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HETERARYLAMINATION AND HETERARYLSULFIDATION OF 2-CHLORO-1-AZAAZULENES

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Abstract – Heteroarylamination and heteroarylsulfidation of 2-chloro-1-azaazulenes (1) were investigated. Palladium catalyzed coupling of 2-amino-1-azaazulenes (2) with 1 underwent to give bis(1-azaazulen-2-yl)amine derivatives in good yields, but the reaction of 2-mercapto-1-azaazulenes (4) with 1 did not give good results in the same conditions. The reaction of 4 with 1 under basic conditions gave bis(1-azaazulen-2-yl) sulfide derivatives in good yields. Heteroarylamino-substitution was proceeded on the reaction of 4-amino-3-mercapto-4H-1,2,4-triazoles (6) with 1 in BuOH under reflux, whereas heteroarylsulfido-substitution was proceeded on the reaction of 6 with 1 in the presence of NaH in dioxane.

The chemistry of azaazulenes1 is of interest for their physiological properties2,3 as well as physical and chemical properties. Aryl amines have a potential functionality in pharmaceutical drug candidates,4-8 therefore Pd-catalyzed amination of aryl halides has attracted attention.9 Recently, we reported that heteroarylamination of ethyl 2-chloro-1-azaazulene-3-carboxylate proceeded well by Pd-catalyzed amination.10 In the extension of the chemistry, we examined the reaction of 2-chloro-1-azaazulenes with 2-amino-1-azaazulenes, mercapto-1-azaazulenes, and 4-amino-3-mercaptop-4H-1,2,4-triazoles. Treatment of 2-chloro-1-azaazulene (1a) with 2-amino-1-azaazulene (2a) in the presence of Pd2(dba)3, Xantphos, and Cs2CO3 in dioxane under reflux for 4 h gave bis(1-azaazulen-2-yl)amine (3aa) in 39% yield. The 1H NMR spectrum of 3aa was symmetrical and the 13C NMR spectrum showed 9 signals; this showed that heteroarylamination occurred at amino group at C-2, and not at N-1 of 1-azaazulene nuclei. Similar treatment of 1b, 1c, and 1d with 2a and 2b gave 3ba (70%), 3ca (63%), and 3db (43%).
respectively. Although the yields were slightly low as the case, the usefulness of Pd-catalyzed heteroarylamination was certified for the synthesis of bis(1-azaazulen-2-yl)amine derivatives.

![Scheme 1](image)

Next, we investigated the reaction of 2-chloro-1-azaazulenes with 2-mercapto-1-azaazulenes. Treatment of 1b with 4a in the presence of Pd$_2$(dba)$_3$, Xantphos, and Cs$_2$CO$_3$ in dry 1,4-dioxane for 24 h under reflux gave 5ba in 50% yield. In a similar manner, the reaction of 1c with 4a gave 5ca (38%). Although the coupling products were obtained, the yields were not so well, and it is considered that the occurrence of S$_N$Ar reaction was within the bounds of possibility, because it is known that S$_N$Ar reaction occurs in the reaction of 2-chloro-1-azaazulenes with good nucleophile, such as alkoxide and sulfoxide. In addition, the possibility of poisoning of Pd-catalyst by S-atom would be considered. Therefore, we performed the reaction of 1a with 4a in the presence of NaH in dry 1,4-dioxane for 4 h under reflux, and 5aa was obtained in 88% yield. In a similar manner, the reaction of 1b and 1c with 4a and 4b gave 5ba (71%), 5ca (80%), and 5cb (85%), respectively. Thus, the reaction of 2-mercapto-1-azaazulenes in the presence of base was preferred to undergo the S$_N$Ar reaction on S-atom and gave bis(1-azaazulen-2-yl) sulfides, and heteroarylamination on N-1 atom of 4 did not proceed.

![Scheme 2](image)

Next, for comparison of the reactivity of SH and NH$_2$ groups in the reaction, we adopted 4-amino-3-mercapto-4$H$-1,2,4-triazoles (6) as reagents, which have SH and NH$_2$ groups in a molecule.
In addition, the mercapto group in 6 could have thione-form, therefore it is considered that the mercapto group of 6 would be a poor nucleophile. Thus, we treated 1b with 6a in the presence of Pd\(_2\)(dba)\(_3\), Xantphos, and Cs\(_2\)CO\(_3\) in dioxane at 120 °C for 24 h, but the reaction showed complex feature and no distinct product was isolated. Then we treated 1b with 6a in BuOH under reflux for 30 min. Interestingly, the S\(_\text{N}\)Ar reaction by the NH\(_2\) group occurred and 7a was obtained in 92% yield. In the \(^1\)H NMR spectrum of 7a, two singlet signals owing to NH and SH appeared at \(\delta\) 10.58 and 13.99. In the IR spectrum of 7a, an NH signal appeared at 3292 cm\(^{-1}\). From the results, we assigned the structure. In a similar manner, the reaction of 1b with 6b and 6c gave 7b (98%) and 7c (43%), respectively.

![Scheme 3](image)

On the contrary, when 1b was treated with 6a in the presence of NaH in dry 1,4-dioxane for 10 h under reflux, the S\(_\text{N}\)Ar reaction by the sulfido group occurred and 8a was obtained in 91% yield. In the \(^1\)H NMR spectrum of 8a, a 2H singlet signal owing to NH\(_2\) appeared at \(\delta\) 5.45, and in its IR spectrum, signals owing to NH\(_2\) appeared at 3251 and 3156 cm\(^{-1}\). From the results, we assigned the structure. Similar reaction of 1b with 6b gave 8b in 85% yield, but the reaction of 1b with 6c gave no good result. It is observed that 6c decomposed by the treatment with NaH, therefore use of more weak base would be required. So we examined the reaction of 1b with 6c in the presence of K\(_2\)CO\(_3\) and 18-crown-6 in dry dioxane under refluxed for 1 h, and obtained 8c in 92% yield. In a similar manner, the reaction of 1b with 6a and 6b gave 8b (92%) and 8c (86%), respectively. Thus, each heteroarylamination and heteroarylsulfidation of 2-chloro-1-azaazulenes was achieved in the reaction of 1b with 6.
**EXPERIMENTAL**

Mps were measured using a Yanagimoto micro-melting apparatus and uncorrected. \(^1\)H NMR spectra (including HH-COSY and CH-COSY NMR) were recorded on a Bruker AVANCE 400S (400 MHz) and \(^{13}\)C NMR spectra were recorded on a Bruker AVANCE 400S (100.6 MHz) using CDCl\(_3\) as a solvent with tetramethyldisilane as an internal standard unless otherwise stated; \(J\) values are recorded in Hz. IR spectra were recorded for KBr pellets on a Nicolet FT-IR AVATAR 370DTGS unless otherwise stated. Electronic spectra were recorded with JASCO V-570 spectrophotometer. Elemental analyses were taken with a Perkin Elmer 2400II. Kieselgel 60 was used for column chromatography.

**Reaction of 2-chloro-1-azaazulenes with 2-amino-1-azaazulenes**

Typical procedure: Under argon atmosphere, a mixture of 1\(a\) (0.046 g, 0.28 mmol), 2\(a\) (0.030 g, 0.20 mmol), Xantphos (0.008 g, 0.014 mmol), Pd\(_2\)(dba)\(_3\) (0.011 g, 0.012 mmol), Cs\(_2\)CO\(_3\) (0.081 g, 0.240 mmol) in dry 1,4-dioxane (6 mL) was refluxed for 4 h, then water (20 mL) was added. The mixture was extracted with CHCl\(_3\). The extract was dried over Na\(_2\)SO\(_4\), and evaporated. Chromatography of the residue with CHCl\(_3\)-AcOEt (1 : 1) gave 3\(aa\) (0.022 g, 39%).

In a similar manner, reaction of 1\(b\), 1\(c\), and 1\(d\) with 2\(a\) and 2\(b\) gave 3\(ba\) (70%), 3\(ca\) (63%), and 3\(db\) (43%), respectively.

3\(aa\): Red powders (from CH\(_2\)Cl\(_2\)-hexane), mp 197-199 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 7.54 (2H, like t, \(J\) 9.2, H-7,7'), 7.58 (2H, like t, \(J\) 9.1, H-5,5'), 7.64 (2H, s, H-3,3'), 7.66 (2H, like t, \(J\) 10.2, H-6,6'), 8.19 (2H, d, \(J\) 9.6, H-4,4'), 8.32 (2H, dm, \(J\) 10.7, H-8,8'), and 11.6 (1H, s, NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 103.1, 129.0, 129.5, 130.2, 130.3, 132.5, 147.2, 157.3, and 163.3; \(\nu_{\max}\) / cm\(^{-1}\) 3366 (NH); \(\lambda_{\max}\) (CH\(_2\)Cl\(_2\)) nm (log \(\varepsilon\)) 260 (4.43), 282 (4.50), 339 (4.32), 411(4.34), 468 (4.11, sh), 485 (4.15), 514 (4.02, sh), and 570 (3.32, sh).

Anal. Calcd for C\(_{18}\)H\(_{13}\)N\(_3\): C, 79.68; H, 4.83; N, 15.49. Found: C, 79.77; H, 4.82; N, 15.49.

3\(ba\): Orange needles (from CH\(_2\)Cl\(_2\)-hexane), mp 189-193 °C; \(^1\)H NMR \(\delta\) 1.55 (3H, t, \(J\) 7.1, Me), 4.57 (q, \(J\) 7.1, OCH\(_2\)), 7.54 (1H, ddd, \(J\) 10.4, 9.5, and 1.2, H-5'), 7.60 (1H, ddd, \(J\) 10.0, 9.7, and 1.2, H-7'), 7.66 (1H, ddd, \(J\) 10.4, 9.7, and 0.9, H-6'), 7.69 (1H, td, \(J\) 10.0, and 0.8, H-7), 7.79 (1H, ddd, \(J\) 10.0, 9.8, and 0.3, H-6), 7.83 (1H, ddd, \(J\) 9.9, 9.8, and 0.9, H-5), 8.33 (1H, dd, \(J\) 9.5 and 0.9, H-4'), 8.36 (1H, d, \(J\) 10.0, H-8'), 8.37 (1H, s, H-3'), 8.51 (1H, dd, \(J\) 10.0 and 0.8, H-8), 9.15 (1H, d, \(J\) 9.9, H-4), and 10.71 (1H, s, NH); \(^{13}\)C NMR \(\delta\) 14.7, 60.6, 100.2, 103.9, 129.2, 130.0, 130.6, 131.5, 132.1, 132.8, 133.2, 133.3, 133.5, 134.4, 147.2, 148.4, 156.7, 160.6, 161.6, 163.5, and 165.4; \(\nu_{\max}\) / cm\(^{-1}\) 3280 (NH) and 1660 (C=O); \(\lambda_{\max}\) (CH\(_2\)Cl\(_2\)) nm (log \(\varepsilon\)) 276 (4.58, sh), 288 (4.66), 315 (4.50, sh), 335 (4.47), 420 (4.58), 464 (3.97), and 484 (4.20). Anal. Calcd for C\(_{21}\)H\(_{17}\)N\(_3\)O\(_2\): C, 79.73; H, 4.89; N, 12.24. Found: C, 79.55; H, 5.10; N, 12.03.

3\(ca\): Orange powders (from AcOEt), mp 193-195 °C; \(^1\)H NMR \(\delta\) 7.63 (1H, dd, \(J\) 10.4 and 9.9, H-5'), 7.71 (1H, dd, \(J\) 10.6 and 10.4, H-7'), 7.74 (1H, dd, \(J\) 10.6 and 9.9, H-6'), 7.91 (1H, dd, \(J\) 10.3 and 9.9, H-5), 8.03 (1H, dd, \(J\) 9.9 and 9.8, H-7), 8.04 (1H, t, \(J\) 9.9, H-6), 8.44 (1H, d, \(J\) 10.4, H-4'), 8.45 (1H, d, \(J\) 9.8,
H-8), 9.47 (1H, d, J 10.3, H-4), and 11.02 (1H, br s, NH); $^{13}$C NMR $\delta$ 104.4, 119.8, 129.5, 130.3, 132.3, 132.6, 132.8, 134.6, 135.8, 136.5, 136.7, 137.0, 141.3, 148.3, 156.3, 157.5, 159.6, and 160.0; $\nu_{\text{max}}$ / cm$^{-1}$ 3330 (NH), 1534 and 1324 (NO$_2$); $\lambda_{\text{max}}$ (CH$_2$Cl$_2$) nm (log $\varepsilon$) 270 (4.28), 298 (4.25), 329 (4.50), 348 (4.32, sh), 422 (4.31), 464 (4.11), and 492 (3.97, sh). *Anal.* Calcd for C$_{18}$H$_{12}$N$_4$O$_2$: C, 67.16; H, 4.28; N, 16.21. Found: C, 67.24; H, 4.26; N, 15.93.

3db: Dark red powders (from CHCl$_3$-AcOEt), mp 255-256 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.29 (2H, like t, J 9.1, H-6,6'), 7.32 (2H, t, J 7.6, H-p-Ph), 7.34 (2H, like t, J 9.3, H-5,5'), 7.47 (4H, dd, J 7.6 and 7.3, H-m-Ph), 7.49 (2H, like t, J 10.0, H-7, 7'), 7.78 (4H, d, J 7.3, H-o-Ph), 8.04 (2H, dm, J 10.0, H-8, 8'), and 8.05 (1H, dm, J 9.3, H-4,4') (NH was not observed); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 120.3, 122.6, 126.8, 128.1, 128.6, 130.2, 131.1, 131.8, 131.9, 133.2, 140.1, 151.6, and 163.0; $\nu_{\text{max}}$ / cm$^{-1}$ 3440 (NH); $\lambda_{\text{max}}$ (CH$_2$Cl$_2$) nm (log $\varepsilon$) 289 (4.64), 369 (4.29), 404 (4.08, sh), 468 (4.09, sh), 498 (4.19), 568 (4.40), 603 (4.41), and 650 (4.06, sh). *Anal.* Calcd for C$_{30}$H$_{21}$N$_3$: C, 85.08; H, 5.00; N, 9.92. Found: C, 85.12; H, 5.13; N, 9.74.

**Reaction of 2-chloro-1-azaazulenes with 2-mercapto-1-azaazulenes**

*Typical procedure A:* Under argon atmosphere, a mixture of 1b (0.055 g, 0.233 mmol), 4a (0.036 g, 0.223 mmol), Xantphos (0.0088 g, 0.015 mmol), Pd$_2$(dba)$_3$ (0.0146 g, 0.016 mmol), Cs$_2$CO$_3$ (0.101 g, 0.310 mmol) in dry 1,4-dioxane (6 mL) was refluxed for 24 h under stirring, then water (80 mL) was added. The mixture was extracted with CHCl$_3$. The extract was dried over Na$_2$SO$_4$, and evaporated. Chromatography of the residue with AcOEt gave 5ba (0.040 g, 50%). In a similar manner, reaction of 1c with 4a gave 5ca (38%).

5ba: Reddish brown micro needles (from CH$_2$Cl$_2$-hexane), mp 119 °C (decomp.); $^1$H NMR $\delta$ 1.54 (3H, t, J 7.1, CH$_3$), 4.53 (2H, q, J 7.1, OCH$_2$), 7.62 (1H, like t, J 9.7, H-7'), 7.72 (1H, like t, J 10.2, H-5'), 7.79 (1H, like t, J 10.0, H-6'), 7.83-7.90 (3H, m, H-5,6,7), 8.48 (1H, d, J 10.0, H-8'), 8.57 (1H, dm, J 10.6, H-8), 8.59-8.64 (1H, m, H-4'), and 9.40-9.49 (1H, m, H-4); $^{13}$C NMR $\delta$ 14.5, 60.7, 113.1, 116.5, 129.1, 129.7, 132.7, 132.9, 133.9, 134.3, 134.8, 135.4, 136.7, 137.9, 146.6, 147.2, 157.0, 159.1, 164.0, and 167.3; $\nu_{\text{max}}$ / cm$^{-1}$ 1685 (C=O). *Anal.* Calcd for C$_{21}$H$_{16}$N$_2$O$_2$: C, 69.98; H, 4.47; N, 7.77. Found: C, 70.07; H, 4.32; N, 7.83.

5ca: Red micro needles (from CH$_2$Cl$_2$-hexane), mp 216 °C (decomp.); $^1$H NMR $\delta$ 7.72 (1H, like t, J 9.7, H-5'), 7.82 (1H, like t, J 9.3, H-6'), 7.90 (like t, J 9.8, H-7'), 8.03-8.15 (3H, m, H-5,6,7), 8.60 (1H, d, J 9.8, H-4'), 8.68 (1H, dm, J 9.6, H-8'), 8.69 (1H, dm, J 9.8, H-8), and 9.65 (1H, dm, J 9.6, H-4); $^{13}$C NMR $\delta$ 117.5, 123.3, 129.3, 129.9, 134.7, 135.1, 135.2, 135.8, 135.9, 136.4, 137.8, 138.1, 139.8, 140.5, 145.0, 146.8, 157.2, and 163.5; $\nu_{\text{max}}$ / cm$^{-1}$ 1481, 1394 (NO$_2$). *Anal.* Calcd for C$_{18}$H$_{12}$N$_2$O$_2$: C, 64.85; H, 3.33; N, 12.60. Found: C, 65.02; H, 3.32; N, 12.81.

*Typical procedure B:* A mixture of 4a (0.151 g, 0.936 mmol) and 60% NaH (0.047 g, 1.17 mmol) in...
dioxane (10 mL) was stirred for 30 min at rt. Then 1a (0.212 g, 1.23 mmol) was added to the mixture, and the mixture was refluxed for 4 h then water (20 mL) was added. The mixture was extracted with CHCl$_3$. The extract was dried over Na$_2$SO$_4$, and evaporated. Chromatography on alumina of the residue with CHCl$_3$-AcOEt (1 : 1) gave 5aa (0.240 g, 88%).

In a similar manner, reaction of 1b and 1c with 4a and 4b gave 5ba (71%), 5ca (80%), and 5cb (85%), respectively.

5aa: Red micro needles (from CH$_2$Cl$_2$-hexane), mp 217-219 ºC; $^1$H NMR (CDCl$_3$) $\delta$ 7.78 (2H, s, H-3,3$'$), 7.63 (dd, 2H, ddd, J 10.2, 9.9, and 1.3, H-7,7$'$), 7.76 (2H, ddd, J 10.2, 9.9, and 1.0, H-6,6$'$), 8.41 (2H, d, J 9.9, H-4,4$'$), and 8.58 (2H, dd, J 10.1 and 1.3, H-8,8$'$); $^{13}$C NMR $\delta$ 114.5, 129.4, 130.0, 133.4, 134.0, 136.6, 146.8, 157.8, and 164.4. Anal. Calcd for C$_{18}$H$_{12}$N$_2$S: C, 74.97; H, 4.19; N, 9.71. Found: C, 74.75; H, 4.32; N, 9.84.

5cb: Yellow micro needles (from CH$_2$Cl$_2$-hexane), mp 203-204 ºC; $^1$H NMR (DMSO-d$_6$) $\delta$ 7.99-8.06 (1H, m, H-5), 8.08-8.13 (2H, m, H-5$'$,7$'$), 8.17-8.22 (3H, m, H-5$'$,7$'$,8$'$), 8.63 (1H, d, J 9.5, H-8), 8.87-8.94 (2H, m, H-4$'$,8$'$), and 9.61-9.68 (1H, m, H-4); $^{13}$C NMR $\delta$ 134.1, 134.7, 134.8, 135.0, 135.3, 135.4, 135.7, 138.3, 139.1, 139.3, 140.4, 157.6, 163.1, and 164.1; $\nu_{\text{max}}$ / cm$^{-1}$ 1485, 1304 (NO$_2$); $\lambda_{\text{max}}$ nm (log $\varepsilon$) 253 (4.55), 286 (4.32), 335 (4.37), 351 (4.37), 387 (4.28), and 465 (2.89, sh). Anal. Calcd for C$_{17}$H$_{10}$N$_4$O$_2$S: C, 61.07; H, 3.01; N, 16.76. Found: C, 61.26; H, 3.07; N, 16.52.

Reaction of ethyl 2-chloro-1-azaazulene-3-carboxylate with 4-amino-3-mercapto-4H-1,2,4-triazoles

Typical procedure: A mixture of 1b (0.059 g, 0.25 mmol), 4-amino-3-mercapto-4H-1,2,4-triazole (6a) (0.059 g, 0.51 mmol) in BuOH (5 mL) was refluxed for 30 min. To the mixture hexane was added, and the trituration of the mixture gave yellow solid. The solid was collected by filtration and washed with Et$_2$O to give 7a (0.073 g, 92%) as yellow powders.

In a similar manner, reaction of 1b with 6b and 6c gave 7b (98%) and 7c (43%), respectively.

7a: Yellow powders (from CH$_2$Cl$_2$-hexane), mp 169 ºC (decomp.); $^1$H NMR (DMSO-d$_6$) $\delta$ 1.41 (3H, t, J 7.1, Me), 4.46 (2H, q, J 7.1, OCH$_2$), 8.03-8.13 (3H, m, H-5,6,7), 8.32-8.40 (2H, m, H-4$'$,8$'$), 9.19 (1H, dm, J 9.9, H-4), 10.58 (1H, br s, NH), and 13.99 (1H, s, SH); $\nu_{\text{max}}$ / cm$^{-1}$ 3292 (NH), 1673 (C=O); $\lambda_{\text{max}}$ (DMSO) nm (log $\varepsilon$) 290 (4.66), 361 (3.85), and 435 (3.65). Anal. Calcd for C$_{14}$H$_{13}$N$_5$O$_2$S·H$_2$O: C, 50.44; H, 4.54; N, 21.01. Found: C, 50.15; H, 4.46; N, 21.30.

7b: Yellow powders (from CH$_2$Cl$_2$-hexane), mp 217 ºC (decomp.); $^1$H NMR (DMSO-d$_6$) $\delta$ 1.43 (3H, t, J 7.1, Me), 2.43 (3H, s, Me), 4.47 (2H, q, J 7.1, OCH$_2$), 8.05-8.12 (3H, m, H-5,6,7), 8.34-8.38 (1H, m, H-8), 9.19 (1H, dm, J 9.8, H-4), 10.48 (1H, br s, NH), and 14.86 (1H, s, SH); $\nu_{\text{max}}$ / cm$^{-1}$ 3270 (NH), 1701 (C=O); $\lambda_{\text{max}}$ (EtOH) nm (log $\varepsilon$) 243 (4.32), 260 (4.27), 290 (4.58), 354 (3.85), and 427 (3.33). Anal. Calcd for C$_{15}$H$_{15}$N$_5$O$_2$S·2H$_2$O: C, 49.31; H, 5.24; N, 19.17. Found: C, 49.29; H, 4.49; N, 19.43.
7c: Yellow powders (from CH₂Cl₂-hexane), mp 215 °C (decomp.);¹H NMR δ 1.40 (3H, t, J 7.1, Me), 4.42 (2H, q, J 7.1, OCH₂), 7.92-8.08 (3H, m, H-5,6,7), 8.25-8.30 (1H, m, H-8), 9.12 (1H, dm, J 10.2, H-4), 14.54 (1H, s, NH), and 14.86 (1H, s, SH); νmax / cm⁻¹ 3286 (NH), 1701 (C=O); λmax (DMSO) nm (log ε) 297 (4.66), 357 (3.94), and 430 (3.53). Anal. Caled for C₁₅H₁₂N₅O₂F₃S: C, 47.00; H, 3.16; N, 18.27. Found: C, 47.19; H, 3.29; N, 18.10.

**Reaction of ethyl 2-chloro-1-azaazulene-3-carboxylate with 4-amino-3-mercapto-4H-1,2,4-triazoles in the presence of base**

**Typical procedure A:** A mixture of 6a (0.1016 g, 0.875 mmol) and 60% NaH (0.071 g, 1.75 mmol) in dioxane (8 mL) was stirred for 30 min at rt. Then 1a (0.212 g, 1.23 mmol) was added to the mixture, and the mixture was refluxed for 10 h, then water (20 mL) was added. The mixture was extracted with CHCl₃. The extract was dried over Na₂SO₄, and evaporated. The mixture was evaporated and the residue was chromatographed with AcOEt to give 1b (0.0051 g, 5%) and 8a (0.1307 g, 91%). In a similar manner, reaction of 1b with 6b gave 8b (85%).

8a: Yellow needles (from CH₂Cl₂-hexane), mp 173 °C (decomp.);¹H NMR δ 1.43 (3H, t, J 7.1, Me), 2.43 (3H, s, Me), 4.47 (2H, q, J 7.1, OCH₂), 5.45 (2H, s, NH₂), 7.92 (1H, ddd, J 10.1, 9.7, and 1.2, H-5), 7.96 (1H, ddd, J 10.1, 9.4, and 1.3, H-6), 8.01 (1H, ddd, J 9.8, 9.4, and 1.3, H-7), 8.47 (1H, d, J 9.8, H-8), 8.53 (1H, s, H-5'), and 9.47 (1H, dd, J 9.7 and 1.3, H-4); ¹³C NMR (DMSO-d₆) δ 14.5, 61.1, 112.3, 133.3, 133.7, 135.8, 136.2, 139.1, 147.1, 147.3, 147.6, 158.9, 163.7, and 166.5; νmax / cm⁻¹ 3251, 3156 (NH), 1698 (C=O); λmax (CH₂Cl₂) nm (log ε) 250 (4.26), 298 (4.57), 355 (4.03), 450 (3.19). Anal. Caled for C₁₅H₁₅N₃O₂S·2H₂O: C, 50.44; H, 4.54; N, 21.01. Found: C, 50.18; H, 4.49; N, 21.22.

8b: Yellow powders (from CH₂Cl₂-hexane), mp 225 °C (decomp.);¹H NMR δ 1.54 (3H, t, J 7.1, Me), 2.62 (3H, s, Me), 4.54 (2H, q, J 7.1, OCH₂), 5.29 (2H, br s, NH₂), 7.91 (1H, ddd, J 10.2, 9.7, and 1.3, H-5), 7.95 (1H, ddd, J 10.2, 9.3, and 1.4, H-6), 8.01 (1H, ddd, J 9.8, 9.3, and 1.4, H-7), 8.47 (1H, d, J 9.8, H-8), and 9.46 (1H, dd, J 9.7 and 1.4, H-4); νmax / cm⁻¹ 3247, 3147 (NH), 1699 (C=O); λmax (CH₂Cl₂) nm (log ε) 251 (4.59), 299 (4.51), 312 (4.31, sh), 357 (4.00), and 453 (3.18). Anal. Caled for C₁₅H₁₅N₃O₂S·2H₂O: C, 49.17; H, 5.50; N, 19.11. Found: C, 49.41; H, 5.35; N, 19.03.

**Typical procedure B:** A mixture of 6a (0.060 g, 0.52 mmol), K₂CO₃ (0.059 g, 0.43 mmol), and 18-crown-6 (0.229 g, 0.87 mmol) in dioxane (5 mL) was stirred for 30 min at rt. Then 1b (0.061 g, 0.26 mmol) was added to the mixture, and the mixture was refluxed for 1 h. The mixture was evaporated and the residue was chromatographed with AcOEt to give 8a (0.074 mg, 92%) as yellow powders. In a similar manner, reaction of 1b with 6b and 6c gave 8b (86%) and 8c (92%), respectively.

8c: Yellow needles (from CH₂Cl₂-hexane), mp 207-210 °C;¹H NMR δ 1.54 (3H, t, J 7.1, Me), 4.55 (2H, q, J 7.1, OCH₂), 5.58 (2H, s, NH₂), 7.95 (1H, ddd, J 10.2, 9.6, and 1.2, H-5), 7.99 (1H, dddd, J 10.2, 9.9,
1.4, and 0.8, H-6), 8.04 (1H, ddd, J 9.9, 9.8, and 1.2, H-7), 8.49 (1H, dd, J 9.8, and 0.8, H-7), and 9.48 (1H, dd, J 9.6 and 1.4, H-4); 13C NMR δ 14.5, 61.2, 112.4, 117.8 (average of 114.6, 116.7, 118.9, and 121.0, q, J 270.9, CF3), 133.6, 133.9, 136.2, 136.6, 139.6, 147.0, 147.5 (average of 147.0, 147.3, 147.6, and 147.9, q, J 39.7, CCF3), 151.4, 158.8, 163.5, and 164.1; vmax / cm
-1 3320, 3193 (NH), 1687 (C=O); λmax (CH2Cl2) nm (log ε) 246 (4.29), 296 (4.63), 352 (4.05), 451 (3.21), and 476 (3.01, sh). Anal. Calcd for C15H12N5O2F3S: C, 47.00; H, 3.16; N, 18.27. Found: C, 46.82; H, 3.21; N, 18.45.

REFERENCES AND NOTES