# Synthesis of Substituted Imidazo[1,5-*a*]pyridines Starting from *N*-2-Pyridylmethylamides Using Lawesson's Reagent and Mercury(II) Acetate

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*Received 28 February 2007; revised 19 April 2007*

**Abstract:** A new method for the synthesis of substituted imidazo[1,5-*a*]pyridines (2-azaindolizines) starting from carboxylic acid and 2-methylaminopyridine is described. The reaction of the obtained *N*-2-pyridylmethylamides with Lawesson's reagent generated the target imidazopyridines, along with the corresponding thioamide intermediates. After a simple filtration on alumina, addition of mercury(II) acetate allowed for total conversion of the thioamides into the imidazopyridines. The reaction conditions, as well as the influence of the substituent in position 3 of the imidazopyridine ring were explored. We also demonstrated that this heterocyclization was racemization free in the presence of a chiral carbon in position α to the heterocycle.

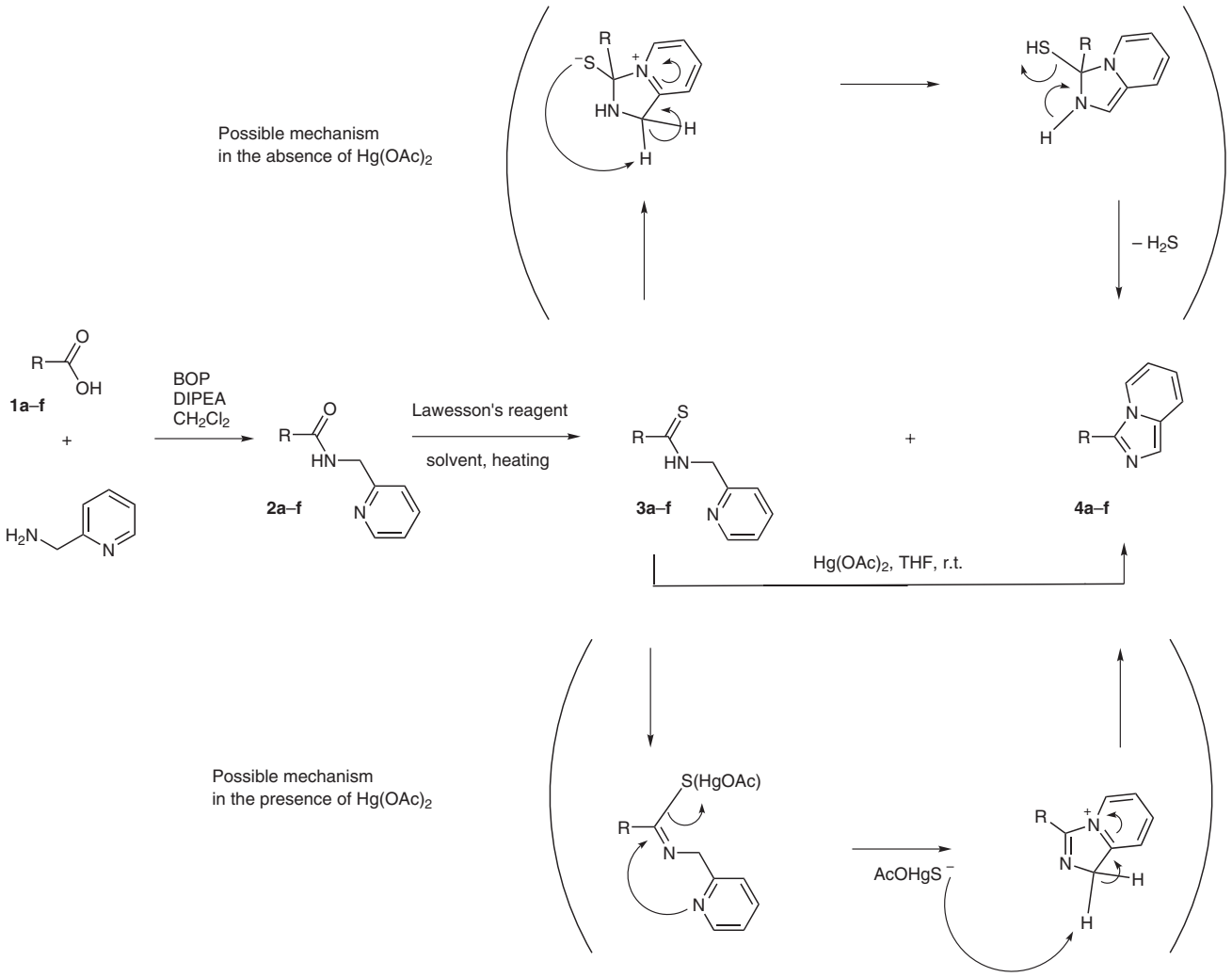
**Key words:** heterocycles, imidazo[1,5-*a*]pyridines, 2-azaindolizines, Lawesson's reagent, mercury(II) acetate

Imidazo[1,5-*a*]pyridines (2-azaindolizines) are an important class of heterocyclic compounds. They express antiviral properties (e.g., HIV-protease inhibitory activities).[1–3] They can also have potential applications in the context of organic light-emitting diodes (OLED)[4–6] and organic thin-layer field effect transistors (FET).[7] Furthermore, they are precursors of N-heterocyclic carbenes,[8,9] whose synthesis and applications are now under active exploration. Therefore, convenient and widely applicable methods allowing the synthesis of these compounds are of interest. Despite this high interest, existing synthetic routes which target imidazo[1,5-*a*]pyridines relying mainly on traditional Vilsmeier-type cyclizations of *N*-2-pyridylmethylamides, are only modestly efficient.[10] Recent advances were described in the synthesis of these compounds via an acetic or polyphosphoric acid mediated condensation pathway,[2,11,12] or via an oxidative pathway.[13–15]

In our ongoing effort to target new bioactive heterocyclic scaffolds, we describe in this paper a new method for the synthesis of substituted imidazo[1,5-*a*]pyridines. The general synthetic route is outlined in Scheme 1. The carboxylic acid **1** is coupled to commercially available 2-methylaminopyridine using BOP [benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate] reagent[16] to give the corresponding *N*-2-pyridylmethylamide **2**. Reaction of **2** with Lawesson's reagent[17] generated the target compound **4** along with the corresponding thioamide intermediate **3**. After a simple filtration on alumina to eliminate the inorganic residues from Lawesson's reagent, the addition of mercury(II) acetate allowed the total conversion of the remaining *N*-2-pyridylmethylthioamide **3** into the imidazo[1,5-*a*]pyridine **4**. A possible mechanism for the cyclization reaction is displayed in Scheme 1. The formation of the thioamide **3** is followed by a nucleophilic attack of the thiocarbonyl group by the nitrogen of the pyridyl moiety. Then a re-aromatization produced the final product **4**. We already proposed this type of mechanism to explain the one-pot formation of 1,2,4-triazolo[4,3-*a*]pyridines,[18] starting from the corresponding acetohydrazide. The fact that a thiophile, for example mercury(II) acetate, is necessary to totally convert the thioamide **3** into the imidazopyridine **4**, contrary to what was observed for the conversion of the thioacetohydrazides into the corresponding triazolopyridines, suggests a lower reactivity of the *N*-2-methylpyridylthioamides compared to the thioacetohydrazides, in this type of desulfurization-promoted cyclization.

Various reaction conditions were tested for the conversion rate of the amide **2** into the imidazopyridine **4**. For this purpose, various solvents, the influence of the reaction temperature, the reaction time, and the number of equivalents of Lawesson's reagent were studied. These different reaction conditions were achieved on the model amide 3-phenyl-*N*-(pyridin-2-ylmethyl)propanamide (**2a**), bearing a phenethyl group (R group). The conversion rates were determined by RP-HPLC analysis at 214 nm. Results are summarized in Table 1. Generally, one equivalent of Lawesson's reagent yielded to slightly better conversion rates compared with 0.5 equivalent (see entries 2 and 4, 6 and 7, 9 and 11, 10 and 12, 13 and 15, except for entries 14 and 16). A reaction time of two hours seemed also to be more favorable than 1 hour for the cyclization reaction (see entries 1 and 2, 3 and 4, 7 and 8, 9 and 10, 11 and 12, 13 and 14). Neither the solvent nor the temperature seemed to have a clear influence on the conversion rate. The best conversion rate was obtained by performing the reaction with one equivalent of Lawesson's reagent for two hours at 80 °C in DME (entry 12). In these experimental conditions, **2a** was totally converted to a mixture of **3a** (46%) and **4a** (54%). In all the reaction conditions tested, a mixture of thioamide **3a** and imidazopyridine **4a** was obtained. After a simple filtration on alumina, the reaction mixture (**3a** and **4a**) was allowed to react with

**SYNTHESIS** 2007, No. 17, pp 2667–2673
Advanced online publication: 08.08.2007
DOI: 10.1055/s-2007-983852; Art ID: P02607SS




**Scheme 1** General synthetic route to imidazo[1,5-*a*]pyridines and possible mechanisms.

$Hg(OAc)_2$ in tetrahydrofuran as solvent to yield only imidazopyridine **4a** after stirring overnight at room temperature.

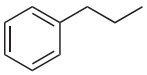
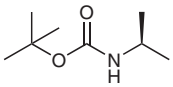
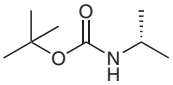
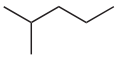
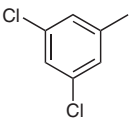
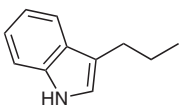
We then attempted to introduce a chiral carbon atom in position α to the imidazopyridine ring, to examine the possible epimerization during the cyclization reaction. For this purpose, we synthesized diastereoisomers **5b** and **5c**, starting from Boc-L- and Boc-D-Alanine, according to Scheme 2. After cyclization under the conditions described in Table 1, entry 12, and treatment with $Hg(OAc)_2$ after an alumina filtration as described previously, the amine function was deprotected in acidic medium and Boc-L-Valine was introduced to yield the two diastereoisomers **5b** and **5c**. The optical purity of these two diastereoisomers was checked by $^1$H NMR spectroscopy. For this purpose, 3 samples were prepared: compounds **5b** and **5c**, and a 50:50 (w/w) mixture of compounds **5b** and **5c** were analyzed by $^1$H NMR in DMSO-$d_6$. We could observe different chemical shifts in the spectra (Figure 1): at 3.70 ppm, corresponding to CH α Val; at 5.60 ppm corresponding to CH α Ala; at 6.80 ppm corresponding to NH amide, $H_6$, and $H_7$ imidazopyridine; and at 8.10 corresponding to NHBoc, $H_5$, and $H_8$ imidazopyridine. In each case, compounds **5b** and **5c** displayed a single signal, whereas the 50:50 (w/w) mixture showed the superposition of two distinct signals corresponding to the two diastereoisomers **5b** and **5c**. We could conclude that the heterocyclization reaction is racemization free for the carbon in a position α to the heterocycle, in the limit of $^1$H NMR detection.

To further investigate the scope of the reaction, several substituents were introduced at the R position, as summarized in Table 2, under the conditions described in Table 1, entry 12, and subsequently treated with 0.5 equivalent of $Hg(OAc)_2$. A wide range of substituents were tolerated (such as alkyl, aryl, heteroaryl groups) which can in some cases lead to the formation of biaryl compound **4e** in good yields. All synthesized compounds were fully characterized by RP-HPLC, LC/MS spectrometry, and $^1$H NMR and $^{13}$C NMR spectroscopy.

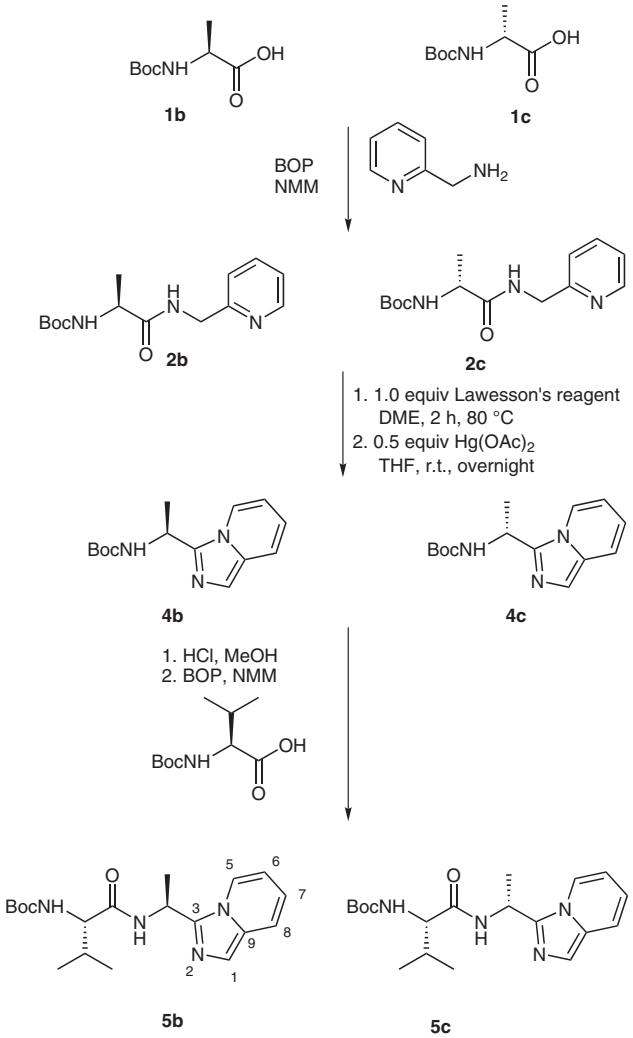
**Table 1** Influence of the Reaction Conditions on the Conversion Rate of **2a** to **3a** and **4a** as Determined by RP-HPLC Analysis at 214 nm

| Entry | Time (h) | Temp (°C) | Solvent | Lawesson's reagent (equiv) | Yield (%) **3a** | Yield (%) **4a** |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 60 | toluene | 0.5 | 55 | 45 |
| 2 | 2.0 | 60 | toluene | 0.5 | 49 | 51 |
| 3 | 1.0 | 60 | toluene | 1.0 | 36 | 45 |
| 4 | 2.0 | 60 | toluene | 1.0 | 31 | 55 |
| 5 | 1.0 | 80 | toluene | 0.5 | 4 | 49 |
| 6 | 1.0 | 60 | DME | 0.5 | 44 | 47 |
| 7 | 1.0 | 60 | DME | 1.0 | 28 | 51 |
| 8 | 2.0 | 60 | DME | 1.0 | 24 | 53 |
| 9 | 1.0 | 80 | DME | 0.5 | 34 | 39 |
| 10 | 2.0 | 80 | DME | 0.5 | 29 | 46 |
| 11 | 1.0 | 80 | DME | 1.0 | 4 | 51 |
| **12** | **2.0** | **80** | **DME** | **1.0** | **46** | **54** |
| 13 | 1.0 | 60 | THF | 0.5 | 44 | 37 |
| 14 | 2.0 | 60 | THF | 0.5 | 49 | 48 |
| 15 | 1.0 | 60 | THF | 1.0 | 42 | 41 |
| 16 | 2.0 | 60 | THF | 1.0 | 42 | 40 |

**Table 2** Variation of the R Substituent

| Compound | R | **2** Yield (%) | **4** Conversion (%)[a] | **4** Yield (%)[b] |
|---|---|---|---|---|
| **1a** |  | 95 | 54 | 80 |
| **1b** |  | 81 | 40 | 76 |
| **1c** |  | 81 | 40 | 76 |
| **1d** |  | 90 | 56 | 83 |
| **1e** |  | 97 | 20 | 69 |
| **1f** |  | 89 | 60 | 85 |

[a] Conversion rate without $Hg(OAc)_2$, determined by RP-HPLC at 214 nm.
[b] Isolated yield after treatment with $Hg(OAc)_2$.




**Scheme 2** Synthesis of L,L- and L,D-imidazopyridine diastereoisomers.

In conclusion, we have presented a new and convenient method for the synthesis of imidazo[1,5-*a*]pyridines allowing the introduction of various substituents at the position 3, including substituents bearing a chiral atom at the α position to the cycle. In this case, the optical integrity of the carbon was conserved, as checked by $^1$H NMR spectroscopy.

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical HPLC chromatograms were performed on a Beckman Gold apparatus composed with the 126 solvent module, the 168 detector and the 32 Karat software. Runs were performed on a VWR Chromolith column (50 × 3.9 mm) at a flow rate of 5 mL/min; from solution A: $H_2O$ with 0.1% TFA to solution B: MeCN with 0.1% TFA in a 3 min gradient. Mass spectra analyses were recorded on a Platform II (Micromass, Manchester, UK) quadrupole mass spectrometer fitted with an electrospray interface. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ at 300 and 75 MHz, respectively, at 300 °K on a Bruker AMX 300 apparatus.

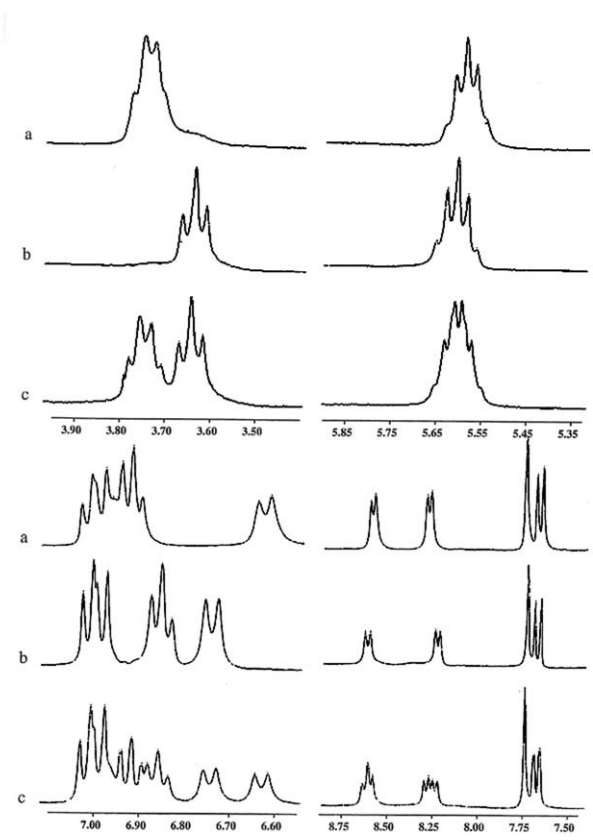



**Figure 1** a) $^1$H NMR spectral data for compound **5b**; b) $^1$H NMR spectral data for compound **5c**; c) $^1$H NMR spectral data for 50:50 (w/w) mixture of compounds **5b** and **5c**.

### *N*-2-Pyridylmethylamides 2; General Procedure

The carboxylic acid **1** (1 equiv) and BOP reagent (1 equiv) were dissolved in a minimum amount of $CH_2Cl_2$. *i*-$Pr_2NEt$ (2.5 equiv) was added under stirring, followed by 2-methylaminopyridine (1.1 equiv). The mixture was stirred for 2 h, then washed with sat. aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried ($Na_2SO_4$), filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–MeOH (100:0 to 95:5) to afford the corresponding *N*-2-pyridylmethylamide.

**2a**

Yield: 95%; $t_R$ = 1.04 min.

$^1$H NMR (DMSO-$d_6$): δ = 2.50 (t, *J* = 8 Hz, C$H_2$CH$_2$Ph, 2 H), 2.82 (t, *J* = 8 Hz, CH$_2$C$H_2$Ph, 2 H), 4.30 (d, 6 Hz, C$H_2$-*o*-pyridyl, 1 H), 7.02–7.26 (m, CHar phenyl, $H_3$ and $H_5$ *o*-pyridyl, 7 H), 7.66 (t, $J_o$ = 8 Hz, $H_4$ *o*-pyridyl, 1 H), 8.38 (br s, NH amide, 1 H), 8.44 (d, $J_{\alpha,\beta}$ = 5 Hz, $H_6$ *o*-pyridyl, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 31.4 (CH$_2$*C*H$_2$Ph), 37.3 (*C*H$_2$CH$_2$Ph), 44.5 (*C*H$_2$-*o*-pyridyl), 121.3 ($C_5$ *o*-pyridyl), 122.4 ($C_3$ *o*-pyridyl), 126.3 ($C_4$ phenyl), 128.6 ($C_3$ and $C_5$ phenyl), 128.7 ($C_2$ and $C_6$ phenyl), 137.1 ($C_4$ *o*-pyridyl), 141.6 ($C_1$ phenyl), 149.0 ($C_6$ *o*-pyridyl), 159.0 ($C_2$ *o*-pyridyl), 171.9 (C=O amide).

ES-MS: *m*/*z* = 241.1 ($MH^+$).

(*S*)-**2b** and (*R*)-**2c**

Yield: 81%; $t_R$ 0.97 min.

$^1$H NMR (DMSO-$d_6$): δ = 1.21 (d, $J$ = 7 Hz, $CH_3$ Ala, 3 H), 1.35 (s, $CH_3$ Boc, 9 H), 4.00 (m, CH α Ala, 1 H), 4.35 (m, C$H_2$-*o*-pyridyl, 2 H), 6.95 (d, $J$ = 7 Hz, N*H*Boc, 1 H), 7.22 (dd, $J_o$ = 8 Hz, $J_{\alpha,\beta}$ = 5 Hz, $H_5$ *o*-pyridyl, 1 H), 7.27 (d, $J_o$ = 8 Hz, $H_3$ *o*-pyridyl, 1 H), 7.70 (t, $J_o$ = 7 Hz, $H_4$ *o*-pyridyl, 1 H), 8.33 (t, $J$ = 6 Hz, NH amide, 1 H), 8.45 (d, $J_{\alpha,\beta}$ = 5 Hz, $H_6$ *o*-pyridyl, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 18.4 ($CH_3$ Ala), 28.5 ($CH_3$ Boc), 44.4 (*C*$H_2$-*o*-pyridyl), 54.0 (CH α Ala), 78.5 (Cq Boc), 121.2 ($C_5$ *o*-pyridyl), 122.5 ($C_3$ *o*-pyridyl), 137.2 ($C_4$ *o*-pyridyl), 148.9 ($C_6$ *o*-pyridyl), 155.6 (C=O Boc), 158.8 ($C_2$ *o*-pyridyl), 173.5 (C=O amide).

ES-MS: $m/z$ = 280.1 ($MH^+$).

**2d**

Yield: 90%; $t_R$ = 1.15 min.

$^1$H NMR (DMSO-$d_6$): δ = 0.87 [d, $J$ = 6 Hz, (C$H_3$)$_2$CH, 6 H], 1.46 [m, (CH$_3$)$_2$C*H*C$H_2$, 3 H], 2.14 [t, $J$ = 8 Hz, (CH$_3$)$_2$CHCH$_2$C$H_2$, 2 H], 4.99 (d, $J$ = 6 Hz, 2 H, C$H_2$-*o*-pyridyl), 7.60 (m, $H_3$ and $H_5$ *o*-pyridyl, 2 H), 8.13 (td, $J_o$ = 8 Hz, $J_m$ = 2 Hz, $H_4$ *o*-pyridyl, 1 H), 8.72 (d, $J_{\alpha,\beta}$ = 5 Hz, $H_6$ *o*-pyridyl, 1 H), 8.27 (br s, NH amide, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 22.2 [(*C*H$_3$)$_2$CH], 27.2 [(CH$_3$)$_2$*C*H], 33.4 [(CH$_3$)$_2$CHCH$_2$*C*H$_2$], 34.3 [(CH$_3$)$_2$CH*C*H$_2$], 47.5 (*C*$H_2$-*o*-pyridyl), 123.3 ($C_5$ *o*-pyridyl), 124.0 ($C_3$ *o*-pyridyl), 141.6 ($C_4$ and $C_6$ *o*-pyridyl), 154.3 ($C_2$ *o*-pyridyl), 172.2 (C=O amide).

ES-MS: $m/z$ = 207.1 ($MH^+$).

**2e**

Yield: 97%; $t_R$ = 1.25 min.

$^1$H NMR (DMSO-$d_6$): δ = 4.55 (d, $J$ = 6 Hz, C$H_2$-*o*-pyridyl, 2 H), 7.21 (dd, $J_o$ = 8 Hz, $J_{\alpha,\beta}$ = 5 Hz, $H_5$ *o*-pyridyl, 1 H), 7.31 (d, $J_o$ = 8 Hz, $H_3$ *o*-pyridyl, 1 H), 7.73 (m, $H_4$ *m*-dichlorophenyl and $H_4$ *o*-pyridyl, 2 H), 7.94 (d, $J_m$ = 2 Hz, $H_2$ and $H_6$ *m*-dichlorophenyl, 2 H), 8.47 (m, $H_6$ *o*-pyridyl, 1 H), 9.48 (t, $J$ = 6 Hz, NH amide, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 53.9 (*C*$H_2$-*o*-pyridyl), 121.4 ($C_5$ *o*-pyridyl), 122.5 ($C_3$ *o*-pyridyl), 126.6 ($C_2$ and $C_6$ *m*-dichlorophenyl), 131.0 ($C_4$ *m*-dichlorophenyl), 134.6 ($C_3$ and $C_5$ *m*-dichlorophenyl), 137.0 ($C_4$ *o*-pyridyl), 137.8 ($C_1$ *m*-dichlorophenyl), 149.2 ($C_6$ *o*-pyridyl), 158.6 ($C_2$ *o*-pyridyl), 164.0 (C=O amide).

ES-MS: $m/z$ = 281.2/283.0 ($MH^+$).

**2f**

Yield = 89%; $t_R$ = 1.03 min.

$^1$H NMR (DMSO-$d_6$): δ = 2.52 (t, $J$ = 8 Hz, C$H_2$CH$_2$-indole, 2 H), 2.93 (t, $J$ = 8 Hz, CH$_2$C$H_2$-indole, 2 H), 4.31 (d, $J$ = 6 Hz, C$H_2$-*o*-pyridyl, 2 H), 6.93 (t, $J_o$ = 7 Hz, $H_5$ indole, 1 H), 7.04 (m, $H_2$, $H_4$ and $H_6$ indole, 3 H), 7.19 (dd, $J$ = 6, 5 Hz, $H_5$ *o*-pyridyl, 1 H), 7.30 (d, $J_o$ = 8 Hz, $H_7$ indole, 1 H), 7.51 (d, $J_o$ = 8 Hz, $H_3$ *o*-pyridyl, 1 H), 7.63 (t, $J_o$ = 8 Hz, $H_4$ *o*-pyridyl, 1 H), 8.37 (t, $J$ = 5 Hz, NH amide, 1 H), 8.45 (d, $J$ = 5 Hz, $H_6$ *o*-pyridyl, 1 H), 10.72 (s, NH indole, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 21.4 (CH$_2$*C*H$_2$-indole), 36.6 (*C*H$_2$CH$_2$-indole), 44.5 (*C*H$_2$-*o*-pyridyl), 111.7 ($C_7$ indole), 114.1 ($C_3$ indole), 118.5 ($C_4$ indole), 118.8 ($C_5$ indole), 121.2 ($C_6$ indole), 121.3 ($C_5$ *o*-pyridyl), 122.3 ($C_3$ *o*-pyridyl), 122.7 ($C_2$ indole), 127.5 ($C_9$ indole), 136.7 ($C_8$ indole), 137.0 ($C_4$ *o*-pyridyl), 149.1 ($C_6$ *o*-pyridyl), 159.2 ($C_2$ *o*-pyridyl), 172.5 (C=O amide).

ES-MS: $m/z$ = 280.1 ($MH^+$).

**Imidazo[1,5-*a*]pyridines 4; General Procedure**

*N*-2-Pyridylmethylamide **2** (1 equiv) and Lawesson's reagent (0.5 equiv) were dissolved in DME (100 mL). The mixture was stirred for 2 h at 80 °C. The solvent was then removed in vacuo. The residue was filtered on alumina (elution with $CH_2Cl_2$). After removal of the solvent under vacuo, the residue was dissolved in THF (50 mL) and Hg(OAc)$_2$ (0.5 equiv) was added. After stirring overnight at r.t., and filtration on Celite, the residue obtained after evaporation of the solvent was purified by flash chromatography on silica gel, eluting with EtOAc–MeOH (100:0 to 95:5) to afford the corresponding imidazo[1,5-*a*]pyridine **4**. None of the thioamide compounds **3a–g** were isolated, except compounds **3b** and **3c**, which were isolated by preparative HPLC to illustrate the reaction scheme. The other thioamides were characterized by RP-HPLC and LC/MS; the results are summarized in Table 3 below.

(*S*)-**3b** and (*R*)-**3c**

$t_R$ = 1.17 min.

$^1$H NMR (DMSO-$d_6$): δ = 1.34 (d, $J$ = 7 Hz, $CH_3$ β Ala, 3 H), 1.38 (s, $CH_3$ Boc, 9 H), 4.44 (t, $J$ = 7 Hz, CH α Ala, 1 H), 4.99 (m, C$H_2$-*o*-pyridyl, 2 H), 7.16 (br s, NH Boc, 1 H), 7.60 (m, $H_3$ and $H_5$ *o*-pyridyl, 2 H), 8.13 (td, $J_o$ = 8 Hz, $J_m$ = 2 Hz, $H_4$ *o*-pyridyl, 1 H), 8.72 (d, $J_{\alpha,\beta}$ = 5 Hz, $H_6$ *o*-pyridyl, 1 H), 10.56 (t, $J$ = 5 Hz, NH thioamide, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 20.8 ($CH_3$ β Ala), 28.1 ($CH_3$ Boc), 47.5 (*C*$H_2$-*o*-pyridyl), 57.0 (CH α Ala), 78.5 (Cq Boc), 123.3 ($C_5$ *o*-pyridyl), 124.0 ($C_3$ *o*-pyridyl), 141.6 ($C_4$ and $C_6$ *o*-pyridyl), 154.3 ($C_2$ *o*-pyridyl), 155.1 (C=O Boc), 207.7 (C=S thioamide).

ES-MS: $m/z$ = 296.2 ($MH^+$).

**4a**

Yield: 80%; $t_R$ = 1.09 min.

$^1$H NMR (DMSO-$d_6$): δ = 3.08 (t, $J$ = 8 Hz, C$H_2$CH$_2$Ph, 2 H), 3.55 (t, $J$ = 7 Hz, CH$_2$C$H_2$Ph, 2 H), 6.98 (t, $J_o$ = 7 Hz, $H_6$ imidazopyridine, 1 H), 7.08 (t, $J_o$ = 8 Hz, $H_7$ imidazopyridine, 1 H), 7.10–7.24 (m, $CH_{Ar}$ phenyl, 5 H), 7.71 (d, $J_o$ = 9 Hz, $H_8$ imidazopyridine, 1 H), 7.96 (s, $H_1$ imidazopyridine, 1 H), 8.41 (d, $J_o$ = 7 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 26.2 (*C*H$_2$CH$_2$Ph), 32.3 (CH$_2$*C*H$_2$Ph), 112.9 ($C_1$ imidazopyridine), 116.7 ($C_6$ imidazopyridine), 119.1 ($C_8$ imidazopyridine), 123.2 ($C_5$ and $C_7$ imidazopyridine), 126.9 ($C_4$ phenyl), 128.7 ($C_2$ and $C_6$ phenyl), 128.9 ($C_3$ and $C_5$ phenyl), 131.5 ($C_9$ imidazopyridine), 137.0 ($C_3$ imidazopyridine), 139.7 ($C_1$ phenyl).

**Table 3** RP-HPLC and LC/MS Characterization of Thioamides **3a**,**d–f**

| Thioamide | Molecular formula | Molecular weight | Exact mass | $t_R$ (min) | ES/MS $m/z$ ($MH^+$) |
|---|---|---|---|---|---|
| **3a** | $C_{15}H_{16}N_2S$ | 256.3659 | 256.1034 | 1.21 | 257.2 |
| **3d** | $C_{12}H_{18}N_2S$ | 222.3497 | 222.1191 | 1.24 | 223.1 |
| **3e** | $C_{13}H_{10}Cl_2N_2S$ | 297.2029 | 295.9942 | 1.44 | 297.0<br>299.0 |
| **3f** | $C_{17}H_{17}N_3S$ | 295.4020 | 295.1143 | 1.56 | 296.0 |

ES-MS: *m*/*z* = 223.2 ($MH^+$).

(*S*)-**4b** and (*R*)-**4c**

Yield: 76%; $t_R$ = 0.98 min.

$^1$H NMR (DMSO-$d_6$): δ = 1.30 (s, $CH_3$ Boc, 9 H), 1.55 (d, *J* = 7 Hz, $CH_3$ Ala, 3 H), 5.27 (t, *J* = 7 Hz, CH α Ala, 1 H), 6.98 (m, $H_6$ and $H_7$ imidazopyridine, 2 H), 7.63 (d, *J* = 5Hz, NH Boc, 1 H), 7.69 (d, *J* = 8 Hz, $H_8$ imidazopyridine, 1 H), 7.80 (s, $H_1$ imidazopyridine, 1 H), 8.32 (d, 6 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 18.1 ($CH_3$ Ala), 28.1 ($CH_3$ Boc), 41.9 (CH α Ala), 78.8 (Cq Boc), 113.3 ($C_1$ imidazopyridine), 115.3 ($C_6$ imidazopyridine), 118.8 ($C_8$ imidazopyridine), 121.6 ($C_7$ imidazopyridine), 122.2 ($C_5$ imidazopyridine), 129.8 ($C_9$ imidazopyridine), 138.3 ($C_3$ imidazopyridine), 155.3 (C=O Boc).

ES-MS: *m*/*z* = 262.2 ($MH^+$).

**5b**

Yield = 82%; $t_R$ = 1.23 min.

$^1$H NMR (DMSO-$d_6$): δ = 0.72 (d, *J* = 7 Hz, $CH_3$ γ Val, 6 H), 1.32 (s, $CH_3$ Boc, 9 H), 1.65 (d, *J* = 7 Hz, $CH_3$ β Ala, 3 H), 1.86 (m, CH β Val, 1 H), 3.75 (m, CH α Val, 1 H), 5.58 (m, CH α Ala, 1 H), 6.64 (d, *J* = 8 Hz, NH amide, 1 H), 6.97 (m, $H_6$ and $H_7$ imidazopyridine, 2 H), 7.70 (d, $J_o$ = 9 Hz, $H_8$ imidazopyridine, 1 H), 7.77 (s, $H_1$ imidazopyridine, 1 H), 8.27 (d, *J* = 7 Hz, NH Boc, 1 H), 8.56 (d, $J_o$ = 7 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 17.9 (Cγ Val), 18.5 (Cγ Val), 19.0 (Cβ Ala), 28.1 ($CH_3$ Boc), 29.8 (Cβ Val), 40.1 (CH α Ala), 60.1 (CH α Val), 78.0 (Cq Boc), 114.4 ($C_1$ and $C_6$ imidazopyridine), 118.4 ($C_8$ imidazopyridine), 121.2 ($C_5$ and $C_7$ imidazopyridine), 130.0 ($C_9$ imidazopyridine), 137.4 ($C_3$ imidazopyridine), 155.4 (CO Boc), 171.6 (C=O amide).

ES-MS: *m*/*z* = 361.2 ($MH^+$).

**5c**

Yield: 78%; $t_R$ = 1.23 min.

$^1$H NMR (DMSO-$d_6$): δ = 0.82 (d, *J* = 7 Hz, $CH_3$ γ Val, 6 H), 1.34 (s, $CH_3$ Boc, 9 H), 1.64 (d, *J* = 7 Hz, $CH_3$ β Ala, 3 H), 1.89 (m, CH β Val, 1 H), 3.64 (m, CH α Val, 1 H), 5.59 (m, CH α Ala, 1 H), 6.75 (d, *J* = 8 Hz, NH amide, 1 H), 6.86 (t, $J_o$ = 7 Hz, $H_6$ imidazopyridine, 1 H), 7.01 (dd, *J* = 9, 6 Hz, $H_7$ imidazopyridine, 1 H), 7.70 (d, $J_o$ = 9 Hz, $H_8$ imidazopyridine, 1 H), 7.76 (s, $H_1$ imidazopyridine, 1 H), 8.22 (d, *J* = 7 Hz, NH Boc, 1 H), 8.59 (d, $J_o$ = 8 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 17.9 (Cγ Val), 18.5 (Cγ Val), 19.0 (Cβ Ala), 28.1 ($CH_3$ Boc), 29.8 (Cβ Val), 40.1 (CH α Ala), 60.1 (CH α Val), 78.0 (Cq Boc), 114.4 ($C_1$ and $C_6$ imidazopyridine), 118.4 ($C_8$ imidazopyridine), 121.2 ($C_5$ and $C_7$ imidazopyridine), 130.0 ($C_9$ imidazopyridine), 137.4 ($C_3$ imidazopyridine), 155.4 (C=O Boc), 171.6 (C=O amide).

ES-MS: *m*/*z* = 361.2 ($MH^+$).

**4d**

Yield: 83%; $t_R$ = 1.17 min.

$^1$H NMR (DMSO-$d_6$): δ = 0.88 [d, *J* = 6 Hz, $(CH_3)_2CH$, 6 H], 1.60 [m, $(CH_3)_2CHCH_2$, 3 H], 3.23 [t, *J* = 8 Hz, $(CH_3)_2CHCH_2CH_2$, 2 H], 7.06 (m, $H_6$ and $H_7$ imidazopyridine, 2 H), 7.73 (d, $J_o$ = 9 Hz, $H_8$ imidazopyridine, 1 H), 7.95 (s, $H_1$ imidazopyridine, 1 H), 8.45 (d, $J_o$ = 7 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 22.3 [$(CH_3)_2CH$], 22.4 [$(CH_3)_2CHCH_2CH_2$], 27.6 [$(CH_3)_2CH$], 34.8 [$(CH_3)_2CHCH_2$], 110.8 ($C_1$ imidazopyridine), 116.7 ($C_6$ imidazopyridine), 119.2 ($C_8$ imidazopyridine), 123.1 ($C_5$ and $C_7$ imidazopyridine), 129.6 ($C_9$ imidazopyridine), 138.0 ($C_3$ imidazopyridine).

ES-MS: *m*/*z* = 189.2 ($MH^+$).

**4e**

Yield: 69%; $t_R$ = 1.35 min.

$^1$H NMR (DMSO-$d_6$): δ = 6.82 (t, $J_o$ = 7 Hz, $H_7$ imidazopyridine, 1 H), 6.94 (dd, $J_o$ = 8, 6 Hz, $H_6$ imidazopyridine, 1 H), 7.68 (m, $H_8$ and $H_1$ imidazopyridine, $H_4$ *m*-dichlorophenyl, 3 H), 7.87 (s, $H_2$ and $H_6$ *m*-dichlorophenyl, 2 H), 8.55 (d, $J_o$ = 7 Hz, $H_5$ imidazopyridine, 1 H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 114.3 ($C_1$ and $C_6$ imidazopyridine), 118.4 ($C_8$ imidazopyridine), 120.3 ($C_5$ and $C_7$ imidazopyridine), 125.7 ($C_2$ and $C_6$ *m*-dichlorophenyl), 127.6 ($C_4$ *m*-dichlorophenyl), 132.1 ($C_9$ imidazopyridine), 134.6 ($C_3$ imidazopyridine, $C_3$ and $C_5$ *m*-dichlorophenyl).

ES-MS: *m*/*z* = 263.0/265.0 ($MH^+$).

**4f**

Yield: 85%: $t_R$ = 1.44 min.

$^1$H NMR (DMSO-$d_6$): δ = 3.21 (t, *J* = 7 Hz, $CH_2CH_2$-indole, 2 H), 3.60 (t, *J* = 8 Hz, $CH_2CH_2$-indole, 2 H), 6.89 (t, $J_o$ = 8 Hz, $H_5$ indole, 1 H), 6.91–7.09 (m, $H_6$ indole, $H_6$ and $H_7$ imidazopyridine, 3 H), 7.10 (s, $H_2$ indole, 1 H), 7.28 (d, $J_o$ = 8 Hz, $H_4$ indole, 1 H), 7.34 (d, $J_o$ = 8 Hz, $H_7$ indole, 1 H), 7.71 (d, $J_o$ = 9 Hz, $H_8$ imidazopyridine, 1 H), 7.99 (s, $H_1$ imidazopyridine, 1 H), 8.35 (d, $J_o$ = 7 Hz, $H_5$ imidazopyridine, 1 H), 10.84 (s, NH indole, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 22.3 ($CH_2CH_2$-indole), 25.7 ($CH_2CH_2$-indole), 110.4 ($C_3$ indole), 111.8 ($C_7$ indole), 112.1 ($C_1$ imidazopyridine), 116.8 ($C_6$ imidazopyridine), 118.2 ($C_4$ indole), 118.8 ($C_5$ indole), 119.2 ($C_8$ imidazopyridine), 121.5 ($C_6$ indole), 123.3 ($C_2$ indole and $C_7$ imidazopyridine), 123.4 ($C_5$ imidazopyridine), 127.1 ($C_9$ indole), 129.6 ($C_9$ imidazopyridine), 136.6 ($C_8$ indole), 137.5 ($C_3$ imidazopyridine).

ES-MS: *m*/*z* = 262.1 ($MH^+$).

## Acknowledgment

We are grateful to Mr. Pierre Sanchez for his indispensable help in obtaining mass spectrometry data, and Mrs. Annie Heitz for her help in interpreting the NMR spectral data.

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