SYNTHESIS OF INDOLO[1,2-b]INDAZOLE DERIVATIVES

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Abstract—New methods to synthesize indolo[1,2-b]indazole derivatives as an extension of available methods and thiol reduction of ketone to methylene peculiar to this skeleton were presented.

INTRODUCTION

We have been involved in the studies of anti-cancer activities of pyrazolo[1,5-a]indole derivatives.1 As an extension of this research we have figured out the structure of indolo[1,2-b]indazole as a next target, and reported a new method to construct this skeleton by intramolecular amination of hydrazine derivatives.2 Even combining a few available methods3 including this new method, known methods are not good enough to synthesize the potential anti-cancer agents with the nucleus of indolo[1,2-b]indazole due to laborious preparation of the starting materials and troubles in introducing a variety of functional groups such as nitro- and halogeno-groups. Also the chemistry of indolo[1,2-b]indazole is totally unexplored. In this report we provide a few supplemental methods to fulfill such kind of shorthand in the synthesis of indolo[1,2-b]indazole derivatives.

RESULTS AND DISCUSSION
Simplest method reported for the construction of indolo[1,2-\(b\)]indazole is a reaction of indazole (2) with 2-fluorobenzaldehyde (1a) in the presence of \(\text{K}_2\text{CO}_3\) in DMF at 110°C, and 11-oxo-11\(H\)-indolo[1,2-\(b\)]indazole (3a) was obtained in 20% yield based on consumed indazole.\(^3\) Reaction mechanism may involve substitution, base-catalyzed cyclization and air-oxidation of alcoholic product. Addition of NaF did not improve the yield of 3a. Although yield was low, the reaction was straightforward, so the scope of this reaction was investigated by using substituted 2-fluorobenzaldehydes. When 5-methoxy-2-fluorobenzaldehyde (1b) was employed, 3b was obtained in low yield (12%), and 2,5-difluorobenzaldehyde (1c) gave 3c in poor yield (7%). Other 2-fluorobenzaldehyde derivatives with 5-Cl, Br and NO\(_2\) substituents were intact in this reaction. 5-Nitro derivative (3d) was synthesized by an alternative method, starting with methyl 5-nitro-2-fluorobenzoate (4). Substitution product (5) obtained by the reaction of lithium salt of 2 with 4 was cyclized by the treatment with LDA, and 3d was obtained in 51.4% isolated yield. Structure of 3d was confirmed by comparing the spectra with those of 3a and 3b. Similar cyclization was also effected with indazole derivative (8). Compound (8) was prepared by coupling
reaction of 2-carboxyphenylhydrazine (6) with masked 1,3-dicarbonyl compound (7a) and following esterification reaction. Cyclization of 8 with LDA gave 7,8,9,10-tetrahydro-11H-indolo[1,2-b]indazole (9) in 41% yield. Similar coupling reaction with unprotected 1,3-dicarbonyl compound (7b) did not give 8 but its regioisomer, 1-(2-ethoxycarbonylphenyl)-4,5,6,7-tetrahydroindazole (65%). The structure of this regioisomer was supported by the observation of NOE between 7'-H and 6-H in ¹H NMR spectrum. These results suggest that hydrazone formation was regioselective and depended upon a species of 1,3-dicarbonyl compound.

Scheme 2

An alternative route to synthesize 7,8,9,10-tetrahydro derivative was also developed (Scheme 2). Starting material (10) was prepared according to the procedure reported for 5-unsubstituted compound starting with 5-methoxy-2-nitrophenyl acetic acid. Carbonyl group of 10 was transferred to acetal, and reduced to indoline (11a) by NaBH₃CN in a mixture of HOAc and MeCN. Treatment of 11a with nitrous acid, reduction of product (11b) with LiAlH₄, and subsequent treatment of N-amino product with silica gel in CH₂Cl₂ overnight permitted air-oxidation to give 1-aminoindole (11c) in 58% overall yield. Deacetallization and cyclization were effected in 80% acetic acid, and 12b was obtained in 91% yield.

Reduction of keto group of 3a to methylene faced with a few difficulties. Reductions by conventional Wolff-Kishner (hydrazine/NaOH) and modified method (tosylhydrazone/NaBH₃CN) failed. 11-Ketone (3a) was readily reduced by sodium borohydride to alcohol (13a). In extraction of 13a, it was critical to use ethyl acetate, since 13a was quite susceptible to air-oxidation. 13a was oxidized to 3a in 84% after 12 h inCDCl₃ when monitored by ¹H NMR spectrum. No notable oxidation was detected in CD₃OD after 24 h of leaving. Acetate (13b) was stable in these conditions. Since 13a was sparingly soluble in CH₂Cl₂,
crude 13a was readily purified by brief washing with cold CH₂Cl₂. Deoxygenation of alcohol (13a) to 14a did not succeed with PdCl₂/NaBH₄⁹ and HSiEt₃/CF₃COOH.¹⁰ In order to use Mozingo reduction, ketone (3a) was treated with ethanedithiol and BF₃ etherate. Thioacetalization was slow (TLC), so that the solution was refluxed to complete reaction (TLC analysis). The product was not thioacetal, but reduction product (14a) in quantitative yield. There are two isomers possible for reduction product, 11H-isomer (14a) and 6H-isomer. Calculation (MOPAC AM1) revealed that 11H-isomer is 6.695 Kcal/mol more stable than 6H-isomer. Hydrogen sulfide is known to reduce carbonyl to methylene group, but thiol reduction observed above has no precedence,¹² thus the scope of this novel reduction was further investigated and result is summarized in Table 1.

Thiol reduction of keto group in 3a to methylene group in 14a was effected by a variety of thiol. In typical procedure a solution of ketone in 20 times mole of thiol was refluxed in the presence of 5 equivalent of BF₃ etherate for 6 h. After cooling upper layer (thiol) was removed by decantation and lower layer was washed with hexane to remove thiol. Work-up with aqueous alkaline solution, and chromatography of crude product yielded odorless reduction product. This reduction was ineffective in the absence of Lewis acid, and in BuSH/KSBu. 9-Fluorenone and 4-oxo-2-phenyl-4H-pyrazolo[1,5-a]indole in above condition resisted to reduction, but yielded dithioacetals. These observations conclude that above thiol reduction is
Table 1. Thiol reduction of 3a to 14a $^a$)

<table>
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<tr>
<th>Entry</th>
<th>RSH</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>$n$-BuSH</td>
<td>98</td>
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<tr>
<td>2</td>
<td>$n$-PrSH</td>
<td>95</td>
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<tr>
<td>3</td>
<td>PhCH$_2$SH</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>4-Me C$_6$H$_4$SH</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>4-Cl C$_6$H$_4$SH</td>
<td>90$^b$</td>
</tr>
<tr>
<td>6</td>
<td>HS(CH$_2$)$_2$SH</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>HS(CH$_2$)$_3$SH</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Dihydrolipoic acid$^c$)</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>Lawesson reagent$^d$)</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$) Reaction procedure in text.

$^b$) 10 Equiv. of BF$_3$ etherate and 24 h period were employed.

$^c$) HS(CH$_2$)$_2$CH(SH)(CH$_2$)$_2$COOH

$^d$) 2.2 Equiv. of reagent in refluxing toluene for 1 h.

peculiar to the ring system of 3a, and its novelty can be interpreted by the participation of the reduction mechanism shown in Scheme 4. The first stage of reduction represented by 16 yields 17 as reduction product and disulfide as oxidation product.$^{13}$ Following protonation to 17, reduction of 18 in a similar manner, and second protonation to 19 eventually yield methylene product 14a. Reduction of thioacetal by thiol is a reported procedure,$^{12,14a}$ and plays a key role in reductive activation of 7-(N-mercaptoalkyl)mitomycins.$^{14b}$ But the observed reduction of keto group to methylene group by thiol has no precedence.

Scheme 4

Reduction with dihydrolipoic acid is noteworthy on the standpoint of odorless procedure. In search of
odorless method,\textsuperscript{14c} we found that a combination of LiAlH$_4$ and AlCl$_3$\textsuperscript{15} was quite effective in reduction of 3a, and 14a was obtained in 71% yield. Since a combination of thiol with BF$_3$ is known to effect in cleaving ether linkage,\textsuperscript{16} reduction of 3b in above reaction condition yielded a mixture of 14b and demethylated product (14d). Demethylation of 14b to 14d in 55% yield was also effected with Lil in refluxing collidine.\textsuperscript{17} Also nitro ketone (3c) was reduced to 14c with intact nitro group in moderate yield. Although above thiol reduction uses thiol of unpleasant odor and is tedious to obtain odorless product, there is no alternative method to reduce 11-keto group in 3c to methylene group in 14c without touching reduction-sensitive nitro group.

Hydrogenation of 3a as in the case of 4-oxopyrazolo[1,5-\textit{a}]indole derivatives\textsuperscript{18} was carried out by 10\%Pd-C/H$_2$ in ethyl acetate, and alcohol (15) with saturated D-ring was obtained in 78\% yield. Similar reduction in methanol containing acetic acid (30\%) yielded 15 (42.3\%), 12a (20.5\%), and 9 (10.7\%). Reduction in acetic acid under pressured hydrogen did not increase a yield of 12a. Catalytic hydrogenation of 14a on 10\%Pd on charcoal gave 12a and PCC oxidation of 15 in the presence of Celite\textsuperscript{19} yielded ketone (9). Similarly 14b afforded 12b in good yield. 2-Phenylindazole was readily hydrogenated to 4,5,6,7-tetrahydro-2-phenylindazole in the similar reaction condition. These chemical behaviors of D-ring in hydrogenation reaction are supported from calculation results (MOPAC AM1). The bond lengths between C-7 and C-8 and between C-9 and C-10 (1.37 Å) are found to be shorter than that of benzene double bond (1.39 Å)(Figure 1). Contrary to ease in hydrogenation, dehydrogenation of 12b to 14b resisted to various reaction conditions (10\%Pd-C in xylene at refluxing temperature; oxidation with MnO$_2$).

![Figure 1](image-url)

\textbf{Figure 1}

\textit{Bond Length (Angstrom) by MOPAC AM1 Calculation}
In summary we have provided various pathways to fulfill the methods in synthesizing a variety of indolo[1,2-b]indazole derivatives. Also spatial chemical behaviors due to the skeleton of indolo[1,2-b]indazole are presented.

**AKNOWLEDGEMENT**

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**EXPERIMENTAL**

Unless otherwise noted, following procedures were employed; chromatography by silica gel; usual work-up by consecutive procedures of washing (saturated brine thrice), drying (Na$_2$SO$_4$), filtration and evaporation in vacuo; IR spectrum in KBr pellet with cm$^{-1}$; chemical shift of NMR spectra (400 MHz) by $\delta$ (ppm) in CDCl$_3$ with tetramethylsilane as internal standard unless otherwise noted; MS spectra by EI ionization. Assignments of NMR spectra were carried out by using COSY, HOHAHA, PNOESY, CHSHF, and LRCHSHF spectra.

**2-Methoxy-11H-indolo[1,2-b]indazol-11-one (3b)**

A solution of 1b (2.31 g, 15 mmol), 2 (3.54 g, 30 mmol) and K$_2$CO$_3$ (2.76 g, 20 mmol) in DMSO (35 mL) was heated at 110 °C for 8 h under extrusion of moisture. Benzaldehyde (1b) (2.31 g, 15 mmol) and potassium carbonate (2.27 g, 16.4 mmol) were supplemented, and heating was resumed for another 8 h to complete reaction (TLC). A mixture was poured into ice-water (100 g), neutralized (1N HCl) and extracted with ether (100 mL x 2) and ethyl acetate (100 mL x 2). The crude product was chromatographed (CH$_2$Cl$_2$ - Hex 3 : 1), and eluate was recrystallized from C$_2$H$_5$OH to give 3b (0.87 g, 11.6%) as red crystals, mp 202.0-203.0 °C (Acetone). MS $m/z$: 250 (M$^+$, 100%), 235(46.0), 207(8.0), 179(8.4). IR: 1708, 1698, 1610, 1479, 1436, 1303, 1226, 1024, 815. $^1$H NMR $\delta$: 3.88 (3H, s), 7.00 (1H, dd, $J= 2.7$, 8.6 Hz), 7.22 (1H, d, $J=2.7$ Hz), 7.30-7.33 (2H, m), 7.52 (1H, d, $J=8.6$ Hz), 7.77-7.84 (2H, m).

2-Fluoro-11H-indolo[1,2-b]indazol-11-one (3c)

A mixture of 2 (0.71 g, 6.0 mmol), 1c (0.32 mL), K$_2$CO$_3$ (1.00 g, 7.2 mmol) and DMSO (7 mL) was heated at 110 °C (bath temperature) for 7 h. 1c (0.32 mL, 7.2 mmol), K$_2$CO$_3$ (1.00 g, 7.2 mmol) and DMSO (7 mL) were added and reaction was resumed for another 10 h. Work-up, chromatography (CH$_2$Cl$_2$-hexane=7 : 1), and recrystallization gave 3c (100 mg, 7.0%) as pale yellow needles, mp 202.0-203.0 °C (C$_2$H$_5$OH). MS m/z: 238(M+, 100), 210(14.4), 182(5.9), 94(6.8). IR: 1704, 1634, 1475, 1211, 821, 800, 743. $^1$H NMR δ: 7.23(1H, td, $^3$J$_{H-F}$=8.5 Hz, $^3$J$_{H-H}$ =8.5 Hz, $^4$J$_{H-H}$ =2.6 Hz), 7.32-7.35 (1H, m), 7.35(1H, d, $J$=9.6 Hz), 7.38(1H, dd, $J$=6.8, 2.5 Hz), 7.59 (1H, dd, $J$=8.4, 3.9 Hz), 7.78-7.87(2H, m). $^{13}$C NMR δ: 112.7($^2$J$_{C-F}$=25.5 Hz), 113.3 ($^3$J$_{C-F}$=8.1 Hz), 120.0, 120.0, 120.1, 120.5($^4$J$_{C-F}$=24.9 Hz), 127.6, 128.1, 130.8($^5$J$_{C-F}$=2.0 Hz), 131.3($^6$J$_{C-F}$=7.4 Hz), 139.4($^7$J$_{C-F}$=2.7 Hz), 154.5, 162.6($^8$J$_{C-F}$=250.1 Hz), 176.4($^9$J$_{C-F}$=2.0 Hz).

2-Nitro-11-oxo-11H-indolo[1,2-b]indazole (3d)

a) To lithium salt prepared by addition of n-BuLi (1.64 M, 14.7 mL, 24.2 mmol) to a solution of 2 (2.59 g, 22.0 mmol) in dry THF (25 mL) at 0 °C for 30 min in dry nitrogen, a solution of 4 (4.37 g, 22.0 mmol) in dry THF (20 mL) was introduced, and the resulting mixture was kept at the same temperature for 3 h, then warmed up to rt. Quenching with 5% NH$_4$Cl (5 mL) and extraction with CH$_2$Cl$_2$ (200 mL) gave the crude product. Chromatography (CH$_2$Cl$_2$-hexane 19 : 1), and recrystallization (CH$_2$Cl$_2$-hexane) yielded 5 (3.20 g, 49.0%), mp 159.5-162.0 °C. IR: 3129, 1743, 1589, 1535, 1520, 1347, 1282, 1132, 771, 749. MS m/z: 298(M$^+$+ 1, 100%), 281(4.2), 266(17.6), 251(3.3), 239(32.7), 220(17.8), 193(9.5), 179(3.8), 164(6.1). HRMS Calcd for M$^+$: 297.0748; Found: 297.0723. $^1$H NMR δ (DMSO-$d_6$): 3.68(3H, s, Me), 7.14(1H, dd, $J$=8.3, 6.6 Hz), 7.35(1H, dd, $J$=8.3, 6.6 Hz), 7.68(1H, d, $J$=8.7 Hz), 7.81(1H, d, $J$=8.3 Hz), 8.17(1H, d, $J$=8.6 Hz), 8.55-8.59(2H, m), 9.00(1H, s). $^{13}$C NMR δ (DMSO-$d_6$): 52.7, 117.4, 121.1, 122.4, 122.6, 124.8,
125.0, 126.1, 126.9, 127.5, 128.5, 142.4, 146.4, 149.5, 165.2. Anal. Calcd for C$_{15}$H$_{11}$N$_3$O$_4$: C, 60.61; H, 3.73; N, 14.13. Found: C, 60.43; H, 3.72; N, 14.05.

b) A LDA solution (2 M in hexane, 1.5 mL, 3 mmol) was added to a solution of 5 (597 mg, 2.0 mmol) in dry THF (50 mL) at –70 °C for 3 min. After 2.5 h of reaction time, the solution (–43 °C) was recooled to –70 °C and another amount of LDA (1.0 mL, 2 mmol) was added. Reaction was completed within 1.5 h, and the mixture was quenched (water and aqueous sodium carbonate), and extracted with CH$_2$Cl$_2$ twice. Chromatography (CH$_2$Cl$_2$) gave 3d, (274 mg, 51.4%), as yellow needle, mp 246.0-246.5 °C (EtOAc). MS m/z: 265(M$^+$, 100), 235(13.2), 219(34.2), 191(5.1), 164(14.5), 163. IR: 1716, 1635, 1532, 1343, 1075, 766, 742, 730. $^1$H NMR δ: 7.38-7.41(2H, m), 7.77(1H, d, $J$=8.1 Hz), 7.79-7.90(2H, m), 8.48-8.52(2H, m).

$^{13}$C NMR δ: 112.4, 120.2, 120.4, 120.4, 120.5, 128.8, 129.1, 130.7, 131.0, 132.0, 147.0, 148.0, 155.6, 175.0(C-11). Anal. Calcd for C$_{14}$H$_7$N$_3$O$_3$: C, 63.40; H, 2.66; N, 15.84. Found: C, 63.60; H, 2.57; N, 16.04.

7,8,9,10-Tetrahydro-11-oxo-11$^H$-indolo[1,2-b]indazole (9)

a) A solution of 6 (1.89 g, 10.0 mmol) and 7a (2.02 g, 12.0 mmol) prepared by acetylation of 7b in ethanol-water (1 : 1, 60 mL) was stirred at 50 °C for 30 min. After addition of 5% sulfuric acid (0.5 mL), the solution was refluxing for 2 h. Extraction with ethyl acetate and washing of the extracts (brine) gave the crude product, which was esterified by the reaction of DCC (3.5 g, 17.0 mmol) and DMAP (0.3 g, 2.5 mmol) in CH$_2$Cl$_2$- C$_2$H$_5$OH (40 mL + 2 mL). Solid isolated was removed, and the filtrate was evaporated in vacuo. The residue was chromatographed (hexane-ether) to give 2-(2-ethoxycarbonylphenyl)-4,5,6,7-tetrahydro-2$^H$-indazole (8) as a colorless oil (1.10 g, 40.6 %). MS m/z: 270(100), 241(27.4), 225(37.6), 198(63.9), 170(16.7). $^1$H NMR δ: 1.17 (3H, t, $J$=7.1 Hz), 1.76-1.86 (4H, m), 2.62 (2H, t, $J$=5.7 Hz), 2.73 (2H, t, $J$=6.3 Hz), 4.21 (2H, q, $J$=7.2 Hz), 7.36 (1H, td, $J$=7.3, 1.3 Hz), 7.37(1H s), 7.46(1H, dd, $J$=7.9, 1.4 Hz), 7.52(1H, td, $J$=7.3, 1.6 Hz), 7.75(1H, dd, $J$=7.7, 1.6 Hz). $^{13}$C NMR δ: 13.9, 20.7, 23.5, 23.5, 23.5, 61.3, 117.6, 124.7, 126.7, 126.9, 127.7, 130.2, 131.6, 139.6, 151.0, 167.4.

b) A solution of 8 (1.32 g, 4.9 mmol) in THF (5 mL) was added at –78 °C to a solution of LDA (2 M in hexane, 2.5 mL, 5.0 mmol) in THF (10 mL) under nitrogen atmosphere, and reaction was continued for 1
h. Quenching (5% NH₄Cl), extraction (CH₂Cl₂, 60 mL), and chromatography (hexane-CH₂Cl₂) of the crude product afforded 9 (0.45 g, 40.9 %) as yellow needle, mp 121.0-121.5 °C (MeOH). MS m/z: 224(M⁺, 100), 196(64.9), 168(9.5), 130(6.8), 102(5.8). IR: 1709, 1625, 1473, 895, 752. ¹H NMR δ: 1.82(4H, m), 2.75(4H, m), 7.13(1H, ddd, \( J =7.6, 7.3, 1.0 \) Hz), 7.31(1H, d, \( J =7.8 \) Hz), 7.48(1H, ddd, \( J =7.8, 7.6, 1.2 \) Hz), 7.56 (1H, d, \( J =7.3 \) Hz). ¹³C NMR δ: 21.0, 22.4, 23.7, 109.9, 120.3, 124.6, 125.4, 128.3, 134.2, 135.4, 143.9, 156.5, 178.0.

\[7,8,9,10\text{-Tetrahydro-2-methoxy-11H-indolo[1,2-b]indazole (12b)}\]

\(a\) 2-(5-Methoxy-2-nitrophenylacetyl)cyclohexanone (5.85 g, 20.1 mmol) prepared from 5-methoxy-2-nitrophenyl acetic acid⁵ was transformed to 2-(5-methoxyindol-2-yl)cyclohexanone (10) by a similar method reported for 5-demethoxylated derivative,⁵ and a solution of 10 in benzene (150 mL) containing p-toluensulfonic acid monohydrate (150 mg) and ethylene glycol (1 mL) was refluxed for 4 h. Dilution with ethyl acetate (200 mL) and usual work-up gave the crude product. Chromatography (hexane-EtOAc 10 : 1) afforded acatal of 10 (3.80 g, 66% overall) as needles, mp 129-130 °C (hexane-EtOAc). MS m/z: 287(M⁺, 100), 244(11.3), 242(13.8), 215(34.0), 200(11.4), 188(21.9), 186(26.6), 175(35.9), 159(19.1). IR: 3374, 1488, 1455, 1208, 1159, 1092, 1035, 924. ¹H NMR δ: 1.38-2.40 (8H, m), 3.01 (1H, dd, \( J =5.0, 10.8 \) Hz), 3.42-3.47(1H, m), 3.57-3.63(1H, m), 3.80-3.86(2H, m), 3.833(3H, s, OMe), 6.26 (1H, s), 6.78 (1H, dd, \( J =2.5, 8.8 \) Hz), 7.03 (1H, d, \( J =2.4 \) Hz), 7.20 (1H, d, \( J =8.8 \) Hz), 8.40 (1H, br s, NH). ¹³C NMR δ: 23.8, 24.8, 29.7, 35.6, 44.8, 55.9, 64.7, 65.0, 100.6, 102.1, 110.2, 111.0, 128.6, 130.99, 140.2, 153.9. Anal. Calcd for C₁₇H₂₁NO₃: C, 71.05; H, 7.37; N, 4.88. Found: C, 70.89; H, 7.29; N, 4.82.

Acetal (0.70 g, 2.4 mmol) in HOAc-MeCN (14 + 7 mL) was reduced with NaBH₃CN (0.40 g, 6.4 mmol) at rt for 4 h. Dilution with ether (150 mL) and usual work-up gave the product. Chromatography (hexane - EtOAc 10 : 1) yielded 11a (0.65g, 92%) as a mixture of isomers, mp 89-91 °C (Hex-EtOAc). MS m/z: 289(M⁺, 75.0), 244(7.8), 215(14.7), 186(11.5), 175(20.7), 159(13.8), 149(100), 147(100), 133(16.0), 117(13.0), 99(26.3). IR: 3350, 1495, 1231, 1141, 1080, 1034, 924, 809. ¹H NMR δ (signals for major isomer): 1.19-1.85 (8H, m), 2.76 (1H, dd, \( J =7.2, 15.1 \) Hz), 3.15 (1H, dd, \( J =9.5, 16.1 \) Hz), 3.73 (3H, s),
3.92-4.08 (4H, m), 4.235 (1H, m), 6.46-6.71 (3H, m). $^{13}$C NMR $\delta$ (signals for major isomers): 23.8, 23.8, 25.1, 35.0, 35.9, 49.6, 56.0, 57.2, 64.3, 64.6, 108.5, 111.2, 111.3, 112.0, 130.2, 145.7, 152.8.

b) A solution of NaNO$_2$ (0.40 g, 5.8 mmol) in water (4 mL) was dropped slowly to the ice-cooled solution of 11a (0.75 g, 2.6 mmol) in dilute HCl (water: 12 mL + 10% HCl: 3 mL). After 20 min of reaction time, the solution was diluted with ethyl acetate (100 mL) and worked up. The crude 11b (0.74 g, 90%) was used in the following step without purification.

c) Nitroso compound (11b) (0.74 g) in dry ether (20 mL) was gradually added to a suspension of LiAlH$_4$ (95%, 0.74 g, 18.5 mmol) in ether (15 mL), and reaction was continued at rt for 12 h. Excess reagent was decomposed with water. Precipitates were removed by filtration, and washed with ether (60 mL). Crude product was dissolved in CH$_2$Cl$_2$ (5 mL), and treated with silica gel (2.0 g) overnight. After filtration the filtrate was evaporated, and residue was chromatographed (hexane-EtOAc 7 : 1) to give 11c (410 mg, 58%), mp 119-121°C (hexane-EtOAc). MS m/z: 302(M+, 100), 287(44.6), 240(15.0), 215(15.8), 201(10.1), 189(17.9), 175(15.0), 159(15.9). IR: 3430, 3345, 1607, 1481, 1446, 1446, 1205, 1157, 1083, 929. $^1$H NMR $\delta$: 1.37-2.10 (8H, m), 3.15-3.19 (2H, m), 3.29-3.34 (1H, m), 3.69-3.75 (2H, m), 3.83 (3H, s), 4.88 (2H, s), 6.22 (1H, s), 6.84 (1H, dd, $J$=2.4, 8.8 Hz), 6.99 (1H, d, $J$=2.4 Hz), 7.41 (1H, d, $J$=8.8 Hz). $^{13}$C NMR $\delta$: 23.9, 25.6, 29.6, 36.8, 42.7, 55.9, 64.7, 65.5, 97.9, 101.8, 110.0, 110.4, 111.1, 125.3, 132.4, 140.9, 154.0.

d) A solution of 11c (250 mg, 0.83 mmol) in 75% acetic acid (8 mL) was stirred at 70-80°C for 30 min. The solution was diluted with water and extracted with ethyl acetate (100 mL). The crude product was chromatographed (hexane-EtOAc 10 : 1), and 12b (180 mg, 91%) was obtained as plates, mp 117-118°C (C$_2$H$_5$OH). MS m/z: 240(M$^+$, 100), 225(28.4), 212(17.6), 183(9.5). IR: 1586, 1488, 1301, 1243, 1130, 1107, 818, 809. $^1$H NMR $\delta$: 1.77-1.89 (4H, m), 2.58 (2H, t, $J$=6.1 Hz), 2.82 (2H, t, $J$=6.1 Hz), 3.70 (2H, s), 3.82 (3H, s), 6.88 (1H, dd, $J$=2.6, 8.6 Hz), 7.10 (1H, t, $J$=1.0 Hz), 7.44 (1H, d, $J$=8.5Hz). $^{13}$C NMR $\delta$: 20.6, 23.4, 23.5, 24.2, 27.67, 55.8, 109.8, 110.7, 112.3, 113.0, 134.7, 134.9, 140.5, 153.4, 156.6. Anal. Calcd for C$_{15}$H$_{16}$N$_2$O: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.84; H, 6.73; N, 11.61.

11-Hydroxy-11H-indolo[1,2-b]indazole (13a)
Reduction of 3a (110 mg, 0.5 mmol) with NaBH₄ (19 mg, 0.5 mmol) in dry methanol (5 mL) was conducted in nitrogen atmosphere at rt for 10 min. Yellow color faded away, and solution was evaporated in vacuo at 40°C. Product was extracted with ethyl acetate and ice-water, and crystalline product (112 mg) were briefly washed with cold CH₂Cl₂ (2 mL x 2) to give 13a (97 mg, 87.4%), mp 207-209°C. IR: 3194, 1518, 1477, 1382, 1057, 747. MS m/z: 222(M⁺, 100), 221(40), 220(48), 205(42), 194(28). HRMS Calcd for C₁₄H₁₀N₂O: 222.0792; Found: 222.0816.

1H NMR (CD₃OD) δ: 6.03(1H, s), 7.18(1H, ddd, J = 8.5, 6.7, 0.9 Hz), 7.35(1H, ddd, J = 8.9, 6.7, 1.1 Hz), 7.41(1H, td, J = 7.5, 1.1 Hz), 7.54(1H, td, J = 7.7, 1.2 Hz), 7.70(1H, dt, J = 8.9, 0.9 Hz), 7.72(1H, d, J = 7.5 Hz), 7.76(1H, d, J = 7.8 Hz), 7.86(1H, dt, J = 8.4, 1.1 Hz).

13C NMR (CD₃OD) δ: 68.1, 112.8, 118.9, 119.2, 121.0, 123.9, 127.4, 128.3, 128.4, 131.0, 140.7, 140.8, 141.8, 154.6. Acetate (13b) was prepared by the reaction of crude 13a with complex of Ac₂O-pyridine (0.5 + 0.5 mL) in 73.1% yield. 13b, mp 177.0-179.0°C (decomp)(hexane). IR: 1742, 1224, 1023, 980, 761, 742. MS m/z: 264(M⁺, 64), 222(50), 221(54), 205(100). HRMS Calcd for C₁₆H₁₂N₂O₂: 264.0899; Found: 264.0934. 1H NMR δ: 6.86(1H, s), 7.16(1H, dd, J = 8.6, 6.7 Hz), 7.32(1H, ddd, J = 8.9, 6.8, 1.1 Hz), 7.34(1H, td, J = 7.6, 1.0 Hz), 7.54(1H, t, J = 7.8 Hz), 7.61(1H, d, J = 7.5 Hz), 7.78(1H, dt, J = 8.5, 1.1 Hz), 7.79(1H, dt, J = 8.8, 1.0 Hz), 7.82(1H, d, J = 7.8 Hz). 13C NMR δ: 20.9, 67.4, 112.4, 118.7, 118.8, 120.5, 123.5, 126.8, 126.9, 127.0, 130.8, 134.5, 135.7, 140.5, 153.6, 171.2.

11H-Indolo[1,2-b]indazole (14a)

a) Thiol-reduction of 11-keto group to 11-methylene group: Typical procedure. A mixture of 3a (1 mmol), n-BuSH (5.4 mL, 20 mmol) and BF₃ etherate (0.63 mL, 5 mmol) was heated at 120°C (bath temperature) for 6 h to complete reaction (TLC analysis). After cooling, upper layer (thiol) was removed, and lower layer was briefly washed with n-hexane twice by decantation. Residual material was treated with aqueous 1M NaOH solution and extracted with CH₂Cl₂. Extracts were washed (saturated brine), dried (Na₂SO₄) and evaporated. Column chromatography (CH₂Cl₂) and recrystallization gave 14a, mp 162.0-164.0°C (isopropyl ether). MS m/z: 206(M⁺, 100), 178 (15.1), 152 (4.4), 151(4.5), 103(8.3). IR: 3055, 1621, 1478, 1450, 1399, 1369, 1298, 1095, 934, 845, 757, 740. 1H NMR δ: 4.11(2H, s), 7.03(1H,
dd, \( J = 8.4, 8.4 \) Hz), 7.24(2H, m), 7.40(1H, \( t, J = 7.8 \) Hz), 7.48(1H, \( d, J = 7.5 \) Hz), 7.61(1H, \( d, J = 8.4 \) Hz), 7.73(1H, \( d, J = 8.9 \) Hz), 7.82(1H, \( d, J = 7.8 \) Hz). NOE was observed between 10-H\(_2\) and 1-H. \( ^{13} \)C NMR \( \delta \): 28.6, 112.2, 117.1, 118.5, 119.6, 121.6, 126.0(2xC), 126.4, 128.3, 134.6, 137.2, 140.7, 153.3. Anal. Calcd for C\(_{14}\)H\(_{10}\)N\(_2\): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.13; H, 4.78; N, 13.56.

b) Reduction with LAH-AlCl\(_3\) complex: A solution of 3a (200 mg, 0.91 mmol) in dry ether (20 mL) was introduced to the reagent prepared by adding a solution of AlCl\(_3\) (700 mg, 5.25 mmol) in dry ether (10 mL) to a suspension of LiAH\(_4\) (300 mg, 7.9 mmol) in dry ether (5 mL). The solution was refluxed for 6 h to complete reduction (TLC analysis). After quenching (C\(_2\)H\(_5\)OH, 5 mL), the solution was suction-filtered. Inorganics were washed with ether (50 mL). Filtrate and washings were worked up, and chromatography (CH\(_2\)Cl\(_2\)-Hexane 5 : 1) gave 14a (133 mg, 71.0%).

2-Nitro-11H-indolo[1,2-b]indazole (14c)

A mixture of 3d (376 mg, 1.4 mmol), \( n\)-BuSH (20 mL, 187 mmol) and BF\(_3\) etherate (0.5 mL, 3.9 mmol) was refluxed for 8 h. Work-up and short column chromatography (CH\(_2\)Cl\(_2\) + 5% EtOAc) gave 14c (153 mg, 43%), mp 240-245 °C (decomp). MS \( m/z \): 251(M\(^+\), 100), 234(14.1), 221(8.7), 205(89.2), 177(10.5), 176(12.1), 151(6.1), 150(5.0). \(^1\)H-NMR \( \delta \): 4.29(2H, s), 7.16 (1H, ddm, \( J = 8.5, 6.7 \) Hz), 7.37(1H, ddd, \( J = 8.9, 6.7, 1.1 \) Hz), 7.72(1H, dm, \( J = 8.5 \) Hz), 7.80(1H, d, \( J = 8.9 \) Hz), 7.99(1H, d, \( J = 9.3 \) Hz), 8.45 - 8.48(2H, m). \(^{13} \)C NMR \( \delta \): 28.9, 112.2, 117.5, 118.8, 119.8, 121.9, 122.8, 125.5, 127.9, 135.7, 139.0, 145.1, 146.1, 154.5. Anal. Calcd for C\(_{14}\)H\(_9\)N\(_3\)O\(_2\): C, 66.93; H, 3.61; N, 16.73. Found: 66.95; H, 3.63; 16.81.

2-Methoxy- and 2-hydroxy-11H-indolo[1,2-b]indazol-11-one, (14b) and (14d)

a) A mixture of 3b (500 mg, 2 mmol) in \( n\)-butanethiol (12 ml) and BF\(_3\) etherate (2.5 ml, 19.7 mmol) was refluxed for 6 h. Crude product was recrystallized from methanol, and crystalline product was chromatographed (CH\(_2\)Cl\(_2\)-CH\(_3\)COCH\(_3\) 10 : 1) to give 14b (240 mg, 51%), mp 213-214 °C. (CH\(_2\)Cl\(_2\)-CH\(_3\)COCH\(_3\)). MS \( m/z \): 236(M\(^+\), 100), 221(20.1), 193(19.3), 165(19.5). HRMS Calcd for C\(_{13}\)H\(_{12}\)N\(_2\)O: 236.0950; Found: 236.0925. IR: 1603, 1485, 1435, 1264, 1246, 825, 742. \(^1\)H NMR \( \delta \): 3.88 (3H, s), 4.13
(2H, s), 7.01 (1H, dd, J=2.3, 8.6 Hz), 7.11 (1H, t, J=7.6 Hz), 7.16 (1H, d, J=2.1 Hz), 7.31 (1H, ddd, J=1.1, 6.7, 8.8 Hz), 7.70 (1H, d, J=8.4 Hz), 7.80 (1H, d, J=8.9 Hz), 7.81 (1H, d, J=8.9 Hz). 13CNMR δ: 28.9, 55.9, 112.6, 112.8, 113.1, 117.3, 118.3, 119.3, 121.4, 126.0, 134.5, 136.3, 136.5, 153.0, 158.6. The mother liquor of above recrystallization was evaporated and the residue was crystallized from HOAc to give 14d (160 mg, 36%), mp 270°C (decomp). MS m/z: 222(100, M+), 194(9.2), 165(17.0). IR: 3046, 1602, 1476, 1270, 1254, 827, 748. HRMS Calcd for C14H10N2O: 222.0793; Found: 222.07861.

H 1H NMR δ(DMSO-d6): 4.24(2H, s), 6.90(1H, dd, J=2.3, 8.4 Hz), 7.08(1H, t, J=7.6 Hz), 7.12(1H, d, J=2.4 Hz), 7.27(1H, ddd, J=1.2, 6.7, 8.2 Hz), 7.64(1H, d, J=8.4 Hz), 7.68(1H, d, J=8.7 Hz), 7.77(1H, d, J=8.3 Hz). 13C NMR δ(DMSO-d6): 28.5, 112.2, 113.8, 114.3, 116.8, 117.6, 119.8, 120.6, 125.4, 132.3, 136.4, 136.9, 151.9, 156.3.

b) A mixture of 14b (118 mg, 0.47 mmol), and LiI (236 mg, 1.0 mmol) in collidine (5 mL) was refluxed for 10 h. After cooling solution was treated with aqueous 3N HCl (10 mL), and extracted with ethyl acetate to give 14d (55 mg, 50%).

Catalytic hydrogenation of ketone (3a).

a) 10%Pd-C/H2/EtOAc. Reduction of 3a (50 mg) in ethyl acetate (15 mL) with H2/10%Pd-C (17 mg), and chromatography of the crude product gave 11-hydroxy-11H-indolo[2,3-b]indazole (15a) (39 mg, 76%), colorless rod, mp 209.0-210.0 °C (EtOAc). MS m/z: 226(M+, 100), 209(11.1), 198(12.8), 197(18.1), 181(6.0), 170(8.5), 121(7.3). IR: 3195, 1622, 1485, 1354, 1051, 756. 1H NMR δ(DMSO-d6): 1.75(4H, m), 2.63(4H, m), 5.63(1H, d, J=7.6 Hz, 11-H. Singlet after D2O addition), 5.96(1H, d, J=7.6 Hz, OH), 7.14(1H, td-like m), 7.34(1H, m), 7.35(1H, dd, J=6.8, 1.2 Hz), 7.51(1H, d, J=7.3 Hz). 13C NMR δ(DMSO-d6): 19.8, 22.7(2 x C), 23.6, 65.4, 108.8, 112.5, 123.9, 125.9, 129.1, 138.0, 139.2, 143.8, 153.3.

b) 10%Pd-C/H2/MeOH-HOAc. A solution of 3a (46 mg) and 10% Pd-C (20 mg) in HOAc-MeOH(7 + 3 mL) was hydrogenated. Chromatography (CH2Cl2 + 5%, 8%, 10%, 50% EtOAc) gave 9 (5 mg, 10.7%), 12a (9 mg, 20.5%), 15 (20 mg, 42.3%).
7,8,9,10-Tetrahydro-11H-indolo[1,2-b]indazole (12a)

A solution of 14a (42.6 mg) in ethyl acetate (20 mL) was reduced with hydrogen over 10% Pd-C (18.9 mg) for 1 d. Crystallization of the crude product gave 12a (27 mg) as colorless plate, mp 113.0-114.5 °C (EtOAc). MS m/z: 210(M⁺, 100), 206(18.4), 195(16.8), 183(21.4), 182(24.2), 181(25.5), 169(17.7), 160(9.2), 153(24.4), 142(17.6), 141(20.4). HRMS Calcd for C₁₄H₁₄N₂: 210.1157; Found: 210.1188. IR: 3058, 1623, 1603, 1486, 747. ¹H NMR δ: 1.83(4H, m), 2.58(2H, t-like m), 2.82(2H, t-like m), 3.71(2H, s), 7.11(1H, td, J=7.4, 1.0 Hz), 7.343(1H, t, J=7.8 Hz), 7.40(1H, d, J=7.8 Hz), 7.54(1H, d, J=7.8 Hz). ¹³C NMR δ: 20.6, 23.4, 23.4, 24.2, 27.4, 109.7, 110.8, 123.4, 126.0, 127.9, 133.1, 140.7, 141.10, 154.2.

Oxidation of 15 to 9

Alcohol (15) (45 mg, 0.20 mmol) was oxidized with a mixture of PCC (99 mg, 0.46 mmol) and Celite (122 mg) suspended in CH₂Cl₂ (20 mL) for 3.5 h at rt.¹⁸ Dilution with ether, filtration via Florisil pad, washing of Florisil with ether, and evaporation of the filtrate and washings gave yellow residue (45 mg). Chromatography (CH₂Cl₂) and recrystallization of yellow crystals (37 mg, 83%) from methanol yielded 9 (22 mg).

Catalytic hydrogenation of 14b to 12b

A solution of 14b (30 mg) and 10% Pd-C (10 mg) in ethyl acetate (4 mL) was stirred in hydrogen atmosphere for 12 h. Catalyst was removed and the filtrate was evaporated. Chromatography of the product (CH₂Cl₂) gave 12b (26 mg).

REFERENCES AND NOTES

13. Reduction of **3a** with 4-chlorothiophenol permitted to isolated disulfide in 70% yield. When dithioacetal was subjected to the same reaction condition, product was obtained in good yield.