Short communication

Microwave-Assisted Synthesis of Benzofuran-3(2*H*)-ones

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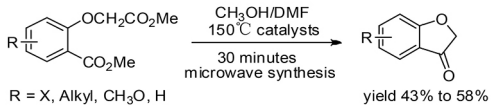
Abstract

A new method for the synthesis of benzofuran-3(2*H*)-ones under microwave conditions was developed. The reaction conditions were screened, and the scope of benzoate substrates was investigated. The results showed that our method could provide rapid access to these important dihydrobenzofuranones in 43% to 58% yields.

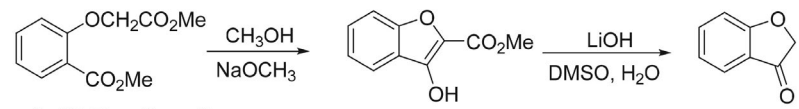


Keywords: Benzofuranones; microwave-Assisted Synthesis; cyclization, dihydrobenzofuranones

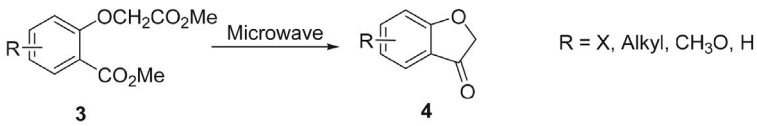
1. Introduction

Benzofuranone is an important pharmacophore in medicinal and natural products,[1] in addition to being a very common motif in organic synthesis.[2] The previously reported classical synthesis of benzofuranones involved two steps, as shown in **Scheme 1:** cyclization of methyl 2-(2-methoxy-2-oxoethoxy)benzoate to give methyl 3-hydroxybenzofuran-2-carboxylate, and subsequent Krapcho reaction of it to provide benzofuran-3(2*H*)-one. While this method seems to be simple and reliable theoretically, the yield in the Krapcho reaction is typically not very high (40% to 60%, as revealed in our experiments); furthermore, prolonged reaction with heating is required in both the steps. Recently, microwave-assisted synthesis has seen widespread use in many kinds of organic reactions,[3] especially in the synthesis of heterocyclic compounds.[4] This is a quick and facile method for organic synthesis, often giving higher product yields and allowing for easier isolation.[5] However, microwave synthesis of

Previous work:[8]



Our work:



Scheme 1: The proposal of the research work.

benzofuranones has seldom been reported.[6] We have adopted the microwave-assisted synthesis to obtain the desired benzofuranones for our study on chiral dihydrobenzofuranones.[7]

2. Experimental

All commercial reagents were purchased from Sigma-Aldrich, Alfa-Aesar, and Acros and used without further purification, unless otherwise specified. The progress of the reaction was monitored by Thin-layer Chromatography. Microwave reactions were carried out in a Biotage Initiator system (Biotage Initiator +, Sweden), and the temperature of the reaction mixture was measured using the external IR sensor present in the instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometers operating at 400 MHz and 100 MHz, respectively. The peaks were internally referenced to TMS (0.00 ppm) or to the residual undeuterated solvent signal. Peak multiplicities are reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. All melting points were measured using an SGWX-4 micro melting point apparatus and are reported uncorrected. IR spectra were recorded as KBr disks on a Perkin-Elmer FT-IR spectrometer.

General procedure for the preparation of compounds 2 (2a as a model). To a solution of **1a** (5 mmol) in CH_3OH (25 mL) concentrated sulfuric acid was added dropwise (10 drops). After stirring under reflux for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to afford **2a**.

General procedure for the preparation of compounds 3 (3a as a model). To a solution of **2a** (304 mg, 2 mmol) in acetone (10 mL) K_2CO_3 (966 mg, 7 mmol) and $BrCH_2CO_2Me$ (367 mg, 2.4 mmol) were added. After stirring under reflux for 3 h, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate = 3:1 as the eluent to give **3a** (417 mg, 93%) as a white solid.

Methyl 2-(2-methoxy-2-oxoethoxy)benzoate (3a):[9] White solid; yield: 93%; m.p. 49–50 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2950, 1771, 1725, 1598, 1582, 1494, 1439, 1258. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, J_1 = 1.6 Hz, J_2 = 7.7 Hz, 1H), 7.48–7.42 (m, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.74 (s, 2H), 3.91 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 166.5, 157.6, 133.6, 132.2, 121.9, 121.4, 114.4, 66.8, 52.5, 52.3; HRMS (ESI): calcd. for $C_{11}H_{12}NaO_5$ $[M+Na]^+$: 247.0577; found: 247.0578.

Methyl 2-(2-methoxy-2-oxoethoxy)-3-methylbenzoate (3b): Yellow oil; yield: 81%; FT-IR (KBr, ν_{max}/cm^{-1}): 2953, 1765, 1728, 1593, 1466, 1434, 1275. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 4.60 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.6, 156.4, 135.6, 133.0, 129.6, 124.6, 124.5, 70.6, 52.4, 52.3, 16.3; HRMS (ESI): calcd. for $C_{12}H_{14}NaO_5$ $[M+Na]^+$: 261.0733; found: 261.0734.

Methyl 2-(2-methoxy-2-oxoethoxy)-4-methylbenzoate (3c): White solid; yield: 92%; m.p. 47–49 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2947, 1733, 1609, 1573, 1505, 1428, 1255. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.69 (s, 1H), 4.72 (s, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 166.4, 157.9, 144.8, 132.3, 122.8, 118.4, 115.4, 66.9, 52.5, 52.2, 22.0; HRMS (ESI): calcd. for $C_{12}H_{14}NaO_5$ $[M+Na]^+$: 261.0733; found: 261.0737.

Methyl 4-chloro-2-(2-methoxy-2-oxoethoxy)benzoate (3d): White solid; yield: 87%; m.p. 88–89 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2964, 1755, 1723, 1595, 1573, 1488, 1253, 773. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 1H), 7.04 (dd, J_1 = 8.4, J_2 = 1.8, 1H), 6.88 (d, J = 1.8 Hz, 1H), 4.73 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 165.6, 158.3, 139.4, 133.3, 122.2, 119.7, 114.9, 66.7, 52.6, 52.4; HRMS (ESI): calcd. for $C_{11}H_{11}ClNaO_5$ $[M+Na]^+$: 281.0187; found: 281.0189.

Methyl 5-methoxy-2-(2-methoxy-2-oxoethoxy)benzoate (3e):[10] White solid; yield: 81%; m.p. 81–83 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2960, 1759, 1725, 1588, 1565, 1503, 1436, 1220, 1206. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 3.2 Hz, 1H), 7.00 (dd, J_1 = 3.2 Hz, J_2 = 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 4.66 (s, 2H), 3.91 (s, 3H), 3.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.3, 154.6, 152.0, 122.5, 119.8, 118.0, 116.1, 68.5, 56.0, 52.5, 52.4; HRMS (ESI): calcd. for $C_{12}H_{14}NaO_6$ $[M+Na]^+$: 277.0683; found: 277.0683.

Methyl 5-ethyl-2-(2-methoxy-2-oxoethoxy)benzoate (3f): Colorless oil; yield: 85%; FT-IR (KBr, ν_{max}/cm^{-1}): 2960, 2875, 1760, 1731, 1612, 1589, 1498, 1437, 1255. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 2.3 Hz, 1H), 7.28–7.25 (m, 1H), 6.83 (d, J = 8.5 Hz, 1H), 4.70 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 166.7, 155.7, 137.9, 133.0, 131.3, 121.2, 114.9, 67.2, 52.4, 52.3,

28.0, 15.7; HRMS (ESI): calcd. for $C_{13}H_{16}NaO_5$ $[M+Na]^+$: 275.0890; found: 275.0892.

Methyl 2-ethyl-6-(2-methoxy-2-oxoethoxy)benzoate (3g): Colorless oil; yield: 82%; FT-IR (KBr, ν_{max}/cm^{-1}): 2970, 2955, 1761, 1732, 1601, 1585, 1470, 1435, 1254. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.64 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 168.6, 154.8, 143.2, 130.6, 124.2, 122.2, 110.0, 66.4, 52.4, 52.4, 26.7, 15.5; HRMS (ESI): calcd. for $C_{13}H_{16}NaO_5$ $[M+Na]^+$: 275.0890; found: 275.0887.

General procedure for the preparation of compounds 4 (4a as a model). K_3PO_4 (159 mg, 0.75 mmol) was added to a solution of **3a** (224 mg, 1 mmol) in DMF (1.0 mL) and MeOH (0.5 mL). The mixture was heated at 150 °C for 30 min under stirring and 300 W microwave irradiation power. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (5 mL). The resulting organic layer was washed with 1 N HCl (5 mL) and dried (Na_2SO_4). The organic layer was then concentrated and purified by column chromatography using petroleum ether/ethyl acetate = 10:1 as the eluent and further purified on a gel column to give **4a** (58 mg, 43%) as a yellow solid.

Benzofuran-3(2*H*)-one (4a):[11] Yellow solid; yield: 43%; m.p. 95–98 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2933, 1723, 1614, 1591, 1473, 1466, 1317. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 174.2, 138.1, 124.3, 122.2, 121.4, 113.9, 74.9; HRMS (ESI): calcd. for $C_8H_7O_2$ $[M+H]^+$: 135.0441; found: 135.0444.

7-Methylbenzofuran-3(2*H*)-one (4b):[12] Yellow solid; yield: 52%; m.p. 86.5–87.5 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2925, 1704, 1603, 1497, 1451, 1434, 1323. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 4.64 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 173.0, 138.5, 124.1, 122.1, 121.5, 120.8, 74.9, 14.4; HRMS (ESI): calcd. for $C_9H_8NaO_2$ $[M+Na]^+$: 171.0417; found: 171.0414.

6-Methylbenzofuran-3(2*H*)-one (4c):[13] Yellow solid; yield: 47%; m.p. 85–86 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2927, 1705, 1619, 1594, 1495, 1449, 1325. ^1H NMR (400 MHz, $CDCl_3$): 7.55 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.61 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 174.8, 150.2, 123.8, 123.8, 119.0, 113.8, 75.1, 22.7; HRMS (ESI): calcd. for $C_9H_8NaO_2$ $[M+Na]^+$: 171.0417; found: 171.0422.

6-Chlorobenzofuran-3(2*H*)-one (4d):[14] Yellow solid; yield: 58%; m.p. 126–127 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 3065, 1703, 1612, 1589, 1438, 1320, 794. ^1H NMR (400 MHz, $CDCl_3$): 7.60 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.08 (dd, J_1 = 8.2, J_2 = 1.6 Hz, 1H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 174.3, 144.3, 125.1, 123.3, 120.0, 114.3, 75.5; HRMS (ESI): calcd. for $C_8H_6ClO_2$ $[M+H]^+$: 169.0051; found: 169.0053.

5-Methoxybenzofuran-3(2*H*)-one (4e):[15] Yellow solid; yield: 55%; m.p. 90–92 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2941, 2837, 1713, 1601, 1490, 1433, 1343, 1248. ^1H NMR (400 MHz, $CDCl_3$): 7.26–7.23 (m, 1H), 7.09–7.05 (m, 2H), 4.65 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 169.6, 155.2, 128.2, 121.3, 114.7, 104.0, 75.7, 56.1; HRMS (ESI): calcd. $C_9H_9O_3$ $[M+H]^+$: 165.0546; found: 165.0549.

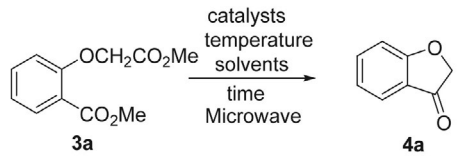
5-Ethylbenzofuran-3(2*H*)-one (4f): Yellow solid; yield: 45%; m.p. 117–119 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2966, 1717, 1621, 1598, 1491, 1458, 1317. ^1H NMR (400 MHz, $CDCl_3$): 7.50–7.44 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.62 (s, 2H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 172.9, 138.5, 138.4, 122.4, 121.3, 113.5, 75.2, 28.2, 15.8; HRMS (ESI): calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.0754; found: 163.0753.

4-**Ethylbenzofuran-3(2H)-one (4g)**: Yellow solid; yield: 49%; m.p. 100–101 °C; FT-IR (KBr, ν_{max}/cm^{-1}): 2972, 1725, 1617, 1586, 1479, 1447, 1322. ^1H NMR (400 MHz, $CDCl_3$): 7.51–7.46 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 4.58 (s, 2H), 3.01 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 174.8, 146.4, 137.8, 121.6, 118.7, 111.0, 74.7, 24.9, 14.7; HRMS (ESI): calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.0754; found: 163.0757.

3. Results and Discussion

First, various conditions, including temperature, reaction time, catalyst, and solvent, for the microwave-assisted cyclization reaction using methyl 2-(2-methoxy-2-oxoethoxy)benzoate were extensively screened (Table 1). The results showed that the temperature was the key factor influencing the reaction, and that the optimal temperature for cyclization was 150 °C (Table 1, entries 1–6). The reaction was fast and proceeded to completion in 30 min (entries 1–42). The solutions were subsequently examined. Cosolvent systems seemed to be better than single solvents (Table 1, entries 1–8). Among the catalysts investigated, K_3PO_4, CH_3CO_2K, and Cs_2CO_3 were more efficient during these common alkaline salts (Table 1, entries 19–31). Combined with the temperature, the reaction time, the catalyst, and the solution, the optimum condition was achieved with the best yield 43% (Table 1, entry 25).

Table 1: Optimization of Reaction Conditions for Microwave-assisted Synthesis of Benzofuranones

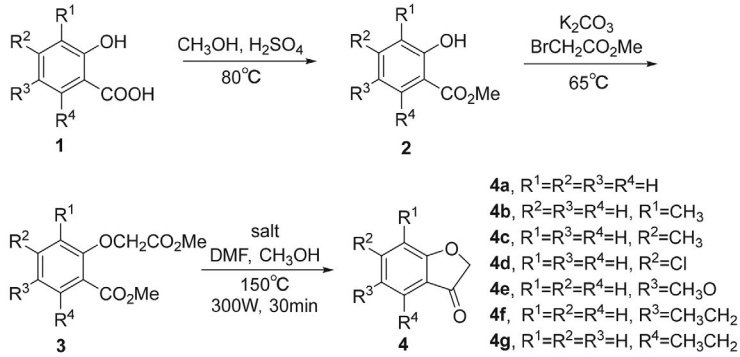


3a **4a**

Entry	*T* (°C)	Time (min)	Catalyst (eq)	Solvent	Yield[f] (%)
1	60	20	K_2CO_3 (1.0)	CH_3OH/DMF[b]	0
2	100	20	K_2CO_3 (1.0)	CH_3OH/DMF	0
3	120	20	K_2CO_3 (1.0)	CH_3OH/DMF	0
4	140	20	K_2CO_3 (1.0)	CH_3OH/DMF	17
5	150	20	K_2CO_3 (1.0)	CH_3OH/DMF	23
6	170	20	K_2CO_3 (1.0)	CH_3OH/DMF	19
7	150	20	K_2CO_3 (1.0)	DMF	8
8	170	20	K_2CO_3 (1.0)	DMF	7
9	170	20	K_2CO_3 (1.0)	DMSO[c]	7
10	140	20	K_2CO_3 (1.0)	DMF	8
11	140	30	K_2CO_3 (1.0)	DMF	10
12	150	15	K_2CO_3 (1.0)	DMF	6
13	150	20	K_2CO_3 (1.0)	DMSO	9
14	190	20	K_2CO_3 (1.0)	DMSO	5
15	150	20	K_2CO_3 (0.5)	DMF	7
16	150	30	K_2CO_3 (0.75)	MEG[d]	15
17	170	20	K_2CO_3 (0.5)	MEG	8
18	170	20	K_2CO_3 (0.75)	MEG	13
19	150	30	K_2CO_3 (0.75)	CH_3OH/DMF	27
20	150	20	Cs_2CO_3 (0.5)	CH_3OH/DMF	31
21	150	30	Cs_2CO_3 (0.75)	CH_3OH/DMF	37
22	150	30	Cs_2CO_3 (0.5)	MEG	12
23	150	30	Cs_2CO_3 (0.5)	CH_3OH/DMF	34
24	150	30	K_3PO_4 (0.5)	CH_3OH/DMF	39
25	150	30	K_3PO_4 (0.75)	CH_3OH/DMF	43
26	150	30	K_3PO_4 (1.0)	CH_3OH/DMF	37
27	150	30	K_3PO_4 (0.75)	MEG	23
29	150	30	$NaHCO_3$ (0.75)	CH_3OH/DMF	17
30	150	30	$NaHCO_3$ (1.0)	CH_3OH/DMF	15
31	150	30	$NaHCO_3$ (0.75)	MEG	11
32	150	30	$NaHCO_3$ (0.75)	DMSO	9
33	150	30	Na_2CO_3 (1.0)	CH_3OH/DMF	28
34	150	30	Na_2CO_3 (0.75)	CH_3OH/DMF	33
35	150	30	$C_2H_{10}N_6 \cdot H_2CO_3$[a] (0.5)	CH_3OH/DMF	13
36	150	30	$C_2H_{10}N_6 \cdot H_2CO_3$ (0.75)	CH_3OH/DMF	17
37	150	30	$C_2H_{10}N_6 \cdot H_2CO_3$ (0.75)	CH_3OH	0
38	150	30	$C_2H_{10}N_6 \cdot H_2CO_3$ (0.75)	DMF	11
39	150	30	Ag_2CO_3 (0.75)	CH_3OH/DMF	0
40	150	30	K_2CO_3 (0.75)	DMF/CH_3CH_2OH	13
41	150	30	K_2CO_3 (0.75)	CH_3OH/DMAC[e]	15
42	150	30	CH_3CO_2K (0.75)	CH_3OH/DMF	38

[a] Guanidine Carbonate. [b] *N*,*N*-Dimethylformamide. [c] Dimethyl Sulfoxide. [d] Ethylene Glycol.
[e] *N*,*N*-Dimethylacetamide. [f] Isolated yield.

Next, scope of the substrates was investigated, as shown in Scheme 2. In order to observe the effect of the functional group at different positions on the benzene ring, phenyl compounds **3** were prepared from easily available 2-hydroxybenzoic acids **1** with alkyl, alkoxy, or halogen substituents. Esterification of **1** provided compounds **2**, which upon etherification with methyl 2-bromoacetate furnished the target products **3**. Cyclization of **3** under the optimal microwave conditions was performed as depicted in Scheme 2. All the substrates **3** could give the corresponding benzofuran-3(2*H*)-ones and the product yields were only slightly different from those in our experiments (43% to 58%).



Entry	*T* (°C)	Time (min)	Catalyst (eq)	Solvent	Yield[f] (%)
4a	150	30	K_3PO_4 0.75	CH_3OH/DMF[b]	43
4b	150	30	CH_3CO_2K 0.75	CH_3OH/DMF	52
4c	150	30	K_3PO_4 0.75	CH_3OH/DMF	47
4d	150	30	CH_3CO_2K 0.75	CH_3OH/DMF	58
4e	150	30	K_3PO_4 0.75	CH_3OH/DMF	55
4f	150	30	Cs_2CO_3 0.75	CH_3OH/DMF	45
4g	150	30	K_3PO_4 0.75	CH_3OH/DMF	49

[b] *N*,*N*-Dimethylformamide. [f] Isolated yield.

Scheme 2: Preparation of different benzoates and their cyclization under microwave condition.

4. Conclusions

In conclusion, a new synthetic route to benzofuran-3(2*H*)-ones was established. The proposed method provides rapid and facile access to these important motifs, although the yields are still low and need to be improved in a future study.

5. Acknowledgements

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Povzetek

V prispevku je opisan razvoj nove metode za sintezo benzofuran-3(2*H*)-onov z uporabo mikrovalov. Podan je pregled reakcijskih pogojev in širši nabor benzoatnih substratov. Predstavljeni rezultati kažejo, da opisana metoda omogoča hitro pripravo dihidrobenzofuranonov s 43 % do 58 %-nim izkoristkom.