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Large-scale synthesis of new cyclazines, 5-thia-1,8*b*-diazaacenaphthylene-3-carboxylic acid derivatives having the peripheral 12π-electron ring system

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Abstract—The 5-thia-1,8b-diazaacenaphthylenes (**2** and its ester, **8**) are new cyclazines, in which a paramagnetic ring is present in the peripheral 12π-electron ring system. Three convenient methods of preparing **8** have been developed. One involved thioglycolation of a new compound, 5-fluoroimidazo[1,2-*a*]pyridine (**6b**), followed by the Duff reaction gave **8** in 64% yield without chromatographic purification.

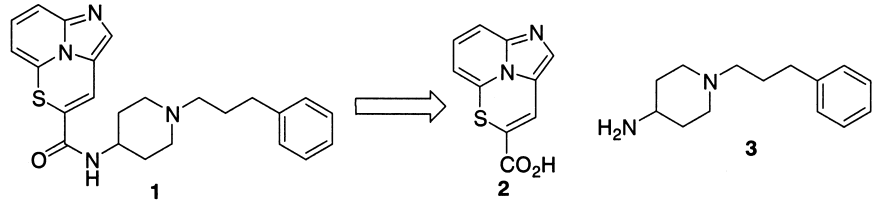
1. Introduction

The 5-thia-1,8*b*-diazaacenaphthylenes (**1**,**2** and **8**) are new cyclazines with fused tricyclic ring systems having an internal nitrogen atom and 5, 6, and 6-members.[1] These heteroaromatic compounds were revealed to have a planar structure by X-ray crystallographic analysis. The ^{1}H NMR data on these cyclazines showed unique properties between those of stable 'aromatic' and unstable 'antiaromatic' ring systems, and suggested the contribution of a paramagnetic ring present in the peripheral 12π-electron ring system.[2] Among these products, *N*-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenaphthylen-4-carboxamide (**1**) reduced the amount of low and very low density lipoprotein cholesterol and triglycerides in hamsters, and has potential for preventing atherosclerosis.[3] Hence, preparation of **1** for large-scale was required to support toxicological evaluation. Compound **1** consists of 5-thia-1,8*b*-diazaacenaphthylene-4-carboxylic acid (**2**) and 4-amino-1-(3-phenylpropan-1-yl)piperidine (**3**) as shown in Scheme 1. In this paper, we describe the large-scale production of **2** as a segment of **1**.

2. Results and discussion

2.1. Synthesis of 7b

Ethyl (imidazo[1,2-*a*]pyridin-5-ylthio)acetate (**7b**) as a precursor of carboxylic acid (**2**) was synthesized, as shown in Scheme 2. The sulfide (**7b**) was early prepared by thiolation of 5-chloroimidazo[1,2-*a*]pyridine (**6a**) with aqueous NaSH solution, followed by treatment with ethyl bromoacetate.[2,3] However, this reaction took more than 60 h



Scheme 1.

Keywords: 5-thia-1,8*b*-diazaacenaphthylene; cyclazine; 5-fluoroimidazo[1,2-*a*]pyridine; Duff reaction; 12π-electron ring system.
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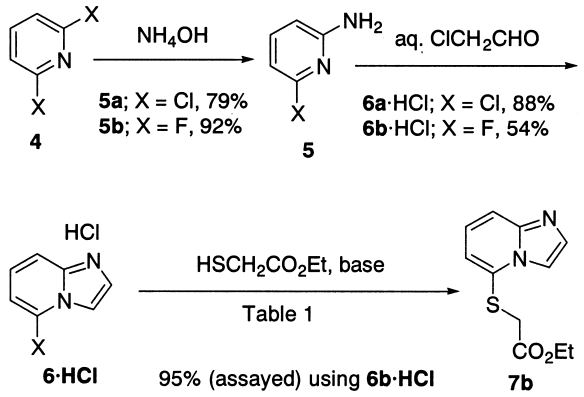


Scheme 2.

Table 1. Reaction of **6** with $HSCH_2CO_2Et$ (1.2 equiv.) in DMF

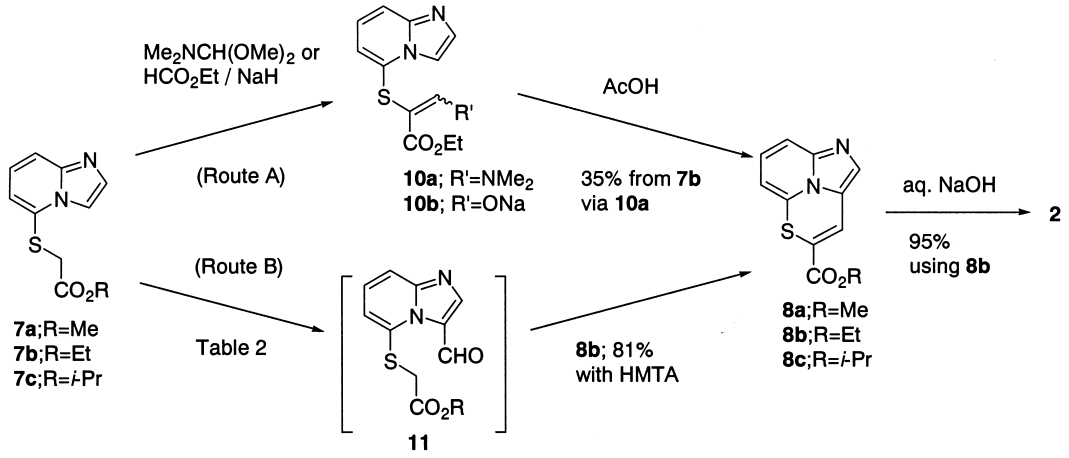
Entry	Substrate	Base (equiv.)	Conditions	Yield of **7b** (%)[a]
1	**6a** (free)	Et_3N (1.0)	70°C, 2 h	62
2	**6a** (free)	Pyridine (1.0)	70°C, 5 h	87
3	**6a** (free)	–	70°C, 7 h	87
4	**6a·HCl**	Et_3N (1.0)	70°C, 7 h	81
5[b]	**6a·HCl**	Et_3N (2.5)	80°C, 4 h	61
6[b]	**6b·HCl**	Et_3N (2.5)	Rt, 2 h	95

[a] Assayed by HPLC.
[b] Thioglycolate (1.5 equiv.) was used.

at 100°C to give 5-mercaptoimidazo[1,2-*a*]pyridine (**9**) and the product contained a large quantity of sulfur as an impurity. This approach was impractical for large-scale production as tedious chromatographic purification was needed. To avoid contamination by sulfur, we conducted the thioglycolation of 5-halogenoimidazo[1,2-*a*]pyridine (**6**)[4] and described the optimization of these reaction conditions as shown in Table 1. The reaction of 5-chloroimidazo[1,2-*a*]pyridine (**6a**) and ethyl thioglycolate using triethylamine in DMF gave **7b** in 62% yield with **9** as by-product. The replacement reaction of **6a** at 70°C in DMF with pyridine or without a base gave **7b** in 87% yield, respectively (entry 2 and 3). These results showed that the presence of a stronger base affected yield and the decomposition of **7b** providing **9**. Moreover, the reaction conditions requiring a higher temperature produced a tar-product. The thioglycolation of a new compound, 5-fluoroimidazo[1,2-*a*]pyridine (**6b**), was prepared by the condensation of chloroacetaldehyde and 2-amino-6-fluoropyridine (**5b**) from 2,6-difluoropyridine (**4b**)[5], was also carried out. The reaction of **6b** hydrochloride salt (**6b·HCl**) with ethyl thioglycolate and triethylamine in DMF at room temperature afforded **7b** in 95% yield (entry 6).

2.2. Synthesis of 8b using 7b

The new cyclazine **8b** was synthesized by two independent methods using **7b**, as shown in Scheme 3. First, we attempted to synthesize **8b** by the formylation of **7b** at the α-position of the ester, followed by a electrophilic reaction



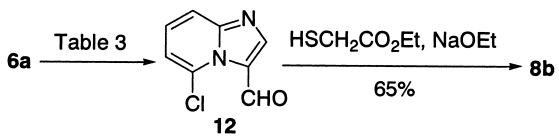
Scheme 3.

Table 2.

Entry	Substrate	Reagent (equiv.), solvent (v/w)	Conditions	Yield (%)[a]
1	**7b** (R=Et)	$POCl_3$ (5), DMF (5.5)	80°C, 21 h	31[b]
2	**7b** (R=Et)	$(CH_2)_6N_4$ (2), AcOH (8.5)	90°C, 8 h	81[b]
3	**7b** (R=Et)	$(CH_2)_6N_4$ (1.7), AcOH (5)	100°C, 6 h	79
4	**7a** (R=Me)	$(CH_2)_6N_4$ (1.7), AcOH (5)	100°C, 5 h	59
5	**7c** (R=*i*-Pr)	$(CH_2)_6N_4$ (1.7), AcOH (5)	100°C, 7 h	81

[a] Assayed by HPLC.
[b] Isolated yield.

(Route C)



Scheme 4.

Table 3.

Entry	Reagents (equiv.)	Conditions	Yields (%)[a]	
			12	**6a**
1	$POCl_3$ (12), DMF	90–100°C, 3 h	31	69
2	Cl_2CHOMe (1.5), $SnCl_4$ (1.5), CH_2Cl_2	Rt, 2 h	8	69
3	Cl_2CHOMe (1.5), $TiCl_4$ (4), CH_2Cl_2	Rt, 3 h	21	59
4	$(CH_2)_6N_4$ (2), AcOH	85°C, 5 h	56 (18)[b]	–
5	Imidazole (1), Ac_2O, then NaOH	125°C, 1 h	Multi-spots	
6	*n*-BuLi (1.5), DMF (1.5), THF	−60°C, 1 h, then rt, 2 h	Multi-spots	

[a] Assayed by HPLC.
[b] Isolated yield.

at the 3-position of imidazo[1,2-*a*]pyridine (route A). Compound **7b** reacted with *N*,*N*-dimethyformamide dimethyl acetal or NaH–ethyl formate to give α-formylester derivatives **10**. The treatment of **10** at 80°C in acetic acid successfully produced the desired **8b** as a purple crystal. Second, the preparation of **8b** was carried out by the formylation of **7b** at the 3-position of imidazo[1,2-*a*]pyridine followed by intramolecular condensation (route B). The treatment of **7b** with phosphorous oxychloride ($POCl_3$) in DMF[6] also gave **8b** in 30–50% yield with **7b** hydrochloride salt (**7b·HCl**), without compound **11**. It was thought that the formation of **7b·HCl** in the Vilsmeier reaction caused the lack of electrophilicity at the 3-position. Therefore, we conducted the formylation of **7b** at the 3-position without a strong acid to prevent the formation of **7b** salt. As shown in Table 2, the formylation of **7b** with hexamethylenetetramine (HMTA)[7] at 100°C using acetic acid as solvent gave **8b** in 81% isolated yield. Because of the stability of **7** to heat, the yields of the Duff reaction[7] were affected by the substituted group of ester under the same conditions (Me<Et<*i*-Pr). The hydrolysis of **8b** with aqueous NaOH solution quantitatively gave the desired compound **2**.

2.3. Synthesis of 8b using 12

Furthermore, an alternative synthetic method of synthesizing **8b** was developed as shown in Scheme 4 (route C).[8] We synthesized 5-chloro-3-formylimidazo[1,2-*a*]pyridine (**12**) and described the optimization of these reactions as shown in Table 3. The Duff reaction of **6a** gave 5-chloro-3-formylimidazo[1,2-*a*]pyridine (**12**) in 56% yield, as assayed by HPLC, although other reagents such as $POCl_3$–DMF and dichloromethylmethylether–titanium tetrachloride gave lower yields. The treatment of **12** with ethyl thioglycolate and sodium ethoxide resulted in thiolation and successive intramolecular condensation to give **8b** in 65% yield.

3. Conclusion

We developed three independent pathways for the synthesis of a new cyclazine, 5-thia-1,8*b*-diazaathenaphtalene (**8b**). The reaction of 5-fluoroimidazo[1,2-*a*]pyridine hydrochride (**6b·HCl**) from 2,6-difuloropyridine (**4b**) and thioglycolate, followed by treatment with HMTA, gave **8b** in particularly good yield. The hydrolysis of **8b** quantitatively gave the desired compound **2**. This process allows for large-scale production without the need for a chromatographic method.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus, and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. Column chromatography was performed with a Wakogel C-200 (75–150 μm) system. HPLC was performed on a YMC-Pack ODS-A302 column (6 i.d.×150 mm) with 0.05 M aqueous KH_2PO_4 solution–MeCN (55:45) at 25°C. Detection was effected with a Shimadzu SPD-10A spectrophotometric detector at 254 nm. Elemental analyses and MS spectra were carried out by Takeda Analytical Research Laboratories, Ltd.

4.1.1. 2-Amino-6-chloropyridine (5a). A solution of 2,6-dichloropyridine (100.0 g, 675.7 mmol) and 25% aqueous NH_4OH solution (600 mL) was stirred for 5 h at 125°C under a pressure of ca. 0.2 MPa. It was then cooled to room temperature and stirred for 2 h. The resulting solid was collected by filtration, washed with water (100 mL) and dried at 40°C in vacuo to give **5a** (68.6 g, 79%) as a white solid, mp 70–71°C. Anal. calcd for $C_5H_5ClN_2$: C, 46.71; H, 3.92; N, 21.79; Cl, 27.58. Found: C, 46.45; H, 3.81; N, 21.69; Cl, 27.53. ^{1}H NMR ($CDCl_3$): δ=4.56–4.84 (2H, brs), 6.37 (1H, d, J=8.1 Hz), 6.63 (1H, d, J=7.5 Hz), 7.35 (1H, dd, J=8.1, 7.5 Hz). IR (KBr): ν=1635, 1548, 1471, 1427, 1184, 781, 686 cm^{-1}.

4.1.2. 6-Chloroimidazo[1,2-*a*]pyridine hydrochloride salt (6a·HCl). Crystal **5a** (3600 g, 28.0 mol) was dissolved in EtOH (28 L) at 60°C. Aqueous chloroacetoaldehyde solution (40%, 18.5 L, 112.2 mol) was added dropwise to the resulting solution over 3 h at 50–60°C, and the whole was refluxed for 10 h, cooled to room temperature and concentrated. A mixture of AcOEt and EtOH (1:1, 5.5 L) was added to the resulting mixture, and the whole was stirred for 2 h at 25–35°C. The resulting solid was collected by filtration and dried in vacuo to give **6a·HCl** (4200 g, 79%) as a white solid. After the mother liquor was concentrated, a mixture of AcOEt and EtOH (1:1, 1.5 L) was added to the resulting solution, and the whole was stirred for 2 h at 25–35°C. The resulting solid was collected by filtration and dried in vacuo to give **6a·HCl** (488 g, 9%) as a white solid, mp 166°C (decomposition). Anal. calcd for $C_7H_6Cl_2N_2$: C, 44.47; H, 3.20; N, 14.82; Cl, 37.51. Found: C, 44.21; H, 3.23; N, 14.65; Cl, 37.22. ^{1}H NMR (D_2O): δ=7.51–7.54 (1H, m), 7.82–7.84 (2H, m), 7.93 (1H, d, J=2.1 Hz), 8.16 (1H, d, J=2.1 Hz). IR (KBr): ν=1644, 1510, 1209, 759 cm^{-1}.

4.1.3. 2-Amino-6-fluoropyridine (5b). A solution of 2,6-difluoropyridine (75.0 g, 651.7 mmol) and 25% aqueous NH_4OH solution (375 mL) was stirred for 5 h at 125°C under a pressure of ca. 1.4 MPa. It was then cooled to 0°C and stirred for 2 h at the same temperature. The resulting solid was collected by filtration and dried at 40°C in vacuo to give **5b** (67.2 g, 92%) as a white solid, mp 57–58°C. Anal. calcd for $C_5H_5FN_2$: C, 53.57; H, 4.50; N, 24.97; F, 16.95. Found: C, 53.44; H, 4.45; N, 24.97; F, 17.25. ^{1}H NMR ($CDCl_3$): δ=4.33–4.74 (2H, brs), 6.16–6.19 (1H, m), 6.28–6.30 (1H, m), 7.46 (1H, dd, J=8.0, 8.0 Hz). IR (KBr): ν=1619, 1571, 1527, 1228, 781 cm^{-1}.

4.1.4. 6-Fluoroimidazo[1,2-*a*]pyridine hydrochloride salt (6b·HCl). To a solution of **5b** (40.0 g, 356.8 mmol) and water (400 mL) was added dropwise 40% aqueous chloroacetoaldehyde solution (119 mL, 715.5 mmol) at 60°C. The mixture was stirred for 2 h at the same temperature and then cooled to room temperature. AcOEt (200 mL×2) was added to the reaction mixture and separated. The aqueous solution was adjusted to pH 9 with saturated $NaHCO_3$ solution. After extraction with AcOEt (200 mL×3), the organic layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was dissolved in THF (120 mL) and 4.68N HCl–AcOEt (76 mL) was added dropwise to the solution in an ice-bath. The resulting solid was collected by filtration, washed with AcOEt–THF and dried in vacuo to give **6b·HCl** (33.0 g, 54%) as a white solid, mp 185°C (decomposition). Anal. calcd for $C_7H_6ClFN_2$: C, 48.72; H, 3.50; N, 16.23; Cl, 20.54; F, 11.01. Found: C, 48.37; H, 3.51; N, 15.92; Cl, 20.41; F, 10.99. ^{1}H NMR (D_2O): δ=7.24 (1H, m), 7.78 (1H, d, J=9.1 Hz), 7.98–8.10 (2H, m), 8.15 (1H, m). IR (KBr): ν=1671, 1573, 1544, 1265, 755 cm^{-1}.

4.1.5. Ethyl (imidazo[1,2-*a*]pyridin-5-ylthio)acetate (7b, using 6b·HCl). Ethyl thioglycolate (2.8 mL, 26.1 mmol) was added to a suspension of **6b·HCl** (3.0 g, 17.4 mmol), triethylamine (6.1 mL, 43.5 mmol), and DMF (30 mL) at room temperature under an argon atmosphere, and the mixture was stirred for 2 h under the same conditions to give **7b** (95%, assayed by HPLC). An analytically pure sample of **7b** was obtained by chromatography on silica-gel with AcOEt as a brown oil. MS (EI)=m/z 237 (M^+, calcd 237.3). ^{1}H NMR ($CDCl_3$): δ=1.17 (3H, t, J=7.1 Hz), 3.62 (2H, s), 4.12 (2H, q, J=7.1 Hz), 7.06 (1H, d, J=7.1 Hz), 7.11 (1H, dd, J=7.1, 8.8 Hz), 7.64 (1H, d, J=8.8 Hz), 7.71 (1H, s), 7.91 (1H, s). IR (neat): ν=1731, 1488, 1294, 784 cm^{-1}.

4.1.6. Ethyl 5-thia-1,8*b*-diazaathenaphtalene-4-carboxylate (8b using 7b via 10a, route A). A solution of **7b** (1.2 g, 5.0 mmol), *N*,*N*-dimethylformamide dimethyl acetal (1.0 mL, 7.5 mmol) and DMF (12 mL) was stirred for 2 h at 80°C, cooled to room temperature, and mixed with water (10 mL). After extraction with AcOEt (24 mL), the organic layer was washed with brine (12 mL×2), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica-gel with AcOEt to give crude **10a** (0.94 g, including AcOEt and DMF, analyzed by ^{1}H NMR) as a brown oil. ^{1}H NMR ($CDCl_3$): δ=1.21 (3H, t, J=7.1 Hz), 3.27 (6H, s), 4.18 (2H, q, J=7.1 Hz), 6.58 (1H, d, J=7.1 Hz), 7.18 (1H, dd, J=7.1, 8.8 Hz), 7.45 (1H, d, J=9.0 Hz), 7.73 (1H, s), 7.79 (1H, s), 8.19 (1H, s). A solution of crude **10a** (0.73 g) and AcOH (7 mL) was stirred for 3 h at 80°C, cooled to room temperature, and concentrated. Water (2.5 L) was added to the resulting residue. After extraction with AcOEt (14 mL), the organic layer was washed with water (12 mL×2). Water (12 mL) was added to the organic solution, and the mixture was adjusted to pH 9 with saturated $NaHCO_3$ solution. The aqueous layer was separated, and the organic layer was washed with brine (12 mL×2) and concentrated in vacuo. The residue was purified by chromatography on silica-gel with AcOEt to give **8b** (0.56 g, 35% from **7b**) as a purple solid, mp 166–167°C. Anal. calcd for $C_{12}H_{10}N_2O_2S{\cdot}0.1H_2O$: C, 58.10; H, 4.14; N, 11.29; S, 12.91. Found: C, 57.81; H, 3.92; N, 11.14; S, 13.29. ^{1}H NMR ($CDCl_3$): δ=1.35 (3H, t, J=7.1 Hz), 4.28 (2H, q, J=7.1 Hz), 5.72–5.75 (1H, m), 6.58–6.65 (2H, m), 6.86 (1H, s), 7.06 (1H, s). IR (KBr): ν=1697, 1617, 1481, 1270, 1228, 1157, 1045 cm^{-1}.

4.1.7. 8b using 7b (route B). A solution of **7b** (288.4 g, 1.23 mol), HMTA (342.2 g, 2.44 mol) and AcOH (2.5 L) was stirred for 8 h at 90°C, cooled to room temperature and concentrated. Water (2.5 L) was added to the resulting residue. After extraction with AcOEt (2.5 L), the organic layer was washed with water (2.5 L×2). Water (0.5 L) was added to the organic solution, and the mixture was adjusted to pH 9 with 30% NaOH solution at below 15°C. The aqueous layer was separated, and the organic layer was washed with water (2 and 0.8 L) and concentrated in vacuo. The residue was triturated with *n*-hexane (1 L), collected by filtration, and dried in vacuo to give **8b** (238.5 g, 79%) as a purple solid. Compound **8b** (4.7 g, 2%) was recovered from the mother solution.

4.1.8. 8b using 6b·HCl via 7b. Ethyl thioglycolate (28.5 mL, 260.7 mmol) was added to a suspension of **6b·HCl** (30.0 g, 173.8 mmol), triethylamine (60.5 mL, 434.5 mmol), and DMF (300 mL) at room temperature under an argon atmosphere, and the whole was stirred for 2 h under the same conditions (88%, assayed by HPLC).

AcOEt (900 mL) was added to the reaction mixture, and extracted with 1N HCl (300 mL×2). The aqueous solution was adjusted to pH 9 with saturated $NaHCO_3$ solution, and extracted with AcOEt (300 mL×2). The organic layer was washed with 5% aqueous NaCl solution (90 mL×2), dried (Na_2SO_4) and concentrated in vacuo to give crude **7b** (31.8 g, 77%, assayed by HPLC) as a light-brown oil.

A solution of crude **7b** (31.8 g, 134.2 mmol), HMTA (32.9 g, 234.9 mmol) and AcOH (270 mL) was stirred for 4 h at 105–110°C, cooled to room temperature, and concentrated. AcOEt (500 mL) was then added to the resulting residue. The organic layer was washed with water (280 mL×3), concentrated in vacuo, and again water (222 mL) was added to the resulting residue. The resulting solid was collected by filtration, and dried in vacuo to give **8b** (21.1 g, 64%) as a purple solid.

4.1.9. 5-Chloro-3-formylimidazo[1,2-*a*]pyridine (12). A solution of **6a** (17.2 g, 112.7 mmol), HMTA (31.6 g, 225.4 mmol) and AcOH (170 mL) was stirred for 5 h at 85°C (56%, assayed by HPLC), cooled to room temperature, and concentrated. Water (150 mL) and 2-butanone (150 mL) were then added to the reaction mixture. The mixture was adjusted to pH 9 with 30% NaOH solution, the aqueous layer was separated, and the aqueous solution was extracted with 2-butanone (150 mL). The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica-gel with AcOEt to give **12** (3.6 g, 18%) as a white solid, mp 157–159°C. Anal. calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51; Cl, 19.63. Found: C, 53.13; H, 2.85; N, 15.46; F, 19.49. ^{1}H NMR ($CDCl_3$): δ=7.20 (1H, d, J=7.4 Hz), 7.44 (1H, dd, J=7.4, 8.9 Hz), 7.76 (1H, d, J=8.9 Hz), 8.50 (1H, s), 10.71 (1H, s). IR (KBr): ν=2952, 2921, 2854, 1648, 1502, 1459 cm^{-1}.

4.1.10. 8b using 12 (route C). NaOEt (210 mg, 3.2 mmol) was added to a solution of **12** (448 mg, 2.7 mmol), ethyl thioglycolate (0.36 mL, 3.2 mmol), and EtOH (10 mL), and the whole was refluxed for 3 h. After the mixture had cooled to room temperature and been concentrated, AcOEt (10 mL) was added to the resulting residue. The organic solution was then extracted with 1N HCl solution (5 mL×2), and the aqueous solution was adjusted to pH 9 with 1N NaOH solution in an ice-bath and extracted with AcOEt (10 mL×2). The organic layer was washed with water (10 mL×2), dried (Na_2SO_4) and concentrated in vacuo. The residue was triturated with diisopropyl ether (20 mL), and collected by filtration to give **8b** (430 mg, 65%) as a white solid.

4.1.11. 5-Thia-1,8*b*-diazaacenaphthylene-4-carboxylic acid (2). 1N NaOH solution (120 mL) was added to a solution of **8b** (15.0 g, 60.9 mmol), and the whole was stirred for 1 h at 35–40°C. Water (60 mL) was added to the reaction mixture and washed with AcOEt (96 mL). The aqueous solution was added dropwise to 1N HCl solution (80 mL), and stirred for 1 h at room temperature. The resulting solid was collected by filtration, and washed successively with water and acetone to give **2** (12.7 g, 96%) as an orange solid, mp 272–273°C. Anal. calcd for $C_{10}H_6N_2O_2S\cdot H_2O$: C, 50.84; H, 3.41; N, 11.86; S, 13.57. Found: C, 50.84; H, 3.22; N, 12.09; S, 13.47. ^{1}H NMR (DMSO-d_6): δ=5.99 (1H, d, J=7.0 Hz), 6.62 (1H, d, J=9.2 Hz), 6.70 (1H, dd, J=7.0, 9.2 Hz), 6.91 (1H, s), 7.15 (1H, s), CO_2H was not found. IR (KBr): ν=3450, 1635, 1338, 781 cm^{-1}.

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