

# **ORIGINAL PAPER**

# An alternative synthetic process of p-acetaminobenzenesulfonyl chloride through combined chlorosulfonation by HClSO<sub>3</sub> and PCl<sub>5</sub>

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p-Aminobenzene sulfonamide (sulfanilamide, SN) is the simplest and most-used sulfonamide medicine. The key step of SN production via the commonly used chlorosulfonic acid routine is the synthesis of p-acetaminobenzenesulfonyl chloride (P-ASC). A large amount of HSO<sub>3</sub>Cl has to be used in the traditional process, which results in serious environmental problems. In this study, an alternative chlorosulfonic acid process to synthesize P-ASC was investigated by partially substituting HSO<sub>3</sub>Cl by PCl<sub>5</sub> as the chlorination agent. Compared with the traditional process, the molar ratio of HSO<sub>3</sub>Cl to acetanilide (the main raw material) can be decreased from 4.96 to 2.1 using CCl<sub>4</sub> as the diluent; also, addition of a small amount of NH<sub>4</sub>Cl was found to significantly increase the P-ASC yield. Operating conditions of the reaction were studied first by single-factor experiments and later by orthogonal experiments to obtain optimum operating conditions under which the P-ASC yield can reach as high as 86.3 %.

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**Keywords:** *p*-aminobenzene sulfone chloride, chlorosulfonation process, HSO<sub>3</sub>Cl, PCl<sub>5</sub>, *p*-aminobenzene sulfonamide

## Introduction

Sulfonamides are the second most-used antibacterial medicine just after antibiotics. They are stable, cheap and have a very broad antimicrobial spectrum (Fidock et al., 2004; Huang et al., 2001; Zhao et al., 2008). Among the sulfonamide medicines, *p*aminobenzene sulfonamide (sulfanilamide, SN) has the simplest molecular structure and the highest annual production. There are two main routines for the production of SN: chlorobenzene and chlorosulfonic acid (Martin et al., 1943; Martin & Hirt, 1947; Galat, 1944). In the chlorobenzene process (Gao et al., 2002), raw material, chlorobenzene, is first sulfonated and chlorinated to chlorobenzene sulfonyl chloride using liquid SO<sub>3</sub> as the sulfonation agent and liquid SOCl<sub>2</sub> as the chlorination agent, the intermediate is further ammoniated to give SN under high temperature and high pressure using Cu<sub>2</sub>O as the catalyst. This process has the advantage of generating a lower amount of waste acid. However, it requires severe operating conditions and the large amount of exhaust gas generated in the process is non-recyclable making its industrial application very limited. In the chlorosulfonic acid process (Gao et al., 2002; Meng, 1995; Zhang, 1991; Zeng, 1981; Fan et al., 2005), SN is prepared from acetanilide which is first sulfonated and chlorinated to pacetaminobenzenesulfonyl chloride (P-ASC) using an excess of chlorosulfonation acid as a combined chlorination and sulfonation agent. Afterwards, P-ASC is

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Fig. 1. Scheme of the experimental set-up. 1 – heater; 2 – four-neck flask; 3 – water/ice bath; 4 – feed inlet; 5 – thermometer; 6 – stirrer; 7 – condenser.

ammoniated and hydrolyzed to produce SN. Raw materials for this process are easy to obtain and the operating conditions are fairy mild, which is why it is the most used industrial process for SN production. However, during the production of P-ASC, an excess of HSO<sub>3</sub>Cl with the molar ratio of HSO<sub>3</sub>Cl to acetanilide as high as 5.0 has to be used in order to obtain the required product yield. After the reaction, the reaction mixture is treated with water which reacts with HSO<sub>3</sub>Cl to generate mixed H<sub>2</sub>SO<sub>4</sub>/HCl acidic solution and HCl gas. P-ASC is obtained as a crystal precipitate. In this process, HCl gas can be recovered by water-scrubbing producing pure HCl while the mixed acidic solution, after being filtered to obtain crude product, can only be sold as a low value byproduct since it contains a significant amount of impurities. Finally, the crude product is washed with water to obtain the final product, which generates a significant amount of waste acidic water resulting in serious environment problem (Li, 2002).

With the aim to decrease the amount of  $HSO_3Cl$ , an alternative chlorosulfonic acid process for the synthesis of P-ASC, in which  $PCl_5$  is used to partially replace  $HSO_3Cl$  as the chlorination agent, is proposed. A diluent,  $CCl_4$ , is introduced to reduce the viscosity of the reaction system, and a small amount of  $NH_4Cl$ is added into the chlorination process to increase the P-ASC yield. The results show that the alternative routine not only decreases the amount of  $HSO_3Cl$  but also significantly increases the product yield.

### Experimental

Acetanilide (Analytical Grade, AR) was purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China); PCl<sub>5</sub> (AR) was from Tingxin Chemical Reagent Co. Ltd. (Shanghai, China); CCl<sub>4</sub> (AR) from Chuandong Chemical Co. Ltd. (Chongqing, China);  $\mathrm{HSO}_3\mathrm{Cl}$  (Industrial Grade) from Changshou Chemical Co. Ltd. (Chongqing, China); and the standard P-ASC sample was obtained from Changshou Chemical Plant (> 99 %, Chongqing, China). All the reagents were used without further purification.

In a 250 mL four-neck flask (Fig. 1), 7.3 mL of  $HSO_3Cl$  were mixed with  $CCl_4$  at a volume ratio of  $HSO_3Cl: CCl_4 = 1: 3.4$  at room temperature. Then, 7.00 g of acetanilide were added in seven batches under stirring; the interval between each batch was 3 min during which the temperature was maintained at  $(15 \pm 2)$  °C by an ice bath. After the addition was completed, the system was stirred for another 10 min at  $(15 \pm 2)$  °C. Afterwards, the reaction system was heated up to  $60\,^{\circ}$ C to perform the sulfonation reaction. After 60 min, when the reaction was close to the end, 0.277 g of NH<sub>4</sub>Cl was added. Subsequently, 11.9 g PCl<sub>5</sub> were added into the system in three batches, the interval between each batch was 10 min. Then, the temperature was increased to  $72\,^{\circ}$ C at which the chlorination reaction proceeded for 3 h. After the synthesis reaction, most CCl<sub>4</sub> was removed under vacuum and ice water was added to remove POCl<sub>3</sub>, HSO<sub>3</sub>Cl, and PCl<sub>5</sub>, which also makes P-ASC crystalling out from the water  $((5 \pm 0.2)$  °C). The reaction mixture was then kept still for liquid-liquid separation of the remaining CCl<sub>4</sub> for recycling. The crude product, obtained by filtration, was washed several times using deionized water until the pH of the washing water was neutral (pH > 6), and dried in a vacuum oven for 3 h at  $50^{\circ}$ C to obtain the final product (10.4 g, white crystals). Purity of the P-ASC product was determined to be 98.2 % by the argentometric method whose basic principle is to measure the Cl<sup>-</sup> content in the product using standard AgNO<sub>3</sub> solutions (Kealey & Haines, 2002).

During the P-ASC synthesis, the dissolution of acetanilide in HSO<sub>3</sub>Cl is a strongly exothermic process



Fig. 2. Scheme of the sulfonation reaction.

while both the sulfonation and chlorination reactions are weakly exothermic. Since the whole process is accompanied by the generation of HCl gas, a water adsorption device was added to the experimental set to recover HCl gas from the system. Moreover, a  $H_2O$  flux condenser was used to recirculate the reactive solvent.

The melting point of P-ASC was measured by an XRC21 microscopic melting point apparatus (Sichuan University Scientific Instrument Co. Ltd., Chengdu, China). IR spectrum of P-ASC was recorded on a MAGMA–IR550 spectrometer (Nicolet Company, USA) using the KBr pressing pellet method.

The product solved in methanol was analyzed using an Agilent 1100 HPLC system (UK), equipped with a Diamonsil C18 (4.6 mm × 250 mm, 5 µm) column and a UV 254 detector. Operating conditions were: temperature 40 °C; injection volume of the sample 25 µL; flow phase methanol/water ( $\varphi_r = 60 : 40$ ); flow rate of the flow phase 1 mL min<sup>-1</sup>.

Finally, <sup>1</sup>H-NMR spectrum of the product dissolved in CDCl<sub>3</sub> was recorded on a Bruker AV500 NMR spectrometer (Switzerland) with  $Si(CH_3)_4$  as the internal reference.

#### **Results and discussion**

#### Reaction mechanism

Traditional chlorosulfonation process to synthesize P-ASC from acetanilide actually contains two sequential reactions (Li et al., 2007; Song, 1990; Kong et al., 1998): acetanilide (I) is sulfonated to pacetamidobenzene sulfonic acid (II) (Fig. 2) which is then chlorinated to P-ASC (III) (Fig. 3a). In the traditional process, HSO<sub>3</sub>Cl is both the sulfonation and the chlorination agents and it also serves as a diluent maintaining low viscosity of the reaction system.

Among the two reactions for P-ASC synthesis, sulfonation is fast and HSO<sub>3</sub>Cl has very high sulfonation efficiency, consequently, the conversion rate of the sulfonation reaction is close to 100 % (Meier & Tronich, 1992; Xin et al., 2006; Su & Yang, 2002; Su & Hao, 2005). On the other hand, the chlorination reaction is slow and the efficiency of HSO<sub>3</sub>Cl as the chlorination agent is low. Therefore, a new chlorination agent was employed in this study to partially substitute HSO<sub>3</sub>Cl



Fig. 3. Schemes of the chlorination reaction: using HSO<sub>3</sub>Cl (A) as the chlorination agent; using PCl<sub>5</sub> (B) as the chlorination agent.

as the chlorination agent with the aim to decrease the amount of HSO<sub>3</sub>Cl and to increase the chlorination efficiency. The comparison of several commonly used chlorination agents, e.g., SOCl<sub>2</sub> (Moore, 2003), SO<sub>2</sub>Cl<sub>2</sub> (Castaner et al., 1991), PCl<sub>3</sub>, trichloromethyl benzene, PCl<sub>5</sub>, resulted in the selection of PCl<sub>5</sub> due to its high chlorination efficiency and easy treatment of byproducts (Emerson & Ifalade, 2005). Reaction scheme with PCl<sub>5</sub> as the chlorination agent is presented in Fig. 3b, the byproducts being POCl<sub>3</sub> and HCl. As with HSO<sub>3</sub>Cl, excess POCl<sub>3</sub> can be removed by its reaction with water (Eqs. (1) and (2)), generated HCl gas as well as that from the chlorination reaction can be recovered by water scrubbing to produce hydrochloric acid.

$$HSO_3Cl + H_2O \Leftrightarrow H_2SO_4 + HCl \tag{1}$$

$$POCl_3 + 3H_2O \Leftrightarrow H_3PO_4 + 3HCl$$
 (2)

In the traditional chlorosulfonation process to synthesize P-ASC, HSO<sub>3</sub>Cl not only serves as the chlorination and sulfonation agent but also as the diluent maintaining low viscosity of the reaction system. Partial substitution of HSO<sub>3</sub>Cl by PCl<sub>5</sub> as the chlorination agent in the improved process decreases the amount of HSO<sub>3</sub>Cl, which leads to an increase of the reaction system's viscosity and pronounced decrease of the P-ASC yield. An alterative diluent has to be introduced to effectively reduce the viscosity of the reaction system. Owing to the extremely high activity of HSO<sub>3</sub>Cl and PCl<sub>5</sub>, the candidate diluent has to be very inert. In this work,  $CCl_4$  was used as the diluent, however, since  $CCl_4$  is to be banned worldwide in the near future due to its damage to the ozone layer, an environmentally friendly diluent is being actively searched for.

It has also been found experimentally that the addition of a small amount of  $NH_4Cl$  during the chlorination stage increases the product yield significantly. Although detailed mechanism of  $NH_4Cl$  reaction requires further investigation, it is believed that  $NH_4Cl$ acts as a phase transfer catalyst which can affect the distribution of reactants and products between the two phases ( $CCl_4$  phase and  $HSO_3Cl$  phase) due to



Fig. 4. IR spectra of the standard P-ASC sample (A) and the product (B).

the "salting-out" effect and the participation of chloride ions in the surface ion-pairing (Boekman et al., 1992).

## Product characterization

Melting point of the synthesized product was determined to be  $(141.3 \pm 1.2)$  °C, while its literature value is between 141 °C and 149 °C (Pence & Winter, 1939; Smiles & Stewart, 1925; Pouchert, 1970). Since the prepared product is not 100 % pure, the measured value is within a reasonable range confirming thus the prepared product to be P-ASC.

Fig. 4 compares the IR spectrum of the standard P-ASC sample (line A) with that of the prepared product (line B). It can be seen that the two spectra are almost identical, which further verifies the identification of the product as P-ASC of high purity. In the spectra, the characteristic peaks at 1371.1 cm<sup>-1</sup> and 1170.3 cm<sup>-1</sup> can be attributed to the symmetric stretching of O=S=O. The three intense peaks at 3307.3 cm<sup>-1</sup>, 3264.5 cm<sup>-1</sup>, and 1681.8 cm<sup>-1</sup> correspond to the amide group. The peaks at 3050.6 cm<sup>-1</sup>, 1495.0 cm<sup>-1</sup>, 1558.1 cm<sup>-1</sup>, 1584.7 cm<sup>-1</sup>, and 1605.7 cm<sup>-1</sup> correspond to the benzene ring, while the peak at 839.0 cm<sup>-1</sup> proves that the benzene ring was parasubstituted (Pouchert, 1970; Lin et al., 2009).

HPLC chromatogram (Fig. 5) of the product shows three peaks: the first one at t = 0.977 min was attributed to the flow phase (void volume); the second at t = 2.289 min corresponds to the impurities; while the last one at t = 3.115 min belongs to P-ASC. Quantitative analysis via the peak area normalization method indicated that the product purity is 98.7 %, which confirmed the result of the argentometric method (98.2 %).

Fig. 6 shows the <sup>1</sup>H-NMR spectrum of the product, which exhibits three major peaks except three baseline peaks corresponding to the impurities. The



Fig. 5. HPLC chromatogram: void volume (t = 0.977 min), impurities (t = 2.289 min), and P-ASC (t = 3.115 min). Product purity determined using the area normalization method is 98.7 %.



Fig. 6. <sup>1</sup>H-NMR spectrum of the product dissolved in  $CDCl_3$  with  $Si(CH_3)_4$  as the internal reference. The spectrum exhibits three major peaks corresponding to the four types of hydrogen atoms in P-ASC while the three base-line peaks are attributed to impurities.

peak at  $\delta = 2.189$  was attributed to methyl hydrogen atoms. The two double-peaks at  $\delta = 7.7$  and  $\delta = 7.9$ correspond to the four hydrogen atoms in the benzene ring; peaks at  $\delta = 7.7$  contain an overlapping peak corresponding to the hydrogen atom in —NH—. The <sup>1</sup>H-NMR spectra show that two types of hydrogen atoms exist in the benzene ring of the products, which further confirms that the benzene ring is parasubstituted. If the benzene ring was ortho-substituted, four different types of hydrogen atoms would exit in the benzene ring.

### Affecting factors of synthesis reaction

The aim of the improved process is to decrease the consumption of  $HSO_3Cl$  by using  $PCl_5$  to partially replace  $HSO_3Cl$  as the chlorination agent; however, it has been found that the dose of  $HSO_3Cl$  cannot be less than a critical range, where the molar ratio of  $HSO_3Cl$  and acetanilide is around 2.0; otherwise, the P-ACS yield decreases remarkably (Fig. 7) even at a very high dose of  $PCl_5$ . Accordingly, the molar ratio of



Fig. 7. P-ASC yield at different amounts of HSO<sub>3</sub>Cl. Other operating conditions are: molar ratio of PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 1.40, 0.1, and 4.0, respectively; sulfonation time – 1 h; chlorination time – 3 h; sulfonation temperature – 54 °C; chlorination temperature – 66 °C; stirring intensity – medium.



Fig. 8. P-ASC yield at different amounts of PCl<sub>5</sub>. Other operating conditions are: molar ratio of HSO<sub>3</sub>Cl, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 2.0, 0.1, and 4.0, respectively; sulfonation time – 1 h; chlorination time – 3 h; sulfonation temperature – 54 °C; chlorination temperature – 66 °C; stirring intensity – medium.

 $HSO_3Cl$  and acetanilide was set to 2.0 and the effect of  $PCl_5$  and  $CCl_4$  dosage, reaction time and temperature on the product yield was investigated. Fig. 8 displays the P-ASC yield versus the molar ratio of  $PCl_5$ to acetanilide, the results show that the P-ASC yield increases with an increase in the  $PCl_5$  amount until a plateau, when the molar ratio of  $PCl_5$  to acetanilide is higher than 1.4, was reached.

The effect of the sulfonation and chlorination temperatures on the product yield is shown in Figs. 9 and 10, respectively. Both results show that the P-ASC yield first increases with an increase of the reaction temperature until a maximum is reached, and then decreases with a further increase of the reaction temperature. Optimum sulfonation temperature is around 58 °C and the decrease of the product yield at higher temperatures is believed to be due to the enhancement of side reactions. Optimum chlorination temperature



Fig. 9. P-ASC yield at different sulfonation temperatures (T<sub>s</sub>). Other operating conditions are: molar ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 2.0, 1.4, 0.1, and 4.0, respectively; sulfonation time – 1 h; chlorination time – 3 h; chlorination temperature – 66 °C; stirring intensity – medium.



Fig. 10. Effect of chlorination temperature (T<sub>c</sub>). Other operating conditions are: molar ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 2.0, 1.4, 0.1, and 4.0, respectively; sulfonation time – 1 h; chlorination time – 3 h; sulfonation temperature – 54 °C; stirring intensity – medium.

is around 70  $^{\circ}$ C, the decrease of the product yield at higher temperatures is caused by the enhancement of side reactions, decomposition of HSO<sub>3</sub>Cl and the evaporation of the solvent.

The chlorosulfonation reaction takes about 4.5 h to be completed in the traditional process, and it was also reported that the chlorination process is slower and requires longer time (Galat, 1944; Li et al., 2007; Song, 1990; Kong et al., 1998; Meier & Tronich, 1992). Figs. 11 and 12 show the effect of the sulfonation and chlorination time on the P-ASC yield. The results indicate that the product yield first increases with an increase of both sulfonation and chlorination time and decreases with a further increase in the reaction time after reaching a maximum value. Optimum sulfonation and chlorination times are around 1.0 h and 3.0 h, respectively; longer reaction time leads to a decrease of the P-ASC yield,



Fig. 11. P-ASC yield at different sulfonation times (t<sub>s</sub>). Other operating conditions are: molar ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 2.0, 1.4, 0.1, and 4.0, respectively; chlorination time – 3 h; sulfonation temperature – 54 °C; chlorination temperature – 66 °C; stirring intensity – medium.

which is also due to the enhancement of the side reactions.

## Orthogonal experiments

Based on the single-factor experiments, a group of orthogonal experiments was employed to study the importance of the affecting factors and to obtain the optimum operating conditions. Since there are nine essential affecting factors including the material ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, CCl<sub>4</sub>, and NH<sub>4</sub>Cl, the time and temperature of both sulfonation and chlorination reaction, and the stirring intensity (Li, 2005; Montgomery, 2004); and also the interactive effect of sulfonation temperature and time, chlorination temperature and time, material ratio of HSO<sub>3</sub>Cl to PCl<sub>5</sub>, material ratio of CCl<sub>4</sub> to NH<sub>4</sub>Cl are interesting, the  $L_{27}(3^{13})$  design was selected. Affecting factors and their values in the orthogonal experiments are listed in Table 1, where columns numbers 4, 8, 9, and 11 studies the interactive effects of factors 1 and 2, factors 10 and 12, factors 6 and 12, and factors 3 and 5, respectively. Experimental design and results are shown in Tables 2 and 3, where the range value (R) indicates the affecting degree of each affecting factor. The larger the



Fig. 12. P-ASC yield at different chlorination times (t<sub>c</sub>). Other operating conditions are: molar ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub> to acetanilide – 2.0, 1.4, 0.1, and 4.0, respectively; sulfonation time – 1 h; sulfonation temperature – 54 °C; chlorination temperature – 66 °C; stirring intensity – medium.

range value, the more important the corresponding factor. K is the average product yield corresponding to each level of every affecting factor. From the K values, optimum operating conditions can be determined by choosing the level of each factor corresponding to the largest K value (Table 2). Afterwards, verification experiments were done at the optimum operating conditions to confirm the results of orthogonal experiments and to obtain the highest product yield.

The range analysis in Table 2 demonstrates that the HSO<sub>3</sub>Cl amount (R = 11.9), sulfonation temperature (R = 8.26) and the chlorination time (R = 6.90)are the major affecting factors while the sulfonation time, amount of CCl<sub>4</sub>, PCl<sub>5</sub>, and NH<sub>4</sub>Cl or the stirring intensity have minor effect on the product yield. The study on the effect of several factors (Table 3) shows that the interaction between the amount of NH<sub>4</sub>Cl and  $CCl_4$  has the most significant effect on the product yield (R = 7.10). The addition of NH<sub>4</sub>Cl increases the P-ASC yield; however, it also increases the viscosity of the reaction system, which is unfavorable to the chlorination reaction. Since an increase in the CCl<sub>4</sub> amount can reduce the viscosity of the reaction system, the addition of a suitable amount of  $CCl_4$  can increase the effect of  $NH_4Cl$ . Table 4 (obtained from Table 2)

Table 1. Factors and levers of the  $L_{27}(3^{13})$  orthogonal experiments: sulfonation temperature  $(T_s)$ , sulfonation time  $(t_s)$ , chlorination time  $(t_c)$ , molar ratio of compound to acetanilide

Factor number	1	2	3	4	5	6	7	8	9	10	11	12	13
Level	$\frac{T_{\rm s}}{^{\circ}{\rm C}}$	$\frac{t_{\rm s}}{\rm h}$	$\frac{T_{\rm c}}{^{\circ}{\rm C}}$	$1 \times 2$	t <sub>c</sub> h	HSO <sub>3</sub> Cl	$\mathrm{CCl}_4$	$7 \times 12$	$3 \times 5$	$PCl_5$	$6 \times 10$	NH <sub>4</sub> Cl	Stiring intensity
$\begin{array}{c}1\\2\\3\end{array}$	50 55 60	$0.5 \\ 1.0 \\ 1.5$	62 67 72		$2.5 \\ 3.0 \\ 3.5$	1.9 2.0 2.1	$3.0 \\ 4.0 \\ 5.0$			$1.10 \\ 1.25 \\ 1.40$		0 0.1 0.2	High Medium Low

**Table 2.** Design and results of the  $L_{27}(3^{13})$  orthogonal experiment: sulfonation temperature ( $T_s$ ), sulfonation time ( $t_s$ ), chlorinationtemperature ( $T_c$ ), chlorination time ( $t_c$ ), molar ratio of compound to acetanilide, stirring intensity: 1 - low, 2 - medium,3 - high

Factor number	1	2	3	5	6	7	10	12	13	
Experiment	$T_{\rm s}$	$t_{\rm s}$	$T_{\rm c}$	$t_{ m c}$	HSO <sub>3</sub> Cl C	CCL	$PCl_5$	NH <sub>4</sub> Cl	Stiring intensity	Yield
	$^{\circ}\mathrm{C}$	h	$^{\circ}\mathrm{C}$	h		0014				%
1	1	1	1	1	1	1	1	1	1	61.90
2	1	1	1	2	$^{2}$	2	2	$^{2}$	2	62.08
3	1	1	1	3	3	3	3	3	3	71.74
4	1	2	2	1	1	1	2	3	3	53.64
5	1	2	2	2	2	2	3	1	1	73.10
6	1	2	2	3	3	3	1	2	2	72.90
7	1	3	3	1	1	1	3	2	2	68.04
8	1	3	3	2	$^{2}$	2	1	3	3	74.80
9	1	3	3	3	3	3	2	1	1	64.72
10	2	1	2	1	2	3	3	2	3	70.18
11	2	1	2	2	3	1	1	3	1	74.64
12	2	1	2	3	1	2	2	1	2	51.50
13	2	2	3	1	$^{2}$	3	1	1	2	70.01
14	2	2	3	2	3	1	2	2	3	78.44
15	2	2	3	3	1	2	3	3	1	70.59
16	2	3	1	1	$^{2}$	3	2	3	1	79.43
17	2	3	1	2	3	1	3	1	2	76.04
18	2	3	1	3	1	2	1	$^{2}$	3	48.85
19	3	1	3	1	3	2	1	3	2	81.09
20	3	1	3	2	1	3	2	1	3	69.27
21	3	1	3	3	$^{2}$	1	3	$^{2}$	1	74.14
22	3	2	1	1	3	2	3	$^{2}$	1	78.28
23	3	2	1	$^{2}$	1	3	1	3	2	77.12
24	3	2	1	3	$^{2}$	1	2	1	3	70.42
25	3	3	2	1	3	2	2	1	3	83.07
26	3	3	$^{2}$	$^{2}$	1	3	3	2	1	72.66
27	3	3	$^{2}$	3	2	1	1	3	2	71.17
$K_1$	66.99	68.50	69.54	71.74	63.73	69.83	70.83	68.89	72.16	—
$K_2$	68.85	71.61	69.20	73.12	71.70	69.26	68.22	69.51	69.99	—
$K_3$	75.25	71.0	72.34	66.23	75.66	72.00	72.04	72.69	68.93	—
R	8.26	3.10	3.14	6.90	11.9	2.74	3.82	3.80	3.23	—

shows that the combination of the molar ratio of  $CCl_4$  to acetanilide of 5.0 and the molar ratio of  $NH_4Cl$  to acetanilide of 0.2 results in the highest product yield; verification experiments also showed that the product yield does not increase when the amounts of  $CCl_4$  and  $NH_4Cl$  are further increased.

Optimum operating conditions of the P-ASC synthesis were determined from Table 2 as: sulfonation temperature of 60 °C; sulfonation time of 1.0 h; chlorination temperature of  $72^{\circ}$ C; chlorination time of 3 h; molar ratio of  $HSO_3Cl$  to acetanilide of 2.1; molar ratio of  $CCl_4$  to acetanilide of 5.0; molar ratio of PCl<sub>5</sub> to acetanilide of 1.4; molar ratio of NH<sub>4</sub>Cl to acetanilide of 0.2; stirring intensity high. The verification experiments demonstrated that the P-ASC yield can reach 86.3 % under optimum operating conditions, the yield being significantly higher than that of the traditional process, (82.4%) for lab-scale and 77\% for the industrial process) with the molar ratio of HSO<sub>3</sub>Cl to acetanilide as high as 4.96 (Li et al., 2007). Since the orthogonal experiments showed that the molar ratio of  $PCl_5$  to acetanilide has a minor effect on the

product yield, the P-ASC yield at the molar ratio of  $PCl_5$  to acetanilide of 1.10 (Level 1) and 1.25 (Level 3) was also studied when other conditions were fixed, and the P-ASC yield reached 84.3 % and 85.4 %, respectively. Therefore, in the scale production of P-ASC using the alternative process, the molar ratio of  $PCl_5$  to acetanilide can be adjusted according to the cost evaluation with little sacrifice of the product yield.

When the molar ratio of  $PCl_5$  to acetanilide was 1.1, the alternative process generated 6.6 mol of HCl, 1.1 mol of  $H_3PO_4$ , and 1.1 mol of  $H_2SO_4$  for producing a mol of P-ASC. Total amount of  $H^+$  was 12.1 mol, by 0.22 mol more than that generated using the traditional process (3.96 mol of HCl and 3.96 mol of  $H_2SO_4$ ). However, since most HCl gas can be recovered to hydrochloric acid, the amount of aqueous acid was significantly decreased in the alternative process, which reduces the amount of the low value byproduct of mixed acid and the waste acidic water generated during the washing of crude product.

The experiments show that  $CHCl_3$  is also a suitable solvent; the yield of P-ASC can reach as high as

Factor number	4	9	8	11
Experiment	$1 \times 2$	$3 \times 5$	$7 \times 12$	$6 \times 10$
1	1	1	1	1
2	1	2	2	2
3	1	3	3	3
4	$^{2}$	2	$^{2}$	3
5	$^{2}$	3	3	1
6	$^{2}$	1	1	$^{2}$
7	3	3	3	$^{2}$
8	3	1	1	3
9	3	2	$^{2}$	1
10	3	$^{2}$	1	1
11	3	3	$^{2}$	$^{2}$
12	3	1	3	3
13	1	3	2	3
14	1	1	3	1
15	1	$^{2}$	1	2
16	2	1	3	2
17	2	$^{2}$	1	3
18	2	3	2	1
19	2	3	1	1
20	2	1	2	2
21	2	$^{2}$	3	3
22	3	1	2	3
23	3	$^{2}$	3	1
24	3	3	1	2
25	1	$^{2}$	3	2
26	1	3	1	3
27	1	1	2	1
$K_1$	71.30	70.86	72.29	69.62
$K_2$	69.826	70.20	65.85	72.27
$K_3$	69.97	70.10	72.95	69.20
R	1.47	0.798	7.10	3.07

**Table 3.** Design and results of the  $L_{27}(3^{13})$  orthogonal experiment: interactive effect

**Table 4.** Product yield under different  $CCl_4$  : acetanilide and<br/> $NH_4Cl$  : acetanilide mole ratios

$\begin{array}{c} \mathrm{CCl}_4 \\ \mathrm{NH}_4 \mathrm{Cl} \end{array}$	3.0	4.0 Yield/%	5.0	
0	68.39	72.55	75.55	
0.1	76.68	67.75	65.55	
0.2	71.8	57.3	77.8	

86.5 % with an identical synthesis procedure. However, since the boiling point of  $CHCl_3$  is only  $61.15 \,^{\circ}C$ , the sulfonation and chlorination temperatures have to be decreased and the reaction time has to be prolonged.

### Conclusions

An alternative chlorosulfonic acid process to synthesize P-ASC was investigated by partially substituting  $HSO_3Cl$  with  $PCl_5$  as the chlorination agent. Compared with the traditional process, the alternative process uses lower amount of  $HSO_3Cl$ , which can alleviate the limitations of the traditional process in generating a large amount of mixed acid byproduct and waste acidic water. In the alternative process, the decrease of the HSO<sub>3</sub>Cl amount leads to an increase of the reaction system's viscosity, which can be solved by introducing  $CCl_4$  as a diluent. Moreover, the addition of a small amount of NH<sub>4</sub>Cl was found to increase the P-ASC yield significantly. The factors affecting the synthesis reaction include the material ratio of HSO<sub>3</sub>Cl, PCl<sub>5</sub>, NH<sub>4</sub>Cl, and CCl<sub>4</sub>, sulfonation temperature and time, and the chlorination temperature and time. These were investigated first by single-factor experiments and later by orthogonal experiments to determine the optimum operating conditions under which the P-ASC yield can reach up to 86.3 %.

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