JOC*Note*

Nucleophilic Aromatic Substitution of Methacrylamide Anion and Its Application to the Synthesis of the Anticancer Drug Bicalutamide

Bang-Chi Chen,* Rulin Zhao, Stacey Gove, Bei Wang, Joseph E. Sundeen, Mark E. Salvati, and Joel C. Barrish

Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543

bangchi.chen@bms.com

Received September 19, 2003

Abstract: The anticancer drug (*R*,*S*)-biscaltamide was prepared in three steps in >90% overall yield. A key step in the new synthesis involved a new nucleophilic aromatic substitution reaction of methacrylamide anion.

(*R*,*S*)-Bicalutamide, sold under the name Casodex, is the leading nonsteroidal antiandrogen used for the treatment of prostate cancer.[1−5] Two methods have been previously reported for the synthesis of (*R*,*S*)-bicalutamide, both starting from an expensive material, 4-amino-2-trifluoromethylbenzonitrile.[6,7] The overall yields were approximately 50−70% and chromatographic separations of products were required.[6,7] We now describe a new synthesis of (*R*,*S*)-biscaltamide which uses a much less expensive starting material, 4-fluoro-3-trifluoromethylbenzonitrile, and is featured by a new nucleophilic aromatic substitution reaction involving methacrylamide anion.

Nucleophilic aromatic substitution of aryl fluorides with amino nucleophiles including anions generated from simple amides is an important method for the preparation of aniline derivatives.[8] Such a reaction with acrylamides as nucleophiles has not, however, been reported. We envisioned that the nitrogen anion generated from methacrylamide **2** would react with electron-deficient aryl fluorides such as **3** to give the desired coupling product **4** (Scheme 1).[9]

Thus, treatment of a mixture of methacrylamide **2** and 4-fluoro-2-trifluorobenzonitrile **3** in DMF with 2.6 equiv of NaH afforded smoothly compound **4** in 97% yield after quenching the reaction and isolating the product by filtration. Under these reaction conditions, the potential side reaction at the methyl group was not detected. More importantly, the potential base promoted polymerization of the resulted product **4** was not observed due presumably to an immediate deprotonation of the aryl amide proton in **4** by excess base once it is formed, which deactivated the α,β-unsaturated carbon−carbon double bond and prevented it from undergoing nucleophilic addition.

The *N*-arylmethacrylamide **4** was next oxidized to the corresponding epoxide **5** using a combination of hydrogen peroxide and trifluoroacetic anhydride instead of the previously reported *m*-CPBA.[6] The desired epoxide **5** was isolated in 98% yield. Epoxide ring opening with 4-fluorothiophenol followed by oxidation of the resulted sulfide with the combination of hydrogen peroxide and trifluoroacetic anhydride afforded (*R*,*S*)-bicalutamide in 97% isolated yield.

In summary, a new nucleophilic aromatic substitution reaction of methacrylamide anion with electron deficient aryl fluoride has been successfully demonstrated. This new reaction made it possible to use the much less expensive 4-fluoro-2-trifluoromethylbenzonitrile as a starting material for the synthesis of the important anticancer drug (*R*,*S*)-Bicalutamide.

Experimental Section

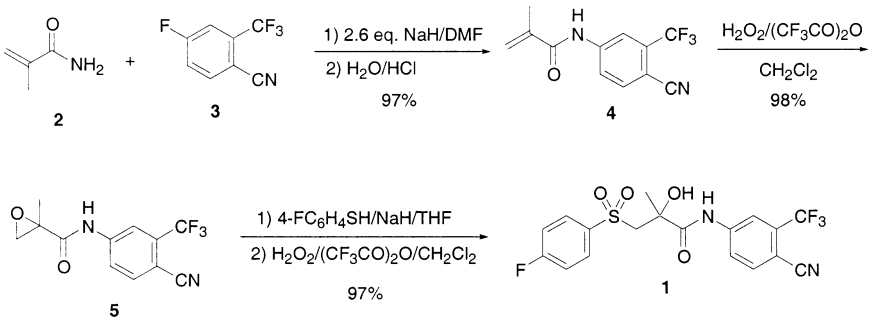
***N*-(4-Cyano-3-trifluorophenyl)methacrylamide 4.** To a solution of methacrylamide (**2**, 153.0 g, 1.80 mol) in 800 mL of DMF was added 4-cyano-3-trifluoromethylphenyl fluoride (**3**, 200.0 g, 1.06 mol) at room temperature. The solution was cooled in a methanol/dry ice bath to −20 °C. To this cooled solution was added sodium hydride (102.0 g, 2.70 mol), portionwise, while keeping the reaction temperature below 70 °C. The reaction mixture was allowed to cool to room temperature and stirred for 4 h under a nitrogen atmosphere. Water (915 mL) was added followed by 18% HCl (250 mL) and hexane (970 mL). The resulted slurry was allowed to stir overnight. The solid was filtered and washed with water (3 × 150 mL) and and hexane (100 mL). The solid was dried at 60 °C overnight to give the titled compound **4** (260.0 g, 97%): mp 137−139 °C (lit.[6b] mp 137−139 °C); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 1.9, 8.5 Hz, 1H), 7.69 (bs, 1H), 7.62 (d, J = 8.5 Hz, 1H), 5.69 (s, 1H), 5.44 (t, J = 1.5 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 18.9, 104.2, 116.2, 118.0, 121.2, 122.1, 122.6, 123.9, 126.6, 133.8, 136.2, 140.3, 142.9, 167.6. Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; F, 22.42; N, 11.02. Found: C, 56.53; H, 3.36; F, 22.52; N, 10.96.

***N*-(4-Cyano-3-trifluorophenyl)methacrylamide Epoxide 5.** To a stirred solution of *N*-[4-cyano-3-(trifluoromethyl)phenyl]-methacrylamide (1.8 g, 7.08 mmol) and dichloromethane (10 mL) was added hydrogen peroxide (1.22 mL, 42.5 mmol). The flask was then put in a water bath at room temperature. Trifluoroacetic anhydride (5 mL, 35.40 mmol) was added slowly. The reaction was stirred and checked by HPLC. After 1 h and 40 min, the reaction mixture was transferred to a separation funnel using dichloromethane (35 mL). The organic layer was then washed with distilled water (15 mL), saturated aqueous sodium bisulfite (4 × 15 mL), saturated sodium bicarbonate (3 × 15 mL), and brine (15 mL), dried over magnesium sulfate, filtered,

(1) Schellhammer, P. *Exp. Opin. Invest. Drugs* **1999**, *8*, 849.
(2) Goa, K. L.; Spencer, C. M. *Drugs Aging* **1998**, *12*, 401.
(3) Dalton, J. T.; Mukherjee, A.; Zhu, Z.; Kirkovsky, L.; Miller, D. D. *Biochem. Biophys. Res. Commun*. **1998**, *244*, 1.
(4) Furr, B. J. A. *Eur. Urol*. **1996**, *29* (Suppl 2), 83. Furr, B. J. A.; Tucker, H. *Urology* **1996**, *47 (*Suppl 1A*)*, 13.
(5) Maucher, A. von Angerer, E. *J. Cancer Res. Clin. Cocol*. **1993**, *119*, 669.
(6) (a) Tucker, H.; Crook, J. W.; Chesterson, G. J. *J. Med. Chem*. **1988**, *31*, 954. (b) Tucker, H. EP 100172 A1, February 8, 1984; *Chem. Abstr*. **1984**, *101*, 54739.
(7) James, K. D.; Ekwuribe, N. N. *Synthesis* **2002**, 850.
(8) Spange, S.; Seifert, A.; Mueller, H.; Hesse, S.; Jaeger, C. *Angew. Chem., Int. Ed*. **2002**, *41*, 1729. Norris, D.; Chen, P.; Barrish, J. C.; Das, J.; Moquin, R.; Chen, B.-C.; Guo, P. *Tetrahedron Lett*. **2001**, *42*, 4297. Fleming, I.; Loreto, M. A.; Wallace, I. H. M.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349.
(9) For recent reports on amidation of aryl halides including the copper catalyzed preparation of *N*-aryl α,β-unsaturated amides, see: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421 and references therein.

10.1021/jo035377c CCC: $25.00
Published on Web 12/02/2003

SCHEME 1. Nucleophilic Aromatic Substitution Reaction of Methacrylamide Anion and Synthesis of (*R*,*S*)-Biscaltamide (1)



concentrated, and dried to give the titled compound as a white solid (1.94 g, 98.6% yield): mp 151−152 °C (lit.[6b] mp 149−150 °C); ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.05 (dd, J = 1.9, 8.5 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 3.16 (s, 2H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 17.0, 54.5, 57.0, 105.0, 115.8, 117.7, 121.1, 122.3, 123.8, 126.5, 133.9, 136.2, 141.7, 169.8. Anal. Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.34; H, 3.36; F, 21.09; N, 10.37. Found: C, 53.10; H, 3.14; F, 21.09; N, 10.32.

***N*-(4-Cyano-3-trifluoromethylphenyl)α-methyl-α-hydroxy-*β*-(4-fluorophenylsulfonyl)propanamide (Bicalutamide) 1.** To a mixture of sodium hydride (19.3 g, 0.80 mol) in THF (333 mL) was added a solution of 4-fluorobenzenethiol (81.8 mL, 0.77 mol) in THF (248 mL) at 0 °C. The temperature was kept below 25 °C during the addition. This mixture was stirred for 5 min. A solution of *N*-(4-cyano-3-trifluorophenyl)methacryalmide epoxide (166.0 g, 0.61 mol) in THF (830 mL) was added slowly. The reaction mixture was stirred at room temperature for 2 h. THF was distilled off. The mixture was diluted with ethyl acetate (885 mL), transferred to a separation funnel, and washed with brine (220 mL) and water (440 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to give a clean oil. The oil was dissolved with dichloromethane (1.5 L) to give a solution, to which was added 30% hydrogen peroxide (141.6 mL, 4.91 mol). The mixture was cooled to −55 °C. Trifluoroacetic anhydride (520.6 mL, 3.69 mol) was added slowly while keeping the reaction temperature between −15 and 0 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 16 h. Ice−water (500 mL) and brine (500 mL) were added, and the resulting slurry was stirred for 20 min. The slurry was filtered, washed with MTBE, and dried to give the titled compound (255.2 g, 97% yield): mp 195 °C (lit.[6a] mp 191−193 °C); ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 8.44 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.93 (m, 2H), 7.38 (t, J = 8.4 Hz, 2H), 6.42 (s, 1H), 3.95 (d, J = 14.7 Hz, 1H), 3.72 (d, J = 14.7 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 27.5, 63.7, 73.5, 102.3, 116.2, 116.3, 117.8, 117.8, 121.5, 123.2, 124.2, 131.7, 136.5, 137.5, 143.6, 163.9, 166.4, 174.1. Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; F, 17.66; N, 6.51; S, 7.45. Found: C, 49.94; H, 3.25; F, 17.76; N, 6.39; S, 7.75.

JO035377C