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Communications to the Editor

An Improved Synthesis of Rimonabant: Anti-Obesity Drug#

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Abstract:

A novel, cost-effective, and efficient process was developed for the large-scale synthesis of Rimonabant 1, an anti-obesity drug. The process involves the conversion of 4-chloro propiophenone 2 to cyclized acid 6 as a key intermediate that afforded Rimonabant 1 in good yield.

Introduction

Rimonabant[1] **1** (Figure 1) is a selective antagonist of cannabinoid type 1 (CB1) receptor. This is the first member of a new class of compounds that elicits pharmacological activity by interacting with the endocannabinoid system (ECS). The ECS is purportedly found to be involved in the regulation of food intake and CNS reward system. CB1 receptors are located in the brain as well as in the several human tissues, including adipocytes.[1]

The discovery of Rimonabant[2,3] (**1**) as a potent CB1 receptor antagonist opens avenues for further characterization of the cannabinoid pharmacophore in its relationship to the binding domain of cannabinoid receptor. Synthesis of **1** and its analogs are extensively explored.[4–7] The product patent route,[8] as shown

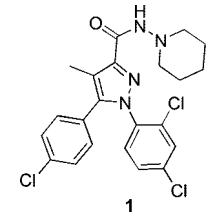

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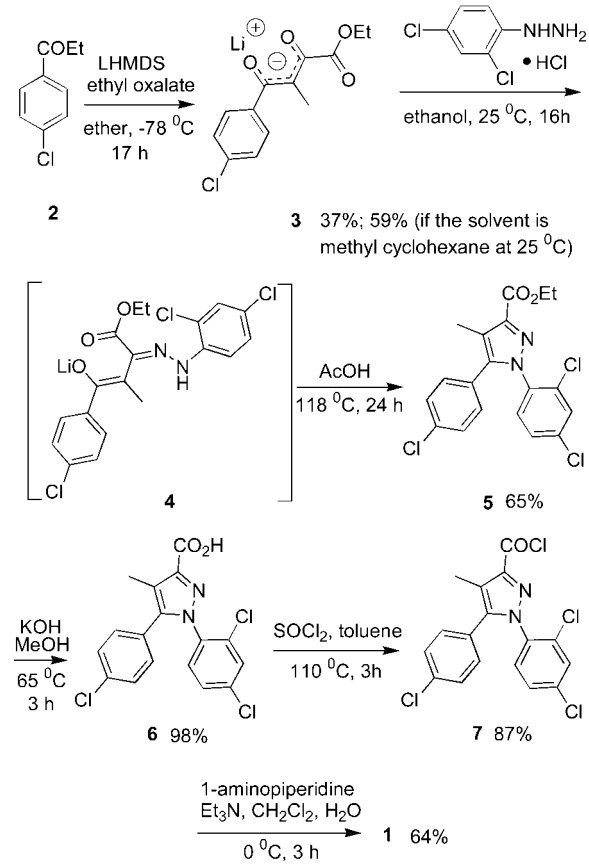
Figure 1. **APIs structural framework.**

Scheme 1. **Precedented Synthetic Approach**



in Scheme 1, involves overall six tedious steps, and the transformations are not efficient. Synthesis of **1** commences with 4-chloropropiophenone (**2**), which upon condensation in the presence of LHMDS with ethyl oxalate affords the lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (**3**) in poor yield. Barth et al.[8] also found that the yield of

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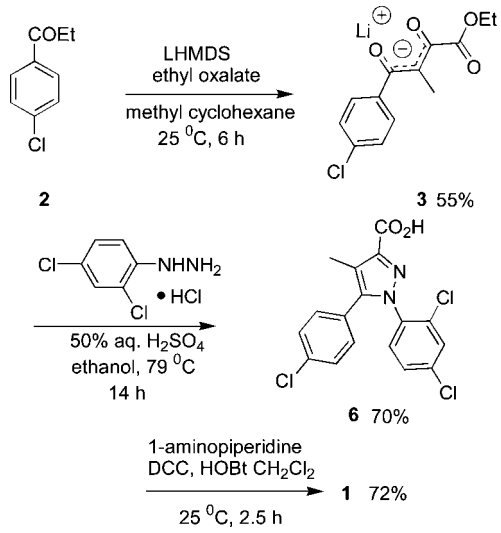
Scheme 2. **Novel Synthetic Approach**



the condensation step to **3** can be improved upon replacing the solvent, ether from methyl cyclohexane. The substrate, 2,4-dichlorophenylhydrazine (**4**) is subjected to a solution of lithium salt **3** in ethanol to afford hydrazone **5** in moderate yield. Saponification of **5** yields **6**, and subsequent treatment of the resultant **6** with thionyl chloride affords acid chloride **7** in excellent yield. Finally, the amidation is achieved to afford **1** in good to moderate yields.

Results and Discussion

It is well-established fact that the acid-catalyzed or -mediated de-esterification or hydrolysis can be rendered in an efficient manner, and we took the advantage of this trivial fact and designed our synthetic route that proved to be non-infringing and cost-effective; this paper is all about exploring the acid-catalyzed hydrolysis and amidation concept to afford **1**.

As presented, with the improved synthesis of **1** in Scheme 2, we were able to synthesize advanced intermediate **6** only in two steps. Preparation of the lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (**3**) itself was improved by changing the solvent and temperature, and the reaction time was also reduced to 6 from 17 h as compared to the product patent route (where ether as a solvent at −78 °C was used). Acid-mediated cyclization followed by de-esterification afforded **6** in good yield. Finally, the synthesis of **1** was accomplished by exploiting DCC-mediated amidation. There are certain advantages to our Scheme 2 over the product patent route as presented in Scheme 1: (i) no cryogenic temperature required in the preparation of **3**, also evidenced in the product patent route, (ii) acid-mediated cyclization followed by hydrolysis afforded intermediate **6**, which avoids the basic hydrolysis and use of the hazardous reagent $SOCl_2$, (iii) high-yielding amidation, and (iv) our synthesis to **1** was achieved in three steps in comparison to the overall six steps involved in the product patent route.

In conclusion, we accomplished novel and improved synthesis of **1** and significant cost reduction was realized in the production of **1**.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, on a Varian Gemini 200 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin–Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on a HP-5989a LC–MS spectrometer. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without any purification.

Preparation of Lithium Salt of Ethyl 4-(4-Chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate 3. A mixture of methyl cyclohexane (300 mL) and lithium hexamethyl disilazane (300 mL, 1.07 mol) was charged into a round bottom flask under nitrogen atmosphere and cooled to 15–25 °C. To this solution was added a solution of chloropropiophenone (**2**, 50.0 g, 1 mol) in methyl cyclohexane (125 mL) over a period of 30–45 min, and the mixture was stirred for 2.5 h. To this mixture diethyl oxalate (47.8 g, 1.1 mol) was added over a period of 30–45 min and was stirred for 17 h. On the completion of the reaction (TLC), the solid material was filtered and washed with methyl cyclohexane (100 mL). The wet solid was taken up with methyl cyclohexane (250 mL) and charged into a round bottom flask, and the mixture was stirred about 45 min, filtered, and washed with methyl cyclohexane (100 mL), followed by being dried under vacuum for about 3 h to afford lithium salt of 4-(4-chloro phenyl)-3-methyl-2,4-dioxo ethyl butyrate (**3**, 45.1 g, 55.2%).

Preparation of 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid 6. A mixture of 4-(4-chlorophenyl)-3-methyl-2, 4-dioxo-ethyl butyrate (**3**, 8.0 g, 1 mol), ethanol (200 mL), 2,4-dichlorophenyl hydrazine (6.2 g, 1 mol), and 50% sulfuric acid (80.0 mL) was heated to reflux for 4–6 h. On the completion of the reaction (TLC), the solvent was removed under reduced pressure, the second lot of 50% sulfuric acid (160 mL) was added, and the mixture was heated to reflux for 6–8 h. On completion of reaction (TLC), the mixture was cooled to 25–35 °C, and the reaction mass was poured into ice–water (200 mL), stirred about 15 min, filtered, washed with water (80 mL), and dried under vacuum for about 2 h. A mixture of the wet solid and water (220 mL) was stirred about 10 min at ambient temperature, adjusted to pH 10–12 with caustic lye (2.2 mL), and washed with petroleum ether. The aqueous layer was separated, adjusted to pH 2 with 12 N hydrochloric acid (2.0 mL), and stirred about 15 min at 25–35 °C. The Solid material was filtered, washed with water (1000 mL), and dried at 35 °C to constant weight to afford 5-(4-chloro phenyl)-1-(2,4-dichloro phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (**6**, 7.7g, 70%).

Preparation of 5-(4-Chloro phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Piperdin-1-yl Amide 1. A mixture of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (**4**, 45.0 g, 1 mol) in dichloromethane (450 mL) and hydroxybenztriazole (HOBt, 18.7 g, 1.2 mol) was stirred about 10 min. To this solution was added a solution of dicyclohexyl carbodiimide (DCC, 29.3 g, 1.2 mol) in dichloromethane (900 mL) over a period of 15–30 min, and the mixture was stirred about 1.5 h at ambient

temperature. On completion of reaction (TLC), the solution was cooled to 0–5 °C, stirred about 45 min, then the dicyclohexyl urea was filtered and washed with dichloromethane (135 mL), and the solvent of the filtrate was removed under reduced pressure. A mixture of the above crude, dichloromethane (900 mL), and potassium carbonate (15.4 g, 1 mol) was stirred for 10 min, a solution of 1-amino piperdine (11.8 g, 1.0 mol) in dichloromethane (450 mL) was added over a period of 15–30 min, and the mixture was stirred for 45–60 min at ambient temperature. On completion of reaction (TLC), the reaction mixture was cooled to 0–5 °C and stirred for 45 min, and precipitated hydroxy benztriazole was filtered, washed with dichloromethane (135 mL), and the solvent of the filtrate was removed under reduced pressure. To the above crude was added petroleum ether (450 mL), and the mixture was stirred for 45 min at 50 °C, filtered, washed with petroleum ether (225 mL), and dried in air to constant weight.

A mixture of the above solid in acetone (225 mL) was heated to reflux, 12 N hydrochloric acid (10 mL) was slowly added, and the mixture was stirred for 30 min, cooled to 0–5 °C, and stirred for 45 min. Finally the precipitated solid was filtered and washed with acetone (45 mL). The wet solid was charged in methanol (225 mL) and adjusted to pH 10–12 with caustic lye (8.0 mL), and DM water (450 mL) was added. After the solution was stirred for 45 min at ambient temperature, the solid material was filtered, washed with DM water (450 mL), and dried at 50 °C under high vacuum to constant weight to afford 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperdin-1-yl amide (**1**, 39.6 g, 72%).

Structures of all intermediates were confirmed by HPLC and ^{1}H NMR.

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