PRACTICAL SYNTHESIS OF 1*H*-INDAZOLE-3-CARBOXYLIC ACID AND ITS DERIVATIVES

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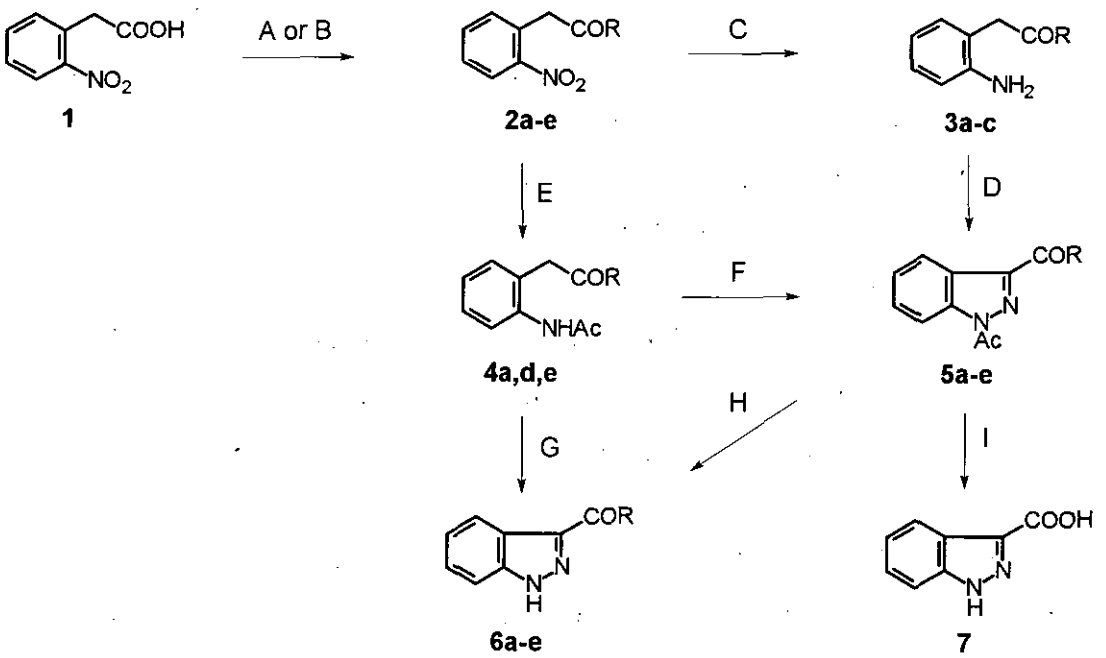
Abstract -- A practical and convenient synthesis of 1*H*-indazole-3-carboxylic acid and its amide and ester derivatives from the corresponding derivatives of 2-nitrophenylacetic acid was described.

Indazoles are attracted much attention as indole bioisosteres; indazole-3-carboxylic acid derivatives were reported to show various activities such as antifertility, antiarthritic, and serotonin 5-HT3 receptor antagonistic activities.[1] We also reported serotonin 5-HT3 receptor antagonistic activity of indazole-3-carboxamides and -carboxylates.[2] Although many indazole-3-carboxylic acid derivatives were prepared from 1*H*-indazole-3-carboxylic acid (**7**) as a starting material, the reported methods[3] for the synthesis of the acid (**7**) have limitations from a point of view on yields, reaction conditions, and starting materials. Moreover, there have been few reports on the synthesis of the indazole-3-carboxylic acid derivatives from starting materials other than the acid (**7**). Only the patent method[4] for the synthesis of isopropyl 1*H*-indazole-3-carboxylates *via* reduction of isopropyl 2-nitrophenylacetates with iron to the corresponding amino esters, followed by acetylation and cyclization with isoamyl nitrite seems to be applicable to the large-scale synthesis of 1*H*-indazole-3-carboxylic acid esters. However this method suffers from the by-production of oxindole in the reduction step and the inapplicability to the primary alkyl analogues because their amino esters produce oxindole with greater facility than the isopropyl analogue.

In order to obtain a practical route to the acid (**7**), therefore, we examined the improved synthesis of 1*H*-indazole-3-carboxamides and -carboxylates (**5a-e** and **6a-e**), which are the precursors of **7**, from the corresponding derivatives (**2a-e**) of 2-nitrophenylacetic acid (**1**). The synthetic routes *via* the Steps A~I are illustrated in Scheme and the results are summarized in Table.



a : R = N O ; **b** : R = N ; **c** : R = NHPr^n ; **d** : R = OMe ; **e** : R = OEt

Reaction conditions: A-1) i) $SOCl_2$, DMF, DCE, 35 - 40 ℃, ii) amine, 20 - 25 ℃; A-2) i) CDI, AcOEt, room temperature, ii) amine, 15 - 20 ℃; B) MeOH or EtOH, conc. H_2SO_4, reflux; C) Fe, IPA, aqueous 5% NH_4Cl, reflux; D) i) Ac_2O, toluene, room temperature → 90℃, ii) *t*-BuONO, 90 - 95 ℃; E) H_2 / 5% Pd-C, Ac_2O, toluene or AcOH, room temperature; F) *t*-BuONO, Ac_2O, toluene or AcOH, 90 - 95 ℃; G-1) *t*-BuONO, toluene or AcOH, 90 - 95℃; G-2) aqueous 34% $NaNO_2$, Ac_2O, AcOH, 90 - 95 ℃; H) i) NaOH (2 equivs), H_2O, 60℃, ii) aqueous 20% HCl; I) i) NaOH (3 - 7 equivs), H_2O, reflux, ii) aqueous 20% HCl.

Scheme . Synthetic Routes to Compounds (**2 - 7**) *via* Steps A ~ I

Table. Yields of Compounds (**2** - **7**) *via* Steps A ~ I

Compd	Step	Yield[a] (%)	Compd	Step	Yield[a] (%)	Compd	Step	Yield[a] (%)
2a	A-1	89	**4a**	E	(95)	**6a**	H	92
2a	A-2	(84)	**4d**	E	(97)	**6b**	H	91
2b	A-1	87	**4e**	E	(97)	**6c**	H	85
2b	A-2	(95)	**5a**	D	85	**6d**	G-1	71
2c	A-2	(89)	**5a**	F	76	**6d**	G-2	70
2d	B	95	**5b**	D	78	**6e**	G-1	75
2e	B	(94)	**5c**	D	63	**6e**	G-2	70
3a	C	(92)	**5d**	F	87	**7**	I	(96-98)[c]
3b	C	(93)	**5d**	B,E,F	87 [b]			
3c	C	(93)	**5e**	F	83			

[a] Yields were isolated yields of purified products (unpurified products in brackets) based on the corresponding precursors unless otherwise noted. The unpurified compounds were proved to be sufficient grade for further reactions by tlc and/or hplc analyses. [b] From **1**.

[c] From **5a, d, e**.

The 2-nitrophenylacetamides (**2a-c**) were prepared by treatment of **1** with $SOCl_2$ (Step A-1) or *N,N'*-carbonyldiimidazole (CDI) (Step A-2), followed by amidation. Reduction of **2a-c** was accomplished by dropping an aqueous 5% NH_4Cl solution into a refluxing mixture of **2a-c** and Fe in isopropyl alcohol (IPA) to afford 2-aminophenylacetamides (**3a-c**) in excellent yields together with negligible yield (below 1%) of oxindole (Step C). Acetylation of **3a-c**, followed by cyclization with *tert*-butyl nitrite gave 1-acetyl-1*H*-indazole-3-carboxamides (**5a-c**) (Step D). Although this route is quite useful for the preparation of the amides and bulky alkyl esters which afford the corresponding stable amino compounds, it is inapplicable to the primary alkyl esters for the reason described above. The 2-nitrophenylacetates (**2d, e**) were prepared in the usual way (Step B). Catalytic hydrogenation of **2d, e** with 5% Pd-C in the presence of Ac_2O gave 2-acetylaminophenylacetates (**4d,e**) in excellent yields with no detectable amount of oxindole (Step E). Cyclization of the esters (**4d,e**) with

tert-butyl nitrite proceeded smoothly in the presence of Ac_2O in AcOH or toluene to afford 1-acetyl-1*H*-indazole-3-carboxylates (**5d, e**) (Step F). Under the same conditions as in Steps E and F, the nitro amide (**2a**) gave the amide (**5a**) in good yield *via* the acetylaminophenylacetamide (**4a**). Thus, this route has the advantage of applicability to a wide variety of 1*H*-indazole-3-carboxamides and -carboxylates. Furthermore, it can be operated without isolation of the intermediates and indeed the ester (**5d**) was obtained in 87% overall yield from **1** *via* Steps B, E, and F.

In the absence of Ac_2O, on the other hand, a similar treatment of **4d, e** with *tert*-butyl nitrite resulted in cyclization accompanied with deacetylation to afford 1*H*-indazole-3-carboxylates (**6d, e**) (Step G-1). The esters (**6d, e**) were also obtained by treatment of **4d, e** with aqueous 34% $NaNO_2$ in the presence of Ac_2O in AcOH (Step G-2). Under the same conditions as in Steps G-1 and G-2, however, the amide (**4a**) failed to give the corresponding deacetylated amide (**6a**); it gave a dirty reaction mixture from which no crystalline product could be isolated. The amides (**6a-c**) were obtained by deacetylation of the amides (**5a-c**) with NaOH (2 equivs) in water under mild conditions (Step H).

Finally, hydrolysis of the amide (**5a**) and esters (**5d, e**) with NaOH (3-7 equivs) in water under refluxing for 1.5-3 h afforded the acid (**7**) in nearly quantitative yields (Step I), whereas the amides (**5b, c**) resisted the hydrolysis, and a large excess of NaOH (10-20 equivs) and prolonged reaction time (15-24 h) were requisite for completion of the hydrolysis.

The present method can be easily scaled up and provides practical and high-yield route to a wide variety of 1*H*-indazole-3-carboxamide and -carboxylate derivatives from 2-nitrophenylacetic acid (**1**), not *via* the acid (**7**). The acid (**7**) is accessible from these amide and ester derivatives by hydrolysis.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded on a Shimadzu FTIR-8100M spectrophotometer. ^{1}H-Nmr spectra were recorded on a Varian Gemini-200 spectrometer using TMS as an internal standard in $CDCl_3$.

Typical Procedure for Step A-1. 4-(2-Nitrophenylacetyl)morpholine (2a): To a suspension of **1** (45.3 g, 0.25 mol) and DMF (0.5 ml) in 1,2-dichloroethane (DCE) (250 ml) was added dropwise

$SOCl_2$ (35.7 g, 0.30 mol) at 35-40 ℃ over a period of 15 min and the mixture was stirred for 2 h at the same temperature. After being cooled to 20℃, a solution of morpholine (65.3 g, 0.75 mol) in DCE (50 ml) was added dropwise at 20-25 ℃ over a period of 30 min and the mixture was stirred for 2 h at 20 ℃. The precipitates were filtered off and washed with DCE (50 ml). The filtrate was washed successively with aqueous 10% HCl (200 ml) and water (300 ml), dried (Na_2SO_4), treated with charcoal, and concentrated *in vacuo*. The residual solid was recrystallized from IPA to give **2a** (55.8 g, 89%) as pale yellow needles, mp 135-137 ℃; ir (KBr): ν 1650, 1525, 1350, 1240, 730 cm^{-1}; ^1H nmr: δ 3.55-3.82 (m, 8H, morpholine ring), 4.04 (s, 2H, ArC*H*$_2$), 7.35 (dd, 1H, J = 1.5, 7.5 Hz, Ar), 7.46 (ddd, 1H, J = 1.5, 7.5, 8.0 Hz, Ar), 7.59 (td, 1H, J = 1.5, 7.5 Hz, Ar), 8.11 (dd, 1H, J = 1.5, 8.0 Hz, Ar). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.51; H, 5.68; N, 11.23.

In the same manner, **1-(2-Nitrophenylacetyl)piperidine (2b)** was obtained in 87% yield as pale yellow crystals by recrystallization from toluene-hexane and identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step A-2 .

Typical Procedure for Step A-2. 1-(2-Nitrophenylacetyl)piperidine (2b): To a suspension of **1** (45.3 g, 0.25 mol) in AcOEt (250 ml) was added portionwise CDI (44.6 g, 0.275 mol) at room temperature over a period of 5 min and the mixture was stirred for 2 h at room temperature. After being cooled to 15 ℃, a solution of piperidine (25.5 g, 0.30 mol) in AcOEt (20 ml) was added dropwise at 15-20 ℃ over a period of 20 min and the mixture was stirred for 1 h at 20 ℃. The reaction mixture was washed with aqueous 10% HCl (250 ml), dried (Na_2SO_4), and concentrated to dryness *in vacuo*. The residue was washed with hexane to give **2b** (59.1 g, 95%) as a pale yellow solid, which was used in the next step without further purification. An analytical sample was obtained by recrystallization from diisopropyl ether (IPE) as pale yellow prisms, mp 76-77 ℃; ir (KBr): ν 1635, 1520, 1350, 730 cm^{-1}; ^1H nmr: δ 1.50-1.78 (m, 6H) and 3.40-3.62 (m, 4H, piperidine ring), 4.06 (s, 2H, ArC*H*$_2$), 7.33 (dd, 1H, J = 1.5, 7.5 Hz, Ar), 7.43 (ddd, 1H, J = 1.5, 7.5, 8.0 Hz, Ar), 7.57 (td, 1H, J = 1.5, 7.5 Hz, Ar), 8.09 (dd, 1H, J = 1.5, 8.0 Hz, Ar). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C,62.89; H, 6.50; N, 11.28. Found: C, 62.97; H, 6.62; N, 11.35.

In the same manner, other amides (**2a, c**) were prepared in sufficient purity for further reactions without purification.

4-(2-Nitrophenylacetyl)morpholine (2a) was obtained in 84% yield by collecting the precipitates from the reaction mixture and washing with AcOEt and identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step A-1.

***N*-n-Propyl-2-nitrophenylacetamide (2c):** 89% yield, off-white powder, mp 104-105 ℃ (IPE); ir (KBr): ν 3300, 1640, 1520, 1360 cm^{-1}; ^1H nmr: δ 0.90 (t, 3H, J = 7.5 Hz, Me), 1.51 (sext, 2H, J = 7.5 Hz, CH_2Me), 3.22 (dt, 2H, J = 6.0, 7.5 Hz, $NHCH_2$), 3.82 (s, 2H, $ArCH_2$),5.82 (bs, 1H, NH), 7.40-7.66 (m, 3H, Ar), 8.30 (dd, 1H, J = 1.2, 8.0 Hz, Ar). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.48; H, 6.21; N, 12.57.

Typical Procedure for Step B. Methyl 2-Nitrophenylacetate (2d): A mixture of **1** (272.0 g, 1.5 mol) in MeOH (1.0 l) containing conc. H_2SO_4 (30 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (1.0 l) and the resulting solution was washed with aqueous 5% NaOH (1.0 l), dried (Na_2SO_4), and evaporated *in vacuo*. The residual oil was purified by distillation to give **2d** (277.9 g, 95%) as a pale yellow oil, bp 135-138 ℃/6 mbar (lit.,[5] bp 264 ℃). In a similar manner, **Ethyl 2-Nitrophenylacetate (2e)** was obtained in 94% yield as a pale yellow solid, which was used in the next step without purification, mp 62-63℃ (IPE) (lit.,[6] mp 65.5 ℃).

Typical Procedure for Step C. 4-(2-Aminophenylacetyl)morpholine (3a): To a suspension of **2a** (50.0 g, 0.20 mol) and reduced iron (40.2 g, 0.72 mol) in IPA (300 ml) was added dropwise a solution of NH_4Cl (11.2 g, 0.21 mol) in water (200 ml) under gentle refluxing over a period of 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residual oil was dissolved in $CHCl_3$ (350 ml) and the solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was crystallized from hexane to afford **3a** (40.6 g, 92%) as a pale yellow solid, which was pure enough for use in the next step without further purification. An analytical sample was obtained by recrystallization from IPE as colorless needles, mp 93-95 ℃; ir (KBr): ν 3450, 3350, 1630, 1460, 1210 cm^{-1}; ^1H nmr: δ 3.58 (s, 4H) and 3.63 (s, 4H, morpholine ring), 3.66 (s, 2H, $ArCH_2$), 4.0-5.1 (br, 2H, NH_2), 6.66-6.77 (m, 2H, Ar), 6.95-7.13(m, 2H, Ar). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.38; H, 7.43; N, 12.75.

In the same manner, other aminophenylacetamides (**3b, c**) were prepared in sufficient purity for further reactions without purification.

1-(2-Aminophenylacetyl)piperidine (3b): 93% yield, colorless plates, mp 72-74 ℃ (IPE); ir (KBr): ν 3400, 1610, 1470, 1260 cm^{-1}; ^1H nmr: δ 1.39-1.68 (m, 6H) and 3.49-3.59 (m, 4H, piperidine ring), 3.66 (s, 2H, ArC*H*$_2$), 4.30-5.20 (br, 2H, NH_2), 6.65-6.75 (m, 2H, Ar), 6.98-7.11 (m, 2H, Ar). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.62; H, 8.43; N, 12.88.

***N*-n-Propyl-(2-aminophenyl)acetamide (3c):** 93% yield, colorless plates, mp 67-68 ℃ (IPE); ir (KBr): ν 3250, 1640, 1625, 1560, 1495, 755 cm^{-1}; ^1H nmr: δ 0.85 (t, 3H, J = 7.5 Hz, Me), 1.46 (sext, 2H, J = 7.5 Hz, C*H*$_2$Me), 3.15 (dt, 2H, J = 7, 7.5 Hz, NHC*H*$_2$), 3.45 (s, 2H, ArC*H*$_2$), 4.12 (bs, 2H, NH_2), 5.65 (bs, 1H, CONH), 6.68-6.79 (m, 2H, Ar), 6.99-7.16 (m, 2H, Ar). *Anal.* Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.69; H, 8.33; N, 14.55.

Typical Procedure for Step D. 4-(1-Acetyl-1*H*-indazole-3-carbonyl)morpholine (5a): To a solution of **3a** (20.0 g, 0.09 mol) in toluene (100 ml) was added Ac_2O (30.7 g, 0.3 mol) at room temperature and then the mixture was heated to *ca.* 90℃. To this mixture was added dropwise *tert*-butyl nitrite (90%) (20.6 g, 0.18 mol) over a period of 20 min at 90-95 ℃ and the resulting mixture was stirred for 1.5 h at *ca.* 95 ℃. After evaporation of the volatiles, the residue was dissolved in $CHCl_3$ (200 ml) and the solution was washed with aqueous 5% K_2CO_3 (150 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residual solid was recrystallized from IPA to give **5a** (20.9 g, 85%) as light brown needles. An analytical sample was obtained by recrystallization from EtOH as pale yellow needles, mp 113-115 ℃; ir (KBr): ν 1740, 1630, 1510, 1380 cm^{-1}; ^1H nmr: δ 2.77 (s, 3H, Ac), 3.71-4.04 (m, 8H, morpholine ring), 7.43 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 7.61 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 8.25 (dt, 1H, J = 1.0, 8.0 Hz, Ar), 8.43 (dt, 1H, J = 1.0,8.0 Hz, Ar). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.44; H, 5.40; N, 15.39.

In the same manner, other 1-acetylindazole-3-carboxamides (**5b,c**) were prepared.

1-(1-Acetyl-1*H*-indazole-3-carbonyl)piperidine (5b): 78% yield, pale yellow needles, mp 110-111 ℃ (IPE); ir (KBr): ν 1740, 1620, 1505, 1380, 750 cm^{-1}; ^1H nmr: δ 1.60-1.80 (m, 6H, piperidine ring), 2.77 (s, 3H, Ac), 3.68-3.89 (m, 4H, piperidine ring), 7.41 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 7.59 (ddd, 1H, J = 1.0, 7.0, 8.5 Hz, Ar), 7.96 (dt, 1H, J = 1.0, 8.0 Hz, Ar), 8.44 (dt, 1H, J = 1.0, 8.5 Hz, Ar). *Anal.* Calcd for $C_{15}H_{17}N_3O_3$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.60; H, 6.46; N, 15.41.

***N*-n-Propyl-1-acetyl-1*H*-indazole-3-carboxamide (5c):** 63% yield, colorless plates, mp 113-115℃ (IPA); ir (KBr): ν 3300, 1730, 1650, 1560, 1360, 1330, 1200, 760 cm^{-1}; ^1H nmr: δ 1.02 (t, 3H, J = 7.5 Hz, CH_2*Me*), 1.72 (sext, 2H, J =7.5 Hz, *C*H_2Me), 2.81 (s, 3H, Ac), 3.50 (dt, 2H, J = 7.0, 7.5 Hz, NHC*H*$_2$), 7.08 (bs, 1H, NH), 7.44 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 7.59 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 8.39-8.46 (m, 2H, Ar). *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.50; H, 6.10; N, 17.10.

Typical Procedure for Step E. Methyl 2-Acetylaminophenylacetate (4d): Hydrogenation of **2d** (48.8 g, 0.25 mol) in the presence of 5% Pd-C (50% wet, 5.0 g) and Ac_2O (102.1 g, 1.0 mol) in toluene (300 ml) was carried out under vigorous stirring at room temperature and atmospheric pressure until *ca.* 18 l of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was washed with hexane to give **4d** (50.6 g, 97%) as off-white powder with sufficient purity for further reactions. An analytical sample was obtained by recrystallization from IPE as colorless needles, mp 93-95 ℃ (lit.,[7] mp 90 ℃).

In a similar manner, other amide and ester (**4a, e**) were prepared in sufficient purity for further reactions without purification.

4-(2-Acetylaminophenyl)morpholine (4a): 95% yield, colorless prisms, mp 144-146℃ (AcOEt); ir (KBr): ν 3275, 1670, 1630, 1510, 1230, 1110, 760 cm^{-1}; ^1H nmr: δ 2.22 (s, 3H, Ac), 3.57-3.74 (m, 8H, morpholine ring), 3.71 (s, 2H, *C*H_2), 7.00-7.14 (m, 2H, Ar), 7.24-7.34 (m, 1H, Ar), 8.06 (d, 1H, J = 8.0 Hz, Ar). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.03; H, 6.88; N, 10.66.

Ethyl 2-Acetylaminophenylacetate (4e): 97% yield, colorless plates, mp 64-66 ℃ (IPE) (lit.,[7] mp 66 ℃).

Typical Procedure for Step F in AcOH. Methyl 1-Acetyl-1*H*-indazole-3-carboxylate (5d): To a solution of **4d** (41.4 g, 0.2 mol) and Ac_2O (40.9 g, 0.4 mol) in AcOH (100 ml) was added dropwise *tert*-butyl nitrite (90%) (25.2 g, 0.22 mol) over a period of 20 min at 90-95 ℃. After being stirred for 0.5 h at *ca.* 95 ℃, the resulting mixture was poured into water (1.0 l) and stirred for 1 h at room temperature. The precipitates were collected by filtration and dissolved in $CHCl_3$ (200 ml). The solution was washed with aqueous 5% K_2CO_3 (150 ml), dried (Na_2SO_4), and evaporated

in vacuo. The residual solid was recrystallized from EtOH to give **5d** (37.9 g, 87%) as colorless needles, mp 111-112 ℃; ir (KBr): ν 1730, 1715, 1500, 1320, 1250, 1190, 770 cm^{-1}; ^1H nmr: δ 2.88 (s, 3H, Ac), 4.08 (s, 3H, OMe), 7.47 (ddd, 1H, J = 1.0, 7.5, 8.5 Hz, Ar), 7.61 (ddd, 1H, J = 1.2, 7.5, 8.0 Hz, Ar), 8.23 (ddd, 1H, J = 1.0, 1.2, 8.0 Hz, Ar), 8.47 (dt, 1H, J = 1.0, 8.5 Hz, Ar). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.44; H, 4.65; N, 12.75.

In Toluene. Ethyl 1-Acetyl-1*H*-indazole-3-carboxylate (5e): A solution of **4e** (22.2 g, 0.1 mol) and Ac_2O (30.7 g, 0.3 mol) in toluene (100 ml) was treated with *tert*-butyl nitrite (90%) (12.6 g, 0.11 mol) in the same manner as above. After evaporation of the volatiles, the residue was dissolved in $CHCl_3$ (200 ml) and the solution was washed with aqueous 5% K_2CO_3 (150 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residual solid was recrystallized from IPA to give **5e** (19.3 g, 83%) as off-white needles. An analytical sample was obtained by further recrystallization from IPA as colorless needles, mp 87-88 ℃ (lit.,[1b] mp 93 ℃).

In the same manner, **4-(1-Acetyl-1*H*-indazole-3-carbonyl)morpholine (5a)** was obtained in 76% yield as colorless prisms by recrystallization from IPA and identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step D.

Methyl 1-Acetyl-1*H*-indazole-3-carboxylate (5d) *via* Steps B, E, and F: A mixture of **1** (181.2 g, 1.0 mol) in MeOH (700 ml) containing conc. H_2SO_4 (15 ml) was refluxed for 4 h. After removal of the solvent, the residue was dissolved in toluene (1.0 l) and the solution was washed successively with aqueous 5% NaOH (500 ml) and brine, and dried (Na_2SO_4). To the organic solution were added Ac_2O (510 g, 5.0 mol) and 5% Pd-C (50% wet, 27.0 g), and the mixture was hydrogenated in the same manner as described in Step E. The catalyst was removed by filtration. To this filtrate was added dropwise *tert*-butyl nitrite (90%) (124.0 g, 1.08 mol) over a period of 20 min at 90-95 ℃ and the resulting mixture was stirred for 1 h at *ca.* 95 ℃. After evaporation of the volatiles, the residue was recrystallized from EtOH to give **5d** (189.9 g, 87%), which was identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step F, as pale yellow needles.

Typical Procedure for Step G-1 in AcOH. Ethyl 1*H*-Indazole-3-carboxylate (6e): To a solution of **4e** (17.7 g, 0.08 mol) in AcOH (40 ml) was added dropwise *tert*-butyl nitrite (90%) (10.1 g, 0.088 mol) over a period of 20 min at 90-95 ℃ and the mixture was stirred for 0.5 h at *ca.* 95 ℃. The

mixture was poured into cold water (500 ml) and stirred for 1 h. The precipitates were collected by filtration and dissolved in $CHCl_3$ (150 ml). The solution was washed with aqueous 5% K_2CO_3 (100 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residual solid was recrystallized from aqueous EtOH to give **6e** (11.4 g, 75%) as light yellow needles. An analytical sample was obtained as colorless needles by further recrystallization from EtOH, mp 135-136 ℃ (lit.,[3a] mp 136-137 ℃).

In Toluene. Methyl 1*H*-Indazole-3-carboxylate (6d): To a solution of **4d** (20.8 g, 0.10 mol) in toluene (100 ml) was added dropwise *tert*-butyl nitrite (90%) (12.6 g, 0.11 mol) over a period of 20 min at 90-95 ℃ and the resulting mixture was stirred for 1.5 h at *ca.* 95 ℃. After evaporation of the volatiles, the residue was dissolved in $CHCl_3$ (200 ml). The solution was washed with aqueous 5% K_2CO_3 (150 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residual solid was washed with hexane and recrystallized from aqueous EtOH to give **6d** (12.5 g, 71%) as pale yellow leaflets, mp 168-170 ℃ (lit.,[3a] mp 168-169 ℃).

Typical Procedure for Step G-2. Methyl 1*H*-Indazole-3-carboxylate (6d): To a solution of **4d** (8.3 g, 0.04 mol) and Ac_2O (13.0 g, 0.12 mol) in AcOH (40 ml) was added dropwise a solution of sodium nitrite (3.4 g, 0.05 mol) in water (10 ml) over a period of 15 min at 90-95 ℃ and the mixture was stirred for 1.5 h at *ca.* 95 ℃. The reaction mixture was poured into water (500 ml) and stirred for 1 h. The precipitates were collected by filtration and dissolved in $CHCl_3$ (200 ml). The solution was washed with aqueous 5% K_2CO_3 (150 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residual crystals were washed with hexane and recrystallized from aqueous EtOH to give **6d** (4.9 g, 70%), which was identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step G-1, as colorless leaflets.

In the same manner, **Ethyl 1*H*-Indazole-3-carboxylate (6e)** was obtained in 70% yield and identified by comparison of its ir spectrum with that of an authentic sample prepared *via* Step G-1.

Typical Procedure for Step H. 4-(1*H*-Indazole-3-carbonyl)morpholine (6a): After a suspension of **5a** (13.7 g, 0.05 mol) and NaOH (4.0 g, 0.1 mol) in water (300 ml) had been stirred for 30 min at 60 ℃, aqueous 20% HCl (20 ml) was added and the mixture was stirred for 1 h at room temperature. The precipitates were collected by filtration, washed with water, and recrystallized from EtOH to give **6a** (10.6 g, 92%) as colorless needles, mp 178-179 ℃; ir (KBr): ν 3150, 1600, 1570, 1490,

1110, 750 cm^{-1}; ^1H nmr: δ 3.65-4.25 (m, 8H, morpholine ring), 7.28 (ddd, 1H, J= 1.5, 7.0, 8.5 Hz, Ar), 7.43 (ddd, 1H, J= 1.0, 7.0, 8.0 Hz, Ar), 7.51 (ddd, 1H, J= 1.0, 1.5, 8.5 Hz, Ar), 8.15 (dt, 1H, J= 1.0, 8.0 Hz, Ar). *Anal.* Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.15; H, 5.60; N, 18.03.

In the same manner, other 1*H*-indazole-3-carboxamides (**6b, c**) were prepared.

1-(1*H*-Indazole-3-carbonyl)piperidine (6b): 91% yield, colorless prisms, mp 206-208 ℃ (EtOH) (lit.,[3b] mp 201.5-203.5 ℃).

***N*-n-Propyl-1*H*-indazole-3-carboxamide (6c):** 85% yield, colorless needles, mp 135-136 ℃ (AcOEt-hexane); ir (KBr): ν 3150, 1620, 1550, 1470, 755 cm^{-1}; ^1H nmr: δ 1.01 (t, 3H, J = 7.5 Hz, Me), 1.68 (sext, 2H, J = 7.5 Hz, CH_2Me), 3.49 (dt, 2H, J = 6.5, 7.5 Hz, $NHCH_2$), 7.12 (b, 1H, NH), 7.28 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 7.42 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz, Ar), 7.51 (dt, 1H, J = 1.0, 7.0 Hz, Ar), 8.43 (dd, 1H, J = 1.0, 8.0 Hz, Ar). *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.06; H, 6.37; N, 20.64.

Typical Procedure for Step I. 1*H*-Indazole-3-carboxylic Acid (7): A suspension of **5d** (441.0 g, 2.02 mol) and NaOH (243.0 g, 6.07 mol) in water (2.2 l) was stirred for 1.5 h under refluxing. After being cooled to room temperature, water (1.0 l) was added and the mixture was acidified with aqueous 20% HCl (1.2 l) and stirred for 1 h at room temperature. The precipitates were collected by filtration and washed with water to give **7** (320.0 g, 97%) as off-white powder, the purity of which was 99.9% with hplc analysis. An analytical sample was obtained by recrystallization from EtOH as colorless needles and sublimed at *ca.* 270 ℃ (lit.,[3d] mp 267-268 ℃).

In the same manner, the ester (**5e**) afforded the acid (**7**) in 98% yield. The amide (**5a**) (356.0 g, 1.3 mol) was refluxed with NaOH (360.0 g, 9.0 mol) in water (2.8 l) for 3 h and worked up in the same manner as above to afford the acid (**7**) (203.0 g, 96%).

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Received, 12th August, 1996