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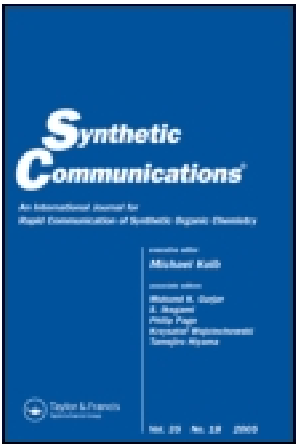

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# Novel Synthetic Routes of 3-Methoxypropanal from Glycerol

Jin Chen [a] & Xiaohua Du [a]

[a] State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou, China

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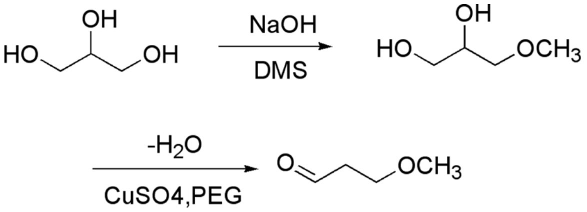
# NOVEL SYNTHETIC ROUTES OF 3-METHOXYPROPANAL FROM GLYCEROL

**Jin Chen and Xiaohua Du**
State Key Laboratory Breeding Base of Green Chemistry–Synthesis Technology, Zhejiang University of Technology, Hangzhou, China

## GRAPHICAL ABSTRACT



**Abstract** *A new synthesis of 3-methoxypropanal from glycerol was presented. With this new approach, the conversion of glycerol to 3-methoxypropanal can be effected in moderate yield using catalysts of copper sulfate and polyethylene glycol (PEG).*

**Keywords** Copper sulfate; dehydration; glycerol; 3-methoxypropanal; PEG

Glycerol has been a well-known chemical made fats and oils by saponification for more than two centuries. Recently, a large surplus of glycerol has been formed as a by-product in manufacturing biodiesel fuel by transesterification of seed oils with methanol. About 100 kg of pure glycerol is obtained from one ton of biodiesel production.[1] Studies have shown that the glycerol commodity market is very limited, and any increase in biodiesel production will cause a sharp decline in price. Obviously, how this additional glycerol can be used wisely has become an urgent issue, particularly how glycerol itself or some of its derivatives can find new applications in the chemical industry. In recent years, new opportunities for the conversion of glycerol into value-added chemicals have attracted intensive interest.[2]

Compound 3-methoxypropanal is a valuable intermediate in organic synthesis and has been used to synthesize agricultural chemical, such as imazamox.[3] It is also useful for the synthesis of a series of N-(3-methoxypropyl)-N-arylmethylpiperidin-4-amines, which are inhibitors of both serotonin and norepinephrine reuptake.[4]

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Address correspondence to Xiaohua Du, State Key Laboratory Breeding Base of Green Chemistry–Synthesis Technology, Zhejiang University of Technology, Hangzhou, 310014, China. E-mail: duxiaohua@zjut.edu.cn

Furthermore, it also found its application in synthesizing the flavor methyl jasmonate.[5] The methods of preparing this compound include oxidation of 3-methoxypropanol with pyridinium chlorochromate,[6] hydroformylation of methoxy-ethene using catalysts of low-valent cobalt and rhodium,[7] rearrangement of 2-methoxymethyl-oxirane under erbium triflate catalysis in dichloromethane,[8] and addition reaction of acrolein with saturated alcohols in the presence of catalysts.[9]

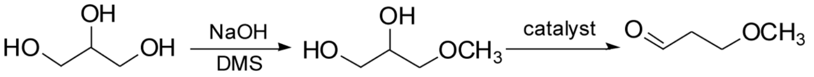
However, studies on converting 3-methoxy-1,2-propanediol to 3-methoxypropanal are seldom performed. Herein we report a new method for the synthesis of 3-methoxypropanal from glycerol (Scheme 1). The reaction was carried out in two steps. First, we prepared 3-methoxy-1,2-propanediol by a literature procedure.[10] Then it was converted to 3-methoxypropanal by dehydration. Some efforts have been made to choose the proper catalysts to obtain better results.

This study first focused on the feasibility of producing 3-methoxypropanal by dehydration of 3-methoxy-1,2-propanediol using heterogeneous catalyst in a single-stage reaction. The products were distilled when the reactions were completed. The results for the dehydration of 3-methoxy-1,2-propanediol are summarized in Table 1.

In our study, catalysis of sulfuric acid, p-toluene sulfonic acid, sodium bisulfate monohydrate, and copper sulfate were examined. A trace amount of product was observed. Copper-chromite catalyst showed high selectivity in the dehydration of glycerol to acetol,[11] but it was not effective in this reaction (Table 1, entry 1). Conventional dehydration catalysts such as sulfuric acid and p-toluene sulfonic acid were active for dehydrating 3-methoxy-1,2-propanediol, but low selectivity showed in this reaction (Table 1, entries 2 and 3). Then we investigated the performance of acidic ionic liquids in the absence of any solvents, but most reactions did not occur at all (Table 1, entries 10 and 11) and some showed low selectivity (Table 1, entries 12–15). On the other hand, sodium bisulfate monohydrate and copper sulfate catalysts are superior to the other screened catalysts, and the corresponding yields reached 21% and 30%, respectively. So copper sulfate and sodium bisulfate monohydrate catalysts were selected for further studies.

In an attempt to improve the method, we also tried adding phase-transfer catalysts to the system to facilitate the migration of the reactant in the heterogeneous system, such as polyethylene glycol (PEG), β-cyclodextrins (β-CD), tetrabutylammonium bromide (TBAB), or using the mixture of two phase-transfer catalysts. The reactions were carried out using the present reaction conditions, and the results are presented in Table 2.

As expected, better concentrations and yields were achieved when adding 2.5% β-CD or PEG400 into sodium bisulfate monohydrate catalyst (Table 2, entries 2 and 3), while lower selectivity was shown when adding TBAB into the reaction (Table 2, entry 1). When more PEG400 (15%) was added, we obtained higher concentration and yield (Table 2, entry 4). Similarly, 15% β-CD or PEG400 were added into copper sulfate catalyst (Table 2, entries 5 and 6); particularly PEG displayed an apparent



**Scheme 1.** Synthetic route of 3-methoxypropanal from glycerol.

**Table 1.** Synthesis of 3-methoxypropanal catalyzed by various catalysts

| Entry | Catalyst (15 wt%) | Distillate[a] (g) | Concentration[b] (%) | Yield (%) |
|---|---|---|---|---|
| 1 | $CuCr_2O_4$ | 0 | 0 | 0 |
| 2 | p-$MeC_6H_4SO_3H$ | 1.77 | 12 | 6 |
| 3 | $H_2SO_4$ | 2.05 | 11 | 5 |
| 4 | $NaHSO_4 \cdot H_2O$ | 1.89 | 44 | 21 |
| 5 | $Na_2HPO_4$ | 0 | 0 | 0 |
| 6 | $CuSO_4 \cdot 5H_2O$ | 2.01 | 41 | 20 |
| 7 | $CuSO_4$ | 2.3 | 51 | 30 |
| 8 | $Cu(HSO_4)_2$ | 1.92 | 36 | 17 |
| 9 | $KHSO_4$ | 1.13 | 27 | 8 |
| 10 | $[BMIM][HSO_4]$ | 0 | 0 | 0 |
| 11 | $[HSO_3\text{-}PMIM][HSO_4]$ | 0 | 0 | 0 |
| 12 | $[HSO_3\text{-}BMIM][HSO_4]$ | 0.51 | 31 | 4 |
| 13 | $[HSO_3\text{-}BPy][HSO_4]$ | 1.65 | 24 | 10 |
| 14 | $[BMIM][CF_3SO_3]$ | 1.02 | 12 | 3 |
| 15 | $[TEPSA][HSO_4]$[c] | 1.77 | 30 | 13 |

[a] The amount of distillate.

[b] The concentration of 3-methoxypropanal in the distillate was analyzed by GC.

[c] N,N,N-Triethyl-N-propanesulfonic acid ammonium hydrogen sulfate.

**Table 2.** Concentration and yield of 3-methoxypropanal by mixed catalysts

| Entry | Catalyst (wt%) | Distillate[a] (g) | Concentration[b] (%) | Yield (%) |
|---|---|---|---|---|
| 1 | $NaHSO_4 \cdot H_2O$ (15)<br>TBAB (2.5) | 2.07 | 12 | 6 |
| 2 | $NaHSO_4 \cdot H_2O$ (15)<br>β-CD (2.5) | 1.37 | 42 | 15 |
| 3 | $NaHSO_4 \cdot H_2O$ (15)<br>PEG400 (2.5) | 2.08 | 44 | 23 |
| 4 | $NaHSO_4 \cdot H_2O$ (15)<br>PEG400 (15) | 2.26 | 48 | 27 |
| 5 | $CuSO_4$ (15)<br>β-CD (15) | 1.96 | 28 | 14 |
| 6 | $CuSO_4$ (15)<br>PEG400 (15) | 2.07 | 59 | 31 |
| 7 | $CuSO_4$ (15)<br>PEG200 (15) | 2.4 | 20 | 12 |
| 8 | $CuSO_4$ (15)<br>PEG600 (15) | 2.48 | 63 | 39 |
| 9 | $CuSO_4$ (15)<br>PEG800 (15) | 2.35 | 21 | 12 |
| 10 | $NaHSO_4 \cdot H_2O$ (15)<br>PEG600 (7.5)<br>β-CD (7.5) | 2.12 | 53 | 28 |
| 11 | $CuSO_4$ (15)<br>PEG600 (7.5)<br>β-CD (7.5) | 2.05 | 54 | 28 |
| 12 | $NaHSO_4 \cdot H_2O$ (7.5)<br>$CuSO_4$ (7.5) | 2.07 | 38 | 19 |

[a] The amount of distillate.

[b] The concentration of 3-methoxypropanal in the distillate was analyzed by GC.

positive effect (Table 2, entry 6). A series of PEG200–800 was investigated (Table 2, entries 7–9), and we found the greatest enhancement was recorded with adding PEG600 (Table 2, entry 8), which afforded 63% content and 39% yield. Moreover, we used the mixture of copper sulfate and sodium bisulfate monohydrate catalysts (Table 2, entry 12) and added the mixture of PEG600 and β-CD into copper sulfate or sodium bisulfate monohydrate catalysts (Table 2, entries 10 and 11). However, the results were not improved. The possible reason for this phenomenon is the metal cation coordination ability of PEG causes heterogeneous catalysts to have better solubility.

## CONCLUSION

In summary, we have developed a novel and simple method for the synthesis of 3-methoxypropanal from glycerol in the presence of copper sulfate and PEG600. Although it affords a moderate yield (39%) now, this methodology provides a new application of glycerol, and such conversion can facilitate the replacement of petroleum by renewable resources.

## EXPERIMENTAL

### General Procedure for the Preparation of 3-Methoxy-1, 2-propanediol

A three-necked flask equipped with a stirrer, a thermometer, and a distillatory was charged with glycerol and 50% aqueous sodium hydroxide in the molar ratio of glycerol/NaOH 3:1. The mixture was heated to about 120 °C under reduced pressure to distill water formed in the synthesis. Then dimethyl sulfate (DMS) was added dropwise to the resulting sodium glycerate at 120–125 °C in the molar ratio DMS/NaOH 0.5:1. The resulting $Na_2SO_4$ was filtered off. After distillation of the bottom in a vacuum and repeated fractionation, 3-methoxy-1,2-propanediol was isolated by vacuum distillation, yield 59%.

### General Procedure for the Preparation of 3-Methoxypropanal

3-Methoxy-1,2-propanediol (4 g) and catalyst were added into a 25-ml, magnetically stirred reactor equipped with a thermometer, a condenser, and a distillatory. The reaction mixture was heated to about 200 °C under atmospheric pressure, and then the product was distilled. The reaction was completed in 30 min to an hour, and dark residues were left. At the end of the reaction, the distillates were weighed and analyzed with a gas chromatograph. The products were purified by fractional distillation in vacuum. The structures of the products were confirmed by $^{1}H$ NMR, $^{13}C$ NMR, and HRMS. $^{1}H$ NMR and $^{13}C$ NMR spectra were obtained on Bruker Avance III 500-MHz instrument for $^{1}H$ at 500 MHz and for $^{13}C$ at 125 MHz using $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra (HRMS) were recorded on a Waters Premier TOF-MS instrument with CI source.

## Data for 3-Methoxypropanal

$^1$H NMR ($CDCl_3$), δ: 9.78–9.79 (t, $J = 1.8$ Hz, 1H, CHO), 3.72–3.75 (t, $J = 6.0$ Hz, 2H, $CH_2$), 3.36 (s, 3H, $CH_3$), 2.66–2.69 (td, $J = 6.0$, 1.8 Hz, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$), δ: 201.07, 66.08, 58.70, 43.65. HRMS ($CI^+$) calculated for $C_4H_8O_2$: 88.0524. Found: 88.0515.

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