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Synthesis of a TRPV1 Receptor Antagonist

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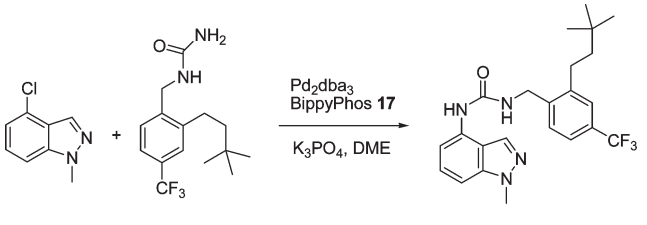
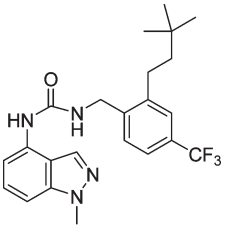


8 **9** **1**

A five-step synthesis of a TRPV1 receptor antagonist **1** is described. The key step involves a novel palladium-catalyzed amidation reaction of 4-chloro-1-methylindazole **8** with the benzyl urea **9** to form the unsymmetrically substituted urea **1**.

TRPV1 receptor antagonists represent a non-NSAID, nonopiate approach for pain management[1] with reduced potential for substance abuse.[2] Compound **1** is a novel, potent, and selective TRPV1 receptor antagonist.[3]

Retrosynthetically, compound **1** can readily be disconnected at the urea moiety. Ureas, and in particular, *N*-aryl and *N*-heteroaryl ureas, have found a ubiquitous position in a number of biologically active targets.[4] They are usually constructed from the couplings of amines with isocyanates, activated esters, or carbamates. An initial synthesis of **1** employed the treatment of aniline, **4**, with *N*,*N*-disuccinimidyl carbonate to form an activated carbamate that was condensed with amine **7** to give the unsymmetrically substituted urea **1** (Scheme 1). A drawback found with this route was the instability of aminoindazole **4**. In addition, synthesis of **4** proved tedious due to the need to separate the aminoindazole **4** from the benzophenone byproduct. Thus, a more robust synthesis was needed to support the development of **1**.



1

Even though C−N cross-couplings have become common in the synthetic repertoire,[5] few examples of *N*-arylation of ureas have been reported and even fewer have described the couplings of chloro-arenes in this transformation.[6] Recently, our laboratory reported a new method for the preparation of unsymmetrically substituted ureas utilizing palladium-catalyzed amidation[7] employing a Pd/bippyphos[8] catalytic system. We report here the application of this methodology in a concise synthesis of compound **1** utilizing the novel coupling reaction between 4-chloro-1-methylindazole, **8**, and benzyl urea, **9** (Scheme 2).

Chloroindazole **8** was prepared from readily available 2-chloro-6-fluorobenzaldehyde **10** by treatment of **10** with excess methyl hydrazine to afford chloroindazole **8** in one step (Scheme 3). However, about 5% of the regioisomer **14** was observed in the product.

To gain insight into the formation of regioisomer **14**, we monitored the reaction by NMR. The addition of methylhydrazine to a slurry of potassium carbonate and **10** in DMSO caused a large and immediate exotherm (1120 J/g of **10**).[9] ^{1}H NMR analysis suggested rapid formation of a ~2:1 mixture of aminals at ambient temperature which were tentatively assigned as **11a** and **11b** (Figure 1). The aminals converged

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(9) The reaction was monitored in an Omincal super chemical reactivity calorimeter.

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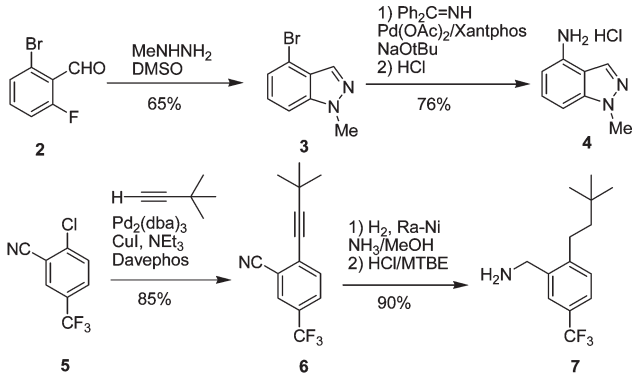
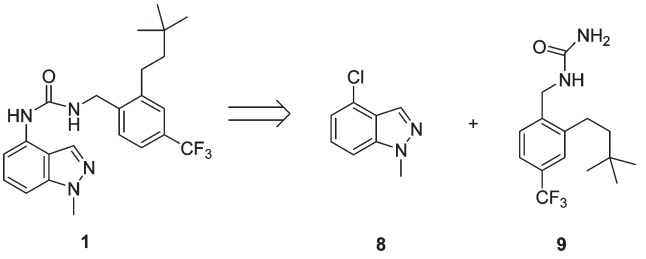
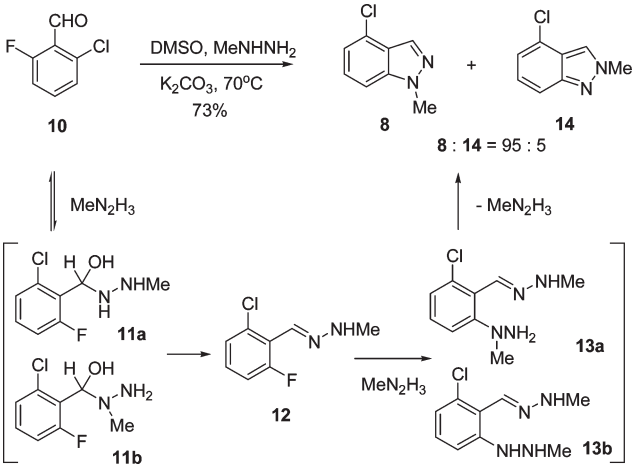
SCHEME 1. First Generation Synthesis of 1



SCHEME 2. Retrosynthetic Analysis of 1



SCHEME 3. Synthesis of Chloroindazole 8



into hydrazone **12** with little to no formation of indazoles **8** and **14**. The formation of the indazoles presumably involves substitution of the aryl fluoride with another molecule of methyl hydrazine, followed by cyclization of **13a** and **13b**[10] (Scheme 3).

(10) Exposure of **12** to the reaction conditions without excess MeN_2H_3 resulted in complex product mixtures while heating **12** with excess MeN_2H_3 cleanly gave **8** and **13** mixtures. See also: Lukin, K.; Hsu, M. C.; Fernando, D.; Leannna, M. R. *J. Org. Chem.* **2006**, *71*, 8166.

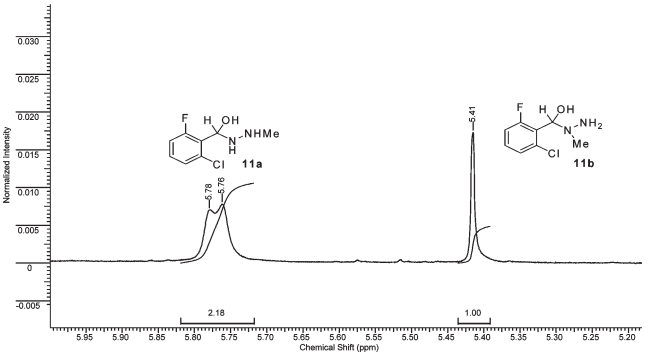
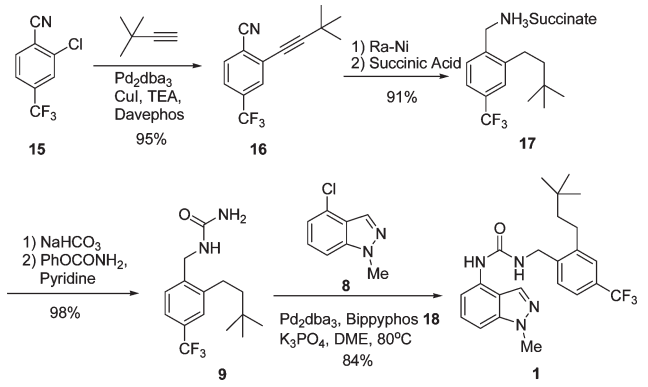


FIGURE 1. NMR of **10**, $MeNHNH_2$ (3 equiv), and DMSO-d_6 at 25 °C/100 min.

SCHEME 4. New Synthesis of 1 with a Novel Urea Coupling Reaction



The ratio of compounds **8** vs. **14** was not significantly affected by equivalents of methylhydrazine either. DMSO proved optimal of the solvents screened (NMP, DME, toluene, DMAC, DMF) in terms of conversion.

Benzyl urea **9** was prepared via a three-step sequence from 3-chloro-4-cyanobenzotrifluoride, **15** (Scheme 4).[11] Sonogashira coupling of aryl chloride **15** with 3,3-dimethylbut-1-yne is accomplished by using Davephos ligand[12] in triethylamine at 65 °C. Deactivated aryl chlorides are typically not competent substrates for Sonogashira couplings;[13] however, the use of the hindered ligand combined with triethylamine as a solvent proved capable of providing the substituted alkyne in >95% yield. It was noted that using THF as a cosolvent decreased the reaction rate. With copper iodide the reaction rates were slightly higher. Slow addition of 3,3-dimethylbut-1-yne minimized oligomerization of the acetylene.

Hydrogenation of **16** was carried out with Ra−Ni under basic conditions at 50 °C. Reduction of the nitrile and alkyne was observed to be rapid while the final alkene reduction proceeded over the course of several hours.[14] The final

(11) Lukin, K. A.; Hsu, M. C.; Fernando, D. P.; Kotecki, B. J.; Leanna, M. R. U.S. Pat. Appl. US2007244178.

(12) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) An initial screen of a series of hindered ligands resulted in Davephose as the best ligand for the reaction.

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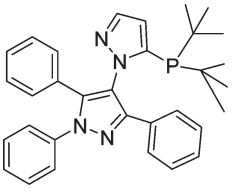
(14) The reaction was monitored by HPLC. Aliquots were taken out to identify the reaction intermediates.

benzylic amine **17** is isolated as the succinate salt providing a purification point without the need of chromatography. Benzyl urea **9** was formed by reacting the benzylic amine **17** with phenyl carbamate (1.07 equiv) and *N*,*N*-diisopropylethylamine (2 equiv) in 2-methyl-THF.

To determine the preferred conditions for the coupling between benzyl urea **9** with chloroindazole **8**, we screened ligands and catalyst first. Two ligands, 1′-binaphthyl-2-di-*tert*-butylphosphine and Bippyphos[8] **18**, provided high conversions for the coupling when complexed with a palladium source. Bippyphos precomplexed with $Pd_2(dba)_3$ with 2:1 ratio in DME provided an optimal rate for the reaction. The complete conversion was achieved with 0.5 mol % of the catalyst.



18

Bippyphos

Milled potassium phosphate tribasic was found to be the most efficient base for the reaction with more reactive surface. The catalyst was preformed by mixing the benzyl urea, $Pd_2(dba)_3$, BippyPhos, K_3PO_4, and DME separately for 30 min at 50 °C. The aryl chloride was then added and the mixture heated to 80 °C for 15 to 20 h. This protocol gave consistent rates and yields.[7]

Purification entailed an aqueous workup followed by sequential exposure of an ethyl acetate solution of the product to a thiourea bound resin and activated carbon. The thiourea resin and the carbon proved necessary to remove residual levels of palladium from the product prior to crystallization from aqueous isopropanol.[15] The product was obtained in > 99.5% purity after crystallization with 5% product loss in the mother liquor.

In summary, we have developed a concise, robust, and scalable synthesis for the TRPV1 receptor antagonist **1**. The synthesis involves a novel coupling reaction between benzyl urea and chloroindazole with readily available[16] nonproprietary Bipyphos as the ligand as well as a high-yielding Sonogashira coupling of an aryl chloride. Compound **1** was delivered by this process to support development efforts.

Experimental Section

4-Chloro-1-methyl-1*H*-indazole 8. Methyl hydrazine (47.3 g, 1.03 mol, 5 equiv) was added to a slurry of potassium carbonate (55.0 g, 0.4 mol), 2-chloro-6-fluorobenzaldehyde **10** (32.1 g, 0.2 mol), and DMSO (317 g) at ambient temperature. The mixture was then heated at 70 °C for 7 days. The mixture was cooled to ambient and diluted with water (250 mL) and methyl *tert*-butyl ether (950 mL). The upper organics were separated and the lower layer was re-extracted with methyl-*tert*-butyl ether (910 mL). The combined organics were washed with 10% citric acid (125 mL) and water (125 mL) and concentrated to oil. To the oil was added water (125 mL). The resulting solid was filtered, washed with water, and dried at 30 °C to yield 27.4 g of crude **8**.

Water (40 mL) was added to a solution of crude **8** (27.4 g) in methanol (40 mL) at 0 °C. The resulting solid was filtered and washed with 33% methanol/67% water (150 mL total) followed by water. A yield of 24.5 g of off-white solid were obtained after drying under vacuum at 30 °C. Yield: 73%. Purity of the solid was 98.5% with 1.34A% of N-2 isomer. ^{1}H NMR (400 MHz, DMSO) δ 4.06 (s, 3H), 7.19 (dd, J = 0.5, 7.5 Hz, 1 H), 7.37 (dd, J = 7.3, 8.5 Hz, 1H), 7.62 (td, J = 0.8, 8.5 Hz, 1H), 8.07 (d, J = 4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 35.8, 108.6, 119.5, 121.8, 124.2, 126.4, 129.9, 140.0; HRMS (ESI) calcd for $C_8H_8ClN_2$ m/z 167.03705 [M + H], found m/z 167.03697.

3-(3,3-Dimethylbut-1-ynyl)-4-cyanobenzotrifluoride 16. To a flask was added Pd_2dba_3 (0.405 g, 0.44 mmol), DavePhos (0.6884 g, 1.75 mmol), and CuI (0.1655 g, 0.87 mmol). It was then purged with nitrogen and degassed triethylamine (100 mL) was added. To this was added 3-chloro-4-cyanobenzotrifluoride **15** (36.2 g, 176 mmol). The mixture was heated to 65 °C and 3,3-dimethylbutyne (23.7 g, 288 mmol) was then slowly added over 2 h. The mixture was heated for an additional 2 h. The mixture was diluted with isopropyl acetate (150 mL). Then it was washed twice with water (150 mL) and twice with 10% aqueous citric acid (150 mL). The organics were diluted with methanol (40 mL) and the volume reduced in vacuo to 60 mL. This was repeated twice with 190 mL of methanol and the residual material was diluted to 250 g with methanol and used in the next step as a solution. Assay yield was 95% with 97% HPLC purity. A solid sample was obtained by removing all of the solvent for the analyses. ^{1}H NMR (400 MHz, DMSO) δ 1.32 (s, 9H), 7.86 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 28.0, 30.1, 74.7, 106.8, 115.9, 117.7, 124.7, 127.1, 127.9, 132.3, 132.6,133.6; HRMS (ESI) calcd for $C_{14}H_{13}F_3N$ m/z 252.09946 [M + H], found m/z 252.09944.

4-Aminomethyl-3-(3,3-dimethylbutyl)benzotrifluoride Succinate Salt 17. To a flask containing Raney Nickel (19 g) was added 3-(3,3-dimethylbut-1-ynyl)-4-cyanobenzotrifluoride **16** in methanol (134 g, 14.9 wt % **16**), potassium hydroxide (0.23 g, 4.1 mmol)), and additional methanol (44.3 g). The mixture was pressurized with hydrogen and agitated for 42 h. The solution was filtered and the cake washed with methanol (20 g). To the solution was added succinic acid (10.65 g, 90 mmol). The solution was reduced in vacuo to 100 mL and diluted with isopropanol (100 mL) and concentrated again to 100 mL. The slurry was filtered and the wetcake washed with isopropanol (120 mL). The cake was dried under vacuum at 35 °C to give a white solid with 91% yield as the monosuccinate salt in > 97A% purity.[17] ^{1}H NMR (400 MHz, DMSO) δ 0.96 (s, 9H), 1.35−1.39 (m, 2 H), 2.30 (s, 4H), 2.62−2.67 (m, 2H), 3.99 (s, 2H), 7.51 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 27.2, 29.0, 30.5, 31.2, 39.9, 44.8, 122.1, 125.0, 127.5, 127.8, 128.3, 139.7, 141.7, 174.1; HRMS (ESI) calcd for $C_{14}H_{21}F_3N$ m/z 260.16206 [M + H], found m/z 260.16273.

1-(2-(3,3-Dimethylbutyl)-4-(trifluoromethyl)benzyl)urea 9. To a solution of 4-aminomethyl-3-(3,3-dimethylbutyl)benzotrifluoride succinate salt **17** (14 g, 37 mmol) in toluene (150 mL) was added 70 mL of 5% NaOH. Then it was mixed and layers were separated. The organic layer was washed twice with 5% $NaHCO_3$ (50 mL) followed by 20% brine (50 mL). It was then

(15) The initial levels of Pd were > 2000 ppm, yet after treatment with thiourea capped resin and carbon, the levels could be brought down to less than 35 ppm with less than 1% of the product lost in the treatments. The Pd level was further dropped with the final crystallization.

(16) It is commercially available in variant quantities from Aldrich and Digital Special Chemicals.

(17) HPLC method: Zorbax RX-C8; 5 um (4.6 mm × 250 mm); 1.0 mL/min; 90:10 H_2O (0.1% H_3PO_4):CH_3CN then to 1:99 in 15 min, held at 1:99 for 10 min, and then to 90:10 in 1 min and held for 4 min; 220 nm wavelength. The reaction mixture is dissolved in 50:50 H_2O (0.1% H_3PO_4):CH_3CN at 1.0 mg/mL at 5 uL for injection. Retention time for **16** is 10.5 min

concentrated and chased with 2-methyl-THF to give benzylamine free base in 99.8% yield. To a slurry of phenyl carbamate (5.12 g, 37 mmol) in 2-methyl-THF (25 mL) was added *N*,*N*-diisopropylethylamine (8.77 g, 68 mmol) and benzylamine/2-methyl-THF solution (total solvent ca. 50 mL). The mixture was stirred at 45 °C overnight and cooled to 20 °C. Isopropyl acetate (55 mL) was added and the organic layer was then washed twice with 5% NaOH (50 mL each) followed by three times with 20% NaCl (50 mL each). The organic layer was concentrated and chased with methanol to ca. 30 mL. To the residue was added 40 mL of methanol. The resulting mixture was heated to 50−60 °C and water (80 mL) was slowly added. The slurry was cooled to 20 °C, filtered, and washed with 50% aqueous methanol followed by water. The wet cake was dried at 55 °C to give 18.8 g of urea **9** as a white solid in 98% yield with 99.6% HPLC purity.[18] ^{1}H NMR (400 MHz, DMSO) δ 0.96 (s, 9H), 1.37−1.41 (m, 2 H), 2.61−2.65 (m, 2H), 4.25 (d, J = 8 Hz, 2H), 5.57 (s, 2H), 6.40 (t, J = 8 Hz, 1H), 7.39−7.51 (m, 3H); ^{13}C NMR (101 MHz, DMSO) δ 27.0, 29.1, 30.5, 39.9, 44.7, 121.9, 124.8, 126.7, 127.0, 127.4, 141.1, 142.4, 157.8. HRMS (ESI) calcd for $C_{15}H_{22}F_3N_2O$ m/z 303.16787 [M + H], found m/z 303.16796.

1-[2-(3,3-Dimethylbutyl)-4-trifluoromethylbenzyl]-3-(1-methyl-1*H*-indazol-4-yl)urea 1. To a flask was added urea **9** (20 g, 66.2 mmol), potassium carbonate (21.04 g, 99.2 mmol), Pd_2dba_3 (606 mg, 0.66 mmol), and bippyphos **18** (1.34 g, 2.65 mmol). After being purged with nitrogen, the mixture was diluted with sparged dimethoxyethane (DME, 260 mL). The mixture was heated to 50 °C for 30 min. Indazole **8** (13.23 g, 79.4 mmol) in 40 mL of sparged DME was added to the catalyst mixture at 50 °C. The mixture was heated to 80 °C for 18 h. The mixture was cooled to ambient, filtered, and concentrated to approximately 150 g. The residue was chased twice with isopropanol (2 × 500 mL). The remaining material was diluted to ca. 230 g with isopropanol and heated to 65 °C. Water (182 g) was slowly added at 65 °C and the solution cooled to 0 °C. The slurry was stirred at 0 °C for 1 h and filtered, then the cake was washed with 45% water/methanol (100 mL). The solids were dried at 40 °C to give 24.0 g of product **1** as a white solid in 84% yield. ^{1}H NMR (400 MHz, DMSO) δ 0.96 (s, 9H), 1.42−1.46 (m, 2 H), 2.67−2.71 (m, 2H), 3.98 (s, 3H), 4.44 (d, J = 8 Hz, 2H), 6.79 (t, J = 5.8 Hz, 1H), 7.13 (d, J = 8 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.50−7.55 (m, 3H), 7.63 (d, J = 7.3 Hz, 1H), 8.03 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 27.2, 29.1, 30.5, 35.4, 40.0, 44.9, 102.1, 106.9, 114.9, 122.1, 125.0, 126.6, 127.1, 127.4, 127.8, 129.1, 132.4, 139.9, 141.5, 141.6, 154.1. HRMS (ESI) calcd for $C_{23}H_{28}F_3N_4O$ m/z 433.22097 [M + H], found m/z 433.22083.

(18) HPLC condition: Zorbax C8 column; 4.6 × 250 mm; 205 nm detection; run time 38 min; injection volume 5 uL; flow rate 1 mL/min; oven temperature 30 °C; gradient elution 20% acetonitrile/80% (0.1% aq H_3PO_4) to 80% acetonitrile/20% (0.1% aq H_3PO_4) in 7 min, hold 23 min then back to 20% acetonitrile/80% (0.1% aq H_3PO_4) in 5 min, hold for 3 min. Retention time for **16** is 7.3 min and for **9** is 10.1 min.

Acknowledgment. We would like to thank Dr. Timothy Robbins for preparing Bippyphos, Christopher Ling for HRMS analysis of all compounds, and Dr. Zhe Wang for the reaction heat analysis.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **8**, **9**, **16**, **17**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.