Organic Process Research & Development

Article

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New and Efficient Synthetic Approaches for the Regioisomeric and Iminium Impurities of Clopidogrel Bisulfate†

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ABSTRACT: New and concise synthetic routes have been devised for the regioisomeric and iminium impurities of clopidogrel bisulfate. The synthesis features utilization of commercially available starting materials and simple reactions.

INTRODUCTION

Clopidogrel bisulfate (Figure 1) is a potent oral antiplatelet agent often used in the treatment of coronary artery disease and

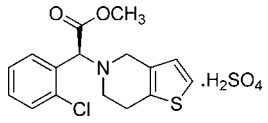


Figure 1. Structure of clopidogrel bisulfate.

peripheral vascular and cerebrovascular diseases. Clopidogrel works by helping to prevent harmful blood clots.[1] It is marketed by Bristol-Myers Squibb and Sanofi-Aventis under the trade name Plavix, which is the world's second-highest-selling pharmaceutical with sales of $5.9 billion. The mechanism of action of clopidogrel is irreversible blockade of the adenosine diphosphate (ADP) receptor $P2Y_{12}$, which is important in platelet aggregation. Studies have shown that clopidogrel is more effective in blocking platelet aggregation than aspirin and ticlopidine even at a much lower dosage.[2]

A literature survey on clopidogrel bisulfate revealed the presence of various pharmacoepia-listed impurities, such as related compound A, related compound B (regioisomer), related compound C, and related compound D.[3,4] Mohan et al. reported a new impurity, clopidogrel iminium, which is the principle oxidative impurity of clopidogrel bisulfate.[5]

In view of stringent quality requirements,[6] quantification of an impurity present in the active pharmaceutical ingredient (API) is receiving significant importance from the regulatory authorities as well as pharmaceutical companies. Hence, there is a considerable demand for a substantial quantity of impurity standards. Often, the pharmacoepial impurity standards are available, but with unaffordable prices. Therefore, easily accessible synthetic routes with the lowest cost are sought after. In the present study, we focused on the synthesis of the regioisomer and the iminium impurity of clopidogrel bisulfate (Figure 2).

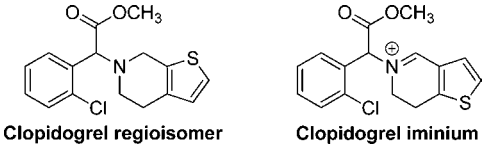


Figure 2. Structures of clopidogrel regioisomer and clopidogrel iminium.

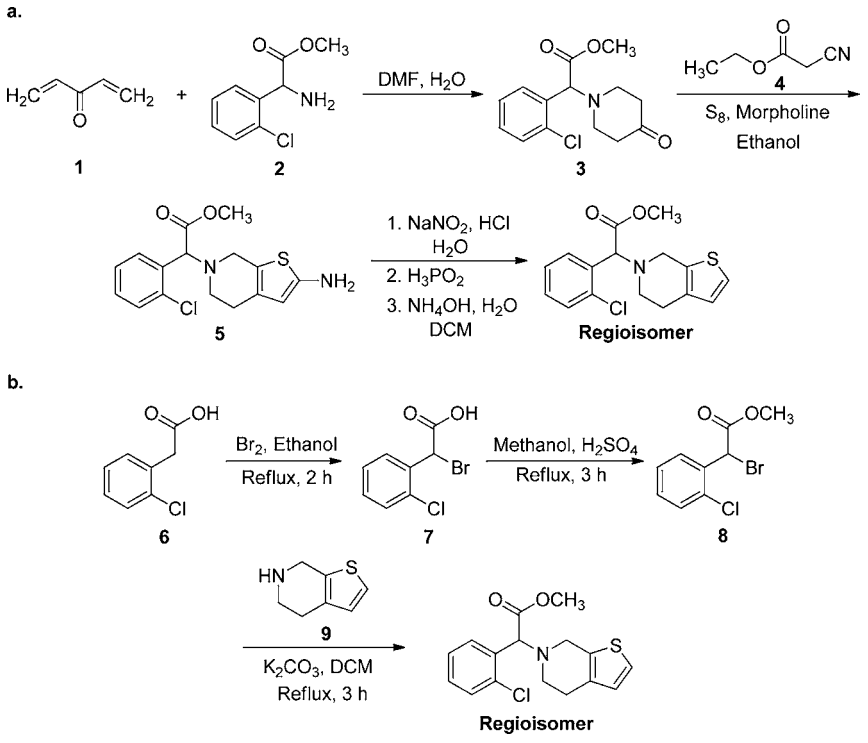
Extensive literature search revealed that two different synthetic routes have been reported for regioisomer (Scheme 1).[7−10] The first synthetic route (Scheme 1a) involves reaction of vinyl ketone **1** with glycine derivative **2** to provide intermediate **3**, which upon reaction with ethyl cyanoacetate (**4**) furnished compound **5**. Finally, diazotization followed by reduction using H_3PO_2 resulted in clopidogrel regioisomer with an overall yield of 36%. Another route (Scheme 1b) involves bromination of acid derivative **6** followed by esterification of bromo derivative **7**. Then, condensation of compound **8** and thieno-piperidine **9** furnished the clopidogrel regioisomer. Thieno-piperidine **9** is not commercially available and was synthesized as shown in the synthetic Scheme 2. However, these synthetic approaches have some disadvantages, such as lower overall yield (36%), usage of expensive and commercially unavailable starting material **1**, a higher number of steps (seven steps, including the preparation of **9**), usage of corrosive reagent bromine, pyrophoric reagent LAH, and expensive reagents $NaBH_4$ and $SnCl_2$. The iminium impurity was isolated from the peroxide degradation by preparative HPLC. Isolation of impurities by preparative HPLC is a laborious process. To the best of our knowledge, there is no commercial source nor a reported synthesis for iminium impurity. In view of the disadvantages associated with the synthesis of clopidogrel regioisomer and clopidogrel iminium, we intended to devise simple and short synthetic approaches. Herein we report a facile three-step synthesis for the regioisomer with an overall yield of 59% and a single-step synthesis for iminium impurity with 70% yield from the commercially available starting materials.

†Dr. Reddy's communication no. IPDO-IPM-00331

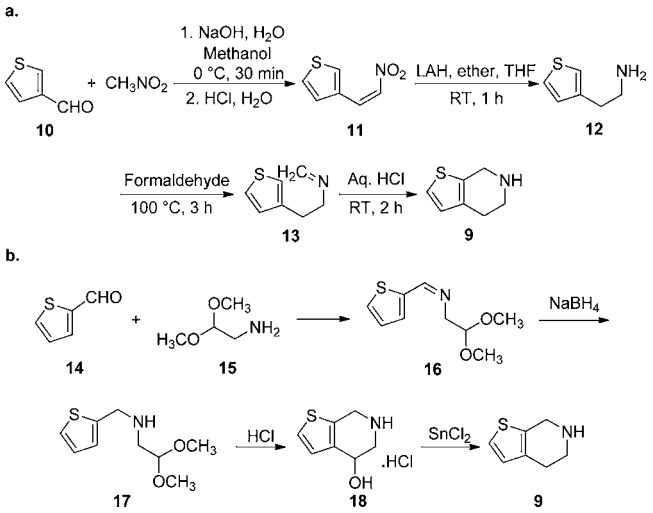
Received: May 2, 2012
Published: August 15, 2012

dx.doi.org/10.1021/op300110m | Org. Process Res. Dev. 2012, 16, 1523−1526

Scheme 1. Reported synthetic schemes for the clopidogrel regioisomer



Scheme 2. Reported synthetic schemes for thieno-piperidine 9



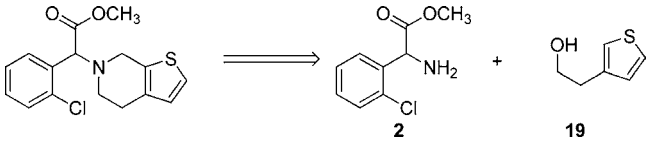


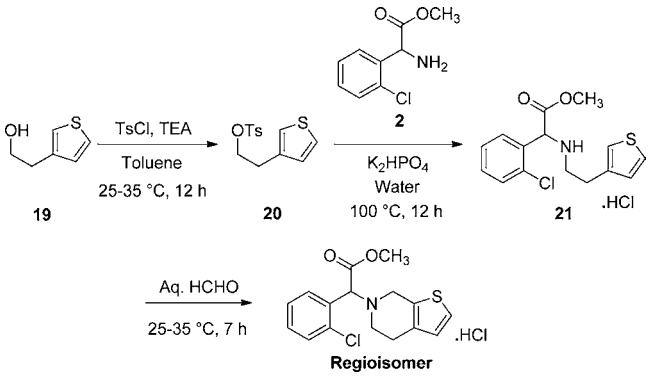
Figure 3. Retro-synthetic pathway of regioisomer.

RESULTS AND DISCUSSION

The retro synthetic analysis indicated that the regioisomer can be synthesized from the commercially available starting materials (see Figure 3).

On the basis of the retrosynthetic pathway, methyl 2-amino-(2-chlorophenyl)acetate (**2**) and 2-(thiophene-3-yl)ethanol (**19**) were identified as starting materials. Compound **19** was reacted with the *p*-toluenesulfonyl chloride in the presence of triethylamine in toluene followed by a typical workup that afforded the compound **20** with 99.2% purity in 93% yield. The thus-obtained tosyl derivative **20** was subjected to reaction with compound **2** in the presence of dipotassium hydrogen phosphate in water medium to afford *N*-alkylated compound **21** in 71% yield with 99.0% purity. Finally, compound **21** was converted into the hydrochloride salt of the regioisomer with 99.5% purity in 90% yield under Pictet–Spengler reaction conditions (Scheme 3). This newly designed synthetic scheme involves utilization of simple reactions and cheaply available reagents with an overall yield of 59%; thus, it is advantageous over the reported synthetic routes for the regioisomer.

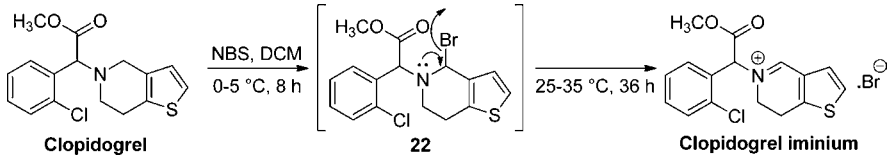
Scheme 3. New synthetic scheme for the clopidogrel regioisomer



Having developed a new and efficient synthetic route for regioisomer, we focused on moving towards the clopidogrel iminium impurity. In the reported literature clopidogrel iminium impurity was isolated from the peroxide degradation, which

dx.doi.org/10.1021/op300110m | *Org. Process Res. Dev.* 2012, 16, 1523–1526

Scheme 4. Synthetic scheme for clopidogrel iminium impurity



involves treatment of clopidogrel bisulfate with hydrogen peroxide at 80 °C for 3 h followed by isolation using preparative liquid chromatography (LC).[5] To have a straightforward synthesis, we embarked upon designing a synthetic route for the iminium impurity. On the basis of the structure of the clopidogrel iminium impurity, it was envisioned that bromination of clopidogrel and subsequent elimination of bromine would result in the bromide salt of the clopidogrel iminium impurity. Therefore, clopidogrel was subjected to bromination in the presence of *N*-bromosuccinimide (NBS) to provide a reaction intermediate, the bromo derivative **22** that upon warming converted into the bromide salt of clopidogrel iminium impurity in 70% yield with 99.5% purity (Scheme 4). Synthesis of clopidogrel iminium impurity following the newly developed synthetic route is simple and more cost-effective than the reported isolation method by preparative HPLC.

CONCLUSION

In conclusion, we have developed new and efficient synthetic approaches for the regioisomer and iminium impurity of clopidogrel bisulfate. These synthetic routes are concise, and start from the commercially available materials, and provide easy access to the synthesis of the regioisomer and the iminium impurity of chlopidogrel bisulfate.

EXPERIMENTAL SECTION

The ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, DMSO-d_6, and a mixture of $CDCl_3$ and DMSO-d_6 on a Varian Gemini 400 MHz, FT NMR spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS (δ 0.0), DMSO-d_6 (δ 39.50) and $CDCl_3$ (δ 77.0). FT IR spectra were recorded on the solid state as KBr dispersion using Perkin-Elmer 1650 FT IR spectrophotometer. The mass spectra (70 eV) were recorded on an HP-5989A LC−MS spectrometer. Melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. A liquid chromatograph equipped with a variable-wavelength UV detector and integrator was used in recording HPLC data.

2-(Thiophen-3-yl)ethyl Tosylate (20). To a solution of *p*-toulenesulfonyl chloride (40.8 g, 0.2140 mol) in toluene (100 mL) was added 2-(thiophene-3-yl)ethanol (**19**, 25 g, 0.1950 mol) and triethylamine (32.5 g, 0.3212 mol) at 0−5 °C. Then temperature was raised to 25−35 °C and stirred for 12 h. The unwanted solid was filtered and washed with toluene (2 × 25 mL). Total filtrates were combined, washed with water (2 × 50 mL) and concentrated below 70 °C under reduced pressure to furnish 51.4 g (93%) of brown colored oily compound with 99.2% purity by HPLC. IR (KBr, cm^{-1}): 3091, 1610, 1519, 1316, 1257, 1196, 1153, 824, 789; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 6.4 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 1H), 6.96 (s, 1H), 6.86 (d, J = 5.2 Hz,1H), 4.20 (t, J = 7.0 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 136.4, 133.0, 129.9, 128.3, 128.1, 125.9, 122.2, 70.0, 29.8, 21.7; Anal. Calcd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.0; S, 22.71; Found: C, 55.32; H, 5.04; S, 22.70.

Methyl 2-(2-Chlorophenyl)-2-(2-(thiophen-3-yl)ethylamino)acetate Hydrochloride (21). A mixture of compound **2** (25 g, 0.1252 mol), compound **20** (42.4 g, 0.1501 mol), dipotassium hydrogen phosphate (43.5 g, 0.2497 mol), and water (12.5 mL) was stirred at 100 °C for 12 h. Then the reaction mixture was cooled to room temperature, ethyl acetate (125 mL) and water (125 mL) were charged, and the mixture was stirred for 30 min. The aqueous layer was separated and extracted with ethyl acetate (25 mL). The combined organic layer was washed with water (50 mL), and aqueous HCl was slowly added (35%, 13.5 mL, 0.1294 mol) and stirred for 30 min at 10−15 °C. The resultant reaction mixture was heated to 60 °C, stirred for 15 min, and then cooled to 10−15 °C and stirred for 45 min. The precipitated solid was filtered and washed with ethyl acetate (25 mL). The wet solid was dried at 65 °C under reduced pressure to provide 31 g (71%) of a white solid with 99.0% purity by HPLC. Mp: 169 °C; IR (KBr, cm^{-1}): 3444, 3068, 2921, 1741, 1583, 1436, 1325, 1269, 1219, 1190, 1039, 786, 755; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.55−7.48 (m, 3H), 7.27 (s, 1H), 6.99 (d, J = 4.8 Hz, 1H), 5.58 (s, 1H), 3.74 (s, 3H), 3.17−3.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 136.6, 134.8, 131.7, 130.5, 130.4, 128.5, 127.9, 127.3, 126.0, 122.2, 58.6, 53.7, 45.8, 26.3; HRMS (ESI): Calcd for $C_{15}H_{16}ClNO_2S$ (M^+ + H) 310.0669, Found 310.0656.

Methyl 2-(2-Chlorophenyl)-2-(4,7-dihydrothieno[2,3-*c*]pyridin-6(5*H*)-yl)acetate Hydrochloride (Clopidogrel Regioisomer). The mixture of compound **21** (15 g, 0.0433 mol) and aq formaldehyde solution (37%, 120 mL, 1.3875 mol) was stirred for 7 h at 25−35 °C. The precipitated solid was filtered, washed with acetone (15 mL), and dried at 65 °C under reduced pressure to afford 14 g (90%) of an off-white solid with 99.5% purity by HPLC. Mp: 148 °C; IR (KBr, cm^{-1}): 2953, 1757, 1591, 1434, 1325, 1243, 1220, 1159, 1063; ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37−7.30 (m, 2H), 7.14 (d, J = 4.8 Hz, 1H), 6.80 (d, J = 5.6 Hz, 1H), 5.10 (s, 1H), 3.97 (d, J = 8.0 Hz, 2H), 3.75 (s, 3H), 3.06 (d, J = 4.4 Hz, 2H), 2.82 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 169.5, 134.0, 132.4, 129.7, 129.6, 129.4, 127.0, 126.3, 122.7, 65.8, 52.0, 48.9, 47.5, 23.9; HRMS (ESI): Calcd for $C_{16}H_{17}ClNO_2S$ (M^+ + H) 322.0669, Found 322.0670.

5-[(2-Chlorophenyl)methoxycarbonylmethyl]-6,7-dihydrothieno[3,2-*c*]pyridin-5-ium Bromide (Clopidogrel Iminium). To a solution of clopidogrel (25 g, 0.0777 mol) in dichloromethane (500 mL) was added *N*-bromosuccinimide (14 g, 0.0786 mol) at 0−5 °C over a period of 15 min. The resultant reaction mixture was stirred for 8 h at 0−5 °C, warmed to room temperature, and stirred for 36 h. The reaction mixture was concentrated under reduced pressure below 55 °C. Acetone (50 mL) was charged and stirred for 1 h at room temperature. The precipitated solid was filtered and washed with acetone (5 mL); the wet solid was dried at 55 °C under reduced pressure to furnish 21.8 g (70%) of pale-yellow solid with 99.5% purity by HPLC. Mp: 157 °C; IR (KBr, cm^{-1}): 3039, 2903, 1738, 1621, 1512, 1225, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.92 (d, J = 8.8 Hz,

dx.doi.org/10.1021/op300110m | *Org. Process Res. Dev.* 2012, 16, 1523−1526

1H), 7.59 (d, J = 4.8 Hz, 1H), 7.44−7.37 (m, 4H), 7.30 (d, J = 5.2 Hz, 1H), 4.45−4.38 (m, 1H), 3.84 (s, 3H), 3.82−3.74 (m, 1H), 3.57−3.48 (m, 1H), 3.33−3.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 162.0, 152.9, 134.9, 133.6, 132.4, 130.9, 128.9, 128.8, 128.5, 127.7, 127.3, 71.2, 54.1, 47.6, 23.6; HRMS (ESI): Calcd for $C_{16}H_{15}ClNO_2S$ (M^+) 320.0512, Found 320.0523.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the management of Dr. Reddy's Laboratories Ltd., IPDO, Bachupally, for supporting this work.

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