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SUPERACID CYCLIZATION OF CERTAIN ALIPHATIC SESQUITERPENE DERIVATIVES IN IONIC LIQUIDS

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Superacid cyclization was demonstrated for the first time to be successful in those ionic liquids with functional groups that are stable in the reaction medium using aliphatic sesquiterpene derivatives as examples.

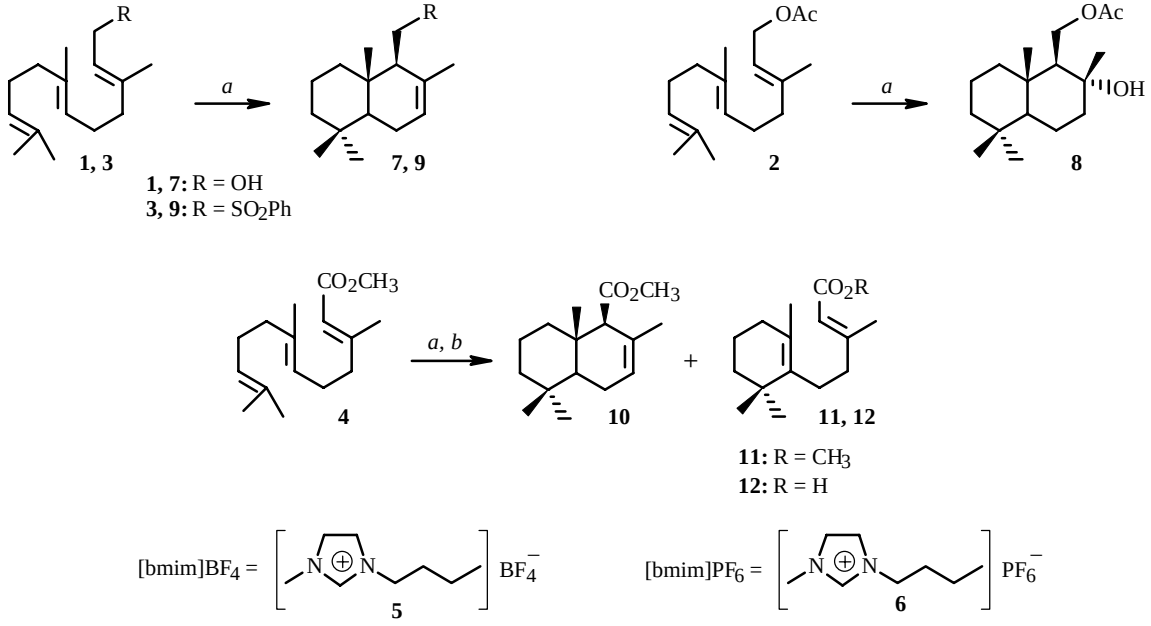
Key words: ionic liquids, superacids, cyclization, sesquiterpenoids.

Ionic liquids have recently found use in organic synthesis thanks to several of their important properties such as a broad temperature range at which reactions can be carried out, the simplicity of working up reaction mixtures, nonvolatility, the ability to be regenerated and used repeatedly, etc. [1-5].

Despite the use of the liquids as reaction media in many organic reactions, their application for carrying out electrophilic cyclization of terpenoids has not been reported. It is well known that this reaction plays an important role in the development of biomimetic synthetic methods for many cyclic terpenoids, among which are practically important compounds.

Existing information on biomimetic cyclization of regularly constructed terpenoids demonstrated convincingly that the preferred reagents for it are superacids at low temperatures. The reaction is chemically and structurally selective and stereospecific [6].

It seemed interesting to determine if superacid cyclization could be carried out in suitable ionic liquids and its efficiency.



a. FSO_3H (5 equiv), [bmim]BF_4 **5**, CH_2Cl_2, -45°C, 15 min; *b*. 10% KOH, EtOH, boiling for 2 h.

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TABLE 1. Cyclization of Aliphatic Sesquiterpenoids **1-4** by Fluorosulfonic Acid in Ionic Liquids **5** and **6**

Substrate	Substrate mass, mg (mmol)	CH_2Cl_2 volume, mL	Ionic liquid **5** or **6** volume, mL	Reaction temperature, °C	Reaction time, min	Product composition, %		
						cyclic product	hydrocarbons	polymers
1	70 (0.315)	1.4	0.70 (**5**)	-45	15	36 (**7**)	19	45
1	72 (0.324)	1.5	0.72 (**5**)	-45	5	33 (**7**)	15	52
1	65 (0.293)	1.3	0.65 (**6**)	0	5	0 (**7**)	69	31
2	88 (0.333)	1.8	0.88 (**5**)	-45	15	32 (**8**)	29	39
3	64 (0.185)	1.3	0.64 (**5**)	-45	30	89 (**9**)	0	11
3	22 (0.064)	0.4	0.20 (**6**)	0	5	73 (**9**)	0	27
4	44 (0.169)	0.9	0.44 (**5**)	-45	30	86 (**10**) and 5 (**11**)	0	9
4	46 (0.169)	0.9	0.46 (**6**)	0	15	41 (**10**) and 7 (**11**)	0	51

We investigated the reactions of several aliphatic sesquiterpene derivatives with fluorosulfonic acid in ionic liquids. The substrates were *E*,*E*-farnesol (**1**), its acetate (**2**), *E*,*E*-farnesylphenylsulfone (**3**), and the methyl ester of *E*,*E*-farnesylic acid (**4**). The ionic liquids were (1-butyl-3-methylimidazolium) tetrafluoroborate [bmim]BF_4 (**5**) and (1-butyl-3-methylimidazolium) hexafluorophosphate [bmim]PF_6 (**6**). Ionic liquid **5** was preferred because reactions can be carried out at from -45 to -50°C in it. As mentioned above, superacid cyclization in ordinary solvents is carried out at from -70 to -80°C. Ionic liquid **6** solidifies at 0°C. This would have a substantial effect on the product yields. Table 1 lists the results and reactions conditions. CH_2Cl_2 was used as a co-solvent because of the high viscosity of the ionic liquids.

The best results for reactions carried out in **5** were obtained for cyclization of **3** and **4**. The yields of bicyclic **9** [7] and **10** [8] were 89 and 86%, respectively. For farnesol and its acetate, which contain functional groups that are sensitive to the acids, the yields of bicyclic **7** and **8** [9] were relatively low (36 and 32%, respectively) because rather large quantities of hydrocarbons were formed. Apparently the functional groups of both starting **1** and **2** and cyclization products **7** and **8** were solvolyzed. For cyclization of **4**, a small quantity (5%) of the ester of β-monocyclofarnesyl acid **11** and the product of full cyclization **10** were formed. Esters **10** and **11** were separated by selective saponification of monocyclic ester **11** on boiling the products in alcoholic KOH for 2 h. Acid **12** was separated by methylation with diazomethane. Ester **11** was identified by comparison with an authentic sample prepared by the previously reported method [10].

If the cyclization was carried out in **6**, the yield was high (89%) only for cyclization of **3**. Cyclization of **4** formed a mixture of **10** and **11** in yields of 41 and 7%, respectively. Compounds **1** and **2** reacted with fluorosulfonic acid in [bmim]PF_6 to give only hydrocarbons and polymeric products.

In all instances products were isolated pure by column chromatography over silica gel and were identified spectrally and chromatographically by comparison with authentic samples.

Thus, we demonstrated for the first time that ionic liquids can be used successfully for superacid cyclization of terpene esters and phenylsulfones, i.e., compounds containing functional groups that are stable in the acidic medium.

EXPERIMENTAL

Melting points were determined on a Boetius heating stage. PMR [and ^{13}C NMR] spectra were recorded in $CDCl_3$ on a Bruker AC-80 (80 and 30 MHz, respectively) and Gemini 300 (300 and 75 MHz, respectively) spectrometers with TMS internal standard. IR spectra were recorded in CCl_4 on a Specord 74 spectrophotometer. Column chromatography used Merck 60 silica gel (70-230 mesh). TLC used Silufol UV-25 plates. Spots were developed by $Ce(SO_4)_2$ (0.1%) in H_2SO_4 (2 N) with subsequent heating at 80°C for 5 min.

Superacid Cyclization of Aliphatic Sesquiterpenoids in Ionic Liquids. General Method. Solutions of **1-4** in the appropriate volume of ionic liquids **5** or **6** and CH_2Cl_2 were cooled to the temperatures listed in Table 1, stirred, and treated with the corresponding volume of fluorosulfonic acid (5 equiv) in CH_2Cl_2 cooled to the same temperature. The mixtures were stirred for the times shown in Table 1, treated with Et_3N (0.75 equiv), and extracted with hexane (3 × 25 mL). The hexane extract was washed successively with water, H_2SO_4 solution (10%), water, saturated $NaHCO_3$ solution, and water, dried over anhydrous

Na_2SO_4, and filtered. Solvent was removed in vacuo. The reaction products were chromatographed over SiO_2. Table 1 lists the results.

(±)-Drimenol (7) from 1. IR spectrum (ν, cm^{-1}): 3627, 3450, 1664, 1030, 834. PMR spectrum (δ, ppm): 0.80 (3H, s), 0.86 (6H, s), 1.76 (3H, s), 2.20 (1H, br.s), 3.67 (2H, m), 5.38 (1H, m). Compound **7** was identified by comparison of the spectral properties with those in the literature [11].

(±)-Driman-8α,11-diol 11-Monoacetate (8) from 2. IR spectrum (ν, cm^{-1}): 3585, 3485, 1735, 1240, 1030. PMR spectrum (δ, ppm): 0.78 (3H, s), 0.83 (3H, s), 0.85 (3H, s), 1.17 (3H, s), 2.02 (3H, s), 3.44 (2H, m). Compound **8** was identified by comparison of the spectral properties with those in the literature [11].

(±)-Drimenylphenylsulfone (9) from 3. IR spectrum (ν, cm^{-1}): 1320, 1145. PMR spectrum (δ, ppm, J/Hz): 0.68 (3H, s), 0.83 (3H, s), 0.86 (3H, s), 1.70 (3H, s), 2.63 (1H, br.s), 3.12 (2H, d, J = 5), 5.48 (1H, br.s), 7.52-7.93 (5H, m). Compound **9** was identified by comparison of the spectral properties with those in the literature [7].

Methyl Ester of (±)-Drim-7-en-11-oic Acid (10) from 4. IR spectrum (ν, cm^{-1}): 1730, 1640, 1380, 1362, 860. PMR spectrum (δ, ppm): 0.90 (6H, s), 0.95 (3H, s), 1.58 (3H, s), 2.88 (1H, br.s), 3.63 (3H, s), 5.46 (1H, m). Compound **10** was identified by comparison of the spectral properties with those in the literature [8].

(±)-β-Monocyclofarnesyl Acid (12) from 4. IR spectrum (ν, cm^{-1}): 1244, 1423, 1635, 1685, 2866, 2927, 2958, 3411, 3469. PMR spectrum (300 MHz, δ, ppm, J/Hz): 1.00 (6H, s), 1.39-1.45 (2H, m), 1.52-1.59 (2H, m), 1.61 (3H, s), 1.91 (2H, t, J = 6), 2.1-2.19 (5H, m), 2.21 (3H, d, J = 1.2), 5.73 (1H, d, J = 1.2). ^{13}C NMR spectrum (75 MHz,δ, ppm): 19.39, 19.60, 19.96, 27.14, 28.71, 32.91, 35.18, 39.90, 41.91, 114.69, 128.17, 136.17, 164.02, 172.38.

Methyl Ester of (±)-β-Monocyclofarnesyl Acid (11) from 12. IR spectrum (ν, cm^{-1}): 1028, 1070, 1147, 1221, 1358, 1383, 1435, 1647, 1720, 2866, 2935. PMR spectrum (300 MHz, δ, ppm, J/Hz): 0.99 (6H, s), 1.39-1.41 (2H, m), 1.51-1.59 (2H, m), 1.60 (3H, s), 1.91 (2H, t, J = 6), 2.1-2.19 (4H, m), 2.20 (3H, d, J = 1.2), 3.69 (3H, s), 5.70 (1H, d, J = 1.2). ^{13}C NMR spectrum (75 MHz,δ, ppm): 19.05, 19.59, 19.93, 27.17, 28.69, 32.89, 35.15, 39.89, 41.60, 50.95, 114.71, 128.04, 136.26, 161.18, 167.52.

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REFERENCES

1. T. Welton, *Chem. Rev.*, **99**, 2071 (1999).
2. P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed. Engl.*, **39**, 3772 (2000).
3. D. Zhao, M. Wu, and Y. M. Kou, *Catalysis Today*, **74**, 157 (2002).
4. S. N. V. K. Aki, J. F. Brennecke, and A. Samanta, *Chem. Commun.*, 413 (2001).
5. J. G. Huddleston and R. D. Rogers, *Chem. Commun.*, 1765 (1998).
6. P. F. Vlad, *Pure Appl. Chem.*, **65**, 1329 (1993).
7. V. Kulcitki, N. Ungur, and P. F. Vlad, *Tetrahedron*, **54**, 11925 (1998).
8. P. F. Vlad, N. D. Ungur, and V. T. Nguen, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2507 (1995).
9. P. F. Vlad, N. D. Ungur, and V. B. Perutskii, *Khim. Prir. Soedin.*, 793 (1986).
10. A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1424 (1965).
11. P. F. Vlad, N. D. Ungur, V. Kh. Nguen, and V. B. Perutskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2494 (1995).