Synthesis of indolo[2,1-*a*]isoquinolines by CF_3COOH-induced cyclization

Yasuhiro Wada,[1,2] Nobuhito Kurono,[1,3*] Hisanori Senboku,[1,4] and Kazuhiko Orito[1*]

[1]*Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University*

[2]*Pharmaceutical Research Center, Asahi Kasei Pharma Corporation*

[3]*Department of Integrated Human Sciences, Hamamatsu University, School of Medicine*

[4]*Division of Applied Chemistry, Faculty of Engineering, Hokkaido University*

Correspondence

Nobuhito Kurono, Department of Integrated Human Sciences, Hamamatsu University, School of Medicine, Hamamatsu, Shizuoka, Japan.

Email: chrono@hama-med.ac.jp

Abstract

Indolo[2,1-*a*]isoquinoline alkaloids and related compounds have been known to have interesting biological activities such as antileukemic and antitumor activities. We found that 1-(3,4-dimethoxyphenethyl)indole gave 2,3-dimethoxyindolo[2,1-*a*]isoquinoline and 1-(3,4-dimethoxyphenylacetyl)indole gave 2,3-dimethoxy-6-oxoindolo[2,1-*a*]isoquinoline, respectively, by an intramolecular cyclization carried out in boiling trifluoroacetic acid.

Keywords

Indolo[2,1-*a*]isoquinoline, intramolecular cyclization, trifluoroacetic acid, 1-phenethylindole

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4078

This article is protected by copyright. All rights reserved.

Accepted Article

INTRODUCTION

We have been interested in construction of an indolo[2,1-*a*]isoquinoline ring system, the structural feature of which has been found in dibenzopyrrocoline alkaloids.[1,2] Some of them have been shown to exhibit interesting biological activities[3] including antileukemic and antitumor activities,[3a,3b,3c] nonsteroidal antiestrogen,[3e] and anti-tubulin activity.[3f] Most of the reported methods for the synthesis of such alkaloids and related indolo[2,1-*a*]isoquinolines[4-7] involve the procedures ending up with the formation of the fused indole ring. We have also reported some synthetic methods, such as radical cyclization,[5j] K_2CO_3-DMF induced cycloamination,[5m,5n,5o] or phosphine-free Pd(0)-catalyzed cycloamination,[5t] which have been developed for cyclization in route A shown in Figure 1. The present study deals with a new method for route B, which completes with an isoquinoline nucleus fusion. The results will be added in a limited number of the successful or very promising methods for the alkaloid syntheses in route B.[5i,7c,7f,7k]

RESULTS AND DISCUSSION

One of the most basic and efficient methods for the preparation of berbines, a structural feature of the protoberberine alkaloids, is the intramolecular acid-catalyzed cyclization so-called Pictet-Spengler isoquinoline synthesis.[8]

N-Phenethyl-1,2-dihydroisoquinolines **2**, which can be prepared by $LiAlH_4$ reduction of isoquinolinium salts **1**, have been converted to the corresponding berbines **3** in heated mineral acids.[9] It was reported by Dyke that acid-treatment (conc. HCl) of carbostyril **4**, which can be prepared by oxidation of **1** with $K_3[Fe(CN)_6]$, afforded 8-oxoberbines **5**,[9c] as shown in Figure 2. Dyke also reported a similar method for the preparation of **3** and **5** starting with disproportionation of **1** with alkali and ending up with the Pictet-Spengler cyclization of the resultant **2** and **4**, respectively. [9d]

On the other hand, under such acidic conditions, indoles cause polymerizations due to their enamine and imine properties to form their dimers or trimers, depending on experimental conditions, as reported before.[10] We tried to test the ring-closure in route B using *N*-phenethylindole **6**. Its treatments under the Dyke's Pictet-Spengler conditions using conc. HCl afforded a trace amount of terahydroindoloisoquinoline **7** in a dark brown tarry substance. The use of diluted HCl solutions also afforded a colored tarry mixture but none of **7**.

We shifted the reaction conditions from those mineral acids to organic acids. Soon, we found that boiling CF_3COOH (bp 72.4 °C) induced the desired ring-closure in **6**.

This article is protected by copyright. All rights reserved.

Accepted Article

When a 0.1 M solution of **6** in CF_3COOH was refluxed under nitrogen for 9-12 h, tetrahydroindoloisoquinoline **7** formed in a 3:2 ratio with the 3-trifluoroacetylindole **8**, as shown in Scheme 1. **7** was air-sensitive, and, on standing in the air overnight, all converted to **9**, which was obtained in 50% isolated yield together with 3-trifluoroacetylindole **8** in 33% yield. This trifluoroacetylation is easily explained to have occurred due to the nucleophilicity of the indole enamine system enhanced by its *N*-alkylation, and could not be avoided even in use of a wet CF_3COOH (CF_3COOH : H_2O = 10:1). The product ratio and yields were the almost same as those of the above dry version. Prolonged reaction times did not change the product ratio of 3:2. The use of the catalytic amount of CF_3COOH (10 mol%) in boiling benzene for 9 h did not consume **6** at all. We have known that the treatment with hot BF_3•Et_2O induces an efficient intramolecular triple cyclization of an indole derivative leading to a pentacyclic nucleus of the Aspidosperma alkaloids.[11] Under a similar condition, a BF_3•Et_2O solution of the indole **6** was heated at 80 °C for 10 h, but no cyclization occurred at all. A catalytic amount of *p*-TsOH (0.1 eq) have been successfully used in boiling toluene for the Pictet-Spengler isoquinoline synthesis to produce tetrahydro-β-carbolines.[12] Under the same condition, indole **6**, however, did not undergo the cyclization and even in use of an increased amount of *p*-TsOH (2 eq), and was recovered unchanged after 10 h. In addition, treatment of **6** (0.1 M) in CCl_3COOH at 80 °C, followed by the air-oxidation, afforded **9** in a yield less than 20%.

In contrast, cyclization of *N*-acylindole derivative **10** in boiling CF_3COOH proceeded more slowly and selectively, compared with that of **6**, to afford 6-oxoindoloisoquinoline **11** 24 h later in 93% isolated yield (Scheme 1). The result may be explained that the nucleophilicity of indole was effectively reduced by its *N*-acylation, so that the competitive trifluoroacetylation was entirely suppressed, and the cyclization occurred specifically. It should be noted that the conversion of **10** to **11** has been carried out in a BF_3•Et_2O/$(CF_3)_2CHOH$ system developed by Nishina.[7k]

CONCLUSIONS

The Pictet-Spengler type treatment, which is useful for preparation of protoberberine alkaloids, has been limited for cyclization of the acid-sensitive substrates, such as indole derivatives. Indoles polymerize to their dimers or trimers under strongly acidic conditions. Cyclization of an acid-sensitive *N*-phenethylindole **6** was carried out in boiling CF_3COOH for 9 h to afford an air-sensitive tetrahydroindolo[2,1-*a*]isoquinoline **7**, being isolated as its dihydro derivative **9** (50%), and a byproduct, 3-trifluoroacetylindole **8** (33%), competitively. In contrast, under the same condition, an

This article is protected by copyright. All rights reserved.

N-protected indole, *N*-phenylacetylindole **10**, was selectively converted to a 6-oxoindolo[2,1-*a*]isoquinoline **11** (93%) 24 h later.[13] Dibenzopyrrocoline alkaloids and related compounds, indolo[2,1-*a*]isoquinolines, have been known to have interesting biological activities. We believe that such compounds will be provided efficiently along with the present methodology.

EXPERIMENTAL

General Remarks: Melting points were measured with a Yanagimoto micro melting point apparatus, and were uncorrected. The IR spectra were recorded with a JASCO IR-810 spectrometer. The ^{1}H NMR (270 or 400 MHz) and ^{13}C NMR (67.8 or 100.4 MHz) spectra were recorded with a JEOL JNM-JX270 or ECX-400P FT NMR spectrometer, and the samples were prepared with $CDCl_3$ (99.8 atom- % D; containing 0.03 % v/v, tetramethylsilane; Aldrich Co.), unless otherwise noted. The chemical shifts were reported in ppm, relative to tetramethylsilane. The LR- and HR-EI-MS spectra were determined with a JEOL JMS-HX110, JEOL JMS-FABmate or JEOL JMS-700TZ mass spectrometer. Elemental analyses were performed with Yanako MT-6 CHN CORDER and Dionex DX-500 at the Analytical Laboratory of Faculty of Pharmaceutical Science, Hokkaido University.

***N*-(3,4-Dimethoxyphenethyl)indole (6).** To a stirred solution of NaH (0.324 g of 60% dispersion in mineral oil, used by washing with hexane 3 times, 8.0 mmol) in anhydrous THF (10 mL) at r.t. was added dropwise a solution of indole (0.89 g, 7.6 mmol) in dry THF (7 mL) at –78 °C under Ar. The reaction mixture was stirred at r.t. for 30 min. To this, a solution of 1-(3,4-dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)ethane (2.70 g, 8.0 mmol)[14] in dry THF (9 mL) was dropwise added at rt. The mixture was heated at reflux overnight, quenched with water (20 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The extracts were washed with water (3 x 15 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue (2.55 g) was subjected to column chromatograpy on silica gel (30 % hexane–CH_2Cl_2) to afford a colorless oil (1.99 g), which was distilled under reduced pressure to give **6** as a colorless oil (1.68 g, 79 %), bp 200 °C/0.3 mmHg; IR (neat): 1605, 1505 cm^{-1}; ^{1}H NMR (270 MHz): δ 3.03 (t, 2H, CH_2, *J* = 7.2 Hz), 3.68 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.32 (t, 2H, CH_2, *J* = 7.2 Hz), 6.34 (d, 1H, 2'-H, *J* = 2.0 Hz), 6.42 (d, 1H, 3-H, *J* = 3.2 Hz), 6.64 (dd, 1H, 6'-H, *J* = 8.2, 2.0 Hz), 6.76 (d, 1H, 5'-H, *J* = 8.2 Hz), 6.89 (d, 1H, 2-H, *J* = 3.2 Hz), 7.10 (dt, 1H, 5- or 6-H, *J* = 8.3, 1.3 Hz) , 7.19 (dt, 1H, 5- or 6-H, *J* = 8.3, 1.3 Hz), 7.31 (br. d, 1H, 7-H, *J* = 8.3 Hz), 7.61 (br. d, 1H, 4-H, *J* = 8.3 Hz) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 36.1 (CH_2), 48.2 (CH_2), 55.6 (OCH_3), 55.8 (OCH_3), 100.8 (CH), 109.3 (C), 111.2 (CH), 112.0 (CH), 119.2 (CH),

This article is protected by copyright. All rights reserved.

Accepted Article

120.5 (CH), 120.9 (CH), 121.3 (CH), 128.0 (CH), 128.6 (CH), 131.1 (C), 135.6 (C), 147.6 (C), 148.7 (C) ppm; EI-MS: m/z 281 (M^+, 19.4), 151 (19.3), 130 (100), 103 (7.5), 77 (8.6). *Anal*. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.59; H, 6.72; N, 4.89.

Cyclization of 6. A stirred mixture of **6** (29 mg, 0.1 mmol) in CF_3COOH (1 mL) was refluxed under nitrogen for 9 h. The cooled reaction mixture was quenched with a saturated Na_2CO_3 solution (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 layers were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was essentially a 3:2 mixture (30 mg) of air-sensitive 2,3-dimethoxy-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinoline (**7**) [^{1}H NMR (270 MHz): δ 2.44 (dd, 1H, 5- or 6-H, *J* = 15.9, 3.7 Hz), 2.95-3.04 (m, 1H, 5- or 6-H), 3.12 (dd, 1H, 12-H, *J* = 15.2, 3.5 Hz), 3.32 (ddd, 1H, 5- or 6-H, *J* = 13.6, 12.3, 3.9 Hz), 3.52 (dd, 1H, 12-H, *J* = 15.2, 9.2 Hz), 3.80 (s, 3H, OCH_3), 3.86-3.90 (s, 3H, OCH_3 and m, 1H, 5- or 6-H), 4.84 (br. d, 1H, 12a-H, *J* = 7.7 Hz), 6.47 (s, 1H, 1- or 4-H), 6.65 (s, 1H, 4- or 1-H), 6.61-6.66 and 7.04-7.09 (each m, each 2H, 8-, 9-, 10-, and 11-H) ppm. These are essentially identical with the reported spectral data.[4c,5f]] and *N*-(3,4-dimethoxyphenethyl)-3-trifluoroacetylindole (**8**), and allowed to stand in air overnight, and subjected to preparative TLC on silica gel (CH_2Cl_2). A fraction with R_f 0.5–0.6 gave colorless crystals 14 mg (50 %), mp 180–181 °C (CH_2Cl_2–CH_3OH), which was identical in all respects with 2,3-dimethoxy-5,6-dihydroinolo[2,1-*a*]isoquinoline (**9**) (lit. [5e] mp 147 °C; lit. [5o] mp 177.5–179.5 °C; lit. [4c] mp 183–185 °C). ^{1}H NMR (270 MHz): δ 3.12 (t, 2H, 5-H, *J* = 6.6 Hz), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.23 (t, 2H, 6-H, *J* = 6.6, Hz), 6.76 (s, 1H, 1- or 4-H), 6.77 (s, 1H, 4- or 1-H), 7.09 (dt, 1H, 10- or 9-H, *J* = 7.9, 0.8 Hz), 7.19 (dt, 1H, 9- or 10-H, *J* = 7.9, 1.0 Hz), 7.24 (s, 1H, 12-H), 7.32 (br. d, 1H, 8- or 11-H, *J* = 7.9 Hz), 7.61 (br. d, 1H, 11- or 8-H, *J* = 7.9 Hz) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 28.7 (CH_2), 40.2 (CH_2), 56.0 (OCH_3), 56.1 (OCH_3), 95.1 (CH), 107.3 (CH), 108.7 (CH), 111.2 (CH), 119.7 (CH), 120.4 (CH), 121.3 (CH), 121.6 (C), 124.9 (C), 128.9 (C), 135.8 (C), 136.6 (C), 148.3 (C), 148.7 (C) ppm.

These are essentially identical with the reported spectral data.[5o,5r] A less mobile fraction with R_f 0.2–0.4 gave **8** as a colorless oil (13 mg, 33%); IR (neat): 1664 (C=O) cm^{-1}; ^{1}H NMR (270 MHz): δ 3.09 (t, 2H, CH_2, *J* = 6.7 Hz), 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.42 (t, 2H, CH_2, *J* = 6.7 Hz), 6.39 (d, 1H, 2'-H, *J* = 2.0 Hz), 6.51 (dd, 1H, 6'-H, *J* = 8.0, 2.0 Hz), 6.75 (d, 1H, 5'-H, *J* = 8.0 Hz), 7.36-7.42 (m, 3H, 5-, 6-, and 7-H), 7.55 (q, 1H, 2-H, *J* = 1.7 Hz), 8.37-8.42 (m, 1H, 4-H) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$) : δ 35.6 (CH_2), 49.4 (CH_2), 55.7 (OCH_3), 55.9 (OCH_3), 109.1 (C), 110.2 (CH),

Accepted Article

This article is protected by copyright. All rights reserved.

111.5 (CH), 111.7 (CH), 116.9 (q, CF_3, J = 291.0 Hz), 120.7 (CH), 122.7 (CH), 123.9 (CH), 124.5 (CH), 127.0 (C), 129.4 (C), 136.3 (C), 137.8 (q, CH, J = 5.0 Hz), 148.3 (C), 149.2 (C), 174.7 (q, CO, J = 35.5 Hz) ppm; EI-MS: m/z 377 (M^+, 34.7), 308 (47.2), 226 (8.1), 151 (100), 129 (12.0); HR-MS calcd for $C_{20}H_{18}NF_3O_3$ 377.12385, found 377.12371.

***N*-(3,4-Dimethoxyphenylacetyl)indole (10).** According to Illi's procedure,[15] when a mixture of indole (38 mg, 0.3 mmol), Bn_4NHSO_4 (2.3 mg, 0.006 mmol), NaOH (254 mg, 6.4 mmol) and 3,4-dimethoxyphenylacetyl chloride (prepared by treatment of 3,4-dimethoxyphenylacetic acid (90 mg, 0.45 mmol), with excess $SOCl_2$ (0.5 mL) in benzene at r.t. overnight, followed by removal of the excess reagent and the solvent in vacuo) in CH_2Cl_2 (2 mL) was stirred at r.t. for 1 h. The reaction mixture was filtered through a thin pad of powdered $MgSO_4$. The solvent was evaporated, and the residue (59 mg) was purified by preparative TLC (R_f 0.4–0.5, 2% EtOAc–CH_2Cl_2) to give **10** as colorless crystals (23 mg, 24%), mp 127–128 °C (benzene–hexane); IR (Nujol): 1706 (C=O) cm^{-1}; ^{1}H NMR (270 MHz): δ 3.857(s, 3H, OCH_3), 3.862 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.62 (d, 1H, 3-H, J = 3.9 Hz), 6.84 (s, 3H, 2', 5', and 6'-H), 7.24–7.38 (m, 2H, 5- and 6-H), 7.52 (d, 1H, 2-H, J = 3.9 Hz), 7.55 (dd, 1H, 7-H, J = 7.3, 1.3 Hz), 8.50 (br. d, 1H, 4-H, J = 8.2 Hz) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 42.6 (CH_2), 55.8 (2 OCH_3), 109.4 (CH), 111.4 (CH), 112.1 (CH), 116.7 (CH), 120.8 (CH), 121.3 (CH), 123.8 (CH), 124.8 (CH), 125.2 (CH), 125.8 (C), 130.2 (C), 135.7 (C), 148.3 (C), 149.2 (C), 169.5 (CO) ppm; EI-MS: m/z 295 (M^+, 74.8), 178 (100), 163 (13.8), 151 (71.3), 117 (13.0). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.76. Found: C, 73.39; H, 5.93; N, 4.76.

Cyclization of 10. A stirred mixture of **10** (29 mg, 0.1 mmol) in CF_3COOH (1 mL) was refluxed for 24 h under nitrogen. The cooled reaction mixture was quenched with a saturated Na_2CO_3 solution (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 layers were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue (28 mg) was purified by preparative TLC (3% MeOH–CH_2Cl_2). A band with R_f 0.3–0.5 gave **11** as a colorless solid, 27 mg (0.9 mmol, 93%), mp 165–167 °C. An analytical sample was prepared by recrystallization from MeOH, mp 167–169 °C (lit. [7k] mp 142-143 °C); IR (Nujol): 1656 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (dd, 1H, 12β-H, J = 15.1, 10.8 Hz), 3.62 (d, 1H, 5β-H, J = 18.5 Hz), 3.64 (dd, 1H, 12α-H, J = 15.1, 9.2 Hz), 3.78 (dd, 1H, 5α-H, J = 18.5, 4.0 Hz), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.40 (ddd, 1H, 12a-H (α-H), J = 10.8, 9.2, 4.0 Hz), 6.74 (s, 1H, 1- or 4-H), 6.77 (s, 1H, 4- or 1-H), 7.07 (t, 1H, 10-H, J = 8.0 Hz), 7.25 (d, 1H, 11-H, J = 8.0 Hz), 7.27 (t, 1H, 9-H, J = 8.0

Accepted Article

This article is protected by copyright. All rights reserved.

Hz), and 8.22 (d, 1H, 8-H, J = 8.0 Hz) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 34.5 (CH_2), 39.6 (CH_2), 56.1 (OCH_3), 56.2 (OCH_3), 61.3 (CH), 107.6 (CH), 110.4 (CH), 116.5 (CH), 124.1 (CH), 124.5 (CH), 125.1 (C), 127.3 (C), 127.8 (CH), 129.8 (C), 141.9 (C), 148.2 (C), 148.8 (C), 167.0 (CO) ppm; EI-MS: m/z 295 (M^+, 100), 278 (15.8), 266 (15.8), 253 (12.7). *Anal*. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.93; H, 5.93; N, 4.67.

Accepted Article

REFERENCES AND NOTES

[1] For a review, see: I. W. Eliott, In The Alkaloids, Academic Press, Orlando, **1987**, Vol. 31, pp 101-116.

[2] a) J. G. Ewing, K. Hughes, E. Ritchie, W. C. Taylor, *Nature* **1952**, 169, 618; b) J. G. Ewing, K. Hughes, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1953**, 6, 78; c) M. Leboeuf, A. Cavé, A. Ranaivo, H. Moskowitz, *Can. J. Chem.* **1989,** 67, 947; d) S.-x. Qiu, C. Liu, S.-x. Zhao, Z.-c. Xia, N. R. Farnsworth, R. Norman, H. H. S. Fong, *Tetrahedron Lett.* **1998**, 39, 4167.

[3] a) R. Ambros, S. Von Angerer, W. Wiegrebe, *Arch. Pharm.* **1988**, 321, 481; b) R. Ambros, S. Von Angerer, W. Wiegrebe, *Arch. Pharm.* **1988**, 321, 743; c) R. Ambros, M. R. Schneider, S. von Angerer, *J. Med. Chem.* **1990**, 33, 153; d) T. Polossek, R. Ambros, S. von Angerer, G. Brandl, B. Mannschreck, E. von Angerer, *J. Med. Chem.* **1992**, 35, 3537; e) R. A. Magarian, L. B. Overacre, S. Singh, K. L. Meyer, *Curr. Med. Chem.*, **1994**, 1, 61; f) M. Goldbrunner, G. Loidl, T. Polossek, A. Mannschreck, E. von Angerer, *J. Med. Chem.* **1997**, 40, 3524; g) G. A. Kraus, V. Gupta, M. Kohut, N. Singh, *Bioorg. Med. Chem. Lett.* **2009**, 19, 5539.

[4] For synthesis of dibenzopyrrocoline alkaloids and related compounds by benzyne methods, see: a) T. Kametani, K. Ogasawara, *J. Chem. Soc. C* **1967**, 2208; b) F. Benington, R. D. Morin, *J. Org. Chem.* **1967**, 32, 1050; c) T. Kametani, T. Terui, K. Fukumoto, *Yakugaku Zasshi* **1968**, 88, 915; d) T. Kametani, T. Terui, K. Fukumoto, *Yakugaku Zasshi* **1968**, 88, 1388; e) T. Kametani, K. Fukumoto, T. Nakano, *J. Heterocycl. Chem.* **1972**, 9, 1363; f) T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Suzuki, K. Fukumoto, *Chem. Pharm. Bull.* **1973**, 21, 766; g) T. Kametani, S. Shibuya, S. Kano, *J. Chem. Soc. Perkin Trans. I* **1973**, 1212; h) I. Ahmad, M. Gibson, *Can. J. Chem.* **1975**, 53, 3660; i) S. V. Kessar, S. Batra, U. K. Nadir, S. S. Gandhi, *Ind. J. Chem.* **1975**, 13, 1109; j) C.-P. Mak, A. Brossi, *Heterocycles* **1979**, 12, 1413; k) J. M. Boente, L. Castedo, A. Rodriguez de Lera, J. M. Saá, M. Suau, M. C. Vidal, *Tetrahedron Lett.* **1983**, 24, 2295; l) N. Atanes, E. Guitian, C. Saá, L. Castedo, J. M. Saá, *Tetrahedron Lett.* **1987**, 28, 817; m) A. I. Meyers, T. M. Sielecki, *J. Am. Chem. Soc.* **1991**, 113,

This article is protected by copyright. All rights reserved.

Accepted Article

2789; n) A. I. Meyers, T. M. Sielecki, D. C. Crans, R. W. Marshman, T. H. Nguyen, *J. Am. Chem. Soc.* **1992**, 114, 8483, and see also ref. 3a-f.

[5] For methods by other typical reactions; *via* oxidative coupling, a) R. Robinson, S. Sugasawa, *J. Chem. Soc.* **1932**, 789; b) C. Schopf, K. Thierfelder, *Liebigs Ann. Chem.* **1932**, 497, 22; c) J. Harley-Mason, *J. Chem. Soc.* **1953**, 1465; d) U. Hess, K. Hiller, R. S. Schroeder, *J. Prackt. Chem.* **1977**, 319, 568; *via* Bischler-Napieralski cyclization, e) S. Sugasawa, K. Mizukami, *Pharm. Bull.* **1955**, 3, 42; *via* photocyclization, f) I. Ninomiya, J. Yasui, T. Kiguchi, *Heterocycles* **1977**, 6, 1855; *via* anionic cyclization, g) S. Takano, S. Satoh, K. Ogasawara, *Heterocycles* **1987**, 26, 1483; h) S. Yasuda, T. Hirasawa, S. Yoshida, M. Hanaoka, *Chem. Pharm. Bull.* **1989**, 37, 1682; i) A. N. C. Lötter, R. Pathak, T. S. Sello, M. A. Fernandes, W. A. L. van Otterlo, C. B. de Koning, *Tetrahedron* **2007**, 63, 2263; *via* radical cyclization, j) K. Orito, S. Uchiito, Y. Satoh, T. Tatsuzawa, R. Harada, M. Tokuda, *Org. Lett.* **2000**, 2, 307; k) M. Menes-Arzate, R. Martinez, R. Cruz-Almanza, J. M. Muchowski; Y. M. Osormio; L. D. Muranda, *J. Org. Chem.* **2004**, 69, 4001; l) S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim, S. S. Rahman, *Tetrahedron* **2005**, 61, 2689 and see also ref. 5h; *via* cyclization with K_2CO_3-DMF, m) K. Orito, M. Miyazawa, H. Suginome, *Heterocyclic Commun.*, **1995**, 1, 239; n) K. Orito, M. Miyazawa, R. Kanbayashi, M. Tokuda, H. Suginome, *J. Org. Chem.*, **1999**, 64, 6583; o) K. Orito, R. Harada, S. Uchiito, M. Tokuda, *Org. Lett.*, **2000**, 2, 1799; *via* Pschorr cyclization, p) K. K. Mathew, K. N. Menon, *Proc. Indian Acad. Sci.* **1949**, 29A, 361; q) I. W. Elliot, Jr. *J. Org. Chem.* **1982**, 47, 5398; *via* Ni or Pd-catalyzed intramolecular amination, r) R. Omar-Amrani, A. Thomas, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* **2003**, 5, 2311; s) Z. Vincze, A. B. Bíró, M. Csékei, G. Timáiri, A. Kotschy, *Synthesis* **2006**, 1375; t) R. Harada, N. Nishida, S. Uchiito, Y. Onozaki; N. Kurono, H. Senboku, M. Tokuda, T. Ohkuma, K. Orito, *Eur. J. Org. Chem.* **2012**, 2012, 366.

[6] For methods *via* metal-catalyzed cycloaddition leading to the formation of substituted indolo[2,1-*a*]isoquinolines, a) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010,** 12, 2068; b) A. K. Verma, R. R. Jha, R. Chaudhary, R. K. Tiwari, K. Rakesh, K. S. K. Reddy, A. Danodia, *J. Org. Chem.* **2012**, 77, 8191; c) Y.-Q. Xia, L. Dong, *Org. Lett.* **2017**, 19, 2258; d) H. Sun, C. Wang, Y.-F. Yang, P. Chen, T.-D. Wu, X. Zhang, Y. Huang, *J. Org. Chem.* **2019,** 79, 11863; e) H. K. Lee, P. D. Q. Dao, Y.-s. Kim, C. S. Cho, *Synthesis* **2018**, 50, 3243; f) G. Chen, X. Zhang, R. Jia, B. Li, X. Fan, *Adv. Synth. Catal.* **2018**, 360, 3781; g) X. Yang, H. Lu, X. Zhu, L. Zhou, G. Deng, Y. Yang, Y. Liang, *Org. Lett.* **2019**, 21, 7284; h) S. Borthakur, S. Sama, S. Gogoi, *Org.*

This article is protected by copyright. All rights reserved.

Lett. **2019**, 21, 7878; i) T.-S. Zhang, Q. Zhao, W.-J. Hao, S.-J. Tu, B. Jiang, *Chem. Asian J.* **2019**, 14, 1042; j) S. Thavaselvam, K. Parthasarathy, *Org. Lett.* **2020**, 22, 3810.

[7] For the other methods; a) A. A. Akhrem, A. M. Moiseenkov, A. I. Poselenov, Dokl. Akad. Nauk SSSR **1972**, 203, 95. b) V. Pabuccuohlu, M. D. Rozwadowska, A. Brossi, *Arch. Pharm.* **1991**, 324, 29; c) J. Cruces, J. C. Estévez, R. J. Estévez, L. Castedo, *Heterocycles* **2000**, 53, 1041; d) A. Padwa, A. G. Waterson, *Tetrahedron* **2000**, *56*, 10159; e) O. Barun, S. Chakrabati, H. Junjappa, H. Ila, *J. Org. Chem.* **2001**, 66, 4457; f) F. J. Reboredo, M. Treus, J. C. Estévez, L. Castedo, R. J. Estévez, *Synlett* **2003**, 1603; g) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148; h) S.-C. Liu, X.-X. Zhang, Z.-J. Shi, Y.-W. Ren, B. Li, W. Zhang, *Adv. Synth. Catal.* **2009**, 351, 2839; i) A. K. Verma, M. Joshi, S. Megha, V. P. Singh, *Org. Lett.* **2011**, 13, 1630; j) G. A. Kraus, J. Beasley, *Tetrahedron Lett.* **2013**, 54, 5597; k) N. Morimoto, K. Morioka, H. Suzuki, Y. Takeuchi, Y. Nishina, *Org. Lett.* **2016**, 18, 2020; l) S. Gundala, M. R. Guda, A. F. Khasanov, D. S. Kopchuk, A. P. Krinochkin, S. Santra, G. V. Zyryanov, P. Venkatapuram, J. R. Garcia, V. N. Charushin, *Mendeleev Commun*. **2019**, 29, 369, and see also ref. 3g.

[8] W. M Whaley, T. R. Govindachari, *Org. React.* **1951**, 6, 74.

[9] a) J. W. Huffman, E. G. Miller, *J. Org. Chem.* **1960**, 25, 90; b) A. R. Battersby, D. J. Le Count, S. Garratt, R. I. Thrift, *Tetrahedron* **1961**, 14, 46; c) D. W. Brown, S. F. Dyke, *Tetrahedron* **1966**, 22, 2429; d) T. R. Govindachari, K. Nagarajan, *Ind. J. Chem.* **1970**, 8, 763.

[10] a) G. F. Smith, *Advances in Heterocyclic Chemistry*; A. R. Katrizky, Ed.; Academic Press: New York and London, **1963**, Vol. 2, pp 287-309; b) N. Tajima, T. Hayashi, S. Nakatsuka, *Tetrahedron Lett.* **2000**, 41, 1059.

[11] E. Wenkert, K. Orito, D. P. Simmons, *Tetrahedron* **1983**, 39, 2719.

[12] R. Grigg, S. M. William, D. T. MacPherson, V. Sridharan, S. Suganthan, M. Thornton-Pett, J. Zhang, *Tetrahedron* **2000**, 56, 6585.

[13] The work described in this paper is included in Dr. Yasuhiro Wada's Master Thesis (14 Feb, 2005).

[14] S. A. Sadek, G. P. Basmadjian, P. M. Hsu, J. A. Rieger, *J. Med. Chem.* **1983**, 26, 947.

[15] V. O. Illi, *Synthesis* **1979**, 387.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Accepted Article

This article is protected by copyright. All rights reserved.

FIGURE LEGENDS

Figure 1. Synthetic approaches to indolo[2,1-*a*]isoquinolines.

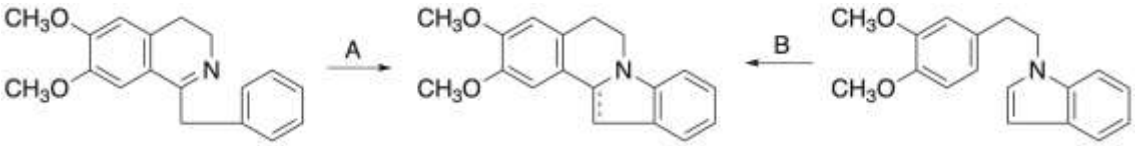
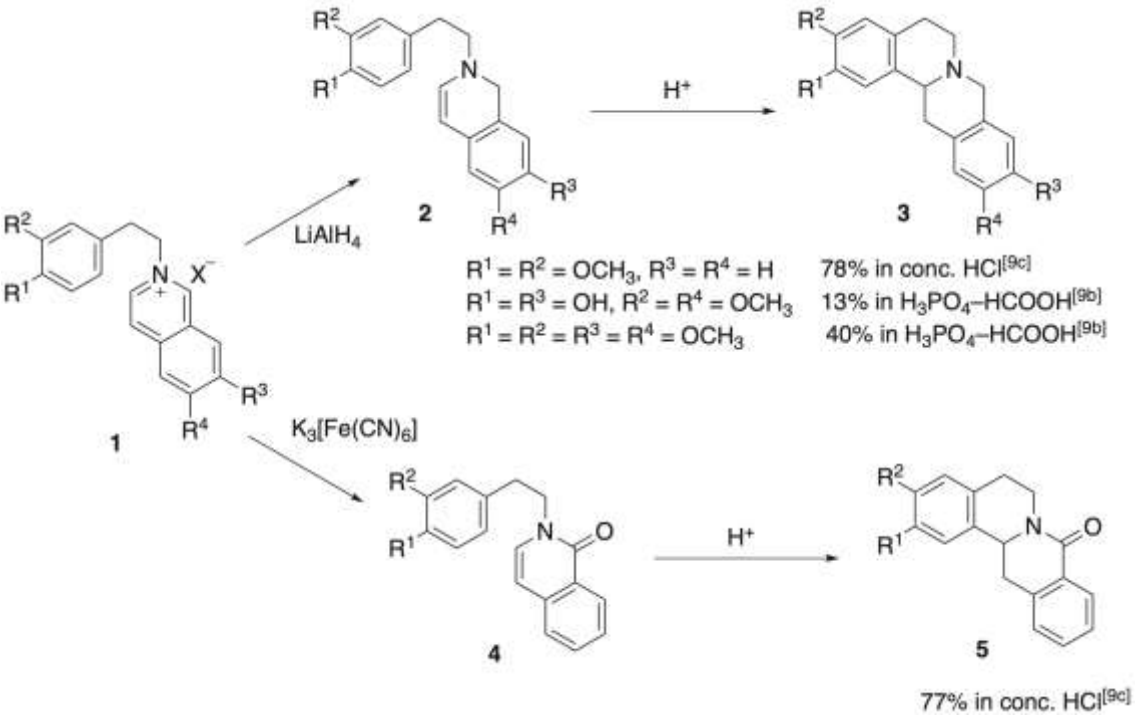


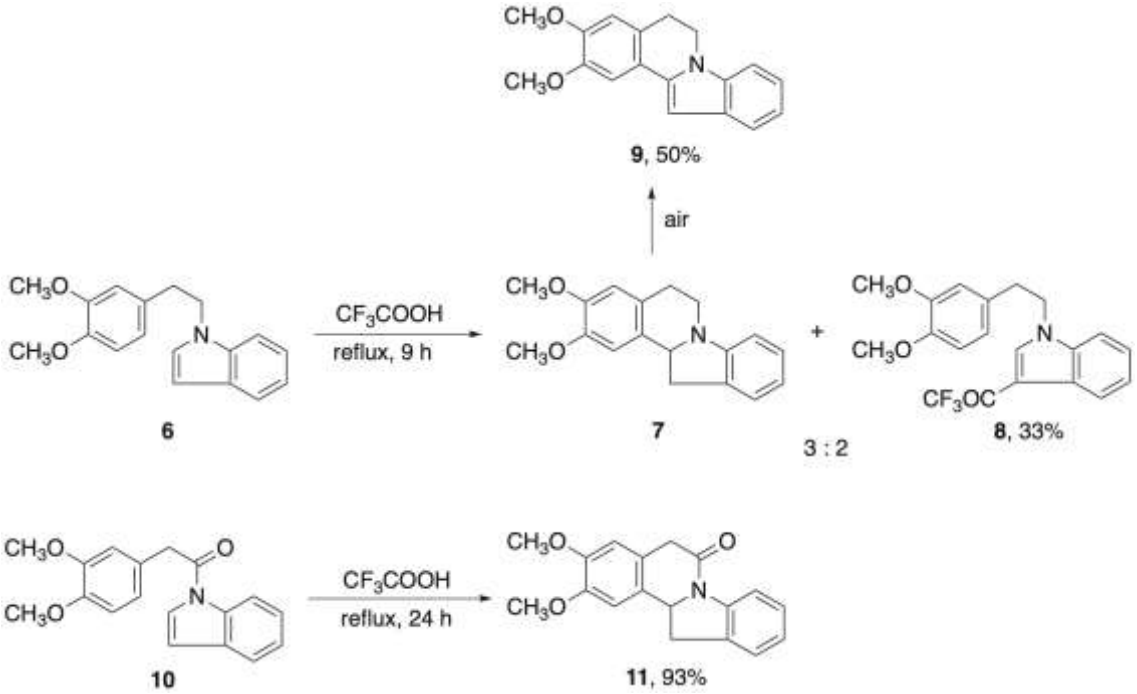
Figure 2. Reported intramolecular acid-catalyzed cyclizations of *N*-phenethyl-1,2-dihydroisoquinolines.



Scheme 1. Intramolecular cyclization of *N*-phenethylindoles **6** and **10** in boiling CF_3COOH.

Accepted Article

This article is protected by copyright. All rights reserved.



Accepted Article

This article is protected by copyright. All rights reserved.