A New and Convenient Synthesis of 3-Aryl-3-hydroxyisoindol-1-ones and Their Aza Analogs

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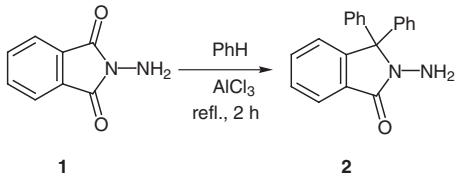
Abstract: A simple and convenient synthesis of 3-aryl-3-hydroxyisoindol-1-ones and their aza analogs is described. The utility of this synthesis is demonstrated by the preparation of 4-arylphthalazinones and their aza analogs.

Key words: aluminum trichloride, hydrazides, hydroxyazaisoindolinones, pyrrolopyridinediones, 1-arylpyridopyridazinones

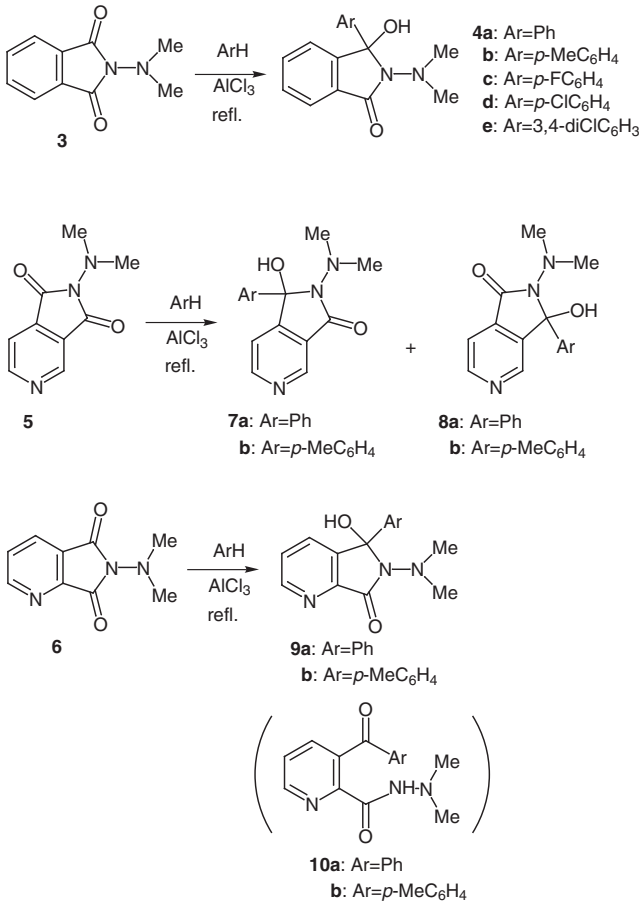
3-Subustituted-3-hydroxyisoindol-1-ones and the corresponding hydroxyazaisoindolinones are important synthetic building blocks for the preparation of bio-active compounds and, accordingly, have received much synthetic attention.[1] Ismail et al. reported that the reaction of *N*-aminophthalimide (**1**) with arenes in the presence of $AlCl_3$ under mild reaction conditions gives the ring opened compound, 2-aroylbenzoic acid hydrazide.[2] We recently reported that reaction of **1** with benzene in the presence of $AlCl_3$ produces 3,3-diphenyl-2,3-dihydroisoindol-1-one (**2**) by an initial Friedel–Crafts alkylation of benzene by the imide carbonyl in a process that is assisted by the neighboring nitrogen atom.[3]



1 **2**

Scheme 1

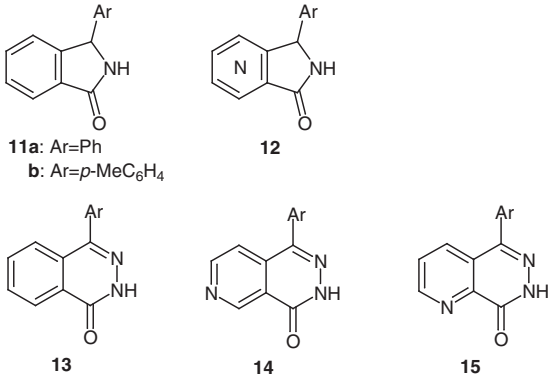
In an extension of this work, we have now investigated the reaction of *N*-(*N*,*N*-dimethylamino)phthalimide (**3**) with arenes in the presence of $AlCl_3$. In this case, using our previous reaction conditions, only one phenyl group was introduced to the imide carbonyl to yield 3-hydroxy-3-phenyl-2,3-dihydroisoindol-1-one (**4a**) in high yield. Presumably, the steric bulk of the dimethylamino group prevents introduction of the second aryl group. Previously reported syntheses of 3-subustituted-3-hydroxyisoindol-1-ones typically involve addition of an organometallic reagent to a protected phthalimide. For example, the reaction of **3** with a stoichiometric amount of Grignard or organolithium reagents under low temperature has been reported.[1] The present synthetic method is found to be applicable for the synthesis of not only **3** but also pyrrolopyridinediones **5** and **6** as depicted in Scheme 2.



Scheme 2

Reaction of the aza analog **5** with benzene and toluene in the presence of $AlCl_3$ gave a mixture consisting predominantly of **7** and a lesser amount of **8**, whereas the similar reaction of **6** interestingly gave only **9**. The procedure is notable for its simplicity and products are formed in high yield. The structures of **7**, **8** and **9** were established on the basis of ^1H and ^{13}C NMR, IR and mass spectra. The ^{13}C NMR spectrum of **9** measured in $CDCl_3$ shows two carbonyl carbon signals and one signal for the tertiary carbon, which suggests the presence of an equilibrium of **9** with the ring opened compound **10** in $CDCl_3$. Furthermore, these structures were unambiguously determined by converting them to the known **14** and **15** (*vide infra*).

Based on the published report of the transformation of **4a** to 3-phenylphthalimidine (**11a**),[1] a similar conversion of **7** and **8** to the corresponding aza analogs **12** would appear



Figure

attractive. Furthermore, **4**, **7** and **9** proved to be useful intermediates for the synthesis of phthalazinones **13** and their aza analogs **14** and **15** simply through reaction with hydrazine. Although **14** and **15** have obvious important synthetic applications, and possess interesting chemical properties, the difficulty in synthesizing pyridine starting materials required for their synthesis has precluded extensive study. Thus, previous synthetic methods have involved the construction of the lactam unit from lithiated pyridine derivatives[4,5] or from *N*-hydroxyquinolinimide.[6] According to our method presented here, **4**, **7** and **9**, readily synthesized with a simple operation, can be transformed by reaction with hydrazine hydrate to **13**, **14** and **15**, respectively. Thus, the present methodology represents an effective and simple route for the synthesis of 3-aryl-3-hydroxyisoindol-1-ones and their aza analogs. These compounds will serve as useful starting points for further transformations to biologically important compounds.

Mps were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR 810 spectrometer. ^{1}H NMR spectra were measured at 270 MHz on JEOL JNM-EX270 or at 500 MHz on JNM-A500 with TMS as an internal reference. ^{13}C NMR spectra were measured at 67.8 MHz on JEOL JNM-EX270 spectrometer with TMS as an internal reference. Mass spectra were measured with a JEOL JMS-700 spectrometer using direct inlet system. Elemental analyses were performed at the Microanalytical Laboratory of this University. All reagents and solvents are available commercially and purchased from Aldrich Chem. Co. and Tokyo Kasei Kogyo Co. and used without further purification. 2-(Dimethylamino)isoindol-1,3-dione (**3**) is a known compound.[7]

2-(Dimethylamino)-3-hydroxy-3-phenyl-2,3-dihydroisoindol-1-one (4a); Typical Procedure

To a solution of **3** (0.30 g, 1.58 mmol) in anhyd benzene (15 mL) was added $AlCl_3$ (1.68 g, 12.6 mmol) and the reaction mixture was refluxed for 2 h. After addition of H_2O (20 mL) to the mixture with ice cooling, the aqueous layer was basified with 10% NaOH (10 mL) and was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (EtOAc/benzene, 1:3) to give **4a** (0.39 g, 93%) as a white solid; mp: 174−175 ºC (benzene/hexane) (Lit.[1] mp: 173−174 ºC).

IR (KBr): ν = 3200, 1680, 1520 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.87 (s, 6H, 2 × CH_3), 3.64 (s. 1H, OH), 7.18−7.26 (m, 1H, ArH), 7.30−7.32 (m, 3H, ArH), 7.32−7.53 (m, 4H, ArH), 7.76−7.85 (m, 1H, ArH).

MS (EI): *m/z* (%) = 268 (M^+), 209 (100).

2-(Dimethylamino)-3-hydroxy-3-(4-methylphenyl)-2,3-dihydroisoindol-1-one (4b)

The procedure was the same as described above except that the reaction mixture was refluxed for 1 h.

Yield: 92%; white crystals; mp: 154−156 ºC (EtOAc/hexane).

IR (KBr): ν = 3200, 1689, 1620, 1520 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 2.88 (s, 6H, 2 × CH_3), 3.57 (s, 1H, OH), 7.15 (d, 2H, *J* = 8.0 Hz, ArH), 7.18−7.24 (m, 1H, ArH), 7.34 (d, 2H, *J* = 8.0 Hz, ArH), 7.42−7.53 (m, 2H, ArH), 7.76−7.83 (m, 1H, ArH).

MS (EI): *m/z* (%) = 282 (M^+), 223 (100).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.24; H, 6.28; N, 9.85.

2-Dimethylamino-3-(4-fluorophenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (4c)

The procedure was the same as described above except that the reaction mixture was stirred for 9 h at 50 ºC (oil bath temperature).

Yield: 65%; white crystals; mp: 145−146 ºC (diisopropylether).

IR (KBr): ν = 3200, 1680, 1620, 1510 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (s, 6H, 2 × CH_3), 3.67 (s, 1H, OH), 7.03 (d, 2H, *J* = 8.9 Hz, ArH), 7.20 (d, 1H, *J* = 7.6 Hz, ArH), 7.43 (dd, 2H, *J* = 8.9, 7.6 Hz, ArH), 7.46−7.53 (m, 2H, ArH), 7.78 (d, 1H, *J* = 7.6 Hz, ArH).

MS (EI): *m/z* (%) = 286 (M^+), 59 (100).

Anal. Calcd for $C_{16}H_{15}N_2O_2F$: C, 67.12; H, 5.28; N, 9.78. Found: C, 67.03; H, 5.36; N, 9.73.

2-Dimethylamino-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (4d)

The procedure was the same as described above except that the reaction mixture was stirred for 2.5 h at 90 ºC (oil bath temperature).

Yield: 77%; white crystals; mp: 162−164 ºC (Et_2O/hexane).

IR (KBr): ν = 3200, 1680, 1620, 1500 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.87 (s, 6H, 2 × CH_3), 3.46 (s, 1H, OH), 7.16−7.24 (m, 1H, ArH), 7.31 (d, 2H, *J* = 8.7 Hz, ArH), 7.39 (d, 2H, *J* = 8.7 Hz, ArH), 7.45−7.55 (m, 2H, ArH), 7.77−7.84 (m, 1H, ArH).

MS (EI): *m/z* (%) = 304 (M^++2), 302 (M^+), 59 (100).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.54; H, 4.99; N, 9.29.

2-Dimethylamino-3-(3,4-dichlorolphenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (4e)

The procedure was the same as described above except that $AlCl_3$ (10 molar equiv) was used and the reaction mixture was stirred for 8 h at 130 ºC (oil bath temperature).

Yield: 58%; white crystals; mp: 154−156 ºC (EtOAc/hexane).

IR (KBr): ν = 3250, 1690, 1475, 1365 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.13 (s, 6H, 2 × CH_3), 3.51 (s, 1H, OH), 7.18−7.24 (m, 1H, ArH), 7.20 (dd, 1H, *J* = 8.4, 2.2 Hz, ArH), 7.40 (d, 1H, *J* = 8.4 Hz, ArH), 7.47−7.58 (m, 2H, ArH), 7.56 (d, 1H, *J* = 2.2 Hz, ArH), 7.76−7.85 (m, 1H, ArH).

MS (EI): *m/z* (%) = 340 (M^++4), 338 (M^++2), 336 (M^+), 59 (100).

Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_2$: C, 56.99; H, 4.18; N, 8.31. Found: C, 57.04; H, 4.15; N, 8.32.

2-(Dimethylamino)pyrrolo[3,4-*c*]pyridine-1,3-dione (5); Typical Procedure

A mixture of 3,4-pyridinedicarboxylic anhydride (1.00 g, 6.71 mmol) and 1,1-dimethylhydrazine (0.40 g, 6.71 mmol) in THF (30 mL) was refluxed for 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in Ac_2O (20 mL) and heated under refluxed for 2 h. HOAc was evaporated under reduced pressure and the crude residue was dissolved in EtOAc (60 mL). The organic layer was washed with 10% Na_2CO_3 (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (EtOAc) to give **5** (0.84 g, 71%) as a pale yellow solid; mp: 141−142 ºC (EtOAc/hexane).

IR (KBr): ν = 1790, 1740, 1710, 1610 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 3.40 (s, 6H, 2 × CH_3), 7.74 (dd, 1H, *J* = 4.8, 1.1 Hz, ArH), 9.09 (d, 1H, *J* = 4.8 Hz, ArH), 9.14 (s, 1H, ArH).

MS (EI): *m/z* (%) = 191 (M^+), 149 (100).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.52; H, 4.73; N, 21.99. Found: C, 56.54; H, 4.74; N, 21.98.

6-(Dimethylamino)pyrrolo[3,4-*b*]pyridine-5,7-dione (6)

Under the same condition used for **5**, 2,3-pyridinedicarboxylic anhydride gave **6** (71%) as a pale yellow solid; mp: 140−142 ºC (EtOAc/hexane).

IR (KBr): ν = 1800, 1780, 1750, 1730 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 3.06 (s, 6H, 2 × CH_3), 7.64 (dd, 1H, *J* = 4.8, 1.1 Hz, ArH), 8.16 (d, 1H, *J* = 4.8 Hz, ArH), 9.00 (s, 1H, ArH).

MS (EI): *m/z* (%) = 191 (M^+), 149 (100).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.46; H, 4.78; N, 21.95.

2-(Dimethylamino)-1-hydroxy-1-phenyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (7a) and 2-(Dimethylamino)-3-hydroxy-3-phenyl-2,3-dihydropyrrolo[3,4-*c*]pyridin-1-one (8a); Typical Procedure

To a solution of **5** (0.20g, 1.05 mmol) in anhyd benzene (10 mL) was added $AlCl_3$ (0.70 g, 5.23 mmol) and the reaction mixture was refluxed for 1 h. After addition of H_2O (10 mL) to the mixture with ice cooling, the aqueous layer was basified with 10% NaOH (10 mL) and was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (1,4-dioxane/benzene, 1:3) to give **7a** (0.195 g, 77%) and **8a** (0.034 g, 14%).

7a (Major Isomer):

Pale yellow crystals; mp: 175−176 ºC (EtOAc/hexane).

IR (KBr): ν = 3400, 1700, 1620 cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 2.72 (s, 6H, 2 × CH_3), 7.24 (s, 1H, OH), 7.26 (dd, 1H, *J* = 1.6, 0.8 Hz, ArH), 7.06−7.08 (m, 5H, ArH), 8.75 (d, 1H, *J* = 5.1 Hz, ArH), 8.92 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$/MeOH-d_4, 30:1, v/v): δ = 45.0, 90.8, 118.7, 126.6, 126.8, 128.7 129.1, 137.3, 143.8, 152.5, 157.2, 165.0.

MS (EI): *m/z* (%) = 269 (M^+), 59 (100).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 67.03; H, 5.63; N, 15.60.

8a (Minor Isomer):

Pale yellow crystals; mp: 148−150 ºC (EtOAc/hexane).

IR (KBr): ν = 3400, 1710, 1620, 1610 cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 2.71 (s, 6H, 2 × CH_3), 7.26 (s, 1H, OH), 7.31−7.42 (m, 5H, ArH), 7.72 (dd, 1H, *J* = 5.1, 1.1 Hz, ArH), 8.47 (s, 1H, ArH), 8.80 (d, 1H, *J* = 5.1 Hz, ArH).

^{13}C NMR ($CDCl_3$/MeOH-d_4, 30:1, v/v): δ = 44.9, 90.1, 120.6, 126.3, 129.0, 129.6, 135.5, 137.7, 143.0, 145.7, 146.4, 161.0.

MS (EI): *m/z* (%) = 269 (M^+), 59 (100).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.81; H, 5.55; N, 15.52.

2-(Dimethylamino)-1-hydroxy-1-(4-methylphenyl)-1,2-dihydropyrrolo[3,4-*c*]pyridin-3-one (7b) and 2-(Dimethylamino)-3-hydroxy-3-(4-methylphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridin-1-one (8b)

Compounds **7a** and **7b** were obtained by reaction of **5** with toluene using the same procedure as above.

7b (Major Isomer):

Yield: 61%; pale yellow crystals; mp: 163−165 ºC (EtOAc/hexane).

IR (KBr): ν = 3400, 1710, 1620, 1520 cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 2.72 (s, 6H, 2 × CH_3), 7.15 (d, 2H, *J* = 10.8 Hz, ArH), 7.19 (s, 1H, OH), 7.20−7.28 (m, 3H, ArH), 8.74 (d, 1H, *J* = 4.9 Hz, ArH), 8.90 (d, 1H, *J* = 0.8 Hz, ArH).

^{13}C NMR ($CDCl_3$/MeOH-d_4, 30:1, v/v): δ = 21.1, 45.2, 90.4, 117.8, 126.0, 126.1, 129.3, 134.5, 138.8, 144.4, 152.7, 155.5, 164.8.

MS (EI): *m/z* (%) = 283 (M^+), 59 (100).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.81; H, 6.08; N, 15.05.

8b (Minor Isomer):

Yield: 17%; pale yellow crystals; mp: 93−95 ºC (EtOAc/hexane).

IR (KBr): ν = 3400, 1720, 1620, 1600 cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 2.71 (s, 6H, 2 × CH_3), 7.15 (d, 2H, *J* = 8.1 Hz, ArH), 7.18 (s, 1H, OH), 7.26 (d, 2H, *J* = 8.1 Hz, ArH), 7.70 (dd, 1H, *J* = 5.0, 1.1 Hz, ArH), 8.45 (d, 1H, *J* = 1.1 Hz, ArH), 8.78 (d, 1H, *J* = 5.0 Hz, ArH).

^{13}C NMR ($CDCl_3$/MeOH-d_4, 30:1, v/v): δ = 21.1, 44.9, 90.6, 117.6, 126.2, 129.3, 134.3, 138.9, 139.9, 142.8, 143.5, 149.0, 164.2.

MS (EI): *m/z* (%) = 283 (M^+), 59 (100).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.70; H, 6.01; N, 14.74.

6-(Dimethylamino)-5-hydroxy-5-phenyl-5,6-dihydropyrrolo[3,4-*b*]pyridin-7-one (9a); Typical Procedure

To a solution of **6** (0.05 g, 0.26 mmol) in anhyd benzene (10 mL) was added $AlCl_3$ (0.18 g, 1.31 mmol) and the reaction mixture was refluxed for 0.5 h. After addition of H_2O (10 mL) to the mixture with ice cooling, the aqueous layer was basified with 10% Na_2CO_3 (10 mL) and was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (EtOAc) to give **9a** (0.69 g, 98%) as a pale yellow solid, mp: 142−143 ºC (EtOAc/hexane).

IR (KBr): ν = 3300, 1700, 1660, 1600, 1500 cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 2.73 (s, 6H, 2 × CH_3), 7.13 (s, 1H, OH), 7.30−7.41 (m, 5H, ArH), 7.54 (d, 1H, *J* = 8.1, 4.8 Hz,

ArH), 7.64 (dd, 1H, *J* = 8.1, 1.5 Hz, ArH), 8.75 (dd, 1H, *J* = 4.8, 1.5 Hz, ArH).

Mixture of 9a and 10a:
^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.62, 2.91 (s, 6H, 2 × CH_3), 7.33–7.46 (m, 2H, ArH), 7.46–7.59 (m, 2H, ArH), 7.67–7.79 (m, 2H, ArH), 8.48 (br s, 1H, NH), 8.65 (dd, 0.8H, *J* = 4.8, 1.8 Hz, ArH), 8.79 (dd, 0.2H, *J* = 5.4, 2.7 Hz, ArH).

^{13}C NMR (DMSO-d_6): δ = 40.0, 88.4, 126.3, 126.9, 127.9, 128.0, 131.2, 138.7, 142.5, 148.3, 151.1, 163.8.

Mixture of 9a and 10a:
^{13}C NMR ($CDCl_3$): δ = 45.3, 47.4, 89.3, 125.9, 126.2, 126.6, 128.4, 128.6, 128.8, 129.1, 131.3, 133.0, 136.4, 137.0, 137.2, 138.2, 141.3, 147.3, 148.6, 151.9, 160.5, 164.7, 194.9.

MS (EI): *m/z* (%) = 269 (M^+), 59 (100).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.90; H, 5.60; N, 15.61.

6-(Dimethylamino)-5-hydroxy-5-(4-methylphenyl)-5,6-dihydropyrrolo[3,4-*b*]pyridin-7-one (9b)
In the same manner as described above, **9b** was obtained by reaction of **6** with toluene in 97% yield as a white solid; mp: 120–124 °C (EtOAc/hexane).

IR (KBr): ν = 3320, 1710, 1690, 1600 cm^{-1}.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 2.73 (s, 6H, 2 × CH_3), 7.06 (s, 1H, OH), 7.14 (d, 2H, *J* = 8.4 Hz, ArH), 7.25 (d, 2H, *J* = 8.4 Hz, ArH), 7.43 (dd, 1H, *J* = 8.1, 4.9 Hz, ArH), 7.61 (dd, 1H, *J* = 8.1, 1.9 Hz, ArH), 8.74 (dd, 1H, *J* = 4.9, 1.9 Hz, ArH).

^{13}C NMR (DMSO-d_6): δ = 20.6, 44.3, 88.3, 126.3, 126.8, 128.5, 131.1, 135.7, 137.2, 142.6, 148.3, 151.2, 163.8.

Mixture of 9b and 10b:
^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.35, 2.38 (s, 3H, CH_3), 2.62, 2.92 (s, 6H, 2 × CH_3), 7.19 (d, 2H, *J* = 8.1 Hz, ArH), 7.55 (d, 1H, *J* = 7.7, 4.5 Hz, ArH), 7.61 (d, 2H, *J* = 8.1 Hz, ArH), 7.74 (dd, 1H, *J* = 7.7, 1.8 Hz, ArH), 8.49 (br s, 1H, NH), 8.63 (dd, 0.7H, *J* = 4.5, 1.5 Hz, ArH), 8.64 (dd, 0.2H, *J* = 5.0, 2.0 Hz, ArH).

Mixture of 9b and 10b:
^{13}C NMR ($CDCl_3$): δ = 21.1, 21.7, 47.4, 89.4, 125.9, 126.2, 126.5, 129.1, 129.4, 131.2, 134.8, 136.6, 137.1, 138.6, 141.5, 143.8, 147.2, 148.5, 151.7, 160.5, 164.7, 194.7.

MS (EI): *m/z* (%) = 283 (M^+), 224 (100).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.69; H, 6.05; N, 14.83. Found: C, 67.69; H, 6.05; N, 14.68.

4-Phenyl-2*H*-phthalazin-1-one (13a); Typical Procedure
A mixture of **4a** (0.16 g, 0.58 mmol) and H_2NNH_2•H_2O (0.5 mL, 10.3 mmol) was stirred for 2 h at 100 °C. After the excess hydrazine was removed under reduced pressure, the crude product was chromatographed on a silica gel column (EtOAc/hexane, 1:3) to give **13a** (0.12 g, 95%) as a white solid; mp: 246–247 °C (EtOH) (Lit.[2] mp: 232–234 °C).

4-(4-Methylphenyl)-2*H*-phthalazin-1-one (13b)
In the same manner as described above, **4b** gave **13b** (88%) as a white solid; mp: 261–263 °C (benzene) (Lit.[2] mp: 259–260 °C).

1-Phenyl-3*H*-pyrido[3,4-*d*]pyridazin-4-one (14a); Typical Procedure
A mixture of **7a** (0.10 g, 0.37 mmol) and H_2NNH_2•H_2O (1.8 mL, 36.3 mmol) was stirred for 0.5 h at 100 °C and then H_2O (20 mL) was added to the mixture with ice cooling. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (EtOAc) to give **14a** (0.07 g, 86%) as a pale yellow solid; mp: 253–254 °C (EtOAc).

IR (KBr): ν = 3150, 1675, 1600 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.52–7.60 (m, 6H, ArH), 9.00 (d, 1H, *J* = 5.5 Hz, ArH), 9.79 (s, 1H, ArH), 10.57 (br s, 1H, NH).

MS (EI): *m/z* (%) = 223 (M^+, 100), 139 (18).

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.80; H, 4.16; N, 18.81.

1-(4-Methylphenyl)-3*H*-pyrido[3,4-*d*]pyridazin-4-one (14b)
In the same manner as described above, **7b** gave **14b** (98%) as a white solid; mp: 235–236 °C (EtOAc).

IR (KBr): ν = 3150, 1680, 1600 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.47 (s, 3H, CH_3), 7.38 (d, 2H, *J* = 8.1 Hz, ArH), 7.48 (d, 2H, *J* = 8.1 Hz, ArH), 7.62 (d, 1H, *J* = 5.5 Hz, ArH), 9.00 (d, 1H, *J* = 5.5 Hz, ArH), 9.78 (s, 1H, ArH), 10.82 (br s, 1H, NH).

MS (EI): *m/z* (%) = 237 (M^+, 100), 222 (49).

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.80; H, 4.76; N, 17.68.

5-Phenyl-7*H*-pyrido[2,3-*d*]pyridazin-8-one (15a); Typical Procedure
A mixture of **9a** (0.20 g, 0.74 mmol) and H_2NNH_2•H_2O (3.5 mL, 72.8 mmol) was stirred for 2 h at 100 °C and then H_2O (20 mL) was added to the mixture with ice cooling. The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a silica gel column (EtOAc) to give **15a** (0.15 g, 91%) as a pale yellow solid; mp: 249–250 °C (EtOAc) (Lit.[6] mp: 240–242 °C).

5-(4-Methylphenyl)-7*H*-pyrido[2,3-*d*]pyridazin-8-one (15b)
In the same manner as described above, **9b** gave **15b** (98%) as a white solid; mp: 253–256 °C (EtOAc) (Lit.[6] mp: 243–244 °C).

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