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Microwave Irradiated Cross Coupling of Carboxylic Acids and Crotyl Bromides: Efficient Application to Make Arachidonic Acid Esters

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Abstract

A microwave irradiated palladium-catalyzed reaction of carboxylic acids and crotyl type bromides creates series of esters in good to high yields. This facile ester synthesis then is applied to make esters from arachidonic acid, salicylic acid, folic acid, and aspirin efficiently.

Keywords

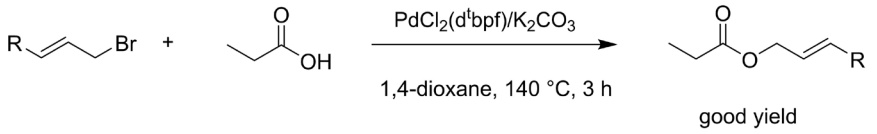
Arachidonic Acid Esters by Cross Coupling, Microwave

1. Introduction

Esters are common chemicals with extensive applications in medicine, biology, chemistry, and material sciences [1]-[7]. Esters used not only as solvents but also are in perfumes, essential oils, agriculture and food flavorings, antioxidant, plastics, detergents, and for many other purposes. Isoamyl acetate (odor of banana), ethyl butanoate (odor of mango), methyl 2-methylbutanoate (odor of pineapple), vitamin C, cocaine, etc., are some common interesting examples occurring in the nature. The enormous use of transition metal complexes to activate organic molecules makes them viable visions for developing catalytic processes with high selectivity and atom economy. This work focusses to find a facile way of making esters by microwave irradiated cross-coupling reaction of carboxylic acids, allyl type halides, in the presence of palladium-catalyst (**Scheme 1**) and apply that effective cross coupling method to synthesize arachidonic acid esters, and folic acid esters, etc.

2. Results and Discussion

Recently, $PdCl_2(d^tbpf)$ complex has been successfully employed as a catalyst in



Scheme 1. Propionic acid ester from Propionic acid and alkyl halides.

various organic transformations involving potassium organotrifluoroborates [8] [9] [10] [11] [12]. The higher cone angle of P-Pd-P in $PdCl_2(d^tbpf)$ may be improve its effectiveness as a catalyst. In order to see further application of this palladium complex, we thought to explore cross coupling reactions of carboxylic acids with 3-Bromo-1-phenyl-1-propene **2a** and 1-bromo-2-butene **2b**. We began our study with 3-bromo-1-phenyl-propene **2a** and various carboxylic acids as substrates with the load of 3 mole % $PdCl_2(d^tbpf)$. The reactions worked well when microwaved for 30 min. We turned our attention to optimization the reaction conditions and found 0.5 mole % catalyst works quite good with 3 h reaction time.

The results with 3-bromo-1-phenyl-1-propene **2a** summarize in Figure 1. In case of cinnamic acid best result obtained with 3 mole % $PdCl_2(d^tbpf)$ (Entry 10, Figure 1).

We also unzipped the cross coupling of carboxylic acids with 3-bromo-2-butene **2b**. The reactions went very sluggish but with 3.0 mole % catalyst the desired products form in moderate yields. The results with 3-bromo-2-butene **2b** summarize in Figure 2. In case of hexanoic acid and 2-octenoic acid, 0.5 mole % of catalyst worked well when treated with 1-bromo-2-butene **2b** (Figure 2, Entries 2, 3).

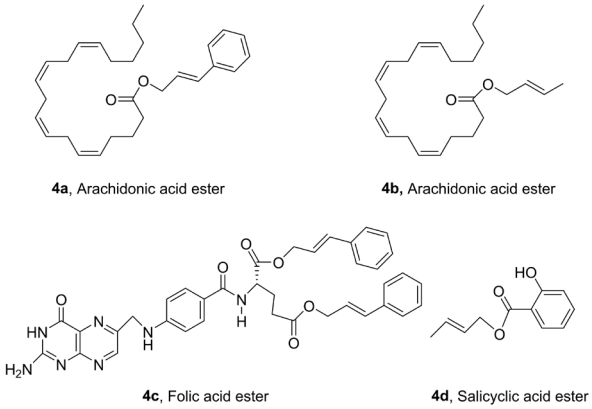
It is a further object of the investigation to see the application of these methods and make the esters from arachidonic acid, folic acid, salicylic acids, etc. In fact, arachidonic acid, folic acid, salicylic acid, all form the corresponding esters when treated with halides **2a** and **2b**. Examples such as **4a**, **4b**, **4c**, and **4d** present in Scheme 2.

Our goal is to examine the significant biological effect of these new esters and report in due courses. Arachidonic and folic acid esters are useful biologically active compounds [13] [14] [15] [16] [17]. The probable catalytic cycle for this new transformation proposes in Scheme 3. This new method is eco-friendly, atom-economy, and sustainable green chemistry synthetic process. This new process will have potential value for complex ester synthesis.

3. Procedure

The synthesis of ester **3a** from propionic acid **1a** and 3-bromo-1-phenyl-1propene **2a** is a representative one. A dry clean microwave vial was loaded with potassium carbonate (0.207 g, 1.5 mmol), $PdCl_2(d^tbpf)$ (0.002 g, 0.0025 mmol), then capped the vial with septum and flushed with argon. After adding propionic acid (37.5 μL, 0.5 mmol), 3-bromo-1-phenyl-propene **2a** (82.0 μL, 0.55 mmol) via micro syringe, and 1,4-dioxane (5.0 mL) in the microwave reaction vial, the result-

ing mixture was irradiated at 140˚C for 3 h. The crude reaction product filtered through sintered funnel and concentrate. For purification, the crude product passed through alumina using hexane/dichloromethane (100/1) as eluents. The purified product **3a** obtained was 87% in yield (Figure 1, entry 1). Compound **3a**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 5H), 6.57 (d, J = 15.8 Hz, 1H), 6.21 (dt, J = 6.44 Hz, 1H), 4.66 (d, J = 6.48 Hz, 2H), 2.30 (q, J = 7.56 Hz, 2H), 1.09 (t, J = 7.56 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz)



Scheme 2. New esters from arachidonic, folic, and salicylic acids.

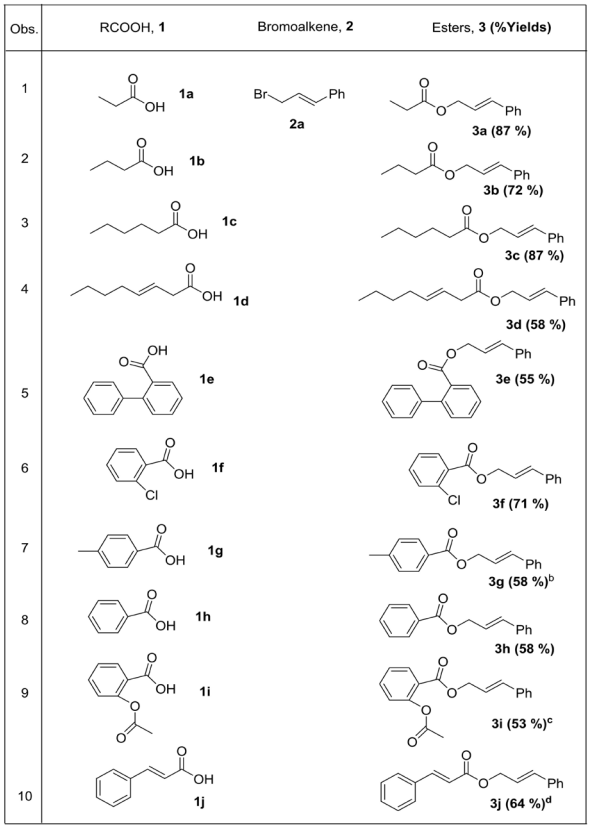


Figure 1. Esters from cross coupling of carboxylic acids and bromoalkenes[a]. [a]All yields are isolated yields; [b]*α*-adduct is minor product; [c]Mixture of E; and Z [d]Compound 3 j formed by adding 3 mole % $PdCl_2$(d^{t}bpf).

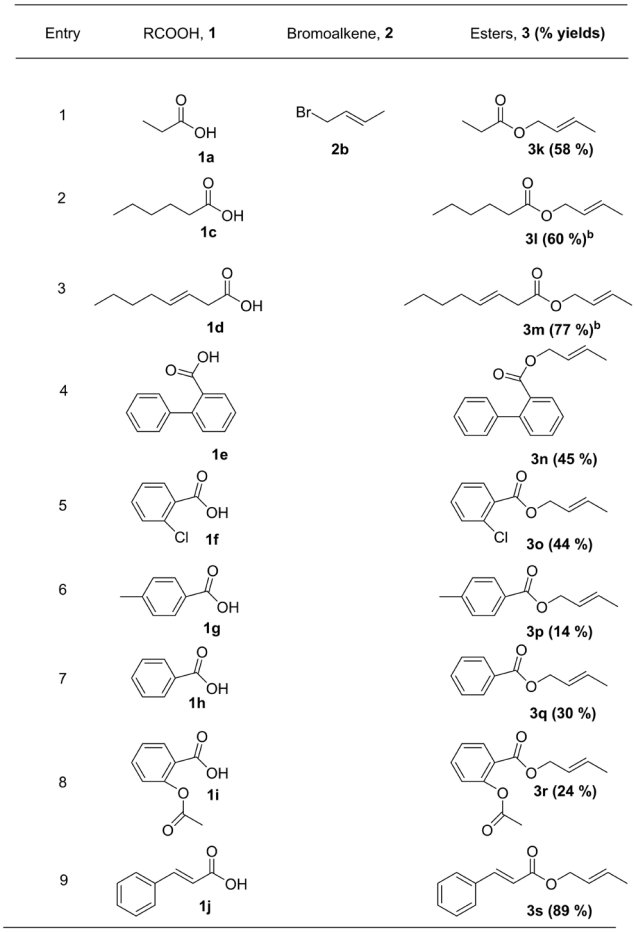
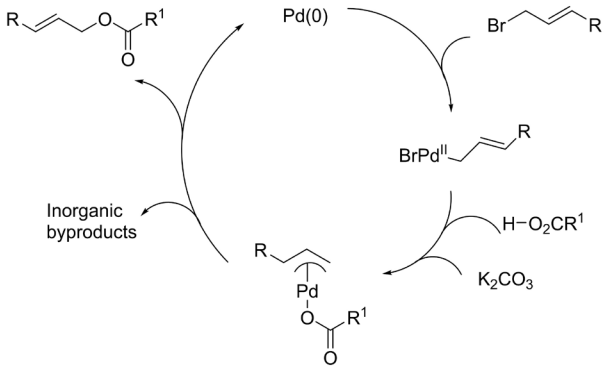


Figure 2. Esters from cross coupling of carboxylic acids and 3-bromo-2-butene2b[a]. [a]Reactions run with the load of 3 mole % $PdCl_2(d^tbpf)$; [b]3 l and 3 m products form with 0.5 mole % load of $PdCl_2(d^tbpf)$.



Scheme 3. Catalytic cycle of esters from R^1COOH and crotyl halide.

3.1. Figure 1

Compound **3a**, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 5H), 6.57 (d, J = 15.8 Hz, 1H), 6.21 (dt, J = 6.44 Hz, 1H), 4.66 (d, J = 6.48 Hz, 2H), 2.30 (q, J = 7.56 Hz, 2H), 1.09 (t, J = 7.56 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 136.2, 134.1, 128.6, 128.5, 128.0, 126.6, 123.3, 64.9, 27.6, 9.1;

Compound **3b**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 5H,), 6.56 (d, J = 15.88 Hz, 1H), 6.20 (dt, J = 6.4 Hz, 1H), 4.65 (d, J = 6.4 Hz, 2H), 2.25 (t, J = 7.4 Hz, 2H), 1.61 (q, J = 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 136.2, 134.9, 128.5, 127.9, 126.5, 123.3, 64.7, 36.1, 18.4, 13.6;

Compound **3c**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 5H), 6.56 (d, J = 15.88 Hz, 1H), 6.20 (dt, J = 6.4 Hz, 1H), 4.65 (d, J = 6.4 Hz, 2H), 2.27 (t, J = 7.48 Hz, 2H), 1.58 (t, J = 7.4 Hz, 2H), 1.24 (m, 4H), 0.81 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 136.2, 133.9, 128.5, 127.9, 126.5, 126.0, 123.3, 64.7, 34.2, 31.2, 24.6, 22.2, 13.8;

Compound **3d**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (m, 5H), 6.57 (d, J = 15.92 Hz, 1H), 6.20 (dt, J = 6.44 Hz, 1H), 5.48 (q, J = 5.36 Hz, 1H), 4.66 (d, J = 6.44 Hz, 1H), 2.99 (d, J = 5.4 Hz, 2H), 1.96 (m, 2H), 1.25 (m, 6H), 0.80 (t, J = 6.40 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 135.0, 134.1, 128.6, 126.6, 123.2, 121.3, 65.1, 38.1, 32.1, 31.3, 22.1, 13.9;

Compound **3e**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 - 7.24 (m, 13H,), 6.35 (d, J = 15.88 Hz, 1H), 5.89 (dt, J = 6.4 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 142.4, 141.3, 136.2, 133.8, 131.2, 130.6, 129.7, 128.4, 128.3, 128.0, 127.8, 127.1, 126.5, 122.5, 65.3;

Compound **3f**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 - 7.31 (m, 8H), 6.81 (d, J = 15.88 Hz, 1H), 6.45 (dt, J = 6.44 Hz, 1H), 5.04 (dt, J = 6.44 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 136.2, 134.7, 132.6, 131.5, 128.6, 128.2, 126.7, 122.8, 66.1;

Compound **3g**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 - 7.16 (m, 7H), 6.65 (d, J = 15.92 Hz, 1H), 6.29 (dt, J = 7.48 Hz, 1H), 4.87 (d, J = 6.36 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 143.7, 134.1, 129.7, 128.8, 128.6, 127.9, 126.6, 126.1, 123.4, 65.3, 21.7;

Compound **3h**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 - 7.28 (m, 10H), 6.81 (d, J = 15.88 Hz, 1H), 6.46 (dt, J = 6.4 Hz, 1H), 5.04 (d, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 134.3, 133.0, 129.7, 128.6, 128.4, 128.1, 127.9, 126.1, 123.3, 65.5;

Compound **3i**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 - 7.01 (m, 9H), 6.63 (d, J = 15.88 Hz, 1H), 6.28 (m, 1H), 4.84 (d, J = 6.48, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 164.3, 150.6, 140.0, 134.6, 133.9, 131.9, 128.8, 128.6, 127.9, 126.6, 123.8, 122.8, 65.7, 21.0;

Compound **3j**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 16.0 Hz, 1H), 7.34 - 7.15 (m, 10 H), 6.62 (d, J = 15.88 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 6.28 (dt, J = 6.48 Hz, 1H), 4.78 (d, J = 6.44 Hz, 2H); ^{13}C NMR (Acetone-D6, 100 MHz) δ 171.0, 149.8, 141.6, 139.6, 138.2, 135.4, 134.0, 133.3, 131.6, 128.9, 123.1, 69.7.

3.2. Figure 2

Compound **3k**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.46 (m, 1H), 5.27 (m, 1H), 4.16 (d, J = 6.4 Hz, 2H), 1.99 (q, J = 7.52 Hz, 2H), 1.40 (d, J = 6.52, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 130.1, 125.2, 64.3, 29.9, 26.8, 17.0, 8.49;

Compound **3l**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (m, 1H), 5.49 (m, 1H), 4.42 (d, J = 6.42 Hz, 2H), 2.23 (t, J = 7.64 Hz, 2H), 1.65 (d, J = 6.44 Hz, 3H), 1.55 (m, 2H), 1.23 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173. 5, 131.0, 125.1, 64.9, 34.2, 31.2, 22.2, 17.0, 13.7;

Compound **3m**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (m, 1H), 5.51 (m, 2H), 4.48 (d, J = 6.48 Hz, 1H), 3.00 (d, J = 5.44 Hz, 2H), 2.00 (m, 2H), 1.69 (m, 3H), 1.29 (m, 6H), 0.86 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 134.8, 131.3, 125.121.4, 65.2, 38.1, 32.1, 331.3, 22.1, 17.7, 13.8;

Compound **3n**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 - 7.32 (m, 9H), 5.5 (m, 1H), 5.27 (m, 1H), 4.47 (d, J = 6.52, 2H), 1.08 (d, J = 6.48, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 142.4, 141.4, 137.3, 131.2, 130.6, 129.7, 128.5, 128.0, 127.1, 124.5, 60.5, 17.7;

Compound **3o**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 - 7.18 (m, 4H), 5.80 (m, 1H), 5.63 (m, 1H), 4.69 (d, J = 6.4 Hz, 2H), 1.68 (d, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) d 165.5, 137.3, 133.6, 132.4, 131.9, 131.0, 126.5, 124.7, 116.3, 66.2, 17.8;

Compound **3p**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.58 (m, 1H), 5.68 (m, 1H), 4.71 (d, J = 6.36 Hz, 2H), 2.38 (s, 3H), 1.72 (d, J = 6.2 Hz, 3H), 0.80 (t, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 143.5, 131.1, 129.6, 127.6, 125.2, 124.4, 65.4, 17.8;

Compound **3q**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 - 7.49 (m, 5H), 5.89 (m, 1H), 5.73 (m, 1H), 4.74 (d, J = 6.32, 2H), 1.74 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 133.9, 131.7, 130.2, 126.4, 66.0, 17.9;

Compound **3r**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 - 7.06 (m, 4H), 5.85 (m, 1H), 5.65 (m, 1H), 4.67 (d, J = 6.52 Hz, 2H), 2.30 (s, 3H), 1.72 (d, J = 6.52 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 164.3, 150.6, 133.7, 131.8, 125.9, 124.8, 123.7, 65.8, 21.0, 17.7;

Compound **3s**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 - 7.42 (m, 5H, 1H), 6.55 (d, J = 16.06 Hz, 1H), 5.76 (m, 2H), 4.60 (d, J = 6.4 Hz, 2H), 1.7 (m, 3H);

Compound **4a**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (m, 5H), 6.56 (d, J = 13.4 Hz, 1H), 6.20 (dt, J = 6.44 Hz, 1H), 5.28 (m, 8H), 4.64 (d, J = 6.48 Hz, 2H), 2.72 (m, 6H), 2.29 (t, J = 7.6 Hz, 2H), 1.98 (m, 4H), 1.65 (t, J = 7.4 Hz, 2H), 1.20 (m, 6H), 0.80 (m, 3H);

Compound **4b**, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (m, 1H), 5.56 (m, 1H), 5.35 (m, 8H), 4.47 (d, 6.5 Hz, 2H), 2.77 (m, 6H), 2.30 (m, 2H), 2.08 (m, 4H), 1.75 (m, 2H, 3H), 1.27 (m, 6H), 0.86 (m, 3H);

Compound **4c**, major peak: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.87 (s, 1H), 9.56 (s, 1H), 9.54 (s, 1H), 7.17 (m, aromatic), 6.5 - 6.25 (d, dt), 4.97 (m, 2H X 2).

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Conflicts of Interest

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

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