

Efficient Cross-Coupling Reaction of Aryltrifluoroborates and Aroyl Chlorides for the Synthesis of Fluorine Substituted Aromatic Ketones

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Abstract

The direct aroylation of ArCOPdCl with potassium aryltrifluoroborates establishes a new cross-coupling synthetic tool for the synthesis of various fluorine substituted benzophenones. The new microwave irradiated process is very efficient and produce high yield benzophenone products within minutes.

Keywords

ArBF₃K, Aroyl Chlorides, Direct Aroylation to Ketones, Minute Reaction

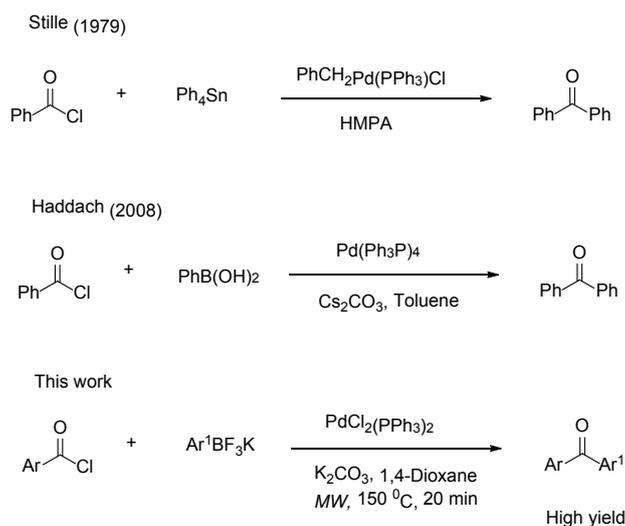
1. Introduction

The selective functionalization of potassium aryltrifluoroborates into fluoro-substituted aromatic ketones is an important synthetic task. Fluoro-substituted aromatic ketones are very active pharmaceutical ingredients useful for pharmaceutical application such as anti-inflammatory effects. Introducing fluorine moiety is demanding methodology in medicinal chemistry to adjust binding affinity of small molecules for biological targets and control metabolic reactivity [1] [2]. Fluorinated benzophenones served as starting point for the synthesis of many small benzophenone analogs. Transition metal catalyst, especially palladium, is very popular in organic synthesis because it has a unique ability to activate various organic compounds. This activation can catalyze the formation of new bonds. J. K. Stille first successfully developed the direct cross-coupling reaction of organotin compounds and benzoyl chlorides for benzophenone synthesis [3] [4]. Haddach also has reported a similar cross-coupling reaction by using

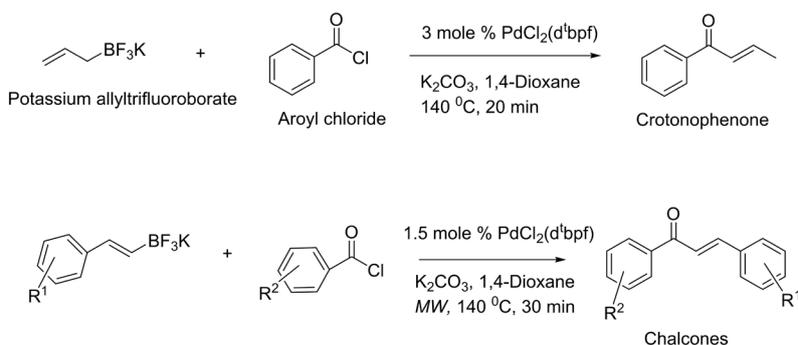
arylboronic acids [5] [6]. In this work, a new reaction method establishes for the direct arylation reaction of potassium aryltrifluoroborates and ArCOCl in the presence of PdCl₂(Ph₃P)₂ (Scheme 1).

2. Results and Discussion

This direct arylation reaction combines PdCl₂(Ph₃P)₂ with K₂CO₃, as a new catalyst system along with potassium aryltrifluoroborates and fluoro substituted aryl chlorides in a dry microwave vial under argon. The resulting mixture microwave in 1,4-dioxane at 150 °C for 20 min and obtained high yield products of various fluoro substituted benzophenones. Recently, new synthetic methods for crotonophenones by cross coupling of potassium allyl trifluoroborate with aryl chlorides, and chalcones from potassium styryl trifluoroborates and aryl chlorides have been established [7] [8]. In both cases, PdCl₂ (d'bpf) complex has shown remarkable catalyst effect for successful transformations (Scheme 2). In line with those findings, it has assumed that same catalyst system would work for cross coupling of aryl trifluoroborates with aryl chlorides. Surprisingly, no desired benzophenones observed as major products.



Scheme 1. Aryltrifluoroborates for arylation reactions.



Scheme 2. Organotrifluoroborates and direct arylation to crotonophenones and chalcones.

After further investigation with several palladium complexes and bases to find a suitable conditions for arylation of potassium aryltrifluoroborates under microwave irradiation, the effective catalyst effect of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ complex has been observed and successfully synthesize series of fluoro-substituted aromatic ketones in high yields.

The results summarize in **Figure 1**. It appears that 1,4-dioxane as the solvent system gave successful results in cross-coupling reaction. The biggest challenge of this project was the formation of homo-coupling product instead of cross coupling. Often times the ArBF_3K reacts with itself giving biphenyl as homo coupling product that observed in GC-MS. This problem is mostly overcome by applying 3 mole % $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ as catalyst.

The mechanism for the direct cross-coupling reaction of potassium organotrifluoroborates and benzoyl chlorides proposes in **Scheme 3**. The catalytic cycle involves the palladium insertion by oxidative addition followed by ligand exchange with the K_2CO_3 . Then occurring transmetalation of organoboron species to the organopalladium, followed by forming the desired cross coupling product by reductive elimination.

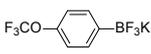
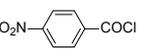
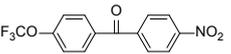
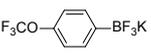
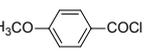
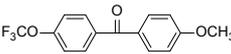
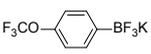
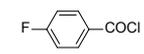
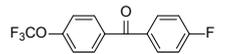
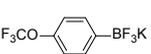
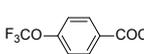
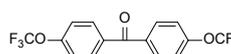
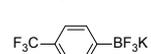
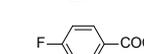
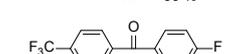
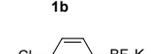
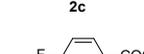
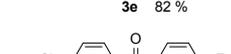
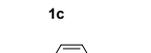
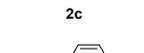
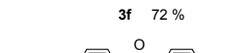
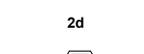
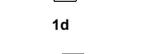
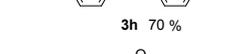
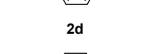
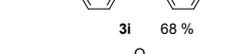
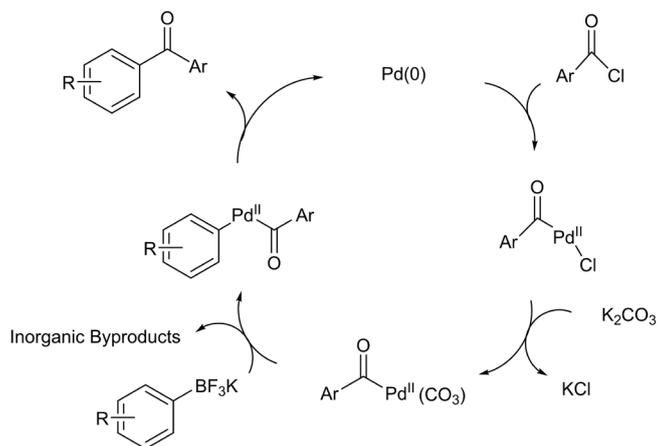
| Obs | ArylBF ₃ K 1 | Aroyl Chloride 2 | Cross-coupling Ketone 3 |
|-----|--|---|---|
| 1 |  1a |  2a |  3a 86 % |
| 2 |  1a |  2b |  3b 78 % |
| 3 |  1a |  2c |  3c 80 % |
| 4 |  1a |  2d |  3d 90 % |
| 5 |  1b |  2c |  3e 82 % |
| 6 |  1c |  2c |  3f 72 % |
| 7 |  1c |  2d |  3g 80 % |
| 8 |  1d |  2d |  3h 70 % |
| 9 |  1e |  2d |  3i 68 % |
| 10 |  1e |  2c |  3j 65 % |

Figure 1. Cross-coupling of ArylBF_3K and ArCOCl for Fluorinated ketones^a. ^aIsolated products separated by silica gel chromatography.



Scheme 3. Catalytic cycle for direct arylation of ArylBF₃K.

3. Conclusions

This work demonstrates the novel application of potassium aryltrifluoroborates with aryl chlorides for cross coupling reaction. A new catalyst system is established. The application of microwave heating drastically reduced the amount of time to 20 minutes. Usually this type of coupling requires 8 - 24 hours heating in conventional heating system. The direct arylation of potassium aryltrifluoroborates is great addition to the direct arylation of potassium styryltrifluoroborates, potassium allyltrifluoroborate, and potassium crotyltrifluoroborate.

Experimental

Synthesis of aryl trifluoroborates (BF₃K); the starting material

ArBF₃K is synthesized from boronic acid. In a typical synthesis, in a round bottom flask with a stirrer, about 20 mL of methanol was added to 20 mmol of boronic acid. This mixture was completely dissolved in the methanol. The solution was clear. On a separate small beaker, 120 mmol (about 9.36 g) potassium hydrogen fluoride (KHF₂) was dissolved in 20 mL of DI water. This KHF₂ solution then added to the methanol mixture while the mixture was stirring vigorously. This resulting thick mixture was on vigorous stirring for 4 hours. The solvent in the mixture dried up by using rotary evaporator followed by high vacuo for complete dry. To remove excess KHF₂ from the crude product, 250 mL of boiled acetone added into the mixture. The clear liquid part of the mixture then filtered through sintered funnel and the filtrate evaporated in a rotary evaporator until it was completely dry. To recrystallize the mixture, the product was dissolved in minimum amount of acetonitrile (CH₃CN) followed by adding diethyl ether until solid crystal formed. The crystallized solid potassium aryltrifluoroborate product was collected in high yields.

Synthesis of 4-fluoro-4'-trifluoromethylbenzophenone is a representative one.

A small dry microwave reaction vial loaded with 0.5 mmol of potassium (4-trifluoromethyl)phenyltrifluoroborate, 2 mmol of K₂CO₃ and 0.015 mmol of PdCl₂(Ph₃P)₂ (11.0 mg). The vial was capped with air-tight septum followed by

Compound **3h**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.79 - 7.22 (m, 8H), $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 195.2, 152.1, 137.1, 135.8, 131.9, 129.9, 128.4, 120.2, $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -57.6.

Compound **3i**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.19 - 7.30 (m, 8H), 2.45 9s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 195.0, 170.8, 153.2, 132.2, 131.8, 130.2, 129.1, 120.2, 21.6; $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -57.6.

Compound **3j**, $^1\text{H NMR}$ (Acetone- d_6 , 400 MHz) δ 7.36 - 6.91 (m, 8H), 1.96 (s, 3H); $^{13}\text{C NMR}$ (Acetone- d_6 , 100 MHz) δ 184.5, 134.2, 124.6, 122.8, 122.7, 120.2, 119.8, 106.1, 11.5.

Compound **3k**, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.83 - 6.97 (m, 8H), 3.90 (s, 3H); $^{19}\text{F NMR}$ (CDCl_3 , 400 MHz) δ -57.6 [product **3k** from potassium (4-methoxy) phenyltrifluoroborate and 4-trifluoromethoxy benzoyl chloride was not added in **Figure 1** due to limited space].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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