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Microwave-promoted cross-coupling of acid chlorides with arylboronic acids: a convenient method for preparing aromatic ketones

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Abstract—Simple catalytic systems for cross-coupling reactions of acyl chlorides with arylboronic acids under microwave conditions were tested. Microwave irradiation facilitated the reaction course. Mild reaction conditions afford the symmetrical and unsymmetrical aryl ketones in reasonable to high yields within a short time. A wide range of substrates bearing an electron-donating or an electron-withdrawing substituent on aryl ring of acid chloride as well as on boronic acid were examined and high yields of ketones were produced.

1. Introduction

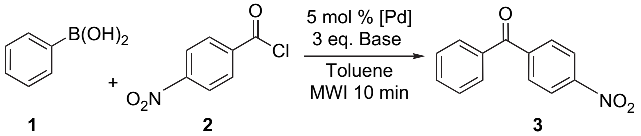
Aromatic ketones are important building blocks for a large number of natural products and are most frequently prepared by a Friedel–Crafts type reaction.[1] Suzuki cross-coupling reaction[2] is a very attractive method for the formation of carbon–carbon single bonds between boronic acids and alkenyl or arylhalides, which is demonstrated in several review articles devoted to this field of chemistry.[3–5] The cross-coupling reaction between arylboronic acids, carbon monoxide (1 atm), and aryl iodides in the presence of palladium catalyst and base also provided biaryl ketones in high yields.[6]

On the other hand in the recent review[7] are just three papers,[8–10] describing Pd-catalyzed reaction of different acyl chlorides with boronic acids. To get good yields of the product it is necessary to heat the reaction mixture for several hours up to 100 °C, or to prolong the reaction time up to several days. This was also the case when aliphatic acid chlorides as well as unsaturated acyl chlorides were used as the substrates.[11,12] Coupling of substituted benzoyl chlorides with phenylboronic acid proceeded at room temperature in a short time in the case when equivalent amount of copper(I) thiophene-2-carboxylate was used as a co-catalyst.[13] Several non-traditional methods have been developed for the Suzuki–Miyaura synthesis of unsymmetrical biaryls such as high intensity ultrasound,[14,15] which accelerates the reactions of aryl iodides and aryl bromides, and especially microwave irradiation,[16–18] which also promotes the reaction of aryl chlorides.

The main goal of our work was to examine if Suzuki–Miyaura coupling of arylboronic acids with acyl chlorides can be promoted by microwave irradiation. The second aim was also to find out if this reaction can be used also for the preparation of unusually substituted aryl ketones.

2. Results and discussion

At the beginning of our work we decided to examine the effect of the catalytic system (Pd source and base) on the course of Suzuki cross-coupling of phenylboronic acid with 4-nitrobenzoyl chloride (Scheme 1, Table 1). While our work was in progress an interesting paper appeared, describing a very rapid reaction of arylboronic acids with different acyl chlorides by grinding reactants with $PdCl_2$ and Na_2CO_3.[19] We decided to test this catalytic system in toluene under MWI too. Catalytic systems $PdCl_2$ and Na_2CO_3 (entry 1) and $Pd(OAc)_2$ and K_2CO_3 (entry 2) was not effective under MWI.



Scheme 1.

Keywords: Palladium; Cross-coupling reaction; Boronic acid; Acyl chlorides; Ketones; Microwave irradiation.

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Table 1. Effect of catalyst systems on the Suzuki–Miyaura coupling of phenylboronic acid with 4-nitrobenzoyl chloride in toluene, under MWI, reaction time 10 min

Entry	[Pd]	Base	Yield **3** (%)
1	$PdCl_2$	Na_2CO_3	n.d.
2	$Pd(OAc)_2$	K_2CO_3	n.d.
3	$Pd[PPh_3]_4$	Cs_2CO_3	93 (13)[a]
4	$PdCl_2(PPh_3)_2$	$K_3PO_4 \cdot 1.5H_2O$	91 (79)[a]
5	$PdCl_2(PPh_3)_2$	$K_3PO_4 \cdot 1H_2O$	35 (25)[a]
6	$PdCl_2(PPh_3)_2$	K_3PO_4	8

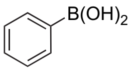
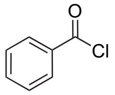
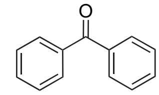
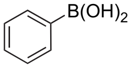
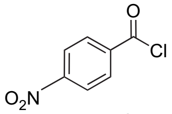
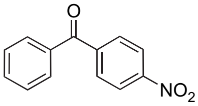
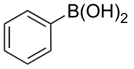
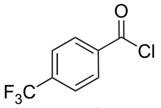
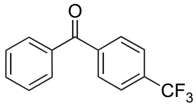
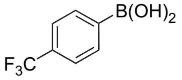
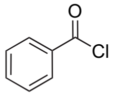
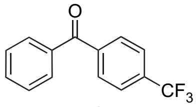
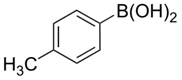
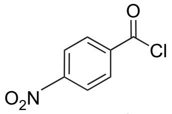
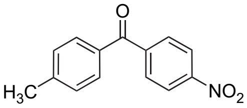
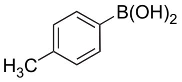
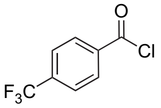
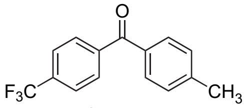
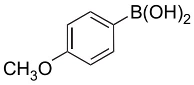
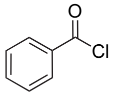
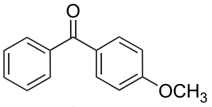
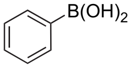
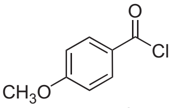
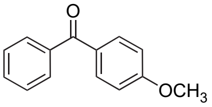
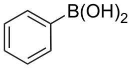
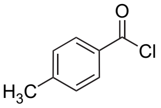
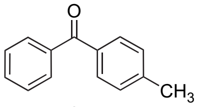
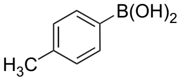
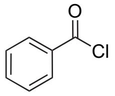
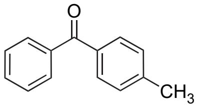
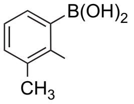
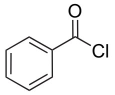
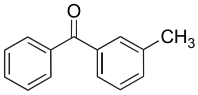
[a] On oil bath for 10 min.

On the other hand $Pd(PPh_3)_4$ and Cs_2CO_3 (entry 3) was found to be the best catalyst system because the cross-coupling product **3** was isolated in 93% yield. Control experiment, without microwave irradiation gave only 13% yield of product **3**. We decided to test also $PdCl_2(PPh_3)_2$ and K_3PO_4 as catalyst system (entries 4–6), and we found that results are very dependent on the quality of potassium phosphate, which is in accord with Ref. 11.

Our next aim was to test the applicability of the catalytic system $Pd(PPh_3)_4$ and Cs_2CO_3 for Suzuki coupling of different arylboronic acids with various acid chlorides. Results are summarized in Table 2.

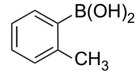
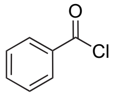
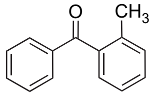
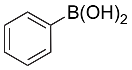
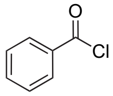
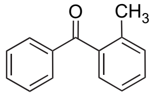
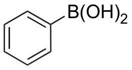
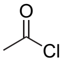
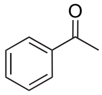
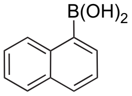
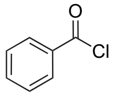
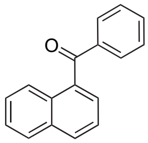
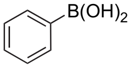
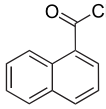
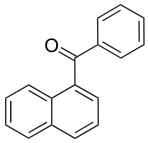
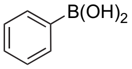
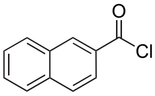
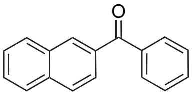
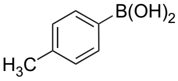
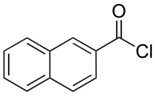
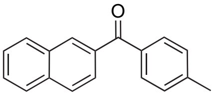
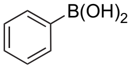
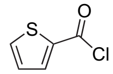
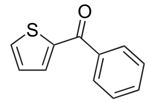
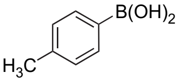
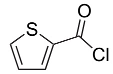
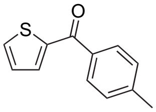
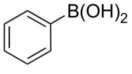
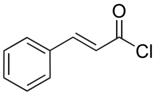
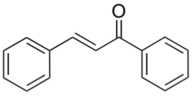
The present methodology is important because it provided the ketones in high yields within a short reaction time (10 min). The reactions of acid chlorides bearing electron-withdrawing (entries 2, 3) and electron-donating (entries 8, 9) groups proceed in good to high yields. Heteroaromatic acid chloride such as 2-furyl (entries 19, 20) afforded the corresponding ketones in 72 and 74% isolated yields. Alkyl- and alkenyl-acid chlorides (entries 14, 21) gave no desired product. The reactions with arylboronic acids bearing electron-donating groups (entries 5–7, 10–12) gave reasonable

Table 2. Effect of the substituent on acid chlorides and of arylboronic acids on the microwave-promoted Suzuki-type coupling catalyzed by $Pd(PPh_3)_4$ in toluene with Cs_2CO_3 as the base, rt, 10 min

Entry	Arylboronic acid	Acid chloride	Ketone	Product	Yield (%)
1				**4**	68[21]
2				**3**	93[20]
3				**5**	90[22]
4				**5**	18[22]
5				**6**	60[23]
6				**7**	57[24]
7				**8**	49[21]
8				**8**	73[21]
9				**9**	60[21]
10				**9**	80[21]
11				**10**	74[22]

(*continued*)

Table 2. (*continued*)

Entry	Arylboronic acid	Acid chloride	Ketone	Product	Yield (%)
12				**11**	61[22]
13				**11**	41[22]
14				**12**	0
15				**13**	77[25]
16				**13**	74[25]
17				**14**	80[22]
18				**15**	50[26]
19				**16**	74[27]
20				**17**	72[28]
21				**18**	0

to high yield of the cross-coupling products. A sterically hindered 2-methylphenylboronic acid (entry 12) gave 61% yield of the product **11**. On the other hand, the reaction of benzoyl chloride with arylboronic acid bearing electron-withdrawing CF_3-group (entry 4) gave only 18% yield of 4-(trifluoromethyl)benzophenone **5**, but this product **5** was obtained in 90% yield when phenylboronic acid with 4-(trifluoromethyl)benzoyl chloride was used (entry 3).

3. Conclusion

In summary we found that microwave irradiation had positive effect on the Suzuki reaction of acid chlorides with arylboronic acids. Catalytic system ($Pd(PPh_3)_4$ and Cs_2CO_3) under microwave irradiation gave ketones in good to high yields in moist toluene (water content in toluene was not controlled). The present methodology is important because it provides a new convenient method for the synthesis of diaryl ketones.

4. Experimental

4.1. General

All microwave experiments were carried out in the Initiator-Biotage reactor (power setting 260 W, 10 min at 98 °C). The reactions were performed in an argon atmosphere. All the products were analyzed by ^{1}H NMR and GC–MS and compared with the authentic samples of the products. The ^{1}H NMR spectra were measured at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. GC–MS measurements were performed on a gas chromatograph Trace GC 2000 Series Thermoquest CE Instruments with a flame ionization detector and a Voyager GC–MS Thermoquest Finnigan in SCAN-mode. Mass spectral data were obtained by cyclic scanning from 15 to 350 mass units with a cyclic time of 0.2 s. Transfer line temperature was 200 °C. Quadrupole conditions were as follows: electron energy 70 eV, emission current 150 μA, and ion source temperature 150 °C. Each GC peak was inspected for constancy of MS pattern in order to detect possible overlapping compounds and to measure their retention time. Melting points were determined on a Kofler hot stage.

4.2. Reactions under thermal heating

Base Cs_2CO_3 (1.5 mmol, 0.488 g) and $Pd(PPh_3)_4$ (5 mol %, 0.029 g) catalyst were added to the solution of phenylboronic acid (0.5 mmol, 0.061 g) and 4-nitrobenzoyl chloride (1 mmol 0.186 g) in 7 mL solvent of toluene. The reaction mixture was heated on the oil bath at 98 °C for 10 min. The solution was washed with sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, product **3** was separated by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) and identified by spectroscopic analyses. Compound **3**: 13%; Mp 137–138 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (2H, t, J=8.0 Hz), 7.64 (1H, d, J=7.6 Hz), 7.81 (2H, d, J=7.9 Hz), 7.94 (2H, d, J=8.4 Hz), 8.35 (2H, d, J=8.4 Hz). ^1H NMR spectroscopy and melting point were compared with the authentic samples of the product.[20]

4.3. Reactions under microwave irradiation

Base Cs_2CO_3 (1.5 mmol, 0.488 g) and $Pd(PPh_3)_4$ (5 mol %, 0.029 g) catalyst were added to the solution of phenylboronic acid (0.5 mmol, 0.061 g) and 4-nitrobenzoyl chloride (1 mmol, 0.186 g) in 7 mL solvent of toluene. The reaction mixture was microwave-irradiated for 10 min. The solution was washed with sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, product **3** was separated by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) and identified by spectroscopic analyses. Compound **3**: 93%; Mp 137–138 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (2H, t, J=8.0 Hz), 7.64 (1H, d, J=7.6 Hz), 7.81 (2H, d, J=7.9 Hz), 7.94 (2H, d, J=8.4 Hz), 8.35 (2H, d, J=8.4 Hz). ^1H NMR spectroscopy and melting point were compared with the authentic samples of the product.[20]

The same procedure was used for preparation of product **4–18**. All products were found to be identical (^1H NMR data) with the data described in literature.[20–28]

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