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Regiospecific synthesis of 3-alkyl-4-hydroxybenzimidazoles as intermediates for an expedient approach to potent EP3 receptor antagonists

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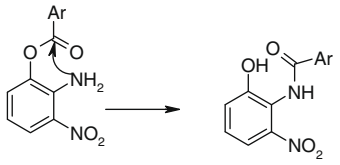
ABSTRACT

Regiospecific construction of 3-alkyl-4-hydroxybenzimidazoles is detailed. The synthetic route involves a novel O- to N-acyl transfer reaction to address the observed exclusive O-acylation of 2-amino-3-nitrophenol starting material. This efficient route provides the targeted 3-alkyl-4-hydroxybenzimidazoles in good yields, in five steps, without the use of chromatographic purification. These key intermediates were subsequently elaborated, as shown, to provide acylsulfonamide-derived potent EP_3 receptor antagonists.

During the course of an investigation into the generation of EP_3 receptor antagonists, we sought to construct a series of 3-alkyl-4-alkoxybenzimidazoles as potential EP_3 receptor antagonists. Traditionally, 3-alkyl-4-hydroxybenzimidazoles have been generated through the reduction of the 3-nitro-2-alkyl-2-amido-phenol[1] or sulfamidephenol[2] derivatives followed by ring closure. A related approach involves ring closure of 3-amido-2-alkyl-2-aminophenol derivatives to arrive at the 3-alkyl-4-hydroxybenzimidazoles,[3] whereas 2-amino-3-alkyl-benzimidazoles have been produced through cyclizations of 2-alkylamino-3-thiourea-anisoles[4] or via the intermediate cyclic ureas.[5] Procedures to selectively alkylate either N1 or N3 of 4-hydroxy/alkoxybenzimidazole derivatives have been met with limited success[1c,5] with the majority of these protocols[6] resulting in the generation of a mixture of regioisomers.

In this Letter, we describe the regiospecific generation of 3-alkyl-4-hydroxybenzimidazoles via a five-step synthetic sequence that results in high yields of the targeted molecules. The current report emphasizes the ease of the sequence wherein no chromatographic purification is required through the isolation of the 3-alkyl-4-hydroxybenzimidazole. Subsequent to the submission of our initial communication of this synthetic route,[7] a similar approach was reported by the Johnson & Johnson group.[8] The utility of this reaction scheme is exemplified here by further elaboration of the key intermediates **6** and **14** to give rise to potent EP_3 receptor antagonists **9** and **17**, respectively.

The initial synthetic sequence was intended to involve direct N-acylation of 2-amino-3-nitrophenol (**1**) to furnish the expected amides **3** or **11**. However, due to the electron-withdrawing ability of the C-3 nitro substituent lowering the nucleophilicity of the C-2 amino substituent, we observed exclusive O-acylation of the phenol functionality when limiting equivalent of acyl chloride (1 equiv), and **1** were used in the presence of DMAP (1.0 equiv) in CH_2Cl_2.[9] Evidence for exclusive O-acylation include (a) absorbances in the IR spectrum of compound **10** at 1742 cm^{-1} for ester C=O, and 3492 and 3382 cm^{-1} for the typical NH_2 asymmetrical and symmetrical N–H stretches and (b) a broad singlet at δ 6.19 in the ^1H NMR integrating for two protons. We reasoned out that the O-acylated compound could be transformed into the respective N-acylated compound via an intramolecular acyl transfer procedure.[10] A five-membered transition state for this reaction appeared feasible (Scheme 1). In addition, the resulting amides, **3** and **11**, are expected to be more thermodynamically stable than the corresponding esters **2** and **10**. Also, the reverse amide-to-ester conversion is unlikely in the presence of excess base due to the deprotonation of amides **3** and **11**. Indeed, both amides **3** and **11** were prepared in high yields and purity upon the treatment of compounds **2** and **10** with sodium hydride in THF, cleanly and in an essentially quantitative yield (Scheme 2). Relevant spectral data for compound **11** include an IR absorption at 3341 and 1650 cm^{-1} for the phenol hydroxyl and amide carbonyl absorptions, respectively. The ^1H NMR spectrum of compound **11** included absorptions at δ 11.16 and 9.77 for the phenolic and amide proton absorptions, respectively. Hydrogenation of the nitro compound **3** was accomplished to afford the amine derivative **4** in a quantita-



Scheme 1. Intramolecular O-acyl to N-acyl migration.

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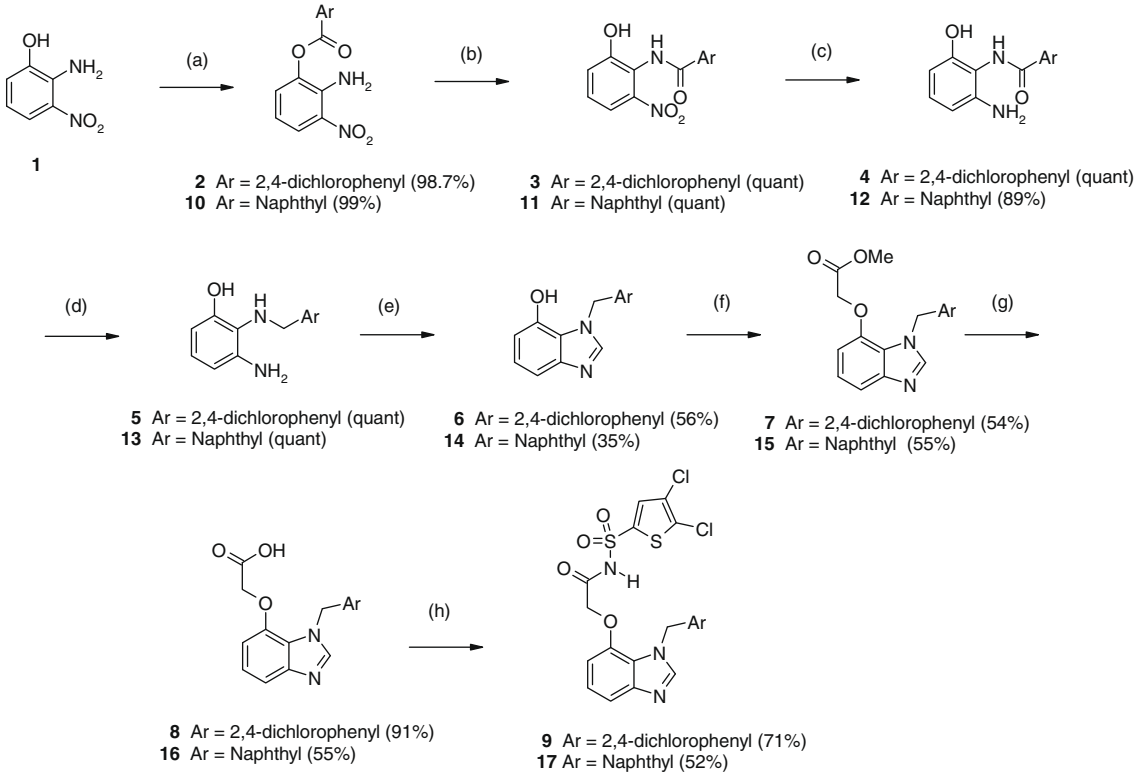

Scheme 2. Reagents and conditions: (a) for **2**: 2,4-dichlorobenzoyl chloride, DMAP, CH_2Cl_2, 20 °C, 16 h; for **10**: 2-naphthoyl chloride, DMAP, CH_2Cl_2, 20 °C, 16 h; (b) NaH, THF; (c) for **4**: H_2, Raney nickel, EtOH, rt, 16 h; for **12**: $SnCl_2{\cdot}2H_2O$ (10 equiv), 6 N aq HCl, EtOH, 70 °C, 1 h; (d) BH_3, THF; (e) $HC(OEt)_3$, pTsOH, EtOH, 75 °C, 1 h; (f) methyl bromoacetate, K_2CO_3, DMF, rt, 16 h; (g) 15% aqueous NaOH, EtOH, H_2O, rt, 16 h; (h) 4,5-dichlorothiophene-2-sulfonamide, EDCI, DMAP, CH_2Cl_2, rt, 4 h.

tive yield. Alternatively, compound **11** was reduced using tin chloride conditions to provide the amine compound **12** (89% yield).

Condensation of **5** with triethyl orthoformate in EtOH in the presence of *p*-toluenesulfonic acid provided the 3-alkyl-4-hydroxybenzimidazole **6** after purification by a simple trituration. Exposure of compound **13** under similar conditions provided compound **14**. The respective 4-hydroxybenzimidazoles 6 and **14** were subjected to the O-alkylation with bromoacetic acid methyl ester followed by the NaOH-mediated hydrolysis to yield the respective acids **8** and **16**. The final coupling of key pharmacophore component 4,5-dichlorothiophene-2-sulfonamide was achieved with EDCI/DMAP to afford the targeted molecules **9** and **17**. These peri-substituted benzimidazole analogs have previously been reported to be potent and isoform selective EP_3 receptor anatagonists.[11]

In conclusion, the procedure described in this Letter[12] allows for the expeditious access to 3-alkyl-4-hydroxybenzimidazoles 6 and **14** in overall good yields without requiring chromatographic purification. The final products were obtained following chromatographic purification yielding compounds **9** and **17** in 20% and 25% overall unoptimized yield, respectively, via the eight-step sequence as shown in Scheme 2. Both high yields and feasibility of the synthetic sequence is expected to be amenable to scale up of 4-substituted benzimidazoles and respective parallel synthesis of their derivatives.

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10. A literature report by Griffiths, D. W.; Bender, M. L. *Bioorg Chem.* **1975**, 4, 84–92, points out that intramolecular acyl transfers of this type have been measured and occur as much as 10^5 times faster than the transfer of the acyl group to the surrounding water molecules, would support the authors notion of the stated acyl migration being intramolecular. However, in the absence of cross-over experiments inter-molecular acyl migration could not be ruled out.
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12. Synthesis of compound **9** is provided as a representative example. *Synthesis of 2,4-dichloro-benzoic acid 2-amino-3-nitro-phenyl ester* (**2**): To a 500 mL, round-bottomed, one-necked flask equipped with a magnetic stir bar and a septum was added 2-amino-3-nitrophenol (4.25 g, 27.6 mmol), anhydrous CH_2Cl_2 (140 mL), 4-(dimethylamino)pyridine (3.37 g, 27.6 mmol), and 2,4-dichlorobenzoyl chloride (5.78 g, 3.87 mL, 27.6 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and the mixture was washed with H_2O (2 × 200 mL), dried (Na_2SO_4), and concentrated to give 8.91 g (98.7%) of a yellow-orange solid. ^1H NMR analysis indicated the material **2** was pure enough to carry on to the next step. ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (br s, 2H), 6.77 (dd, J = 8.5, 8.0 Hz, 1H), 7.43 (m, 1H), 7.45 (m, 1H), 7.60 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 8.10 (dd, J = 8.5, 1.5 Hz, 1H) ppm.

Synthesis of 2,4-dichloro-N-(2-hydroxy-6-nitro-phenyl)-benzamide (**3**)*:* To a 500 mL, round-bottomed, one-necked flask containing **2** (8.91 g, 27.2 mmol) was added a magnetic stir bar and anhydrous THF (300 mL) and the reaction vessel was placed under a N_2 atmosphere. Sodium hydride (1.08 g, 44.9 mmol, 60% in oil dispersion) was added in portions cautiously to the stirring reaction mixture over a period of 2 min. After an additional 2 min, H_2 gas evolution occurs (fairly rapidly) and a slight exotherm was observed. The mixture was stirred at room temperature for 1 h. TLC analysis at this time shows reaction complete. The mixture was allowed to stir at room temperature overnight. The mixture was cautiously quenched through the slow addition of water (50 ml) dropwise and then in small portions. The mixture was poured into EtOAc (1 L) and water (200 mL). The aqueous layer was acidified to a pH ~1 with 1 N aqueous HCl and extracted. The layers were separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give **3**, (9.36 g) as a tan solid. ^{1}H NMR (500 MHz, CDCl3) δ 7.34 (t, J = 8.0 Hz, 1H), 7.44 (m, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.0, 1.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 8.74 (s, 1H), 10.62 (br s, 1H) ppm.

Synthesis of N-(2-amino-6-hydroxy-phenyl)-2,4-dichloro-benzamide (**4**): To a 250 mL hydrogenation vessel was added an aqueous slurry of Raney nickel (700 mg) and it was cautiously diluted with EtOH (60 mL). Compound **3** (700 mg, 2.14 mmol) was added as a solid. The sides of the vessel were rinsed with EtOH (10 mL) and the mixture was subjected to hydrogenation in a Parr shaker at 50 psi of H_2 gas at room temperature overnight. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with EtOH (400 mL). The filtrate was concentrated in vacuo to give a quantitative yield of a dark brown solid, **4**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.74 (br s, 2H), 6.15 (dd, J = 8.0, 2.0 Hz, 1H), 6.23 (dd, J = 8.0, 1.0 Hz, 1H), 6.81 (dd, apparent t, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0, 2.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 9.20 (v br s, 2H) ppm. MS (ESI$^+$) Calcd (M) 296; Found: 297.4 (M+H).

Synthesis of 3-amino-2-(2,4-dichloro-benzylamino)-phenol (**5**): To a 250 mL round-bottomed, one-necked flask equipped with a magnetic stir bar, a reflux condenser and placed under a N_2 atmosphere was added compound **4** (635 mg, 2.14 mmol). Anhydrous THF (31 mL) was added followed by dropwise addition of 1 M BH_3 in THF (8.6 mL, 8.6 mmol). The reaction mixture was heated at reflux overnight. The reaction was cooled and cautiously quenched by dropwise addition of methanol (50 mL). The resulting mixture was concentrated on a rotary evaporator. The residue was again dissolved in methanol (50 mL) and reconcentrated. This redissolution of the residue in methanol and reconcentration was repeated two more times to give a quantitative yield of a brown oil, **5**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.38 (br s, 2H), 4.35 (br s, 1H), 4.61 (s, 2H), 6.05 (dd, J = 8.0, 1.5 Hz, 1H), 6.15 (dd, J = 8.0, 1.5 Hz, 1H), 6.51 (t, J = 8.0 Hz, 1H), 7.36 (dd, J = 8.5, 2.0 Hz, 1H), 7.53 (m, 2H), 8.85 (br s, 1H) ppm. MS (API$^+$) Calcd (M) 282.02, Found: 283.2 (M+H).

Synthesis of 3-(2,4-dichloro-benzyl)-3H-benzoimidazol-4-ol (**6**)*:* To a 20 mL vial containing a magnetic stir bar was added compound **5** (980 mg, 3.46 mmol) and absolute EtOH (8 mL). To this stirring suspension were added triethyl orthoformate (0.634 mL, 3.81 mmol) and *p*-toluenesulfonic acid monohydrate (33 mg, 0.173 mmol). The vial was capped and placed in an oil bath at 75 °C for 1 h. At this time the cap was removed from the vial and the oil bath temperature was increased to 95–100 °C, boiling off the solvent. The last traces of solvent were removed under high vacuum. The residue was triturated twice with 1:1 hexanes/acetone (6 mL each time) and the resulting dark brown solid was filtered and dried to give **6**, 570 mg (56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.70 (s, 2H), 6.55 (overlapping doublets, apparent triplet, J = 8.5, 8.0 Hz, 2H), 6.98 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 9.85 (s, 1H) ppm. MS, Calcd (M) 292.02; Found (ESI$^+$): 293.5, Found (ESI$^-$): 291.1.

Synthesis of [3-(2,4-dichloro-benzyl)-3H-benzoimidazol-4-yloxy]-acetic acid methyl ester (**7**)*:* To a 5 mL vial containing a magnetic stir bar and compound **6** (60 mg, 0.204 mmol) were added anhydrous DMF (0.8 mL), anhydrous potassium carbonate (34 mg, 0.246 mmol), and methyl bromoacetate (24 μL, 0.246 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to give a residue which was dissolved in 1:1 hexanes/acetone (1 mL) and was purified by column chromatography on flash silica gel (6 g) utilizing 4:1 hexanes/acetone followed by 7:3 hexanes/acetone as eluent to give **7**, 40 mg (54%) of a semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.66 (s, 2H), 5.77 (s, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 7.11 (dd, J = 8.5, 2.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H) ppm. MS (ESI$^+$) Calcd (M+H) 365.7; Found: 365.6.

Synthesis of [3-(2,4-dichloro-benzyl)-3H-benzoimidazol-4-yloxy]-acetic acid (**8**)*:* To a 50 mL round-bottomed, one-necked flask containing compound **7** (32 mg, 0.088 mmol) were added absolute ethanol (0.5 mL), water (0.5 mL), and 15% aqueous sodium hydroxide (25 μL, 93 μmol). The reaction mixture was allowed to stir at room temperature overnight. The mixture was concentrated in vacuo to give a solid. The solid was dissolved in water (3 mL) and made acidic through the addition of 1 N aqueous HCl (0.25 mL). pH of the solution was 2–3 by litmus paper. The resulting precipitate was filtered and dried. The aqueous filtrate was extracted with EtOAc (3 × 1 mL) and the organic extracts were concentrated in vacuo to give a solid. This solid was combined with the isolated precipitate to give 28 mg (91%), **8**, as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.69 (s, 2H), 5.80 (s, 2H), 6.70 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 2.0 Hz, 1H), 8.32 (s, 1H), 12.95 (br s, 1H) ppm. LC/MS = 95%, MS (ESI$^+$) Calcd (M+H) 349.2; Found: 349.2.

Synthesis of 4,5-dichloro-thiophene-2-sulfonic acid {2-[3-(2,4-dichloro-benzyl)-3H-benzoimidazol-4-yloxy]-acetyl}-amide (**9**)*:* To a 3 mL vial containing a magnetic stir bar and compound **8** (21 mg, 0.060 mmol) was added anhydrous CH_2Cl_2 (2 mL) followed by DMAP (14.7 mg, 0.120 mmol), which made the solution homogenous. 4,5-Dichlorothiophene-2-sulfonamide (15.5 mg, 0.066 mmol) was added followed by EDCI (23 mg, 0.12 mmol). The reaction was stirred at room temperature for 4 h and then diluted with CH_2Cl_2 and water (5 mL each). The aqueous layer was made acidic through the addition of 1 N aqueous HCl until a pH of 2–3 was reached (litmus paper). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were concentrated in vacuo and dried under vacuum. The resulting solid was triturated with hot CH_2Cl_2 (3 mL) and the cooled solution was filtered and dried to give 26 mg (71%) of **9** as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.59 (s, 2H), 5.91 (s, 2H), 6.85 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.33 (dd, J = 8.5, 2.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 8.98 (s, 1H). LC/MS = 97.8% purity, MS (ESI$^+$) Calcd (M+H) 564.4; Found: 564.4