Notes

Novel Syntheses of 2,3-Disubstituted Benzofurans

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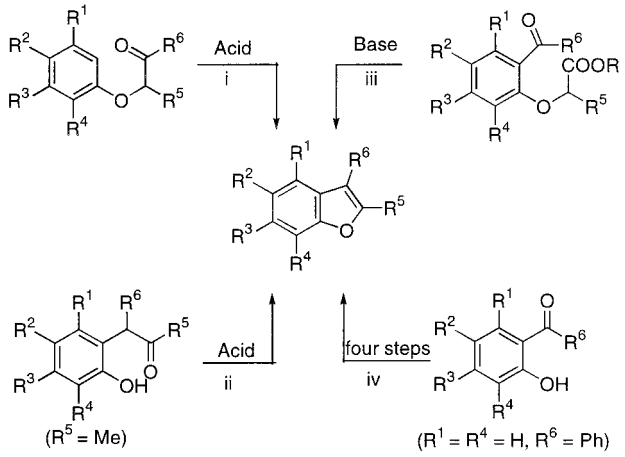
Introduction

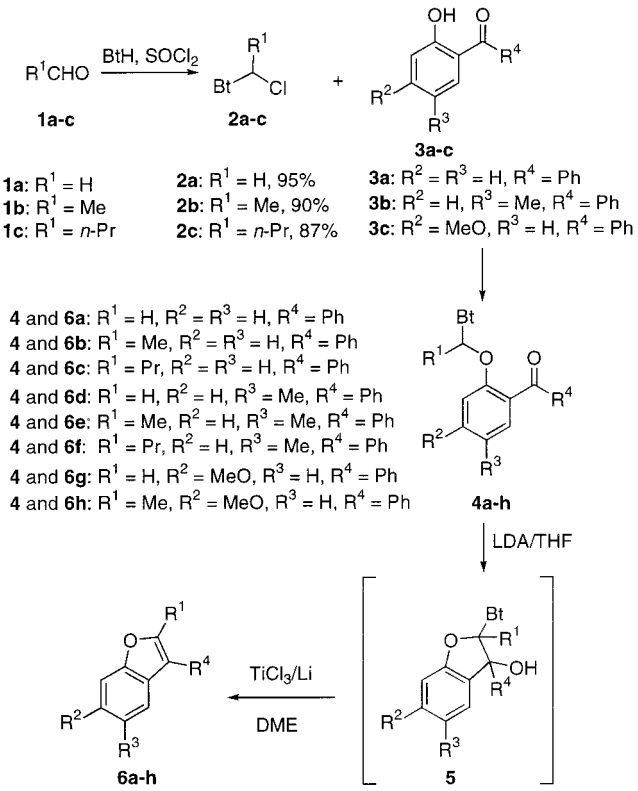
Benzofurans possess a broad range of biological activities, are constituents of important natural products, and have been the subject of extensive experimental studies.[1a−c] Major synthetic strategies utilized include the following (Scheme 1): (i) dehydrative cyclization of α-(phenoxy)-alkyl ketones;[2a−e] (ii) dehydration of *o*-hydroxybenzyl ketones under acidic conditions;[3a−b] (iii) decarboxylation of *o*-acylphenoxyacetic acids or esters on treatment with a base;[4a−d] (iv) cyclofragmentation of oxiranes, prepared in three or four steps from the corresponding *o*-hydroxybenzophenones;[5] and (v) palladium(II)-catalyzed cyclization of arylacetylenes.[6a−d]

We now disclose the preparation of 2,3-disubstituted benzofurans by reactions of *o*-hydroxyphenyl ketones **3a**−**c** or *o*-(1-hydroxy-2,2-dimethylpropyl)phenol **8** with 1-benzotriazol-1-ylalkyl chlorides **2a**−**c** in two or three steps (Schemes 2 and 3). These new approaches make the variety of benzofurans readily available by simple procedures and in good overall yields and complements a previous benzotriazole-mediated preparation of benzofurans.[7]

Scheme 1



Scheme 2



Results and Discussion

Compounds **2a**−**c** (available from aldehydes, benzotriazole, and thionyl chloride in 87−96% yields[8]) were treated with sodium salts of *o*-hydroxybenzophenones **3a**−**c** or of **8** to afford the corresponding intermediates **4a**−**h** (Table 1) and **9a**,**b** in excellent yields (Schemes 2

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Scheme 3

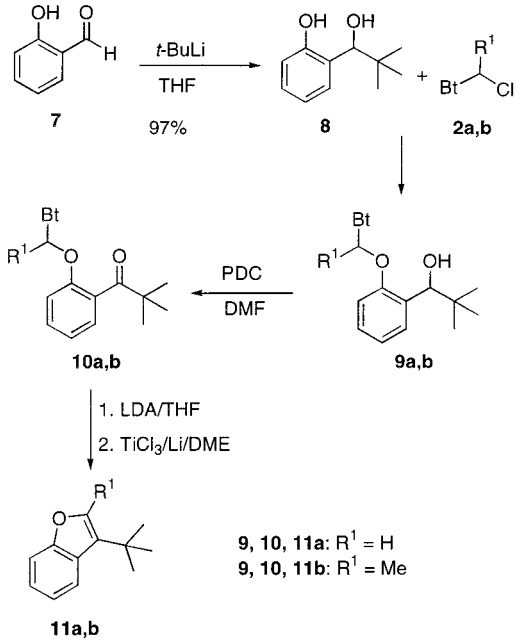

Table 1. Preparative Yields of Ortho-Substituted Phenones 4a−h and Benzofurans 6a−h

	R^1	R^2	R^3	R^4	**4** (yield, %)	**6** (yield, %)
a	H	H	H	Ph	97	65[5]
b	Me	H	H	Ph	87	55[11]
c	*n*-Pr	H	H	Ph	85	65
d	H	H	Me	Ph	99	60[12]
e	Me	H	Me	Ph	95	57[13]
f	*n*-Pr	H	Me	Ph	87	40
g	H	MeO	H	Ph	98	70[14]
h	Me	MeO	H	Ph	97	56[15]

Table 2. Preparative Yields of Ortho-Substituted Phenyl-2,2-dimethyl-1-propanols 9a,b, Ortho-Substituted Phenyl-2,2-dimethyl-1-propanones 10a,b, and Benzofurans 11a,b

	R^1	**9** (yield, %)	**10** (yield, %)	**11** (yield, %)
a	H	99	97	60[16]
b	Me	95	98	56[17]

and 3). The structures of **4a**−**h** and **9a**,**b** are supported by their ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectra of **4a**−**h** and **9a**,**b** showed the disappearance of the phenolic proton signal (5.0−6.0 ppm) of the *o*-hydroxyphenyl ketones and the appearance of a new set of signals at 7.0−8.2 ppm characteristic for the N-substituted benzotriazole group. The ^{13}C NMR spectra of **4a**−**h** and **9a**,**b** also showed new signals around 110, 120, 124, 127, 132, and 146 ppm, corresponding to the N-substituted benzotriazole. Compounds **9a**,**b** were treated with pyridinium dichromate to afford intermediates **10a**,**b** in yields of 97−98% (Table 2).

Intermediates **4a**−**h** or **10a**,**b** were treated with an equivalent amount of LDA in THF at temperatures ranging from −78 to +20 °C to give the corresponding 2-(benzotriazol-1-yl)-3-substituted-2,3-dihydro-1-benzofuran-3-ols of type **5**. Compounds **5** without further purification were treated with an equivalent amount of low-valent titanium reagent (prepared by heating $TiCl_3$ and Li under reflux in DME for 5 h under argon protection)[9a] in DME under reflux for 12−24 h to give the corresponding benzofurans **6a**−**h** and **11a**,**b**. To support the reaction path proposed, we isolated and characterized the intermediate **5a**. The structure of **5a** was deduced from its ^{1}H NMR, ^{13}C NMR, and DEPT spectra. The ^{1}H NMR spectrum of **5a** shows some change compared to that of compound **4a** in the aromatic region (7.00−8.00 ppm), and the characteristic singlet of the methylene protons (6.44 ppm) of **4a** disappeared. The signal at 3.93 ppm present in the spectrum of **5a** disappeared after addition of D_2O, suggesting the existence of an OH group. In the ^{13}C NMR spectrum of **5a**, the signals corresponding to the carbonyl (195.5 ppm) and methylene (74.8 ppm) fragments of **4a** have disappeared. Two new signals (at 83.5 and 97.8 ppm) in the ^{13}C spectrum of **5a** were assigned to the two aliphatic carbons connected to the OH and the benzotriazole groups. DEPT reveals that the number of even carbons and odd carbons is 7 and 13, respectively. These data taken together confirm the structure of **5a**. In previous work,[9b] we showed that pairs of diastereomers of type **5** each gave the same olefin on low-valent Ti treatment.

The structures of benzofurans **6a**−**h** and **11a**,**b** were assigned by their ^{1}H and ^{13}C NMR. The ^{1}H NMR spectra of **6a**−**h** and **11a**,**b** show no signals corresponding to those assigned to the N-substituted benzotriazole groups of intermediates **4a**−**h** or **10a**,**b** (7.0−8.2 ppm). In the ^{13}C NMR spectra, the sets of signals assigned to the N-substituted benzotriazole groups of **4a**−**h** or **10a**,**b** (around 110, 120, 124, 127, 132, 146 ppm) have disappeared. The new ^{13}C signal at 140−155 ppm was assigned to C(2) of benzofurans **6a**−**h** and **11a**,**b**.

In summary, an efficient and simple route to benzofurans was developed from α-benzotriazolylalkyl chlorides and *o*-hydroxyphenyl ketones. The sequence works well for 3-aryl- and 3-*tert*-butylbenzofurans but could not be extended to other 3-alkyl analogues.

Experimental Section

General Methods. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard for ^{1}H (300 MHz) or a solvent as the internal standard for ^{13}C (75 MHz). Microanalyses were performed on a Carlo Erba-1106 elemental analyzer. Benzene and toluene were dried over molecular sieves. Column chromatography was conducted with silica gel 200−425 mesh.

1-Benzotriazol-1-ylalkyl chlorides **2a**−**c** were synthesized according to the previously published procedure.[10]

General Procedure for the Preparation of Ortho-Substituted Benzophenones 4a−h. To a stirred solution of 1-(2-hydroxyphenyl)ketones **3** (3 mmol) in ethanol (20 mL) was added NaOH (120 mg, 3 mmol) at room temperature, and the reaction mixture was stirred for 5 h. Ethanol was removed from the reaction mixture *in vacuo*. The residue was dissolved in DMF; to the solution obtained was added the corresponding 1-benzotriazol-1-ylalkyl chloride **2** (3 mmol), and the reaction mixture was stirred at 70 °C for 12 h. After the starting materials were consumed, the reaction mixture was poured into ice−water and extracted with diethyl ether. Ether was removed *in vacuo*, and the residue was purified by column chromatography on silica gel.

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[2-(1-Benzotriazol-1-ylmethoxy)phenyl](phenyl)methanone (4a): white needles (hexanes/ethyl acetate 5:1); mp 72−74 °C (97%); ^{1}H NMR δ 6.44 (s, 2H), 7.08 (dt, J = 7.5, 1.8 Hz, 1H), 7.21−7.47 (m, 9H), 7.55−7.60 (m, 2H), 7.93−7.98 (m, 1H); ^{13}C NMR δ 74.3, 109.7, 115.2, 119.4, 122.8, 124.2, 127.8, 128.0, 129.2, 129.3, 130.2, 131.6, 132.3, 132.8, 137.0, 145.8, 153.2, 195.3. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.36; H, 4.53; N, 12.79.

Preparation of 2-(1-Benzotriazol-1-yl)-3-phenyl-2,3-dihydro-1-benzofuran-3-ol (5a). To a stirred solution of the ortho-substituted phenone **4a** (494 mg, 1.5 mmol) in THF was added LDA (2.0 M, 0.85 mL, 1.7 mmol) at −78 °C. The reaction mixture was stirred at the same temperature overnight and then quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel to afford compound **5a** (97%) as white plates: mp 167−168 °C; ^{1}H NMR δ 3.93 (s, 1H), 7.05 (t, J = 3.9 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.25−7.45 (m, 10H), 7.87 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 83.5, 97.8, 110.9, 111.2, 120.1, 123.4, 124.6, 125.3, 125.6, 128.3, 128.5, 129.0, 130.7, 131.4, 133.3, 143.1, 146.0, 158.0. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.82; H, 4.91; N, 12.79.

General Procedure for the Preparation of Benzofurans 6a−h. To a stirred solution of ortho-substituted phenones **4** (1.5 mmol) in THF was added LDA (2.0 M, 0.85 mL, 1.7 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature overnight. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was directly used in the next step, for which $TiCl_3$ (277 mg, 1.8 mmol), Li (38 mg, 5.4 mmol), and DME (15 mL) were loaded in a three-necked round-bottom flask under argon. The reaction mixture was heated under reflux for 5 h to generate the Ti(0) species. A solution of the crude product in DME (10 mL) was added to the Ti(0) solution and heated under reflux for 24 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel.

3-Phenyl-1-benzofuran (6a): white plates (hexanes); mp 40−43 °C (65%) (lit.[5,10] mp 40−42 °C); ^{1}H NMR δ 7.22−7.37 (m, 3H), 7.45 (t, J = 7.5 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.76 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 111.9, 120.6, 122.4, 123.1, 124.7, 126.6, 127.7, 129.1, 132.2, 141.4, 156.0.

Preparation of 2-(1-Hydroxy-2,2-dimethylpropyl)phenol 8. To a solution of the aldehyde **7** (2.83 g, 23 mmol) in THF (10 mL) was added *t*-BuLi (1.7 M, 30 mL, 51 mmol) at −78 °C, and the reaction mixture was stirred for 4 h in the temperature range from −78 to 0 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl at 0 °C and extracted with diethyl ether, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate 4:1) to afford compound **8** (97%) as white needles: mp 54−55 °C (no lit. mp provided[18]); ^{1}H NMR δ 0.94 (s, 9H), 3.64−3.67 (m, 1H), 4.46 (d, J = 3.3 Hz, 1H), 6.74−6.86 (m, 3H), 7.12 (t, J = 6.9 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR δ 26.0, 37.1, 84.5, 117.0, 118.6, 124.1, 128.5, 129.6, 156.0.

General Procedure for the Preparation of the Intermediates 9. To a stirred solution of 2-(1-hydroxy-2,2-dimethylpropyl)phenol **8** (540 mg, 3 mmol) in ethanol (20 mL) was added NaOH (120 mg, 3 mmol) at room temperature, and the reaction mixture was stirred for 5 h. Ethanol was removed from the reaction mixture *in vacuo*. The residue was dissolved in DMF, the corresponding 1-benzotriazol-1-ylalkyl chloride **2** (3 mmol) was added, and the reaction mixture was stirred at 70 °C for 12 h. After the starting materials were consumed, the reaction mixture was poured into ice−water and extracted with diethyl ether. Ether was removed *in vacuo*, and the residue was purified by column chromatography on silica gel.

1-[2-(1-Benzotriazol-1-ylmethoxy)phenyl]-2,2-dimethyl-1-propanol (9a): white plates (hexanes/ethyl acetate 5:1); mp 97−98 °C (99%); ^{1}H NMR δ 0.83 (s, 9H), 3.24 (d, J = 3.3 Hz, 1H), 4.74 (d, J = 3.0 Hz, 1H), 6.40 (s, 2H), 6.95 (t, J = 7.0 Hz, 1H), 7.08−7.24 (m, 3H), 7.34 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 25.4, 35.9, 73.8, 74.3, 109.3, 113.0, 119.3, 121.9, 124.1, 127.6, 127.7, 129.0, 132.0, 132.2, 145.4, 153.2. Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.78. Found: C, 69.31; H, 7.36; N, 13.78.

General Procedure for the Preparation of the Intermediates 10. To a solution of an intermediate **9** (1.7 mmol) in DMF (10 mL) was added pyridinium dichromate (3.2 g, 8.5 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with diethyl ether, and the organic fraction was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel.

1-[2-(1-Benzotriazol-1-ylmethoxy)phenyl]-2,2-dimethyl-1-propanone (10a): white needles (hexanes/ethyl acetate 5:1); mp 103−104 °C (97%); ^{1}H NMR δ 1.05 (s, 9H), 6.44 (s, 2H), 6.90−6.99 (m, 2H), 7.18 (s, 2H), 7.27 (t, J = 7.5 Hz, 1H), 7.40(t, J = 7.5 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 26.2, 44.4, 74.4, 109.4, 114.7, 119.4, 122.2, 124.1, 126.1, 127.8, 129.5, 131.9, 132.3, 145.6, 151.2, 211.8. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.63; H, 6.11; N, 13.55.

General Procedure for the Preparation of Benzofurans 11a,b. To a stirred solution of ortho-substituted phenones **10** (1.5 mmol) in THF was added LDA (0.85 mL, 2.0 M, 1.7 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature overnight. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was directly used in the next reaction as follows. $TiCl_3$ (277 mg, 1.8 mmol), Li (38 mg, 5.4 mmol), and DME (15 mL) were loaded in a three-necked round-bottom flask under argon. The reaction mixture was heated under reflux for 5 h to generate the Ti(0) species. A solution of the crude product in DME (10 mL) was added to the Ti(0) solution, and the reaction mixture was heated under reflux for 24 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel.

3-*tert*-Butyl-1-benzofuran (11a): white plates (hexanes/ethyl acetate 10:1); mp 65−66 °C [lit.[16] mp 66−68 °C] (60%); ^{1}H NMR δ 1.43 (s, 9H), 7.19−7.30 (m, 2H), 7.34 (s, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 29.9, 30.9, 111.6, 121.6, 121.8, 123.6, 126.9, 130.2, 139.3, 156.0.

Supporting Information Available: Experimental data for **4b−h**, **6b−h**, **9b**, **10b,** and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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