Res Chem Intermed
DOI 10.1007/s11164-015-2132-0

Synthetic optimization of rosiglitazone and related intermediates for industrial purposes

Ge Meng[1] · Meilin Zheng[1] · Mengshu Dong[2] · Yang Gao[1] · Aqun Zheng[3] · Zhenyu Li[1] · Ruizhi Hu[1]

Received: 22 October 2014 / Accepted: 4 June 2015

Abstract As an important newly Food and Drug Administration (FDA)-approved drug for treating diabetes, rosiglitazone (**1**) has received much attention from researchers in many areas. To search for an economical and convenient synthesis method for **1**, we explored the reaction conditions and workup of a scalable five-step synthetic route by an orthogonal method to determine the best condition for each reaction step. The starting materials are commercially available, including 2-chloropyridine (**2**), *N*-methylethanolamine (**3**), 4-fluorobenzaldehyde (**4a**) or 4-hydroxybenzaldehyde (**4b**), and 1,3-thiazolidine-2,4-dione (**5**). The five sequential reaction steps are cyclization, alkylation, etherification, condensation, and reduction, having optimal yield of 90, 99, 59, 75, and 91 %, respectively. The best overall yield to synthesize rosiglitazone based on compound **2** was 40 %, being suitable for industrial purposes, using water as a green solvent and avoiding column chromatography during the last three reaction steps.

Keywords Rosiglitazone · Avandia · BRL49653 · Synthesis technology · Optimization · Intermediates

✉ Ge Meng
mengge@mail.xjtu.edu.cn

[1] School of Pharmacy, Health Science Center, Xi'an Jiaotong University, Xi'an 710061, Shaanxi, People's Republic of China

[2] School of Software Engineering, Xi'an Jiaotong University, Xi'an 710049, Shaanxi, People's Republic of China

[3] School of Science, Xi'an Jiaotong University, Xi'an 710049, Shaanxi, People's Republic of China

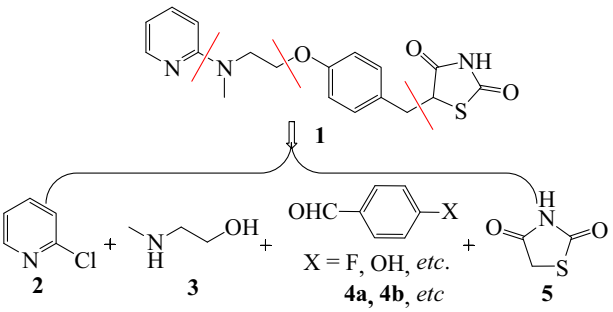
Published online: 17 June 2015

Introduction

Besides its well-known antihyperglycemic activity, rosiglitazone (**1**, Avandia, BRL 49653, by GlaxoSmithKline, Scheme 1) also displays various other biological activities [1, 2], such as anti-inflammatory [3], anti-cancer [4], increasing dendritic spine density [5], anti-Alzheimer's disease [6], anti-ulcerative colitis [7], anti-pancreatitis [8], anti-acanthosis nigricans [9], inducing brown adipose tissue (BAT) recruitment [10], stimulating nitric oxide (NO) synthesis [11], and diminishing NO synthase cofactor [12].

Retrosynthetic analysis of **1** indicated four main materials, including 2-chloropyridine (**2**), *N*-methylethanolamine (**3**), 4-fluorobenzaldehyde (**4a**) or its equivalent hydroxybenzaldehyde (**4b**), and 1,3-thiazolidine-2,4-dione (**5**) (Scheme 1). Although many improved synthesis methods for **1** have been reported, including a microwave (MW)-assisted approach [13], a solid-phase (SP) protocol [14], a polymer-supported (PS) method [15], and a semiconvergent approach [16], the linear synthesis route remains the reliable option to obtain this product efficiently [2], being a four-step route requiring more than 36 h to afford the final product [17]. Considering that MW, SP, and PS methods are not suitable for industrial scale-up, many pharmaceutical industries still adopt linear methods involving column chromatography to separate intermediates to provide bulk pharmaceutical chemicals (BPCs) [17]. Optimization for economical and convenient synthesis conditions might provide some suggestions for companies to reduce production costs, improving each step of the linear synthesis protocol for **1**, which is still required from the global perspective.

The yield for each step in the process to synthesize **1** varies significantly based on various factors such as mole ratio, reaction time, and catalyst. There is still scope to improve the productive cost efficiency by optimizing the reaction conditions of this practical linear synthesis route based on the following five sequential reaction steps: Intermediate **6** is first obtained via alkylation on secondary amine **3** with pyridine chloride **2**. Further etherification of alcohol **6** with 4-fluorobenzaldehyde (**4a**) affords **7** [18]. Knoevenagel condensation between aldehyde **7** and **5** provides the intermediate **8**. Reduction of the double bond of compound **8** with $NaBH_4$ under basic condition gives the target drug **1**. The main material 1,3-thiazolidine-2,4-dione



Scheme 1 Retrosynthetic analysis of rosiglitazone (**1**)

(**5**) was synthesized directly from 2-chloroacetic acid (**9**) and thiourea (**10**) via cyclization in either hydrochloride or water using our previously improved methods [19, 20]. The optimal overall yield of this linear synthesis route for **1** was 40 % (Scheme 2).

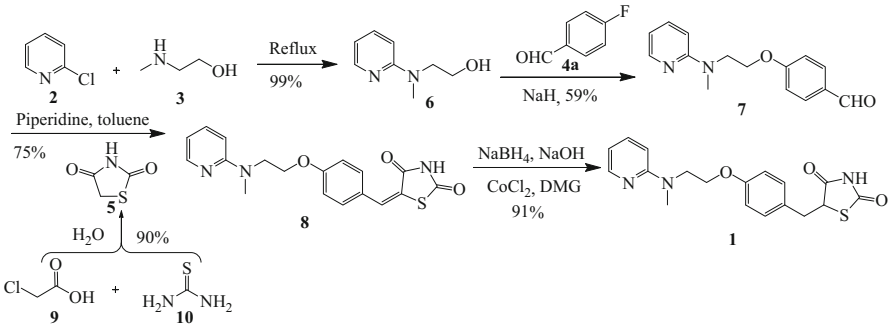
Results and discussion

As an important synthon for **1** and other related glitazones, 1,3-thiazolidine-2,4-dione (**5**) was earlier obtained from 2-iminothiazolidine-4-one hydrochloride salt via cyclization between 2-chloroacetic acid (**9**) or its ester and thiourea (**10**) under concentrated hydrochloride or sulfuric acid. The 2-iminothiazolidine-4-one HCl salt was isolated and then neutralized with sodium hydroxide to give 2-iminothiazolidine-4-one as free base, which was hydrolyzed under concentrated hydrochloride condition to give **5**. This early method was improved via a one-pot procedure (84 %) [19] or a green synthesis method by our group recently (79 %) [20].

Subsequent research on this cyclization reaction indicated that the yield of both the one-pot and green methods could be enhanced by adjusting the amount and concentration of solvent. Therefore, we designed an experiment to explore the effects of different levels of these factors, aiming for better yield based on the well-established orthogonal theory (Tables 1, 2).

The results showed that this cyclization process happened in both water and hydrochloride solution with various concentrations (Table 3), the latter of which could slightly influence the yield. However, in water solution, the yield was mainly dependent on the concentration of the reactant. The greater the amount of water used for a certain amount of reactant, the lower the yield, which could be explained by the solubility of the product **6** in water. Excess amount of solvent would lead to heavy loss during the workup and recovery difficulties.

2-(*N*-Methyl-*N*-(pyridin-2-yl)amino)ethanol (**6**) is an intermediate for both the linear and convergent synthetic routes for rosiglitazone. Since hydrochloride is also the main side-product of the same reaction, it is necessary to use an excess amount of **2** above the theoretical mole ratio of **2** to **3** (1:1) as an acid catcher. Based on this



Scheme 2 Linear synthesis route for rosiglitazone (**1**)

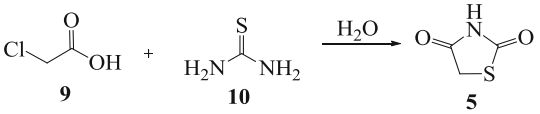
Table 1 Different levels of main factors in synthesis of intermediate **5**

Factor	Level				
	1	2	3	4	5
A: solvent	Hydrochloric acid (12 mol/L)	Hydrochloric acid (6 mol/L)	Hydrochloric acid (4 mol/L)	Hydrochloric acid (3 mol/L)	Water
B: ratio (**9**/solvent, mol/L)	10	6.67	4.00	3.33	2.00

Table 2 Experimental plan for intermediate **5** by orthogonal design method

Entry	Level	
	Factor A: solvent	Factor B: ratio (solvent/**9**, L/mol)
1	1	4
2	2	3
3	3	3
4	4	3
5	5	3
6	5	2

Table 3 Optimization result for synthesis of 1,3-thiazolidine-2,4-dione (**5**)



9 **10** **5**

Entry	Solvent	Time (h)	Ratio (**9**/solvent, mol/L)	Yield (%)[a]	M.p. (°C)	Yield (%)[b]
1	Hydrochloric acid (12 mol/L)	11	3.33	83	126–127	84 [19, 20]
2	Hydrochloric acid (6.0 mol/L)	8	4.00	82	126–127	
3	Hydrochloric acid (4.0 mol/L)	8	4.00	67	126–127	
4	Hydrochloric acid (3.0 mol/L)	8	4.00	69	126	
5	Water	8	4.00	77	126–127	
6	Water	10	6.67	90	124–125	

[a] Isolated yield of product (**5**)

[b] Yield obtained from the reaction sequence used in industry

reaction mechanism and our experience, the yield of this tertiary amine **6** is dependent on two main factors, viz. mole ratio and reaction time. Therefore, eight main levels of these factors and experimental plans were designed according to the orthogonal method to explore both factors efficiently at the same time, as shown in Tables 4 and 5, respectively. The experimental results showed that the yield of **6** depended on the ratio of the materials to a large extent.

The best yield was achieved when the volume ratio of **2** to **3** (v/v) was set between 4.0 and 5.0, and the reaction time was set between 9 and 10 h (entry 6, Table 6). If the ratio was very low, material **3** could not be consumed completely, increasing the amount of side-products. If the ratio was too high, recovering the excess amount of material **2** was a difficult task requiring long distillation time, which could lead to an increased amount of side-products. Both of the extreme conditions led to low yield of **6**. Overprolonging the reaction time could increase the side-products and lower the yield of intermediate **6** (entry 7, Table 6). The relevant details of these results are summarized in Table 6.

In comparison with literature [16], the improvements of this reaction step can be summarized in the following two aspects: the workup involved no ammonium chloride, and the reaction time was reduced from 13 to 9 h [16]. Although compound **2** was used in excess amount, it could be recycled via distillation.

As the specific intermediate for the linear synthesis route, aldehyde **7** can be obtained by many methods. In this work, only two main methods were investigated for etherification between **4a** and **6** (Table 7).

Method 1 using sodium hydride is the industrial approach to afford intermediate **7**. Dimethylformamide (DMF) was used as the solvent, with a high boiling point leading to inconvenient workup. Sodium hydride is an unstable, hazardous reagent. The yield of this step is relatively lower than other reactions of this route, so improving this reaction was important to influence the overall yield. Method 2 using a phase-transfer catalyst (PTC) and potassium hydroxide as the acid catcher could be carried out under heating or microwave condition. The PTC used in a mixed solution of toluene and water was tetrabutylammonium hydrogen sulfate (TBAHS) or tetrabutylammonium bromide (TBAB). The yield for forming the ether bond could be assisted by the microwave condition. Although the yield under MW condition using TBAHS as the PTC was reported to be the best (90 %), optimization of this method was not investigated as MW is usually not suitable for industrialization. Only the effect of economical TBAB on this reaction was investigated as an alternative to PTC.

The crude product **7** could be directly used in Knoevenagel condensation to provide (*Z*)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]-methylene]-1,3-

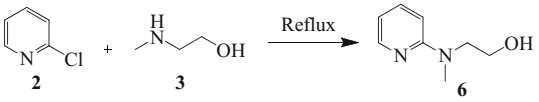
Table 4 Different levels of main factors for synthesizing intermediate **6**

Factor	Level							
	1	2	3	4	5	6	7	8
A: ratio (**2**/**3**, v/v)	3.0	3.5	4.0	4.6	4.8	5.0	5.3	5.5
B: time (h)	5	6	9	10	12	15	16	17

Table 5 Design of experimental plan for **6** by orthogonal method

Entry	Level	
	Factor A: ratio (**2/3**, v/v)	Factor B: reaction time
1	1	3
2	2	3
3	3	5
4	4	5
5	5	2
6	6	3
7	7	6
8	8	4

Table 6 Optimization results for synthesis of **6**



2 **3** **6**

Entry	A: mole ratio (**2/3**, v/v)	B: reaction time (h)	Yield (%)[a]	Yield (%)[b]
1	3.0	9	84	77 [17]
2	3.5	9	89	
3	4.0	12	99	
4	4.6	12	98	
5	4.8	6	97	
6	5.0	9	99	
7	5.3	15	90	
8	5.5	10	97	

[a] Isolated yield of product (**6**)

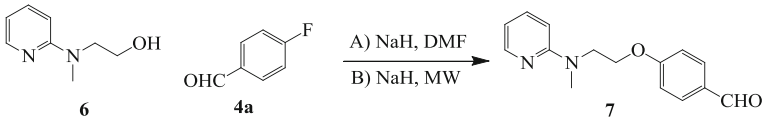
[b] Yield obtained from the reaction sequence used in industry

thiazolidine-2,4-dione (**8**), which could also be used for the next reduction step without further purification. The research into this reaction showed that the yield was high (75 %) when 1,3-thiazolidine-2,4-dione (**5**) was used in slight excess (mole ratio of **7**:**5** = 1:1.1) above the required equivalent. Toluene was better than methanol as an effective solvent system to enhance the yield.

The final product **1** was obtained from **8** via reduction with sodium borohydride under basic condition containing a catalytic amount of cobalt chloride hexahydrate and dimethylglyoxime (DMG) with yield of 91 %. The final step in the linear synthesis of **1** was improved in this work based on the reported method in the following three main aspects:

Firstly, lithium borohydride was reported to reduce **8** to **1** with yield of 76 %. Reduction of the exocyclic double bond involved use of boron lithium, which is too expensive for industrial purposes [22]. It was also necessary to add some DMF with

Table 7 Comparison of two synthesis methods for **7**



6 **4a** **7**

Entry	Method and reagents	Time	Temperature (°C)	Yield (%)[a]	Yield (%)[b]
1	NaH and DMF	24 h	25	59	47 [21]
2	TBAB and microwave	40 min	85	53	

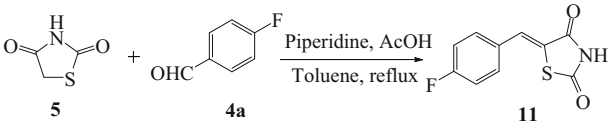
[a] Isolated yield of product (**7**)

[b] Yield obtained from the reaction sequence used in industry

slight heating when using sodium borohydride for the reduction, the yield of which is only 70 %. Our improved procedures involved use of sodium borohydride with direct dissolution of **8** in water before adding aqueous NaOH. This might allow complete dissolution of **8** in water to form the sodium salt of **8** without addition of any extra organic solvent. The reaction was kept at room temperature with high yield of 91 %.

Secondly, sodium borohydride should be dissolved in extremely dilute aqueous sodium hydride solution before addition to the basic aqueous solution of material. The procedures include use of the inverse addition manner to improve the troublesome procedures. To be specific, basic solution of **8** was added with cobalt chloride, dimethylglyoxime (DMG) before adding with sodium boron hydride powder at room temperature, which could be manipulated more conveniently than described in literature.

Thirdly, intermediate **8** was prepared via Knoevenagel condensation between 1,3-thiazolidine-2,4-dione (**5**) and an unpurified intermediate of 4-[2-[*N*-methyl-*N*-(2-pyridyl)]amido]ethoxybenzaldehyde (**7**) prepared from 4-fluorobenzaldehyde (**4a**). Therefore, it is possible that unpurified material **4a** might remain in the crude product of the unpurified intermediate **7**. Under the same basic Knoevenagel condensation condition, **4a** could condense with 1,3-thiazolidine-2,4-dione (**5**) also to give 5-(4-fluorobenzylidene) 1,3-thiazolidine-2,4-dione (**11**) as the main side-product (Scheme 3). The side-product **11** could be easily removed by adjusting the pH of the reaction mixture after completing the reduction, avoiding column chromatography. Therefore, the target compound **1** was purified easily by adjusting pH, which is quite suitable for industrial purposes.



5 **4a** **11**

Scheme 3 Formation of **11** during the linear synthesis route

Experimental

All materials were obtained from commercial suppliers and used as received. Melting points were taken on an X-1 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet FT-IR 360 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-300 (400 MHz) spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in δ. Mass spectra were measured on a HP5988A instrument by direct inlet at 70 eV.

General procedures for synthesis of target molecule and intermediates

*Synthesis of 1,3-thiazolidine-2,4-dione (**5**)*

2-Chloroacetic acid (**9**, 39.6 g, 420 mmol) and thiourea (**10**, 31.9 g, 420 mmol) were mixed together in a flask, to which water (60.0 mL) was added. The reaction mixture was heated to reflux for 10 h, then allowed to cool down to room temperature. Large amounts of solid appeared from the mixture, which were collected by filtering over vacuum and washed with a small amount of ice water (10.0 mL). The filter cake was dried under vacuum to give the product **5** (44.3 g, 90 %), m.p. 126–127 °C. *lit* m.p. 125–126 °C [19], IR (KBr, cm^{-1}): 3130 (ν_{N-H}), 2821 (ν_{C-H}), 1670 ($\nu_{C=O}$).

*Synthesis of 2-(N-methyl-N-(pyridin-2-yl)amino)ethanol (**6**)*

2-Chloropyridine (**3**, 16.1 mL, 19.3 g, 169.7 mmol, $d = 1.20$ g/mL, b.p. 166.0 °C) and *N*-methylethanolamine (**2**, 80.5 mL, 75.7 g, 1.01 mol, $d = 0.94$ g/mL, b.p. 158.1 °C) were added into a clean flask. The reaction mixture was heated to reflux for 9 h. The reaction process was monitored by thin-layer chromatography (TLC). After 9 h of heating, the reaction mixture was condensed under vacuum. The excess amount of **2** was recovered. The residue was allowed to cool down to room temperature and was then added with some ice water (100 mL). The mixture was extracted with dichloromethane (150 mL × 3). The organic layers were combined and washed with saturated brine solution (150 mL), and dried over sodium sulfate. The final product **6** was obtained after filtration and concentration under vacuum as clear yellow oil (25.6 g, 99 %) (b.p. 112–115 °C at 0.8 Torr [23]). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (m, 1H, pyridine-6-H), 7.44 (m, 1H, pyridine-4-H), 6.54 (m, 1H, pyridine-3-H), 6.51 (m, 1H, pyridine-5-H), 3.80 (t, 2H, CH_2OH), 3.67 (t, 2H, $R^1R^2NCH_2CH_2OH$), 3.03 (s, 3H, CH_3N). Compound **6** could be used directly in the next step without further purification.

*Synthesis of 4-[2-[N-methyl-N-(2-pyridyl)]amido]ethoxybenzaldehyde (**7**)*

Method 1 Using sodium hydride: 2-[*N*-methyl-*N*-(2-pyridyl)]amidoethanol (**6**, 4.42 mL, 5.00 g, 32.9 mmol, $d = 1.13$ g/mL, b.p. 281 °C) and anhydrous DMF

(60.0 mL) were mixed together in a three-necked flask, to which sodium hydride (70 %, 2.30 g, 95.8 mmol) was added portionwise. Nitrogen protection was applied after the addition of sodium hydride, and the speed of hydrogen gas evolution was abated. 4-Fluorobenzaldehyde (**4a**, 7.76 mL, 9.00 g, 72.5 mmol, $d = 1.16$ g/mL, b.p. 181 °C) was then added dropwise to the mixture, keeping the temperature below 50 °C. The reaction mixture was kept at r.t. for 24 h while monitoring with TLC, then concentrated by evaporating DMF partially. The mixture became turbid after diluting with cold water (30.0 mL), which was adjusted with aqueous hydrochloride (2.0 mol/L) to pH = 3. The mixture was extracted with dichloromethane (30.0 mL × 3) to remove the unused material **6**. Aqueous sodium hydroxide (5.0 mol/L) was added to the aqueous layer to modulate the pH to 11 again, followed by extraction with dichloromethane (30.0 mL × 3). The combined organic phase was washed with brine (30.0 mL × 2), dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, eluent: chloroform/methanol, v/v = 10:1) to provide the crude product (5.00 g, 59 %), which was recrystallized with ethyl acetate/petroleum ether (v/v = 1:1) to afford white crystal **7** (4.20 g, 50 %), m.p. 66–67 °C [13]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H, CHO), 8.17 (d, 1H, $J = 4.0$ Hz, pyridine-6-H), 7.83 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.48 (t, 1H, $J = 12.0$ Hz, pyridine-4-H), 7.02 (d, 2H, $J = 8.0$ Hz, Ar–H), 6.58 (m, 1H, pyridine-3-H), 6.53 (d, 1H, pyridine-5-H), 4.30 (t, 2H, OCH_2CH_2N), 4.03 (t, 2H, OCH_2CH_2N), 3.15 (s, 3H, CH_3N).

Method 2 Using tetrabutylammonium bromide (TBAB): 2-[*N*-methyl-*N*-(2-pyridyl)]amidoethanol (**6**, 2.30 mL, 2.60 g, 16.8 mmol), 4-fluorobenzaldehyde (**4b**, 1.81 mL, 2.10 g, 16.8 mmol), potassium hydroxide (2.80 g, 50.4 mmol), tetrabutylammonium bromide (TBAB, 0.60 g, 1.70 mmol), water (0.50 mL), and toluene (10.0 mL) were put into a three-necked flask. The reaction mixture was put into a microwave reactor with power of 800 W. Heating was kept under 80 °C for 40 min to complete the reaction. The residue was extracted with dichloromethane (50 mL × 3). The organic layers were combined and washed with water, then dried over anhydrous sodium sulfate. The filtrate was concentrated before separating via stepwise column chromatography (eluent: petroleum/ethyl acetate ester, v/v = from 10:1 to 7:1) to give the crude product **7** (2.30 g, 53 %), which was recrystallized from ethyl acetate ester/petroleum (v/v = 1:1) to give needle-like white crystals as pure **7** (1.80 g, 41 %), m.p. 65–66 °C, *lit*. viscous liquid [16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H, CHO), 8.17 (d, 1H, $J = 4.0$ Hz, pyridine-6-H), 7.83 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.48 (t, 1H, $J = 12.0$ Hz, pyridine-4-H), 7.02 (d, 2H, $J = 8.0$ Hz, Ar–H), 6.58 (m, 1H, pyridine-3-H), 6.53 (d, 1H, pyridine-5-H), 4.30 (t, 2H, OCH_2CH_2N), 4.03 (t, 2H, OCH_2CH_2N), 3.15 (s, 3H, CH_3N).

*Synthesis of (Z)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]-methylene]-1,3-thiazolidine-2,4-dione (**8**)*

4-[2-[*N*-Methyl-*N*-(2-pyridyl)]amido]ethoxybenzaldehyde (**7**, 9.00 g, 35.1 mmol), 1,3-thiazolidine-2,4-dione (**5**, 6.20 g, 52.7 mmol), and toluene (60.0 mL) were put into a three-necked flask and stirred until dissolving, to which was added a few drops of piperidine (about 0.5 mL) under nitrogen atmosphere. The mixture was

heated to reflux for 6 h until reaction completion. Large amounts of yellow solid precipitated from the solution after cooling down to room temperature. Methanol (10.0 mL) was added to the reaction mixture with stirring for 10 min before filtering. The filter cake was washed with a small amount of cold methanol and dried under vacuum to give yellow powder as the crude product **8** (9.40 g, 75 %), m.p. 196–200 °C. Yellow crystals were obtained after recrystallization with ethanol as the pure product (8.50 g, 80 %), m.p. 196–197 °C, *lit.* m.p. 197–198 °C [13]. ^{1}H NMR (400 MHz, DMSO) δ: 8.0 (d, 1H, pyridine-6-H), 7.7 (s, 1H, Ar–CH=), 7.5 (m, 3H, pyridine-4-H & O–Ar–H), 7.1 (m, 2H, O–Ar–H), 6.6 (m, 1H, pyridine-3-H), 6.5 (m, 1H, pyridine-5-H), 4.2 (t, 2H, OCH_2 CH_2N), 3.9 (t, 2H, OCH_2CH_2N), 3.0 (s, 3H, CH_3N); EI MS *m/z* (%): 355.0 ($[M]^+$, 3), 221.0 (35), 150.1 (100).

*Synthesis of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]-methyl]-1,3-thiazolidine-2,4-dione (**1**)*

(*Z*)-5-[[4-[2-(Methyl-2-pyridinylamino)ethoxy]phenyl]-methylene]-1,3-thiazolidine-2,4-dione (**8**, 3.60 g, 10.1 mmol) was mixed in water (450 mL) with stirring, to which was added aqueous sodium hydroxide (0.5 mol/L) to pH = 11 until the material **8** dissolved completely. The solution was added with cobalt chloride hexahydrate (0.20 g, 0.84 mmol), DMG (0.20 g, 1.72 mmol), and sodium boron hydride (4.50 g, 120 mmol). The mixture was kept at room temperature for 24 h until the reaction was complete. The insoluble residue was removed by filtration. The filtrate was adjusted with hydrochloride to pH = 3, then a small amount of solids appeared. The filtrate from the second filtration was adjusted to pH 6–7 with aqueous sodium hydroxide, then a large amount of solids appeared from the solution and was collected by filtration. The filter cake was washed with a small amount of water and dried under vacuum to give the final product **1** (0.80 g), m.p. 154–155 °C. The filtrate was extracted with dichloromethane (50.0 mL × 3), washed with saturated brine (50.0 mL × 2), and dried over anhydrous sodium sulfate. The solid was obtained via filtration and concentration as the second portion of **1** (2.50 g, total amount: 3.30 g, crude yield: 91 %). Pale-white crystals were obtained via recrystallization from ethanol as pure **1** (1.80 g, 50 %), m.p. 154–156 °C, *lit.* m.p. 152–153 °C [16], m.p. 154–155 °C [13]. ^{1}H NMR (400 MHz, DMSO) δ: 12.00 (s, 1H, NH), 8.07 (d, 1H, J = 8.0 Hz, pyridine-6-H), 7.48 (t, 1H, J = 8.0 Hz, pyridine-4-H), 7.12 (d, 2H, J = 8.0 Hz, Ar–H), 6.86 (d, 2H, J = 8.0 Hz, Ar–H), 6.63 (d, 1H, J = 8.0 Hz, pyridine-3-H), 6.55 (m, 1H, pyridine-5-H), 4.84 (m, 1H, thiazolidine-5-H), 4.09 (t, 2H, OCH_2CH_2N), 3.88 (t, 2H, OCH_2CHN), 3.05 (m, 2H, CH_2Ar), 2.49 (s, 3H, CH_3N); EI MS m/z (%): 342.0 (3), 107.1 (100), 223.1 (5).

Conclusions

Rosiglitazone was synthesized from commercially available materials via a five-step linear synthetic route with improved overall yield of 40 % (based on **2**). Optimization for each reaction step was designed and explored using an orthogonal

method on the linear synthesis route to determine the best conditions. The yield for each reaction step was 90, 99, 59, 75, and 91 %, respectively. The three main aspects of the improvement in the final step offered a practical and reliable technological protocol to synthesize **1** efficiently. The newly improved workup of the final reaction step offers an alternative method to afford the purified product without column chromatography, including purification of the final target compound **1**, intermediate **6**, and intermediate **8**. All the improved manipulations in the related procedures are conveniently suitable for industrial purposes.

Acknowledgments The authors would like to thank the Returned Overseas Chinese Scholars, State Education Ministry (SRF for ROCS, SEM), P. R. China (2011) and Technology Research and Development Program of China, International Cooperation (2013KW31-04) for financial support. The project was also sponsored by the Cooperation Project between Xi'an Jiaotong University and Weifang Keli Chemical Limited Company, P. R. China (2013).

References

1. B.B. Lohray, V. Bhushan, B.P. Rao, G.R. Madhavan, N. Murali, K.N. Rao, A.K. Reddy, B.M. Rajesh, P.G. Reddy, R. Chakrabarti, J. Med. Chem. **41**(10), 1619–1630 (1998)
2. B.C. Cantello, M.A. Cawthorne, D. Haigh, R.M. Hindley, S.A. Smith, P.L. Thurlby, Bioorg. Med. Chem. Lett. **4**(10), 1181–1184 (1994)
3. P. Mohanty, A. Aljada, H. Ghanim, D. Hofmeyer, D. Tripathy, T. Syed, W. Al-Haddad, S. Dhindsa, P. Dandona, J. Clin. Endocr. Metab. **89**(6), 2728–2735 (2004)
4. S.S. Palakurthi, H. Aktas, L.M. Grubissich, R.M. Mortensen, J.A. Halperin, Cancer Res. **61**(16), 6213–6218 (2001)
5. J. Brodbeck, M.E. Balestra, A.M. Saunders, A.D. Roses, R.W. Mahley, Y. Huang, Proc. Natl. Acad. Sci. **105**(4), 1343–1346 (2008)
6. M. Risner, A. Saunders, J. Altman, G. Ormandy, S. Craft, I. Foley, M. Zvartau-Hind, D. Hosford, A. Roses, Pharmacogenomics J. **6**(4), 246–254 (2006)
7. J.D. Lewis, G.R. Lichtenstein, J.J. Deren, B.E. Sands, S.B. Hanauer, J.A. Katz, B. Lashner, D.H. Present, S. Chuai, J.H. Ellenberg, Gastroenterology **134**(3), 688–695 (2008)
8. C. Chen, S. Xu, W.-X. Wang, Y.-M. Ding, K.-H. Yu, B. Wang, X.-Y. Chen, Arch. Med. Res. **40**(2), 79–88 (2009)
9. A. Romo, S. Benavides, Ann. Pharmacother. **42**(7–8), 1090–1094 (2008)
10. W.T. Festuccia, P.-G. Blanchard, D. Richard, Y. Deshaies, Am. J. Physiol. Regul. Integr. Comparat. Physiol. **299**(1), R159–R167 (2010)
11. J.G. Boyle, P.J. Logan, M.-A. Ewart, J.A. Reihill, S.A. Ritchie, J.M. Connell, S.J. Cleland, I.P. Salt, J. Biol. Chem. **283**(17), 11210–11217 (2008)
12. P. Linscheid, U. Keller, N. Blau, D.J. Schaer, B. Müller, Biochem. Pharmacol. **65**(4), 593–598 (2003)
13. S.L. Gaonkar, H. Shimizu, Tetrahedron **66**(18), 3314–3317 (2010)
14. K.M. Brummond, J. Lu, J. Org. Chem. **64**(5), 1723–1726 (1999)
15. X. Li, C. Abell, B.H. Warrington, M. Ladlow, Org. Biomol. Chem. **1**(24), 4392–4395 (2003)
16. D.V. Jawale, U.R. Pratap, R.A. Mane, Bioorg. Med. Chem. Lett. **22**(2), 924–928 (2012)
17. B.C. Cantello, M.A. Cawthorne, G.P. Cottam, P.T. Duff, D. Haigh, R.M. Hindley, C.A. Lister, S.A. Smith, P.L. Thurlby, J. Med. Chem. **37**(23), 3977–3985 (1994)
18. S. Raza, S.P. Srivastava, D.S. Srivastava, A.K. Srivastava, W. Haq, S. Katti, Eur. J. Med. Chem. **63**, 611–620 (2013)
19. G. Meng, Z.-Y. Li, M.-L. Zheng, Org. Prep. Proced. Int. **40**(6), 572–574 (2008)
20. G. Meng, Y. Gao, M.-L. Zheng, Org. Prep. Proced. Int. **43**(3), 312–313 (2011)
21. T. Sohda, K. Mizuno, Y. Momose, H. Ikeda, T. Fujita, K. Meguro, J. Med. Chem. **35**(14), 2617–2626 (1992)
22. R.G. Giles, N.J. Lewis, J.K. Quick, M.J. Sasse, M.W.J. Urquhart, L. Youssef, Tetrahedron **56**, 4531–4537 (2000)
23. M.K. Chmielewski, V. Marcha, J. Cieslak, A. Grajkowski, V. Livengood, U. Munch, A. Wilk, S.L. Beaucage, J. Org. Chem. **68**(26), 10003–10012 (2003)