Acylations of 2-Isopropenyl-2,3-dihydrobenzofurans

Seiji YAMAGUCHI, Aiko MIYATA, Mariko UENO, Takayuki HASE, Kenichi YAMAMOTO, and Yoshiyuki KAWASE*

Department of Chemistry, Faculty of Science, Toyama University, Gofuku, Toyama 930

(Received July 11, 1983)

Synopsis. Methoxy-substituted 2-isopropenyl-2,3-dihydrobenzofurans were prepared from methoxy-substituted phenols and 1,4-dibromo-2-methyl-2-butene in one-step reactions. Their acylations with acetic acid-trifluoroacetic anhydride or *N*-methylformanilide-phosphoryl chloride were studied.

In our previous paper, we reported a new preparative method of 2-isopropenyl-2,3-dihydrobenzofuran (**1**) from phenol and 1,4-dibromo-2-methyl-2-butene and its acylations with acetic acid-trifluoroacetic anhydride (acetylation) or with *N*-methylformanilide-phosphoryl chloride (formylation).[1] Some naturally occurring hydroxy or methoxy-substituted 2-isopropenyl-2,3-dihydrobenzofuran derivatives having an acetyl group in 5 or 7 position have been reported.[2-8] Now, we report the preparation of methoxy-substituted 2-isopropenyl-2,3-dihydrobenzofurans and their acylations.

By the method used before, 2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**3**) was obtained from *p*-methoxyphenol and 1,4-dibromo-2-methyl-2-butene. From *m*-methoxyphenol, a mixture of 4-methoxy **2** and 6-methoxy derivative **4** was obtained. But 7-methoxy derivative **5** was not obtained by this method, it was prepared by dehydration of 2-(1-hydroxy-1-methylethyl)-7-methoxy-2,3-dihydrobenzofuran with phenyl isocyanate.

Acetylations were run with acetic acid-trifluoroacetic anhydride at room temp for 3 h and formylations were run with *N*-methylformanilide-phosphoryl chloride at 90 °C for 1 h. Thier yields are summarized in Table 1. Phosphoryl chloride which used in formylations is a weaker acid than trifluoroacetic acid which derived from trifluoroacetic anhydride in the acetylations. Therefore, formylations can run at higher temp than acetylations, and the former showed better yields than the latter. In all 2-isopropenyl-2,3-dihydrobenzofurans, the position 5 was the most reactive. In 5-methoxy derivative **3**, formylation at 90 °C afforded 6-formyl compound **9b**, but acetylation at room temp could not afford any acetylated compound.

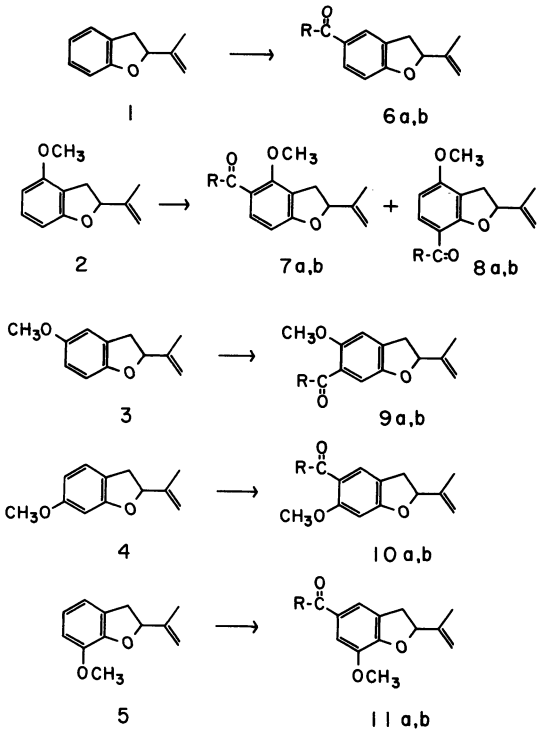
TABLE 1. ACYLATIONS OF 2-ISOPROPENYL-2,3-DIHYDROBENZOFURANS

2-Isopropenyl-2,3-dihydrobenzofuran	Acylated position	Yield/%	
		Acetylation[a]	Formylation[b]
1	5	45.9[c]	20.9[c]
2	5	14.5[d]	27.9[d]
	7	21.7[d]	55.7[d]
3	6	0	24.8
4	5	32.0	46.7
5	5	12.8	64.1

a) With acetic acid-trifluoroacetic anhydride at room temp for 6 h (**1**) or 3 h (**2**—**5**). b) With *N*-methylformanilide-phosphoryl chloride at 90 °C for 1 h. c) Reported in our previous paper.[1] d) Calcd by the methoxy signal ratio in the ^{1}H-NMR spectra.

The structure of the acyl compounds were determined by the coupling constants among aromatic hydrogens in their ^{1}H-NMR spectra. The yields of **7a, b** and **8a, b** were calculated by methoxy signal ratio in their ^{1}H-NMR spectra. By addition of europium tris-dipivaloylmethanate, the methoxy signal of 5-acyl compound **7a, b** shifted to a low field than that of 7-acyl compound **8a, b**, perhaps because they have different chelating structures.

The spectral data of **11a** agreed with the data of the natural compound reported by Bohlmann *et al.*[3]



Experimental

The boiling points and melting points were uncorrected (in boiling points: 1 mmHg=133.322 Pa); the IR spectra were measured on a Hitachi EPI-S2 spectrophotometer, and the ^{1}H-NMR spectra, on a JEOL JNM-MH-60 spectrometer.

Preparation of Methoxy-substituted Dihydrobenzofurans (2—8). By the method described in our previous paper,[1] **3** was obtained from *p*-methoxyphenol and a mixture of **2** and **4** was obtained from *m*-methoxyphenol. The mixture was separated on silica gel with cyclohexane. **2**. Yield: 2.4%; ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 2.8 (1H, dd, J=16+9 Hz), 3.2 (1H, dd, J=16+9 Hz), 3.8 (3H,s), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.1 (1H, t, J=9 Hz), 6.2 (1H, d, J=9 Hz), 6.3 (1H, d, J=9 Hz), 6.9 (1H, t, J=9 Hz); Found: C, 75.96; H, 7.19%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. **3**. Yield: 59.3%; bp 110—117 °C (2 mmHg); ^{1}H-NMR (CCl_4): δ=1.8

(3H, s), 3.0 (1H, dd, J=16+9 Hz), 3.3 (1H, dd, J=16+9 Hz), 3.8 (3H, s), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.1 (1H, t, J=9 Hz), 6.6— 6.8 (3H,m); Found: C, 75.76; H, 7.69%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. **4**. Yield: 13.8%; ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 2.9 (1H, dd, J=16+9 Hz), 3.2 (1H, dd, J=16+9 Hz), 3.7 (3H, s), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.1 (1H,t,J=9 Hz), 6.2 (1H, d, J=2 Hz), 6.2 (1H, dd, J=9+2 Hz), 6.9 (1H, d, J=9 Hz); Found: C, 75.65; H, 7.33%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

Dehydrative Preparation of 5. By the method similar to that described in our previous paper,[1] 7-methoxy-2,3-dihydrobenzofuran-2-carboxylic acid[9] gave methyl 7-methoxy-2,3-dihydrobenzofuran-2-carboxylate: yield, 86.6%; bp 172—173.5 °C (17 mmHg); IR (neat): 1760 cm^{-1}; ^{1}H-NMR (CCl_4): δ=3.3 (1H, dd, J=16+8 Hz), 3.4 (1H, dd, J=16+9 Hz), 3.7 (3H, s), 3.8 (3H, s), 5.1 (1H, dd, J=9+8 Hz), 6.6 (3H, s); Found: C, 63.50; H, 5.91%. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%. The product was converted to 2-(1-hydroxy-1-methylethyl)-7-methoxy-2,3-dihydrobenzofuran: yield, 53.0%; IR (neat) 3400 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.2 (3H, s), 1.3 (3H,s), 2.2 (1H, broad s), 3.1 (1H, dd, J=16+9 Hz), 3.2(1H, dd, J=16+8 Hz), 3.8 (3H, s), 4.6 (1H, dd, J=9+8 Hz), 6.7 (3H, s); Found: C, 68.99; H, 7.90%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. A mixture of 2-(1-hydroxy-1-methylethyl)-7-methoxy-2,3-dihydrobenzofuran (1.02 g, 4.90 mmol) and phenyl isocyanate (5.85 g, 4.90 mmol) was refluxed for 10 h.[10] After the reaction, the mixture was distilled. The fraction boiling at 118—136 °C (2 mmHg) (0.679 g, 72.9%) showed two peaks (5:1) in GLC. The mixture was separated into components by silica gel chromatography. The fractions eluted with 1:4 benzene–hexane gave 2-isopropyl-7-methoxybenzofuran (101 mg, 10.8%); ^{1}H-NMR (CCl_4): δ=1.4 (6H, d, J=7 Hz), 3.1 (1H, m, J=7 Hz), 3.9 (3H, s), 6.2 (1H, s), 6.6 (1H, t, J=5 Hz), 6.9 (2H, d, J=5 Hz); Found: C, 75.47;H, 7.14%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. The fractions eluted with 2:3 benzene–hexane gave 2-isopropenyl-7-methoxy-2,3-dihydrobenzofuran (**5**) (258 mg, 27.7%); ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 3.0 (1H, dd, J=15+9 Hz), 3.2 (1H, dd, J=15+9 Hz), 3.8 (3H, s), 4.8 (1H, broad s), 5.1 (1H, broad s), 5.1 (1H, t, J=9 Hz), 6.6 (3H, s); Found: C, 75.74; H, 7.12%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

Acylations of Methoxy-substituted Dihydrobenzofurans 2—5. By a method similar to that described in our previous paper,[1] dihydrobenzofuran **2—5** was acetylated with acetic acid and trifluoroacetic anhydride for 3 h at room temp, and was formylated with *N*-methylformanilide and phosphoryl chloride for 1 h at 90 °C. In case of the acylations of **2**, mixtures were obtained; the spectrum of the acetylated compounds showed two methoxy signals at 3.85 (**8a**) and 3.88 ppm (**7a**) (relative intensity 3:2), which shifted to 3.87 and 4.03 ppm by the addition of europium trisdipivaloylmethanate, and the spectrum of the formylated compounds showed signals at 3.84 (**8b**) and 3.93 ppm(**7b**) (relative intensity 2:1), which shifted to 3.90 and 4.06 ppm by similar treatment. Their yields were calculated by the methoxy signal ratio in their ^{1}H-NMR spectra.

The yields of acyl dihydrobenzofurans **7a**, **b**—**11a**,**b** are summarized in Table 1. And their physical data are listed below.

Mixture of **7a** and **8a**; bp 225—240 °C (14.5 mmHg) (bath temp); IR (neat): 1670 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.8 (s, **7a** and **8a**), 2.45 (s, **7a**), 2.48 (s, **8a**), 3.0 (dd, J=16+10 Hz, **7a** and **8a**), 3.4 (dd, J=16+10 Hz, **7a** and **8a**), 3.85 (s, **8a**) 3.88 (s, **7a**), 4.95 (broad s, **7a** and **8a**), 5.1 (broad s, **7a** and **8a**), 5.3 (t, J=10 Hz, **7a** and **8a**), 6.43 (d, J=10 Hz, **8a**), 6.55 (d, J=10 Hz, **7a**), 7.65 (d, J=10 Hz, **7a**), 7.75 (d, J=10 Hz, **8a**); Found: C, 72.22; H, 6.99%. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%. **10a**; mp 111— 112 °C (recrystallized from cyclohexane); IR (KBr disk): 1650 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 2.6 (3H, s), 3.0 (1H, dd, J=16+9 Hz), 3.2 (1H, dd, J=16+9 Hz), 3.8 (3H, s), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.2 (1H, t, J=9 Hz), 6.4 (1H, s), 7.7 (1H, s); Found: C, 72.23; H, 7.08%. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%. **11a**: bp 230—255 °C (15 mmHg); IR (neat): 1670 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 2.4 (3H, s), 3.0 (1H, dd, J=16+9 Hz), 3.3 (1H, dd, J=16+9 Hz), 3.9 (3H, s), 4.9 (1H, broad s), 5.1(1H, broad s), 5.2 (1H, t, J=9 Hz), 7.3 (2H, s); Found: C, 72.23; H, 7.08%. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%. Mixture of **7b** and **8b**; bp 220—265 °C (14.5 mmHg); IR (neat): 1635 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.8 (s, **7b** and **8b**), 3.0 (dd, J=16+8 Hz, **7b** and **8b**), 3.3 (dd, J= 16+8 Hz, **7b** and **8b**), 3.84 (s, **8b**), 3.93 (s, **7b**), 4.9 (s, **7b** and **8b**), 6.39 (d, J=9 Hz, **8b**), 6.51 (d, J=9 Hz, **7b**), 7.53 (d, J=9 Hz, **8b**), 7.63 (d, J=9 Hz, **7b**), 10.08 (s, **8b**), 10.14 (s,**7b**); Found: C, 71.15; H,6.50%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%. **9b**; mp 64—66 °C (recrystallized from cyclohexane); IR (KBr disk): 1670 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.7 (3H, s), 3.0 (1H, dd, J=16+8 Hz), 3.3 (1H, dd, J=16+8 Hz), 3.7 (3H, s), 4.8 (1H, broad s), 5.0(1H, broad s), 5.1 (1H, t, J=8 Hz), 6.7 (1H, s), 6.9 (1H, s), 10.2 (1H, s); Found: C, 71.62; H, 6.70%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%. **10b**; mp 97—99 °C (recrystallized from cyclohexane); IR (KBr disk): 1680 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.7 (3H, s), 3.0 (1H, dd, J=16+9 Hz), 3.2 (1H, dd, J=16+9 Hz), 3.9 (3H, s), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.2 (1H, t, J=9 Hz), 6.3 (1H, s), 7.5 (1H, s), 10.1 (1H, s); Found: C, 71.32; H, 6.35%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%. **11b**;Benzene eluted oil; IR (neat): 1690 cm^{-1}; ^{1}H-NMR (CCl_4): δ=1.8 (3H, s), 3.1 (1H, dd, J=16+9 Hz), 3.3 (1H, dd, J=16+9 Hz), 3.8 (3H, s), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.2 (1H, t, J=9 Hz), 7.1 (2H, s), 9.7 (1H, s); Found: C, 71.30; H, 6.43%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

References

1) S. Yamaguchi, S. Kondo, K. Shimokawa, O. Inoue, M. Sannomiya, and Y. Kawase, *Bull. Chem. Soc. Jpn.*, **55**, 2500 (1982).

2) W. A. Bonner and J. I. DeGraw, Jr., *Tetrahedron*, **18**, 1295 (1962).

3) F. Bohlmann and M. Grenz, *Chem. Ber.*, **103**, 90 (1970).

4) M. Hirotani, J. O'Reilly, and D. M. X. Donnell, *Tetrahedron Lett.*, **1977**, 651.

5) R. D. Allan, R. L. Correll, and R. J. Wells, *Tetrahedron Lett.*, **1969**, 4673.

6) R. D. Allan, R. J. Wells, and J. K. MacLeod, *Tetrahedron Lett.*, **1970**, 3945.

7) F. Bohlmann, J. Jakupovic, A. Schuster, R. M. King, and H. Robinson, *Phytochemistry*, **21**, 161 (1982).

8) J. I. DeGraw, Jr., D. M. Bowen, and W. A. Bonner, *Tetrahedron*, **19**, 19 (1963).

9) B. Libis and E. Habicht, Ger. Offen., 1927393 (1970); *Chem. Abstr.*, **72**, P43426x (1970).

10) Refluxing for 5 h gave a mixture of 7-methoxy-2-isopropenyl-2,3-dihydrobenzofuran (21.9%) and 7-methoxy-2-isopropylbenzofuran (9.3%); longer refluxing caused an isomerization of the dihydrobenzofuran **5** to the benzofuran.