HETEROCYCLES, Vol. 81, No. 6, 2010, pp. 1459 - 1466. © The Japan Institute of Heterocyclic Chemistry
Received, 15th March, 2010, Accepted, 23rd April, 2010, Published online, 26th April, 2010
DOI: 10.3987/COM-10-11947

CONVENIENT SYNTHESIS OF 1,3-DIHYDROISOBENZOFURANS BY HYDRIODIC ACID-CATALYZED CYCLIZATION OF 2-VINYLBENZYL ALCOHOLS

Kazuhiro Kobayashi,* Kazuaki Shikata, Yuri Fujii, Shuhei Fukamachi, Miyuki Tanmatsu, and Hisatoshi Konishi

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – A new and short process has been developed for the preparation of 1,1,3-tri- and 1,1,3,3-tetra-substituted 1,3-dihydroisobenzofurans (phthalanes) from α-substituted 2-bromostyrenes. The method involves addition of α-substituted 2-lithiostyrenes, generated by the bromine-lithium exchange between α-substituted 2-bromostyrenes and butyllithium, to aliphatic aldehydes or ketones, followed by hydriodic acid catalyzed cyclization of the resulting 2-vinylbenzyl alcohols.

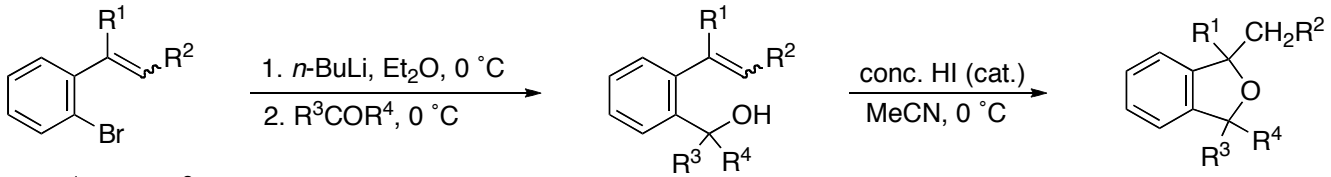
INTRODUCTYION

We previously described a convenient synthesis of 1,1,3-tri- and 1,1,3,3-tetra-substituted 1,3-dihydroisobenzofurans.[1] This synthesis commences with α-substituted 2-bromostyrenes and involves iodocyclization of the corresponding 2-vinylbenzyl alcohols, obtained by successive treatment of α-substituted 2-bromostyrenes with butyllithium and carbonyl compounds, to give 1-iodomethyl-1,3-dihydroisobenzofurans. These iodomethyl derivatives are exposed to the reduction with tributyltin hydride to afford the corresponding 1-methyl derivatives. As part of our investigation to explore the potential of the hydriodic acid mediated cyclization of appropriately *ortho*-substituted styrene derivatives for the synthesis of benzene-fused heterocycles,[2] we found that when 2-vinylbenzyl alcohols (**2**) were treated with a catalytic amount of concentrated hydriodic acid, cyclization took place to afford 1,3-dihydroisobenzofurans (**3**).[3] In this paper we report on the results of our investigation, which have shown that the sequence offers a more convenient and general method for the synthesis of 1,3-dihydroisobenzofurans. A range of previously unknown and potentially important[4] 1,3-dihydroisobenzofurans have been thus synthesized via this process. A few methods for the synthesis

of this class of heterocycles have been reported so far.[5] However, these suffer from limited generality and/or troublesome preparation of the precursors.

RESULTS AND DISCUSSION

The synthetic approach that led to the formation of 1,3-dihydroisobenzofurans (**3**) from 2-bromostyrenes (**1**) is illustrated in Scheme 1. It involves addition of α-substituted 2-lithiostyrenes, generated by the bromine-lithium exchange between α-substituted 2-bromostyrenes (**1**) and butyllithium, to aliphatic aldehydes or ketones according to the conditions reported previously by us[1] to give the corresponding 2-vinylbenzyl alcohols (**2**) in moderate to fair yields. Subsequently, these alcohol derivatives were subjected to treatment with a catalytic amount of concentrated hydriodic acid in acetonitrile at 0 ˚C to give the desired 1,1,3-tri- and 1,1,3,3-tetra-substituted 1,3-dihydroisobenzofurans (**3**) in the yields summarized in Table 1. Protonation at β-position of the styrene moiety of **2** generates a benzyl cation intermediate. Intramolecular attack of the hydroxy-oxygen on this cation center followed by removal of a proton gives rise to **3**. In many cases, trace amounts of the corresponding indene derivatives, which arose from cyclization of the benzyl cation intermediates generated from acid mediated dehydroxylation of 2-vinylbenzyl alcohols (**2**), were detected in the reaction mixtures. When other weaker acids, such as hydrobromic acid and hydrochloric acid, were used, the reactions required extended reaction times or higher reaction temperatures and much more complicated reaction mixtures of products were obtained.



1a R^1 = Me, R^2 = H
1b R^1 = Ph, R^2 = H
1c R^1 = *m*-Tol, R^2 = H
1d R^1 = *m*-Tol, R^2 = Me
1e R^1 = *p*-Tol, R^2 = H
1f R^1 = 4-$MeOC_6H_4$, R^2 = H
1g R^1 = 4-$MeOC_6H_4$, R^2 = Me

Scheme 1

Table 1 indicates that the yields of the products (**3**) are generally moderate to fair. However, it should be noted that 1,1,3-trisubstituted 1,3-dihydroisobenzofurans (**3c**) and (**3d**) were obtained in lower yields compared to those of 1,1,3,3-tetrasubstituted derivatives, as can be seen from entries 3 and 4. The reactions required extended reaction times and resulted in somewhat intractable mixtures of products, though the reason for these results is not clear yet. Similarly, when 2-(β-methylvinyl)benzyl alcohols (**1d**) and (**1g**) were subjected to cyclization under conditions similar to those stated above, the

corresponding 2-ethyl derivatives (**2g**) and (**2k**) were obtained in lower yields (entries 7 and 11, respectively). The β-methyl substituents may make difficulty in cyclization.

Table 1. Preparation of 1,3-Dihydrobenzoisofurans (**3**) from **1**, via **2**.

Entry	**1**	R^3	R^4	**2** (Yield/%)[a]	Time/min	**3** (Yield/%)[a]
1	**1a**	$(CH_2)_5$		**2a** (63)[b]	5	**3a** (62)
2	**1a**	Me	Et	**2b** (54)	5	**3b** (54)
3	**1a**	*t*-Bu	H	**2c** (53)	30	**3c** (36)
4	**1a**	*i*-Pr	H	**2d** (59)	30	**3d** (33)
5	**1b**	$(CH_2)_5$		**2e** (67)[b]	5	**3e** (65)
6	**1c**	$(CH_2)_5$		**2f** (71)	5	**3f** (61)
7	**1d**	$(CH_2)_5$		**2g** (60)	20	**3g** (39)
8	**1e**	$(CH_2)_5$		**2h** (73)	5	**3h** (58)
9	**1f**	$(CH_2)_5$		**2i** (78)	5	**3i** (61)
10	**1f**	Me	Me	**2j** (50)	5	**3j** (52)
11	**1g**	$(CH_2)_5$		**2k** (67)	20	**3k** (43)

[a] Isolated yields. [b] Ref. 1.

In summary, the above-mentioned experiments have revealed that 1,1,3-tri- and 1,1,3,3,-tetra-substituted 1,3-dihydroisobenzofuran derivatives can be conveniently prepared from α-substituted 2-bromostyrenes in two-steps. Although the overall yields for the present addition/cyclization sequence are not so high, it provides an efficient method for the general synthesis of this class of molecules, because the starting materials are readily available and the operations are very simple.

EXPERIMENTAL

The melting point of compound (**3c**) was obtained on a Laboratory Devices MEL-TEMP II melting apparatus and is uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) m were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 1-Bromo-2-(1-methylethenyl)benzene (**1a**),[6] 1-bromo-2-(1-phenylethenyl)benzene (**1b**),[7] (2-bromophenyl)(3-methylphenyl)methanone,[8] 1-bromo-2-[1-(4-methylphenyl)ethenyl]benzene (**1e**),[9] 1-bromo-2-[1-(4-methoxyphenyl)ethenyl]benzene (**1f**),[10] and 1-bromo-2-[1-(4-methoxyphenyl)-prop-1-enyl]benzene (**1g**)[10] were prepared by the appropriate reported methods. All other chemical used in this study were commercially available.

1-Bromo-2-[1-(3-methylphenyl)ethenyl]benzene (1c). This compound was prepared by treating (2-bromophenyl)(3-methylphenyl)methanone[7] with methylenetriphenylphosphorane in THF at 0 ˚C in 83% yield; a colorless oil; R_f 0.48 (hexane); IR (neat) 1601 cm^{-1}; ^{1}H NMR δ 2.32 (s, 3H), 5.24 (s, 1H), 5.82 (d, J = 0.9 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.10 (s, 1H), 7.17–7.22 (m, 2H), 7.30–7.36 (m, 2H), 7.60 (dd, J = 7.8, 1.4 Hz, 1H). Anal. Calcd for $C_{15}H_{13}Br$: C, 65.95; H, 4.80. Found: C, 65.73; H, 5.03.

1-Bromo-2-[1-(3-methylphenyl)prop-1-enyl]benzene (1d). This compound was prepared by treating (2-bromophenyl)(3-methylphenyl)methanone[8] with ethylenetriphenylphosphorane in THF at 0 ˚C in 69% yield; a mixture of stereoisomers (E:Z = ca. 2:8); a pale-yellow oil; R_f 0.51 (hexane); IR (neat) 1603 cm^{-1}; ^{1}H NMR δ 1.61 (d, J = 7.3 Hz, 2.4H), 1.91 (d, J = 6.9 Hz, 0.6H), 2.30 (s, 2.4H), 2.32 (s, 0.6H), 5.82 (q, J = 6.9 Hz, 0.2H), 6.32 (q, J = 7.3 Hz, 0.8H), 6.97–7.05 (m, 3H), 7.09–7.22 (m, 2.4H), 7.26 (d, J = 7.3 Hz, 0.8H), 7.34 (ddd, J = 7.8, 7.3, 1.4 Hz, 0.8H), 7.53 (d, J = 7.8 Hz, 0.2H), 7.65 (d, J = 7.8 Hz, 0.8H). Anal. Calcd for $C_{16}H_{15}Br$: C, 66.91; H, 5.26. Found: C, 66.89; H, 5.31.

2-Vinylbenzyl Alcohol Derivatives (2). These compounds were prepared by treating the 2-lithiostyrene derivatives, generated from 2-bromostyrene derivatives (**1**), with carbonyl compounds according to the procedure described in our earlier paper.[1] See ref. 1 for the physical and spectral data for **2a** and **2e**. Physical and spectral data for new products are as follows.

2-[2-(1-Methylethenyl)phenyl]butan-2-ol (2b): a pale-yellow oil; R_f 0.51 (1:10 THF–hexane); IR (neat) 3564, 3466, 1634 cm^{-1}; ^{1}H NMR δ 0.80 (t, J = 7.3 Hz, 3H), 1.56 (s, 3H), 1.82 (dq, J = 14.7, 7.3 Hz, 1H), 1.95 (dq, J = 14.7, 7.3 Hz, 1H), 2.17 (dd, J = 1.4, 0.9 Hz, 3H), 3.04 (s, 1H), 4.86 (dq, J = 1.4, 0.9 Hz, 1H), 5.18 (quint, J = 1.4 Hz, 1H), 7.00 (dd, J = 7.8, 1.4 Hz, 1H), 7.17 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.21–7.27 (m, 2H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.01; H, 9.68.

2,2-Dimethyl-2-[2-(1-methylethenyl)phenyl]propan-1-ol (2c): a pale-yellow oil; R_f 0.29 (1:10 THF–hexane); IR (neat) 3418, 1639 cm^{-1}; ^{1}H NMR δ 0.93 (s, 9H), 1.73 (d, J = 3.0 Hz, 1H), 2.06 (d, J = 1.4 Hz, 3H), 4.82 (d, J = 3.0 Hz, 1H), 4.88 (s, 1H), 5.21 (quint, J = 1.4 Hz, 1H), 7.09 (dd, J = 7.3, 1.8 Hz, 1H), 7.22 (td, J = 7.3, 1.8 Hz, 1H), 7.26 (td, J = 7.3, 1.8 Hz, 1H), 7.54 (dd, J = 7.3, 1.8 Hz, 1H). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.25; H, 9.97.

2-Methyl-1-[2-(1-methylethenyl)phenyl]propan-1-ol (2d): a pale-yellow oil; R_f 0.38 (1:10 THF–hexane); IR (neat) 3402, 1639 cm^{-1}; ^{1}H NMR δ 0.72 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1,68 (d, J = 3.1 Hz, 1H), 1.99–2.04 (m, 1H), 2.06 (s, 3H), 4.54 (dd, J = 7.8, 3.1 Hz, 1H), 4.84 (d, J = 0.9 Hz, 1H), 5.22 (d, J = 0.9 Hz, 1H), 7.11 (dd, J = 7.8, 1.4 Hz, 1H), 7.23 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.30 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.91; H, 9.66.

1-{2-[1-(3-Methylphenyl)ethenyl]phenyl}cyclohexanol (2f): a pale-yellow oil; R_f 0.29 (1:20 THF–hexane); IR (neat) 3566, 3462, 1601 cm^{-1}; ^{1}H NMR δ 1.16–1.19 (m, 1H), 1.47–1.88 (m, 9H), 2.02

(br s, 1H), 2.31 (s, 3H), 5.17 (s, 1H), 5.82 (s, 1H), 7.06–7.09 (m, 3H), 7.15–7.19 (m, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.34 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H). Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 86.17; H, 8.27.

1-{2-[1-(3-Methylphenyl)prop-1-enyl]phenyl}cyclohexanol (2g): a mixture of stereoisomers (*E*:*Z* = ca. 3:7); a pale-yellow oil; R_f 0.50 (1:10 THF–hexane); IR (neat) 3564, 3468, 1601 cm^{-1}; ^1H NMR δ 1.11–1.31 (m, 1H), 1.43–1.88 (m, 11.1H), 1.93 (d, *J* = 6.9 Hz, 0.9 H), 2.01 (s, 0.7H), 2.29 (s, 2.1H), 2.31 (s, 0.9H), 2.49 (s, 0.3H), 5.78 (q, *J* = 6.9 Hz, 0.3H), 6.27 (q, *J* = 6.9 Hz, 0.7H), 6.97–7.30 (m, 6.3H), 7.34 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 0.7H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 0.3H), 7.54 (dd, *J* = 7.8, 1.4 Hz, 0.7H). Anal. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55. Found: C, 86.14; H, 8.78.

1-{2-[1-(4-Methylphenyl)ethenyl]phenyl}cyclohexanol (2h): a pale-yellow oil; R_f 0.33 (1:20 THF–hexane); IR (neat) 3564, 3466, 1609 cm^{-1}; ^1H NMR δ 1.12–1.21 (m, 1H), 1.46–1.88 (m, 9H), 2.07 (s, 1H), 2.32 (s, 3H), 5.14 (s, 1H), 5.81 (s, 1H), 7.06 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H). Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 86.08; H, 8.26.

1-{2-[1-(4-Methoxyphenyl)ethenyl]phenyl}cyclohexanol (2i): a pale-yellow oil; R_f 0.30 (1:15 THF–hexane); IR (neat) 3564, 3477, 1607 cm^{-1}; ^1H NMR δ 1.15–1.20 (m, 1H), 1.47–1.86 (m, 9H), 2.17 (s, 1H), 3.79 (s, 3H), 5.09 (s, 1H), 5.75 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.33 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.64; H, 8.13.

2-{2-[1-(4-Methoxyphenyl)ethenyl]phenyl}propan-2-ol (2j): a pale-yellow oil; R_f 0.18 (1:15 THF–hexane); IR (neat) 3557, 3472, 1607 cm^{-1}; ^1H NMR δ 1.53 (s, 6H), 2.44 (s, 1H), 3.79 (s, 3H), 5.13 (s, 1H), 5.78 (d, *J* = 0.9 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.23–7.28 (m, 3H), 7.33 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.39; H, 7.41.

1-{2-[1-(4-Methoxyphenyl)prop-1-enyl]phenyl}cyclohexanol (2k): a mixture of stereoisomers (*E*:*Z* = ca. 4:6); a pale-yellow oil; R_f 0.50 (1:5 THF–hexane); IR (neat) 3420, 1607 cm^{-1}; ^1H NMR δ 1.13–1.19 (m, 1H), 1.28–1.88 (m, 10.8H), 1.94 (d, *J* = 7.3 Hz, 1.2H), 2.11 (s, 0.6H), 2.54 (s, 0.4H), 3.77 (s, 1.8H), 3.79 (s, 1.2H), 5.73 (q, *J* = 7.3 Hz, 0.4H), 6.18 (q, *J* = 6.9 Hz, 0.6H), 6.79 (d, *J* = 9.2 Hz, 1.2H), 6.84 (d, *J* = 8.7 Hz, 0.8H), 6.98 (dd, *J* = 7.8, 1.4 Hz, 0.6H), 7.09 (dd, *J* = 7.8, 1.4 Hz, 0.4H), 7.15 (d, *J* = 9.2 Hz, 1.2H), 7.17–7.20 (m, 1.2H), 7.24–7.29 (m, 1H), 7.33 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 0.6H), 7.42 (dd, *J* = 7.8 1.4 Hz, 0.4H), 7.53 (dd, *J* = 7.8, 1.4 Hz, 0.6H). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.95; H, 8.14.

Typical Procedure for the Preparation of 1,3-Dihydroisobenzofuran (Phthalane) (3). 3',3'-Dimethyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3a).[1,5a] To a stirred solution of 1-[2-(1-methylethenyl)phenyl]cyclohexanol (**2a**) (0.29 g, 1.3 mmol) in MeCN (9 mL) at 0 °C was added a drop

of concentrated HI. After 5 min, saturated aqueous $NaHCO_3$ (10 mL) was added and the MeCN was evaporated. The organic materials were extracted with Et_2O three times (10 mL each) and the combined extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel (1:10 Et_2O–hexane) to afford **3a** (0.18 g, 62%). The physical and spectral data for this product were identical to those reported previously.[1,5a]

1-Ethyl-1,3,3-trimethyl-1,3-dihydroisobenzofuran (3b): a pale-yellow oil; R_f 0.56 (1:10 Et_2O–hexane); IR (neat) 2972, 1450, 1101, 993, 968, 754 cm^{-1}; ^1H NMR δ 0.80 (t, J = 7.3 Hz, 3H), 1.48 (s, 3H), 1.52 (s, 6H), 1.74–1.88 (m, 2H), 7.04 (dd, J = 8.7, 2.3 Hz, 1H), 7.09 (dd, J = 8.2, 1.8 Hz, 1H), 7.25–7.28 (m, 2H); ^{13}C NMR δ 8.82, 29.50, 29.82, 31.32, 34.91, 83.97, 87.00, 120.64, 120.93, 127.34, 127.40, 144.62, 146.78; MS *m/z* 190 (M^+, 14), 175 (100). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.95; H, 9.78.

3-(1,1-Dimethylethyl)-1,1-dimethylisobenzofuran (3c): a pale-yellow solid; mp 103–106 °C (hexane–Et_2O); IR (KBr) 2963, 1477, 1159, 1040, 1014, 758 cm^{-1}; ^1H NMR δ 0.99 (s, 9H), 1.41 (s, 3H), 1.56 (s, 3H), 4.91 (s, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.21 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H); MS *m*/z 203 [$(M–1)^+$, 36], 57 (100). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.15; H, 10.15.

3-(1-Methylethyl)-1,1-dimethylisobenzofuran (3d): a pale-yellow oil; R_f 0.56 (1:10 Et_2O–hexane); IR (neat) 2968, 1456, 1157, 1009, 758 cm^{-1}; ^1H NMR δ 0.84 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.45 (s, 3H), 1.54 (s, 3H), 2.01–2.10 (m, 1H), 5.10 (d, J = 3.7 Hz, 1H), 7.09 (dd, J = 8.2, 1.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.23–7.28 (m, 2H); MS *m*/z 189 [$(M–1)^+$, 100]. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.81; H, 10.51.

3'-Methyl-3'-phenyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3e).[1,5a] The physical and spectral data for this product were identical to those reported previously.[1,5a]

3'-Methyl-3'-(3-methylphenyl)-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3f): a pale-yellow oil; R_f 0.26 (hexane); IR (neat) 2930, 1605, 1447, 1172, 1036, 968, 752 cm^{-1}; ^1H NMR δ 1.33–1.41 (m, 1H), 1.56–1.93 (m including s at 1.83, 12H), 2.33 (s, 3H), 7.01 (d, J = 7.3 Hz, 1H), 7.11 (dd, J = 7.8, 1.4 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.25–7.27 (m, 3H), 7.35 (d, J = 7.8 Hz, 1H), 7.39 (s, 1H); MS *m*/z 292 (M^+, 52), 277 (100). Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 86.00; H, 8.30.

3'-Ethyl-3'-(3-methylphenyl)-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3g): a pale-yellow oil; R_f 0.52 (1:15 THF–hexane); IR (neat) 2932, 1605, 1446, 1144, 1040, 982, 752 cm^{-1}; ^1H NMR δ 0.80 (t, J = 7.3 Hz, 3H), 1.32–1.41 (m, 1H), 1.48–1.55 (m, 2H), 1.64–2.01 (m, 8H), 2.16 (dq, J = 14.7, 7.3 Hz, 1H), 2.33 (s, 3H), 7.00 (d, J = 7.3 Hz, 1H), 7.07 (dd, J = 7.8, 0.9 Hz, 1H), 7.18 (dd, J = 7.8, 7.3 Hz, 1H), 7.25 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.28 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.35 (dd, J = 7.8, 1.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.43 (s, 1H); MS *m*/z 306 (M^+, 100). Anal. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55. Found: C, 85.96; H, 8.57.

3'-Methyl-3'-(4-methylphenyl)-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3h): a pale-yellow oil; R_f 0.54 (1:15 THF–hexane); IR (neat) 2930, 1607, 1446, 1184, 1035, 968, 813, 752 cm^{-1}; ^1H NMR δ 1.32–1.40 (m, 1H), 1.54–1.92 (m including s at 1.83, 12H), 2.30 (s, 3H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.22–7.26 (m, 4H), 7.44 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR δ 20.95, 22.41, 22.44, 25.42, 31.52, 38.09, 39.51, 85.77, 86.77, 120.91, 122.18, 125.18, 127.36, 127.49, 128.69, 136.13, 144.82, 145.47, 146.29; MS *m*/z 292 (M^+, 100). Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 86.26; H, 8.36.

3'-(4-Methoxyphenyl)-3'-methyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3i): a pale-yellow oil; R_f 0.53 (1:15 THF–hexane); IR (neat) 2932, 1611, 1446, 1176, 1036, 966, 754 cm^{-1}; ^1H NMR δ 1.32–1.39 (m, 1H), 1.58–1.91 (m including s at 1.83, 12H), 3.77 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.19 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.24–7.27 (m, 2H), 7.45 (d, *J* = 8.7 Hz, 2H); MS *m*/z 308 (M^+, 19), 293 (100). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.70; H, 7.80.

1-(4-Methoxyphenyl)-1,3,3-trimethyl-1,3-dihydroisobenzofuran (3j): a pale-yellow oil; R_f 0.38 (1:7 THF–hexane); IR (neat) 2974, 1611, 1456, 1248, 1163, 1036, 829, 756 cm^{-1}; ^1H NMR δ 1.48 (s, 3H), 1.61 (s, 3H), 1.85 (s, 3H), 3.78 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.12 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.20 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.27–7.31 (m, 2H), 7.42 (d, *J* = 8.7 Hz, 2H); MS *m*/z 268 (M^+, 15), 253 (100). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.29; H, 7.72.

3'-Ethyl-3'-(4-methoxyphenyl)-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran] (3k): a pale-yellow oil; R_f 0.36 (1:49 Et_2O–hexane); IR (neat) 2932, 1611, 1456, 1247, 1174, 1040, 827, 754 cm^{-1}; ^1H NMR δ 0.80 (t, *J* = 7.3 Hz, 3H), 1.31–1.40 (m, 1H), 1.48–1.56 (m, 1H), 1.60–1.99 (m, 9H), 2.15 (dq, *J* = 14.7, 7.3 Hz, 1H), 3.77 (s, 3H), 6.83 (d, *J* = 9.2 Hz, 2H), 7.07 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.23–7.32 (m, 3H), 7.49 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR δ 9.00, 22.43, 22.54, 25.49, 36.58, 38.04, 38.70, 55.16, 85.42, 89.63, 113.21, 120.92, 122.31, 126.39, 127.29, 127.35, 139.54, 143.76, 147.02, 158.08; MS *m*/z 322 (M^+, 8.0), 293 (100). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.86; H, 8.13.

REFERENCES

1. K. Kobayashi, K. Shikata, S. Fukamachi, and H. Konishi, *Heterocycles,* 2008, **75**, 599.
2. (a) K. Kobayashi, T. Nagaoka, S. Fukamachi, Y. Shirai, O. Morikawa, and H. Konishi, *Synthesis*, 2007, 3032; (b) K. Kobayashi, K. Hayashi, C. Nam, S. Fukamachi, and H. Konishi, *Heterocycles*, 2008, **75**, 1225; (c) K. Kobayashi, S. Fukamachi, and H. Konishi, *Heterocycles*, 2008, **75**, 2301; (d) K. Kobayashi, S. Fujita, and H. Konishi, *Heterocycles*, 2008, **75**, 2555; (e) K. Kobayashi, D. Nakai, K. Hayashi, and H. Konishi, *Heterocycles*, 2008, **75**, 3025.
3. A hydrochloric acid or acetyl bromide catalyzed cyclization of α,α-diaryl-2-(1-methylethenyl)benzyl alcohols forming the corresponding 1,3-dihydroisobenzofurans has been reported: D. Hellwinkel, G. Aulmich, and W. Warth, *Chem. Ber.*, 1980, **113**, 3275.
4. Some 1,3-dihydroisobenzofuran derivatives have recently been shown to have biological activity:

(a) J. Madsen, P. Merachtsaki, P. Davoodpoyr, M. Bergström, B. Langström, K. Andersen, C. Thomsen, L. Martiny, and G. M. Knudsen, *Bioorg. Med. Chem.*, 2003, **11**, 3447. Natural products having this system have recently been isolated from the nature: (b) J. K. Harper, A. M. Arif, E. J. Ford, G. A. Strobel, J. A. Porco, Jr., D. P. Tomer, K. L. Oneill, E. M. Heider, and D. M. Grant, *Tetrahedron,* 2003, **59**, 2471; (c) X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang, and J. Shi, *J. Nat. Prod.*, 2004, **67**, 1661; (d) N. H. Lee, J. B. Gloer, and D. T. Wicklow, *Bull. Korean Chem. Soc.*, 2007, **28**, 877; (e) R. Tago, S. Yamauchi, M. Maruyama, K. Akiyama, T. Sugahara, T. Kishida, and Y. Koba, *Biosci. Biotecnol. Biochem.*, 2008, **72**, 1032.

5. (a) M. Yus, F. Foubelo, and J. V. Ferrández, *Tetrahedron,* 2003, **59**, 2083; (b) V. Capriati, S. Florio, R. Luisi, and B. Musio, *Org. Lett.*, 2005, **7**, 3749; (c) M. Guiso, A. Betrow, and C. Marra, *Eur. J. Org. Chem.*, 2008, 1967.
6. I. Fleming and M. Woolias, *J. Chem. Soc., Perkin Trans. 1,* 1979, 829.
7. M. E. Jason, *Tetrahedron Lett.*, 1982, **23**, 1635.
8. S. Karagoz, D. K. Astley, and S. T. Astley, *Appl. Organomet. Chem.*, 2000, **14**, 341.
9. S. Fukamachi, H. Konishi, and K. Kobayashi, *Heterocycles,* 2009, **78**, 169.
10. K. Kobayashi, T. Kozuki, S. Fukamachi, and H. Konishi, *Heterocycles*, 2010, **81**, 163.