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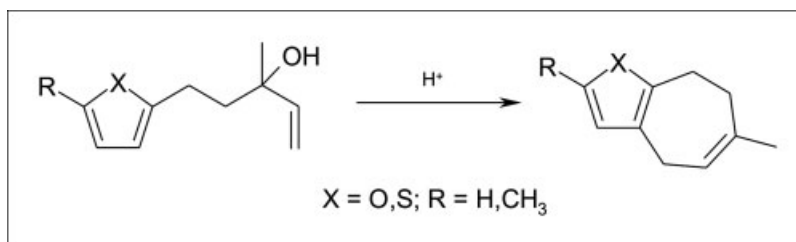
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2,6-Dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan and 2,6-dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]thiophene were prepared by direct cyclization of 3-methyl-5-(5-methylfuran-2-yl)-pent-1-en-3-ol and 3-methyl-5-(5-methylthiophen-2-yl)-pent-1-en-3-ol, respectively.

INTRODUCTION

Cyclic furan and thiophene derivatives have attracted increased attention due to their potential use as basic synthetic building blocks. Especially, in pharmaceutical drug design, a variety of heterocycles are used as pharmacophores [1,2].

Although many methods have been devised for the synthesis of furan (thiophene) core and cycloheptane ring, the formation of both condensed rings has rarely been reported. 5,6,7,8-Tetrahydro-4*H*-cyclohepta[*b*]furan has been prepared by Herz and Juo [3] through the conversion of 3,6-dihydro-1,2-dioxin derivative obtained in a 1,3-diene photo-oxygenation process. The same fused furan has been synthesized from 2-(2-phenylsulfanyl-allyl)-cycloheptanon via its cyclization under acidic conditions [4] and its 2-methyl derivative by mercuric triftalete-catalyzed cyclization of 2-prop-2-ynyl-cycloheptanone [5]. The corresponding thiophene analogues are reported to be available in a multistep transformation of 5-thiophene pentanoyl chloride [6]. We have found only one report on the preparation of 7,8-dihydro-4*H*-cyclohepta[*b*]furan (thiophene) in the 1-furyl (thienyl)-2-vinylcyclopropane Cope rearrangement [7].

RESULTS AND DISCUSSION

Working on the synthesis of furyl analogues of acyclic monoterpenes [8], we could observe that the formic acid catalyzed allylic rearrangement of furyl-derived tertiary allylic alcohol **1** did not yield primary alcohols and/or their formates as main components of the product mixture. The main compound composed 60% of the reaction mixture (gc) was isolated by flash chromatography in a yield of 45%. Its ^{1}H and ^{13}C NMR analyses revealed the presence of six *sp*^{2} carbon atoms in the molecule indicating thereby a bicyclic structure of **2** (Scheme 1).

The double bond position in the seven-membered ring was unambiguously confirmed by heteronuclear multiple bond correlation (HMBC) experiment. Heteronuclear long–range correlations ($^2J_{C—H}$ and $^3J_{C—H}$) between ^{13}C-3a (117.37 ppm) and protons 3, 4, 5, 8, and between ^{13}C-8a (149.19 ppm) and protons 3, 4, 7, 8 were used to distinguish correctly between structure **2** and presumable structure of its 5,8-dihydro-isomer that would have very similar one-dimensional ^{1}H and ^{13}C NMR spectra. Table 1 includes complete ^{1}H and ^{13}C assignments of compound **2**.

The second major product (ca. 35% of a crude material) was an E/Z-mixture (5:1) of formate **3**, the structure of which was proved by MS and NMR. No substrate alcohol was detectable in the gc trace of the crude reaction product. This reflects the ease of tertiary allylic carbocation formation from the alcohol. So, the reaction in the presence of formic acid likely proceeds through a cation and the formation of the bicyclic compound can be clarify by the participation of the allylic carbocation in a two-pathway mechanism (Scheme 2).

Although, in general the 2-positions at furan ring are more reactive than the 3-ones, the first intramolecular electrophilic attack on C-3 carbon atom seems to come into consideration (Path A) assuming the charge distribution as the kinetic criterion. Similarly, an intramolecular carbocationic attack on C-3 position in a 2,5-disubstituted furan moiety of 2-furyl benzo[b]furan derivatives leading

Scheme 1. Transformation of furyl-derived tertiary allylic alcohol **1** to 2,6-dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (**2**) and formate **3**.
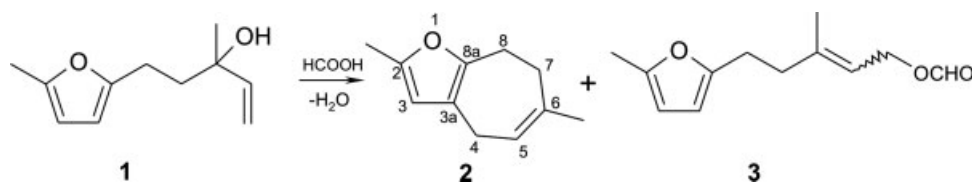
to benzofuro-oxaazulene derivatives had been reported by Russian team [9]. Worth mentioning is that the gas-phase alkylation of 2-methylfuran occurs preferentially at β-position with high charge densities [10]. In our work, the charge distribution has been determined by theory calculations at B3LYP/6-31G(d) (Gaussian 03W ver. 6.1) for allylic carbocation. The charge densities are −0.18 and −0.19 for C3 and C4, respectively, and −0.46 for the oxygen. However, the rearrangement of 5/6 spiro-intermediate to 7,8-dihydro-4*H*-cyclohepta[*b*]furan skeleton is also a considerable reaction path (Path B).

Based on these observations, an attempt to apply the method for the preparation of some other 7,8-dihydro-4*H*-cyclohepta[*b*]furan and 7,8-dihydro-4*H*-cyclohepta[*b*]thiophene derivatives was made (Scheme 3).

However, under similar reaction conditions, the yield of the isolated compounds not containing methyl substituent in the aromatic ring (**5a, 5b**) was much poorer (13%). Presumably, it is a consequence of competitive intermolecular reactions which resulted in formation of much polymeric material. Alcohols **4a** and **4b** reacted rapidly and the process was difficult to control under changing conditions studied (e.g., dilution, temperature 0°C).

It should be pointed out that the substrate alcohols are easily obtainable from the corresponding furyl and thienyl butanones and their acid catalyzed cyclization can also be of some value for the access to furan and thiophene derivatives with seven-membered ring. To the best of our knowledge, there are no reports on the direct use of tertiary allylic alcohol derivatives for annulation of any hetero- or carbo-cycles.

EXPERIMENTAL

The courses of all reactions, composition products and their purity were checked by means of thin layer chromatography (TLC) and capillary gas chromatography (gc). A THF 1*M* solution of vinyl magnesium bromide was purchased from Aldrich®. The final products were isolated by flash chromatography (silica gel:hexane/ethyl acetate in ratio 100:2.5). gc-ms (mass spectra) were obtained with a Carlo Erba gc coupled to MD 800 Fisons Instruments at 70 eV. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.90 MHz) were recorded in CDCl$_3$ on a Bruker instrument.

2,6-Dimethyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (2). 1 g (5.5 mmol) of allylic alcohol **1** [6] in hexane (5 mL) was added dropwise to a stirred mixture of hexane (20 mL) and concentrated formic acid (20 mL) at room temperature. The

stirring was continued for another 3 h and then 10 cm^3 of water was added. The crude product was extracted with hexane (2 × 20 mL), washed neutral with water and dried over anhydrous sodium sulphate. Furan derivative **2** was isolated by flash chromatography in a yield of 405 mg (45%). Anal. Calcd for C$_{11}$H$_{14}$O: C, 81.44; H, 8.70. Found: C, 81.19; H, 8.68.

^{1}H NMR, ^{13}C NMR data: see Table 1. ms: *m/z* 162 (M$^+$, 100), 147 (90), 129 (40), 119 (85), 105 (50), 91 (50), 79 (20), 77 (25), 65 (10), 43 (30).

Formic acid 3-methyl-5-(5-methyl-furan-2-yl)-pent-2-enyl ester (3). E-isomer, ^{1}H NMR: δ 8.06 (s, 1H), 5.84 (m, 2H), 5.40 (t, *J* = 7.5 Hz, 1H), 4.69 (d, *J* = 7.5 Hz, 2H), 2.69 (m, 2H), 2.35 (m, 2H), 2.24 (s, 3H), 1.74 (s, 3H). ^{13}C NMR: δ 160.89 (d), 153.37 (s), 150.21 (s), 142.03 (s), 118.27 (d), 105.72 (d), 105.46 (d), 60.50 (t), 37.82 (t), 26.41 (t), 16.29 (q), 13. 37 (q). ms: *m/z* 208 (M$^+$, 7), 162 (3), 96 (6), 95 (100), 94 (3), 67 (3), 65 (2), 53 (2), 43 (6), 41 (4). Z-isomer, ^{1}H NMR: δ 8.03 (s, 1H), 5.84 (m, 2H), 5.39 (t, *J* = 7.5 Hz, 1H), 4.56 (t, *J* = 7.5 Hz, 2H), 2.68 (m, 2H), 2.37 (m, 2H), 2.24 (s, 3H), 1.77 (s, 3H). ^{13}C NMR: δ 160.89 (d), 152.91 (s), 150.43 (s), 141.79 (s), 119.37 (d), 105.88 (d), 105.78 (d), 60.20 (t), 30.75 (t), 26.43 (t), 23.12 (q), 13.37 (q). ms: *m/z* 208 (M$^+$, 7), 162 (3), 96 (6), 95 (100), 94 (3), 67 (3), 65 (2), 53 (2), 43 (6), 41 (4).

6-Methyl-7,8-dihydro-4*H*-cyclohepta[*b*]furan (5a). To a stirred mixture of hexane (40 mL) and concentrated formic acid (10 mL) 1 g (6 mmol) of allylic alcohol **4a** [5] was dropped in hexane (5 mL) at room temperature. The stirring was continued for 20 min and then 10 mL of water was added. The crude product was extracted with hexane (2 × 20 mL), washed neutral with water, and dried over anhydrous sodium sulphate. Furan derivative **5a** was isolated by flash chromatography in a yield of 117 mg (13%). Anal. Calcd for C$_{10}$H$_{12}$O: C, 81.04; H, 8.16. Found: C, 80.93; H, 12.11.

^{1}H NMR: δ 7.15 (d, *J* = 1.68 Hz, 1H), 6.10 (d, *J* = 1.75 Hz, 1H)), 5.74 (tq, *J* = 5.92, 1.52 Hz, 1H), 3,05 (d, *J* = 4.8 Hz, 2H), 2.73 (m, 2H), 2.36–2.41 (m, 2H), 1.81 ppm (d, *J* = 1 Hz, 3H).

Table 1
^{1}H- and ^{13}C-NMR data of **2** (Bruker 700 MHz, 176 MHz, CDCl$_3$).

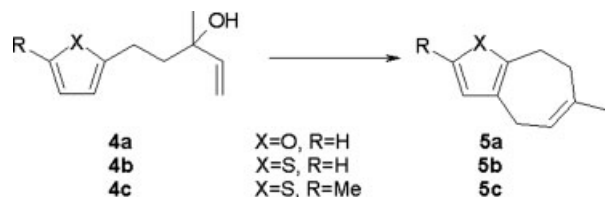|	700 MHz (ppm) ^{1}H	176 MHz (ppm) ^{13}C
2	–	147.99
3	5.69 (s)	108.01
3a	–	117.37
4	3.00 (d, *J* = 5.2 Hz)	23.59
5	5.73 (td, *J* = 5.9, 1.3 Hz)	124.57
6	–	138.52
7	2.38 (m)	29.72
8	2.69 (m)	24.83
8a	–	149.19
2-Me	2.20 (s)	13.22
6-Me	1.81 (s)	25.03

Scheme 2. Plausible mechanisms of 2,6-dimethyl-7,8-dihydro-4H-cyclohepta[b]furan (**2**) formation from **1**.
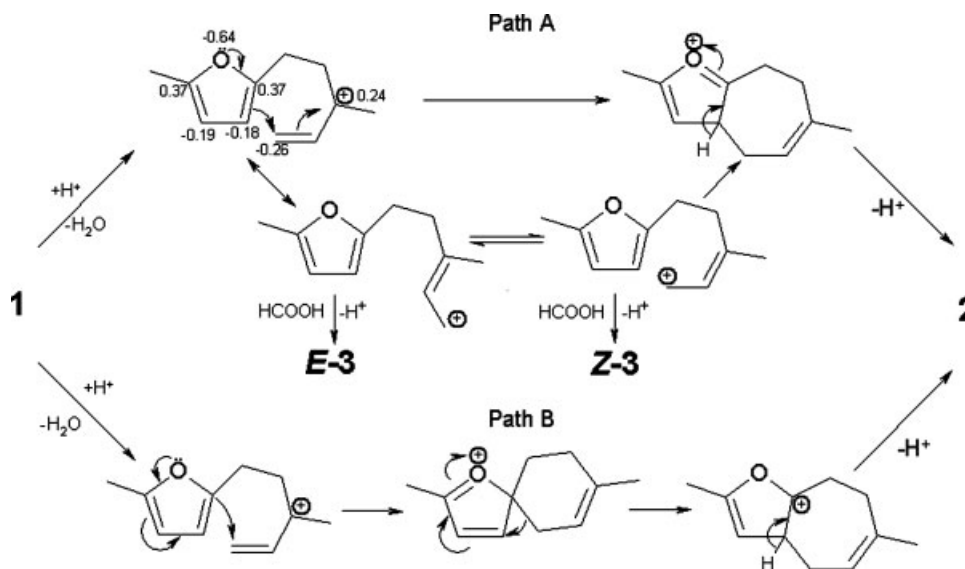
^{13}C NMR: δ 151.19 (s), 138.63 (d), 138.62 (s), 125.47 (d), 116.62 (s), 112.06 (d), 29.56 (t), 24.48 (t), 23.87 (q), 23.54 (t). ms: *m/z* 148 (M$^+$, 100), 133 (60), 119 (25), 115 (30), 105 (65), 91 (45), 77 (15), 65 (15), 55 (20), 39 (20).

3-Methyl-5-thiophen-2-yl-pent-1-en-3-ol (4b). To a 1*M* solution of vinyl magnesium bromide in THF (33 mL, 0.035 mol), 5 g (0.032 mol) of 4-thiophen-2-yl-butan-2-one [11] was added dropwise for 20 min. The reagents were stirred for 2 h at room temperature and thereafter the mixture was poured into ice-water (6 g), and a 30% solution of ammonium chloride (30 mL) was added. The crude product was extracted with toluene (3× 50 mL), washed neutral with water and dried over anhydrous sodium sulfate. Toluene was vacuum removed and the residue was distilled to give alcohol **4b** in 74% yield; b.p., 92°C/0.4 mmHg. ^{1}H NMR: δ 7.10 (m, 1H), 6.90 (m, 1H), 6.78 (m, 1H), 5.93 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.26 (dd, *J* = 10.7, 0.7 Hz, 1H), 5.10 (dd, *J* = 10.7, 0.7 Hz, 1H), 2.86 (m, 2H), 1.93 (m, 2H), 1.33 ppm (s, 3H). ^{13}C NMR: δ 145.07 (s), 144.45 (d), 126.48 (d), 124.13 (d), 123.87 (d), 112.21 (t), 73.00 (s), 43.92 (t), 28.01 (q), 24.47 (t). ms: *m/z* 182 (M$^+$, 21), 164 (48), 149 (72), 135 (18), 115 (17), 111 (23), 97 (100), 80 (15), 71 (65), 43 (20).

6-Methyl-7,8-dihydro-4H-cyclohepta[b]thiophene (5b). The compound was prepared from alcohol **4b** in the same manner

like furan derivative **5a** (yield 13%). Anal. Calcd for C$_{10}$H$_{12}$S: C, 73.11; H, 7.37. Found: C, 73.41; H, 7.37. ^{1}H NMR: δ 6.92 (d, *J* = 5 Hz, 1H), 6.70 (d, *J* = 5 Hz, 1H), 5.62 (t, *J* = 5 Hz, 1H), 3.34 (d, *J* = 5 Hz, 2H), 2.96 (m, 2H), 2.37 (m, 2H), 1.75 ppm (s, 3H). ^{13}C NMR: δ 137.73 (s), 137.52 (s), 136.36 (s), 129.52 (d), 121.85 (d), 119.94 (d), 31.91 (t), 28.01 (t), 25.87 (q), 25.76 (t). ms: *m/z* 164 (M$^+$, 100), 149 (85), 135 (55), 115 (50), 97 (10), 91 (22), 77 (15), 69 (10), 65 (8), 45 (7).

3-Methyl-5-(5-methylthiophen-2-yl)-pent-1-en-3-ol (4c). The alcohol was prepared from 4-(5-methylthiophen-2-yl)-butan-2-one (6) in the same fashion like **4b** in a yield of 75%; b.p., 97°C/1.5 mmHg. ^{1}H NMR: δ 6.54 (m, 2H), 5.93 (dd, *J* = 10.75, 17.25 Hz, 1H), 5.21 (d, *J* = 17.25 Hz, 1H), 5.12 (d, *J* = 10.75 Hz, 1H), 2.81 (m, 2H), 2.42 (s, 3H), 1.88 (br.m, 2H), 1.33 ppm (s, 3H). ^{13}C NMR: δ 144.50 (d), 142.98 (s), 137.22 (s), 124.57 (d), 123.81 (d), 112.10 (t), 73.01 (s), 43.88 (t), 27.25 (q), 24.20 (t), 15.18 (q). ms: *m/z* 196 (M$^+$, 22), 178 (30), 163 (45), 149 (17), 129 (18), 125 (23), 111 (100), 97 (15), 80 (20), 71 (27).

2,6-Dimethyl-7,8-dihydro-4H-cyclohepta[b]thiophene (5c). Starting from alcohol **4c** the thiophene derivative **5c** was obtained by the same procedure as given earlier for compound **2** (yield 46%). Anal. Calcd for C$_{11}$H$_{14}$S: C, 74.10; H, 7.91. Found: C, 74.48; H, 7.89. ^{1}H NMR: δ 6.36 (s, 1H), 5.60 (t, *J* = 5.1 Hz, 1H), 3.24 (d, *J* = 5 Hz, 2H), 2.86 (t, *J* = 6.25 Hz, 2H), 2.27–2.44 (m, s; 5H), 1.74 ppm (s, 3H). ^{13}C NMR: δ 137.67 (s), 135.81 (s), 134.94 (s), 133.93 (s), 127.74 (d), 121.99 (d), 31.91 (t), 27.93 (t), 25.93 (t), 25.67 (q), 14.76 (q). ms: *m/z* 178 (M$^+$, 100), 163 (95), 148 (35), 135 (20), 129 (40), 115 (15), 105 (12), 91 (20), 77 (18), 59 (15).

REFERENCES AND NOTES

[1] Davies, H. M. L.; Hedley, S. J. Chem Soc Rev 2007, 36, 1109.

Scheme 3. Transformation of allylic alcohols into 7,8-dihydro-4H-cyclohepta[b]furan and 7,8-dihydro-4H-cyclohepta[b]thiophene derivatives.

4a	X=O, R=H
4b	X=S, R=H
4c	X=S, R=Me

5a
5b
5c

[2]   Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Barszcz, T.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. J Med Chem 2008, 51, 6927.

[3]   Herz, W.; Juo, R. R. J Org Chem 1985, 50, 618.

[4]   Chen, W.; Zhao, X.; Lu, L.; Cohen, T. Org Lett 2006, 8, 2087.

[5]   Imagawa, H.; Kurisaki, T.; Nishizawa, M. Org Lett 2004, 6, 3679.

[6]   Frejd, T.; Karlsson, J. O.; Gronowitz, S. J Org Chem 1981, 46, 3132.

[7]   Maas, G.; Hummel, Ch. Chem Ber 1980, 113, 3679.

[8]   Kula, J.; Sikora, M.; Hammad, D.; Bonikowski, R.; Balawejder, M.; Nowicki, J. Flavour Fragrance J 2005, 20, 487.

[9]   Butin, A. V.; Gutnov, A. V.; Abaev, V. T. Chem Heterocycl Compd 1998, 34, 762.

[10]   Robin, D.; Hoppilliard, Y.; Audier H. Org Mass Spectrom 1988, 23, 370.

[11]   Dujardin, G.; Poirier, J. M. Bull Soc Chim Fr 1994, 131, 900.