An improvement to the preparation of prasugrel hydrochloride

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An efficient synthesis of prasugrel, a thienopyridine ADP-receptor antagonists, is described. A thienopyridine intermediate was prepared by N-protection, boric acid substitution and N-substitution. After acid hydrolysis of the methyl ether and subsequent acetylation, prasugrel was obtained with a total yield of 50% after seven linear steps from 4,5,6,7-tetrahydrothieno [3,2-c]pyridine and 2-bromo-1-cyclopropyl-2-(2- fluorophenyl)ethan-1-one as raw materials.

Keywords: prasugrel, boric acid substitution, platelet inhibitor

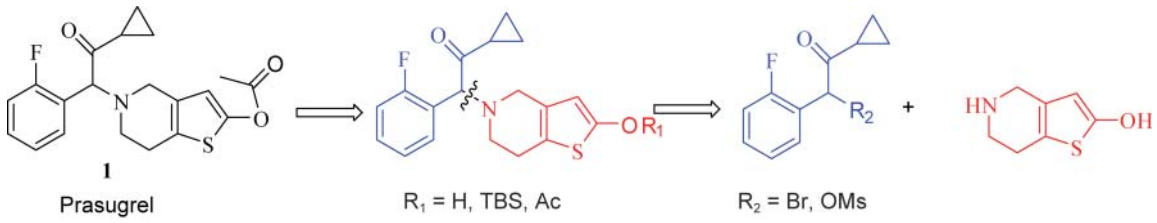
Prasugrel is a novel thienopyridine prodrug that is rapidly metabolised to its active platelet-inhibitory metabolite (R-138727) which exerts antiplatelet activity through antagonism of P2Y (12) receptors.[1] Prasugrel has found extensive use as a major thienopyridine ADP-receptor antagonist with a safer, higher, faster, and more consistent level of inhibition of platelet aggregation compared to similar drugs that are used for the treatment of cardiovascular disease such as ticlopidine and clopidogrel.[2–7] Due to the sharp increase in the number of people suffering from cardiovascular disease, the need for prasugrel to treat cardiovascular disease is growing. Considerable effort has been spent on developing simple and practical synthetic routes for the preparation of prasugrel **1** (Scheme 1).[8–11] In 1993, Hiroyuki synthesised prasugrel **1** from the C-2 enol 4,5,6,7-tetrahydrothieno [3,2-c]pyridine hydrochloride and 2-bromo-1-cyclopropyl-2-(2-fluorophenyl) ethanone.[8] Stepankova synthesised this compound from 2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl methanesulfonate and 5,6,7,7a-tetrahydrothieno [3,2-c]pyridin-2(4H)-one hydrochloride.[9] Given the relatively low yield and unavoidable impurities (Scheme 2),[8–12] there is still room for improvement. We report here an improved synthetic route for the preparation of prasugrel hydrochloride.

The synthesis started from 4,5,6,7-tetrahydrothieno[3,2-c]-pyridine **7** (Scheme 3) which was obtained from Sigma-Aldrich Co. compound **8** was prepared in 92% yield[8,13] after N-protection reaction with triphenylchloromethane in CH_2Cl_2. Compound **8** was converted to compound **9** in 96% yield by reacting with trimethyl borate. Removal of the triphenylmethyl protecting group was performed at r.t. (TsOH, THF), to give compound **10** in 89% yield. Compound **10** was then reacted with 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethan-1-one **12** which was prepared according to the procedure of H. Stepankova, and J. Hajicek.[9] Compound **11** was obtained in 93% yield after purification. Compound **11** was then oxidised and acetylated to give prasugrel **1** in 85% yield via the key intermediate **4**. After treatment with an acetone solution of hydrogen chloride, prasugrel hydrochloride was isolated in 88% yield.

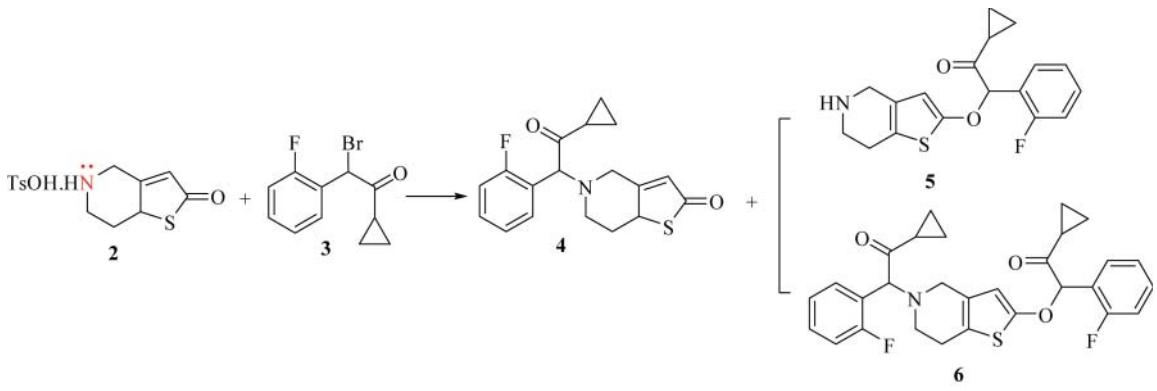
In conclusion, a highly efficient and practical approach to prasugrel hydrochloride has been developed by borate esterification. In this process, the boronate group was successfully used to generate the 2-oxo group to avoid the formation of by-products attached to the oxo group. Its ease of work-up, high yield, fairly mild reaction conditions and no unavoidable impurities provide an improved access to prasugrel. The overall yield of the route is 50% for seven steps. Other applications of this process are under investigation in our laboratory.

Experimental

Melting points were determined with a SGW X-4 micro melting point apparatus. ^{1}H NMR spectras were recorded using Avance 400 MHz



Scheme 1



Scheme 2

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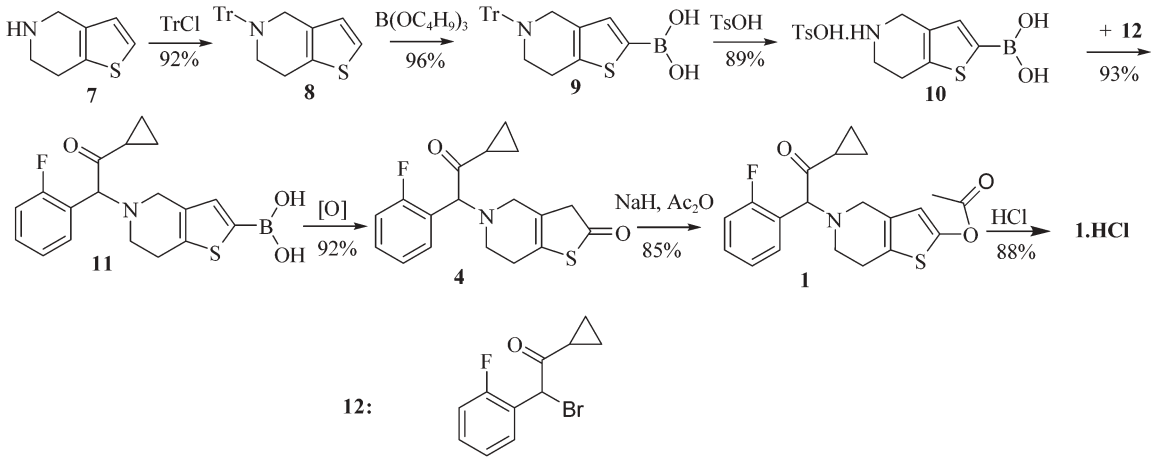

Reagents and conditions: (a) NaOH, TrCl, CH_2Cl_2, 92%; (b) *n*-BuLi, $B(OBu)_3$, THF, 0 °C, 96%; (c) TsOH, THF, 89%; (d) **12**, EtOH, Et_3N, 50 °C, 93%. (e) EtOH, HOAc, H_2O_2, 0 °C, 92%; (f) NaH, Ac_2O, DMF, 0 °C, 85%; and (g) acetone, HCl.

Scheme 3

spectrometer. ESI-MS were recorded on Dionex MSOPlus mass spectrometer. High resolution mass spectra were recorded on Finnigan MAT XL95 mass spectrometer.

5-Trityl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**8**): The hydrochloride of 4,5,6,7-tetrahydrothieno [3,2-c]pyridine **7** (140.4 g, 0.8 mol) was added to a mixture of CH_2Cl_2 (500 mL) and 4M sodium hydroxide solution (420 mL, 1.68 mol), and stirred at room temperature for 15 min. This solution was kept at room temperature while triphenylchloromethane (234.0 g, 0.84 mol) was added in portions. After the addition, the mixture was stirred at room temperature for 8 h. Then H_2O (500 mL) was added to the reaction mixture. The layers were separated, the organic layer was washed with sat. NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide the crude product. This was recrystallised from EtOAc to give compound **8** (280.4 g) as a white solid in 92% yield. M.p. 162–164 °C. (lit [13] 150–151 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.3 Hz, 6H), 7.39–7.24 (m, 6H), 7.19 (t, *J* = 7.3 Hz, 3H), 7.06 (d, *J* = 5.0 Hz, 1H), 6.67 (d,*J* = 5.1 Hz, 1H), 3.45 (s, 2H), 3.01 (s, 2H), 2.63 (s, 2H). ESI-MS *m/z*: 382.2 $(M+H)^+$.

(5-Trityl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)boronic acid (**9**):[14] A magnetically stirred solution containing compound **8** (19 g, 50 mmol) in THF (50 mL) was treated with 2.5M hexane solution of *n*-BuLi (30 mL, 0.075 mol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at –10 °C for two hours, and then trimethylborate (19 mL, 0.075 mol) in THF (50 mL) was added slowly over half hour. The mixture was stirred at –10 °C for 1 h before EtOAc (100 mL) was added. The layers were separated, the organic layer was washed first with sat. $NaHCO_3$, and then with sat. NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated to provide the product (20.4g) as a pale yellow viscous liquid in 96% yield. ^{1}H NMR (δ, $CDCl_3$): 7.55–7.57 (m, 6H), 7.29–7.34 (m, 7H), 7.09–7.20 (m, 3H), 3.25–3.48 (m, 2H), 3.06–3.10 (m, 2H), 2.61–2.68 (m, 2H). ESI-MS *m/z*: 426.4 $(M+H)^+$.

TsOH salt of (4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)boronic acid (**10**): *p*-Toluenesulfonic acid (17.2 g, 0.1 mol) was added to a solution of compound **9** (42.5 g, 0.1 mol) in 300 mL of THF, while keeping the internal temperature between 0 and 5 °C. After the addition was complete, stirring was continued for another hour at room temperature. The white solid which formed was filtered, and washed with THF. After drying below 60 °C, compound **10** (31.6 g) was obtained in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 2H), 8.25 (s, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.21 (s, 2H), 3.53–3.17 (m, 2H), 3.04 (t, *J* = 5.8 Hz, 2H), 2.29 (s, 3H). MS-ESI (*m/z*): 378.3 $[M+Na]^+$.

(5-(2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)boronic acid (**11**): Triethylamine (34.5 g, 0.25 mol) was added to a solution of compound **10** (28.4 g, 0.08 mol) in 150 mL of absolute ethanol under a nitrogen atmosphere. The mixture was stirred vigorously at 50 °C, and a solution of compound **12** (22.6 g, 0.088 mol) in absolute ethanol (50 mL) was added. The mixture was stirred for another 8 h at 50 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum to remove enthanol, saturated NaCl solution (300 mL) and ethyl acetate (400 mL) were added, and the layers were separated. The organic layer was washed with saturated NaCl (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product. This was recrystallised from a mixture of EtOAc and petroleum ether to give compound **11** (26.8 g) as a pale yellow solid in 93% yield. M.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–6.91 (m, 4H), 5.33 (s, 1H), 4.89 (s, 1H), 3.66 (d, *J* = 24.7 Hz, 2H), 3.19–1.88 (m, 4H), 1.66 (s, 1H), 0.97–0.56 (m, 4H). MS-ESI (*m/z*): 360 $[M+H]^+$. HRMS Calcd for $C_{18}H_{19}BFNO_3S$ $(M + H)^+$ requires 360.2224, found 360.2217.

1-Cyclopropyl-2-(2-fluorophenyl)-2-(2-hydroxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethan-1-one (**4**): Acetic acid was added until a pH of 5 was reached to a solution of compound **11** (18.0 g, 0.05 mol) in absolute ethanol (100 mL) under a nitrogen atmosphere below 4 °C. Then 30% hydrogen peroxide (6.8 g, 0.06 mol) was added slowly. After the addition, the mixture was stirred and warmed slowly to room temperature for 4 h. The reaction was quenched with saturated sodium thiosulfate solution (50 mL). Then the reaction mixture was concentrated under vacuum to remove enthanol. Saturated $NaHCO_3$ (100 mL) and ethyl acetate (100 mL) were added, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product. This was recrystallised from isopropyl ether to give compound **4** (15.2 g) as a pale yellow solid in 92% yield. M.p. 124–126 °C. (lit [8] 123–125 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.11 (m, 4H), 6.05 (d, *J* = 8.7 Hz, 1H), 4.87 (t, *J* = 7.9 Hz, 1H), 4.10 (ddd, *J* = 12.5, 5.7, 1.3 Hz, 1H), 3.95 (ddd, *J* = 15.6, 12.3, 1.9 Hz, 1H), 3.10 (ddd, *J* = 12.0, 9.8, 3.5 Hz, 1.5H), 2.85 (d, *J* = 12.3 Hz, 0.5H), 2.54 (td, *J* = 12.2, 1.6 Hz, 0.5H), 2.43–2.22 (m, 1.5H), 2.16–2.00 (m, 1H), 2.01–1.74 (m, 1H), 1.11–1.00 (m, 2H), 0.97–0.71 (m, 2H). MS-ESI (*m/z*): 332 $[M+H]^+$.

Prasugrel (**1**): 60% Sodium hydride (0.44 g, 0.011 mo1) was added to a magnetically stirred solution containing compound **4** (3.31 g, 10 mmol) in DMF (20 mL) and Ac_2O (0.38 mL, 40mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. The white solid was formed after adding 100 mL of ice-water. The white solid was filtered, and washed with Et_2O. After drying under 60 °C, prasugrel **1** (3.2 g) was obtained in 85% yield. M.p. 120–121 °C. (lit [13] 119–121 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.02 (m, 4H), 6.26 (s, 1H), 4.83 (s, 1H), 3.52 (q, *J* = 14.3 Hz, 2H), 2.95–2.59 (m, 4H), 2.32–2. 25 (m, 1H), 2.24 (s, 3H), 1.11–0.91 (m, 2H), 0.91–0.59 (m, 2H). MS: ESI (*m/z*): 374 $[M+ H]^+$.

Prasugrel hydrochloride (**1**)**·HCl**: acetone solution of hydrogen chloride was added to a magnetically stirred solution containing

prasugrel **1** (3.73 g, 10 mmol) in acetone (15 mL) until a pH of 3 was reached at 0 °C under a nitrogen atmosphere. The reaction was stirred for another 12 h at 0 °C. The white solid which formed was filtered, and washed with Et_2O. After drying under 40 °C, 3.6 g of prasugrel hydrochloride **1·HCl** was obtained in 88% yield. The purity of the product was higher than 99.7%.

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