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Synthetic Improvements in the Preparation of Clopidogrel

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Abstract:

Synthetic improvements in the preparation of clopidogrel are described. The synthesis was accomplished in four steps or one-pot in above 70% overall yield. The process featured PTC catalyzed alkaline hydrolysis of the key intermediate 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetonitrile and highly effective kinetic resolution of racemic clopidogrel using L-camphorsulphonic acid in toluene and has been successfully used in a 50-kg pilot test.

Introduction

(*S*)-(+)-Clopidogrel bisulfate (Plavix, Figure 1) is an orally active inhibitor of platelet aggregation now marketed as an antithrombotic agent which was licensed by Sanofi in 1986. It is an adenosine diphosphate (ADP) receptor antagonist indicated for the reduction of atherosclerotic events including myocardial infarction, ischemic stroke, and vascular death in patients with atherosclerosis. Clopidogrel works by helping to prevent harmful blood clots.[1] Recent studies have shown that clopidogrel is more effective in blocking platelet aggregation than aspirin and ticlopidine even at much lower dosage.[2] A dosage of 75 mg of clopidogrel has been shown to be more effective than a dosage of 325 mg of aspirin, [3] and as a consequence, this compound has captured the interest of a number of synthetic groups as a target for commercial total synthesis.[4]

There were mainly two kinds of syntheses of clopidogrel. One was from the derivatives of α-halogenphenyl acetate by alkylation with 4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine, **3**.[5] The second was from the derivatives of α-aminophenylacetic acid.[6] All of these methods have suffered several industrial inconveniences, including unsatisfactory yield and efficiency, high raw material cost, and environmental impact.

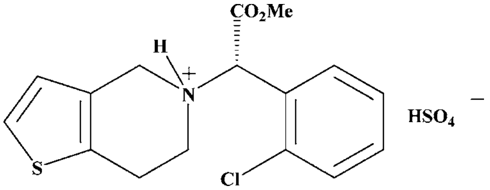
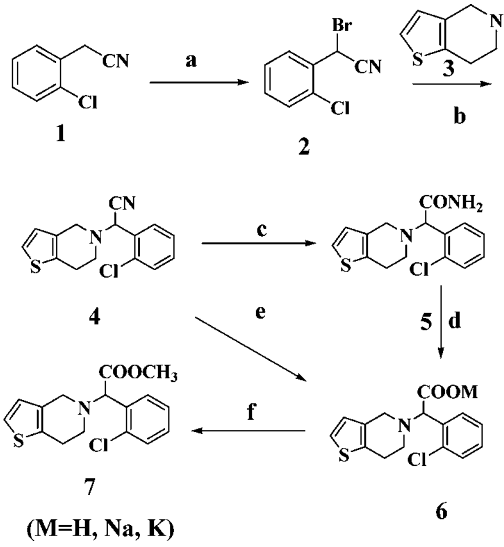


Figure 1. **(*S*)-(+)-Clopidogrel bisulfate.**

Results and Discussion

Herein we report synthetic improvements in the preparation of clopidogrel starting from 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridine-5(4H)-yl)acetonitrile, **4**, which is a key intermediate in our process, that can be cheaply and effectively prepared from commercially available **3** and α-bromo-2-chlorophenyl acetonitrile, **2**, which is from the bromination of 2-chlorophenyl acetonitrile **1** (Scheme 1). As far as we know, our synthetic route and the whole process are effective, facile, and economical.

Scheme 1[a]



[a] Reagents and conditions: (a) Br_2, 100−110 °C, 6 h, 86%; (b) $NaHCO_3$, methanol, reflux, 3 h, 85%; (c) TEBA, 10−20% NaOH (aq), methanol, reflux, 12 h, 96%; (d) TEBA, 40−50% NaOH (aq), methanol, reflux, 12 h, 95%; (e) TEBA, 40−50% NaOH (aq), methanol, reflux, 12 h, 95%; (f) TEBA, methanol, NaOH, dimethyl sulfate, 40 °C, 12 h; 87%; TEBA = triethylbenzylammonium chloride.

In contrast to our syntheses, Pandey and his co-workers reported a Strecker synthesis of nitrile **4** by reacting amine **3** with sodium cyanide and 2-chlorobenzaldehyde in high

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(1) (a) Gurbel, P. A.; O'Connor, C. M.; Cummings, C. C.; Serebruany, V. L. *Pharmacol. Res.* **1999**, *40*(2), 107−111. (b) Yang, L. H.; Hoppensteadt, D.; Fareed, J. *Thromb. Res.* **1998**, *92*, 83−89.

(2) (a) Coukell, A. J.; Markham, A. *Drugs* **1997**, *54*, 745−751. (b) Boneu, B.; Destelle, G. *Thromb. Haemostasis* **1996**, *76*, 939−943.

(3) Valeriano, M.; Daverio, P.; Bianchi. S. U.S. Patent 2004/0024012A1, 2004.

(4) (a) Pandey, B.; Lohray, V. B.; Lorhray. B. B. U.S. Patent 2002/0177712A1, 2002. (b) Kumar, A.; Vyas, K. D.; Barve, S. G. WO Patent 2005/104663A2, 2005. (c) Castaldi, G.; Barreca, G.; Bologna. A. U.S. Patent 2005/0143414A1, 2005. (d) Valeriano, M.; Daverio, P.; Bianchi. S. U.S. Patent 6737411B2, 2004.

(5) (a) Bousquet, A.; Calet, S.; Heymes, A. U.S. Patent 5,132,435, 1992. (b) Bousquet, A.; Musolino, A. U.S. Patent 6,573,381 B1, 2003. (c) Bouisset, M.; Radisson, J. U.S. Patent 5,036,156, 1991.

(6) (a) Castro, B.; Dormoy, J; Previero, A. U.S. Patent 6,080,875, 2000. (b) Descamps, M.; Radisson, J. U.S. Patent 5,204,469, 1993.

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yield.[7] Acid **6** and clopidogrel were prepared from amide **5** by methanolysis in large excess of concentrated sulfuric acid, and the amide **5** was prepared from nitrile **4** by alkaline hydrolysis in alcohol. They also reported that clopidogrel could be synthesized from nitrile **4** in one step, but they did not offer the details or related descriptions of direct esterification of nitrile **4** in their patents. In fact, we could only obtain **5** or a small amount of **6** according to the methods they offered, and the direct acid hydrolysis of **4** to clopidogrel had few real applications in commercial production for the reported low yield (38%). Herbert also reported the conversion of nitrile **4** to the final product **7** through methanolysis of **5** in 28% yield.[8] It seems that the direct alkaline hydrolysis of nitrile **4** to acid **6** is difficult under general circumstances.

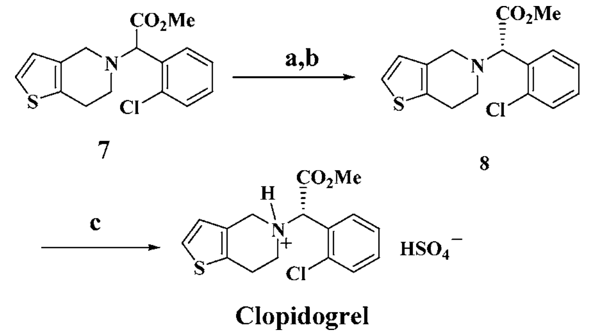
To our delight, we have found that direct alkaline hydrolysis of nitrile **4** to acid **6** could be accomplished almost quantitatively in the mixed solvent and high concentration of inorganic strong base in the presence of phase transfer catalyst, whereas by controlling the concentration of base ($<20\%$), amide **5** may also be obtained selectively. To the best of our knowledge, there are no successful analogous reports for this direct alkaline hydrolysis of nitrile **4** to acid **6**.

Bromination of 2-(2-chlorophenyl) acetonitrile (**1**) without solvent at 100−110 °C afforded 2-bromo-2-(2-chlorophenyl)-acetonitrile **2** in 86% separated yield (above 95% conversion). [9,10] To reduce dibromination, it was better to add bromine dropwise in a period of more than 2 h and in a little excess quantity, such as 1.1 equiv. **3** is commercially available or can be synthesized from 2-(2-thienyl)ethylamine in two steps in 90% overall yield.[11]

2 was alkylated with **3** to give nitrile **4** in above 85% separated yield in the presence of at least one equivalent of base in polar solvent. The resulting nitrile **4** was directly hydrolyzed to acid **6** in high concentration ($>35\%$) of strong bases (e.g., KOH, NaOH) in water and alcohols, e.g., BuOH in the presence of phase transfer catalysts (PTC) almost quantitatively ($>95\%$ yield).[12] The concentration of base and PTC are crucial for this direct conversion, at lower base concentration, amide **5** was the main product, while without PTC, almost no acid **6** could be obtained. The final product was obtained by esterification of acid **6** in refluxing methanol and at least 2 equiv of concentrated sulfuric acid in more than 70% yield or esterification with dimethyl sulfate in the presence of sodium hydroxide in 75% yield. Unreacted acid **6** was easily recycled by forming salt.[13]

Our experiments also show that the whole process of the synthesis of **6** could be taken in one-pot or without strict separation and purification. After simple washing off of HBr, amine **3** and $NaHCO_3$ were added directly to the brominated intermediate **2** to form nitrile **4**. The reactants were alkaline hydrolyzed to form the salt of **6**; after cooling, a highly pure ($>98\%$) salt of **6** was obtained in above 75% yield.

Scheme 2[a]



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Clopidogrel

[a] Reagents and conditions: (a) L-CSA. H_2O, toluene, 48 h, 93%, ee > 99.5%; (b) $NaHCO_3$, acetone, reflux, 6 h; (c) H_2SO_4, 0 °C, 12 h, 95% (two steps).

Our synthetic route and the whole process for racemic clopidogrel were simple, easily controlled, industrially economical, and environmental friendly in excellent total yield, and the starting materials were commercially available and cheap. Furthermore, all these conversions or reaction steps could be taken in one-pot just by the simple filtration of the potassium salt of **6**.

The process described above has been used in a 50-kg pilot scale, wherein high-quality racemic clopidogrel bisulfate was obtained in four steps from commercially inexpensive available materials in over 70% overall separated yield.

For the manufacture of (*S*)-clopidogrel,currently, there were mainly three known processes. Each of these processes relies on classical resolution, enzymatic techniques, or asymmetric synthesis to introduce the sole chiral center into the molecule. While the classical resolution of clopidogrel is still the main method in industry and shows advantages in cost and method flexibility, the reported methods of classical resolution of clopidogrel using L-CSA (10-L-camphorsulphonic acid) were all in acetone,[14] methyl *tert*-butyl ether,[15] or in the cosolvent of DMF.[16] The reported resolution yield in acetone was 67.8% or lower, but we could not repeat these procedures, and almost no desired chiral isomer was obtained; in the cosolvent, the resolution, yield, and efficiency were unsatisfactory, the recovery of the solvents was rather difficult, and no exact results were reported. To our surprise, when only 0.45−0.55 equiv of L-CSA was used and only in toluene, we found a highly selective and effective kinetic resolution method of racemic clopidogrel in above 98.3% ee and 88% total yield (Scheme 2). Qualified clopidogrel was obtained in above 99.5% ee just by washing with cold isopropanol. From the scope of literature searched and to the best of our knowledge, our resolution method is the most effective and economical one until now.

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(7) Pandey, B.; Lohray, V. B.; Lorhray, B. B. CN Patent 1487943A, 2004.

(8) Burgos, A.; Herbert, J. M.; Simpson, I. *J. Labelled Cmpd. Radiopharm* **2000**, *43*, 891−898.

(9) Robb, C. M.; Schultz, E. M. *Org. Synth.* **1948**, *28*, 55−58.

(10) Lodewijk, E.; Khatri, H. N. EP Patent 0342118A1, 1989.

(11) (a) Venkatesan, A. M.; Agarwal, A.; Abe, T. *J. Med. Chem.* **2006**, *49*, 4623−4637. (b) El Ashry, E. S. H.; Ramadan, E. S.; Abdel Hamid, H. M. *Synlett* **2004**, *4*, 723−725.

(12) (a) Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E. *Org. Process Res. Dev.* **2005**, *9*, 774−781. (b) Watson, T. J. N.; Horgan, S. W.; Shah, R. S. *Org. Process Res. Dev.* **2000**, *4*, 477−487. (c) Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, *2*(16), 2423−2425.

(13) The sodium/potassium salt of **6** is hardly soluble in cold water and most organic solvents.

(14) (a) Badorc, A.; Frehel, D. U.S. Patent 4,847,265, 1989. (b) Bakonyi, M.; Nagy, M. C.; Bako, E. M. U.S. Patent 6,258,961 B1, 2001.

(15) Tarur, V. R.; Sathe, D. G.; Sawant, K. D. WO Patent 2006/087729A1, 2006.

(16) Valeriano, M.; Daverio, P.; Bianchi, S. U.S. Patent 2005/0049275A1, 2005.

Conclusion

In summary, an effective synthetic pathway beyond the coverage of the present patents for the commercial preparation of clopidogrel bisulfate starting from commercially available materials has been accomplished in four separated steps or in a one-pot procedure in above 70% overall yield. Highly effective and selective kinetic resolution of clopidogrel using L-CSA in toluene is presented. The whole process and all of the procedures are environmental friendly, economical, industrially reliable, and easily scaled up.

Experimental Section

Materials and Instruments. All solvents and reagents were purchased from the suppliers and used without further purification. The IR spectra were performed on a NICOLET MX-1E FT-IR instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer in $CDCl_3$, DMSO-d_6, or D_2O with Me_4Si (TMS) as internal standard at room temperature. Mass spectra were obtained with a Bruker Daltonics Data Analysis 3.2.

HPLC analyses were performed on Schimadzu LC-12ATVP according to the following conditions: (1) column, Shimpack VP-ODS (150 mm × 4.6 mm, 5 μm); eluent, 80:20 methanol/water; flow rate 1 mL/min; temperature, 30 °C; wavelength 240 nm. (2) Column, Chiral-AGP (150 mm × 4.0 mm + 10 mm × 4.0 mm, 5 μm); eluent, 83:17 sodium acetate (aq, pH 6.2)/acetonitrile; flow rate 0.8 mL/min; temperature, 30 °C; wavelength 225 nm.

2-Bromo-2-(2-chlorophenyl)acetonitrile (2). Bromine (176 g, 1.1 mol) was added over a period of 3 h to 2-(2-chlorophenyl)acetonitrile (151.5 g, 1 mol) with stirring at 105−110 °C and was reacted for another 3 h. Then butyl acetate (250 mL) and sodium bisulfate (11.4 g, 0.11 mol) were added at 30 °C. After 15 min stirring, the mixture was filtered, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent was done in vacuum to afford **2** (200 g, 86%): mp: 110 °C /15 mmHg; IR (cm^{-1}): 2969, 2253, 1589.0, 1472, 1445, 1194, 1051, 765, 725, 646; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.83 (1 H, m), 7.38−7.45 (4 H, m), 5.87 (1 H, s).

2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridine-5(4H)-yl)acetonitrile (4). 3 (98.7 g, 0.43 mol), **2** (70.2 g, 0.4 mol), sodium hydrogen carbonate (84 g, 1.0 mol), and methanol (300 mL) were combined and refluxed for 3 h. Then the mixture was stirred at 5 °C for more than 30 min, filtered, washed with water and cold methanol, and dried to give **4** (98 g, 85%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.35−7.72 (4 H, m), 7.08 (1 H, d, $J = 5.1$), 6.69 (1 H, d, $J = 5.1$), 5.32 (1 H, s), 3.78 (1 H, d, $J = 13.7$), 3.65 (1 H, d, $J = 13.7$), 2.8−3.0 (4 H, m); ^{13}CNMR (300 MHz, $CDCl_3$): δ 136.46, 132.78, 132.38, 130.69, 130.46, 130.38, 129.90, 126.73, 124.96, 123.01, 115.09, 59.12, 49.30, 47.66, 25.47.

2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridine-5(4H)-yl)acetic Acid (6). The mixture of **4** (60 g, 0.22 mol), TEBA (1.0 g), NaOH (aq 360 g, 40−50%), and butanol (100 mL) was refluxed for 12 h. After cooling to room temperature, the solution was neutralized with HCl (aq 35−37%) to pH 8 and then acidified with acetic acid to pH 4−5. The suspension was filtered, washed, and dried to give **6** (61 g, 95%). IR (cm^{-1}): 3439.5, 2849.1, 1691.3, 1628.3, 1474.4, 1351.3, 1329.3, 1035.6, 890.0, 847.6, 756.5, 748.4; ^{1}HNMR (300 MHz, DMSO): δ 10.3−14.3 (1 H, br), 7.35−7.64 (4 H, m), 7.26 (1 H, d, $J = 5.1$), 6.8 (1 H, d, $J = 5.1$), 4.7 (1 H, s), 3.61−3.65 (2 H, dd, $J = 10.8$), 2.78−2.85 (4 H, m).

Methyl(2-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4H)-acetate (7). The mixture of acid **6** (60 g, 0.198 mol), TEBA (1.2 g), methanol (250 mL), and NaOH (aq 20%, 60 g) was refluxed for 30 min. After cooling to about 10 °C, Me_2SO_4 (40 g, 0.317 mol) was added dropwise. The solution was reacted at 40 °C for 12 h. After removal of methanol, butyl acetate (150 mL) was added. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After removal of solvent by vacuum, brown oil was obtained (54.7 g, 87%). IR (cm^{-1}): 3452, 2554.5, 1752.3, 1630.5, 1591.0, 1437.8, 1187.6, 882.0, 867.2, 847.7, 772.4; ^{1}HNMR (300 MHz, D_2O): δ 7.65 (1 H, d, $J = 8.0$), 7.5−7.6 (3 H, m), 7.3 (1 H, d, $J = 5.2$), 6.7 (1 H, d, $J = 4.7$), 5.9 (1 H, s), 4.2−4.4 (2 H, m), 3.8 (3 H, s), 3.7−3.8 (2 H, m), 3.2 (2 H, s).

Kinetic Resolution of Racemic Clopidogrel. L-CSA·$1H_2O$ (13.3 g, 0.053 mol) was added batchwise into the solution of racemic **7** (32 g, 0.10 mol) and toluene (140 mL) at room temperature. After stirring at 50 °C for 1 h, the mixture was cooled to room temperature, stirred, and seeded for another 48 h. It was then filtered, washed, and dried to give a white solid (25.7 g, ee = 99.6%). Then a mixture of the white solid (25.7 g, 0.046 mol), $NaHCO_3$ (3.9 g, 0.046 mol), and acetone (100 mL) was refluxed for 6 h. After the mixture was cooled to −5 °C, filtered, and washed with cold acetone, then H_2SO_4 (98%, 4.6 g, 0.046 mol) was added dropwise into the filtrate, stirring continuously at 0 °C for 12 h. (*S*)-(+)-Clopidogrel bisulfate (18.4 g, 88%, ee = 99.5%) was obtained by the usual filtering, washing, and drying.

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Supporting Information Available

Spectrograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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