SYNTHESIS OF 4-SUBSTITUTED 2-CARENES IN NOVEL IMIDAZOLINIUM IONIC LIQUIDS

F. Macaev,[1] K. Gavrilov,[2] V. Muntyanu,[1] E. Styngach,[1] L. Vlad,[1] L. Bets,[1] S. Pogrebnoi,[1] and A. Barba[1]

UDC 547.596/598+547.854.021

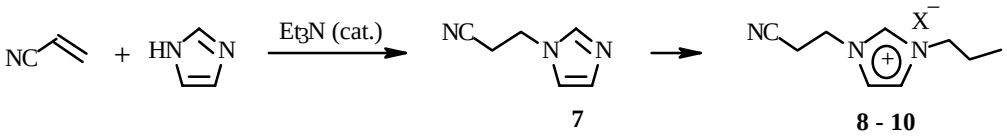
4-Acetyl-, 4-acetoxymethyl-, and 4-hydroxymethyl-2-carenes were synthesized using novel ionic liquids.

Key words: (+)-3-carene, 4-substituted 2-carenes, 2-(1*H*-1-imidazolyl)ethylcarbonitrile, ionic liquids.

Derivatives of the monoterpene 3-carene (**1**) such as (+)-4α-acetyl-2-carene (**2**), (+)-4α-hydroxymethyl-2-carene (**3**), and (+)-4α-acetoxymethyl-2-carene (**4**) are widely used to synthesize optically active 1,3-disubstituted 2,2-dimethylcyclopropanes [1], including precursors of commercially important insecticides [2-6]. Known methods for preparing **2-4** include heating **1** with $ZnCl_2$ in Ac_2O solution or with paraformaldehyde in AcOH solution [7-9]. Syntheses of **5** and **6** from the corresponding epimers **2** and **3** have also been reported [3, 7].

Ionic liquids (IL) have in the last decade become of interest in organic synthesis. However, examples of the synthesis of 4-substituted 2-carenes using IL have not appeared [1, 10-14]. Furthermore, researchers have paid attention mainly to testing commercially available IL salts of *N*,*N*′-dialkyl substituted imidazoles whereas functionalized analogs, e.g., carbonitriles, have been little studied [11].

Herein we report the ability to synthesize 4-substituted 2-carenes based on **1** using salts **8-10** as catalyst and solvent. These were prepared using 2-(1*H*-1-imidazolyl)ethylcarbonitrile (**7**).



7 **8 - 10**

8: X = Br; **9:** X = BF_4; **10:** X = PF_6

It was found that holding an equimolar mixture of **1**, Ac_2O, and 6 mole % **8**, **9**, or **10** at +50°C enhances the Kondakov reaction.

The catalytic activity of melts of the synthesized imidazole salts is probably due to initial formation of an acylium ion from Ac_2O that involves the nitrile associated with the anion [14, 15]. Table 1 gives the reaction conditions and yields of **2** and **5**.

Judging from GC data and the integrated intensities of the *gem*-dimethyl and acetyl groups in the PMR spectrum, the reaction product is a mixture of two compounds in a 95:5 ratio. Signals assigned to the major product agreed with literature data for **2** [7] whereas those for the minor product agreed well with those assigned to 4β-acetyl-2-carene (**5**). Moreover, the difference in the chemical shifts of the geminal methyls of the minor and major isomers at 0.23 and 0.16 ppm, respectively, in combination with the position of the H-3 signal provides additional confirmation of the proposed structures [7].

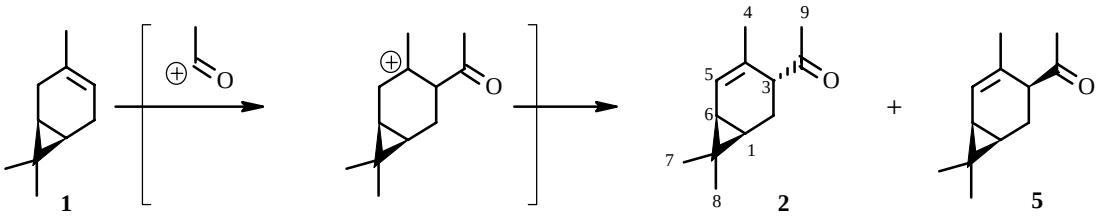
The carbonium ion formed by addition of the acyl cation to the Δ^3-double bond of **1** is stabilized by elimination of a proton to regenerate a Δ^2-double bond (Scheme 1).

1) Institute of Chemistry, Academy of Sciences of Moldova, ul. Akademicheskaya, 3, Kishinev, MD-2028, Republic of Moldova; 2) S. I. Esenin Ryazan′ State University, fax 373-22-73-99-54, e-mail: flmacaev@cc.acad.md. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 114-116, March-April, 2007. Original article submitted November 13, 2006.

 0009-3130/07/4302-0136

TABLE 1. Reaction Conditions and Yield of **2** and **5**

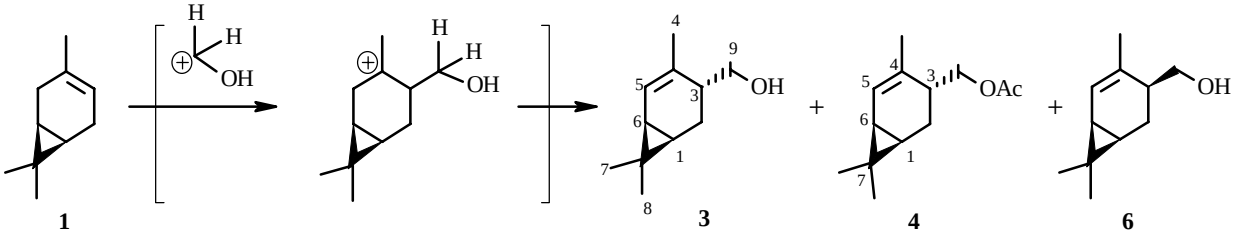
IL	Amount of IL	Total yield of **2** and **5**, %	Reaction time, h
8	6 mole %	32.58	49
	melt	36.7	25
9	6 mole %	38.26	46
10	6 mole %	29.21	48



Scheme 1.

The preferential formation of **2** is due to the directing effect of the 2,2-dimethylcyclopropane group [7]. Carrying out the reaction in a melt of **8** halves the time and slightly increases the yield. If the reaction is carried out in a melt of **9** or **10**, the 2,2-dimethylcyclopropane ring opens and produces a complicated product mixture in addition to the acetylation reaction.

Attempted hydroxymethylation of **1** using paraformaldehyde in a melt of the aforementioned salts or with a catalytic amount of $ZnCl_2$ added to the reaction mixture was unsuccessful. Only for a melt of **9** did addition of a stoichiometric amount of AcOH lead to a Prins reaction. The α-hydroxy carbonium ion produced by binding of a proton to formaldehyde reacts with **1** to give the β-hydroxy carbonium ion that is stabilized by elimination of a proton to regenerate a Δ^2-double bond.



The reaction products were isolated by column chromatography over silica gel. The less polar fraction contained **4** (38% yield), the physical chemical constants of which were analogous to those published [7-9]. The polar fraction was a mixture of compounds in a 9:1 ratio according to GC and signal intensities of the *gem*-dimethyl group in the PMR spectrum. The positions of the characteristic singlets for three methyls at 0.87, 1.05, 1.75 and 0.85, 0.96, and 1.69 ppm agreed with those reported previously [7-9] for epimeric 4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-ylmethanols **3** and **6**.

Thus, 4-substituted 2-carenes were synthesized from (+)-3-carene using novel 1-(2-ethylcarbonitrile)-3-propyl-1*H*-imidazol-3-ium salts, which differ from the traditional solvents (Ac_2O, AcOH) in being nonvolatile and catalytic.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 spectrophotometer; PMR and ^{13}C NMR spectra, on Bruker AC-E 200 (200.13 and 50.32 MHz) and Bruker AC-80 (80 and 20 MHz) spectrometer as 2-3% solutions in $CDCl_3$ or DMSO-d_6 with TMS internal standard. Specific rotation was measured on a A1-EPO polarimeter. GC was performed on a Chrom-5 chromatograph with a FI detector, glass column (1.2 × 3 mm), SE-30 (5%) stationary phase on Chromaton N-AW-DMCS (0.16-0.20 mm), and He carrier gas (40 cm^3/min flow rate). Column chromatography used silica gel (SiO_2) L 40/100, 100/160 μ (Czech Rep.) and 40/63 μ (Fluka); TLC, Silufol plates (Czechoslovakia). Compounds were detected by phosphomolybdic acid (5%) in EtOH with subsequent heating or dipping of plates in acidified aqueous $KMnO_4$ (2%). Imidazole, acrylonitrile, KBF_4, and KPF_6 were reagent grade (Aldrich).

(+)-(1*S*,6*R*)-3,7,7-Trimethylbicyclo[4.1.0]hept-2-ene (**1**, Aldrich, 90%) gave n_D^{20} 1.4726 and $[\alpha]_D^{26}$ +15.7° (*l* = 1, without solvent).

Synthesis of a Mixture of [(1*R*,3*R*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-yl]-1-ethanol (2) and [(1*R*,3*S*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-yl]-1-ethanol (5). A mixture of **2** and **5** was prepared by two methods. a) A mixture of **1** (1 g, 7.3 mmol) and Ac_2O (0.83 g, 8 mmol) was treated with **8**, **9**, or **10** (0.44 mmol). The reaction mixture was stirred with heating [50-55°C, TLC monitoring, benzene:CCl_4 (1:1) eluent] and extracted with hexane (3 × 10 mL). The extract was washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. Solvent was distilled off. The solid (1.1 g) was purified over a SiO_2 (45 g) column with elution by hexane to afford a colorless mixture of **2** and **5** (for yield, see Table 1), n_D^{20} 1.4869, $[\alpha]_D^{20}$ +346.5° (*c* 1.33, $CHCl_3$), $C_{12}H_{18}O$. PMR spectrum of the major isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79, 1.02 (3H each, s, H-7, H-8), 0.93-1.05 (2H, m, H-1, H-6), 1.18-1.68 (2H, m, H-2), 1.73 (3H, s, H-4), 2.08 (3H, s, H-9), 3.18, 3.22 (1H, dd, H-3, $J_{3,2\alpha}$ = 6.4, $J_{3,2\beta}$ = 10.6), 5.4-5.6 (1H, m, H-5).

b) Stirring **1** (1 g, 7.3 mmol) and Ac_2O (0.83 g, 8 mmol) in **8**, **9**, or **10** (3 g) and work up analogously to that described in a) gave a mixture of **2** and **5** identical to that described above.

Synthesis of (1*R*,3*S*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-ylmethyl Acetate (4). Stirring a mixture of **1** (1.36 g, 10 mmol), AcOH (0.6 g, 10 mmol), and paraformaldehyde (0.3 g, 10 mmol) at 50-55°C in **9** (5 g) for 20 h [TLC monitoring, $CHCl_3$:acetone (9.5:0.5) eluent] and extraction by ether (3 × 50 mL) gave a solid (1.8 g) that was chromatographed over a column of SiO_2 (60 g) with elution by hexane to afford colorless **4** (0.79 g), yield 38%, $[\alpha]_D^{20}$ +132° (*c* 3.1, $CHCl_3$), n_D^{20} 1.4765, $C_{13}H_{20}O_2$; lit. [8] $[\alpha]_D^{20}$ +122° and [9] $[\alpha]_D^{20}$ +133.6°. IR spectrum (ν, cm^{-1}): 1380, 1385 (CMe_2), 1670 (C=CH), 1740 (CO_2).

PMR spectrum (200.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87, 1.06 (3H each, s, Me_2C), 0.8-1.08 (2H, m, H-1, H-6), 1.69-1.72 (3H, m, MeC=), 1.82-2.2 (2H, m, H-2), 2.06 (3H, s, MeCO), 2.35-2.55 (1H, m, H-3), 3.92, 4.03 (2H, dd, $J_{3,2\alpha}$ = 2.1, $J_{3,2\beta}$ = 6.4, CH_2O), 5.42-5.58 (1H, m, H-5).

^{13}C NMR spectrum (20 MHz, $CDCl_3$): 15.01 and 22.65 [C($\underline{C}H_3$)$_2$], 16.90 (C-6), 20.82 ($\underline{C}H_3CO$), 21.80 (C-2), 23.11 (C-7), 37.60 (C-3), 23.24 (C-1), 27.61 ($\underline{C}H_3$–C=), 65.86 (CH_2O), 122.12 (C-5), 136.04 (C-4), 170.76 (CO_2).

Synthesis of a Mixture of (1*R*,3*R*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-ylmethanol (3) and (1*R*,3*S*,6*S*)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-ylmethanol (6). Elution of the hydroxymethylation products (1.36 g) of **1** (see synthesis of **4**) by hexane:ethylacetate (7:3) gave a mixture of **3** and **6** (0.48 g), yield 29%, $[\alpha]_D^{20}$ +101.9° (*c* 1.84, $CHCl_3$), $C_{11}H_{18}O$.

PMR spectrum of the major isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87, 1.05 (3H each, s, H-7, H-8), 0.7-1.08 (2H, m, H-1, H-6), 1.75 (3H, s, H-4), 1.81-2.13 (2H, m, H-2), 2.37-2.60 (1H, m, H-3), 3.92, 4.03 (2H, dd, $J_{3,9\alpha}$ = 2.0, $J_{3,9\beta}$ = 6.4, H-9), 4.7 (1H, OH), 5.49-5.6 (1H, m, H-5).

Synthesis of 2-(1*H*-1-Imidazolyl)ethylcarbonitrile (7). A solution of imidazole (40 g, 0.59 mol) in toluene (80 mL) was treated with acrylonitrile (33.85 g, 0.59 mol) and Et_3N (0.1 mL). The mixture was stirred at 60-65°C for 30 h. The solvent was distilled off to afford **7** (oil, 71 g, 99.75%), $C_6H_7N_3$. IR spectrum (ν, cm^{-1}): 2250 (CN).

PMR spectrum (80 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.69 (2H, t, J = 6.5, H-1, propionitrile), 4.13 (2H, t, J = 6.94, H-2, propionitrile), 6.88-7.01 (2H, m, H-4, H-5, imidazole), 7.43 (1H, s, H-1, imidazole).

Synthesis of 1-(2-Ethylcarbonitrile)-3-propyl-1*H*-imidazol-3-ium Bromide (8). A mixture of **7** (2.13 g, 0.018 mol) and propylbromide (2.17 g, 0.022 mol) in acetone (5 mL) was stirred at room temperature for 15 h [TLC, $CHCl_3$:propan-2-ol (3:7) eluent]. Solvent and the excess of starting bromide were distilled off to afford **8** (4.14 g of salt), yield 96.5%, yellow oil, $C_9H_{14}BrN_3$. IR spectrum (ν, cm^{-1}): 630 (Br), 1460, 1565 (C=C), 2250 (CN), 740, 2890, 2940, 2965 (aliphatic).

PMR spectrum (80 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (3H, t, J = 7.4, H-3, propyl), 1.6-1.91 (2H, m, H-2, propyl), 3.30 (2H, t, J = 6.5, H-1, propionitrile), 4.29 (2H, t, J = 6.4, H-2, propionitrile), 4.56 (2H, t, J = 6.5, H-1, propyl), 7.8-7.9 (2H, m ,H-4, H-5, imidazole), 9.47 (1H, s, H-2, imidazole.

^{13}C NMR spectrum (20 MHz, DMSO-d_6): 10.23 (C-3, propyl), 18.87 (C-1, propionitrile), 22.74 (C-2, propyl), 44.42 (C-1, propionitrile), 50.45 (C-1, propyl), 117.54 (C-4, imidazole), 118.23 (CN), 122.42 (C-5, imidazole), 122.70 (C-2, imidazole).

Synthesis of 1-(2-Ethylcarbonitrile)-3-propyl-1*H*-imidazol-3-ium Tetrafluoroborate (9). A solution of **8** (25 g, 0.102 mol) in acetone (25 mL) was treated in portions (4 g) with KBF_4 (12.85 g, 0.102 mol). The mixture was stirred at room temperature for 30 h. The solvent was distilled off. The solid was extracted with CH_2Cl_2 (3 × 70 mL). The combined extract

was dried over Na_2SO_4. The solvent was distilled off to afford **9** (22.69 g), yield 88.3%, yellow oil, $C_9H_{14}BF_4N_3$. IR spectrum (ν, cm^{-1}): 1020 (BF), 1455, 1570 (C=C), 2260 (CN), 740, 2895, 2985 (aliphatic).

PMR spectrum (80 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.79 (3H, t, J = 7.49, H-3, propyl), 1.65-1.92 (2H, m, H-2, propyl), 3.34 (2H, t, J = 6.64, H-1, propionitrile), 4.20 (2H, t, J = 6.95, H-2, propionitrile), 4.57 (2H, t, J = 6.41, H-1, propyl), 7.9-8.03 (2H, m, H-4, H-5, imidazole), 9.58 (1H, s, H-2, imidazole).

^{13}C NMR spectrum (20 MHz, DMSO-d_6): 10.32 (C-3, propyl), 18.86 (C-1, propionitrile), 22.82 (C-2, propyl), 44.50 (C-1, propionitrile), 50.55 (C-1, propyl), 117.62 (C-4, imidazole), 118.40 (CN), 122.49 (C-5, imidazole), 122.79 (C-2, imidazole).

Synthesis of 1-(2-ethylcarbonitrile)-3-propyl-1*H*-imidazol-3-ium hexafluorophosphate (10) was prepared analogously to **9** using equimolar amounts of **8** and KPF_6. Yield 96.6%, yellow oil, $C_9H_{14}F_6N_3P$. IR spectrum (ν, cm^{-1}): 850 (PF), 1460, 1570 (C=C), 2260 (CN), 750, 2895, 2995 (aliphatic). PMR spectrum (80 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.50, H-3, propyl), 1.58-1.94 (2H, m, H-2, propyl), 3.15 (2H, t, J = 6.64, H-1, ethyl), 4.14 (2H, t, J = 6.95, H-2, propionitrile), 4.48 (2H, t, J = 6.42, H-1, propyl), 7.66-7.77 (2H, m, H-4, H-5, imidazole), 9.16 (1H, s, H-2, imidazole).

^{13}C NMR spectrum (20 MHz, DMSO-d_6): 10.45 (C-3, propyl), 19.01 (C-1, propionitrile), 22.96 (C-2, propyl), 44.63 (C-1, propionitrile), 50.74 (C-1, propyl), 117.77 (C-4, imidazole), 120.30 (CN), 122.85 (C-5, imidazole), 122.91 (C-2, imidazole).

ACKNOWLEDGMENT

The work was supported by Moldova—Russia projects No. 06.21 CRF and No. 06-03-90898-Mol-a.

REFERENCES

1. F. Z. Macaev and A. V. Malkov, *Tetrahedron*, **62**, 9 (2006).
2. F. Z. Macaev, *Izv. Akad. Nauk, Ser. Khim.*, **8**, 1480 (2000).
3. F. Z. Macaev, F. Z. Galin, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, **3**, 517 (1995).
4. F. Z. Macaev, F. Z. Galin, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, **2**, 305 (1995).
5. G. A. Tolstikov, F. Z. Galin, F. Z. Macaev, V. N. Ignatyuk, V. S. Sultanova, and R. G. Davletov, *Zh. Org. Khim.*, **26**, 1671 (1990).
6. G. A. Tolstikov, F. Z. Galin, F. Z. Macaev, and V. N. Ignatyuk, *Zh. Org. Khim.*, **25**, 2633 (1989).
7. P. J. Kropp, D. C. Hecker, and T. J. Flant, *Tetrahedron*, **24**, 1385 (1968).
8. G. Ohloff, H. Farnow, and W. Philipp, *Liebigs Ann. Chem.*, **6132**, 43 (1958).
9. M. Muhlstadt and P. Richter, *Chem. Ber.*, **100**, 1892 (1967).
10. J. H. Davis, *Chem. Lett.*, **33**, 1072 (2004).
11. N. Jain, A. Kumar, S. Chauhan, and S. M. S. Chauhan, *Tetrahedron*, **61**, 1015 (2005).
12. C. Baudequin, J. Baudoux, J. Levillan, D. Cahard, A. C. Gaumont, and J. C. Plaquevent, *Tetrahedron: Asymmetry*, **14**, 3081 (2003).
13. K. Binnemans, *Chem. Rev.*, **105**, 4148 (2005).
14. I. J. B. Lin and C. S. Vasam, *J. Organomet. Chem.*, **690**, 3498 (2005).
15. K. Nakanishi, *Infrared Absorption Spectroscopy. Practical*, Holden—Day, San Francisco (1962).