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A More Sustainable Process for the Preparation of the Muscarinic Acetylcholine Antagonist Umeclidinium Bromide

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Abstract: A more sustainable process for the synthesis of the long-acting muscarinic acetylcholine antagonist umeclidinium bromide is described. Specifically, we report the synthesis of ethyl 1-(2-chloroethyl)-4-piperidinecarboxylate, a key intermediate in the preparation of umeclidinium bromide, in good yields using triethylamine, as well as the identification and characterization of the by-product formed in this reaction. This new method of synthesis leads to an improvement of the yield, compared with the previous reported protocols using potassium carbonate as base (65.6% versus 38.6%). Moreover, in the last synthetic step of the process to obtain umeclidinium bromide we were able to replace the use of toxic solvents (acetonitrile/chloroform) by water. The use of this green solvent allowed the precipitation of the API from the reaction medium with high purity and in high yield. Overall, we have developed a more efficient and green process for the synthesis of the umeclidinium bromide active pharmaceutical ingredient with a higher overall yield (37.8% versus previously reported overall yield of 9.7%).

Introduction

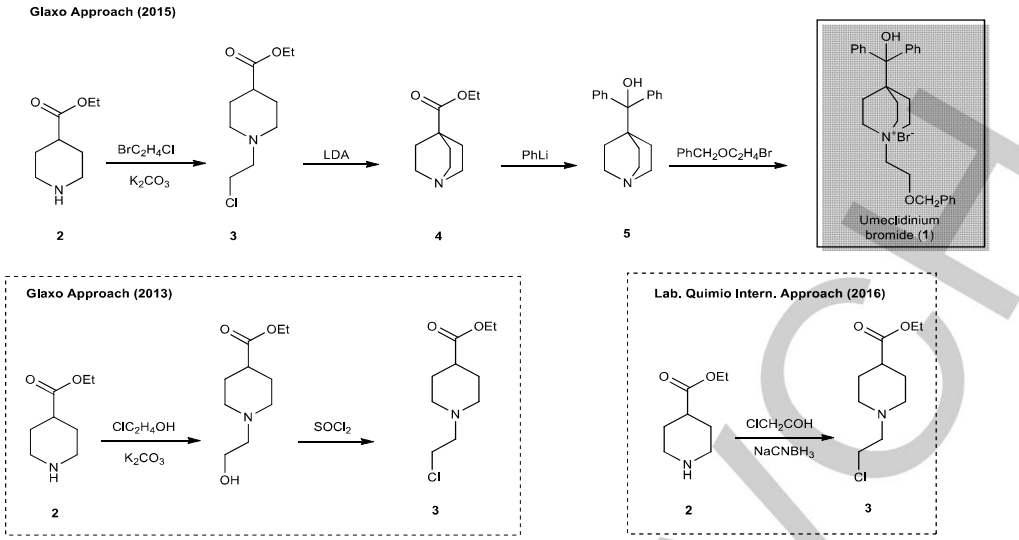
Chronic obstructive pulmonary disease (COPD) is a multi-component disease characterized to be preventable, however there is no cure and is considered one of the major causes of death worldwide.[1] An increase of this disease is expected due to continued exposure to COPD risk factors, as cigarrete smoking, indoor and outdoor pollution, chemicals, and an ageing population.[2-4] According to World Health Organization (WHO), globally, is estimated that the disease caused about 3 million deaths in 2015 (that is, 5% of all deaths globally in that year). WHO predicts that COPD will become the third leading cause of death worldwide by 2030.[1]

COPD is associated with an enhanced chronic inflammatory response, which leads to airway abnormalities and also some architectural distortion of the lung parenchyma. The cough, sputum production, and dyspnea are very common symptoms in individuals affected with this disease.[5-6] Due to the fast world population growth, pharmaceuticals will have an increasingly prominent role in the health care of the future generations. Therefore, the development of efficient processes that can deliver more safer, effective and affordable medicines is vital.

There are several therapeutic options to relieve COPD symptoms and provide a good quality of life for people suffering from this disease. Synthetic corticosteroids, as fluticasone propionate and fluticasone furoate, can be used in the management of COPD. They act on glucocorticoid receptor complexes, regulating C-reactive protein and inflammatory cytokines and cells.[7] These corticosteroids can be used in combination with long-acting muscarinic receptor antagonists (LAMAs). The LAMAs also exhibit anti-inflammatory effects and anti-remodeling effects such as inhibition of mucus gland hypertrophy.[8] One example is the umeclidinium bromide (**1**) (Scheme 1), a potent muscarinic acetylcholine receptor antagonist identified in 2009.[9] This molecule was approved by the US FDA at the end of 2013 as a highly effective active pharmaceutical ingredient (API) for the maintained treatment of stable COPD.[10-12]

The first process to obtain umeclidinium bromide (**1**) was disclosed by GlaxoSmithKline and comprises a synthetic route with four steps starting from ethyl isonipecotate (**2**) (Scheme 1).[13] In the first step, ethyl 1-(2-chloroethyl)piperidine-4-carboxylate (**3**) is obtained by a nucleophilic addition of ethyl isonipecotate (**2**) to 1-bromo-2-chloroethane, in the presence of potassium carbonate in acetone.[13] Under these mild conditions, product **3** is isolated, by chromatography, in low yield (38.6%). This low yield compromises the overall yield of the synthetic process to obtain the API **1**. More recently, two other synthetic methods to obtain the intermediate **3** were reported (Scheme 1) [14-15] but both of them present some security risks to be used in a large scale synthesis (e.g. use of toxic reagents, use of high temperatures, release of hydrogen). The second and third synthetic steps involve the intramolecular cyclization of compound **3** (yield of 95.7%), followed by reaction of **4** with phenyl lithium (yield of 60.7%), to obtain compound **5**. umeclidinium bromide (**1**) is then obtained by reaction of intermediate **5** with benzyl 2-bromoethyl ether, in a mixture of chloroform and acetonitrile, in 43.3%.[13]

Although this process allows obtaining umeclidinium bromide (**1**) with an overall yield of 9.7% it has some limitations for the pharmaceutical industry in terms of toxicity of the solvents/reagents used. Therefore, the search for more efficient and green synthetic alternatives to this method of synthesis are required.



Scheme 1. The first process described by GlaxoSmithKline for the preparation of umeclidinium bromide (**1**) and reported processes for the preparation of intermediate **3**.

Results and Discussion

Herein we present our results on the optimization of this process of synthesis of umeclidinium bromide (**1**) by improving the yields of the first and last synthetic steps and applying greener synthetic methods. In order to improve the yield of **3** we studied the effect on the reaction of changing the temperature, the base or the solvent (Table 1). Using the reaction conditions reported by GlaxoSmithKline (acetone as solvent and potassium carbonate as base)[13] we evaluated the effect of changing the temperature from room temperature to 56 ºC (Entries 1-2). The higher yield of compound **3** was obtained when the reaction was performed at 25º C (Entry 1). Then, a screening of solvents was performed (acetonitrile, THF, DCM and toluene).

Table 1. Reaction conditions for the preparation of ethyl 1-(2-chloroethyl)-4-piperidinecarboxylate (**3**).

Base	Solvent[a]	*T* [ºC] [b]	Yield [%][c]
K_2CO_3	Acetone	rt	38.6[13]
K_2CO_3	Acetone	56	18.6
K_2CO_3	CH_3CN	rt	11.1
K_2CO_3	THF	rt	35.9
K_2CO_3	DCM	rt	25
K_2CO_3	Toluene	rt	11.5
K_2HPO_4	Acetone	rt	58.4
$KHCO_3$	Acetone	rt	33.8
NEt_3	Acetone	rt	65.6

[a] THF: tetrahydrofuran, DCM: dichloromethane. [b] rt – room temperature. [c] Isolated yield after flash chromatography (silica gel, 1:1 *n*-hexane/EtOAc).

In all cases, the yield of compound **3** reduced compared to the reaction using acetone as solvent (Entries 3-6 versus Entry 1). Finally, we studied the effect on the reaction of using other bases. The yield of compound **3** was increased when the base used was dipotassium phosphate (pKa = 12.4) (Entry 7) or triethylamine (pKa = 10.7) (Entry 9), while it reduced when the base was potassium bicarbonate (pKa = 10.3) (Entry 8). Comparing with GlaxoSmithKline approach, the yield of compound **3** was increased to 65.6% using triethylamine as base. Using these reaction conditions, we isolated a by-product in 14% yield (Scheme 2). We also tested the use of other bases such as pyridine, DMAP, DIPEA and DBU. Unfortunately, the amount of the crude obtained was too low, so the isolation of the product was not carried out.

We then focused our attention on the optimization of the last synthetic step described in Scheme 1. The reported yield for this reaction is low and the solvents used, a mixture of acetonitrile/chloroform, are not ideal for industrial application. These solvents should be limited in pharmaceutical products because of their inherent toxicity. Using 1.5 equivalents of benzyl 2-bromoethyl ether, we explored the effect of other solvents and temperatures on the reaction (Table 2). Comparing with the yields obtained by GlaxoSmithKline approach, in all reactions the yields were improved to 53.4-82.2%. The highest yield was obtained by using THF as solvent (82.2%, Entry 1). The yields were lower when the reactions were performed in a mixture of water/acetone (1:1) (53.4%, Entry 5) or ethanol (62.9%, Entry 10). Quite interestingly, even when water was used as solvent the final product was obtained in very good yields (64.3-74.2%, Entries 6-9). While in water, the higher yields were obtained with a temperature of 60ºC (Entry 6), in toluene the reaction temperature had almost no impact in the reaction yield (Entries 3-4). Moreover, the precipitation of umeclidinium bromide was induced at 2–4 ºC for the reactions developed in water, while in the other cases it was required to evaporate to dryness the solvent to obtain the final product in a less pure form. This efficient process allowed obtaining directly the umeclidinium bromide (**1**) from the reaction medium with good purity (confirmed by HPLC).

Table 2. Reaction conditions for the preparation of umeclidinium bromide (1).

Entry	Volume [mL]	Solvent[a]	*T* [ºC]	Yield [%]
1	30	THF	60	82.2[b]
2	30	acetone	60	75.7[b]
3	30	toluene	60	79.6[b]
4	30	toluene	reflux	81.0[b]
5	30	water/acetone (1:1)	60	53.4[b]
6	30	water	60	74.2[c]
7	20	water	60	71.6[c]
8	30	water	reflux	64.3[c]
9	20	water	reflux	68.3[c]
10	30	ethanol	60	62.9[b]

[a] THF: tetrahydrofuran. [b] Isolated yield after evaporation to dryness of the solvent. [c] Isolated yield after precipitation from the reaction medium.

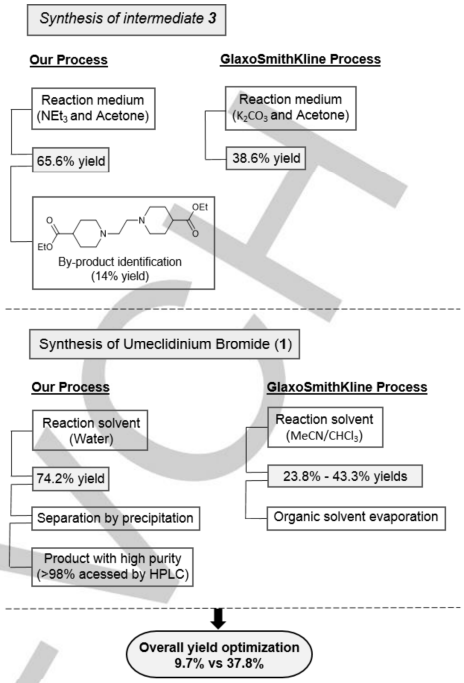
The reaction in water at a temperature of 60ºC (entry 6) was also performed in a larger scale (starting from 2.56 mmol of compound **5**). In this scale the reaction outcome was almost identical with a yield of 76.9%. Using the optimized steps (step 1 - entry 9, Table 1; step 4 - entry 6, Table 2) Umeclidium Bromide (**1**) was obtained with an overall yield of 37.8%.

A comparison of the impurity profile of the final product obtained from the two different routes (GSK and ours) showed that the absolute purity obtained following GSK route is 95.9%, while following our higher scale route is 98.9%. Moreover, the amounts of toxic solvents present in each sample were quantified. The sample prepared following GSK route presented: CH_3CN (662 ppm), AcOEt (44 ppm), and $CHCl_3$ (407 ppm). The sample prepared following our route only presented *n*-heptane (39 ppm).

Finally, we evaluated if the optimized process could be developed using directly the mixture of intermediate **3** and by-product to synthesize the final product. Using this approach and starting from 25.95 mmol of compound **2**, intermediate **5** was obtained in 23% yield and with high purity (99.3% by HPLC). Reaction with benzyl 2-bromoethyl ether led to umeclidinium bromide (**1**) in an overall yield of 19.3% and HPLC purity of 98.1%.

Conclusions

Overall, the new protocols developed in these two synthetic steps allow a considerable improvement of the overall yield of the process described in Scheme 1 (from 9.7%[13] to 37.8%). Additionally, in the final synthetic step the solvents acetonitrile and chloroform were replaced by water, the solvent of choice in green chemistry. This change in the reaction conditions allowed obtaining the API directly from the reaction medium by precipitation. This optimized process (Scheme 2) represents a clear advantage for the large scale synthesis of umeclidinium bromide (**1**) by the pharmaceutical industry.



Scheme 2. Advantages of the proposed process comparing with the GlaxoSmithKline approach reported in 2005.

Experimental Section

General Information: All reagents and solvents were obtained from commercial suppliers and were used without further purification. Thin layer chromatography was performed using Merck Silica Gel 60 F_{254} plates and visualized by UV light. Merck Silica Gel (230-400 mesh) was used for flash column chromatography. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Fourier 300. ^{1}H and ^{13}C-NMR chemical shifts are reported in parts per million (ppm, δ) referenced to the solvent used. Proton coupling constants (*J*) are expressed in hertz (Hz). Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS experiment was performed on Micromass® Quattro Micro triple quadrupole (Waters®, Ireland) with an electrospray in positive ion mode (ESI+), ion source at 120 ºC, capillary voltage of 3.0 kV and source voltage of 30V, at the Liquid Chromatography and Mass Spectrometry Laboratory, Faculty of Pharmacy, University of Lisbon. LC-MS experiments to determine the purity of the compounds were performed on a Waters Alliance 2695 Separations Module, equipped with a PDA detector set at 220 nm.

General procedure for the synthesis of ethyl 1-(2-chloroethyl)piperidine-4-carboxylate (3): To a solution of ethyl isonipecotate (**2**) (0.8 mL, 5.19 mmol) in the corresponding solvent (8.6 mL) was added the appropriate base (7.79 mmol) followed by 1-bromo-2-chloroethane (0.48 mL, 10.38 mmol). The reaction mixture was stirred for 24h at the corresponding temperature and then concentrated under vacuum. The resulting residue was treated with water and extracted with diethyl ether. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under vacuum. The purification of the crude was performed by flash chromatography on silica gel (1:1 *n*-heptane/ethyl acetate) resulting in the desired compound (colourless liquid). The ^{1}H-NMR of ethyl 1-(2-chloroethyl)-4-

piperidinecarboxylate (**3**) was in accordance with the one reported [13]. By-product: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.11 (q, J = 5.25 Hz, 4H), 2.99 – 2.76 (m, 4H), 2.47 (s, 4H), 2.30 – 2.20 (m, 2H), 2.07 – 1.99 (m, 6H), 1.90 – 1.84 (m, 4H), 1.79 – 1.66 (m, 4H), 1.23 (t, *J* = 6.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.3, 60.5, 56.4, 53.7, 41.3, 28.4, 14.4. MS (ESI) m/z calcd for $C_{18}H_{32}N_2O_2$: 340, found 341 $[M + H]^+$.

General Procedure for the synthesis of umeclidinium bromide (1) [Entries 1-5 and 10, Table 2]: To a solution of compound **5** (0.20 g, 0.68 mmol) in the corresponding solvent (20 or 30 mL) was added benzyl 2-bromoethyl ether (0.16 mL, 1.02 mmol). The solution was stirred at the mentioned temperature, during 24h. The reaction mixture was cooled down and the solvent was removed under vacuum. The resulting solid was washed with ethyl acetate (5x20 mL) and *n*-hexane (5x20 mL). The resulting white solid was then dried under vacuum to afford umeclidinium bromide (**1**) as a white powder.

General Procedure for the synthesis of umeclidinium bromide (1) [Entries 6-9, Table 2]: To a solution of compound **5** (0.20 g, 0.68 mmol) in water (20 or 30 mL) was added benzyl 2-bromoethyl ether (0.16 mL, 1.02 mmol). The solution was stirred at the temperature indicated in table 2, during 24h. The reaction mixture was slowly cooled to 2-4^{0}C, forming a white solid. The product was filtrated under vacuum and the excess of bromide was removed by washing the compound with ethyl acetate (20 mL) and *n*-hexane (5x20 mL). The white solid was then dried under vacuum to afford umeclidinium bromide (**1**) as a white powder. The ^{1}H-NMR of umeclidinium bromide (**1**) was in accordance with the one reported.[13]

Experimental procedure for the preparation of umeclidinium bromide (1) in large scale starting from ethyl isonipecotate, and without removing the by-product: To a solution of ethyl isonipecotate (4.0 mL, 25.95 mmol) in acetone (43.0 mL) was added triethylamine (5.45 mL, 38.95 mmol) followed by 1-bromo-2-chloroethane (4.32 mL, 52.14 mmol). The reaction mixture was stirred for 17h at 25ºC. *n*-Heptane (43.0 mL) was added and acetone was removed under vacuum. This procedure was repeated twice. Then, water (43 mL) was added and the resulting solution was extracted with *n*-heptane (2x43 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under vacuum. After, *n*-heptane (11.50 mL) was added, and the solution was placed at 0ºC during 1h and at -20ºC for 16h, followed by filtration. The solution obtained was concentrated under vacuum. The obtained residue (3.57 g) was dissolved in THF (89.6 mL), under nitrogen atmosphere, and the solution was cooled to -50ºC. LDA (1.0 M in hexanes/THF 20.72 mL, 20.72 mmol) was added at -50ºC during 25 min. The reaction mixture was allowed to warm up to room temperature over 16h. The reaction was quenched with saturated aqueous solution of K_2CO_3 (74.4 mL) and extracted with ethyl acetate (3x74.4 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under vacuum, to give an orange oil (3.02 g).

The orange oil (3.02 g) was dissolved in THF (36.7 mL). The resulting solution was slowly added to a solution of phenyllithium (1.9 M in 70 cyclohexane/30 ether, 33.7 mL, 64.1 mmol), under nitrogen atmosphere, at -30ºC during 25 min. The reaction mixture was allowed to warm up to room temperature over 16h. The reaction was quenched with water (15 mL) and then evaporated to dryness under vacuum. Water (60.2 mL) and ethyl acetate (60.2 mL) were added, causing a white solid to crash out. This solid was filtered off under vacuum, to give 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (**5**) as a white powder (1.76 g, three steps yield: 23.0%). HPLC purity: 99.3%.

To a suspension of 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (**5**) (1.76 g, 5.83 mmol) in water (258.0 mL) was added ((2-bromoethoxy)methyl)benzene (1.40 mL, 9.01 mmol) and heated up to reflux. The solution was stirred during 24h. The reaction mixture was slowly cooled to room temperature and stirred for 2h at a temperature between 2-4ºC. The product was filtrated under vacuum and the excess of bromide was removed by washing the compound with *n*-heptane (20.0 mL). Umeclidinium bromide (**1**) was obtained as a white solid and then dried under vacuum (2.55 g, 84.0%). HPLC purity: 98.1%.

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Supplementary data

Supplementary data associated with this article can be found in the online version. These data include: ^{1}H and ^{13}C NMR spectra of by-product; HPLC chromatograms of compound **1**.

Keywords: COPD • green solvents • industrial chemistry• triethylamine • umeclidinium bromide

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