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An efficient procedure for the synthesis of 3-aryl-4-methoxy-2(5*H*)-furanones by using the microwave-promoted Suzuki–Miyaura coupling reactions

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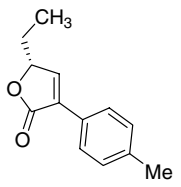
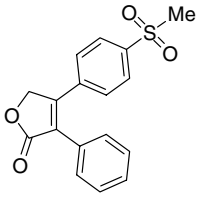
Abstract—The Suzuki–Miyaura coupling reactions of 3-bromo-2(5*H*)-furanones with a variety of arylboronic acids, promoted by microwave heating, efficiently generate 3-aryl-2(5*H*)-furanones. This remarkably rapid process serves as the foundation for a simple method to rapidly construct 3-aryl-2(5*H*)-furanone libraries.

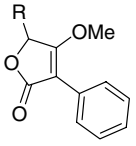
Molecules possessing the 2(5*H*)-furanone moiety, a frequently found substructure in natural products and biologically active compounds, have received considerable attention in the contexts of plant protection,[1] antifungal,[2] antibacterial,[3] and anti-inflammatory agents.[4] Especially interesting in this regard are incrustoporin (**1**)[5] and rofecoxib **2**[6] (Vioxx®), which exhibit potent fungicidal and selective COX-II inhibitory activity, respectively. Even though Vioxx has been recently recalled from the market, questions remain about whether the net benefits of the drug outweigh its risks. It is has been reported that some osteoarthritis and rheumatoid arthritis sufferers claim that Vioxx is the only drug that alleviates pain without causing severe ulcers.



(-)-Incrustoporin (**1**)



Rofecoxib (Vioxx®, **2**)



3

Clearly, the search for 2(5*H*)-furanone containing substances that possess the same levels of COX-II inhibitory activity as Vioxx, but have fewer side effects, remains a significant challenge. The most common among the limited number of methods available for the preparation of 3-aryl-4-methoxy-2(5*H*)-furanones **3** are thermal, photolytic, and oxidative ring expansion reactions of 4-hydroxy-2-cyclobutenones.[7] Another route for the synthesis of these compounds involves the regioselective K-Selectride reduction of substituted maleic anhydrides.[8] Although both of these procedures produce 3-aryl-4-methoxy-2(5*H*)-furanones in high yields with high regioselectivities, a general, efficient approach that enables the introduction of a wide variety of substituents at the C-3 position is desirable.

The Suzuki–Miyaura coupling reaction[9] appears to offer the most direct approach for rapid construction of 3-substituted-2(5*H*)-furanones.[10,11] Worthington and his co-workers described the Suzuki–Miyaura reaction of 3-bromo-5-methyl-2(5*H*)-furanone that affords 3-arylfuranones.[12] However, the yields of these processes were unsatisfactory (36–56%) even when microwave heating conditions were employed. Based on the results of our recent investigations of the Suzuki–Miyaura coupling reactions,[13] we felt that the use of microwave heating[14] to accelerate the process would enhance reaction efficiencies and lead to a functional group tolerant methodology that would enable a high-speed construction of 3-substituted-2(5*H*)-furanones. In order to provide

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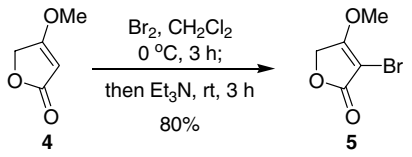


Scheme 1.

support for this proposal, we have investigated the microwave-promoted Suzuki–Miyaura coupling reactions of 3-bromo-4-methoxy-2(5*H*)-furanone (**5**) with arylboronic acids.

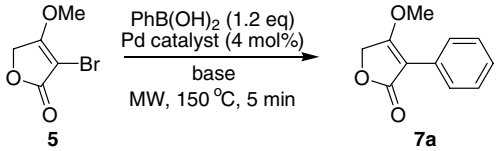
The starting 3-bromo-4-methoxy-2(5*H*)-furanone (**5**) was prepared in a high yield via sequential bromination and base-mediated elimination reactions of commercially available 4-methoxy-2(5*H*)-furanone (**4**) (Scheme 1).[15] The Suzuki–Miyaura reactions of 3-bromo-2(5*H*)-furanone **5** with phenylboronic acid (**6a**) in the presence of several palladium catalysts were explored. The data given in Table 1 illustrate that the use of $Pd(PPh_3)_4$ (4 mol %) in combination with Cs_2CO_3 (3.0 mol-equiv) in 1,4-dioxane and microwave irradiation at 150 °C for 5 min (entry 1) led to the formation of 4-methoxy-3-phenyl-2(5*H*)-furanone (**7a**) in 42% yield. We observed that the use of aprotic polar solvents, such as CH_3CN and DMF, gave lower reaction efficiencies (entries 2 and 3). When the reactions were carried out employing a palladium(II) precursor catalyst, such as $Pd(PPh_3)_2Cl_2$, the yields increased (entries 4–7). Also, changing the base from Cs_2CO_3 to K_2CO_3 caused a small increase in the yield of the formation of **7a** (entry 5) and the use of K_3PO_4 as a base led to a further improvement in the yield to 66% (entry 6).

Previous observations made in our earlier studies of the Suzuki–Miyaura reaction in aqueous media[13] suggested that the use of H_2O as a co-solvent would positively impact this process. Indeed, the reaction of 3-bromo-2(5*H*)-furanone **5** with phenylboronic acid in 4:1 dioxane/H_2O provided the coupling product **7a** in 74% yield (entry 7). When $Pd(PPh_3)_4$ and Na_2CO_3 were employed to promote the reaction in this solvent system, the yield of **7a** increased to 76% yield (entry 8). Finally, the optimal yield of 85% was obtained when 2.4 equiv of Na_2CO_3 was used (entry 9); but it is important to note that small changes in the amount of the base employed lead to variations in reaction efficiencies in the range of 76–85%.

With the optimized reaction conditions in hand, the Suzuki–Miyaura reactions of 3-bromo-2(5*H*)-furanone **5** with a wide range of arylboronic acids were explored. The results (Table 2) demonstrated that these processes produced coupling products **7a**–**l** in moderate to high yields.[16] The coupling reactions took place with both electron-deficient (entries 4–6) and electron-rich (entries 2 and 8) arylboronic acids. In addition, the Suzuki–Miyaura coupling reactions of **5** with the sterically demanding substrates (entries 9 and 10), such as the *ortho*-methyl- and *ortho*-fluorophenylboronic acids, proceeded to afford the corresponding coupling products **7i** and **7j** in respective yields of 67% and 65%. However, the process was less effective with 2-thienylboronic acid, giving the coupling product **7l** in 52% yield (entry 12).

In summary, we have demonstrated that the Suzuki–Miyaura reactions of 3-bromo-4-methoxy-2(5*H*)-furanone with arylboronic acids, under microwave irradiation conditions, serves as a general and highly efficient method for the synthesis of 3-aryl-4-methoxy-2(5*H*)-furanones. Further studies are underway in our laboratory to evaluate the biological properties of the 2(5*H*)-furanones produced in the current effort.

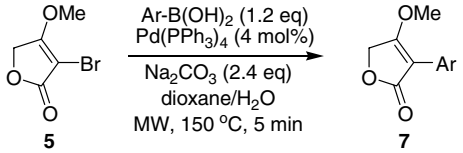
Table 1. Suzuki–Miyaura coupling of 3-bromo-4-methoxy-2(5*H*)-furanone with phenylboronic acid[a]

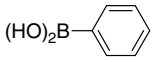
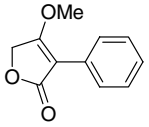
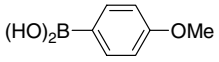
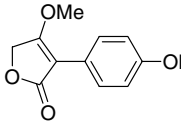
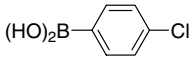
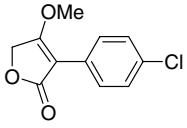
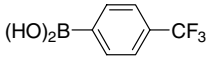
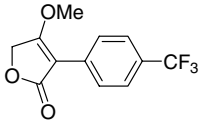
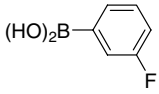
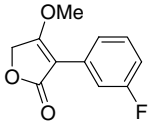
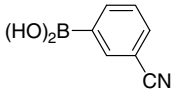
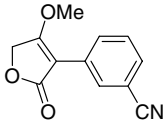
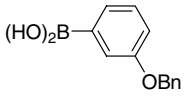
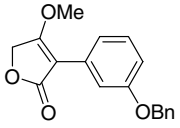
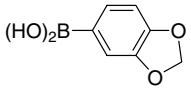
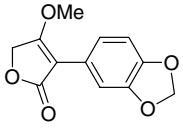
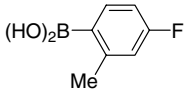
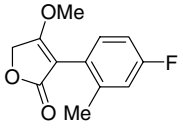
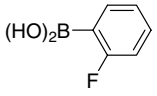
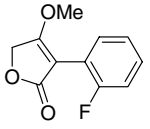
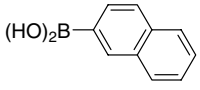
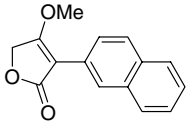


Entry	Pd Source	Base	Solvents	Yield[b] (%)
1	$Pd(PPh_3)_4$	Cs_2CO_3	Dioxane	42
2	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	26
3	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	0[c]
4	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	Dioxane	55
5	$Pd(PPh_3)_2Cl_2$	K_2CO_3	Dioxane	60
6	$Pd(PPh_3)_2Cl_2$	K_3PO_4	Dioxane	66
7	$Pd(PPh_3)_2Cl_2$	K_3PO_4	Dioxane/H_2O (4/1)	74
8	$Pd(PPh_3)_4$	Na_2CO_3	Dioxane/H_2O (4/1)	76
9	$Pd(PPh_3)_4$	Na_2CO_3 (2.4 equiv)	Dioxane/H_2O (4/1)	85
10	$Pd(PPh_3)_4$	Na_2CO_3 (1.8 equiv)	Dioxane/H_2O (4/1)	78

[a] Reaction conditions: **5** (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), $Pd(PPh_3)_4$ (4 mol %), base (3.0 mmol), microwave 150 °C, 5 min.
[b] Isolated yields.
[c] Furanone **5** was not recovered and biphenyl was obtained as a major product.

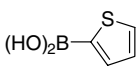
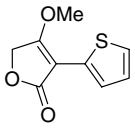
Table 2. Suzuki–Miyaura coupling of 3-bromo-4-methoxy-2(5*H*)-furanone with boronic acid[a]



Entry	Boronic acid		Product		Yield[b] (%)
1		**6a**		**7a**	85
2		**6b**		**7b**	76
3		**6c**		**7c**	70
4		**6d**		**7d**	67
5		**6e**		**7e**	68
6		**6f**		**7f**	60
7		**6g**		**7g**	70
8		**6h**		**7h**	77
9		**6i**		**7i**	67
10		**6j**		**7j**	65
11		**6k**		**7k**	69

(*continued on next page*)

Table 2 (*continued*)

Entry	Boronic acid	Product	Yield[b] (%)
12	 **6l**	 **7l**	52

[a] Reaction conditions: **5** (1.0 mmol), $ArB(OH)_2$ (1.2 mmol), $Pd(PPh_3)_4$ (4 mol %), Na_2CO_3 (2.4 mmol), dioxane/H_2O (4 mL/1 mL), microwave 150 °C, 5 min.
[b] Isolated yields.

Acknowledgments

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16. *General procedure*. All reactions were conducted by using a Biotage Initiator EXP™ microwave reactor. To a thick-wall borosilicate glass vial (10 mL) were added 3-bromo-2(5*H*)-furanone **5** (1 mmol), $Pd(PPh_3)_4$ (4 mol %), arylboronic acid (1.2 mmol), and Na_2CO_3 (2.4 mmol) sequentially. The mixture was dissolved in dioxane/H_2O (4 mL/1 mL) and degassed with argon for 5 min. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 150 °C for 5 min. After cooling to room temperature, the mixture was diluted with EtOAc, dried over $MgSO_4$, and filtered through Celite. The filtrate was concentrated in vacuo giving a residue which was subjected to silica gel flash column chromatography (EtOAc/hexanes). The spectral data for **7c**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 2H, $J = 8.7$ Hz), 7.39 (d, 2H, $J = 8.7$ Hz), 4.87 (s, 2H), 4.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 172.2, 133.2, 128.7, 128.4, 127.7, 101.6, 64.4, 58.0; MS (EI) m/z $[M]^+$ for $C_{11}H_9ClO_3$: calcd 224.02, found 224 (100), 195 (62), 152 (65), 123 (25).