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An efficient approach to the key intermediate of rosuvastatin

Abstract: An efficient synthetic approach to the synthesis of the 5-pyrimidinecarbaldehyde **2**, which is the key intermediate of rosuvastatin, involves the aerobic oxidation of the 5-pyrimidinemethanol **1** in the presence of $Co(NO_3)_2$, dimethylglyoxime ($DmgH_2$), and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under mild reaction conditions. The method does not require the use of hazardous or expensive chemicals and is suitable for scale-up.

Keywords: aerobic oxidation; key intermediate; 5-pyrimidinecarbaldehyde; rosuvastatin.

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Introduction

Statins [1, 2] such as atorvastatin [3, 4] and rosuvastatin (Figure 1) [5, 6] are very effective inhibitors [7] of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGR) and are the most powerful lipid-lowering agents in use for people with or at risk of cardiovascular disease [8]. Rosuvastatin [9] has been called a super statin because it appears to reduce low-density lipoprotein (LDL) cholesterol to a greater degree than competitors in its class without additional adverse effects. Rosuvastatin is approved for the treatment of elevated LDL cholesterol (dyslipidemia) [10], total cholesterol (hypercholesterolemia), and/or triglycerides (hypertriglyceridemia).

A well-known key intermediate for the synthesis of rosuvastatin is 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-methanesulfonamido)-5-pyrimidinecarbaldehyde (**2** in Scheme 1). Many methodologies [11–15] for the synthesis of compound **2** have been developed over the past decade (Scheme 1). However, most of them have shortcomings, such as harsh conditions, use of expensive catalysts, long reaction time, unsatisfactory yields, and tedious work-up. We now report a greatly improved synthesis of **2**.

Results and discussion

Oxidation of alcohols to the corresponding aldehydes or ketones is of importance in fundamental research and industrial manufacturing. Developing new and efficient catalytic technologies for the selective aerobic oxidation of alcohols has attracted much attention because of the obvious advantages of dioxygen, such as abundance, low cost, and non-toxicity of the byproduct (H_2O) [16–19]. Our current research interest is focused on the development of the catalytic oxidation system for pharmaceuticals and their intermediates. In this report, we describe an efficient approach, which is based on the work of Jing et al. [20], to the synthesis of **2** by the aerobic oxidation of **1** (Scheme 1). The methodology of Jing was greatly expanded by us by using readily available and inexpensive reagents. To the best of our knowledge, this is the first example of the preparation of **2** by using the three-component catalytic system, namely cobalt nitrate/dimethylglyoxime/2,2,6,6-tetramethylpiperidine-1-oxyl, abbreviated as [$Co(NO_3)_2$/$DmgH_2$/TEMPO]. This methodology is amendable to scaling-up (Scheme 1).

The starting alcohol **1** was derived in high yield from 4-fluorobenzaldehyde as previously described [12]. The aerobic oxidation of **1** with 1.0 mol% of $Co(NO_3)_2$, 1.0 mol% of TEMPO, and 4.0 mol% of $DmgH_2$ proceeded smoothly in

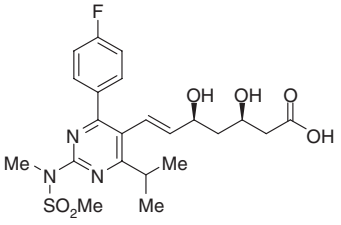
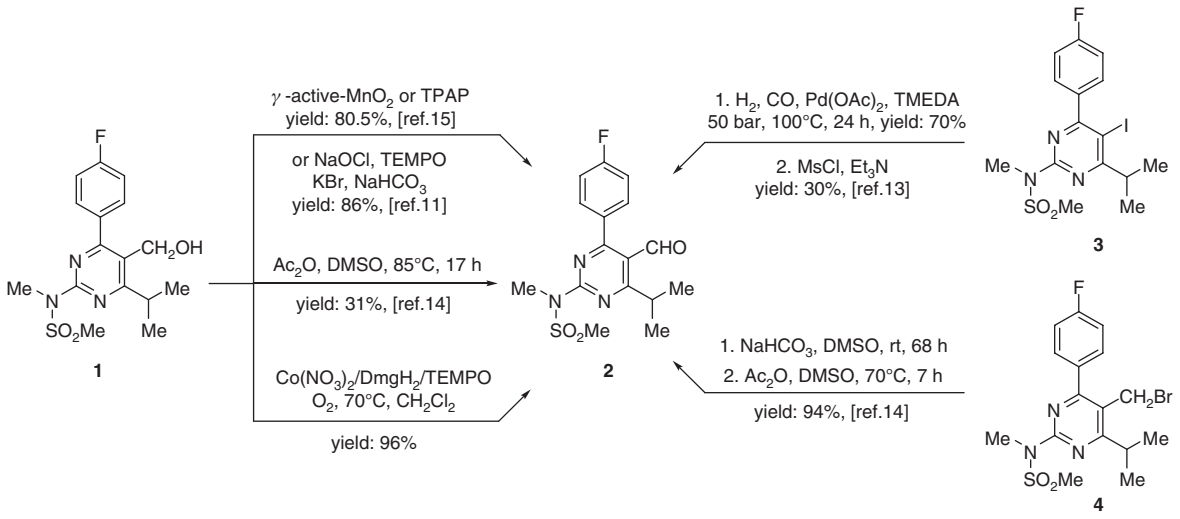


Figure 1 Chemical structure of rosuvastatin.



Scheme 1 Synthesis of 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-methanesulfonamido) -5-pyrimidinecarbaldehyde (**2**).

dichloromethane under 0.4 MPa pressure of O_2 at 70°C for 3 h. The desired product **2** was obtained in 96% yield. The method is suitable for scale-up.

Experimental

General commercially available chemicals were all reagent grade. Melting points (mp) were determined on a Buchi 535 capillary melting apparatus. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Mercury Plus Varian 400 spectrometer. ESI mass spectra were acquired on a Thermo Scientific LCQ spectrometer. IR spectra were determined on a Nicolet NEXUS-470 FT-IR spectrometer in KBr pellets.

Synthesis of 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-methanesulfonamido) -5-pyrimidinemethanol (1)

This compound was obtained as a white solid by using the known procedure described previously [12]; yield 93%; purity 99.5% (HPLC); white solid; mp 131.9–132.8°C {ref. [14], mp 131.5°C (DSC onset) and 133.6°C (DSC peak)}; ^{1}H NMR (DMSO-d_6): δ 1.26 (d, 6H, J = 5.2 Hz), 3.45 (s, 3H), 3.65 (m, 4H), 4.4 (s, 2H), 7.37 (m, 2H), 7.86 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 177.7, 165.5, 164.4, 162.5, 157.8, 134.6, 132.1, 132.0, 122.5, 115.8, 115.6, 56.3, 42.1, 33.7, 31.2, 22.5; MS (ESI): m/z 354.1 ([M+H]$^+$, 100), 355.1 ([M+2]$^+$, 18), 356.6 ([M+3]$^+$, 7), 376.0 ([M+Na]$^+$, 10%); IR: ν 3537, 2935, 1597, 1546, 1510, 1365, 1325, 1228, 1143, 1120, 1001, 952, 854, 812 cm^{-1}.

Synthesis of 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-methanesulfonamido) -5-pyrimidinecarbaldehyde (2)

A 100 mL autoclave reactor, equipped with an efficient mechanical stirrer, was charged with 35.34 g (0.10 mol) of **1**, 0.156 g of TEMPO (1.0 mol%), 0.183 g of $Co(NO_3)_2$ (1.0 mol%), 0.464 g of $DmgH_2$ (4.0 mol%), and 50 mL of dichloromethane. The pressure of O_2 in the sealed reactor was kept under 0.4 MPa for 3 h. During this period of time the atmosphere inside the reactor was refilled with fresh oxygen three times and the mixture was stirred and heated to 70°C. Then the mixture was cooled to room temperature and treated with dichloromethane (100 mL). Then the suspension was filtered and the clear filtrate was washed with water (150 mL) and a saturated aqueous solution of sodium chloride (100 mL). Concentration under reduced pressure followed by trituration of the residue with cyclohexane gave the desired compound **2** (yield 33.7 g, 96%) as a white solid; purity 99% (HPLC); mp 177.5–178.9°C {ref. [14], mp 178.2°C (DSC onset) and 179.1°C (DSC peak)}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J = 5.2 Hz), 3.62 (s, 3H), 3.61 (s, 3H), 4.02 (m, 1H), 7.21 (m, 2H), 7.64 (m, 2H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 190.5, 179.1, 169.8, 165.5, 163.5, 158.8, 132.7, 132.6, 119.6, 116.1, 115.90, 42.5, 33.1, 32.1, 21.7; MS (ESI): m/z 352.2 ([M+H]$^+$, 100), 353.2 ([M+2]$^+$, 18), 354.1 ([M+3]$^+$, 5%); IR: ν 2976, 1685, 1600, 1533, 1508, 1444, 1315, 1230, 1157, 1126, 956, 902, 854, 808, 779 cm^{-1}.

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