HETEROCYCLES, Vol. 78, No. 12, 2009, pp. 3065 - 3072. © The Japan Institute of Heterocyclic Chemistry
Received, 31th July, 2009, Accepted, 15th September, 2009, Published online, 17th September, 2009
DOI: 10.3987/COM-09-11806

HETEROARYLAMINATION AND HETEROARYLSULFIDATION OF 2-CHLORO-1-AZAAZULENES

Eiko Yoshioka,[1] Kazuya Koizumi,[1] Shinya Yamazaki,[1] Hiroyuki Fujii,[2] and Noritaka Abe[1]*

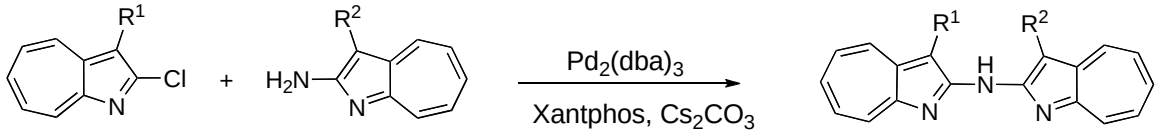
[1]Graduate School of Medicine, and Department of Biology and Chemistry, Faculty of Science, Yamaguchi University, Yoshida, Yamaguchi 753-8512, Japan
[2] Science Research Center, Yamaguchi University, Yamaguchi 753-8512, Japan

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-4*H*-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 azaazulenes[1] is of interest for their physiological properties[2,3] 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 heteroarylaminatition 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-mercapto-4*H*-1,2,4-triazoles.

Treatment of 2-chloro-1-azaazulene (**1a**) with 2-amino-1-azaazulene (**2a**) in the presence of $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 in dioxane under reflux for 4 h gave bis(1-azaazulen-2-yl)amine (**3aa**) in 39% yield. The ^{1}H NMR spectrum of **3aa** was symmetrical and the ^{13}C 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.



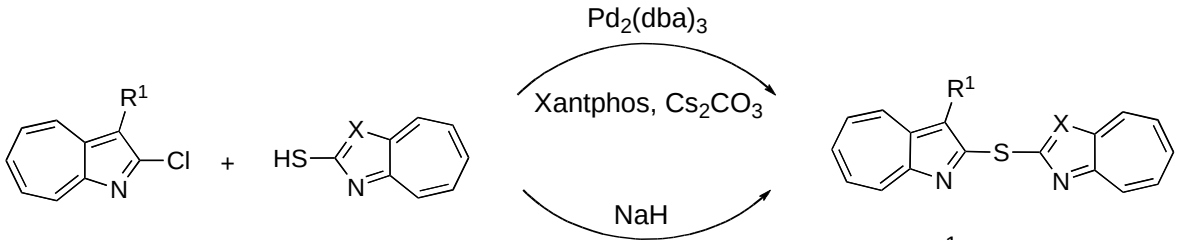
1a : R^1 = H
1b : R^1 = CO_2Et
1c : R^1 = NO_2
1d : R^1 = Ph

2a : R^2 = H
2b : R^2 = Ph

3aa : R^1= R^2 = H
3ba : R^1 = CO_2Et, R^2 = H
3ca : R^1 = NO_2, R^2 = H
3db : R^1 = R^2= Ph

Scheme 1

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_2CO_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_NAr reaction was within the bounds of possibility, because it is known that S_NAr reaction occurs in the reaction of 2-chloro-1-azaazulenes with good nucleophile, such as alkoxide and sulfoxide.[1] 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_NAr reaction on S-atom and gave bis(1-azaazulen-2-yl) sulfides, and heteroarylamination on N-1 atom of **4** did not proceed.



1a : R^1 = H
1b : R^1 = CO_2Et
1c : R^1 = NO_2

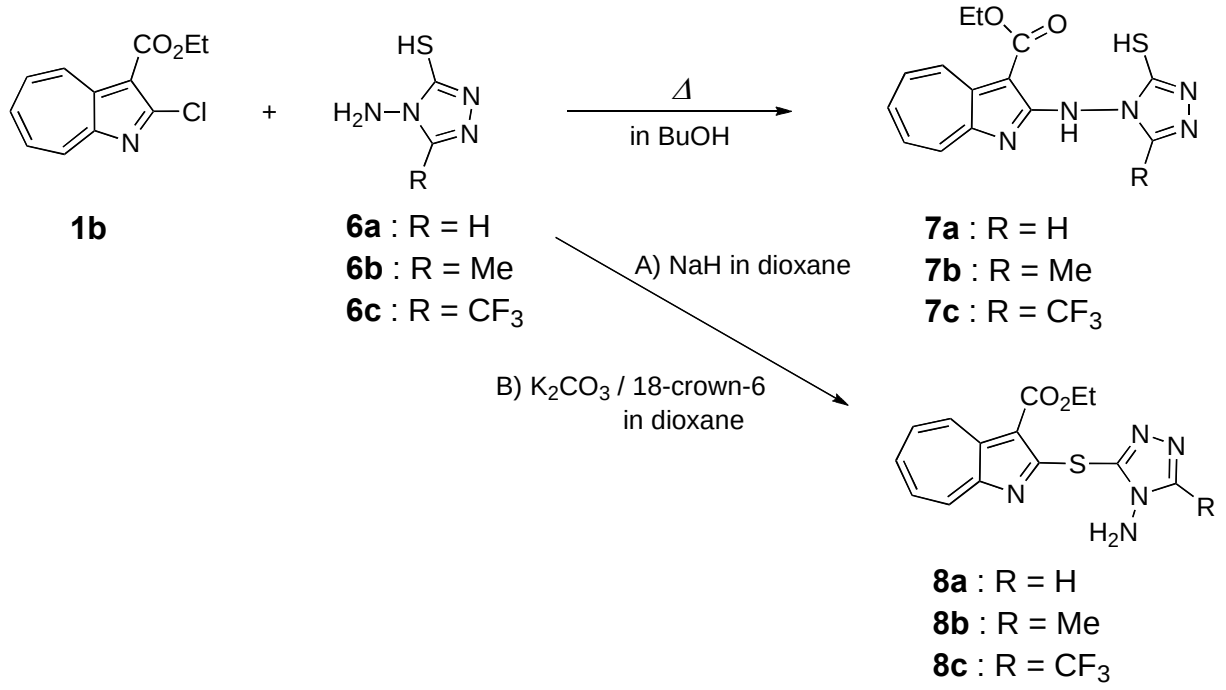
4a : X = CH
4b : X = N

5aa : R^1 = H, X = CH
5ba : R^1 = CO_2Et, X = CH
5ca : R^1 = NO_2, X = CH
5cb : R^1 = NO_2, X = N

Scheme 2

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_2CO_3 in dioxane at 120 ºC 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_NAr reaction by the NH_2 group occurred and **7a** was obtained in 92% yield. In the ^1H NMR spectrum of **7a**, two singlet signals owing to NH and SH appeared at δ 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

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_NAr reaction by the sulfido group occurred and **8a** was obtained in 91% yield. In the ^1H NMR spectrum of **8a**, a 2H singlet signal owing to NH_2 appeared at δ 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_2CO_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 tetramethylsilane 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 **1a** (0.046 g, 0.28 mmol), **2a** (0.030 g, 0.20 mmol), Xantphos (0.008 g, 0.014 mmol), $Pd_2(dba)_3$ (0.011 g, 0.012 mmol), Cs_2CO_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_2SO_4, and evaporated. Chromatography of the residue with $CHCl_3$-AcOEt (1 : 1) gave **3aa** (0.022 g, 39%).

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

3aa: Red powders (from CH_2Cl_2-hexane), mp 197-199 ºC; ^{1}H NMR (DMSO-d_6) δ 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) δ 103.1, 129.0, 129.5, 130.2, 130.3, 132.5, 147.2, 157.3, and 163.3; ν_{max} / cm^{-1} 3366 (NH); λ_{max} (CH_2Cl_2) nm (log ε) 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, 15.35.

3ba: Orange needles (from CH_2Cl_2-hexane), mp 189-193 ºC; ^{1}H NMR δ 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 δ 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; ν_{max} / cm^{-1} 3280 (NH) and 1660 (C=O); λ_{max} (CH_2Cl_2) nm (log ε) 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 $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.55; H, 5.10; N, 12.03.

3ca: Orange powders (from AcOEt), mp 193-195 ºC; ^{1}H NMR δ 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 δ 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; ν_{max} / cm^{-1} 3330 (NH), 1534 and 1324 (NO_2); λ_{max} (CH_2Cl_2) nm (log ε) 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 $C_{18}H_{12}N_4O_2$·1/3AcOEt: 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 ºC; ^{1}H NMR (DMSO-d_6) δ 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) δ 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; ν_{max} / cm^{-1} 3440 (NH); λ_{max} (CH_2Cl_2) nm (log ε) 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_2CO_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_2SO_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_2Cl_2-hexane), mp 119 °C (decomp.); ^{1}H NMR δ 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 δ 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; ν_{max} / cm^{-1} 1685 (C=O). *Anal*. Calcd for $C_{21}H_{16}N_2O_2S$: 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_2Cl_2-hexane), mp 216 °C (decomp.); ^{1}H NMR δ 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 δ 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; ν_{max} / cm^{-1} 1481, 1394 (NO_2). *Anal*. Calcd for $C_{18}H_{11}N_3O_2S$: 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_2SO_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_2Cl_2-hexane), mp 217-219 ºC; ^{1}H NMR ($CDCl_3$) δ 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'), 7.81 (2H, ddd, *J* 10.2, 9.9, and 1.0, H-5,5'), 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 δ 114.5, 129.4, 130.0, 133.4, 134.0, 136.6, 146.8, 157.8, and 164.4. *Anal*. Calcd for $C_{18}H_{12}N_2S$: 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_2Cl_2-hexane), mp 203-204 ºC; ^{1}H NMR δ 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), 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 δ 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; ν_{max} / cm^{-1} 1485, 1304 (NO_2); λ_{max} nm (log ε) 253 (4.55), 286 (4.32), 335 (4.37), 351 (4.37), 387 (4.28), and 465 (2.89, sh). *Anal*. Calcd for $C_{17}H_{10}N_4O_2S$: 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-4*H*-1,2,4-triazoles

Typical procedure: A mixture of **1b** (0.059 g, 0.25 mmol), 4-amino-3-mercapto-4*H*-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_2O 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_2Cl_2-hexane), mp 169 ºC (decomp.); ^{1}H NMR (DMSO-d_6) δ 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 (1H, m, H-8), 8.81 (1H, s, H-5'), 9.19 (1H, dm, *J* 9.9, H-4), 10.58 (1H, br s, NH), and 13.99 (1H, s, SH); ν_{max} / cm^{-1} 3292 (NH), 1673 (C=O); λ_{max} (DMSO) nm (log ε) 290 (4.66), 361 (3.85), and 435 (3.65). *Anal*. Calcd for $C_{14}H_{13}N_5O_2S\cdot H_2O$: C, 50.44; H, 4.54; N, 21.01. Found: C, 50.15; H, 4.46; N, 21.30.

7b: Yellow powders (from CH_2Cl_2-hexane), mp 217 ºC (decomp.); ^{1}H NMR (DMSO-d_6) δ 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); ν_{max} / cm^{-1} 3270 (NH), 1701 (C=O); λ_{max} (EtOH) nm (log ε) 243 (4.32), 260 (4.27), 290 (4.58), 354 (3.85), and 427 (3.33). *Anal*. Calcd for $C_{15}H_{15}N_5O_2S\cdot 2H_2O$: C, 49.31; H, 5.24; N, 19.17. Found: C, 49.29; H, 4.49; N, 19.43.

7c: Yellow powders (from CH_2Cl_2-hexane), mp 215 ºC (decomp.); ^{1}H NMR δ 1.40 (3H, t, *J* 7.1, Me), 4.42 (2H, q, *J* 7.1, OCH_2), 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); ν_{max} / cm^{-1} 3286 (NH), 1701 (C=O); λ_{max} (DMSO) nm (log ε) 297 (4.66), 357 (3.94), and 430 (3.53). *Anal*. Calcd for $C_{15}H_{12}N_5O_2F_3S$: 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-4*H*-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 (0.07 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 $CHCl_3$. The extract was dried over Na_2SO_4, 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 CH_2Cl_2-hexane), mp 173 ºC (decomp); ^{1}H NMR δ 1.43 (3H, t, *J* 7.1, Me), 2.43 (3H, s, Me), 4.47 (2H, q, *J* 7.1, OCH_2), 5.45 (2H, s, NH_2), 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); ^{13}C NMR (DMSO-d_6) 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; ν_{max} / cm^{-1} 3251, 3156 (NH), 1698 (C=O); λ_{max} (CH_2Cl_2) nm (log ε) 250 (4.26), 298 (4.57), 355 (4.03), 450 (3.19). *Anal*. Calcd for $C_{19}H_{15}N_3O_2S\cdot H_2O$: C, 50.44; H, 4.54; N, 21.01. Found: C, 50.18; H, 4.49; N, 21.22.

8b: Yellow powders (from CH_2Cl_2-hexane), mp 225 ºC (decomp.); ^{1}H NMR δ 1.54 (3H, t, *J* 7.1, Me), 2.62 (3H, s, Me), 4.54 (2H, q, *J* 7.1, OCH_2), 5.29 (2H, br s, NH_2), 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); ν_{max} / cm^{-1} 3247, 3147 (NH), 1699 (C=O); λ_{max} (CH_2Cl_2) nm (log ε) 251 (4.59), 299 (4.51), 312 (4.31, sh), 357 (4.00), and 453 (3.18). *Anal*. Calcd for $C_{15}H_{15}N_5O_2S\cdot 2H_2O$: 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), K_2CO_3 (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 CH_2Cl_2-hexane), mp 207-210 ºC; ^{1}H NMR δ 1.54 (3H, t, *J* 7.1, Me), 4.55 (2H, q, *J* 7.1, OCH_2), 5.58 (2H, s, NH_2), 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); ^{13}C 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, $\underline{C}F_3$), 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, $\underline{C}CF_3$), 151.4, 158.8, 163.5, and 164.1; ν_{max} / cm^{-1} 3320, 3193 (NH), 1687 (C=O); λ_{max} (CH_2Cl_2) nm (log ε) 246 (4.29), 296 (4.63), 352 (4.05), 451 (3.21), and 476 (3.01, sh). *Anal.* Calcd for $C_{15}H_{12}N_5O_2F_3S$: C, 47.00; H, 3.16; N, 18.27. Found: C, 46.82; H, 3.21; N, 18.45.

REFERENCES AND NOTES

1. For reviews see, N. Abe, '*Recent Research Developments in Organic and Bioorganic Chemistry*'2001, **4**, 14, Transworld Research Network; T. Nishiwaki and N. Abe, *Heterocycles*, 1981, **15**, 547; M. Kimura, *Yuki Gosei Kagaku Kyokai Shi*, 1981, **39**, 690.
2. T. Ishikawa and A. Zeimoto, *Jpn. Kokai Tokkyo Koho*, JP 1999, 11,255,746.
3. M. Nagahara, J. Nakano, M. Miura, T. Nakamura, and K. Uchida, *Chem. Pharm. Bull*., 1994, **42**, 2491.
4. D. Lednicer, *Strategies for Organic Drug Synthesis and Design*; John Wiley and Sons, New York, 1998.
5. S. Tasler, J. Mies, and M. Lang, *Adv. Synth. Catal*., 2007, **349**, 2286.
6. R. Jiang, D. Duckett, W. Chen, J. Habel, Y. Y. Ling, P. Lograsso, and T. M. Kamenecka, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6378.
7. W. Huang, W. Zheng, D. J. Urban, J. Inglese, E. Sidransky, C. P. Austin, and C. J. Thomas, *Bioorg. Med. Chem. Lett*., 2007, **17**, 5783.
8. P. Ballard, B. C. Barlaam, R. H. Bradbury, A. Dishington, L. F. A. Hennequin, D. M. Hickinson, I. M. Hollingsworth, J. G. Kettle, T. Klinowska, D. J. Oglivie, S. E. Pearson, J. S. Scott, A. Suleman, R. Whittaker, E. J. Williams, R. Wood, and L. Wright, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6326.
9. For the reviews on the Pd-catalyzed amination reactions, see (a) J. F. Hartwig, *Angew. Chem. Int. Ed*., 1998, **37**, 2046; (b) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res*., 1998, **31**, 805; (c) B. H. Yang and S. L. Buchwald, *J. Organometal. Chem*., 1999, **576**, 125; D. Prim, J.-M. Campagne, D. Joseph, and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.
10. K. Koizumi, K. Shimabara, A. Takemoto, S. Yamazaki, N. Yamauchi, H. Fujii, M. Kurosawa, T. Konakahara, and N. Abe, *Heterocycles*, 2009, **79**, 319.