CONCISE SYNTHESIS OF (±)-CLOPIDOGREL VIA CARBOXYLATION OF BENZYLAMINE WITH CO₂

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GRAPHICAL ABSTRACT

Abstract A concise and efficient synthesis of (±)-clopidogrel, an antithrombotic agent, is achieved by inserting CO₂ at the benzylic position as the key reaction without using any toxic transition metals. The overall yield of the synthetic process is 38% and the salient features include operationally simple process chemistry and fewer steps.

Keywords Antithrombatic agent; clopidogrel; CO₂ insertion; Plavix

INTRODUCTION

(S)-Methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate, also known as (S)-clopidogrel (1a), is marketed as hydrogen sulfate salt. It is a potent antiaggregant and antithrombotic drug demonstrated in several experimental models of thrombosis[1] and was the second top-selling drug worldwide in 2005 with the commercial trade name of Plavix. It was marketed and licensed by Sanofi in 1986. The drug was launched on the market following a successful clinical evaluation[2] and studies, which has shown that it tends to block the platelet aggregation more than aspirin 2 and ticlopidine 3, even at much lower dosage.[3] Clopidogrel (1a) has an absolute S configuration[4] and the corresponding R enantiomer is totally devoid of antiaggregating activity. Because of the high biological activity of (S)-clopidogrel, many organic chemists are interested in synthesizing it via chiral or resolution pathway.

There are mainly two kinds of strategies known for its synthesis, such as (i) substitution reaction of 2-chlorophenylglycine or derivatives of 2-chloromandelic acid...
and (ii) attack of nitrogen nucleophile onto α-halogen substituted phenyl acetonitrile or phenyl acetate, both involving SN2 substitution reaction. Many other recent methods are known for the synthesis of clopidogrel such as SN2 displacement,\(^5\) stereoselective hydrogenation,\(^6\) Mannich-type multicomponent reaction,\(^7\) Cu(II)-catalyzed oxidative coupling reaction,\(^8\) and patented methods,\(^9\) involving the resolution of \((\pm/C_6\text{-}C_6\text{-})\text{-clopidogrel}\) using 10-L-camphorsulfonic acid (L-CSA) or its precursor α-amino ester using D- or L-tartaric acid. Some of these intermediates in turn were obtained via simple SN2 displacement reactions and NaCN addition on imines.\(^{9a}\) Some of these reported methods do utilize highly poisonous cyanide as nucleophile and highly expensive toxic transition metals as catalyst in existing methods of its synthesis. Thus, there is a need for an efficient synthesis of \((\pm/C_6\text{-}C_6\text{-})\text{-clopidogrel}\) \((\pm/C_6\text{-}C_6\text{-})\text{-}1\) with one carbon homologation using insertion of CO\(_2\) at the benzylic position,\(^{10}\) and this strategy has not been reported previously.

**RESULTS AND DISCUSSION**

CO\(_2\) insertion for an alternative energy sources is a topic of current interest because of the constant rise in global warming and atmospheric CO\(_2\) concentrations.\(^{11}\) Because it is an attractive one-carbon source for organic synthesis, due to its low cost, low toxicity, and ease of handling, we were interested in its utility in some of organic transformations to synthesize the various substituted cyclic carbonates and propargylic acids.\(^{12}\) Herein, we present a concise synthesis of \((\pm/C_6\text{-}C_6\text{-})\text{-clopidogrel}\) \((\pm/C_6\text{-}C_6\text{-})\text{-}1\) by insertion of CO\(_2\) at the benzylic position as the key reaction from readily available and cheap starting materials.

Retroynthetic analysis of \((\pm/C_6\text{-}C_6\text{-})\text{-clopidogrel}\) \((\pm/C_6\text{-}C_6\text{-})\text{-}1\) reveals that α-amino ester 7 could be visualized as the key intermediate, which in turn can be obtained from the insertion of CO\(_2\) at the benzylic position in Boc-protected benzylamine 8 derived from 2-chlorobenzaldehyde (4).

Accordingly, the synthesis of \((\pm/C_6\text{-}C_6\text{-})\text{-clopidogrel}\) \((\pm/C_6\text{-}C_6\text{-})\text{-}1\) was undertaken starting from commercially available 2-chlorobenzaldehyde (4). The condensation of 2-chlorobenzaldehyde (4) with thiophene-2-ethanolamine in CH\(_2\text{Cl}_2\) and anhydrous MgSO\(_4\)
at room temperature provided the corresponding imine. The subsequent reduction of imine using NaBH₄ in methanol at 0 °C gave the N-substituted-2-chlorobenzylamine 5, which was then protected as Boc-carbamate 6 by treating it with (Boc)₂O in CH₃CN at room temperature. (The ¹H NMR spectrum of 6 showed the presence of rotameric proton signals at δ 1.41 (brs, 4H), and 1.49 (brs, 5H) as two broad singlets for nine Boc-methyl protons and at δ 4.45 (brs, 1H) and 4.55 (brs, 1H) as two broad singlets for two benzyllic protons. Its ¹³C NMR spectrum also displayed the presence of rotameric carbon signals at δ 155.3, and 155.6 for carbonyl carbon present in the Boc group.) Insertion of CO₂ at benzyllic position of carbamate 6 was achieved by using n-BuLi as a strong base with the bubbling of CO₂ at −78 °C in dry tetrahydrofuran (THF) to provide the α-amino acid as its lithium salt, as indicated by the formation of turbid pale yellow solution after 3 h. Subsequently, α-amino acid salt was treated with NaHCO₃ and MeI in dimethylformamide (DMF), which gave the α-amino ester 7 in 65% yield. To make this process in an asymmetric fashion, CO₂ was bubbled to a solution containing carbamate 6, (+)-sparteine (1 equiv),[¹³] and n-BuLi at −78 °C. However, we ended up with the α-amino ester 7 in only 3% ee. The Boc group in α-amino ester 7 was deprotected using trifluoroacetic acid in CH₂Cl₂ at 25 °C, followed by electrophilic aromatic cyclization (Pictet–Spengler type) on the thiophene ring was achieved, on treatment with paraformaldehyde in one pot at 10 °C. It was then quenched with saturated NaHCO₃ solution, which furnished the (±)-clopidogrel free base, (±)-1, in 68% yield and whose spectral data are in complete agreement with those reported in the literature.[⁵]

CONCLUSION

In conclusion, a concise synthesis of (±)-clopidogrel with an overall yield of 38% is described. The key reaction employed here is the insertion of CO₂ at the benzyllic position, which has been unprecedented for its synthesis. The salient features include fewer steps and avoiding the use of toxic transition metals.

EXPERIMENTAL

All reactions were carried out under a nitrogen atmosphere. Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical thin-layer chromatography (TLC) was done on precoated silica-gel plates (Kieselgel 60 F₂₅₄, Merck). Column chromatographic purifications were done with 230- to 400-mesh silica gel. NMR spectra were recorded in CDCl₃ on AV 200 and AV 400 MHz Bruker NMR spectrometers.
All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). Infrared (IR) spectra were recorded in CHCl₃ using Shimadzu FTIR-8400 spectrophotometer. Liquid chromatography–mass spectrometry (LC-MS) was carried out on a Thermo Finnigan Surveyor MSQ LC-MS instrument.

**N-(2-Chlorobenzyl)-2-(thiophen-2-yl)ethan-1-amine (5)**

2-(Thiophen-2-yl)ethan-1-amine (3.3 g, 25.63 mmol) in CH₂Cl₂ (15 mL) and anhydrous Na₂SO₄ were added to a stirred solution of 2-chlorobenzaldehyde (3 g, 21.36 mmol) in CH₂Cl₂ (60 mL) at 25 °C. The reaction mixture was allowed to stir at the same temperature for 30 min. This was followed by the addition of MeOH (30 mL) and NaBH₄ (2 g, 53.4 mmol) at 0 °C, and this mixture was allowed to stir for 30 min. It was then quenched with saturated NH₄Cl solution. The solvents were evaporated in rotavapour and the residue was extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the crude benzylamine. Silica-gel column chromatographic purification of the crude product using petroleum ether / EtOAc / Et₃N (70:25:5) gave benzylamine 5 (4.9 g) as a yellow liquid.

Yield: 4.9 g, 92%; IR (CHCl₃, cm⁻¹): νmax 3440, 3331, 2912, 2826, 1471, 1441, 1049, 1037, 752, 696; ¹H NMR (200 MHz, CDCl₃): δ 1.61 (br s, 1H), 2.84–2.98 (m, 2H), 2.99–3.11 (m, 2H), 3.89 (s, 2H), 6.78–6.85 (m, 1H), 6.86–6.96 (m, 1H), 7.11 (dd, J = 5.1, 1.1 Hz, 1H), 7.15–7.26 (m, 2H), 7.28–7.40 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 30.4, 50.3, 50.9, 123.4, 124.9, 124.9, 126.7, 128.1, 129.4, 129.9, 133.6, 137.5, 142.3. Analysis: C₁₃H₁₄ClNS requires C, 62.02; H, 5.61; N, 5.56; S, 12.73. Found: C, 61.89; H, 5.72; N, 5.71; S, 12.65%.

**tert-Butyl-(N-2-chlorobenzyl)-(N’-2-(thiophen-2-yl)ethyl) carbamate (6)**

(Boc)₂O (3.9 g, 18 mmol) in dry CH₃CN (10 mL) was added to a solution of the benzyl amine 5, (2.3 g, 9 mmol), triethylamine (1.38 mL, 9.93 mmol), and DMAP (0.6 g, 4.51 mmol) in dry CH₃CN (20 mL) under nitrogen at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 7 h. The reaction mixture was then quenched with water, the solvent was evaporated, and the crude product was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Silica-gel column chromatographic purification of the crude product using petroleum ether / EtOAc (95:5) gave carbamate 6 (2.7 g) as a colorless liquid.

Yield: 2.7 g, 85%; IR (CHCl₃, cm⁻¹): νmax 3019, 2981, 2839, 2400, 1698, 1612, 1585, 1368, 1216, 1035, 1167; ¹H NMR (500 MHz, CDCl₃): δ 1.41 (brs, 4H), 1.49 (brs, 5H), 3.00 (brs, 1H), 3.07 (brs, 1H), 3.41 (brs, 1H), 3.49 (brs, 1H), 4.45 (brs, 1H), 4.55 (brs, 1H), 6.75 (brs, 1H), 6.89 (dd, J = 5.0, 3.5 Hz, 1H), 7.10 (d, J = 5.2 Hz, 1H), 7.16–7.29 (m, 3H), 7.33 (d, J = 7.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 28.4, 29.0, 47.6, 48.9, 49.1, 49.2, 76.7, 77.3, 80.0, 96.2, 123.7, 125.2, 126.9, 128.0,
Methyl-2-((tert-butoxycarbonyl)(2-(thiophen-2-yl)ethyl)amino)-2-(2-chlorophenyl)acetate (7)

n-BuLi (2.96 mL, 4.7 mmol) was added dropwise to a stirred solution of carbamate 6 (1.5 g, 4.3 mmol) in dry THF, at –78 °C under N₂ atmosphere for 15 min. CO₂(1 atm) gas was bubbled through the reaction mixture and allowed to stir for 3 h until it formed a pale yellow turbid solution. This was followed by the addition of NaHCO₃ (540 mg, 6.39 mmol) and MeI (1.5 g, 10.65 mmol) in DMF and stirred for further 3 h at 25 °C. The reaction mixture was quenched with saturated NH₄Cl solution, and the solvent was evaporated under reduced pressure. The obtained crude mixture was extracted with EtOAc (3 × 15 mL) and washed with brine (3 × 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. Silica-gel column chromatographic purification of the crude product using petroleum ether / EtOAc (90:10) as eluent gave α-amino ester 7 (1.13 g) as a colorless liquid.

Yield: 1.13 g, 65%; IR (CHCl₃, cm⁻¹): νmax 2977, 1751, 1696, 966, 756; ¹H NMR (200 MHz, CDCl₃): δ 1.51 (s, 9H), 2.32–2.35 (m, 1H), 3.01–3.04 (m, 1H), 3.15–3.23 (m, 1H), 3.38–3.53 (m, 1H), 3.79 (s, 3H), 6.13 (brs, 1H), 6.52 (brs, 1H), 6.78–6.82 (m, 1H), 7.01 (d, J = 4.9 Hz, 1H), 7.22–7.35 (m, 3H), 7.43–7.48 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 28.3, 29.5, 47.6, 52.2, 60.0, 60.8, 80.5, 96.0, 123.2, 124.6, 126.6, 126.9, 130.0, 133.1, 135.4, 141.1, 154.4, 155.3, 170.8. LCMS (ESI, m/z) calculated for C₂₀H₂₄ClNO₄SNa (M+Na)⁺ 432.1; found 432.13. Analysis: C₂₀H₂₄ClNO₄S required C, 55.49; H, 5.59; N, 3.24; S, 7.37%.

Methyl 2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate (±)-Clopidogrel (1)

Trifluoroacetic acid (0.25 mL, 3.2 mmol) was added to a solution of α-amino ester 7 (435 mg, 1.06 mmol) in dry CH₂Cl₂ and kept under stirring for 4 h at room temperature. Subsequently, paraformaldehyde (38 mg, 1.3 mmol) was added to the reaction mixture and allowed to stir for 24 h at room temperature. It was then quenched with saturated NaHCO₃ solution at 0 °C and further stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with water (2 × 10 mL) and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Silica-gel column chromatographic purification of the crude product using petroleum ether/EtOAc gave (±)-clopidogrel 1 (0.24 g) as a pale yellowish liquid.

Yield: 0.24 g, 70%; IR (CHCl₃, cm⁻¹): νmax 2977, 1741, 1654, 1434, 1203, 1167, 1042, 755; ¹H NMR (200 MHz, CDCl₃): δ 2.88 (brs, 4H), 3.53–3.78 (m, 5H), 4.89 (s, 1H), 6.65 (d, J = 5.2 Hz, 1H), 7.04 (d, J = 5.2 Hz, 1H), 7.22–7.25 (m, 1H), 7.28–7.32 (m, 1H), 7.35–7.44 (m, 1H), 7.56–7.80 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 25.5, 48.3, 50.7, 52.1, 67.7, 76.4, 77.6, 96.2, 122.8, 125.2, 127.2, 129.4, 129.8, 130.0, 133.1,
133.8, 134.7, 171.0. Analysis: $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}$ required C, 59.72; H, 5.01; N, 4.35; S, 9.96. Found: C, 59.61; H, 4.95; N, 4.15; S, 9.76%.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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