Synthesis of 5-Aminosalicylic Acid using Kolbe-Schmidt Reaction Under Supercritical Conditions

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5-Aminosalicylic acid is one of the preferred drugs in clinical treatment of inflammatory bowel disease, so it has important significance to investigate the process of its preparation. In this work, 5-aminosalicylic acid was synthesized by Kolbe-Schmidt reaction under supercritical conditions. Supercritical CO_2 serves as both reactant and reaction medium in the reaction. The effects of various conditions, such as pressure, temperature, reaction time and stir speed, on the yield of 5-aminosalicylic acid were investigated. As the supercritical CO_2 has high diffusion coefficient, high solubility, high mass transfer efficiency and effective heat transfer capacity, the reaction can be carried out in a homogenizing situation. The experimental results show that more than 90.5 % of the yield of 5-aminosalicylic acid can be obtained under the optimal reaction parameters such as pressure (9.0 MPa), temperature (140 °C), reaction time (2.5 h) and stir speed (300 rpm). The results indicate that, in supercritical state, Kolbe-Schmidt reaction can be carried out with high speed at much lower temperature compared to that of the traditional technology and the product quality and production efficiency is also enhanced.

Key Words: 5-Aminosalicylic acid, Synthesis, Kolbe-Schmidt reaction, Supercritical fluids reaction.

INTRODUCTION

5-Aminosalicylic acid (5-ASA drugs known as Masalazine) is an important chemical raw material of medicine and dye, is also a main material of salazosulfapyridine for treating inflammatory bowel disease[1], which has a similar treatment. 5-Aminosalicylic acid could carry on several reactions because of three active reactive groups of hydroxyl and carboxyl on the ring, so it can be used to make a variety of reactive dyes with good quality in the dye industry.

5-Aminosalicylic acid is typically synthesized *via* the Kolbe-Schmidt reaction[2,3]. At present, the main manufacturing techniques for 5-aminosalicylic acid include suspension reaction, gas-solid phase reaction and solvent process, among others. However, these techniques universally suffer from certain limitations, including high energy consumption, long reaction times, low yields, complicated operation and pollution-causing tendencies. Moreover, they haven't been enhanced so far.

In view of the drawbacks mentioned above, we developed a method of synthesizing 5-aminosalicylic acid under supercritical conditions. Supercritical fluids (SCFs) can be defined as a compound, mixture or element that is in a state above its critical pressure (Pc) and critical temperature (Tc). The density-dependent properties of an supercritical fluids solvent (*e.g.*, solubility, diffusivity, viscosity and heat capacity) can be manipulated with relatively small changes in temperature and pressure. By far, the most commonly used fluid is CO_2[4] because it is inexpensive, non-toxic, environmentally benign, non-flammable and has low critical constants (Tc = 31.1 °C, Pc = 7.38 MPa). Super critical CO_2 (scCO$_2$) has very low surface tension, low viscosity and a high diffusion rate. Furthermore, scCO$_2$ forms fully homogeneous single-phase mixtures with many reagents over a wide range of compositions.

The objective of the present study is to synthesize 5-aminosalicylic acid through the Kolbe-Schmidt reaction under supercritical conditions, in which CO_2 serves as both the solvent and reagent. We also discuss the effects of reaction pressure, temperature, time and stir speed on the yield of 5-aminosalicylic acid. In this way, we may obtain some insights regarding the Kolbe-Schmidt reaction under supercritical conditions and lay a preliminary experimental foundation for the theory of supercritical reactions.

EXPERIMENTAL

p-Aminophenol and sodium hydroxide were purchased from Tianjin Fine Chemical Corporation (China) and used as received. A high pressure autoclave (model HA221-50-06) was sourced from by Hainan, China.

Methods: The synthesis of 5-aminosalicylic acid from the Kolbe-Schmidt reaction involves three steps. First, sodium *p*-aminophenol is obtained from the reaction of *p*-aminophenol and sodium hydroxide:
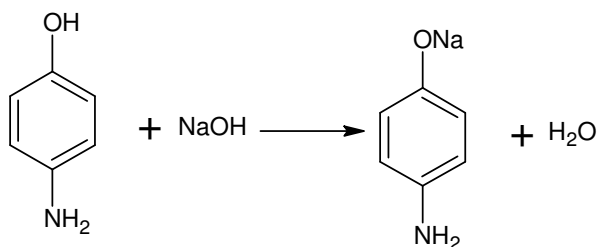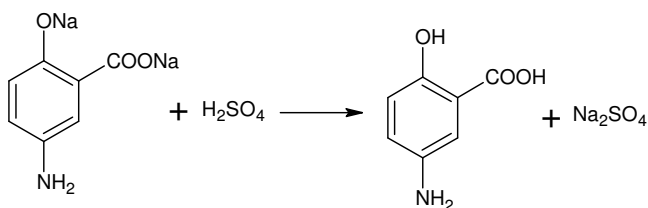
Scheme-I: First step of a Kolbe-Schmidt reaction

Then, carboxylation of sodium *p*-aminophenol with CO_2 follows:
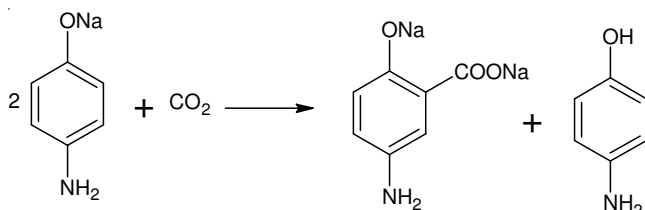
Scheme-II: Second step of a Kolbe-Schmidt reaction

Finally, 5-aminosalicylic acid is obtained after acid washing:

Scheme-III: Purification of 5-aminosalicylic acid

On the Kolbe-Schmidt reaction mechanism there is no conclusive explanation[5-7]. The more acknowledged mechanism is that illustrated above. The main side effects are as follows:

$$2NaOH + CO_2 \longrightarrow Na_2CO_3 + H_2O$$
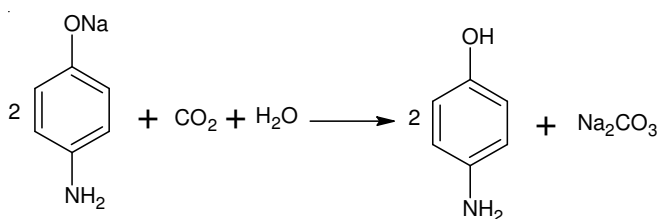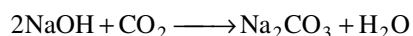
Scheme-IV: Side products of the Kolbe-Schmidt reaction

Formation of sodium *p*-aminophenol: The influence of molar ratio of *p*-aminophenol and sodium hydroxide was studied and the optimum ratio was determined to be 1.1:1. The initial amount of *p*-aminophenol and sodium hydroxide were put into a three-necked flask and stirred for about 15 min. The system was heated until the solution became viscous. The solution then transferred to a vacuum drying equipment. The initial vacuum drying took place at a pressure of 0.08-0.09 MPa and a temperature of 140-150 ºC. The mixer was cooled when a small amount of water flowed out from vacuum dryer. Next, sodium *p*-aminophenol was ground and put into a vacuum dryer. The second vacuum drying proceeded at a pressure of 0.08-0.09 MPa and a temperature of 130-140 ºC. When water no longer flowed out, the mixer was cooled, weighed and placed into a vacuum dryer in storage.

Carboxylation: Carboxylation reaction carried out in an autoclave. The autoclave was sealed after specific amounts of sodium *p*-aminophenol were added into it. With heating and stirring, CO_2 was loaded into autoclave until it reached a pre-selected value. And the temperature was also adjusted to a specific value. At the required pressure and temperature the reaction proceeded for a pre-defined length of time.

Refining: After a pre-determined reaction time, the reaction was quenched. The temperature of the autoclave was quickly reduced to below 80 ºC with cold water and CO_2 was simultaneously drained away from the autoclave. The mixer in the autoclave was removed into a 1 L beaker. Some sulfuric acid was added in succession to the beaker until the pH value was adjusted to roughly 2-3, crude salicylic acid was obtained by filtration. This was dried, weighed and packed. Afterwards, some of the product was transferred into a solution which contained about 225 mL distilled water, 75 mL conc. hydrochloric acid and amount of activated carbon. And this solution needed to boil for 10 min. Then activated carbon was filtered and the pH value was adjusted to roughly 2-3 with 30 per cent sodium hydroxide and almost colourless solid was separated out. The obtained solid was dried for 2 h after washing, finally got slightly grayish white crystals and packed.

An UV752 spectrometer was used to test the concentration of the prepared 5-aminosalicylic acid. An FTIR200 spectrometer was used to obtain the spectra of the prepared 5-aminosalicylic acid over the range of 4000-400 cm^{-1}. ^{1}H NMR spectra were recorded on a Varian spectrometer at 200-900 MHz. Electric and magnetic fields sport ions (electrically charged atoms, molecules or molecular fragments) according to their mass charge ratio detection method after separation. The melting point was measured by a WRR model melting point apparatus.

RESULTS AND DISCUSSION

Effect of pressure on the yield of 5-aminosalicylic acid: Supposing a temperature of 140 ºC, a reaction time of 2.5 h and stir speed of 300 rpm, the influence of reaction pressure on the 5-aminosalicylic acid yield is shown in Fig. 1. From Fig. 1, it is concluded that on the whole, the 5-aminosalicylic acid yield increases with increasing pressure. However, the effect of slightly increasing pressure on the yield is not very obvious when the pressure is below 5 MPa. The main reason for this is that, although the pressure increases, the reaction still proceeds as a gas-solid phase reaction, in which the reaction rate is mainly influenced by the mass transfer progress. Under a relative high pressure, CO_2 and sodium *p*-aminophenol molecules reach equilibrium, so that this equilibrium cannot be broken by increasing pressure. Accordingly, the yield remains relative steady. When pressure increases and exceeds 6 MPa, CO_2 transforms to sub-supercritical CO_2. At this point, CO_2 has some properties of a sub-fluid, therefore causing an increase in the mass transfer coefficient and yield. This phenomenon becomes more clear[8] when pressure nearly reaches the critical point (7.38 MPa). Due to the low precision of the pressure gauge in the laboratory, the pressure may have exceeded the supercritical point. When pressure exceeds 9.0 MPa, the distinct
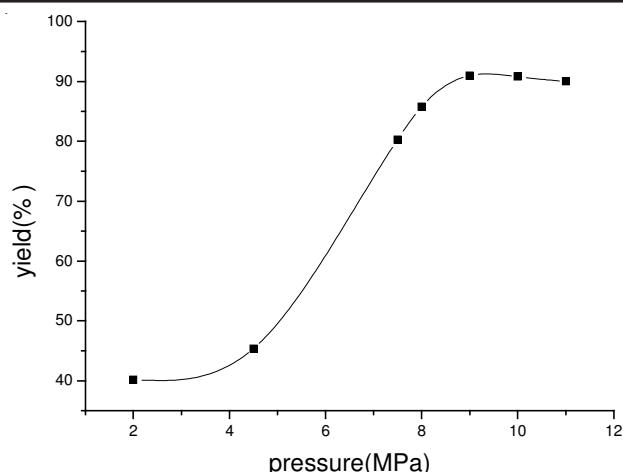
Fig. 1. Relationship between pressure and yield of 5-aminosalicylic acid

Fig. 2. Relationship between temperature and yield of 5-aminosalicylic acid

effect on the yield of 5-aminosalicylic acid is not observed. This is because the mass transfer coefficient of CO_2 and sodium *p*-aminophenol molecules is essentially constant in supercritical fluids. The coefficient does not change obviously by increasing pressure. The mechanism of supercritical fluids is not very explicit at present and further tests need to be done to draw further conclusions.

Above the supercritical pressure, the yield increases only a little, but the energy consumption is more. To avoid wasting energy, a pressure of 9.0 MPa is deemed suitable for actual use.

Effect of temperature on the yield of 5-aminosalicylic acid: Supposing a reaction pressure of 9.0 MPa, a reaction time of 2.5 h and stir speed of 300 rpm, the influence of the reaction temperature on 5-aminosalicylic acid yield is shown in Fig. 2. As shown in Fig. 2, temperature is the key factor in controlling the Kolbe-Schmidt reaction. The density of the oxygenic negative ion of sodium *p*-aminophenol and the electron cloud of the benzene ring is high, whereas the electron cloud of CO_2 is low. Thus, it can be considered a weak electrophile and only a highly activated benzene ring can react with it. When temperatures are below 80 °C, sodium *p*-aminophenol cannot react however high the pressure may be or how vigorously it is stirred. This can be confirmed in the experiment. Increasing the temperature gradually increases the yield of 5-aminosalicylic acid. When the temperature reaches 140 °C, the yield is maximum, then the yield begins to decrease. This is because the increasing temperature is conducive to the proliferation and infiltration of the sodium salt and $scCO_2$ makes heterogeneous gas-solid reactions become homogeneous reaction. The reaction improvement of the mass transfer and heat transfer characteristics reaches maximum, thus the reaction speed is greatly accelerated and local side effects caused by overheating is avoided, the reaction can occur in the lower temperature and the yield is enhanced. However, when the temperature rises to a certain degree, the yield begins to decrease because of the increase in the amount of by-products and the decomposition of products.

Effect of time on the yield of 5-aminosalicylic acid: Supposing a temperature of 140 °C, pressure of 9.0 MPa and stir speed of 300 rpm, the influence of reaction time on the yield of 5-aminosalicylic acid is shown in Fig. 3. As the results
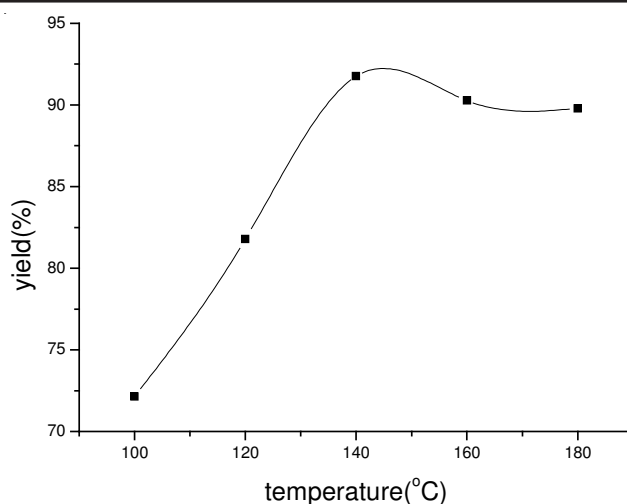
in Fig. 3 show, the influence of time on the yield of 5-aminosalicylic acid is apparent. The optimal reaction time is 2.5 h and the yield shows a decreasing trend whether the reaction time is enhanced or reduced. This is because, under supercritical conditions, both the solubility of $scCO_2$ on sodium *p*-aminophenol and its mass transfer coefficient are very high. The $scCO_2$ can quickly combine with sodium *p*-aminophenol and reach equilibrium. This consequently shortens the reaction time significantly compared with traditional methods. As the reaction proceeds, the amount of sodium *p*-aminophenol present in the system decreases and the reaction rate begins to decrease. At the same time, the decomposition of the products and side reactions gradually increase. As a result, the yield decreases.
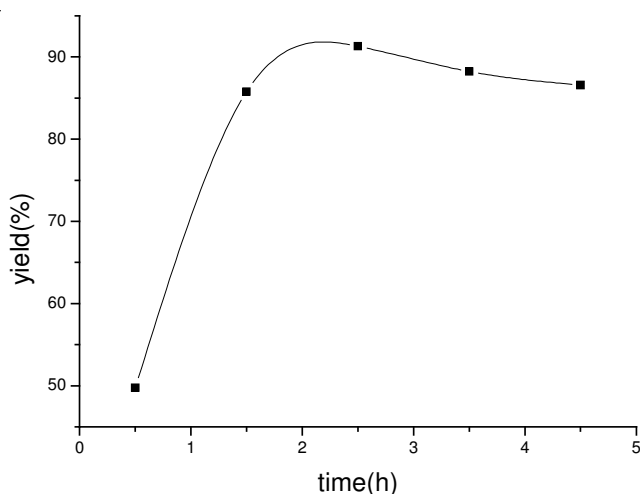

Fig. 3. Relationship between time and yield of 5-aminosalicylic acid

Effect of stir speed on the yield of 5-aminosalicylic acid: Supposing a temperature of 140 °C, pressure of 9.0 MPa and a reaction time of 2.5 h, the influence of stir speed on the 5-aminosalicylic acid yield is shown in Fig. 4. From Fig. 4, it is concluded that on the whole, increasing the stir speed gradually increases the yield of 5-aminosalicylic acid. However, when the stir speed reaches up to 300 rpm later, this effect is not obvious. On comparison with conventional methods stirring intensity is greatly decreased. This is due to the fact that sodium
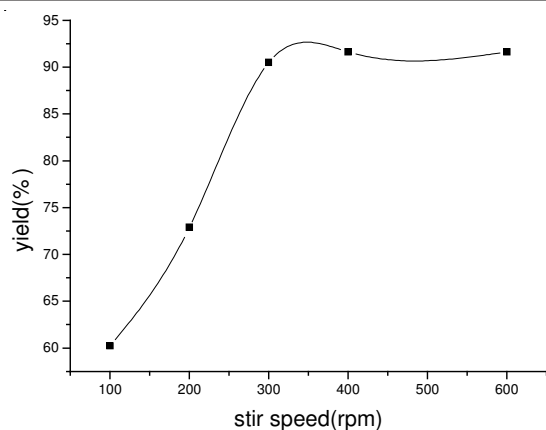
Fig. 4. Relationship between stir speed and yield of 5-aminosalicylic acid

salt can not be completely dissolved in scCO$_2$ fluid, but this solution has fundamentally changed the heterogeneous nature of the traditional Kolbe-Schmidt reaction, so that the whole system is similar to the same phase, so the stirring intensity is less important than traditional crafts.

Characterization of the product: Crude 5-aminosalicylic acid with scCO$_2$ is powder and grayish yellow. Refined 5-aminosalicylic acid is light gray-white needle crystallization and its melting point is 276-277 °C.

FTIR analysis of the prepared 5-aminosalicylic acid: The spectrum of the prepared 5-aminosalicylic acid is shown in Fig. 5. FTIR analysis shows that the four strong absorption peaks at 1650-1450 cm^{-1} are due to the ν(C-C) of the benzene ring. The appearance of the -OH group is proved by a moderately strong absorption peak at 3500-3200 cm^{-1}. The two strong peaks at 1320-1280 and 1240-1200 cm^{-1} are due to δ(O-H) and ν(C-O) of the -OH group in benzene, separately. The weak bands at 3400-2500 and 1450-1410 cm^{-1}, 950-870 cm^{-1} are assigned to the νC-H and δO-H of the -OH group in -COOH, respectively. The νC=O of the C=O group is identified from its bands at 1700-1680 cm^{-1}. The two weak absorption peaks at 3500-3400 cm^{-1} are the νN-H of the -NH group. The δN-H of the -NH group and benzene ring are similar, may mutually overlapping or covering up, so it is difficult to distinguish. The presence of the C-N group is supported by a moderately strong absorption peak at 1340-1250 cm^{-1}.
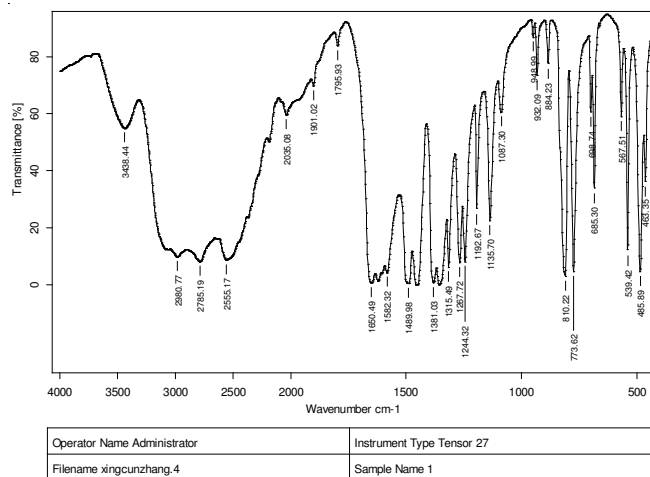

Fig. 5. FTIR spectra of the refined 5-aminosalicylic acid

^{1}H NMR analysis of the prepared 5-aminosalicylic acid: The ^{1}H NMR spectrum in Fig. 6 shows that the peaks at δ = 6.661-6.683 δ = 6. 836-6.865 and δ = 7.120-7.126 are H in the structure of benzene ring. However the protons of -OH, -NH$_2$ and -COOH don't appear. The reason is due to the situation between the rapid proton exchange and the formation of salt when the molecule has several active hydrogen groups, such as containing -COOH, -OH and -NH$_2$, *etc*.
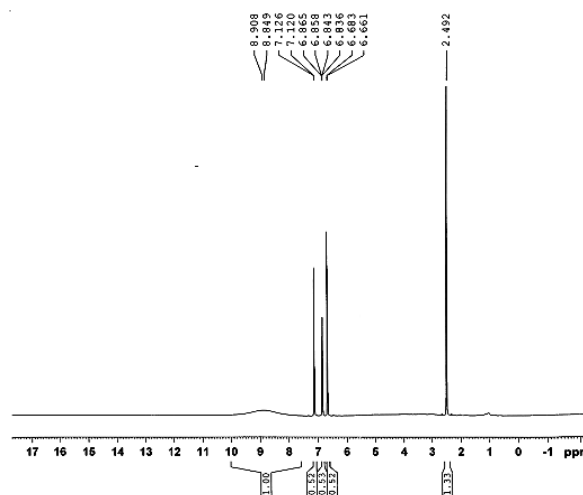

Fig. 6. Chemical structure(a) and ^{1}H NMR spectrum (b) of refined 5-aminosalicylic acid

Mass spectra of the prepared 5-aminosalicylic acid: The mass spectra is shown in Fig. 7. The appearance of the molecular ion peak is proved by m/z = 153, the two fragment ion peaks at m/z = 107 and m/z = 79 are due to strip CO. The fragment ion peaks at m/z = 135 and m/z = 52 are ascribed to strip H$_2$O and CNH, respectively. The cracking method is in the following manner:
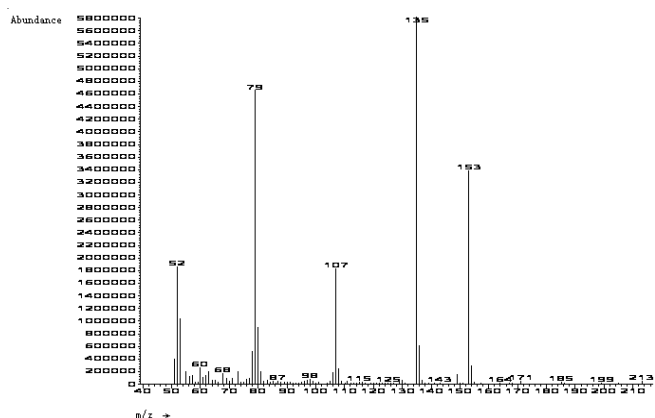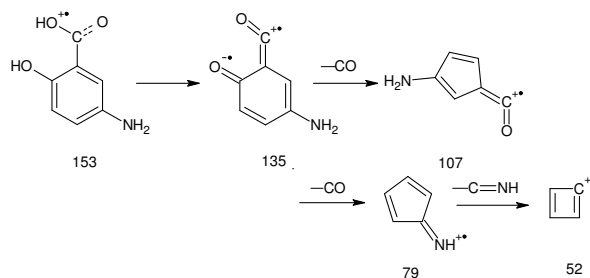

Fig. 7. Mass spectra of the refined 5-aminosalicylic acid

These results clearly show that the product structure is correct.

Conclusion

Because of the high diffusion coefficient, high solubility, high mass transfer efficiency and effective heat transfer capacity of $scCO_2$, the synthesis of 5-aminosalicylic acid by the Kolbe-Schmidt reaction under supercritical conditions can be conducted in the homogeneous phase. In supercritical state, mass transfer occurs more rapidly and uniformly compared to traditional technology. Consequently, the reaction temperature is reduced and the reaction time is greatly shortened. Kolbe-Schmidt reaction can be carried out with high speed and short time at much lower temperature.

Because $scCO_2$ serves as both solvent and reactant in the reaction, no additional solvent needed and $scCO_2$ non-toxic and non-flammable, there are no problems with pollution and solvent recovery. Therefore, the process becomes much simpler than that used by conventional methods.

The optimal reaction parameters in synthesizing 5-aminosalicylic acid in $scCO_2$ are as follows: temperature of 140 °C, pressure of 9.0 MPa, reaction time of 2.5 h, stir speed of 300 rpm. The yield and purity of 5-aminosalicylic acid can reach as high as 90.5 and 96 % at these conditions, respectively.

Based on these results, synthesizing 5-aminosalicylic acid by the Kolbe-Schmidt reaction in $scCO_2$ is expected to considerably decrease the cost of 5-aminosalicylic acid production. The new technology is feasible and offers promising prospects for industrial production.

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