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Note

Microwave promoted Suzuki reactions between aroyl chlorides and boronic acids catalyzed by heterogeneous and homogeneous phosphine-free palladium catalysts

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ABSTRACT

Suzuki cross-coupling reactions between arylboronic acids and aroyl chlorides with phosphine-free palladium catalysis under microwave irradiation were performed to obtainment of aromatic ketones in good yields within short times. Heterogeneous and homogeneous catalysts were studied as well as their influence in the reaction selectivity relative to homocoupling of the boronic acids.

1. Introduction

Aromatic ketones are important building blocks in organic synthesis. This class of compounds is present in natural products and as active pharmaceuticals ingredients. Sulisobenzone (**1**) (Fig. 1), for example, is an aromatic ketone used as absorber of UVB and UVA light in sunscreens [1]. Ketoprofen (**2**) is a non-stereoidal anti-inflammatory drug (NSAID) that inhibits prostaglandin production in the body [2]. The flavonoid naringenin (**3**) is present in grapefruits and is regarded as having an antioxidant and an anti-inflammatory activity in human health [3].

Aromatic ketones are most frequently prepared by Friedel–Crafts acylation of aromatic compounds [4] but this method is not regioselective. Mixtures of regioisomers difficult to separate can be obtained instead. Moreover the drastic conditions employed in Friedel–Crafts reaction cannot be suitable for several substrates [5]. Nucleophilic addition of organometallic compounds to carboxylic acids derivatives is another available approach to the synthesis of ketones [6]. However, low yields can be achieved due to the formation of tertiary alcohols.

Palladium-catalyzed C–C bond formation methodologies have been proved as effective tools in organic synthesis [7–11]. Regarding these methodologies, organic halides and triflates are the most employed electrophiles. A lot of efforts, however, have been put recently into employing cheap aryl sources like arene-diazonium salts [12–15] and carboxylic acids derivatives [16,17] as electrophiles in the couplings. Acid chlorides, for instance, can be employed successfully in the arylation of alkenes (Heck reaction) [18–20], or in the acylation of terminal alkynes to obtain ynones [21]. Palladium-catalyzed cross-couplings, like the Suzuki [22] and Stille reactions [23,24], between acyl chlorides and organometallic compounds can be considered as a regioselective route to aromatic ketones [25–30]. Suzuki cross-coupling is a superior methodology because of the mild conditions, functional groups tolerance, effectiveness and regioselectivity. Furthermore boronic acids are compounds of low toxicity and great stability.

Microwave assisted reactions is an area of increasing research because of the reduced chemical reaction times, increased yields, reduced side reactions and high reproducibility reported in the literature [31]. Since pioneers researches in the arena of microwave-assisted Suzuki reactions [32,33], several works were

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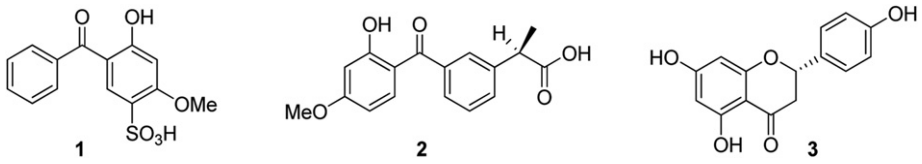


Fig. 1. Examples of important aromatic ketones.

published dealing with the development of palladium-catalyzed Suzuki reactions under microwave irradiation.

Bumagin and co-workers [34–36] studied the Suzuki reaction between acid chlorides and boronic acids in aqueous acetone with $Pd(OAc)_2$ or $PdCl_2$ as pre-catalysts. These researchers prepared various aromatic ketones in high yields. The development of anhydrous protocols is desirable for those acid chlorides most prone to hydrolysis. Since in the previous reports concerning anhydrous protocols [37,38] soluble phosphine-bound palladium compounds were employed as pre-catalysts, we decided to investigate the reaction between aroyl chlorides and boronic acids catalyzed by phosphine-free catalysts. Supported catalysts as well as non-supported ones were employed as pre-catalysts under microwave irradiation.

2. Results and discussion

Our initial investigation started with the cross-coupling reaction of benzoyl chloride and phenylboronic acid (Scheme 1) with $Na_3PO_4.12H_2O$ as the base, in toluene as solvent. Different reaction conditions were tested with the aim of investigating their influence on the selectivity. The results obtained were summarized in Table 1.

In a general manner it could be observed that better selectivities toward benzophenone (**6**) were achieved when Pd_2dba_3 was employed as catalyst. Formation of biphenyl (**7**) was favoured when supported catalysts were employed (entries 1–4), with exception of $Pd/BaSO_4$ for which almost the same selectivity of Pd_2dba_3 (entry 5) was observed (see entry 3 *versus* entry 5). Conversions to the coupling products were considered as total since benzoyl chloride and the benzoic acid have not been detected by the GC–MS analysis.

Although the selectivity toward benzophenone with Pd/C as catalyst was not good, this selectivity could be improved by the decrease of the reaction temperature from 120 °C to 80 °C (entries 1 and 6). Apparently, biphenyl formation under Pd/C catalysis is favoured at higher temperatures. When Pd/C was employed under conventional heating utilizing a pre-heated oil bath at the temperature of 120 °C the selectivity toward benzophenone was better than under microwave heating (Table 1; entry 1[a,b]). As Pd/C is as strong microwave absorber, higher surface temperatures are achieved under microwave irradiation than under conventional heating, so these high superficial temperatures can lead to greater amounts of biphenyl.

Pd/C was shown to be an effective catalyst when acetonitrile was used as solvent (entry 7) instead of toluene. This better result can be attributed to a better solubilization of the base in a solvent with higher polarity. When acetonitrile was used as solvent with Pd_2dba_3 as the palladium source, although this catalytic system afforded excellent selectivity, the reaction was slower and high amount of benzoyl chloride was recovered (entry 8). The better solubility of the base in acetonitrile resulted in the hydrolysis of the benzoyl chloride with the detection of great amounts of benzoic acid.

We have also investigated the effect of phase transfer catalysts in the reaction between benzoyl chloride and phenylboronic acid catalyzed by Pd_2dba_3 (entries 9–10). Among the phase transfer catalysts studied, better results were obtained with the most hydrophilic ones (PEG and [Bmim]Cl). PEG -200 was found to be an excellent choice, probably because besides promoting a better solubilization of the base, it prevents the hydrolysis of the acyl chloride.

Ogura and co-workers [39] reported that hydrated bases resulted better than the anhydrous ones. These authors [39] attributed the better efficiency of the hydrated bases to the water activation of the boron species in the transmetalation step of the coupling without a consequent hydrolysis of the acyl chloride. Therefore, in our initial experiments (Table 1) we utilized $Na_3PO_4 \cdot 12H_2O$ as the base. After irradiation, it was observed the solidification of the base when $Na_3PO_4 \cdot 12H_2O$ was employed [40]. This fact was not observed when K_2CO_3 and K_3PO_4 were employed as base and the better selectivity was found with K_2CO_3.

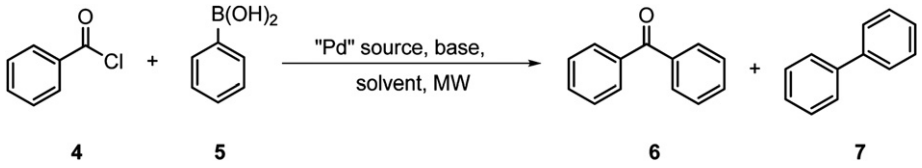
In the majority of the reaction time, potency was maintained in 10 W and temperature in 120 °C. The temperature and potency profile for the reactions with Pd_2dba_3 as catalyst, under microwave irradiation, are shown in Fig. 2.

To further comprehend the scope and limitations of the cross-coupling reaction between acid chlorides and boronic acids catalyzed by Pd_2dba_3, a variety of acid chlorides and boronic acids were tested (Table 2, Scheme 2).

High yields (79–99%) to aromatic ketones were achieved for the Suzuki cross-coupling reactions between aryl boronic acids and aroyl chlorides under microwave irradiation with Pd_2dba_3 as catalyst (K_2CO_3), without phosphine ligands.

Biphenyls were obtained as by-products in the couplings between boronic acids and aroyl chlorides. Biphenyls can be produced by two pathways: the homocoupling of the boronic acids (Scheme 3a) and the decarbonylative coupling between the acyl chloride and the boronic acid (Scheme 3b).

Products from the decarbonylative coupling were found in entries 2–4 (Table 2). In entry 1 (Table 2), the same product is produced in both pathways. Aroyl chlorides can be employed as arylating agents in Heck couplings [20,40–42]. In the present work, it was observed that the same tendency to the decarbonylation process was not observed in the Suzuki couplings, since in all cases ketones were obtained as the principal product.



Scheme 1. Suzuki reaction between benzoyl chloride and phenylboronic acid.