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Synthesis of Flurbiprofen *via* Suzuki Reaction Catalyzed by Palladium Charcoal in Water

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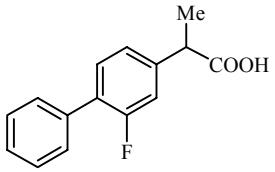
Abstract: Flurbiprofen **1**, an excellent nonsteroidal antiinflammatory drug, was synthesized in 5 steps in 69% overall yield. The key step of constructing the biaryl fragment was successfully achieved *via* Pd/C-catalyzed Suzuki coupling reaction in water using sodium tetraphenylborate as phenylation reagent.

Keywords: Flurbiprofen, Suzuki coupling, Pd/C, sodium tetraphenylborate.

Flurbiprofen **1** is a commercially available nonsteroidal antiinflammatory and analgesic drug[1]. Several synthetic routes towards the compound have recently been reported. The biaryl unit has been constructed by means of Ullmann reaction[2] or by modified Gomberg reaction[3] as a key step. However, in all these procedures, a large volume of benzene was used, which would be harmful to environment and human. The yield is generally also moderate. Schlosser and co-worker[4] reported a new synthetic route to flurbiprofen. The key steps were selective deprotonation of 3-fluorotoluene and 4-methyl-2-fluorobiphenyl with *t*-BuLi in the presence of *t*-BuOK at −75 °C.



Flurbiprofen **1**

Palladium charcoal-catalyzed, ligandless Suzuki reaction, involving tetraarylborates in water has recently been reported by our group[5]. We have successfully synthesized two nonsteroidal antiinflammatory drugs, felbinac and fenbufen, in excellent yields by this new strategy. In this communication, as continuing of our previous research, a new facile approach towards the synthesis of flurbiprofen *via* Suzuki reaction catalyzed by

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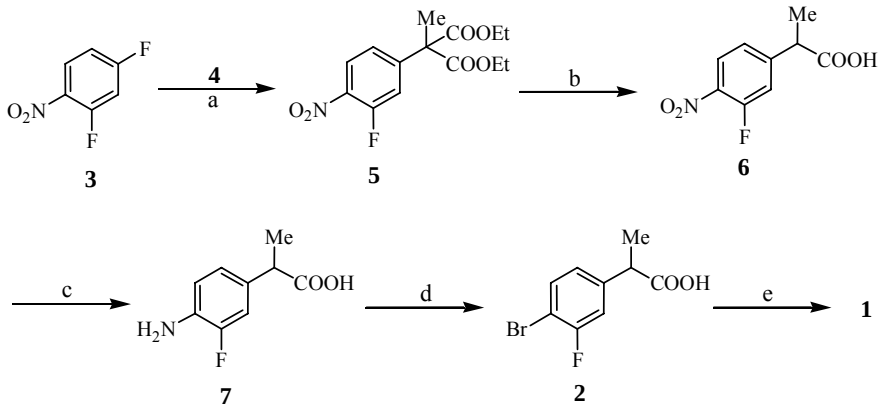
Scheme 1



a) ethyl methylmalonate **4**, NaOH, DMF, r.t.; b) HOAc, H_2SO_4, H_2O, reflux, 87% (2 steps); c) H_2, Pd/C, r.t., 98%; d) $NaNO_2$, 40% HBr, CuBr, H_2O, 83%; e) Ph_4BNa, Na_2CO_3, 0.05 mol% 5% Pd/C, H_2O, reflux in air for 1 h, 98%. Overall yield: 69%.

palladium charcoal for the construction of the biaryl fragment was described (**Scheme 1**). The bromoaryl carboxylic acid **2** was used as a key intermediate, which was easily synthesized from 2,4-difluoronitrobenzene **3** and ethyl methylmalonate **4**. Thus, **2** was coupled with sodium tetraphenylborate, a highly reactive and non-toxic phenylation reagent, in water in the presence of 0.05 mol% 5% Pd/C. This Suzuki coupling reaction could complete within 1 h in air and the target compound **1** was obtained in excellent yield (98%) with high purity determined by HPLC analysis. The structure was confirmed by ^{1}H NMR and ^{13}C NMR. The overall yield for all the steps was 69%, higher than any of reported yield. This mild and environmental friendly procedure is suitable and convenient for bulk synthesis.

Experimental

Melting points were determined with a X-4 digital melting point apparatus (Beijing Taike Apparatus Co. Ltd.) and the thermometer was uncorrected. All materials were commercially available and were used without further purification. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded by using a Brucker ARX-300 spectrometer. TMS was used as an internal standard. MS spectrum was recorded by the instrument of Agilent 1100 series LC-MSD-Trap-SL (ESI: 4000 V). HPLC analysis of the target compound was performed on a C_{18} reversed-phase column (5 μ, 200×4.6 mm) using 20 mmol ammonium acetate buffer (pH 3.0) : methanol (20 : 80, v/v) as the mobile phase at a flow rate of 1.0 mL/min. The UV detector was set at 242 nm.

Ethyl 2-(3-fluoro-4-nitrophenyl)methylmalonate **5**: NaOH (6.40 g，0.16 mol) was added to a 500 mL two-necked round bottom flask, charged with 2,4-difluoronitrobenzene **3** (28.64 g, 0.18 mol), ethyl methylmalonate **4** (26.91 g, 0.15 mol) and DMF (200 mL). The mixture was stirred at room temperature for 4.5 h. Then saturated brine was added and the product was extracted with CH_2Cl_2 (100 mL×3). The

combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and then concentrated to give 62.60 g clear brown oil **5**, which was used directly in next step without further purification.

3-Fluoro-4-nitro-α-methylphenylacetic acid **6**: To the prepared **5**, water (160 mL), HOAc (225 mL, 3.93 mol) and concentrated H_2SO_4 (64 mL, 1.18 mol) were added. After the mixture was refluxed for 24 h, the product was extracted with CH_2Cl_2 (100 mL×3) and washed with brine. The organic layer was treated with aqueous K_2CO_3 until pH 10, and the separated aqueous layer was acidified with 3 mol/L HCl, extracted with CH_2Cl_2, which was then washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, 27.82 g red brown clear oil **6** was obtained. Yield for two steps was 87% (lit.[3d]91%).

4-Amino-3-fluoro-α-methylphenylacetic acid **7**: To a 500 mL flask were charged **6** (26.20 g, 0.12 mol), ethanol (240 mL) and 5% Pd/C (50% water wet, 2.62 g, 10% w/w). **6** was hydrogenated at room temperature overnight under atmospheric H_2 pressure. 21.52 g white crystal **7** was obtained. M.p. 109-110 °C, yield: 98% (lit.[3d]m.p. 113-115 °C, yield: 97%). ^{1}H NMR ($CDCl_3$, δ ppm) 7.01-6.96 (dd, 1H, J = 12.0, 1.6 Hz, 2-Ar-CH), 6.91-6.88 (m, 1H, 6-Ar-CH), 6.76-6.70 (m, 1H, 5-Ar-CH), 6.01 (br s, 3H, NH_3^+), 3.65-3.58 (q, 1H, J = 7.1 Hz, CH), 1.47-1.45 (d, 3H, J = 7.2 Hz, CH_3).

4-Bromo-3-fluoro-α-methylphenylacetic acid **2**: **7** (4.58 g, 0.025 mol) was reacted with $NaNO_2$ (1.90 g, 0.027 mol) and 40% w/w HBr (14.7 mL, 0.10 mol) in 30 mL water at 0-5 °C to give diazonium of **7**. A 100 mL three-necked flask was charged with freshly prepared CuBr[6] (2.01 g, 0.014 mol), 40% w/w HBr (2.2 mL, 0.015 mol), and the mixture was heated to 60 °C. The above diazonium solution was added dropwise to the flask. After being refluxed for 3 h, the mixture was extracted with CH_2Cl_2, washed with brine and dried over anhydrous Na_2SO_4. 5.12 g white product **2** was obtained by flash chromatography with CH_2Cl_2 as eluent. M.p. 56-58 °C, yield: 83%. MS(*m/z*): 200.8 $[M–CO_2–H]^-$ & 202.8 $[M+2–CO_2–H]^-$; 244.8 $[M–H]^-$ & 246.8 $[M+2–H]^-$; 490.8 $[2M–H]^-$ & 492.8 $[2M+2–H]^-$ & 494.8 $[2M+4–H]^-$. ^{1}H NMR ($CDCl_3$, δ ppm) 10.00-11.00 (br s, 1H, COOH), 7.53-7.51 (t, 1H, J = 7.8 Hz, 5-Ar-CH), 7.14-7.11 (dd, 1H, J = 9.0, 1.8 Hz, 2-Ar-CH), 7.02-6.99 (dd, 1H, J = 8.2, 1.5 Hz, 6-Ar-CH), 3.76-3.69 (q, 1H, J = 7.1 Hz, CH), 1.53-1.50 (d, 3H, J = 7.2 Hz, CH_3).

3-Fluoro-4-phenyl-α-methylphenylacetic acid **1**: To a 50 mL flask equipped with a stirring bar and a condenser were charged water (10 mL), Na_2CO_3 (0.212 g, 2.00 mmol), **2** (0.247g, 1.00 mmol), sodium tetraphenylborate (0.092 g, 0.27 mmol) and 5% Pd/C (50% water wet, 2 mg, 0.05 mol%). The mixture was refluxed for 1 h, quenched with 3 mol/L HCl. The precipitate was filtered, washed with water and dried. The residue was dissolved in THF to remove Pd/C. The yield determined by HPLC was 98%. Then the solution was concentrated to give white crystal **1**. M.p. 110-113°C (lit.[3d] 111-113.5°C). ^{1}H NMR ($CDCl_3$, δ ppm) 7.51-7.55 (m, 2H), 7.49-7.37 (m, 4H), 7.21-7.16 (m, 2H), 3.85-3.78 (q, 1H, J = 7.1 Hz, CH), 1.60-1.57 (d, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$ δ ppm) 180.4 (COOH), 161.3 & 158.0 (3-Ar-C), 140.9 & 140.8, 135.4, 130.9 & 130.8 (5-Ar-C), 128.9, 128.4, 128.2 & 128.0 (4-Ar-C), 127.7 (4′-Ar-C), 123.7 & 123.7 (6-Ar-C), 115.5 & 115.2 (2-Ar-C), 44.8 (CH), 18.0 (CH_3).

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