

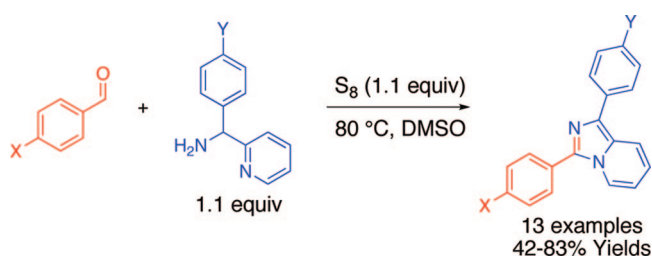
Synthesis of Fluorescent 1,3-Diarylated Imidazo[1,5-*a*]pyridines: Oxidative Condensation–Cyclization of Aryl-2-Pyridylmethylamines and Aldehydes with Elemental Sulfur as an Oxidant

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Oxidative condensation–cyclization of aldehydes and aryl-2-pyridylmethylamines proceeded in the presence of a stoichiometric amount of elemental sulfur as an oxidant in the absence of catalyst. The reaction gave a variety of 1,3-diarylated imidazo[1,5-*a*]pyridines in good to high yields. The products showed fluorescence emission in a wavelength range of 454–524 nm. The quantum yields of 1,3-diarylated imidazopyridines were greatly improved compared to those of the parent 3-monosubstituted compounds.

Recently, considerable interest has been focused on imidazo[1,5-*a*]pyridines because of their wide applicability.^{1–4} For

example, the compounds including an imidazo[1,5-*a*]pyridine moiety show interesting properties applicable to OLED² and FET.³ They also give a new class of *N*-heterocyclic carbenes.⁴ However, efficient and common synthetic routes to imidazo[1,5-*a*]pyridines have not been established.^{5–9} Therefore, it has been difficult to investigate their properties systematically. In the course of our studies on thioamide transformations,¹⁰ we developed a synthesis of 3-substituted imidazo[1,5-*a*]pyridines via the oxidative desulfurization–cyclization of readily available *N*-2-pyridylmethylthioamides using iodine as an oxidant.¹¹ This reaction gives a series of imidazo[1,5-*a*]pyridine derivatives in good to excellent yields, and the resulting 3-substituted imidazo[1,5-*a*]pyridines and their sulfur-bridged dimers show a variety of fluorescence emissions. It is promising that the introduction of additional π -systems into imidazo[1,5-*a*]pyridines influences their photophysical properties. To prepare 1,3-diarylated imidazo[1,5-*a*]pyridines with added π -systems, we attempted to synthesize the thioamide substrates *N*-(aryl-2-pyridylmethyl)thioamides by the Willgerodt–Kindler reaction of benzaldehyde, aryl-2-pyridylmethylamine, and elemental sulfur.¹² As a result, elemental sulfur acted not only as a sulfurizing agent but also as a simple oxidant under the reaction conditions, and the aldehyde and amine underwent formal oxidative condensation–cyclization to give the 1,3-diarylated imidazo[1,5-*a*]pyridines directly in low yields. To our knowledge, there has been no previous report of oxidative cyclization of this type with such a mild oxidant in the absence of a catalyst.¹³ We report here an oxidative condensation–cyclization of aromatic aldehydes and aryl-2-pyridylmethylamines using a stoichiometric amount of elemental sulfur as an oxidant in the absence of a catalyst.

As an example of our attempt to synthesize the thioamide substrates **4**, 2-pyridyl-4-tolylmethylamine (**2c**) was reacted with benzaldehyde (**1b**) in the presence of a stoichiometric amount

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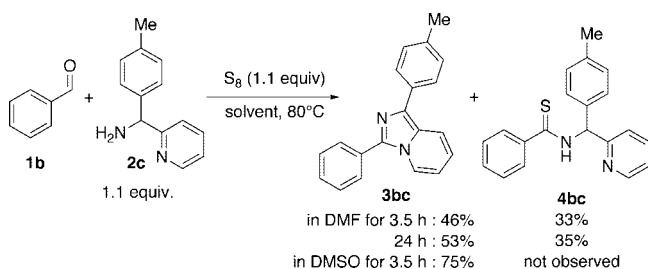
(13) The copper-catalyzed oxidative cyclization of the corresponding *N*-(2-pyridyl)arylmethylamines with molecular oxygen as an oxidant has been reported. See ref 8a.

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SCHEME 1. Attempted Synthesis of *N*-(Aryl-2-pyridylmethyl)-thioamide^a


^a The yields were determined by ¹H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

of elemental sulfur at 80 °C in DMF for 3.5 h. The reaction gave 1-(4-tolyl)-3-phenylimidazo[1,5-*a*]pyridine (**3bc**) and *N*-(2-pyridyl-4-tolylmethyl)benzencarbothioamide (**4bc**) in respective yields of 46% and 33%. The reaction was allowed to run for a longer time to improve the yield of imidazopyridine **3bc**, but the product distribution did not change after 24 h (Scheme 1). The solvent system was then optimized, and we found that the cyclization reaction took place efficiently in DMSO; **3bc** was obtained in 75% NMR yield (64% isolated yield) with no thioamide formation.

The scope of substrates was investigated, and the results are summarized in Table 1. Under the optimal conditions, the desired cyclization products were obtained in good to high yields regardless of the substituents. On the other hand, the time dependence of the product yields revealed the reactivities of the substrates and the stabilities of the products under the reaction conditions. For example, the reaction of an electron-rich aldehyde **1c** and amine **2d** proceeded quite rapidly to give the cyclization product **3cd** in 78% yield after 3.5 h, and most of the starting materials were consumed at this stage. The yield then significantly dropped to 41% after 24 h and multiple spots were observed in TLC analysis. These results suggest that while such electron-rich substrates are highly reactive, the corresponding products may be unstable under these conditions. In contrast, even after a prolonged reaction time, no significant decomposition of the products was detected in the reaction of electron-deficient substrates, particularly *p*-CF₃-phenyl-substituted amine **2a**. The reactions with **2a** furnished the cyclized products **3aa–ca** in yields of 69–82% after 12–30 h.

During our investigation of the reaction conditions, the formation of ketone **5**, which may occur via the oxidation of an aryl-2-pyridylmethylamine moiety followed by hydrolysis, was observed (Scheme 2). A similar oxidation of **2b** in the absence of aldehyde took place to give the ketone **5b** in 66% yield, though the reaction required a longer time for conversion. These results indicate that oxidation of the diarylmethylamine moiety by elemental sulfur as an oxidant takes place under these reaction conditions.¹⁴

A reaction sequence that includes the formation of thioamide **4** under the Willgerodt–Kindler reaction conditions¹⁵ followed by cyclization involving the elimination of H₂S is a possible pathway for the present reaction. However, thioamides scarcely undergo such an elimination of H₂S under neutral conditions.

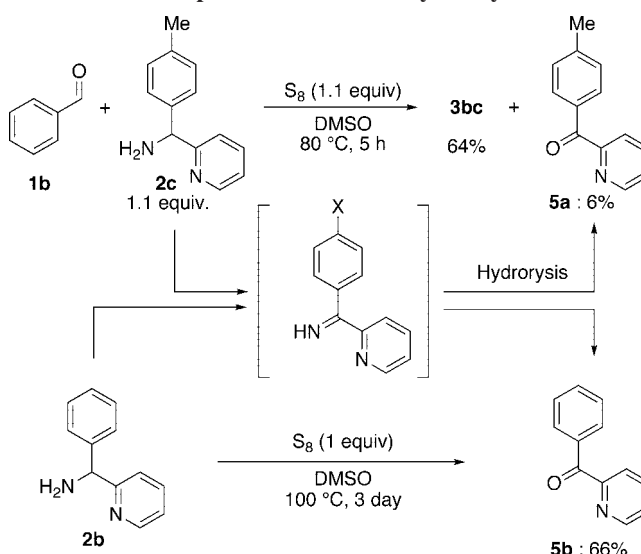
TABLE 1. Oxidative Condensation–Cyclization of Aldehydes and Aryl-2-pyridylmethylamines in the Presence of Elemental Sulfur^{a,b}

$X = \text{CF}_3 : 1a$
 $H : 1b$
 $\text{OMe} : 1c$

$Y = \text{CF}_3 : 2a$
 $H : 2b$
 $\text{Me} : 2c$
 $\text{OMe} : 2d$

Aldehyde	Amine			
	electron rich		electron deficient	
3aa	3ab	3ac	3ad	
45% (3.5 h) 69% (12 h) 60% (24 h)	42% (3.5 h) 66% (24 h)	65% (3.5 h) 56% (24 h)	42% (3.5 h) 50% (16 h) 44% (24 h)	
3ba	3bb	3bc	3bd	
54% (3.5 h) 74% (24 h) 82% (30 h)	62% (3.5 h) 74% (10 h) 67% (24 h)	64% (3.5 h) 81% (6 h) 74% (24 h)	63% (3.5 h) 50% (24 h)	
3ca	3cb	3cc	3cd	
63% (3.5 h) 76% (16 h) 71% (24 h)	79% (3 h) 77% (3.5 h) 65% (24 h)	69% (3.5 h) 83% (4.5 h) 67% (24 h)	78% (3.5 h) 41% (24 h)	

^a All reactions were carried out with **1** (0.5 mmol), **2** (0.55 mmol), and S₈ (0.55 mmol) in DMSO (0.5 mL) at 80 °C. ^b Isolated yields. Optimal yields are listed in boldface.

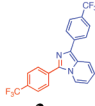
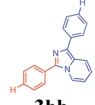
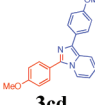
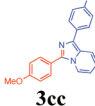
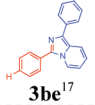
SCHEME 2. Simple Oxidation of Diarylmethylamine


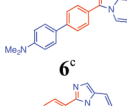
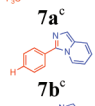
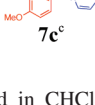
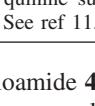
In fact, the resulting thioamides **4** were intact under these reaction conditions in DMF even for a long reaction time, while significant amounts of the corresponding imidazopyridines **3** were formed in the same reaction solution (Scheme 1). Also,

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TABLE 2. Representative Photophysical Properties of the Obtained Imidazo[1,5-*a*]pyridines^a

entry	compound	UV/Vis		Fluorescence	
		λ_{\max} (nm)	log ϵ	λ_{em} (nm)	Φ_{F} ^b
1	 3aa	325	4.24	480	0.16
2	 3bb	308	4.18	454	0.14
3	 3cd	303	4.31	479	0.22
4	 3cc	303	4.31	521	0.13
5	 3be¹⁷	314	4.47	524	0.21

6	 6^c	348	4.41	488	0.32
7	 7a^c	340	4.12	459	0.04
8	 7b^c	317	4.25	461	0.05
9	 7c^c	306	4.05	469	0.04

^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 ^c See ref 11.

isolated thioamide **4bd** was heated at 80 °C in DMSO for 4 h in the presence or absence of elemental sulfur, but no reaction took place and the starting **4bd** was recovered quantitatively in both cases. These results suggest that the present cyclization did not proceed via the formation of thioamide. On the other hand, although the details of the oxidation step in the present reaction are unclear, the reduced sulfur species, hydrogen sulfide, was detected by a lead(II) acetate test of the atmosphere over the reaction mixture after the reaction. This result obviously suggests that elemental sulfur acted as a stoichiometric oxidant in the present reaction.

An additional aryl group at C1 greatly influences the emission maxima (λ_{em}) and fluorescent quantum yields of the imidazo[1,5-*a*]pyridines. Selected results are shown in Table 2.¹⁶ Imidazopyridines bearing the same aryl groups on C1 and C3 (**3aa**, **3bb**, and **3cd**) show emission colors similar to those of parents **7** ($\lambda_{\text{em}} = 454\text{--}480$ nm vs $\lambda_{\text{em}} = 459\text{--}469$ nm), whereas the

quantum yields of emissions are increased 3- to 4-fold to $\Phi_{\text{F}} = 0.14\text{--}0.22$ (entries 1–3 vs. 7–9). Although the reason for this result is not yet clear, **3cc** shows a dramatically red-shifted emission ($\lambda_{\text{em}} = 521$ nm, entry 4). A similar large red-shifted emission is observed with imidazopyridine bearing a highly electron-donating 4-dimethylaminophenyl group at C1 (**3be¹⁷**) ($\lambda_{\text{em}} = 524$ nm, entry 5). In contrast, imidazopyridine bearing a similar electron-donating 4-dimethylaminobiphenyl group at C3 (**6**) does not show such large red-shifted emission ($\lambda_{\text{em}} = 488$ nm, entry 6) though the quantum yield is greatly improved ($\Phi_{\text{F}} = 0.32$). Notably, Stork's shifts ($\Delta\lambda_{\text{em}} - \lambda_{\text{max}}$) of **3cc** and **3be** reach over 210 nm.

In summary, we have developed an oxidative condensation–cyclization of aromatic aldehydes **1** and aryl-2-pyridylmethyl amines **2** leading to 1,3-diarylated imidazo[1,5-*a*]pyridines **3**. The reaction took place efficiently with a stoichiometric amount of elemental sulfur as a mild oxidant in the absence of a catalyst, and this simple protocol readily furnishes 1,3-diarylated imidazo[1,5-*a*]pyridines on demand. In addition, the products showed a wide variety of fluorescent emissions at wavelengths of 454–524 nm. Also, the quantum yields of 1,3-diarylated imidazopyridines **3** were greatly improved compared to those of the parent 3-monosubstituted compounds. These synthetic improvements and photofunctional diversity imply that the imidazo[1,5-*a*]pyridines can be potentially used as easily tunable photofunctional materials. Further studies on the development of a diversity-oriented introduction of a π -conjugated system into an imidazo[1,5-*a*]pyridine skeleton and theoretical studies on the absorption and emission properties of these substances are underway.

Experimental Section

General Procedure for the Synthesis of 1,3-Diarylated Imidazo[1,5-*a*]pyridines. To a solution of aldehyde (0.5 mmol) in DMSO (0.5 mL) at room temperature was added elemental sulfur (0.55 mmol). To the resulting solution was added aryl-2-pyridylmethylamine (0.55 mmol), and the mixture was stirred at 80 °C. At the indicated time, the reaction mixture was poured onto ice and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with 20 mL of brine. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to give the desired 1,3-diarylated imidazo[1,5-*a*]pyridine. The yields of the products except for **3be** are listed in Table 1.

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Supporting Information Available: General experimental procedures for the synthesis of amine **2**, characterization data, and copies of ¹H NMR and ¹³C NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO900415Y

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