

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

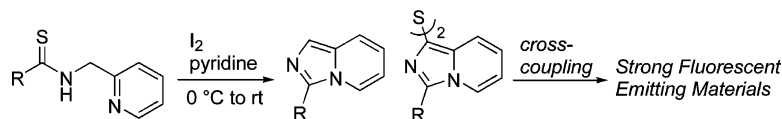
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ABSTRACT



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 carbenes⁵ 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) Degeoey, 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.

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

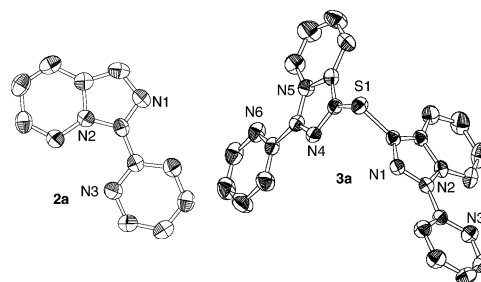


Figure 1. ORTEP plots of the molecular structures of 2-azaindolizine **2a** and sulfur-bridged 2-azaindolizine dimer **3a** (thermal ellipsoids drawn at the 50% probability level). Hydrogen atoms have been omitted for clarity.

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

$\text{R}-\text{C}(=\text{S})\text{NHCH}_2\text{Py} \xrightarrow[\text{THF, 0}^\circ\text{C then rt, 15 min}]{\text{I}_2(3 \text{ equiv}), \text{Pyridine}(3 \text{ equiv})} \text{2-azaindolizine } \mathbf{2} + \text{sulfur-bridged dimer } \mathbf{3}$				
R = 2-Py-, 1a 4-F-C ₆ H ₄ -, 1f Ph-, 1b 4-Me-C ₆ H ₄ -, 1g 4-MeO-C ₆ H ₄ -, 1c 4-Me ₂ N-C ₆ H ₄ -, 1h 4-F ₃ C-C ₆ H ₄ -, 1d 2-thenyl-, 1i 4-Br-C ₆ H ₄ -, 1e <i>i</i> Pr-, 1j				
entry	substrate 1	scale (mmol)	product	yield (%) ^b
1		1		89 ^c
2		31		84
3		1		89
4		23		95
5		1		89 ^d
6		3		89
7		9		87
8		3		83
9		10		81
10		1		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.

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%

(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)Cl₃ did not give the desired 3-(4-bromophenyl)-2-azaindolizine under the traditional Vilsmeier conditions⁶ (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

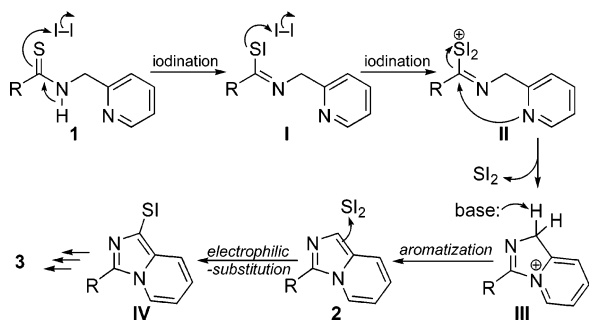
entry	substrate	solvent	yield(%)	
			2	3
1	1a	THF	57	32
2	1a	DMF	29	45
3	1b	DMF	47	31
4	1c	DMF	26	66
5	1d	DMF	51	35

^a Reactions were carried out at rt for 21 h.

yield, whereas reaction of the CF₃-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**

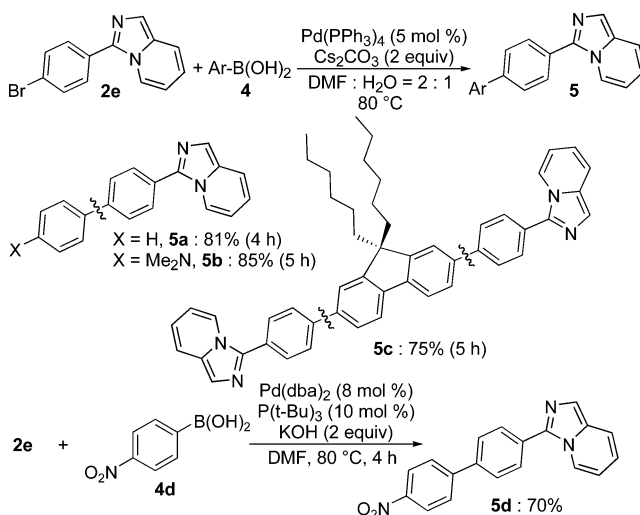


pathway, deprotonation of the *N*-2-pyridylmethyl thioamide **1** by pyridine, followed by iodination at sulfur, gives intermediate **I**. Subsequent iodination, again at sulfur, takes place to form the electrophilic intermediate **II**, which undergoes intramolecular substitution by the pyridine nitrogen 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 tetrakis(triphenyl)phosphine 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 σ (R^2 = 0.95) and λ_{abs} of **3** = 322 + 37.04 σ (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 SCl₂ 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

entry	compound	UV/vis ^a		fluorescence ^a	
		λ_{max} (nm)	$\log \epsilon$	λ_{max} (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
6	3b	357	4.56	513	0.02
		277	4.21		
7	3c	322	4.28	518	0.03
		276	4.34		
8	3d	312	4.35	512	0.03
		276	4.22		
9	5a	342	4.41	415	0.07
10	5b	334	4.23	488	0.32
11	5c	348	4.41	447	0.22
		357	4.87		

^a Measured in CHCl₃. ^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** Φ_{F} = 0.32, entry 10), contrasted with **2b** (Φ_{F} = 0.07) and **5a** (Φ_{F} = 0.07). The fluorene-substituted analogue **5c** has both the strongest UV absorption and the highest fluorescence quantum yield ($\log \epsilon$ = 4.87, Φ_{F} = 0.22, entry 11) in this series and shows a strong blue emission (λ_{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.

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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>.

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