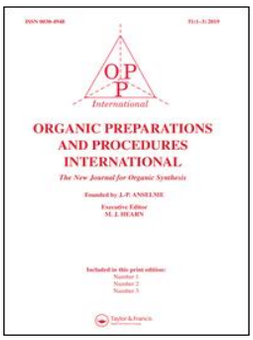

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Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

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To cite this article: Vinodh Guvvala, Venkatesan Chidambaram Subramanian & Jayashree Anireddy (2019): Development of a Novel and Scalable Process for the Synthesis of a Key Cangrelor Intermediate, Organic Preparations and Procedures International, DOI: 10.1080/00304948.2019.1677442

To link to this article: https://doi.org/10.1080/00304948.2019.1677442

Published online: 07 Nov 2019.

Organic Preparations and Procedures International, 0:1–7, 2019

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2019.1677442

Development of a Novel and Scalable Process for the Synthesis of a Key Cangrelor Intermediate

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Cangrelor (*Figure 1*) is a parenteral drug that reversibly inhibits the P2Y12 receptor; like ticagrelor, it does not require metabolic activation. It has a rather short half-life of 3 to 4 minutes;[1,2] and, with an infusion of 4 µg/kg per minute, peak inhibition occurs after 15 minutes. Cangrelor also has a rapid offset, with normal levels of platelet aggregation returning after 60 minutes. Inhibitors of platelet activation and aggregation are substances that are useful during percutaneous coronary intervention and other catheterization techniques in order to reduce bleeding complications and in the treatment of acute coronary syndromes and clotting disorders in general. One class of antiplatelet agents includes the inhibitors of the $P2Y_{12}$ receptor, a G-protein coupled purinergic receptor which is an important component of platelet activation.[3] Cangrelor (trade name kengreal in the US and kengrexal in Europe) was approved by the United States Food and Drug Administration in 2015.

In continuation of our ongoing research to improve the process and identify impurities[4–6] we now report a novel, convenient, and readily scalable approach for the synthesis of the key intermediate of cangrelor. A detailed study has been undertaken to identify, synthesize and characterize the cangrelor intermediates using up-to-date spectral techniques (IR, NMR, and HRMS).

The synthesis of cangrelor has been reported in the literature starting from 2-mercaptoadenosine[7,8] (*Scheme 1*). The synthesis involves seven stages and additional purifications to get cangrelor. During the synthesis, compound **5** serves as a key precursor. This material is highly expensive. The reported preparation of this compound involves four steps. However, the preparation suffers from certain drawbacks, most importantly the availability of the starting material as being difficult to access. A lot of purification procedures were involved in each stage, and these present difficulties in scale-up. Therefore, a synthetic route starting from more readily available and cheaper substrates was sought. The synthetic process reported in the literature[7–11] shows that the

Received August 31, 2018; in final form July 3, 2019.
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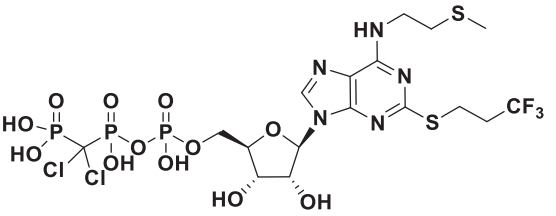
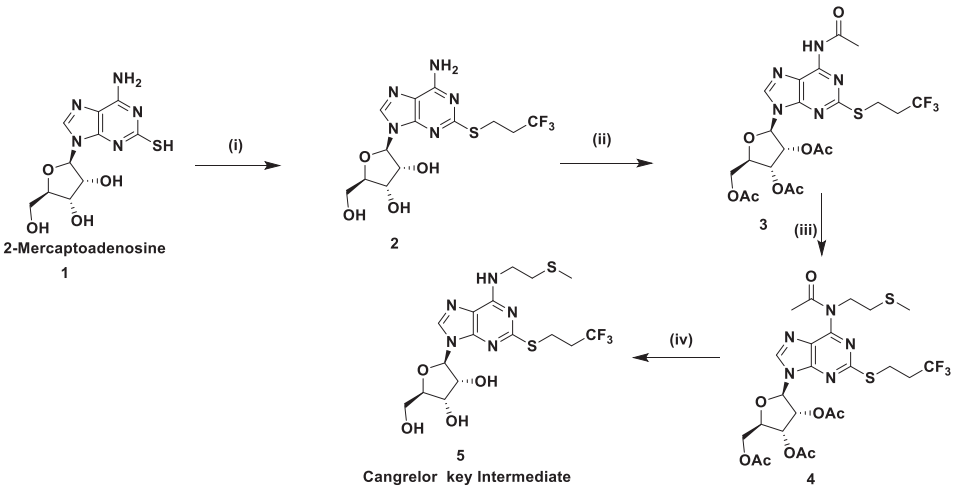


Figure 1. Cangrelor.

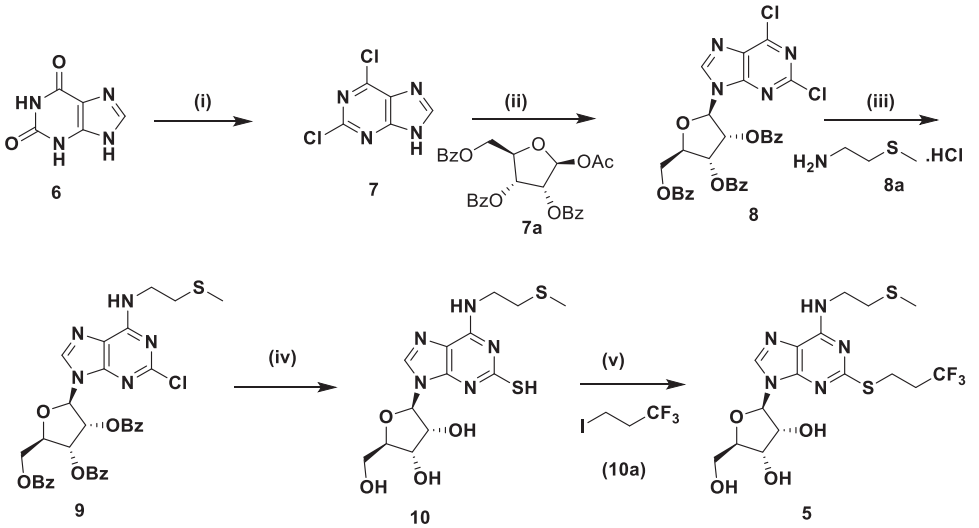


Reagents and conditions: i) $CF_3CH_2CH_2I$, NaOH, H_2O; ii) Ac_2O, NaOAc; iii) NaH, DMF, $ClCH_2CH_2SMe$; iv) MeO-, MeOH, heat.

Scheme 1. Synthesis of cangrelor key intermediate **5** from 2-mercaptoadenosine (**1**).

2-mercaptoadenosine (**1**) was *S*-alkylated with 1-iodo-3,3,3-trifluoropropane in the presence of NaOH to give trifluoropropyl sulfide (**2**). This was followed by acetylation of **2** using acetic anhydride in the presence of anhydrous sodium acetate at 80 °C to provide **3**. In our hands, during the acetate formation, we observed penta-acetate and tri-acetates along with the required tetra-acetate (**3**), to the extent of about 20–30% (LC-MS analysis). These materials are difficult to remove. Further N-alkylation with methylthioethyl chloride in the presence of NaH yielded **4**. Hydrolysis of the resulting **4** with 0.1M NaOH in refluxing MeOH furnished the 2,6-difunctionalized adenosine derivative of cangrelor, the desired key intermediate **5** (*Scheme 1*).

To avoid such drastic conditions as the use of sodium hydride in DMF, we starting from the easily and commercially available 2,6-dichloropurine. Halide substituents on the purine system display a leaving group ability which decreases in the series C-6 > C-2.[12] We envisioned that, if the difference in reactivity is sufficiently large, 2,6-dichloropurine (**7**) could also be used as the starting material to construct the key intermediate **5**. With the protocol described above, the synthesis is started from **7** which can be directly synthesized from xanthine (**6**). The later compound was prepared according to the literature procedure.[13] Then, **7** was subjected to the Hilbert – Johnson glycosylation reaction[14–18] with fully protected ribose in the presence of Lewis acid TMSOTf to



Reagents and conditions: i) $POCl_3$, Base; ii) DBU, TMSOTf, ACN, 75-80ºC; iii) Et_3N, Ethanol ,70-75ºC, 4 h; iv) NaSH H_2O, DMF, NaI, 120ºC; v) NaOH, MeOH/H_2O, r.t.

Scheme 2. Synthesis of cangrelor key intermediate **5** from xanthine (**6**).

give the β-anomer (**8**) in good yield without any additional purification. The HPLC purity of the isolated compound was >98%. The IR spectrum of compound **8** showed a band at 1728 cm^{-1} attributed to the ester groups of the benzoate. In addition other signals at 1558 and 1267 cm^{-1} confirmed the C = N and C-O of the purine and ribose functionalities. Besides, the ^{1}H NMR spectrum of compound **8** showed two doublets of doublets at δ 4.73 (H-5'), 4.88 (H-5''), a multiplet at δ 6.12-6.20 (H1' & H2') and a doublet at 6.48 (H4') attributed to the ribose ring. Other signals were observed in the aromatic region due to the purine ring. Subsequently, introduction of the amine group on the C-6 position was successfully accomplished by treatment of compound **8** with (methylthio)ethan-1-amine hydrochloride in the presence of triethylamine in ethanol at 70-75 °C. This cleanly produced the C-6 amination compound only. The hydrochloride salt of (methylthio)ethan-1-amine had been prepared in three steps from 2-chloroethaneamine hydrochloride (**8a**) by the literature procedure.[19] The IR spectrum of the compound **9** displayed a band at 3372 (NH) cm^{-1} to confirm that the amination took place. The structure of the compound was further confirmed by NMR and HRMS analysis.

After successful introduction of the amino alkyl group on the C-6 position of pyrimidine, our attention turned towards introduction of the SH group on C-2. For that compound **9** was treated with 60% sodium hydrogen sulfide in the presence of dimethyl formamide at 120 °C for 44–48 hours to give thiol (**10**). During the course of the reaction in addition to the expected thiol formation we found that the benzoate groups also got deprotected due to the highly basic nature (pH 9.5–10.00) of the reaction medium. The structure was confirmed by the absence of ester bands in the IR spectrum. This was further evidenced by the absence of peaks in the aromatic region in the ^{1}H NMR associated with the benzoyl group. The structure was additionally supported by ^{13}C NMR and HRMS analysis (see Experimental Section).

After successful introduction of the thiol group at the C-2 position, further *S*-alkylation[20] was performed by coupling with trifluoropropyl iodide (**10a**) in the presence of

sodium hydroxide in methanol at room temperature to give the final nucleoside analogue (**5**) in good yield (*Scheme 2*). The ^{1}H and ^{13}C NMR data are in good agreement with the reported values.[7] Finally the cangrelor core is synthesized in five linear steps in a simple methodology without any additional purification techniques. The compound is isolated in good yield with greater than 99.6% of purity (HPLC analysis).

In conclusion, an alternative efficient and novel synthetic route to cangrelor key intermediate **5** was developed. The target was obtained with >99.5% purity without any additional purifications. This improved method involves five steps starting from readily and cheaply available xanthine. The developed process is scalable, cost effective, with simplified reaction workup, and avoids the use of costly metal catalysts or chromatography. It may be commercially viable for synthesis in large quantities compared to previous methods discussed above.

Experimental Section

General

The starting material 2,6-dichloro-9*H*-purine was prepared by using a literature procedure from xanthine.[13] Other materials, solvents, and reagents were of commercial origin and used without additional operations. The HPLC analysis was performed on an Agilent model no. 1200 series (Chemstation software) using the Inertsil ODS column C-18, 100 × 2.1 mm, 3.5 µm with gradient elution mobile phases A (5 mM of ammonium carbonate adjusted with acetic acid to pH 3.2) and B (acetonitrile:methanol 70:30). The gradient profile was as follows: 10% of B in 3 min, 10–60% B in 12 min, 60–85% B in 20 min, 85% B in 38 min and re-equilibration of the column from 38 to 45 min with 10% of B with 45 min runtime using 10 µL injection volumes with 0.3 mL flow rate under 272 nm. All stages and intermediate core samples were neutralized and diluted with the mobile phase and filtered through a 0.22 micron membrane filter before injection.

The IR spectra were recorded on a Shimadzu FTIR Spectrophotometer (PRESTIGE-21) using the KBr disc technique. The ^{1}H and ^{13}C NMR spectral analyses were carried out on a Bruker instrument (300 MHz). The samples were dissolved in DMSO-d_6, $CDCl_3$ and the NMR spectrum was measured by using tetramethylsilane (TMS) as an internal standard. HRMS ESI-TOF positive ion mass spectra were recorded on an Agilent Q-TOF 6530 instrument. Melting points in °C were recorded on DSC-60 Shimadzu instrument and were uncorrected.

(2R,3R,4R,5R)-2-((Benzoyloxy)methyl)-5-(2,6-dichloro-9H-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (8)

A mixture of 2,6-dichlorpurine (**7**) (50 g, 0.2645 mol) and 1-O-acetyl-2,3,5-tri-O-benzoyl-[3-D-ribofuranose **7a** (146.7 g, 0.291 mol) was dried by co-evaporation with anhydrous acetonitrile (2 x 250 mL). The resultant mixture was taken in anhydrous acetonitrile (500 mL), DBU (118.4 mL, 0.7936 mol) was added followed by dropwise addition of trimethylsilyl trifuoromethylsulfonate (191.52 mL, 1.058 mol) over a period of 30 minutes under an argon atmosphere. After completion of the addition, the reaction temperature was raised to 70–80 °C and was stirred at the same temperature for about 4 h. The reaction mixture was then diluted with dichloromethane (1.0 L) and washed

with saturated sodium bicarbonate solution (1.0 L x 2) followed by brine (2 x 500 mL). The organic layer was concentrated under reduced pressure and the resultant solid obtained was recrystallized from 10% v/v DMSO/water and gave a white solid (Yield: 150 g, (89%); HPLC purity: 98.6%), mp 82–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, 1H, H5', $J = 12.0$ & 3.6 Hz), 4.88 (dd, 1H, H5", $J = 12.3$ & 3.6 Hz,), 6.12–6.20 (m, 2H, H1' & H2'), 6.48 (d, 1H, H4', $J = 6.0$ Hz), 4.91–4.96 (m, 1H, H3'), 8.30 (s, 1H, H8), 7.35-8.08 (m, 15H, phenyl ring protons); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.48, 130.05, 130.01, 153.62, 152.48, 81.66, 74.44, 71.69, 87.12, 63.62, 165.10, 165.28, 165.43, 128.22, 128.74, 128.77, 128.89, 129.18, 129.76; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{31}H_{22}Cl_2N_4O_7$ 655.07632, found 655.07653; IR (KBr, cm^{-1}): 1728, 2925, 2956, 1595, 1558, 1267.

Anal. Calcd for $C_{31}H_{22}Cl_2N_4O_7$: C, 58.78; H, 3.50; Cl, 11.19; N, 8.85. Found: C, 58.82; H, 3.48; Cl, 11.22; N, 8.89.

(2R,3R,4R,5R)-2-((Benzoyloxy)methyl)-5-(2-chloro-6-((2-(methylthio)ethyl)amino)-9H-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (9)

To a mixture of glucosylated 2,6-dichlorpurine **8** (40 g, 0.0631mol) and (methylthio)ethan-1-amine hydrochloride **8a** (11.28 g, 0.088 mol) in ethanol (1.0 L), triethylamine (26.62 mL, 0.1894 mol) was added. The reaction mixture was heated to 70–75 °C for about 4 hours. Then the reaction mixture was cooled to 0 °C. The resultant solid was filtered and washed with cold ethanol (200 mL) and gave a white solid (Yield: 37.36 g (86%); HPLC purity: 97.99%), mp 79–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (brs, 2H, H1"), 2.79 (t, 2H, H2"), 2.14 (s, 3H, H3"), 5.06-5.07 (m, 1H, H1'), 6.16 (t, 1H, H2', $J = 5.4$ Hz), 5.99 (t, 1H, H3', $J = 5.1$ Hz), 6.85 (d, 1H, H4', $J = 5.4$ Hz), 4.65 (dd, 1H, H5', $J = 12.0$ & 3.3 Hz), 4.77 (dd, 1H, H5', $J = 12.6$ & 2.4 Hz), 7.29-8.15 (m, 16H, phenyl ring protons & H8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.40, 138.31, 86.99, 84.77, 74.42, 70.40, 62.04, 32.47, 14.53; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{31}ClN_5O_7S$ 688.16327, found 688.16319; IR (KBr, cm^{-1}): 3372, 1728, 2919, 2954, 1616, 1601.

Anal. Calcd for $C_{34}H_{31}ClN_5O_7S$: C, 59.34; H, 4.39; Cl, 5.15; N, 10.18; S, 4.66. Found: C, 59.30; H, 4.37; Cl, 5.18; N, 10.14; S, 4.71.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(2-mercapto-6-((2-(methylthio)ethyl)amino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (10)

To a stirred solution of compound **9** (35 g, 0.05086 mol), in N,N-dimethyl formamide (525 mL), 60% sodium hydrogen sulfide hydrate (22.58 g, 0.3051 mol) was added followed by NaI (3.81 g, 0.0254 mol). The resultant reaction mixture was heated to 120 °C for 62 hours. After completion of the reaction as monitored by HPLC, the reaction mixture was concentrated to one-third and poured into water. The precipitated salts were filtered off and the filtrate was washed with dichloromethane (3 x 350 mL). Then, the aqueous layer pH was adjusted to 4.5 using acetic acid. The solid obtained was filtered and washed with water. The resultant solid was recrystallized from aqueous ethanol (525 mL) and dried under reduced pressure to give a pale yellow solid (Yield: 17.0 g, (90%), HPLC purity: 99.52%), mp 139–141 °C; ^{1}H NMR (300 MHz, DMSO-*d*6) δ 2.12 (s, 3H, H3"), 2.72 (t, 2H, H2"), 3.65-3.67 (m, 2H, H1"), 8.00 (s, 1H, H8), 3.41 (dd, 1H,

H5'a, $J = 5.1$ & 11.7 Hz), 3.50 (dd, 1H, H5'b, $J = 3.9$ & 11.7 Hz), 3.95 (t, 1H, H1', $J = 5.1$ Hz), 4.02 (t, 1H, H2', $J = 4.8$ Hz) 3.78 (t, 1H, H3', $J = 4.5$ Hz), 5.92 (d, 1H, H4', J = 4.2 Hz); ^{13}C NMR (DMSO-*d*6, 75 MHz) δ 154.98, 152.9, 145.01, 118.21, 97.21, 89.20, 72.97, 71.20, 61.50, 53.10, 34.91, 15.20; HRMS (ESI) m/z: $(M + H]^+$ calcd for $C_{13}H_{20}N_5O_4S_2$ 374.09567, found 374.09695; IR (KBr, cm^{-1}): 3365, 3305, 2924, 2956, 1618, 1596.

Anal. Calcd for $C_{13}H_{20}N_5O_4S_2$: C, 41.81; H, 5.13; N, 18.75; S, 17.17. Found: C, 41.78; H, 5.11; N, 18.69; S, 17.21.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(6-((2-(methylthio)ethyl)amino)-2-((3,3,3-trifluoropropyl)thio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5)

To a stirred solution of compound **10** (20 g, 0.0536 mol), in methanol: water (360 mL: 120 mL), 1M sodium hydroxide solution (132 mL) was added. The resultant solution was cooled to 0 °C then 1,1,1-trifluoro-3-iodopropane **10a** (9.14 mL, 0.0803 mol) was added slowly at the same temperature. Then the reaction mixture was stirred at room temperature for 8-9 hours. After completion of the reaction as monitored by HPLC, the reaction mass was concentrated to remove methanol and filtered and washed with cold methanol (200 mL) to give an off-white solid (Yield: 24.0 g, (95%), HPLC purity: 99.5%), mp 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10 (s, 3H, SCH_3), 2.65–2.81 (m, 4H, NCH_2CH_2 + $SCH_2CH_2CF_3$), 3.27 (m, 2H, SCH_2), 3.51–3.70 (m, 4H, NCH_2 + H-5'a + H-5'b), 3.92 (m, 1H, H-4'), 4.11 (m, 1H, H-3'), 4.56 (m, 1H, H-2'), 5.09 (t, 1H, $J = 5.0$ Hz, OH), 5.21 (d, 1H, $J = 4.8$ Hz, OH) 5.46 (d, 1H, $J = 6.3$ Hz, OH), 5.83 (d, 1H, $J = 6.3$ Hz, H-1'), 8.14 (brs, 1H, NH), 8.28 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.63, 22.90, 32.77, 39.07, 33.16, 33.53, 33.88, 34.25, 61.62, 70.57, 73.58, 85.71, 87. 51, 138.95, 117.56, 121.24, 124.92, 128.60, 132.28, 149.58.07, 154.03, 162.57; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{23}F_3N_5O_4S_2$ 470.11436, found 470.11606; IR (KBr, cm^{-1}): 3339, 3270, 2928, 2980, 1623, 1584.

Acknowledgments

The authors are grateful to Gland Pharma Limited, Hyderabad, for providing facilities to carry out the work. We thank the Synthesis R&D team of Gland Pharma for fruitful discussions in the prediction of the structure.

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