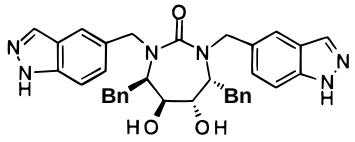
Efficient Synthesis of 5-(Bromomethyl)- and 5-(Aminomethyl)-1-THP-Indazole

Jung-Hui Sun,* Christopher A. Teleha, Jia-Sheng Yan, James D. Rodgers, and David A. Nugiel*

The DuPont Merck Pharmaceutical Company, P.O. Box 80500, Wilmington, DE 19880-0500

Received February 27, 1997

The indazole ring system has an interesting chemistry and is an effective pharmacophore in medicinal chemistry.[1] Recently, we disclosed an extremely potent cyclic urea-based human immunodeficiency virus protease (HIVPR) inhibitor (K_i = 0.018 nM) with excellent antiviral activity (IC_{90} = 8 nM), using 5-methyl-1*H*-indazole as the P2/P2′ substituent (**1**).[2] Molecular modeling of **1**

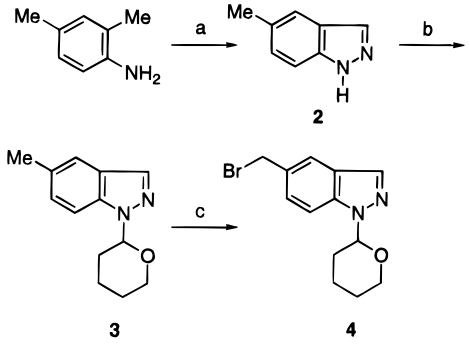


1

bound in the active site of HIVPR showed key hydrogen bonds between each indazole nitrogen and backbone NH and carbonyl groups of Asp 30. Unlike other benzofused heterocycles examined, the potent enzyme inhibitory activity of **1** translated efficiently to whole cell antiviral activity. These favorable properties make the indazole moiety an attractive target for future analogs. Therefore, we needed an expedient synthesis of the title indazole **4**; a key intermediate in the synthesis of **1**. In addition, we prepared the analogous aminomethyl derivative **9**. This allows introduction of the indazole moiety in a complimentary nucleophilic fashion compared to an electrophilic process used with bromide **4**.

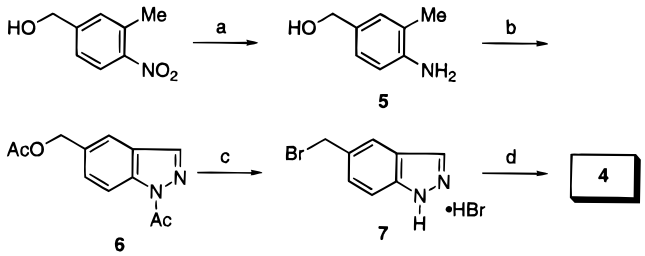
Our initial approach to the desired indazole **4** is shown in Scheme 1. This strategy relied on a radical-promoted benzylic bromination late in the synthetic scheme. Using the same reaction conditions reported by Huisgen and Bast,[3] 2,4-dimethylaniline was converted to 5-methyl-1*H*-indazole (**2**) in 30% yield. Next, the indazole 1-nitrogen was regioselectively functionalized with a tetrahydropyranyl (THP) protecting group in 69% yield. The acidic reaction media results in high regioselectivity.[4] Attempts at introducing other acid-labile protecting groups (MEM, SEM), requiring base-promoted reaction conditions, gave a mixture of N-1- and N-2-protected indazoles. Initially, this did not seem to be a problem since the protecting group would ultimately be removed in subsequent chemical manipulations. Unfortunately, the radical-promoted bromination step proceeded in modest yield for the SEM-

Scheme 1[a]



[a] Reagents and conditions: (a) Ac_2O/AcOH, $NaNO_2$, HNO_3, HCl hydrolysis, 30%; (b) DHP, PPTS, CH_2Cl_2, 69%; (c) NBS, AIBN, CCl_4, 31%.

Scheme 2[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOH, 97%; (b) Ac_2O/KOAc, *n*-amyl nitrite, cat. 18-crown-6, $CHCl_3$, 58%; (c) 48% aqueous HBr, 92%; (d) DHP, THF, reflux, 79%.

protected analog. The final product was difficult to handle and had to be stored as a frozen benzene solution to prevent polymerization. Radical bromination of **3**, using NBS in refluxing CCl_4, gave bromide **4** in 31% yield. The low yield was probably due to the reactivity of the aminal hydrogen on the THP group, leading to decomposition of the starting material.

This initial sequence had two major problems we wished to address: (i) inefficient assembly of the indazole ring system and (ii) inefficient installation of the bromomethyl functionality. Both of these issues were addressed in our second approach shown in Scheme 2. Commercially available 3-methyl-4-nitrobenzyl alcohol provides a versatile benzylic alcohol handle for conversion to the bromomethyl entity using non-radical-based methodology. In addition, the indazole ring system is assembled using a phase-transfer-promoted protocol.[5] Facile reduction of the nitro group was accomplished using hydrogen and 10% palladium on carbon to give the aniline **5** in 97% yield.[6] Preforming the diacetate of **5** with acetic anhydride, followed by nitrosation with *n*-amyl nitrite in the presence of catalytic amounts of 18-crown-6, gave the desired indazole **6** in 58% yield. The phase-transfer protocol allows for anilide nitrosation and rearrangement under mild conditions without the use of a strong acid. To our knowledge, this is the first example of this transformation with a benzylic ester-containing substrate.

(1) (a) Elderfield, R. C. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley & Sons, Inc.: New York, 1957; Vol. 5, p 162. (b) Behr, L. C.; Fusco, R.; Jarobe, C. H. In *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Wiley, R. H., Ed.; International Wiley Science: New York, 1969; p 289. (c) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 5, p 167. For more recent examples see: Ruchardt, C.; Hassman, V. *Liebigs Ann. Chem.* **1980**, 908. Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1992**, *48*, 325.

(2) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *BioMed. Chem. Lett.* **1996**, *6*, 2919.

(3) Huisgen, R.; Bast, K. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 650.

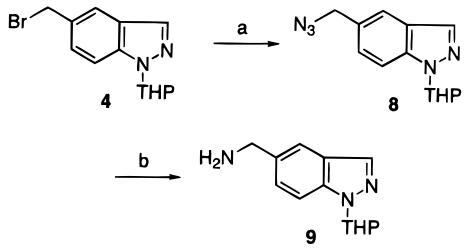
(4) Alonso, G.; Diez, C.; Garcia-Munoz, G.; De las Heras, F. G.; Navarro, P. *J. Carbohydr., Nucleosides, Nucleotides* **1976**, *3*(3), 157−67.

(5) Bartsch, R. A.; Yang, I.-W. *J. Heterocycl. Chem.* **1984**, *21*, 1063. Phase-transfer-promoted indazole formation was also observed as a byproduct in the synthesis of biarenes. See: Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594.

(6) Nayar, M. R. G.; Francis, J. D. *Indian J. Chem. Sect. B* **1983**, *22B*, 776.

S0022-3263(97)00375-7 CCC: $14.00

Scheme 3[a]



[a] Reagents and conditions: (a) NaN_3, DMF, 90 °C, quant; (b) LAH, THF, 0 °C, 98%.

The next reaction removes both acetate groups and introduces the benzylic bromide in one step.[7] Treating indazole **6** with 48% aqueous HBr at 25 °C for 16 h gave the desired 5-(bromomethyl)-1*H*-indazole (**7**) in 92% yield as the HBr salt. It was critical to isolate **7** as the salt to reduce the indazole nitrogen's nucleophilicity and suppress polymerization. This salt was taken on crude to the next step. Any attempt to purify this material as its free base led to decomposition. Heating indazole **7** with 3,4-dihydro-2*H*-pyran in refluxing THF gave the desired product **4** in 79% yield. The importance of the THP protecting group becomes evident. Any attempt at introducing nitrogen protecting groups, using base-promoted reaction conditions, would lead to decomposition of **7**. Bromide **4** could be stored indefinitely at 0 °C without much evidence of decomposition.

Scheme 3 details the conversion of bromide **4** to amine **9**. Facile displacement of the benzylic bromide was accomplished using sodium azide in DMF to give **8** in quantitative yield. The crude azide was carried onto the next step without purification. Reduction of the azide was accomplished with LAH in THF to give the desired amine **9** in 98% yield. This material was of sufficient purity (96.8% by HPLC) to be used in subsequent reactions without further purification and could be stored at 0 °C indefinitely.

In conclusion, we presented a short, efficient synthesis of two useful intermediates on a multigram scale. The indazole ring system was assembled using a phase-transfer-catalyzed protocol, further expanding this reaction's scope. A one-pot conversion provided 5-(bromomethyl)-1*H*-indazole from intermediate **6** in 92% yield. Regioselective introduction of the THP protecting group gave the title compound **4**. An efficient conversion of bromide **4** to amine **9** proceeded in 98% yield without chromatography. These intermediates should provide easy and useful ways of introducing the indazole moiety into future medicinal targets.

Experimental Section

All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Commercial reagents were used as received without additional purification. THF was distilled from sodium benzophenone ketyl. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using tetramethylsilane as an internal standard. Melting points are uncorrected. TLC was performed on E. Merck 15719 silica gel plates. Flash chromatography was carried out using EM Science silica gel 60 (230−400 mesh). Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ.

(7) Initially, a two-step protocol was used to produce indazole **7** from **6**, which involved removing the acetate groups with K_2CO_3/MeOH and treating the subsequent 5-(hydroxymethyl)-1*H*-indazole with 48% HBr in 42% overall yield.

5-Methyl-1*H*-indazole (2). Using the procedure reported by Huisgen and Bast,[3] 2,4-dimethylaniline was converted to 5-methyl-1*H*-indazole in 30% yield. **2**: mp 103−107 °C (lit.[4] mp 111 °C); ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 7.53 (s, 1 H), 7.40 (d, J = 8.9 Hz, 1 H), 7.22 (d, J = 8.9 Hz, 1 H), 2.40 (s, 3 H).

5-Methyl-1-(2-tetrahydropyranyl)indazole (3). A mixture of **2** (6.63 g, 0.05 mol), 3,4-dihydro-2*H*-pyran (10.3 mL, 0.113 mol), and PPTS (0.12 g, 0.6 mmol) in CH_2Cl_2 (50 mL) was heated to reflux for 5 h. The reaction was poured into saturated $NaHCO_3$ (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with 5% aqueous citric acid (50 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Chromatography (silica gel, 10% EtOAc/hexane) gave the product as an oil (7.57 g, 69%). **3**: ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H), 7.47 (m, 2 H), 7.21(d, J = 9.5 Hz, 1 H), 5.68 (dd, J = 9.4, 2.4 Hz, 1 H), 4.02 (br, 1 H), 3.72 (dd, J = 10.6, 3.0 Hz, 1 H), 2.57 (m, 1 H), 2.44 (s, 3 H), 2.2−2.0 (m, 2 H), 1.8−1.6 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.6, 134.7, 131.9, 129.9, 126.5, 121.4, 111.1, 86.7, 68.8, 30.8, 26.6, 24.0, 22.6; CIMS (NH_3) m/z 234 (M + NH_4^+), 217 (M + H^+). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.39; H, 7.46; N, 12.95. Found: C, 72.66; H, 7.42; N, 13.05.

4-(Hydroxymethyl)-2-methylaniline (5). A mixture of 3-methyl-4-nitrobenzyl alcohol (21.05 g, 0.126 mol) and 10% palladium on carbon (2.0 g) in 200 mL of EtOH was hydrogenated at rt. After completion of the reaction, the catalyst in the reaction mixture was removed by filtration. The solvent was evaporated and the residue dried in a vacuum to give **5** as a yellow solid (17.22 g, 97%). **5**: mp 72−75 °C; ^{1}H NMR ($CDCl_3$) δ 7.06 (s, 1 H), 7.03 (d, J = 8.0 Hz, 1 H), 6.66 (d, J = 7.7 Hz, 1 H), 4.53 (s, 1 H), 3.62 (br, 2 H), 2.17 (s, 3 H); CIMS (NH_3) m/z 172 (M + 2 X NH_3 + H^+, 100), 155 (M + NH_4^+).

1-Acetyl-5-(acetoxymethyl)indazole (6). A mixture of **5** (16.58 g, 0.12 mol), acetic anhydride (34.0 mL, 0.36 mol) and potassium acetate (23.71 g, 0.24 mol) in 240 mL of $CHCl_3$ was stirred at rt for 3 h, refluxed for 2 h, and stirred at rt overnight. Then *n*-amyl nitrite (32 g, 0.27 mol) and 18-crown-6 (1.59 g, 6.0 mmol) were added and the mixture heated at reflux for 28 h. After being cooled to rt, the reaction mixture was added to acetic anhydride (10 mL) and stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (400 mL), washed with saturated $NaHCO_3$ (200 mL), water, and brine, and dried (Na_2SO_4) and the solvent evaporated to give a dark brown solid. Chromatography (silica gel, 15% EtOAc/hexane) gave **6** as a yellow solid (16.98 g, 58%). **6**: mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 8.8 Hz, 1 H), 8.13 (d, J = 0.8 Hz, 1 H), 7.75 (d, J = 0.7 Hz, 1 H), 7.56 (dd, J = 8.8, 1.5 Hz, 1 H), 5.23 (s, 2 H), 2.79, (s, 3 H), 2.12 (s, 3 H); CIMS (NH_3) m/z 267 (M + 2 X NH_3 + H^+, 100), 250 (M + NH_4^+). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.22; N, 12.06. Found: C, 62.07; H, 5.07; N, 11.91.

5-(Bromomethyl)-1*H*-indazole Hydrogen Bromide (7). A mixture of **6** (10 g, 0.043 mol) in 50 mL of 48% HBr was stirred at rt for 16 h. The solid was collected on a Buchner funnel, washed with 48% HBr, and dried in a vacuum desiccator with P_2O_5 and NaOH to give **7** as a light tan solid (11.58 g, 92%), which was used for the next reaction without further purification. **7**: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 8.09 (d, J = 0.8 Hz, 1 H), 7.86 (s, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.43 (dd, J = 8.8, 1.5 Hz, 1 H), 4.87 (s, 2 H); CIMS (NH_3) m/z 230, 228 (M + NH_4^+), 213, 211 (M + H^+).

5-(Bromomethyl)-1-(2-tetrahydropyranyl)indazole (4). A mixture of **7** (16.54 g, 0.057 mol) and 3,4-dihydro-2*H*-pyran (9.53 g, 0.113 mol) in THF (400 mL) was refluxed for 2 h and stirred at rt overnight. The reaction solution was diluted with 1 L of CH_2Cl_2, washed with saturated $NaHCO_3$, water, and brine, and dried ($MgSO_4$) and the solvent evaporated. Chromatography (silica gel, EtOAc/hexane 0−20%) gave **4** as a beige solid (13.3 g, 79%). **4**: mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 7.73 (s, 1 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.45 (dd, J = 8.8, 1.5 Hz, 1 H), 5.72 (dd, J = 9.4, 2.4 Hz, 1 H), 4.66 (s, 2 H), 4.04−4.00 (m, 1 H), 3.79−3.70 (m, 1 H), 2.62−2.49 (m, 1 H), 2.18−2.06 (m, 2 H), 1.84−1.57 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.2, 134.0, 130.9, 128.0, 124.8, 121.4, 110.8, 85.5, 67.4, 34.5, 29.4, 25.1, 22.5; CIMS-(NH_3) m/z 314, 312 (M + NH_4^+, 100), 297, 295 (M + H^+); IR (KBr) 3406, 3208, 2938, 2864, 2528, 1692, 1640, 1538, 1440, 1364, 1308, 1282, 1246, 1200, 1136, 1078, 1038, 1012, 908, 816 cm^{-1}. Anal. Calcd for $C_{13}H_{15}BrN_2O$: C, 52.90; H, 5.12; N, 9.49; Br, 27.07. Found: C, 52.62; H, 5.31; N, 9.35; Br, 27.03.

Preparation of 4 by Radical Bromination of 3. A solution of NBS (1.065 g, 5.99 mmol) and AIBN (13.5 mg, 0.08 mmol) in CCl_4 (80 mL) was heated to 60 °C, and a solution of **3** (0.99 g, 4.58 mmol) in CCl_4 (20 mL) was added. After continued heating at this temperature overnight, the reaction was cooled to 0 °C and filtered and the filtrate washed with water. After the organic layer was dried ($MgSO_4$) and the solvent removed at reduced pressure, the residue was chromatographed (silica gel, 17% EtOAc/hexane) to give the product as a yellow oil (414 mg, 31% yield), which slowly crystallized upon standing, mp 64−67 °C. This material was identical in every respect to that prepared from **7**.

5-(Azidomethyl)-1-(2-tetrahydropyranyl)indazole (8). A solution of bromide **4** (3.0 g, 0.01 mol) in dry DMF (30 mL) was treated with sodium azide (2.64 g, 0.041 mol) in one portion and heated to 90 °C for 30 min. The reaction mixture was cooled and poured into water (100 mL) and extracted with ether (150 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to give azide **8** as an oil (2.6 g, quant). No further purification was needed. **8**: oil; ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 7.63 (s, 1 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 1 H), 5.72 (dd, J = 9.4, 2.4 Hz, 1 H), 4.38 (s, 2 H), 4.04−4.00 (m, 1 H), 3.76−3.68 (m, 1 H), 2.62−2.49 (m, 1 H), 2.15−2.03 (m, 2 H), 1.99−1.52 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.3, 133.9, 128.4, 127.1, 124.8, 120.8, 110.8, 85.4, 67.4, 55.0, 29.4, 25.1, 22.5; ESIMS m/z 258 (M + H$^+$, 100); HRMS calcd for $C_{13}H_{16}N_5O_1$ (M + H$^+$) 258.1355, found: 258.1360.

5-(Aminomethyl)-1-(2-tetrahydropyranyl)indazole (9). A solution of azide **8** (2.6 g, 0.01 mol) in THF (30 mL) was cooled to 0 °C using an ice bath and treated with LAH (10.2 mL, 1.0 M in THF) via syringe over 10 min. After 1 h, the reaction mixture was quenched by the dropwise addition of a 1.0 M solution of NaOH (1.5 mL). The reaction mixture was allowed to reach rt, diluted with EtOAc (60 mL), dried with Na_2SO_4, and filtered (Celite). The filter cake was washed with an additional portion of EtOAc (20 mL), and the organic layers were combined and evaporated to give essentially pure amine **9** (2.31 g, 98%). An analytical sample was purified by chromatography (silica, 10% MeOH/CH_2Cl_2/1% concd NH_4OH). **9**: oil; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.53 (s, 1 H), 7.48 (d, J = 8.8 Hz, 1 H), 7.29 (d, J = 8.8 Hz, 1 H), 5.62 (dd, J = 9.4, 2.4 Hz, 1 H), 3.97−3.93 (m, 1 H), 3.85 (s, 2 H), 3.70−3.62 (m, 1 H), 2.83 (bs, 2 H), 2.56−2.43 (m, 1 H), 2.09−1.96 (m, 2 H), 1.76−1.50 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.2, 133.7, 126.8, 124.8, 119.0, 110.3, 85.3, 67.4, 46.0, 29.4, 25.1, 22.6; ESIMS m/z 232 (M + H$^+$, 33), 215 (M + H$^+$ − 17, 100); HRMS calcd for $C_{13}H_{18}N_3O$ (M + H$^+$) 232.1500, found 232.1447. Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.42; N, 18.17. Found: C, 67.18; H, 7.31; N, 18.45.

JO970375B