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Research Article

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Novel synthesis of 8-mercaptomethone via pulegon and disodium tetrasulphide ignited by Dowex® 50WX4

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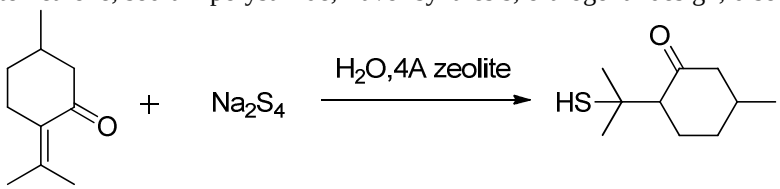
ABSTRACT

An improved synthesis of 8-mercaptomethone by utilizing sodium polysulfide instead of the H_2S was developed. An L^9 orthogonal array of the Taguchi method was implemented to investigate the effects of experimental conditions to prepare 8-mercaptomethone according to yields. The optimal conditions were determined by using Na_2S_4, H_2O to react with pulegone accelerated by adding the Dowex® 50WX4 under conventional heating for 12h. In comparison with conventional methods, the prominent features of this procedure are experimental simplicity, without toxic H_2S and the use of water as a green solvent.

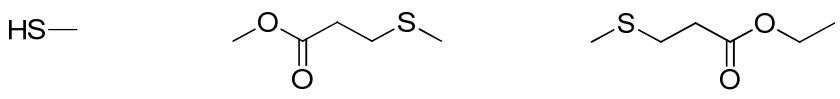
Keywords: 8-mercaptomethone; sodium polysulfide; flavor synthesis; orthogonal design; disodium tetrasulphide



1 **2** **3**

INTRODUCTION

flavor[1-3], a special high concentration of additives which can affect the taste of the food, has been widely applied to various areas of food production. It can give the vivid original taste of some food, enhance the food flavor and cover up some bad tastes. All these advantages make the flavor becoming a research focus of food science and synthetic chemistry[4]. Sulfur flavors play an important role in existing food spices[5-6]. Among them, thiols fragrance compounds are a major kind of sulfur-containing spices and an significant intermediate to synthesis other sulfur spices. With the development of analytical techniques, more and more sulfur compounds were detected in food. In sulfur spices, methyl mercaptan **4**[7], methyl 3-methylthiopropionate acid methyl ester **5** [8]and ethyl 3-methylthiopropionate **6** [9]was found in pineapple and other food substance.



4 **5** **6**

Several well-established synthetic methods for the formation of the mercaptan, commonly used alkyl halide to react with thiourea, getting the product and reacted with base[10-11]. The synthetic methods of 8-mercaptomethone **3**, literature reported that using Lewis acids as catalyst, such as Al_2O_3. The yields of 8-mercaptomethone was only 9%, among the products, the trans isomer was 43%, the cis isomer was 7% and another 39% of raw materials

unconverted[12]. Good conversions to prepare 8-mercaptomethone were reported for the reactions of pulegone with liquid H_2S. The pulegone was placed into the autoclave, then cooled to -75℃ as well as adding the liquid H_2S, increased the volume, and then closed the autoclave to react 16 hours. The yields can reach to 73% , but this process is quite difficult in the industrial production[13].

The prevalence of sulfur flavors compounds has resulted in a continuous demand for the development of flexible and greener synthetic methods for this structural moiety. Sodium polysulfide containing two or more atoms of sulfur in the molecule was used chiefly in the manufacture of sulfur dyes , insecticides , batteries , and synthetic vulcanized rubber. Moreover, this water-soluble granular powder is widely used as ligands in coordination chemistry. To the best of our knowledge, there is no literature precedent for the synthesis of 8-mercaptomethone utilizing sodium polysulfide instead of the liquid H_2S. We herein report a new methodology that involves an environmentally friendly process that avoids H_2S.

In this work, an L^9 orthogonal Taguchi design was applied in order to investigate the change of synthesis conditions including the number of sulfur in sodium polysulfide(Na_2S_X), solvent, catalyst and synthesis time concentration on 8-mercaptomethone to gain a better understanding about the effect of mentioned parameters in 8-mercaptomethone synthesis process.

The objectives of this work are: (1) to suggest a method for the synthesis of 8-mercaptomethone by using an environmentally friendly process, (2) to apply the Taguchi robust design method on the optimization of properties and to obtain the optimal synthesis conditions of 8-mercaptomethone .

EXPERIMENTAL SECTION

2.1. Synthesis of 8-mercaptomethone

A 200ml round-bottomed flask was charged with pulegone **1**, sodium polysulfide and solvent, which were stirred at 70℃under conventional heating. The mixture was diluted with water, acidified with hydrochloric acid to neutral and cooled to room temperature. The crude product was isolated by filtration and the filter cake was washed by warm water with a temperature of 35℃-40℃. All the products were isolated, and their isolated yields are given in Table 2. Identities of the products were established by comparison of their physical and spectral data with those of reported compounds.

2.2. Characterization

All the substrates and solvents were commercially available and purified before use. ^1H and ^{13}C NMR spectra were recorded on a BRUKER AV-300 spectrometer at 300.13 and 75.47 MHz, respectively. The mass spectrometric analyses (HRMS) were performed using a JMS-700 MStation High Resolution JEOL Mass Spectrometer with a source temperature of 230◦C, an ionization energy of 70 eV, and an ionization trap current of 300A. Melting points were measured with a differential scanning calorimeter (Shimadzu DSC-50) and were uncorrected. The standard heating rate for all compounds was 10℃/ min.

2.3. Orthogonal array and experimental parameters

Orthogonal design is one of the most time-saving and effective methods for the studies involving multiple variables in order to find out which factors (or variables) influence to the most extent properties of the target product. In this study, orthogonal design was adopted.

The L^9 orthogonal array of the Taguchi method was chosen in our studies. The factors (variables) and levels for L^9 orthogonal array design are listed in Table 1. Four factors were considered: Na_2S_X and solvent, catalyst and synthesis time. For each factor, three levels were selected in order to eliminate the influence and validate the results. Nine experimental runs derived from the L^9 orthogonal array design are shown in Table 2. The yields of 8-mercaptomethone was taken as measured responses. Applying the simple factorial design for study of the assigned three levels of each parameter, the numbers of permutations would be 81. However, the fractional factorial design reduced the number of experiments to 9[14-15].

Table 1 Factors and levels for L^9 orthogonal array

Levels	Factors			
	A	**B**	**C**	**D**
	Na_2S_X	Solvent	Catalyst	Time(h)
K_1	1	Methanol	ZnCl	8
K_2	2	H_2O	--	10
K_3	4	THF	Dowex® 50WX4	12

RESULTS AND DISCUSSION

3.1. Effects of experimental conditions on the final products crystallinity

The optimization of 8-mercaptomethone parameters was investigated with an orthogonal design L_9 (3^4). The factors were the Na_2S_X (A),solvent (B), catalyst (C) and synthesis time (D). The factors and the corresponding levels used in the orthogonal design are shown in Table 1. Nine experimental trials were performed according to the orthogonal design and the results are also shown in Table 2. The K and R values were calculated and listed in Table 2.

Table 2 Design matrix based on L^9 orthogonal array

Formula No.	A Na_2S_X	B Solvent	C Catalyst	D Time(h)	Response	Yields(%)
1	1	Methanol	ZnCl	8	K_1	48.2%
2	1	H_2O	--	10	K_2	39.6%
3	1	THF	Dowex® 50WX4	12	K_3	47.3%
4	2	Methanol	--	12	K_4	43.4%
5	2	H_2O	Dowex® 50WX4	8	K_5	54.6%
6	2	THF	ZnCl	10	K_6	49.2%
7	4	Methanol	Dowex® 50WX4	10	K_7	59.3%
8	4	H_2O	ZnCl	12	K_8	62.5%
9	4	THF	--	8	K_9	39.2%
K_{i1}	45.0	50.3	53.3	47.3		
K_{i2}	53.6	52.2	40.7	49.4		
K_{i3}	53.7	45.2	53.7	51.1		
$R(K_{max}-K_{min})$	8.7	7	13	3.8		

The responses from each experiment is denoted as K_1, K_2,…, K_9 for phase yields. The average response for each factor was computed at each level, and labeled as Kij, where i represent a factor and j a level. For example, for the factor of catalyst at level of ZnCl, the average response was calculated as $(K_1+K_6+K_8)/3$; for the factor of time at level of 8 h, the average response was calculated as $(K_1+K_5+K_9)/3$. The results are summarized in Table 2. From the average responses, the $K_{max}–K_{min}$ was calculated, where K_{max} and K_{min} were the largest and smallest values among the K_{ij} respectively. According to the largest donating rule, the largest $K_{max}–K_{min}$ value indicates the most significant influence to the yields of 8-mercaptomethone.

Based on the mentioned details and the results given in Table 2, the following conclusions can be made.

Catalyst, as it was expected, was the most significant factor that influenced the yields of 8-mercaptomethone. According to K_{cj}, it was difficult for sodium polysulfide to release H_2S without catalyst, ZnCl and Dowex® 50WX4 are acidic catalyst, which suggests that sodium polysulfide could slow release H_2S under acidic or potentially acidic conditions.

The number of sulfur in sodium polysulfide was the second important factor affected the yields of 8-mercaptomethone. According to K_{Aj} values, the number of sulfur in sodium polysulfide means the alkaline of sodium polysulfide, H_2S was easier to release in acidic conditions

The effect of solvent was close to the effect of sodium polysulfide. Based on K_{Bj} values, protic solvent, such as H_2O and Methanol can easier to combine with sulfur anion than aprotic solvent and release H_2S.

Reaction time, in the selected range from 8 to 12 hours, based on K_{Dj} values, in which changes of synthesis time did not affect the the yields of 8-mercaptomethone so much. But the yields of 8-mercaptomethone increased with increasing time means the reaction become more completely along with the time.

3.2. Confirmation of orthogonal design results

In Table 2, all of four factors had an influence on the yields of the 8-mercaptomethone, the influence of factors on the mean yields of 8-mercaptomethone decreased in the order: catalyst, Na_2S_X, solvent and time (C>A>B>D). The analysis of variance of the yields also indicated that the catalyst, the Na_2S_X and the solvent had obvious influence on yields of the target compounds, while time had no significant impact. According to Table 2, the average yields under every level can be concluded as, $A_3>A_2>A_1$,$B_2>B_1>B_3$,$C_3>C_1>C_2$,$D_3>D_2>D_1$, respectively. Therefore, the optimum condition of synthesizing 8-mercaptomethone was $A_3B_2C_3D_3$ as follows: the Na_2S_X was Na_2S_4, the solvent was H_2O, the catalyst was Dowex® 50WX4, and the time was 12 hours. This indicated that the yields could be enhanced using a combination of those factors at different levels in the preparation process

Under the optimized conditions, Pulegone, Na_2S_4 and H_2O, which were stirred at 70◦C under conventional heating for 12 h. Besieds, adding the Dowex® 50WX4 into the raection. The yields of 8-mercaptomethone was 67.3%.

CONCLUSION

In summary, we described a facile and practical method toward the synthesis of 8-mercaptomethone in good yields using sodium polysulfide as the substitute for H_2S. Apply the Taguchi robust design method on the optimization of properties and to obtain the optimal synthesis conditions of 8-mercaptomethone. The present work could find diverse applications in view of the power of the synthesis methods as a valid and green alternative. Further studies to develop new clean methodology toward the synthesis of biologically active sulfur compounds are in progress.

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