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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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 carbene,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-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate] reagent16 to give the corresponding N-2-pyridylmethylamide 2. Reaction of 2 with Lawesson’s reagent17 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 acetoxydrazide. The fact that a thiophile, for example mercury(II) acetate, is necessary to totally convert 3 into 4, contrary to what was observed for the conversion of the thioacetoxydrazides into the corresponding triazolopyridines, suggests a lower reactivity of the N-2-methylpyridylthioamides compared to the thioacetoxydrazides, 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 3a and imidazopyridine 4a. We already proposed this mechanism for the cyclization reaction (see entries 1 and 2, 3 and 4, 7 and 8, 9 and 10, 11 and 12, 13 and 15, except for entries 14 and 16). A reaction time of two hours was allowed 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
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 $a$ 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 $a$ Val; at 5.60 ppm corresponding to NH amide, H$_6$, and H$_5$ imidazopyridine; and at 8.10 corresponding to NHBOc, H$_5$, and H$_4$ 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 $a$ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Lawesson’s reagent (equiv)</th>
<th>Yield (%) 3a</th>
<th>Yield (%) 4a</th>
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Table 2  Variation of the R Substituent

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<th>4 Conversion (%)a</th>
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<tr>
<td>1f</td>
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<td>60</td>
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</table>

a Conversion rate without Hg(OAc)₂, determined by RP-HPLC at 214 nm.
b Isolated yield after treatment with Hg(OAc)₂.
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 1H 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: H2O 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. 1H and 13C NMR spectra were recorded in DMSO-d6 at 300 and 75 MHz, respectively, at 300 °K on a Bruker AMX 300 apparatus.

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 1H NMR spectroscopy.

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N-2-Pyridylmethylamides 2; General Procedure

The carboxylic acid 1 (1 equiv) and BOP reagent (1 equiv) were dissolved in a minimum amount of CH2Cl2. i-Pr2NEt (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 NaHCO3 (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried (Na2SO4), 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.

Yield: 95%; tR = 1.04 min.

1H NMR (DMSO-d6): δ = 2.50 (t, J = 8 Hz, CH2CH2Ph, 2 H), 2.82 (t, J = 8 Hz, CH2CH2Ph, 2 H), 4.30 (d, 6 Hz, CH2-0-pyridyl, 1 H), 7.02–7.26 (m, CHar phenyl, H3 and H50-pyridyl, 7 H), 7.66 (t, Jo = 8 Hz, H40-pyridyl, 1 H), 8.38 (br s, NH amide, 1 H), 8.44 (d, Ja,b = 5 Hz, H60-pyridyl, 1 H).

13C NMR (DMSO-d6): δ = 31.4 (CH2CH2Ph), 37.3 (CH2CH2Ph), 44.5 (CH2-0-pyridyl), 121.3 (C1, o-pyridyl), 122.4 (C1, o-pyridyl), 126.3 (C2, phenyl), 128.6 (C4, C6 and C7 phenyl), 128.7 (C2 and C4 phenyl), 137.1 (C3, o-pyridyl), 141.6 (C1, phenyl), 149.0 (C0, o-pyridyl), 159.0 (C2, o-pyridyl), 171.9 (C=O amide).

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

Yield: 95%; tR = 1.04 min.

Figure 1  a) 1H NMR spectral data for compound 5b; b) 1H NMR spectral data for compound 5c; c) 1H NMR spectral data for 50:50 (w/w) mixture of compounds 5b and 5c.
Synthesis of Imidazo[1,5-α]pyridines Starting from N-2-Pyridylmethylamides

2d

Yield: 90%; \( t_k = 1.15 \) min.

1H NMR (DMSO-\( d_6 \)): \( \delta = 0.87 \) [\( d, J = 6 \) Hz, \( CH_2 \alpha CH_3 \), \( 6 \) H], 1.46 \( [m, (CH_2)_2 CHCH_2 \), \( 3 \) H], 2.14 \( [t, J = 6 \) Hz, \( CH_2 \alpha CHCH_2 \), \( 2 \) H], 4.99 \( [d, J = 6 \) Hz, \( 2 \) H, \( CH_2 \alpha pyridyl \), \( 1 \) H], 7.83 \( [t, J = 8 \) Hz, \( J_{\alpha - \beta} = 5 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H], 8.45 \( [d, J_{\alpha - \beta} = 5 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H].

13C NMR (DMSO-\( d_6 \)): \( \delta = 122.5 \) (C3 \( \alpha pyridyl \), \( 2 \) H), 154.3 (C2 \( \alpha pyridyl \), \( 1 \) H), 7.27 \( (d, J = 8 \) Hz, \( H_3 \alpha pyridyl \), \( 1 \) H), 7.70 \( (t, J = 5 \) Hz, \( H_4 \alpha pyridyl \), \( 1 \) H), 8.33 \( (t, J = 6 \) Hz, \( NH \) amide, \( 1 \) H), 8.45 \( (d, J_{\alpha - \beta} = 5 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H).

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

Imidazo[1,5-α]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 purified by flash chromatography on silica gel, eluting with EtOAc–MeOH (100:0 to 95:5) to afford the corresponding imidazo[1,5-α]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.

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

\( t_k = 1.17 \) min.

1H NMR (DMSO-\( d_6 \)): \( \delta = 1.34 \) (d, \( J = 7 \) Hz, CH\( \alpha \) Ala, \( 3 \) H), 1.38 \( (s, CH_2 \alpha Boc, \) \( 9 \) H), 4.44 \( (t, J = 7 \) Hz, \( CH \alpha CH_2 \) phenyl, \( 5 \) H), 7.16 \( (br s, NH \) Boc, \( 1 \) H), 7.60 \( (m, H_2 \alpha indole \), \( 1 \) H), 8.72 \( (d, J_{\alpha - \beta} = 5 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H), 8.27 \( (br s, NH \) amide, \( 1 \) H).

13C NMR (DMSO-\( d_6 \)): \( \delta = 22.2 \) [(CH\( \alpha \)CH\( \alpha \)], 27.2 [(CH\( \alpha \)CH\( \alpha \)], 33.4 [(CH\( \alpha \)CH\( \alpha \)], 47.5 \( (CH_2 \alpha pyridyl \), \( 123.3 \) (C3 \( \alpha pyridyl \), \( 124.0 \) (C3 \( \alpha pyridyl \), \( 141.6 \) (C4 and C6 \( \alpha pyridyl \), \( 154.3 \) (C2 \( \alpha pyridyl \), \( 172.2 \) (C=O amide).

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

2f

Yield: 89%; \( t_k = 1.03 \) min.

1H NMR (DMSO-\( d_6 \)): \( \delta = 2.52 \) (d, \( J = 8 \) Hz, \( CH_2 \alpha indole \), \( 2 \) H), 2.93 \( (t, J = 8 \) Hz, \( CH_2 \alpha phenyl \), \( 2 \) H), 4.31 \( (d, J = 6 \) Hz, \( CH_2 \alpha pyridyl \), \( 2 \) H), 6.93 \( (t, J = 7 \) Hz, \( H_2 \alpha indole \), \( 1 \) H), 7.04 \( (m, H_2 \alpha Boc \) and H4 \( \alpha indole \), \( 3 \) H), 7.19 \( (d, J = 5 \) Hz, \( H_4 \alpha pyridyl \), \( 1 \) H), 7.30 \( (d, J_{\alpha - \beta} = 5 \) Hz, \( H_3 \alpha pyridyl \), \( 1 \) H), 7.51 \( (d, J = 8 \) Hz, \( H_4 \alpha pyridyl \), \( 1 \) H), 7.63 \( (t, J = 8 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H), 8.37 \( (t, J = 5 \) Hz, \( NH \) amide, \( 1 \) H), 8.45 \( (d, J = 5 \) Hz, \( H_2 \alpha pyridyl \), \( 1 \) H).

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

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

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<th>Thioamide</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Exact mass</th>
<th>( t_k ) (min)</th>
<th>ES-MS ( m/z ) (MH(^+))</th>
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<tbody>
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ES-MS: m/z = 223.2 (MH⁺).

(5) 4b - and (R)-4c

Yield: 76%; tₑ = 0.98 min.

1H NMR (DMSO-d₆): δ = 1.30 (s, CH₃ Boc, 9 H), 1.55 (d, J = 7 Hz, CH₃ Ala, 3 H), 5.27 (t, J = 7 Hz, CH α Ala, 1 H), 6.98 (m, H4 and H1 imidazopyridine, 2 H), 7.18 (d, J = 5 Hz, NH Boc, 1 H), 7.69 (d, J = 8 Hz, H6 imidazopyridine, 1 H), 7.80 (s, H7 imidazopyridine, 1 H), 8.32 (d, 6 Hz, H8 imidazopyridine, 1 H).

13C NMR (DMSO-d₆): δ = 18.1 (CH₃ Ala), 28.1 (CH₃ Boc), 41.9 (CH β Ala), 78.8 (Cq Boc), 113.3 (C, imidazopyridine), 115.3 (C6 imidazopyridine), 118.8 (C5 imidazopyridine), 121.6 (C7 imidazopyridine), 122.2 (C4 imidazopyridine), 129.8 (C9 imidazopyridine), 138.3 (C3 imidazopyridine), 155.3 (C=O Boc).

ES-MS: m/z = 262.2 (MH⁺).

5b

Yield: 82%; tₑ = 1.23 min.

1H NMR (DMSO-d₆): δ = 0.72 (d, J = 7 Hz, CHγ Val, 6 H), 1.32 (s, CH₂ Val, 9 H), 1.65 (d, J = 7 Hz, CHβ Val, 3 H), 1.86 (m, CHβ Val, 1 H), 3.75 (m, CHα Val, 1 H), 5.58 (m, CHβ Ala, 1 H), 6.64 (d, J = 8 Hz, NH amide, 1 H), 6.97 (m, H4 and H1 indole, 2 H), 7.70 (d, J = 9 Hz, H6 imidazopyridine, 1 H), 7.77 (s, H7 imidazopyridine, 1 H), 8.27 (d, J = 7 Hz, NH Boc, 1 H), 8.56 (d, J = 7 Hz, H8 imidazopyridine, 1 H).

13C NMR (DMSO-d₆): δ = 17.9 (Cγ Val), 18.5 (Cγ Val), 19.0 (Cβ Ala), 28.1 (CHβ Boc), 29.8 (Cβ Val), 40.1 (CH α Ala), 60.1 (CHα Val), 78.0 (Cq Boc), 114.4 (C, and Cβ imidazopyridine), 118.4 (C4 imidazopyridine), 121.2 (C and C7 imidazopyridine), 130.0 (C, imidazopyridine), 137.4 (C imidazopyridine), 155.4 (C=O Boc), 171.6 (C=O amide).

ES-MS: m/z = 361.2 (MH⁺).

5c

Yield: 78%; tₑ = 1.23 min.

1H NMR (DMSO-d₆): δ = 0.82 (d, J = 7 Hz, CHγ Val, 6 H), 1.34 (s, CH₃ Val, 9 H), 1.64 (d, J = 7 Hz, CHβ Val, 3 H), 1.89 (m, CHβ Val, 1 H), 3.64 (m, CHβ Val, 1 H), 5.59 (m, CHα Val, 1 H), 6.75 (d, J = 8 Hz, NH amide, 1 H), 6.86 (t, J = 7 Hz, H4 imidazopyridine, 1 H), 7.01 (dd, J = 9, 6 Hz, H8 imidazopyridine, 1 H), 7.70 (d, J = 9 Hz, H6 imidazopyridine, 1 H), 7.76 (s, H7 imidazopyridine, 1 H), 8.22 (d, J = 7 Hz, NH Boc, 1 H), 8.59 (d, J = 8 Hz, H8 imidazopyridine, 1 H).

13C NMR (DMSO-d₆): δ = 17.9 (Cγ Val), 18.5 (Cγ Val), 19.0 (Cβ Ala), 28.1 (CHβ Boc), 29.8 (Cβ Val), 40.1 (CHα Val), 60.1 (CHα Val), 78.0 (Cq Boc), 114.4 (C, and Cβ imidazopyridine), 118.4 (C4 imidazopyridine), 121.2 (C, and C7 imidazopyridine), 130.0 (C, imidazopyridine), 137.4 (C, imidazopyridine), 155.4 (C=O Boc), 171.6 (C=O amide).

ES-MS: m/z = 361.2 (MH⁺).

4d

Yield: 83%; tₑ = 1.17 min.

1H NMR (DMSO-d₆): δ = 0.88 (d, J = 6 Hz, CHα Val, 6 H), 1.60 (m, CHα CH(CH₂)₃, 3 H), 2.33 (t, J = 8 Hz, CH₃(CH₂)₃CH₂CH₃, 2 H), 7.06 (m, H4 and H1 imidazopyridine, 2 H), 7.73 (d, J = 9 Hz, H6 imidazopyridine, 1 H), 7.95 (s, H7 imidazopyridine, 1 H), 8.45 (d, J = 7 Hz, H8 imidazopyridine, 1 H).

13C NMR (DMSO-d₆): δ = 22.3 [(CH₃)₂CH], 22.4 [(CH₃)₂CHCH₂CH₃], 27.6 [(CH₃)₂CH], 34.8 [(CH₃)₂CHCH₂CH₃], 110.8 (C imidazopyridine), 116.7 (C imidazopyridine), 119.2 (C₈ imidazopyridine), 123.1 (C, and C7 imidazopyridine), 129.6 (C, imidazopyridine), 138.0 (C, imidazopyridine).

ES-MS: m/z = 189.2 (MH⁺).

4e

Yield: 69%; tₑ = 1.35 min.

1H NMR (DMSO-d₆): δ = 6.82 (t, J = 7 Hz, H4 imidazopyridine, 1 H), 6.94 (dd, J = 8, 6 Hz, H6 imidazopyridine, 1 H), 7.68 (m, H4 and H1 imidazopyridine, H8 dichlorophenyl, 3 H), 7.87 (s, H, and H6 dichlorophenyl, 2 H), 8.55 (d, J = 7 Hz, H8 imidazopyridine, 1 H).

13C NMR (75 MHz, DMSO-d₆): δ = 114.3 (C, and C6 imidazopyridine), 118.4 (C4 imidazopyridine), 120.3 (C1 and C7 imidazopyridine), 125.7 (C2 and C6 dichlorophenyl), 127.6 (C4 dichlorophenyl), 132.1 (C1 imidazopyridine), 134.6 (C3 imidazopyridine, C5, and C6 dichlorophenyl).

ES-MS: m/z = 263.0/265.0 (MH⁺).

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References