Iodine-mediated cyclization of *N*-thioacyl-1-(2-pyridyl)-1,2-aminoalcohols and their subsequent condensation leading to the formation of novel bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes†

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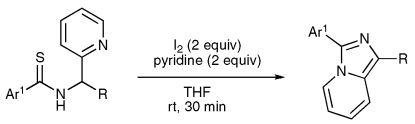
The treatment of *N*-thioacyl-1-(2-pyridyl)-1,2-aminoalcohols with iodine and pyridine in THF at room temperature for 30 min leads to the formation of bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes as green solids in good to high yields.

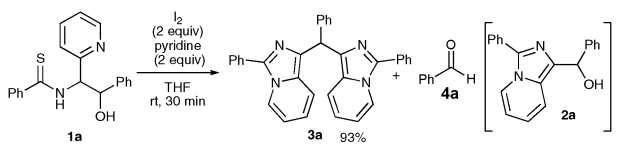
Triarylmethanes are among the most interesting family of organic compounds, since they have unique properties that are applicable to organic materials,[1] leuco dyes[2] and chemical biological probes.[3] However, most members of this group are simple derivatives that have 6 π-electron aryl and heteroaryl groups linked to the methane carbon.[4] Also, growing attention has been given to nitrogen-containing 10 π-electron heterocycles[5] that contain the imidazo[1,5-*a*]pyridine ring system, since these substances have applicability as metal ligands,[6] photophysical materials[7] and biologically-related probes.[8] As part of recent studies focusing on the synthesis and properties of imidazo[1,5-*a*]pyridines,[9] we developed a novel method for their preparation through a process that involves desulfurative cyclization of *N*-2-pyridylmethyl thioamides (Scheme 1).[9a] Below, we describe applications of this process to the synthesis of bis(1-imidazo[1,5-*a*]pyridyl)-arylmethanes, starting with *N*-thioacyl-1,2-aminoalcohols.

To explore potential applications of this new cyclization process, *N*-thioacyl-1,2-aminoalcohol **1a** was treated with I_2 and pyridine at room temperature in THF (Scheme 2).

The thioamide **1a** was completely consumed within 30 min, but, unlike the reaction shown in Scheme 1, the corresponding imidazopyridine **2a** was not produced. Instead, the bis(1-imidazo-[1,5-*a*]pyridyl)phenylmethane **3a** was generated as a green solid in



Scheme 1 Desulfurative cyclization of *N*-2-pyridylmethyl thioamides.



Scheme 2 Synthesis of bis(1-imidazopyridyl)phenylmethane.

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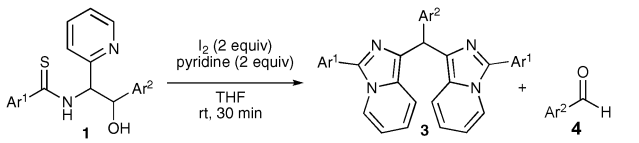
Table 1 Reaction of *N*-thioacyl-1,2-aminoalcohols **1** with I_2 in the presence of pyridine



Entry	**1**	Ar^1	Ar^2	**3**	Yield (%)[a]
1	**1b**	Ph	C_6H_4OMe-4	**3b**	72
2	**1c**	Ph	C_6H_4Cl-4	**3c**	81
3	**1d**	Ph	C_6H_4Me-4	**3d**	100
4	**1e**	4-$MeOC_6H_4$	C_6H_4OMe-4	**3e**	72
5	**1f**	2-Pyridyl	C_6H_4OMe-4	**3f**	54
6	**1g**	2-Pyridyl	C_6H_4Cl-4	**3g**	77
7	**1h**	2-Thienyl	C_6H_4OMe-4	**3h**	62
8	**1i**	2-Thienyl	C_6H_4Cl-4	**3i**	45

[a] Isolated yields.

93% yield along with benzaldehyde (**4a**). Although pyrrole-, imidazole- and indole-containing triarylmethanes are known,[10] to our knowledge, **3a** is the first example of a triarylmethane that possesses a nitrogen-containing 10 π-electron aromatic moiety. Furthermore, the intensive green color of **3a** is suggestive of extended electron delocalization, yet **3a** contains two imidazo-[1,5-*a*]pyridyl moieties that are linked to a central sp^3-hybridized carbon and, therefore, they are not conjugated.

A variety of *N*-thioacyl-1-(2-pyridyl)-1,2-aminoalcohols **1**, readily prepared by the reaction of dianions derived from *N*-(2-pyridyl)methyl aromatic thioamides with aromatic aldehydes,[11] were subjected to reaction with iodine in the presence of pyridine (Table 1). In all cases, the triarylmethane products **3** were selectively produced as green solids in moderate to high yields along with the corresponding aromatic aldehydes **4**. The presence of electron-withdrawing and electron-donating substituents on the aromatic rings of the reactants did not affect the efficiency of the reactions (entries 1–3). Heteroaromatic rings, including pyridyl and thienyl, can also be incorporated into the products of these reactions (entries 5–8). One of the reasons for the lower than expected isolated yields of these processes has to do with the lability of the triarylmethane products when exposed to light. Therefore, purification of these products by column chromatography on silica gel was carried out under conditions that avoid light.

The structures of the bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes were elucidated by carrying out X-ray crystallographic analysis of **3g**.‡ An ORTEP plot of the X-ray data obtained from **3g** is shown in Fig. 1. The central carbon atom (C7) in this substance

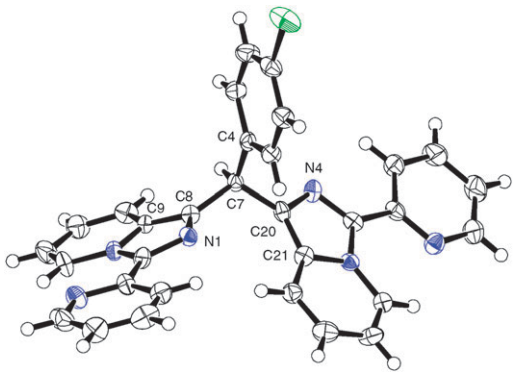
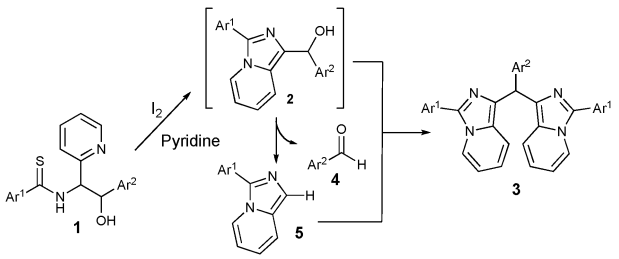


Fig. 1 X-Ray molecular structure of **3g**. Selected bond lengths (Å) and angles (°): C7–C8, 1.519(6); C7–C20, 1.508(6); C7–C4, 1.533(6); C8–N1, 1.361(5); C20–N4, 1.362(5); C4–C7–C8, 110.0(3); C8–C7–C20, 115.8(3); C4–C7–C20, 111.4(3); C4–C7–C8–C9, 125.7(4); C4–C7–C20–C21, 90.9(5).



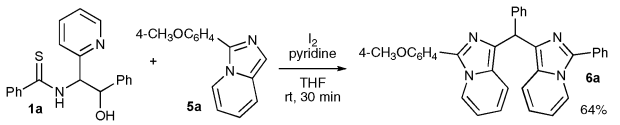
Scheme 3 A plausible reaction pathway for bis(1-imidazo[1,5-*a*]-pyridyl)arylmethanes **3**.

has a slightly distorted tetrahedral geometry. The dihedral angles between the aromatic ring and the two imidazo[1,5-*a*]pyridyl groups are 90.7(6) and 125.5(5)°. The two imidazo[1,5-*a*]pyridyl groups are not coplanar, but rather their planes deviate by 35.79°.

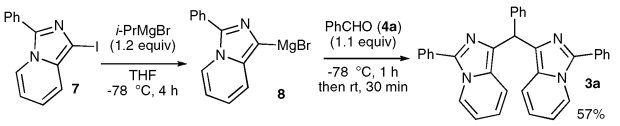
A plausible mechanistic pathway for the reactions that form the bis(1-imidazo[1,5-a]pyridyl)arylmethanes **3** is shown in Scheme 3. The initial stage of this process involves iodine-mediated oxidative desulfurative cyclization of **1** to form the 1-(hydroxy)arylmethylimidazo[1,5-*a*]pyridine intermediate **2**. Elimination of an aryl aldehyde **4** from **2** then occurs to give the imidazo[1,5-*a*]pyridine **5**. One possible route for the final stage of this process involves condensation of two molecules of **5** with aldehyde **4**. However, this process is not likely, since no reaction is observed to take place between isolated **5** and **4** in the presence of iodine and pyridine. Consequently, it is likely that the alternative pathway, involving Friedel–Crafts reaction of **5** with **2** occurs under the reaction conditions to give the observed products **3**.

If the Friedel–Crafts reaction serves as the final step of this process, reactions of **2** with electron-rich imidazo[1,5-*a*]pyridine **5**, would be more rapid than those with unsubstituted analogs. Thus, by carrying out the process in the presence of electron-rich imidazo[1,5-*a*]pyridines, it is likely that unsymmetrically substituted products would be generated. In fact, the reaction of **1a** with iodine and pyridine in the presence of imidazo[1,5-*a*]-pyridine **5a** proceeds to produce the unsymmetrically substituted product **6a** along with 22% yield of the recovered starting material **5a** (Scheme 4).

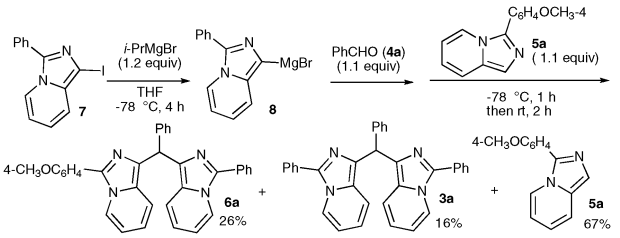
Evidence for the intermediacy of 1-(hydroxy)arylmethyl-imidazo[1,5-*a*]pyridines **2** in this pathway was gained by



Scheme 4 Iodine-mediated reaction of *N*-thioacyl-1,2-aminoalcohol **1a** and imidazo[1,5-*a*]pyridine **5a**.



Scheme 5 Reaction of imidazo[1,5-*a*]pyridylmagnesium bromide **8** with benzaldehyde (**4a**).

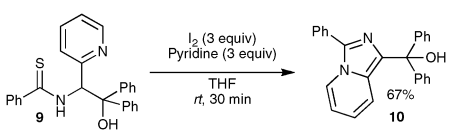


Scheme 6 Reaction of **8** with **4a** and **5a**.

investigating the chemistry of independently prepared substances. For example, the addition of 1-imidazo[1,5-*a*]pyridyl magnesium bromide **8**, generated by the reaction of **7** with *i*-PrMgBr, to benzaldehyde (**4a**) (Scheme 5) was observed to produce **3a** in good yield. In this process, two molecules of **8** are incorporated into the final product. An identical reaction, carried out in the presence of imidazo[1,5-*a*]pyridine **5a**, yields a mixture of the unsymmetric product **6a** and the symmetric analog **3a**, along with recovered **5a** (Scheme 6). Extensively studied Friedel–Crafts reactions of electron-rich arenes with aromatic alcohols and aldehydes to form triarylmethanes, promoted by Brønsted or Lewis acid catalysts, have been extensively studied.[12] Even though the Friedel–Crafts reactions taking place in the current scheme do not require added acids, it is possible that hydroiodic acid, generated as a byproduct in the initial step of the cyclization of **1** with I_2 and pyridine, may serve in this capacity. Alternatively, iodine itself might catalyze the Friedel–Crafts reaction.[13]

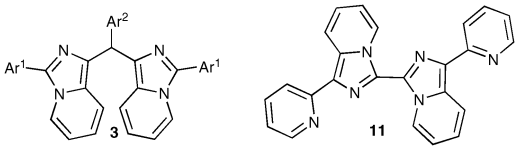
In order to explore a possible strategy for the preparation of tetraarylmethanes bearing imidazo[1,5-*a*]pyridyl groups, we investigated the reaction of *N*-thioacyl-1,2-aminoalcohol **9** with iodine and pyridine. However, in this case, only the desulfurative cyclization process occurs to form **10** as a brown solid (Scheme 7).[14]

Finally, information was obtained about the electronic properties of the bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes. UV-vis spectra of $CHCl_3$ solutions of these substances contain the maxima and molar extinction coefficients listed in Table 2. The longest wavelength absorption maximum of **3a** at 604 nm



Scheme 7 Reaction of **9** with I_2 in the presence of pyridine.

Table 2 UV-vis spectra of **3**, **5a** and **11**



Entry	3	Ar^1	Ar^2	λ/nm (log ε)[a]
1	**3a**	Ph	Ph	242(4.35), 329(4.28), 604(2.97)
2	**3b**	Ph	C_6H_4OMe-4	244(4.27), 320(4.18), 465(3.66), 602(4.14)
3	**3c**	Ph	C_6H_4Cl-4	255(4.15), 320(4.85), 611(3.50)
4	**3d**	Ph	C_6H_4Me-4	244(4.21), 327(4.17), 604(3.26)
5	**3e**	4-$MeOC_6H_4$	C_6H_4OMe-4	254(4.54), 317(4.52), 464(3.19), 618(3.56)
6	**3f**	2-Pyridyl	C_6H_4OMe-4	250(4.39), 363(4.50), 621(2.79)
7	**3g**	2-Pyridyl	C_6H_4Cl-4	249(4.35), 360(4.40), 630(2.89)
8	**3h**	2-Thienyl	C_6H_4OMe-4	229(4.37), 347(4.35), 633(2.54)
9	**3i**	2-Thienyl	C_6H_4Cl-4	253(4.41), 345(4.32), 644(2.53)
10	**5a**	4-$MeOC_6H_4$	Ph	248(4.33), 317(4.51), 495(3.19), 618(3.56)
11	**11**	Ph		240, 265, 338[b]

[a] Measured in $CHCl_3$. [b] Ref. 7.

is red-shifted by more than 150 nm compared with that of the parent imidazo[1,5-*a*]pyridine **5a**, despite the fact that no conjugation exists between the two imidazo[1,5-*a*]pyridyl groups in the former substance. More interesting is the fact that compound **11**, in which the two imidazo[1,5-*a*]pyridyl groups are fully conjugated, shows its longest wavelength absorption maximum at only 338 nm (entry 11).[7] Similarly, the longest wavelength absorption maximum of **10**, consisting of two phenyl groups and one imidazo[1,5-*a*]pyridyl group, is at 328 nm. The introduction of a methoxy or a chlorine substituent to the aromatic ring attached to the central sp^3 carbon atom has almost no effect on the absorption maxima of these substances (entries 2–4). In contrast, the introduction of a methoxy group to the aromatic ring connected to the imidazo[1,5-*a*]pyridyl group causes a slight red shift (entry 5). Furthermore, substitution of these same aromatic groups by a 2-pyridyl or a 2-thienyl moiety brings about a red-shift of *ca.* 20 and 30 nm, respectively.

In summary, the results of this effort demonstrate that sequential, iodine and pyridine promoted cyclization–condensation reactions of *N*-thioacyl-1-(2-pyridyl)-1,2-amino-alcohols, derived from secondary thioamides and aromatic aldehydes, take place to produce triarylmethanes that bear nitrogen-containing 10 π-electron, imidazo[1,5-*a*]pyridyl groups. The synthesis of unsymmetrically substituted members of this family can be achieved by the reaction of *N*-thioacyl-1,2-aminoalcohols in the presence of imidazo[1,5-*a*]pyridines that contain different substituents from those present in the alcohols. The bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes formed in this manner are green substances that have longest wavelength absorption maxima at *ca.* 600 nm. Additional applications of this chemistry to produce new classes of triarylmethanes are under current investigation.

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Notes and references

‡ Crystallographic data for bis(1-imidazo[1,5-*a*]pyridyl)(4-chlorophenyl)-methane (**3g**) $C_{31}H_{21}ClN_6$, monoclinic space group $P2_1/c$, a = 11.262(6), b = 10.562(6), c = 20.766(12) Å, β = 96.078(7)°, V = 2456(2) Å^3, Z = 4, D_{calcd} = 1.387 Mg m^{-3}, 19 735 reflections measured, 5616 unique (R_{int} = 0.0806). $R1$ = 0.1074 ($I > 2\sigma(I)$), w$R2$ = 0.2600 (all data), GOF(F^2) = 1.

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