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An Efficient Process for The Synthesis of Anti-Obesity Drug Rimonabant

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A convenient and cost effective synthetic process has been developed for the synthesis of an anti-obesity drug rimonabant (**1**). The process involves the condensation of 4-chloro propiophenone with diethyl oxalate to get the diketo ester (**3**), which upon reaction with N-amino piperidine followed by acid catalyzed cyclization with 2,4-dichloro phenyl hydrazine hydrochloride afforded rimonabant (**1**) in good overall yield.

Key Words: Rimonabant, Anti-obesity drug, Diketo ester.

INTRODUCTION

Obesity is a serious and chronic medical condition that continues to spread rapidly throughout the world. It is estimated that obesity affects about 30 % of the adult population in the Western world and many people who are afflicted with obesity also suffer from subsequent comorbidities, including diabetes, hypertension, cardiovascular disease, cancer and arthritis[1]. Although modifications of lifestyle may be the preferred approach for the management of obesity, these modifications often prove to be insufficient or unsustainable. Currently, there are a few drugs available in the market for the treatment of obesity.

Rimonabant **1** is a selective antagonist of cannabinoid type 1 (CB1) receptor[2,3]. Recently, it has been approved in the EU for the treatment of obesity. 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[4].

The discovery of rimonabant **1**, a potent CB1 receptor antagonist with nanomolar affinity[5,6], provides a unique chemical tool for further characterization of the cannabinoid pharmacophore in its relationship to the binding domain of cannabinoid antagonists. Rimonabant is the prototypic cannabinoid CB1 receptor against, as a novel and effective pharmacotherapy for drug addiction and obesity-related disorders.

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Synthesis of **1** and its analogues are extensively reported in the literature[7-11]. Product patent route[12] as shown in **Scheme-I** involves six tedious stages for the preparation of **1** with an overall yield of 20 %. Cost-effective synthesis of rimonabant was recently reported by our colleagues and involves four steps with an over all yield of 28 %[13]. The product patent route starts with the condensation[14] of 4-chloro propiophenone (**2**) with diethyl oxalate in the presence of lithium hexamethyl disilazane to give the lithium salt of ethyl -4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate (**3**), which on treatment with 2,4-dichlorophenyl-hydrazine hydrochloride in ethanolic medium gave hadrazone (**4**). Hydrazone **4** on cyclization in acetic acid results **5** in moderate yields. Saponification of **5** gave the acid **6**, which on subsequent treatment with thionyl chloride afforded the acid chloride **7** in good yield. Finally amidation of **7** with N-amino piperidine gave rimonabant (**1**).

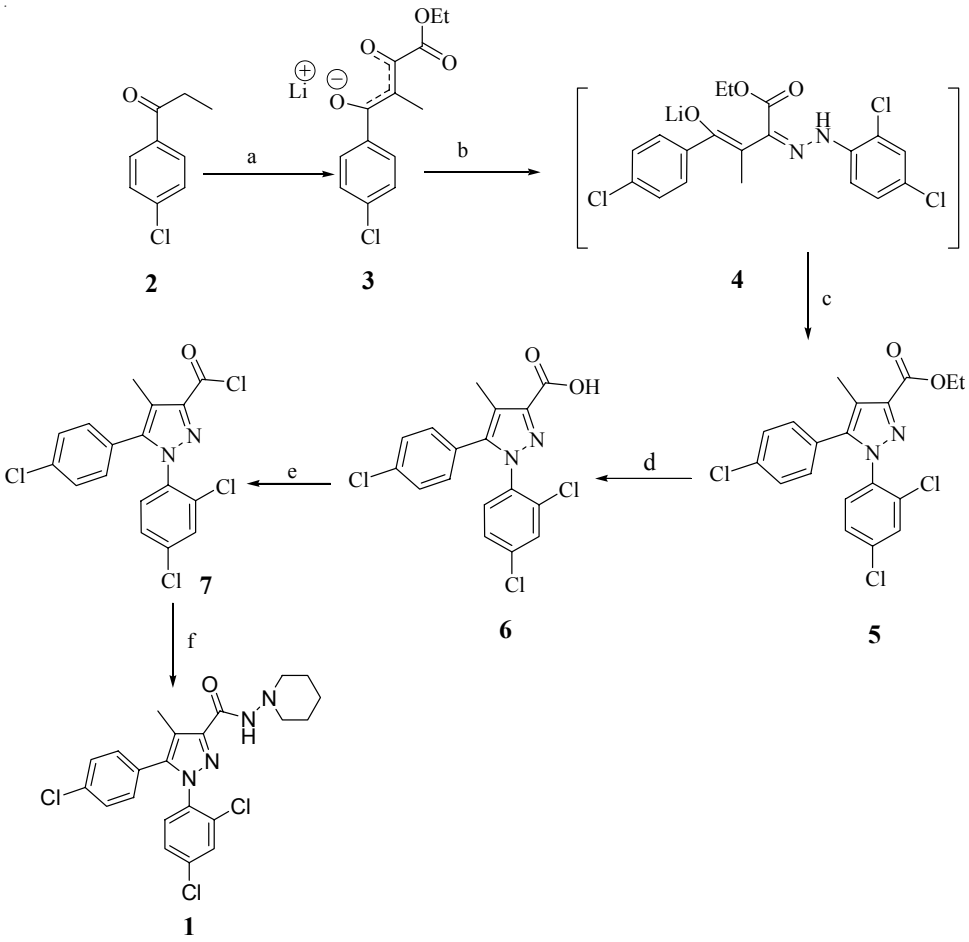
EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ using 200 MHz on a Varian Gemini FT NMR spectrometer; the chemical shifts are reported in ppm (parts per million) relative to tetramethylsilane (TMS) as the internal standard. 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 HP-5989A LC/MS spectrometer. The melting points were determined by using the capillary method on POLOMAN.The solvents and reagents were used without further purification. Reactions were carried out under nitrogen atmosphere unless otherwise noted.

Preparation of ethyl-2,4-dioxo-3-methyl-4-(4-chlorophenyl)-butanoate (8): To a mechanically stirred solution of lithium hexamethyl disilazane (LiHMDS) (300 mL, 1.07 mol 1.0 M solution in hexane) in cyclohexane (300 mL) was added a solution of 4-chloropropiophenone (50 g, 1 mol) in cylcohexane (125 mL) at 15-20 °C under nitrogen atmosphere over a period of 30-45 min. After stirring for 1 h, diethyl oxalate (47.8 g, 1.1 mol) was added over a period of 10 min. The cold bath was removed and the reaction mixture was stirred for 6 h. The precipitated yellow solid was filtered and washed with cyclohexane (100 mL). The solid was sequentially partitioned thrice between 1 N HCl and methylene dichloride. The organic phase was dried over sodium sulfate and evaporated under reduced pressure to give the title compound as an orange coloured residue. The crude product was crystallized in hexane to yield 57 g of diketoester as a yellow solid.

IR (KBr, ν_{max}, cm^{-1}): 1754 (C=O), 1698 (C=O), 1670 (C=O), 2960 (CH_3 aliphatic), 1587, 1456 (C=C aromatic); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.3 (t, *J* = 7.1 Hz, 3H), 1.45 (d, *J* = 7.1 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 5.0 (q, *J* = 7.1 Hz, 1H), 7.5 (t, *J* = 7.1 Hz, 3H), 7.93 (d, *J* = 8.8 Hz, 2H), Mass: 269.1 (M^+ + 1).

Preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (1): To a stirred solution of diketoester **8** (18.0 g, 0.067 mol) in absolute ethanol (180 mL) was added N-amino piperidine (6.78 g, 0.067 mol) at room temperature under inert atmosphere. The reaction mixture



Reagents and conditions: (a) LiHMDS, methyl cyclohexane, diethyl oxalate, 15-20 °C, 20 h, 60 %; (b) 2,4-dichlorophenyl hydrazine hydrochloride, ethanol, 25 °C, 16 h, 70 %; (c) acetic acid, 118 ºC, 24 h, 65 %; (d) KOH, methanol, 65 ºC, 3 h, 98 %; (e) thionyl chloride, toluene, 110 ºC, 3 h, 87 %; (f) 1-amino piperidine, triethyl amine, methylene dichloride, water, 0 ºC, 3 h, 64 %.

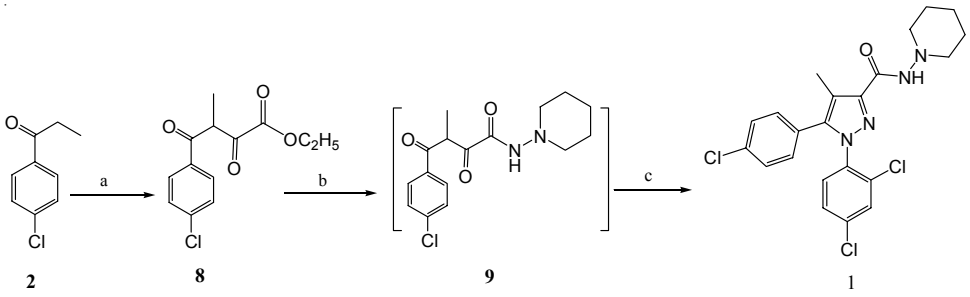
Scheme-I

was stirred for 1 h at ambient temperature. After disappearance of diketoester by TLC 2,4-dichlorophenyl hydrazine hydrochloride (16.5 g, 0.077 mol) was added to the above reaction mixture and reaction mixture was maintained for 3 h at ambient temperature. After completion of the reaction, solvent was evaporated under reduced pressure. The crude product was dissolved in 100 mL of ethyl acetate and washed twice with 50 mL of saturated sodium chloride solution. The solvent was evaporated under reduced pressure to give the crude residue which was crystallized in diisopropyl ether to yield 20.5 g of the title compound **1**.

Melting point 159 °C; IR (KBr, ν_{max}, cm^{-1}): 3390 (N-H), 1658 (C=O, amide), 2937 (CH, aliphatic), 1606, 1500 (C=C aromatic). ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 1.35 (m, 2H), 1.58 (m, 4H), 2.21 (s, 3H), 2.78 (t, *J* = 5.4 Hz, 4H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 10.8 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 9.1 (s, 1H). HRMS: calculated for $C_{22}H_{21}N_4OCl_3$ 462.07, found 462.07. Mass (m/z) 462 (M^+).

RESULTS AND DISCUSSION

In present studies, a facile synthetic route which comprises two-stage process for the title compound, rimonabant (**1**) is reported. The synthesis was started with the preparation of diketo ester **8** in a straightforward manner. Thus, treatment of the anion generated from 4-chloro propiophenone (**2**) and LiHMDS with diethyl oxalate afforded the diketo ester **8** in 70 % yield. A number of different reaction variables were explored in order to gain a more thorough understanding of the reaction. The cyclohexane and methyl cyclohexanes were found to be the best solvent for the reaction. Diketo ester **8** on condensation with N-amino piperidine gave the intermediate 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide (**9**), which on *in situ* cyclization with 2, 4-dichloro phenylhydrazine hydrochloride produced desired compound **1** in good yield.



2 **8** **9** 1

Reagents and conditions: (a) LiHMDS, methyl cyclohexane, diethyl oxalate, 15-20 °C, 6 h, 1 N HCl, 70 %; (b) N-amino piperdine, ethanol, room temperature, 1 h; (c) 2,4-dichloro phenyl hydrazine HCl, ethanol, room temperature, 3 h, 65 %.

Scheme-II

In summary, **Scheme-II** represents a safe, economically competitive synthesis of rimonabant over the earlier synthesis. To the best of our knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to high yields (45 % overall yield) and minimizing the number of stages.

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