Facile two-step synthesis of 3-substituted indazoles using diazo(trimethylsilyl)methylmagnesium bromide†

Yoshiyuki Hari,*[a] Ryosuke Sone[b] and Toyohiko Aoyama*[b]

Received 17th April 2009, Accepted 17th April 2009
First published as an Advance Article on the web 22nd May 2009
DOI: 10.1039/b907796k

Diazo(trimethylsilyl)methylmagnesium bromide readily reacted with various ketones and aldehydes to give the corresponding 2-diazo-(2-trimethylsilyl)ethanols. These were efficiently converted to indazoles bearing hydroxymethyl units at the 3-position by intermolecular [3 + 2] cycloaddition with benzynes.

Introduction

Indazole, an aza analog of indole, is a very attractive pharmacophore for drug discovery and a number of its derivatives are known to possess potent pharmacological activity including anti-inflammatory, anti-tumor or anti-HIV activity.[1,2] However, efficient methods for the preparation of indazole derivatives are still lacking. For instance, the introduction of electrophiles at the 3-position of indazoles is very difficult and can only be achieved by quite limited approaches.[3,4] Thus, the development of more efficient and convenient methodologies is in great demand.

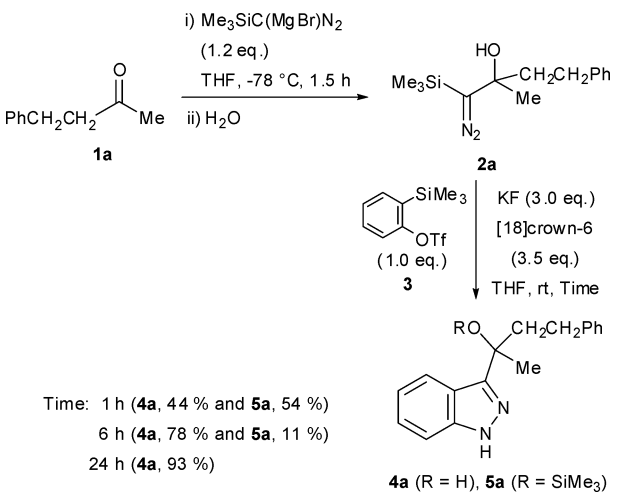
Intermolecular [3 + 2] cycloaddition between diazomethane derivatives and benzynes would be a powerful methodology towards facilitating the synthesis of indazoles bearing various substituents at the 3-position (eqn (1)).[5] However, the diazomethane derivatives used would mainly be limited to diazoketones, diazoacetates, or phenyl- and trimethylsilyl-diazomethanes due to problems with the safety of handling and with the inherent stability of diazomethanes.

(1)

We have engaged in the development of new synthetic methods using trimethylsilyldiazomethane (Me_3SiCHN_2)[6] and recently found that its magnesium bromide salt [$Me_3SiC(MgBr)N_2$][7] smoothly reacted with simple carbonyl compounds to efficiently and readily afford the corresponding 2-diazo-(2-trimethylsilyl)ethanols,[8] which were converted to multi-substituted pyrazoles by intermolecular [3 + 2] cycloaddition reactions with propiolates.[9] Thus, we applied this method using $Me_3SiC(MgBr)N_2$ to a greater variety of carbonyl compounds as electrophiles and investigated the [3 + 2] cycloaddition reaction of the resulting 2-diazo-(2-trimethylsilyl)ethanols with benzynes towards the convenient synthesis of various 3-substituted indazoles. In this paper, we wish to describe the details of our results on this new methodology in indazole synthesis.

Results and discussion

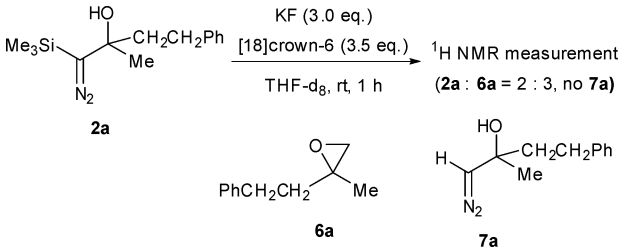
Initially, as shown in Scheme 1, the reaction of the 2-diazo-(2-trimethylsilyl)ethanol **2a**, prepared from 4-phenylbutan-2-one **1a** and $Me_3SiC(MgBr)N_2$, with (2-trimethylsilyl)phenyl triflate **3**[10] in the presence of KF and [18]crown-6 in THF was examined using three different reaction times (1 h, 6 h, and 24 h). When the reaction was carried out for 1 h, **3** disappeared by TLC and the desired indazole **4a** bearing a hydroxymethyl unit at the 3-position and its *O*-trimethylsilyl derivative **5a** were obtained in 44% and 54% yields from **1a**, respectively. Increasing the reaction time led to a significant increase in the yield of **4a** along with a reduction in that of **5a**, indicating that the trimethylsilyl group of **5a** was gradually removed by KF. The reaction for 24 h gave only **4a** in 93% yield. When, in the absence of **3**, **2a** was treated with KF in THF-d_8 for 1 h, ^{1}H NMR analysis of the reaction mixture showed that **2a** and epoxide **6a** existed as a 2:3 mixture and no desilylated diazoalcohol **7a** was detected (Scheme 2). This result suggests that the resulting **7a** immediately decomposed to **6a** due to its lability. Therefore, the [3 + 2] cycloaddition reaction giving indazoles would be expected to occur between **2a**, not **7a**, and benzyne generated from **3** (Scheme 3).



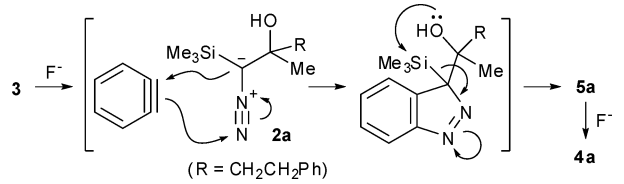
Scheme 1 Examination of the reaction time.

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: hari@phs.osaka-u.ac.jp; Fax: +81 6 6879 8201; Tel: +81 6 6879 8201*
[b]*Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho, Nagoya 467-8603, Japan. E-mail: aoyama@phar.nagoya-cu.ac.jp; Fax: +81 52 836 3439; Tel: +81 52 836 3439*

† Electronic supplementary information (ESI) available: Characterization data for 2-diazo-(2-trimethylsilyl)ethanols, and ^{1}H and ^{13}C spectra for all new compounds. See DOI: 10.1039/b907796k



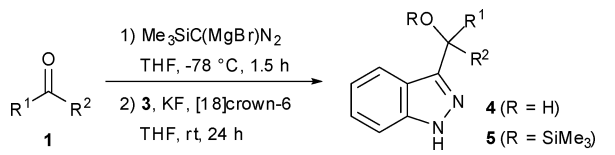
Scheme 2 ^{1}H NMR experiment.



Scheme 3 Plausible reaction mechanism.

Next, the synthesis of 3-substituted indazoles using other carbonyl compounds was surveyed and the results were summarized in Table 1. When 4-methoxybenzophenone **1b** was used, the corresponding 3-substituted indazole **4b** was obtained in 74% yield in two steps (entry 1). Other ketones **1c–f** bearing aromatics as well as heteroaromatics, like pyridine and thiophene, also afforded desired indazoles **4c–f** in good to high yields (66–82%)(entries 2–5). Moreover, the dimethyl acetal moiety in **1g** was tolerated under the reaction conditions to give **4g** in 74% yield (entry 6). Interestingly, this reaction system was applicable to even β-ketoester **1h** with an active methylene moiety and an ester group and the desired **4h** was obtained in 59% yield (entry 7).[11] Reaction of $Me_3SiC(MgBr)N_2$ with an α,β-unsaturated ketone exclusively proceeded through 1,2-addition to give the corresponding diazoalcohol which was converted to **4i** in 68% yield from **1i** (entry 8). In the case of bulky ketone **1j**, silylated indazole **5j** was isolated in 58% yield as a major product together with **4j** (18% yield). However, successive

Table 1 Synthesis of 3-substituted indazoles from carbonyl compounds[a]



Entry	Substrate	R^1	R^2	Yield[b] (%)
1	**1b**	4-MeOPh	Ph	**4b**, 74
2	**1c**	Ph	Me	**4c**, 77
3	**1d**	4-CF_3Ph	Me	**4d**, 69
4	**1e**	2-Pyridyl	Me	**4e**, 66
5	**1f**	2-Thienyl	Me	**4f**, 82
6	**1g**	$(MeO)_2CHCH_2$	Me	**4g**, 74
7	**1h**	$MeOCOCH_2$	Me	**4h**, 59
8	**1i**	(*E*)-PhCH=CH	Me	**4i**, 68
9	**1j**	*i*-Pr	Et	**4j**, 18; **5j**, 58 (**4j**, 79[c])
10	**1k**	*i*-Pr	H	**4k**, 43
11	**1l**	4-MeOPh	H	**4l**, 46

[a] In all reactions, $Me_3SiC(MgBr)N_2$ (1.1–1.2 eq.), **3** (1.0 eq.), KF (3.0 eq.) and [18]crown-6 (3.5 eq.) were used. See ESI† for details. [b] Isolated yield from **1**. [c] Treatment with 10% hydrochloric acid for 10 min before work-up of the reaction mixture was performed.

treatment with 10% HCl aq. after the reaction afforded **4j** in 79% yield with complete desilylation of **5j** (entry 9). Aromatic and aliphatic aldehydes **1k** and **1l** also gave the corresponding indazoles **4k** and **4l**, though the yields were somewhat low (43–46%) compared with those from ketones (entries 10 and 11).

Under the same reaction conditions, other benzyne precursors **8–10** also underwent the cycloaddition reaction with **2a** (Fig. 1). Thus, the use of naphthyl derivative **8** as a benzyne precursor gave the corresponding benzoindazole **11a** in 81% yield. Reaction with *m*-methoxybenzyne generated from **9** afforded a 1:1.2 separable mixture of **12a** and **12a′** in 67% yield.[12] Similarly, the benzyne precursor **10** furnished a mixture of **13a** and **13a′** in 74% yield (**13a**:**13a′** = 1:2).[12]

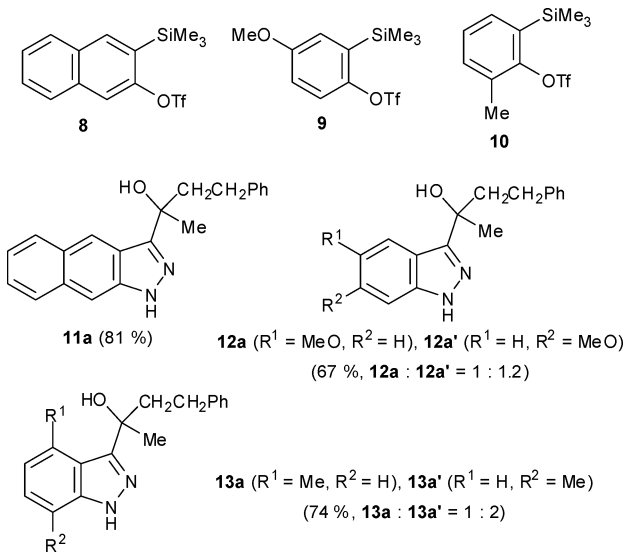
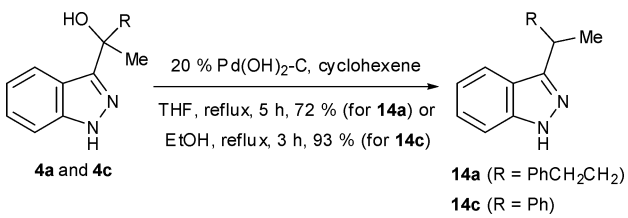


Fig. 1 Structures of benzyne precursors used and indazoles synthesized.

In addition, we also found that hydrogenolysis of the (3-hydroxymethyl)indazoles **4a** and **4c** using palladium hydroxide readily gave the corresponding 3-alkyl congeners **14a** and **14c** (Scheme 4).



Scheme 4 Hydrogenolysis of **4a** and **4c**.

Conclusions

We have achieved the facile and two-step synthesis of 3-substituted indazoles from carbonyl compounds. To our knowledge, this is the first example of indazole synthesis using 2-diazoethanols and the present method would be very valuable for the preparation of indazoles possessing 3-hydroxymethyl units.

Experimental

General

All melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer (^{1}H, 270 MHz; ^{13}C, 67.8 MHz). MS spectra (bp = base peak) were recorded on a JEOL JMS-SX-102A spectrometer. A solution of $MgBr_2$ in Et_2O–toluene (1:1) was prepared from $MgBr_2$ etherate (Aldrich) dried well under reduced pressure at 100 °C, anhydrous Et_2O and anhydrous toluene. Carbonyl compounds **1a–l** were distilled prior to use.

Representative procedure of 3-substituted indazoles

Under an argon atmosphere, *n*-BuLi (1.66 M in hexane solution, 0.72 mL, 1.2 mmol) was added to a solution of $TMSCHN_2$ (1.77 M in hexane solution, 0.68 mL, 1.2 mmol) in anhydrous THF (5 mL) at −78 °C and the mixture was stirred at −78 °C for 20 min. After the addition of $MgBr_2$ [1.00 M in toluene–Et_2O (1:1) solution, 1.20 mL, 1.2 mmol], the mixture was further stirred at −78 °C for 20 min. 4-Phenyl-2-butanone **1a** (150 μL, 1.0 mmol) was added to the above mixture at −78 °C and the mixture was further stirred at −78 °C for 1.5 h. After the addition of H_2O (1 mL) at −78 °C, the mixture was extracted with EtOAc (30 mL × 3). The organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give unpurified **2a**[8] (261 mg), which was dissolved in THF (5 mL) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **3** (243 μL, 1.0 mmol), KF (183 mg, 3.0 mmol) and [18]crown-6 (925 mg, 3.5 mmol) were added. After being stirred at room temperature for 24 h, the mixture was filtered through a short pad of Celite® and the filtrate was concentrated *in vacuo*. The residue was diluted with EtOAc, then the EtOAc solution was washed with 1M $KHCO_3$ (10 mL × 3), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give **4a** (249 mg, 93% from **1a**).

2-(1*H*-Indazol-3-yl)-4-phenylbutan-2-ol (4a). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ:1.78 (s, 3H), 2.31–2.45 (m, 3H), 2.63–2.76 (m, 1H), 4.15 (br s, 1H), 6.98 (d, 2H, J = 6.5 Hz), 7.05–7.16 (m, 4H), 7.27 (dd, 1H, J = 7.5, 8.0 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.84 (d, 1H, J = 8.0 Hz), 11.05 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 29.31, 30.47, 44.72, 73.41, 110.15, 119.29, 120.51, 121.26, 125.45, 126.65, 128.09, 128.14, 141.93, 142.02, 151.11. IR (neat) ν: 3256 cm^{-1}. MS (EI): m/z = 266 (M$^+$, 2.2), 161 (bp). HRMS (EI): calcd for $C_{17}H_{18}N_2O$ (M$^+$), 266.1419, found, 266.1420.

(1*H*-Indazol-3-yl)(4-methoxyphenyl)(phenyl)methanol (4b). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ:3.69 (s, 3H), 4.80 (br s, 1H), 6.73 (d, 2H, J = 9.0 Hz), 6.87 (dd, 1H, J = 6.5, 8.0 Hz), 6.96 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 8.5 Hz), 7.14–7.23 (m, 6H), 7.32–7.36 (m, 2H), 11.17 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 55.13, 78.89, 110.08, 113.08, 120.61, 120.94, 121.75, 126.29, 127.25, 127.58, 127.75, 128.99, 137.61, 141.33, 145.47, 150.74, 158.53. IR (neat) ν: 3259 cm^{-1}. MS (EI): m/z = 330 (M$^+$, 29.3), 312 (bp). HRMS (EI): calcd for $C_{21}H_{18}N_2O_2$ (M$^+$), 330.1368, found, 330.1365.

1-(1*H*-Indazol-3-yl)-1-phenylethanol (4c).[3]

1-[4-(trifluoromethyl)phenyl]-1-(1*H*-indazol-3-yl)ethanol (4d). White powder; m.p. 151–153 °C. ^{1}H-NMR (acetone-d_6) δ: 2.12 (s, 3H), 5.27 (br s, 1H), 6.95 (dd, 1H, J = 7.0, 8.0 Hz), 7.26 (dd, 1H, J = 7.0, 8.5 Hz), 7.49 (d, 1H, J = 8.5 Hz), 7.61–7.69 (m, 3H), 7.79 (d, 2H, J = 8.0 Hz), 12.10 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ: 31.22, 74.63, 110.50, 120.48, 121.25, 122.79, 125.24 (q, $^1J_{C\text{-}F}$ = 270 Hz), 125.34 (q, $^3J_{C\text{-}F}$ = 4 Hz), 126.60, 128.61 (q, $^2J_{C\text{-}F}$ = 32 Hz), 142.62, 151.32, 153.47 (q, $^4J_{C\text{-}F}$ = 1 Hz). IR (neat) ν: 3283 cm^{-1}. MS (EI): m/z = 306 (M$^+$, 20.3), 291 (bp). HRMS (EI): calcd for $C_{16}H_{13}F_3N_2O$ (M$^+$), 306.0980, found, 306.0979.

1-(Pyridin-2-yl)-1-(1*H*-indazol-3-yl)ethanol (4e). Colorless crystals; m.p. 150–151 °C. ^{1}H-NMR (acetone-d_6) δ: 2.05 (s, 3H), 6.07 (br s, 1H), 6.94 (dd, 1H, J = 7.5, 8.0 Hz), 7.21–7.26 (m, 2H), 7.45–7.54 (m, 2H), 7.64–7.75 (m, 2H), 8.55 (d, 1H, J = 4.5 Hz), 12.07 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ: 29.88, 74.85, 110.43, 120.32, 121.11, 121.40, 122.71, 122.81, 126.41, 137.61, 142.51, 147.80, 150.87, 165.05. IR (nujol) ν: 3250 cm^{-1}. MS (EI): m/z = 239 (M$^+$, 44.3), 224 (M$^+$ − CH_3, bp). HRMS (EI): calcd for $C_{14}H_{13}N_3O$ (M$^+$), 239.1059, found, 239.1054.

1-(1*H*-Indazol-3-yl)-1-(thiophen-2-yl)ethanol (4f). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (s, 3H), 4.99 (br s, 1H), 6.79–6.86 (m, 2H), 6.95 (dd, 1H, J = 7.0, 8.0 Hz), 7.13 (d, 1H, J = 5.0 Hz), 7.18–7.24 (m, 2H), 7.48 (d, 1H, J = 8.0 Hz), 11.58 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 30.93, 72.72, 110.22, 119.48, 120.47, 121.41, 124.05, 124.65, 126.33, 126.48, 141.51, 150.28, 151.21. IR (neat) ν: 3259 cm^{-1}. MS (EI): m/z = 244 (M$^+$, 33.7), 229 (M$^+$ − Me, 78.1), 145 (bp). HRMS (EI): calcd for $C_{13}H_{12}N_2OS$ (M$^+$), 244.0670, found, 244.0670.

2-(1*H*-Indazol-3-yl)-4,4-dimethoxybutan-2-ol (4g). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (s, 3H), 2.33 (dd, 1H, J = 7.5, 14.5 Hz), 2.54 (dd, 1H, J = 4.0, 14.5 Hz), 3.21 (s, 3H), 3.26 (s, 3H), 4.51 (dd, 1H, J = 4.0, 7.5 Hz), 4.74 (br s, 1H), 7.11 (dd, 1H, J = 7.0, 8.0 Hz), 7.32 (dd, 1H, J = 7.0, 8.5 Hz), 7.44 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.0 Hz), 11.27 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 30.00, 43.85, 52.47, 53.59, 72.03, 102.74, 109.94, 120.03, 120.20, 121.91, 126.31, 141.49, 150.88. IR (neat) ν: 3271 cm^{-1}. MS (EI): m/z = 250 (M$^+$, 7.8), 161 (bp). HRMS (EI): calcd for $C_{13}H_{18}N_2O_3$ (M$^+$), 250.1318, found, 250.1317.

Methyl 3-hydroxy-3-(1*H*-indazol-3-yl)butanoate (4h). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (s, 3H), 2.92, 3.43 (AB, 2H, J = 16.0 Hz), 3.63 (s, 3H), 4.86 (br s, 1H), 7.14 (dd, 1H, J = 7.0, 8.0 Hz), 7.34 (dd, 1H, J = 7.0, 8.5 Hz), 7.41 (d, 1H, J = 8.5 Hz), 8.09 (d, 1H, J = 8.0 Hz), 10.74 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 29.25, 44.69, 51.81, 71.66, 109.75, 120.17, 120.42, 122.14, 126.60, 141.47, 150.47, 173.54. IR (neat) ν: 3277, 1715 cm^{-1}. MS (EI): m/z = 234 (M$^+$, 18.5), 161 (bp). HRMS (EI): calcd for $C_{12}H_{14}N_2O_3$ (M$^+$), 234.1005, found, 234.0999.

(*E*)-2-(1*H*-Indazol-3-yl)-4-phenylbut-3-en-2-ol (4i). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (s, 3H), 4.20 (br s, 1H), 6.66 (d, 1H, J = 16.0 Hz), 6.69 (d, 1H, J = 16.0 Hz), 7.01 (dd, 1H, J = 7.5, 8.0 Hz, Ar), 7.12–7.30 (m, 7H), 7.83 (d, 1H, J = 8.0 Hz), 11.56 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 28.74, 73.11, 110.17, 119.65, 120.42, 121.57, 126.40, 126.50, 127.32, 127.93, 128.24, 134.50, 136.35, 141.60, 149.86. IR (neat) ν: 3254 cm^{-1}. MS (EI):

$m/z = 264$ (M^+, 1.2), 245 (bp). HRMS (EI): calcd for $C_{17}H_{16}N_2O$ (M^+), 264.1263, found, 264.1284.

3-(1*H*-Indazol-3-yl)-2-methylpentan-3-ol (4j). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (t, 3H, $J = 7.5$ Hz), 0.73 (d, 3H, $J = 7.0$ Hz), 1.08 (d, 3H, $J = 7.0$ Hz), 2.11 (dq, 2H, $J = 7.5$, 7.5 Hz), 2.29 (sep, 1H, $J = 7.0$ Hz), 3.51 (br s, 1H), 7.13 (dd, 1H, $J = 7.0$, 8.0 Hz), 7.37 (dd, 1H, $J = 7.0$, 8.5 Hz), 7.46 (d, 1H, $J = 8.5$ Hz), 7.81 (d, 1H, $J = 8.0$ Hz), 10.21 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 8.28, 16.59, 17.75, 31.16, 37.34, 78.42, 109.92, 119.74, 120.37, 121.57, 126.60, 141.99, 150.25. IR (neat) ν: 3258 cm^{-1}. MS (EI): $m/z = 218$ (M^+, 4.7), 175 (bp). HRMS (EI): calcd for $C_{13}H_{18}N_2O$ (M^+), 218.1419, found, 218.1418.

1-(1*H*-Indazol-3-yl)-2-methylpropan-1-ol (4k). White powder; m.p. 133–134 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.83 (d, 3H, $J = 7.0$ Hz), 1.12 (d, 3H, $J = 7.0$ Hz), 2.21–2.33 (m, 1H), 4.68 (dd, 1H, $J = 4.5$, 7.5 Hz), 5.40 (d, 1H, $J = 4.5$ Hz), 7.15 (dd, 1H, $J = 7.5$, 8.0 Hz), 7.41 (dd, 1H, $J = 7.5$, 8.0 Hz), 7.57 (d, 1H, $J = 8.0$ Hz), 7.98 (d, 1H, $J = 8.0$ Hz), 12.80 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 19.11, 19.20, 34.00, 73.78, 109.82, 119.23, 120.70, 121.41, 125.53, 140.88, 147.75. IR (nujol) ν: 3144 cm^{-1}. MS (EI): $m/z = 190$ (M^+, 10.9), 147 (bp). HRMS (EI): calcd for $C_{11}H_{14}N_2O$ (M^+), 190.1106, found, 190.1108.

(1*H*-Indazol-3-yl)(4-methoxyphenyl)methanol (4l). Colorless crystals; mp 140–143 °C. ^{1}H-NMR (acetone-d_6) δ: 3.71 (s, 3H), 5.08 (br s, 1H), 6.23 (s, 1H), 6.85 (d, 2H, $J = 8.5$ Hz), 7.00 (dd, 1H, $J = 7.0$, 8.0 Hz), 7.27 (dd, 1H, $J = 7.0$, 7.5 Hz), 7.44–7.49 (m, 3H), 7.74 (d, 1H, $J = 8.0$ Hz), 12.08 (br s, 1H). ^{13}C-NMR (acetone-d_6) δ: 55.33, 71.46, 110.60, 113.99, 120.46, 121.23, 122.13, 126.65, 128.15, 136.62, 142.48, 149.45, 159.40. IR (nujol) ν: 3192 cm^{-1}. MS (EI): $m/z = 254$ (M^+, 67.3), 236 (bp). HRMS (EI): calcd for $C_{15}H_{14}N_2O_2$ (M^+), 254.1055, found, 254.1055.

2-(1*H*-Indazol-3-yl)-4-phenyl-2-(trimethylsilyloxy)butane (5a). Yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (s, 9H), 1.91 (s, 3H), 2.27–2.41 (m, 2H), 2.54–2.67 (m, 2H), 7.06–7.21 (m, 6H), 7.28–7.37 (m, 2H, Ar), 8.05 (d, 1H, $J = 8.0$ Hz), 10.52 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 2.18, 27.78, 30.91, 46.50, 76.43, 109.58, 120.16, 121.10, 122.86, 125.41, 126.37, 128.09, 128.18, 141.50, 142.35, 151.14. IR (neat) ν: 3213 cm^{-1}. MS (EI): $m/z = 338$ (M^+, 1.1), 323 (M^+ – Me, 31.9), 233 (bp). HRMS (EI): calcd for $C_{20}H_{26}N_2OSi$ (M^+), 338.1815, found, 338.1813.

3-(1*H*-Indazol-3-yl)-2-methyl-3-(trimethylsilyloxy)pentane (5j). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.20 (s, 9H), 0.86–0.92 (m, 9H), 2.02–2.15 (m, 1H), 2.17–2.27 (m, 1H), 2.30–2.43 (m, 1H), 7.08 (dd, 1H, $J = 7.0$, 8.0 Hz), 7.29 (dd, 1H, $J = 7.0$, 8.5 Hz), 7.36 (d, 1H, $J = 8.5$ Hz), 8.06 (d, 1H, $J = 8.0$ Hz), 10.11 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 2.73, 9.00, 17.99, 18.34, 31.99, 39.31, 84.37, 109.52, 119.86, 122.91, 123.86, 125.93, 141.26, 149.30. IR (neat) ν: 3175 cm^{-1}. MS (EI): $m/z = 275$ (M^+ – Me, 39.5), 247 (bp). HRMS (EI): calcd for $C_{15}H_{23}N_2OSi$ (M^+ – Me), 275.1580, found, 275.1582.

2-(1*H*-benzo[*f*]indazol-3-yl)-4-phenylbutan-2-ol (11a). Orange syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (s, 3H), 2.43–2.54 (m, 3H), 2.66–2.78 (m, 1H), 4.21 (br s, 1H), 6.94–7.07 (m, 5H), 7.21–7.33 (m, 2H), 7.63–7.66 (m, 2H), 7.83 (d, 1H, $J = 8.0$ Hz), 8.42 (s, 1H), 11.31 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 28.93, 30.50, 44.57, 73.71, 104.96, 120.16, 120.88, 123.13, 125.40, 125.77, 127.21, 128.02, 128.05, 128.37, 129.01, 132.46, 140.56, 141.78, 151.16. IR (neat) ν: 3283 cm^{-1}. MS (EI): $m/z = 316$ (M^+, 31.8), 298 (bp). HRMS (EI): calcd for $C_{21}H_{20}N_2O$ (M^+), 316.1576, found, 316.1572.

2-(5-Methoxy-1*H*-indazol-3-yl)-4-phenylbutan-2-ol (12a). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (s, 3H), 2.31–2.50 (m, 3H), 2.67–2.78 (m, 1H), 3.83 (s, 3H), 7.02–7.12 (m, 4H), 7.16–7.23 (m, 3H), 7.31 (d, 1H, $J = 9.0$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 29.12, 30.56, 44.56, 55.85, 73.43, 101.16, 110.95, 118.82, 119.79, 125.51, 128.14, 128.18, 137.86, 142.15, 150.56, 154.22. IR (neat) ν: 3263 cm^{-1}. MS (EI): $m/z = 296$ (M^+, 7.0), 236 (bp). HRMS (EI): calcd for $C_{18}H_{20}N_2O_2$ (M^+), 296.1525, found, 296.1519.

2-(6-Methoxy-1*H*-indazol-3-yl)-4-phenylbutan-2-ol (12a′). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (s, 3H), 2.27–2.45 (m, 3H), 2.68–2.79 (m, 1H), 3.86 (s, 3H), 6.79–6.83 (m, 2H), 7.06–7.14 (m, 3H), 7.17–7.23 (m, 2H), 7.71 (d, 1H, $J = 9.5$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 29.43, 30.56, 44.85, 55.52, 73.19, 91.00, 112.74, 114.27, 122.17, 125.53, 128.17, 128.23, 142.20, 143.42, 159.61. IR (neat) ν: 3296 cm^{-1}. MS (EI): $m/z = 296$ (M^+, 4.9), 192 (bp). HRMS (EI): calcd for $C_{18}H_{20}N_2O_2$ (M^+), 296.1525, found, 296.1522.

2-(4-Methyl-1*H*-indazol-3-yl)-4-phenylbutan-2-ol (13a). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (s, 3H), 2.33–2.50 (m, 2H), 2.61–2.67 (m, 2H), 2.83 (s, 3H), 3.22 (br s, 1H), 6.96 (d, 1H, $J = 4.0$ Hz), 7.09–7.13 (m, 3H), 7.18–7.25 (m, 4H), 9.98 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 23.33, 29.40, 30.68, 44.73, 73.08, 107.43, 119.82, 123.03, 125.51, 126.72, 128.18, 128.20, 132.03, 142.27, 142.91, 151.32. IR (neat) ν: 3271 cm^{-1}. MS (EI): $m/z = 280$ (M^+, 7.4), 175 (bp). HRMS (EI): calcd for $C_{18}H_{20}N_2O$ (M^+), 280.1576, found, 280.1573.

2-(7-Methyl-1*H*-indazol-3-yl)-4-phenylbutan-2-ol (13a′). Yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (s, 3H), 2.31–2.40 (m, 3H), 2.50 (s, 3H), 2.71–2.77 (m, 1H), 3.69 (br s, 1H), 7.03–7.21 (m, 7H), 7.70 (d, 1H, $J = 8.0$ Hz), 10.25 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 16.78, 29.34, 30.52, 44.70, 73.28, 118.83, 119.04, 119.84, 120.96, 125.45, 126.65, 128.09, 128.18, 142.15, 151.78. IR (neat) ν: 3416 cm^{-1}. MS (EI): $m/z = 280$ (M^+, 1.8), 262 (bp). HRMS (EI): calcd for $C_{18}H_{20}N_2O$ (M^+), 280.1576, found, 280.1562.

Representative procedure for hydrogenation of 4a

20% $Pd(OH)_2$-C (70 mg, 0.1 mmol) and cyclohexene (1 mL, 10 mmol) were added to a solution of **4a** (53 mg, 0.2 mmol) in THF (5 mL). After being refluxed for 5 h, the mixture was filtered through filter paper and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give **14a** (36 mg, 72%).

3-(1-Methyl-3-phenylpropyl)-1*H*-indazole (14a)

Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (d, 3H, $J = 7.0$ Hz), 2.00–2.13 (m, 1H), 2.23–2.37 (m, 1H), 2.53–2.70 (m, 2H), 3.34 (sext, 1H, $J = 7.0$ Hz), 7.08–7.16 (m, 4H), 7.20–7.26 (m, 2H), 7.31–7.42 (m, 2H), 7.71 (d, 1H, $J = 8.0$ Hz), 10.15 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 20.52, 32.70, 33.97, 38.35, 109.83, 119.95, 120.44, 121.27, 125.54, 126.50, 128.14, 128.30, 141.27, 142.20, 151.07. IR (neat) ν: 3178 cm^{-1}. MS (EI): $m/z = 250$ (M^+, 8.7), 146 (bp). HRMS (EI): calcd for $C_{17}H_{18}N_2$ (M^+), 250.1470, found, 250.1474.

3-(1-Phenylethyl)-1*H*-indazole (14c)

White powder, m.p. 115–118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (d, 3H, J = 7.0 Hz), 4.58 (q, 1H, J = 7.0 Hz), 7.01 (dd, 1H, J = 7.0, 8.0 Hz), 7.16–7.35 (m, 6H), 7.40 (d, 2H, J = 8.5 Hz), 9.97 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.02, 38.94, 109.55, 120.18, 120.72, 121.54, 126.25, 126.52, 127.47, 128.37, 141.32, 144.76, 150.09. IR (nujol) ν: 3182 cm^{-1}. MS (EI): m/z = 222 (M^+, 63.0), 207 (bp). HRMS (EI): calcd for $C_{15}H_{14}N_2$ (M^+), 222.1157, found, 222.1144.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI), the Osaka University Life Science Young Independent Researcher Support Program (Japan Science and Technology Agency), a Grant-in-Aid for Research in Nagoya City University and a Grant-in-Aid from Asahi Kasei Pharma Co. Award in Synthetic Organic Chemistry, Japan.

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