Pharmaceutical Chemistry Journal *Vol. 32, No. 10, 1998*

BETA-IONONE SYNTHESIS USING ANHYDROUS HYDROGEN FLUORIDE

Yu. D. Markovich,[1] A. V. Panfilov,[1] A. A. Zhirov,[1] A. T. Kirsanov,[1] L. A. Gorbach,[1] and K. A. Taraskin[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 32, No. 10, pp. 45 – 47, October, 1998.

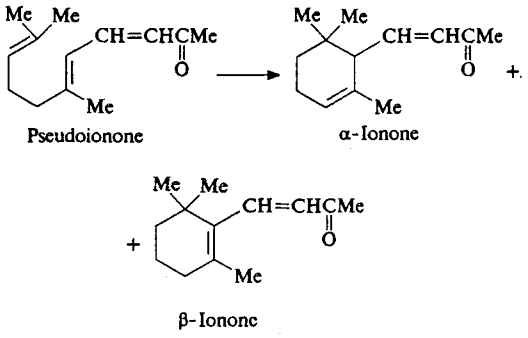
Original article submitted April 6, 1998.

The main commercially significant method of β-ionone synthesis is based on the cyclization of pseudoionone. The process is conducted in an inert solvent medium with a large excess of a strong mineral acid (pK_a –3) [1 – 3]. In the stage of β-ionone isolation, the acid is neutralized with an aqueous alkali, this treatment resulting in the accumulation of a large amount of waste products.

The purpose of this investigation was to search for a new cyclization agent, which can be regenerated after use in the reaction.

As is known, anhydrous hydrogen fluoride is capable of regenerating carbocations from unsaturated compounds [4]. The rather low boiling temperature of hydrogen fluoride (19.5°C) allows it to be readily removed from the mixture upon reaction.

In this connection, it was expedient to study the cyclization of pseudoionone with the aid of hydrogen fluoride. The cyclization proceeds according to the following scheme:



The yields and isomer compositions of cyclic ionones, dependent on the molar ratio of the reagents, are presented in Table 1.

Pseudoionone was added with stirring to anhydrous hydrogen fluoride, and the temperature of the reaction mixture was controlled within 2 – 3°C for 15 – 20 min using an external cooling system. After evaporating the excess hydrogen fluoride in vacuum and neutralizing the residue with potassium fluoride, the products were distilled in vacuum. As seen from the data given in Table 1, the cyclization of pseudoionone to β-ionone requires not less than 7.5 mole hydrogen fluoride.

We have investigated the effect of temperature on the yield and isomer composition of the cyclization products for the pseudoionone/hydrogen fluoride molar ratio 1 : 10. The results are presented in Table 2.

TABLE 1. Yields and Isomer Compositions of Ionones Obtained by Pseudoionone Cyclization under the Action of Anhydrous Hydrogen Fluoride

Pseudoionone / HF molar ratio	Yield of cyclic ionones, %	Isomer composition, %	
		α-ionone	β-ionone
1 : 1.0	–	initial pseudoionone	
1 : 5.0	70	48.0	52.0
1 : 7.5	80	7.0	93.0
1 : 10.0	90	2.0	98.0
1 : 15.0	90	1.5	98.5

TABLE 2. Effect of Temperature on the Yield and Composition of Cyclic Ionones

Reaction mixture temperature, °C	Yield of cyclic ionones, %	Isomer composition, %	
		α-ionone	β-ionone
– 10	80.0	7.5	92.5
– 5	82.9	5.0	95.0
– 2	89.4	2.0	98.0
0	92.4	1.7	98.3
5	92.5	1.5	98.5
10	90.8	1.5	98.5
15	85.0	1.5	98.5
40*	72.0	1.5	98.5
100*	43.0	1.5	98.5

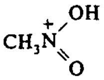
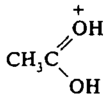
* Reaction mass heated to the indicated temperature upon mixing.

---

[1] "Belvitaminy" Joint-Stock Company, Belgorod, Russia.

0091-150X/98/3210-0557$20.00

TABLE 3. Effect of Conjugated Acids in Pseudoionone Cyclization

Conjugated base	Conjugated Acid	pK_a of conjugated acid	HF / pseudoionone / conjugated acid molar ratio	Isomer composition, %	
				α-ionone	β-ionone
–	–	–	5 : 1 : 0.00	43	57
CH_3NO_2	 $CH_3\overset{+}{N}(OH)=O$	– 12.0	5 : 1 : 0.25	21	79
$CH_3C(O)OH$	 $CH_3C(OH)_2^+$	– 6.5	5 : 1 : 0.25	33	67
$(C_2H_5)_2O$	$(C_2H_5)_2\overset{+}{O}H$	– 3.5	5 : 1 : 0.25	25	75
CH_3OH	$CH_3\overset{+}{O}H_2$	– 2.0	5 : 1 : 0.25	28	72

These data indicate that the maximum yield of β-ionone is achieved for pseudoionone cyclization with anhydrous hydrogen fluoride at a temperature of 0 – 10°C.

It was also of interest to study cyclization processes involving agents stronger than the sulfuric and fluorosulfonic acids used previously. According to the theory of acids and bases, promising results could be expected upon using strong conjugated acids formed by protonation of weak organic bases [5].

In order to establish the effect of conjugated acids on the yield of cyclic ionones, we performed a series of experiments (Table 3) in which the ratio of pseudoionone to hydrogen fluoride (1 : 5) was selected so as to provide that a considerable amount of α-ionone would form in the reaction mixture.

The data of Table 3 indicate that adding compounds forming conjugated acids to the reaction mixture leads to an increasing fraction of β-ionone in the products.

TABLE 5. β-Ionone under the Action of Anhydrous Hydrogen Fluoride

Characteristic	Experiment					
	1	2	3	4	5	6
Charged, g: pseudoionone	49.9	49.9	49.9	49.9	49.9	49.0
hydrogen fluoride	52.0	57.2	78.0	39.0	31.2	25.0
Pseudoionone / HF molar ratio	1 : 10	1 : 11	1 : 15	1 : 7.5	1 : 6.0	1 : 5.0
Cyclization temperature, °C	– 2	+ 5	+ 5	0	+ 5	+ 5
HF distilled:						
weight, g	49.9	56.0	75.6	38.0	30.6	24.0
% of theoretical	96.0	98.0	97.0	97.8	98.0	96.0
Neutralizing agent:						
type	$CaCO_3$	KF	$CaCO_3$	KF	$CaCO_3$	$CaCO_3$
amount, g	3.0	4.3	3.5	3.6	1.0	1.4
Ionone yield, g	46.7	46.8	46.8	45.8	44.8	46.2
Composition, %:						
β-ionone	98.5	98.6	98.6	98.0	97.0	61.0
α-ionone	1.5	1.4	1.4	2.0	3.0	39.0
Relative yield of β-ionone, %	92.2	92.5	92.5	90.0	87.1	80.0

TABLE 4. Yields and Compositions of Cyclic Ionones Obtained by α-Ionone Isomerization in the Presence of Anhydrous Hydrogen Fluoride

α-Ionone / HF molar ratio	Yield of cyclic ionones, %	Isomer composition, %	
		α-ionone	β-ionone
1 : 5.0	90	40.0	60.0
1 : 7.5	92	10.0	90.0
1 : 10.0	91	2.7	97.3
1 : 15.0	93	1.5	98.5

Then we studied the effect of water on the direction of pseudoionone cyclization. For this purpose, 2, 5, or 10 wt.% water was added to anhydrous hydrogen fluoride taken in a tenfold excess with respect to pseudoionone. The reagents were mixed at 0 – 5°C and kept at this temperature for 15 min. It was found that the α- to β-ionone ratio in the reaction product was 8 : 92, 15 : 85, and 40 : 60 wt.%, respectively. Thus, the proportion of α-ionone increases with the water content.

It was of interest from both a theoretical and practical standpoint to study the possibility of α-ionone isomerization to β-ionone under the action of anhydrous hydrogen fluoride (note that hydrogen fluoride was not previously considered as a possible agent for the isomerization of cyclic ionones). The experimental data are summarized in Table 4.

The data presented in Table 4 show that hydrogen fluoride leads to the isomerization, but a sufficiently effective process would require a tenfold excess of this reagent.

Thus, our investigation led to a new reagent that can be used for the synthesis of α-ionone proceeding from pseudoionone and β-ionone [6].

EXPERIMENTAL PART

The course of the reaction was monitored and the composition of the products was checked by thin-layer chromatography (TLC). The analyses were performed on a CAMAG TLC-Scanner using Kieselgel $60F_{254}$ plates (Merck). The plates were eluted in a diethyl ether – chloroform (2 : 98 v / v) solvent system.

The gas chromatography (GC) analyses were conducted on a Varian Aerograph VA-3700 system equipped with a plasma-ionization detector and metal columns (1 m × 3 mm). The immobile phase was 10 % Carbowax-20H on W-HP chromosorb (80 / 100 μm fraction). The evaporator temperature was equal to that of the detector (200°C). The programmed temperature rise from 120 to 180°C in the column thermostat was performed at a rate of

5 °C / min; the carrier gas supply rate was 30 ml / min.

The pseudoionone cyclization was effected in a cooled metal reactor equipped with a mechanical stirrer, reflux cooler, temperature control system, and a copper tube reaching the reactor bottom (used for the dosed adding of pseudoionone). The reactor was charged with 52 g (2.6 mole) of anhydrous hydrogen fluoride. Then 49.9 g (0.26 mole) of freshly distilled pseudoionone was added with intensive stirring, the rate of the reagent supply being controlled so as to maintain the reaction mixture temperature within 0 – 5°C. After completing the pseudoionone introduction, the reaction mixture was stirred at the same temperature for 15 – 20 min. In the next step, hydrogen fluoride was evaporated at a residual pressure of 15 Torr with intensive stirring of the mixture. Hydrogen fluoride was condensed using two metal traps connected in series and cooled to – 50°C, the total amount collected being 48.5 g. The residual reaction mass was poured into a vessel containing 60 ml petroleum ether and 5 g of anhydrous potassium fluoride. This mixture was stirred at room temperature for 30 min. The precipitate was filtered and washed on the filter with petroleum ether (2 × 5 ml). The solvent was distilled off and the residue was subjected to fractional distillation in vacuum to collect the fraction boiling at 92 – 95°C at 3 Torr. Yield, 92.5%. The product contains 2% α-ionone and 98% β-ionone.

β-Ionone appears as an oily transparent yellowish liquid with $n_D^{20} = 1.5175$.

Table 5 shows the results of a series of experiments on pseudoionone cyclization.

Using a procedure similar to that described above, we conducted a reaction between 50 g (0.25 mole) α-ionone and 52 g (2.6 mole) anhydrous hydrogen fluoride and obtained 45 g (90%) β-ionone. The product contains 2.7% α-ionone and 97.3% β-ionone.

REFERENCES

1. FRG Patent No. 1000377 (1957); *Chem. Abstr.*, **53**, 18889b (1959).
2. UK Patent No. 814226 (1958); *Chem. Abstr.*, **53**, 18981b (1959).
3. FRG Patent Application No. 2027344 (1971); *Chem. Abstr.*, **76**, 46341j (1972).
4. C. E. Coor, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1865).
5. A. Gordon and R. Ford, *The Chemist's Companion. A Handbook of Practical Data*, Techniques, and References, Wiley, New York (1976).
6. A. V. Panfilov, Yu. D. Markovich, A. A. Zhirov, et al., RF Patent No. 2075473; *Byull. Izobret.*, No. 8 (1997).