Supporting Information for *Angew. Chem. Int. Ed.* Z16751

Regioselective Cross-Coupling Reactions as an Entry into Biologically Relevant Bithiazoles. First Total Synthesis of Cystothiazole^^E

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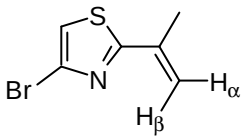
4-Bromo-2-isopropenylthiazole

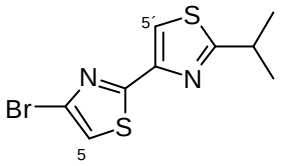


C_6H_6BrNS

34.6 mL of a solution (1.5 M in hexane, 52.0 mmol) of *t*-butyllithium were added at –78°C to a solution of 3.15 g (26.0 mmol) 2-bromopropene in 60 mL diethylether. After stirring for 15 min at –78°C 32.5 mL (1.0 M in THF, 32.5 mmol) of a $ZnCl_2$-solution were added and the reaction mixture was allowed to warm up to 25°C keeping the temperature for 30 min. This solution was cannulated quantitavely to a suspension of 4.86 g (20.0 mmol) 2,4-dibromothiazole (**6**) and 1.16 g (5 mol-%) $Pd(PPh_3)_4$ in 50 mL THF. Upon stirring for 1 h, the reaction was quenched by addition of 40 mL saturated aqueous NH_4Cl-solution. The aqueous phase was extracted three times with 100 mL diethylether and the combined organic extracts were washed with 50 mL brine and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo the residue was purified by column chromatrography (pentane/diethylether, 95:5). 3.90 g (96%) 4-bromo-2-isopropenylthiazole could be isolated as a dark yellow oil, which was immediately subjected to further conversions due to its tendency to polymerize.

^{1}H NMR (200 MHz): δ = 2.22 (s, 3 H, C*H*$_3$), 5.35 (d, b, ^2J = 1.5 Hz, 1 H, H_α), 5.87 (s, b, 1 H, H_β), 7.14 (s, 1 H, H_{arom}). – ^{13}C NMR (50 MHz): δ = 20.7 (CH_3), 116.8 (CH_{arom}), 117.8 (C*C*H$_2$), 125.8 (CBr), 137.7 (CH_3*C*CH$_2$), 170.6 (SCN).

4-Bromo-2-[4´-(2´isopropyl)-thiazoyl]-thiazol



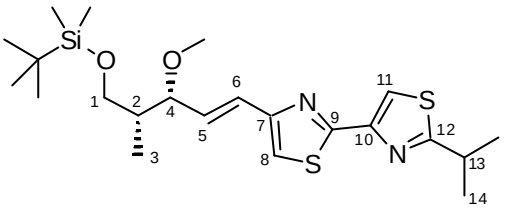
3

$C_9H_9BrN_2S_2$

15.0 mL of a solution (1.5 M in hexane, 22.5 mmol) of *t*-butyllithium were added at –78°C to a solution of 2.20 g (10.7 mmol) 4-bromo-2-isopropylthiazole (**7**) in 50 mL diethylether. After stirring for 15 min at –78°C 16.0 mL (1.0 M in THF, 16.0 mmol) of a $ZnCl_2$-solution were added and the reaction mixture was allowed to warm up to 25°C keeping the temperature for 30 min. A suspension of 1.70 g (7.00 mmol) 2,4-dibromothiazole (**6**) and 245 mg (5 mol-%) $Pd(PPh_3)Cl_2$ in 50 mL THF was cannulated quantitavely to the prepared organozinc-solution. Upon refluxing for 16 h, the reaction was quenched by addition of 40 mL saturated aqueous NH_4Cl-solution. The aqueous phase was extracted three times with 100 mL diethylether and the combined organic extracts were washed with 50 mL brine and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo the residue was purified by column chromatrography (pentane/diethylether, 99:1). 2.06 g (97%) 4-Bromo-2-[4´-(2´isopropyl)-thiazoyl]-thiazol (**3**) could be isolated as a yellow solid.

^{1}H NMR (200 MHz): δ = 1.36 (d, ^3J = 6.8 Hz, 6 H, CH_3), 3.28 (sept., ^3J = 6.8 Hz, 1 H, CH), 7.16 (s, 1 H, H-5), 7.80 (s, 1 H, H-5´). – ^{13}C NMR (50 MHz): δ = 23.5 (CH_3), 33.7 [*C*H(CH_3)$_2$], 116.1 (C-5), 117.6 (C-5´), 126.2 (C-4), 147.9 (C-4´), 164.3 (C-2), 179.3 (C-2´)

Bithiazole 12



12

$C_{22}H_{36}N_2O_2S_2Si$

565 mg (4.75 mmol) catecholborane were added slowly to neat 760 mg (3.16 mmol) 1-*tert*-butyldimethylsiloxy-3(R)-methoxy-2(R)-methyl-4-pentyne (**11**). After keeping the reaction mixture at 25°C for 5 min, the temperature was risen to 70°C for 1 h and afterwards to 95°C for further 2 h. The reaction mixture was allowed to cool to room temperature and 6.5 mL water were added. After vigorous stirring for 1 h 10 mL ethanol were added to dissolve the formed white precipitate. This solution was quantitatively added to a solution of 365 mg (1.26 mmol) 4-bromo-2-[4´-(2´isopropyl)-thiazoyl]-thiazol (**3**), 73 mg (5 mol-%) $Pd(PPh_3)_4$ and 6.3 mL (3.73 mmol) of an aqueous 10% CsOH-solution in 60 mL benzene. The reaction mixture was heated to 95°C for 24 h. After cooling to room temperature and addition of 40 ml water the aqueous phase was extracted two times with 100 mL CH_2Cl_2 and two times with 100 mL pentane. The combined organic extracts were washed with 100 mL brine, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. Flash chromatrography (pentane/diethylether, 95:5) provided 537 mg (94%) of the desired compound **12** as a yellow oil.

^{1}H NMR (250 MHz): δ = 0.02 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 0.92 (d, ^3J = 6.2 Hz, 3 H, H-3), 1.41 [d, ^3J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.82 (virt. sept., ^3J = 6.2 Hz, 1 H, H-2), 3.31 (s, 3 H, OCH_3), 3.33 [sept., ^3J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.48 (dd, ^2J = 9.7 Hz, ^3J = 5.7 Hz, 1 H, CHHOSi), 3.60 (dd, ^2J = 9.7 Hz, ^3J = 6.7 Hz, 1 H, CHHOSi), 3.85 (virt. t, ^3J = 5.0 Hz, 1 H, $CHOCH_3$), 6.53 (m, 2 H, H-5, H-6), 7.05 (s, 1 H, H-8), 7.84 (s, 1 H, H-11). – ^{13}C NMR (62.9 MHz): δ = - 5.5 [$Si(CH_3)(CH_3)$], - 5.4 [$Si(CH_3)(CH_3)$], 11.6 (CH_3), 18.2 [$SiC(CH_3)_3$], 23.1 [2 C, $CH(CH_3)_2$], 25.9 [$SiC(CH_3)_3$], 33.3 [$CH(CH_3)_2$], 41.0 [$OCH_2CH(CH_3)CH(OCH_3)$], 57.1 (OCH_3), 64.8 (CH_2O), 82.1 [$CH(CH_3)CH(OCH_3)$], 114.9 (C-11), 115.0 (C-8), 124.8 (C-6), 132.2 (C-5), 148.7 (C-10), 154.4 (C-7), 162.7 (C-9), 178.6 (C-12)