An Improved Synthesis of (4-{4-Hydroxy-3-isopropyl-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetic Acid (NH-3)

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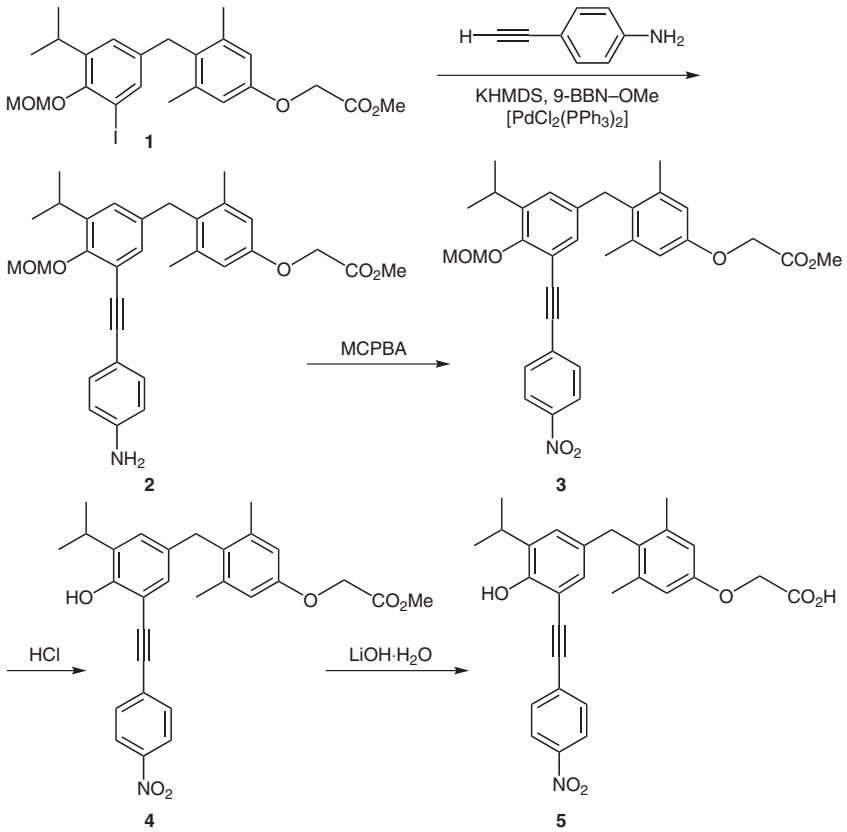
Abstract: Sonogashira coupling of methyl {4-[3-iodo-5-isopropyl-4-(methoxymethoxy)benzyl]-3,5-dimethylphenoxy}acetate with (trimethylsilyl)acetylene afforded the corresponding (trimethylsilyl)ethynyl derivative in quantitative yield. Copper-free palladium-catalyzed coupling of this intermediate with 1-iodo-4-nitrobenzene afforded methyl (4-{3-isopropyl-4-(methoxymethoxy)-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetate in high yield. Saponification of the ester group, followed by the removal of the methoxymethyl group afforded (4-{4-hydroxy-3-isopropyl-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetic acid (NH-3).

Key words: coupling, Sonogashira coupling, palladium catalysis, 1-iodo-4-nitrobenzene, hydrolysis

Thyroid receptors (TRs) exert profound effects on development and homeostasis in mammals.[1] Development of TR antagonists is of current interest because of their potential clinical use in treatment of thyrotoxicosis and hyperthyroidism.[2] The compound known as NH-3 (**5**, Scheme 1) selectively and completely blocks TR and shows in vivo activity in a tadpole tail resorption assay.[3] A recent study[4] describes the pharmacological profile of **5** in rats.

Compound **5** was previously synthesized as shown in Scheme 1.[5] The key step was the Suzuki–Miyaura coupling of 5′-iodinated intermediate **1** with the boronate derivative of 4-ethynylaniline to afford 5′-(phenylethynyl) intermediate **2** in 58% yield on a 2.3 mmol scale.[6] This reaction required cannula transfer of the boronate deriva-



Scheme 1

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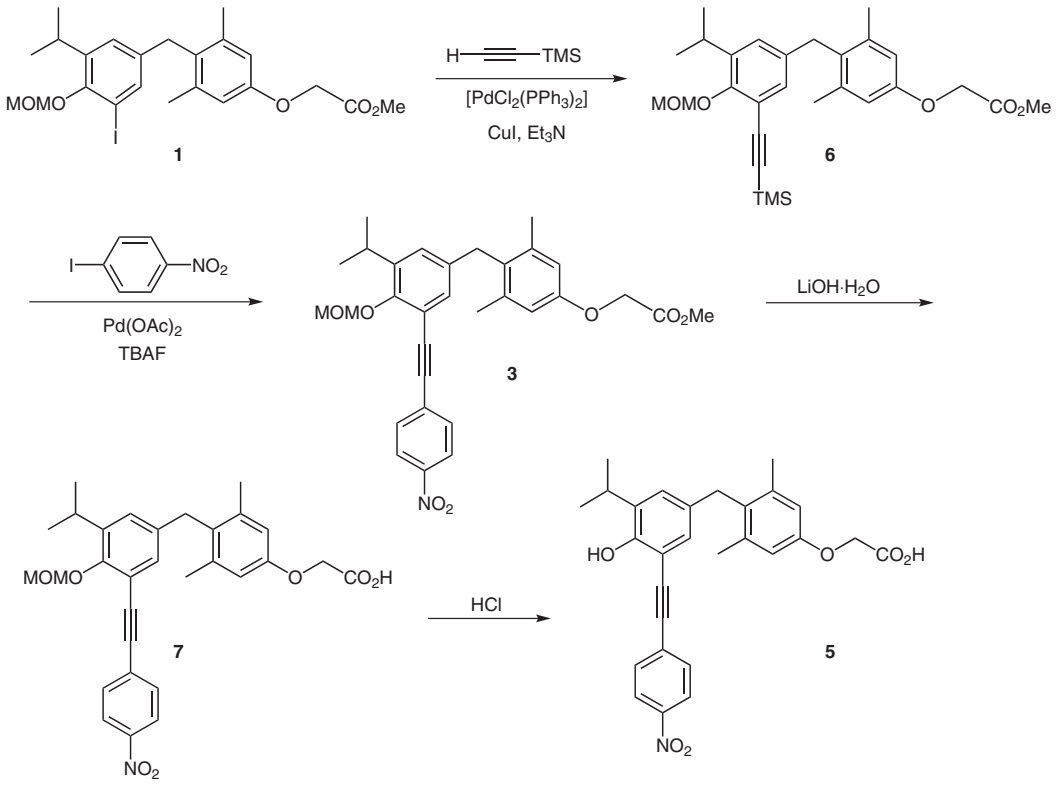

Scheme 2

tive, generated in situ under basic conditions with 9-methoxy-9-borabicyclo[3.3.1]nonane in anhydrous tetrahydrofuran at –78 °C, to a mixture containing **1** and dichlorobis(triphenylphosphine)palladium(II) and further refluxing of the mixture for 15 hours. Subsequent *m*-chloroperoxybenzoic acid oxidation of **2** gave nitro compound **3**[5] in 61% yield, and in an overall yield of 35% from **1** to **3**. Compound **3** was then converted into target compound **5** via a standard deprotection and hydrolysis sequence.

As part of an ongoing research program, gram-scale quantities of **5** were required. Unfortunately, attempts to replicate the synthetic sequence of **1** to **3** were not successful, possibly due to the stringent experimental conditions. Therefore, a more efficient, scalable, and potentially more versatile synthesis of **5** was developed (Scheme 2).

Sonogashira[7] coupling of 5′-iodinated intermediate **1**, obtained according to the literature procedure,[6] with (trimethylsilyl)acetylene afforded (trimethylsilyl)ethynyl intermediate **6** in quantitative yield under mild conditions (Scheme 2). This reaction was performed on a 10 mmol scale and could be scaled up readily. Subsequent reaction of **6** with 1-iodo-4-nitrobenzene, tetrabutylammonium fluoride, and palladium(II) acetate afforded intermediate **3** in 76% yield. Conversion of **3** into target compound **5** according to the literature procedure (Scheme 1) produced a product mixture, which, in addition to **5**, contained traces of impurities[8] that could not be removed. Reversing the final sequence, **3** was first hydrolyzed with lithium hydroxide to give acid **7** in quantitative yield (Scheme 2). Subsequent hydrogen chloride deprotection of the methoxymethyl group from **4** afforded **5** in 73% yield. The overall yield of **5** from **1** was 55% (4 steps), compared to the literature yield of 17% (4 steps).

In summary, an efficient and scalable synthesis of NH-3 has been developed. This general method can be used to synthesize other NH-3 analogues and would provide products without benzofuran impurities.[6]

Reagents were obtained from Aldrich Chemical Company and were used as received unless mentioned otherwise. Melting points were determined on a Fisher–John's apparatus and are uncorrected. HRMS was performed at the University of Michigan, Ann Arbor, MI. The ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$, with TMS as internal standard, were recorded on a Bruker Avance spectrometer (300 MHz). Mass spectra were run on a Perkin-Elmer Sciex APR150 EX mass spectrometer outfitted with APCI (atmospheric pressure chemical ionization) or ESI (turbospray) sources. Flash column chromatography was carried out on a CombiFlash Companion system using Isco prepacked silica gel columns or by using E. Merck silica gel 60 (230–400 mesh). Analytical TLC was carried out on EMD silica gel 60 F_{254} TLC plates. Elemental analyses were done by Atlantic Microlab Inc., Norcross, GA.

Methyl (4-{3-Isopropyl-4-(methoxymethoxy)-5-[(trimethylsilyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetate (6)

A soln of **1** (5.12 g, 10 mmol) in Et_3N (120 mL) was degassed by having argon bubbled through it for 10 min. [$PdCl_2(PPh_3)_2$] (350 mg, 0.5 mmol) and CuI (95 mg, 0.5 mmol) were added to the solution. (Trimethylsilyl)acetylene (1.57 g, 16 mmol) was added, and the mixture was stirred at r.t. under argon for 3 h. Then the mixture was filtered through a pad of Celite, which was subsequently washed with Et_3N (100 mL). The filtrate and the washings were combined and evaporated under vacuum. Purification of the residue by column chromatography (silica gel, EtOAc–hexane, 1:9) afforded **6**.

Pale brown oil; yield: 4.82 g (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9 H), 1.14 (d, *J* = 6.9 Hz, 6 H), 2.19 (s, 6 H), 3.38 (hept, *J* = 6.9 Hz, 1 H), 3.59 (s, 3 H), 3.81 (s, 3 H), 3.88 (s, 2 H), 4.6 (s, 2 H), 5.18 (s, 2 H), 6.63 (s, 2 H), 6.80 (s, 1 H), 6.91 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.2, 20.5, 23.3, 26.3, 33.8, 52.1, 57.4, 65.3, 97.9, 99.6, 102.5, 114.1, 116.3, 126.8, 129.9, 135.5, 138.6, 141.8, 154.6, 155.9, 169.6.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{38}NaO_5Si$: 505.2386; found: 505.2378.

Methyl (4-{3-Isopropyl-4-(methoxymethoxy)-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetate (3)

$Pd(OAc)_2$ (110 mg, 0.49 mmol) was added to a stirred soln of **6** (4.67 g, 9.67 mmol) and 1-iodo-4-nitrobenzene (2.4 g, 9.67 mmol) in anhyd THF (55 mL) under argon. A 1.0 M solution of TBAF in THF (9.6 mL) was then added. The dark-colored mixture was stirred at r.t. for 70 min and then at 65 °C for 10 min. The mixture was cooled to r.t., poured into sat. aq $NaHCO_3$ (220 mL) and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine (250 mL), dried (Na_2SO_4), and evaporated under vacuum. Flash column purification of the residue (silica gel, EtOAc–hexane, 10:90 to 20:80) afforded **3**.

Yellow solid; yield: 3.91 g (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.9 Hz, 6 H), 2.22 (s, 6 H), 3.40 (hept, *J* = 6.9 Hz, 1 H), 3.62 (s, 3 H), 3.82 (s, 3 H), 3.93 (s, 2 H), 4.64 (s, 2 H), 5.22 (s, 2 H), 6.65 (s, 2 H), 6.84 (s, 1 H), 7.05 (s, 1 H) 7.63 (d, *J* = 8.9 Hz, 2 H), 8.20 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 23.2, 26.4, 33.7, 52.1, 57.5, 65.2, 90.9, 92.4, 99.9, 114.2, 115.5, 123.5, 127.9, 129.6, 129.7, 130.2, 132.0, 136.0, 138.5, 142.2, 146.8, 154.2, 156.0, 169.5.

ESI-MS: *m*/*z* = 532.6 [M + H]$^+$.

(4-{3-Isopropyl-4-(methoxymethoxy)-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetic Acid (7)

A soln of $LiOH·H_2O$ (312 mg, 7.44 mmol) in H_2O (16 mL) was added to a stirred suspension of **3** (1.59 g, 3 mmol) in MeOH (120 mL). After stirring at r.t. for 50 min, the mixture was heated to reflux, to give a clear solution. After the mixture had stirred for another 20 min at r.t., the solvent was removed under vacuum. The residue was treated with H_2O (80 mL), acidified to pH 1 with 1 N aq HCl, and extracted with CH_2Cl_2 (1 × 100 mL, 2 × 50 mL). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4). Evaporation of the solvent under vacuum afforded **7**.

Yellow foamy solid; yield: 1.55 g (100%); mp 90–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.9 Hz, 6 H), 2.07 (s, 6 H), 3.37 (hept, *J* = 6.9 Hz, 1 H), 3.59 (s, 3 H), 3.82 (s, 2 H), 4.47 (s, 2 H), 5.19 (s, 2 H), 6.60 (s, 2 H), 6.78 (s, 1 H), 6.99 (s, 1 H) 7.54 (d, *J* = 8.8 Hz, 2 H), 8.13 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 23.3, 26.4, 33.7, 57.5, 66.1, 91.0, 92.3, 99.9, 114.5, 115.5, 123.7, 127.9, 129.5, 129.9, 130.1, 131.9, 135.9, 138.5, 142.3, 146.9, 154.3, 155.6, 174.8.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{31}NNaO_7$: 540.1998; found: 540.2000.

Anal. Calcd for $C_{30}H_{31}NO_7·0.5H_2O$: C, 68.43; H, 6.13; N, 2.66. Found: C, 68.53; H, 5.98; N, 2.75.

(4-{4-Hydroxy-3-isopropyl-5-[(4-nitrophenyl)ethynyl]benzyl}-3,5-dimethylphenoxy)acetic Acid (5, NH-3)

Concd aq HCl (3.6 mL) was added to a stirred solution of **7** (1.00 g, 1.93 mmol) in THF (44 mL), and the mixture was stirred at r.t. for 18 h. It was then filtered and the filtrate was evaporated under vacuum. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (20 mL). The organic layer was washed with brine (30 mL), dried (Na_2SO_4), and evaporated under vacuum. Purification of the residue on an ISCO prepacked silica column (MeOH–CH_2Cl_2, 2:98 to 15:85) afforded a yellow solid (753 mg). This material was dissolved in CH_2Cl_2 (10 mL) and treated with hexane (60 mL). The precipitated solid was collected and dissolved again in warm CH_2Cl_2 (25 mL). The CH_2Cl_2 solution was treated with hexane (160 mL). The precipitate was collected, washed with hexane, and dried under vacuum; this afforded **5**.

Yellow solid; yield: 669 mg (73%); mp 173–174 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.9 Hz, 6 H), 2.23 (s, 6 H), 3.26 (hept, *J* = 6.9 Hz, 1 H), 3.90 (s, 3 H), 4.69 (s, 2 H), 5.69 (br, 1 H), 6.67 (s, 2 H), 6.71 (s, 1 H), 7.02 (s, 1 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 8.22 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 22.3, 27.6, 33.6, 64.9, 89.4, 93.9, 107.9, 114.2, 123.7, 127.3, 128.7, 129.4, 130.6, 131.8, 132.1, 134.7, 138.8, 147.2, 152.5, 155.4, 172.5.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{27}NNaO_6$: 496.1736; found: 496.1741.

Anal. Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96. Found: C, 70.80; H, 5.91; N, 3.07.

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