ORGANIC LETTERS

2006
Vol. 8, No. 24
5621−5624

Synthesis of 2-Azaindolizines by Using an Iodine-Mediated Oxidative Desulfurization Promoted Cyclization of *N*-2-Pyridylmethyl Thioamides and an Investigation of Their Photophysical Properties

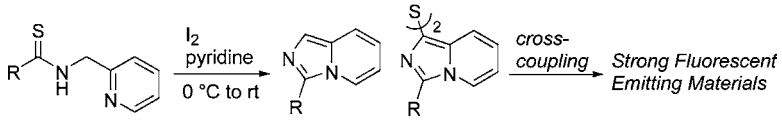
Fumitoshi Shibahara,* Asumi Kitagawa, Eiji Yamaguchi, and Toshiaki Murai*

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan

fshiba@gifu-u.ac.jp; mtoshi@gifu-u.ac.jp

Received September 26, 2006

ABSTRACT



Iodine-mediated, oxidative desulfurization promoted cyclization of *N*-2-pyridylmethyl thioamides serves as an efficient and versatile method for the preparation of 2-azaindolizines (imidazo[1,5-a]pyridines) and rare 2-azaindolizine sulfur-bridged dimers. The 2-azaindolizines prepared in this manner are readily converted to a variety of fluorescent compounds by using transition-metal-catalyzed cross-coupling reactions.

Bicyclic heteroaromatics, in which the nitrogen atom is located at ring-fusion positions, comprise an important family of compounds owing to their unique photophysical and biological properties.[1] Recently, increasing attention has been given to members of this family that contain the imidazo[1,5-a]-pyridine (2-azaindolizine) skeleton.[2−5] Potential applications of these substances have been actively probed in the context of organic light-emitting diodes (OLED)[2] and organic thin-layer field effect transistors (FET).[3] In addition, 2-azaindolizines have been investigated as pharmaceuticals (eg., HIV-protease inhibitors)[4] and as precursors of N-heterocyclic carbenes[5] whose synthesis and applications are now under active exploration. Despite this high interest, existing synthetic routes which target 2-azaindolizines, relying mainly on traditional Vilsmeier-type cyclizations of *N*-2-pyridylmethyl amides, are only modestly efficient.[6] Consequently, an efficient synthetic approach to a wide variety of 2-azaindolizines is in strong demand.[7,8] Methods that enable preparation of 2-azaindolizines, which contain functional groups that can be transformed to π-conjugated systems, would be

(1) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Black Science: Oxford, U.K., 2000; Chapter 25.

(2) (a) Nakatsuka, M.; Shimamura, T. Jpn. Kokai Tokkyo Koho JP 2001035664; *Chem. Abstr.* **2001**, *134*, 170632. (b) Tominaga, G.; Kohama, R.; Takano, A. Jpn. Kokai Tokkyo Koho JP 2001006877; *Chem. Abstr.* **2001**, *134*, 93136. (c) Kitazawa, D.; Tominaga, G.; Takano, A. Jpn. Kokai Tokkyo Koho JP 2001057292; *Chem. Abstr.* **2001**, *134*, 200276.

(3) Nakamura, H.; Yamamoto, H. PCT Int. Appl. WO 2005043630; *Chem. Abstr.* **2005**, *142*, 440277.

(4) (a) Degoey, D. A.; Flentge, C. A.; Flosi, W. J.; Grampovnik, D. J.; Kempf, D. J.; Klein, L. L.; Yeung, M. C.; Randolph, J. T.; Wang, X. C.; Yu, S. U.S. Pat. Appl. Publ. U.S. 2005148623; *Chem. Abstr.* **2005**, *143*, 133693. (b) Kim, D. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129. See Supporting Information for full list of authors.

(5) (a) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290. (b) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207. (c) Hahn, F. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1348.

(6) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834.

(7) For recent advances in the synthesis of 2-azaindolizines via an acetic acid mediated condensation pathway, see: (a) Wang, J.; Mason, R.; VanDerveer, K.; Feng, D.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415. (b) Dyers, J. W. L., Jr.; Mason, R., Jr.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353 and references cited therein.

(8) For recent advances in the synthesis of 2-azaindolizines via an oxidative pathway, see: (a) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962. (b) Bluhm, M. E.; Folli, C.; Pufky, D.; Kröger, M.; Walter, O.; Döring, M. *Organometallics* **2005**, *24*, 4139 and references cited therein.

10.1021/ol0623623 CCC: $33.50
Published on Web 10/25/2006

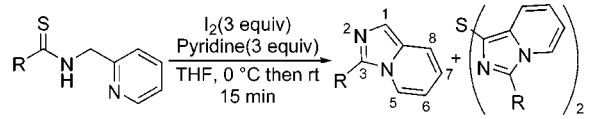
particularly attractive because they can be used to generate substances with fine-tuned photophysical properties.

Below, we describe a new procedure to access 2-azaindolizines that relies on iodine-mediated, oxidative desulfurization promoted cyclizations of *N*-2-pyridylmethyl thioamides.[9,10] Also, efforts leading to the introduction of aromatic substituents into the 2-azaindolizine product by using a transition-metal-catalyzed cross-coupling reaction is described. Finally, the photophysical properties of the derived 2-azaindolizines are reported.

In initial studies exploring the iodine-mediated, oxidative desulfurization promoted cyclization process, *N*-2-pyridylmethyl-2-pyridinecarbothioamide (**1a**) was reacted with iodine (3 equiv) in the presence of pyridine (3 equiv) in THF for 15 min (entry 1 in Table 1). The reaction generated the 2-azaindolizine **2a** in 89% yield along with a rare compound, the sulfur-bridged 2-azaindolizine dimer **3a**[11] in 7% yield. The structures **2a** and **3a** were confirmed by X-ray crystallographic analysis (Figure 1).[12] A wide range of thioamides **1** participate in this cyclization reaction (entries 2−10), efficiently yielding the corresponding 2-azaindolizines **2** independent of the electronic nature of substituents on the aromatic rings. Moreover, the reactions can be carried out on a multigram scale with the same efficiencies observed in corresponding small-scale reactions (entries 2, 4, 5, 7, and 9). It is noteworthy that this process is used to generate the bromo-2-azaindolizine **2e**, a possible precursor for transition-metal-catalyzed cross-coupling reactions.[13] Heteroaromatic substituents in the starting material (e.g., **1a** and **1i**) do not alter the efficiencies of the reaction (entries 1 and 9), but the alkyl-substituted substrate **1j** reacts to give the 2-azaindolizine **2j** in slightly lower yield (entry 10). In this case, decomposition of the product **2j** was observed during purification.

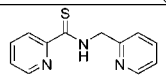
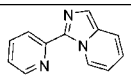
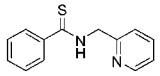
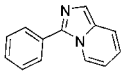
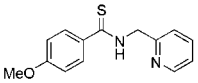
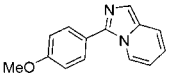
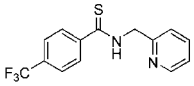
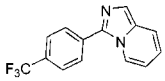
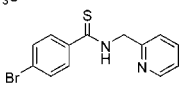
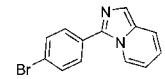
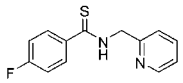
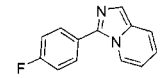
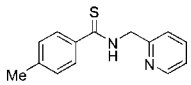
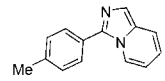
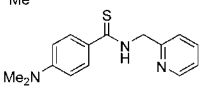
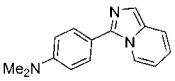
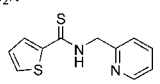
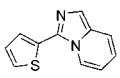
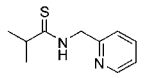
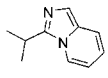
Attention was given to the formation of the sulfur-bridged dimer **3**. Reaction of **1a** with iodine and pyridine in THF for 21 h leads to formation of 2-azaindolizine **2a** in 57% and the sulfur-bridged dimer **3a** in 32% yield (entry 1 in Table 2). Reaction of these substrates in DMF affords **3a** in an elevated 45% yield (entry 2). Likewise, other thioamides **1b**−**d** are converted to analogous sulfur-bridged dimers **3** (entries 3−5). Interestingly, reaction of thioamide **1c**, which contains an aromatic OMe substituent, produces **3c** in 66%

Table 1. Iodine-Mediated Oxidative Desulfurization Promoted Cyclization of Thioamides **1** Leading to 2-Azaindolizines **2**[a]



R = 2-Py-, **1a**; Ph-, **1b**; 4-MeO-C_6H_4-, **1c**; 4-F_3C-C_6H_4-, **1d**; 4-Br-C_6H_4-, **1e**; 4-F-C_6H_4-, **1f**; 4-Me-C_6H_4-, **1g**; 4-Me_2N-C_6H_4-, **1h**; 2-thenyl-, **1i**; *i*Pr-, **1j**

2 **3**

entry	substrate **1**	scale (mmol)	product		yield (%)[b]
1		1		**2a**	89[c]
2		31		**2b**	84
3		1		**2c**	89
4		23		**2d**	95
5		1		**2e**	89[d]
6		3		**2f**	89
7		9		**2g**	87
8		3		**2h**	83
9		10		**2i**	81
10		1		**2j**	59

[a] Iodine and pyridine were added to a 0.5 M THF solution of thioamides **1** at 0 °C, and then the reaction mixture was stirred at rt for 15 min. [b] Isolated yields. [c] Sulfur-bridged 2-azaindolizine dimer **3a** was also isolated in 7% yield. [d] 10 mmol scale: 80% yield.

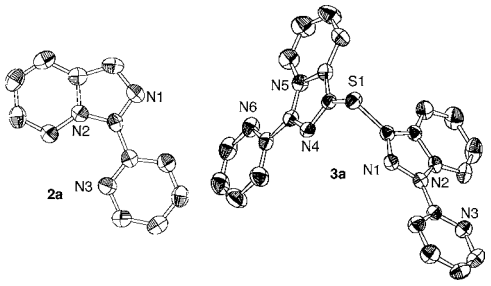


Figure 1. ORTEP plots of the molecular structures of 2-azaindolizine **2a** and sulfur-bridged 2-azaindolizine dimer **3a** (thermal ellipsoids drawn at the 50% probability level). Hydrogen atoms have been omitted for clarity.

(9) Starting thioamides are readily prepared by the three-component Willgerodt−Kindler reaction of an aldehyde, amine, and elemental sulfur. See: Brown, E. V. *Synthesis* **1975**, 358.

(10) For examples of our recent studies on thioamides, see: (a) Murai, T.; Niwa, H.; Kimura, T.; Shibahara, F. *Chem. Lett.* **2004**, *33*, 508. (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (c) Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, *70*, 8148. (d) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312.

(11) As only one example of compound **3**, **3b**, was reported, see: Glover, E. E.; Vaughan, K. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, *21*, 2595.

(12) See Supporting Information.

(13) The reaction of 2-pyridylmethyl 4-bromobenzenecarboamide with $P(O)Cl_3$ did not give the desired 3-(4-bromophenyl)-2-azaindolizine under the traditional Vilsmeier conditions[6] (in toluene under reflux for 4 h), but instead, insoluble material was precipitated.

Table 2. Iodine-Mediated Desulfurization−Cyclization of **1** Leading to Sulfur-Bridged 2-Azaindolizine Dimer **3**[a]

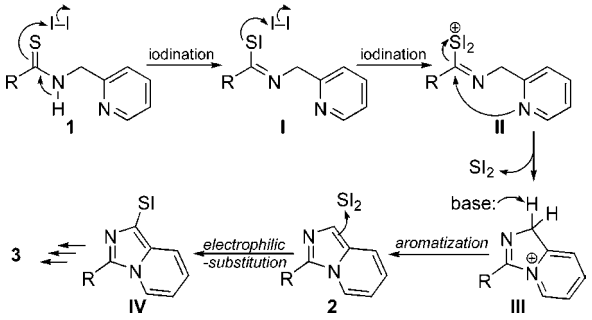
entry	substrate	solvent	yield(%) **2**	yield(%) **3**
1	**1a**	THF	57	32
2	**1a**	DMF	29	45
3	**1b**	DMF	47	31
4	**1c**	DMF	26	66
5	**1d**	DMF	51	35

[a] Reactions were carried out at rt for 21 h.

yield, whereas reaction of the CF_3-substituted thioamide **1d** gives **3d** in lower yield (entry 5).

A plausible mechanism for the novel cyclization reaction leading to 2-azaindolizines is displayed in Scheme 1. In the

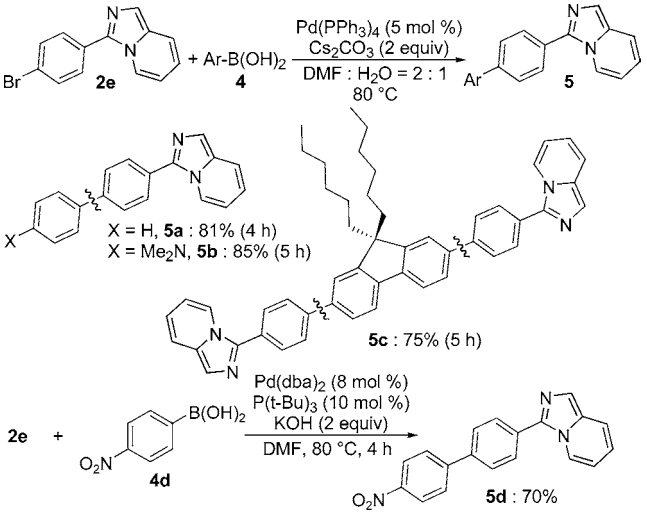
Scheme 1. Plausible Mechanism for Formation of 2-Azaindolizines **1** and Sulfur-Bridged Dimers **3**



pathway, deprotonation of the *N*-2-pyridylmethyl thioamide **1** by pyridine, followed by iodination at sulfur, gives intermediate **I**. Subsequent iodination, again at sulfur, takes place to form the electrophilic intermediate **II**, which undergoes intramolecular substitution by the pyridine nitrogen at the imino carbon to form **III**. Finally, aromatization of **III** by deprotonation forms 2-azaindolizines **2**.[14] In this mechanistic route, the sulfur atom of the starting thioamides **1** is formally oxidized to form a sulfur (+II) species (presumably sulfur diiodide).[14b] Electrophilic substitution reaction by sulfur diiodide on the initially formed 2-azaindolizine **2** yields intermediate **IV**, which serves as a precursor to the sulfur-bridged dimer **3**.[15] This proposal is in accord with the observation that thioamides bearing an electron-donating group give higher yields of **3**.

Suzuki−Miyaura coupling reactions of the bromine-substituted 2-azaindolizine **2e** with arylboronic acids were examined to extend the π-conjugated system of 2-azaindolizines (Scheme 2).[16] These reactions take place with high

Scheme 2. Suzuki−Miyaura Coupling Reactions of **2e**



efficiency under the general Suzuki−Miyaura coupling conditions. For example, reaction of **2e** and phenylboronic acid in the presence of tetrakistriphenylphosphine palladium(0) and cesium carbonate in aqueous DMF efficiently provides the phenylated product, 3-biphenyl-2-azaindolizine **5a**, in 81% yield. 4-Dimethylaminophenylboronic acid **4b** and fluorene diboronic acid **4c** also react to generate coupling products **5b** and **5c** in high yields. Although highly electron-deficient 4-nitrophenylboronic acid **4d** does not participate in a coupling reaction with **2e** under the typical conditions, the reaction proceeds smoothly when a combination of Pd(dba)$_2$, tri-*tert*-butyl phosphine, and KOH in DMF are used.

Photophysical studies reveal that π-conjugating substituents have a great influence on absorption and emission maxima (λ_{abs} and λ_{em}) and fluorescent quantum yields of the 2-azaindolizines (Table 3).[17,18] The λ_{abs} values of 2-azaindolizines bearing electron-donating groups on the phenyl ring, such as **2c** (306 nm) and **3c** (312 nm), are blue-shifted, and those with electron-withdrawing phenyl substitution, such as **2d** (340 nm) and **3d** (342 nm), are red-shifted, compared to the unsubstituted analogues, **2b** (317 nm) and **3b** (322 nm) (entries 2−4 and 6−8). A linear relationship is observed between the λ_{abs} values of **2** and **3** and the Hammett constants of the phenyl substituents in the expressions λ_{abs} of **2** $= 315 + 49.51\sigma$ ($R^2 = 0.95$) and λ_{abs} of **3** $= 322 + 37.04\sigma$ ($R^2 = 1.00$).[19] However, the λ_{em} values of **2b**−**d** and **3b**−**d** are less affected by phenyl substituents (entries 2−4 and 6−8). The λ_{em} values of **3b**,**c** (512−518 nm, entries 6−8), where a sulfur atom is present at the 2-azaindolizine

(14) For related oxidative desulfurization reactions, such as (a) glycosidation via oxidative activation of a thioether, see: Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576. (b) For oxidative desulfurization−fluorination, see: Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1973. Also see review: (c) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

(15) The reaction of 2-azaindolizine **2b** and SCl_2 provides **3b**: see ref 11.

(16) For a recent review of the Suzuki−Miyaura coupling reaction, see: Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366 and references cited therein.

(17) See Supporting Information for full detailed analytical data (Table S1).

(18) Demas, J. N.; Crosby, G. A. *J. Phys. Chem.* **1971**, *75*, 991.

(19) See Supporting Information (Figures S1 and S2).

Table 3. Selected Photophysical Properties of the Conjugated 2-Azaindolizines

		UV/vis[a]		fluorescence[a]	
entry	compound	λmax (nm)	log ε	λmax (nm)	Φ_F[b]
1	**2a**	348	4.04	425	0.02
2	**2b**	317	4.25	461	0.07
3	**2c**	306	4.05	469	0.05
4	**2d**	340	4.12	459	0.04
5	**3a**	273	4.27	480	0.02
		357	4.56		
6	**3b**	277	4.21	513	0.02
		322	4.28		
7	**3c**	276	4.34	518	0.03
		312	4.35		
8	**3d**	276	4.22	512	0.03
		342	4.41		
9	**5a**	334	4.23	415	0.07
10	**5b**	348	4.41	488	0.32
11	**5c**	357	4.87	447	0.22

[a] Measured in $CHCl_3$. [b] Quantum yields (Φ_F) were determined with reference to quinine sulfate in 0.1 M aqueous sulfuric acid (excited at 350 nm).[18]

1-position, are significantly red-shifted relative to those of **2b**−**d** (459−469 nm, entries 2−4). Furthermore, the λ_{em} values of **2a** (425 nm, entry 1) and **3a** (480 nm, entry 5), each of which bears a 2-pyridyl group at C-3, are considerably blue-shifted in contrast to those of **2b** (461 nm) and **3b** (513 nm). Interestingly, in spite of the usual large red-shift of its λ_{abs}, **5a** containing a C-3 phenyl-extended π-system has a λ_{em} value (415 nm, entry 9) that is significantly blue-shifted in comparison to **2b**. Moreover, the fluorescence quantum yields (Φ_F) are dramatically enhanced when the electron-donating 4-dimethylaminophenyl group is present at C-3 (e.g., **5b** $\Phi_F = 0.32$, entry 10), contrasted with **2b** ($\Phi_F = 0.07$) and **5a** ($\Phi_F = 0.07$). The fluorene-substituted analogue **5c** has both the strongest UV absorption and the highest fluorescence quantum yield ($\log \epsilon = 4.87$, $\Phi_F = 0.22$, entry 11) in this series and shows a strong blue emission ($\lambda_{em} = 447$ nm).

In summary, we have developed an efficient synthetic method to prepare functionalized 2-azaindolizines from readily available thioamides. In addition, the Suzuki−Miyaura coupling based protocol was developed to further extend π-conjugation in the 2-azaindolizines. This enabled preparation of 2-azaindolizines that have high fluorescence emission efficiencies. The advantage of this strategy is that it can be used to generate 2-azaindolizines with finely tuned absorption and emission properties for applications in advanced functional organic materials and medicinal chemistry. Further studies aimed at introducing novel functionality into the 2-azaindolizine skeleton and at theoretically probing the emission properties of these substances are underway.

Acknowledgment. This work was supported by Grant-in-Aids for Young Scientists (No. 17750084) and for Scientific Research on Priority Area (No. 18037024, "Advanced Molecular Transformations of Carbon Resources") from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by the research foundation for the Electrotechnology of Chubu.

Supporting Information Available: General experimental procedures, characterization data for all new compounds, X-ray crystallographic files (CIF) for compounds **2a** and **3a**, UV/vis and fluorescent spectra (Table S1), and Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0623623