ISSN(PRINT) : 2320 -1967
ISSN(ONLINE) : 2320 -1975

GLOBAL SCIENTIFIC INC.

ChemXpress

ORIGINAL ARTICLE

CHEMXPRESS 4(4), 325-329, (2014)

Reductive step for preparation of rosiglitazone

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Received : 25th October, 2013 ; Revised : 02nd January, 2014 ; Accepted : 12th January, 2014

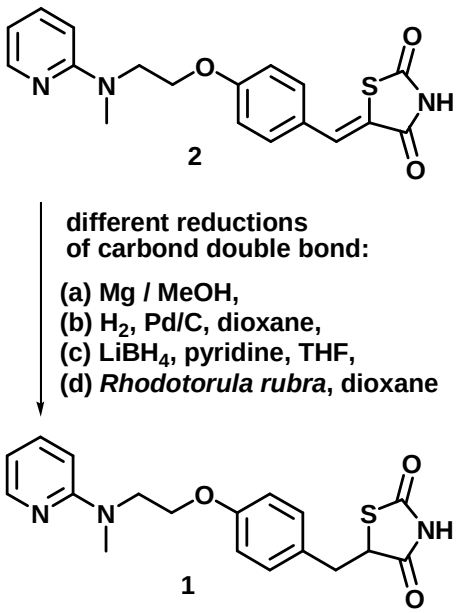
Abstract : An improved process has been developed for the production of rosiglitazone based on reductive transformation of substituted 5-benzylidenethiazolidin-2,4-dione. Sodium borohydride was used as reducing agent and divalent cobalt complex with dimethyglyoxim as catalyst. Reaction temperatures as well as dosage modes of the reducing agent and catalyst have been identified as significantly important parameters of the process. The discussed procedure ensures very high conversions and yields of the reductive transformation.

Keywords : Rosiglitazone; Thiazolidine-2,4-diones (TZD's); Sodium borohydride; Cobalt(II) chloride; Dimethylglyoxim.

INTRODUCTION

Rosiglitazone 1 belong to the group of thiazolidine-2,4-diones (TZD's), so called glitazones, which are characterized by a positive effect on insulin resistance, and increase bodies' sensitivity to insulin[1-3].

Reductive transformations of 5-benzylidenethiazolidin-2,4-dione 2 play the crucial role in the chemical synthesis of 1 (Scheme 1). The first way how to carry out this reduction is procedure with magnesium in methanol[4], furthermore reductions by means of catalytic hydrogenation[5], by means of lithium borohydride in pyridine[6], as well as by means of biochemical processes[7]. Another interesting approach based on the sodium borohydride and divalent cobalt complex with dimethylglyoxim (DMG) as catalyst was used for preparation other TZD's[8]. This approach frequently suffers from reduction stalling after 80% con-



Scheme 1 : Reductive transformations of carbon double bond on the intermediate 2 leading to rosiglitazone 1

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versions. Attempts to restart this reduction by adding more reducing agent or catalyst were supposedly unsuccessful[8]. Our need for large quantities of 1 led us to develop a scalable synthesis for this compound in pharmaceutical quality.

DISCUSSION

At beginning, we tried the earlier described reductive procedures (Scheme 1) and we recognized some serious troubles. Our preliminary experiments by means of widely cited method based on magnesium in methanol[4] failed unexpectedly due to production of complex mixtures including decomposition of rosiglitazone. On the other hand, the catalytic hydrogenation[5] is selective but it is characterized by economically unacceptable consumption of expensive catalyst. Unfortunately, the most commonly used catalytic hydrogenation suffers from consumption of big amount of palladium catalyst in this case probably due to catalyst poison which is originated from sulphur contained in the structure of reduced compound as well as in the product. After catalytic hydrogenation we have focused on the procedure based on sodium borohydride and cobalt chloride-dimethylglyoxime catalyst as potentially suitable method for synthesis of 1 (Scheme 2).

It was found that high or better absolute conversion of 2 to 1 is the limiting factor of this process because we were not able to remove residual content of 2 effectively under limit 0.1 % during isolation and crystallization. For that reason the conversion of starting material at level 99.9 % and more was taken as the main criterion for set-up of optimal reaction conditions.

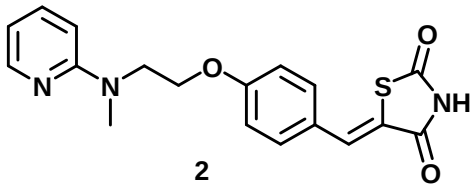
The reductions of the compound 2 to the rosiglitazone were carried out in the following way. First, the starting material 2 was dissolved in an aqueous solution of sodium hydroxide. While the reaction mixture was kept at selected temperature ±2 °C, solution of catalyst (solution of $CoCl_2.6H_2O$ and DMG in the mixture of water and DMF) and then aqueous solution of sodium borohydride were added into it. Molar ratios were as follows: 1.0 (2) : 0.015 ($CoCl_2$) : 0.2 (DMG) : 2.1 ($NaBH_4$). It was found that reaction temperature and dosage mode of reducing agent and catalyst has significant influence on the final result of reduction. Both were tested in detail.

Reaction temperature

The influence of reaction temperature was tested at following values: 30, 45, 55 and 65 °C. The characteristic S-shaped curves as relationship of degree of conversion on reaction time under different temperatures have been obtained by means of HPLC analyses of reaction mixtures (Figure 1). Suitable reaction rates and conversion of 2 were observed at 55 and 65°C.

Dosage mode

Dosage mode of both reduction agent and catalyst was tested as the second parameter. The obtained results are summarised by means of the characteristic S-shaped curves describing relationships of the degree of conversion on reaction time under different dosage modes (Figure 2). The procedure is characterized by adding the dose of the catalyst and the dose of the reducing agent to the solution of 2 which was heated to the selected temperature. These doses are repeated in cycles characterized by the same time intervals between additions. The constant temperature is held throughout the whole course of the reaction. The results indicate the high sensitivity of catalyst as well as sodium borohydride to temperature (Figure 2) and therefore the reaction temperature around 55 °C was selected for



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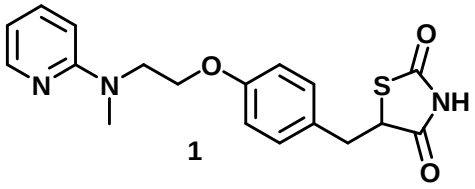
criterion for optimization:
degree of conversion more than 99.9 %

reducing agent: **$NaBH_4$**
catalyst: **$CoCl_2*6H_2O$, DMG, DMF**
reaction medium: **water and NaOH**
other: **temperature 30-65 °C, dosing based on gradual addition of catalyst and reduction agent**



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Scheme 2 : Method selected for reduction of 2 to 1.

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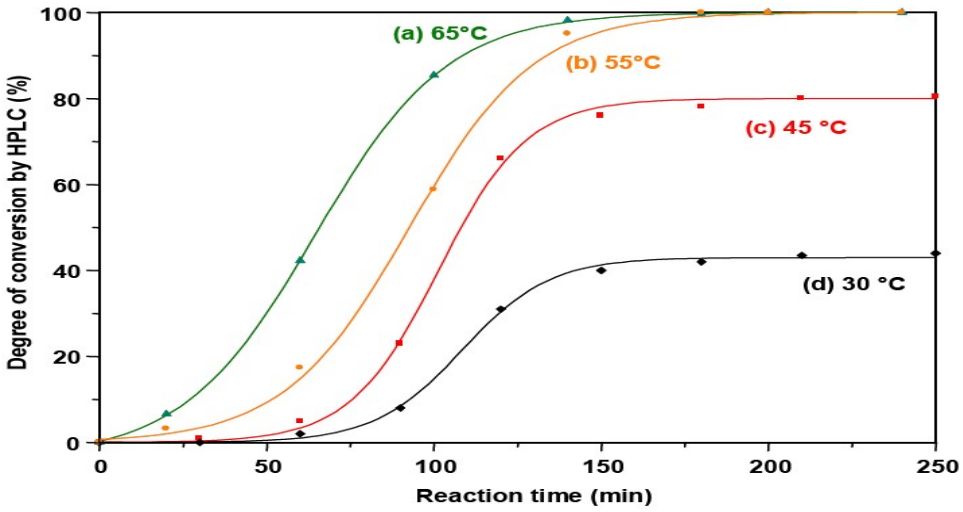

Figure 1 : Relationships of degree of conversion on reaction time under different reaction temperatures, catalyst and reducing agent were added in five doses at 50 minutes intervals, catalyst always as the first.

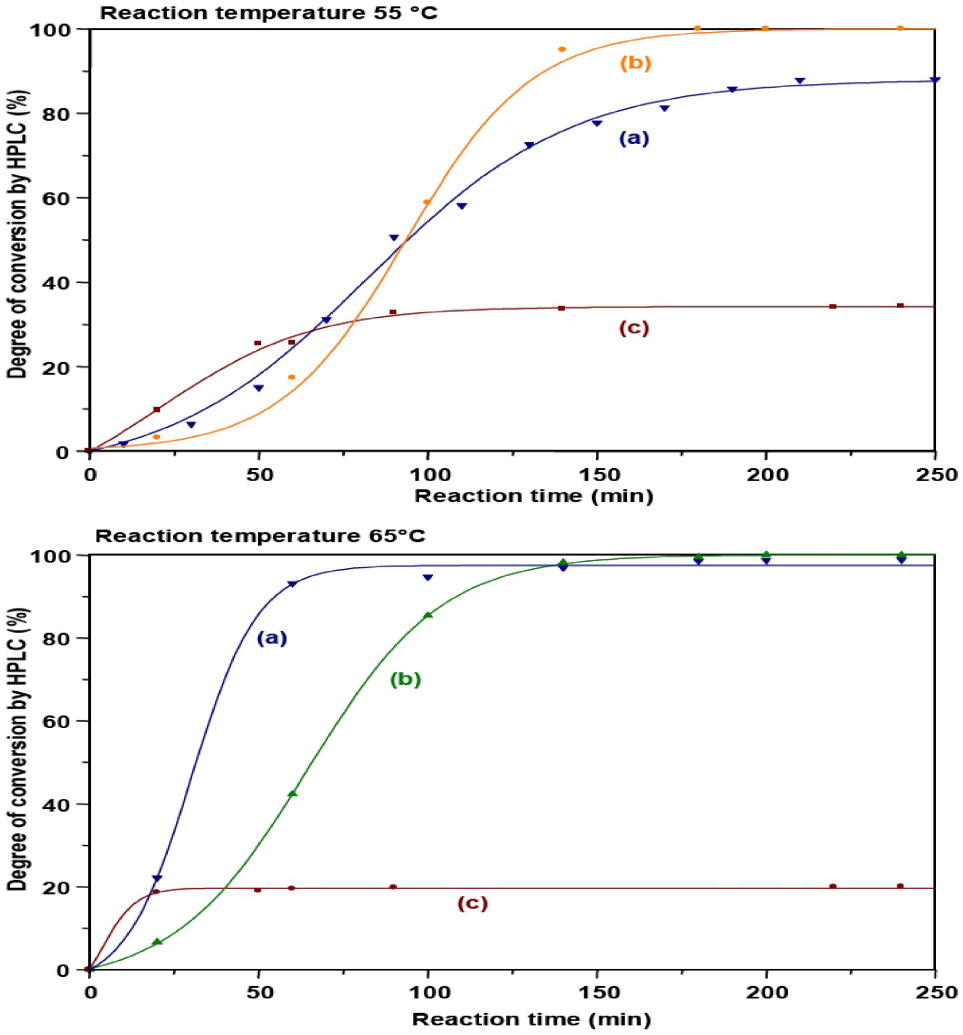

Figure 2 : Relationships of degree of conversion on reaction time at temperatures 65 °C and 55 °C, (a) reducing agent added at once at the beginning of reaction, catalyst added in five doses at 50 minutes intervals, (b) catalyst and reducing agent were added in five doses at 50 minutes intervals, catalyst always as the first, (c) catalyst added at once at the beginning of reaction, reducing agent added in five doses at 50 minutes intervals.

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scale up experiments due to better stability booth, catalyst and reducing agent. The influence of temperature and dosage mode is significantly higher in the case of catalyst; see Figure 2, curves (c) when catalyst is added once at the beginning of reaction.

Scalable process

The reaction conditions used in case scale-up experiments are very similar to the conditions used during lab-scale experiments, e.g. the reaction temperature 55 °C, five of the dosage cycles and the same quantity of reagent and catalyst in each cycle. On the other hand, the interval between cycles was prolonged from 50 to 60 minutes. The molar ratios between starting material 2 and sodium borohydride were changed from the original ratio 1:2.1 to 1:2.8. The reason for that is better reproducibility between scales. These conditions show very good reproducibility if we compare both laboratory and larger scale (Figure 3).

EXPERIMENTAL SECTION

^{1}H NMR spectra were measured with the Bruker Avance 500 spectrometer with the measuring frequency of 500.131 MHz. The spectra were measured in DMSO-d_6 solutions, chemical shifts were related to TMS (δ = 0.00 ppm). HPLC chromatograms were measured with the EliteLachrom device made by the Hitachi Company. A column filled with stationary phase RP-18e was used for the analyses, column temperature 25 °C. As the mobile phase a mixture of acetonitrile (80 %) and 0.1M aqueous solution of ammonium formate (20 %) adjusted to pH 5.0 with formic acid was used. The measurements were carried out in the isocratic mode with the flow rate of mobile phase 1 ml/min, overall analysis time was 20 min. Spectrophotometric detection at the wavelength of 266 nm was used. DMF was used as the solvent for the preparation of the samples to be analysed (20 µl of reaction mixture to 5 ml DMF), 10 µl of the prepared solution were used for the injection.

Synthesis of rosiglitazone 1 (general procedure)

Procedure consists of five parts as follows:

(1) Preparation of the catalyst

120 g of cobalt(II) chloride hexahydrate and 800 g of dimethylglyoxime were dissolved in 12.0 l DMF yielding a clear blue-green solution (ca 15 l).

(2) Preparation of the solution of the reducing agent

3.63 kg of sodium borohydride was dissolved in 30 l of a 0.1 M solution of sodium hydroxide under cooling in ice.

(3) Carrying out the reduction reaction

1.68 kg of sodium hydroxide and, subsequently, 12.0 kg of 2 were dissolved in 120 l of water. The obtained solution was stirred and heated to a temperature of 55±2 °C until a solution was formed. The catalyst was added (1/5 of the volume according to point

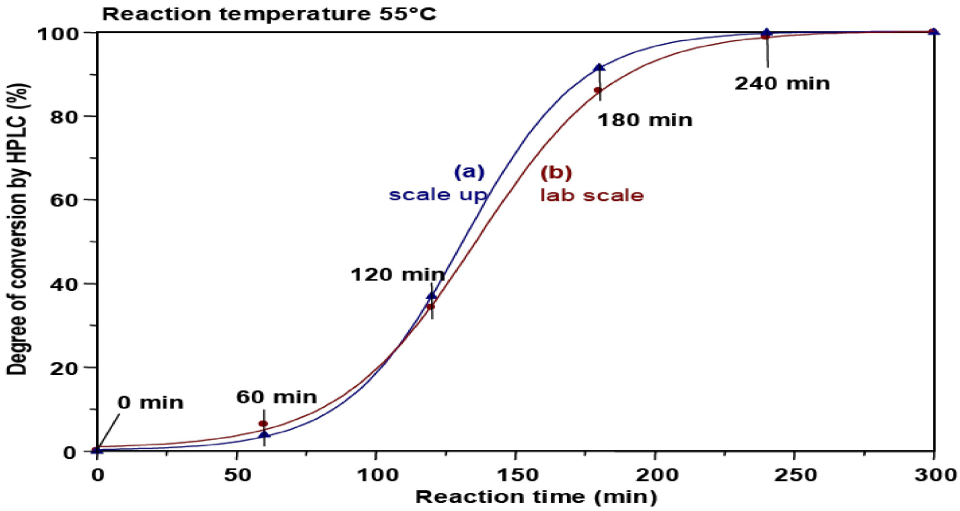

Figure 3 : Relationships of degree of conversion on reaction time at temperature 55 °C, catalyst and reducing agent were added in five doses at 60 minutes intervals, catalyst always as the first, (a) scale up experiment characterised by use of 4 kg of 2(b) lab scale experiment characterised by use of 10 g of 2.

(1), during ca 1 minute) into the solution, then the reducing agent was added (1/5 of the volume according to point (2), during ca 2 minutes) and the mixture was subsequently stirred at 55±2 °C for 60 minutes. The addition of the catalyst (1/5 of the volume according to point (1)) and of the reducing agent (1/5 of the volume according to point (2)), including the stirring and heating of the reaction mixture at 55±2 °C, were repeated in the same way four times more, including 60 minutes pauses between the individual additions. The total reaction time was approximately 300 minutes.

(4) Isolation of the crude product

60 l of ethyl acetate, 26 l of hydrochloric acid (1:1) and 60 l of a 10 % solution of sodium hydrogen carbonate were added into the reaction mixture according to point (3). The precipitated lumpy suspension was filtered, washed with water (6x20 l) and ethanol (3x20 l) and dried in a vacuum drier at 70 °C until a constant weight. The crude product was obtained (11.2 kg, yield 93 %).

(5) Crystallization

Crude product (11.0 kg) was mixed with 20 l of acetic acid; the resulting suspension was stirred and slowly heated to a temperature of 70-80 °C for 15 minutes. Then, heating was stopped and 100 l of ethanol was added in four doses to the stirred solution over 70 minutes, and the temperature of the suspension reached 30 °C. The resulting suspension was filtered; the cake washed with ethanol (2x15 l), the solid was dried under vacuum to constant weight. The product with a melting point of 155-156 °C and HPLC 99.90% was obtained. The yield of crystallization was 86.4% (9.5 kg), overall yield of the reductive step was 80.3%; ^{1}H NMR (DMSO-D_6), δ (ppm): 3.03-3.37 (m, 2H); 3.09 (s, 3H, CH_3); 3.92 (t, 2H); 4.13 (t, 2H); 4.88 (dd, 2H); 6.60 (dd, 1H); 6.67 (d, 1H); 6.91 (d, 2H); 7.17 (d, 2H); 7.53 (dd, 1H); 8.11 (dd, 1H); 12.02 (br s, 1H, NH).

CONCLUSION

The method of the reduction of carbon double bond has been chosen for the production of rosiglitazone 1 from substituted 5-benzylidenethiazolidin-2,4-dione 2 based on sodium borohydride as reducing agent and divalent cobalt complex as catalyst. Conversions of starting substrate more than 99.9 % are achieved after optimization of the procedure. Overall yields of the reductive step including crystallization of the crude product were around 80 %. Obtained rosiglitazone 1 is characterised by very high purity around 99.9 % determined by HPLC. It was found that reaction temperature and dosage mode of both, the reducing agent and catalyst has significant influence on the final result of reduction. The deficient stability of the catalytic system and reducing agent implicate necessity of incremental addition of catalyst as well as sodium borohydride in repeated doses at appropriate reaction temperature.

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