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A Short Synthesis of 2,3,4-Trihydrodibenzofuranes

M. Deshmukh[1,*], **D. Kharade**[2], and **S. D. Shirke**[2]

[1] Institute of Organic Chemistry, Karl-Franzens University, A-8010 Graz, Austria
[2] Department of Chemistry, Shivaji University, Kolhapur-416004, India

Summary. Treatment of 2-phenoxypropionic acid with polyphosphoric acid gave substituted benzofuran-3-ones (**2a–h**), which were converted into 2,3,4-trihydrodibenzofuran-3-ones (**4a–h**) *via* the compounds **3a–h**. *Clemmensen* reduction of the compounds **4a–h** gave the 2,3,4-trihydrodibenzofuranes (**5a–h**).

Keywords. Benzofuran-3-ones; 2,3,4-Trihydrodibenzofuran-3-ones.

Eine einfache Synthese von 2,3,4-Trihydrobenzofuranen

Zusammenfassung. Behandlung von 2-Phenoxypropionsäure mit Polyphosphorsäure lieferte die substituierten Benzofuran-3-one (**2a–h**), welche über **3a–h** in die 2,3,4-Trihydrodibenzofuran-3-one (**4a–h**) übergeführt wurden. Durch *Clemmensen*-Reduktion von **4a–h** wurden die gewünschten 2,3,4-Trihydrobenzofurane (**5a–h**) erhalten.

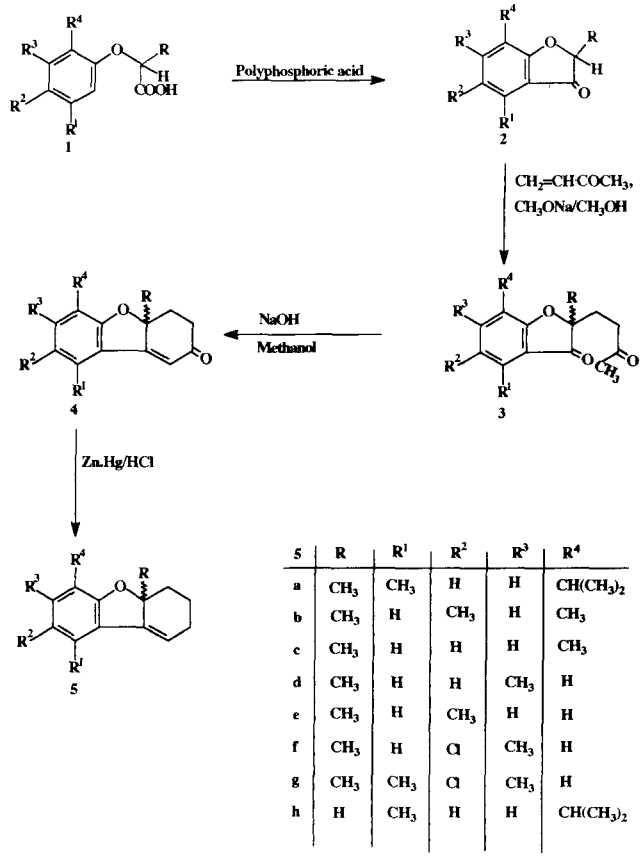
Introduction

Benzofuran derivatives are of specific interest because of their antibacterial and antifungal activities [1–4]. The estrogenic activity [5] of some furocoumarins has been extensively recorded. Recently, syntheses of benzocondensed furanes, benzofuranopyrazoles and benzofuranopyrimidines have been reported [6–9]. We now report an easy synthesis of new tricyclic dibenzofuran derivatives.

The strategy employed for the synthesis of the desired compounds involved the polyphosphoric acid catalysed cyclization of the corresponding 2-phenoxypropionic acids **1** to benzofuran-3-ones **2a–h**, followed by reaction with methylvinylketone in the presence of sodium methoxide to give compounds **3a–h**. The latter are cyclized by methanolic alkali to obtain **4a–h**. *Clemmensen* reduction of compounds **4a–h** yields the desired 2,3,4-trihydrodibenzofuranes **5a–h**. The overall yield of this 4 step preparation is 60 to 80%.

Experimental

All chemicals were of AR grade and used without further purification. Melting points were taken by the open capillary method and are uncorrected. Proton magnetic resonance spectra were recorded using *TMS* as an internal standard with a Perkin–Elmer R-32 90 MHz spectrometer. IR spectra were recorded on a Shimazdu IR-437 spectrometer. Column chromatography was carried out using E.



5	R	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H	$CH(CH_3)_2$
b	CH_3	H	CH_3	H	CH_3
c	CH_3	H	H	H	CH_3
d	CH_3	H	H	CH_3	H
e	CH_3	H	CH_3	H	H
f	CH_3	H	Cl	CH_3	H
g	CH_3	CH_3	Cl	CH_3	H
h	H	CH_3	H	H	$CH(CH_3)_2$

Table 1. Yields and melting points of **2b–h** and **3b–h**. All compounds gave satisfying elemental analyses

Compound	Yield (%)	M.p. (°C)	Molecular formula	Molecular weight
2a	50	88	$C_{13}H_{16}O_2$	204.3
2b	60	90	$C_{11}H_{12}O_2$	176.2
2c	62	87	$C_{10}H_{10}O_2$	162.2
2d	60	100	$C_{10}H_{10}O_2$	162.2
2e	58	85	$C_{10}H_{10}O_2$	162.2
2f	55	93	$C_{10}H_9O_2Cl$	196.7
2g	59	82	$C_{11}H_{11}O_2Cl$	210.7
2h	60	79	$C_{12}H_{14}O_2$	190.2
3a	82	124	$C_{17}H_{22}O_3$	274.4
3b	75	98	$C_{15}H_{18}O_3$	246.3
3c	78	92	$C_{14}H_{16}O_3$	232.3
3d	69	114	$C_{14}H_{16}O_3$	232.3
3e	77	105	$C_{14}H_{16}O_3$	232.3
3f	68	97	$C_{14}H_{15}O_3Cl$	266.3
3g	75	91	$C_{15}H_{17}O_3Cl$	280.8
3h	73	85	$C_{16}H_{20}O_3$	260.3

Table 2. IR and ^{1}H NMR spectral data of compounds **2a–h** and **3a–h**

Compound	IR (KBr) ν (cm^{-1})	NMR ($CDCl_3$) δ (ppm)
2a	1710 (C=O), 1600 (C=C), 1060 (C–O–C)	1.1 (d, J = 7.5 Hz, 6H), 1.5 (d, J = 7 Hz, CH_3), 2.3 (s, CH_3), 3.2 (m, CH), 4.6 (q, J = 7 Hz, OCH), 6.9–7.3 (m, 2H, arom.)
2b	1710 (C=O), 1600 (C=C), 1060 (C–O–C)	1.55 (d, J = 7.5 Hz, CH_3), 2.35 (s, 6H), 4.95 (q, J = 7 Hz, OCH), 6.55–7.15 (m, 2H, arom.)
2c	1715 (C=O), 1595 (C=C), 1065 (C–O–C)	1.5 (d, J = 7 Hz, CH_3), 2.3 (s, CH_3), 4.95 (q, J = 7 Hz, OCH), 6.9–7.2 (m, 3H, arom.)
2d	1710 (C=O), 1605 (C=C), 1065 (C–O–C)	1.55 (d, J = 7 Hz, CH_3), 2.3 (s, CH_3), 4.75 (q, J = 7 Hz, OCH), 6.9–7.2 (m, 3H, arom.)
2e	1700 (C=O), 1600 (C=O), 1070 (C–O–C)	1.52 (d, J = 7 Hz, CH_3), 2.3 (s, CH_3), 4.76 (q, J = 7 Hz, OCH), 6.6–7.1 (m, 3H arom.)
2f	1710 (C=O), 1600 (C=C), 1070 (C–O–C), 760 (C–Cl)	1.53 (d, J = 7.5 Hz, CH_3), 2.3 (s, CH_3), 4.75 (q, J = 7 Hz, OCH), 6.6–7.15 (m, 2H, arom.)
2g	1715 (C=O), 1600 (C=C), 1065 (C–O–C), 760 (C–Cl)	1.58 (d, J = 7.5 Hz, 6H), 2.35 (s, 6H), 4.7 (q, J = 7 Hz, OCH), 7.0 (s, 1H, arom.)
2h	1710 (C=O), 1605 (C=C), 1070 (C–O–C)	1.1 (d, J = 7.5 Hz, 6H), 2.3 (s, CH_3), 3.2 (m, CH), 4.74 (s, CH_2CO), 6.6–7.15 (m, 2H, arom.)
3a	1710 (C=O), 1700 (C=O), 1600 (C=C), 1070 (C–O–C)	1.1 (d, J = 7.5 Hz, 6H), 1.3 (t, J = 7 Hz, CH_2), 1.8 (s, CH_3), 2.1 (s, $COCH_3$), 2.4 (t, J = 7 Hz, $COCH_2$), 2.3 (s, CH_3), 3.2 (m, CH), 6.9–7.3 (m, 2H, arom.)
3b	1715 (C=O), 1700 (C=O), 1600 (C=C), 1065 (C–O–C)	1.3 (t, J = 7.0 Hz, CH_2), 1.65 (s, CH_3), 2.1 (s, $COCH_3$), 2.35 (s, 6H), 2.45 (t, J = 7 Hz, $COCH_2$), 6.1–7.1 (m, 2H, arom.)
3c	1710 (C=O), 1700 (C=O)	1.33 (t, J = 7 Hz, CH_2), 1.6 (s, CH_3), 2.15 (s, $COCH_3$), 2.3 (s, CH_3), 2.4 (t, J = 7 Hz, $COCH_2$), 6.4–7.2 (m, 2H, arom.)
3d	1710 (C=C), 1700 (C=O) 1605 (C=C), 1070 (C–O–C)	1.32 (t, J = 7 Hz, CH_2), 1.62 (s, CH_3), 2.12 (s, $COCH_3$), 2.35 (s, CH_3), 2.45 (t, J = 7 Hz, $COCH_2$), 6.9–7.15 (2H, arom.)
3e	1720 (C=O), 1700 (C=O) 1600 (C=C), 1065 (C–O–C)	1.33 (t, J = 7.1 Hz, CH_2), 1.65 (s, CH_3), 2.15 (s, $COCH_3$), 2.32 (s, CH_3), 2.4 (t, J = 7 Hz, $COCH_2$), 6.6–7.15 (m, 3H, arom.)
3f	1715 (C=O), 1695 (C=O) 1600 (C=C), 1065 (C–O–C) 760 (C–Cl)	1.32 (t, J = 7 Hz, CH_2), 1.62 (s, CH_3), 2.15 (s, $COCH_3$), 2.35 (s, CH_3), 2.45 (t, J = 7 Hz, $COCH_2$), 7.25 (m, 2H, arom.)
3g	1720 (C=O), 1700 (C=O), 1605 (C=C), 1070 (C–O–C), 760 (C–Cl)	1.35 (t, J = 7 Hz, CH_2), 1.65 (s, CH_3), 2.13 (s, $COCH_3$), 2.33 (s, 6H), 2.4 (t, J = 7 Hz, $COCH_2$), 7.15 (s, 1H, arom.)
3h	1715 (C=O), 1700 (C=O), 1600 (C=C), 1070 (C–O–C)	1.1 (d, J = 7.5 Hz, 6H), 1.3 (t, J = 7 Hz, CH_2), 2.1 (s, $COCH_3$), 2.4 (t, J = 7 Hz, $COCH_2$), 2.3 (s, CH_3), 3.2 (m, CH), 5.1 (t, OCH), 6.6–7.15 (m, 2H, arom.)

Merck silica gel-G (100–200 μ particle size). 2-Phenoxypropionic acids were prepared from substituted phenols and 2-chloropropionic acid as starting material by a known method [10].

General procedure for the preparation of benzofuran-3-(1H)-ones (**2**)

0.045 mol of the corresponding 2-phenoxypropionic acid were added to a stirred solution of 10.0 g in 15 ml phosphorus pentoxide orthophosphoric acid. The reaction mixture was heated for 2 h at 80 °C, cooled and poured in ice-water (200 ml). The neutralization of the reaction mixture with sodium bicarbonate gave a gummy solid which was dissolved in chloroform. Removal of the solvent under vacuum gave a brownish mass which was recrystallized from methanol to furnish **2** (cf. Tables 1 and 2).

General procedure for the preparation of 2-(butan-3-'one-1'-yl)-benzofuran-3(1H)-ones (**3**)

A solution of 12.7 mmol of **2** in methanol (10 ml) was treated with a 1*M* sodium methoxide solution in methanol (10 ml) and methylvinylketone (12.7 mmol). The reaction mixture was refluxed for 6 h cooled and the solvent removed under reduced pressure. The residue was treated with ice-water (100 ml) and the separated semisolid mass was dissolved in ether. Removal of ether gave a solid which was crystallized from methanol (cf. Tables 1 and 2).

General procedure for the preparation of 1,2,3-trihydrodibenzofuran-3-ones (**4**)

A solution of 10 mmol of **3** in methanol (10 ml) was heated with 2*N* sodium hydroxide (10 ml) on a steam bath for 6 h, cooled, concentrated and neutralized with 2*N* hydrochloric acid. The separated solid was extracted with chloroform and the solvent was removed under reduced pressure to obtain a solid which was recrystallized from methanol (cf. Tables 3 and 4).

Table 3. Yields and melting points of **4a–h** and **5a–h**. All compounds gave satisfying elemental analyses

Compound	Yield (%)	M.p. (°C)	Molecular formula	Molecular weight
4a	60	85	$C_{17}H_{20}O_2$	256.3
4b	72	164	$C_{15}H_{16}O_2$	228.3
4c	74	132	$C_{14}H_{14}O_2$	214.3
4d	70	120	$C_{14}H_{14}O_2$	214.3
4e	68	145	$C_{14}H_{14}O_2$	214.3
4f	72	185	$C_{14}H_{13}O_2Cl$	248.7
4g	73	144	$C_{15}H_{15}O_2Cl$	262.8
4h	69	172	$C_{16}H_{18}O_2$	242.3
5a	50	110	$C_{17}H_{22}O$	242.3
5b	68	95	$C_{15}H_{18}O$	214.3
5c	72	92	$C_{14}H_{16}O$	200.3
5d	57	90	$C_{14}H_{16}O$	200.3
5e	73	96	$C_{14}H_{16}O$	200.3
5f	80	84	$C_{14}H_{15}OCl$	234.8
5b	65	88	$C_{15}H_{17}OCl$	248.8
5h	82	110	$C_{16}H_{20}O$	228.3

General procedure for the preparation of 1,2,3-trihydrodibenzofuranes (**5**)

To a solution of 7.0 mmol of in **4** toluene (20 ml) and a suspension of mercuric chloride and zinc chloride (10 g) in concentrated hydrochloric acid (15 ml) was added. The reaction mixture was refluxed for 26 h, cooled and the separated organic layer was dissolved in ether. Removal of the solvent under reduced pressure gave a solid which was recrystallized from methanol (cf. Tables 3 and 4).

Table 4. IR and ^{1}H NMR spectral data of compounds **4a–h** and **5a–h**

Compound	IR (KBr) ν(cm^{-1})	NMR ($CDCl_3$) δ(ppm)
4a	1650 (C=O) 1600 (C=C)	1.1 (d, J = 7.5 Hz, 6H), 1.32 (t, J = 7 Hz, CH_2), 1.6 (s, CH_3), 2.35 (s, CH_3), 2.4 (t, J = 7 Hz, $COCH_2$), 3.3 (m, CH), 6.9–7.3 (m, 2H, arom.), 8.15 (s, =CH)
4b	1650 (C=O), 1600 (C=C)	1.25 (t, J = 7 Hz, CH_2), 1.55 (s, CH_3), 2.35 (s, 6H) 2.4 (t, J = 7 Hz, $COCH_2$), 6.9–7.1 (m, 2H, arom.), 8.15 (s, =CH)
4b	1645 (C=O), 1600 (C=C),	1.3 (t, J = 7 Hz, CH_2), 1.55 (s, CH_3), 2.3 (s, CH_3), 2.45 (t, J = 7 Hz, $COCH_2$), 6.7–7.1 (m, 3H, arom.), 8.18 (s, =CH)
4d	1650 (C=O), 1605 (C=C), 1070 (C–O–C)	1.25 (t, J = 7 Hz, 2H, CH_2), 1.58 (s, CH_3), 2.35 (s, CH_3), 2.42 (t, J = 7 Hz, $COCH_2$), 6.7–7.1 (m, 3H, arom.), 8.15 (s, =CH)
4e	1650 (C=O), 1600 (C=C), 1065 (C–O–C)	1.28 (t, J = 7 Hz, CH_2), 1.52 (s, CH_3), 2.35 (s, CH_3), 2.43 (t, J = 7 Hz, $COCH_2$), 6.6–7.15 (m, 3H, arom.), 8.2 (s, =CH)
4f	1645 (C=O), 1600 (C=C), 1070 (C–O–C), 755 (C–Cl)	1.3 (t, J = 7 Hz, CH_2), 1.55 (s, CH_3), 2.3 (s, CH_3), 2.45 (s, $COCH_2$), 7–7.2 (m, 2H, arom.), 8.17 (s, =CH)
4g	1650 (C=O), 1605 (C=C), 1065 (C–O–C), 760 (C–Cl)	1.32 (t, J = 7 Hz, CH_2), 1.58 (s, CH_3), 2.35 (s, 6H), 2.43 (t, J = 7 Hz, $COCH_2$), 7.15 (s, 1H, arom.), 8.2 (s, =CH)
4h	1645 (C=O), 1600 (C=C),	1.1 (d, J = 7.5 Hz, 6 H), 1.3 (q, J = 7.5 Hz), 2.4 (t, J = 7.5 Hz, $COCH_2$), 3.2 (m, CH), 4.8 (s, OCH), 6.6–7.1 (m, 2H, arom.), 8.12 (s, =CH)
5a	1600 (C=C), 1060 (C–O–C)	0.9 (m, CH_2), 1.1 (d, J = 7 Hz, 6H), 1.3 (t, J = 7 Hz, CH_2), 1.55 (s, CH_3), 2.2 (t, J = 7 Hz, CH_2), 2.35 (s, CH_3), 3.2 (m, CH), 6.16 (t, J = 7 Hz, =CH), 6.8–7.15 (m, 2H, arom.)
5b	1600 (C=C), 1065 (C–O–C)	0.8 (m, CH_2), 1.35 (t, J = 7 Hz, CH_2), 1.55 (s, CH_3), 2.2 (q, CH_2), 2.35 (s, 6H), 6.2 (t, J = 7 Hz, =CH), 6.9–7.2 (m, 2H, arom.)
5c	1605 (C=C), 1070 (C–O–C)	0.85 (m, 2H, CH_2), 1.3 (t, J = 7 Hz, CH_2), 1.58 (s, CH_3), 2.18 (q, J = 7 Hz, CH_2), 2.35 (s, CH_3), 6.18 (t, J = 7 Hz, =CH), 6.9–7.15 (m, 3H, arom.)
5d	1600 (C=O) 1065 (C–O–C)	0.8–0.95 (m, CH_2), 1.32 (t, J = 7 Hz, CH_2), 1.56 (s, CH_3), 2.15 (q, J = 7 Hz, CH_2), 2.3 (s, CH_3), 6.2 (t, J = 7 Hz, =CH), 6.9–7.2 (m, 3H, arom.)

Table 4. (continued)

Compound	IR (KBr) $\nu(cm^{-1})$	NMR ($CDCl_3$) δ(ppm)
5e	1605 (C=C), 1070 (C–O–C)	0.8–0.92 (m, CH_2), 1.33 (t, $J = 7$ Hz, CH_2), 1.57 (s, CH_3), 2.18 (q, $J = 7$ Hz, CH_2), 2.35 (s, CH_3), 6.18 (t, $J = 7$ Hz, =CH), 6.6–7.1 (m, 3H, arom.)
5f	1600 (C=C), 1065 (C–O–C) 760 (C–Cl)	0.85–0.95 (m, CH_2), 1.3 (t, $J = 7$ Hz, CH_2), 1.5 (s, CH_3), 2.22 (q, $J = 7$ Hz, CH_2), 2.28 (s, CH_3), 6.18 (t, $J = 7$ Hz, =CH), 6.9–7.2 (m, 2H, arom.)
5g	1605 (C=C), 1070 (C–O–C), 760 (C–Cl)	0.8–0.9 (m, CH_2), 1.35 (t, $J = 7$ Hz, CH_2), 2.2 (q, $J = 7$ Hz, CH_2), 2.35 (s, 6H), 6.18 (t, $J = 7$ Hz, =CH), 7.1 (s, 1H, arom.)
5h	1600 (C=C), 1070 (C–O–C)	0.9 (m, CH_2), 1.1 (d, $J = 7.5$ Hz, 6H), 1.4 (q, $J = 7$ Hz, CH_2), 2.2 (q, $J = 7$ Hz, CH_2), 2.35 (s, CH_3), 3.2 (m, CH), 4.8 (t, $J = 7.5$ Hz, OCH), 6.6 (s, =CH), 6.5–7.15 (m, 2H, arom.)

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