S U P P O R T I N G I N F O R M A T I O N

Tunable Carbon–Carbon and Carbon–Sulfur Cross–Coupling of Boronic Acids with 3,4-Dihydro-pyrimidine-2-thiones

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EXPERIMENTAL PROCEDURES

General Methods. TLC analysis was performed on Merck precoated 60 F_{254} plates. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX360 instrument in $CDCl_3$ or DMSO-d_6, operating at 360 and 90 MHz, respectively. IR spectra were taken on a Perkin-Elmer 298 spectrophotometer in KBr pellets. Mass spectra were taken on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (negative or positive APCI) mode.

HPLC Analysis. For reaction monitoring and quality (purity) control of the synthesized compounds a Shimadzu LC-10 system, that included LC10-AT(VP) pumps, an autosampler (SIL-10AXL), and a dual wavelength UV detector set at 215 and 280 nm was used. The separations were carried out using a C18 reversed phase analytical column, LiChrospher 100 (E. Merck, 100 x 3 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradients were applied at a flow rate of 0.5 mL/min: linear increase from solution 30 % B to 100% solution B in 7 min, hold at 100% solution B for 1 min.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out using the Emrys™ Synthesizer from PersonalChemistry AB (Uppsala), including proprietary Workflow Manager software (version 2.1). All experiments were carried out in sealed microwave process vials utilizing the standard absorbance level (300 W maximum power). Reaction times under microwave conditions reflect total irradiation times rather than actual reaction times at a given temperature. A detailed description of this single-mode microwave reactor with integrated robotics was recently published (ref. 16).

Typical Procedure for the Preparation of 2-Aryl-3,4-Dihydropyrimidines 2a,b from Methylthioethers via Microwave Heating (Scheme 2). A microwave process vial was charged with a stir bar. To the vessel were added DHPM **1a** (72.6 mg; 0.25 mmol), $PhB(OH)_2$ (45.7 mg; 0.375 mmol), Cu(I) thiophene-2-carboxylate (CuTC) (142.9 mg; 0.75 mmol) and $Pd(PPh_3)_4$ (14.4 mg; 5.0 mol%). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous THF was added (5 ml). The reaction vessel was irradiated at 130°C for 25 min (Emrys Synthesizer, Personal Chemistry AB, Uppsala). After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel. (hexanes/ethyl acetate 3:1) to

provide product **2a** (82% yield) as a semi-solid (>98 % purity by HPLC, 215 nm). Dihydropyrimidine **2b** was obtained in analogous fashion from Methlythioether **1b** (86%).

DHPM **2a:** ^{1}H NMR ($CDCl_3$): 1.22 (t, *J* = 7.5 Hz, 3H), 2.5 (s, 3H), 4.12 (q, *J* = 7.5 Hz, 2H), 5.8 (s, 1H), 7.24-7.32 (m, 3H), 7.40-7.43 (m, 3H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): 14.2, 29.7. 57.3, 59.9, 126.7, 127.1, 127.5, 128.5, 128.8, 131.2, 133.6, 145.0; IR (KBr): 1700, 1660, 1500 cm^{-1}; MS (pos. APCI): m/z 321 (M+1).
DHPM **2b**: ^{1}H NMR ($CDCl_3$): δ 1.13 and 1.27 (2d, *J* = 7.5 each, 6H), 2.49 (s, 3H), 5.04 (m, 1H), 5.91 (s, 1H), 7.41-7.52 (m, 4H), 7.73-7.78 (m, 3H), 8.11 (d, *J* = 8.5, 1H), 8.25 (s, 1H); MS (pos. APCI): m/z 380 (M+1), (neg. APCI) m/z 378 (M-1).

Procedure for Carbon-Carbon Cross-Coupling of DHPM 3a with $PhB(OH)_2$ (Scheme 3). A microwave process vial was charged with a stir bar. To the vessel were added DHPM **3a** (69.1 mg, 0.25 mmol), PhB(OH)2 (45.7 mg, 0.375 mmol), Cu(I) thiophene-2-carboxylate (CuTC) (142.9 mg, 0.75 mmol) and Pd(PPh3)4 (8.7 mg, 3.0 mol %). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous THF was added (5 ml). The reaction vessel irradiated at 100 °C for 25 min (Emrys Synthesiser, Personal Chemistry AB, Uppsala). After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 3:1) to yield dihydropyrimidine **2a** as a semi-solid:
DHPM **2a**: ^{1}H NMR (CDCl3): 1.22 (t, J = 7.5 Hz, 3H), 2.5 (s, 3H), 4.12 (q, J = 7.5 Hz, 2H), 5.8 (s, 1H), 7.24-7.32 (m, 3H), 7.40-7.43 (m, 3H), 7.46 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H); ^{13}C NMR (CDCl3): 14.2, 29.7. 57.3, 59.9, 126.7, 127.1, 127.5, 128.5, 128.8, 131.2, 133.6, 145.0; IR (KBr): 1700, 1660, 1500 cm-1; MS (pos. APCI): m/z 321 (M+1). All spectrosopic data were identical to material obtained starting from DHPM **1a** (see above).

Procedure for the Carbon-Sulfur Cross-Coupling of DHPM 3a with $PhB(OH)_2$. (Preparation of 6-Methyl-4-phenylsulfanyl-1,4-dihydro-pyrimidine-5-carbocyclic acid ethyl ester 4) (Scheme 4). A microwave process vial was charged with a stir bar. To the vessel were added DHPM **3a** (90.6 mg; 0.33 mmol), $PhB(OH)_2$ (121.9 mg; 1 mmol), phenanthroline (118.9 mg; 0.66 mmol), $Cu(OAc)_2$ (59.9 mg; 0.33 mmol), 4Å molecular sieves powder (250 mg) and 1,2-dichlorethane (5 ml). The reaction vessel was sealed and irradiated at 85°C for 45 min (Emrys Synthesizer, Personal Chemistry AB, Uppsala). After cooling, the mixture was transferred to a round bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel. (hexanes/ethyl acetate 3:1).
DHPM **4** (ca 2:1 mixture of 1,4- and 3,4-dihydrotautomers): **A** : ^{1}H NMR ($CDCl_3$): δ 2.23 (t, *J* = 7.5, 3H), 3.32 (s, 3H), 4.00 (q, *J* = 7.5, 2H), 5.40 (s, 1H), 7.13-7.40 (m, 10H), 9.77 (s, 1H). ^{13}C NMR: δ 14.5 (CH3), 17.8 (CH3), 53.4 (C4), 59.2 (CH2), 98.9 (C5) 126.6-134.6 (phenyls) 145.2 (C(phenyl)-S), 146.5 (C6), 150.0 (C2), 166.4 (C=O). **B**: ^{1}H NMR ($CDCl_3$): δ 1.11 (t, *J* = 7.5, 3H), 3.32 (s, 3H), 3.99 (q, *J* = 7.5, 2H), 5.26 (s, 1H), 7.13-7.40 (m, 10H), 8.80 (s, 1H). ^{13}C NMR: δ 14.5 (CH3), 23.1 (CH3), 59.2 (CH2), 60.1 (C4), 104.0 (C5) 126.6-134.6 (phenyls) 144.4 (C(phenyl)-S), 155.8 (C6), 159.7 (C2), 166.3 (C=O). MS (pos. APCI): m/z 353 (M+1), (neg. APCI) m/z 351 (M-1).

General Procedure of the Biginelli Cyclocondensation for the Preparation of 4-(2-chloro-4-fluoro-phenyl)-6methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester 5 (Table 1). A microwave process vial was charged with a stir bar. To the vessel were added 2-chloro-4-fluorobenzaldehyde (79.3 mg; 0.5 mmol), methyl acetoacetate (63,8 mg; 0.55 mmol), thiourea (114 mg; 1.5 mmol), $Yb(OTf)_3$ (31.5 mg; 10 mol%) and MeCN (1 ml). The reaction vessel was sealed and irradiated at 120°C for 20 min (Emrys Synthesizer, Personal Chemistry AB, Uppsala). After cooling, the reaction mixture was

poured onto ice/water. The formed precipitate was separated by filtration, washed with H_2O and dried to yield 87% of DHPM **5** (95% HPLC purity) which was direclty used in the next step.
DHPM **5**: ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H), 3.48 (s, 3H), 5.59 (s, 1H), 7.19-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.39-7.43 (m, 1H), 9.62 (s, 1H), 10.42 (s, 1H); MS (pos. APCI): m/z 315 (M+1).

DHPMs **6a-e** were obtained as oils in >95% HPLC purity following the general procedure for carbon-carbon bond formation described above for compound **3a** and $PhB(OH)_2$. For specific catalyst loading and reaction times, see Table 1 in the manuscript:

DHPM **6a**: ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H), 3.64 (s, 3H), 6.09 (s, 1H), 6.94 (m, 1H), 7.29-7.47 (m, 4H), 7.67 (m, 2H); MS (pos. APCI): m/z 359 (M+1), (neg. APCI) m/z 357 (M-1).

DHPM **6b**: ^{1}H NMR ($CDCl_3$): δ 2.56 (s, 3H), 3.64 (s, 3H), 6.08 (s, 1H), 6.94 (m, 1H), 7.17 (m, 1H), 7.30 (m, 1H), 7.38 (m, 2H), 7.63 (m, 2H); MS (pos. APCI): m/z 393 (M+1).

DHPM **6c**: ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.57 (s, 3H), 3.63 (s, 3H), 6.07 (s, 1H), 6.93 (m, 1H), 7.16 (m, 1H), 7.25-7.32 (m, 2H), 7.42 (m, 1H), 7.50 (s, 1H); MS (pos. APCI): m/z 373 (M+1).

DHPM **6d**: ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H), 3.63 (s, 3H), 6.10 (s, 1H), 6.83 (m, 1H), 6.92-6.94 (m, 2H), 7.14-7.16 (m, 1H), 7.29-7.33 (m, 1H), 7.98 (s, 1H); MS (pos. APCI): m/z 394 (M+1).

DHPM **6e**: ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H), 3.63 (s, 3H), 6.01 (s, 1H), 6.92-6.95 (m, 1H), 7.03-7.06 (m, 1H), 7.12-7.15 (m, 1H), 7.30-7.32 (m, 1H), 7.38-7.39 (m, 1H), 7.45-7.47 (m, 1H); MS (pos. APCI): m/z 365 (M+1), (neg. APCI) m/z 363 (M-1).