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Communications to the Editor

An Improved Process for Pioglitazone and Its Pharmaceutically Acceptable Salt†

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Abstract:

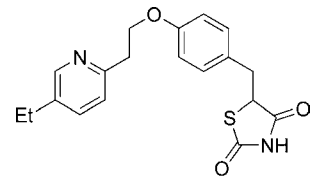
An improved process for pioglitazone (1) is described. The process features high-yielding transformations employing inexpensive reagents and recoverable solvents.

Introduction

Pioglitazone **1** (Figure 1) is a benzylthiazolidinedione derivative approved as a drug for the management of diabetes. Pioglitazone **1** is found to stimulate peroxisome proliferator-activated receptor gamma (PPARγ) in order to modulate the transcription of the insulin sensitive genes that are involved in glucose and lipid metabolism.[1]

The synthetic routes for pioglitazone **1**, as described in a previous patent,[2] are shown in Scheme 1 where reaction involves protection of 5-ethyl-2-pyridyl ethanol, **2**, with a *p*-toluene sulfonyl group to obtain intermediate **3**. Subsequently, this intermediate was subjected to nucleophilic substitution. In particular, the reaction between intermediate **3** and *p*-hydroxybenzaldehyde **4** in the presence of sodium hydroxide afforded intermediate **5**. The reaction between intermediate **5** and thiazolidinedione **6**, employing Knoevenagel conditions, afforded penultimate intermediate **7**.

Moreover, the reduction of intermediate **7** in the presence of Pd/C/H_2 at 25 °C yielded the desired compound **1**. In another disclosure,[3] $CoCl_2 \cdot 6H_2O/NaBH_4$/dimethyl glyoxime system was also used for such a reduction to obtain **1**. Additionally, there is a completely different approach (Scheme 1b)[4] where



1

Figure 1. **Structure of pioglitazone 1.**

starting material **2** was condensed with *p*-substituted fluorobenzene to obtain intermediates **8** and **9**. Raney Ni/HCO_2H-mediated reductive hydrolysis of cyano derivative **9** afforded aldehyde intermediate **5** which can be converted to title compound **1** as per the procedure described in Scheme 1a. Intermediate **8** was subjected to a cascade of reactions to obtain bromo derivative **10**. In this particular strategy, catalytic hydrogenation, diazotization, bromination, Cu metal insertion across the aromatic carbon and bromo functionality, followed by reaction with methyl acrylate was performed to afford **10**. Subsequently, intermediate **10** was further utilized in the condensation with thiourea and acid-catalyzed hydrolysis to render desired species **1**. Despite the proven potential of these procedures in Scheme 1 (a and b), there are certain disadvantages: (a) transformation from **2** to **3** was high yielding, but the enrichment of E2 elimination impurity during the reaction leading to the cumbersome isolation and purification of intermediate **5**, (b) expensive Pd metal was used in the reduction of **7** to **1**, (c) a plant-unfriendly, pyrophoric non-nucleophilic base, NaH, is employed in the transformation of **8** or **9** from **2**, (d) a cascade of reactions, involving expensive metal (Pd), toxic acid (HBr, and diazonium chloride intermediate, was performed to yield intermediate **10**, and (e) use of expensive partially recoverable solvents, e.g., dioxane, THF and CH_2Cl_2. A convergent approach involving condensation of **4** and **6** to obtain **1** is also precedented.[5]

Herein, we present our efforts to avoid all of the disadvantageous factors involved in Scheme 1 (a and b) and achieve a cost-effective, high-yielding, and moderately greener process for pioglitazone **1** and its pharmaceutically acceptable HCl salt.

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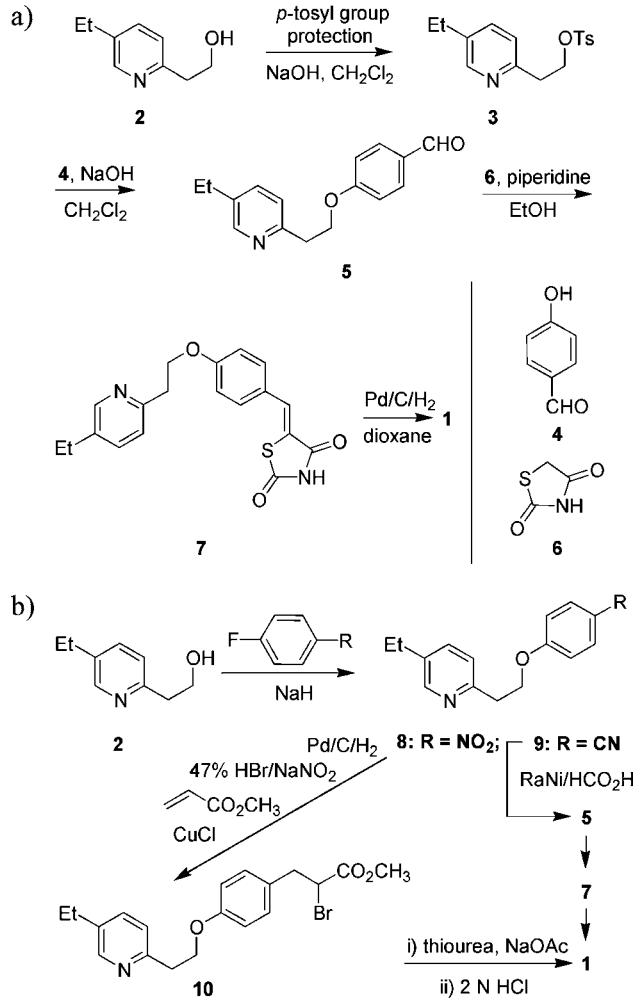
Scheme 1. **Precedented synthetic approach**



Results and Discussion

In our endeavor to improve the process, the synthesis of pioglitazone **1**, as shown in Scheme 2, starts with the protection of 5-ethyl-2-pyridyl ethanol **2** with the methyl sulfonyl group to obtain intermediate **11**. Subsequently, this intermediate was subjected *in situ* to nucleophilic substitution. In particular, the reaction between intermediate **11** and *p*-hydroxybenzaldehyde, **4**, in presence of potassium carbonate afforded intermediate **5**. The reaction between intermediate **5** (not isolated) and thiazolidinedione **6**, employing Knoevenagel conditions, afforded penultimate intermediate **7** in 50% yield and 99% purity for the three steps. Moreover, the reduction of intermediate **7** in the presence of Co (II) salts as a catalyst at 30 °C yielded the desired compound **1** in 90−98% yield and 98% purity.

In one of the reactions, following the literature procedure,[3] 15 mol % $CoCl_2 \cdot 6H_2O/NaBH_4$/dimethyl glyoxime system afforded **1** in 98% yield and 98% purity. This reduction was also performed, in the presence of 15 mol % $Co(NO_3)_2 \cdot 6H_2O/NaBH_4$/dimethyl glyoxime as a catalytic system, that gave rise to the product **1** in same yield and purity. However, cobalt ammonium sulfate as a catalyst, instead of cobalt chloride or nitrate, did not offer better yields although the purity was found to be same. Pharmaceutically acceptable salt of **1** was prepared by employing 1.5 equiv of aq HCl and isopropanol in 90% yield and >99.7% purity (ICH grade).

Scheme 2. **Improved synthetic approach: route A (feasibility) and B (after optimization)**

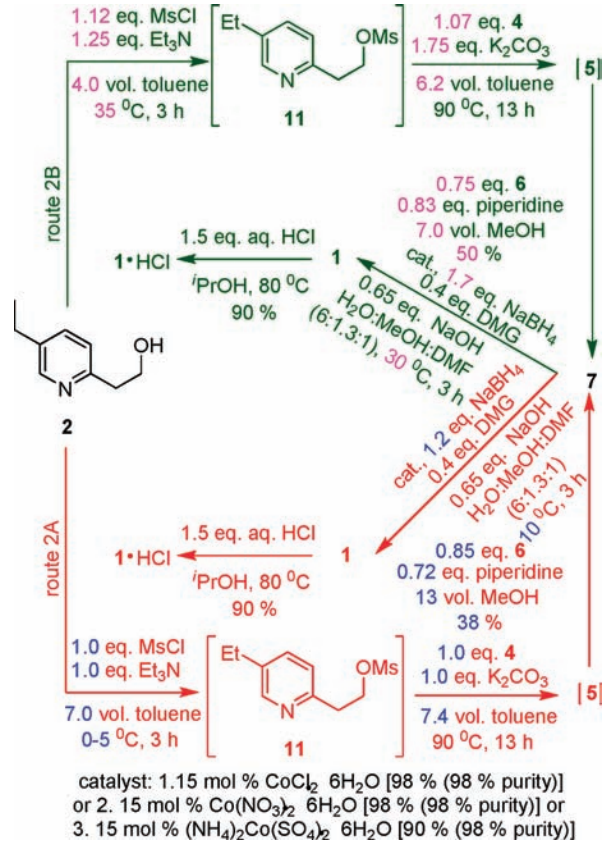


Table 1. **Optimization of solvent quantity used in the synthesis of intermediate 11**

		toluene quantity		yield of **11**	
entry	quantity of **2** (g)	(mL)	vol	(g)	(%)
1	25	75	3.0	33.7	88.8
2	25	100	4.0	34.9	92.0
3	25	125	5.0	33.8	89.1

The process that we developed at our end was optimized to find out the best possible conditions for the synthesis of **1**. The optimization of every step is described in detail as given below:

Optimization of Solvent Quantity Used in the Synthesis of Intermediate 11. Preparation of **11** involves mesylation of 2-(5-ethyl-2-pyridyl) ethanol **2**, employing methanesulfonyl chloride and triethylamine in toluene. During feasibility studies, 7 volumes of toluene were used as shown in Scheme 2 (route 2A). We anticipated that the volume of the solvent can further be optimized to a lesser quantity. With 3 volumes of solvent, a thick reaction mass was observed; however, with 4 or 5 volumes of solvent the stirring of the reaction mass was found to be efficient [Table 1 (entry 2)]. In this study, except for the solvent, all other parameters were the same as in Scheme 2 (route 2A).

Eventually, we could perform the reaction with 4 volumes of toluene and the detailed investigation is summarized in Table 1.

Optimization of Triethylamine Equivalence in the Synthesis of 11. As mentioned before, preparation of **11** involves triethylamine in toluene medium. During feasibility studies 1.0 equiv of triethylamine was used as shown in Scheme 2 (route 2A). In order to improve the yield, we reasoned that the quantity

Table 2. **Optimization of triethylamine equivalence in the synthesis of 11**

entry	quantity of **2** (g)	triethylamine quantity (mL)	triethylamine quantity equiv	yield of **11** (g)	yield of **11** (%)	purity by HPLC (%)
1	25	23.0	1.0	32.9	87	61
2	25	25.8	1.12	33.1	87	70
3	**25**	**28.8**	**1.25**	**34.6**	**91**	**80**
4	25	31.2	1.35	34.9	92	81
5	25	34.6	1.5	34.4	91	82

Table 3. **Optimization of methanesulfonyl chloride equivalents in the synthesis of 11**

entry	quantity of **2** (g)	MsCl quantity (mL)	MsCl quantity equiv	yield of **11** (g)	yield of **11** (%)	purity by HPLC (%)
1	25	19.0	1.0	30.2	80	78
2	**25**	**21.2**	**1.12**	**32.9**	**87**	**84**
3	25	23.7	1.25	33.1	87	55
4	25	25.6	1.35	32.4	85	75

Table 4. **Optimization of temperature in the synthesis of 11**

entry	quantity of **2** (g)	temperature (°C)	yield of **11** (g)	yield of **11** (%)	purity by HPLC (%)
1	25	0–5	32.9	87	85
2	**25**	**25–35**	**33.3**	**89**	**88**
3	25	−5–0	33.0	87	85
4	25	45–50	24.2	64	83

of base could be detrimental and can be optimized to adequate quantity. With 1.12 equiv of triethylamine, a lesser purity of the product was observed. Additionally, different quantities of base were investigated but the best combination of purity and yield, considering the amount of base, was observed with 1.25 equiv of triethylamine as shown in Table 2 (entry 3). In this study, except for toluene and triethyl amine, all other parameters were the same as in Scheme 2 (route 2A).

Optimisation of Methanesulfonyl Chloride Equivalence in the Synthesis of 11. As a part of our strategy, the number of equivalents of methanesulfonyl chloride in the preparation of **11** is also optimized. During feasibility studies 1.0 equiv of methanesulfonyl chloride was used as shown in Scheme 2 (route 2A). In order to improve the yield, we anticipated that the quantity of mesylating reagent could also be detrimental. Employing 1.12 equiv of methanesulfonyl chloride as shown in Table 3 (entry 2), we obtained the product with the best yield and purity. In the different reactions with the increased amount of methylsulfonyl chloride, we isolated the product with the lower yield and purity as shown in Table 3. In this study, except for toluene, triethylamine, and methanesulfonyl chloride, other reaction conditions remained the same as in Scheme 2 (route 2A).

Optimization of Temperature in the Synthesis of 11. Temperature always plays a pivotal role in the synthesis; therefore, as a part of our strategy preparation of **11** at different temperatures is also studied. During feasibility studies, the reaction was conducted at 0−5 °C as shown in Scheme 2 (route 2A). In order to improve the yield, during optimization, we performed the reaction at 25−35 °C and isolated the product with best purity and yield as shown in Table 4 (entry 2). In the different reactions at lower or higher temperatures, we were not able to isolate the product with better yield and purity as shown in Table 4.

Table 5. **Optimization of solvent quantity used in the synthesis of intermediate 5**

entry	quantity of organic layer containing **11** (mL)	toluene quantity (mL)	toluene quantity vol	yield of **5** (g)	yield of **5** (%)	purity by HPLC (%)
1	150	185	7.4	31.3	74.1	72.8
2	**150**	**155**	**6.2**	**32.4**	**76.7**	**80.8**
3	150	100	4.0	–	–	–

Table 6. **Optimization of equivalents of 4-hydroxybenzaldehyde 4 in the preparation of 5**

entry	quantity of organic layer containing **11** (mL)	quantity of **4** (g)	quantity of **4** equiv	yield of **5** (g)	yield of **5** (%)	purity by HPLC (%)
1	150	18.2	0.9	33.5	79.3	76.1
2	150	20.2	1.0	33.1	78.4	80.9
3	**150**	**21.6**	**1.07**	**33.8**	**80.0**	**85.4**
4	150	24.2	1.2	32.6	77.2	84.2

In this way we optimized the reaction conditions involved in the preparation of **11** as shown in Scheme 2, route 2B.

Optimization of Solvent Quantity in the Preparation of 5. Preparation of **5** involves condensation of 4-hydroxybenzaldehyde **4** and 2-(5-ethyl-2-pyridyl)ethyl methanesulfonate **11** using potassium carbonate in toluene. During feasibility studies 7.4 volumes of toluene were used as shown in Scheme 2, route 2A. As per our optimization strategy, we realized that the volume of the solvent can further be optimized to a lesser quantity. With 4 volumes of solvent, a thick reaction mass was observed; however, with 6.2 volumes as shown in Table 5 (entry 2) of solvent the stirring of the reaction mass was found to be efficient. In this study, except for the solvent, all other parameters remained the same as in Scheme 2 (route 2A).

Optimization of Equivalence of 4-Hydroxybenzaldehyde 4 in the Preparation of 5. Condensation of 4-hydroxybenzaldehyde **4** with 2-(5-ethyl-2-pyridyl)ethyl methanesulfonate **11** leads to the synthesis of **5**. During feasibility studies 1 equiv of **4** was used as shown in Scheme 2 (route 2A). After optimization, the yield and purity in the preparation of **5** were found to be optimal with 1.07 equiv of **4** (Table 6, entry 3). In different reactions, less or more than 1.07 equiv of **4** was found to be inefficient (entries 1, 2, and 4). In this study, except for the volume of the solvent and quantity of **4**, all other parameters remained the same as in Scheme 2 (route 2A).

Optimization of Potassium Carbonate Quantity in the Preparation of 5. Condensation of 4-hydroxybenzaldehyde **4** with 2-(5-ethyl-2-pyridyl) ethyl methane sulfonate **11** using potassium carbonate in toluene leads to the synthesis of **5**. During feasibility studies 1.0 equiv of potassium carbonate was used as shown in Scheme 2 (route 2A). After optimization, 1.75 equiv of potassium carbonate was found to be sufficient to obtain best yield and purity of **5** as shown in Table 7 (entry 2). In different reactions, less or more than 1.75 equiv of base did not offer better results.

The optimized reaction conditions involved in the preparation of **5** are shown in Scheme 2 (route 2B).

Optimization of Methanol Quantity in the Preparation of 7. Preparation of **7** involves the condensation of 2,4-thiozolidinedione **6** and **5** using piperidine base in methanol. As shown in Scheme 2 (route 2A), 13 volumes of methanol were used. After optimization, 7 volumes of the methanol were

Table 7. **Optimization of equivalents of potassium carbonate in the preparation of 5**

entry	quantity of organic layer containing **11** (mL)[a]	quantity of K_2CO_3 (g)	quantity of K_2CO_3 equiv	yield of **5** (g)	yield of **5** (%)	purity by HPLC (%)
1	175	34.3	1. 5	32.3	76.5	82.2
2	**175**	**40.0**	**1.75**	**33.8**	**80.0**	**85.4**
3	175	57.1	2.5	31.8	75.3	86.0
4	175	22.8	1.0	30.2	71.5	79.3
5	175	17.1	0.75	28.4	67.2	76.6

[a] 175 mL of organic layer is equal to 33 g of **11**.

Table 8. **Optimization of methanol quantity in the preparation of 7**

entry	**5** (g)	methanol (vol)	yield (g)	yield (%)	purity (%)
1	**25**	**7.0**	**23.3**	**67.1**	**96.2**
2	25	10.0	23.5	67.7	95.9
3	25	12.0	23.3	67.1	98.2

Table 9. **Optimization of equivalents of 2,4-thiozolidinedione in the preparation of 7**

entry	**5** (g)	**6** (equiv)	yield (g)	yield (%)	purity (%)
1	25	0.68	22.6	65.1	95.7
2	25	0.85	23.2	66.8	96.1
3	**25**	**0.75**	**23.2**	**66.8**	**97.6**
4	25	0.94	22.9	65.9	96.8
5	25	0.61	21.7	62.5	95.19

Table 10. **Optimization of piperidine quantity in the preparation of 7**

entry	**5** (g)	piperidine (equiv)	yield (g)	yield (%)	purity (%)
1	25	0.64	22.8	65.6	97.4
2	25	0.72	22.8	65.6	98.3
3	**25**	**0.83**	**25.5**	**73.4**	**94.52**
4	25	0.95	23.6	68.0	96.7

found to be sufficient for effective stirring and solubility of the substrates, Table 8 (entry 1). In this study, except for the volume of solvent, all other parameters were the same as in Scheme 2 (route 2A).

Optimization of Equivalents of 2,4-Thiozolidinedione in the Preparation of 7. In feasibility studies, 0.85 equivalent of 2,4-thiozolidinedione **6** was used to prepare **7** as shown in Table 9 (entry 2). After optimization, 0.75 equivalent of **6** was found to be sufficient to afford **7** in better yield and purity [Table 9 (entry 3)]. In this study, except for the volume of solvent and equivalents of **6**, all other parameters were the same as in Scheme 2 (route 2A).

Optimization of Piperidine Quantity in the Preparation of 7. As mentioned in Scheme 2, preparation of **7** involves the condensation of **6** and **5** using piperidine base in methanol. In feasibility studies, 0.72 equiv of piperidine was used for the preparation of **7** [Scheme 2 (route 2A)]. After optimization, 0.83 equiv of piperidine base was found to be sufficient to effect the transformation [(Table 10 (entry 3)]. In this study, except for the volume of solvent, equivalents of **6** and equivalents of piperidine base, all other parameters remained the same as in Scheme 2 (route 2A).

Table 11. **Optimization of quantity of sodium borohydride in the preparation of 1**

entry	**7** (g)	sodium borohydride (g)	sodium borohydride (equiv)	yield (g)	yield (%)	purity by HPLC (%)
1	20	2.1	1.0	18.2	90.4	88.77
2	20	2.6	1.2	18.5	91.9	90.73
3	20	3.0	1.4	18.5	91.9	94.16
4	20	3.2	1.5	19.0	94.4	97.21
5	20	4.0	1.9	18.2	90.4	98.69
6	**20**	**3.6**	**1.7**	**19.1**	**94.9**	**98.14**
7	20	4.9	2.3	18.0	89.4	98.08

The optimized reaction conditions involved in the preparation of **7** are shown in Scheme 2 (route 2B).

Optimization of Quantity of Sodium Borohydride in the Preparation of 1. Preparation of **1** involves reduction of **7** using sodium borohydride in aq methanol and DMF. Dimethyl glyoxime and cobalt chloride hexahydrate was used as a catalyst. In feasibility studies, 1.2 equiv of sodium borohydride was used for the preparation of **1** as shown in Scheme 2 (route 2A). After optimization, 1.7 equiv of sodium borohydride was found to be sufficient to effect the transformation with high yield and purity [Table 11 (entry 6)].

An improved process presented in Scheme 2 (route 2B), appears to be advantageous over the existing synthesis, e.g. (a) transformation from **2** to **11** was high yielding, and the enrichment of E2 elimination impurity during the reaction was avoided up to greater extent [the route described in the patent (Scheme 1a) yields 30−40% E2 elimination impurity; however, in our optimized process (Scheme 2, route 2B) it was found to be only 5−8%]; (b) expensive Pd metal was replaced with Co (II) salts as a catalyst in the reduction of **7** to **1**; (c) plant-unfriendly, pyrophoric, non-nucleophilic base, NaH, was completely avoided as we developed a process analogous to Scheme 1a; (d) similarly, a cascade of reactions involving expensive metal (Pd), toxic acid (HBr), and diazonium chloride intermediate was avoided to yield intermediate **10**, as the process analogous to Scheme 1b was not developed; and (e) expensive, partially recoverable solvents, e.g., dioxane, THF, and CH_2Cl_2, were replaced with toluene, methanol, and isopropanol.

Conclusions

We have developed an improved process for pioglitazone **1** which appears to be more compatible with industrial scale and has some advantages over the existing synthesis.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. The ^1H and ^{13}C spectra were measured in DMSO-d_6 using 200 or 400 MHz on a Varian Gemini and Varian Mercury plus 2000 FT NMR spectrometer; the chemical shifts were reported in δ ppm. IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on an HP 5989 A LC−MS spectrometer. The melting points were determined by using the capillary method on Polmon (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

Preparation of 5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzilidene]-2,4-thiazolidinedione (7). To a stirring solution of triethylamine (57.6 L, 413 mol), 2-(5-ethyl-2-pyridyl)ethanol (50 kg, 331 mol), and toluene (200 L) at about 25 °C was added slowly (200 g/min) methanesulfonyl chloride (42.5 kg, 371 mol) for about 25 min. After stirring for 3 h at 25 °C, the separated solid was filtered and washed with toluene (60 L). The obtained filtrate was washed with 4% sodium bicarbonate solution (60 L). The layers were separated, the aqueous phase was extracted with toluene (50 L), and the combined organic layers were washed with water (2 × 60 L). To the organic layer containing intermediate **11** were added 4-hydroxybenzaldehyde (43.2 kg, 354 mol) and potassium carbonate (80 kg, 579 mol) in one portion at 25 °C. After stirring for 13 h at 90 °C, the reaction mass was cooled to 50 °C in 1 h and quenched with water (250 L) under stirring. The layers were separated, the aqueous phase was extracted with toluene (2 × 150 L), and the combined organic layers were washed with 5% sodium hydroxide solution (250 L). The clear organic layer was distilled completely under vacuum below 65 °C to afford the crude compound **5** (68.6 kg), in 81.2% yield and >83.0% purity (unsuccessful attempts were made to distill the product at below <250 °C). To a solution of **5** in methanol (450 L) were added piperidine (23.3 kg, 274 mol) and 2,4-thiozolidinedione (29.1 kg, 248 mol) at 25 °C. After stirring for 13 h at 65 °C, the reaction mass was cooled in 1 h to 25 °C and diluted with methanol (195 L) under stirring. The pH of reaction mass was adjusted to about 6−6.5 by using acetic acid (35 L) followed by addition of methanol (130 L) under stirring for about 15 min. After stirring for 1.5 h at 65 °C, the reaction mass was cooled to 25 °C in 1 h, and the separated solid was filtered and washed with methanol (65 L) and dried under vacuum at 65 °C for 4 h to afford compound **7** (58.6 kg) in 50% yield and >98.9% purity. Spectroscopic data were found to be in agreement with the data collected from an authentic sample of intermediate **7**.

Preparation of 5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolinedione (1). To a stirring solution of compound **7** (60 kg, 169 mol) in methanol (120 L), water (420 mL), and 4% sodium hydroxide solution (78 L) was added a solution of cobalt nitrate hexahydrate (0.75 kg, 2.5 mol) in dimethyl glyoxime (7.8 kg, 67.2 mol) and dimethyl formamide (90 L) at 35 °C. Subsequently, a mixture of sodium borohydride (11.1 kg dissolved in water 120 L) and 4% sodium hydroxide solution (27 L) was added slowly (150 mL/min) at 20 °C over a period of 3 h. After additional stirring for 3 h, the charcoal (3 kg) was added to the reaction mass and the stirring continued for about 30 min at 20 °C. The reaction mixture was passed through the Celite bed, and the pH of the filtrate was adjusted within the range of 6.5−7.0 using acetic acid (24 L). After stirring for 45 min at 25 °C, the separated solid was filtered, washed with water (60 L) and methanol (2 × 75 L), and dried under vacuum at 70 °C for 8 h to afford compound **1** (59.2 kg) in 98% yield and >98% purity. Spectroscopic data were found to be in agreement with the data collected from an authentic sample of pioglitazone **1**.[1]

Preparation of Pioglitazone Hydrochloride (1·HCl) salt. To a stirring solution of compound **1** (50 kg, 141 mol) in isopropyl alcohol (250 L) was added hydrochloric acid (75 L) over the period of 10 min at 25 °C and heated to 80 °C to achieve clear solution. After additional stirring for 45 min, the clear solution was in 1 h cooled to about 25 °C, and the separated solid was filtered and washed with isopropyl alcohol (50 L) and dried under vacuum at 70 °C for 4 h to afford **1**·HCl (49.6 kg) in 90% yield and >99.7% purity. Spectroscopic data were found to be in agreement with the data collected from authentic sample of pioglitazone **1**.[1]

^{1}H NMR (400 MHz, DMSO-d_6) 12.08 (s, 1H), 8.73 (d, 1H, J = 1.6 Hz), 8.43 (dd, 1H, J = 2.0, 8.0 Hz), 8.01 (d, 1H, J = 8.0 Hz), 7.16 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 4.88 (dd, 1H, J = 4.4, 8.8 Hz), 4.34 (t, 2H, J = 6.2 Hz), 3.55 (t, 2H, J = 6.2 Hz), 3.30 (dd, 1H, J = 4.4, 14.0 Hz), 3.06 (dd, 1H, J = 8.8, 14.0 Hz), 2.80 (q, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.6 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) 175.6, 171.5, 156.9, 151.0, 145.2, 141.3, 139.8, 130.3, 129.0, 127.1, 114.4, 65.4, 52.8, 40.1, 39.9, 39.7, 39.5, 39.2, 39.0, 38.8, 36.2, 32.1, 24.5, 14.5; IR (KBr) 2928, 2742, 1743, 1694, 1616, 1510, 1461, 1313, 1243, 1038, 850, 712 cm^{-1}; HRMS (Cl) calcd For $C_{19}H_{20}N_3O_3S$ (M^+) 356.44; found (MH^+) 357.5.

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