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A method for the regioselective synthesis of 1-alkyl-1*H*-indazoles

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ABSTRACT

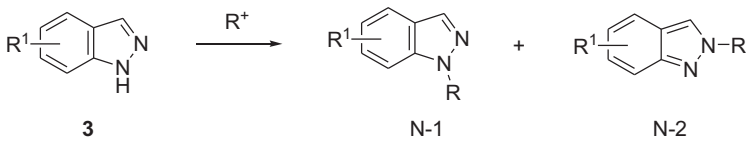
A method for the regioselective synthesis of 3-unsubstituted 1-alkyl-1*H*-indazoles, starting with 2-halobenzonitriles and *N*-alkylhydrazines, is described. The two-step reaction pathway proceeds through the intermediacy of 1-alkyl-3-amino-1*H*-indazoles followed by reductive deamination.

1. Introduction

The indazole ring system is recognized to be a highly effective pharmacophore in medicinal chemistry as well as being the core of important nitrogen-containing heterocycles that show a broad range of biological activities, such as nitric oxide synthase[1] and HIV protease[2] inhibitors, anti-inflammatory,[3] antitumor,[4] and anti-cancer[5] agents, and serotonin 5-HT3 receptor antagonists.[6] A variety of methods for the preparation of indazoles have been reported.[7] The developed approaches include diazotization of 2-alkylaniline derivatives followed by cyclization under basic conditions,[8] base promoted cyclization of (*o*-alkylaryl)azosulfides derived from 2-alkylaniline derivatives,[9] [3+2] cycloadditions of arynes with diazo compounds or hydrazones,[10] condensation reactions of *o*-haloaryl carbonyls or salicylaldehydes with hydrazine,[11] and cyclization reactions of *o*-aminobenzoximes in the presence of bases.[12] Although methods for regioselective synthesis of indazoles have been described,[12–20] only a few of these are applicable to the regioselective synthesis of 1-alkyl-1*H*-indazoles.[13,14,15b,16,20] Thus, methods for the regioselective synthesis of 1-alkyl-1*H*-indazoles remain in demand.

2. Results and discussion

As a part of a recent research effort, we required 3-unsubstituted 1-alkyl-1*H*-indazoles as synthetic intermediates. The most straightforward route to access these substances involves treatment of 3-unsubstituted 1*H*-indazoles with alkylating agents. However, the regiochemistry of these processes is highly dependent on the nature of alkylating agent and, in general, mixtures of *N*-1 and *N*-2 alkylated products are typically produced (Eq. 1). For example, methylation of 5-nitro-1*H*-indazole using iodomethane (NaH, THF, 0 °C, 2 h) results in formation of a mixture of 5-nitro-1-methyl-1*H*- and 5-nitro-2-methyl-2*H*-indazoles in a 55:45 ratio. Moreover, varying the solvent, temperature and base employed in this reaction failed to improve the selectivity.



3 N-1 N-2 **Eq (1)**

A common method for the preparation of 3-substituted 1-alkyl-1*H*-indazoles involves cyclization of an arylhydrazone, derived

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from reaction of an arylketone possessing a leaving group in the *ortho*-position with an alkylhydrazine.[14,16] We envisioned that 3-unsubstituted 1-alkyl-1*H*-indazoles could be generated utilizing an analogous process in which an arylketone is replaced by an arylaldehyde. However, treatment of methylhydrazine and a mesylate, derived from reaction of 5-bromo-2-hydroxy-benzaldehyde with mesyl chloride, in refluxing xylene in the presence of NH_4OAc for 3 h gave only the corresponding hydrazone product, and an increase in the time for this reaction to 14 h resulted in the formation of multiple products.

Owing to these observations, our attention turned to the use of other substrates. 3-Aminoindazoles, obtained by using a variety of methods,[21–23] are known to have valuable biological activities in several therapeutic areas.[24] Wheeler et al. described a procedure for the regioselective synthesis of 3-amino-1-methyl-1*H*-indazoles utilizing reactions of 2-fluorobenzonitriles with methylhydrazine.[20] We hypothesized that this process, when coupled with the novel reductive deamination reaction of arylamines that produces aromatic hydrocarbons described by Doyle and Picciionello et al.,[24,25] would serve as a regioselective two-step method for the preparation of 3-unsubstituted 1-alkyl-1*H*-indazoles. The viability of this proposal was demonstrated in the studies described below.

As the results displayed in Scheme 1 and Table 1 show, reactions of members of a series of 2-halobenzonitriles, containing either electron-donating or -withdrawing groups, with methylhydrazine in ethanol efficiently produce the corresponding 3-amino-1-methyl-1*H*-indazoles **2**. Reductive deamination reactions of the 3-amino-1-methyl-1*H*-indazole products **2** with *tert*-butyl nitrite in either $CHCl_3$, DMF or THF generated 3-unsubstituted-1-methyl-1*H*-indazoles **3** in high yields. It should be noted that the deamination reaction of 3-amino-1-methyl-5-nitro-1*H*-indazole (**2e**) in THF or $CHCl_3$ gave a product that was expected to be 1-methyl-5-nitro-1*H*-indazole (**3e**). In order to confirm its structure, this substance was subjected to catalytic hydrogenation, which yielded 1-methyl-5-amino-1*H*-indazole.

4. Experimental section

4.1. General

All commercially available chemicals were used without further purification. TLC analyses were run on a TLC glass plate (Silica gel 60 F_{254}) and were visualized using UV and a solution of phosphomolybdic acid in ethanol (5 wt %) or *p*-anisaldehyde stain. Flash chromatography was performed using silica gel (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line) 77.0]. Mass spectra were recorded under fast atom bombardment (FAB) or electron impact ionization (EI) conditions. High-resolution mass spectra were recorded by electron impact ionization with a magnetic sector analyzer.

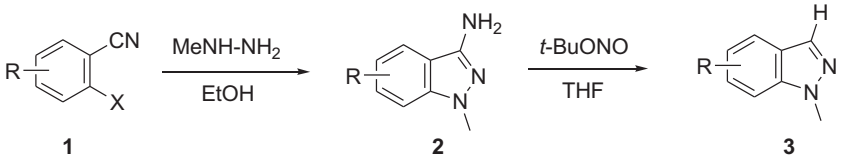
4.2. Synthesis

*4.2.1. General procedure for synthesis of 3-amino-1-methyl-1H-indazole **2**.* A mixture of benzonitrile **1** (10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) was heated to reflux overnight. The mixture was cooled to rt and then concentrated. H_2O (10.0 mL) and EtOAc (20.0 mL) were added to the residue. The organic layer was washed with H_2O (10.0 mL), brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica-gel chromatography by using EtOAc/hexanes (1:1) as eluent to give the product **2**.

*4.2.1.1. 1-Methyl-1H-indazol-3-ylamine (**2a**).* As described in the general procedure, reaction of 2-fluorobenzonitrile **1a** (1.21 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.35 g, 92%). Solid (EtOAc/hexanes=3:1), mp 94–95 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.13 (br s, 2H), 6.96 (dd, *J*=8.6, 7.2 Hz, 1H), 7.15 (d, *J*=8.6 Hz, 1H), 7.30 (dd, *J*=8.0, 7.2 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6 (CH_3), 108.5 (CH), 114.3 (C), 118.2 (CH), 119.4 (CH), 126.7 (CH), 141.3 (C), 146.9 (C); MS *m*/*z* (rel intensity) 148 (M^++H, 100), 133 (5). These data are in agreement with those reported in the literature.[26]

*4.2.1.2. 4-Fluoro-1-methyl-1H-indazol-3-amine (**2b**).* As described in the general procedure, reaction of 2,6-difluorobenzonitrile **1b** (1.39 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.42 g, 86%). Solid (EtOAc/hexanes=1:1), mp 125–126 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 3438, 3308, 3206, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.12 (br s, 2H), 6.54 (dd, *J*=9.0, 6.0 Hz, 1H), 6.88 (d, *J*=6.0 Hz, 1H), 7.18 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 35.0 (CH_3), 102.7 (CH), 104.6 (CH), 128.2 (CH), 144.0 (C), 145.5 (C), 155.1 (C), 158.4 (C); MS *m*/*z* (rel intensity) 165 (M^+, 100), 122 (28); HRMS $[M]^+$ for $C_8H_8N_3$: 165.0702, found 165.0708.

*4.2.1.3. 5-Fluoro-1-methyl-1H-indazol-3-amine (**2c**).* As described in the general procedure, reaction of 2,5-difluorobenzonitrile



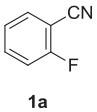
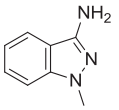
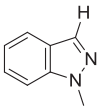
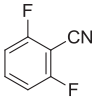
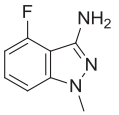
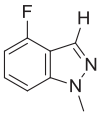
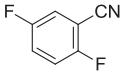
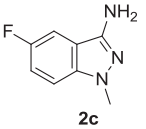
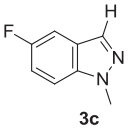
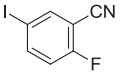
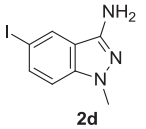
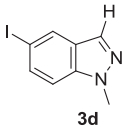
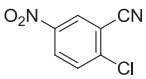
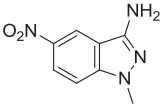
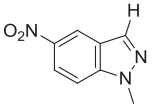
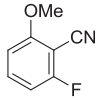
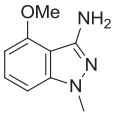
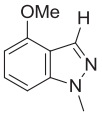
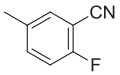
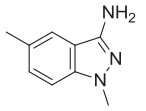
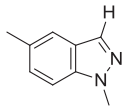
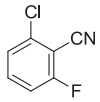
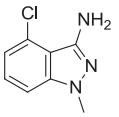
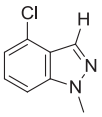
Scheme 1. Regioselective synthesis of 1-methyl-1*H*-indazoles via 1-methyl-3-amino-1*H*-indazoles.

In order to determine if this methodology is suitable for the preparation of other 1-alkyl-1*H*-indazoles, reactions of ethyl hydrazine and benzyl hydrazine with the respective benzonitriles **1b** and **1e** were examined. As the results displayed in Scheme 2 show, application of the two-step procedure gave the corresponding 1-ethyl- (**3j**) and 1-benzyl- (**3i**) 1*H*-indazoles in high yields. Other hydrazines, such as phenylhydrazine (Ph–NH–NH_2) and isopropylhydrazine (Me_2CH–NH–NH_2) were examined and both reactions gave a mixture of multiple products. Based on the results, a plausible mechanism is proposed and shown in Scheme 3.

3. Conclusion

In summary, the study described above has resulted in the development of an alternative, two-step method for the regioselective synthesis of 3-unsubstituted 1-alkyl-1*H*-indazoles starting with *N*-alkylhydrazines and 2-halobenzonitriles.

Table 1
Regioselective synthesis of 1-methyl-3-amino-1*H*-indazoles and 1-methyl-1*H*-indazoles

Entry	SM **1**	Indazole **2**	Yield (%)[a]	Indazole **3**	Yield (%)[a]
1	 **1a**	 **2a**	92	 **3a**	91
2	 **1b**	 **2b**	86	 **3b**	91
3	 **1c**	 **2c**	80	 **3c**	84
4	 **1d**	 **2d**	92	 **3d**	85
5	 **1e**	 **2e**	94	 **3e**	83
6	 **1f**	 **2f**	91	 **3f**	88
7	 **1g**	 **2g**	90	 **3g**	82
8	 **1h**	 **2h**	94	 **3h**	85

[a] Isolated yield.

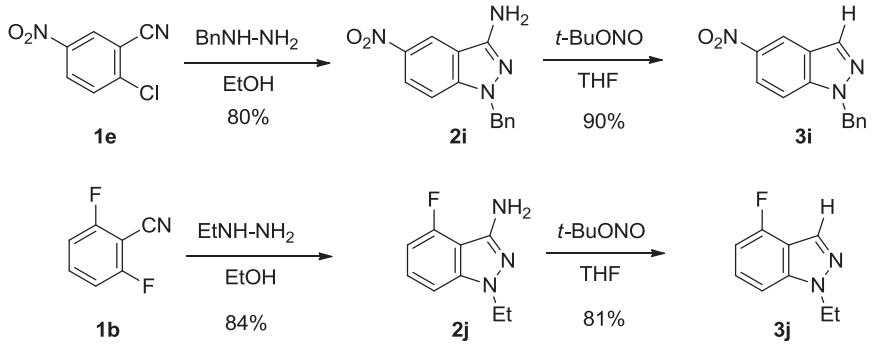
1c (1.39 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.32 g, 80%). Solid (EtOAc), mp 76–77 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.13; IR (neat) 3363, 3187, 1532, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.85 (br s, 2H), 7.06–7.13 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 34.9 (CH_3), 103.5 (CH), 109.5 (CH), 113.7 (C), 116.1 (CH), 138.5 (C), 146.6 (C), 154.8 (C), 158.0 (C); MS *m*/*z* (rel intensity) 165 (M^+, 100), 147 (16); HRMS $[M]^+$ for $C_8H_8FN_3$: 165.0702, found 165.0696.

*4.2.1.4. 5-Iodo-1-methyl-1H-indazol-3-amine (**2d**).* As described in the general procedure, reaction of 2-fluoro-5-iodobenzonitrile **1d** (2.47 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (2.52 g, 92%). Solid (EtOAc), mp 151–152 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 3418, 3280, 3178, 1648 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.74 (s, 3H), 5.58 (s, 2H), 7.21 (d, *J*=8.7 Hz, 1H), 7.49 (dd, *J*=8.7, 1.5 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 35.5 (CH_3), 80.4 (C), 112.0 (CH), 117.7 (C), 130.1 (CH), 134.8 (CH), 140.8 (C), 148.4 (C); MS *m*/*z* (rel intensity) 273 (M^+, 100), 258 (3); HRMS $[M]^+$ for $C_8H_8IN_3$: 272.9763, found 272.9760.

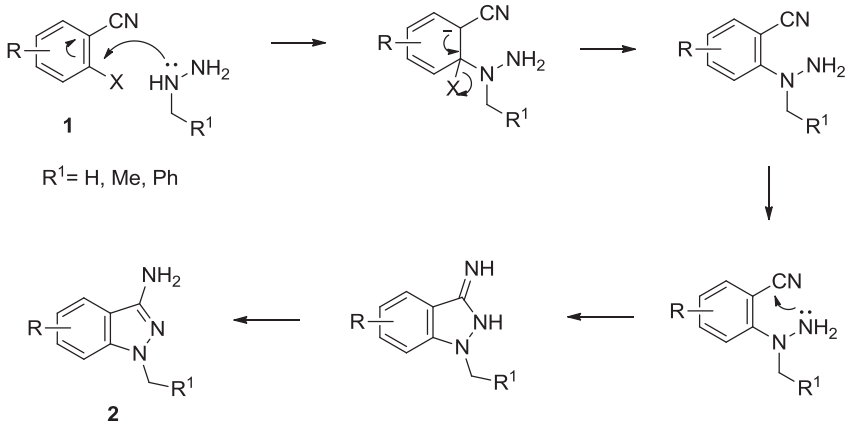
*4.2.1.5. 1-Methyl-5-nitro-1H-indazol-3-ylamine (**2e**).* As described in the general procedure, reaction of 2-fluoro-5-nitrobenzonitrile **1e** (1.66 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.81 g, 94%). Solid (EtOH), mp 226–227 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 3336, 3194, 1616, 1329 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.14 (br s, 2H), 7.47 (d, *J*=9.4 Hz, 1H), 8.11 (dd, *J*=9.4, 2.1 Hz, 1H), 8.90 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.9 (CH_3), 110.0 (CH), 114.5 (C), 120.7 (CH), 122.3 (CH), 139.6 (C), 143.0 (C), 152.4 (C); MS *m*/*z* (rel intensity) 193 (M^++1, 100), 163 (60). These data are in agreement with those reported in the literature.[21i]

*4.2.1.6. 4-Methoxy-1-methyl-1H-indazol-3-ylamine (**2f**).* As described in the general procedure, reaction of 2-fluoro-6-methoxybenzonitrile **1f** (1.51 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.61 g, 91%). Solid (EtOAc), mp 139–140 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 3428, 3298, 3178, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.90 (s, 3H), 4.38 (br s, 2H), 6.25 (d, *J*=7.5 Hz, 1H), 6.71 (d, *J*=8.4 Hz, 1H), 7.17 (dd, *J*=8.4, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.8 (CH_3), 55.2 (CH_3), 97.3 (CH), 101.5 (CH), 105.2 (C), 128.4 (CH), 143.4 (C), 147.4 (C), 155.1 (C); MS *m*/*z* (rel intensity) 177 (M^+, 100), 162 (20); HRMS $[M]^+$ for $C_9H_{11}N_3O$: 177.0902, found 177.0896.

*4.2.1.7. 1,5-Dimethyl-1H-indazol-3-ylamine (**2g**).* As described in the general procedure, reaction of 2-fluoro-5-methylbenzonitrile **1g** (1.35 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.45 g, 90%). Solid (EtOAc), mp 149–150 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR



Scheme 2. Regioselective synthesis of 1-alkyl-1*H*-indazoles via 1-alkyl-3-amino-1*H*-indazoles.



Scheme 3. Plausible mechanism.

(neat) 3448, 3289, 3180, 2364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.72 (s, 2H), 3.78 (s, 3H), 7.07 (d, J=8.4 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.08 (CH_3), 34.8 (CH_3), 108.3 (CH), 114.6 (C), 118.5 (CH), 172.7 (C), 128.9 (CH), 140.33 (C), 146.3 (C); MS m/z (rel intensity) 161 (M^+, 100), 160 (48); HRMS $[M]^+$ for $C_9H_{11}N_3$: 161.0953, found 161.0961.

*4.2.1.8. 4-Chloro-1-methyl-1H-indazol-3-amine (**2h**).* As described in the general procedure, reaction of 2-chloro-6-fluorobenzonitrile **1h** (1.55 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.70 g, 94%). Solid (EtOAc/hexanes=1:2), mp 131–132 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.2; IR (neat) 3438, 3299, 1616, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.49 (br s, 2H), 6.85 (d, J=8.4 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 7.13 (t, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.8 (CH_3), 107.3 (CH), 111.5 (C), 118.3 (CH), 126.6 (C), 127.4 (CH), 142.4 (C), 146.8 (C); MS m/z (rel intensity) 181 (M^+, 100), 138 (25); HRMS $[M]^+$ for $C_8H_8ClN_3$: 181.0407, found 181.0400.

*4.2.1.9. 1-Benzyl-5-nitro-1H-indazol-3-amine (**2i**).* As described in the general procedure, reaction of 2-chloro-5-nitrobenzonitrile **1e** (0.91 g, 5.0 mmol), Et_3N (5.06 g, 50.0 mmol) and benzyl hydrazine HCl (2.93 g, 15.0 mmol) in EtOH (20.0 mL) afforded the title compound (1.07 g, 80%). Solid (EtOAc), mp 253–254 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.18; IR (neat) 3428, 1597, 1468, 1329 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.44 (s, 2H), 6.19 (s, 2H), 6.66 (d, J=9.3 Hz, 1H), 7.24–7.37 (m, 5H), 8.14 (dd, J=9.3, 2.1 Hz, 1H), 8.94 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 52.3 (CH_2), 110.1 (CH), 114.9 (C), 120.7 (CH), 122.5 (CH), 128.3 (CH), 128.4 (CH×2), 129.4 (CH×2), 138.3 (C), 139.9 (C), 142.9 (C), 152.6 (C); MS m/z (rel intensity) 268 (M^+, 56), 91 (100); HRMS $[M]^+$ for $C_{14}H_{12}N_4O_2$: 268.0960, found 268.0968.

*4.2.1.10. 1-Ethyl-4-fluoro-1H-indazol-3-amine (**2j**).* As described in the general procedure, reaction of 2,6-difluorobenzonitrile **1b** (0.70 g, 5.0 mmol), Et_3N (5.06 g, 50.0 mmol) and ethyl hydrazine oxalate (2.25 g, 15.0 mmol) in EtOH (20.0 mL) afforded the title compound (0.75 g, 84%). Solid (EtOAc), mp 64–65 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.45; IR (neat) 3428, 3280, 3201, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J=7.2 Hz, 3H), 4.11 (q, J=7.2 Hz, 2H), 4.31 (br s, 2H), 6.52 (dd, J=10.5, 7.8 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 7.10–7.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (CH_3), 43.1 (CH_2), 102.3 (CH), 104.5 (CH), 127.7 (CH), 143.1 (C), 145.5 (C), 155.2 (C), 158.5 (C); MS m/z (rel intensity) 179 (M^+, 88), 164 (100); HRMS $[M]^+$ for $C_9H_{10}FN_3$: 179.0859, found 179.0852.

*4.2.2. General procedure for synthesis of indazole **3**.* A mixture of 3-amino-1-methyl-1*H*-indazole **2** (3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) was heated to reflux for 1 h. The mixture was cooled to rt and then concentrated. H_2O (10.0 mL) and EtOAc (20.0 mL) were added to the residue. The organic layer was washed with H_2O (10.0 mL), brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica-gel chromatography by using Et_2O/hexanes (1:4) as eluent to give the product **3**.

*4.2.2.1. 1-Methyl-1H-indazole (**3a**).* As described in the general procedure, reaction of 1-methyl-1*H*-indazol-3-amine **2a** (0.44 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.34 g, 86%). Solid (EtOAc/hexanes (1:3)), mp 49–50 °C; TLC (EtOAc/hexane (1:4)) R_f=0.2; IR (neat) 2947, 1597, 1218, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3H), 7.11–7.15 (m, 1H), 7.37 (br d, J=4.1 Hz, 2H), 7.71 (dd, J=8.0, 1.0 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (CH_3), 108.9 (CH), 120.3 (CH), 121.0 (CH), 123.9 (C), 126.1 (CH), 132.6 (CH), 139.7 (C). These data are in agreement with those reported in the literature.[20]

*4.2.2.2. 4-Fluoro-1-methyl-1H-indazole (**3b**).* As described in the general procedure, reaction of 4-fluoro-1-methyl-1*H*-indazol-3-amine **2b** (0.50 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.41 g, 91%). Solid (EtOAc), mp 36–37 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 2919, 1634, 1584, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 6.74 (dd, J=10.2, 7.8 Hz, 1H), 7.13 (d, J=8.4, 1.2 Hz, 1H), 7.26–7.30 (m, 1H), 8.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8 (CH_3), 104.8 (CH), 114.1 (C), 127.1 (CH), 129.1 (CH), 142.3 (C), 154.1 (C), 157.4 (C); MS m/z (rel intensity) 150 (M^+, 100), 122 (15); HRMS $[M]^+$ for $C_8H_7FN_2$: 150.0593, found 150.0602.

*4.2.2.3. 5-Fluoro-1-methyl-1H-indazole (**3c**).* As described in the general procedure, reaction of 5-fluoro-1-methyl-1*H*-indazol-3-amine **2c** (0.50 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.38 g, 84%). Oil; TLC (EtOAc/hexanes (1:2)) R_f=0.5; IR (neat) 2947, 1505, 1209, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 7.10–7.17 (m, 1H), 7.28–7.33 (m, 2H), 7.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7 (CH_3), 104.7 (CH), 109.9 (CH), 115.6 (CH), 123.7 (CH), 132.6 (C), 136.9 (C), 156.1 (C); MS m/z (rel intensity) 150 (M^+, 100), 122 (21); HRMS $[M]^+$ for $C_8H_7FN_2$: 150.0593, found 150.0599.

*4.2.2.4. 5-Iodo-1-methyl-1H-indazole (**3d**).* As described in the general procedure, reaction of 5-iodo-1-methyl-1*H*-indazol-3-amine **2d** (0.82 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.66 g, 85%). Solid (EtOAc), mp 172–173 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.4; IR

(neat) 2928, 1666, 1477, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 7.14 (dd, J=8.7 Hz, 1H), 7.56 (dd, J=8.7, 1.2 Hz, 1H), 7.86 (s, 1H), 8.04 (d, J=1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6 (CH_3), 83.7 (C), 110.7 (CH), 126.3 (C), 129.9 (CH), 131.6 (CH), 134.4 (CH), 138.8 (C); MS m/z (rel intensity) 258 (M^+, 100), 131 (26); HRMS $[M]^+$ for $C_8H_7IN_2$: 257.9654, found 257.9658.

*4.2.2.5. 1-Methyl-5-nitro-1H-indazole (**3e**).* As described in the general procedure, reaction of 1-methyl-5-nitro-1*H*-indazol-3-amine **2e** (0.58 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.44 g, 83%). Solid (MeOH), mp 161–162 °C; TLC (EtOAc/hexanes (1:4)) R_f=0.2; IR (neat) 3030, 1634, 1496, 1329 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (s, 3H), 7.42 (d, J=9.2 Hz, 1H), 8.16 (s, 1H), 8.24 (dd, J=9.2, 2.1 Hz, 1H), 8.68 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0 (CH_3), 109.2 (CH), 118.9 (CH), 121.4 (CH), 123.0 (C), 135.6 (CH), 141.5 (C), 142.3 (C). These data are in agreement with those reported in the literature.[27]

*4.2.2.6. 4-Methoxy-1-methyl-1H-indazole (**3f**).* As described in the general procedure, reaction of 4-methoxy-1-methyl-1*H*-indazol-3-amine **2f** (0.53 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.43 g, 88%). An oil; TLC (EtOAc/hexanes (1:4)) R_f=0.2; IR (neat) 2938, 1588, 1496, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.00 (s, 3H), 6.42 (d, J=7.5 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 7.26 (t, J=8.1 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (CH_3), 55.3 (CH_3), 99.2 (CH), 101.6 (CH), 115.8 (C), 127.4 (CH), 130.5 (CH), 141.6 (C), 153.7 (C); MS m/z (rel intensity) 162 (M^+, 100), 147 (30); HRMS $[M]^+$ for $C_9H_{10}N_2O$: 162.0793, found 162.0789.

*4.2.2.7. 1,5-Dimethyl-1H-indazole (**3g**).* As described in the general procedure, reaction of 1,5-dimethyl-1*H*-indazol-3-amine **2g** (0.48 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.36 g, 82%). Solid (EtOAc), mp 60–61 °C; TLC (EtOAc/hexanes (1:4)) R_f=0.2; IR (neat) 2920, 2374, 1565, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.03 (s, 3H), 7.18–7.28 (m, 2H), 7.47 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 35.5 (CH_3), 108.5 (CH), 120.0 (CH), 124.4 (C), 128.3 (CH), 129.8 (C), 132.0 (CH), 138.6 (C); MS m/z (rel intensity) 146 (M^+, 100), 131 (17); HRMS $[M]^+$ for $C_9H_{10}N_2$: 146.0844, found 146.0840.

*4.2.2.8. 4-Chloro-1-methyl-1H-indazole (**3h**).* As described in the general procedure, reaction of 4-chloro-1-methyl-1*H*-indazol-3-amine **2h** (0.54 g, 3.0 mmol) and *tert*-butyl nitrite (1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.42 g, 85%). oil; TLC (EtOAc/hexanes (1:2)) R_f=0.5; IR (neat) 3086, 2928, 1616, 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 7.06 (dd, J=8.1, 3.0 Hz, 1H), 7.22–7.23 (m, 2H), 8.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7 (CH_3), 107.4 (CH), 119.9 (C), 123.1 (C), 126.4 (C), 126.6 (CH), 131.2 (CH), 140.6 (C). These data are in agreement with those reported in the literature.[11c]

*4.2.2.9. 1-Benzyl-5-nitro-1H-indazole (**3i**).* As described in the general procedure, reaction of 1-benzyl-5-nitro-1*H*-indazol-3-amine **2h** (0.48 g, 3.0 mmol) and *tert*-butyl nitrite (0.84 g, 1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.68 g, 90%). White solid (EtOAc), mp 125–126 °C; TLC (EtOAc/hexanes (1:2)) R_f=0.45; IR (neat) 3122, 2956, 1514, 1329 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 2H), 7.18–7.39 (m, 6H), 8.16–8.22 (m, 2H), 8.70 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.6 (CH_2), 109.6 (CH), 118.9 (CH), 121.5 (CH), 123.5 (C), 127.2 (CH×2), 128.3 (CH), 128.9 (CH×2), 135.6 (C), 136.0 (CH), 141.2 (C), 142.4 (C); MS m/z (rel intensity) 253 (M^+, 61), 252 (25); HRMS $[M]^+$ for $C_{14}H_{11}N_3O_2$: 253.0851, found 253.0849.

*4.2.2.10. 1-Ethyl-4-fluoro-1H-indazole (**3j**).* As described in the general procedure, reaction of 1-ethyl-4-fluoro-1*H*-indazol-3-amine **2i** (0.54 g, 3.0 mmol) and *tert*-butyl nitrite (0.84 g, 1.0 mL, 8.1 mmol, 2.7 equiv) in THF (12.0 mL) afforded the title compound (0.40 g, 81%). Oil; TLC (EtOAc/hexanes (1:4)) R_f=0.55; IR (neat) 2984, 2928, 1588, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (t, J=7.2 Hz, 3H), 4.39 (q, J=7.2 Hz, 2H), 6.73 (dd, J=9.9, 7.5 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.22–7.29 (m, 1H), 8.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (CH_3), 44.0 (CH_2), 104.4 (CH), 104.7 (CH), 126.9 (CH), 129.1 (CH), 141.6 (C), 154.2 (C), 157.6 (C); MS m/z (rel intensity) 164 (M^+, 70), 149 (100); HRMS $[M]^+$ for $C_9H_9FN_2$: 164.0750, found 164.0755.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.03.042.

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