An efficient synthesis of 2-amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one, a potent BACE1 inhibitor

Ping Zhou,* Michael Malamas, and Albert J. Robichaud

Chemical Sciences, Wyeth Research, CN 8000 Princeton, NJ 08543
E-mail: zhoup3@wyeth.com, pbzhou@yahoo.com

Dedicated to Professor Franklin A. Davis on the occasion of his 70th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.609

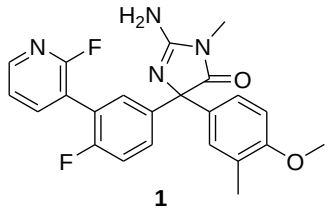
Abstract

An efficient method has been developed for the synthesis of 2-amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one, a potent BACE1 inhibitor for the potential treatment of Alzheimer's Disease. The new method features a Friedel-Crafts reaction between 3-bromo-4-fluorophenylacetic acid and 2-methoxytoluene followed by DMSO mediated α-oxidation of the resulting 1,2-diarylethanone to give an α-diketone. Subsequent aminohydantoin formation and Suzuki coupling led to the target molecule in greater than 70% overall yield.

Keywords: Alzheimer's Disease (AD), BACE1 inhibitor, Friedel-Crafts reaction, α-oxidation, aminohydantoin, Suzuki coupling

Introduction

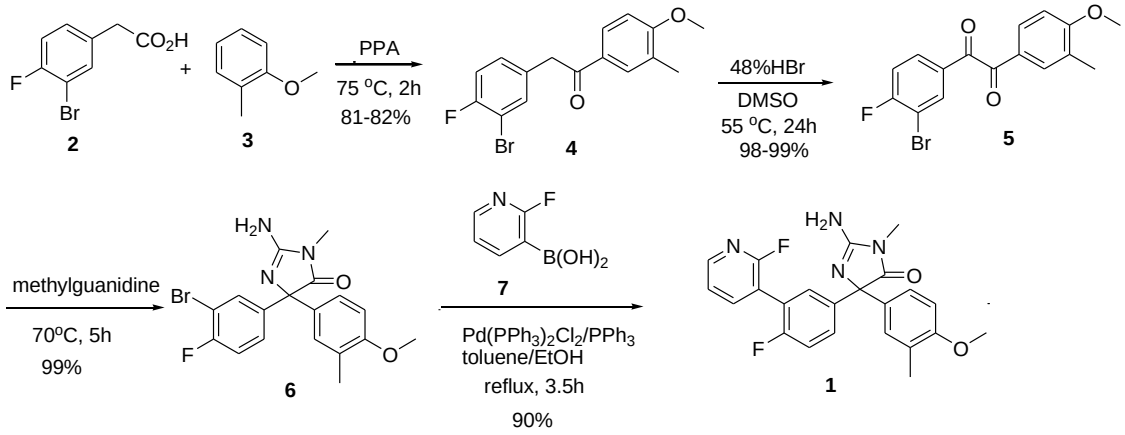
Alzheimer's Disease (AD) is a neurodegenerative disease that leads to progressive decline in cognitive function and ultimately incapacitation and death.[1-4] The amyloid cascade is a leading hypothesis for the cause of AD. According to this hypothesis, processing of the amyloid precursor protein (APP) by β-secretase (β-site APP Cleaving Enzyme or BACE1) followed by γ-secretase releases the putative Aβ peptide, which has been implicated in the neurodegeneration associated with the disease. BACE1 is a type I membrane associated aspartyl protease and is rate-limiting in this proteolytic process. Based on the key role of BACE1 in the β-amyloid cascade, inhibition of BACE1 is considered a prominent therapeutic target for treating AD.[5-8] In this regard, we recently reported that 2-amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one **1** was a potent BACE1 inhibitor (BACE1 IC_{50} 40 nM).[9]



1

Compound **1** was originally prepared in seven transformations from commercially available 2-bromo-1-fluoro-4-methylbenzene and 4-methoxy-3-methylbenzoic acid.[9] While this original method was successfully used to prepare enough of the desired final product **1** for initial biological tests, the low overall yield and multiple tedious purifications made this route inefficient for large scale synthesis to support further in vivo evaluation. In this report, we describe a new and efficient synthesis of the target compound using readily commercially available 3-bromo-4-fluorophenylacetic acid **2** and 2-methoxytoluene **3** as starting materials (Scheme 1)

Thus, Friedel-Crafts reaction of **2** with 2-methoxytoluene **3** in PPA gave the corresponding ketone **4** in 82% yield.[10] Treatment of **4** with HBr in DMSO afforded the key 1-(3-bromo-4-fluorophenyl)-2-(4-methoxy-3-methylphenyl)ethane-1,2-dione intermediate **5**,[11] which was isolated in essentially quantitative yield by simple addition of water and filtration of the crystalline product.



Scheme 1. New synthesis of 2-amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one 1.

With a large quantity of **5** in hand, we began to optimize the aminohydantoin formation and Suzuki coupling step. We found that the formation of aminohydantoin **6** could be best carried out by treating **5** and methylguanidine in a mixture of dioxane and ethanol at 70°C for 5 hr, instead of refluxing overnight, the conditions initially employed.[12] In this way, compound **6** was isolated

in 99% yield. For the subsequent Suzuki coupling of **6** with boronic acid **7**, we found $Pd(PPh_3)_2Cl_2/PPh_3$ is superior to the more commonly used $Pd(PPh_3)_4$, and provided **1** in 90% yield.[13]

In summary, a new and efficient method has been developed for the synthesis of 2-amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one, a potent BACE1 inhibitor for the potential treatment of Alzheimer's disease. The new method features a Friedel-Crafts reaction between 3-bromo-4-fluorophenylacetic acid and 2-methoxytoluene, followed by DMSO mediated α-oxidation of the resulting 1,2-diarylethanone to give key α-diketone intermediate **5**. Subsequent aminohydantoin formation and Suzuki coupling led to the target molecule in 71% overall yield. This new synthesis not only avoids multiple time consuming chromatographic separations, but also shortens the reaction sequence from seven to four steps. Furthermore, the overall yield was greatly improved from a variable 10-26% to 71% with less expensive starting materials employed. In addition we expect that the new two step method that was developed for the rapid large scale synthesis of 1,2-diketones will find broad applications in organic and medicinal chemistry due to the versatility of these building blocks. The preparation of a variety of synthetically and/or biologically important compounds such as imidazoles,[14] 2-thioxoimidazolidin-4-one and imidazolidine-2,4-diones,[15] quinoxalines,[16] and 1,2,3,4-tetrahydroquinoxalines can be effected from these key intermediates.[17]

Experimental Section

2-(3-Bromo-4-fluorophenyl)-1-(3-methoxy-4-methylphenyl)ethanone 4. A mixture of the (3-bromo-4-fluorophenyl)acetic acid (**2**, 58 g, 250 mmol), 1-methoxy-2-methylbenzene (**3**, 37 mL, 300 mmol) and polyphosphoric acid (290 g) was placed in a three necked round bottom flask. The reaction mixture was mechanically stirred at 75 ºC for 3 h (open flask). The reaction was cooled to room temperature. To the resulting deep red solution was added ice-water (300 mL) slowly to decompose the excess polyphosphoric acid. A gummy solid was formed. The aqueous solution was decanted and the resulting gummy solid was dissolved in EtOAc (600 mL). The organic solution was washed with 1N aqueous NaOH (2x200 mL), H_2O (200 mL), brine (200 mL), dried ($MgSO_4$) and concentrated to give a wet solid, which was triturated with hexane (300 mL) to give a solid. The solid was collected by filtration, washed with hexane (100 mL), air-dried to give the first crop product (64.3 g, 76%). The mother liquid was concentrated and triturated with hexane to give the second crop product (4.5 g, 5%, total yield 81%). White solid: mp 75-77 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H), 3.83 (s, 3H), 4.32 (s, 2H), 7.02 (d, J = 8.66 Hz, 1H), 7.26 (m, 2H), 7.56 (m, 1H), 7.80 (s, 1H), 7.90 (m, 1H); MS m/z 335.0 $[M-H]^-$; HRMS: Calcd for $C_{16}H_{14}BrFO_2$ $[M+H]^+$, 337.0239; Found: 337.0245.

Synthesis of 1-(3-bromo-4-fluorophenyl)-2-(3-methoxy-4-methylphenyl)ethane-1,2-dione 5. To a stirred solution of 2-(3-bromo-4-fluorophenyl)-1-(3-methoxy-4-methylphenyl)ethanone (**4**,

64.3 g, 190 mmol) in DMSO (323 mL) was add an aqueous HBr (48% in water, 65 mL) slowly at room temperature. The solution was stirred in an open flask at 55 ºC for 18 h. The reaction mixture was cooled and quenched with ice-water (300 mL). The solid was collected by filtration, washed with water (2x200 mL) and air-dried to give the product (65.0 g, 97%). Light yellow solid: mp 118-120 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H), 3.87 (s, 3H), 7.10 (d, J = 8.54 Hz, 1H), 7.56 (m, 1H), 7.75 (m, 2H), 7.90 (m, 1H), 8.17 (m, 1H); MS m/z 351.0 $[M+H]^+$; HRMS: Calcd for $C_{16}H_{12}BrFO_3$ $[M+H]^+$, 351.0027; Found: 351.0021.

2-Amino-4-(3-bromo-4-fluorophenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one 6. To a stirred solution of 1-(3-bromo-4-fluorophenyl)-2-(3-methoxy-4-methylphenyl)ethane-1,2-dione (**5**, 46.7 g, 133 mmol) and N-methylguanidine hydrochloride (24.2 g, 221 mmol) in EtOH (500 mL), dioxane (500 mL) and H_2O (100 mL) was added Na_2CO_3 (39.0 g, 368 mmol) in one portion at room temperature. After heating the reaction at 70 ºC for 5h, the reaction mixture was cooled and concentrated. The residue was portioned between EtOAc (350 mL) and H_2O (300 mL). The organic layer was separated, washed with H_2O (300 mL), brine (200 mL), dried ($MgSO_4$) and filtered through a plug of Celite, washed with EtOAc (2x50 mL). The filtrate was concentrated to dryness to the titled compound in quantitative yield (54.0 g) as a solid: mp 108-110 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H), 3.30 (s, 3H), 3.72 (s, 3H), 6.67 (br, 2H), 6.83 (d, J = 8.49, 1H), 7.15 (m, 1H), 7.29 (m, 1H), 7.45 (m, 1H), 7.65 (m, 1H); MS m/z 406.1 $[M+H]^+$; HRMS: Calcd for $C_{18}H_{17}BrFN_3O_2$ $[M+H]^+$, 406.0561; Found: 406.0559.

2-Amino-4-(4-fluoro-3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxy-3-methylphenyl)-1-methyl-1*H*-imidazol-5(4*H*)-one 1. To a stirred solution of 2-amino-5-(3-bromo-4-fluorophenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5- dihydro-4H-imidazol-4-one, **1**, (32.0 g, 78.8 mmol) in EtOH (480 mL) and toluene (480 mL) was added 2-fluoropyridine-3-boronic acid (**7**, 23 g, 163.2 mmol), bis(triphenylphosphino)palladium(II) chloride (2.8 g, 4.0 mmol), triphenylphosphine (1.1 g, 4.2 mmol) and Na_2CO_3 (17.8 g, 167.9 mmol) at room temperature. The reaction mixture was refluxed for 3.5 h, cooled and concentrated. The residue was dissolved in EtOAc and filtered through a plug of silica gel with EtOAc. The filtrate was concentrated to a small volume when it was treated with HCl (240 mL, 1N, in Et_2O) solution. The mixture was triturated with Et_2O and the solid was collected by filtration. The solid was dissolved in EtOH and adjusted pH to ~12 with sat. Na_2CO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by a short column (silica gel, EtOAc/hexane: 50-100%/50-0%, 2.0M NH_3 in EtOH/EtOAc: 10/90) to afford the titled compound (30.1 g, 90%) as white solid: mp 123-124 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 3H), 2.95 (s, 3H), 3.71 (s, 3H), 6.64 (br, 2H), 6.83 (d, J = 8.61 Hz, 1H), 7.22 (m, 3H), 7.50 (m, 3H), 7.97 (m, 1H), 8.29 (m, 1H); MS m/z 423.2 $[M+H]^-$; HRMS: Calcd for $C_{23}H_{20}F_2N_4O_2$ $[M+H]^+$, 423.1627; Found: 423.1626.

Acknowledgements

The authors acknowledge the members of the Wyeth Discovery Analytical Chemistry group for analytical and spectral determinations, and Dr. David P. Rotella for helpful discussions.

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