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An efficient synthesis of 2-aryl-3-methoxy-2-cycloalkenones via Suzuki–Miyaura reaction under microwave irradiation

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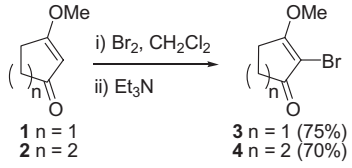
Abstract—The Suzuki–Miyaura coupling reaction of α-bromocycloalkenones with arylboronic acids has been developed by using microwave heating. This method provides a simple and rapid construction of small molecule libraries of α-arylcycloalkenones with high efficiency.

The Suzuki–Miyaura coupling reaction provides a convenient access to the carbon–carbon bond formation with high efficiency.[1] Recently, the use of microwave heating for the coupling reaction is of great interest to synthetic chemists due to the high-speed construction of versatile chemical entities.[2,3] Although, a plethora of methods has been established on the development of the Suzuki–Miyaura reaction of aryl (including heteroaryl) halides or triflates under microwave irradiation, cross-coupling reaction of vinyl halides, in particular of α-halocycloalkenones,[4] remains an attractive area for investigation using a microwave-promoted approach. A number of α-arylcycloalkenones served as key synthetic intermediates for the development of biologically active pharmaceuticals[5] and agrochemicals.[6] In the event, α-halocycloalkenones have been coupled with 4-fluorophenylboronic acid using Suzuki–Miyaura conditions previously,[5b] but not under microwave irradiation. Therefore, we envisioned a systematic study of this type of reaction with various arylboronic acids. In this paper, we described the rapid and efficient synthesis of 2-aryl-3-methoxy-2-cycloalkenones via Suzuki–Miyaura reaction under microwave irradiation.



Scheme 1.

The required 2-bromo-3-methoxy-2-cyclopentenone (**3**) and its 6-membered analog (**4**) were prepared via sequential bromination and base-mediated elimination reactions of the corresponding cycloalkenones (Scheme 1).[7] Subsequently, we examined the Suzuki–Miyaura reaction of α-bromocyclopentenone **3** with phenylboronic acid in the presence of a suitable palladium catalyst. As illustrated in Table 1, our initial attempt was focused on the use of $Pd(PPh_3)_4$ (4 mol%) in combination with K_3PO_4 (3.0 equiv) in 1,4-dioxane while microwave heating at 150 °C for 5 min (entry 1). This reaction provided 2-phenyl-2-cyclopentenone **5a** in 58% yield. Based on a GC analysis, the starting α-bromocyclopentenone **3** remained (10%) and biphenyl was obtained as a by-product (7% GC yield). As a next step, we screened a range of solvents such as THF, CH_3CN, and DMF to figure out the solvent effects (entries 2–4). The results obtained from reactions using solvents other than dioxane turned out to be inferior. Changing a base from K_3PO_4 to Na_2CO_3, only trace amount of product **5a** was detected by GC (entry 5). In contrast, the use of Cs_2CO_3 significantly improved the reaction yield up to 72% (entry 6).

Keywords: Suzuki reaction; Palladium; Boronic acid; Microwave; Cycloalkenone.
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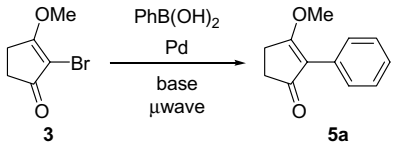
Table 1. Suzuki–Miyaura coupling of α-bromocyclopentenone **3** with phenylboronic acid[a]



3 **5a**

Entry	Pd source	Base	Solvent	Temp (°C)	Yield[b] (%)
1	$Pd(PPh_3)_4$	K_3PO_4	Dioxane	150	59
2	$Pd(PPh_3)_4$	K_3PO_4	THF	150	35
3	$Pd(PPh_3)_4$	K_3PO_4	CH_3CN	150	42
4	$Pd(PPh_3)_4$	K_3PO_4	DMF	150	22
5	$Pd(PPh_3)_4$	Na_2CO_3	Dioxane	150	3[f]
6	$Pd(PPh_3)_4$	Cs_2CO_3[d]	Dioxane	150	72
7	$Pd(PPh_3)_4$	K_3PO_4	Dioxane/H_2O	150	77
8	$Pd(PPh_3)_4$	K_3PO_4	Dioxane/H_2O	130	61
9	$Pd(PPh_3)_2Cl_2$	K_3PO_4	Dioxane/H_2O	150	27
10	$PdCl_2$	K_3PO_4	Dioxane/H_2O	150	4
11	$Pd(OAc)_2$	K_3PO_4	Dioxane/H_2O	150	23
12[c]	$Pd(PPh_3)_4$	K_2CO_3	Dioxane/H_2O	150	80
13[c]	$Pd(PPh_3)_4$	Na_2CO_3[d]	Dioxane/H_2O	150	89
14[c]	$Pd(PPh_3)_4$	Na_2CO_3[d]	Dioxane/H_2O	150[e]	58[g]

[a] Reaction conditions: cyclopentenone **3** (1.0 mmol), $PhB(OH)_2$ (1.3 mmol), Pd (4 mol%), base (3.0 mmol), and solvent (4 mL) using a sealed tube under microwave irradiation for 5 min.
[b] Isolated yield.
[c] 1.2 mmol of $PhB(OH)_2$ was used.
[d] 2.4 mmol of base was used.
[e] Conventional oil bath heating was applied.
[f] GC yield.
[g] Biphenyl was detected by GC–MS (20% GC yield).

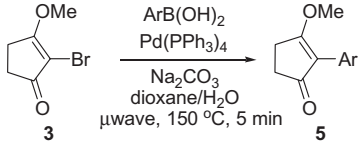
Based on a number of reports regarding the Suzuki–Miyaura reaction in aqueous media,[8] we decided to use H_2O as a co-solvent. In the event, we were pleased to observe that the reaction using dioxane/H_2O (4:1) provided the coupling product **5a** in 77% yield (entry 7). However, decreasing reaction temperature to 130 °C resulted in lower yield due to incompletion of reaction (entry 8). Next, we carried out reactions using palladium(II) precursor catalysts such as $Pd(PPh_3)_2Cl_2$, $PdCl_2$, and $Pd(OAc)_2$, but the reactions provided **5a** in poor yield (entries 9–11). With the result of entry 7, we attempted to find an optimum condition by changing bases. With K_2CO_3, the reaction furnished **5a** in 80% yield (entry 12). Employing a weaker base, Na_2CO_3, the coupling yield increased up to 89% (entry 13). Therefore, we selected this protocol as the optimum condition. Finally, we examined thermal effects of microwave heating compared to conventional heating. The identical reaction using preheated conventional oil bath at 150 °C provided the coupling product **5a** in lower yield due to the significant production of biphenyl (entry 14).

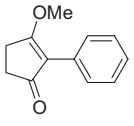
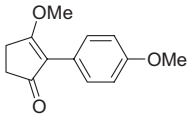
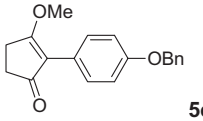
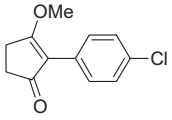
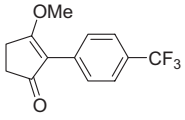
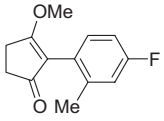
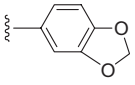
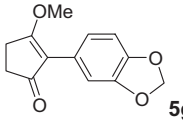
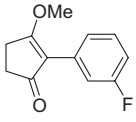
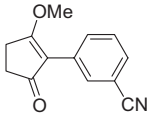
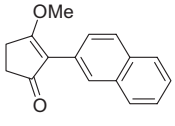
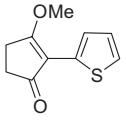
Using the optimized reaction conditions (Table 1, entry 13), we performed the microwave-promoted Suzuki–Miyaura reaction of α-bromocyclopentenone **3** with a variety of arylboronic acids. As illustrated in Table 2, we obtained the coupling products **5a**–**k** in good to excellent yields.[9] It is noteworthy that the coupling reaction tolerates both electron-withdrawing and -donating substituents of arylboric acids. In addition, the reaction with *ortho*-substituted one also proceeded smoothly to afford coupling product **5f** in excellent yield (entry 6). In case of 2-thienylboronic acid, however, the reaction was slightly sluggish to give **5k** in a moderate yield. Whereas yields of the coupling reaction obtained herein are compatible to those described in the previous report under conventional heating,[5b] reaction time could be remarkably shortened.

For further exploration of the Suzuki–Miyaura coupling reaction, we applied this method to α-bromocyclohexenone **4** for a synthesis of the corresponding α-arylcyclohexenone **6**. As highlighted in Table 3, the reactions under microwave irradiation proceeded smoothly to afford coupling products **6a**–**j** in good yields irrespective of electronic and steric properties of the arylboronic acids. It was found that the reaction conditions were mild enough for the coupling of arylboronic acid in the presence of a base-sensitive ester functional group (entry 8).

In summary, we have demonstrated that an efficient and rapid synthesis of α-arylcycloalkenones can be achieved via the Suzuki–Miyaura coupling reaction using microwave irradiation. Such a rapid construction of small molecule libraries may prompt for the development of biologically active molecules. Currently, our laboratory is on due course for a further application of this reaction.

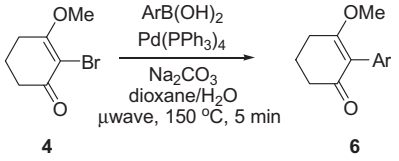
Table 2. Suzuki–Miyaura coupling of α-bromocyclopentenone **3** with arylboronic acids[a]

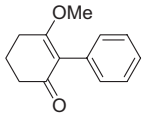
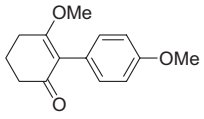
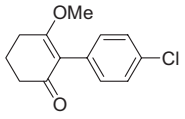
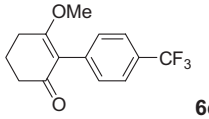
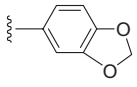
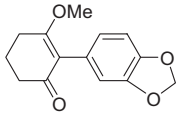
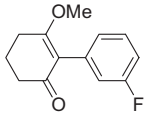
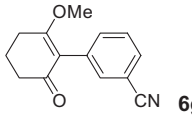
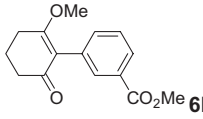
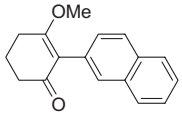
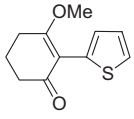


Entry	Ar	Product	Yield[b] (%)
1	Ph	 **5a**	89
2	4-MeO–C_6H_4	 **5b**	83
3	4-BnO–C_6H_4	 **5c**	82
4	4-Cl–C_6H_4	 **5d**	72
5	4-CF_3–C_6H_4	 **5e**	77
6	2-Me–4-F–C_6H_3	 **5f**	84
7		 **5g**	83
8	3-F–C_6H_4	 **5h**	78
9	3-CN–C_6H_4	 **5i**	75
10	2-Naphthyl	 **5j**	83
11	2-Thienyl	 **5k**	52

[a] Reaction conditions: α-bromocyclopentenone **3** (1.0 mmol), $ArB(OH)_2$ (1.2 mmol), $Pd(PPh_3)_4$ (4 mol%), Na_2CO_3 (2.4 mmol), dioxane/H_2O, microwave 150 °C, 5 min.
[b] Isolated yields.

Table 3. Suzuki–Miyaura coupling of α-bromocyclohexenone **4** with arylboronic acids[a]



Entry	Ar	Product	Yield[b] (%)
1	Ph	 **6a**	79
2	4-MeO–C_6H_4	 **6b**	76
3	4-Cl–C_6H_4	 **6c**	78
4	4-CF_3–C_6H_4	 **6d**	68
5		 **6e**	73
6	3-F–C_6H_4	 **6f**	72
7	3-CN–C_6H_4	 **6g**	64
8	3-CO_2Me–C_6H_4	 **6h**	70
9	2-Naphthyl	 **6i**	72
10	2-Thienyl	 **6j**	60

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

Acknowledgments

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9. General procedure: all reactions were conducted by using Biotage Initiator EXP™ microwave reactor. To a thick-wall borosilicate glass vial (5 mL) was added α-bromocyclopentenone **3** or -cyclohexenone **4** (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 over 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 rt, the mixture was diluted with EtOAc, dried over $MgSO_4$, and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by silica gel flash column chromatography with EtOAc/hexanes as eluents. Spectral data for **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, $J =$ 8.9 Hz), 6.91 (d, 2H, $J = 8.9$ Hz), 4.01 (s, 3H), 3.81 (s, 3H), 2.81–2.79 (m, 2H), 2.60–2.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 184.0, 158.4, 129.4, 123.3, 118.2, 113.5, 56.8, 55.2, 33.8, 24.5; IR (neat) ν 3001, 2954, 1670, 1595, 1508, 1452, 1356, 1290, 1248, 1171, 1053, 1028, 937, 843 cm^{-1}; MS (EI) m/z $[M + H]^+$ for $C_{13}H_{15}O_3$ calcd: 219.10. Found: 219.1 (55), 218.4 (69), 217.6 (87), 203.0 (90), 174.9 (21), 160.5 (87), 146.8 (53), 132.9 (100), 118.9 (53).