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Process Improvements of Prasugrel Hydrochloride: An Adenosine Diphosphate Receptor Antagonist†

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ABSTRACT: An improved process for the synthesis of prasugrel hydrochloride with an overall yield of 58%, 99.9% purity, and meeting all other quality requirements is described.

INTRODUCTION

Prasugrel hydrochloride (5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride), is a novel platelet inhibitor developed by Daiichi Sankyo & Co. for acute coronary syndrome (ACS). The United States Food and Drug Administration (USFDA) approved the use of prasugrel for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI).[1] Prasugrel is a member of the thienopyridine class of adenosine diphosphate (ADP) receptor inhibitors, like ticlopidine and clopidogrel. These agents reduce the aggregation ("clumping") of platelets by irreversibly binding to $P2Y_{12}$ receptors. Compared to clopidogrel, prasugrel inhibits ADP-induced platelet aggregation more rapidly and more consistently in healthy volunteers and in patients with coronary artery disease, including those undergoing PCI.[2]

Though many synthetic schemes were reported for the synthesis of prasugrel,[3−7] *N*-alkylation of thienopyridine derivative **2** with cyclopropyl ketone derivative **3** followed by acetylation and hydrochloride salt formation is the convenient and the most practiced route.[8−14] Most of the reported processes using this synthetic route involve isolation of the *N*-alkylated compound **4** followed by acetylation with a low overall yield. Moreover isolation of compounds **4** and **5** involves tedious workup process including extraction, evaporation of the solvent followed by isolation of the solid product using solvent and anti-solvent technique.[8−10] In recently reported processes[11−14] acetylation was carried out without isolation of the *N*-alkylated compound **4**, but involved the usage of a relatively expensive base, diisopropylethyl amine, cumbersome workup process for the isolation of the solid product, lower purity, and a moderate overall yield. Considering these disadvantages we intended to develop an efficient and commercially viable process for prasugrel HCl, we have subjected this synthetic route to further studies. In this article, we describe an improved process with an overall yield of 58% for three steps including *N*-alkylation, acetylation, and hydrochloride salt formation, examining all the disadvantages associated with the reported processes.

RESULTS AND DISCUSSION

Our improved process also starts with the *N*-alkylation using commercially available materials, **2** and **3** (Scheme 1). The initial experiments carried out for the reaction of **2** and **3** in *N*,*N*-dimethylformamide using potassium carbonate resulted in low yield and purity. These experiments indicated that the solvent and the base are to play a major role in the *N*-alkylation reaction.

Various solvents were examined for the reaction of **2** and **3** including acetonitrile, dichloromethane, acetone, isopropyl alcohol, ethyl acetate, and *N*,*N*-dimethylformamide. Apart from acetonitrile all other solvents furnished either lower yield or less purity; experimental results are presented in Table 1. Hence, the use of acetonitrile would be appropriate for the reaction of **2** and **3**.

After selecting the acetonitrile as a solvent for the *N*-alkylation reaction, another key parameter was studied by screening of bases. Using sodium bicarbonate and potassium bicarbonate, very little product formation was observed, whereas triethylamine resulted in very low purity. On the other hand higher yield and purity were obtained using sodium carbonate as a base. On the basis of these results, sodium carbonate was found to be the suitable base for the reaction of **2** and **3** (Table 2).

The solid byproduct was filtered after completion of the *N*-alkylation reaction, and the filtrate was used without isolation of compound **4** in the next reaction, acetylation. This reaction was carried out using acetic anhydride in the presence of a base and catalytic amount of 4-dimethylaminopyridine. Without 4-dimethylaminopyridine, the rate of reaction is found to be slow and requires more than 15 h for the completion of the reaction, whereas the catalytic amount of 4-dimethylaminopyridine completed the acetylation within 4 h. The reported

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Scheme 1. Synthetic scheme for prasugrel hydrochloride

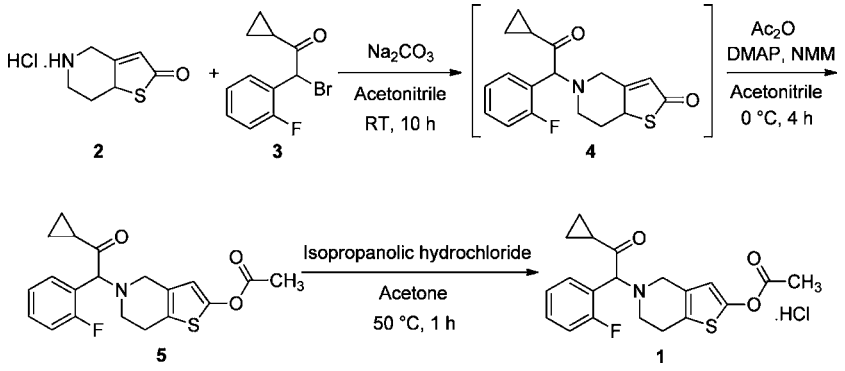

Table 1. Screening of solvents for the reaction of 2 and 3

entry	solvent	purity (%)	yield (%)[a]
1	acetonitrile	90.1	85
2	acetone	83.3	74
3	dichloromethane	63.8	75
4	*N*,*N*-dimethylformamide	65.2	70
5	isopropyl alcohol	75.0	61
6	ethyl acetate	82.6	80

[a]Isolated yield (solvent was evaporated to obtain the oily compound).

Table 2. Screening of base for the N-alkylation reaction

entry	base	purity (%)	yield (%)[a]
1	triethylamine	55.6	90
2	sodium bicarbonate[b]	–	–
3	sodium carbonate	94.7	95
4	potassium bicarbonate[b]	–	–
5	potassium carbonate	91.0	84

[a]Isolated yield. [b]Product formation is very low, therefore not isolated.

processes involve the use of triethylamine[10,11] and diisopropyl ethylamine[12,13] as a base. However, our experimental results revealed that the use of *N*-methylmorpholine as a base would increase the yield and the purity significantly (Figure 1).

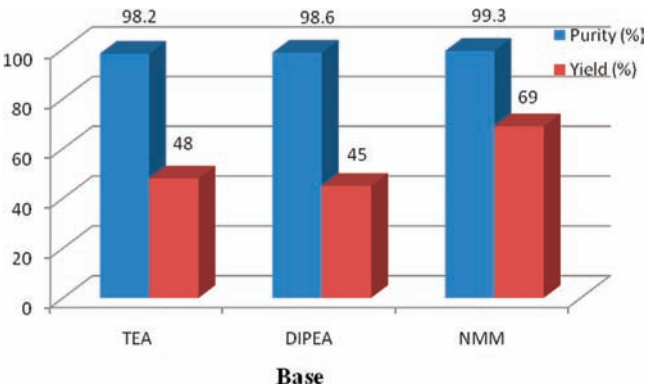

Figure 1. Selection of base for acetylation.

After studying the parameters of the key process, we focused the attention on the workup process. In the processes reported, after completion of the acetylation reaction, the product was extracted with a solvent followed by evaporation of the solvent and isolation of the solid using either a mixture of solvents[10] or a single solvent.[11,13] This tedious workup process was significantly simplified by isolating the solid directly from the reaction mixture by addition of water. Recrystallization from the mixture of acetonitrile and water provided high-quality prasugrel (>99.7% purity by HPLC).

Having achieved high purity of prasugrel, our next task was to study the prasugrel hydrochloride salt formation. Preparation of prasugrel hydrochloride according to the process reported[8] using aqueous hydrochloric acid in acetone resulted in more desacetyl prasugrel **4** (~0.25%). This indicates that, prasugrel is more susceptible to the desacetylation in aqueous hydrochloric acid medium. Therefore, to control the desacetylation and avoid the aqueous medium, isopropanolic hydrochloride was used instead of aqueous hydrochloric acid. Applying this modification, formation of desacetyl prasugrel **4** was significantly reduced (<0.10%).

It was also observed that, the temperature of hydrochloride salt formation reaction plays a major role on acetone content in the final solid. At lower temperatures (≤40 °C) higher acetone content was observed, while at higher temperatures (≥45 °C) the acetone content was well within the limit (5000 ppm). It was found that 50 °C would be optimum for the prasugrel hydrochloride salt formation (Figure 2). 2-Chloropropane, the

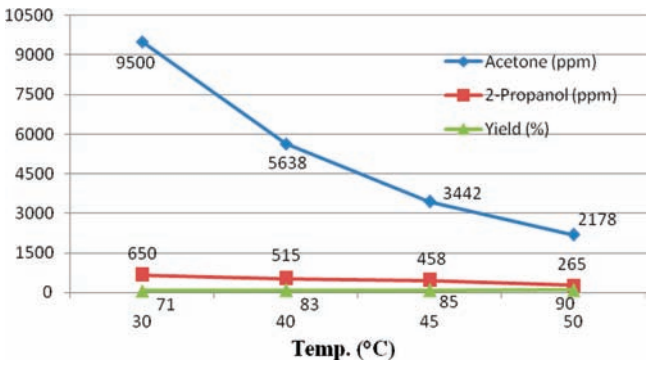

Figure 2. Effect of temperature on residual solvents.

byproduct formed from the isopropanolic hydrochloride during the salt formation reaction was observed around 12 ppm in the prasugrel hydrochloride.

Further, it was identified that the concentration of isopropanolic hydrochloride also had a significant influence on the acetone content. The acetone content is higher when the concentration of isopropanolic hydrochloride is high (Figure 3). The reason for the higher content of acetone in the solid may be explained by acetone being trapped in the crystal lattice due to the fast crystallization when the higher

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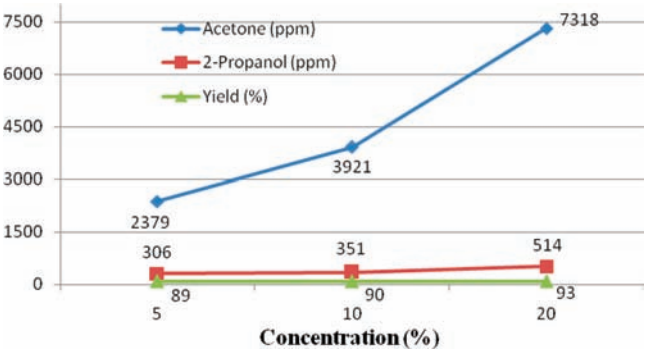

Figure 3. Effect of isopropanolic HCl concentration on residual solvents.

concentration of isopropanolic hydrochloride is used. The experimental results indicates that, 5% isopropanolic hydrochloride is preferable for the preparation of prasugrel hydrochloride.

Finally, the redesigned process furnished the prasugrel hydrochloride with an overall yield of 58% (from three steps, *N*-alkylation, acetylation, and hydrochloride salt formation), around 99.9% purity and meeting other quality parameters (Table 3).

CONCLUSION

In conclusion, we have developed an efficient and commercially viable process for the synthesis of prasugrel hydrochloride, meeting all the quality requirements with an overall yield of 58% and high purity (~99.9% by HPLC).

EXPERIMENTAL SECTION

A liquid chromatograph equipped with variable wavelength UV detector and integrator was used in recording HPLC. Mass spectra were obtained using a 4000-Q-trap LC−MS/MS mass spectrometer. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ at 500 and 125 MHz, respectively, on Unity INOVA (Varian 500 MHz) FT NMR spectrometer, the chemical shifts are reported in δ ppm relative to TMS (δ 0.00 ppm) and $CDCl_3$ (δ 77.00 ppm). IR spectra were recorded on a Perkin-Elmer FT IR instrument (KBr pellet method). The thermal analysis was carried out on DSC Q1000 TA. The thermogram was recorded from 40 to 220 °C under the nitrogen flow of 50 mL/min at a heating rate of 10 °C/min. The solvents and reagents were used without further purification.

5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (Prasugrel base). To a suspension of **3** (10.55 kg, 89% assay, 36.5208 mol), sodium carbonate (8.5 kg, 80.1887 mol) in acetonitrile (35 L) was added **2** (7.0 kg, 36.5192 mol) at 25−35 °C. The resulting reaction mixture was stirred for 10 h at 25−35 °C. The solid byproduct was filtered off, and the obtained filtrate was cooled to 0 °C. *N*-Methylmorpholine (7.39 kg, 73.0598 mol), 4-dimethylaminopyridine (49 g, 0.4011 mol), and then acetic anhydride (5.6 kg, 54.8535 mol) were added at 0 °C and stirred for 4 h. Water was charged (49 L) and stirred for 1 h at 0 °C; the precipitated solid was filtered and washed with the mixture of acetonitrile (7 L) and water (7 L). The wet solid was transferred into acetonitrile (35 L), heated to 50 °C, and stirred for 10 min. The resulting clear solution was cooled to 0 °C, and water (28 L) was added and stirred for 2 h. The solid precipitate was filtered and washed with a mixture of acetonitrile (35 L) and water (35 L). The wet solid was dried for 6 h at 60 °C to furnish 9.0 kg (66.0%) of the title compound with 99.8% purity by HPLC; DSC: 120−122 °C; Mass: 374 $(M + H)^+$; IR (KBr, cm^{-1}): 3085, 2989, 1758, 1703, 1585, 1493, 1368, 1193; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (t, J = 7.5 Hz, 1H), 7.32 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 9.0 Hz, 1H), 6.26 (s, 1H), 4.83 (s, 1H), 3.55 (d, J = 14.0 Hz, 1H), 3.48 (d, J = 14.0 Hz, 1H), 2.89 (m, 1H), 2.79 (m, 2H), 2.76 (m, 1H), 2.28 (m, 1H), 2.26 (s, 3H), 1.03 (m, 2H), 0.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 167.8, 162.5, 160.1, 149.5, 130.6, 129.2, 125.7, 124.4, 121.8, 115.9, 111.9,71.5, 50.5, 48.4, 24.9, 20.7, 18.4, 12.1, 11.5.

Prasugrel Hydrochloride. To a solution of prasugrel base, **5** (6 kg, 16.0668 mol) in acetone (60 L) was added isopropanolic hydrochloride (11.16 L, assay 5.0%, 15.2876 mol) slowly at 50 °C and stirred for 1 h. The reaction mixture was cooled to room temperature and filtered. The wet solid was washed with acetone (6 L) and dried under reduced pressure at 70 °C to furnish 5.8 kg (88.0%) of the title compound with 99.91% purity by HPLC; DSC: 191.8 °C. Residual solvents: acetonitrile: ND, acetone: 1973 ppm, isopropyl alcohol: 278 ppm, 2-chloropropane: 8 ppm. Mass: 374 $(M + H)^+$; IR (KBr, cm^{-1}): 3086, 2957, 2436, 2387, 1758, 1690, 1593, 1493, 1326, 1213; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0 (m, 1H), 7.55 (m, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 9.0 Hz, 1H), 6.40 (br, 1H), 5.72 (br, 1H), 4.65−2.88 (m, 6H), 2.30 (s, 3H), 1.82 (br, 1H), 1.30−0.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 167.2, 161.0, 151.3, 133.3, 132.6, 126.1, 123.2, 122.4, 116.5, 115.2, 110.9, 66.4, 49.5, 47.6, 22.2, 20.6, 19.8, 13.2.

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Notes

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Table 3. Final quality data of prasugrel hydrochloride

		residual solvents (ppm)				
entry	purity (%)	acetone	isopropanol	acetonitrile	2-chloropropane	yield (%)[a]
1	99.91	1973	278	ND	8	58.1
2	99.90	2675	347	ND	9	58.0
3	99.91	2763	381	ND	12	57.8

[a]Overall isolated yield; ND = not detected.

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