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# Suzuki-Miyaura Cross-Coupling for Synthesis of Key Intermedi-Ates of Ketoprofen and Bifonazole Analogues †

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**Abstract:** Aromatic ketones are important compounds because of their utility as synthetic intermediates, applications as light absorbing compounds and biological activities. Bifonazole (antifungal) and Ketoprofen (anti-inflammatory) are commercial drugs having aryl ketones as synthetic intermediates. Suzuki coupling reaction is a C-C bond forming procedure catalyzed by palladium species under a basic medium. Acyl chlorides can be used as electrophiles in Suzuki couplings resulting in aryl ketones. In this work, selectivity in Suzuki coupling reactions between acid chlorides and boronic acids, the catalytic system for such reactions and other aspects of the reaction are studied. Intermediates of interest are: 4-bromobenzophenone, 4-phenylbenzophenone and 3-bromobenzophenone.

**Keywords:** Suzuki; bifonazole; ketoprofen; 4-bromobenzopheenone; 4-phenylbenzophenone and 3-bromobenzophenona

## 1. Introduction

Aromatic ketones can make up the skeleton of natural or synthetic molecules. In organic synthesis, these ketones are very important, as they can be transformed both to generate new organic functions and to extend the carbon chain [1]. This structural framework is present in several compounds with biological activity: for example, the anti-inflammatory Ketoprofen, the antipsychotic and the neuroleptic Haloperidol, the antidepressant Bupropion and Quercetin, a natural flavonoid with anticancer activity (Figure 1).

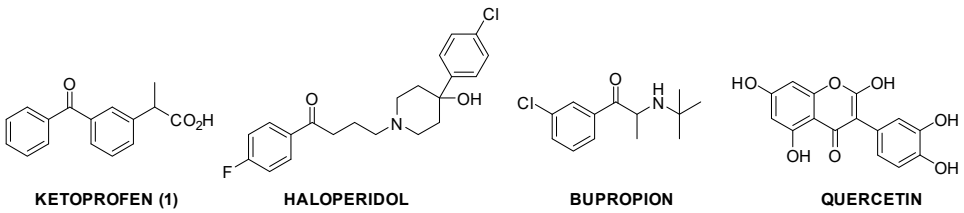


**Figure 1.** Examples of drugs with aromatic ketone moiety.

In our research group, we apply Suzuki couplings as synthetic tool to obtain compounds of biological importance [2,3]. The Suzuki coupling provides for the formation of a C-C bond by the reaction between a boron organometallic and an electrophile (halide or pseudohalide) under palladium catalysis and in the presence of a base [4–7]. Carboxylic acids and their derivatives can also be employed as electrophiles in

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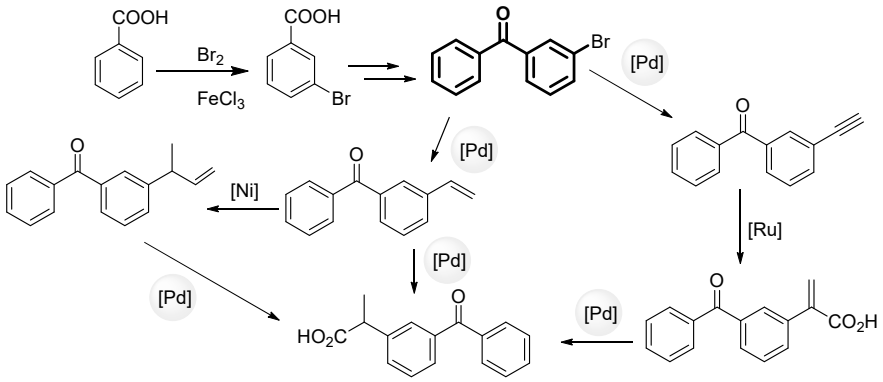
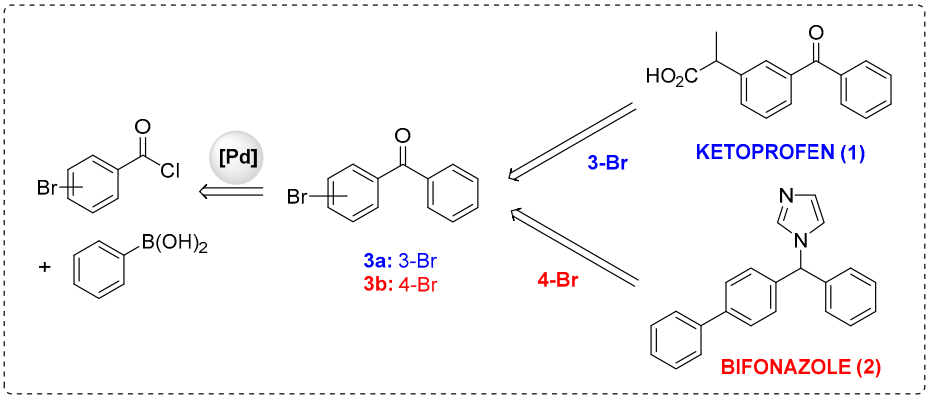
palladium-catalyzed coupling reactions, and if they are used in Suzuki reactions, they can generate ketones as products [8–12].

Rammimger and collaborators reported the use of transition metal-catalyzed couplings in the synthesis of ketoprofen (**1**) (Scheme 1) [13]. However, these researchers did not use a coupling reaction to generate the key intermediate bromobenzophenone, but in the subsequent steps. Instead, they brominated benzoic acid, converted it to the acid chloride and performed a Friedel-Crafts acylation with benzene. The couplings were used to introduce the side chain into the aromatic ring. Friedel-Crafts acylations, however, cannot be carried out with benzenes substituted by strongly electron-withdrawing groups, which reduces the scope of the reaction. Reactions using carboxylic acid derivatives and lithium or magnesium organometallics may require protective protocols, limit the functional groups that can be present, require drying solvents, low temperatures, etc. Suzuki couplings, on the other hand, occur with boron organometallics, which are non-toxic, easily manipulated and commercially available. In addition, boron organometallics with strongly electron-withdrawing substituents can be used.




**Scheme 1.** Ketoprofen synthesis by Rammimger and collaborators.

Both the anti-inflammatory ketoprofen (**1**) and the antifungal bifonazole (**2**) can be obtained from a bromobenzophenone. While ketoprofen (**1**) and its analogues can be synthesized from the benzophenone brominated at position 3, bifonazole (**2**) and its analogues can be prepared from the benzophenone brominated at position 4 (Scheme 2). In the present work, we employed the palladium-catalyzed Suzuki reaction between bromobenzoyl chlorides and boronic acids to prepare two bromobenzophenones that are key synthetic intermediates in the syn-theses of ketoprofen (**1**) and bifonazole (**2**).

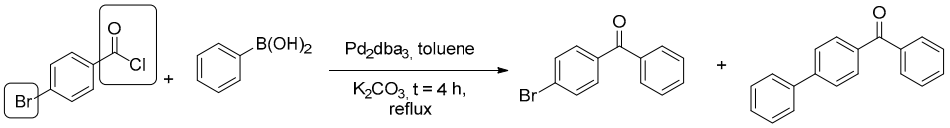



**Scheme 2.** Key synthetic intermediates in the synthesis of ketoprofen and bifonazole.

## 2. Results and Discussion

### *2.1. Study of the Selectivity of Suzuki Coupling: Acid Chlorides Versus Bromides*

Both acyl chlorides and bromides can be electrophiles in the Suzuki reaction. Different halides have different Suzu-ki coupling reactivities depending on the energy required to break the C-X bond. Studies were therefore begun with 4-bromobenzoyl chloride in order to check the selectivity of the reaction with respect to the two electrophilic centers present in the molecule (Scheme 3). Martins and collaborators reported the study of the reaction between dif-ferent acid chlorides and boronic acids under microwave irradiation. It was found that the use of an inorganic base in toluene was efficient in promoting coupling with minimization of hydrolysis [11]. The researchers found that the best yields were obtained with the Pd2dba3 precatalyst. When applying heterogeneous precatalysts (e.g., Pd/BaSO4), the addition of PEG-200 accelerated the reaction. Based on Martins' work, we evaluated catalytic sys-tems and the influence of reaction conditions on chloride versus bromide selectivity (Scheme 3).




**Scheme 3.** Reaction between 4-bromobenzoyl chloride and phenylboronic acid.

In the initial reaction condition, potassium carbonate was selected as the inorganic base in toluene with 5 mol % of the Pd2dba3 precatalyst (10% Pd). Through GC-MS analysis, we observed that acid chloride is more reactive under the reaction conditions, with ketone being the favored product (Figure 2). The first peak of sig-nificant intensity has a retention time of 18.537 min (78%) and the corresponding mass spectrum indicates a molecular ion in 260 with an isotopic pattern consistent with the presence of a bromine in the structure (M/(M + 2) ratio approximately 1:1) (Figure 2). The 13% of 4-phenylbenzophenone was identified, with a retention time of 23.389 min. This is the product of the coupling of phenylboronic acid with the bromobenzophenone formed in the previous coupling, at the acyl electrophilic center. In Figure 3, the mass spectrum of this ketone is shown (Figure 3).

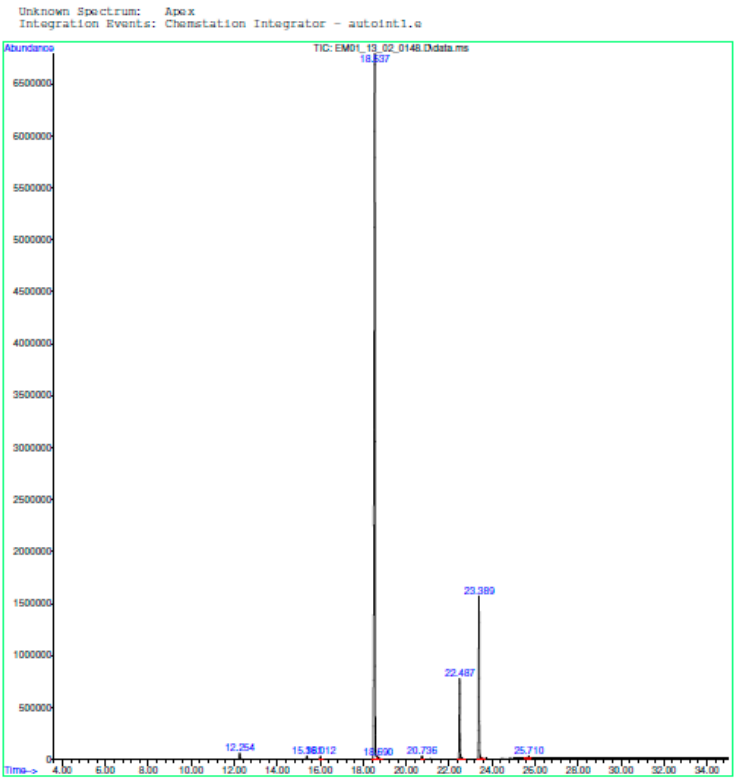


**Figure 2.** Chromatogram of the reaction mixture.

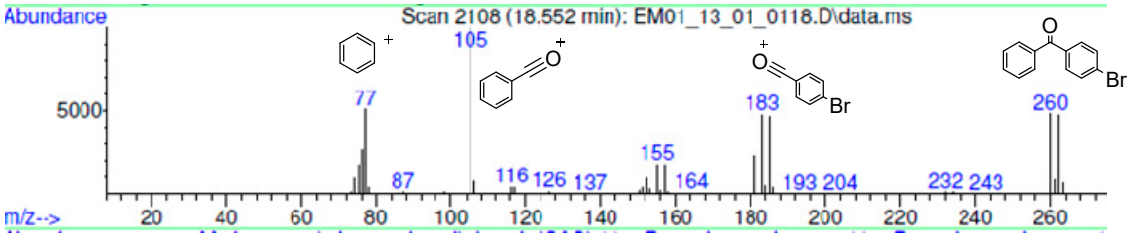



**Figure 3.** Mass spectrum of the bromobenzophenone **3b.**

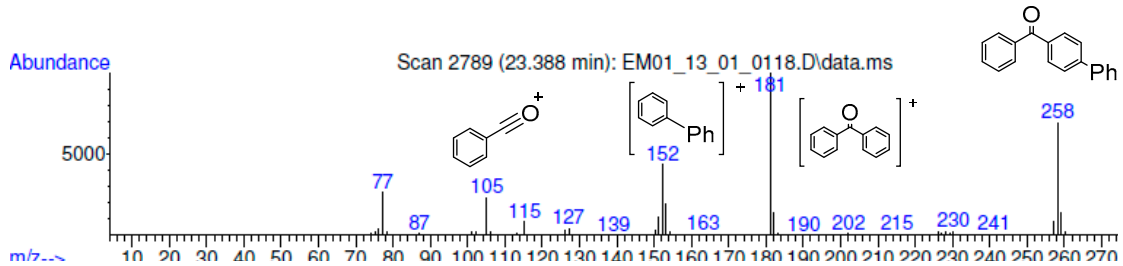



**Figure 4.** Mass spectrum of the 4-phenylbenzophenone.

*2.2. Study of the Influence of Reaction Conditions on the Suzuki Coupling between the 4-bromobenzoyl Chloride and Phenylboronic Acid*

The reaction conditions were changed in an attempt to reduce 4-phenylbenzophenone formation (Table 1). The condition in which the least formation of 4-phenylbenzophenone was as described in Entry in Table 1.

**Table 1.** Study of reaction conditions to maximize the formation of 4-bromobenzophenone.

| | $PhB(OH)_2$ (mmol) | $Pd_2dba_3$ | Toluene | Yield % |
|---|---|---|---|---|
| 1 | 0.52 mmol | 1.00% | 1.0 mL | 80% |
| 2 | 0.52 mmol | 0.50% | 1.0 mL | 81% |
| 3 | 0.52 mmol | 0.25% | 1.0 mL | 86% |
| 4 | 0.50 mmol | 0.50% | 1.0 mL | 71% |
| 5 | 0.50 mmol | 0.50% | 1.0 mL | 76% |
| 6 | 0.52 mmol | 0.50% | 2.5 mL | 76% |
| 7 | 0.52 mmol | 0.25% | 2.5 mL | 67% |
| 8 | 0.52mmol | 0.10% | 2.5 mL | 70% |

* 0.50 mmol of 4-bromobenzoyl chloride was used in all reactions.

After purification of the crude product by column chromatography, 4-bromobenzophenone was obtained as a white solid with a melting point of 80 °C (m.p. = 79–81 °C, Sigma Aldrich, St. Louis, MI, USA), being characterized by spectroscopy in the infrared region (IR) and 1H nuclear magnetic resonance ($^1$H-NMR). The $^1$H-NMR spectrum indicates a substitution pattern for benzophenone (two doublets with coupling constant $J$ = 9 Hz). We can notice that the monosubstituted ring hydrogens are the most unshielded (doublet around 7.781–7,767 ppm/Hc,c') this can be due to the inductive withdrawal effect of electrons exerted by the carbonyl (Figure 4).

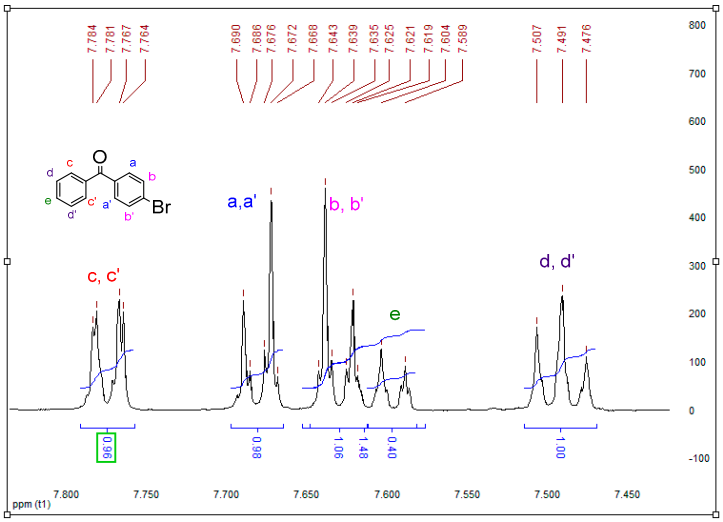



**Figure 4.** $^{1}$H-NMR spectrum of the pure 4-bromobenzophenone.

When 1.0% Pd/$BaSO_4$ in toluene was used, 4-phenylbenzophenone (23.735 min) was obtained in 70% yield as observed when analyzed by gas chromatography. 4-Bromobenzophenone (18.830 min) was present in 28%. With the addition of a drop of PEG-200, 10% of 4-bromobenzophenone (RT = 18.882 min) and 88% of 4-phenylbenzophenone (RT = 23.729 min) were formed, which indicates that the addition of PEG favors double coupling, that is, the coupling between the acyl chloride and the bromide. The double coupling is interesting for the synthesis of bifonazole itself, since the ring present in the biphenyl formed is phenyl. However, this double coupling is interesting in the formation of bifonazole analogues where the A ring is the same as the C ring. In this case, the use of Pd2dba3 provided the synthesis of 4-bromoacetophenone, which can be coupled sequentially with another boronic acid to provide a structure with the three different aromatic rings as intermediates for bifonazole analogues.

### *2.3. Synthesis of the Key Intermediate to Obtain Ketoprofen*

Since in the coupling reactions with 4-bromobenzoyl chloride we were successful in obtaining 4-bromobenzophenone **3b,** this protocol was extended to the formation of 3-bromobenzophenone **3a.**

Thus, the study began using 0.5% mmol of $Pd_2dba_3$ in 1.0 mL of toluene and 2 equivalents of base $CO_3$) in relation to the limiting chloride. After 4 h of reaction, 3-phenylbenzophenone was observed in a greater proportion than 3-bromobenzophenone. It was then decided to reduce the amount of base used in the reaction; expecting that the Suzuki reaction would be slower, both in the chloride portion and in the bromide portion. When using 1.3 equivalents of base for the reaction, the c.c.f. carried out after 1.5 h indicated the pres-ence of 3-bromobenzophenone and the beginning of formation of the biaryl-containing ketone. Thus, the reaction was stopped, isolated, and the crude product was analyzed by $^{1}$H-NMR (Figure 5).

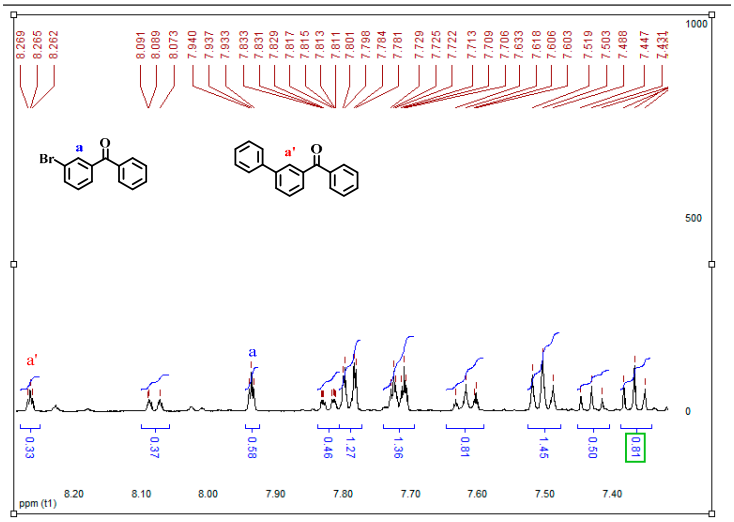



**Figure 5.** [1]H-NMR spectrum of 3-bromobenzophenone.

## 3. Experimental Procedure

*Typical Suzuki Couplings between Bromobenzoyl Chlorides and Phenylboronic Acid*

In a 10 mL flask equipped with a magnetic stirrer were added: 4-bromobenzoyl chloride (0.5 mmol), phenylboronic acid (0.52 mmol), $K_2CO_3$ (1.0 mmol) and $Pd_2dba_3$ (5 mol%; 0.025 mmol). Then, toluene (1.0 mL) was added. The reaction mixture was left under magnetic stirring and reflux for 4 h with the aid of an oil bath. At the end of the reaction, washing was carried out with 1.5 M sodium hydroxide solution (2 times of 5 mL). The aqueous phase was extracted and treated with ethyl acetate (3 times of 5 mL). To the organic phase of the extraction, anhydrous sodium sulfate was added, and the solvent was evaporated using a rotary evaporator. The product thus obtained was called crude product. This product was purified by silica flash chromatography using an ethyl acetate/hexane mixture as eluent starting at 10%.

## 4. Conclusions

Homogeneous catalysts seem to favor the formation of bromobenzophenones **3a** and **3b**, while the heterogeneous catalyst favors "double coupling", that is, a sequence of couplings in both acyl chloride and bromide, generating biphenylbenzophenone. The use of a phase transfer catalyst led to the conversion to the double coupling product in higher concentrations, probably by facilitating the mass transport processes that deter-mine heterogeneous catalysis.

In reactions with 3-bromobenzoyl chloride, it was necessary to reduce the amount of base used to minimize the formation of double coupling. We consider that this occurred because this electrophile is more reactive for the Suzuki reaction, so the "activation" of the phenylboronic acid through the use of the base makes coupling faster at both electrophilic points present.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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