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Cesium fluoride and tetra-*n*-butylammonium fluoride mediated 1,4-N→O shift of disubstituted phenyl ring of a bicalutamide derivative

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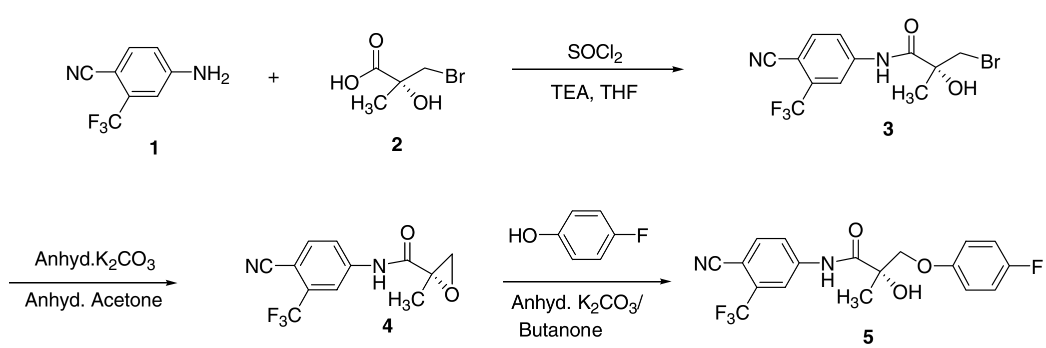
Abstract—A novel 1,4-N→O migration of a disubstituted phenyl ring was observed during N-methylation of a bicalutamide derivative, (2*S*)-2-(*tert*-butyldimethylsilanyloxy)-*N*-(4-cyano-3-trifluoromethylphenyl)-3-(4-fluorophenoxy)-2-methylpropionamide, in the presence of CsF-Celite/acetonitrile and desilylation of (2*S*)-2-(*tert*-butyldimethylsilanyloxy)-*N*-(4-cyano-3-trifluoromethylphenyl)-3-(4-fluorophenoxy)-2,*N*-dimethylpropionamide in tetra-*n*-butylammonium fluoride/THF. Both NMR and X-ray analysis confirmed the structure of the 1,4-N→O disubstituted phenyl ring migrated product.

Bicalutamide (Casodex) is a well-known drug for the treatment of prostate cancer. Our group has been synthesizing several bicalutamide derivatives that showed androgen receptor (AR) agonist activity.[1–4] In continuation of our work to prepare such compounds, we planned to synthesize the prodrug by following the reaction steps shown in Scheme 1 (reaction of the substituted aniline **1** with acid **2**[5] to give amide **3**,[6] followed by the formation of epoxide **4**[7] that subsequently reacts with *p*-fluorophenol to give ether **5**[7]), and then by replacing the amide hydrogen of **5**[7] by diethylphosphonate. The diethylphosphate of **5** was proposed to be a prodrug



Scheme 1. Schematic route for the synthesis of compound **5**.

Keywords: 1,4-N→O migration; CsF mediated rearrangement; Tetra-*n*-butylammonium fluoride mediated rearrangement.
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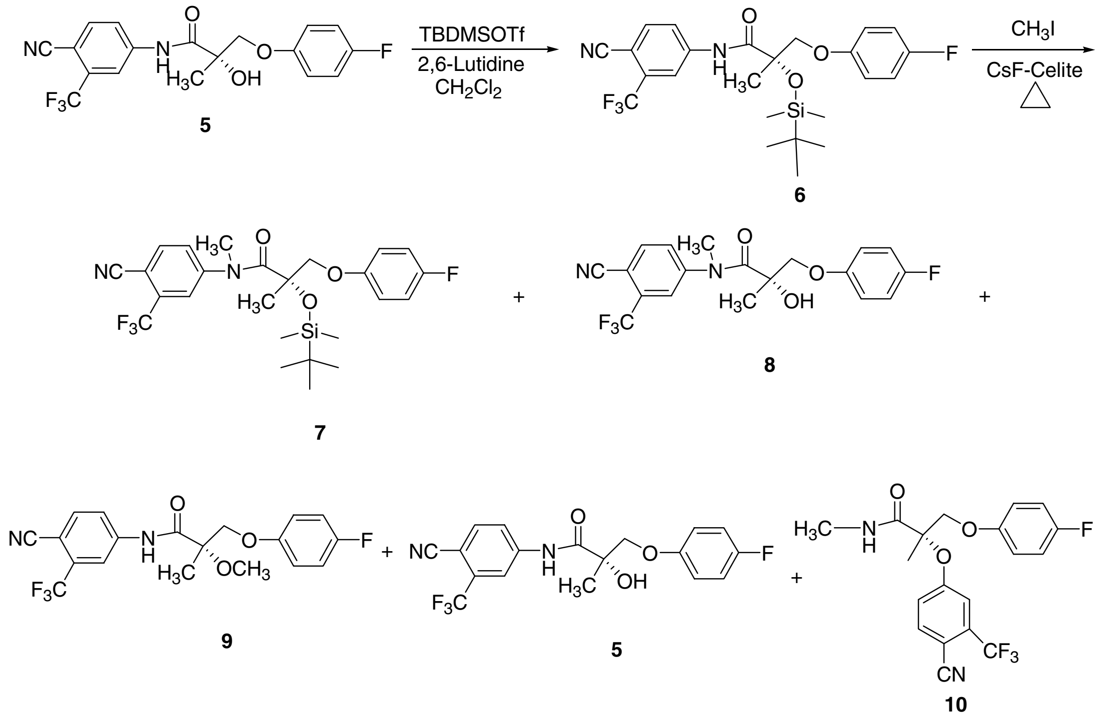
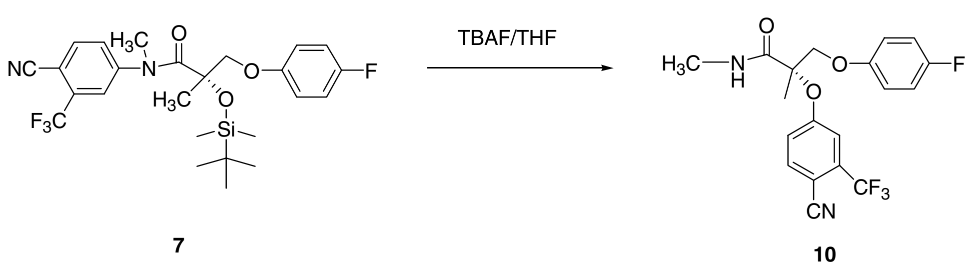


Scheme 2. Schematic route for the synthesis of compounds **6**–**10**.

of **5**. In an attempt at preparing the prodrug, we protected the hydroxyl group of compound **5**[7] using *tert*-butyldimethylsilyl trifluoromethane sulfonate with 2,6-lutidine in DCM to get (2*S*)-2-(*tert*-butyldimethylsilanyloxy)-*N*-(4-cyano-3-trifluoromethylphenyl)-3-(4-fluorophenoxy)-2-methylpropionamide **6**[8] (Scheme 2), and then tried to substitute the amide hydrogen of compound **6**[8] by diethylphosphonate using diethylchlorophosphonate in the presence of various bases like NaOH, NaH, and $NaNH_2$ under stirring conditions at room temperature. In all these cases, we did not get the N-substituted derivative of **6**.[8] Then, we changed our interest towards preparing *N*-methyl and *N*-benzyl derivatives of compound **6**[8] via N-alkylation using methyl iodide or benzyl bromide under stirring conditions at room temperature in a K_2CO_3/acetone or KOH/THF medium. Surprisingly, no N-alkylated compounds were obtained. Recently, Bayer and co-workers[9] described a CsF-Celite/alkyl halide/acetonitrile combination method to alkylate carboxamides and several nitrogen heterocycles. This report encouraged us to use CsF-Celite as a solid base that enforces N-methylation of **6**[8] with methyl iodide in anhydrous acetonitrile. As a result, we observed methylation at the amide coupled with 1,4-N→O migration of the disubstituted phenyl ring of compound **6**[8] thus yielding (2*S*)-2-(4-cyano-3-trifluoromethylphenoxy)-3-(4-fluorophenoxy)-2,*N*-dimethylpropionamide **10**[10] as the major product (37%). The actual target compound **7**[10] was obtained only in 16% yield along with the desilylated alcohol **8**[10] (10%), the methoxyether **9**[10] (11%), and compound **5**[7] (22%) (Scheme 2). All these compounds were separated by column chromatography (1:9 to 6:4 ethyl acetate/hexane). In addition, when compound **7**[10] was desilylated using tetra-*n*-butylammonium fluoride in dry THF, the same 1,4-N→O shift of the disubstituted phenyl ring was observed exclusively thus yielding compound **10**[11] (55%) rather than the expected compound **8**[10] (Scheme 3).

Initially, we had difficulties assigning the correct structure to compound **10**.[10,11] Desilylation and single methylation were evident from the analysis of both mass spectrometry and NMR data. In the NMR, the NH proton appeared as a quartet indicating a scalar coupling constant of 4.5 Hz with the added methyl group. Since we had never observed bond breaking for the amide



Scheme 3. Schematic route for the synthesis of compound **10** from desilylation of compound **7**. Compound **10** is the only product from this reaction.

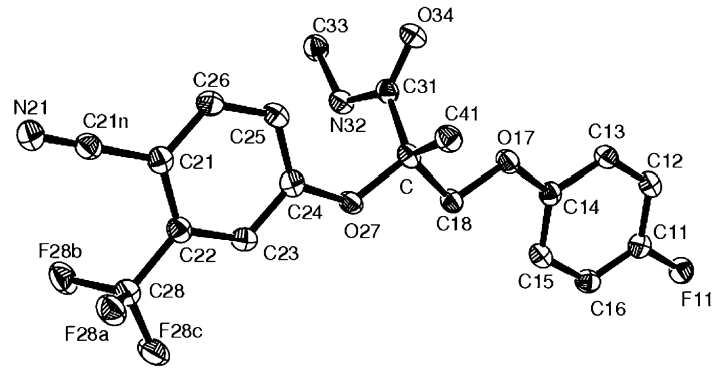


Figure 1. X-ray crystal structure of compound **10**.

group in the synthesis of many analogs of **7**,[10] we initially attributed the NH quartet to a scalar coupling across the hydrogen bond ($^{3h}J_{HH}$), formed by NH···O–CH_3 in a structure similar to that of compound **9**.[10] However, density functional theory (DFT) calculations,[12–15] utilizing the coupled perturbed DFT (CP-DFT) approach for NMR spin–spin coupling constants published by Cremer and co-workers,[15] indicated at most 0.1 Hz for the $^{3h}J_{HH}$ spin–spin coupling constant, clearly ruling out this type of structure.[12–15] The MS did not lead to characteristic fragmentation peaks to make an unambiguous structure assignment for compound **10**.[10,11] In the end, we were able to grow crystals successfully in benzene suitable for X-ray structural analysis. The result of the X-ray analysis revealed the actual structure for compound **10**,[10,11] clearly indicating a 1,4-N→O migration of the disubstituted phenyl ring of the amide group (Fig. 1).[16,17] The structure of **10**[10,11] explained the appearance of the NMR spectra. Remaining compounds were confirmed by spectroscopy methods without difficulty.

In conclusion, we have found that the CsF-Celite and tetra-*n*-butylammonium fluoride mediated reactions of compounds **6**[8] and **7**,[10] respectively, initiates a novel 1,4-N→O shift of disubstituted phenyl. The novel structure of compound **10**[10,11] was confirmed by detailed spectroscopic studies, quantum mechanics calculations, and X-ray structural analysis.

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6. (2*R*)-3-Bromo-*N*-(4-cyano-3-trifluoromethylphenyl)-2-hydroxy-2-methylpropionamide. Thionyl chloride (4.60 g, 38.71 mmol) was added drop wise to a solution of (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid **2** (7.1 g, 38.71 mmol) in anhydrous THF (25 mL) under nitrogen atmosphere at 0 to −5 °C, and stirred at the same temperature for 2 h to give the corresponding acid chloride, which was treated in situ with a solution of compound **1** (6.0 g, 32.26 mmol) in anhydrous THF (20 mL) followed by triethyl amine (8.16 g, 80.65 mmol) at 0 to −5 °C. The reaction mixture was allowed to attain room temperature, and then refluxed overnight. The reaction mixture was concentrated under reduced pressure, and extracted with ethyl acetate. The organic layer was washed with 5% HCl, saturated $NaHCO_3$ solution, followed by water. The solvent was dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and recrystallized with ethyl acetate and hexane to yield **3** as a yellow powder (8.61 g, 76%). Mp 133–134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.52 (s, 1H, –NH), 8.54 (s, 1H, ArH), 8.30 (dd, $J = 1.8$, 1.8 Hz, 1H, ArH), 8.10 (d, $J = 8.7$ Hz, 1H, ArH), 6.40 (s, 1H, OH), 3.82 (d, $J = 10.5$ Hz, 1H, –CH_2), 3.57 (d, $J = 10.2$ Hz, 1H, –CH_2), 1.48 (s, 3H, –CH_3). MS (ESI−) *m/z* 350 $(M-H)^-$.
7. (2*S*)-*N*-(4-Cyano-3-trifluoromethylphenyl)-3-(4-fluorophenoxy)-2-hydroxy-2-methylpropionamide. Anhydrous K_2CO_3 (3.94 g, 28.4 mmol) was added to a solution of compound **3** (5.00 g, 14.2 mmol) in acetone (25 mL), and the reaction mixture was refluxed for 2 h. The mixture was concentrated to dryness, the obtained residue was dissolved in water, and extracted with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4, and removed under reduced pressure to give epoxide **4** as oil which was used in the next step without further purification. A solution of the above epoxide in 2-butanone (25 mL) was treated with anhydrous K_2CO_3 (3.94 g, 28.4 mmol) and 4-fluorophenol (1.600 g, 14.2 mmol), the mixture was stirred at reflux overnight, and evaporated to dryness. The residue was dissolved in water and extracted with ethylacetate, washed with brine solution, dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude residue was purified by flash column chromatogra-

phy (1:9 ethyl acetate/hexane) to give 3.0 g (55%) of **5** as a yellow oil, which was recrystallized from DCM to furnish white colored crystals. Mp 128–129 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (br s, 1H, –NH), 8.56 (s, 1H, ArH), 8.31 (d, $J = 8.7$ Hz, 1H, ArH), 8.10 (d, $J = 8.7$ Hz, 1H, ArH), 7.11–7.05 (m, 2H, ArH), 6.95–6.91 (m, 2H, ArH), 6.26 (br s, 1H, OH), 4.20 (d, $J = 9.6$ Hz, 1H, –CH_2), 3.96 (d, $J = 9.6$ Hz, 1H, –CH_2), 1.43 (s, 3H, –CH_3). MS (ESI−) *m*/*z* 381 $(M-H)^-$.

8. (2*S*)-2-(*tert*-Butyldimethylsilanyloxy)-*N*-(4-cyano-3-trifluoromethylphenyl)-3-(4-fluorophenoxy)-2-methylpropionamide. To a solution of compound **5** (4.00 g, 10.46 mmol) in dichloromethane (75 mL) was added *tert*-butyldimethylsilyl trifluoromethane sulfonate (3.32 g, 12.56 mmol), and 2,6-lutidine (2.24 g, 20.93 mmol) at 0 °C. The mixture was stirred at ambient temperature overnight, and diluted with water. The water layer was extracted with ethyl acetate, the combined organic layers were dried with anhydrous Na_2SO_4, and the solvents were evaporated under reduced pressure. The resulting crude residue was purified by flash column chromatography (5:95 ethyl acetate/hexane) to afford 3.85 g (99%) of **6** as a colorless oil. (Recovered starting material yield 1.00 g, 25%.) ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H, –NH), 8.32 (s, 1H, ArH), 8.16 (d, $J = 8.4$ Hz, 1H, ArH), 8.08 (d, $J = 8.4$ Hz, 1H, ArH), 7.14–7.08 (m, 2H, ArH), 6.97–6.92 (m, 2H, ArH), 4.26 (d, $J = 10.2$ Hz, 1H, –CH_2), 4.11 (d, $J = 10.2$ Hz, 1H, –CH_2), 1.55 (s, 3H, –CH_3), 0.91 (s, 9H, 3 × –CH_3), 0.14 (d, $J = 7.8$ Hz, 6H, 2 × –CH_3). MS (ESI+) *m*/*z* 519 $(M+Na)^+$.
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10. To a stirred solution of compound **6** (0.946 g, 1.94 mmol) in anhydrous acetonitrile (20 mL) was added CsF-Celite (0.442 g, 2.91 mmol) and methyl iodide (0.551 g, 3.88 mmol). The mixture was heated for 5 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, filtered, and the precipitate was washed with ethyl acetate. The combined filtrates were evaporated under reduced pressure, and the crude residue was purified by flash column chromatography (1:9 to 6:4 ethyl acetate/hexane) afforded compounds **5** (0.149 g, 22%), **7** (0.144 g, 16%), **8** (0.070 g, 10%), **9** (0.077 g, 11%), and **10** (0.259 g, 37%). (Recovered starting material yield 0.087 g, 9%.) Data for **7**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, $J = 8.1$ Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.82 (d, $J = 8.1$ Hz, 1H, ArH), 7.18–7.12 (m, 2H, ArH), 7.00–6.96 (m, 2H, ArH), 4.25 (d, $J = 9.9$ Hz, 1H, –CH_2), 4.01 (d, $J = 9.9$ Hz, 1H, –CH_2), 3.50 (s, 3H, –NCH_3), 1.60 (s, 3H, –CH_3), 0.79 (s, 9H, 3 × –CH_3), 0.02 (d, $J = 4.8$ Hz, 6H, 2 × –CH_3); MS (ESI+) *m*/*z* 533 $(M+Na)^+$. **8**: Mp 85–86 °C ^{1}H NMR (DMSO-d_6) δ 7.91 (d, $J = 8.4$ Hz, 1H, ArH), 7.28 (d, $J = 1.8$ Hz, 1H, ArH), 7.18–7.09 (m, 3H, ArH), 6.99–6.93 (m, 2H, ArH), 5.38 (s, 1H, OH), 4.10 (d, $J = 9.6$ Hz, 1H, –CH_2), 3.81 (d, $J = 9.9$ Hz, 1H, –CH_2), 3.69 (s, 3H, –NCH_3), 1.42 (s, 3H, –CH_3); MS (ESI+) *m*/*z* 419 $(M+Na)^+$. **9**: Mp 96–97 °C ^{1}H NMR (300 MHz, $CDCl_3$-d_6) δ 9.09 (s, 1H, –NH), 8.09 (d, $J = 2.1$ Hz, 1H, ArH), 7.98 (dd, $J = 2.1$, 1.8 Hz, 1H, ArH), 7.80 (d, $J = 8.4$ Hz, 1H, ArH), 7.00–6.92 (m, 2H, ArH), 6.87–6.77 (m, 2H, ArH), 4.27 (d, $J = 9.6$ Hz, 1H, –CH_2), 4.11 (d, $J = 10.2$ Hz, 1H, –CH_2), 3.49 (s, 3H, –OCH_3), 1.53 (s, 3H, –CH_3); MS (ES+) *m*/*z* 419 $(M+Na)^+$. **10**: Mp 88–89 °C ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (q, $J = 4.5$ Hz, 1H, –NH), 8.09 (d, $J = 8.4$ Hz, 1H, ArH), 7.52 (d, $J = 2.4$ Hz, 1H, ArH), 7.39 (dd, $J = 2.4$, 2.4 Hz, 1H, ArH), 7.15–7.06 (m, 2H, ArH), 7.00–6.91 (m, 2H, ArH), 4.31 (q, $J = 10.8$ Hz, 2H, –CH_2), 2.66 (d, $J = 4.5$ Hz, 3H, –$NHCH_3$), 1.60 (s, 3H, –CH_3); MS (ESI+) *m*/*z* 419 $(M+Na)^+$.
11. To a solution of **7** (0.063 g, 0.123 mmol) in anhydrous THF (10 mL) was added TBAF 1 M solution in THF (0.064 g, 0.247 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, diluted with ethyl acetate, and extracted with water. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was dissolved in DCM, and evaporated to give compound **10** (0.027 g, 55%).
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