HETEROCYCLES, Vol. 92, No. 5, 2016, pp. 900 - 909. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 16th February, 2016, Accepted, 4th March, 2016, Published online, 10th March, 2016
DOI: 10.3987/COM-16-13440

DEVELOPMENT OF MADELUNG-TYPE INDOLE SYNTHESIS USING COPPER-CATALYZED AMIDATION/CONDENSATION STRATEGY

Masahiro Abe, Charline Denneval, Kanako Nozawa-Kumada, and Yoshinori Kondo*

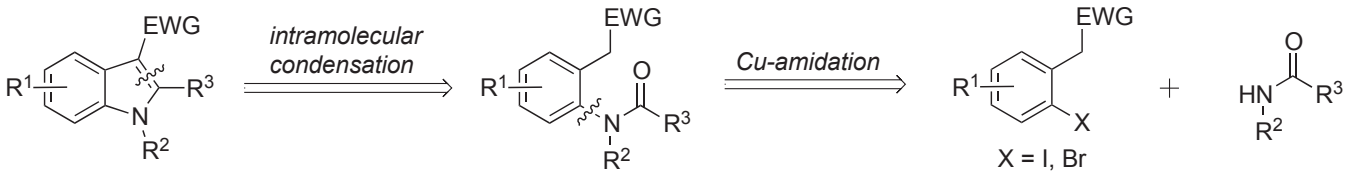
Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aramaki Aza Aoba, Aobaku, Sendai 980-8578, Japan; E-mail:ykondo@m.tohoku.ac.jp

Abstract – A new method for Madelung-type indole synthesis was investigated, and it was found that the amidation of 2-iodophenylacetonitrile with various alkanamides proceeds smoothly in the presence of CuI and a diamine ligand. The subsequent cyclization of the C-N coupling products takes place under the coupling reaction conditions.

INTRODUCTION

Indoles are one of the most ubiquitous heterocycles in biologically active natural products, and the indole moiety appears as a substructure of numerous pharmaceuticals, agrochemicals and functional materials.[1] The substituted indoles have been referred to as privileged structures for drug discovery[2] and the study of indole syntheses has been an important research area for synthetic chemists.[3] The Madelung indole synthesis is one of the most versatile methods for the synthesis of 2,3-substituted indoles, which involves intramolecular cyclization of an *N*-(2-alkylphenyl)alkanamide with a strong base at elevated temperatures.[4] The most common conditions employed include potassium alkoxide at temperatures of 200-300 °C and also use reactive bases like LDA or *n*-BuLi. Relevant intramolecular condensation reactions have been investigated for indole ring construction that provide various 2,3-substituted indole derivatives.[5] A modified Madelung-type cyclization for the preparation of indole-3-carboxylate derivatives has also been investigated using the phenylalkanamide substrates with a cyanomethyl or an alkoxylcarbonylmethyl group.[6] Although this cyclization method is considered to be useful, the drawback lies on the limited construction of the anilide substrate for the cyclization. On the other hand, transition-metal-catalyzed amidation of aryl halides has been widely investigated and the Cu-catalyzed Goldberg amidation reaction has also been well employed with the important finding of considerable acceleration by organic ligands.[7] In order to develop a new Madelung-type indole synthesis, we have designed a new tandem one-pot Cu-catalyzed amidation/cyclization process from

2-halophenylacetonitrile or 2-halophenylacetates for 3-substituted indoles as shown in Scheme 1. Recently, *ortho*-selective iodination of phenylacetic acid derivatives in the presence of palladium catalyst was reported by Yu *et al.*[8] and the methodology is considered to be advantageous for the access to the substrates for this Cu-catalyzed amidation/intramolecular condensation strategy. The strong bases have been employed for the Madelung cyclization, but we anticipated that the one–pot amidation/condensation procedure would be able to be achieved by an appropriate choice of substrates and reaction conditions.

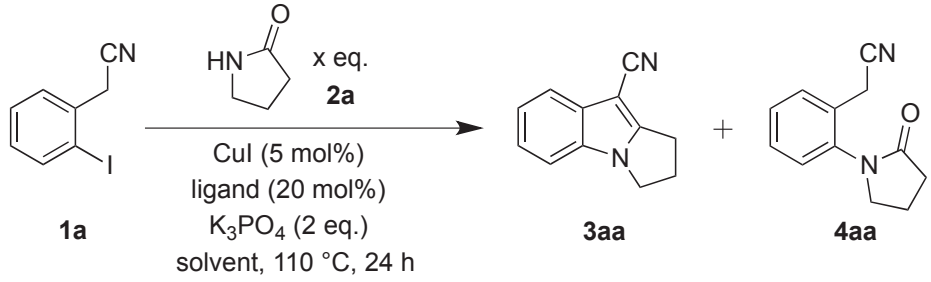


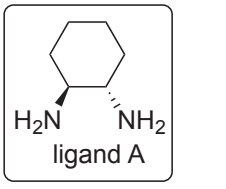
Scheme 1. Synthetic strategy of sequential amidation/condensation

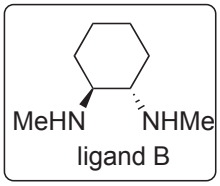
RESULTS AND DISCUSSION

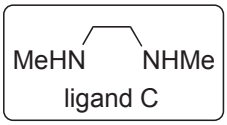
We started with the reaction of 2-iodophenylacetonitrile and 2-pyrrolidone. The reaction was carried out in the presence of CuI, ligand A, K_3PO_4 in toluene 110 °C for 24 h and the amidated product **4aa** was obtained with the cyclized cyanoindole **3aa**. In order to convert amidated product **4aa** to cyclized cyanoindole **3aa**, we initially focused our study on the solvent effect of this reaction. We anticipated that intramolecular cyclization reaction would proceed smoothly in more soluble solvents for K_3PO_4. Dioxane gave a lower yield (29%) while DMF gave a good yield (75%) and no amidated product **4aa** was detected (Table 1, entries 2, 3).

Table 1. Optimization of conditions for amidation/condensation







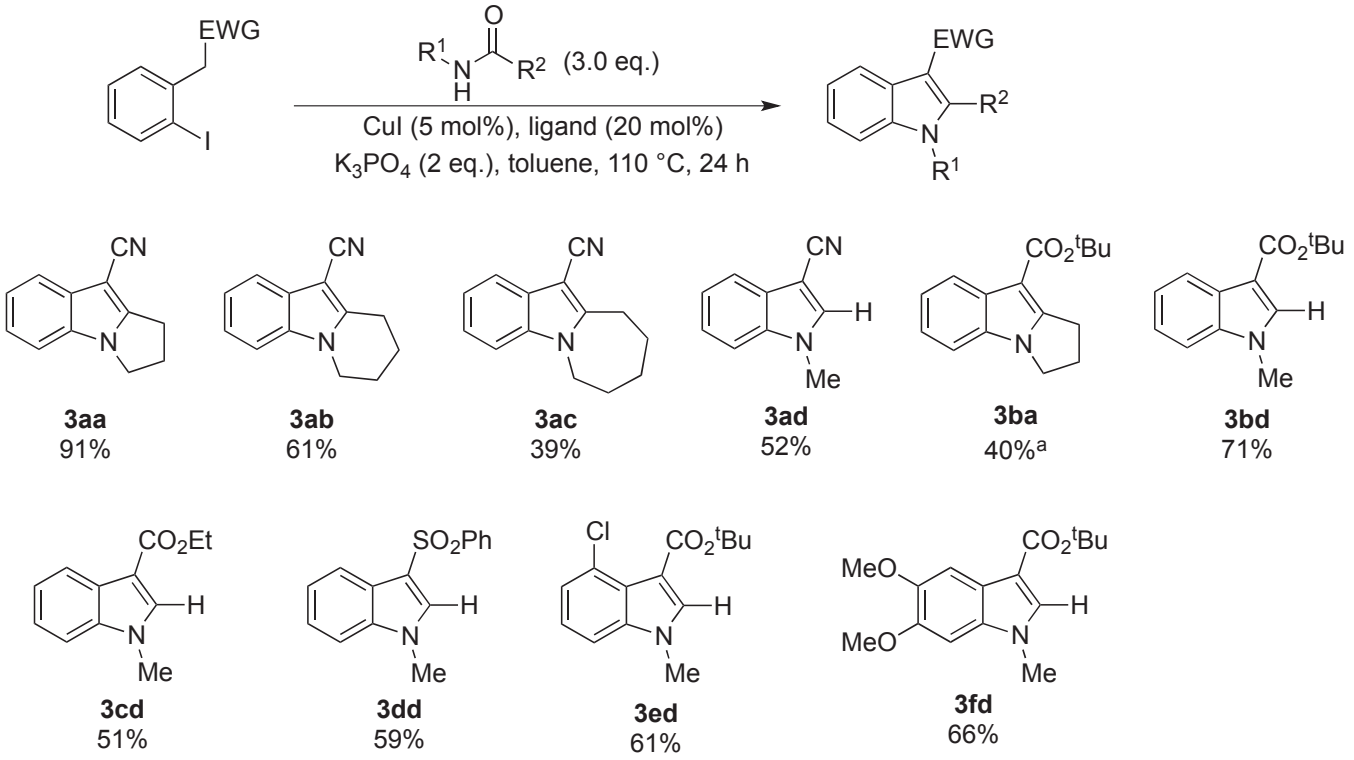


entry	x	solvent	ligand	**3aa** (%)	**4aa** (%)
1[a]	1.2	toluene	A	45	46
2[a]	1.2	dioxane	A	29[b]	55[b]
3[a]	1.2	DMF	A	75[b]	nd[b,c]
4	2.0	toluene	A	78	7[b]
5	3.0	toluene	A	91	0
6	3.0	toluene	B	29[b]	0
7	3.0	toluene	C	28[b]	0

isolated yield. [a] with 10 mol% ligand. [b] NMR yield. [c] not detected.

By increasing an amount of 2-pyrrolidone in toluene, amidated product **4aa** was successfully altered in the cyclized cyanoindole **3aa** (entries 4, 5). We observed that with 3 equiv of 2-pyrrolidone in toluene, this reaction afforded only the desired product **3aa** in the highest yield (entry 5).

The role of the excess amide in the cyclization is not clear, but one plausible explanation is that the amide proton works to activate carbonyl of the amidated product to render it more electrophilic or to activate the nitrile to make the methylene proton more acidic. Among the ligands which were reported to be effective for the amidation by Buchwald's group, ligand B and ligand C were ineffective for this reaction (entries 6, 7). With these optimized conditions in hand, the substrate scope of this method was explored (Scheme 2). At first, the scope was investigated by coupling a range of alkanamides to 2-iodophenylacetonitrile. It was found that the reactions including 6 and 7 member ring amides proceed with lower yields when the more hindered cyclic amides were used (**3ab**, **3ac**). This method was also effective for formamide (**3ad**). Other aryl iodide substrates with EWG (electron-withdrawing group) functionalized methylene were examined for the amidation/condensation. For instance, *tert*-butoxycarbonyl (**3ba**, **3bd**), ethoxycarbonyl (**3cd**), and phenylsulfonyl (**3dd**) were suitable as EWGs. In case of **3ba**, higher temperature was needed to complete the cyclization reaction. As expected, the halogen group on the aromatic ring can be selectively amidated with a preference for the iodo substituted position (**3ed**).

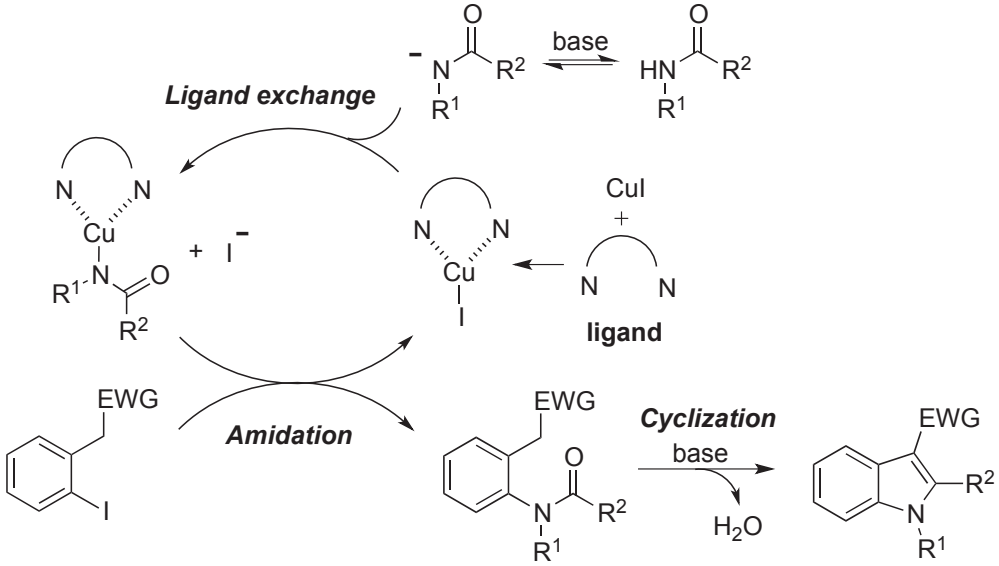


isolated yield. [a] at 150 °C

Scheme 2. Synthesis of diversely functionalized indole derivatives

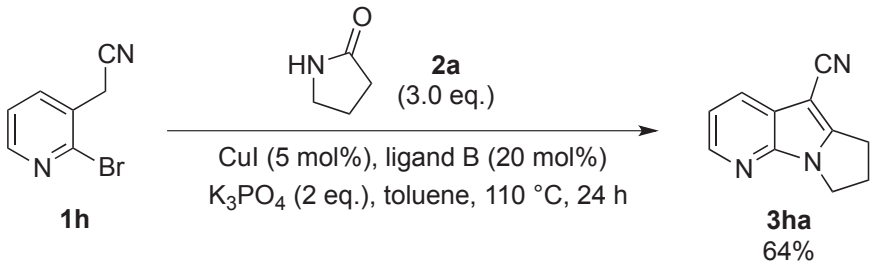
The substrate bearing two electron-donating groups on the aromatic ring whose electronic effects are considered to be unfavorable for both Cu-catalyzed amidation and subsequent condensation, was tolerated for this reaction (**3fd**). When *N*-methylacetamide was used for the reaction with **1a**, the amidation did not proceed and the dehalogenation of the substrate was observed.

The plausible reaction pathway for this indole formation *via* amidation/condensation is described in Scheme 3. The amides are also considered to play an important role for enhancing cyclization other than acting as a nucleophile as suggested in Table 1, entries 1, 4, 5.



Scheme 3. Plausible mechanism for indole formation

Our next interest was to focus on the synthesis of azaindole using the methodology. Azaindoles have attracted much attention due to their physicochemical and pharmacological properties, and can be considered as a bioisostere of an indole or purine moiety.[9] We investigated the 7-azaindole synthesis using 2-(2-bromopyridin-3-yl)acetonitrile as a substrate in the presence of 5 mol% CuI, 20 mol% ligand A, 3 equiv. 2-pyrrolidone and the reaction mixture was heated in toluene at 110 °C for 24 h. The reaction gave the desired 7-azaindole derivative **3ha** in 29% yield. By using ligand B in place of ligand A, the coupling reaction proceeded smoothly in higher yield and the product was obtained in 64% (Scheme 4).



Scheme 4. Synthesis of azaindolecarbonitrile

CONCLUSION

It was found that the amidation of 2-iodophenylacetonitrile with various alkanamides proceeds smoothly in the presence of CuI and a diamine ligand. The subsequent cyclization of the C-N coupling products takes place under the coupling reaction conditions. The use of copper catalyzed process is considered to be attractive from the viewpoint of potential economic advantages.[10] A new Cu-catalyzed straightforward synthesis of 3-functionalized indoles is demonstrated.[11] Further studies on the scope of the substrate and the application of the methodology are underway.

EXPERIMENTAL

General: Unless otherwise noted, reactions were carried out under an argon atmosphere using dry solvents. Melting points (mp) were determined with a Yazawa micro melting point apparatus and uncorrected. Infrared (IR) data were recorded on Shimadzu software. The spectra were acquired in 32 scans per spectrum at a resolution of four, and absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). NMR data were recorded on either a JEOL AL400 spectrometer (395.75 MHz for ^{1}H, 99.50 MHz for ^{13}C) or a JEOL ECA600 spectrometer (600.172 MHz for ^{1}H, 150.907 MHz for ^{13}C). Chemical shifts are expressed in δ (parts per million, ppm) values, and coupling constants (*J*) are expressed in hertz (Hz). ^{1}H NMR spectra were referenced to a tetramethylsilane (TMS) as an internal standard or to a solvent signal ($CDCl_3$: 7.26 ppm). ^{13}C NMR spectra were referenced to a solvent signal ($CDCl_3$: 77.16 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = double doublet, m = multiplet, br.s = broad singlet. Low and high resolution mass spectra (LRMS and HRMS) were obtained from Mass Spectrometry Resource, Graduate School of Pharmaceutical Sciences, Tohoku University, on a JEOL JMS-DX303 and JMS-700 spectrometer respectively.

General procedure for indole synthesis by Cu-catalyzed amidation reaction. A dried re-sealable vial with a Teflon stir bar was charged with amide (3.0 equiv, 1.5 mmol), CuI (5 mol%, 0.025 mmol), K_3PO_4 (2.0 equiv, 1.0 mmol). The vial was sealed with a rubber septum and evacuated and refilled with argon three times through a syringe needle. Under an argon atmosphere, toluene (0.5 mL), *trans*-1,2-diaminocyclohexane (20 mol%, 0.1 mmol) and aryl halide (0.50 mmol) were each added via syringe. The rubber septum was then removed and quickly replaced with a Teflon screw cap and the reaction mixture was stirred at 110 °C for 24 h. The resulting suspension was allowed to reach room temperature and filtered through a pad of silica gel eluting with AcOEt (10 mL). The filtrate was concentrated and the residue was purified by flash chromatography to afford a pure product.

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (3aa). Obtained as colorless prisms (83 mg, 91%) (Recrystallized from AcOEt/hexane, mp 128–130 °C). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.70

(quintet, J = 7.3 Hz, 2H), 3.18 (t, 2H, J = 7.3 Hz), 4.14 (t, J = 7.3 Hz, 2H), 7.22–7.28 (m, 3H), 7.65–7.67 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 24.7, 26.8, 44.9, 77.7, 110.6, 116.5, 119.4, 121.8, 122.7, 132.0, 132.2, 152.9. LRMS (EI) *m/z*: 182 (M^+). HRMS: Calcd. for $C_{12}H_{10}N_2$: 182.0844. Found: 182.0828. IR (neat, cm^{-1}): 2924, 2852, 2211, 1544, 1452, 1423, 1302, 1242, 1119, 1026, 1011 cm^{-1}.

6,7,8,9-Tetrahydropyrido[1,2-*a*]indole-10-carbonitrile (3ab). Obtained as yellow prisms (60 mg, 61%) (Recrystallized from AcOEt/hexane, mp 104–105 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.92–1.98 (m, 2H), 2.08–2.14 (m, 2H), 3.08 (t, J = 6.8 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 7.22–7.31 (m, 3H), 7.62–7.66 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 19.8, 22.6, 23.3, 42.6, 109.7, 116.5, 118.9, 122.3, 122.7, 127.4, 135.5, 146.3. LRMS (EI) *m/z*: 196 (M^+), 168 (M^+–28). HRMS: Calcd. for $C_{13}H_{12}N_2$: 196.1000. Found: 196.0977. IR (neat, cm^{-1}): 2956, 2936, 2925, 2854, 2202, 1532, 1490, 1477, 1456, 1445, 1422, 1361, 1351, 1318, 1270, 1258, 1246, 1195, 1163, 1093, 1046, 1016, 934, 902, 824, 757, 748 cm^{-1}.

7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carbonitrile (3ac). Obtained as yellow prisms (41 mg, 39%) (Recrystallized from AcOEt/hexane, mp 133–134 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.76–1.83 (m, 4H), 1.89–1.95 (m, 2H), 3.08 (t, J = 5.8 Hz, 2H), 4.20 (t, J = 4.9 Hz, 2H), 7.20–7.33 (m, 3H), 7.6 (d, J = 7.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 26.8, 27.5, 28.6, 30.8, 45.5, 84.3, 109.7, 116.8, 119.4, 121.8, 123.0, 127.2, 136.1, 151.7. LRMS (EI) *m/z*: 210 (M^+). HRMS: Calcd. for $C_{14}H_{14}N_2$: 210.1157. Found: 210.1146. IR (neat, cm^{-1}): cm^{-1}.2928., 2854, 2207, 1529, 1475, 1462, 1427, 1359, 1331, 1249, 1206, 1184, 1086, 985, 747, 739 cm^{-1}.

1-Methyl-indole-3-carbonitrile (3ad). Obtained as colorless prisms (41 mg, 52%) (Recrystallized from AcOEt/hexane, mp 61–63 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.84 (s, 3H), 7.25–7.40 (m, 3H), 7.54 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 33.7, 85.6, 110.4, 116.0, 119.9, 122.2, 124.0, 127.9, 135.6, 136.1. LRMS (EI) *m/z*: 358 (M^+), 91 (M^+–267). HRMS: Calcd. for $C_{10}H_8N_2$: 357.9967. Found: 357.9950. IR (neat, cm^{-1}): 3113, 3057, 3041, 2211, 1530, 1458, 1420, 1378, 1358, 1334, 1250, 1204, 1158, 1126, 1066, 1009, 936, 848, 767, 750 cm^{-1}.

***tert*-Butyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (3ba).** Obtained as colorless prisms (51 mg, 40%) (Recrystallized from AcOEt/hexane, mp 161–162 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.63 (s, 9H), 2.59 (quintet, J = 7.3 Hz, 2H), 3.23 (t, J = 7.3 Hz, 2H), 4.03 (t, J = 7.3 Hz, 2H), 7.14–7.22 (m, 3H), 8.07–8.09 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 21.8, 22.3, 24.4, 40.0, 75.0, 96.4, 105.4, 117.1, 117.2, 126.6, 128.3, 148.2, 160.8. LRMS (EI) *m/z*: 257 (M^+), -201 (M^+–56), 156 (M^+–101). HRMS: Calcd. for $C_{16}H_{19}NO_2$ 257.1416. Found: 257.1404. IR (neat, cm^{-1}): 2978, 2932, 2891, 2681, 1673, 1540, 1507, 1473, 1452, 1424, 1391, 1368, 1335, 1301, 1288, 1247, 1206, 1165, 1154, 1126, 1110, 1018, 1008, 935, 885, 784,750 cm^{-1}.

***tert*-Butyl 1-methyl-1*H*-indole-3-carboxylate (3bd).** Obtained as yellow oil. (82 mg, 71%) ^1H NMR

(400 MHz, $CDCl_3$/TMS) δ (ppm): 1.63 (s, 9H), 3.73 (s, 3H), 7.26 (br.s, 3H), 7.67 (s, 1H), 8.14 (br.s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 28.7, 33.3, 79.8, 108.8, 109.7, 121.66, 121.69, 122.6, 126.7, 135.1, 137.3, 164.7. LRMS (EI) *m/z*: 231 (M^+), 175 (M^+–56), 158 (M^+–73). HRMS: Calcd. for $C_{14}H_{17}NO_2$ 231.12593. Found: 231.12502. IR (neat, cm^{-1}): 3112, 3053, 3004, 2975, 2931, 2881, 1685, 1616, 1533, 1466, 1424, 1390, 1379, 1366, 1337, 1277, 1266, 1231, 1167, 1149, 1099, 1059, 1004, 933, 855, 831, 774, 747, 714 cm^{-1}.

Ethyl 1-methyl-1*H*-indole-3-carboxylate (3cd). Obtained as colorless prisms (52 mg, 51%) (Recrystallized from hexane, mp 73–74 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.39-1.42 (t, J = 7.3 Hz, 3H), 3.76 (s, 1H), 4.34-4.40 (q, J = 7.3 Hz, 2H), 7.23-7.32 (m, 3H), 7.73 (s, 1H), 8.15–8.20 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7, 33.4, 59.7, 107.3, 109.8, 121.7, 121.9, 122.8, 126.7, 135.2, 137.3, 165.2. LRMS (EI) *m/z*: 203 (M^+), 158 (M^+-56). HRMS: Calcd. for $C_{12}H_{13}NO_2$ 203.0946. Found: 203.0934. IR (neat, cm^{-1}): 3117, 3053, 2991, 2938, 2901, 1679, 1533, 1521, 1479, 1429, 1390, 1371, 1336, 1272, 1233, 1163, 1153, 1128, 1104, 1032, 1014, 929, 879, 851, 829, 777, 771, 751, 739 cm^{-1}.

1-Methyl-3-(phenylsulfonyl)-1*H*-indole (3dd). Obtained as colorless needless (80 mg, 59%) (Recrystallized from AcOEt/hexane, mp 167–168 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.76 (s, 1H), 7.23–7.30 (m, 3H), 7.39–7.45 (m, 3H), 7.74 (s, 1H), 7.91–7.94 (m, 1H), 7.99–8.02 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 33.7, 110.5, 115.0, 119.8, 122.5, 123.7, 124.3, 126.7, 129.1, 132.5, 133.8, 137.4, 143.6. LRMS (EI) *m/z*: 271 (M^+). HRMS: Calcd. for $C_{15}H_{13}NO_2S$ 271.06670. Found: 271.06591. IR (neat, cm^{-1}): 3116, 1515, 1457, 1443, 1382, 1329, 1299, 1289, 1250, 1173, 1143, 1129, 1118, 1080, 1025, 1015, 999, 982, 847, 756, 745, 719 cm^{-1}.

***tert*-Butyl 4-chloro-1-methyl-1*H*-indole-3-carboxylate (3ed).** Obtained as colorless prisms (81 mg, 61%) (Recrystallized from hexane, mp 120 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.61 (s, 9H), 3.78 (s, 3H), 7.16–7.23 (m, 3H), 7.69 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 28.6, 33.6, 80.5, 108.5, 109.8, 123.2, 123.5, 123.7, 127.1, 136.5, 139.0, 163.5. LRMS (EI) *m/z*: 265 (M^+), 209 (M^+–56), 192 (M^+–73). HRMS: Calcd. for $C_{14}H_{16}ClNO_2$ 265.08696. Found: 265.08587. IR (neat, cm^{-1}): 3117, 2977, 2932, 2918, 1708, 1559, 1527, 1472, 1448, 1421, 1389, 1363, 1335, 1231, 1200, 1181, 1160, 1147, 1113, 1065, 1041, 1005, 948, 874, 858, 848, 829, 781, 767, 743, 725 cm^{-1}.

***tert*-Butyl 5,6-dimethoxy-1-methyl-1*H*-indole-3-carboxylate (3fd).** Obtained as colorless prisms (96 mg, 66%) (Recrystallized from AcOEt/hexane, mp 187–189 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.63 (s, 9H), 3.73 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 6.74 (s, 1H), 7.54 (s, 1H), 7.64 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 28.6, 33.5, 56.1, 56.3, 79.57, 93.0, 103.0, 108.3, 119.8, 131.4, 133.0, 146.5, 147.3, 164.8. LRMS (EI) *m/z*: 291 (M^+), 235 (M^+–56). HRMS: Calcd. for $C_{16}H_{21}NO_4$

291.14706. Found: 291.14675. IR (neat, cm^{-1}): 3007, 2968, 2940, 2908, 2833, 1686, 1533, 1506, 1486, 1456, 1448, 1368, 1359, 1311, 1272, 1261, 1240, 1210, 1171, 1139, 1095, 1058, 1037, 1025, 941, 864, 851, 831, 804, 771 cm^{-1}.

7,8-Dihydro-6*H*-pyrido[3,2-*b*]pyrrolizine-5-carbonitrile (3ha). Obtained as colorless prisms (59 mg, 64%) (Recrystallized from AcOEt/hexane, mp 167–169 °C). ^1H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.74 (quint, J = 4.9 Hz, 2H), 3.25 (t, J = 4.9 Hz, 2H), 4.31 (t, J = 4.9 Hz, 2H), 7.19 (dd, J = 5.5 Hz, J = 3.0 Hz, 1H), 7.94–7.96 (m, 1H), 8.33 (d, J = 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 25.2, 26.9, 44.5, 76.89, 115.5, 117.9, 125.0, 127.9, 143.9, 144.0, 153.8. LRMS (EI) *m/z*: 183 (M^+), 156 (M^+–27). HRMS: Calcd. for $C_{11}H_9N_3$ 183.0796. Found: 183.0790. IR (neat, cm^{-1}): 3051, 2966, 2938, 2906, 2217, 1595, 1566, 1540, 1482, 1448, 1426, 1416, 1381, 1372, 1347, 1317, 1297, 1282, 1230, 1211, 1163, 1128, 1033, 982, 938, 861, 802, 797, 774 cm^{-1}.

ACKNOWLEDGEMENT

This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 23390002), a Grant-in-Aid for Challenging Exploratory Research (No. 25670002) from Japan Society for the promotion of Science, a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysis” (No. 23105009) and the project “Platform for Drug Discovery, Informatics, and Structural Life Science” from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES

1. (a) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry*, ed. by A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, Vol. 4, p 313; (b) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, E. F. V. Scriven, and C. W. Birds, Pergamon, Oxford, 1996, Vol. 2, p 119; (c) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, E. F. V. Scriven, and C. W. Birds, Pergamon, Oxford, 1996, Vol. 2, p 207.
2. D. A. Horton, G. T. Bourne, and M. L. Smythe, *Chem. Rev*., 2003, **103**, 893.
3. For recent reviews on indole synthesis, see: (a) D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195; (b) R. Vicente, *Org. Biomol, Chem*., 2011, **9**, 6469; (c) J. J. Song, J. T. Reeves, D. R. Fandrick, Z. Tan, N. K. Yee, and C. H. Senanayake, *ARKIVOC*, 2010, **i**, 390; (d) J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, and C. H. Senanayake, *Chem. Soc. Rev.*, 2007, **36**, 1120; (e) G. R. Humphrey and J. T. Kuethe, *Chem. Rev*., 2006, **106**, 2875.
4. (a) F. T. Tyson, *J. Am. Chem. Soc*., 1941, **63**, 2024; (b) W. J. Houlihan, V. A. Parrino, and Y. Uike, *J. Org. Chem*., 1981, **46**, 4511.

5. (a) C. D. Jones, *J. Org. Chem*., 1972, **37**, 3624; (b) Y. Ito, K. Kobayashi, and T. Saegusa, *J. Am. Soc*., 1977, **99**, 3532; (c) K. Wojciechowski and M. Makosza, *Synthesis*, 1986, 651; (d) G. Bartoli, M. Bosco, R. Dalpozzo, and P. E. Todesco, *J. Chem. Soc., Chem. Commun*., 1988, 807; (e) T. Fukuyama, X. Chen, and G. Peng, *J. Am. Chem. Soc*., 1994, **116**, 3127; (f) A. Fürstner and A. Hupperts, *J. Am. Chem. Soc*., 1995, **117**, 4468; (g) K. Miyashita, K. Tsuchiya, K. Kondoh, H. Miyabe, and T. Imanishi, *Heterocycles*, 1996, **42**, 513; (h) H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, and T. Fukuyama, *J. Am. Chem. Soc*., 1999, **121**, 3791; (i) A. Takeda, S. Kamijo, and Y. Yamamoto, *J. Am. Chem. Soc*., 2000, **122**, 5662; (j) Y. Nakamura and T. Ukita, *Org. Lett*., 2002, **4**, 2317; (k) K. Nakao, Y. Murata, H. Koike, C. Uchida, K. Kawamura, S. Mihara, S. Hayashi, and R. W. Stevens, *Tetrahedron Lett*., 2003, **44**, 7269; (l) G. A. Kraus and H. Guo, *Org. Lett*., 2008, **10**, 3061; (m) C. Seong, C. M. Park, J. Choi, and N. S. Park, *Tetrahedron Lett*., 2009, **50**, 1029; (n) L. Zhou and M. P. Doyle, *J. Org. Chem*., 2009, **74**, 9222.
6. (a) M. A. Bobko, K. A. Evans, A. C. Kaura, L. E. Schuster, and D.-S. Su, *Tetrahedron Lett*., 2012, **53**, 200; (b) D. A. Wacker and P. Kasireddy, *Tetrahedron Lett*., 2002, **43**, 5189; (c) E. O. M. Orlemans, A. H. Schreuder, P. G. M. Conti, W. Verboom, and D. N. Reinhoudt, *Tetrahedron*, 1987, **43**, 3817.
7. (a) W.-S. Huang, R. Xu, R. Dodd, and W. C. Shakespeare, *Tetrahedron Lett*., 2014, **55**, 441; (b) E. Racine, F. Monnier, J.-P. Vors, and M. Taillefer, *Org. Lett*., 2011, **13**, 2818; (c) E. R. Strieter, B. Bhayana, and S. L. Buchwald, *J. Am. Chem. Soc*., 2009, **131**, 78; (d) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito, and J. F. Hartwig, *J. Am. Chem. Soc*., 2008, **130**, 9971; (e) W. Cheng, J. Li, D. Fang, C. Feng, and C. Zhang, *Org. Lett*., 2008, **10**, 4565; (f) C.-Z. Tao, J. Li, Y. Fu, L. Liu, and Q.-X. Guo, *Tetrahedron Lett*., 2008, **49**, 70; (g) C. P. Jones, K. W. Anderson, and S. L. Buchwald, *J. Org. Chem*., 2007, **72**, 7968; (h) S.-L. Zhang, L. Liu, Y. Fu, and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546; (i) X. Lv and W. Bao, *J. Org. Chem*., 2007, **72**, 3863; (j) J. Yuen, Y.-Q. Fang, and M. Lautens, *Org. Lett*., 2006, **8**, 653; (k) E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc*., 2005, **127**, 4120; (l) W. Deng, Y.-F. Wang, Y. Zou, L. Liu, and Q.-X. Guo, *Tetrahedron Lett*., 2004, **45**, 2311; (m) H.-J. Cristau, P. P. Cellier, J.-F. Spindler, and M. Taillefer, *Chem. Eur. J*., 2004, **10**, 5607; (n) J. H. Lange, L. J. F. Hofmeyer, F. A. Hout, S. J. M. Osanabrug, P. C. Verveer, C. G. Kruse, and R. W. Feenstra, *Tetrahedron Lett*., 2002, **43**, 1101; (o) A. Klapars, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc*., 2002, 7421; (p) A. Klapars, J. C. Antilla, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc*., 2001, **123**, 7727.
8. (a) X.-C. Wang, Y. Hu, S. Bonacorst, Y. Hong, R. Burrell, and J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 10326; (b) T.-S. Mei, D.-H. Wang, and J.-Q. Yu, *Org. Lett*., 2010, **12**, 3140.
9. (a) J.-Y. Mérour, S. Routier, F. Suzenet, and B. Joseph, *Tetrahedron*, 2013, **69**, 4767; (b) F. Popowycz, S. Routier, B. Joseph, and J.-Y. Mérour, *Tetrahedron*, 2007, **63**, 1031; (c) J. J. Song, J. T.

Reeves, F. Gallou, Z. Tan, N. K. Yee, and C. H. Senanayake, *Chem. Soc. Rev*., 2007, **36**, 1120; (d) J. Jadhav, S. Khanapaure, R. Kurane, R. Salunkhe, and G. Rashinkar, *Tetrahedron Lett*., 2013, **54**, 6858.

10. (a) D. S. Surry and S. L. Buchwald, *Chem. Sci*., 2010, **1**, 13; (b) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed*., 2009, **48**, 6954; (c) D. Ma and Q. Cai, *Acc. Chem. Res*., 2008, **41**, 1450; (d) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed*., 2008, **47**, 3096; (e) G. Evano, N. Blanchard, and M. Toumi, *Chem. Rev*., 2008, **108**, 3054.
11. For recent Cu catalyzed indole synthesis, see: (a) Z. Zhu, J. Yuan, Y. Zhou, Y. Qin, J. Xu, and Y. Peng, *Eur. J. Org. Chem*., 2014, 511; (b) X. Xiao, T.-Q. Chen, J. Ren, W.-D. Chen, and B.-B. Zeng, *Tetrahedron Lett*., 2014, **55**, 2056; (c) S. Cacchi, G. Fabrizi, and A. Goggiamani, *Org. Biomol. Chem*., 2011, **9**, 641; (d) H. Wang, Y. Li, L. Jiang, R. Zhang, K. Jin, D. Zhao, and C. Duan, *Org. Biomol. Chem*., 2011, **9**, 4983; (e) R. C. Hodgkinson, J. Schulz, and M. C. Willis, *Org. Biomol. Chem*., 2009, **7**, 432; (f) F. Melkonyan, A. Topolyan, M. Yurovskaya, and A. Karchava, *Eur. J. Org. Chem*., 2008, 5952; (g) F. Liu and D. Ma, *J. Org., Chem.*, 2007, **72**, 4844; (h) L. Ackermann, *Org. Lett*., 2005, **7**, 439; (i) K. Hiroya, S. Itoh, and T. Sakamoto, *J. Org. Chem*., 2004, **69**, 1126.