CYCLIZATION OF ISOPRENOID COMPOUNDS

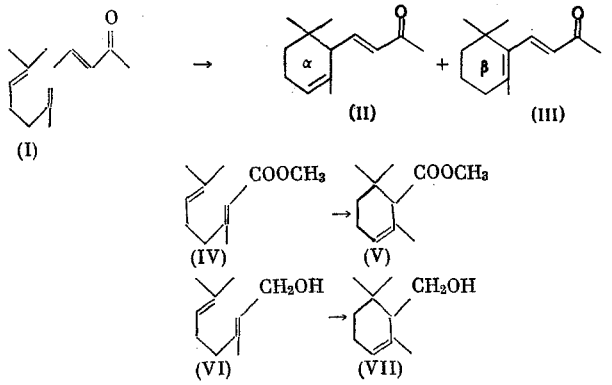
COMMUNICATION 27.* FLUOROSULFONIC ACID AS A PROMISING NEW CYCLIZATION AGENT

M. Kurbanov, A. V. Semenovskii, and V. A. Smit

UDC 542.91:547.315:546.16'226

Previously while studying the structural and steric direction of the acid-catalyzed cyclization of isoprenoids we developed a method for running the cyclization at low temperatures under the influence of 100% H_2SO_4 [2], which makes it possible to obtain cyclic isoprenoids in good yield, and assures a stereospecificity of the process and, as a rule, a quite high degree of structural selectivity [3]. However, sulfuric acid, which protonates the terminal double bond of the acyclic isoprenoid molecule, is capable of giving the corresponding acyclic sulfoesters, especially in those cases where the cyclization is retarded by the involvement of the conjugated double bond, for example, in the cyclization of geranic ester [1]. Taking into account the fact that the formation of sulfoesters is undoubtedly one of the factors responsible for the progress of secondary processes during the cyclization, we began a search for other cyclization agents, which possess the advantages of sulfuric acid, but lack the ability of forming addition products. Fluorosulfonic acid proved to be such a cyclization agent, which shows little inclination to form fluorosulfonates and is capable of sharply increasing the rate of the cyclization reaction. The present investigation is devoted to a study of the characteristic features associated with this and the advantages of fluorosulfonic acid, including its use for synthesis purposes.

As the object of study we selected certain typical isoprenoids that contained various functional groups, in particular, also those that cannot be satisfactorily converted to cyclic products under the influence of the commonly used reagents. The reaction was run in conventional manner [3, 4] in an inert solvent of the type of the nitroparaffins or liquid SO_2. Previously we had shown [5] that a suitable method for the synthesis of predominantly the α-(II) or the β-ionones (III) by the cyclization of pseudoionone requires the use of substantial amounts of H_2SO_4 (2-6 mole/mole of ketone). As can be seen from Table 1, 0.5-1.0 mole of FSO_3H is sufficient in order to run the cyclization of (I) in satisfactory yield (Expts. 2-5). Both the yield and the composition of the reaction products is independent of the isomeric composition of the starting ψ-ionone, the same as in the case of cyclization under the influence of H_2SO_4. In Table 1 are also given data on the cyclization of (I) under identical conditions under the influence of H_2SO_4, which clearly show how much less active this reagent is than FSO_3H (see Expts. 5 and 6)



*See [1] for Communication 25.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 390-394, February, 1973. Original article submitted January 27, 1972.

TABLE 1. Cyclization of ψ-Ionone under the Influence of FSO_3H (Solvent = 10 ml/g of starting compound)

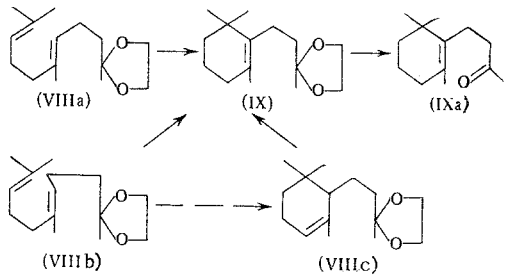
Expt. No.	ψ-Ionone (I)	Amount of FSO_3H, M/M of starting compound	T., °C	Time, min	Composition of mixture of reaction products, %		
					cyclic product		starting compound
					(II)	(III)	
1	cis + trans (6.7)	0,05	20	100	—	—	100
2	trans (6.7)	0,10	20	120	30	12	53
3*	cis + trans (6.7)	0,50	25	5	58	31	11
				15	74	26	—
4	trans (6.7)	1,00	—30	120	32	6	62
5	trans (6 7)	1,00	—10	10	84	16	—
6†	cis + trans (6.7)	1,00	—10	60	13	3	84

*The preparative experiment under these conditions gave a 65% yield.

†The experiment was run with 100% H_2SO_4.

This difference proved to be even more striking when going over to geranic ester (IV) (Table 2). In this case it is possible to run the reaction even with catalytic amounts of FSO_3H, and at –25° it is sufficient to use 0.05 mole of FSO_3H per mole of (IV) in order to obtain the α-cyclogeranic ester (V) in good yield (Expt. 1). For comparison we will state that at least 2.5 mole of H_2SO_4 is required for the successful cyclization of (IV) under the influence of H_2SO_4.

The possibility of running the reaction with small amounts of acid made it possible to study the cyclization of acid–labile isoprenoids. Thus, the use of FSO_3H makes it possible to accomplish the cyclization of geraniol (VI) on the ionone type with a 62% yield of (VII) (Expt. 4), whereas with sulfuric acid this product is obtained in ~30% yield [7], while the principal direction of the reaction is the formation of p-methane derivatives. The cyclization of the cis- and trans-geranylacetone ketals (VIII) was successfully accomplished under the influence of FSO_3H in amounts ranging from 0.1 to 0.5 mole/mole of compound (Expts. 5-7), in which connection the ketal protection is retained here. This transformation cannot be accomplished under the influence of either H_2SO_4 or BF_3, for here the cleavage of the ketal grouping and the formation of bicyclic products occur. It is interesting that the β-cyclo product (IX) is formed during the cyclization of the trans, as well as the cis isomer of (VIIIa) and (VIIIb), although the predominant formation of the α-cyclo product (VIIIc) from (VIIIb) could be expected [8]. This result is apparently associated with the ease of the isomerization: (VIIIc)→(IX). Actually, the authentic (VIIIc) under the conditions for the cyclization of (VIIIa) is completely converted to (IX). The indicated reaction can serve as a convenient method for the preparation of dihydro-β-ionone (IXa), an important intermediate in the synthesis of terpenoids



Consequently, as a result of the performed studies it was found that fluorosulfonic acid as a cyclization agent has a number of important advantages over sulfuric acid, which are apparently associated with the inability of FSO_3H to form either fluorosulfonates or associates of the type of intimate ion pairs. In other words, FSO_3H probably facilitates a greater "degree of development" of the carbcation center at C_2 of the isoprenoid molecule, which leads to an acceleration of the cyclization reaction. In our opinion, the above enumerated examples are sufficient to consider fluorosulfonic acid as being a promising new reagent in the reaction for the acid-catalyzed cyclization of isoprenoids.

EXPERIMENTAL METHOD

The preparation of the starting compounds (I), (IV), (VI), and (VIIIa, b) was described previously [9-12]. The cyclization products were analyzed by GLC (2% of neopentyl glycol succinate deposited on Chromosorb

TABLE 2. Cyclization of Acyclic Isoprenoids under the Influence of FSO_3H (Solvent = 10 ml/g of starting compound)

Expt. No.	Starting compound	Amount of FSO_3H, M/M of starting compound	T., °C	Time, min	Composition of mixture of reaction products, %		Total yield, %
					cyclic product	starting compound	
1	Geranic ester (IV) (mixture of cis-trans isomers)	0,05	—25	120	93	7	72
2	The same	0,05	0	30	87	13	70
3	Geraniol (VI)	0,5	—70	60	20	80	
4	"	1	—70	5	~100	—	62
5	trans-Geranylacetone ketal (VIIIa)	0,5	—20	5	~100	—	60
6	cis-Geranylacetone ketal (VIIIb)	0,5	—20	5	~100	—	55
7	trans-Geranyl acetone ketal (VIIIa)	0,1	+20	20	~100	—	65

W, 2 m × 4 mm glass column, flame-ionization detector, 50-60 ml/min of N_2, temperature 125° (A conditions), 95° (B conditions), 140° (C conditions), and 155° (D conditions). The NMR spectra were taken on an R-12 instrument in CCl_4 solution. The chemical shifts (δ) are given relative to HMDS as the internal standard. The IR spectra were taken on a UR-10 instrument. The conditions and results of all of the cyclization experiments are summarized in Tables 1 and 2, and only some of the typical experiments are given below.

Cyclization of Pseudoionone (see Table 1, Expt. 5). With stirring, to a solution of 1.0 g of trans-6,7-trans-8,9-pseudoionone (I) in 9 ml of absolute nitromethane at –10° was added in 30 sec a chilled mixture of 0.30 ml of 100% FSO_3H in 2 ml of nitromethane. After keeping at this temperature for 10 min the reaction mass was decomposed under cooling (–20°) with an ether solution of triethylamine. Then it was washed with sodium bicarbonate solution, water, and dried over sodium sulfate. The solvent was then distilled off and the residue was vacuum-distilled. We obtained 0.80 g (77%) of product with bp 75-78° (0.65 mm); $n_D^{19.5}$ 1.5040. Based on the GLC data (A conditions), the product contains 84% of α-ionone (II) and 16% of β-ionone (III).*

Cyclization of Methyl Ester of Geranic Acid (see Table 2, Expt. 1). To a stirred solution of 5 g of the methyl ester of geranic acid (IV) (mixture of cis–trans isomers) in 50 ml of nitropropane at –25° was added in 30 sec a solution of 0.08 ml of 100% FSO_3H in 1 ml of nitropropane. The mixture was stirred for 2 h and then poured with stirring into 30 ml of ice water containing 20 ml of ether. The water layer was extracted with ether, the combined ether extract was washed in succession with $NaHCO_3$ solution and water, and dried over Na_2SO_4. After distilling of the solvent the residue was distilled to give 3.58 g (72%) of product with bp 54-55° (0.6 mm); n^{20} 1.4640, which, based on the GLC data (B conditions), is the practically pure methyl ester of α-cyclogeranic acid (V); see [13].

Cyclization of Geraniol (see Table 2, Expt. 4). To a stirred solution of 1.15 g of geraniol (VI) in 10 ml of nitropropane, cooled to –70°, was added 0.427 ml of 100% FSO_3H in 2 ml of nitropropane at such a rate that the temperature did not exceed –65° (~1 min). The mixture was held for another 5 min and then decomposed with an ether solution of triethylamine, containing chipped ice, at –50°. After the usual workup we obtained 0.71 g (62%) of product, bp 64-66° (1 mm); n_D^{20} 1.4830, which, based on the GLC data (C conditions) and the IR spectrum, is pure α-cyclogeraniol (VII); see [7].

Cyclization of trans-Geranylacetone Ketal (VIIIa) (see Table 2, Expt. 7). To a stirred solution of 0.90 g of trans-geranylacetone ethylene ketal (VIIIa) in 8 ml of nitromethane at 20° was added 0.022 ml of 100% FSO_3H in 1 ml of nitromethane. The mixture was then stirred for another 20 min. The reaction mass was cooled to –25° and decomposed with a solution of triethylamine in absolute ether. After the usual workup we obtained 0.59 g (65%) of product (IX), bp 80-84° (0.7 mm); n_D^{19} 1.4808. Based on the GLC data (D conditions), the compound is identical with dihydro-β-ionone ethylene ketal (IX). NMR spectrum: 0.92 (–C$(CH_3)_2$–),

*The products in this experiment, as well as in all of the subsequent experiments, were identified by comparison with authentic specimens on the basis of the constants and spectral characteristics (IR and NMR spectra and GLC data).

1.15 (–C(O)(O)–CH_3), 1.5 (C=C–CH_3), 3.7 ppm (–O–CH_2–CH_2–O–); the signals of olefinic protons in the 4.5-5.4 ppm region are absent. The hydrolysis of this product with a 20% solution of H_2SO_4 in dioxane (2 h at 40°) gives dihydro-β-ionone (IXa).

Isomerization of Dihydro-α-Ionone Ketal (VIIIc). With stirring and cooling (–20°), to 0.20 g of (VIIIc) in 1.5 ml of nitromethane was added in 30 sec a solution of 0.024 ml of 100% FSO_3H in 0.5 ml of absolute nitromethane. Then the mixture was stirred at –20° for 15 min. After the usual workup and removal of the solvent by distillation, the product was identified by the GLC method (D conditions) as being the dihydro-β-ionone ketal (IX) by comparison with an authentic specimen.

CONCLUSIONS

It was shown that fluorosulfonic acid can be used as a cyclization agent in the cyclization reactions of isoprenoids, and it has a number of important advantages, and, in particular, it can be used in small amounts (clear down to catalytic amounts), which makes the cyclization structurally more selective and applicable to objects that previously were not amenable to this reaction.

LITERATURE CITED

1. M. Kurbanov, A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 2541 (1971).
2. V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 2193 (1960).
3. V. A. Smit, A. V. Semenovskii, B. A. Rudenko, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 1782 (1963).
4. V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, Izv. Akad. Nauk, 1848 (1959).
5. V. A. Smit, A. V. Semenovskii, V. M. Medvedeva, and V. F. Kucherov, Dokl. Akad. Nauk SSSR, 124, 1080 (1959).
6. V. A. Smit, A. V. Semenovskii, P. F. Vlad, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 312 (1962).
7. V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 470 (1962).
8. V. A. Smit, A. V. Semenovskii, T. N. Chernova, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 1229 (1965).
9. H. Kappeler, H. Gutter, and H. Schinz, Helv. Chim. Acta, 36, 1862 (1953).
10. P. Stadler and P. Oberhausli, Helv. Chim. Acta, 42, 2597 (1959).
11. I. N. Nazarov, B. P. Gusev, and V. I. Gunar, Zh. Obshch. Khim., 28, 1444 (1958).
12. D. N. Kirk, D. K. Patel, and V. Petrow, J. Chem. Soc., 1046 (1957).
13. V. I. Isagulyants and G. A. Serebryanikov, Zh. Obshch. Khim., 9, 917 (1939).