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Short Communication

Monitoring the conversion of cycloheptanone to methyl 7-oxoheptanoate by gas chromatography☆

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Abstract

Methyl 7-oxoheptanoate is an important intermediate required for the synthesis of prostaglandins by three-component coupling methodology. It can be efficiently prepared in two steps from cycloheptanone via the formation of 1-methoxy-1-cycloheptene and its ozonolysis. An efficient and reproducible method for the baseline separation of the components in the reaction mixtures in the above steps by gas chromatography is reported.

1. Introduction

During the course of our studies on prostaglandin synthesis we required methyl 7-oxoheptanoate (**1**) [1,2], and we decided to prepare it by ozonolysis [1] of 1-methoxy-1-cyloheptene (**2**), which in turn can be prepared from cycloheptanone (**3**) and trimethyl orthoformate (**4**) (Fig. 1). Wohl [3] reported a one-step procedure for the synthesis of cyclic enol ethers via intermediate acetals, in which the acetal content could not be judged by GC analysis. No suitable methods [4–6] were available to monitor these reactions by GC and, to our knowledge, there is no report giving conditions for separating a mixture of cycloheptanone (**3**), trimethyl orthoformate (**4**), 1,1-dimethoxycycloheptane (**5**) and 1-methoxy-1-cycloheptene (**2**) simultaneously. In this work, we achieved a baseline separation and developed GC conditions for the quantitative analysis of the reaction mixtures so that these reactions could be optimized for the maximum yield of **1**.

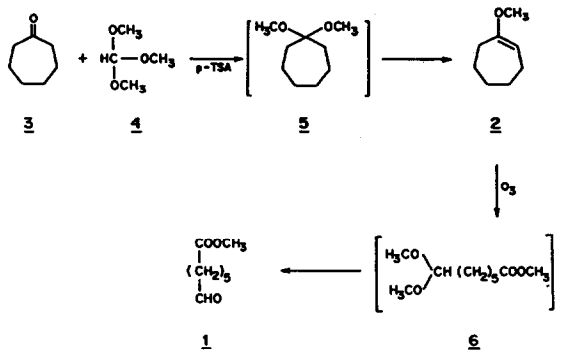

Fig. 1. Conversion of cycloheptanone (**3**) into methyl 7-oxoheptanoate (**1**) via the intermediates **5** and **2**.

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2. Experimental

2.1. Materials and solvents

Cycloheptanone (**3**) and trimethyl orthoformate (**4**) were purchased from Merck (Darmstadt, Germany). *p*-Toluenesulphonic acid (Fluka) was used as received. Other compounds, *viz.*, methyl 7-oxoheptanoate (**1**), 1-methoxy-1-cycloheptene (**2**) and 1,1-dimethoxycycloheptane (**5**), were prepared (see Section 2.2) in our laboratory, isolated in pure form by distillation and characterized by IR, NMR and mass spectrometry. The purified materials were analysed by GC and GC–MS to confirm their retention times.

2.2. Methods

Cycloheptanone was subjected to Wohl's conditions [3] for the preparation of **2**, *i.e.*, a mixture of trimethyl orthoformate, cycloheptanone and *p*-toluenesulphonic acid was stirred at room temperature for 24 h and then heated to remove the methanol liberated. We found that the reaction mixture could be directly heated under reflux (120°C) for 8 h to achieve complete conversion. The progress of this reaction was monitored by GC analysis as described. Further, the **2** thus obtained (after distillation) was subjected to ozonolysis [1] in methanol at −78°C to give **1**. The methanolic solution was analysed directly by GC.

2.3. Apparatus and conditions

A Hewlett-Packard Model 5880 gas chromatograph equipped with dual flame ionization detectors and coupled to a level 4 integrator was used with a stainless-steel column (6 ft. × 1/8 in. O.D.) packed with Chromosorb W HP (80–100 mesh) coated with 10% diethylene glycol succinate (DEGS).

The column was operated at 60°C with the injection port at 40°C above the oven temperature and a detector temperature of 250°C for the separation of methyl formate, methanol and trimethyl orthoformate. However, baseline separation and monitoring of the progress of the reactions were achieved using the same column operated at a detector temperature of 250°C, an oven temperature either isothermal at 90°C or programmed from 90 to 150°C at 20°C/min and an injection port temperature 40°C above the oven temperature. Nitrogen was used as the carrier gas at a flow-rate of 30 ml/min; the hydrogen flow-rate was 30 ml/min and the air flow-rate 350 ml/min.

2.4. Preparation of standard solutions

For quantitative analysis, mixtures of compounds **2** and **3** of different compositions ranging from 1:9 to 10:0 (**2**:**3**) were prepared in dichloromethane, *e.g.*, 10 mg of **2** and 90 mg of **3** were dissolved in 10 ml of dichloromethane. With an injection volume of 2 μl, GC analysis of all the solutions was carried out; calibration graphs for **2** and **3** were plotted separately and were found to be linear. Aliquots of the reaction mixture to be monitored were analysed by GC directly at different intervals.

3. Results and discussion

The separation of a mixture of trimethyl orthoformate (**4**), cycloheptanone (**3**), 1,1-dimethoxycycloheptane (**5**) and 1-methoxy-1-cycloheptene (**2**) was initially tried on 5% OV-101 at 100°C, but **2** and **5** eluted at nearly the same retention time. A baseline separation was successfully achieved using 10% DEGS at 90°C, as shown in Fig. 2. The order of elution was **4** ($t_R = 0.97$), **2** ($t_R = 2.05$), **5** ($t_R = 4.42$) and **3** ($t_R = 7.20$ min). The total time required for the separation of all the components was less than 8 min.

In order to follow the presence of methyl formate and methanol formed during the preparation of **5** and **2**, indicating the progress of the reaction, the reaction mixture was analysed at 60°C on the same column and the order of elution was methyl formate ($t_R = 0.67$), methanol ($t_R = 0.96$) and **4** ($t_R = 2.19$ min). The pro-

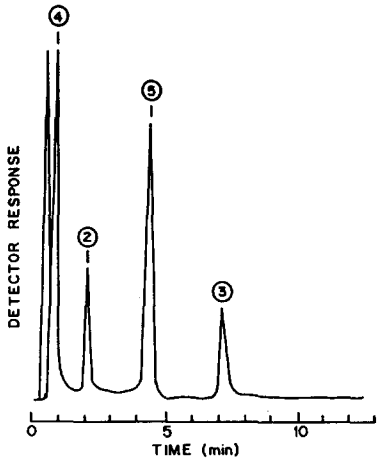

Fig. 2. Gas chromatogram showing separation of the reaction mixture during the conversion of **3** into **2**, obtained using a 10% DEGS column at 90°C. Peaks: 4 = trimethyl orthoformate (**4**) (t_R = 0.97 min); 2 = 1-methoxy-1-cycloheptene (**2**) (t_R = 2.05 min); 5 = 1,1-dimethoxycycloheptane (**5**) (t_R = 4.42 min); 3 = cycloheptanone (**3**) (t_R = 7.20 min).

Table 1

Progress of the reaction monitored by gas chromatography

Reaction conditions	Concentration (%)		
	3	**2**	**5**
Stirred at room temperature for 24 h	12.43	37.64	40.56
Room temperature for 24 h then 120°C for 6 h	–	92	5
120°C for 4 h	1.36	18.00	72.37
120°C for 8 h	–	94.07	2.87

gress of the conversion of **3** into **2** using different reaction conditions was monitored by GC as described and the results are given in Table 1.

In order to determine the accuracy of the method (external standard method), calibration graphs were plotted of area counts on the ordinate *versus* mass in mg on the abscissa. When 2 μl of solution of known concentration were injected under similar conditions, we found that the mass deduced from this graph matched the actual mass. The graphs thus obtained for **2** and **3** were found to be linear with slopes of 1.2 and 1.0, respectively. The results obtained after injecting unknown synthetic mixtures (aliquots from the reaction mixture) are given in Table 2. Statistical evaluation of the method showed that the reproducibility of quantitative measurements is fairly good, as indicated by the standard deviation, ranging from 0.432 to 0.886%.

Compound **2** was subjected to ozonolysis using the reported conditions [1] and the reaction was monitored by GC. The column temperature was programmed from 90 to 150°C at 20°C/min. The chromatogram in Fig. 3 shows the separation between **3**, **6** and **1**, the retention times being 7.20, 12.26 and 13.81 min, respectively (during the reaction a small amount of **2** is converted into the more stable keto form, cycloheptanone). It was assumed that the peak at t_R = 12.26 min was due to the intermediate methyl 7,7-dimethoxyheptanoate, which disappeared after acid hydrolysis with increase in the amount of **1** present (t_R = 13.81 min).

Table 2

Results obtained from calibration graph for different batches

Sample	Concentration of **2** present (mg/ml)	Concentration of **2** found from calibration graph (mg/ml)	Conversion (%)	Standard deviation (%)[a]
A	62	60	96.77	0.886
B	53	51	96.22	0.432
C	55	53	96.36	0.714

[a] Peak area for six determinations.

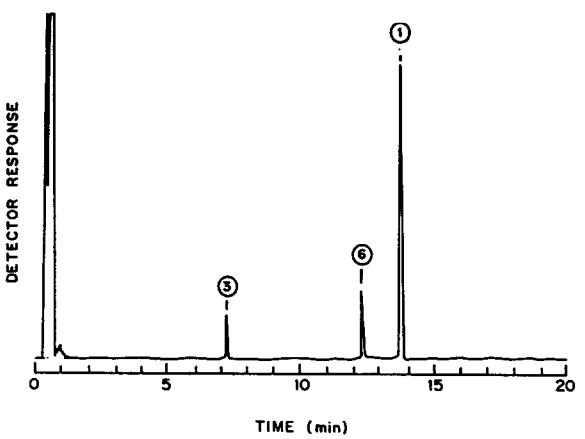

Fig. 3. Gas chromatogram showing the separation of the products after ozonolysis of **2** to **1**. Column, 10% DEGS; temperature, programmed from 90°C (7.5 min) to 150°C at 20°C/min. Peaks: 3 = cycloheptanone (**3**) (t_R = 7.20 min); 6 = methyl 7,7-dimethoxyheptanoate (**6**) (t_R = 12.26 min); **1** = methyl 7-oxoheptanoatc (**1**) (t_R = 13.81 min).

4. Conclusions

A clear separation of **2** and **3** was achieved by selecting suitable column and temperature conditions for GC. This was especially useful as the usual TLC technique was not satisfactory. Further conversion of **2** into **1** could also be monitored directly in the reaction mixture.

5. References

[1] M. Suzuki, T. Kawagishi, A. Yanagisawa, T. Suzuki, N. Okamura and R. Noyori, *Bull. Chem. Soc. Jpn.*, 61 (1988) 1299.
[2] L. Van Hijfte and M. Kelb, *Tetrahedron*, 48 (1992) 6393.
[3] R.A. Wohl, *Synthesis*, (1974) 38.
[4] M. Verzele, M. Acke and M. Anteunis, *J. Chem. Soc.*, (1963) 5598.
[5] K. Schank and W. Pack, *Chem. Ber.*, 102 (1969) 1892.
[6] H.O. House, L.J. Czula, M. Gall and H.D. Olmstead, *J. Org. Chem.*, 34 (1969) 2324.