2 (s), 163.5 (dd, J = 254, 10 Hz), 157.5 (dd, J = 257, 11 Hz), 141.1 (s), 137.7 (m), 135.4 (s), 133.7 (s), 128.9 (s), 126.1 (m), 124.8 (s), 123.7 (d, J = 4 Hz), 109.9 (t, J = 26 Hz), 108.3 (dd, J = 24, 3 Hz); MS, m/e 216 (M$^+$). Anal. Calcd for $C_{13}H_6F_2O$: C, 72.23; H, 2.80. Found: C, 72.05; H, 2.67.

2,5,7-Trifluorofluorenone and 4,5,7-Trifluorofluorenone. These were prepared as a mixture as described for **2c**. They were separated by preparative HPLC with 1% ethyl acetate in hexanes as eluent. The major component, which eluted first, was the 2,5,7-derivative (38%). An analytical sample was prepared by recrystallization from ethyl acetate/hexanes: ^{13}C NMR δ 189.9 (s), 163.4 (dd, J = 264, 9 Hz), 163.2 (d, J = 251 Hz), 157.2 (dd, J = 256, 11 Hz), 137.8 (s), 136.9 (s), 135.9 (d, J = 6), 125.7 (m), 124.9 (m), 121.6 (d, J = 23 Hz), 112.5 (d, J = 24 Hz), 110.2 (t, J = 26 Hz), 108.7 (d, J = 24 Hz); MS, m/e 234 (M$^+$). Anal. Calcd for $C_{13}H_5F_3O$: C, 66.68; H, 2.15. Found: C, 66.68; H, 1.99.

The minor component was the 4,5,7 derivative (13%). An analytical sample was prepared by recrystallization from ethyl acetate/hexanes: ^{13}C NMR δ 189.9 (s), 164.0 (dd, J = 255, 9 Hz), 156.7 (dd, J = 261, 11 Hz), 156.5 (d, J = 258 Hz), 137.3 (m), 136.2 (s), 131.2 (d, J = 8 Hz), 126.4 (d, J = 16 Hz), 123.9 (d, J = 22 Hz), 123.0 (d, J = 17 Hz), 120.8 (s), 110.6 (t, J = 26 Hz), 108.7 (d, J = 24 Hz); MS, m/e 234 (M$^+$). Anal. Calcd for $C_{13}H_5F_3O$: C, 66.68; H, 2.15. Found: C, 66.48; H, 2.05.

7-Fluoro-3-azafluorenone (2b). A solution of sodium nitrate (3.5 g, 51 mmol) in degassed water (50 mL) was added slowly to a solution of amine **8b** (9.5 g, 44.0 mmol) in a mixture of concentrated sulfuric acid (50 mL) and water (2 L) while the temperature was maintained between 0 and 5 °C. Urea (ca. 1 g) was added and the solution was transfered to a 3-L photoreactor and irradiated at 30 °C for 2 h. Concentrated ammonium hydroxide was added and the resulting mixture was extracted with methylene chloride (4 × 500 mL). The organic extract was dried and concentrated, and the residue was chromatographed on alumina with acetate/methylene chloride/hexanes (1/1/3) to give a yellow solid. This was recrystallized from ethanol to give **2b** as a yellow powder (4.5 g, 51%): ^{13}C NMR δ 191.8, 163.9 (d, J = 252 Hz), 151.5, 141.9, 140.3, 138.9, 136.9, 135.5 (d, J = 7 Hz), 122.7 (d, J = 8 Hz), 121.9 (d, J = 23 Hz), 117.4, 112.9 (d, J = 24 Hz). Anal. Calcd for $C_{12}H_6FNO$: C, 72.36; H, 3.04. Found: C, 72.16; H, 3.09.

3-Azafluorenone. This was prepared as for **2b** to give a yellow crystalline solid (49%): mp 124–125 °C (lit.[6] mp 132–133 °C); ^{13}C NMR δ 192.7, 151.6, 143.0, 142.0, 140.0, 137.3, 135.3, 133.3, 129.7, 125.1, 121.1, 117.0.

7-Methoxy-3-azafluorenone. This was prepared as for **2b** to give an orange crystalline solid (44%): ^{13}C NMR δ 193.1, 161.4,

150.7, 141.3, 140.4, 137.9, 135.6, 135.1, 122.3, 121.3, 117.2, 110.1, 55.8. Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29. Found: C, 73.40; H, 4.38.

7-Methyl-3-azafluorenone (2e). A solution of sodium nitrite (500 mg, 7.22 mmol) in water (20 mL) was added to a solution of 2-amino-5-methylphenyl 4-pyridyl ketone (1.30 g, 6.13 mmol) in water (350 mL) and sulfuric acid (10 mL) at 0–5 °C. After 15 min, urea (1.0 g) was added, followed by tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (70 mg, 0.093 mmol) and copper(II) acetate monohydrate (250 mg, 1.25 mmol). The solution was then photolyzed for 1.5 h through pyrex optics at 25 °C. Concentrated ammonium hydroxide (80 mL) was added and the resulting solution was extracted with methylene chloride (100 × 5 mL). The organic extracts were dried and concentrated. The residue was chromatographed on alumina (50 g) with methylene chloride/ethyl acetate/hexanes (1/1/3) to give a yellow solid (530 mg), which contained the desired fluorenone along with 3-methylphenyl 4-pyridyl ketone in a ratio of 5:1 (by integration of the methyl resonances in the ^1H NMR spectrum). A portion of the yellow solid (200 mg) in ethanol (5 mL) was treated with picric acid (164 mg) in ethanol (5 mL) to give a yellow precipitate immediately. This was recrystallized from ethanol (100 mL) to give an orange-yellow solid (305 mg), which was treated with 2 M sodium hydroxide (50 mL) and methylene chloride (50 mL). The organic layer was dried and concentrated to give pure **2e** (130 mg, 29%) as a yellow solid: mp 103–104 °C; ^{13}C NMR δ 193.3, 151.3, 141.8, 140.5, 140.3, 140.2, 137.7, 136.0, 133.6, 125.9, 121.1, 117.2, 21.4. Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 79.90; H, 4.72.

7-Chloro-3-azafluorenone. This was prepared as for **2b** to give a yellow crystalline solid (31%): ^{13}C NMR δ 191.8, 151.9, 142.2, 141.3, 139.9, 136.8, 136.1, 135.1, 134.8, 125.6, 122.3, 117.4. Anal. Calcd for $C_{12}H_6ClNO$: C, 66.84; H, 2.80. Found: C, 67.01; H, 2.78.

7-Chloro-2-azafluorenone and 7-Chloro-4-azafluorenone. These were prepared as for **2b** to give a mixture of isomers, which was separated by chromatography on alumina with methylene chloride/ethyl acetate/hexanes (1/1/3). The first band was the 4-aza derivative, obtained as a light yellow solid (37%), which was then sublimed under vacuum: ^{13}C NMR δ 190.3, 164.3, 154.3, 141.6, 137.2, 136.2, 134.9, 131.6, 128.2, 124.5, 123.4, 122.1. Anal. Calcd for $C_{12}H_6ClNO$: C, 66.84; H, 2.80. Found: C, 66.79; H, 2.90.

The second band was eluted with a 4% methanolic solution of the above eluent system to obtain a brownish yellow solid, which was sublimed under vacuum to give the 2-aza derivative as a light yellow solid (37%): ^{13}C NMR δ 191.2, 156.1, 150.8, 145.3, 139.9, 137.7, 135.2, 134.6, 127.9, 125.0, 122.9, 115.3. Anal. Calcd for $C_{12}H_6ClNO$: C, 66.84; H, 2.80. Found: C, 66.38; H, 2.46.

6-Chloro-3-azafluorenone. This was prepared as for **2b** to give a yellow crystalline solid (25%): mp 218–219 °C; ^1H NMR δ 8.90 (s, 1 H), 8.76 (d, J = 4 Hz, 1 H), 7.67 (d, J = 8 Hz, 1 H), 7.64 (d, J = 2 Hz, 1 H), 7.54 (d, J = 4 Hz, 1 H), 7.36 (dd, J = 8, 2 Hz, 1 H); ^{13}C NMR δ 191.5, 152.4, 144.9, 142.3, 142.1, 140.5, 136.4, 131.7, 129.9, 126.3, 121.9, 117.4; IR 1720 (s), 1600 (s); MS, m/e 215 (M^+ for ^{35}Cl). Anal. Calcd for $C_{12}H_6ClNO$: C, 66.84; H, 2.80. Found: C, 66.65; H, 2.69.

7-Methyl-2-azafluorenone and 7-Methyl-4-azafluorenone. These were prepared as for **2e** to give a mixture of isomers, which was separated by chromatography on alumina with methylene chloride/ethyl acetate/hexanes (1/1/3). The first band was the 4-aza derivative, obtained as a yellow solid (43%): ^{13}C NMR δ 192.0, 165.4, 153.9, 141.6, 141.1, 135.9, 135.2, 131.2, 128.5, 124.9, 122.8, 120.8, 21.6; MS, m/e 195 (M^+). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 80.01; H, 4.64.

The second band was the 2-aza derivative, a light yellow solid (21%): ^{13}C NMR δ 193.0, 155.8, 152.0, 145.1, 142.2, 139.3, 135.5, 134.3, 128.5, 125.4, 121.7, 115.1, 21.6; MS, m/e 195 (M^+). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 79.47; H, 4.64.

5,7-Difluoro-2-azafluorenone and 5,7-Difluoro-4-azafluorenone. These were prepared as for **2c** except that the photochemical reaction mixture was maintained below 5 °C. The mixture of isomers that was obtained was separated by HPLC with 20% ethyl acetate in hexanes. The first band was the 4-aza species, obtained as a yellow solid (37%): ^{13}C NMR δ 189.1, 164.9 (dd, J = 257, 10 Hz), 163.0, 157.5 (dd, J = 263, 11 Hz), 154.9, 138.3 (m), 131.9 (d, J = 16 Hz), 128.2, 125.1 (m), 122.9 (d, J = 9 Hz), 111.0 (m), 108.5 (m); MS, m/e 217 (M^+). Anal. Calcd for $C_{12}H_5F_2NO$: C, 66.37; H, 2.32. Found: C, 66.21; H, 2.05.

The second band was the 2-aza species, a light yellow solid (26%): ^{13}C NMR δ 190.0, 165.2 (dd, J = 258, 10 Hz), 158.6 (dd, J = 260, 12 Hz), 156.5, 148.3, 145.5, 137.3, 127.9, 124.0 (d, J = 13 Hz), 118.3 (m), 110.2 (m), 108.9 (d, J = 24 Hz); MS, m/e 217 (M^+). Anal. Calcd for $C_{12}H_5F_2NO$: C, 66.37; H, 2.32. Found: C, 66.44; H, 2.23.

4-Methyl-5,7-difluoro-2-azafluorenone and 2-Methyl-5,7-difluoro-4-azafluorenone. These were prepared as for the fluorenones immediately above, except that the photosensitizer system was as for **2e** [Ru(II)/Cu(II)]. The mixture of isomers obtained was separated by chromatography on alumina with 25% ethyl acetate in hexanes. The first band was the 4-aza derivative, obtained as a yellow solid (27%): ^{13}C NMR δ 189.4, 164.6 (dd, J = 256, 10 Hz), 160.6, 157.2 (dd, J = 262, 11 Hz), 155.1, 138.5 (m), 133.1, 132.4, 128.1, 125.3 (m), 110.9 (t, J = 26 Hz), 108.4 (d, J = 23 Hz), 18.6; MS, m/e 231 (M^+). Anal. Calcd for $C_{13}H_7F_2NO$: C, 67.54; H, 3.05. Found: C, 67.65; H, 3.23.

The second band was the 2-aza derivative, which was eluted with 50% ethyl acetate in hexanes and was a light yellow solid (38%): ^{13}C NMR δ 190.5, 165.0 (dd, J = 257, 10 Hz), 159.1, 157.1 (dd, J = 259, 11 Hz), 147.2, 143.4, 138.1 (m), 128.6, 127.8 124.0 (m), 110.6 (t, J = 27 Hz), 108.9 (d, J = 24 Hz), 18.6 (d, J = 15 Hz); MS, m/e 231 (M^+). Anal. Calcd for $C_{13}H_7F_2NO$: C, 67.54; H, 3.05. Found: C, 67.50; H, 2.91.

3-Methyl-5,7-difluoro-2-azafluorenone and 3-Methyl-5,7-difluoro-4-azafluorenone. These were prepared as for those immediately above to give a mixture of isomers, which was separated by chromatography on alumina with 25% ethyl acetate in hexanes. The first band was the 4-aza species, obtained as a yellow solid (34%): ^{13}C NMR δ 189.0, 165.7, 164.8 (dd, J = 256, 10 Hz), 163.3, 157.3 (dd, J = 263, 11 Hz), 138.9 (m), 132.0, 125.8 (m), 122.3, 110.7 (t, J = 25 Hz), 108.4 (d, J = 24 Hz), 25.4; MS, m/e 231 (M^+). Anal. Calcd for $C_{13}H_7F_2NO$: C, 67.54; H, 3.05. Found: C, 67.27; H, 2.81.

The second band was the 2-aza species, which was eluted with 50% ethyl acetate in hexanes and was a light yellow solid (11%): ^{13}C NMR δ 189.7, 166.9, 165.1 (dd, J = 255, 9 Hz), 158.5 (dd, J = 259, 12 Hz), 148.7, 145.0, 138.1 (m), 125.8, 124.0 (d, J = 13 Hz), 118.1 (d J = 3 Hz), 110.1 (t, J = 26 Hz), 108.4 (m), 25.6; MS, m/e 231 (M^+). Anal. Calcd for $C_{13}H_7F_2NO$: C, 67.54; H, 3.05. Found: C, 67.39; H, 3.22.

2,5,7-Trifluoro-4-azafluorenone. This was prepared as for **2b**. The photolysis solution was concentrated, chromatographed on alumina with ethyl acetate/dichloromethane/hexanes (1/1/3, v/v/v), followed by sublimation at 100 °C (0.5 mm), to give the title fluorenone as a yellow solid (46%): ^{13}C NMR δ 187.8 (s), 164.6 (dd, J = 257, 10 Hz), 159.4 (d, J = 260 Hz), 158.6 (s), 157.2 (dd, J = 263, 11 Hz), 142.7 (d, J = 26 Hz), 138.7 (d, J = 4 Hz), 129.6 (s), 124.7 (m), 119.4 (d, J = 20 Hz), 111.4 (d, J = 25 Hz), 108.8 (m); MS, m/e 235 (M^+). Anal. Calcd for $C_{12}H_4F_3NO$: C, 61.29; H, 1.71. Found: C, 61.12; H, 1.59.

Attempted Preparation of 3-Methyl-5,7-difluoro-4-azafluorenone by Diazotization and Photolysis of 2-Amino-5-methyl-3-pyridyl 3,5-Difluorophenyl Ketone (11). The amine **11** (1.0 g, 4.0 mmol) was suspended in water (25 mL) and concentrated sulfuric acid (10 mL) was added with cooling. The resulting solution was treated with sodium nitrite (0.34 g, 4.9 mmol) in water (2 mL) while the temperature was maintained between 0 and 5 °C. Pyridone **12** quickly precipitated as a yellow solid (0.80 g, 80%): mp 240–241 °C; ^1H NMR (DMSO-d_6) δ 7.69 (d, J = 3 Hz, 1 H), 7.5–7.3 (m, 4 H), 2.1 (s, 3 H); ^{19}F NMR (DMSO-d_6) δ 109.2 (m); IR (KBr) 3424 (w), 1666 (s), 1621 (s), 1594 (s); HRMS, m/e 249.060 46 (calcd 249.060 14).

5-Methylnicotinic Acid (15). 3,5-Lutidine (100 g, 0.930 mol) was added to a mechanically stirred solution of potassium permanganate (295 g, 1.87 mol) in water (4.5 L). The temperature of the stirred mixture rose to 43 °C over 5 h. It was heated at 45 °C overnight, the precipitated manganese dioxide was filtered and washed with hot water, and the filtrate and washings were concentrated to a volume of ca. 500 mL. This was acidified with 2 M hydrochloric acid and the precipitated dicarboxylic acid (**16**) was filtered. The precipitate was washed with water, and the combined filtrate and washings were evaporated to dryness. The

residue was boiled with ethanol (3 × 200 mL) and filtered. Concentration of the filtrate yielded **15** as a colorless solid (34.7 g, 27%) in two crops: mp 214–216 °C (lit.[19] mp 215–216 °C); ^{1}H NMR (DMSO-d_6) δ 8.96 (d, J = 2 Hz, 1 H), 8.69 (d, J = 2 Hz, 1 H), 8.15 (br s, 1 H), 2.41 (s, 3 H); IR (KBr) 3244–2082 (br), 1723 (s); MS, m/e 137 (M^+).

Methyl 5-Methylnicotinate (17). Acid **15** (10.0 g, 73.0 mmol) was added to methanol (100 mL), which was saturated with dry hydrogen chloride. The mixture was heated under reflux overnight, cooled, and poured into crushed ice (200 g). It was made slightly alkaline by adding solid sodium carbonate and then extracted with ether (5 × 100 mL). The ether solution was washed with water, dried, and concentrated to yield ester **17** as a colorless crystalline solid (8.0 g, 73%). The solid was suitable for reduction and was used as such in the next step without further purification. A small portion of the sample was recrystallized from hexanes: mp 41–43 °C (lit.[20] mp 45–46 °C); ^{1}H NMR δ 9.07 (d, J = 2 Hz, 1 H), 8.66 (d, J = 2 Hz, 1 H), 8.13 (br s, 1 H), 3.96 (s, 3 H), 2.40 (s, 3 H); IR 1725 (s), cm^{-1}; MS, m/e 151 (M^+).

5-Methyl-3-pyridylmethanol (18). A solution of ester **17** (33.8 g, 0.224 mol) in anhydrous ether (400 mL) was added dropwise with stirring to a suspension of LAH (17.0 g, 0.45 mol) in ether (400 mL) maintained at −78 °C. As soon as the addition started, the color of the suspension turned green. Halfway through the addition, a green ball-like semisolid formed and the suspension turned yellow. After the addition was complete, the suspension was stirred at −78 °C for 30 min and then ethyl acetate (60 mL) was added dropwise at this temperature. The mixture was allowed to warm to about 5 °C and then water (60 mL) was added dropwise. The white solid was filtered and washed with ether, and the filtrate and washings were dried and concentrated to give a yellow oil. This was distilled under reduced pressure to give **18** as a colorless liquid (21.7 g, 80%): bp 130 °C (1.5 mm) (lit.[21] bp 125 °C (1.3 mm)); ^{1}H NMR δ 8.33 (d, J = 2 Hz, 1 H), 8.21 (d, J = 2 Hz, 1 H), 7.56 (br s, 1 H), 6.38 (br s, 1 H), 4.66 (s, 2 H), 2.26 (s, 3 H); IR 3606 (m), 3187 (br); MS, m/e 123 (M^+).

5-Methylnicotinaldehyde (19). Oxalyl chloride (12.4 mL, 0.14 mol) in methylene chloride (300 mL) was placed in a three-necked flask fitted with two addition funnels and a stirrer. Dimethyl sulfoxide (21.0 mL, 0.3 mol) in methylene chloride (60 mL) was placed in one addition funnel, and the other one contained the alcohol **17** (15.2 g, 0.123 mol) in methylene chloride (120 mL). The contents of the flask were cooled to −60 °C and dimethyl sulfoxide was added over a period of 20 min. Stirring was continued for 20 min, followed by addition of the alcohol solution during 20 min. After the mixture was stirred at −60 °C for 20 min, triethylamine (84 mL, 0.60 mol) was added over a period of 10 min. The cooling bath was removed and the suspension was allowed to warm to room temperature. Water (360 mL) was added, the yellow organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 75 mL). The combined organic solution was dried and concentrated to give an orange-yellow liquid. Distillation at reduced pressure gave the title aldehyde as a colorless liquid (13.5 g, 91%): bp 130 °C (20 mm) (lit.[21] bp 68 °C (0.5 mm)): ^{1}H NMR δ 10.20 (s, 1 H), 8.92 (d, J = 2 Hz, 1 H), 8.73 (d, J = 2 Hz, 1 H), 8.00 (br s, 1 H), 2.46 (s, 3 H); IR 1700 (s) cm^{-1}; MS, m/e 121 (M^+).

6-Methyl-3-pyridylmethanol. This was prepared as above for **18** from methyl 6-methylnicotinate in 75% yield as a colorless liquid which then solidified to give a white crystalline solid: mp 42–44 °C (lit.[22] mp 46 °C); ^{1}H NMR δ 8.33 (d, J = 2 Hz, 1 H), 7.63 (dd, J = 8, 2 Hz, 1 H), 7.13 (d, J = 8 Hz, 1 H), 5.88 (br s, 1 H), 4.66 (s, 2 H), 2.46 (s, 3 H); IR 3630 (m), 3200 (br) cm^{-1}; MS, m/e 123 (M^+).

6-Methylnicotinaldehyde. This was prepared as above for 5-methylnicotinaldehyde in 83% yield as a colorless liquid: bp 95 °C (20 mm) (lit.[23] bp 78 °C); ^{1}H NMR δ 10.16 (s, 1 H), 8.97 (d, J = 2 Hz, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 2.66 (s, 3 H); IR 1705 (s) cm^{-1}; MS, m/e 121 (M^+).

5-Methylnicotinamide (20). A solution of acid **15** (60 g, 0.44 mol) in thionyl chloride (500 mL) was heated under reflux overnight. Excess thionyl chloride was removed by distillation under reduced pressure, and the crude acid chloride was suspended in anhydrous 1,2-dichloroethane (300 mL) and cooled to −30 °C. Ammonia gas was passed through the cold suspension for 30 min and the resulting solution was allowed to warm to room temperature. The mixture was concentrated, and the residue was boiled with ethyl acetate (5 × 150 mL) and filtered. Concentration of the filtrates yielded the amide as a dark yellow solid in several crops. This was further purified by three recrystallizations from ethyl acetate to give **20** as a colorless solid (40 g, 67%): mp 163–165 °C; ^{1}H NMR (DMSO-d_6) δ 8.95 (d, J = 2 Hz, 1 H), 8.59 (d, J = 2 Hz, 1 H), 8.10 (br s, 2 H), 7.57 (br s, 1 H), 2.36 (s, 3 H); IR (KBr) 3337 (br) 3161 (m), 1658 (s) cm^{-1}; HRMS, m/e 136.063 37 (calcd 136.063 66).

5-Methyl-3-aminopyridine (21). Finely powdered amide **20** (8.6 g, 0.063 mol) was added portionwise with stirring to a hypobromite solution prepared from bromine (10.0 g, 0.063 mol) and a solution of potassium hydroxide (53.6 g) in water (930 mL). After the mixture was stirred at room temperature for 1 h, it was heated at 70 °C for 15 min and then cooled. The solution was acidified with glacial acetic acid and filtered from the dark-red precipitate. The filtrate was made strongly alkaline with sodium hydroxide and extracted with chloroform (5 × 100 mL). The organic solution was washed with water (75 mL), brine (75 mL), dried, and concentrated to give a brown residue. This was distilled to give **21**, bp 155 °C (21 mm), which crystallized immediately as a colorless solid (4.6 g, 67%): mp 56–58 °C (lit.[16b] mp 57–59 °C); ^{1}H NMR δ 7.87 (d, J = 3 Hz, 1 H), 7.80 (d, J = 2 Hz, 1 H), 6.73 (m, 1 H), 3.97 (br s, 2 H), 2.17 (s, 3 H); IR 3455 (m), 3380 (m), 1615 (s) cm^{-1}; MS, m/e 108 (M^+).

5-Methyl-3-fluoropyridine (22). A solution of amine **21** (11.0 g, 0.102 mol) in a mixture of 48–50% fluoboric acid (50 mL) and ethanol (75 mL) was cooled to −10 °C and isoamyl nitrite (34 mL, 0.252 mol) was added dropwise with stirring. The diazonium fluoborate began to precipitate after a few milliliters of isoamyl nitrite had been added. After the addition was complete, the suspension was stirred at −10 °C for 20 min and then poured into a mixture of absolute ethanol (75 mL) and ether (100 mL), which was cooled to −78 °C. The resulting mixture was filtered, and the precipitate was washed with cold absolute ethanol (2 × 50 mL), cold dry ether (2 × 50 mL), and cold dry hexanes (2 × 50 mL). The white solid, dampened with hexanes, was transferred to a 1-L round-bottomed flask fitted with a condenser, containing hexanes (100 mL) at 0 °C. The mixture was allowed to warm to room temperature to initiate slow decomposition. When it appeared to be complete, the mixture was heated under reflux for 30 min and cooled and the hexane solution was decanted. This solution was extracted with 2 M hydrochloric acid (2 × 50 mL), and the extracts were added to the original flask. The mixture was warmed to remove all hexanes. The resulting mixture was made slightly alkaline (NaOH) and steam distilled. The distillate was saturated with sodium sulfate, and the organic layer was separated and dried over sodium hydroxide pellets. Distillation yielded **22** as a colorless liquid (8.0 g, 71%): bp 136 °C (760 mm) (lit.[16b] bp 139 °C (760 mm)); ^{1}H NMR δ 8.30 (m, 2 H), 7.25 (m, 1 H), 2.35 (s, 3 H); ^{19}F NMR δ 129.0 (dd, J = 8, 2 Hz); IR 3051 (m), 2987 (s), 1606 (s) cm^{-1}; MS, m/e 111 (M^+).

5-Fluoronicotinic Acid (23). A mixture of fluoropyridine **22** (11.4 g, 0.103 mol) and water (800 mL) was heated under reflux. Potassium permanganate (34.8 g, 0.221 mol) was added to the refluxing solution, 10.7 g at first, and the remaining in small portions over a period of about 3 h, as the solution decolorized. The unreacted 3-methyl-5-fluoropyridine (1.5 g) was removed by distillation, the residue in the flask was filtered while hot, and the precipitate was washed with hot water (200 mL). The combined filtrate and washings were concentrated to a volume of ca. 200 mL and acidified with 2 M hydrochloric acid until precipitation was complete. The solid was filtered, the filtrate evaporated to about 50 mL, and more hydrochloric acid was added to pre-

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cipitate more solid. The solid was recrystallized from water to give **23** as a white crystalline solid (8.3 g, 66%): mp 192–194 °C (lit.[16b] mp 195–197 °C; ^{1}H NMR (DMSO-d_6) δ 9.03 (t, J = 2 Hz, 1 H), 8.83 (d, J = 3 Hz, 1 H), 8.12 (m, 1 H); ^{19}F NMR (DMSO-d_6) δ 126.8 (dd, J = 8, 2 Hz); IR (KBr) 3067 (s), 2462 (br), 1713 (s) cm^{-1}; MS, m/e 141 (M$^+$).

Methyl 5-Fluoronicotinate (24). A suspension of acid **23** (8.3 g, 0.059 mol) in ether (75 mL) was cooled to 0 °C and an ethereal solution of diazomethane (ca. 0.13 mol) was added dropwise with stirring. The acid gradually dissolved and the solution was allowed to warm to room temperature and stirred overnight. The unreacted starting material (0.2 g) was removed by filtration and the filtrate was concentrated to give a light yellow solid. Recrystallization from hexanes gave the ester **24** as a colorless crystalline solid (8.8 g, 99%): mp 47–48 °C (lit.[24] mp 50.0–50.5 °C); ^{1}H NMR δ 9.13 (m, 1 H), 8.71 (d, J = 3 Hz, 1 H), 8.06 (m, 1 H), 4.02 (s, 3 H); ^{19}F NMR δ 127.1 (dd, J = 8, 2 Hz); IR 1731 (s), 1294 (s) cm^{-1}; MS, m/e 155 (M$^+$).

5-Fluoro-3-pyridylmethanol (25). This was prepared as above for **18** in 70% yield as a colorless liquid: bp 123 °C (0.4 mm) (lit.[25] bp 83–85 °C (0.01–0.05 mm); ^{1}H NMR δ 8.33 (m, 2 H), 7.53 (td, J = 9, 2 Hz, 1 H), 5.02 (s, 1 H), 4.78 (s, 2 H); ^{19}F NMR δ 127.1 (dd, J = 8, 2 Hz); IR 3608 (m), 3271 (br), 1608 (s), 1435 (s) cm^{-1}; MS, m/e 127 (M$^+$).

5-Fluoronicotinaldehyde (26). This was prepared as above for **19** in 91% yield, as a colorless liquid: bp 90 °C (22 mm) (lit.[15] bp 71–76 °C (10 mm)); ^{1}H NMR δ 10.23 (d, J = 2 Hz, 1 H), 8.98 (s, 1 H), 8.79 (d, J = 2 Hz, 1 H), 7.92 (td, J = 9, 2 Hz, 1 H); ^{19}F NMR δ 125.6 (d, J = 7 Hz); IR 3001 (m), 2846 (m), 1704 (s), 1580 (s) cm^{-1}; MS, m/e 125 (M$^+$).

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Supplementary Material Available: The preparations and spectral properties of most of the derivatives **6–8** (39 compounds, 9 pages). Ordering information is given on any current masthead page.

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Reaction of Tosylamide Monosodium Salt with Bis(halomethyl) Compounds: An Easy Entry to Symmetrical *N*-Tosyl Aza Macrocycles

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A one-step, general procedure for a variety of *N*-tosyl aza macrocycles (including aza-crown ethers, pyridino- and bipyridino-aza-crown analogues, and azacyclophanes), by reaction of appropriate bis(halomethyl) precursors with tosylamide monosodium salt (TsNHNa) in *N,N*-dimethylformamide, is described. In polymethyl-substituted 2,11-diaza[3.3]cyclophane systems, the methyl substituents play an important role in inducing stereospecific ring closures. Thus, coupling of 1,4-bis(chloromethyl)-2,5-dimethylbenzene (**15b**) with TsNHNa produced only one of the two possible diastereomeric dimers, to which chiral structure **16db** was assigned by means of the chiral Eu(dcm)$_3$ shift reagent. This stereochemical assignment was confirmed by a single-crystal X-ray study on **16d**. Detosylation of *N*-tosyl aza macrocycles to the free polyamino macrocycles by reductive (Na–NH$_3$) or hydrolytic (90% H_2SO_4) methods, followed by N-methylation (CH_2O–HCO_2H), was also accomplished in excellent yield. The ^{1}H NMR spectra of 2,11-diaza[3.3]cyclophanes and 2,11-diaza[3.3](2,6)pyridinophanes are discussed in terms of conformation and conformational mobility.

Introduction

Synthetic aza macrocycles are well-known for their binding properties toward either inorganic[1] or organic[2] cations, anions,[3] and neutral molecules.[4] Selective binding of certain cations by multifunctional aza macrocycles has resulted in their use as models for carrier molecules in the study of active ion transport phenomena in liquid membrane systems.[5] Furthermore, macrocyclic (poly)amines have been further functionalized to improve ligand–cation binding or change ligand–cation selectivity,[6] provide secondary binding sites,[7] impart biological activity to the macrocycle,[8] and prepare polymer-bound reagents.[9]

Conventional strategies for the preparation of these compounds rely upon the availability of suitable acyclic mono- or polyamino precursors.[10] Lehn[8,11] developed a generally useful procedure for the preparation of diaza macrocycles, which is based on the high-dilution reaction of a diamine with a diacid dichloride to form a macrocyclic

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