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A convenient ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols and 2-aryl-2,2-dialkylacetaldehydes

Makoto Yamashita,* Yujirou Ono and Hiroyuki Tawada

Chemical Development Laboratories, Takeda Chemical Industries, Ltd, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan

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Abstract—A new and simple route for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols is described. In the presence of an acid catalyst phenols react with 2-aryl-2,2-dialkylacetaldehydes, prepared in good yield from 2-arylacetonitriles in 2 steps, to give 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans. Electron-donating substituents were required on the phenols in order to give 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans in good yield.

1. Introduction

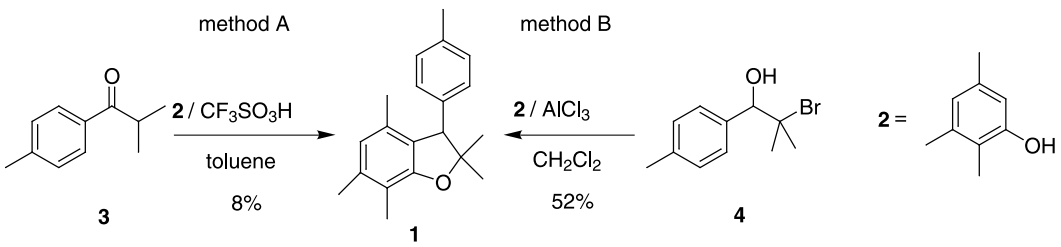
2,3-Dihydrobenzofuran derivatives are useful as key intermediates in the synthesis of a variety of biologically active compounds.[1] For example, 2,3-dihydrobenzofurans were developed for the treatment of traumatic and ischchemic central nervous system (CNS) injury,[1a] and 2,3-dihydro-5-benzofuranamines are said to be useful in treating arteriosclerosis, hepatopathy, and cerebrovascular disease.[1c]

In our laboratories, we have required a facile and efficient synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans to support one of our drug development programs. Although various methods for the preparation of 3-unsubstituted-2,2-dialkyl-2,3-dihydrobenzofurans have been reported,[2] there are only a few reports of the synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans,[1a,3] and none of them are suitable for large scale manufacture. In this paper we wish to describe a new simple, economical, and practical process for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans.

2. Results and discussion

2.1. Preliminary studies for the preparation of 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1)

Two synthetic methods[2c,e] were investigated for the preparation of dihydrobenzofuran **1**, as shown in Scheme 1. In method A, the propiophenone derivative **3**[4] was reacted with 2,3,5-trimethylphenol (**2**) in the presence of CF_3SO_3H to afford the desired dihydrobenzofuran in low yield. Method B, involving the reaction of phenol **2** with the alcohol derivative **4**, prepared from 2-bromo-4′-methylisobutyrophenone (**5**)[5] (see Section 4), in the presence of $AlCl_3$ gave the desired dihydrobenzofuran **1** in moderate yield.



Scheme 1.

Keywords: 2,3-Dihydrobenzofurans; Phenols; Aldehydes; Wagner–Meerwein rearrangement.
* Corresponding author. Tel.: +81-6-6300-6797; fax: +81-6-6300-6251; e-mail address: yamashita_makoto@takeda.co.jp

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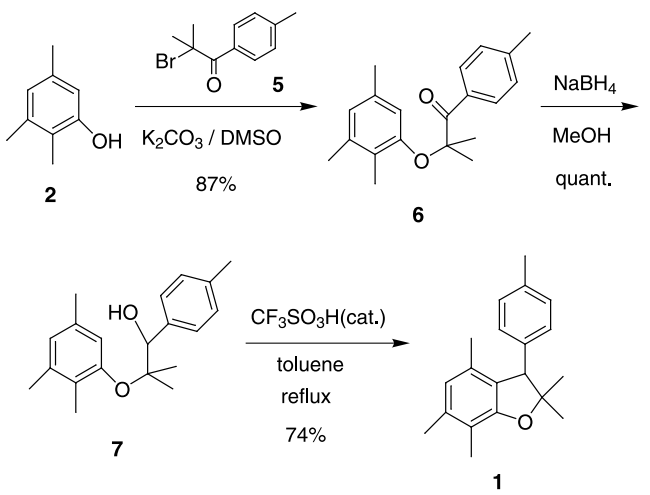
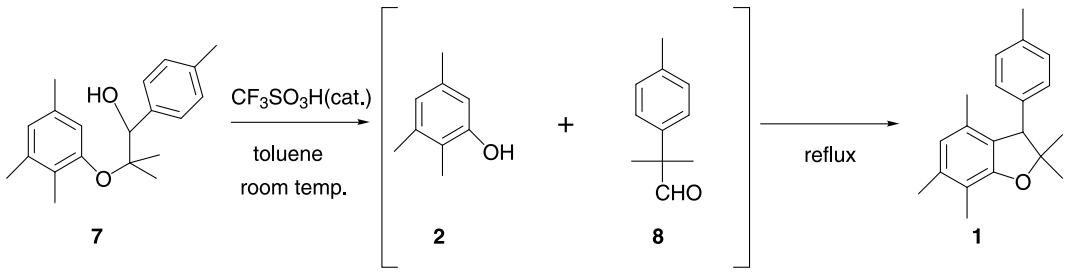
However, as neither of these processes were sufficiently high yielding for our purpose, we decided to investigate a new approach, using an intramolecular cyclization reaction of alcohol derivative **7**, to synthesize dihydrobenzofuran **1** (Scheme 2). Intermediate **7** was prepared from phenol **2** by alkylation with **5**[5] in the presence of potassium carbonate to give 2-methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-one (**6**) in 87% yield. Subsequent reduction of **6** with $NaBH_4$ in MeOH gave 2-methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-ol (**7**) in quantitative yield. The cyclization reaction of **7** was then performed using 0.1 equiv. of CF_3SO_3H in refluxing toluene for 1 h to afford the dihydrobenzofuran **1** in 74% yield.



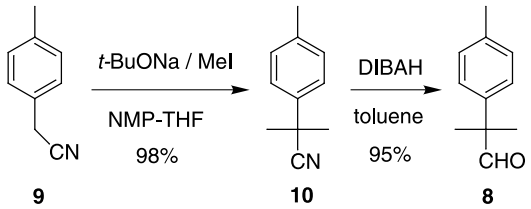
Scheme 2.



Scheme 3.

When the cyclization reaction was carried out at room temperature, **1** was only obtained in low yield and two unknown products were formed. When the reaction mixture was refluxed for a further hour the dihydrobenzofuran **1** was obtained. Isolated the two unknown products by silica gel column chromatography suggested their structures to be phenol **2** and 2-methyl-2-(4-methylphenyl)propanal (**8**), from ^{1}H NMR and Mass spectrometry {^{1}H NMR ($CDCl_3$); C*H*O for 9.47 ppm, MS (EI); *m*/*e*=162 (M^+)} (Scheme 3).

The aldehyde structure was confirmed by comparison with the spectral data of an authentic sample, which was prepared by Schaffner's method.[6] Aldehyde **8** was obtained by oxidation of the corresponding alcohol prepared in two steps, and we also synthesized aldehyde **8** by an alternative synthetic method, as shown in Scheme 4. Treatment of 4-methylbenzylcyanide (**9**) with MeI[7] (4 equiv.) in the presence of *t*-BuONa (4 equiv.) gave 2-methyl-2-(4-methylphenyl)propionitrile (**10**) in 98% yield, and subsequent reduction[8] of **10** with DIBAH (1.3 equiv.) gave aldehyde **8** in 95% yield.

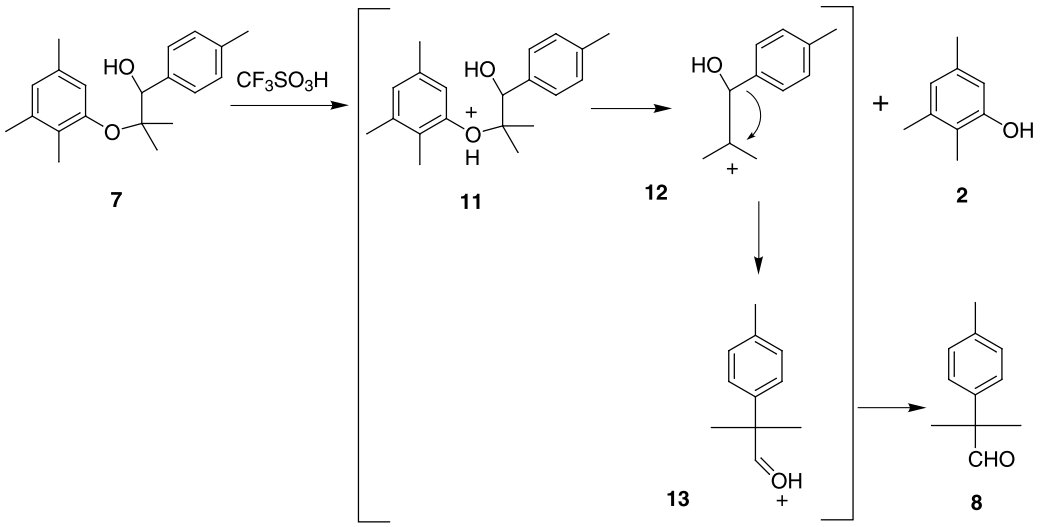


Scheme 4.

We considered that the reaction mechanism for the formation of phenol **2** and aldehyde **8** from **7** is similar to the Wagner–Meerwein rearrangement[9] shown in Scheme 5. Treatment of **7** with CF_3SO_3H in toluene at room temperature initially cleaves the ether bond and leads to the formation of **2** and cation **12**, which then undergoes Wagner–Meerwein type rearrangement to form aldehyde **8**.

2.2. Exploration of a new convenient ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols and 2-aryl-2,2-dialkylacetaldehydes

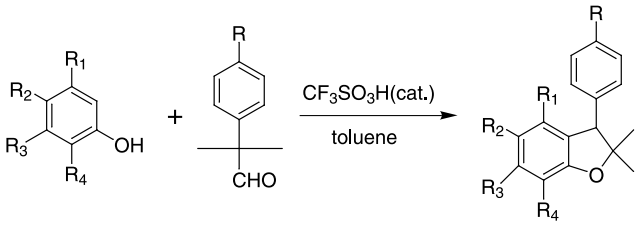
The identification of phenol **2** and aldehyde **8** as intermediates in the cyclization reaction prompted us to explore a new ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans. According to this result, it should be possible to obtain dihydrobenzofuran **1** by reaction of phenol **2** with aldehyde **8** in the presence of an acid catalyst. When phenol **2** was reacted with aldehyde **8** in the presence of a catalytic amount of CF_3SO_3H in refluxing toluene, dihydrobenzofuran **1** was obtained in 75% yield. Various acids were evaluated in this reaction (eg. $AlCl_3$, BF_3/Et_2O, $TiCl_4$, $SnCl_4$, $ZnCl_2$, H_2SO_4, $MeSO_3H$, PPA, *p*-TsOH, CF_3SO_3H), but CF_3SO_3H was found to be superior to the others in terms of yield. The reaction was carried out with other phenols and aldehydes to investigate the scope of this new method for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans, and phenols **2**, **14a–c** and aldehydes **8**, **15a–c** were examined (Scheme 6, Table 1). Reaction of 2,3,5-trimethylphenol (**2**) and *p*-cresol (**14a**) with aldehydes **8**, **15a–c** afforded dihydrobenzofurans **1**, **16–22** in good yield (entry 1–8). However, reaction of phenol (**14b**) and



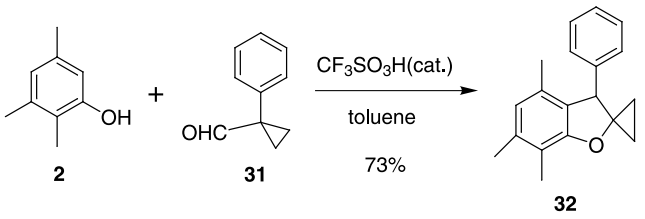
Scheme 5.

p-chlorophenol (**14c**) with aldehydes **8**, **15a–c** gave dihydrobenzofurans **23–30** in low yield (entry 9–16).

These results indicate that although electron-donating substituents are required on the phenols for good conversion, the substituents on the aldehydes have little effect on the reaction, and therefore a variety of 2-aryl-2,2-dialkylacetaldehydes may be used. For example, reaction of phenol **2** with 1-phenylcyclopropanecarbaldehyde (**31**) afforded 4,6,7-trimethyl-3-phenyl-3*H*-spiro-[1-benzofuran-2,1′-cyclopropane] (**32**) in good yield (Scheme 7).



Scheme 6.



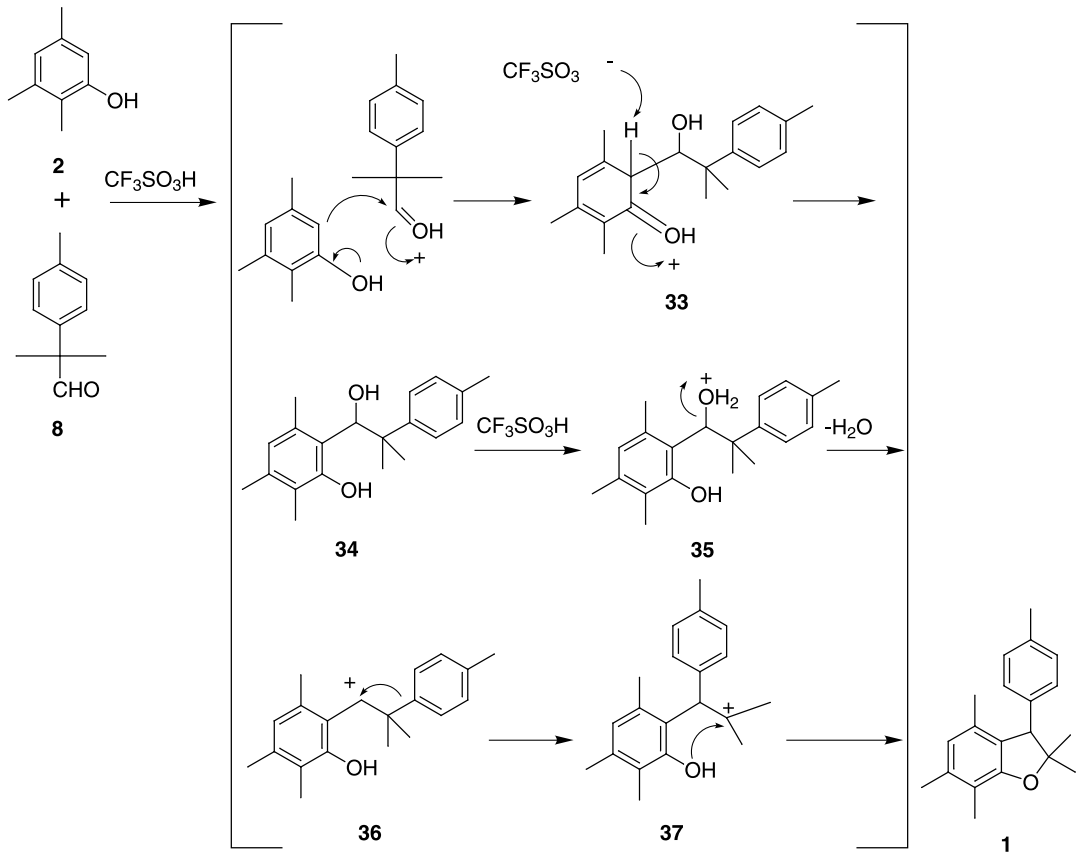
Scheme 7.

The proposed reaction mechanism for this process is shown in Scheme 8. In the presence of CF_3SO_3H, phenol **2** and aldehyde **8** initially form **34**, which after protonation followed by dehydration, leads to cation **36**, which then

Table 1. Reaction[a] of phenols and 2-aryl-2,2-dialkylacetaldehydes

Entry	Phenols					Aldehydes		Temperature	Time	Products	
		R1	R2	R3	R4		(R)	(°C)	(h)		(yield %)
1	**2**	CH_3	H	CH_3	CH_3	**8**	CH_3	110	1	**1**	75[b]
2	**2**	CH_3	H	CH_3	CH_3	**15a**	OCH_3	110	1	**16**	77[b]
3	**2**	CH_3	H	CH_3	CH_3	**15b**	H	110	1	**17**	90[b]
4	**2**	CH_3	H	CH_3	CH_3	**15c**	Cl	110	1	**18**	85[b]
5	**14a**	H	CH_3	H	H	**8**	CH_3	110	2	**19**	52[b]
6	**14a**	H	CH_3	H	H	**15a**	OCH_3	25	17	**20**	60[b]
7	**14a**	H	CH_3	H	H	**15b**	H	25	15	**21**	62[b]
8	**14a**	H	CH_3	H	H	**15c**	Cl	25	17	**22**	65[b]
9	**14b**	H	H	H	H	**8**	CH_3	110	1	**23**	11[c]
10	**14b**	H	H	H	H	**15a**	OCH_3	25	15	**24**	6[c]
11	**14b**	H	H	H	H	**15b**	H	25	15	**25**	8[c]
12	**14b**	H	H	H	H	**15c**	Cl	25	17	**26**	32[c]
13	**14c**	H	Cl	H	H	**8**	CH_3	110	2	**27**	8[c]
14	**14c**	H	Cl	H	H	**15a**	OCH_3	110	2	**28**	11[c]
15	**14c**	H	Cl	H	H	**15b**	H	25	15	**29**	7[c]
16	**14c**	H	Cl	H	H	**15c**	Cl	25	17	**30**	13[c]

[a] Reaction conditions: 1.0 equiv. of phenols, 1.0 equiv. of aldehydes, 0.1 equiv. (entry 1–5) or 0.5 equiv. (entry 6–16) of CF_3SO_3H, toluene was used as solvent.
[b] Isolated yield.
[c] Not isolated yield but HPLC analyses. The structure of **23–30** was just assigned by LC-Ms.



Scheme 8.

undergoes Wagner–Meerwein type rearrangement and cyclization to form the desired product **1**.

3. Conclusions

We have developed a new and convenient ring formation reaction for the synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans using phenols and 2-aryl-2,2-dialkylacetaldehydes, and its reaction mechanism was elucidated. The ease and utility of this method indicates that it may be applicable to the industrial manufacture of 3-aryl-2,2-dialkyl-2,3-dihydrobenzohurans, and investigations are in progress.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. NMR spectra were run at 300 MHz on a Bruker DPX-300 spectrometer. Chemical shifts are reported as δ values using tetramethylsilane as an internal standard and the coupling constants (J) are given in Hz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. All column chromatography was performed on Merck Silica gel 60 (0.063–0.200 mm). The HPLC data in Table 1 was obtained under the following conditions: detector, ultraviolet absorption photometer (wavelength 230 nm); column, YMC-Pack ODS-A302 (4.6 mm i.d.×150 mm); mobile phase, 0.02 M KH_2PO_4 aqueous solution/MeCN (20/80); flow rate, 1.0 ml/min; column temperature, 25 °C. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and HPLC analysis. Elemental analysis and mass spectra were carried out by Takeda Analytical Research Laboratories, Ltd.

4.1.1. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 1, Method A). A solution of phenol **2** (1.36 g, 10 mmol), 4′,2-dimethylpropiophenone (**3**)[4] (1.62 g, 10 mmol) and CF_3SO_3H (3.73 g, 25 mmol) in toluene (13.6 ml) was refluxed for 3 h. The reaction mixture was cooled to room temperature, and aqueous NaOH (6 M, 10 ml) was added. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **1** (0.21 g, 8%) as a white crystalline powder. Mp 119–120 °C. IR (cm^{-1}, KBr) 1457, 1511, 1589, 3436; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.49 (3H, s), 1.83 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 2.30 (3H, s), 4.09 (1H, s), 6.48 (1H, s), 6.5–7.1 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.1, 19.3, 20.9, 24.8, 29.8, 57.5, 88.5, 115.4, 123.0, 126.2, 128.4, 128.8, 132.0, 136.0, 136.7, 137.3, 157.3. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.67, H, 8.74.

4.1.2. 2-Bromo-2-methyl-1-(4-methylphenyl)propan-1-ol (4). A solution of 2-bromo-4′-methylisobutyrophenone (**5**)[5] (5.0 g, 20.7 mmol) in MeOH (50 ml) was cooled to 10 °C,

and $NaBH_4$ (0.24 g, 6.3 mmol) was added and stirred for 4 h. To the reaction mixture was added aqueous HCl (1 M, 8 ml) and the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and water, the organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **4** (4.2 g, 84%) as a colorless oil. IR (cm^{-1}, neat) 1101, 1384, 3540; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (3H, s), 1.73 (3H, s), 2.33 (3H, s), 2.77 (1H, bs), 4.77 (1H, s), 7.14 (2H, d, J=8.0 Hz), 7.27 (2H, d, J=8.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.0, 27.3, 31.6, 74.8, 81.9, 127.7, 128.4, 134.9, 137.8; MS (EI): m/z 242 (M^+); HRMS (EI) calcd for $C_{11}H_{15}BrO$ (M^+) 242.0306. Found: 242.0281.

4.1.3. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 1, Method B). A solution of **2** (0.28 g, 2 mmol) and **4** (0.5 g, 2 mmol) in dichloromethane (5 ml) was cooled to 5 °C, and $AlCl_3$ (0.27 g, 2 mmol) was added. The mixture was stirred at room temperature for 20 h and diluted with toluene and aqueous HCl (6 M). The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **1** (0.3 g, 52%) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 118–119 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.84, H, 8.65.

4.1.4. 2-Methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-one (6). A suspension of phenol **2** (13.6 g, 100 mmol) and K_2CO_3 (27.6 g, 200 mmol) in DMSO (68 ml) was warmed to 35 °C, and **5**[5] (42.2 g in 68 ml of DMSO, 175 mmol) was added and stirred for 24 h. MeOH (95 ml) and water (95 ml) were added to the reaction mixture, which was stirred at 40 °C for 1 h. The precipitate was filtered, washed with MeOH/H_2O (1:1) twice to give the crude product. The crude cake was dissolved in refluxing MeOH (204 ml), and then water (68 ml) was added and it was cooled to 40 °C. After stirring at 40 °C for 1 h, the precipitate was collected by filtration, washed with MeOH/H_2O (3:1) and water, and dried in vacuo at 50 °C to afford **6** (25.8 g, 87.0% based on **2**) as a white crystalline powder. Mp 115–117 °C. IR (cm^{-1}, KBr) 1141, 1604, 1664, 2985; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (6H, s), 2.05 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.34 (3H, s), 6.18 (1H, s), 6.54 (1H, s), 7.18 (2H, d, J=8.3 Hz), 8.23 (2H, d, J=8.3 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 12.0, 20.0, 20.9, 21.5, 25.9, 84.7, 115.3, 124.2, 124.4, 129.0, 130.1, 132.1, 134.9, 137.7, 143.4, 153.2, 202.4. Anal. calcd for $C_{20}H_{24}O_2$ (296.40): C, 81.04, H, 8.16. Found: C, 80.74, H, 7.90.

4.1.5. 2-Methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-ol (7). To a suspension of **6** (25.2 g, 85 mmol) in MeOH (252 ml) was added $NaBH_4$ (2.6 g, 69 mmol), and the mixture was stirred at 35 °C for 3 h under nitrogen gas purge. The reaction mixture was cooled to 15 °C and adjusted to pH 7 at 20 °C with aqueous HCl (1 M), and the whole was concentrated in vacuo. The residue was diluted with toluene and water, the organic layer was separated, washed with water, dried over sodium sulfate and concentrated in vacuo to afford **7** (25.4 g) quantitatively as a colorless oil. The product was subsequently used without further purification. IR (cm^{-1}, neat) 1128, 1298, 2981, 3558; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s), 1.22 (3H, s), 2.13 (3H, s), 2.22 (3H, s), 2.25 (3H, s), 2.34 (3H, s), 3.38 (1H, bs), 4.87 (1H, s), 6.72 (1H, s), 6.74 (1H, s), 7.13 (2H, d, J=8.3 Hz), 7.34 (2H, d, J=8.3 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.2, 20.3, 20.7, 21.0, 21.1, 22.8, 80.5, 84.2, 121.6, 126.0, 127.8, 128.4, 134.9, 136.7, 137.2, 137.9, 152.7. Anal. calcd for $C_{20}H_{26}O_2$ (298.42): C, 80.50, H, 8.78. Found: C, 80.71, H, 8.65; MS (CI): m/z 299 $(M+H)^+$.

4.1.6. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 2). A solution of **7** (25.4 g, 85 mmol) and CF_3SO_3H (1.28 g, 8.5 mmol) in toluene (127 ml) was refluxed for 1 h. The reaction mixture was cooled to 50 °C before aqueous NaOH (1 M, 76 ml) was added and then the mixture was stirred at 35 °C for 30 min. The organic layer was separated and washed with water and concentrated in vacuo. The residue was diluted with 2-propanol (76 ml) and heated to 60 °C, and water (76 ml) was added dropwise at the same temperature. The mixture was cooled to room temperature and stirred for 1 h. The precipitate was filtered, washed with 2-propanol/H_2O (1:1) twice and dried in vacuo at 50 °C to afford **1** (17.6 g, 74.0% based on **6**) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 119–120 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.54, H, 8.79.

4.1.7. Reaction of (7) with CF_3SO_3H at room temperature. A solution of **7** (1.0 g) and CF_3SO_3H (0.05 g) in toluene (6 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with aqueous $NaHCO_3$ and separated. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford phenol **2** (305 mg) as a white crystalline powder, aldehyde **8** (353 mg) as a colorless oil, and benzofuran **1** (169 mg) as a white crystalline powder.

4.2. General procedure for the preparation of 2-aryl-2,2-dialkylacetaldehydes

4.2.1. 2-Methyl-2-(4-methylphenyl)propanal (8). A solution of *t*-BuONa (19.9 g, 207 mmol) in 1-methyl-2-pyrrolidone/THF (1:1, 68 ml) was cooled to 5 °C, and a solution of 4-methylbenzylcyanide (**9**) (6.8 g, 52 mmol) and methyl iodide (12.9 ml, 207 mmol) was added maintaining the reaction temperature below 10 °C. After the mixture was stirred for 1 h, diluted with aqueous HCl (3 M) and toluene, the organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried over sodium sulfate and concentrated in vacuo to afford 2-methyl-2-(4-methylphenyl)propionitrile (**10**) (8.1 g, 98%) as a red-brown oil, which was used in the next reaction without further purification. IR (cm^{-1}, neat) 815, 1513, 2235, 2981; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (6H, s), 2.35 (3H, s), 7.17–7.22 (2H, m), 7.33–7.37 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 29.0, 36.6, 124.5, 124.8, 129.4, 137.4, 138.4; MS (EI): m/z 159 (M^+). A solution of **10** (8.1 g, 51 mmol) in toluene (81 ml) was cooled to −50 °C, and DIBAH (1.5 M

in toluene, 42 ml, 63 mmol) was added dropwise maintaining the reaction temperature below −40 °C and stirred for 1 h. Aqueous HCl (6 M) was added to the reaction mixture, which was stirred at room temperature for 30 min. The organic layer was separated, washed with aqueous HCl (2 M), aqueous $NaHCO_3$ and brine successively, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **8** (7.8 g, 93% based on **9**) as a colorless oil. IR (cm^{-1}, neat) 1514, 1728, 2973; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (6H, s), 2.33 (3H, s), 7.14–7.24 (4H, m), 9.47 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.8, 22.3, 49.9, 126.5, 129.4, 136.8, 138.0, 202.1; MS (EI): *m/z* 162 (M^+); HRMS (EI) calcd for $C_{11}H_{14}O$ (M^+) 162.1045. Found: 162.1034.

The following compounds were obtained according to the general procedure.

4.2.2. 2-Methyl-2-(4-methoxyphenyl)propanal (15a). Yield 72%, colorless oil. IR (cm^{-1}, neat) 1254, 1514, 1724, 2971; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (6H, s), 3.80 (3H, s), 6.88–6.93 (2H, m), 7.17–7.22 (2H, m), 9.44 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.4, 49.6, 55.1, 114.1, 127.7, 132.9, 158.6, 202.0. Anal. calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13, H, 7.92. Found: C, 73.77, H, 7.99; MS (EI): *m/z* 178 (M^+).

4.2.3. 2-Methyl-2-phenylpropanal (15b). Yield 70%, colorless oil. IR (cm^{-1}, neat) 1448, 1496, 1722, 2981; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (6H, s), 7.25–7.30 (3H, m), 7.35–7.40 (2H, m), 9.49 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.3, 50.3, 125.2, 126.5, 127.1, 128.4, 128.7, 141.1, 202.0; MS (EI): *m/z* 148 (M^+); HRMS (EI) calcd for $C_{10}H_{12}O$ (M^+) 148.0888. Found: 148.0878.

4.2.4. 2-Methyl-2-(4-chlorophenyl)propanal (15c). Yield 87%, colorless oil. IR (cm^{-1}, neat) 1105, 1495, 1724, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (6H, s), 7.18–7.23 (2H, m), 7.32–7.36 (2H, m), 9.47 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.4, 49.9, 128.0, 128.8, 133.1, 139.6, 201.4; MS (EI): *m/z* 182 (M^+); HRMS (EI) calcd for $C_{10}H_{11}ClO$ (M^+) 182.0499. Found: 182.0481.

4.2.5. 1-Phenylcyclopropanecarbaldehyde (31). Yield 90%, colorless oil. IR (cm^{-1}, neat) 1446, 1498, 1711, 2823; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.41 (2H, m), 1.54–1.58 (2H, m), 7.29–7.36 (5H, m), 9.28 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.0, 37.3, 127.5, 128.5, 129.9, 137.4, 200.8; MS (EI): *m/z* 146 (M^+); HRMS (EI) calcd for $C_{10}H_{10}O$ (M^+) 146.0732. Found: 146.0726.

4.3. General procedure for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans using phenols and 2-aryl-2,2-dialkylacetaldehydes

4.3.1. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 6). A suspension of phenol **2** (0.84 g, 6.2 mmol), aldehyde **8** (1.0 g, 6.2 mmol) and CF_3SO_3H (0.09 g, 0.62 mmol) in toluene (6.2 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature, and aqueous NaOH (1 M) was added before it was stirred for 30 min. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/39) to afford **1** (1.3 g, 75%) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 118–120 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.67, H, 8.72; MS (EI): *m/z* 280 (M^+).

The following compounds were obtained according to the general procedure.

4.3.2. 2,2,4,6,7-Pentamethyl-3-(4-methoxylphenyl)-2,3-dihydrobenzofuran (16). Yield 77%, white crystalline powder. Mp 105–106 °C. IR (cm^{-1}, KBr) 825, 1088, 1248, 1510, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.48 (3H, s), 1.84 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 3.76 (3H, s), 4.07 (1H, s), 6.48 (1H, s), 6.5–7.2 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.0, 19.3, 24.8, 29.7, 55.0, 57.1, 88.5, 113.4, 115.4, 123.0, 126.3, 129.5, 131.9, 132.5, 136.7, 157.2, 158.2. Anal. calcd for $C_{20}H_{24}O_2$ (296.40): C, 81.04, H, 8.16. Found: C, 80.81, H, 7.92; MS (EI): *m/z* 296 (M^+).

4.3.3. 2,2,4,6,7-Pentamethyl-3-phenyl-2,3-dihydrobenzofuran (17). Yield 90%, white crystalline powder. Mp 89–91 °C. IR (cm^{-1}, KBr) 698, 1090, 1456, 2979; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.50 (3H, s), 1.83 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 4.12 (1H, s), 6.48 (1H, s), 6.5–7.3 (5H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.6, 18.0, 19.3, 24.8, 29.8, 57.9, 88.5, 115.5, 123.0, 126.1, 126.5, 128.1, 128.6, 132.0, 136.9, 140.4, 157.4. Anal. calcd for $C_{19}H_{22}O$ (266.38): C, 85.67, H, 8.32. Found: C, 85.52, H, 8.19; MS (EI): *m/z* 266 (M^+).

4.3.4. 2,2,4,6,7-Pentamethyl-3-(4-chlorophenyl)-2,3-dihydrobenzofuran (18). Yield 85%, white crystalline powder. Mp 110–112 °C. IR (cm^{-1}, KBr) 831, 1084, 1489, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.49 (3H, s), 1.83 (3H, s), 2.13 (3H, s), 2.23 (3H, s), 4.08 (1H, s), 6.48 (1H, s), 6.5–7.3 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.0, 19.3, 24.8, 29.7, 57.2, 88.3, 115.6, 123.1, 125.7, 128.3, 129.9, 131.8, 132.3, 137.2, 139.0, 157.3. Anal. calcd for $C_{19}H_{21}OCl$ (300.82): C, 75.86, H, 7.04, Cl, 11.79. Found: C, 75.82, H, 6.99, Cl, 11.66; MS (EI): *m/z* 300 (M^+).

4.3.5. 2,2,5-Trimethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (19). Yield 52%, colorless oil. IR (cm^{-1}, neat) 1251, 1491, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.56 (3H, s), 2.24 (3H, s), 2.33 (3H, s), 4.26 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.83 (1H, s), 6.95–6.99 (3H, m), 7.07–7.15 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 20.9, 24.0, 28.8, 58.1, 89.7, 109.2, 126.3, 128.7, 128.8, 128.9, 129.5, 130.3, 130.6, 136.5, 136.7, 156.8; MS (EI): *m/z* 252 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O$ (M^+) 252.1514. Found: 252.1511.

4.3.6. 2,2,5-Trimethyl-3-(4-methoxyphenyl)-2,3-dihydrobenzofuran (20). Yield 60%, pale yellow oil. IR (cm^{-1}, neat) 1250, 1491, 1512, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.55 (3H, s), 2.25 (3H, s), 3.79 (3H, s), 4.25 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.82–6.86 (3H, m), 6.95–7.02 (3H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.7, 55.1, 57.7, 89.8, 109.2, 113.6, 126.2, 128.7,

129.5, 129.8, 130.7, 131.8, 156.7, 158.6; MS (EI): *m/z* 268 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O_2$ (M^+) 268.1463. Found: 268.1443.

4.3.7. 2,2,5-Trimethyl-3-phenyl-2,3-dihydrobenzofuran (21). Yield 62%, pale yellow oil. IR (cm^{-1}, neat) 1252, 1491, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.57 (3H, s), 2.24 (3H, s), 4.29 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.84 (1H, s), 7.07–7.10 (2H, m), 7.24–7.30 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.8, 58.5, 89.7, 109.3, 126.3, 126.9, 128.2, 128.8, 128.9, 129.5, 130.3, 130.4, 139.8, 156.8; MS (EI): *m/z* 238 (M^+); HRMS (EI) calcd for $C_{17}H_{18}O$ (M^+) 238.1358. Found: 238.1353.

4.3.8. 2,2,5-Trimethyl-3-(4-chlorophenyl)-2,3-dihydrobenzofuran (22). Yield 65%, colorless oil. IR (cm^{-1}, neat) 1093, 1252, 1491, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.55 (3H, s), 2.24 (3H, s), 4.25 (1H, s), 6.72 (1H, d, *J*=8.1 Hz), 6.81 (1H, s), 6.96–7.03 (3H, m), 7.25–7.28 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.8, 57.9, 89.5, 109.4, 126.1, 128.4, 129.1, 129.6, 129.7, 129.9, 130.2, 132.8, 138.4, 156.8; MS (EI): *m/z* 272 (M^+); HRMS (EI) calcd for $C_{17}H_{17}ClO$ (M^+) 272.0968. Found: 272.0944.

4.3.9. 4,6,7-Trimethyl-3-phenyl-3*H*-spiro[1-benzofuran-2,1′-cyclopropane] (32). Yield 73%, pale yellow oil. IR (cm^{-1}, neat) 698, 1084, 1296, 1450, 2939; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01–2.05 (1H, m), 2.15 (3H, s), 2.18 (3H, s), 2.24 (3H, s), 2.46–2.53 (1H, m), 2.76–2.85 (2H, m), 3.92–3.95 (1H, m), 6.55 (1H, s), 7.17–7.42 (3H, m), 7.57–7.60 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.7, 17.9, 19.2, 23.2, 35.1, 49.0, 90.9, 116.1, 123.0, 124.7, 127.3, 127.4, 128.1, 128.3, 128.9, 131.2, 137.1, 142.4, 158.7. Anal. calcd for $C_{19}H_{20}O$ (264.36): C, 86.32, H, 7.63. Found: C, 86.18, H, 7.86; MS (EI): *m/z* 264 (M^+).

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