Synthesis of Heterocyclic Compounds *via* Nucleophilic Aroylation Catalyzed by Imidazolidenyl Carbene

Yumiko SUZUKI,* Tomonori TOYOTA, Akira MIYASHITA, and Masayuki SATO

School of Pharmaceutical Sciences, University of Shizuoka; 52–1 Yada, Suruga-ku, Shizuoka 422–8526, Japan.
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Xanthones and acridones were synthesized from 3,4-difluoronitrobenzene and 2-fluorobenzaldehydes in two or three steps. The key step was nucleophilic aroylation catalyzed by imidazolidenyl carbene. The nucleophilic aroylation of 3,4-difluoronitrobenzene afforded 2,2′-difluoro-4-nitrobenzophenones. The cyclization of the difluorobenzophenones with *O*-nucleophile and *N*-nucleophile yielded 3-nitroxanthones and 3-nitroacridones, respectively. Indazole, quinolino[2,3-*b*]quinoxaline, and thianaphtho[2,3-*b*]quinoxaline derivatives were also synthesized *via* nucleophilic aroylation of 2,3-dichloroquinoxaline followed by cyclization with nucleophiles.

Key words nucleophilic aroylation; *N*-heterocyclic carbene; organocatalysis; xanthone; acridone

N-Heterocyclic carbenes (NHCs) are nucleophilic and excellent σ-donors. They readily form complexes with transition metals. Since 1990s, the use of NHCs as ligands has lead to significant advancements in the area of Pd-catalyzed carbon–carbon bond-forming reactions,[1] Ru-catalyzed olefin metathesis,[2] and Rh-catalyzed hydrosilylations.[3—5] NHCs have also attracted significant attention as organocatalysts. Several reactions have been catalyzed by NHCs, for *e.g.*, benzoin condensation,[6—11] Stetter reaction,[12—14] transesterification/acylation reaction,[15,16] and cyanosilylation.[17—19]

We have previously reported NHC-catalyzed nucleophilic substitution on aromatic heterocyclic rings.[20—22] It was considered impossible to introduce aroyl groups directly into the electron-deficient positions of aromatic rings in the conventional electrophilic acylation reaction—Friedel–Crafts reaction. In this NHC-catalyzed reaction, the aroyl groups (derived from aromatic aldehydes) are directly introduced into heteroarenes by nucleophilic aromatic substitution under the catalysis of 1,3-dimethylimidazolidenyl carbene **2** that is obtained from 1,3-dimethylimidazolium iodide (**1**) (Chart 1). In other words, aromatic ketones can be synthesized from aldehydes and heterocyclic compounds by NHC catalysis in a single step.

We have recently broadened the scope of reaction substrates to include benzene rings by using fluoride ion as a leaving group.[23] Aroylation was presented as a new method to synthesize benzophenone derivatives from fluorobenzenes and benzaldehydes. The reaction mechanism is shown in Chart 2.

In order to develop a new synthetic route to heterocyclic compounds, we examined NHC-catalyzed aroylation as a tool for the syntheses of heterocycles. In this study, we report the syntheses of xanthones **6**, acridones **7**, and other heterocyclic compounds *via* NHC-catalyzed aroylation (Chart 3).

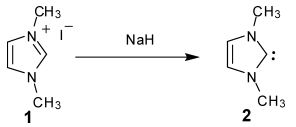


Chart 1

Results and Discussion

Among the xanthone and acridone families, there are quite a few compounds that are reported to exhibit bioactivities such as antitumor, antibacteria, and antivirus.[24—29] From both chemical and pharmaceutical viewpoints, it would be significant to provide a new synthetic route to these heterocyclic compounds.

There are two major routes to synthesize xanthones.[30] The first one is based on the cyclization of 2-hydroxybenzophenones,[31—33] and the second involves the cyclodehydration of *o*-phenoxybenzoic acids.[34—36] Our method is based on the cyclization of 2,2′-difluorobenzophenones **5** prepared by NHC-catalyzed aroylation of 3,4-difluoronitrobenzene (**3**)

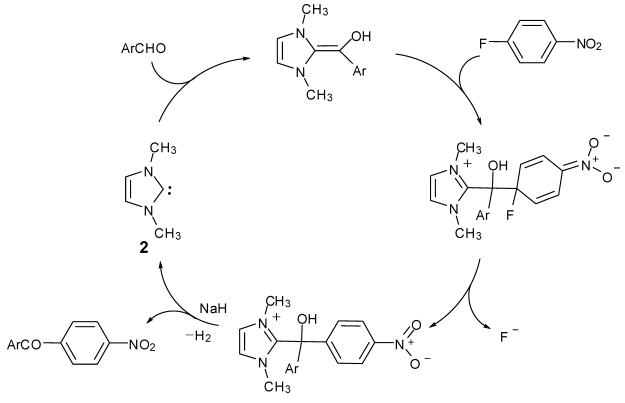


Chart 2. Reaction Mechanism of Aroylation of 4-Fluoronitrobenzene

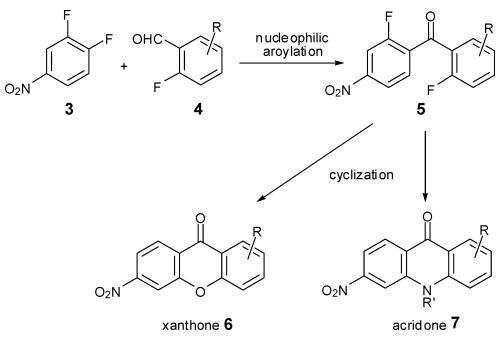
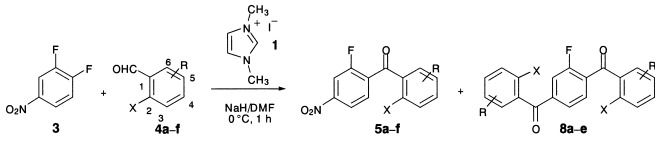


Chart 3

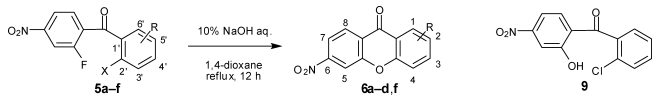
* To whom correspondence should be addressed. e-mail: suzuyumi@u-shizuoka-ken.ac.jp

Table 1. Nucleophilic Aroylation of 3,4-Difluoronitrobenzene (**3**) with Benzaldehydes **4a**—**f**



Entry	Aldehyde	R	X	Benzophenone	Yield (%)	Diketone	Yield (%)
1	**4a**	H	F	**5a**	70	**8a**	1
2	**4b**	4-F	F	**5b**	63	**8b**	8
3	**4c**	5-F	F	**5c**	63	**8c**	8
4	**4d**	6-F	F	**5d**	35	**8d**	2
5	**4e**	H	Cl	**5e**	64	**8e**	7
6	**4f**	6-Cl	F	**5f**	27	**8f**	—

Table 2. Synthesis of Xanthones



Entry	Benzophenone			Xanthone		
	R	X		R		Yield (%)
1	H	F	**5a**	H	**6a**	65
2	4′-F	F	**5b**	3-F	**6b**	30
3	5′-F	F	**5c**	2-F	**6c**	33
4	6′-F	F	**5d**	1-F	**6d**	35
5	H	Cl	**5e**	H	**6a**	12[a]
6	6′-F	Cl	**5f**	1-Cl	**6f**	62

a) Along with **6a**, compound **9** was obtained in 30% yield.

and fluorobenzaldehydes **4** (Chart 2). Two *o*-fluoro substituents of benzophenones **5** are replaced by an oxygen nucleophile in a reaction with aqueous alkali to afford a xanthone structure.

The first step in the synthesis of xanthone is the preparation of 2,2′-difluorobenzophenones **5**. The aroylation of 3,4-difluoronitrobenzene (**3**) was carried out according to the method we reported previously.[23] The NHC—imidazolidenyl carbene **2**—was generated *in situ* from the precursor 1,3-dimethylimidazolium iodide (**1**) and used as a catalyst. The reaction of **3** with benzaldehydes **4a**—**f**, which have 2-fluoro or 2-chloro substituents, produced the corresponding benzophenones **5a**—**f** in 27—70% yields, along with the recovery of the starting materials and diketones **8a**—**e** (Table 1). In the reaction with 2,6-disubstituted benzaldehydes (**4d**, **f**), the steric hindrance caused by two *ortho*-substituents seems to lower the yields (entries 4, 6). Nitro group behaves as a leaving group in nucleophilic aromatic substitutions. The nitro groups of major products **5a**—**e** were substituted with benzoyl groups by nucleophilic aroylation to yield **8a**—**e**.

Cyclization to xanthones was conducted by the treatment of benzophenones **5a**—**f** with 10% aqueous solution of sodium hydroxide in refluxing 1,4-dioxane (Table 2). Two fluorine atoms—*ortho* to carbonyl group of **5a**—**d**—were continuously replaced by one oxygen atom to form xanthones **6a**—**d** (entries 1—4). Benzophenone **5e** has 2′-chloro and 2-fluoro substituents instead of two *o*-fluoro groups. The chlorine atom was replaced and **5e** was cyclized to **6a**; however, the yield was poor and a non-cyclized compound 2′-chloro-2-hydroxy-4-nitrobenzophenone (**9**) was obtained in 30% yield (entry 5). It is well known that fluoro substituents are more susceptible to nucleophilic aromatic substitution than chloro substituents. The ring closure of 2′-chloro-2,6′-difluoro-4-nitrobenzophenone (**5f**) took place at 2-position and 6′-position, and the chloro group at 2′-position remained intact. Fluoro groups at 2- and 6′-positions were replaced by an oxgen nucleophile to yield 1-chloro-6-nitroxanthone (**6f**). The product **6d**, which can be produced by the replacement of 2′-chloro group, was not obtained.

The synthesis of acridones was also examined. There are several routes to synthesize acridones[37]—intramolecular nucleophilic substitution of 2′-*O*-substituted 2-aminobenzophenones,[38] acid catalyzed cyclization of *N*-phenylanthranilic acid,[39] and pyrolysis or photolysis of 3-arylanthranils.[40] Analogous to xanthone synthesis, our acridone synthesis is based on the cyclization of 2,2′-difluorobenzophenones by the substitution of two *o*-florines with one *N*-nucleophile.

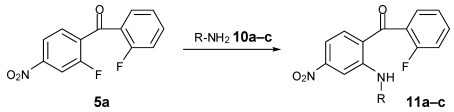
The reaction between difluorobenzophenones **5a** and primary amines **10a**, **b** was carried out in refluxing 1,4-dioxane to obtain 2-amino-4-nitro-2′-fluorobenzophenones **11a**,**b** in good yields (Table 3, entries 1, 2). Acridone **7a** was obtained in 2% yield in the reaction of **10a**. The reaction between benzophenone **5a** and amine **10c** in anisole at 150 °C afforded a 2-amino compound **11c** in 75% yield (Table 3, entry 3). The isolated **10a**—**c** were heated in *N*,*N*-dimethylformamide (DMF) at 150 °C to obtain acridones **7a**—**c** in 55—96% yields (Table 4).

In order to synthesize acridone from benzophenone **5a** in a single step, the reaction of **5a** with **10c** was carried out in DMF at 150 °C for 24 h (Chart 4). The reaction afforded 9-benzyl-4-nitroacridone (**7c**) in 39% yield, but 9-methyl-4-nitroacridone (**7a**) was also produced in 35% yield. It appeared that dimethylamine derived from the DMF reacted with the starting material **5a** to yield **7a**. To avoid this undesired reaction, dimethylsulfoxide (DMSO) was used as a solvent instead of DMF to produce only **7c** in 72% yield.

When methylhydrazine was used as a nucleophile in the cyclization reaction, an indazole derivative **12** was synthesized from **5a** (Chart 5). The indazole structure was formed through the imine formation between **5a** and hydrazine, followed by the intramolecular nucleophilic substitution of *o*-fluorine by methyl-substituted nitrogen.

The syntheses of tetracyclic fused quinoxalines were examined by using the same method as that for xanthone and acridone syntheses (Chart 6). The starting material used was

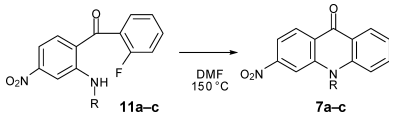
Table 3. Amination of 2,2′-Difluoro-4-nitrobenzophenone (**5a**)



Entry	R	Amine	Solvent	Temp.	Time (h)	Product	Yield (%)
1	Methyl	**10a**	1,4-Dioxane	Reflux	6	**11a**	95[a)]
2	Isopropyl	**10b**	1,4-Dioxane	Reflux	3	**11b**	91
3	Benzyl	**10c**	Anisole	150 °C	3	**11c**	75

a) Along with **11a**, 10-methyl-3-nitroacridone (**7a**) was obtained in 2% yield.

Table 4. Synthesis of Acridones



Entry	R		Time (h)	Product	Yield (%)
1	Methyl	**11a**	12	**7a**	96
2	Isopropyl	**11b**	24	**7b**	55
3	Benzyl	**11c**	24	**7c**	63

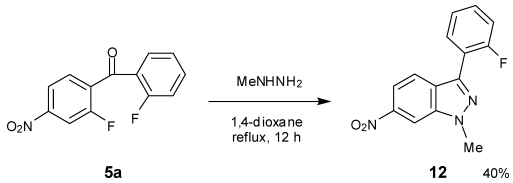


Chart 5. Synthesis of 3-(2-Fluorophenyl)-1-methyl-6-nitroindazole (**12**)

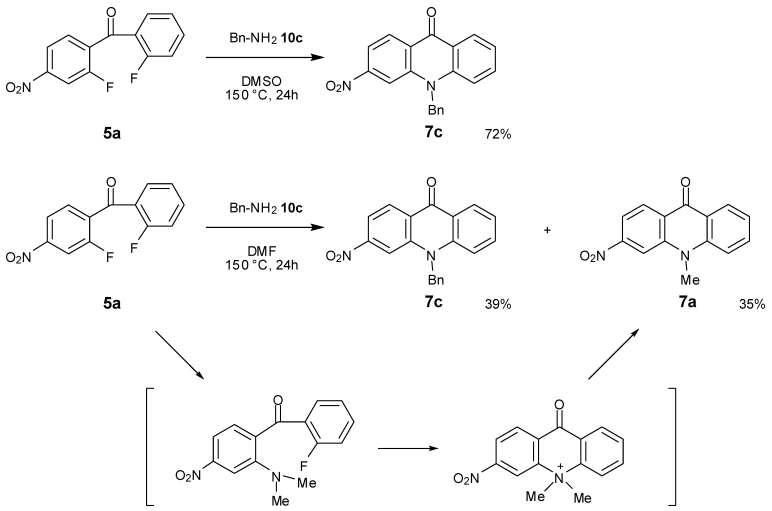


Chart 4

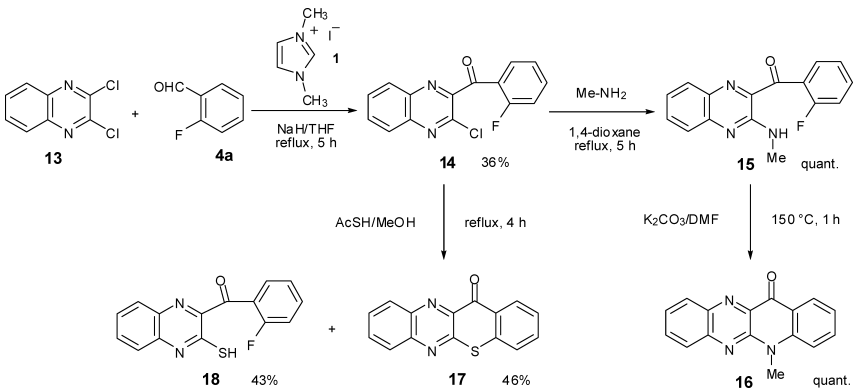


Chart 6. Synthesis of Tetracyclic Compounds *via* Aroylation

2,3-dichloroquinoxaline (**13**). The aroylation of **13** with **4a** (1.2 eq) afforded mono-benzoylated 2-chloro-3-(2-fluorobenzoyl)quinoxaline (**14**). The 2-chloro substituent of quinoxaline **14** was replaced by the reaction with 40% aqueous solution of methylamine (**10a**) to yield a 2-methylamino derivative **15**. Further, **15** was quantitively cyclized to quinolino[2,3-*b*]quinoxaline **16** by treatment with potassium carbonate. The reaction of **14** with thioacetic acid was carried out in refluxing methanol for 4 h. Thianaphtho[2,3-*b*]quinoxaline **17** was produced in 46% yield, along with a non-cyclized compound **18**.

Conclusion

We have developed a new route to synthesize xanthones and acridones. The key step is the *N*-heterocyclic carbene-catalyzed nucleophilic aroylation. The fluorine atom at 4-position of 3,4-difluoronitrobenzene (**3**) was replaced by 2-fluorobenzoyl groups to yield 2,2′-difluorobenzophenones **5**. Two *o*-fluorine atoms of benzophenone **5** were substituted by *O*- and *N*-nucleophiles and cyclized to xanthones and acridones, respectively. The cyclization of **5a** with methylhydrazine afforded 3-phenylindazole **12**. Quinolino[2,3-*b*]quinoxaline and thianaphtho[2,3-*b*]quinoxaline derivatives were synthesized from 2,3-dichloroquinoxaline. To the best of our knowledge, fluorinated xanthones, quinolino[2,3-*b*]quinoxaline, and thianaphtho[2,3-*b*]quinoxaline were synthesized for the first time using the proposed method. We believe that this method could be useful for the synthesis of heterocyclic compounds.

Experimental

General Melting points are determined using the Yazawa micromelting point apparatus without correction. The ^{1}H-NMR (270 MHz) and ^{13}C-NMR (67.8 MHz) spectra were recorded using the JEOL JNM-GSX270 NMR spectrometer. The IR spectra were recorded using the Jasco IR-700 infrared spectrophotometer and the Jasco A-102 infrared spectrophotometer. The GC-MS (EI) spectra were recorded using the JEOL JMS AX505W mass spectrometer. The MS (FAB) spectra were recorded using the JEOL JMS-SX102 mass spectrometer and *m*-nitrobenzyl alcohol as the matrix. Column chromatography was performed using Merck silica gel 60 and silica gel 60 N (spherical, neutral; Kanto Chemical Co., Inc.).

General Procedure Synthesis of Benzophenone Under an argon atmosphere, 60% sodium hydride in oil (160 mg, 4 mmol) was added to a mixture of 3,4-difluoronitrobenzene (**3**) (477 mg, 3 mmol), and benzaldehyde **4a—f** (3.6 mmol), 1,3-dimethylimidazolium iodide (**1**) (224 mg, 1 mmol) in DMF (20 ml). The mixture was stirred at 0 °C for 1 h and poured into ice-water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain benzophenone **5a**—**f** and diketone **8a**—**e**.

2,2′-Difluoro-4-nitrobenzophenone (**5a**): Colorless prisms (recrystallized from dichloromethane/*n*-hexane). mp 93 °C. IR (KBr) cm^{-1}: 1654 (CO), 1526, 1297 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.14 (1H, ddd, J=10.7, 8.3, 0.9 Hz), 7.33 (1H, td, J=7.6, 0.9 Hz), 7.59—7.67 (1H, m), 7.87—7.79 (2H, m), 8.00 (1H, dd, J=9.6, 2.3 Hz), 8.15 (1H, dd, J=8.4, 2.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 112.2 (d, J_{FC}=27.0 Hz), 116.5 (d, J_{FC}=21.8 Hz), 119.5 (d, J_{FC}=4.2 Hz), 124.8 (d, J_{FC}=3.1 Hz), 125.9 (d, J_{FC}=11.4 Hz), 131.0, 131.4 (d, J_{FC}=3.1 Hz), 133.5 (d, J_{FC}=13.5 Hz), 135.7 (d, J_{FC}=9.3 Hz), 150.5 (d, J_{FC}=8.3 Hz), 160.1 (d, J_{FC}=259.5 Hz), 161.6 (d, J_{FC}=256.4 Hz), 187.8. GC-MS (EI) *m/z*: 263 (M^+). *Anal.* Calcd for $C_{13}H_7F_2NO_3$: C, 59.32; H, 2.68; N, 5.32. Found: C, 59.31; H, 2.46; N, 5.30.

4-Nitro-2,2′,4′-trifluorobenzophenone (**5b**): Slightly yellow prisms (recrystallized from *n*-hexane/dichloromethane). mp 84—85 °C. IR (KBr) cm^{-1}: 1652 (CO), 1530, 1290 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 6.90 (1H, ddd, J=10.9, 8.6, 2.3 Hz), 7.06 (1H, dddd, J=8.6, 7.6, 2.3, 1.0 Hz), 7.83 (1H, dd, J=8.6, 6.9 Hz), 7.89 (1H, td, J=8.6, 6.3 Hz), 8.01 (1H, dd, J=9.6, 2.0 Hz), 8.16 (ddd, J=8.6, 2.0, 0.7 Hz). GC-MS (EI) *m/z*: 281 (M^+). *Anal.* Calcd for $C_{13}H_6F_3NO_3$: C, 55.53; H, 2.15; N, 4.98. Found: C, 55.39; H, 2.26; N, 4.91.

4-Nitro-2,2′,5′-trifluorobenzophenone (**5c**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 76—77 °C. IR (KBr) cm^{-1}: 1664 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.13 (1H, td, J=9.2, 4.6 Hz), 7.28—7.36 (1H, m), 7.48—7.54 (1H, m), 7.86 (1H, dd, J=8.6, 6.9 Hz), 8.02 (1H, dd, J=9.6, 2.0 Hz), 8.16 (dd, J=8.6, 2.0 Hz). GC-MS (EI) *m/z* 281 (M^+). *Anal.* Calcd for $C_{13}H_6F_3NO_3$: C, 55.53; H, 2.15; N, 4.98. Found: C, 55.49; H, 2.11; N, 4.62.

4-Nitro-2,2′,6′-trifluorobenzophenone (**5d**): Colorless needles (recrystallized from *n*-hexane/dichloromethane). mp 101—102 °C. IR (KBr) cm^{-1}: 1681 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.02 (2H, td, J=8.2, 1.7 Hz), 7.52 (1H, tt, J=8.2, 6.3 Hz), 7.98—8.05 (2H, m), 8.15 (dd, J=8.6, 2.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 112.2 (dd, J_{FC}=21.8, 3.2 Hz), 112.7 (d, J_{FC}=28.1 Hz), 117.3 (t, J_{FC}=17.5 Hz), 119.5 (d, J_{FC}=4.1 Hz), 131.5 (d, J_{FC}=11.4 Hz), 132.1 (d, J_{FC}=2.1 Hz), 133.8 (t, J_{FC}=10.9 Hz), 151.2 (d, J_{FC}=8.3 Hz), 160.3 (dd, J_{FC}=255.4, 6.2 Hz), 161.0 (d, J_{FC}=295.9 Hz), 183.8. GC-MS (EI) *m/z*: 281 (M^+). *Anal.* Calcd for $C_{13}H_6F_3NO_3$: C, 55.53; H, 2.15; N, 4.98. Found: C, 55.67; H, 1.87; N, 4.69.

2′-Chloro-2-fluoro-4-nitrobenzophenone (**5e**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 86—87 °C. IR (KBr) cm^{-1}: 1666 (CO), 1528, 1291 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.58 (4H, m), 7.91 (1H, dd, J=8.2, 6.9 Hz), 7.99 (1H, dd, J=9.9, 2.0 Hz), 8.14 (ddd, J=8.6, 2.3, 1.0 Hz). GC-MS (EI) *m/z*: 279 (M^+). *Anal.* Calcd for $C_{13}H_7ClFNO_3$: C, 55.83; H, 2.52; N, 5.01. Found: C, 55.77; H, 2.41; N, 4.68.

2′-Chloro-2,6′-difluoro-4-nitrobenzophenone (**5f**): Slightly yellow needles (recrystallized from *n*-hexane/dichloromethane). mp 90—91 °C. IR (KBr) cm^{-1}: 1675 (CO), 1534, 1347 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.12 (2H, td, J=8.2, 1.0 Hz), 7.29 (1H, d, J=8.2 Hz), 7.44 (1H, td, J=8.2, 5.9 Hz), 8.00 (dd, J=10.2, 2.0 Hz), 8.07 (dd, J=8.6, 6.9 Hz), 8.15 (dd, J=8.6, 2.0 Hz). GC-MS (EI) *m/z*: 297 (M^+). *Anal.* Calcd for $C_{13}H_6ClF_2NO_3$: C, 52.46; H, 2.03; N, 4.71. Found: C, 52.73; H, 2.08; N, 4.61.

1,4-Bis(2-fluorobenzoyl)-2-fluorobenzene (**8a**): Yellow prisms (recrystallized from acetone/*n*-hexane). mp 132.5—134 °C. IR (KBr) cm^{-1}: 1651 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.10—7.23 (2H, m), 7.26—7.34 (2H, m), 7.55—7.70 (5H, m), 7.74—7.81 (2H, m). GC-MS (EI) *m/z*: 340 (M^+). *Anal.* Calcd for $C_{20}H_{11}F_3O_2$: C, 70.59; H, 3.20. Found: C, 70.48; H, 3.01.

1,4-Bis(2,4-difluorobenzoyl)-2-fluorobenzene (**8b**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 120—122 °C. IR (KBr) cm^{-1}: 1653 (CO). ^{1}H-NMR ($CDCl_3$) δ: 6.84—7.09 (4H, m), 7.56 (1H, td, J=10.2, 1.3 Hz), 7.63—7.72 (2H, m), 7.76 (dd, J=7.8, 4.6 Hz), 7.84 (td, J=8.6, 6.3 Hz). GC-MS (EI) *m/z*: 376 (M^+). *Anal.* Calcd for $C_{20}H_9F_5O_2$: C, 63.84; H, 2.41. Found: C, 63.84; H, 2.13.

1,4-Bis(2,5-difluorobenzoyl)-2-fluorobenzene (**8c**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 148—150 °C. IR (KBr) cm^{-1}: 1667 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.12 (1H, td, J=8.9, 4.9 Hz), 7.20 (1H, ddd, J=8.9, 4.3, 0.7 Hz), 7.24—7.35 (3H, m), 7.48 (1H, ddd, J=7.9, 5.6, 3.3 Hz), 7.59 (1H, dt, J=10.2, 1.3 Hz), 7.68 (1H, dt, J=7.98, 1.3 Hz), 7.79 (1H, dd, J=7.9, 6.6 Hz). GC-MS (EI) *m/z*: 376 (M^+). *Anal.* Calcd for $C_{20}H_9F_5O_2$: C, 63.84; H, 2.41. Found: C, 63.62; H, 2.20.

1,4-Bis(2,6-difluorobenzoyl)-2-fluorobenzene (**8d**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 153—154 °C. IR (KBr) cm^{-1}: 1665 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.00 (2H, t, J=8.6 Hz), 7.04 (2H, dd, J=8.6, 7.6 Hz), 7.42—7.57 (2H, m), 7.62 (1H, dd, J=10.9, 1.6 Hz), 7.71 (1H, dt, J=8.2, 0.5 Hz), 7.94 (1H, dd, J=8.2, 6.9 Hz). GC-MS (EI) *m/z*: 376 (M^+). *Anal.* Calcd for $C_{20}H_9F_5O_2$: C, 63.84; H, 2.41. Found: C, 63.68; H, 2.28.

1,4-Bis(2-chlorobenzoyl)-2-fluorobenzene (**8e**): Colorless prisms (recrystallized from *n*-hexane/dichloromethane). mp 102—103 °C. IR (KBr) cm^{-1}: 1654 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.36—7.56 (9H, m), 7.63 (1H, dd, J=7.9, 1.7 Hz), 7.81 (1H, dd, J=8.6, 6.9 Hz). GC-MS (EI) *m/z*: 372 (M^+). *Anal.* Calcd for $C_{20}H_{11}Cl_2FO_2$: C, 64.37; H, 2.97. Found: C, 64.20; H, 2.90.

General Procedure for the Synthesis of Xanthone Benzophenone **5a**—**f** (1 mmol) was dissolved in 1,4-dioxane (30 ml) and 10% aqueous solution of sodium hydroxide (5 ml) was added to the solution. The mixture was refluxed for 12 h, cooled, and neutralized with 10% hydrochloric acid. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain xanthone **6a**—**e**.

3-Nitroxanthone (**6a**)[41]: Yellow needles (recrystallized from *n*-hexane/acetone). mp 173.5—174.5 °C. IR (KBr) cm^{-1}: 1664 (CO), 1514, 1343 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.47 (1H, td, J=8.8, 1.5 Hz), 7.57 (1H, d, J=8.8 Hz), 7.82 (1H, ddd, J=8.5, 7.5, 2.0 Hz), 8.19 (1H, dd, J=8.8, 2.0 Hz), 8.36 (1H, dd, J=7.5, 1.5 Hz), 8.41 (1H, d, J=2.0 Hz), 8.53 (1H, d, J = 8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 111.0, 115.0, 115.1, 122.6, 123.0, 125.5,

128.0, 130.0, 134.9, 142.5, 143.0, 150.9, 177.2. GC-MS (EI) *m/z*: 241 (M^+). *Anal.* Calcd for $C_{13}H_7NO_4$: C, 64.74; H, 2.93; N, 5.81. Found: C, 64.78; H, 2.81; N, 5.60.

3-Fluoro-6-nitroxanthone (**6b**): Colorless needles (recrystallized from *n*-hexane/dichloromethane). mp 218 °C. IR (KBr) cm^{-1}: 1662 (CO), 1533, 1346 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.16—7.28 (2H, m), 8.21 (1H, dd, J=8.6, 2.0 Hz), 8.36—8.41 (2H, m), 8.51 (1H, d, J=8.6 Hz). GC-MS (EI) *m/z*: 259 (M^+). *Anal.* Calcd for $C_{13}H_6FNO_4$: C, 60.24; H, 2.33; N, 5.40. Found: C, 60.15; H, 1.94; N, 5.18.

2-Fluoro-6-nitroxanthone (**6c**): Slightly yellow needles (recrystallized from *n*-hexane/dichloromethane). mp 200—201 °C. IR (KBr) cm^{-1}: 1667 (CO), 1528, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.51—7.63 (2H, m), 7.99 (1H, ddd, J=7.9, 2.8, 0.7 Hz), 8.20 (1H, dd, J=8.6, 2.3 Hz), 8.41 (1H, d, J=2.3 Hz), 8.51 (1H, d, J=8.6 Hz). GC-MS (EI) *m/z*: 259 (M^+). *Anal.* Calcd for $C_{13}H_6FNO_4$: C, 60.24; H, 2.33; N, 5.40. Found: C, 60.10; H, 2.15; N, 5.08.

1-Fluoro-6-nitroxanthone (**6d**): Slightly yellow needles (recrystallized from *n*-hexane/dichloromethane). mp 208—209 °C. IR (KBr) cm^{-1}: 1670 (CO), 1523, 1347 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.13 (1H, ddd, J=10.4, 8.6, 1.0 Hz), 7.38 (1H, dt, J=8.6, 1.0 Hz), 7.75 (1H, td, J=8.6, 5.6 Hz), 8.19 (1H, dd, J=8.6, 2.0 Hz), 8.36 (1H, d, J=2.0 Hz), 8.50 (1H, d, J=8.6 Hz). GC-MS (EI) *m/z*: 259 (M^+). *Anal.* Calcd for $C_{13}H_6FNO_4$: C, 60.24; H, 2.33; N, 5.40. Found: C, 60.10; H, 2.23; N, 5.01.

1-Chloro-6-nitroxanthone (**6f**): Colorless needles (recrystallized from *n*-hexane/dichloromethane). mp 212—213 °C (lit.[34,42] 214—216 °C). IR (KBr) cm^{-1}: 1667 (CO), 1525, 1346 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 7.46 (1H, dd, J=7.9, 1.3 Hz), 7.49 (1H, dd, J=8.6, 1.0 Hz), 7.66 (1H, dd, J=8.6, 7.9 Hz), 8.18 (1H, dd, J=8.6, 2.0 Hz), 8.34 (1H, d, J=2.0 Hz), 8.48 (1H, d, J=8.2 Hz). GC-MS (EI) *m/z*: 275 (M^+). *Anal.* Calcd for $C_{13}H_6ClNO_4$: C, 56.65; H, 2.19; N, 5.08. Found: C, 56.79; H, 2.03; N, 4.79.

2′-Chloro-2-hydroxy-4-nitrobenzophenone (**9**): Yellow needles (recrystallized from *n*-hexane/dichloromethane). mp 88—89 °C. IR (KBr) cm^{-1}: 3434 (OH), 1640 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.36—7.55 (5H, m), 7.66 (1H, dd, J=8.8, 2.5 Hz), 7.90 (1H, d, J=2.5 Hz), 11.99 (1H, s). GC-MS (EI) *m/z*: 277 (M^+). *Anal.* Calcd for $C_{13}H_8ClNO_4$: C, 56.23; H, 2.90; N, 5.04. Found: C, 56.11; H, 3.02; N, 4.89.

2′-Fluoro-2-methylamino-4-nitrobenzophenone (11a) Benzophenone **5a** (1.315 g, 5 mmol) was dissolved in 1,4-dioxane (10 ml) and 40% aqueous solution of methylamine (**10a**) (2 ml) was added to the solution. The mixture was refluxed for 6 h and poured into ice-water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain **11a** (1.295 g, 95%) and acridone **7a** (29 mg, 2%). Recrystallization of the crude product from *n*-hexane/acetone yielded crystals of **11a** as orange plates. mp 117—117.5 °C. IR (KBr) cm^{-1}: 3326 (NH), 1629 (CO), 1535, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.08 (3H, d, J=5.4 Hz), 7.17 (1H, t, J=8.9 Hz), 7.25—7.30 (2H, m), 7.42 (1H, td, J=7.3, 2.0 Hz), 7.48—7.58 (3H, m), 8.92 (1H, bs). ^{13}C-NMR ($CDCl_3$) δ: 29.7, 96.1, 106.2, 107.9, 116.2 (d, J_{FC}=21.8 Hz), 120.7, 124.5 (d, J_{FC}=4.2 Hz), 127.9 (d, J_{FC}=16.6 Hz), 129.7 (d, J_{FC}=3.1 Hz), 132.5 (d, J_{FC}=8.3 Hz), 136.5 (d, J_{FC}=2.1 Hz), 152.3 (d, J_{FC}=39.4 Hz), 158.9 (d, J_{FC}=252.2 Hz), 195.0. GC-MS (EI) *m/z*: 274 (M^+). *Anal.* Calcd for $C_{14}H_{11}FN_2O_3$: C, 61.31; H, 4.04; N, 10.21. Found: C, 61.07; H, 3.82; N, 9.99.

2′-Fluoro-2-isopropylamino-4-nitrobenzophenone (11b) Isopropylamine (**10b**) (1.48 g, 25 mmol) was added to a solution of **5a** (1.315 g, 5 mmol) in 1,4-dioxane (10 ml). The mixture was refluxed for 3 h and poured into ice-water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain **11b** (1.372 g, 91%). Recrystallization of the crude product from *n*-hexane/dichloromethane yielded crystals of **11b** as orange plates. mp 83—84 °C. IR (KBr) cm^{-1}: 3314 (NH), 1632 (CO), 1528, 1343 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, d, J=6.5 Hz), 3.88 (1H, octet, J=6.5 Hz), 7.14—7.31 (3H, m), 7.42 (1H, td, J=7.3, 1.7 Hz), 7.48—7.56 (2H, m), 7.60 (1H, d, J=2.3 Hz), 8.92 (1H, bs). GC-MS (EI) *m/z*: 302 (M^+). *Anal.* Calcd for $C_{16}H_{15}FN_2O_3$: C, 63.57; H, 5.00; N, 9.27. Found: C, 63.41; H, 4.64; N, 9.17.

2-Benzylamino-2′-fluoro-4-nitrobenzophenone (11c) Benzylamine (**10c**) (107 mg, 1 mmol) was added to a solution of **5a** (263 mg, 1 mmol) in anisole (10 ml). The mixture was refluxed for 6 h and poured into ice-water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain **11c** (264 mg, 75%). Recrystallization of the crude product from *n*-hexane/dichloromethane yielded crystals of **11c** as orange plates. mp 133—134 °C. IR (KBr) cm^{-1}: 3320 (NH), 1629 (CO), 1526, 1348 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 4.57 (2H, d, J=5.6 Hz), 7.17 (1H, t, J=8.9 Hz), 7.25—7.57 (10H, m), 7.59 (1H, d, J=2.0 Hz), 9.32 (1H, bs). GC-MS (EI) *m/z*: 350 (M^+). *Anal.* Calcd for $C_{20}H_{15}FN_2O_3$: C, 68.57; H, 4.32; N, 8.00. Found: C, 68.44; H, 4.46; N, 7.88.

General Procedure for the Synthesis of Acridone A solution of 2-aminobenzophenone **11a**—**c** (1 mmol) in DMF (10 ml) was stirred at 150 °C for 12 or 24 h and then cooled. Water was added to the solution. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain acridone **7a**—**c**.

10-Methyl-3-nitroacridone (**7a**): Orange needles (recrystallized from *n*-hexane/acetone). mp 209—212 °C (lit.[42] 219—220 °C). IR (KBr) cm^{-1}: 1670 (CO), 1522, 1351 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 7.39 (1H, dd, J=7.8, 6.8 Hz), 7.61 (1H, d, J=8.8 Hz), 7.82 (1H, ddd, J=8.8, 6.8, 1.5 Hz), 8.05 (1H, dd, J=8.3, 2.0 Hz), 8.48 (1H, d, J=2.0 Hz), 8.56 (1H, dd, J=7.8, 1.5 Hz), 8.70 (1H, d, J=8.3 Hz). FAB-MS *m/z*: 255 (M^+). *Anal.* Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.22; H, 3.92; N, 10.88.

10-Isopropyl-3-nitroacridone (**7b**): Orange needles (recrystallized from *n*-hexane/acetone). mp 246—248 °C. IR (KBr) cm^{-1}: 1639 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.86 (6H, d, J=7.3 Hz), 5.23 (1H, septet, J=7.3 Hz), 7.35 (1H, ddd, J=7.9, 6.6, 1.3 Hz), 7.68—7.79 (2H, m), 8.02 (1H, dd, J=8.9, 2.0 Hz), 8.51 (1H, ddd, J=7.9, 1.3, 0.6 Hz), 8.59 (1H, d, J=2.0 Hz), 8.65 (1H, d, J=8.9 Hz). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.01; H, 4.64; N, 9.79.

10-Benzyl-3-nitroacridone (**7c**)[43]: Orange needles (recrystallized from *n*-hexane/dichloromethane). mp 201 °C. IR (KBr) cm^{-1}: 1640 (CO). ^{1}H-NMR ($CDCl_3$) δ: 5.67 (2H, s), 7.22 (2H, dd, J=7.8, 1.9 Hz), 7.32—7.44 (5H, m), 7.69 (1H, ddd, J=8.9, 6.9, 1.6 Hz), 8.00 (1H, dd, J=8.9, 2.0 Hz), 8.26 (1H, d, J=2.0 Hz), 8.53 (1H, dd, J=7.8, 1.6 Hz), 8.67 (1H, d, J=8.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 51.1, 111.3, 115.3, 115.6, 122.8, 122.9, 125.4, 125.6, 127.9, 128.3, 129.5, 129.8, 134.3, 135.1, 142.3, 142.9, 151.1, 177.2. *Anal.* Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.47; H, 4.13; N, 8.35.

Synthesis of 10-Benzyl-3-nitroacridone (7c) from 2,2′-Difluoro-4-nitrobenzophenone (5a) and Benzylamine (10c) A solution of **5a** (263 mg, 1 mmol) and **10c** (107 mg, 1 mmol) in DMSO (20 ml) was stirred at 150 °C for 24 h and then cooled. Water was added to the solution. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain acridone **7c** (241 mg, 73%).

3-(2-Fluorophenyl)-1-methyl-6-nitroindazole (12) Under an argon atomophere, methylhydrazine (576 mg, 12.5 mmol) was added to a solution of **5a** (263 mg, 1 mmol) in 1,4-dioxane (10 ml). The mixture was refluxed for 12 h, cooled, and poured into water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to yield **12** (109 mg, 40%). Recrystallization of the crude product from *n*-hexane/dichloromethane yielded crystals of **12** as yellow needles. mp 165—167 °C. IR (KBr) cm^{-1}: 1513, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 4.26 (3H, s), 7.23—7.39 (2H, m), 7.42—7.50 (1H, m), 7.80 (1H, td, J=7.8, 2.0 Hz), 7.95 (1H, dd, J=9.8, 2.9 Hz), 8.05 (1H, dd, J=8.8, 2.0 Hz), 8.41 (1H, d, J=2.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 36.2, 96.1, 105.8, 115.4, 116.3 (d, J_{FC}=21.8 Hz), 119.9 (d, J_{FC}=14.5 Hz), 123.0 (d, J_{FC}=8.3 Hz), 124.6 (d, J_{FC}=3.1 Hz), 125.5, 130.5 (d, J_{FC}=8.3 Hz), 130.9 (d, J_{FC}=4.2 Hz), 140.0 (d, J_{FC}=22.9 Hz), 146.5, 159.9 (d, J_{FC}=249.1 Hz). GC-MS (EI) *m/z*: 271 (M^+). *Anal.* Calcd for $C_{14}H_{10}FN_3O_2$: C, 61.99; H, 3.72; N, 15.49. Found: C, 61.95; H, 3.54; N, 15.21.

3-Chloro-2-(2-Fluorobenzoyl)quinoxaline (14) Under an argon atmosphere, 60% sodium hydride in oil (520 mg, 13 mmol) was added to a mixture of 2,3-dichloroquinoxaline (**13**) (1.99 g, 10 mmol), and 2-fluorobenzaldehyde (**4a**) (1.49 g, 12 mmol), 1,3-dimethylimidazolium iodide (**1**) (672 mg, 3 mmol) in THF (50 ml). The mixture was refluxed for 5 h and poured into ice-water. After neutralizing the water layer with acetic acid, the products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain recovered **13** (862 mg, 43%) and benzoylquinoxaline **14** (1.08 g, 38%). Recrystallization of the crude product from *n*-hexane/acetone yielded crys-

tals of **14** as colorless prisms. mp 100 °C. IR (KBr) cm^{-1}: 1669 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.11 (1H, ddd, J=11.7, 8.3, 1.0 Hz), 7.38 (1H, td, J=7.8, 1.0 Hz), 7.62—7.71 (1H, m), 7.80—7.92 (2H, m), 8.07—8.13 (3H, m). *Anal.* Calcd for $C_{15}H_8ClFN_2O$: C, 62.84; H, 2.81; N, 9.77. Found: C, 62.68; H, 2.76; N, 9.59.

2-(2-Fluorobenzoyl)-3-methylaminoquinoxaline (15) Quinoxaline **14** (573 mg, 2 mmol) was dissolved in 1,4-dioxane (10 ml) and 40% aqueous solution of methylamine (**10a**) (0.8 ml) was added to the solution. After the mixture was refluxed for 1 h, the methylamine solution (0.4 ml) was added again. The mixture was refluxed for 30 min and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain quinoxaline **15** quantitively. Recrystallization of the crude product from *n*-hexane/acetone yielded crystals of **15** as orange neeedles. mp 189—190 °C. IR (KBr) cm^{-1}: 3368 (NH), 1644 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.21 (3H, d, J=4.9 Hz), 7.16 (1H, ddd, J=9.3, 8.3, 1.0 Hz), 7.25—7.36 (2H, m), 7.51—7.77 (5H, m), 8.19 (1H, bs). *Anal.* Calcd for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30; N, 14.94. Found: C, 68.36; H, 4.25; N, 14.81.

Quinolino[2,3-*b*]quinoxaline 16 A mixture of quinoxaline **14** (281 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) in DMF (5 ml) was stirred at 150 °C for 1 h and then cooled. The mixture was poured into ice-water. The resulting precipitates were filtered and washed with a small amount of cooled ethyl acetate to obtain qunolinoquinoxaline **16** quantitively. Recrystallization of the crude product from *n*-hexane/acetone yielded crystals of **16** as orange needles. mp >300 °C. IR (KBr) cm^{-1}. 1647 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.23 (3H, s), 7.38 (1H, td, J=8.3, 1.0 Hz), 7.65 (1H, d, J=8.8 Hz), 7.73 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.83—7.92 (2H, m), 8.06 (1H, dd, J=8.8, 1.5 Hz), 8.43 (1H, dd, J=8.3, 1.0 Hz), 8.66 (1H, dd, J=8.3, 1.5 Hz). *Anal.* Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.55; H, 4.24; N, 15.98.

Thianaphtho[2,3-*b*]quinoxaline 17 A mixture of benzoylquinoxaline **14** (500 mg, 1.75 mmol) was dissolved in methanol (10 ml) and thioacetic acid (0.5 ml) was added to the solution. After the mixture was refluxed for 2 h, thioacetic acid (0.5 ml) was added again. The mixture was refluxed for another 2 h, cooled, and poured into ice-water. The products are extracted with dichloromethane. The organic layer was concentrated. Sodium hydroxide (2 N) and ethyl acetate were added to the residue. The organic layer was dried over Na_2SO_4 and concentrated to obtain thianaphthoquinoxaline **17** (212 mg, 46%). The water layer was neutralized and the product was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated to obtain compound **18** (212 mg, 43%).

Thianaphtho[2,3-*b*]quinoxaline **17**: Yellow needles (recrystallized from *n*-hexane/acetone). mp 263 °C. IR (KBr) cm^{-1}: 1666 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.54 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.65 (1H, dd, J=8.3, 1.5 Hz), 7.72 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.86 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 7.95 (1H, ddd, J=8.3, 6.8, 1.5 Hz), 8.10 (1H, dd, J=8.3, 1.0 Hz), 8.44 (1H, dd, J=8.3, 1.0 Hz), 8.67 (1H, dd, J=8.3, 1.5 Hz). GC-MS (EI) m/z: 264 (M^+). *Anal.* Calcd for $C_{15}H_8N_2OS$: C, 68.17; H, 3.05; N, 10.60. Found: C, 68.31; H, 3.27; N, 10.26.

2-(2-Fluorobenzoyl)-3-mercaptoquinoxaline (**18**): Orange plates (recrystallized from *n*-hexane/dichloromethane). mp 211.5—212.5 °C. IR (KBr) cm^{-1}: 3228 (SH), 1653 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.08 (1H, dd, J=11.2, 8.7 Hz), 7.31—7.37 (2H, m), 7.46 (1H, td, J=8.3, 1.7 Hz), 7.59—7.66 (2H, m), 7.92 (1H, dd, J=8.3, 1.7 Hz), 8.20 (1H, td, J=7.5, 1.7 Hz), 11.34 (1H, bs). MS (FAB) m/z: 285 (M^{+1}). *Anal.* Calcd for $C_{15}H_9FN_2OS$: C, 63.37; H, 3.19; N, 9.85. Found: C, 63.23; H, 3.18; N, 9.84.

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