Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 3439–3440

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A SHORT SYNTHESIS OF TROGLITAZONE: AN ANTIDIABETIC DRUG FOR TREATING INSULIN RESISTANCE

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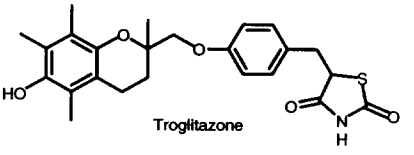
Received 2 August 1999; accepted 3 November 1999

Abstract: Troglitazone was obtained in 5 steps from 4-bromo-1,1-dimethoxy-3-methylbut-2-ene with an overall yield of 7.5%. The formation of the chromane ring was achieved by condensing an unsaturated acetal with trimethylhydroquinone in the presence of bis(trifluoromethylsulfonyl)imide.

Type 2 (non-insulin-dependent) diabetes mellitus affect 3-6% of adults in most industrialised countries and account for over 80 % of all cases of diabetes.[1] Type 2 diabetes develop very gradually over years, because of progressive debilitating defects in both the secretion and action of insulin. Insulin, a peptide hormone produced by β-cells of the pancreatic islets of Langerhans,[2] is the main hormone controlling glucose metabolism. In the early stages of diabetes, the body fails to respond adequately to insulin and the person becomes " insulin resistant ". The search for new agents which can improve the action of insulin is currently led by thiazolidinediones of which troglitazone received approval from FDA in the US in 1997. This compound has a very potent lipid peroxide-lowering activity and caused no adverse effects in preclinical and clinical studies. Troglitazone was first synthetized in 1982 in 8 steps from trimethylhydroquinone and *p*-nitrophenol.[3,4]



Troglitazone

Here, we would like to report the synthesis of troglitazone in 5 steps from bromoacetal **1**[5] and trimethylhydroquinone (TMHQ) **4**.

Reaction of bromoacetal **1** with *p*-hydroxybenzaldehyde **2** (K_2CO_3, NaI) produced unsaturated ether **3**. Compound **3** may reacted with trimethylhydroquinone **4** (TMHQ) in acidic conditions to lead to a 2,2-disubstituted chromene which will be the precursor of troglitazone. Different acids were tested such as $ZnCl_2$, *p*-toluenesulfonic acid, HCl, H_2SO_4, $SnCl_4$ and bis(trifluoromethylsulfonyl)imide (TFSI-H). The best

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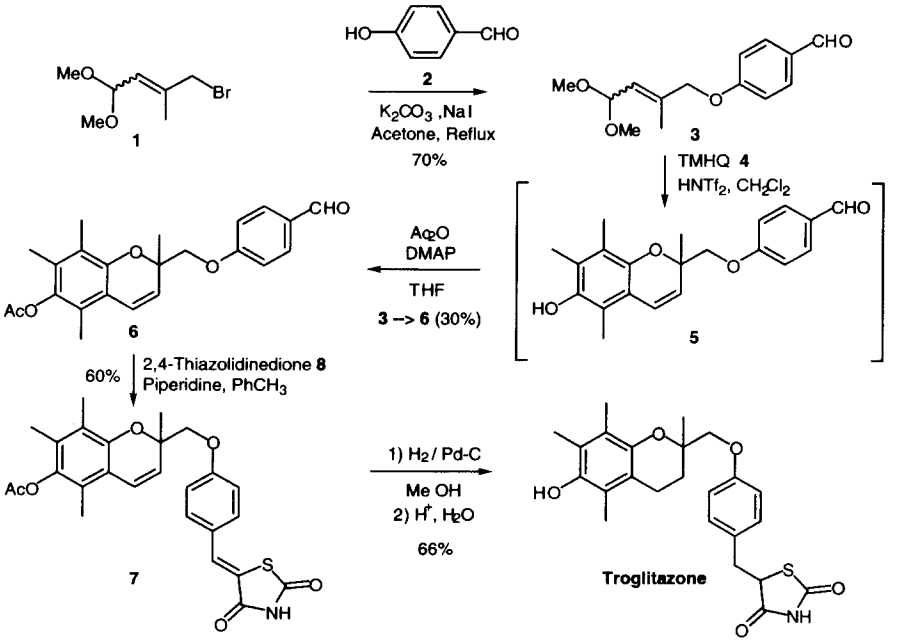
0960-894X/99/$ - see front matter
PII: S0960-894X(99)00630-7

yield of the unstable chromene **5** was obtained when TFSI-H was used (1 equiv of TFSI-H, -78 °C; then -10 °C for 1.5 h). Chromene **5** was not purified but directly acetylated (Ac_2O, 4-dimethylaminopyridine) to produce the acetyl chromene **6** with an overall yield of 30% from acetal **3**. The Knoevenagel condensation of chromene **6** with 2,4-thiazolidinedione, in toluene in the presence of piperidine (0.2 equiv) afforded thiazolidine **7** (60%). After hydrogenation of **7** (H_2/Pd-C, MeOH) and hydrolysis (AcOH/HCl/H_2O: 3/1/1 in MeOH), troglitazone was isolated in 66% yield. Troglitazone was obtained in 5 steps from bromoacetal **1** with an overall yield of 7.5%.

Scheme: Synthesis of troglitazone



Acknowledgements: We thank Rhône-Poulenc Industrialisation for financial support.

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2 - DeFronzo, R. A.; Bonadonna R. C.; Ferrannini, E. *Diabetes Care* **1992**, *15*, 318.

3 - Aizawa, Y.; Kanai, T., Fujita, T.; Hirokoshi, H.; Yoshioka, T. *Heterocycles* **1991**, *32*, 285.

4 - Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K., Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421 and references therein.

5 - Compound **1** was obtained from Rhône-Poulenc. It can also be prepared by treatment of diene **9** with bromine in DMF, followed by the addition of methanol.