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SYNTHESIS OF NEW SAFROL DERIVATIVES BY MODIFYING THE SIDE CHAIN

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SUMMARY

By modifying the side chain with different eights derivatives of safrol have been synthesized functional groups. All obtained compounds are new and their structures are assigned by mass analysis and NMR spectra.

I - INTRODUCTION

Safrol is a natural product, and presents especially in Sassafras oil with 80% abundance. Sassafras oil has been used for long time for treatment of some diseases such as influenza, trouble digestion, stomach and arthritis [1]. Otherwise, Sassafras oil was also used in food and cosmetic industries. Some derivatives of safrol such as heliotropin is a precious perfume used widely in cosmetic industry. Heliotropin was prepared by oxidation of isosafrol [2, 3].

The exploitation and employing of safrol is limited so far. The synthesis of safrol derivatives bearing the active function groups on the side chain is necessary. These derivatives could be transformed to other compounds, which are useful for the research of biologically active molecules. In our previous paper, we described the synthesis of several new safrol derivatives containing nitrogen atom [4]. Herein, we present the synthesis of some safrol derivatives by modifying on the side chain.

II - EXPERIMENTAL

Synthesis of 2 and 3

To a solution of 100 ml formic acid containing 0.12 mol of 30% H_2O_2 solution was added 0.1 mol (16.2 g) of safrol at 0°C. The temperature was kept below 20°C. The reaction solution was stirred at the same temperature for 24 h. The formic acid was removed under diminished pressure. The remaining was neutralized with aqueous 5% NaOH solution, and then extracted with ethyl acetate (4 times). The combined organic extract was dried over Na_2SO_4 and the solvent was removed under diminished pressure. The crud was purified by column chromatography on silicagel eluted with a mixture of hexane/ethyl acetate 75/25 to give **2** and **3** in 35% and 50%, respectively.

Synthesis of 4, 5 and 6

Safrol (0.1 mol, 16.2 g) was dissolved in 100 ml CCl_4 and the solution was cooled to 0°C. To this solution, 0.1 ml of bromine in 50 ml CCl_4 was added. The reaction temperature was kept below 5°C. The reaction was stirred until the bromine was consumed (indicating by disappearance of yellow color of Br_2). The reaction solution was washed twice with water and dried over Na_2SO_4. The solvent was then removed under diminished pressure. The crud was purified on a silica gel column eluted with a mixture of hexane/ethyl acetate 98/2 providing the compound **4** (35%), **5** (15%) and **6** (50%).

Synthesis of 7 and 8

To a solution of 150 ml CCl_4 containing 18.92 g (0.11 mol) of *m*-chloroperbenzoic acid (MCPBA) was added 0.1 mol (16.2 g) safrol at 0°C. The reaction solution was stirred at the same temperature for 8 h. The solution was then washed with 10% NaOH aqueous solution (4 times) and with water (twice). The organic layer was dried over $MgSO_4$ and the solvent was removed under diminished pressure. The crud was chromatographied on a silicagel column eluted with a mixture of hexane/ethyl acetate 98/2 to provide compound **7** in 89% yield. Compound **7** was hydrolyzed with NaOH in MeOH at 60°C giving the diol **8** in 92% yield.

Synthesis of 9

To a solution of 150 ml of 5% KOH aqueous solution containing 0.15 mol of $KMnO_4$ was added 0.1 mol safrol at 20°C. The reaction was stirred for additional 2 h at the same temperature. The solid was filtered off and the filtrate was neutralized with 5% HCl aqueous solution. The precipitate was collected by filtration and dried under reduced pressure to give compound **9** as white solid in 80% yield (mp 210 - 211°C).

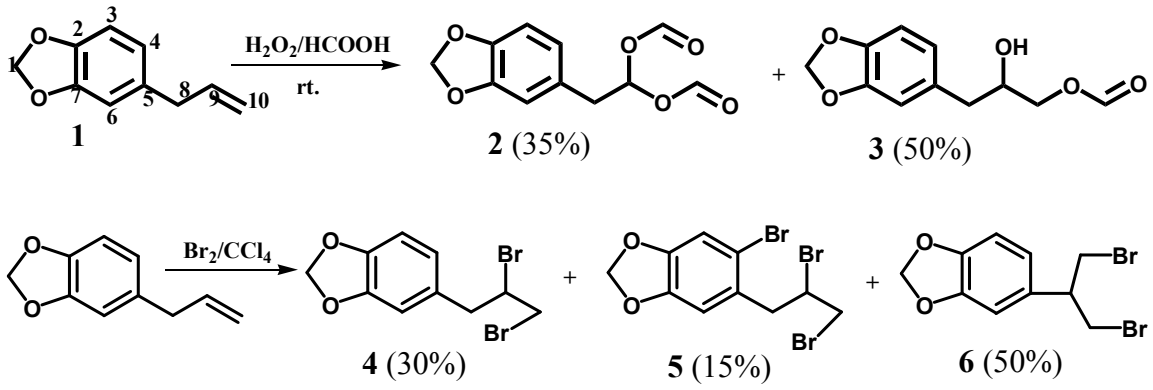
III - RESULTS AND DISCUSSION

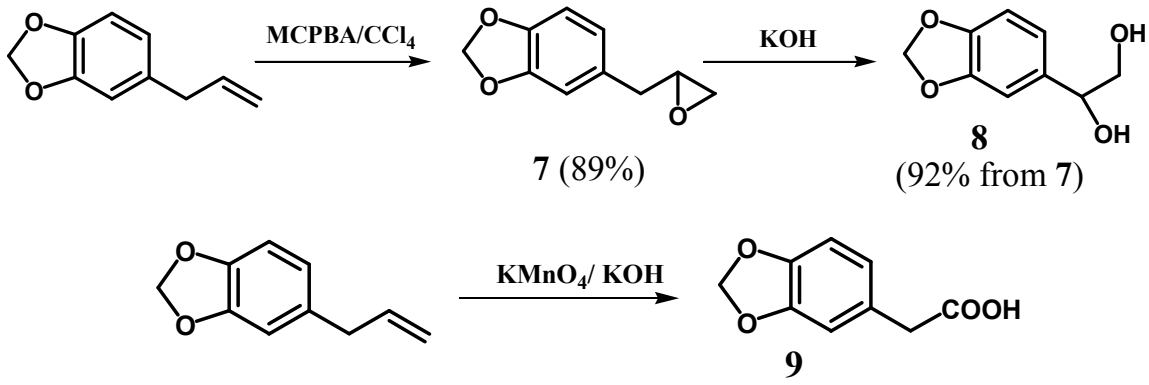
The compounds **2** and **3** were obtained by the oxidation of safrol in the presence of H_2O_2 in aqueous formic acid solution at room temperature for 24 h in 35% and 50% yield, respectively. The structures of **2** and **3** were established by NMR spectra (^1H, ^{13}C, HMQC and HMBC) and mass spectrum. The ^1H and ^{13}C NMR spectra of **3** in $CDCl_3$ showed the loss of the signals of double bond C9-C10. In the mass spectrum (ESI-MS), the protonated molecular ions were observed at m/z 253 and 235 for **2** and **3**, respectively.

The bromination of the double bond of **1** gave a mixture of **4**, **5** and **6** with 30%, 15% and 50% yields, respectively. The structures of **4**, **5** and **6** were determined by NMR spectroscopy and the mass analysis.

On the other hand, the epoxidation of **1** by *m*-chloroperbenzoic acid in CCl_4 at 0°C provided compound **7** in 89% yield [5]. Hydrolysis of **7** in aqueous NaOH at 60°C for 10 h gave the diol **8** in high yield (92%). The structures of **7** and **8** were confirmed by NMR spectra (^1H, ^{13}C, HMQC and HMBC) and mass spectrum.

The oxidation of **1** by $KMnO_4$ in aqueous KOH at 20°C produced the acid **9**. The mass spectrum (ESI-MS) of **9** showed the protonated molecular ion at m/z 181 $[M+H]^+$. The ^{13}C-NMR spectrum of **9** presented the signal of carboxylic group at 176 ppm. This indicated that the double bond was oxidized and the bond C9-C10 was cleaved.





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