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Synthesis of rimonabant regioisomer

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Abstract A novel synthesis route for a rimonabant regioisomer was developed.

Keywords Rimonabant; Anti-obesity; Regioisomer.

Introduction

Impurities' profiling of active pharmaceutical ingredients (APIs) imposes a great challenge in pharmaceutical industries and a renaissance for the same is now seen as an indispensable aspect of drugs and their process development for the following reasons: i) to assure that the elicited pharmacological or toxicological effects are only due to the API and not due to impurities, ii) also to ensure that in the due course of the product formulation and marketing the impurities should not be generated or elevated, and iii) impurities can not be considered always to be inferior, it may have better pharmacological and inferior toxicological properties [1].

When it comes to profiling of impurities generated from chemistry involved in the synthesis it becomes more stringent and demanding. In general, during the synthesis of desired species, traces of certain undesired byproducts used to be observed that we refer impurities. Despite the synthesis of the desired one, our affair also involves identifying and characterizing impurities by means of spectroscopy and other techniques. Since they are present only in traces, the spectroscopic characterization and documentation are practically impossible that enforces us to design route(s) for their synthesis if they are of organic origin.

Results and discussion

Synthesis of **1** and their analogs are extensively explored [2–6]. The only synthesis of regioisomer **2** (Fig. 1) in trace amount (as an impurity) is given in Ref. [7]. Herein, we report a novel synthesis of **2** in moderate yield.

As presented in Scheme 1, we were able to accomplish the synthesis of **2** in three steps. Preparation of the ethyl 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoate (**4**) was achieved by reacting

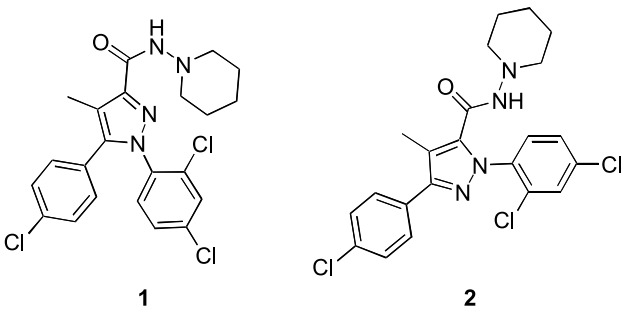

Fig. 1 Rimonabant (**1**) and its regioisomer **2**

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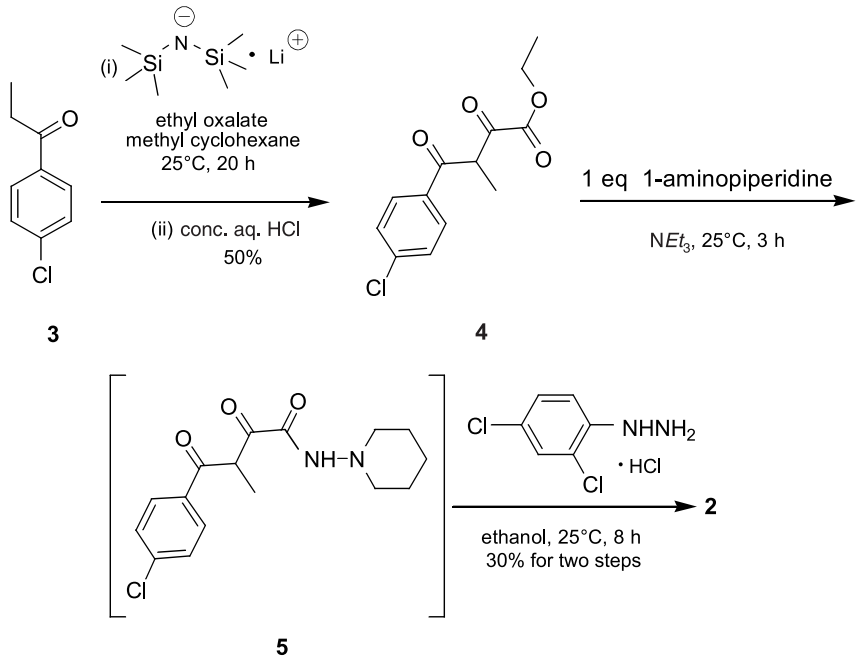

Scheme 1

1-(4-chlorophenyl)propane-1-one (**3**) with ethyl glyoxalate in presence of *LHMDS* followed by treating the resultant with conc. aq. HCl. Triethylamine mediated amidation followed by condensation afforded the desired regioisomer **2** in moderate yield. This successful synthesis proved to be advantageous in identifying the impurity **2** which was formed, in trace amount, during the synthesis [6] of **1** at large scale (200 g). Spectroscopic data of **2** is in agreement with literature [7].

In conclusion we accomplished a novel and improved synthesis for **2**.

Experimental

Unless otherwise stated, all non-aqueous reactions and distillations were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel aluminum supported plates that have been bought from Merck. Visualization was accomplished by irradiation under a 254 nm UV lamp. ^{1}H NMR spectra were recorded on a Varian 400 MHz. Chemical shifts are reported in ppm from tetramethylsilane or with the solvent resonance as the internal standard (CD_3OD 3.31 ppm). IR spectra were taken on Perkin-Elmer equipment. Mass spectra were obtained on a low resonance Q-trap machine in electron spray mode. Melting points were obtained on a Polmon apparatus.

Ethyl 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoate (**4**)
A mixture of 300 cm^3 methylcyclohexane and 300 cm^3 1 *M* solution of lithium hexamethyldisilazane (0.32 mol) was charged into a round-bottom flask under N_2 and cooled to 15–25°C. To this solution was added a solution of 50.0 g **3** (0.30 mol) in 125 cm^3 methylcyclohexane over a period of 45 min and stirred about 2.5 h, then 47.8 g diethyl oxalate (0.33 mol) were added over a period of 30–45 min and stirred about 17 h. On the completion of the reaction (TLC), the solid material was filtered off and washed with 100 cm^3 methylcyclohexane. The solid was dissolved in 250 cm^3 water, filtered, and the *pH* of the filtrate was adjusted to 1–2 by adding conc. hydrochloric acid (24 cm^3). Separated solid was filtered off, the filtrate was extracted with 3×250 cm^3 ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate (20 g) followed by distillation of the solvent at about 55–65°C under reduced pressure of about 700 mm Hg to afford 21.5 g **4** (identical as described in Ref. [7]) as a residue.

N-(Piperidin-1-yl)-3-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-5-carboxamide (**2**)
A mixture of 21.5 g **4** (0.08 mol) in 11.0 cm^3 triethylamine and 8.04 g 1-aminopiperdine (0.08 mol) was stirred about 3 h at ambient temperature. On completion of reaction (TLC), 500 cm^3 ethyl acetate were added and the organic layer was washed with 3×500 cm^3 water, dried over sodium sulfate followed by distillation of the solvent at about 55–65°C under reduced pressure of about 700 mm Hg to afford 19.5 g **5** as a crude material. A solution of 19.5 g **5**, and 12.9 g 2,4-dichlorophenylhydrazine (0.06 mol) in 240 cm^3 ethanol was stirred for 8 h. On completion of the reaction (TLC), the solid was filtered off, washed with 20 cm^3 ethanol, and solvent was

removed at about 55–65°C under reduced pressure of about 700 mm Hg to afford a residue (23.2 g). This was dissolved in 200 cm^3 dichloromethane and stirred about 30 min followed by filtration of solid that was washed with 10 cm^3 dichloromethane. Solvent from the resultant filtrate was distilled completely at about 35–40°C under reduced pressure of about 700 mm Hg to afford 21.5 g of crude compound. This was purified by column chromatography to afford 8.5 g **2** (identical as described in Ref. [7]) in 30% yield. To remove the trace amount of rimonabant (**1**) (identical as described in Ref. [7]), the mixture was separated by dissolving the semi-pure material obtained from column in 50 cm^3 acetone and stirring for about 10 min afforded insoluble rimonabant (**1**) in 0.3 g quantity.

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