TECHNICAL TRANSACTIONS | CZASOPISMO TECHNICZNE
CHEMISTRY | CHEMIA
1-Ch/2015

JOLANTA JAŚKOWSKA*, KAROLINA CHORABIK*, ZBIGNIEW MAJKA**

EFFICIENT METHODS FOR SYNTHESIS OF FLOROL AND ITS DERIVATIVES

OPRACOWANIE WYDAJNEJ METODY SYNTEZY FLOROLU I JEGO POCHODNYCH

Abstract

The paper describes and compares the two methods of synthesis of florol (**1**) (4-methyl-2-(2-methylpropyl) tetrahydro-2H-pyran-4-ol) by the Prins reaction. The first method involves the reaction for obtaining **1** in methylene chloride as solvent at 60°C. The second method applies the preparation of florol (**1**) and other tetrahydrofuran derivatives in solvent-free conditions in room temperature.

Keywords: fragrances, florol, florifol, synthesis of tetrahydropyran derivatives, Pins cyclisations

Streszczenie

W pracy opisano i porównano dwie metody syntezy florolu (**1**) (4-methyl-2-(2-methylpropyl)tetrahydro-2H-pyran-4-ol) na drodze reakcji Prinsa. Pierwsza metoda dotyczyła reakcji otrzymywania **1** w chlorku metylenu jako rozpuszczalniku w 60°C. Druga metoda, w warunkach bezrozpuszczalnikowych w temperaturze pokojowej, obejmowała zarówno syntezę florolu, jak i innych pochodnych tetrahydrofuranu.

Słowa kluczowe: związki zapachowe, florifol, florol, synteza pochodnych tetrahydrofuranu, cyklizacja Prins'a

DOI: 10.4467/2353737XCT.15.102.4050

* Ph.D. Eng. Jolanta Jaśkowska, M.Sc. Eng. Karolina Chorabik Institute of Organic Chemistry and Technology, Cracow University of Technology.
** Ph.D. Eng. Zbigniew Majka, Adamed Pharmaceuticals, Scientific Department.

1. Introduction

Florol (**1**) is also known as Floriffol, Floros, Floral Pyranol, Muguetol. It belongs to fragrance compounds with floral (Lily of the Valley) scent. Floral (**1**) is found in many perfumes such as: "XS for her" (Paco Rabanne) 0.5%, "O oui" (Lancome) 5.5%, "Dazzling Gold" (Estee Lauder) 8.5%, "J'adore" (Dior) 5.6%, "Fragile" (Jean Paul Gaultier) 2.7%, "L'Eau d'Eden" (Cacharel) 0.16%, "Romance" (Ralph Lauren8) 3%, "L'Eau de Kenzo masc" (Kenzo) 1%. This compound exists as four isomers which have a slightly different intensity and odor [1]. Methods for the preparation of florol (**1**) are described in literature based on the reaction Prins [2, 3] or cyclization reaction of the corresponding derivatives [4]. Prins'a reaction is most commonly described in literature by synthesis systems containing system pyran or tetrahydropyran [5-8]. Florol (**1**) can also be used as a starting material to obtain another fragrance compound called Clarycet, which has a smell of herbal-floral with a hint of dried fruit [3, 10, 11].

2. Results and discussions

The aim of the research was to develop efficient methods for synthesis of florol (1) (4-methyl-2-(2-methylpropyl) tetrahydro-2H-pyran-4-ol) (Fig. 1) and its derivatives.

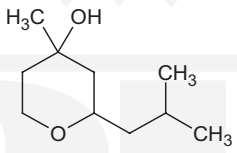

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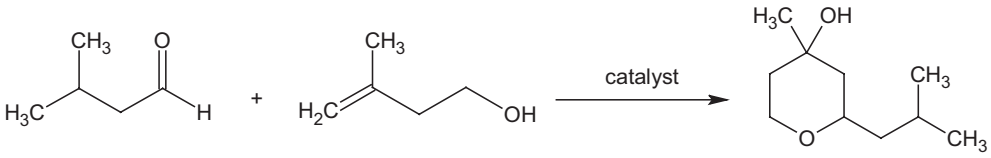
Fig. 1. Florol (4-methyl-2-(2-methylpropyl)tetrahydro-2*H*-pyran-4-ol)

Florol (**1**) was prepared by a Prins cyclization reaction between isovaleraldehyde (**2**) and isoprenol (**3**) (Fig. 2).



2 **3** **1**

Fig. 2. Florol (**1**) synthesis in Prins cyclization reaction

We started our research from the process carried out in dichloromethane as a solvent at a temperature of 60°C (method I), in the next step of the study, we assessed the solvent-free synthesis method at room temperature (method II). In each case, florol (**1**) was obtained in the form of two diastereoisomers (Fig. 3), which corresponds with literature data [3].

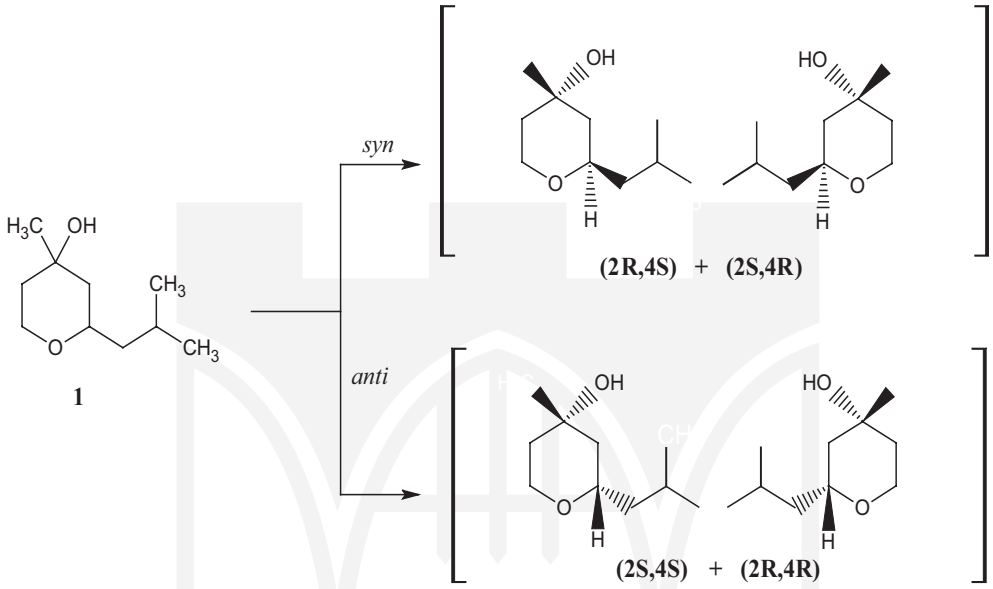


Fig. 3. Diastereoisomers of florol (**1**)

Separation on the chromatographic column (eluent: hexane/ethyl acetate – 3:1) and analysis of the results obtained by TLC, GC-MS and ^{1}H NMR led to the identification of isomers *syn* R_f = 0.20, RT = 5.35 oraz *anti* R_f = 0.35, RT = 5.58.

The synthesis according to method which was described in patent from 2005 [12] results in a 32% yield of the florol (**1**). The process took more than six hours, and the mixture, as already mentioned, required heating. Solvent-free reactions (method II) in the system SiO_2: *p*-toluenesulfonic acid gives a better yield over two hour (39%). This reaction mainly based on literature data, except thata different type was used there and the proportions of SiO_2 were changed [3]. Short reaction time and simplicity of method encouraged us to test the reaction in a wider range. First, the effect of the reaction time on the process was evaluated. It has been observed that the extension of the reaction time to 24 hours allows to increase the yield of florol (**1**) to 55%, and carrying out the process furthermore by 7 days results in a 63% yield. In a next step, the effect of a different catalysts was tested with a process for 24h (Table 1). Acids are most frequently recommended in literature for this type of synthesis catalysts, especially *p*-toluenesulfonic acid and methanesulfonic acid [3, 12]. We also tested other acid catalyst (sulfuric acid), and a catalyst which has a neutral pH (sodium sulfate). Studies show that, in addition to previously used *p*-toluenosulfonoego acid, the process can be carried out also by using methanesulfonic acid (64%) and sulfuric acid (43%) (Table 1). In the case of sodium sulfate, yield of **1** was very low (2%).

Table 1

The influence of the catalyst on the yield of florol (1).
Reaction time 24h

No.	Catalyst	Yield
1	*p*-toluenesulfonic acid	55
2	methanesulfonic acid	64
3	sulfuric acid	43
4	sodium sulfate	2

During the research, we also tested a series of reactions in which the isovalericaldehyde (**2**) is replaced by the other aldehydes **5-8**, to give the compounds based on 2-substituted--4-methyl-tetrahydropiranol **9-12** (Fig. 4). The synthesis was carried out at room temperature for 1h using a catalyst which was the *p*-toluenesulfonic acid.

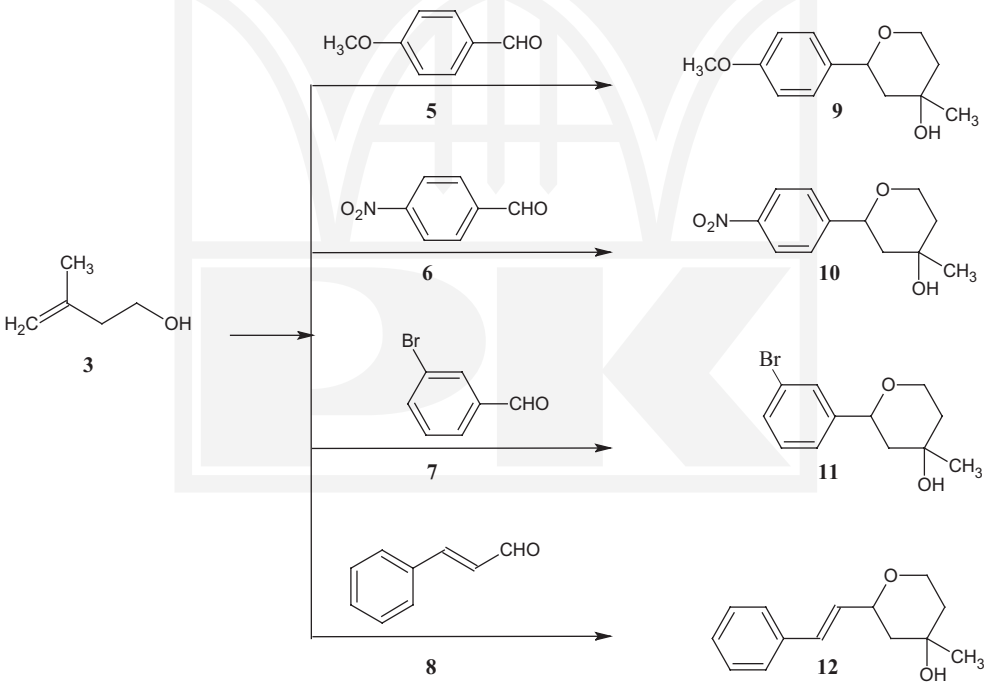


Fig. 4. Synthesis of tetrahydropyran derivatives

Expected compounds **9-12** were obtained with the high yields (Table 2) in comparison with data described in similar reactions in literature [3]. All the synthesized compounds were evaluated by TLC and GC, and their structures were confirmed on the basis of ^{1}H NMR spectra.

Table 2

Synthesis of tetrahydropyran derivatives

No.	Aldehyde structure	Compound	Yield
1	5	9	92
2	6	10	63
3	7	11	91
4	8	12	95

3. Experimental

The reactions were monitored by TLC on silica-gel plates (Merck 60F254) using chloroform/methanol (9:1) as eluent. TLC plates were visualized by exposure to solution *p*-anisaldehyde – sulfuric acid followed by heating on a hot plate. Starting materials, solvents, and reagents were purchased from commercial sources and were used without further purification. The structure of the obtained compounds was confirmed by ^{1}H-NMR, IR, and MS spectral data, and by comparing their physical properties to those described in literature. GC analyzes were performed on the: Varian 3800 GC with autosampler CP8400 and dispenser 1079 Split/splitless. The samples were dissolved in methanol. The prepared sample was injected onto the column of the gas chromatograph (0,5 µl). Column: VF-1 MS 30 m × 0,25 mm × 0,25 µm. Oven: initial temperature:60°C, kept for 1 min, accretion 25°C/min. do 220°C, kept for 4,6 min. Analysis time 12 minutes. An injection port temperature 250°C, split injection: 100:1, 0,5 µl. Carrier gas: helium 99.9995%, flow 1,2 ml/min. FID detector. Air 350 ml/min., hydrogen: 35 ml/min., auxiliary gas (He): 25 ml/min. Data recording with a frequency of 20 Hz. If the purity analysis recorded total ion current chromatogram "FID". Purity is calculated by summing up the area of all peaks in a chromagram and determining the percentage of the surface area of the analyte**.**

Synthesis of florol (**1**) (4-methyl-2-(2-methylpropyl)tetrahydro-2*H*-pyran-4-ol)

Method I

11.4 cm^3 (8.94 g, 0.1038 mol) isovaleraldehyde (**2**) and 0.034 cm^3 (0.051 g, 0.0053 mol) methanesulfonic acid were introduced into a 100 cm^3 flask and mixed at room temperature. Then, the mixture was heated to 60°C and after that 3.14 cm^3 (2.681 g, 0.0311 mol) isoprenol (**3**) was added dropwise to over 3 hours under stirring. After that, the mixture was kept at this temperature for another 3 hours. After cooling, the mixture was neutralized and extracted with methylene chloride. The organic layer was evaporated to give a yellow oil with a characteristic odor. Florol (**1**) as a mixture of two diastereomers was obtained in a yield of 32%.

Method II

General procedure: In a mortar containing silica gel (70-230 mesh) (12.5 g, 0.200 mol) and *p*-toluanesulfonic acid (0.5 g, 0.00029 mol) was added the aldehyde (**2**, **5**-**8**) (0.001 mol) and isoprenol (**3**) (0.0011mol). The resulting mixture was ground for appropriate time.

Reaction was monitored by TLC. After the reaction, the product was washed to remove by using a mixture of hexane/ethyl acetate (3:1). After evaporation of the solvent, the resulting compounds were subjected to TLC analysis, the GC-MS: 172 (*M+1*). Structures were confirmed by ^{1}H NMR.

Syn diastereoisomer: oil, R_f = 0.44, RT = 5,58; ^{1}H NMR σ 0.9 (d, 6H), 1.2 (ddd, 1H), 1.26 (s, 3H), 1.29 (dd, 1H), 1.4-1.5 (m, 3H), 1.61 (td, 1H), 1.71 (hept., 1H), (3.75-3.84 (m, 2H), 3.41 (td, 1H).

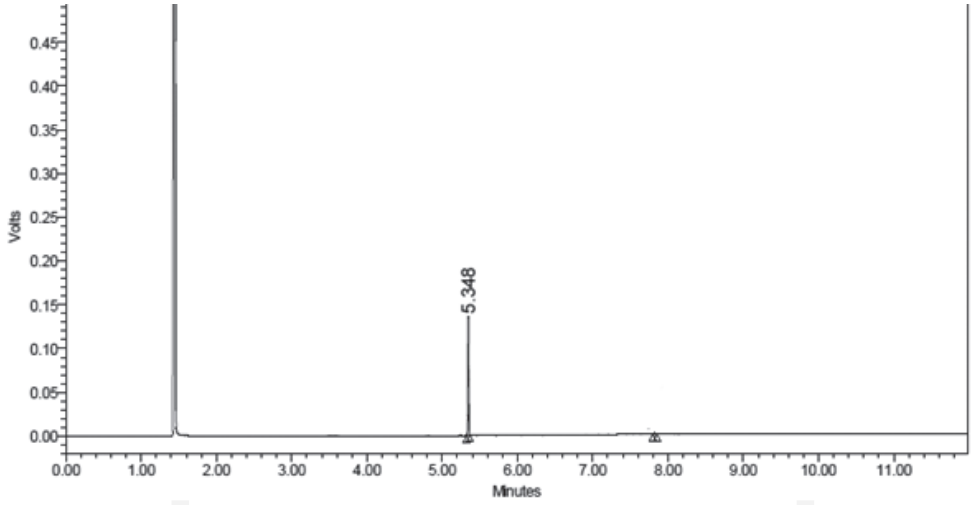


Fig. 5. GC spectra *syn diastereoizomer* (2S, 4S)+(2R, 4R)

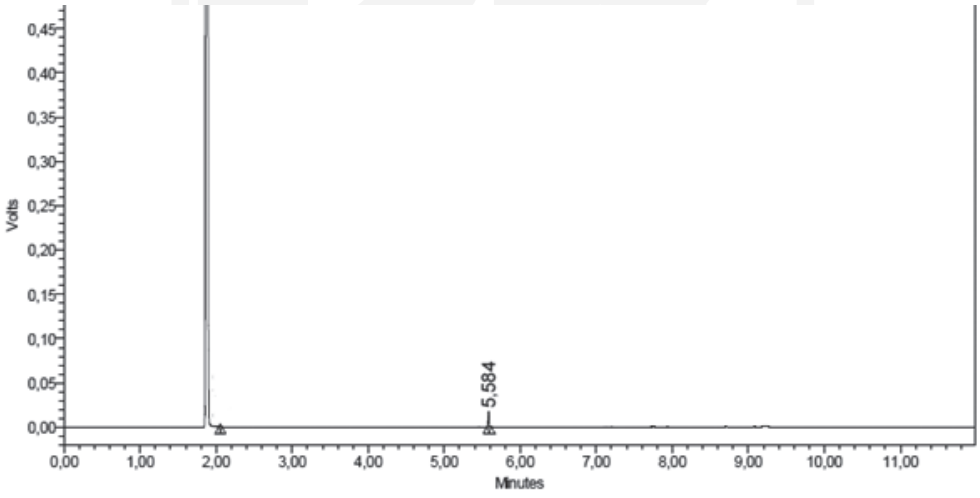


Fig. 6. GC spectra *anti diastereoizomer* (2R, 4S)+(2S, 4R)

Anti diastereoisomer: oil, R_f = 0.20, RT = 5.35, ^{1}H NMR σ 0.8-0.9 (d, 6H), 1.15 (ddd, 1H)1.32 (s, 3H), 1.39 (t, 1H), 1.49 (ddd, 1H), 1.56 (dq, 1H), 1.64 (dt, 1H), 1.69-1.73 (td, 1H), 3.23-3.37 (m, 1H), 3.41 (td, 1H), 3.92 (ddd, 1H).

Tetrahydropyran derivatives **9**-**12** (obtained as a racemic diastereoisomeric mixture) were synthesized by *method II*

2-(4-methoxyphenyl)-4-methyltetrahydro-2*H*-pyran-4-ol (**9**)
Obtained by reaction with 4-methoxybenzaldehyde (**5**) R_f = 0.23, R_f = 0.44 (R_f lit. = 0.31 and 0.46 [3]); RT = 5.63; 5.73; GC-MS: 223 (*M+1*).

4-methyl-2-(4-nitrophenyl)tetrahydro-2*H*-pyran-4-ol (**10**)
Obtained by reaction with 4-nitrobenzaldehyde (**6**) R_f = 0.52, R_f = 0.61 (R_f lit. = 0.42 and 0.61 [3]); RT = 5.62; 5.72; GC-MS: 238 (*M+1*).

2-(3-bromophenyl)-4-methyltetrahydro-2H-pyran-4-ol (**11**)
Obtained by reaction with 3-bromobenzaldehyde (**7**) R_f = 0.18, R_f = 0.28 (R_f lit. = 0.22 and 0.28 [3]); RT = 5.62; 5.72; GC-MS: 271 (*M+1*).

2-(4-ethenylphenyl)-4-methyltetrahydro-2H-pyran-4-ol (**12**)
Obtained by reaction with (2E)-3-phenylprop-2-enal (**8**) R_f = 0.58, R_f = 0.71 (R_f lit. = 0.56 and 0.73 [3]); RT = 5.62; 5.73; GC-MS: 219 (*M+1*).

4. Conclusions

During the research, two methods of synthesis of florol (1) were evaluated. In the solvent-free method, the impact of catalyst and the duration of the process to yield of 1 were also estimated. The universality of this method was confirmed in the reactions leading to a variety of tetrahydropyran derivatives. In each case, the compounds were obtained in the form of two diastereomers.

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