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A New Process of Synthesizing Anandamide Derivatives from Arachidonic Acid in the Presence of Boron Catalyst

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Abstract

Anandamide is part of the cannabinoid group and functions as a neurotransmitter. Anandamide plays a role in depression, pain, appetite, memory, and fertility. Since it is well documented that anandamide analog behaves as probes of the cannabinoid receptor, it is of great interest to find a new method of making new series of anandamide derivatives. Dennis Hall and his group recently reported a direct amidation process of carboxylic acid by ortho-iodo boronic acid. Using ortho-iodo boronic acid as a catalyst, we explore the amidation of arachidonic acid under microwave heating and synthesize anandamide derivatives in high yields.

Keywords

Anandamide, Cross-Coupling, Microwave, Alcohol Amines

1. Introduction

Anandamide is becoming a well-studied compound due to its numerous functions in the human body. [1]-[6] Anandamide (shown in **Figure 1**) is a polyunsaturated fatty acid; it functions as a neurotransmitter and is part of the cannabinoid family. Cannabinoids are compounds that bind to cannabinoid receptors, CB_1 and CB_2. [2] CB_1 and CB_2 receptors are G-protein coupled receptors located in the cell membrane, and they can lead to multiple cellular regulations. G-protein coupled receptors are proteins composed of seven transmembrane domains that lead to cell signaling. CB_1 is located throughout the body, but it is mostly abundant in the brain and the central nervous system. It is responsible for appetite, analgesia, and many other effects. CB_2 is located primarily in the immune system, and it plays a role in anti-inflammatory and immunosuppressive activities.

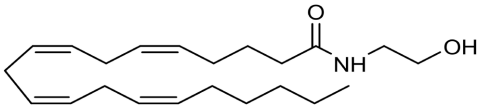


Figure 1. Anandamide.

Anandamide binds and activates both CB_1 and CB_2 receptors, but it's known to primarily bind to CB_1 receptor. Consequently, anandamide plays a role in many aspects of the human body including depression, pain, appetite, memory, and fertility. Furthermore, anandamide has been shown to influence neurodegenerative diseases including analgesia, anxiety, epilepsy, cancer, and Alzheimer's disease. Since the discovery of arachidonic acid in 1992, its under-study has come a long way. Like Δ^9-tetrahydrocannabinol (Δ^9-THC) in marihuana, anandamide has similar cannabinoid effects. Anandamide has a faster start and shorter duration compared to Δ^9-THC in pharmacological tests of analgesia, catalepsy, hypoactivity and hypothermia. Thus making anandamide a perfect example for pharmacological studies.

We used arachidonic acid and different alcohol amines to synthesize anandamide derivatives. Arachidonic acid (shown in **Figure 2**) is a polyunsaturated fatty acid essential to the human body. Arachidonic acid can be synthesized by the human body from linoleic acid. It can also be indigested by the human body through food intake, like milk. Arachidonic acid is found on cell membranes and it composes some of the phospholipids located in the cell membrane. Arachidonic acid has many functions; for example, it's needed for the growth and repair of skeletal muscle tissues. Thus, it plays an important role in cell regulation. In 2012, Denis Hall and his group synthesized a new catalyst, 5-methoxy-2-iodo phenylboronic acid (**Figure 3**), which they applied for direct amidation. [7]-[9]

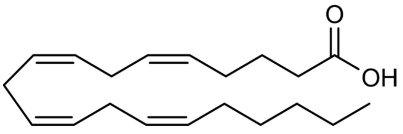


Figure 2. Arachidonic acid.

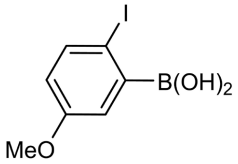
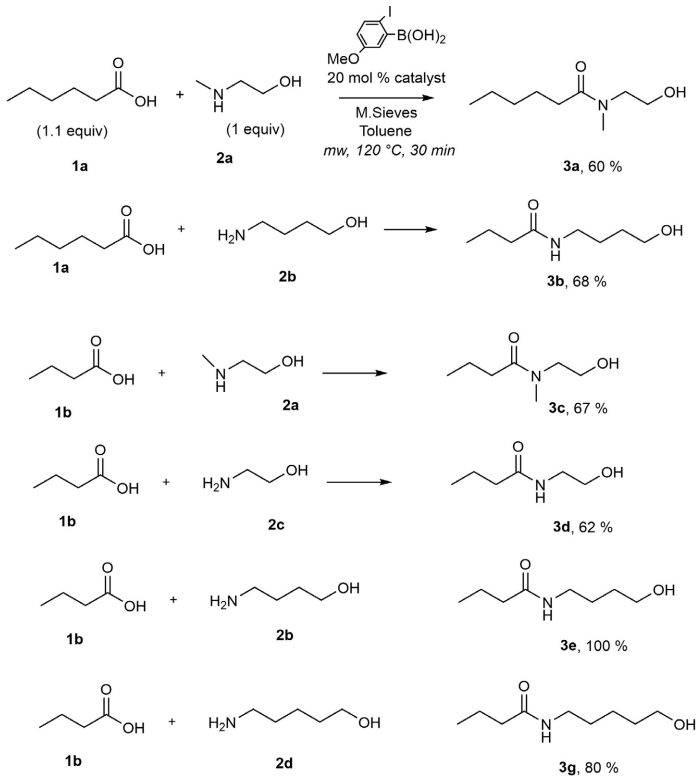


Figure 3. 2-iodo-5-methoxyphenylboronic acid catalyst.

2. Results and Discussion

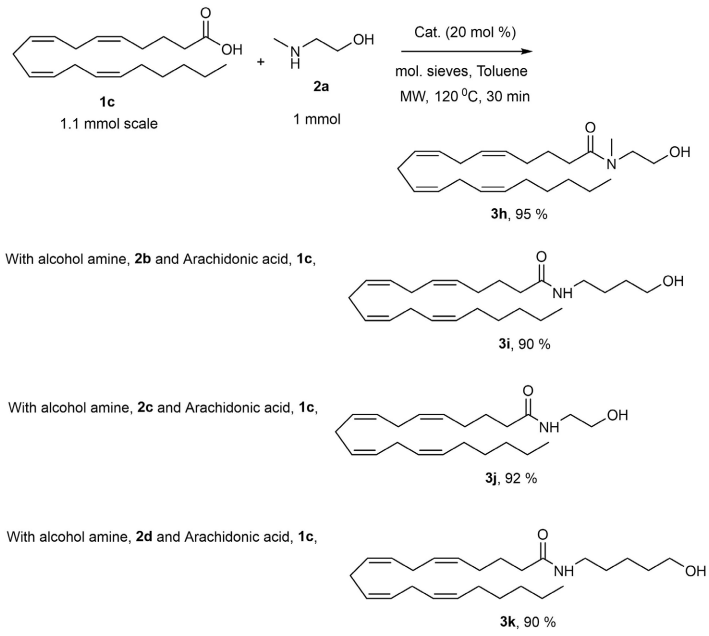
We were able to successfully synthesize various amide products from simple carboxylic acids and alcohol amines. Using Hall's catalyst and our newly developed procedure with microwave heating, we were able to run direct amidation reactions, as shown in **Scheme 1**. The reaction procedure of compound **3a** is a representative one.



[a]All products are purified by silica gel chromatography.

Scheme 1. Reaction of carboxvlic acids and alcohol amines.[a]

We proceeded to synthesize anandamide derivatives. Using this new method that we came up with, we were able to synthesize anandamide derivatives using arachidonic acid and alcohol amines (Scheme 2).



Scheme 2. Anandamide derivatives from arachidonic acid and alcohol amines.

3. Materials and Methods

Amide and anandamide derivatives were synthesized using iodo-boron catalyst and Denis Hall's method for direct amidation. The iodo-boron catalyst was synthesized following the published procedure. Then, we synthesized different amide derivatives to test the best method for amidation using microwave heating. After the optimized method under the microwave, we applied the method for synthesizing anandamide derivatives.

Synthesis of Compound **3a**

In a microwave reaction vial, the catalyst 2-iodo-5-methoxyphenylboronic acid 29.0 mg (20 mol%) was added with hexanoic acid 65 µl (1.1 eq), mol. Sieves (100 mg) and toluene (200 µl) it was then mixed for 10 min. After the 10 min, 2-(methylamino) ethanol 40 µl (1 equiv) was added and mixed. The microwave test tube was then put into the microwave for 30 min at 120˚C. The product was then transferred to a round flask using methanol and then silica gel. It was then evaporated to dry until powder was formed. After evaporation, the product was added to the column chromatography. It was separated catalyst using silica gel and the mixture of hexane and ether acetate in a 25:1 ratio. Once the catalyst was separated from the product, the column was washed with 100 ml of methanol and the product was collected. The purity of the product was tested using CG-MS, ^{1}H NMR, and ^{13}C NMR. LRMS: Calculated for $C_9H_{20}NO_2$ M^+ 174. Found: 174. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.2 (s, H, OH), 3.8 (t, 2H, CH_2), 3.0 (t, 2H, CH_2), 2.3 (s, 3H, CH_3), 2.1 (t, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 0.9 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.1, 61.8, 51.6, 31.6, 31.2, 30.99, 24.4, 22.3, 13.9.

Synthesis of compound **3h**

In a microwave reaction vial, the catalyst 2-iodo-5-methoxyphenylboronic acid 62 mg (0.1 mmol, 20 mol %) was added with arachidonic acid 404 µl (1.1 mmol, 1.1 eq), mol. Sieves (200 mg) and toluene (400 µl) it was then mixed for 10 min. After the 10 min, the 2-(methylamino) ethanol 80 µl (1 mmol, 1 equiv) was added and mixed. The microwave test tube was then put into the microwave for 30 min at 120˚C. The product was then transferred to a round flask using methanol and then silica gel. It was then evaporated to dry until powder was formed. After evaporation, the product was added to the column chromatography. It was separated catalyst using silica gel and the mixture of hexane and ether acetate in a 25:1 ratio. Once the catalyst was separated from the product, the column was washed with 200 ml of methanol and the product was collected. The purity of the product was tested using CG-MS, ^{1}H NMR, and ^{13}C NMR. LRMS: Calculated for $C_{23}H_{39}NO_2$ M^+ 361. Found: 361. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.6 (m, H, CH), 5.6 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 3.8 (m, H, CH), 3.8 (m, H, CH), 3.5 (m, 2H, CH_2), 3.4 (t, 2H, CH_2), 2.9 (t, H, OH), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.3 (m, 2H, CH_2), 2.0 (m, 2H, CH_2), 2.0 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 0.9 (t, 3H, CH_3).

Compound **3i**

LRMS: Calculated for $C_{24}H_{40}NO_2$ M^+ 374. Found: 374. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.7 (m, H, CH), 5.7 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 3.6 (m, H, CH), 3.6 (m, H, CH), 3.5 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 2.9 (t, H, OH), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.2 (t, 2H, CH_2), 2.0 (t, 2H, CH_2), 1.8 (m, 2H, CH_2), 1.8 (m, 2H, CH_2), 1.8 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 0.9 (t, 3H,CH_3).

Compound **3j**

LRMS: Calculated for $C_{22}H_{37}NO_2$ M^+ 347. Found: 347. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.0 (m, H, CH), 5.5 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 5.3 (m, H, CH), 3.8 (m, H, CH), 3.8 (m, H, CH), 3.4 (m, 2H, CH_2), 3.4 (t, 2H, CH_2), 3.0 (t, H, OH), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.3 (m, 2H, CH_2), 2.0 (m, 2H, CH_2), 2.0 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 0.9 (t, 3H,CH_3).

Compound **3k**

LRMS: Calculated for $C_{25}H_{42}NO_2$ M^+ 378. Found: 378. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.1 (m, H, CH), 6.1 (m, H, CH), 5.4 (m, H, CH), 5.4 (m, H, CH), 5.4 (m, H, CH), 5.4 (m, H, CH), 3.7 (m, H, CH), 3.7 (m, H, CH), 3.6 (m, 2H, CH_2), 3.6 (t, 2H, CH_2), 2.9 (t, H, OH), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 2.2 (t, 2H, CH_2), 2.0 (m, 2H, CH_2), 2.0 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 1.3 (m, 2H, CH_2), 0.8 (t, 3H,CH_3).

Synthesis of 2-iodo-5-methoxyphenylboronic acid (Catalyst)

In a three-neck round flask, 3-methoxyphenylboronic acid 1.4 g (9.44 mmol, 1 equiv) was added with silver (I) sulfate 1.62 g (5.2 mmol, 0.55 equiv) and ethanol (30 mL) at room temperature under argon[1]. In a two-neck round flask iodine 2.4 g (9.44 mmol, 1 equiv) was added with ethanol (30 mL) and mixed at room temperature until dissolved under argon. [7] The iodine mixture was then injected dropwise into the three-neck round flask; it was then mixed for around two hours until a color changed. The resulting mixture was then filtered through a Celite 545 pad, evaporated, and put under vacuum for drying. Before extraction, 50 mL of water was added, and the mixture was extracted with ethyl acetate and brine solution. The collected organic layer in ethyl acetate was treated with anhydrous sodium sulfate for complete dehydration. The sodium sulfate is filtered out by filtration through a sintered funnel under reduced pressure. The synthesized boron catalyst in ethyl acetate was collected by using a rotary evaporator under vacuum. The crude product was then subjected to column chromatography using silica gel and a mixture of hexane and ethyl acetate with a 3:1 ratio as eluents. The catalyst was then tested for purity using GC-MS and NMR.

4. Conclusion

We were able to establish an optimum synthetic method for the direct amidation

of simple carboxylic acids with alcohol amines in the presence of metal-free boron catalyst. Following the same reaction conditions, we were also able to synthesize anandamide derivatives from arachidonic acid. We tried Denis Hall's separation method for direct amidation: filtration through a Celite 545 pad, then separation with pH 3, pH 11, brine (NaCl) solution and sodium sulfate for removing water. [7] His method for separation didn't work for our compounds. Then we tried filtration with Celite 545 pad, then separation with ethyl acetate brine solution and sodium sulfate to remove water. This method for separation didn't work as well. We then went for column chromatography, where we used alumina with hexane and ethyl acetate with a 2 to 1 ratio, which didn't work. Also, we went for the column with silica gel instead of hexane only, which didn't work. Column with silica gel with hexane and ethyl acetate 1 to 1 ratio didn't work. Finally, we went for a column with silica gel with hexane and ethyl acetate 25 to 1 ratio, which only separated the catalyst from the product. Thus, then we used a washing method, where you poured methanol as eluent and collected the product with methanol.

Conflicts of Interest

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

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