Res Chem Intermed (2013) 39:2107–2113
DOI 10.1007/s11164-012-0742-3

A convenient method for the synthesis of roflumilast

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Received: 17 May 2012 / Accepted: 22 July 2012 / Published online: 7 August 2012

Abstract A convenient synthetic method has been developed for the synthesis of roflumilast from 4-difluoromethoxy-3-hydroxybenzaldehyde and bromomethyl cyclopropane via O-alkylation, oxidation and N-acylation. With sodium hydroxide as alkali in the last step, the total yield of roflumilast can be up to 68.3 % and the purity of the target product reached 99.2 %. It was obvious that sodium hydroxide showed more economic advantage for scale-up production than sodium hydride or potassium *tert*-butoxide.

Keywords Acylation · Chronic obstructive pulmonary diseases · Roflumilast · Sodium hydroxide

Introduction

Roflumilast is one of the second generation PDE-4 inhibitors and is the first drug to be approved for the treatment of chronic obstructive pulmonary disease (COPD) in Europe in the last 10 years. Now, it is widely used for the treatment of COPD, asthma, pulmonary hypertension and acute respiratory disease syndrome [1–3]. A synthetic route of roflumilast and its pharmacological actions were reported by

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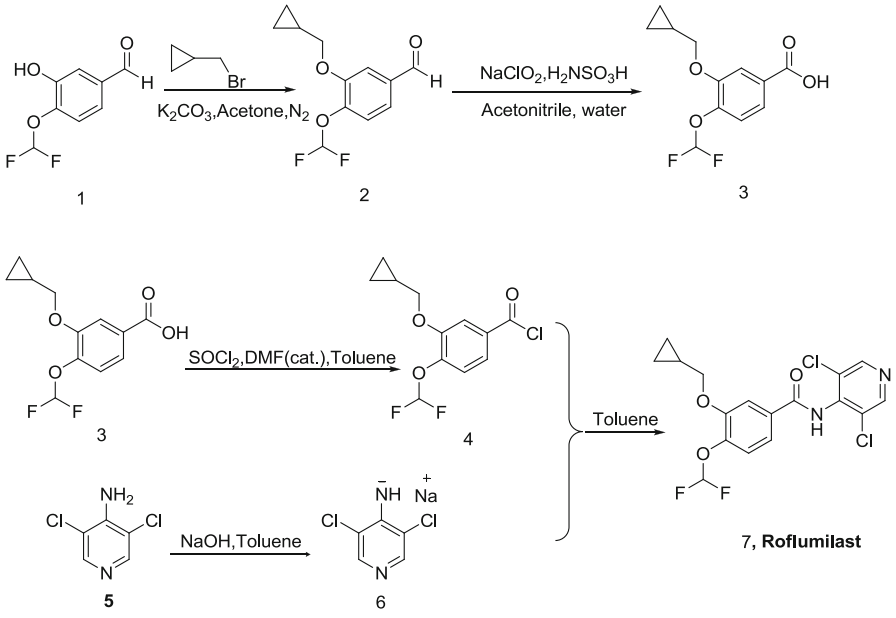
Sorbera et al. [4], the synthetic route consisting of O-alkylation, oxidation and N-acylation reaction, but there was just a scheme and no experimental details were mentioned in that paper. Obviously, the N-acylation reaction is the key step in the synthesis because 3,5-dichloropyridine-4-amine is not a good nucleophile and it is difficult to carry out the nucleophilic substitution reaction under normal reaction conditions. Sodium hydride was first reported to be used to activate the amine [5–7]. But the mineral oil in it is usually troublesome for the purification of the final product, and the hydrogen generated would cause security problems. Kohl et al. [8] intensively studied the synthesis of roflumilast, particularly the effects of alkalis employed in the last step, in which potassium *tert*-butoxide yielded the best results. In addition, alkalis in that paper only included lithium *tert*-butoixde, sodium *tert*-butoxide and potassium *tert*-butoxide, thus developing a new method employing sodium hydroxide in this reaction has good prospect.

Based on the above investigations, with consideration of the convenience of sodium hydroxide, in this paper, we have synthesized roflumilast from 4-difluoromethoxy-3-hydroxybenzaldehyde and bromomethyl cyclopropane, and have employed sodium hydroxide in the last step (Scheme 1). By optimizing the reaction conditions, the total yield of roflumilast can be up to 68.3 %.

Results and discussion

As described in Scheme 1, roflumilast was synthesized via O-alkylation, oxidation, chlorination of the carboxylic acid and N-acylation reaction. The O-alkylation



Scheme 1 Synthesis of roflumilast

reaction has been reported to be achieved in *N*,*N*-dimethylformamide [9], followed by the treatment of the reaction mixture with water and extraction of the aqueous phase by organic solvents, which contributed to effluent burden in the scale-up industrialization. Thus, in this paper, a number of solvents were examined for this reaction and the results are listed in Table 1. It can be seen that polar aprotic solvents would be helpful to the reaction. The O-alkylation reaction in methanol proceeded quite slowly and gave low yield, while higher yield was obtained in ethanol but in 40 h. Only in acetone did the alkylation proceed efficiently to afford the desired compound in satisfactory yield. In order to enhance the reaction time, KI was employed as catalyst and this led to an excellent result. Compound **2** as yellow oil was obtained in the yield of 94.4 %, which was directly used in the next oxidation step without further purification. The oxidation was achieved straightforwardly by sulfamic acid and sodium chlorite in acetonitrile to give the important intermediate, 3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzoic acid in the total yield of 76.5 %.

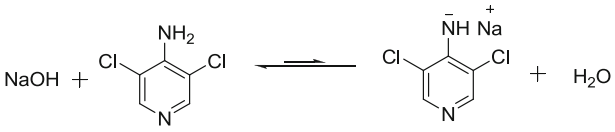
Then, we focused on the investigation of the last step. As seen in Scheme 1, roflumilast was achieved by the N-acylation of compound **5** with compound **4**. Because the nucleophilic ability of 3,5-dichloropyridine-4-amine was low due to the electronic and steric effects, the activation of the amine is required by alkali, such as potassium *tert*-butoxide and sodium hydride [7, 10]. In view of accessibility, convenience and the low cost, we employed sodium hydroxide in this reaction. It can be seen that the amino anion of 3,5-dichloropyridine-4-amine can be obtained in the reverse reaction equilibrium (Scheme 2). And sodium hydroxide showed such low basicity that it was more conductive to the forward equilibrium, which was unfavorable for the generation of the amino anion. Thus, by continuously removing the water, the equilibrium was very favorable for the reverse reaction balance and the amino anion could be generated efficiently. The acyl chloride (compound **4**) can be easily obtained by the chlorination of compound **3** with $SOCl_2$. Then it (compound **4**) was added to the suspending mixture to yield the roflumilast product. So dehydration was of great importance in this reaction, and this could be the main reason for the low yields in the preliminary experiments.

Then, the reactions were performed in the presence of different molar ratios of compounds **3**, **5** and sodium hydroxide to find the effects on the N-acylation reaction. The results are shown in Table 2. The results showed that the yields of roflumilast were all over 80 % under these conditions. And when the molar ratio of compounds **3**, **5** and NaOH was 1:2:4, the reaction gave the best yield of 89.2 % while there was more than 0.5 % of compound **8** in the purified product after repeated crystallization. But compound **8** was less in the final product when the reaction molar ratio was 1:2.5:2.25, which contributed to a higher quality of

Table 1 Effects of solvents on the O-alkylation reaction[a]

Entry	Solvents	Reaction time (h)	Yield %
1	Methanol	>16	45.7
2	Ethanol	40	88.2
3	Acetone	18	91.7
4	Acetone/KI	12	94.4

[a] The yields of compound **2** were detected by HPLC



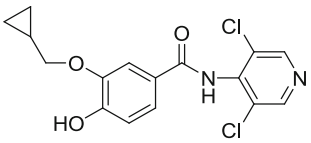
Scheme 2 Formation of the sodium salt of 4-amino-3,5-dichloropyridine

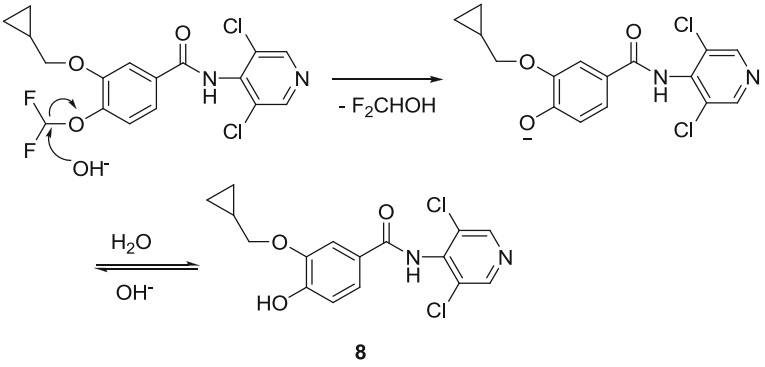
Table 2 Effects of molar ratio on the N-acylation reaction[a]

Entry	Molar ratio of compounds **3**, **5** and NaOH	Yield of 7 %	Content of 8 %
5	1.0:2.0:4.0	89.2	1.2
6	1.0:2.0:2.4	85.1	0.8
7	1.0:2.0:1.8	81.7	0.6
8	1.0:2.5:2.25	87.6	0.5

[a] The reaction was refluxed in toluene for 6 h. The yields and contents were detected by HPLC

Scheme 3 Structure of compound **8**





Scheme 4 The supposed mechanism of the generation of compound **8**

product. In addition, the mass of this compound **8** was measured at 353.9 by a liquid chromatography–mass spectrometry instrument [8]. The structure of it can be seen in Scheme 3, and the supposed mechanism of its formation in Scheme 4. In this figure, the nucleophilic substitution of roflumilast yielded the phenoxy anion, followed by the generation of compound **8**. It can be seen that excess sodium hydroxide contributed to the formation of compound **8**. So the amounts of compound **8** can be decreased by increasing the molar ratio of 3,5-dichloropyridine-4-amine to sodium hydroxide, and this was of great help for the purification of roflumilast. Thus, the optimum molar ratio of compounds **3**, **5** and sodium hydroxide was 1:2.5:2.25.

Table 3 Effects of the reaction temperature and time on the N-acylation reaction[a]

Entry	Reaction temperature (°C)	Reaction time (h)	Yield of 7 %	Yield of 8 %
9	35	6	17.2	0.1
10	110	2	68.5	0.2
11	110	3	81.5	0.2
12	110	6	87.6	0.5
13	110	7	87.3	2.5

[a] The molar ratio of compound **3**, **5** and NaOH in the reactions was 1:2.5:2.25. The yields of were detected by HPLC

In order to further decrease the amount of compound **8**, both the reaction temperature and reaction time were studied. The results are listed in Table 3. We can see that the N-acylation reaction and the generation of compound **8** competed in this reaction system, while the low temperature slowed down the N-acylation reaction process more significantly and this was disadvantageous for the roflumilast product yield. However, the reaction conducted at reflux afforded better yield of the roflumilast, which was 87.6 %. Furthermore, the results showed that the amounts of both compound **8** and roflumilast increased with the extension of the reaction time. So 3 h was the suitable reaction time.

Conclusions

In conclusion, we have developed a convenient synthetic method of roflumilast from 4-difluoromethoxy-3-hydroxybenzaldehyde and bromomethyl cyclopropane via O-alkylation, oxidation and N-acylation reaction. By optimizing the reaction conditions, roflumilast can be obtained in 68.3 % total yield and the purity of the product reached up to 99.2 %. The results showed that, with sodium hydroxide as the alkali in the N-acylation reaction, roflumilast can be obtained at the best yield of 89.2 %. Compared with other methods, the present method has several advantages including convenience, low cost and easy work-up, which allows an easy scale-up.

Experimental

General information

Reagents and solvents were obtained from commercial suppliers. All reactions were monitored by thin layer chromatography using commercial silica gel plates. The purity was detected by HPLC on Agilent 1,100 series. Melting points were observed on YRT-3 Melting Point Tester and were uncorrected. NMR spectra were recorded on Varian Inova-500 and 400 MHz NMR spectrometer with TMS as an internal reference. MS were recorded on a LCQ Advanced MAX mass spectrometer. HR-MS was recorded on MicroOTOF-Q II.

Synthesis of 3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzaldehyde (**2**)

4-(Difluoromethoxy)-3-hydroxybenzaldehyde (compound **1**, 53.16 mmol), K_2CO_3 (79.74 mmol), KI (10.63 mmol) in 250 mL acetone were added to a flask with magnetical stirring under nitrogen atmosphere. After the mixture was refluxed for 0.5 h, bromomethyl cyclopropane (79.74 mmol) was added to the flask within 0.5 h. Then, the mixture was stirred and refluxed for 12 h. After cooled to room temperature, the reaction mixture was filtered and concentrated. The obtained oil was dissolved in ethyl acetate and washed with water for three times. Then, the solvent was evaporated giving the compound **2** in yellow oil with the purity of 90.09 %. And this can be used for the next process without purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.93 (s, 1H, CHO), 7.47 (d, J = 2.5 Hz, 1H, CH of benzene), 7.45 (d, J = 1.5 Hz, 1H, CH of benzene), 7.32 (d, J = 8.0 Hz, 1H, CH of benzene), 6.76 (t, J = 74.5 Hz, 1H, CF_2H), 3.95 (d, J = 7.0 Hz, 2H, OCH_2), 1.35–1.29 (m, 1H), 0.70–0.66 (m, 2H), 0.40–0.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.68 (C=O), 150.88, 145.20, 134.55, 124.65, 121.94 (5 C benzene), 118.27, 115.68, 113.08 (CHF_2), 112.61, 73.98 (CH_2O), 9.89, 3.13. HR-MS (ESI), calcd $C_{12}H_{12}F_2O_3$: $[M+Na]^+$, m/z: 265.0652, found: 265.0650.

Synthesis of 3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzoic acid (**3**) [9, 11]

Compound **2** was dissolved in 100 mL acetonitrile and added to the solution of sulfamic acid (74.42 mmol) in 50 mL water. Then, sodium chlorite (74.42 mmol) in 50 mL water was added slowly at 0–10 °C and the reaction mixture was stirred at 20 °C for 5 h. Then, the acetonitrile was evaporated and the residue was dissolved in 5 wt%. NaOH solution, followed by washing with CH_2Cl_2 for three times. The aqueous solution was acidized by 1 mol/L hydrochloric acid until pH 3. The suspension was filtered and the solid was washed with water and dried to afford compound **3** as white solid (10.50 g, with the purity of 99.82 %). Mp.120 °C (lit. [12] 118–120 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.73 (d, J = 8.0 Hz, 1H, CH of benzene), 7.68 (s, 1H, CH of benzene), 7.24 (d, J = 8.5 Hz, 1H, CH of benzene), 6.75 (t, J = 74.5 Hz, 1H, CF_2H), 3.95 (d, J = 7.0 Hz, 2H, OCH_2), 1.36–1.28 (m, 1H), 0.70–0.66 (m, 2H), 0.40–0.38 (m, 2H). (lit. [12].: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.70 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.72 (t, J = 74.7 Hz, 1H), 3.94 (d, J = 6.6 Hz, 2H), 1.2–1.37 (m, 1H), 0.71–0.65 (m, 2H), 0.41–0.36 (m, 2H).)

Synthesis of 3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzoyl chloride (**4**) [13]

Compound **3** (3.9 mmol) in 50 mL toluene was heated to reflux until dissolving and the water was removed by Dean-Stark apparatus. The solution was then cool to 90 °C, $SOCl_2$ (5.8 mmol) and several drops of DMF were added. The solution was heated at reflux for 3.0 h. Then, it was cooled to room temperature and concentrated to give compound **4** as yellow crystal.

Synthesis of roflumilast (compound **7**)

Sodium hydroxide (15.50 mmol) was added to the mixture of compound **5** (7.75 mmol) in 40 mL toluene. Water was removed by azeotrope distillation. After 2 h, the chloride compound **4** in dry toluene was added and the mixture was stirred at reflux for 6 h. After the reaction mixture was cooled to room temperature, it was washed successively by 1 mol/L hydrochloric acid, saturated sodium bicarbonate solution and water. The organic phase was dried with magnesium sulfate and concentrated to give crude product of roflumilast as yellow solid (1.05 g) in the yield of 89.2 %. It was recrystallized in methanol/water = 90/10 (v/v) to yield the product (99.26 %). Mp. 158 °C (lit. [10] 158 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.56 (s, 2H, 2 CH of pyridine), 7.92 (s, 1H, NH), 7.59 (s, 1H, CH of benzene), 7.50–7.48 (dd, $J_1 = 2.0$ Hz, $J_2 = 6.5$ Hz, 1H, CH of benzene), 7.28 (d, $J = 8.0$ Hz, 1H, CH of benzene), 6.76 (t, $J = 93.5$ Hz, 1H, CF_2H), 3.96 (d, $J = 8.5$ Hz, 2H, OCH_2), 1.36–1.30 (m, 1H), 0.71–0.66 (m, 2H), 0.40–0.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.94 (C=O), 151.15, 148.57, 144.07 (3 C pyridine), 139.89, 131.03, 129.12, 122.54, 120.12, 114.42 (6 C benzene), 117.95, 115.87, 113.79 (CHF_2), 74.43, 10.23, 3.54. HR-MS (ESI), calcd $C_{17}H_{14}Cl_2F_2N_2NaO_3$: $[M+Na]^+$ *m*/*z*: 425.0242, found: 425.0208.

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