HETEROCYCLES, Vol. 98, No. 1, 2019, pp. 63 - 77. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 29th November, 2018, Accepted, 21st December, 2018, Published online, 21st January, 2019
DOI: 10.3987/COM-18-14019

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

Kentaro Okano,* Kazuki Morii, Daichi Mari, and Atsunori Mori

Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan. E-mail: okano@harbor.kobe-u.ac.jp

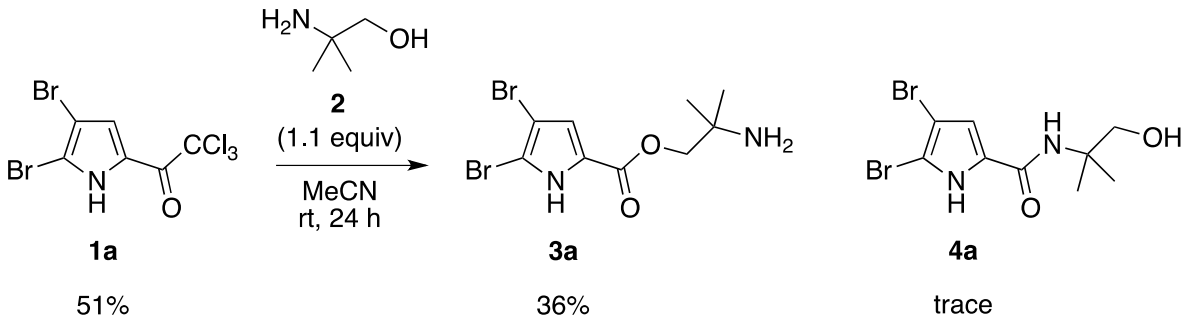
Abstract – A practical synthesis of 4,4-dimethyl-2-oxazolines on pyrrole was achieved via the cyclization of the corresponding amides, which were derived from the trichloroacetylpyrroles. The established conditions were applicable to pyrroles bearing a ketone or an ester moiety. In addition to pyrroles,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

INTRODUCTION

Substituted 2-oxazolines not only abound in nature[1] but are often used as chiral ligands.[2] 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,[3] nucleophilic substitution by organolithium reagents and Grignard reagents,[4] and transition metal-catalyzed C–H functionalization.[5] 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[6] or acid chlorides.[7] The modification of Appel reaction[8] allows the formation of oxazolines from carboxylic acids in one pot, but the elaborate purification processes are sometimes required.[7a] The reaction of nitriles and 2-aminoethanol derivatives requires harsh conditions with Lewis acids under heating conditions.[9] Iminoethers are also employed as nitrile derivatives; however, additional reaction step to form imidates is necessary.[10] One-pot formation of oxazolines has been recently achieved through condensation of an aldehyde and 2-aminoethanol followed by oxidation of the resulting hemiaminal.[11] However, oxidants such as NBS cause the undesired halogenation of the electron-rich pyrrole-2-carbaldehyde or salicylaldehyde.[11b] 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.[12] Herein we report a practical synthesis of 4,4-dimethyl-2-oxazolines on pyrroles from the trichloroacetylated derivatives.

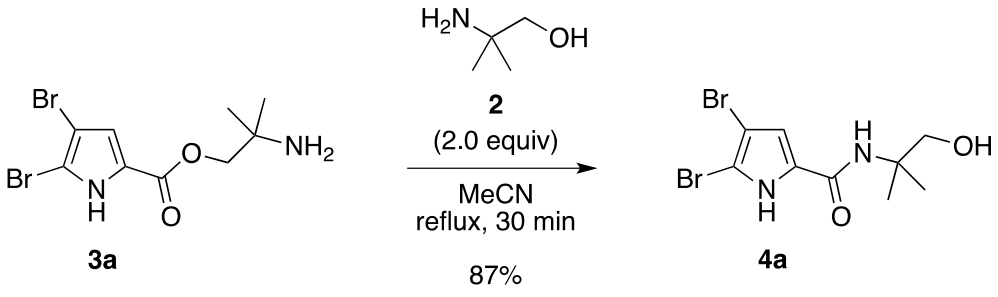
RESULTS AND DISCUSSION

In a preliminary experiment, 2,3-dibromo-5-trichloroacetylpyrrole (**1a**),[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**.[14] Trace amount of the expected amide **4a** was observed in the ^{1}H NMR spectrum of the crude products.



Scheme 1. Formation of ester **3a** from trichloroacetylpyrrole **1a** and 2-amino-2-methyl-1-propanol (**2**)

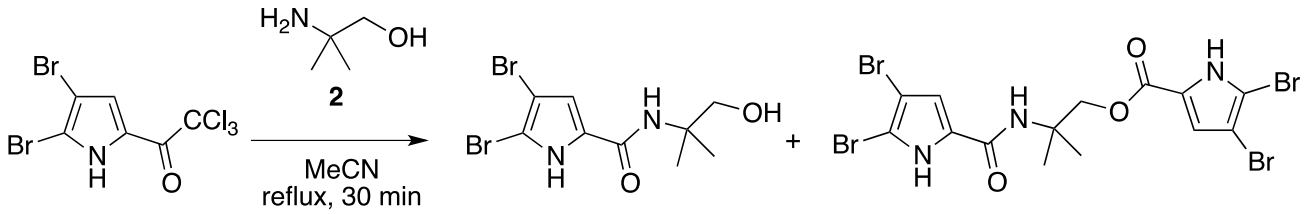
We next examined the formation of amide **4a** from the afore-obtained ester **3a**. After heating at 60 °C for 1 h under neat conditions, ^{1}H NMR spectroscopy showed partial conversion (ca. 10%) of ester **3a** into amide **4a**. Upon heating in refluxing acetonitrile for 30 min in the presence of 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**.



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 ^{1}H 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.

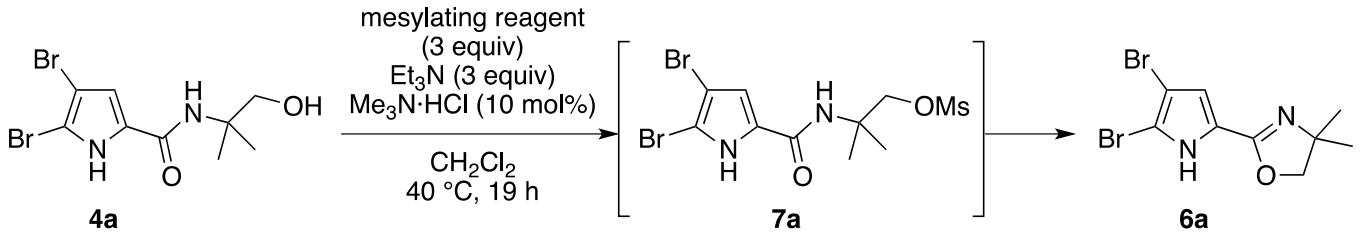
Table 1. Effects of equivalents of the aminoalcohol on the formation of amides



Entry	Equivalent	**4a** [%][a]	**5a** [%][a]
1	1.1	41 (37[c])	25 (29[c])
2	2.0	65	13
3	3.0	70	<5
4	5.0	67 (56[b,c])	–[d] (–[d])

[a] The yield was determined by ^{1}H 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 $Me_3N{\cdot}HCl$[15] and MsCl, the stirring was continued at 40 °C for 19 h to provide oxazoline **6a** in 49% yield.[16] 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 Ms_2O as a mesylating reagent to circumvent the formation of the chloride, which led to significant improvement of the yield of the desired oxazoline **6a**.



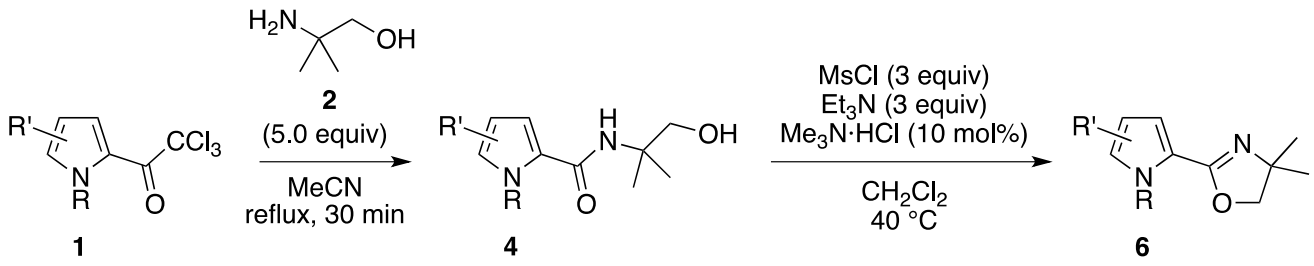
mesylating reagent	
MsCl	49%
Ms_2O	87%

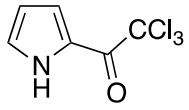
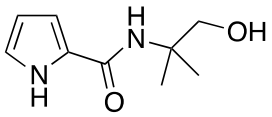
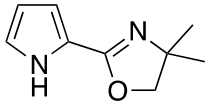
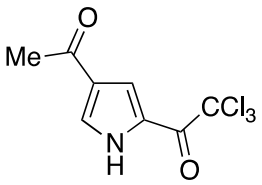
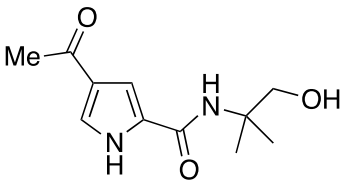
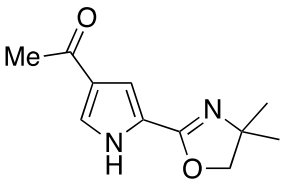
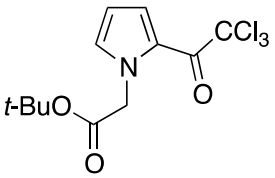
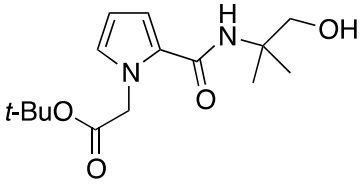
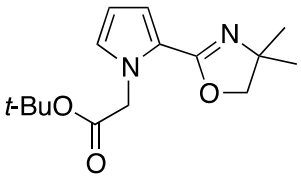
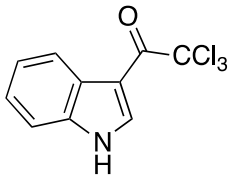
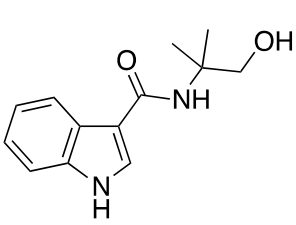
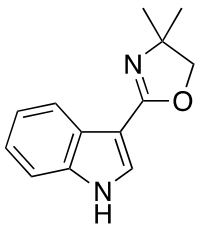
Scheme 3. Formation of oxazoline **6a**

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;[17] 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



Entry	Trichloroacetylpyrrole **1**	Amide **4**	Oxazoline **6**
1	 **1b**	 **4b** 84%	 **6b** 83%
2	 **1c**	 **4c** 52%	 **6c** 53%
3	 **1d**	 **4d** 35%	 **6d** 64%
4[b]	 **1e**	 **4e** 75%	 **6e** 70%

[a] Isolated yield. [b] 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}). ^1H NMR (400 MHz) and $^{13}C\{^1H\}$ NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^1H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, DMSO-d_5: δ 2.50 ppm, tetramethylsilane: δ 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 ($CDCl_3$: δ 77.16 ppm, DMSO-d_6: δ 39.52 ppm, CD_3OD: δ 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® C-300 (45–75 μm, 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_2Cl_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 ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[13] R_f = 0.68 (hexane/CH_2Cl_2 = 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (br s, 1H), 7.33 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.3, 124.0, 123.4, 113.8, 102.6, 94.0.

1-(4-Acetyl-1*H*-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), $AlCl_3$ (1.38 g, 10.4 mmol, 1.3 equiv), $MeNO_2$ (13 mL), and anhydrous CH_2Cl_2 (13 mL). After the resulting solution was cooled to –20 °C, acetyl chloride (1.01 g, 12.9 mmol, 1.6 equiv) in anhydrous CH_2Cl_2 (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 CH_2Cl_2 and water. The aqueous layer was extracted twice with Et_2O (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 CH_2Cl_2/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 ^{13}C NMR spectra were identical to those reported in the literature.[18] R_f = 0.36 (CH_2Cl_2/MeOH = 40:1); ^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (br s, 1H), 7.72 (dd, 1H, *J* = 2.8, 1.2 Hz), 7.70 (dd, 1H, *J* = 3.2, 1.2 Hz), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): 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)-1*H*-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), K_2CO_3 (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/CH_2Cl_2 = 2:1) to provide the title compound as a colorless oil (514.0 mg, 1.57 mmol, 32%). R_f = 0.52 (hexane/CH_2Cl_2 = 1:1); IR (ATR, cm^{-1}): 1744, 1667, 1403, 1387, 1370, 1335, 1239, 1157, 1096, 845, 804; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, 1H, *J* = 4.2, 1.2 Hz), 6.99–6.95 (m, 1H), 6.30 (dd, 1H, *J* = 4.2, 2.4 Hz), 4.92 (s, 2H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{15}O_3N^{35}Cl_3$, 326.0118 $[M+H]^+$; found, 326.0107.

2,2,2-Trichloro-1-(1*H*-indol-3-yl)ethan-1-one (1e): The compound was prepared according to the literature procedure.[19] R_f = 0.29 (hexane/CH_2Cl_2 = 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (br s, 1H), 8.46–8.42 (m, 1H), 8.37 (d, 1H, *J* = 3.2 Hz), 7.49–7.45 (m, 1H), 7.42–7.32 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): 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-1*H*-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/CH_2Cl_2 = 1:1 to CH_2Cl_2/MeOH = 60:1 to 10:1, gradient) to give a crude amine **3a**, which was washed with cold Et_2O (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 (CH_2Cl_2/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, $CDCl_3$): δ 6.92 (s, 1H), 4.04 (s, 2H), 1.19 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 160.7, 126.3, 117.8, 112.3, 95.9, 69.2, 51.5, 24.4; HRMS (DART$^+$) *m/z*: calcd. for $C_9H_{13}O_2N_2{}^{79}Br^{81}Br$, 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)-1*H*-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 (CH_2Cl_2/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-1*H*-pyrrole-2-carboxamido)-2-methylpropyl 4,5-dibromo-1*H*-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 (Et_2O); mp 218–220 °C; IR

(ATR, cm^{-1}): 2928, 1742, 1487, 1365, 1230, 1217, 840, 824; ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 2H), 6.91 (s, 1H), 6.50 (s, 1H), 6.09 (br s, 1H), 4.38 (s, 2H), 1.51 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 161.5, 160.8, 129.4, 125.1, 118.8, 114.7, 108.5, 105.8, 100.6, 99.8, 69.7, 54.9, 24.6; HRMS ($DART^+$) *m/z*: calcd. for $C_{14}H_{14}O_3N_3{}^{79}Br_3{}^{81}Br$, 589.7748 $[M+H]^+$; found, 589.7757.

Gram-scale synthesis of amide 4a (Table 1, entry 4)

4,5-Dibromo-*N*-(1-hydroxy-2-methylpropan-2-yl)-1*H*-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 $CHCl_3$/MeOH to provide the title compound as a colorless solid (948.3 mg, 2.79 mmol, 56%). R_f = 0.27 (CH_2Cl_2/MeOH = 20:1); mp 180–182 °C; IR (ATR, cm^{-1}): 3176, 2973, 2934, 1640, 1632, 1562, 1514, 1454, 1415, 1390, 1366, 1327, 1249, 1223, 1174, 1056, 973, 847, 827; ^1H NMR (400 MHz, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 158.8, 128.9, 113.0, 104.0, 97.7, 67.3, 55.0, 23.8; HRMS ($DART^+$) *m/z*: calcd. for $C_9H_{13}O_2N_2{}^{79}Br^{81}Br$, 340.9323 $[M+H]^+$; found, 340.9330.

General procedure for the formation of oxazoline (Scheme 3)

2-(4,5-Dibromo-1*H*-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), CH_2Cl_2 (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 CH_2Cl_2 (1 mL). After partitioned, the organic layer was washed with water (3 mL). The combined aqueous layer was extracted with CH_2Cl_2 (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/Et_2O = 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 ^{13}C NMR spectra were identical to those described in the following procedure.

The formation of oxazoline using Ms_2O 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), CH_2Cl_2 (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. Ms_2O (281.3 mg, 1.57 mmol, 3.0 equiv) in CH_2Cl_2 (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 CH_2Cl_2 (1 mL). After partitioned, the organic layer was washed with water (3 mL). The combined aqueous layer was extracted with CH_2Cl_2 (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/Et_2O = 2:1) to provide the title compound as a colorless amorphous (147.3 mg, 0.457 mmol, 87%). R_f = 0.47 (hexane/Et_2O = 1:1); mp 112–113 °C; IR (ATR, cm^{-1}): 1652, 1546, 1426, 1191, 1176, 1163, 992, 974, 950; ^1H NMR (400 MHz, $CDCl_3$): δ 6.67 (s, 1H), 4.07 (s, 2H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 121.8, 115.7, 105.8, 99.9, 79.5, 67.4, 28.4; HRMS (DART$^+$) *m/z*: calcd. for $C_9H_{11}ON_2{}^{81}Br_2$, 324.9197 $[M+H]^+$; found, 324.9202.

***N*-(1-Hydroxy-2-methylpropan-2-yl)-1*H*-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 $CHCl_3$ (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 $CHCl_3$ (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 (CH_2Cl_2/MeOH = 20:1) to provide the title compound as a yellow solid (308.7 mg, 1.69 mmol, 84%). R_f = 0.27 (CH_2Cl_2/MeOH = 20:1); mp 118–120 °C; IR (ATR, cm^{-1}): 3296, 1606, 1560, 1529, 1406, 1339, 1133, 1061, 1051, 840; ^1H NMR (400 MHz, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 160.8, 126.9, 121.1, 110.2, 108.4, 67.9, 54.7, 23.9; HRMS (DART$^+$) *m/z*: calcd. for $C_9H_{15}O_2N_2$, 183.1134 $[M+H]^+$; found, 183.1127.

4,4-Dimethyl-2-(1*H*-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 (CH_2Cl_2/MeOH = 20:1). R_f = 0.25 (hexane/Et_2O = 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, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.5, 122.1, 120.2, 112.6, 109.5, 79.0, 67.0, 28.4; HRMS (DART$^+$) *m/z*: calcd. for $C_9H_{13}ON_2$, 165.1028 $[M+H]^+$; found, 165.1025.

4-Acetyl-*N*-(1-hydroxy-2-methylpropan-2-yl)-1*H*-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 Et_2O (10 mL) to give a crude amide. The filtrate was extracted with $CHCl_3$ (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 $CHCl_3$/MeOH to provide the title compound as a colorless solid (232.8 mg, 1.04 mmol, 52%). R_f = 0.18 (CH_2Cl_2/MeOH = 20:1); mp 206–208 °C; IR (ATR, cm^{-1}): 3222, 1659, 1630, 1567, 1532, 1491, 1458, 1434, 1392, 1366, 1354, 1297, 1229, 1147, 1060, 932, 871, 851; ^1H NMR (400 MHz, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): 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 $C_{11}H_{17}O_3N_2$, 225.1239 $[M+H]^+$; found, 225.1247.

1-(5-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-1*H*-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 (CH_2Cl_2/MeOH = 50:1) followed by preparative TLC (CH_2Cl_2/MeOH = 50:1). R_f = 0.45 (CH_2Cl_2/MeOH = 20:1); mp 119–121 °C; IR (ATR, cm^{-1}): 2971, 1649, 1562, 1391, 1296, 1209, 1124, 990, 930, 855; ^1H NMR (400 MHz, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{11}H_{15}O_2N_2$, 207.1134 $[M+H]^+$; found, 207.1134.

***tert*-Butyl 2-(2-((1-hydroxy-2-methylpropan-2-yl)carbamoyl)-1*H*-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, 2.00 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 $CHCl_3$ (2 mL). After partitioned, the aqueous layer was extracted twice with $CHCl_3$ (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 $CHCl_3$ (6 mL) and washed with water (6 mL) three times. The aqueous layer was extracted with $CHCl_3$ (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/Et_2O = 1:2) to provide the title compound as a colorless solid (209.2 mg, 0.706 mmol, 35%). R_f = 0.45 (CH_2Cl_2/MeOH = 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, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{25}O_4N_2$, 279.1814 $[M+H]^+$; found, 279.1824.

***tert*-Butyl 2-(2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1*H*-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). R_f = 0.77 (CH_2Cl_2/MeOH = 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, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{23}O_3N_2$, 279.1709 $[M+H]^+$; found, 279.1704.

***N*-(1-Hydroxy-2-methylpropan-2-yl)-1*H*-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 $CHCl_3$ (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 $CHCl_3$ (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 (CH_2Cl_2/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 (CH_2Cl_2/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, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): 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 $C_{13}H_{17}O_2N_2$, 233.1290 $[M+H]^+$; found, 233.1301.

2-(1*H*-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 heated to 60 °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 (CH_2Cl_2/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 (CH_2Cl_2/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, $CDCl_3$): 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{15}ON_2$, 215.1184 $[M+H]^+$; found, 215.1195.

ACKNOWLEDGMENTS

This work was financially supported by JSPS KAKENHI Grant Numbers JP16K05774 in Scientific Research (C), JP16H01153 and 18H04413 in the Middle Molecular Strategy, and Kawanishi Memorial ShinMaywa Education Foundation. A part of this article is based on results obtained from a project subsidized by the New Energy and Industrial Technology Development Organization (NEDO).

REFERENCES AND NOTES

1. (a) H. R. Onishi, B. A. Pelak, L. S. Gerckens, L. L. Silver, F. M. Kahan, M.-H. Chen, A. A. Patchett, S. M. Galloway, S. A. Hyland, M. S. Anderson, and C. R. H. Raetz, *Science*, 1996, **274**, 980; (b) E. Riego, D. Hernández, F. Albericio, and M. Álvarez, *Synthesis*, 2005, 1907; (c) A. Asano, T. Yamada, T. Taniguchi, M. Sasaki, K. Yoza, and M. Doi, *J. Pept. Sci.*, 2018, **24**, e3120.
2. (a) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; (b) P. Braunstein and F. Naud, *Angew. Chem. Int. Ed.*, 2001, **40**, 680; (c) G. Desimoni, G. Faita, and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561; (d) H. Nishiyama, *Chem. Soc. Rev.*, 2007, **36**, 1133; (e) J. S. Cannon and L. E. Overman, *Acc. Chem. Res.*, 2016, **49**, 2220; (f) K. Morisaki, H. Morimoto, K. Mashima, and T. Ohshima, *J. Synth. Org. Chem. Jpn.*, 2018, **76**, 226.
3. (a) L. DellaVecchia and I. Vlattas, *J. Org. Chem.*, 1977, **42**, 2649; (b) T. D. Harris, B. Neuschwander, and V. Boekelheide, *J. Org. Chem.*, 1978, **43**, 727; (c) E. Wehman, G. Van Koten, and J. T. B. H. Jastrzebski, *J. Organomet. Chem.*, 1986, **302**, C35.
4. A. I. Meyers and W. B. Avila, *J. Org. Chem.*, 1981, **46**, 3881.
5. (a) Y. Ie, N. Chatani, T. Ogo, D. R. Marshall, T. Fukuyama, F. Kakiuchi, and S. Murai, *J. Org. Chem.*, 2000, **65**, 1475; (b) F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani, and S. Murai, *Chem. Lett.*, 2001, 422; (c) S. Oi, E. Aizawa, Y. Ogino, and Y. Inoue, *J. Org. Chem.*, 2005, **70**, 3113; (d) X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78; (e) X. Chen, K. M. Engle, D.-H. Wang, and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094.
6. (a) V. Rosnati and D. Misiti, *Gazz. Chim. Ital.*, 1960, **90**, 584; (b) J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; (c) D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 1972, **13**, 3031; (d) A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270.
7. (a) H. Vorbrüggen and K. Krolikiewicz, *Tetrahedron*, 1993, **49**, 9353; (b) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297.
8. R. Appel, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 801.
9. (a) E. L. Hölljes, Jr. and E. C. Wagner, *J. Org. Chem.*, 1944, **9**, 31; (b) M. Dreme, S. Brunel, M. F. Llauro, P. Le Perchec, J. Garapon, and B. Sillion, *Tetrahedron*, 1984, **40**, 349; (c) C. Bolm, K. Weickhardt, M. Zehnder, and T. Ranff, *Chem. Ber.*, 1991, **124**, 1173.
10. (a) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, 1951, **73**, 3744; (b) M. I. Butt, D. G. Neilson, K. M. Watson, and U. Zakir, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2328.
11. (a) Intramolecular 1,4-hydride shift: M. T. Shipchandler, *J. Heterocycl. Chem.*, 1977, **14**, 305; (b) S. Sayama, *Synlett*, 2006, **17**, 1479; (c) K. Schwekendiek and F. Glorius, *Synthesis*, 2006, 2996; (d) B. T. Hahn, K. Schwekendiek, and F. Glorius, *Org. Synth.*, 2008, **85**, 267; (e) M. Ishihara and H. Togo, *Tetrahedron*, 2007, **63**, 1474.

12. (a) P. Zhou and N. R. Natale, *Synth. Commun.*, 1998, **28**, 3317; (b) R. C. Fuson and B. A. Bull, *Chem. Rev.*, 1934, **15**, 275.
13. J. J. Richards, T. E. Ballard, R. W. Huigens, III, and C. Melander, *ChemBioChem*, 2008, **9**, 1267.
14. The formation of ester was not observed in the case of 2-amino-1-propanol and 2-aminoethanol.
15. Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, and Y. Tanabe, *Tetrahedron*, 1999, **55**, 2183.
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**).
18. D. O. A. Garrido, G. Buldain, M. I. Ojea, and B. Frydman, *J. Org. Chem.*, 1988, **53**, 403.
19. A. H. Essa, R. I. Lerrick, E. Ciftci, R. W. Harrington, P. G. Waddell, W. Clegg, and M. J. Hall, *Org. Biomol. Chem.*, 2015, **13**, 5793.