A Two-step Synthesis of the Anti-cancer Drug (*R*,*S*)-Bicalutamide

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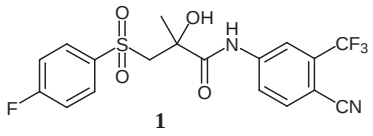
Abstract: A short, efficient synthesis of the non-steroidal antiandrogen (*R*,*S*)-bicalutamide is presented. This new route generates bicalutamide in only two steps with an overall yield of 73%. The key step is a 1,2 addition of a methyl sulfone to a keto-amide.

Key words: addition reaction, aldol reaction, antiandrogen, antitumor agent, keto-amide

The non-steroidal antiandrogen (*R*,*S*)-bicalutamide (**1**), which is sold under the name Casodex®,[1] is the leading antiandrogen used for the treatment of prostate cancer (Figure). The published synthetic route for this compound provides the enantiomeric mixture after four steps in an overall yield of approximately 50%.[2] We now report a more efficient synthetic route (Scheme 1), which provides (*R*,*S*)-bicalutamide in two steps with an overall yield of 73%.



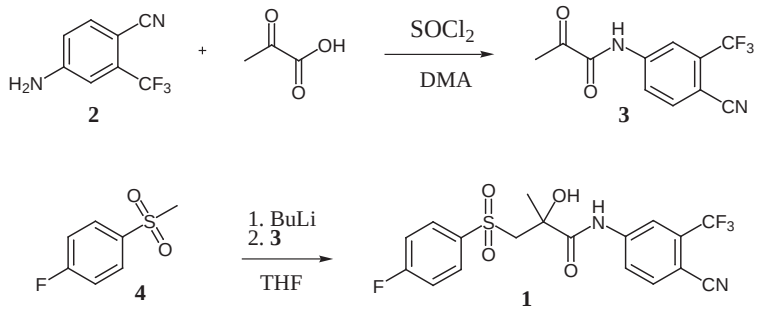
1

Figure

With two strongly electron-withdrawing groups attached, the aniline derivative **2** is a relatively poor nucleophile. When we performed couplings of such anilines with substituted α-hydroxy acids, the yields have generally been rather modest. Similar results have been reported by Tucker, et al.[2,3] and by Ohnmatch, et al.[4] Since the aniline is expensive, we initially considered routes in which this compound would be reserved until the end of the synthesis. However, we reasoned that the yield of coupling could be significantly improved if steric interactions were minimized by having an sp^2 center adjacent to the carboxyl group. We found that when thionyl chloride was added with pyruvate to a solution of **2** in DMA, the α-keto-amide **3** was generated (Scheme 1). When eight equivalents of pyruvate and thionyl chloride were used, the product was obtained in 81% yield after chromatography and crystallization. Stoichiometry was found to be important in the reaction; when only four equivalents of pyruvate and thionyl chloride were used, yields were approximately 65%.

With the use of the methyl sulfone **4**, carbanion addition to the carbonyl would generate bicalutamide in only one more step. Our first approach utilized sodium hydride in an effort to deprotonate **4**, which was then transferred to a solution of the keto-amide **3** with the goal of forming bicalutamide (**1**). Instead, the dimer **6** was the only observed product. This compound likely resulted from deprotonation of the methyl ketone **3** to form the enolate **5**, which underwent an aldol reaction with another keto-amide (Scheme 2). We switched to a stronger base on the premise that the sulfone was not being deprotonated. Adapting the work by Fournier, et al.,[5] we successfully synthesized **1** following the above procedure while using either pentyl magnesium bromide or *n*-butyllithium as the base.

When 1:1 ratios of sulfone to keto-amide were used, yields of bicalutamide were approximately 45%. The low yield was due to a side reaction, which generated a product with a mass corresponding to **6**. It seemed likely that



2 **3** **4** **1**

Scheme 1

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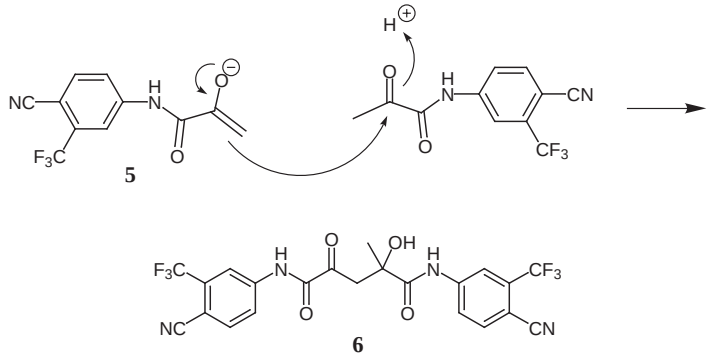

Scheme 2

the alkoxide of the desired reaction product might have been serving as a general base, deprotonating any unreacted keto-amide and thus catalyzing the undesired reaction. We reasoned that if the keto-amide present in the reaction mixture were always exposed to excess quantities of the deprotonated sulfone, then the side reaction would be minimized. When a solution of the keto-amide was added slowly to three equivalents of the deprotonated sulfone, bicalutamide was generated in yields of 90% and higher.

We believe that the ease and speed of this synthetic route, coupled with the cost effectiveness of the approach, will be of great utility in the production of this antineoplastic.

Unless otherwise stated, all reagents were purchased from Aldrich and were used without further purification. All solvents were glass-distilled. Pyruvate and 4-fluorophenyl methyl sulfone (**4**) were purchased from Lancaster. 4-Cyano-3-trifluoromethyl-aniline (**2**) was purchased from Maybridge. Chemical shift values for fluorine atoms are expressed in ppm relative to an external standard of $CFCl_3$. Coupling constants are reported in Hertz. All melting points are uncorrected. Petroleum ether is abbreviated as PE.

***N*-[4-Cyano-3-(trifluoromethyl)phenyl]-2-oxopropanamide (3)**
Pyruvate (3.0 mL, 43 mmol) and SO_2Cl_2 (3.1 mL, 43 mmol) were added simultaneously via syringes over the course of 10 min to a stirring soln of 4-cyano-3-trifluoromethyl-aniline (1.00 g, 5.38 mmol) in 20 mL of dry DMA at r.t. After 10 min, the reaction mixture was diluted with Et_2O (200 mL), extracted with sat. $NaHCO_3$ (3 × 50 mL) and with cold sat. brine (4 × 100 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated by rotary evaporation. The product was purified by silica gel chromatography (EtOAc–hexanes, 1:1) and crystallized from the same solvents. Yield 1.11 g (81%); mp 147–148 °C.

IR (KBr): 3330, 3112, 3065, 1719, 1540 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.1 (s, 1 H, NH), 8.2 (s, 1 H, Ar-H), 8.0 (d, *J* = 8.5, 1 H, Ar-H), 7.8 (d, *J* = 8.5, 1 H, Ar-H), 2.6 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 195.7, 157.7, 140.3, 135.9, 134.2, 122.0, 121.9, 117.4, 115.1, 105.6, 23.9.

^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –62.8.

MS-FAB: (*m*/*z*) = 257 (M + 1).

UV (CH_3CN): λ_{max} = 214, 248, 288 nm.

Anal. Calcd for $C_{11}H_7F_3N_2O_2$: C, 51.57; H, 2.75; N, 10.94. Found: C, 51.69; H, 2.81; N, 10.86.

***N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide (1)**
BuLi (13.0 mmol) was added to a stirring soln of 4-fluorophenyl methyl sulfone (2.49 g, 14.3 mmol) in 13 mL of anhyd THF. After 1 h, a soln of **3** (1.11 g, 4.34 mmol) in 40 mL of anhyd THF was added slowly over the course of 30 min to the stirring reaction. After 20 min, the reaction was brought to neutral pH with 1 M HCl. The contents were diluted with EtOAc (250 mL) and extracted with 1 M HCl (75 mL) and sat brine (75 mL). The aq layers were combined and extracted with EtOAc (2 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated by rotary evaporation. After purification by silica gel chromatography (CH_2Cl_2–EtOAc, 4:1), the product was crystallized from EtOAc–PE. Yield 1.67 g (90%); mp 187 °C.

IR (KBr): 3432, 3338, 3106, 2921, 1699, 1586, 1525 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.1 (s, 1 H, NH), 8.0 (s, 1 H, Ar-H), 7.9 (m, 2 H, Ar-H), 7.8 (m, 2 H, Ar-H), 7.2 (m, 2 H, Ar-H), 5.0 (s, 1 H, OH), 4.0 (d, *J* = 14.5, 1 H, CH_2), 3.5 (d, *J* = 14.5, 1 H, CH_2'), 1.6 (s, 3 H, CH_3).

^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –62.7 (CF_3), –101.5 (Ar-F).

MS-FAB: (*m*/*z*)= 431 (M + 1), 453 (M + Na^+).

UV (CH_3CN): λ_{max} = 216, 270 nm.

Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.35; H, 3.16; N, 6.35.

***N*,*N*′-Bis[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-4-oxopentanediamide (6)**
Mp 165–168 °C.

IR (KBr): 3292, 2234, 1705, 1688, 1524 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO): δ = 10.5 (s, 1 H, NH), 10.3 (s, 1 H, NH), 8.2 (s, 1 H, Ar-H), 8.1 (s, 1 H, Ar-H), 8.0 (d, 1 H, *J* = 8.4, Ar-H), 7.9 (d, 1 H, *J* = 8.2, Ar-H), 7.7 (d, 1 H, *J* = 8.4, Ar-H), 7.7 (d, 1 H, *J* = 8.2, Ar-H), 5.6 (s, 1 H, OH), 2.6 (d, 1 H, *J* = 14.0, CH_2), 2.4 (d, 1 H, *J* = 14.0, CH_2'), 1.5 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, $CDCl_3$/DMSO): δ = 176.2, 170.3, 169.4, 142.0, 141.2, 135.7, 135.4, 133.2, 132.9, 127.5, 122.9, 122.8, 122.6, 118.3, 115.6, 115.3, 106.7, 104.3, 90.0, 73.1, 48.5, 25.0.

^{19}F NMR (282.3 MHz, $CDCl_3$–DMSO): δ = –62.3 (CF_3), –62.5 (CF_3').

HRMS-FAB: (*m*/*z*) [M + H]$^+$ calcd for $C_{22}H_{14}F_6N_4O_4$, 513.0997; found, 513.1001.

UV (CH_3CN): λ_{max} = 267 nm, λ_{min} = 231 nm.

Anal. Calcd for $C_{22}H_{14}F_6N_4O_4$: C, 51.57; H, 2.75; N, 10.94. Found: C, 51.48; H, 2.61; N, 10.65.

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