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Microwave-Assisted Dieckmann Reaction: Efficient One-Step Synthesis of 2-Aroylbenzofuran-3-ols

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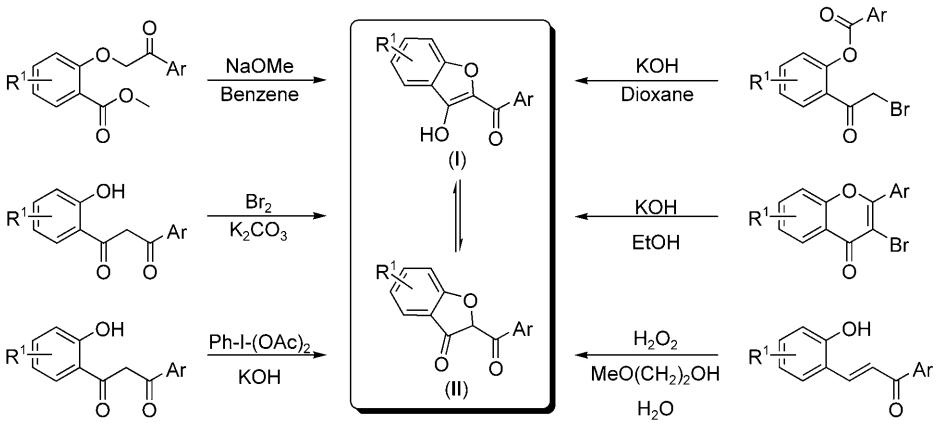
Abstract: This paper describes the first efficient one-step synthesis of 2-aroylbenzofuran-3-ols from the microwave-assisted Dieckmann reaction of substituted methylsalicylates with 2-bromo-1-aroylethanones in alkaline aprotic solvents. This method features excellent yields, short reaction time (15 min) and high functional group compatibility, making it an efficient and practical approach for the synthesis of 2-aroylbenzofuran-3-ols.

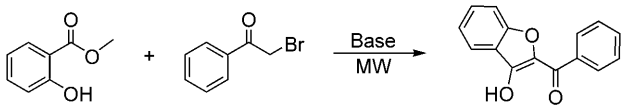
Keywords: 2-aroylbenzofuran-3-ols; cyclization; Dieckmann reaction; microwave irradiation

Benzofuran derivatives are widely distributed in nature, and have attracted increasing interests because of their multiple pharmacological properties and wide applications in drug discovery.[1] For example, 2-aroylbenzofuran-3-ols (**I**, Scheme 1), as a class of typical benzofuran derivatives, not only have unique antitumor and anti-inflammatory activities,[2] but also are useful synthetic intermediates for many drugs.[3] 2-Aroylbenzofuran-3-ols are known to be tautomers of 2-aroylbenzofuran-3-ones (**II**, Scheme 1), and they can be converted to each other under certain conditions.[2a] These tautomers can be prepared by several methods (Scheme 1), including the classic Dieckmann condensation of methyl 2-(2-oxo-2-aroylethoxy)benzoates,[4] cyclocondensation of 2-aroylacetylphenol by bromination,[4a,5] oxidative cyclization of 2-aroylacetylphenol,[6] rearrangement of 3-haloflavones[5c] and biotransformation of 2-hydroxychalcones in cell suspension cultures.[7] However, most of these methods have limited applications because of the poor availability of starting materials and low yields. In addition, they generally require prolonged reaction time and toxic reagents that are not commercially available. Therefore, during the last few decades, major efforts have been made to develop a straightforward approach for the synthesis of 2-aroylbenzofuran-3-ols from readily available starting materials.



Scheme 1. Approaches for the synthesis of 2-aroylbenzofuran-3-ols.

Table 1. Optimization of the microwave-assisted Dieckmann reaction of methyl salicylate with phenacyl bromide.



1a **2a** **3a**

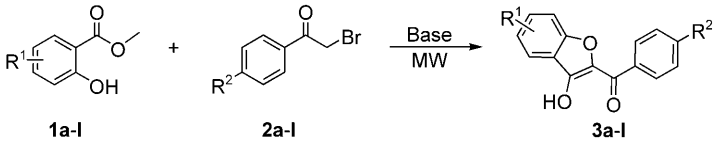
Entry	Solvent	Base	Temp. [°C]	Time [min]	Isolated Yield [%]
1	acetone	NaOAc	80	10	trace
2	acetone	Na_2CO_3	80	10	trace
3	acetone	K_2CO_3	80	10	trace
4	acetone	KOH	80	10	mix.
5	acetone	K_3PO_4	80	10	54
6	toluene	K_3PO_4	80	10	27
7	THF	K_3PO_4	80	10	36
8	1,4-dioxane	K_3PO_4	80	10	35
9	solvent free	K_3PO_4	80	10	trace
10	acetone	K_3PO_4	90	10	88
11	acetone	K_3PO_4	100	10	93
12	acetone	K_3PO_4	110	10	94
13	acetone	K_3PO_4	120	10	89
14	acetone	K_3PO_4	100	5	78
15	acetone	K_3PO_4	100	15	97
16	acetone	K_3PO_4	100	20	96
17	acetone	K_3PO_4	100	25	94

Classic Dieckmann reactions should be able to provide an opportunity for the direct preparation of 2-aroylbenzofuran-3-ols *via* cyclization of methyl 2-(2-oxo-2-aroylethoxy)benzoates. However, it is a highly challenging task to synthesize methyl 2-(2-oxo-2-aroylethoxy)benzoates.[4] The method that was used to prepare methyl 2-(2-oxopropoxy)benzoates could not be transplanted in the synthesis of methyl 2-(2-oxo-2-aroylethoxy)benzoates.[4a] This may be due to the incidental intramolecular condensation reaction of methyl 2-(2-oxo-2-aroylethoxy)benzoates.[4a] This, however, enabled us to develop a new method to synthesize 2-aroylbenzofuran-3-ols from the base-mediated reaction of substituted methyl salicylates with 2-bromo-1-aroylethanones. On the other hand, microwave irradiation, because of its significant enhancement in reaction rates and yields, has emerged as a powerful technique for promoting a variety of chemical reactions.[8] Thus, as part of our ongoing programs to synthesize benzofuran-3-ol derivatives under mild conditions, we describe herein an efficient one-step synthesis of 2-aroylbenzofuran-3-ols *via* microwave-assisted Dieckmann reaction in alkaline aprotic solvents. To the best of our knowledge, this represents an unprecedented example for the direct synthesis of 2-aroylbenzofuran-3-ols from substituted methyl salicylates and 2-bromo-1-aroylethanones as starting materials.

Dieckmann reactions generally proceed in alkaline aprotic solvents to give benzofuran derivatives in poor to moderate yields.[5] Therefore, we firstly investigated the effect of bases, solvents, temperature and reaction time under microwave irradiation. The reaction of methyl salicylate **1a** with phenacyl bromide **2a** in acetone was chosen as a model to optimize the reaction conditions. The results are summarized in Table 1.

As shown in Table 1, compound **3a** could be prepared in good yield only in the presence of potassium phosphate (entries 1–5), and acetone was found to be the best reaction medium (entries 5–9). It should be noted that potassium carbonate was the best base under conventional heating (data not shown). Under the conditions of potassium phosphate and acetone, the yields increased consistently with an increase of the temperature from 80 °C to 100 °C, and were maintained up to 110 °C. Further increase to 120 °C, however, led to a decrease in the yield (entries 10–13). On the other hand, the yields increased with time, i.e., from 78% (5 min) to maximum 97% (15 min) (entries 11 and 14–17). Extending the reaction time longer than 15 min did not change the yield significantly. Taken together, we concluded that, under microwave irradiation, the optimal conditions were 100 °C, 15 min and potassium phosphate in acetone. Then we used these conditions for the microwave-assisted synthesis of 2-aroylbenzofuran-3-ols in the library. The results, together with those obtained under conventional heating for comparison, are shown in Table 2.

Table 2. Microwave-assisted Dieckmann reaction of substituted methyl salicylates **1a–l** with 2-bromo-1-aroylethanones **2a–l**.



1a-l **2a-l** **3a-l**

Compound	R^1 in **1a–l**	R^2	Microwave Irradiation		Conventional Heating	
			Time [min]	Isolated Yield [%]	Time [min]	Isolated Yield [%]
3a	H	H	15	97	360	95
3b	H	MeO	15	94	360	83
3c	H	Me	15	90	360	81
3d	H	Cl	15	92	360	81
3e	5-MeO	H	15	93	360	88
3f	5-MeO	MeO	15	93	360	82
3g	5-MeO	Me	15	93	360	87
3h	5-MeO	Cl	15	89	360	79
3i	3-NO_2	H	15	93	360	71
3j	3-NO_2	MeO	15	88	480	30
3k	3-NO_2	Me	15	87	360	57
3l	3-NO_2	Cl	15	85	360	38

As can be seen from Table 2, moderate to good isolated yields (30–95%) could be achieved under conventional heating, however, the reactions were sluggish (6–8 h) and highly dependent on the starting materials that were used. Prolonging the reaction time or adding excess 2-bromo-1-aroylethanones **2a–l** did not significantly improve the yield. In sharp contrast, under microwave irradiation, the reactions were completed in 15 min and 2-aroylbenzofuran-3-ols were isolated in excellent yields (85–97%). Thus, microwave irradiation increased the yields by 2% to 58%. It should be noted that the electronic properties of the substituents on the aromatic rings of both methyl salicylates and 2-bromo-1-aroylethanones, affected the reaction. When the methyl salicylates bore a strong electron-withdrawing NO_2 group, the yields were relatively low, especially under conventional heating (compounds **3i–l**, Table 2). No product was detected under either conditions in the case of 2-bromo-1-(4-nitrophenyl)ethanone (data not shown). This might be due to the high instability of nitrated 2-bromo-1-aroylethanones under our reaction conditions.

In conclusion, we have developed the first efficient one-step synthesis of 2-aroylbenzofuran-3-ols directly from Dieckmann reaction of substituted methyl salicylates with 2-bromo-1-aroylethanones in acetone under microwave irradiation. This reaction boasts of excellent yields, short reaction time (15 min) and easy manipulation. These advantages ensure its practical applications as an efficient approach for the synthesis of 2-aroylbenzofuran-3-ols.

Experimental Section

General Procedure for Conventional Preparation of 2-Aroylbenzofuran-3-ols 3

2-Benzoylbenzofuran-3-ol (3a) as an example: Phenacyl bromide (1.09 g, 5.5 mmol) and potassium carbonate (2.09 g, 15 mmol) were added to a solution of methyl salicylate (0.76 g, 5.0 mmol) in dry acetone (6 mL). The resulting mixture was refluxed and monitored by TLC. After 6 h, the reaction mixture was filtered and washed with acetone (12 mL). The obtained solid was then dispersed in water (30 mL) and acidified with 3 N HCl. The resulted precipitate was collected by filtration to give one portion of **3a** as a yellow solid; yield: 773 mg (3.24 mmol). The filtrate was concentrated under reduced pressure and subject to chromatography on a silica-gel column (petroleum ether-acetone, 10/1 by volume) to afford another portion of **3a**; yield: 357 mg (1.50 mmol). Thus, compound **3a** was obtained in 95% yield (1.13 g, 4.74 mmol) under conventional heating.

General Procedure for Microwave-Assisted Preparation of 2-Aroylbenzofuran-3-ols 3

2-Benzoylbenzofuran-3-ol (3a) as an example: In a microwave tube, phenacyl bromide (219 mg, 1.1 mmol) and potassium phosphate (318 mg, 1.5 mmol) were added to a solution of methyl salicylate (152 mg, 1.0 mmol) in dry acetone (0.8 mL). Then, the sealed microwave tube was microwave-irradiated at 100 °C for 15 min. Then, the reaction mixture was filtered and washed with acetone (3 mL). The obtained solid was then dispersed in water (10 mL) and acidified with 3 N HCl. The resultant precipitate was collected by filtration to give one portion of **3a** as a yellow solid (yield: 145 mg, 0.61 mmol). The filtrate was concentrated under reduced pressure and subject to chromatography on a silica-gel column (petroleum ether-acetone, 10/1 by volume) to afford

another portion of **3a** (yield: 85 mg, 0.36 mmol). Thus, compound **3a** was obtained in 97% yield (230 mg, 0.97 mmol) under microwave irradiation.

Compounds **3b–l** were synthesized in a similar way. All the compounds were fully characterized by MS and NMR (^{1}H and ^{13}C) (see Supporting Information). Shown below are the structural data of new compounds **3f–l**.

2-(4-Methoxybenzoyl)-5-methoxybenzofuran-3-ol (3f): Negative ESI-MS: $m/z=297.07$ $[M-H]^-$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.89$ (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.87–6.90 (s and dd, overlapped, 2H, H-11 and H-13), 6.99–7.04 (m, 2H, H-2 and H-6), 7.65 (d, $J=8.7$ Hz, 1H, H-14), 8.30–8.35 (m, 2H, H-3 and H-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=55.47$ (MeO), 55.7 (MeO), 95.7 (C-11), 113.3 (C-8), 113.4 (C-114), 113.8 (C-2 and C-6), 122.3 (C-13), 127.3 (C-10), 131.5 (C-3 and C-5), 135.4 (C-4), 158.0 (C-15), 162.3 (C-9), 163.2 (C-12), 163.4 (C-1), 176.3 (C=O).

2-(4-Methylbenzoyl)-5-methoxybenzofuran-3-ol (3g): Negative ESI-MS: $m/z=281.09$ $[M-H]^-$;^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.45$ (s, 3H, Me), 3.99 (s, 3H, OMe), 6.86–6.90 (s and dd, overlapped, 2H, H-11, H-13), 7.31 (d, $J=8.1$ Hz, 2H, H-3 and H-5), 7.66 (dd, $J=8.1$ Hz and 0.9 Hz, 1H, H-14), 8.19 (d, $J=8.1$ Hz, 2H, H-2 and H-6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.7$ (Me), 55.7 (OMe), 95.7 (C-11), 113.4 (C-14), 113.5 (C-13), 122.5 (C-8), 129.2 (C-2 and C-6), 129.3 (C-3 and C-5), 131.8 (C-10), 135.6 (C-4), 143.5 (C-1), 158.6 (C-15), 163.7 (C-12 and C-9), 176.9 (C=O).

2-(4-Chlorobenzoyl)-5-methoxybenzofuran-3-ol (3h): Negative ESI-MS: $m/z=301.07$ $[M-H]^-$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.89$ (s, OMe), 6.87–6.91 (m, 2H, H-11 and H-12), 7.46~7.51 (m, 2H, H-3 and H-5), 7.66 (d, $J=9.2$ Hz, 1H, H-14), 8.22–8.26 (m, 2H, H-2 and H-6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=55.8$ (OMe), 95.7 (C-11), 113.2 (C-14), 113.8 (C-13), 122.7 (C-8), 128.8 (C-2 and C-6), 130.6 (C-3 and C-5), 132.8 (C-10), 135.5 (C-1), 138.9 (C-4), 158.9 (C-15), 164.1 (C-9), 164.5 (C-12), 174.1 (C=O).

2-Benzoyl-7-nitrobenzofuran-3-ol (3i): ESI-MS: $m/z=306.04$ $[M+Na]^+$, 284.06 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=7.53$~7.60 (t and t, overlapped, 3H, H-2, H-6 and H-12), 7.67 (t, $J=7.2$ Hz, 1H, H-1), 8.08 (d, $J=6.9$ Hz, 2H, H-3 and H-5), 8.33 (d, $J=7.8$ Hz, 1H, H-13), 8.38 (d, $J=7.8$ Hz, 1H, H-11); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=123.9$ (C-12), 126.0 (C-11), 126.3 (C-13 and C-8), 129.0 (C-2 and C-6), 129.8 (C-3 and C-5), 133.4 (C-10), 134.4 (C-1), 137.2 (C-14), 137.4 (C-4), 145.4 (C-9), 148.8 (C-15), 182.8 (C=O).

2-(4-Methoxybenzoyl)-7-nitrobenzofuran-3-ol (3j): ESI MS: $m/z=336.11$ $[M+Na]^+$, 314.22 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=3.83$ (s, 3H, OMe), 7.10 (d, $J=8.4$ Hz, 2H, H-2 and H-6), 7.52~7.59 (m, 1H, H-12), 8.18 (d, $J=8.4$ Hz, 2H, H-3 and H-5), 8.29 (d, $J=7.5$ Hz, 1H, H-13), 8.37 (d, $J=7.8$ Hz, 1H, H-11); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=56.3$ (OMe), 114.4 (C-2 and C-6), 123.8 (C-12), 125.8 (C-11), 126.1 (C-8), 129.4 (C-13), 129.5 (C-10), 132.3 (C-3 and C-5), 134.3 (C-14), 137.2 (C-4), 145.1 (C-9), 148.8 (C-15), 163.7 (C-1), 181.2 (C=O).

2-(4-Methylbenzoyl)-7-nitrobenzofuran-3-ol (3k): ESI MS: $m/z=320.13$ $[M+Na]^+$, 298.10 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=2.43$ (s, 3H, Me), 7.37 (d, $J=8.1$ Hz, 2H, H-2 and H-6), 7.55 (t, $J=8.1$ Hz, 1H, H-12), 8.02 (d, $J=7.8$ Hz, 2H, H-3 and H-5), 8.31 (d, $J=7.8$ Hz, 1H, H-13), 8.38 (d, $J=8.1$ Hz, 1H, H-11); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=22.0$ (Me), 123.8 (C-12), 125.9 (C-11), 126.1 (C-13 and C-8), 129.6 (C-2 and C-6), 129.9 (C-3 and C-5), 134.3 (C-10), 134.5 (C-14), 137.2 (C-4), 144.0 (C-1), 145.2 (C-9), 148.8 (C-15), 182.3 (C=O).

2-(4-Chlorobenzoyl)-7-nitrobenzofuran-3-ol (3l): ESI MS: $m/z=340.09$ $[M+Na]^+$, 318.32 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta=7.51$ (t, $J=7.8$ Hz, 1H, H-12), 7.62 (d, $J=8.7$ Hz, 2H, H-2 and H-6), 8.05 (d, $J=8.4$ Hz, 2H, H-3 and H-5), 8.33 (d, $J=7.8$ Hz, 1H, H-13), 8.38 (d, $J=7.8$ Hz, 1H, H-11); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta=123.8$ (C-12), 126.4 (C-11 and C-8), 129.1 (C-2 and C-6), 130.0 (C-13), 131.6 (C-3 and C-5), 134.3 (C-10), 136.3 (C-1), 137.1 (C-14), 138.1 (C-4), 145.6 (C-9), 149.4 (C-15), 181.2 (C=O).

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