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Synthesis of Flavor 3-Methylthiopropionaldehyde Diethyl Acetal

Guan Wei[a], Liu Yuping[b*], Miao Zhiwei[c], Shen Deli[d], Cao YU[e]

School of Food and Chemical Engineering, Beijing technology and business University, Beijing 100048, China

[a]weiwei-nunu@hotmail.com, [b]liuyp@th.btbu.edu.cn, [c]mzwtyytc@163.com, [d]henryshen@126.com, [e]bjgsdxcaoyu@126.com

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Abstract. 3-Methylthiopropionaldehyde diethyl acetal was synthesized from the reaction of 3-methylthiopropional with ethanol and triethyl orthoformate. The effecting factors including the kinds of catalyst, the mole ratio of raw materials, the amount of catalyst and the reaction time were optimized. The structure of product was characterized by gas chromatography, infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance. Additionally, the mechanism of the reaction was speculated; the odor characteristics were evaluated.

Introduction

3-Methylthiopropionaldehyde diethyl acetal (**I**), also known as 1,2-diethoxy-3-methylthio propane, is a colorless liquid with the fruit odor [1] and meat odor [2], It can be widely used in compounding food flavorings [3]. Additionally, it can be also used as intermediate for preparing plant growth regulator [1].

It is a FEMA-GRAS approved flavoring agent, which is listed in Generally Recognized as Safe 24 (FEMA GRAS 24) by the expert panel of the U.S. Flavor and Extract Manufacturer's Association (FEMA). Its FEMA No. is 4590, and it is suggested that its using amount in food is ranged from 0.02 to 0.1ppm [3]. Though some synthetic routes have been reported to the public, materials used in some synthetic routes were either expensive or unavailable. And in other routes, water generated in the processes was not easily carried out by conventional water carrier. For instances, one method is that of Carl's using 3-methylthio propionitrile and ethanol, under acidic condition to obtain the original ester, which was deoxygenized to give the target product by Lithium aluminium hydride, the yield was 73% [4-6]. A second method is that of Masaaki's preparing it by using diphenylphosphinodithioate ester and methyllithium at -40°C in THF, the yield was 97%[7]. A third method is T. Yamanishi's treating 3-chloropropylaldehyde diethyl acetal with sodium salt of methanethiol, the yield was 53% [8]. Raw materials (3-methylthiopropionitrile, biphenyl phosphinodithioate ester, 3-chloropropyl aldehyde diethyl acetal) used in the three methods above are unavailable in the market. The fourth mothod is Claude Clapot's[1] and K. S. Boustany's[9] making 3-methylthiopropional (**II**) react with ethanol, the yield was 66%, but in this method, water generated in the reaction was difficult to be carried out by conventional water carrier. Some literatures reported that acetals can be obtained in good yield by the reactions of aldehydes with triethyl orthoformate(**III**) [10-11].

In this paper, **I** was synthesized by the reaction of Ⅱ with ethanol and **III**. The aims of the work were to study the effect of different catalysts on the yield and to optimize the reaction conditions including the mole ratio of materials, the reaction time and the amount of the catalyst. The yield of **I** was 92%. Necessary works were done to make the role of **III** clear and to speculate the mechanism of the reaction.

Results and discussion

Investigation of different catalysts. In order to find a suitable catalyst, raw materials molar ratio of 3-methylthiopropional (**II**) to ethanol to triethyl orthoformate (**III**) to catalyst is chosen as 0.1mol: 0.3mol: 0.09mol: 0.002mol. Four kinds of catalysts were investigated, respectively. The experimental results are shown in Table 1.

Table1. Effect of different catalysts on the yield of **I**

Catalyst	$NaHSO_4 \cdot H_2O$	Citric Acid	p-Toluenesulfonic Acid	Ammonium Chloride
yield/%	84.6	56.8	81.78	85.5

From the point of yield, ammonium chloride and sodium sulfate monohydrate were better than the other catalysts. Due to the sodium sulfate monohydrate brought in a certain amount of chemical combined water to the reaction system, it may contribute to a lower yield. While ammonium chloride is slightly soluble in the reaction system, it was recycled easily for re-use, therefore, ammonium chloride is more suitable as the catalyst in this experiment.

Effect of the amount of triethyl orthoformate(III) on the yield. Experiments were performed with 0.1mol 3-methylthiopropional, 0.003mol ammonium chloride, 0.3mol ethanol, and the mole of **III** was 0mol, 0.2mol, 0.4mol, 0.06mol, 0.08mol, 0.1mol, 0.12mol, respectively. The results are shown in Fig. 1.

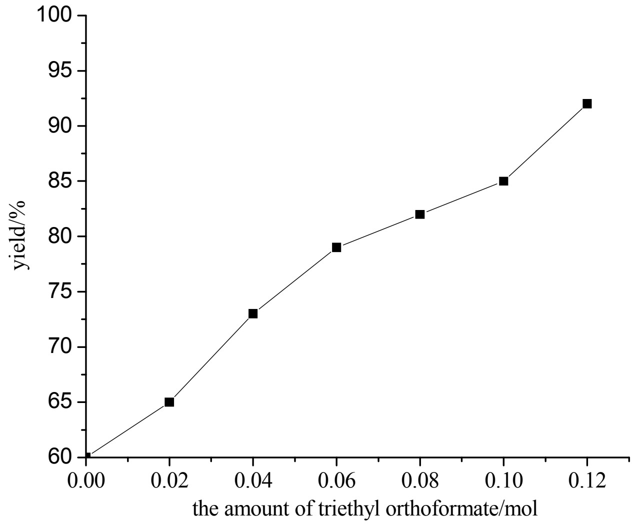

Fig. 1 Effect of the amount of triethyl orthoformate on yield

When there was no **III** in the reaction system, the yield was only 60%. From the Fig. 1, we can know that the amount of **III** had significant effect on the yield. When the amount of **III** reached to 0.12mol, the yield was 92%. Here **III** might play two roles. One was that it might react with water, which is formed in the reaction, to make the reaction go to completion; the other was that it might react with 3-methylthiopropional to give the product.

Effect of the amount of ethanol on the yield. To investigate the influence of the amount of ethanol, two groups of experiments were carried out. One group of experiments were performed on the mole ratio of 3-methylthiopropional to ammonium chloride to **III** was 0.1mol:0.003mol:0.06mol and the amount of ethanol in each reaction was 0.1mol, 0.14mol, 0.22mol, 0.26mol, 0.30mol, 0.34mol, respectively; the other group of experiments was performed on the mole ratio of 3-methylthiopropional to ammonium chloride to **III** was 0.1mol:0.003mol:0.12mol and the amount of ethanol in each reaction was 0.14mol, 0.22mol, 0.26mol, 0.30mol, respectively. The results are shown in Fig. 2.

As the amount of ethanol increased, the yield of I increased slightly under the same amount of **III**. Probably, the effect of the amount of ethanol was not so significantly as the **III**'s effect in the reaction. And the phenomenon was that the broken line of the 0.12mol **III** was above the broken line of the 0.6mol **III**. It also showed that the more orthoformate added, the less water existed and the higher yield reached.

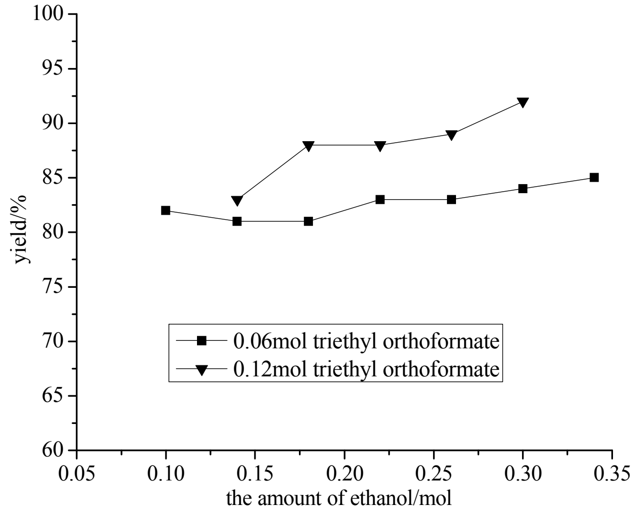

Fig. 2 Effect of the amount of ethanol on yield

Effect of different reaction time on the yield. To find a suitable reaction time, the raw materials molar ratio of 3-methylthiopropional to ethanol to triethyl orthoformate to ammonium chloride was chosen as 0.1mol: 0.3mol: 0.12mol: 0.003mol. The results are shown in Fig. 3.

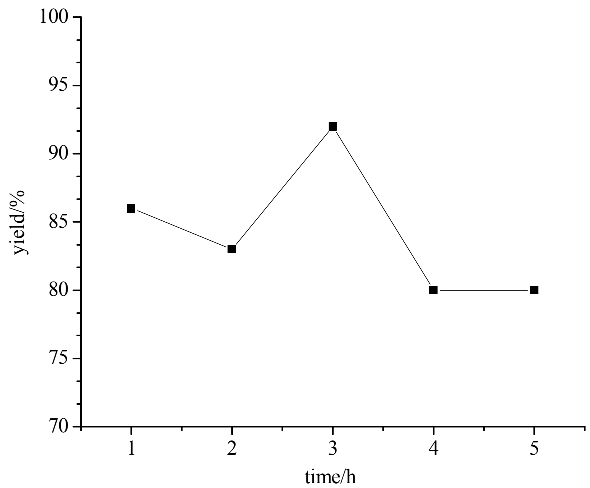

Fig. 3 Effect of reaction time on yield

The results of experiments showed that 3 hour is more suitable for the reaction. A longer reaction time will lead to more side-products, which mainly contain 3-ethyloxypropionaldeheyde diethyl acetal (detected by GC-MS), and the yield of product was lower.

Effect of different amount of catalyst on the yield. To find a suitable amount of catalyst, the raw materials molar ratio of 3-methylthiopropional to ethanol to triethyl orthoformate was chosen as 0.1mol: 0.3mol: 0.12mol. Ammonium chloride was 0.002mol, 0.003mol, 0.004mol, 0.005mol, respectively. The results are shown in Fig. 4.

The results showed that the amount of ammonium chloride has a significant effect on the yield. 0.003mol ammonium chloride was more suitable. When the amount of the ammonium chloride was less than 0.003mol, the amount was not enough for the reaction. When the amount of the ammonium chloride was more than 0.003mol in the reaction system, there were more side-product.

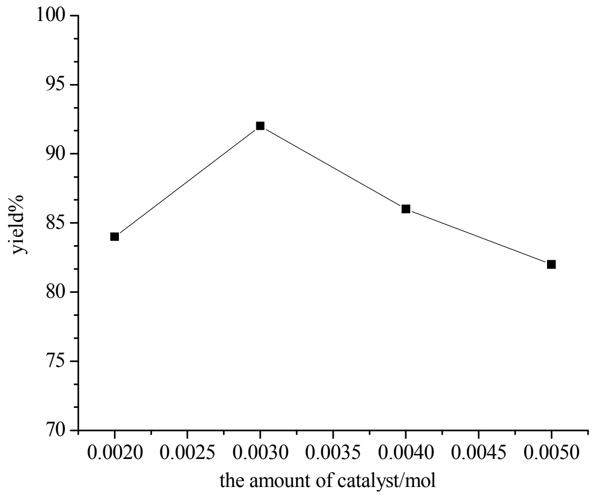

Fig. 4 Effect of different amount of ammonium chloride on yield

The role of the orthoformate in the reaction. For the sake of making a good understanding of the role of the orthoformate and confirming the mechanism of the reaction, an extra experiment was designed. Following the procedure of synthesis of **I**, 3-methylthiopropional reacted with ethanol and trimethyl orthoformate(**IV**), that is, triethyl orthoformate (**III**) was replaced by **IV**, the reaction mixture was analysized by GC-MS and GC. We found that mixture of three acetals was obtained.
The three acetals were 3-methylthiopropionaldehyde dimethyl acetal (**V**), 3-methylthiopropionaldehyd methyl ethyl acetal(**VI**) and 3-methylthiopropionaldehyde diethyl acetal(**I**), respectively. The ratio of **V** to **VI** to **I** is 6: 13: 11. The result indicated that the acetal was formed by four routes at least. It is also confirmed that orthoformate not only played the role of water absorbent, but also participated in the reaction.The water formed in the reaction was eliminated, which may force the chemical equilibrium toward completion and obtain more products. Elimination of water formed in the reaction system is very important, which can ensure higher yield. The speculation of the reaction mechanism is shown in the Fig. 5.

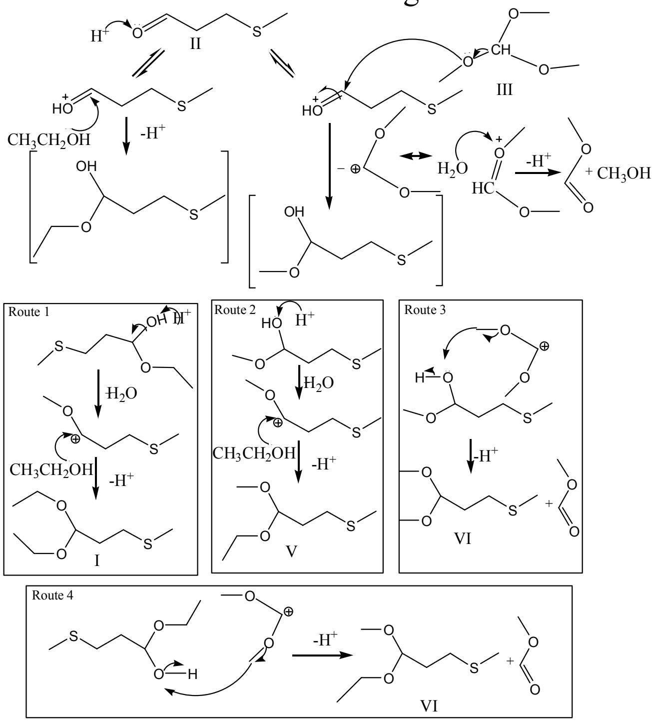

Fig. 5 The speculation of the reaction mechanism

The odor characteristics. The odor evaluation indicated that 3-methylthiopropionaldehyde diethyl acetal has meaty, sauce, savory, and pineapple odor. It can be used for compounding meaty flavoring and fruity flavoring.

Experimental

Reagents and Instruments. triethyl orthoformate, ammonium chloride, anhydrous ethanol, toluenesulfonic acid, sodium bisulfate and citric acid were obtained from Sinopharm Chemical Reagent BeiJing Co., Ltd.(BeiJing, China). 3-methylthiopropional was obtained from TengZhou Ruiyuan Flavor Co., Ltd. (ShanDong, China). The contents were determined on a Varian CP3800 gas chromatograph. Mass spectra were obtained at a Agilent 6890N-5973i gas chromatography-mass spectrometry. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 nuclear magnetic resonance spectrometer. IR spectra were measured on a Nicolet Avater 370 Fourier transform infrared spectrometer.

Synthesis of 3-methylthiopropionaldehyde diethyl acetal(I). Ammonium chloride (0.003mol) was added to a flask equipped with magnetic stirrer, thermometer and reflux condenser. Then 3-methylthiopropional (0.1mol) was added followed by triethyl orthoformate (0.12mol) and ethanol (0.3mol). The mixture was stirred for 3 h at 68 °C~72°C, then the reaction mixture was cooled to bellow 18°C. The reaction mixture was washed with (20 ml×3) sodium chloride solution, and then the aq. layer was extracted with (10 ml×3) ether. The two organic phase were combined and dried with anhydrous sodium sulfate. After filtration, the solvent was removed in rotary evaporator to give pale-yellow clear liquid, which mainly consists of 3-methylthiopropionaldehyde diethyl acetal. The yield of compound **I** was 92%. I.R (KBr, cm^{-1}) 2975, 2878, 2917, 1440, 1344, 1372, 1224, 1060, 965. ^{1}H-NMR ($CDCl_3$, 300MHz, δ ppm) 4.495-4.460 (t, 1H), 3.603-3.328 (m, 4H), 2.437-2.388 (t, 2H) 1.994-1.989 (s, 3H), 1.799-1.7 31(m, 2H), 1.099-1.049 (t, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$, δ ppm) 101.323 (CH), 61.071 (OCH_2), 33.022 (CH_2), 29.297 (SCH_2), 15.139 (SCH_3), 14.991 (CH_3). MS (70 ev) m/z 178($M\cdot^+$), 133($M\text{-}OCH_2CH_3^+$) 118 ($CH_3SCH_2CH_2CH_2OCH_2\cdot^+$), 103($CH_3SCH_2CH_2C^+{=}O$), 85($^+\cdot CH{=}CHCH_2O\ CH_2CH_3$), 75 ($CH_3SCH_2CH_2\cdot^+$), 61 ($CH_3SCH_2\cdot^+$), 47 ($CH_3S\cdot^+$), 29 ($^+\cdot C_2H_5$).

Preparation of the mixture of I , V and VI. The mixture of I, **V** and **VI** were obtained from 0.12mol **IV** following procedure of the synthesis of **I**. The mixture was analyzed by the GC-MS.
Compound **V**. MS (70 ev) m/z 150($M\cdot^+$), 118 ($M\text{-}HOCH_3$), 103 ($CH_3SCH_2CH_2C^+{=}O$), 75 ($CH_3SCH_2\ CH_2\cdot^+$), 61 ($CH_3SCH_2\cdot^+$), 47 ($CH_3S\cdot^+$), 29 ($^+\cdot C_2H_5$).
Compound **VI**. MS (70 ev) m/z 164($M\cdot^+$), 132 ($M\text{-}HOCH_3$) 118 ($CH_3SCH_2CH_2CH_2OCH_2\cdot^+$), 103 ($CH_3\ SCH_2CH_2C^+{=}O$), 85 ($^+\cdot CH{=}CHCH_2OCH_2CH_3$), 75 ($CH_3SCH_2CH_2\cdot^+$), 61 ($CH_3SCH_2\cdot^+$), 47 ($CH_3S\cdot^+$), 29($^+\cdot C_2H_5$).

Odor evaluation. 3-Methylthiopropionaldehyde diethyl acetal was purified in *vacuo*, diluted to 1% with 1,2-propylene glycol, and evaluated by five trained assessors. The evaluation was performed in a room free from odors. A clean strip of odorless absorbent paper(width 0.5～1.0cm, length 10～15cm) was impregnated with the above solution, and the wetted length was about 1～2mm. The paper strip was smelled at certain intervals. At the same time, the odor characteristics were recorded [12].

Conclusions

Ammonium chloride is more suitable catalyst for the synthesis of 3-methylthiopropionaldehyde diethyl acetal. The relative optimal conditions for the synthesis of 3-methylthiopropionaldehyde diethyl acetal are a mole ratio of 3-methylthiopropional to ethanol to triethyl orthoformate to ammonium chloride of 1:3:1.2:0.03, under reflux, and a reaction time of 3h. The yield of

3-methylthiopropionaldehyde diethyl acetal is about 92%. It was confirmed that triethyl orthoformate not only played the role of water absorbent, which was the dominate role, but also participated in the reaction. The odor evaluation indicated that 3-methylthiopropionaldehyde diethyl acetal has meaty, sauce, savory, and pineapple odor.

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