Fused Heterocycles: Synthesis of Some New Imidazo[1,2-a]-pyridine Derivatives

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Abstract: Some new thiazolidines and spirothiazolidines derived from hydrazones of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide, a bioisosteric derivative of isoniazid, were synthesized and characterized by analytical, IR, \(^1\)H- and \(^13\)C-NMR and mass spectral data. Some of the newly synthesized compounds were screened for their antimycobacterial activities. None of the tested compounds showed significant \textit{in vitro} antituberculous activity at 6.25 \(\mu\)g/mL (MIC rifampin 0.031 \(\mu\)g/mL).

Keywords: Imidazo[1,2-a]pyridine, hydrazones, thiazolidines, spirothiazolidines, antituberculous activity.

Introduction

\textit{Mycobacterium tuberculosis} infects over one-third of the world’s population and causes almost three million deaths every year [1]. Isonicotinic acid hydrazide (isoniazid) is one of the primary drugs used in combination with ethambutol, rifampin, streptomycin and pyrazinamide to treat tuberculosis, but the treatment of this disease is still a major health problem due to multi-drug resistant bacterial strains and new antimycobacterial agents, different from available first-line drugs, are urgently needed. As part of our studies on imidazo[1,2-a]pyridine we have recently reported the synthesis of some imidazo[1,2-a]pyridine-3-carboxylic acid hydrazides and related compounds and their antimycobacterial activities [2]. Continuing our search for new antimycobacterial agents we have now
synthesized some new ketone-hyrazones 3a-c, thiazolidines 4a-c and spiro compounds 4d-g incorporating an imidazo[1,2-α]pyridine moiety. These compounds were characterized by their elemental and spectral analyses (IR, 1H-NMR, 13C-NMR and mass spectra).

**Results and Discussion**

The synthetic pathway followed in the preparation of the compounds is outlined in Scheme 1. The starting materials, ethyl 2-methylimidazo[1,2-α]pyridine-3-carboxylate (1) and 2-methylimidazo[1,2-α]pyridine-3-carboxylic acid hydrazide (2), were obtained by previously described methods [3,4].

**Scheme 1**
Condensation of 2 with the appropriate ketones in ethanol yielded the corresponding ketone-hydrazone 3. The hydrazones were reacted with mercaptoacetic acid in dry benzene (Method A) to give cyclocondensation products 4b,d and e in 69.8-72.3 % yields. On the other hand, refluxing a mixture of 2 and the appropriate ketone together with mercaptoacetic acid in dry benzene (Method B) also produced the target compounds 4 but in higher yields (69.7-99.1 %), except in the case of 4b (55.5 %). All the compounds were characterized by their physical data and elemental analyses (Table 1), IR, \(^1\)H- and \(^{13}\)C-NMR and EI mass spectra.

**Table 1. Some physical and analytical data of compounds 3 and 4**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>n</th>
<th>M.p. (°C)</th>
<th>Yield %</th>
<th>Formula (molecular weigh)</th>
<th>Analysis (calcld./found)(%)</th>
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<tr>
<td>3a</td>
<td>CH(_3)</td>
<td>C(_2)H(_5)</td>
<td>-</td>
<td>-</td>
<td>120-5</td>
<td>75.8</td>
<td>C(<em>{13})H(</em>{16})N(_4)O</td>
<td>63.91</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>162-6</td>
<td>62.1</td>
<td>C(<em>{14})H(</em>{16})N(<em>4)O(</em>{1.5})H(_2)O</td>
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<tr>
<td>3c</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>76-8</td>
<td>63.8</td>
<td>C(<em>{15})H(</em>{18})N(_4)O(_2)H(_2)O</td>
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<td>CH(_3)</td>
<td>CH(_3)</td>
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<td>-</td>
<td>222-5</td>
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<td>C(<em>{14})H(</em>{19})N(_4)O(_2)S.H(_2)O</td>
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<tr>
<td>4b</td>
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<td>C(<em>{16})H(</em>{18})N(_4)O(_2)S.H(_2)O</td>
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<td>4d</td>
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<td>-</td>
<td>137-43</td>
<td>75.5</td>
<td>C(<em>{16})H(</em>{18})N(_4)O(_2)S.H(_2)O</td>
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<td>C(<em>{17})H(</em>{20})N(_4)O(_2)S</td>
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<td>C(<em>{17})H(</em>{20})N(_4)O(_2)S</td>
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<td>C(<em>{18})H(</em>{22})N(_4)O(_2)S.H(_2)O</td>
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<td>C(_2)H(_5)</td>
<td>2</td>
<td>142-6</td>
<td>81.7</td>
<td>C(<em>{19})H(</em>{24})N(_4)O(_2)S.H(_2)O</td>
<td>55.86</td>
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</table>
The IR spectra of the starting materials 3 showed C=O bands in the 1654-1679 cm⁻¹ region. A new strong band at 1690-1710 cm⁻¹ in the spectra of 4 provided firm support for ring closure. The most significant evidence for the reaction was the presence of two doublets (dd, 2H, J=16 Hz) at about 3.61 and 3.68 in the ¹H-NMR spectrum of 4b [6]. In the spectra of 4a,c-g, the same protons were observed as singlets (2H) at about 3.40-3.72 ppm due to the lack of chirality. ¹³C-NMR and DEPT (135) spectra of the prototypes (4b,d and, e) were also studied and are detailed. Signals at about 71.44-76.59 ppm, which are not seen in DEPT spectra, were assigned to the quarternary (spiro) carbon atoms. According to the data obtained from DEPT and HETCOR experiments the signals at about 28.80-29.72 ppm were assigned to the CH₂ group located in the thiazolidine moiety [7]. The mass spectra of all the compounds were relatively simple and showed (except for 4g) the peaks due to molecular ions.

Antituberculous Activity

Primary screening was conducted at 6.25 µg/mL against M. tuberculosis H₃⁷Rv. The M. tuberculosis H₃⁷Rv was grown in a medium containing a radiolabeled substrate. Labeled CO₂ produced was detected and quantitated with a BACTEC 460 automatic radiometric system. Compounds giving inhibitions < 90 % (MIC > 6.25 µg/mL, MIC rifampin 0.031 µg/mL) were not evaluated further [5]. None of the compounds showed antituberculous activity at the tested concentration.

Acknowledgements

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Experimental

General

Melting points determined with a Buchi 530 melting point apparatus in open capillaries and are uncorrected. IR (KBr disks) and ¹H- and ¹³C-NMR spectra (DMSO-d₆) were recorded on Perkin Elmer Model 1600 and Bruker AC 200 and DPX 400 instruments, respectively. Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. All starting materials were purchased E. Merck (Darmstadt, Germany).
Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (1) [3].

2-Aminopyridine (0.01 mol) was heated under reflux with ethyl 2-chloroacetoacetate (0.1 mol) in 96% C₂H₅OH (25 mL) for 6h and then cooled. Excess C₂H₅OH was evaporated in vacuo. The residual red oil was partitioned between ether-water. After drying, the ether extracts were evaporated and the residual oil was allowed to crystallize. M.p. 69 °C, yield 45.05%.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (2) [4].

Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (0.01 mol) was heated under reflux with H₂NNH₂ (0.1 mol) in 96% C₂H₅OH (15 mL) for 5h and then cooled. The crystals formed were washed with H₂O, dried and recrystallized from C₂H₅OH (96%). M.p.180 °C, yield 27.16 %.

General procedure for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid (alkylidene / cycloalkylidene) hydrazides 3a-c.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (2, 0.01 mol), the appropriate ketone (0.011 mol), a drop of conc. H₂SO₄ and 96% C₂H₅OH (20 mL) were heated under reflux for 6h. The crude products which precipitated on cooling were filtered and recrystallized from an C₂H₅OH-H₂O mixture.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid sec-butylidenehydrazide (3a): IR: 1654 (C=O) cm⁻¹; ¹H-NMR: δ (ppm) = 1.04 (3H, t, CH₂CH₃), 1.98 (3H, s, CH₃), 2.28 (2H, q, CH₂CH₃), 2.53 (3H, s, 2-CH₃), 7.01 (1H, t, 6-H), 7.38 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.88 (1H, d, 5-H), 10.03 (1H, s, CONH); EIMS (%) = 244 (M⁺, 38), 159 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclopentylidenehydrazide (3b): IR: 1670 (C=O) cm⁻¹; ¹H-NMR: δ (ppm) = 1.68-1.83 (4H, m, cyclopentylidene-3H,4H), 2.34-2.49 (4H, m, cyclopentylidene-2H,5H), 2.54 (3H, s, 2-CH₃), 7.00 (1H, t, 6-H), 7.40 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.89 (1H, d, 5-H), 9.91 (1H, s, CONH); EIMS (%) = 256 (M⁺, 100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclohexylidenehydrazide (3c): IR: 1679 (C=O) cm⁻¹; ¹H-NMR: δ (ppm) = 1.4-1.78 (6H, m, cyclohexylidene 3H,4H,5H), 2.21-2.31 (2H, m, cyclohexylidene-2H,6H, axial), 2.33-2.60 (2H, m, cyclohexylidene-2H,6H, equatorial), 2.52 (3H, s, 2-CH₃), 7.01 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.56 (1H, d, 8-H), 8.86 (1H, d, 5-H), 10.28 (1H, s, CONH); EIMS (%) = 270 (M⁺, 72), 78 (100).
General procedures for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid amides 4a-g.

Method A

A mixture of 3a-c (0.01 mol) and HSCH$_2$COOH (0.15 mol) was heated under reflux for 6h in dry benzene (30 mL) using a Dean-Stark trap for removal of water of condensation. Excess benzene was evaporated in vacuo. The residue was triturated with saturated NaHCO$_3$ until CO$_2$ evaluation ceased and then allowed to stand overnight. The solid thus obtained was filtered, washed with H$_2$O and recrystallized from an C$_2$H$_5$OH-H$_2$O mixture.

Method B

The appropriate ketone (0.011 mol) was added to a solution of 2 (0.01 mol) in dry benzene (30 mL) and the mixture was heated under reflux for 1.5h using a Dean-Stark trap. After cooling HSCH$_2$COOH (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 6h. The compounds were purified using the procedure described under Method A.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-dimethyl-4-oxo-1,3-thiazolidin-3-yl)amide (4a): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 1.36 (6H, s, -C(CH$_3$)$_2$), 2.44 (3H, s, 2-CH$_3$), 3.52 (2H, s, CH$_2$S), 6.88 (1H, t, 6-H), 7.25 (1H, t, 7-H), 7.42 (1H, d, 8-H), 8.65 (1H, d, 5-H), 9.81 (1H, s, CONH); EIMS (%) = 304 (M$^+$, 3), 156 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2-ethyl-2-methyl-4-oxo-1,3-thiazolidin-3-yl)amide (4b): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm$^{-1}$; $^1$H-NMR (CDCl$_3$): δ (ppm) = 1.04 (3H, t, CH$_2$CH$_3$), 1.66 (3H, s, C-CH$_3$), 1.76-1.84,1.92-1.99 (1H, 1H, 2m, CH$_2$CH$_3$), 2.60 (3H, s, 2-CH$_3$), 3.61, 3.68 (1H, 1H, dd, J=16 Hz, CH$_2$S), 6.93 (1H, t, 6-H), 7.34 (1H, t, 7-H), 7.46 (1H, d, 8-H), 9.22 (1H, d, 5-H), 7.93 (1H, s, CONH); $^{13}$C-NMR δ(ppm) = 168.67/161.73 (thiazolidine CO and CONH), 148.19/146.57 (imidazopyridine C$_2$ and C$_{8a}$), 128.19 (imidazopyridine C$_7$), 117.14 (imidazopyridine C$_8$), 114.33 (imidazopyridine C$_3$), 71.44 (thiazolidine C$_2$), 34.72 (CH$_2$CH$_3$), 29.72 (thiazolidine C$_3$), 28.32 (CH$_3$), 16.73 (2-CH$_3$), 9.53 (CH$_2$CH$_3$); EIMS (%) = 318 (M$^+$, 100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-diethyl-4-oxo-1,3-thiazolidin-3-yl)amide (4c): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 0.8 (6H, t, CH$_2$CH$_3$), 1.50-1.65 (4H, m, CH$_2$CH$_3$), 2.40 (3H, s, 2-CH$_3$), 3.40 (2H, s, CH$_2$S), 6.64 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.66 (1H, d, 5-H), 9.72 (1H, s, CONH); EIMS (%) = 332 (M$^+$, 4.5), 46 (100).
2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)amide (4d): IR: 1662 (CONH), 1691 (spiro[4.4]nonane C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 1.67-1.97 (4H, m, spiro-7H,8H), 2.15-2.21 (2H, m, spiro-6H,9H axial), 2.23-2.40 (2H, m, spiro-6H,9H equatorial), 2.64 (3H, s, 2-CH$_3$), 3.72 (2H, s, CH$_2$S), 7.05 (1H, t, 6-H), 7.46 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.98 (1H, s, CONH); $^{13}$C-NMR δ (ppm) = 168.67/161.73 (spiro[4.4]nonane C$_3$ and CONH), 148.05/146.62 (imidazopyridine C$_2$ and C$_{8a}$), 128.25 (imidazopyridine C$_5$), 127.85 (imidazopyridine C$_7$), 117.12 (imidazopyridine C$_8$), 114.74 (imidazopyridine C$_3$), 113.34 (imidazopyridine C$_6$), 76.79 (C$_5$), 39.22 (spiro[4.4]nonane C$_6$ and C$_8$), 29.72 (spiro[4.4]nonane C$_2$), 23.62 (spiro[4.4]nonane C$_7$ and C$_8$), 16.75 (2-CH$_3$); EIMS (%) = 330 (M$^+$, 66.45), 90 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)amide (4e): IR: 1673 (CONH), 1709 (spiro[4.5]decane C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 1.05-2.54 (10H, m, spiro-6H,7H,8H,9H,10H), 2.67 (3H, s, 2-CH$_3$), 3.64 (2H, s, CH$_2$S), 7.07 (1H, t, 6-H), 7.44 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.93 (1H, s, CONH); $^{13}$C-NMR δ (ppm) = 168.67/161.73 (spiro[4.5]decane C$_3$ and CONH), 148.00/146.00 (imidazopyridine C$_2$ and C$_{8a}$), 128.29 (imidazopyridine C$_5$), 127.84 (imidazopyridine C$_7$), 117.11 (imidazopyridine C$_8$), 114.37 (imidazopyridine C$_3$), 73.04 (spiro[4.5]decane C$_5$), 28.80 (spiro[4.5]decane C$_2$), 24.90 (spiro[4.5]decane C$_8$), 23.76 (spiro[4.5]decane C$_6$ and C$_9$), 23.62 (spiro[4.5]decane C$_6$ and C$_{10}$), 16.78 (2-CH$_3$); EIMS (%) = 344 (M$^+$, 92.4), 160 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)amide (4f): IR: 1662 (CONH), 1693 (spiro[4.5]decane C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 0.67 (3H, s, CH$_3$), 1.28-1.63 (9H, m, spiro-6H,7H,8H,9H,10H), 2.43 (3H, s, 2-CH$_3$), 3.43 (2H, s, CH$_2$S), 6.85 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.67 (1H, d, 5-H), 9.79 (1H, s, CONH); EIMS (%) = 358 (M$^+$, 4), 46 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)amide (4g): IR: 1672 (CONH), 1710 (spiro[4.5]decane C=O) cm$^{-1}$; $^1$H-NMR: δ (ppm) = 0.84 (3H, s, CH$_2$CH$_3$), 1.05-1.98 (11H, m, spiro-6H,7H,8H,9H,10H, CH$_2$CH$_3$), 2.64 (3H, s, 2-CH$_3$), 3.64 (2H, s, CH$_2$S), 6.99 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.67 (1H, d, 8-H), 8.86 (1H, d, 5-H), 9.99 (1H, s, CONH); EIMS (%) = 46 (100).

In vitro evaluation of antituberculous activity [5]

A primary screen was conducted at 6.25 µg/mL against *M. tuberculosis* H$_{37}$R$_V$ in BACTEC 12B medium using a BACTEC 460 radiometric system. Compounds 3a-c, 4b,d-e, chosen as prototypes, did not show *in vitro* antituberculous activity at 6.25 µg/mL (MIC rifampin 0.031 µg/mL).
References


*Samples Availability:* Available from the authors.