Microwave-Enhanced One-Pot Synthesis of Diversified 3-Acyl-5-Hydroxybenzofurans

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Received August 7, 2007

The efficient parallel synthesis of small organic molecules is one of the most important methods to speed modern drug discovery. Organic reactions and reaction sequences to prepare target molecules should preferably be facile, fast, and efficient.[1] The resulting products should also be easily and rapidly purified. Microwave technology has proven as a powerful tool for speeding up reactions and the efficient preparation of new target molecules for drug discovery projects in industry and academia.[2] In this paper we report the synthesis of a structurally diverse and medicinally interesting library of 3-acyl-5-hydroxybenzofurans under microwave irradiation.

The importance of the hydroxylated benzofuran scaffold in medicinal chemistry is widely known. Many of those compounds are known as modulators of estrogen receptors,[3] cyclooxygenase-2 inhibitors,[4] antifungal agents,[5] and antioxidant agents.[6] 5-Hydroxybenzofurans are well known because of their reported inhibition of human leukocyte 5-lipoxygenase inhibitors.[7] From the synthetic point of view, the hydroxylated benzofuran rings often appear in the structures of natural products and function as the key intermediate in the synthesis of these complicated molecules, such as angiopreissin A[8] and wedelolactone[9] (Figure 1). Many preparations of 5-hydroxybenzofuran derivatives have been reported and generally involve the intramolecular cyclization of an appropriately substituted benzene ring. For example, the condensation of *p*-methoxyphenol with 2-bromoacetaldehyde diethyl acetal, followed by acid-promoted intramolecular cyclization in benzene, affords 5-methoxybenzofuran in 35% yield.[10] This strategy often involves multistep processes and harsh reaction conditions. 5-Hydroxybenzofurans have also been prepared by the condensation of *p*-benzoquinone with acetyl acetone[11] or ethyl acetoacetate[12] in the presence of a Lewis acid catalyst. The Nenitzescu reaction, the condensation of *p*-benzoquinone with β-aminocrotonic esters,[13] is a classical process for indole synthesis, from which 5-hydroxybenzofurans are often obtained as side products. Chemoselectivity and isolated yields for 5-hydroxybenzofurans are typically low. But 5-hydroxybenzofurans can be generated predominately by the cyclocondensation of *p*-benzoquinone and enaminones despite low yields and sluggish processes.[14]

In this work we focus on the development of efficient, facile, and practical methodology for the rapid preparation

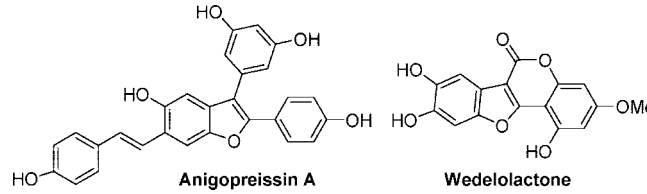
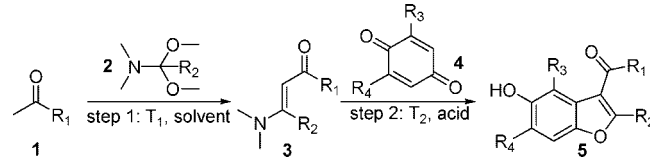


Figure 1. Biologically active hydroxylbenzofurans.

Scheme 1. Two-step synthesis of 5-hydroxybenzofurans.



of the 3-acyl-5-hydroxybenzofuran scaffold under microwave irradiation and its application to solution-phase parallel synthesis of medicinally interesting molecules.

3-Acyl-5-hydroxybenzofurans were first synthesized by Trofimov as early as 1967, by the condensation of *p*-benzoquinone with β-(dimethylamino)vinyl ketones that were prepared from methyl ketones and *N*,*N*-dimethylaminoformamide dimethyl acetal.[15] Initially, we employed this two-step sequence to synthesize 3-benzoyl-5-hydroxybenzofuran under conventional thermal heating for comparison purposes (Scheme 1). Step 1: the reaction of acetophenone **1a** (R_1 = Ph) with dimethylformamide dimethyl acetal **2a** (R_2 = H) was performed in refluxing DMF for 20 h to give intermediate enaminone **3a**, which was unstable on silica gel but could be crystallized (yield 60–70%). Step 2: the condensation of **3a** with *p*-benzoquinone **4a** ($R_3 = R_4$ = H) in acetic acid at room temperature for overnight gave the desired product **5a** in 57% yield. Overall, the two-step sequence delivered the product in low yield (29%) with an extended reaction time (over 24 h). High temperatures were required.

Microwave irradiation has been shown not only to reduce reaction times, but often to provide higher yields of the desired products, as compared to conventional heating methods.[16,17] We therefore conceived of a microwave-assisted one-pot synthesis without isolating the intermediate enaminone **3a**. We screened microwave irradiation conditions (temperature and time), solvents, and acids to optimize the two-step sequence. Initially, step 1 was carried out in dimethylacetamide (DMA) at 170 °C for 10 min under 112 W of microwave irradiation (ramp time 20 s). After cooling, acetic acid and *p*-benzoquinone were added to the mixture and it (**1a**/**2a**/**4a** = 1:1:2) was stirred overnight at room temperature (step 2), and the product was isolated in 67% yield for two steps. When the step 2 reaction was heated in an oil bath at 60 °C for 40 min, the yield was about the same (69% for two steps). Under microwave irradiation, the reaction time can be reduced further to 20 min (60 °C, 71%). Temperatures above 90 °C caused a reduction in yield (37%), suggesting that the thermal energy provided was too high, resulting in an increase in side reactions and/or degradation of the benzofuran product. The temperature for step 1 was

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10.1021/cc070015u CCC: $37.00
Published on Web 08/31/2007

Table 1. Temperature and Time Optimization of the Two-Step One-Pot Synthesis

Entry	T_1[a] (°C)	T_2 (°C)	Yield[c] (%)
1	170	rt, overnight	67
2	170	60, 40 min[b]	69
3	170	60, 20 min	71
4	170	90, 20 min	37
5	150	60, 20 min	40
6	190	60, 20 min	75
7	210	60, 20 min	75

[a] Under μW for 10 min. [b] In oil bath. [c] Isolated yield.

Table 2. Ratio of Reactants and Solvent Optimization of the Two-Step One-Pot Synthesis

Entry	**1a**:**2a**:**4a**	Solvents	Yield[a] (%)
1	1:1:1	DMA	26
2	1:1:1	DMF	57
3	1:1:1.5	DMF	72
4	1:1:2	DMA	48
5	1:1:2	DMF	78
6	1:1:3	DMA	75
7	1:1:3	ethylene glycol	24
8	1:1:3	DMSO	67
9	1:1:3	DMF	81
10	1:1:3	toluene	27
11	1:1:4	DMF	76

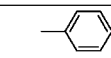
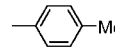
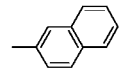
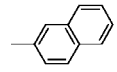
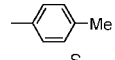
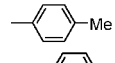
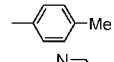
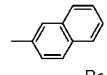
[a] Isolated yield based on initial reactant not present in excess.

optimized by carrying out the reaction for 10 min under microwave irradiation from 150 to 210 °C in increments of 20 °C. The highest yield (75%) for two steps was obtained at T_1 = 190 °C and T_2 = 60 °C, as shown in Table 1.

With the optimized reaction temperature and time, we studied other factors to further improve the chemical yield. The choice of solvent is critical, as the interaction between solvent and microwave greatly affects the temperature profile of the reaction. As shown in Table 2, different solvents were tested in our synthesis of 3-acyl-5-hydroxybenzofurans. Poor yields were obtained in protonic solvent ethylene glycol (24%, entry 7) and nonpolar solvent toluene (27%, entry 10). DMF was an ideal solvent and gave much higher yield than others (entries 2, 3, 5, 9, and 11). The ratio of reactants (**1a**/**2a**/**4a**) was also carefully studied. It was found that an excess of *p*-benzoquinone helped increase the yield for the formation of the benzofuran scaffold. We observed that the addition of one equivalent of *p*-benzoquinone provided only a yield of 57% in DMF (entry 1). One more equivalent of *p*-benzoquinone boosted the yield to 78% in our experiments (entry 5). Addition of three equivalents of *p*-benzoquinone or more has insignificant improvements on the yield (entries 9 and 11). We concluded that using 1.5–2 equivalents of *p*-benzoquinone can deliver the desired product in a satisfactory yield and is also economical. Replacing the acetic acid with Lewis acid, BF_3 etherate, resulted in a reduction of the yield from 78% to 36%.

The power of microwave irradiation was optimized to be 112 W for this one-pot synthesis. The optimum conditions (step 1: T_1 = 190 °C, 10 min, DMF; step 2: T_2 = 60 °C, 20 min, acetic acid, DMF) were sought out for the two-step synthesis of 3-acyl-5-hydroxybenzofurans. Microwave irradiation dramatically improved the yield from 29% to 81% and reduced the reaction time from >24 h to 30 min for this one-pot synthesis.

Table 3. Microwave-Accelerated One-Pot Parallel Synthesis of 3-Acyl-5-Hydroxybenzofuran Library[a]

Entry	R_1	R_2	R_3, R_4	Product	Crude purity (%)	Yield[b] (%)
1		H	H	**5a**	85	78
2		H	H	**5b**	80	75
3		H	H	**5c**	87	85
4		H	H	**5d**	83	74
5		H	H	**5e**	83	77
6		H	H	**5f**	76	68
7		H	H	**5g**	83	80
8		H	H	**5h**	79	74
9	Me	H	H	**5i**	67	59
10		Me	H	**5j**	71	64
11		Me	H	**5k**	70	65
12		Me	H	**5l**	81	74
13		Me	H	**5m**	78	70
14		Me	H	**5n**	75	68
15		H	Br	**5o**	77	74
16		H	Br	**5p**	82	77
17		H	Br	**5q**	71	66
18		H	Br	**5r**	81	75
19		H	Cl	**5s**	76	69
20		H	Cl	**5t**	80	71
21		H	Cl	**5u**	80	75
22		H	Cl	**5v**	74	67
23		H	COOMe H[c]	**5w**	78	72
24		H	COOMe H[c]	**5x**	82	79
25		H	COOMe H[c]	**5y**	80	77
26		H	COOMe H[c]	**5z**	73	68

[a] Reactions were carried out on a 1.0 mmol scale. Step 1: 190 °C, DMF, 10 min; Step 2: 60 °C, DMF, HOAc, 20 min. [b] Isolated yield for two steps. [c] R_3 = COOMe, R_4 = H.

The optimized power of microwave irradiation at 112 W and the optimum conditions (step 1: T_1 = 190 °C, 10 min, DMF; step 2: T_2 = 60 °C, 20 min, acetic acid, DMF) were applied to the parallel synthesis of all the 3-acyl-5-hydroxybenzofurans in the library as shown in Table 3. As part of

our ongoing medicinal chemistry project, the library was diversified by modifying the 2-, 3-, 4-, and 6-positions of the structure of the 5-hydroxybenzofuran scaffold. All the desired products were isolated by flash chromatography and fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. The purity of reaction mixtures was analyzed by TLC, LC–MS, and HPLC. In general, this microwave-assisted method provided a very rapid means of synthesizing 3-acyl-5-hydroxybenzofurans. The desired products were obtained with high crude purity and acceptable isolated yields. On the average, the yield for each single step of the two-step sequence was over 80–90%. The lowest yield was given when acetone was used (59%, entry 9). Aryl groups are more preferable than electron-donating alkyl groups. When both microwave results and conventional preheated oil bath results were compared, we observed a clear improvement in yield and reaction time with microwave heating. The reaction rate was increased by coupling rapid microwave heating and sealed vessel technology. The improved yield of desired product and purity of reaction mixture allow direct high-throughput biological screening. Compounds **5a**, **5b**, **5e**, **5f**, **5h**, **5i**, **5j**, **5n**, **5p**, and **5r** are known structures. Compounds **5c**, **5d**, **5g**, **5k**, **5l**, **5m**, **5o**, **5q**, **5s**, **5t**, **5u**, **5v**, **5w**, **5x**, **5y**, and **5z** are new compounds. All products are stable in refrigerator. Biological evaluation of 3-acyl-5-hydroxybenzofurans is currently underway with respect to some metabolic diseases and may lead to novel chemical entities as drug candidates.

We have developed an efficient method to generate structurally diverse and medicinally interesting 3-acyl-5-hydroxybenzofurans via a one-pot two-step reaction sequence under microwave irradiation. There are not many synthetic procedures as simple as the Nenitzescu process to prepare 5-hydroxybenzofurans and our work makes a simpler process much more efficient. The reaction time was dramatically reduced and chemical yield was significantly improved under microwave irradiation as compared to conventional heating methods. The method was employed to rapidly construct twenty-six 3-acyl-5-hydroxybenzofurans, of which sixteen compounds are new. We expect this method to find extensive applications in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Acknowledgment. This work was supported by Nanyang Technological University and Ministry of Education, Singapore. We thank Dr. David Chen and Professor K.C. Nicolaou for the use of microwave synthesizer in their lab, ICES, Singapore. We also thank Dr. Roderick W. Bates and Dr. Guan-Leong Chua for discussion and help in preparation of the manuscript.

Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC070015U