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An efficient and large scale synthesis of Clopidogrel: Antiplatelet drug

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ABSTRACT

*An efficient and large scale process for clopidogrel (**1**) is described. The process features high yielding transformations employing simple operations and recoverable solvents.*

Keywords: Clopidogrel, Strecker synthesis, Electrophilic cyclization, large scale synthesis.

INTRODUCTION

(S)-(+)-Clopidogrel bisulfate **1•H_2SO_4** (Plavix, Figure 1), is a potent oral antiplatelet agent often used in the treatment of coronary artery, peripheral vascular and cerebrovascular diseases. It is marketed by Bristol-Myers Squibb and Sanofi-Aventis under the trade name Plavix® and licensed by Sanofi in 1986. The mechanism of action of clopidogrel is irreversible blockade of the adenosine diphosphate (ADP) receptor P2Y12 and is important in platelet aggregation, the cross-linking of platelets by fibrin.[1, 2] Recent studies have shown that the clopidogrel is more effective in blocking platelet aggregation than aspirin and ticlopidine even at much lower dosage.[3]

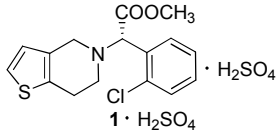


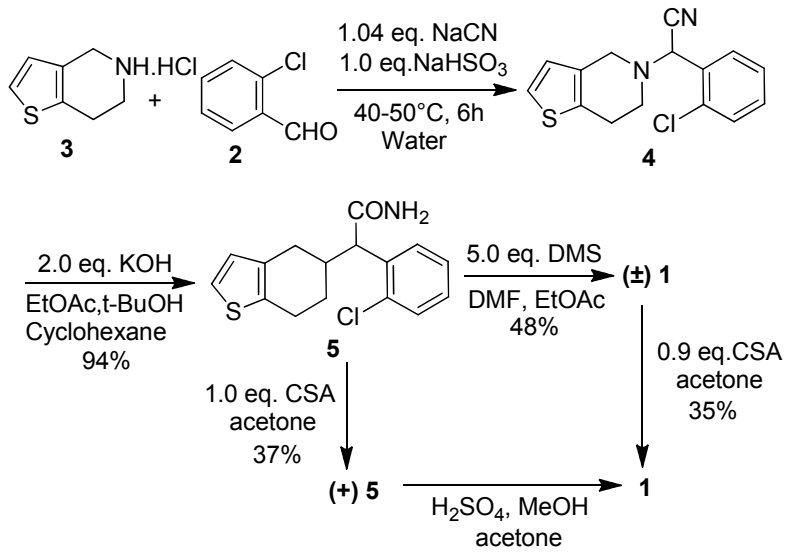
Figure 1. (S)-(+)-Clopidogrel bisulfate

Whilst there are many routes to Clopidogrel,[4-9] we focused on two which have potential for industrial manufacturing with some limitations that can be addressed. The first synthetic route for (S)-(+)-Clopidogrel bisulfate **1•H_2SO_4** as shown in Scheme 1 started with the condensation of *o*-chloro benzaldehyde **2** with 4, 5, 6, 7-tetrahydrothieno [3, 2-c] pyridine **3** by employing Strecker synthesis that afforded cyano intermediate **4**. Subsequently, cyano intermediate **4** converted to amide **5**. Reaction of amide **5** in methanol and acidic reagent afforded racemic Clopidogrel, which was resolved using L-camphorsulfonic acid to afford (S)-(+)-Clopidogrel **1**.

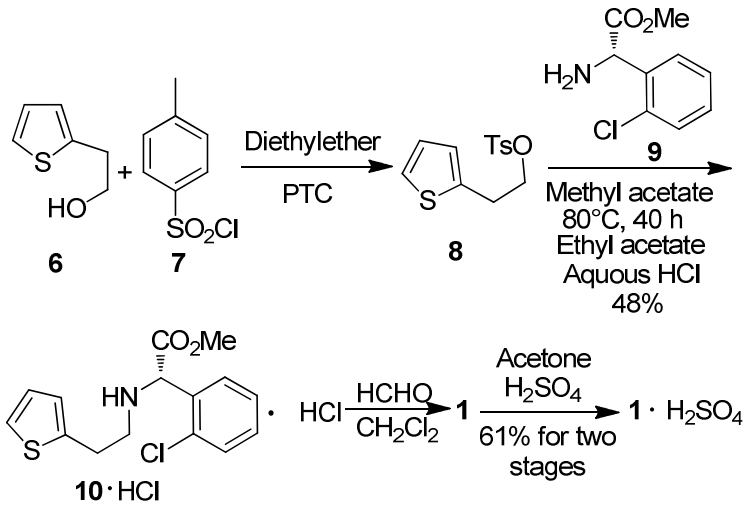
The second synthetic route for preparation of (S)-(+)-Clopidogrel **1** as shown in Scheme 2 commences with tosylation of thiophene-2-ethanol **6** with p-toluenesulfonyl chloride (p-TSA) **7** in the presence of phase transfer catalyst affording 2-(2-Thienyl) ethyl tosylate **8**, which upon reaction with (+)-α-amino-2-chloro phenyl acetic acid methyl ester **9** afforded substituted intermediate **10•HCl**. Finally, this intermediate undergoes reaction with formaldehyde followed by electrophilic cyclization and salt formation to obtain bisulfate salt of **1•H_2SO_4**.

Despite the proven potential of the Scheme 1 and 2, there are certain disadvantages; a) condensation of *o*-chloro benzaldehyde **2** with 4, 5, 6, 7-tetrahydrothieno [3, 2-c] pyridine **3** in water medium is not process friendly due to formation of lumps during the reaction and workup. Moderate yields were obtained by replacing water with organic solvents like methanol and toluene, b) isolation of **5** involves tedious workup process including extraction, washings, evaporation of the solvent and isolation of the solid using non-polar solvent like hexane, c) synthesis of **5** involves usage of a multisolvent system, making the process less viable for commercial production, d) conversion of (+) enantiomer of amide compound **5** to Clopidogrel in acidic medium at high temperature leads to racemisation, e) low yielding during the conversion of **5** to racemic Clopidogrel bisulphate **1**, f) racemisation during the condensation of **8** and **9** and g) use of expensive and partially recoverable solvents like diethyl ether, t-butyl acetate, methyl acetate in high volumes for the synthesis of **10**.

Scheme 1. Precedented Synthetic Approach



Scheme 2. Patented Synthetic Approach



Herein, we present our efforts to avoid all the disadvantageous factors involved in Scheme 1&2 and achieve cost effective, high yielding and moderately greener process for clopidogrel **1** and its pharmaceutically acceptable H_2SO_4 salt.

MATERIALS AND METHODS

Experimental section

Solvents and reagents were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}C spectra were measured in DMSO-d_6 using 200 or 400 MHz on a Varian Gemini & Varian Mercury plus 2000 FT NMR spectrometer; the chemical shift were reported in δ ppm. IR spectrum recorded in the solid state as KBr dispersion using Perkin Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on HP 5989 A LC MS spectrometer. The melting points were determined by using the capillary method on Polmon (Model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

Preparation of (±) -(2-Chlorophenyl)-(6,7-dihydro)-4H -thieno (3, 2-c) pyrid-5- yl) acetamide (5)

To a stirring solution of sodium cyanide (7 kg, 142 mol) and water (35 L) at about 28 °C was simultaneously added slowly o-chlorobenzaldehyde (20 kg, 142 mol) and 6,7-dihydro-4H -thieno (3,2-c) pyridine hydrochloride solution (25 kg in 90 L water) for about 30 minutes. Reaction mass stirred at 60°C for 3 h, dichloromethane (100 L) is added to the reaction mixture at about 28°C. The layers were separated and aqueous phase was extracted with dichloromethane (50 L), combined organic layers were washed with water (50 L). The clear organic layer was distilled completely under vacuum below 40 °C to afford the compound **4**. Compound **4**, t-butanol (200 L), potassium hydroxide (23.2 kg, 414 mol) and water (12 L) is charged into round bottom flask. After stirring for 3 h at 80 °C, the reaction mass was cooled to 25 °C and quenched with water (400 L) under stirring. After stirring for 30 minutes at 28 °C, the separated solid was filtered and washed with water (40 L) and dried and vacuum at 65 °C for 4 h to afford

compound **5** (42.02 Kg) in 92% yield and >98.9 % purity. Spectroscopic data were found to be in agreement with the data collected from authentic sample of intermediate **5**.

Preparation of racemic clopidogrel (1) bisulphate salt

To a stirring solution of methanol (90 L) and sulfuric acid (26 L, 488 mol) was added dimethyl sulfate (15.5 L, 163 mol) at 10°C. After stirring the reaction mixture at 70 °C for 90 minutes, cooled to 28 °C and compound **5** (25 kg, 81 mol) was added. After stirring the reaction mixture at 70 °C for 35 hr cooled to 28 °C. Dichloromethane (125 L) and water (250 L) was added to the reaction mixture at 27 °C. The layers were separated and aqueous phase was extracted with dichloromethane (3 x 50 L), combined organic layers were washed with 5% sodium carbonate solution (2 x 100 L) and water (125 L). The clear organic layer was distilled completely under vacuum below 40 °C to afford the crude racemic Clopidogrel **(±) 1**. To the solution containing Acetone (100 L) and crude racemic clopidogrel was added sulfuric acid at (2.5 L) at 10°C. After stirring at 12 °C for 90 minutes water (2.5 L) is added. After stirring for 55 °C for 15 minutes cooled to 12 °C and further stirred at 12 °C for 90 minutes. The separated solid was filtered and washed with acetone (25 L) and dried under vacuum at 65 °C for 4 h to afford compound **(±) 1** (23.0 Kg) in 67.2% yield and >98.7% purity. Spectroscopic data were found to be in agreement with the data collected from authentic sample of intermediate **(±) 1**.

Preparation of Clopidogrel hydrogen sulphate (1•H_2SO_4) salt

Racemic clopidogrel bisulfate (350 Kg) and dichloromethane (1400 L) was charged into a reactor and cooled to 3 °C. Reaction mixture pH was adjusted to 7.6 with a sodium carbonate solution (190 kg of in 900 L of water). Organic layer was separated, aqueous layer was extracted with dichloromethane (2x350 L) and combined organic layer was washed with water (2x 300 L). The organic layer was then concentrated under vacuum at a temperature of 60 °C. To the resultant residue acetone (1470 L) was added at 30 °C and stirred for clear dissolution. Water (14 L) and L-(-)-camphor sulfonic acid monohydrate (200 kg) was added to the above reaction mass, and stirred for 45 minutes. (+)-Clopidogrel camphor sufonate (0.15 kg) was added as a seed compound and reaction mass was stirred for 18 hr at 30 °C. The separated solid was filtered and washed with acetone (130 L) and dried under vacuum at 42 °C for 10 h to afford (+)-Clopidogrel camphor sufonate (150 kg) in 64.9% yield with chiral purity 99.55%. (+)- Clopidogrel camphor sulfonate obtained above (80 kg) and dichloromethane (350 L) charged into a reactor and cooled to 2 °C. Reaction mixture pH was adjusted to 7.0 with a 10% sodium carbonate solution (80 L). Organic layer was separated, aqueous layer was extracted with dichloromethane (2 x 120 L) and combined organic layer was washed with water (2 x 120 L). The organic layer was then concentrated under vacuum at a temperature of 47 °C. To the resultant residue, 2-butanol (90 L) was added and solvent was distilled off at 53 °C under vacuum of 620 mm Hg. Thereafter, traces of dichloromethane were removed using nitrogen purging for 30 minutes. Solvent 2-butanol (800 L) was added to the reaction mass at 40 °C and stirred for 15 minutes. Activated charcoal (4.0 kg) was added to the reaction mass and stirred for 10 minutes. The reaction mass was then filtered through a leaf filter, online and cartridge filters into another reactor. The filter bed was washed with 2-butanol (100 L). Sulfuric acid (7.3 liters of 98%) was added to the reaction mass slowly at 24 °C. The reaction mass was seeded with 450 g of pure (+)-Clopidogrel bisulfate and maintained for about 12 hr. The reaction mass was then cooled to about 23 °C and maintained for about 2 hr. The separated solid is filtered, and the wet cake was washed with of 2-

butanol (80 L) and cyclohexane (40 L), dried under vacuum at 100 °C for 22 h to afford (+)-Clopidogrel (34.7 kg) in 56.9% yield.

MS (m/z): 322 (M^++1); IR (KBr cm^{-1}): 3121, 3080, 2956, 2852, 2509, 1753.; ^{1}H NMR (200 MHz,$CDCl_3$) δ: 7.50-7.80 (m, 4H), 5.60 (s, 1H), 4.21 (br, s, 2H), 3.10 (br, s, 2H), 7.44 (d, 1H, J = 5.2 Hz), 6.90 (d, 1H, J = 5.2 Hz), 3.45 (br, s, 2H), 3.76(br, s, 3H).

Regeneration of racemic clopidogrel (1) bisulphate salt from (+)-ClopidogreI camphor sulfonate filtrate.

1300 liters of the mother liquor (filtrate) obtained in the process similar to that described in the above after isolation of (+)-clopidogreI camphor sulfonate was taken into a reactor. The solvent was distilled under vacuum at 56°C until a volume of the mother liquor of 775 liters was achieved. Sulfuric acid (30 L, 98%) was slowly added to the above reaction mass at a temperature of 22°C and stirred for 4 hours and 30 minutes. The separated solid was filtered and the solid was washed with acetone (50 L) to yield the racemic Clopidogrel bisulfate. The obtained wet compound is purified by slurred in acetone to afford 105 kg of the title compound with 99.57% of purity.

Preparation of (+)-α-{(2-thien-2-yl)-ethyl amino}-α-(2-chloro phenyl) methyl acetate hydrochloride (10 • HCl).

Thiophene-2-ethanol (100 kg) is added to reaction mass containing toluene (400 L) and para-toluene sulfonyl chloride (163.2 kg) at about 5 °C followed by triethylamine (130 kg) was added at about 5 °C. After stirring for 8 h at 30°C, the separated solid was filtered and washed toluene (100 L). The obtained filtrate was washed with water (200 L); about 250 L of solvent from the reaction mass was collected by distillation. To the resultant reaction mass containing **8** in toluene (250 L) were added dipotassium hydrogen phosphate (336.81 kg), (S)-(+)-isomer of amino-(2-chlorophenyl)-acetic acid methyl ester (130 kg). After stirring for 30 h at 100°C, toluene (380 L) and water (1125 L) was added at 30 °C. The layers were separated, the aqueous phase was extracted with toluene (100 L), and the combined organic phase was washed with water (250 L). To the clear organic layer aqueous HCL (64 L) was added at 10 °C. After stirring for 1 h, separated solid is filtered at 35 °C and washed with toluene (100 L). To the obtained wet compound acetone (1000 L) and aqueous HCl (57 L) were added and heated to 55 °C. After stirring for 15 minutes at 55 °C, reaction mass is cooled to 15 °C, and the separated solid was filtered and washed with acetone (100 L) and dried under vacuum at 60 °C for 4 h to afford 151.2 kg of title compound **10 • HCl** with 99.9% of chemical purity and 99.6% of chiral purity.

[α]D20: +116° (c=1.0 % methanol); MS (m/z): 310.4 (M^+); IR (KBr cm^{-1}): 3465, 2923, 1740, 1219, 1036; ^{1}H NMR (200 MHz,$CDCl_3$) δ: 6.8-8.2 (m, 7H), 5.6 (s, 1H), 3.8 (s, 3H), 10.7 (s, 1H), 3.0-3.2 (m, 2H), 3.4-3.6 (m, 2H).

(+)-Methyl-(2-chlorophenyl)-(6,7-dihydro)-4H-thieno(3,2-c)pyrid-5-yl)acetate bisulfate salt (1 •H_2SO_4)

Suspension of **10 • HCl** salt (100 kg, 289 moles) and aqueous formaldehyde solution (37-41%, 500 L), was stirred for 20-22 h at 30°C. After completion of the reaction, the reaction mass was filtered and dichloromethane (300 L) was added to the filtrate and reaction mass was neutralized (pH = 6.5-7.5) with 10% aqueous sodium carbonate solution. Layers were separated, aqueous

layer was extracted with dichloromethane (2 X 250 L) and the combined organic layer was washed with water (200 L). The organic phase was concentrated under vacuum at below 40 °C to get the syrup. This syrup was diluted with acetone (980 L) and water (20 L). Reaction mixture was cooled to 10-15 °C and H_2SO_4 (98%, 26 kg, 265 moles) was added drop wise to the reaction mixture at 10-15 °C and Clopidogrel bisulfate was added as a seed (1.0 kg, 2.38 moles) to the reaction mixture. The suspension was stirred at 10-15 °C for 4 h and separated solid was filtered and washed with acetone (100 L) and dried at 60-65 °C to give the 95 kg (76% yield and 99.8% HPLC purity) of **1 •H_2SO_4** as off white color solid. MS (m/z): 322 (M^++1); IR (KBr cm^{-1}): 3121, 3080, 2956, 2852, 2509, 1753.; ^{1}H NMR (200 MHz,$CDCl_3$) δ: 7.50-7.80 (m, 4H), 5.60 (s, 1H), 4.21 (br, s, 2H), 3.10 (br, s, 2H), 7.44 (d, 1H, J = 5.2 Hz), 6.90 (d, 1H, J = 5.2 Hz), 3.45 (br, s, 2H), 3.76(br, s, 3H); MP: 171-176°C.

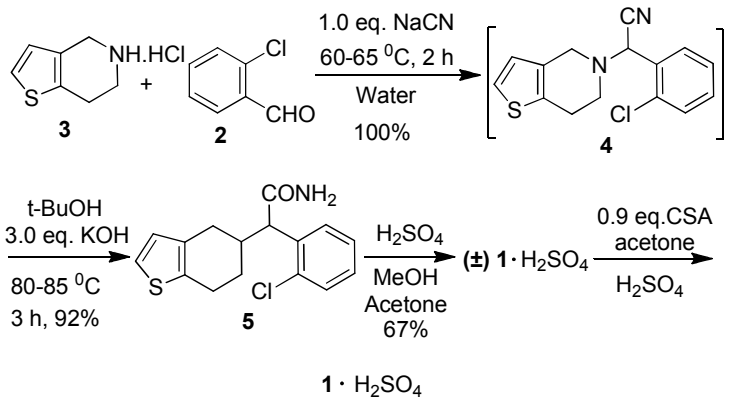
RESULTS AND DISCUSSION

Herein, we reported improved process for the synthesis of Clopidogrel **1**, as shown in Scheme 3, starting with the reaction of *o*-chloro benzaldehyde **2** with 4, 5, 6, 7-tetrahydrothieno [3, 2-c] pyridine **3** by employing Strecker synthesis that afforded intermediate **4**. We avoided lumps formation by addition of *o*-chloro benzaldehyde **2** and 4, 5, 6, 7-tetrahydrothieno [3, 2-c] pyridine **3** solution to the aqueous sodium cyanide at 25-35 °C. Subsequently, this intermediate **4** converted *in situ* to amide intermediate **5** in 92% yields and 98% purity for the two steps. Tedious workup process for the isolation of **5** was significantly simplified by isolating the solid directly from the reaction mixture after completion of reaction. Further, amide compound **5** was converted to racemic clopidogrel **(±) 1** rather than resolution of racemic amide compound **5**. Reaction of amide **5** with methanol in the presence of sulfuric acid and dimethyl sulfate to afford methyl ester **(±) 1** in 67% yield. Desired isomer of Clopidogrel **1** is separated from the racemic Clopidogrel by using L-(-)-camphor sulfonic acid (CSA) as a resolving reagent. Bisulphate salt of Clopidogrel **1** was prepared by employing sulfuric acid.

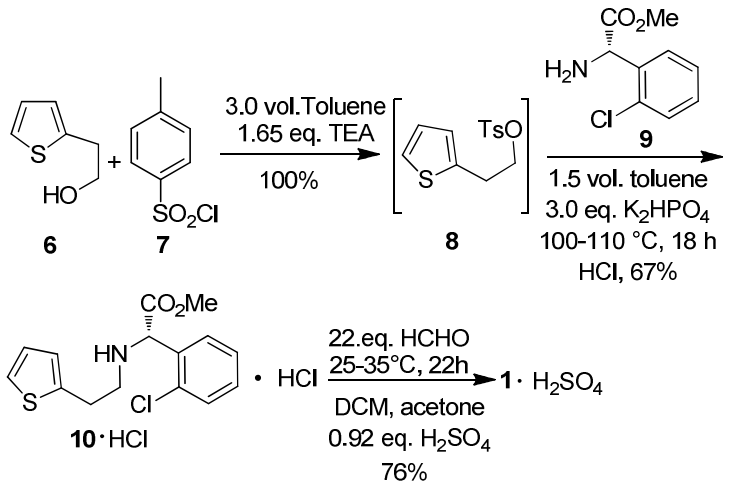
In order to improve the process, the synthesis of Clopidogrel bisulphate **1**•H_2SO_4, as shown in Scheme 4 starts with tosylation of compound **6** with **7** in the presence of triethylamine and toluene. Subsequently, tosyl intermediate **8** was subjected *in situ* to condensation with compound **9** in the presence of dipotassium hydrogen phosphate to afford penultimate intermediate **10** and further reaction with HCl afforded **10** as the HCl salt with overall 67% yield, 99.9% chemical purity and 99.6% chiral purity for two stages. In the reported processes, [5-6] condensation reaction (**8** with **9**) performed in methyl acetate, ethyl acetate and acetonitrile solvent. Isolation of **10** as its HCl salt using aq. HCl in methyl or ethyl acetate solvents we observed corresponding alcohol and acid impurities out of solvent and it further effect the solvent recovery and quality of compound **10**. At our end, we have opted non-hydrolytic, inexpensive and highly recoverable solvents like toluene instead of methyl acetate, ethyl acetate and acetonitrile to avoid solvent impurities.

Apart from the solvent impurities, there are some additional demerits associated with the reported procedures, [5-6] including racemisation in the reaction of **8** and **9** and purification of **10 • HCl** salt. To find the route cause for enhancement of undesired enantiomer (R-isomer) of compound **10**, the following key parameters were studied thoroughly.

Scheme 3. Improved Synthetic Approach



Scheme 4. Improved Synthetic Approach



1. Impact of dipotassium hydrogen phosphate mole ratio in synthesis of 10:

Preparation of compound **10** involves the reaction of tosyl intermediate **8** with compound **9** in the presence of dipotassium hydrogen sulfate. Reactions were conducted by using 1.05, 2.0, 3.0 and 4.0 mole ratio of dipotassium hydrogen sulfate. In this study, the yield and purity were found to be optimal with 3.0 equivalents of dipotassium hydrogen phosphate (Table 1, entry 3). Racemic compound **10** was obtained by using 1.05 equivalent of dipotassium hydrogen phosphate (Table 1, entry 1) and lesser yield and purity were obtained by using 2.0 equivalents of dipotassium hydrogen phosphate as shown in Table 1.

2. Impact of time in the synthesis of 10

Temperature and time always plays pivotal role in synthesis; as a part of our strategy impact of time in the synthesis of compound **10** was studied. Undesired enantiomer of compound **10** was found to increase with the time of the reaction as shown in Table 2. In this study 3.0 equivalents of dipotassium hydrogen phosphate used.

Table1: Screening of dipotassium hydrogen phosphate for the synthesis of 10.

Entry	quantity of **9** (g)	K_2HPO_4 quantity		Yield of **10 • HCl** salt (%)	SOR of **10 • HCl** salt (°)	Purity of **10 • HCl** salt by HPLC (%)
		(g)	(equiv)			
1	20	18.4	1.05	57.8	0.00	95.2
2	25	43.5	2.0	60.0	(+) 59.2	96.47
3	20	52.4	3.0	74.3	(+)109.3	98.53
4	20	69.8	4.0	71.7	(+)107.0	99.57

Table 2: Impact of time in the synthesis of 10

Entry	Time (hours)	Undesired compound **10** (%)	Compound **10** (%)
1	1	1.01	98.99
2	4	1.70	98.30
3	8	2.00	98.00
4	12	2.46	97.54
5	16	2.81	97.19
6	20	2.96	97.04
7	24	3.06	96.93
8	After workup	3.31	96.69

3. Impact of HCl addition temperature in the synthesis of HCl salt of compound 10

Contact of acid with base compound creates platform for the racemisation. Preparation of hydrochloride salt of compound **10** involves reaction of compound **10** with the aqueous hydrochloric acid. To investigate the impact of hydrochloric acid in the synthesis of HCl salt of compound **10**, different reactions were conducted for example dumping of aqueous HCl into reaction mass containing compound **10** at 28 °C, slow addition of HCl and addition of HCl at different temperature. Results are indicated that addition of HCl is not affecting the quality and yield of the HCl salt of compound **10** as shown in Table 3.

Table 3: Screening of HCl addition temperature in the synthesis of HCl salt of compound 10

S.No.	quantity of **9** (g)	HCl addition		Yield of **10 • HCl** salt (%)	Chiral purity of **10 • HCl** salt by HPLC (%)
		Temperature (°C)	Time (minutes)		
1	25	0-5	10-15	71.95	99.72
2	25	10-15	10-15	72.00	99.67
3	25	10-15	Dumping	72.80	99.69
4	25	25-35	10-15	72.60	99.55
5	25	25-35	60-90	72.40	99.62

In view of the above results it was observed that undesired enantiomer was slowly reaching 3-4% in the synthesis of compound **10**. There is a need to develop robust, simple and cost effective process for the purification of hydrochloride salt of compound **10**. Various solvents were examined for the purification of HCl salt of compound **10** including dichloromethane, isopropyl alcohol, ethyl acetate, acetone, 10% aqueous dichloromethane, 10% aqueous ethyl acetate, 10% aqueous isopropyl alcohol, 10% aqueous acetone and mixture of 10% aqueous hydrochloride and acetone. Apart from the mixture of 10% aqueous hydrochloride and acetone all other solvents furnished either lower yield or lesser purity and the results are presented in Table 4.

Table 4: Screening of solvents for the purification of 10•HCl salt

Entry	Name of the solvent	Solvent quantity (equivalents)	Yield of **10 • HCl** salt (%)	Chiral purity of **10 • HCl** salt (%) by HPLC
1	Dichloromethane (DCM)	5	88	98.25
2	Isopropyl alcohol (IPA)	5	96	97.23
3	Ethyl acetate	5	95	97.11
4	Acetone	5	95	98.24
5	10% Aqueous DCM	5	87	98.69
6	10% Aqueous IPA	5	86	97.25
7	10% Aqueous ethyl acetate	5	75	97.10
8	10%Aqueous acetone	5	91	97.23
9	10% aqueous HCl and acetone	5	90	99.67

Hydrochloride salt of penultimate intermediate **10** undergoes condensation with formaldehyde followed by electophilic cyclisation and its salt formation to obtain bisulfate salt of **1** with 78% yield and 99.8% chemical purity and 99.9% chiral purity.

An improved process presented in Schemes 3 and 4, appears to be advantageous over the existing synthesis e.g. a) developed one pot synthesis for the preparation of amide intermediate **5** starts from the reaction of **2** and **3** by employing Strecker synthesis, b) avoided plant unfriendly operations like addition of hazardous sodium cyanide solution to the reaction mixture and formation of the lumps during the reaction of **2** and **3**, c) transformation of **4** to **5** is simplified by significantly by avoiding tedious workup procedure like product extraction from aqueous layer, washings with water and brine solution, distillation of reaction mass and isolation of **5** from non-polar solvent like hexane, d) one pot synthesis for the preparation of intermediate **10**, e) controlled enhancement of undesired isomer of intermediate **10** and developed simple process for the purification of undesired enantiomer of **10** f) expensive and partially recoverable solvents like diethyl ether, t-butyl acetate, methyl acetate were replaced with non-hydrolytic, inexpensive and highly recoverable solvents like toluene.

CONCLUSION

We have developed improved process for Clopidogrel **1** which found to be more compatible with industrial scale and has significant advantages over the existing synthesis.

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