SYNTHESIS OF 4,4-DIMETHYL-2-(2-PYRROLYL)-2-OXAZOLINES

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Abstract – A practical synthesis of 4,4-dimethyl-2-oxazolines on pyrrole was achieved via the cyclization of the corresponding amides, which were derived from the trichloroacetylpyrroles. The established conditions were applicable to pyrroles bearing a ketone or an ester moiety. In addition to pyrroles, the method could be extended to the synthesis of the indole derivative.

INTRODUCTION

Substituted 2-oxazolines not only abound in nature but are often used as chiral ligands. In particular, 4,4-dimethyl-2-oxazolines attached to an aryl group have been utilized in ortho-substitution of aryl carboxylic acid derivatives by electrophilic substitution via the directed lithiation, nucleophilic substitution by organolithium reagents and Grignard reagents, and transition metal-catalyzed C–H functionalization. Many synthetic methods have thus emerged for the formation of the oxazoline moiety. In most cases 4,4-dimethyl-2-oxazolines are synthesized by cyclization of the corresponding amides that are prepared from nucleophilic substitution of 2-aminoethanol derivatives with carboxylic acids or acid chlorides. The modification of Appel reaction allows the formation of oxazolines from carboxylic acids in one pot, but the elaborate purification processes are sometimes required. The reaction of nitriles and 2-aminoethanol derivatives requires harsh conditions with Lewis acids under heating conditions. Iminoothers are also employed as nitrile derivatives; however, additional reaction step to form imidates is necessary. One-pot formation of oxazolines has been recently achieved through condensation of an aldehyde and 2-aminoethanol followed by oxidation of the resulting hemiaminal. However, oxidants such as NBS cause the undesired halogenation of the electron-rich pyrrole-2-carbaldehyde or salicylaldehyde. Trichloroacetyl group is a synthetic equivalent of a carboxylic acid and readily introduced onto pyrrole. Pyrroles bearing a trichloroacetyl group are often less expensive than the corresponding carboxylic acids or acid chlorides; however, their conversion to 4,4-dimethyl-2-oxazolines has been limited. Herein we report a practical synthesis of 4,4-dimethyl-2-oxazolines on pyrroles from the trichloroacetylated derivatives.
RESULTS AND DISCUSSION

In a preliminary experiment, 2,3-dibromo-5-trichloroacetylpyrrole (1a),\textsuperscript{13} which was synthesized by a known literature procedure, was used as a test substrate to examine the formation of the amide with 2-amino-2-methyl-1-propanol (2) (Scheme 1). When a mixture of 1.0 equivalent of trichloroacetylpyrrole 1a and 1.1 equivalents of aminoalcohol 2 was stirred in acetonitrile at room temperature for 24 h, ester 3a was obtained in 36% with 51% recovery of the starting pyrrole 1a.\textsuperscript{14} Trace amount of the expected amide 4a was observed in the $^1$H NMR spectrum of the crude products.

We next examined the formation of amide 4a from the afore-obtained ester 3a. After heating at 60 °C for 1 h under neat conditions, $^1$H NMR spectroscopy showed partial conversion (ca. 10%) of ester 3a into amide 4a. Upon heating in refluxing acetonitrile for 30 min in the presence of aminoalcohol 2, the starting ester 3a was completely consumed to provide the desired amide 4a in 87% yield (Scheme 2). Based on the results that the formation of amide 4a from ester 3a did not take place at room temperature in Scheme 1, ester 3a bearing an amino group was unexpectedly stable to be isolated and identified. These results suggested that the formation of amide 4a from trichloroacetylpyrrole 1a should be conducted at heating conditions to promote the rearrangement of ester 3a to amide 4a.

\textbf{Scheme 1.} Formation of ester 3a from trichloroacetylpyrrole 1a and 2-amino-2-methyl-1-propanol (2)

\textbf{Scheme 2.} Rearrangement of ester 3a to amide 4a
We then performed the same reaction in acetonitrile at reflux to promote the rearrangement of ester 3a to amide 4a (Table 1, entry 1). As we expected, ester 3a was completely consumed in 30 min and the desired amide 4a was isolated in 37% yield. However, diacylated byproduct 5a was obtained in 29% yield. These results indicated that ester 3a underwent the rearrangement to provide the desired amide 4a and that the two methyl groups would reduce nucleophilicity of the primary amine 2, which led to the formation of the substantial amount of the diacylated product 5a. Because several attempts to improve the ratio of these products by using additives such as amines or other solvents proved ineffective, we then investigated the effects of the equivalents of aminoalcohol 2 to increase the yield of the desired amide 4a. The ratio of amide 4a to diacylated byproduct 5a was improved to 5:1 with two equivalents of aminoalcohol 2 (entry 2). The desired amide 4a was exclusively formed in a good yield in the presence of three equivalents of aminoalcohol 2 (entry 3). Finally, clean conversion to the amide 4a was achieved by using five equivalents of the aminoalcohol 2 without observation of the undesired diacylated product 5a in the 1H NMR spectrum of the crude products (entry 4). The reaction could be also performed on a 5-mmol scale to provide the corresponding amide 4a in 56% isolated yield without silica gel column chromatography.

Table 1. Effects of equivalents of the aminoalcohol on the formation of amides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalent</th>
<th>4a [%] a</th>
<th>5a [%] a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>41 (37°)</td>
<td>25 (29°)</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>65</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>70</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>67 (56b,c)</td>
<td>−d (−d)</td>
</tr>
</tbody>
</table>

a The yield was determined by 1H NMR of the crude material using N,N-dimethylformamide as an internal standard. b The reaction was carried out on a 5-mmol scale. c Isolated yield. d Not observed.
Having established the optimal conditions for the selective amide formation, we then focused on the construction of oxazoline (Scheme 3). After the primary alcohol 4a was converted to its mesylate 7a with catalytic Me₃N·HCl and MsCl, the stirring was continued at 40 °C for 19 h to provide oxazoline 6a in 49% yield. The ¹H NMR spectrum of the crude material indicated the generation of the corresponding chloride from the starting alcohol 4a. Prolonged reaction time did not improve the yield of the oxazoline. We then performed the same reaction with Ms₂O as a mesylating reagent to circumvent the formation of the chloride, which led to significant improvement of the yield of the desired oxazoline 6a.

Scheme 3. Formation of oxazoline 6a

With these results in hand, we then examined the scope and limitation of this method (Table 2). After the unsubstituted pyrrole 1b was converted to amide 4b in 84% yield, the resultant amide was subjected to the cyclization conditions using inexpensive MsCl to give the desired oxazoline 6b in 83% yield (entry 1). Apart from the amide 4a bearing the dibrominated pyrrole, amide 4b was smoothly converted to the corresponding oxazoline. The pyrrole 1c bearing an acetyl group was also transformed to the corresponding amide 4c in moderate yield. The subsequent formation of oxazoline proceeded to give the desired product 6c in 53% yield (entry 2). Trichloroacetylpyrrole 1d bearing a tert-butyl ester moiety was transformed to the corresponding amide 4d in low yield; however, the corresponding oxazoline 6d was obtained in 64% yield (entry 3). The method could be applied to indole derivative 1e to provide the corresponding oxazoline 6e (entry 4).

In summary, we have developed a practical synthesis of 4,4-dimethyl-2-oxazolines on pyrrole and indole from the corresponding trichloroacetylated derivatives. The amide formation requires five equivalents of aminoalcohol 2 to prevent the generation of the undesired diacylated product. The established conditions were applicable to substrates bearing a ketone or an ester moiety. The resulting amides were converted to the corresponding oxazolines in good to excellent yields.
Table 2. Scope of this method for the synthesis of 4,4-dimethyl-2-oxazolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Trichloroacetylpyrrole 1</th>
<th>Amide 4</th>
<th>Oxazoline 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image of 1b" /></td>
<td><img src="image2" alt="Image of 4b" /> 84%</td>
<td><img src="image3" alt="Image of 6b" /> 83%</td>
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<tr>
<td>2</td>
<td><img src="image4" alt="Image of 1c" /></td>
<td><img src="image5" alt="Image of 4c" /> 52%</td>
<td><img src="image6" alt="Image of 6c" /> 53%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Image of 1d" /></td>
<td><img src="image8" alt="Image of 4d" /> 35%</td>
<td><img src="image9" alt="Image of 6d" /> 64%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Image of 1e" /></td>
<td><img src="image11" alt="Image of 4e" /> 75%</td>
<td><img src="image12" alt="Image of 6e" /> 70%</td>
</tr>
</tbody>
</table>

*Isolated yield. Acetonitrile was used as solvent instead of dichloromethane.*
EXPERIMENTAL

**General Remarks:** Melting points (mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wave numbers (cm\(^{-1}\)). \(^1\)H NMR (400 MHz) and \(^{13}\)C\{\(^1\)H\} NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for \(^1\)H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard (CHCl\(_3\): \(\delta \) 7.26 ppm, DMSO-\(d_5\): \(\delta \) 2.50 ppm, tetramethylsilane: \(\delta \) 0 ppm) and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Chemical shifts for \(^{13}\)C NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): \(\delta \) 77.16 ppm, DMSO-\(d_6\): \(\delta \) 39.52 ppm, CD\(_3\)OD: \(\delta \) 49.00 ppm).

High-resolution mass spectra (HRMS) were performed on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment. All work-up and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck 60 F\(_{254}\) aluminum sheets precoated with a 0.25 mm thickness of silica gel. Preparative TLC separations were performed on Wako analytical plates (0.25 mm thick) precoated with silica gel 70 F\(_{254}\). Flash column chromatography was performed on Wakogel\(^{\circledR}\) C-300 (45–75 \(\mu\)m, Wako Pure Chemical Industries, Ltd.). Recycling preparative SEC-HPLC was performed with LC-9201 (Japan Analytical Industry Co., Ltd.) equipped with preparative SEC columns (JAI-GEL-1H and JAI-GEL-2H). Anhydrous CH\(_2\)Cl\(_2\) was purchased from Kanto Chemical Co., Inc.

**2,2,2-Trichloro-1-(4,5-dibromo-1\(^H\)-pyrrol-2-yl)ethan-1-one (1a):** A 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-(trichloroacetyl)pyrrole (12.0 g, 56.5 mmol, 1.0 equiv) and CHCl\(_3\) (51 mL). After the solution was cooled to 0 °C, Br\(_2\) (6.70 mL, 131 mmol, 2.3 equiv) was added dropwise to the flask. After stirring at 0 °C for 15 min, the reaction mixture was warmed to room temperature and stirred for 1.5 h, at which time the mixture was treated with water (60 mL). After partitioned, the organic layer was washed with saturated aqueous sodium thiosulfate (80 mL). The combined aqueous layer was extracted with CHCl\(_3\) (80 mL). The combined organic extracts were washed with brine (80 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the corresponding product as a colorless solid (20.4 g, 54.9 mmol, 97%), whose \(^1\)H and \(^{13}\)C NMR spectra were identical to those reported in the literature.\(^{13}\) R\(_f\) = 0.68 (hexane/CH\(_2\)Cl\(_2\) = 1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 9.50 (br s, 1H), 7.33 (s, 1H); \(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl\(_3\)): \(\delta \) 172.3, 124.0, 123.4, 113.8, 102.6, 94.0.
1-(4-Acetyl-1H-pyrrol-2-yl)-2,2,2-trichloroethan-1-one (1c): A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with trichloroacetylpyrrole (1.70 g, 8.00 mmol, 1.0 equiv), AlCl₃ (1.38 g, 10.4 mmol, 1.3 equiv), MeNO₂ (13 mL), and anhydrous CH₂Cl₂ (13 mL). After the resulting solution was cooled to –20 °C, acetyl chloride (1.01 g, 12.9 mmol, 1.6 equiv) in anhydrous CH₂Cl₂ (1.3 mL) was added dropwise to the Schlenk tube. The reaction mixture was stirred at –20 °C for 20 h and poured into ice water (40 mL) to give a white precipitate. The resulting mixture was partitioned between CH₂Cl₂ and water. The aqueous layer was extracted twice with Et₂O (10 mL). The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give analytically pure product (839 mg). The white precipitate was collected by filtration and washed with water. The solid was dissolved in CH₂Cl₂/MeOH, and the resulting solution was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give analytically pure product (1.12 g, combined weight: 1.96 g, combined yield 97%) as a gray solid, whose ¹H and ¹³C NMR spectra were identical to those reported in the literature.¹⁸ R_f = 0.36 (CH₂Cl₂/MeOH = 40:1); ¹H NMR (400 MHz, CDCl₃): δ 9.62 (br s, 1H), 7.72 (dd, J = 2.8, 1.2 Hz), 7.70 (dd, J = 3.2, 1.2 Hz), 2.49 (s, 3H); ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ 192.5, 173.0, 132.4, 127.2, 122.8, 119.6, 94.6, 27.4.

tert-Butyl 2-(2-(2,2,2-trichloroacetyl)-1H-pyrrol-1-yl)acetate (1d): A 50-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-(trichloroacetyl)pyrrole (1.03 g, 4.85 mmol, 1.0 equiv), K₂CO₃ (1.68 g, 12.1 mmol, 2.5 equiv), MeCN (16.2 mL), and tert-butyl bromoacetate (1.05 g, 5.33 mmol, 1.1 equiv). The resulting mixture was heated at 40 °C for 16 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/CH₂Cl₂ = 2:1) to provide the title compound as a colorless oil (514.0 mg, 1.57 mmol, 32%). R_f = 0.52 (hexane/CH₂Cl₂ = 1:1); IR (ATR, cm⁻¹): 1744, 1667, 1403, 1387, 1370, 1335, 1329, 1157, 1096, 845, 804; ¹H NMR (400 MHz, CDCl₃): δ 7.56 (dd, J = 4.2, 1.2 Hz), 6.99–6.95 (m, 1H), 6.30 (dd, J = 4.2, 2.4 Hz), 4.92 (s, 2H), 1.46 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 173.0, 167.0, 133.7, 124.4, 121.8, 109.5, 96.0, 82.6, 52.6, 28.0; HRMS (DART⁺) m/z: calcd. for C₁₂H₁₅O₃N₃ Cl₃, 326.0118 [M+H]+; found, 326.0107.

2,2,2-Trichloro-1-(1H-indol-3-yl)ethan-1-one (1e): The compound was prepared according to the literature procedure.¹⁹ R_f = 0.29 (hexane/CH₂Cl₂ = 1:1); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (br s, 1H), 8.46–8.42 (m, 1H), 8.37 (d, J = 3.2 Hz), 7.49–7.45 (m, 1H), 7.42–7.32 (m, 2H); ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ 176.7, 136.7, 136.2, 127.1, 123.8, 123.1, 121.3, 112.9, 104.8, 96.6.
Synthesis of ester 3a (Scheme 1)

2-Amino-2-methylpropyl 4,5-dibromo-1H-pyrrole-2-carboxylate (3a): A 30-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (499.9 mg, 5.61 mmol, 1.1 equiv), MeCN (5.0 mL), and 1a (1.88 g, 5.09 mmol, 1.0 equiv). The resulting mixture was stirred at room temperature for 24 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/CH₂Cl₂ = 1:1 to CH₂Cl₂/MeOH = 60:1 to 10:1, gradient) to give a crude amine 3a, which was washed with cold Et₂O (30 mL) to provide the title compound as a colorless solid (620.4 mg, 1.82 mmol, 36%). The starting 2-(trichloroacetyl)pyrrole (1a) was recovered in 53% yield (967.6 mg, 2.61 mmol). R_f = 0.26 (CH₂Cl₂/MeOH = 10:1); mp 177–179 °C; IR (ATR, cm⁻¹): 2921, 2908, 2853, 1739, 1487, 1472, 1457, 1373, 1283, 1243, 1217; ¹H NMR (400 MHz, CDCl₃): δ 6.92 (s, 1H), 4.04 (s, 2H), 1.19 (s, 6H); ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ 160.7, 126.3, 117.8, 112.3, 95.9, 69.2, 51.5, 24.4; HRMS (DART⁺) m/z: calcd. for C₉H₁₃O₂N₂Br₂, 338.9344 [M+H]+; found, 338.9350.

Conversion of ester 3a to amide 4a (Scheme 2)

4,5-Dibromo-N-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrrole-2-carboxamide (4a): A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (17.7 mg, 0.199 mmol, 2.0 equiv), 1a (34.0 mg, 0.100 mmol, 1.0 equiv), and MeCN (0.10 mL). The resulting mixture was heated to reflux for 30 min, at which time the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 30:1) to provide the title compound as a colorless solid (29.5 mg, 0.0868 mmol, 87%).

Screening of equivalents of aminoalcohol 2 (Table 1)

A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (10.0 mg, 0.112 mmol, 1.1 equiv), 1a (37.1 mg, 0.100 mmol, 1.0 equiv), and MeCN (0.10 mL). The resulting mixture was heated to reflux for 30 min, at which time the reaction mixture was concentrated under reduced pressure. The yields of 4a and 5a were determined by ¹H NMR analysis using DMF as an internal standard.

Isolation of compound 5a (Table 1, entry 1)

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)-2-methylpropyl 4,5-dibromo-1H-pyrrole-2-carboxylate (5a): The title compound was obtained as a yellow solid in 29% yield (9.4 mg, 0.0159 mmol) with amide 4a in 37% yield (13.7 mg, 0.0403 mmol) from 1a (40.8 mg, 0.110 mmol, 1.0 equiv) according to the above procedure. Purification was performed by preparative TLC. R_f = 0.61 (Et₂O); mp 218–220 °C; IR
Gram-scale synthesis of amide 4a (Table 1, entry 4)

4,5-Dibromo-N-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrrole-2-carboxamide (4a): A 50-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (2.22 g, 24.9 mmol, 5.0 equiv), MeCN (5.0 mL), and 1a (1.85 g, 4.99 mmol, 1.0 equiv). The resulting mixture was heated to reflux for 30 min, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 1 M aqueous hydrochloric acid (10 mL) and filtered. The residue was washed with water (10 mL) to give a crude solid, which was recrystallized from CHCl₃/MeOH to provide the title compound as a colorless solid (948.3 mg, 2.79 mmol, 56%). R_f = 0.27 (CH₂Cl₂/MeOH = 20:1); mp 180–182 °C; IR (ATR, cm⁻¹): 3176, 2973, 2934, 1640, 1632, 1562, 1514, 1454, 1415, 1390, 1366, 1249, 1223, 1174, 1056, 973, 847, 827; ¹H NMR (400 MHz, CDCl₃): δ 9.31 (br s, 1H), 6.53 (s, 1H), 5.77 (br s, 1H), 4.03 (t, 1H, J = 6.0 Hz), 3.66 (d, 2H, J = 6.0 Hz), 1.38 (s, 6H); ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ 158.8, 128.9, 113.0, 104.0, 97.7, 67.3, 55.0, 23.8; HRMS (DART⁺) m/z: calcd. for C₉H₁₃O₂N₂Br₂, 340.9323 [M+H⁺]; found, 340.9330.

General procedure for the formation of oxazoline (Scheme 3)

2-(4,5-Dibromo-1H-pyrrol-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (6a): A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged 4a (170.6 mg, 0.502 mmol, 1.0 equiv), CH₂Cl₂ (2.5 mL), triethylamine (0.21 mL, 1.5 mmol, 3.0 equiv), and trimethylamine hydrochloride (4.8 mg, 0.050 mmol, 0.10 equiv). The resulting mixture was cooled to 0 °C. MsCl (117 µL, 1.51 mmol, 3.0 equiv) was added dropwise to the test tube, and the reaction mixture was stirred at 40 °C for 19 h. The reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (3 mL) and CH₂Cl₂ (1 mL). After partitioned, the organic layer was washed with water (3 mL). The combined aqueous layer was extracted with CH₂Cl₂ (6 mL) three times. The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et₂O = 4:1) followed by SEC-HPLC to provide the title compound as a brown oil (79.6 mg, 0.247 mmol, 49%), whose ¹H and ¹³C NMR spectra were identical to those described in the following procedure.
The formation of oxazoline using Ms₂O instead of MsCl (Scheme 3)

A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 4a (177.8 mg, 0.523 mmol, 1.0 equiv), CH₂Cl₂ (2.6 mL), triethylamine (0.22 mL, 1.6 mmol, 3.0 equiv), and trimethylamine hydrochloride (5.0 mg, 0.052 mmol, 0.10 equiv). The resulting mixture was cooled to 0 °C. Ms₂O (281.3 mg, 1.57 mmol, 3.0 equiv) in CH₂Cl₂ (0.50 mL) was added dropwise to the test tube. The reaction mixture was stirred at 40 °C for 19 h, then treated with saturated aqueous sodium hydrogen carbonate (3 mL) and CH₂Cl₂ (1 mL). After partitioned, the organic layer was washed with water (3 mL). The combined aqueous layer was extracted with CH₂Cl₂ (6 mL) three times. The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/Et₂O = 2:1) to provide the title compound as a colorless amorphous (147.3 mg, 0.457 mmol, 87%). R<sub>f</sub> = 0.47 (hexane/Et₂O = 1:1); mp 112–113 °C; IR (ATR, cm⁻¹): 1652, 1546, 1426, 1191, 1176, 1163, 992, 974, 950; <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 6.67 (s, 1H), 4.07 (s, 2H), 1.33 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl₃): δ 156.4, 121.8, 115.7, 105.8, 99.9, 79.5, 67.4, 28.4; HRMS (DART⁺) m/z: calcd. for C₉H₁₁ON₂₂Br₂, 324.9197 [M+H]+; found, 324.9202.

N-(1-Hydroxy-2-methylpropan-2-yl)-1H-pyrrole-2-carboxamide (4b): A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (889.5 mg, 9.98 mmol, 5.0 equiv), MeCN (2.0 mL), and 1b (427.3 mg, 2.01 mmol, 1.0 equiv). The resulting mixture was heated to reflux for 20 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 1 M aqueous hydrochloric acid (1 mL) and CHCl₃ (2 mL), and partitioned. The organic layer was washed with 1 M aqueous hydrochloric acid (1 mL), water (1 mL), brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The aqueous layers were combined and extracted with CHCl₃ (5 mL) five times. The combined organic extracts were dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 20:1) to provide the title compound as a yellow solid (308.7 mg, 1.69 mmol, 84%). R<sub>f</sub> = 0.27 (CH₂Cl₂/MeOH = 20:1); mp 118–120 °C; IR (ATR, cm⁻¹): 3296, 1606, 1560, 1529, 1406, 1339, 1133, 1061, 1051, 840; <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 9.36 (br s, 1H), 6.95–6.91 (m, 1H), 6.54–6.50 (m, 1H), 6.26–6.21 (m, 1H), 5.87 (br s, 1H), 4.85 (t, 1H, J = 6.4 Hz), 3.67 (d, 2H, J = 6.4 Hz), 1.39 (s, 6H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-d₆): δ 160.8, 126.9, 121.1, 110.2, 108.4, 67.9, 54.7, 23.9; HRMS (DART⁺) m/z: calcd. for C₉H₁₅O₂N₂, 183.1134 [M+H]+; found, 183.1127.
4,4-Dimethyl-2-(1H-pyrrol-2-yl)-4,5-dihydrooxazole (6b): The title compound was obtained as a yellow solid in 83% yield (67.1 mg, 0.409 mmol) from 4b (89.1 mg, 0.491 mmol) according to the general procedure (40 °C, 1.5 h). The crude material was purified by silica gel column chromatography (CH2Cl2/MeOH = 20:1). Rf = 0.25 (hexane/Et2O = 1:1); mp 79–80 °C; IR (ATR, cm–1): 3124, 3076, 2967, 2865, 1739, 1654, 1550, 1426, 1358, 1327, 1191, 1122, 1073, 1035, 1026, 973, 942; 1H NMR (400 MHz, CDCl3): δ 9.19 (br s, 1H), 6.90–6.87 (m, 1H), 6.74–6.71 (m, 1H), 6.25 (dd, 1H, J = 3.2, 2.4 Hz), 4.06 (s, 2H), 1.35 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 157.5, 122.1, 120.2, 112.6, 109.5, 79.0, 67.0, 28.4; HRMS (DART+) m/z: calcd. for C9H13ON2, 165.1028 [M+H]+; found, 165.1025.

4-Acetyl-N-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrrole-2-carboxamide (4c): A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (893.6 mg, 10.0 mmol, 5.0 equiv), MeCN (2.0 mL), and 1c (506.9 mg, 1.99 mmol, 1.0 equiv). The resulting mixture was heated to reflux for 3 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 1 M aqueous hydrochloric acid (2 mL), and filtered. The filter cake was washed with Et2O (10 mL) to give a crude amide. The filtrate was extracted with CHCl3 (3 mL) three times. The combined organic extracts were dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude amide. The combined crude material was recrystallized from CHCl3/MeOH to provide the title compound as a colorless solid (232.8 mg, 1.04 mmol, 52%). Rf = 0.18 (CH2Cl2/MeOH = 20:1); mp 206–208 °C; IR (ATR, cm–1): 3222, 1659, 1630, 1567, 1532, 1458, 1434, 1392, 1366, 1354, 1297, 1229, 1147, 1060, 932, 871, 851; 1H NMR (400 MHz, CDCl3): δ 9.52 (br s, 1H), 7.48 (dd, 1H, J = 3.2, 1.6 Hz), 6.95 (dd, 1H, J = 2.2, 1.6 Hz), 5.98 (br s, 1H), 4.23 (t, 1H, J = 6.0 Hz), 3.67 (d, 2H, J = 6.0 Hz), 2.44 (s, 3H), 1.40 (s, 6H); 13C{1H} NMR (100 MHz, DMSO-d6): δ 192.7, 160.2, 128.5, 126.3, 125.8, 109.5, 67.5, 54.9, 27.0, 23.7; HRMS (DART+) m/z: calcd. for C11H17O3N2, 225.1239 [M+H]+; found, 225.1247.

1-(5-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-1H-pyrrol-3-yl)ethan-1-one (6c): The title compound was obtained as a yellow solid in 53% yield (54.9 mg, 0.266 mmol) from 4c (112.1 mg, 0.500 mmol) according to the general procedure (13 h). The crude material was purified by silica gel column chromatography (CH2Cl2/MeOH = 50:1) followed by preparative TLC (CH2Cl2/MeOH = 50:1). Rf = 0.45 (CH2Cl2/MeOH = 20:1); mp 119–121 °C; IR (ATR, cm–1): 2971, 1649, 1562, 1391, 1254, 1209, 1124, 990, 930, 855; 1H NMR (400 MHz, CDCl3): δ 11.95 (br s, 1H), 7.44 (d, 1H, J = 1.4 Hz), 7.08 (d, 1H, J = 1.4 Hz), 4.11 (s, 2H), 2.40 (s, 3H), 1.33 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 193.6, 157.3, 127.0, 126.3, 121.7, 112.9, 79.4, 67.2, 28.4, 27.4; HRMS (DART+) m/z: calcd. for C11H17O2N2, 207.1134 [M+H]+; found, 207.1134.
**tert-Butyl 2-(2-((1-hydroxy-2-methylpropan-2-yl)carbamoyl)-1H-pyrrol-1-yl)acetate (4d):** A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (894.0 mg, 10.0 mmol, 5.0 equiv), MeCN (2.0 mL), and 1d (651.6 mg, 2.0 mmol, 1.0 equiv). The resulting mixture was heated to reflux for 35 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 1 M aqueous hydrochloric acid (2 mL) and CHCl₃ (2 mL). After partitioned, the aqueous layer was extracted twice with CHCl₃ (2 mL). The combined organic extracts were washed with water (2 mL), brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a brown oil, which was dissolved in CHCl₃ (6 mL) and washed with water (6 mL) three times. The aqueous layer was extracted with CHCl₃ (20 mL) three times. The combined organic extracts were dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide a crude material, which was purified by silica gel column chromatography (hexane/Et₂O = 1:2) to provide the title compound as a colorless solid (209.2 mg, 0.706 mmol, 35%). Rₚ = 0.45 (CH₂Cl₂/Methanol = 20:1); mp 83–84 °C; IR (ATR, cm⁻¹): 3371, 2971, 1742, 1624, 1552, 1522, 1469, 1418, 1368, 1355, 1283, 1236, 1217, 1159, 1066; ¹H NMR (400 MHz, CDCl₃): δ 6.74–6.69 (m, 1H), 6.55 (dd, 1H, J = 4.0, 1.6 Hz), 6.14 (dd, 1H, J = 4.0, 2.6 Hz), 5.89 (br s, 1H), 4.92 (t, 1H, J = 6.0 Hz), 4.91 (s, 2H), 3.62 (d, 2H, J = 6.0 Hz), 1.47 (s, 9H), 1.34 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 168.4, 162.9, 128.1, 125.7, 112.2, 107.9, 82.3, 70.8, 56.4, 51.5, 28.1, 25.0; HRMS (DART⁺) m/z: calcd. for C₁₅H₂₅O₄N₂, 279.1814 [M+H]+; found, 279.1824.

**tert-Butyl 2-(2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1H-pyrrol-1-yl)acetate (6d):** The title compound was obtained as a colorless solid in 64% yield (85.7 mg, 0.308 mmol) from 4d (142.8 mg, 0.482 mmol) according to the general procedure (11 h). The crude material was purified by silica gel column chromatography (hexane/MeOAc = 20:1) followed by preparative TLC (hexane/MeOAc = 20:1). Rₚ = 0.77 (CH₂Cl₂/Methanol = 20:1); mp 51.7–52.3 °C; IR (ATR, cm⁻¹): 1750, 1656, 1470, 1439, 1367, 1352, 1276, 1228, 1155, 1074, 1015, 967, 863; ¹H NMR (400 MHz, CDCl₃): δ 6.77–6.71 (m, 2H), 6.18 (dd, 1H, J = 3.8, 2.6 Hz), 5.05 (s, 2H), 3.93 (s, 2H), 1.46 (s, 9H), 1.29 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 168.3, 155.8, 127.5, 121.3, 114.7, 108.4, 81.7, 77.8, 67.8, 51.2, 28.6, 28.2; HRMS (DART⁺) m/z: calcd. for C₁₅H₂₃O₃N₂, 279.1709 [M+H]+; found, 279.1704.

**N-(1-Hydroxy-2-methylpropan-2-yl)-1H-indole-3-carboxamide (4e):** A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-amino-2-methyl-1-propanol (2) (882.8 mg, 9.90 mmol, 5.0 equiv), MeCN (2.0 mL), and 1e (519.4 mg, 1.98 mmol, 1.0 equiv). The resulting mixture was heated to reflux for 20 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 1 M aqueous hydrochloric acid (1 mL) and CHCl₃ (2 mL). After partitioned,
the organic layer was washed with 1 M aqueous hydrochloric acid (1 mL), water (1 mL), brine (2 mL),
dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The aqueous
layers were combined and extracted with CHCl₃ (5 mL) five times. The combined organic extracts were
dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 30:1 to 20:1, gradient) to provide the
title compound as a yellow amorphous (345.7 mg, 1.48 mmol, 75%). R_f = 0.24 (CH₂Cl₂/MeOH = 20:1);
IR (ATR, cm⁻¹): 1705, 1621, 1579, 1538, 1509, 1454, 1389, 1365, 1338, 1322, 1270, 1243, 1209, 1179,
1134, 1057, 848; ¹H NMR (400 MHz, CDCl₃): δ 9.36 (br s, 1H), 7.88–7.82 (m, 1H), 7.73 (d, 1H, J = 2.8
Hz), 7.47–7.40 (m, 1H), 7.29–7.22 (m, 2H), 6.16 (s, 1H), 5.60 (br s, 1H), 3.74 (d, 2H, J = 3.2 Hz), 1.46 (s,
6H); ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ 165.1, 136.1, 128.1, 126.1, 121.8, 120.9, 120.3, 111.8,
111.3, 68.4, 54.5, 24.1; HRMS (DART⁺) m/z: calcd. for C₁₃H₁₇O₂N₂, 233.1290 [M+H⁺]; found, 233.1301.

2-(1H-Indol-3-yl)-4,4-dimethyl-4,5-dihydrooxazole (6e): To a 20-mL test tube equipped with a
Teflon-coated magnetic stirring bar were charged 4e (115.9 mg, 0.499 mmol, 1.0 equiv), MeCN (2.5 mL),
triethylamine (0.21 mL, 1.5 mmol, 3.0 equiv), and trimethylamine hydrochloride (4.6 mg, 0.0480 mmol,
0.10 equiv). The resulting mixture was cooled to 0 °C. MsCl (117 µL, 1.50 mmol, 3.0 equiv) was added
dropwise to the test tube. The reaction mixture was cooled to 0 °C for 25 h, then treated with saturated
aqueous sodium hydrogen carbonate (3 mL) and EtOAc (3 mL). After partitioned, the aqueous layer was
extracted twice with EtOAc (1 mL). The combined organic extracts were washed with water (3 mL), and
brine (3 mL) respectively, dried over sodium sulfate, and filtered. The filtrate was concentrated under
reduced pressure to give a crude material, which was purified by silica gel column chromatography
(CH₂Cl₂/MeOH = 40:1 to 30:1, gradient) to provide the corresponding product as a colorless solid (74.3
mg, 0.347 mmol, 70%). R_f = 0.35 (CH₂Cl₂/MeOH = 20:1); mp 157–158 °C; IR (ATR, cm⁻¹): 2966, 1630,
1617, 1535, 1452, 1370, 1337, 1281, 1248, 1180, 1159, 1142, 1035, 1012, 961, 841, 820; ¹H NMR (400
MHz, CDCl₃): δ 9.58 (br s, 1H), 8.23–8.15 (m, 1H), 7.71 (s, 1H), 7.39–7.32 (m, 1H), 7.24–7.17 (m, 2H),
4.10 (s, 2H), 1.41 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 160.6, 136.3, 128.3, 125.7, 122.8, 121.5,
121.3, 111.8, 105.0, 78.5, 67.0, 28.7; HRMS (DART⁺) m/z: calcd. for C₁₃H₁₅ON₂, 215.1184 [M+H⁺]; found, 215.1195.

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REFERENCES AND NOTES


14. The formation of ester was not observed in the case of 2-amino-1-propanol and 2-aminoethanol.


16. The amides, which were derived from 2-amino-1-propanol and 2-aminoethanol, required prolonged reaction time for the formation of oxazoline.

17. Prolonged reaction time caused the nucleophilic substitution of the tert-butyl ester with 2-amino-2-methyl-1-propanol (2).
