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An improved synthesis of 2-(1,2,4-thiadiazol-5-yl)pyridine by interception of an intermediate involved in a competing cyclisation reaction

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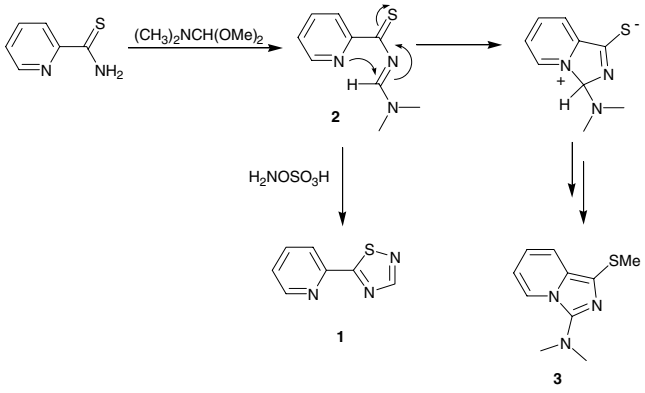
Abstract—Reaction of thiopicolinamide with *N*,*N*′-dimethylformamide dimethyl acetal leads to the formation of 3-(dimethylamino)-1-methylthioimidazo[1,5-*a*]pyridine (**3**). However, the course of the reaction can be diverted to produce the title compound (**1**) in good yield by timely interception of the intermediate thioacylamidine (**2**).

For some time we have been interested in the synthesis and study of new chelating *N*-heterocyclic ligands and their use in coordination and metallosupramolecular chemistry.[1] In particular, we have focussed on the use of ligands incorporating less commonly studied heterocyclic ring systems, such as tetrazoles,[2] 1,2-benzisoxazoles,[3] furoxans,[4] benzotriazoles,[5,6] 1,4,2,5-dioxadiazines,[7] thiazolo[5,4-*d*]thiazoles,[8] 1,2,3-thia(and selena)diazoles,[9] pyridazines,[10] 1,2,5-oxadiazoles and 1,2,5-thiadiazoles.[11,12] We have been particularly attracted to sulfur-containing azole ligands as these seem to impart intriguing properties to the resultant metal complexes.

Within this context, we identified 2-(1,2,4-thiadiazol-5-yl)pyridine (**1**) (Scheme 1) as a potentially useful chelating ligand and were surprised to find that the only literature references to this compound relate to two reports of its use as a ligand involved in ruthenium(II) complexes.[13,14] Neither of these papers have described experimental details of its synthesis, other than a yield (32%), a melting point and an oblique reference to the synthetic method, which cited a two-step synthetic procedure employed by Lin et al.[15] This involved a process in which a thioamide was reacted with *N*,*N*′-dimethylformamide dimethyl acetal to form a thioacylamidine that was subsequently reacted with hydroxylamine-*O*-sulfonic acid to furnish the thiadiazole product. These authors[15] reported the synthesis of the isomeric 3- and 4-substituted pyridines, but not the 2-substituted isomer.



Scheme 1. Synthesis of **1** and **3**.

When we attempted to employ this synthetic route, we found that the reaction of thiopicolinamide with *N*,*N*′-dimethylformamide dimethylacetal led to a different product than the expected amidine **2**. A high-resolution mass spectrometry measurement provided a molecular formula of $C_{10}H_{13}N_3S$ for the product and this was supported by elemental analysis. The ^{1}H NMR spectrum (Fig. 1) clearly showed that this product has reduced aromaticity of the pyridine ring, suggesting a 1,2-fused

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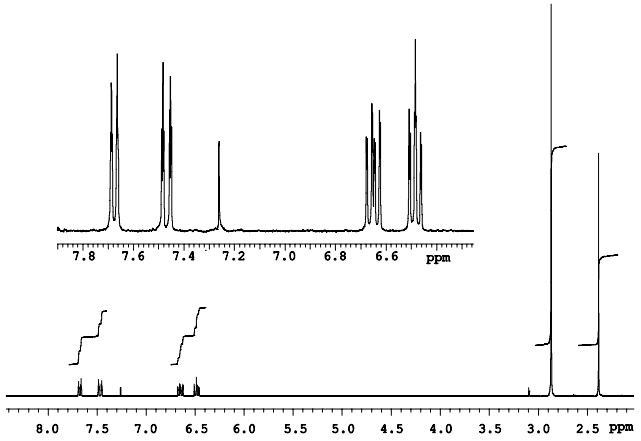

Figure 1. ^{1}H NMR spectrum of **3**.

pyrido subunit, and that it possessed dimethylamino and methylthio substituents. Complete ^{1}H and ^{13}C NMR assignments of this molecule were made, and by comparison of the NMR data with a similar molecule containing an imidazo[1,5-*a*]pyridine system,[16] we identified the product as 3-(dimethylamino)-1-methylthioimidazo[1,5-*a*]pyridine (**3**).[17] We believe that the formation of this new compound is initiated by intramolecular cyclisation of the pyridyl nitrogen onto the amidine carbon of **2**, a process not available to the 3- and 4-pyridyl analogues (Scheme 1). Formation of imidazo[1,5-*a*]pyridines by related cyclisations is known.[18,19]

We next decided to monitor the progress of this reaction by ^{1}H NMR. We found that after combining the reactants for 30 min, the thiopicolinamide was completely consumed and a single compound was formed, the spectrum of which was consistent with it being the desired amidine **2**. However, during the course of the next 90 min, this compound underwent further reaction to generate a mixture of compounds containing the rearranged product **3**.

We felt that the course of the reaction could be intercepted by simply carrying out the two steps without isolation of the intermediate, conveniently turning the synthesis into a 'one-pot' procedure. Accordingly, thiopicolinamide and *N*,*N*′-dimethylformamide dimethyl acetal were combined and allowed to react for 30 min, before hydroxylamine-*O*-sulfonic acid and pyridine in a solvent mixture of methanol/ethanol were added and the resulting mixture was allowed to react at room temperature. By this method, **1** was obtained in 75% yield after workup and purification,[20] which was a considerable improvement over the previously reported yield of 32%.

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17. Preparation of **3**: Thiopicolinamide (0.50 g, 3.6 mmol) and *N*,*N*′-dimethylformamide dimethyl acetal (0.58 mL, 3.6 mmol) were combined and left to stand at rt for 4 d. The methanol produced was removed in vacuo, and the residue chromatographed on silica gel with EtOAc–Pet. ether (1:4) as eluant giving the product (R_f 0.18) as a yellow solid (0.40 g, 54%). mp 34–37 °C (Found: C, 57.72; H, 6.41; N, 20.33; S, 15.72. $C_{10}H_{13}N_3S$ requires C, 57.95; H, 6.22; N, 20.26; S, 15.47). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.38 (3H, s, –SMe), 2.87 (6H, s, $-NMe_2$), 6.48 (1H, ddd, $J = 7.3$, 6.3 1.2 Hz, H6), 6.65 (1H, ddd, $J = 9.3$, 6.3, 1.0 Hz, H7), 7.47 (1H, dt, $J = 9.3$, 1.2 Hz, H8), 7.67 (1H, dt, $J = 7.3$, 1.0 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.10 (–SMe), 42.18 ($-NMe_2$), 111.75 (C6), 118.09 (C8), 118.48 (C7), 119.00 (C1), 120.69 (C5), 129.94 (C8a), 144.39 (C3). $HRMS^{+}$ Calcd m/z for $C_{10}H_{13}N_3S$ 207.0830. Found: 207.0830. $EIMS^{+}$ m/z 207.1 (M^{+}, 100%), 192.0 ($M^{+}-CH_2$, 55%), 78.0 (Py^{+}, 29%).
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20. Preparation of **1**: Thiopicolinamide (0.50 g, 3.6 mmol) and *N*,*N*′-dimethylformamide dimethyl acetal (0.48 mL, 3.6 mmol) were combined and allowed to stand for 30 min. A solution of hydroxylamine-*O*-sulfonic acid (0.49 g, 4.3 mmol) in MeOH (3 mL) and then pyridine (0.58 mL, 7.5 mmol) in EtOH (5 mL) were added and the solution was stirred magnetically at rt for 5 h. The volatiles were removed in vacuo and the residue taken up in CH_2Cl_2 (25 mL) and washed with H_2O (1×10 mL), 0.1 N NaOH (1×10 mL), H_2O (1×10 mL), dried over Na_2SO_4 and concentrated to dryness by rotary evaporation. The residue was chromatographed on silica gel eluting with EtOAc–Pet. ether (1:5) and the product (R_f 0.37) was obtained as a canary-yellow solid (0.44 g, 75%). mp 73–75 °C (lit.[14] 68–69 °C) (Found: C, 51.56; H, 3.08;

N, 25.57; S, 19.92. $C_7H_5N_3S$ requires C, 51.52; H, 3.09; N, 25.75; S, 19.65). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (1H, ddd, $J = 7.32$, 4.88, 1.47 Hz, H5), 7.88 (1H, td, $J = 7.32$, 1.47 Hz, H4), 8.18 (1H, d, $J = 7.81$ Hz, H3), 8.66 (1H, d, $J = 4.39$ Hz, H6), 8.75 (1H, s, H3′); ^{13}C NMR (protonated carbons only) (75 MHz, $CDCl_3$) δ: 120.38 (C3), 126.21 (C5), 137.51 (C4), 149.99 (C6), 163.50 (C3′). HRMS$^+$ Calcd m/z for $C_7H_5N_3S$ 163.0204. Found: 163.0200. EIMS$^+$ m/z 163.0 (M^+, 100%), 136.0 (M^+-CNH, 43%), 104.0 ($PyCN^+$, 53%), 78.0 (Py^+, 26%), 59 ($SCNH^+$, 17%).