Synthesis of an impurity in crude roflumilast

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A simple synthetic method has been developed for the synthesis of 3,4-bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl) benzamide (an impurity in crude roflumilast) from 3,4-dihydroxybenzaldehyde *via* alkylation, oxidation, chlorination and acylation reactions. Acetonitrile was used as the solvent in all the three steps for convenient recovery. The oxidation of 3,4-bis(cyclopropylmethoxy)benzaldehyde (purity, 86.2%) by sodium chlorite afforded the corresponding acid with purity of 99.2%. Finally, N-acylation of 3,5-dichloropyridin-4-amine yielded 3,4-bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl) benzamide. Without column chromatography, the overall yield of the target compound was about 70%.

Keywords: phosphodiesterase 4 inhibitor, purification, N-acylation, acetonitrile, impurity

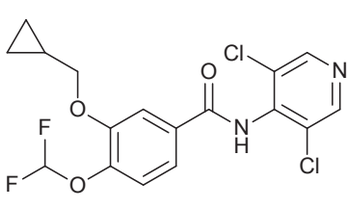
Phosphodiesterases (PDEs) play an important role in various biological processes through decreasing the concentration of cAMP and cGMP.[1–3] Phosphodiesterase 4 (PDE 4) is responsible for the degradation of cAMP in many cell types and has been proposed as an attractive target in various diseases including chronic obstructive pulmonary disease (COPD) and asthma.[4–7] Roflumilast (Fig. 1), acting as the inhibitor of the PDE 4, was developed by Altana AG and became the first drug approved for the treatment of COPD in Europe.[8,9] Further attention has been paid to the pharmacology, synthesis and analysis of roflumilast in the last decade.[10–13] It was reported that 3,4-bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl) benzamide (**1**) (Fig. 1) is one of the impurities in the synthesis of roflumilast [14]. However, the synthesis of the impurity **1** has rarely been mentioned in the literature. Here, a simple synthetic method is described for the preparation of the impurity **1** from 3,4-dihydroxybenzaldehyde *via* alkylation, oxidation and acylation reactions (Scheme 1). Reaction parameters were optimised and acetonitrile was selected as the solvent in all the three steps to make the solvent recovery easier. The total yield of the four-step sequence was about 70%.

Results and discussion

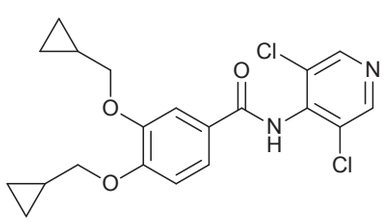
The O-alkylation of 3,4-dihydroxybenzaldehyde **2** with cyclopropylmethyl bromide **3** gave compound **4** mono- and di-alkylated products were expected. In order to increase the yield of the desired compound, several solvents were examined for this reaction. It was found that acetonitrile was promising. It is a polar aprotic solvent, which enhances nucleophilic substitution; and its high boiling point made it possible to carry the reaction at higher temperature to accelerate the reaction. KI was also chosen as the catalyst to improve the conversion and selectivity of the reaction. The effect of KI to this reaction was clear in methanol, ethanol and acetone, but not in acetonitrile. Several bases were evaluated and the results indicated that potassium carbonate exhibited the best performance. Cyclopropyl methyl bromide was added gradually to avoid hydrolysis side reaction. As mentioned above, the reaction parameters were optimised for this nucleophilic substitution. Compound **4** was used directly in the next oxidation step without further purification.

The oxidation of aldehydes to the corresponding carboxylic acids in the presence of sodium chlorite has been widely reported.[15–19] It was claimed that sulfamic acid was used for the chlorine scavenger.[20,21] Methanol, ethanol, t-butanol or acetonitrile as the solvent for the oxidation were found to afford similar results. Since acetonitrile was used in the first step, we chose acetonitrile as the reaction solvent. Compound **5** was recrystallised from toluene in 99.2% purity to avoid impurities into the next step.

The nucleophilic ability of 3,5-dichloropyridin-4-amine was low due to the electronic and steric effects, so sodium hydride was chosen as the base to form the amino anion to enhance its reactivity.[18,22] Acetonitrile, consistent with the previous reactions, was chosen as the solvent for this reaction. 3,4-Bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl) benzamide was obtained as a white solid by the N-acylation of the created anion with the benzoyl chloride **6**. Finally the purified compound **1** was characterised by IR, ^{1}H NMR, ^{13}C NMR and high-resolution mass spectra (HR-MS).



Roflumilast
formula: $C_{17}H_{14}Cl_2F_2N_2O_3$



impurity 1

Fig. 1 The structure of Roflumilast and the impurity **1**.

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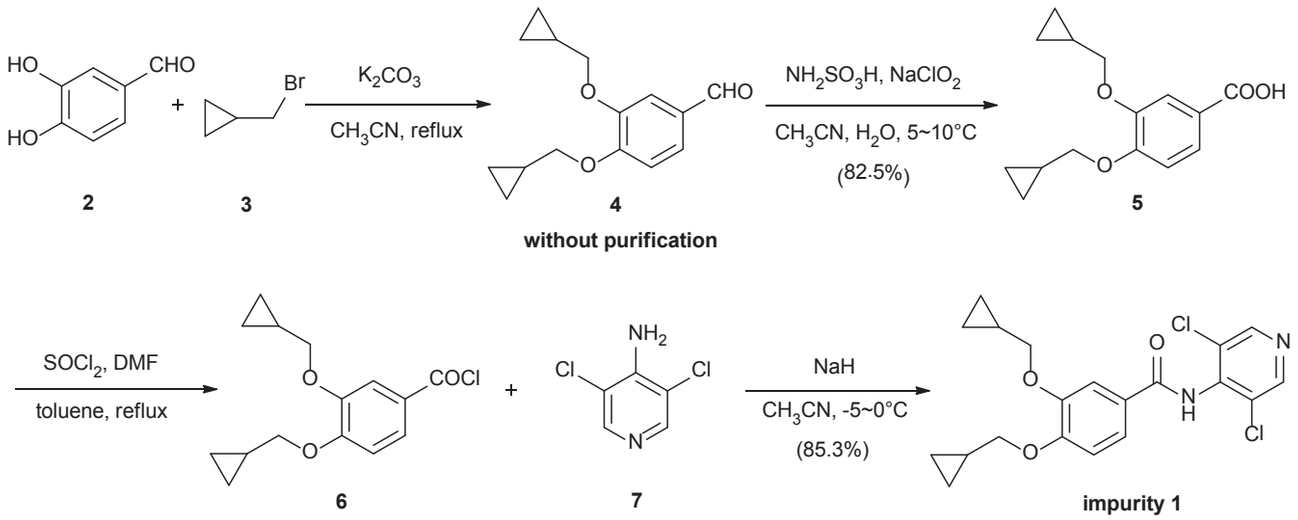

Scheme 1 The synthesis of the impurity **1**.

Experimental

Reagents and solvents used in this study were commercially available. All reactions were monitored by TLC using commercial silica gel plates. The purity of product was detected by HPLC on Agilent 1,100 series. IR spectra were obtained from KBr disk on the FT-IR Bruker Tensor 27. NMR spectra were recorded on Avance III 400 or 600 NMR spectrometer with tetramethylsilane as an internal reference. Melting points were observed on a YRT-3 Melting Point Tester and uncorrected. HR-MS were recorded with a Bruker micrOTOF-QII spectrometer in electrospray ionisation (ESI) mode.

3,4-Bis(cyclopropylmethoxy)benzaldehyde (**4**): Potassium carbonate (4.5 g, 32.56 mmol) was added to the solution of 3,4-dihydroxybenzaldehyde **2** (1.5 g, 10.86 mmol) in acetonitrile (25 mL) with magnetic stirring. It was heated to reflux and stirred for 30 minutes. Then, cyclopropyl methyl bromide **3** (4.4 g, 32.56 mmol) was added dropwise to the reaction mixture and stirred at reflux till no starting material was left (TLC). The reaction mixture was then cooled to 20 °C. After filtration, the filtrate was evaporated to give **4** (2.58 g) as yellow oil with the purity of 86.2%. It was used in the next step without further purification. IR (KBr, ν_{max}/cm^{-1}): 3085–3002 (ν CH on benzene), 2922 (ν CH on cyclopropyl), 2819, 2784 (ν CH on CHO), 1694 (ν C=O), 1589, 1517, 1433 (ν C=C), 1277, 1238 (ν C–O–Ar), 1132, 1121, 1032, 845, 830 (ν CH on benzene). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 9.59 (s, 1 H, CHO), 7.29 (dd, J = 1.8, 8.2 Hz, 1 H, CH on benzene), 7.16 (d, J = 1.8 Hz, 1 H, CH on benzene), 6.92 (d, J = 8.3 Hz, 1 H, CH on benzene), 3.73 (d, J = 7.0 Hz, 2 H, OCH$_2$), 3.67 (d, J = 7.0 Hz, 2 H, OCH$_2$), 1.05 (m, 2 H, CH), 0.37 (t, 4 H, CH$_2$), 0.13 (t, 4 H, CH$_2$). ^{13}C NMR (151 MHz, DMSO-d$_6$): δ 191.3 (C=O), 153.9, 148.5, 129.5, 125.8, 112.6, 111.5 (6 C on benzene), 73.0, 72.9 (2 C on OCH$_2$), 10.0 (2 C on CH), 3.2 (4 C on CH$_2$).

3,4-Bis(cyclopropylmethoxy)benzoic acid (**5**): Compound **4** (2.58 g, 10.68 mmol) was dissolved in acetonitrile (20 mL) and added to a solution of sulfamic acid (1.48 g, 15.24 mmol) in water (10 mL). Then, sodium chlorite (1.53 g, 15.24 mmol) in water (10 mL) was added dropwise to the above reaction mixture at 5–10 °C. Subsequently, the ice bath was removed and the mixture was stirred at room temperature for two hours (monitored by TLC). Then the solvent was evaporated to give a white solid. It was then recrystallised from toluene as white solid **5** (2.35 g, 82.5% yield). M.p. 155–156 °C; IR (KBr, ν_{max}/cm^{-1}): 3079, 3003 (ν CH on benzene), 2952–2550 (ν OH on COOH), 2921, 2877 (ν CH on cyclopropyl), 1680 (ν C=O), 1600, 1586, 1519, 1445 (ν C=C), 1270, 1225 (ν C–O–Ar), 1135–1003, 844, 812 (ν CH on benzene). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 12.64 (s, 1 H, COOH), 7.52 (d, J = 8.3 Hz, 1 H, CH on benzene), 7.42 (s, 1 H, CH on benzene), 7.01 (d, J = 8.4 Hz, 1 H, CH on benzene), 3.90 (d, J = 6.0 Hz, 2 H, OCH$_2$), 3.85 (d, J = 6.0 Hz, 2 H, OCH$_2$), 1.25 (m, 2 H, CH), 0.58 (t, 4 H, CH$_2$), 0.35 (t, 4 H, CH$_2$). ^{13}C NMR (151 MHz, DMSO-d$_6$): δ 167.1 (C=O), 152.3, 147.6, 123.2, 122.7, 113.8, 112.3 (6 C on benzene), 72.9 (2 C on OCH$_2$), 10.0, 10.1 (2 C on CH), 3.2 (4 C on CH$_2$).

3,4-Bis(cyclopropylmethoxy)benzoyl chloride (**6**): Compound **5** (1.49 g, 5.68 mmol) in toluene (48 mL) was heated to reflux until it dissolved and water was removed by Dean–Stark apparatus. Then the solution was cooled to 85 °C. After that, three drops of DMF and thionyl chloride (1.01 g, 8.49 mmol) were added dropwise to the solution. The mixture was stirred at reflux for 3 h (monitored by TLC). Then toluene was evaporated to give a brown oil of 3,4-bis(cyclopropylmethoxy)benzoyl chloride **6**. The residue was dissolved in anhydrous (8 mL) acetonitrile and used for the next step directly. IR (KBr, ν_{max}/cm^{-1}): 3082, 3068 (ν CH on benzene), 2930, 2876 (ν CH on cyclopropyl), 1757 (ν C=O), 1688 (ν C=O), 1583, 1517, 1466 (ν C=C), 1277, 1240 (ν C–O–Ar), 1174, 1132, 1029, 832, 807 (δ CH on benzene). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.79 (dd, J = 2.2, 8.3 Hz, 1 H, CH on benzene), 7.57 (d, J = 2.2 Hz, 1 H, CH on benzene), 6.91 (d, J = 8.6 Hz, 1 H, CH on benzene), 3.97 (d, J = 6.9 Hz, 2 H, OCH$_2$), 3.92 (d, J = 6.8 Hz, 2 H, OCH$_2$), 1.34 (m, 2 H, CH), 0.66 (t, 4 H, CH$_2$), 0.40 (t, 4 H, CH$_2$). ^{13}C NMR (151 MHz, CDCl$_3$): δ 167.2 (C=O), 155.7, 148.7, 127.3, 125.2, 116.3, 112.4 (6 C on benzene), 74.4, 73.9 (2 C on OCH$_2$), 10.2 (2 C on CH), 3.4 (4 C on CH$_2$). HR-MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{15}H_{17}ClO_3$+H$^+$ 263.1283; found 263.1274.

3,4-Bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl) benzamide (**1**): A suspension of sodium hydride (0.50 g, 12.50 mmol) in anhydrous (17 mL) acetonitrile was stirred at –5–0 °C for 20 minutes, then 3,5-dichloropyridin-4-amine **7** (2.33 g, 14.20 mmol) was added to the solution (**CAUTION:** hydrogen gas is liberated). After that, compound **6** dissolved in acetonitrile was added dropwise to the mixture, and the temperature remained unchanged for an hour (monitored by TLC). Then the mixture was filtered, concentrated and dissolved in dichloromethane. The organic phase was washed with 1 M aqueous solution of hydrochloric acid, saturated sodium hydrogen carbonate and brine, then dried with magnesium sulfate. The organic phase was concentrated to give a yellow solid. Then it was recrystallised in methanol to give 3,4-bis(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)benzamide **1** (1.97 g, 85.3% yield) as a white solid. M.p. 206–207 °C; IR (KBr, ν_{max}/cm^{-1}): 3283 (ν NH), 3085, 3010 (ν CH on benzene or pyridine), 2913, 2871 (ν CH on cyclopropyl), 1656 (ν C=O), 1598, 1586 (ν C=C), 1558, 1548 (δ NH), 1500 (ν C=C), 1461 (ν C=C), 1399 (ν C=N), 1303 (ν CONHR), 1278, 1251 (ν C–O–Ar), 1239–1001, 868, 807 (δ CH on benzene), 750 (δ CH on pyridine). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.43 (s, 1 H, NH), 8.74 (s, 2 H, CH on pyridine), 7.64 (d, J = 8.4 Hz, 1 H, CH of benzene), 7.57 (s, 1 H, CH of

benzene), 7.10 (d, J = 8.4 Hz, 1 H, CH of benzene), 3.93 (d, J = 6.8 Hz, 2 H, OCH_2), 3.90 (d, J = 6.8 Hz, 2 H, OCH_2), 1.28 (m, 2 H, CH), 0.59 (t, 4 H, CH_2), 0.36 (t, 4 H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8 (C=O), 152.6, 148.7, 148.5, 142.1, 131.3, 125.2, 122.3, 113.8, 113.3 (11 C on benzene or pyridine), 73.7, 73.5 (OCH_2), 10.7, 10.6, 3.7 (4 C on CH_2). HR-MS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{20}Cl_2N_2O_3+Na^+$ 429.0749; found 429.0753.

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References

1 J.A. Beavo, *Physiol. Rev.*, 1995, **75**, 725.
2 B.J. Lipworth, *Lancet*, 2005, **365**, 167.
3 T. Trian, J.K. Burgess, K. Niimi, L.M. Moir, Q. Ge, P. Berger, S.B. Liggett, J.L. Black and B.G. Oliver, *Plos One*, 2011, **6**, e20000.
4 A. Kodimuthali, S.S.L. Jabaris and M. Pal, *J. Med. Chem*., 2008, **51**, 5471.
5 C.P. Page and D. Spina, *Curr. Opin. Pharmacol.,* 2012, **12**, 275.
6 D.C. Grootendorst, S.A. Gauw, R.M. Verhoosel, P.J. Sterk, J.J. Hospers, D. Bredenbroker, T.D. Bethke, P.S. Hiemstra and K.F. Rabe, *Thorax,* 2007, **62**, 1081.
7 D.V. Ly, M.D. Pedro, P. James, L. Morgan, J.L. Black, J.K. Burgess and B.G.G. Oliver, *Resp. Res.,* 2013, **14**, 127.
8 M.A. Giembycz and S.K. Field, *Drug Des. Dev. Ther.,* 2010, **21**, 147.
9 L.M. Fabbri, B. Beghe, U. Yasothan and P. Kirkpatrick, *Nat. Rev. Drug Discov.,* 2010, **9**, 761.
10 R. Gewald, C. Grunwald and U. Egerland, *Bioorg. Med. Chem. Lett.,* 2013, **23**, 4308.
11 S.L. Zheng, G. Kaur, H.C. Wang, M.Y. Li, M. Macnaughtan, X.C. Yang, S. Reid, J. Prestegard, B.H. Wang and H.M. Ke, *J. Med. Chem.,* 2008, **51**, 7673.
12 N.A. Pinner, L.A. Hamilton and A. Hughes, *Clin. Ther.,* 2012, **34**, 56.
13 S.K. Chen, P. Zhao, Y.X. Shao, Z. Li, C.X. Zhang, P.Q. Liu, X.X. He, H.B. Luo and X.P. Hu, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 3261.
14 G.F. Zhang, CN Patent 102964297, 2013.
15 T. Murakami, H. Matsuda, M. Inadzuki, K. Hirano and M. Yoshikawa, *Chem. Pharm. Bull,* 1999, **47**, 1717.
16 S. Caron, R.W. Dugger, S.G. Ruggeri, J.A. Ragan and D.H.B. Ripin, *Chem. Rev.,* 2006, **106**, 2943.
17 T. Konoike, K. Matsumura, T. Yorifuji, S. Shinomoto, Y. Ide and T. Ohya, *J. Org. Chem.,* 2002, **67**, 7741.
18 M.J. Ashton, D.C. Cook, G. Fenton, J.A. Karlsson, M.N. Palfreyman, D. Raeburn, A.J. Ratcliffe, J.E. Souness, S. Thurairatnam and N. Vicker, *J. Med. Chem.,* 1994, **37**, 1696.
19 D.C. Cook, R.H. Jones, H. Kabir, D.J. Lythgoe, I.M. McFarlane, C. Pemberton, A.A. Thatcher, D.M. Thompson and J.B. Walton, *Org. Process Res. Dev*., 1998, **2**, 157.
20 E. Dalcanale and F. Montanari, *J. Org. Chem.,* 1986, **51**, 567.
21 B.O. Lindgren and T. Nilsson, *Acta Chem. Scand.,* 1973, **27**, 888.
22 B. Kohl, B. Mueller and W. Palosch, WO Patent 2004080967, 2004.