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Microwave-assisted synthesis of the antihyperglycemic drug rosiglitazone

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ABSTRACT

We developed a simple, rapid, high yielding, and environmentally benign microwave assisted total synthesis of rosiglitazone, an antihyperglycemic agent for diabetes mellitus Type II. We used microwave heating successfully to improve reactions in four of six steps and obtain quicker and higher yields. In addition, all intermediates were isolated in good yields with crystallizations only and did not require chromatographic separations.

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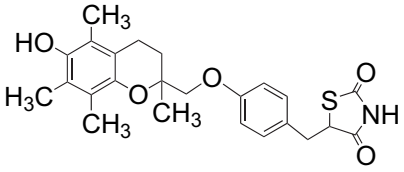
1. Introduction

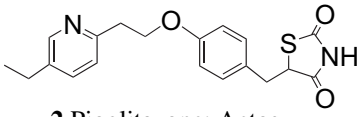
Diabetes mellitus is a complex, chronic, and progressive disease that can eventually adversely affect the functioning of the kidneys, eyes, and nervous and vascular systems. According to the WHO (World Health Organization), at least 170 million people had diabetes in 2006, and most, especially in developed countries, had non-insulin-dependent diabetes mellitus (NIDDM), or more commonly known as diabetes mellitus type II.

Members of the thiazolidinedione drug class,[1] troglitazone(**1**), pioglitazone (**2**), and rosiglitazone (**3**) are well-known as antihyperglycemic drugs used for the treatment of diabetes mellitus type II.[2] (Fig. 1) Rosiglitazone (**3**), known as Avandia by GlaxoSmithKline, is one of the most potent drugs in this class.[3] Although already prevalent throughout the world, it is estimated that currently, at least a third of all cases of NIDDM remain undiagnosed. Moreover, hyperglycemia is increasingly implicated in other metabolic disorders, such as hypertension, atherosclerosis, and obesity. Therefore, hyperglycemia represents an important target for medicinal chemical intervention.[4,5] Apart from its effect on insulin resistance, thiazolidinedione appears to have an *anti*-inflammatory effect.[6] Recent research has suggested that rosiglitazone may also be of benefit to a subset of patients with Alzheimer's disease.[7] The medication may also be effective in the treatment of mild to moderate ulcerative colitis, due to its *anti*-inflammatory properties as a PPAR (peroxisome proliferator-activated receptor) ligand.[8] Recent studies showed that rosiglitazone can be used for the treatment of acute pancreatitis and pancreatitis-associated lung injury.[9]

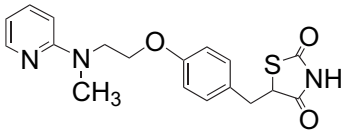
Meanwhile, microwave assisted organic synthesis is a rapidly growing field in organic chemistry.[10] The introduction of dedicated equipments has a large impact on the further development of this



1 Troglitazone: Rezulin (Noscal)



2 Pioglitazone: Actos



3 Rosiglitazone: Avandia

Figure 1. Antihyperglycemic drugs of the thiazolidinedione drug class, troglitazone(**1**), pioglitazone (**2**) and rosiglitazone (**3**).

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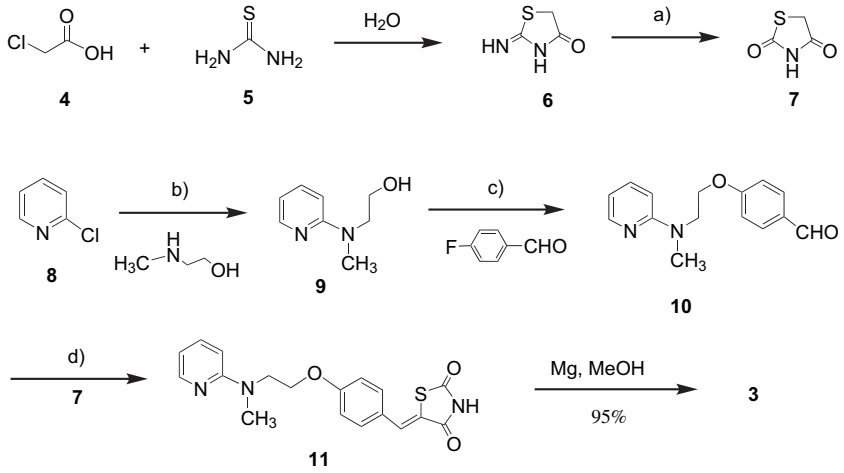


Scheme 1. Synthesis of rosiglitazone (**3**). Conditions and results from (a) to (d) were shown in Table 1.

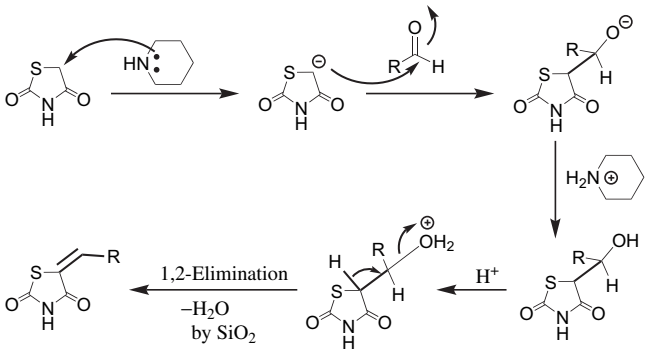
relatively young research field.[11] The study of microwave effects on a molecular level is very interesting and we reported benefits of microwaves in the syntheses of glycopeptides,[12,13] controlling the reaction pathway for glycosylations[14] and glycosylations at low temperatures.[15] On the other hand, making reaction times shorter and expanding the reaction range offered by microwave assisted organic synthesis are suited to the increased demands of industry. In particular the pharmaceutical industry requires the production of a higher number of novel chemical entities, which requires chemists to employ a number of resources to reduce the time for the production of compounds. Microwave radiation provides an alternate to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. In an attempt to develop cost effective and environmentally friendly clean chemistries and in continuation of our research on microwave assisted organic synthesis,[16] synthesis of bioactive heterocycles,[17–19] we are reporting microwave assisted total synthesis of rosiglitazone.

2. Results and discussion

The literature route[20] starts with the synthesis of thiazolidine-2,4-dione (**7**), which is a very important intermediate in the synthesis of glitazones (Scheme 1, Table 1). Monochloroacetic acid (**4**) was treated with thiourea (**5**) in water medium for 1 h at rt and the resulting 2-imino-thiazolidin-4-one (**6**) was successively irradiated with microwave at 140 °C for 10 min to give thiazolidine-2,4-dione (**7**) in 90% yield. The same reaction carried out by conventional heating at 140 °C for 10 min in a sealed tube proceed only a trace amount and required 15 h at 100 °C with yield of only 82%. In the case of the reaction carried out at 100 °C by microwave heating, it required similar reaction time with the case of the conventional heating to yield **7**. Therefore, an advantage of using microwave in this reaction might be just an availability of higher temperature quickly and efficiently. Meanwhile, 2-Chloropyridine (**8**) was condensed with 2-(*N*-methylamino)ethanol without solvent under microwave irradiation to give 2-(Methyl-pyridin-2-ylamino)ethanol (**9**). The reaction was completed at 140 °C in 20 min and isolated (**9**) as pale yellow oil without any side product in 92% yield. The same reaction carried out by conventional method at 140 °C for 20 min formed only 10% of the product (judged by TLC), and required 15 h at 140 °C to be yielded in 85%. In addition, the resulting product was dark brown impure oil, which required high vacuum distillation or column purification. 2-(Methyl-pyridin-2-ylamino)ethanol (**9**) was then coupled with *p*-fluoro benzaldehyde in aqueous toluene with tetrabutylammonium hydrogen sulfate (TBAHS) as a phase-transfer catalysis under microwave heating at 85 °C in 20 min to give 4-[2-(Methyl-pyridin-2-ylamino)ethoxy]-benzaldehyde (**10**) in 90% yield. The same reaction carried out by conventional heating under identical condition did not preceded at all in 20 min and only partially converted even after 15 h. The conventional method described the use of NaH at 80 °C, which is dangerous to handle and results impure product, but the aldehyde (**10**) synthesized by microwave method was able to use directly in the next stage without further purification. Knoevenagel condensation of aldehyde (**10**) with thiazolidine-2,4-dione (**7**) was carried out in a toluene medium in the presence of catalytic amounts of piperidine and acetic acid. Silica gel was used to absorb the water eliminated during the reaction.[21] The reaction was completed in 10 min at 130 °C with 93% yield. To confirm the role of silica gel, the reaction was carried out without the use of silica gel resulted incomplete reaction. The probable mechanism of Knoevengel condensation is shown in Scheme 2. The reaction by conventional method under the same conditions with the case of using microwave did not go on at all but required 15 h with the azeotropic removal of water molecule using the Dean–stark apparatus, and

Table 1
Conditions for Scheme 1. Comparison of the cases of using microwave and conventional method for heating

Reaction	By microwave heating			By conventional heating		
	Conditions	Time	Yield %	Conditions	Time	Yield %
(a)	H_2O 140 °C	10 min	90	H_2O 100 °C	12 h	82
(b)	Solvent free 140 °C	20 min	92	Solvent free 140 °C	15 h	85
(c)	KOH, water, toluene, TBAHS, 85 °C	20 min	90	DMF, NaH 80 °C	8 h	80
(d)	Toluene, piperidine, CH_3COOH, SiO_2, 130 °C	10 min	93	Toluene, piperidine, CH_3COOH, reflux	15 h	85



Scheme 2. Probable mechanism of Knoevenagel condensation in presence of silica gel.

resulted in lower yield and poor quality due to heating for a long time. The reduction of alkene (**11**) was carried out using magnesium metal in methanol at rt to give rosiglitazone (**3**) in 95% yield.

3. Conclusion

In conclusion, we have developed a simple, efficient, cost effective, high yielding, and environmentally friendly total synthesis of rosiglitazone utilizing microwave irradiation as a developed process synthesis of rosiglitazone. We should note here that all intermediates synthesized by aid of microwave heating were not required either high vacuum distillation or column purification. In addition, this is a universal method for syntheses of other members of the thiazolidinedione drug class by coupling suitable aldehydes with a common key intermediate thiazolidine-2,4-dione (**7**). Based on this result, we plan to prepare a thiazolidinedione library with the development of a new microwave assisted synthesizer and the results will be reported in due course.

4. Experimental

4.1. General

All the microwave irradiation experiments were performed in a CEM Discover microwave system and reaction temperatures were monitored by an equipped IR sensor. Chemical reagents and solvents were purchased from Wako Pure Chemical Industries, Ltd. (Japan), Nacalai tesque, Inc. (Japan), Tokyo Kasei (Japan) or Sigma–Aldrich Chemical Co. (USA) and used as supplied unless otherwise stated. Reactions were monitored by TLC, which was performed with 0.25 mm precoated silica gel 60 F_{254} on glass from Merck (Darmstadt, Germany). Compounds were detected under a black-light (UV_{254}). Silica gel N60 (40–50 nm) from Kanto Chemical (Tokyo, Japan) was used for silica gel chromatography. Melting points were determined on an ASONE ATM-01 and are uncorrected. ^{1}H NMR spectra were routinely recorded at 400 MHz on a BRUKER AVANCE 400 spectrometer at 300 K, and chemical shifts were expressed in parts per million downfield shift from tetramethylsilane (δ 0.00 ppm). ^{13}C NMR spectra were routinely recorded at 100 MHz on a BRUKER AVANCE 400 spectrometer at 300 K and. Chemical shifts were expressed in parts per million downfield shift from internal tetramethylsilane (δ 0.00 ppm). Infrared (IR) spectra were recorded on a Shimadzu 8300 IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument.

4.2. Thiazolidine-2,4-dione (7)[20]

A mixture of monochloroacetic acid (**4**, 1.03 g, 10.9 mmol) and thiourea (**5**, 829 mg, 10.9 mmol) in water (2 ml) was introduced into a CEM Discover microwave reaction vessel equipped with a magnetic stirrer. The vessel was sealed and the reaction mixture was stirred for 1 h at rt, successively irradiated by 250 W microwave for 5 min at 140 °C and performed twice successively, cooled to rt and further stirred for 1 h. The formed solid was filtered and recrystallized from hot water to yield **7** (1.15 g, 90%).

Mp 124–125 °C (lit.[20] mp 125 °C); ^{1}H NMR ($CDCl_3$): δ 4.01 (2H, s, CH_2), 12.11 (1H, br s, N*H*); ^{13}C NMR ($CDCl_3$): δ 35.5, 171.1, 171.6; IR (KBr pellet, cm^{-1}): ν 3118, 2814, 1738, 1667, 1388; Anal. Calcd for $C_3H_3NO_2S$: C, 30.76; H, 2.58; N, 11.96%. Found: C, 30.61; H, 2.50; N, 11.88%.

4.3. 2-(Methyl-pyridin-2-ylamino)ethanol (9)[1]

A mixture of 2-chloropyridine (**8**, 506 mg, 4.46 mmol) and 2-(*N*-methylamino)ethanol (673 mg, 8.96 mmol) was introduced into a CEM discover vessel equipped with a magnetic stirrer. The vessel was sealed and the reaction mixture was irradiated by 300 W microwave for 10 min at 140 °C twice successively. The completion of the reaction was monitored by TLC (toluene–ethyl acetate, 1:1). The reaction mass was cooled to rt, diluted with 2 ml water, and extracted into 10 ml ethyl acetate twice. The combined ethyl acetate layer was washed with water, saturated brine, dried over anhyd Na_2SO_4 and concentrated in vacuo to give **9** (621 mg, 92%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ 3.05 (3H, s, NC*H*$_3$), 3.70 (2H, t, J=5.2 Hz, C*H*$_2$CH$_2$), 3.84 (2H, t, J=5.2 Hz, CH$_2$C*H*$_2$), 5.29 (1H, br s, O*H*, exchangeable with D_2O), 6.52–6.58 (2H, m, Ar*H*), 7.44–7.49 (1H, m, Ar*H*), 8.39 (1H, d, J=4.2 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 37.6, 49.7, 66.4, 111.5, 114.8, 137.4, 147.8, 158.2; IR (KBr pellet, cm^{-1}): ν 3069, 2961,1764, 1667, 1485; Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41%. Found: C, 63.20; H, 7.85; N, 18.33%.

4.4. 4-[2-(Methyl-pyridin-2-ylamino)ethoxy]-benzaldehyde (10)[1]

A mixture of **9** (512 mg, 3.36 mmol), 4-fluorobenzaldehyde (422 mg, 3.40 mmol), KOH powder (565 mg, 10.08 mmol), and TBAHS (114 mg, 0.336 mmol) in water (0.5 ml) and toluene (2 ml) was introduced into a CEM Discover microwave vessel equipped with a magnetic stirrer. The vessel was sealed and the mixture was irradiated by microwave for 20 min at 85 °C. The completion of the reaction was monitored by TLC (toluene–ethyl acetate, 1:1). The reaction mass was cooled and diluted with 5 ml water and extracted into 25 ml toluene twice. The combined toluene layer was washed with water, dried over anhyd Na_2SO_4, and concentrated in vacuo to give **10** (778 mg, 90%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ 3.05 (3H, s, 3H, NC*H*$_3$), 4.01 (2H, t, J=5.6 Hz, C*H*$_2$CH$_2$), 4.27 (2H, t, J=5.6 Hz, CH$_2$C*H*$_2$), 6.52–6.58 (2H, m, Ar*H*), 6.99 (2H, d, J=8.6 Hz, Ar*H*), 7.45 (1H, m, Ar*H*), 7.80 (2H, d, J=8.6 Hz, Ar*H*), 8.15 (1H, d, J=4.0 Hz, Ar*H*), 9.83 (1H, s, C*H*O, exchanges with D_2O); ^{13}C NMR ($CDCl_3$): δ 37.3, 48.6, 66.0, 105.1, 111.3, 114.1, 129.2, 131.3, 136.5, 147.0, 157.3, 163.0, 190.1; Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%. Found: C, 70.20; H, 6.25; N, 10.96%.

4.5. (*Z*)-5-{4-[2-(Methyl-pyridin-2-ylamino)ethoxy]-benzylidene}thiazolidine-2,4-dione (11)[1]

A mixture of **10** (504 mg, 1.97 mmol) and **7** (243 mg, 2.07 mmol) in toluene (1 ml) containing piperidine (cat.), acetic acid (cat.), and silica gel (0.1 g) were introduced into a CEM microwave vessel equipped with a magnetic stirrer. The vessel was sealed and the mixture was irradiated by microwave for 20 min at 130 °C. The completion of the reaction was monitored by TLC. The reaction mass was cooled, diluted with 2 ml water, and further cooled to 5–10 °C under stirring. The solid formed was filtered and dissolved in hot methanol (5 ml), and insolubles were removed by filtration. Methanol was removed in vacuo to give **11** (649 mg, 93%) as yellow solid.

Mp 197–198 °C (lit.[1] mp 196–198 °C); ^{1}H NMR (d_6-DMSO): δ 3.04 (s, 3H, NCH_3), 3.92 (2H, t, J=5.7 Hz, CH_2CH$_2$), 4.23 (2H, t, J=5.7 Hz, CH$_2$CH_2), 6.56 (1H, m, ArH), 6.63 (1H, d, J=8.4 Hz, ArH), 7.12 (2H, d, J=8.4 Hz, ArH), 7.49–7.55 (3H, m, ArH), 7.82 (1H, s, C$_6$H$_4$CH=C), 8.09 (1H, d, J=4.8 Hz, ArH), 12.46 (1H, br s, NH, exchanges with D$_2$O); ^{13}C NMR (DMSO-d_6): δ 37.0, 48.3, 65.7, 105.7, 111.5, 115.3, 120.3, 125.5, 131.7, 132.0, 137.2, 147.4, 157.9, 160.1, 167.4, 167.9; Anal. Calcd for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82%. Found: C, 60.72; H, 4.80; N, 11.75%.

4.6. 5-{4-[2-(Methyl-pyridin-2-ylamino)ethoxy]benzyl}-thiazolidine-2,4-dione; rosiglitazone (3)[1]

To a stirred suspension of alkene **11** (495 mg, 1.39 mmol) in methanol (10 mL) were added magnesium turnings (20 mg) and a pinch of iodine at rt, and the mixture was stirred and warmed to initiate the reaction. Magnesium (50 mg) was added portion wise for 30 min. On completion of the addition, the reaction mixture was stirred for 3 h at rt and quenched on ice water (10 mL). The pH was adjusted to 7.0–7.5 using 1 M hydrochloric acid and the mixture was extracted with dichloromethane (10 ml) twice. The combined organic extracts were washed with water (10 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was crystallized from boiling methanol to give **3** (470 mg, 95%) as a white solid.

Mp 154–155 °C (lit.[1] mp 153–155 °C); ^{1}H NMR (DMSO-d_6): δ 3.05 (1H, dd, J=9.2, 14.0 Hz, C$_6$H$_4$CH_2CH), 3.09 (3H, s, NCH_3), 3.28 (1H, dd, J=3.6, and 14.0 Hz, C$_6$H$_4$CH_2CH), 3.92 (2H, t, J=5.6 Hz, CH_2CH$_2$), 4.20 (2H, t, J=5.6 Hz, CH$_2$CH_2), 4.88 (1H, dd, J=4.2, 9.2 Hz, C$_6$H$_4$CH$_2$CH), 6.55–6.80 (2H, m, ArH), 6.85 (2H, d, J=8.4 Hz, ArH), 7.18 (2H, d, J=8.4 Hz, ArH), 7.49 (1H, m, ArH), 8.05 (1H, d, J=4.8 Hz, ArH), 12.05 (1H, br s, NH, exchanges with D$_2$O); ^{13}C NMR (DMSO-d_6): 37.1, 37.2, 48.9, 53.1, 65.5, 105.3, 111.1, 114.0, 127.2, 129.7, 136.8, 146.9, 157.5, 157.6, 170.6, 174.4; Anal. Calcd for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.57%. Found: C, 60.40; H, 5.29; N, 11.50%.

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