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New and convenient approach for synthesis of metconazole

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Abstract In terms of environmental and food supply protection, development of green, efficient, and less toxic pesticides is of great importance and in continuous demand. Metconazole, a triazole antiseptic, possesses such advantages, being environmentally friendly and high efficiency with broad-spectrum activity against bacteria and fungi. However, previously reported synthetic routes for metconazole have many disadvantages, for example, requiring multiple steps, being complicated, and suffering from high cost. We report herein a new, convenient, and high-yield four-step (aldol condensation, dimethylation, hydrogenation, and one-pot triazolation) synthesis for metconazole with relatively low cost.

Keywords Metconazole · Antiseptic · Aldol condensation · Hydrogenation · One-pot triazolation

Introduction

Since the introduction of pesticides, global food production has increased by one-third. Antiseptics, as a type of pesticide, have played an important role in this achievement. However, chemoresistance has increased rapidly due to the long-term use of early antiseptics. Initially, until the 1970s, this problem was solved by Bayer via the development of the first triazole antiseptic, triadimefon [1], which was found to possess low toxicity, high efficiency, and broad-spectrum action against bacteria and fungi. Since this pioneering work, considerable attention has been directed towards development of new triazole antiseptics. Among the numerous triazole

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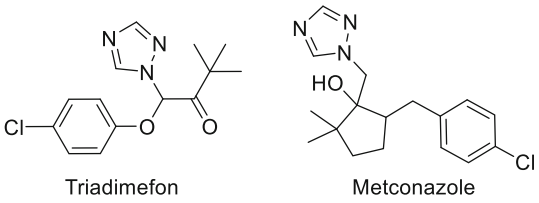


Fig. 1 Triazole antiseptics

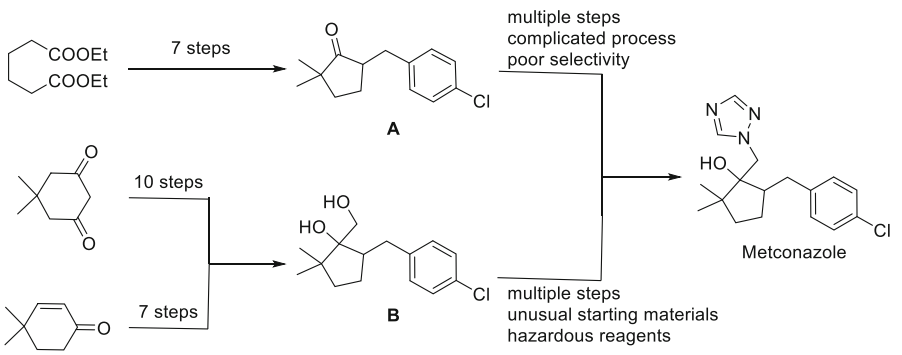
antiseptics, metconazole (Fig. 1), developed by Kureha in the 1990s, has become one of the most widely used pesticides [2]. Over the past few decades, more than 200 patents related to utilization and synthesis of metconazole have been approved.

According to differences in key intermediates, there are two major synthetic routes for metconazole (Scheme 1). 5-(4-Chlorobenzyl)-2, 2-dimethylcyclopentone (**A**) is recognized as one of these key intermediates. In these methods, diethyl adipate is used as starting material. Multiple steps and a complicated synthetic process are required to obtain the target molecule. 5-(4-Chlorobenzyl)-1-hydroxylmethyl-2,2-dimethylcyclopentol (**B**) is recognized as another key intermediate; however, unusual starting materials and hazardous reagents are used in routes that utilize this intermediate, and they require even more steps. Therefore, development of new and convenient routes for synthesis of metconazole is still highly desired.

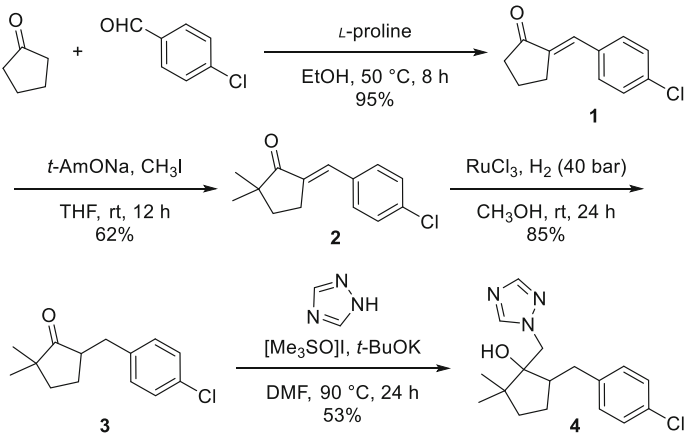
We describe herein a new, simple, short, and economical route for synthesis of metconazole (Scheme 2). Common reactions and readily available reagents are used to obtain the desired product in four steps and 27% total yield. Additionally, the possibility of asymmetric synthesis of metconazole is greatly enhanced by use of asymmetric hydrogenation technology developed in our laboratory [3–9].

Experimental

Commercially available reagents were used without further purification. ^{1}H nuclear magnetic resonance (NMR) (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Varian Mercury Plus 400 spectrometer.



Scheme 1 The two synthetic routes for metconazole



Scheme 2 Synthesis of metconazole

(*E*)-2-(4-Chlorobenzylidene)cyclopentan-1-one (1)

To a flask containing *p*-chlorobenzaldehyde (1.75 g, 12.4 mmol) and L-proline (1.43 g, 12.4 mmol, 1.0 eq) in EtOH (50 mL) was added cyclopentone (1.15 g, 13.6 mmol, 1.1 eq). The reaction mixture was stirred at 50 °C for 8 h. After reaction completion, the solvent was evaporated and toluene (50 mL) was added. The suspension was filtrated to give L-proline (1.36 g, 95% recovery), and the filtrate was evaporated to give crude product **1** as brown solid (2.60 g, 93% purity, 94% yield), which was used directly in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.46 (d, J = 8.6 Hz, 2H, C_6H_4), 7.38 (d, J = 8.6 Hz, 2H, C_6H_4), 7.33 (t, J = 2.8 Hz, 1H, C_6H_4CHC), 2.94 (td, J = 8.0 Hz, 2.8 Hz, 2H, CCH_2CH_2), 2.41 (t, J = 7.9 Hz, 2H, $COCH_2CH_2$), 2.08–2.01 (m, 2H, $CH_2CH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 208.1 (CO), 136.7 ($COC{=}CH(CH_2)$), 135.4 ($C_6H_4CH{=}C$), 134.2 (C_6H_4), 131.8 (C_6H_4), 131.1 (C_6H_4), 129.1 (C_6H_4), 37.9 (CCH_2CH_2), 29.5 ($COCH_2CH_2$), 20.3 ($CH_2CH_2CH_2$).

(*E*)-5-(4-Chlorobenzylidene)-2,2-dimethylcyclopentan-1-one (2)

(*E*)-2-(4-Chlorobenzylidene)cyclopentan-1-one (**1**, 1.00 g, 93% purity, 4.5 mmol) and *t*-AmONa (0.99 g, 9.0 mmol, 2.0 eq) were added to a 50-mL dried flask followed by addition of tetrahydrofuran (THF, 20 mL). After the mixture had been stirred for 0.5 h at 25 °C, CH_3I (2.55 g, 18.0 mmol, 4.0 eq) was added. The mixture was stirred for 12 h at 25 °C before the reaction completed. The mixture was quenched with water and extracted with ethyl acetate (30 mL × 3). The organic phases were combined, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel using petroleum/ethyl acetate (50:1) as eluent to provide faint-yellow product **2** (0.66 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.56 (d, J = 8.0 Hz, 2H, C_6H_4), 7.46 (d, J = 8.0 Hz, 2H, C_6H_4), 7.43 (t, J = 2.8 Hz, 1H, C_6H_4CHC), 2.94 (td, J = 8.0 Hz, 2.8 Hz, 2H, CCH_2CH_2), 1.94 (t, J = 8.0 Hz, 2H, $C(CH_3)_2CH_2CH_2$), 1.21 (s, 6H, $C(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 211.7 (CO), 136.2 (C_6H_4CH), 135.4 ($COCCH(CH_2)$), 134.4 (C_6H_4), 132.1 (C_6H_4), 131.9 (C_6H_4), 129.2 (C_6H_4), 45.1 ($C(CH_3)_2$), 36.0 (CCH_2CH_2), 26.1 (CH_2CH_2C), 24.1 ($C(CH_3)$).

5-(4-Chlorobenzyl)-2,2-dimethylcyclopentan-1-one (3)

(*E*)-5-(4-Chlorobenzylidene)-2,2-dimethylcyclopentan-1-one (**2**, 0.20 g, 0.85 mmol) and $RuCl_3$ (17.6 mg, 0.085 mmol, 0.1 eq) were placed in a 5-mL tube equipped with a magnetic stirrer bar. This tube was then placed into a nitrogen-filled autoclave. CH_3OH (2 mL) was added to the mixture under nitrogen atmosphere. The autoclave was then closed, purged three times with hydrogen, and finally pressurized to 40 bar. The reaction mixture was stirred for 24 h at 25 °C. After reaction completion, the hydrogen gas was slowly released. After evaporation of the solvent, the mixture was purified by flash chromatography on silica gel using petroleum/ethyl acetate (20:1) as eluent to obtain product **3** as colorless oil (172 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 (d, J = 8.0 Hz, 2H, C_6H_4), 7.09 (d, J = 8.0 Hz, 2H, C_6H_4), 3.09–3.05 (m, 1H, $C_6H_4CH_2$), 2.64–2.59 (m, 1H, $C_6H_4CH_2$), 2.47–2.39 (m, 1H, CH_2CHCO), 1.97–1.94 (m, 1H, CH_2CH_2C), 1.77–1.72 (m, 1H, CH_2CH_2C), 1.66–1.48 (m, 2H, CH_2CH_2CH), 1.08 (s, 3H, $C(CH_3)_2$), 1.06 (s, 3H, $C(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 223.5 (CO), 138.5 (C_6H_4), 132.1 (C_6H_4), 130.7 (C_6H_4), 128.6 (C_6H_4), 50.4 ($C(CH_3)_2$), 45.4 ($COCH(CH_2)_2$), 36.5 ($C_6H_4CH_2CH$), 35.6 (CCH_2CH_2), 25.0 ($CHCH_2CH_2$), 24.8 ($C(CH_3)_2$), 23.7 ($C(CH_3)_2$).

1-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorobenzyl)-2,2-dimethylcyclopentan-1-ol (metconazole, 4)

To a dried 25-mL flask containing 1,2,4-triazole (0.43 g, 6.3 mmol, 1.5 eq) was added trimethylsulfoxonium iodide (1.02 g, 4.6 mmol, 1.1 eq) and *t*-BuOK (1.52 g, 13.5 mmol, 3.2 eq). The solvent dimethylformamide (DMF, 8 mL) was then added, and the reaction mixture was stirred for 1 h at 25 °C. Following this, 5-(4-chlorobenzyl)-2,2-dimethylcyclopentan-1-one **3** (1.0 g, 4.2 mmol) in 2 mL DMF was added, and the mixture was stirred at 90 °C for 24 h. After completion, the mixture was cooled down to room temperature, quenched with water, and extracted with ethyl acetate (15 mL × 3). The organic phases were combined, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel using petroleum/ethyl acetate (3:2) as eluent to give metconazole **4** as colorless solid (0.71 g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (s, 1H, $C_2H_2N_3$), 7.98 (s, 1H, $C_2H_2N_3$), 7.22 (d, J = 8.0 Hz, 2H, C_6H_4), 7.06 (d, J = 8.0 Hz, 2H, C_6H_4), 4.29–4.16 (m, 2H, $C_2H_2N_3CH_2$), 3.63 (s, 1H, OH), 2.50–2.47 (m, 1H, $C_6H_4CH_2$), 2.36–2.32 (m, 2H, $C_6H_4CH_2$ + CH_2CHCH_2C), 1.81–1.62 (m, 2H, CH_2CH_2C),

1.45–1.42 (m, 1H, CH_2CH_2CH), 1.34–1.31 (m, 1H, CH_2CH_2CH), 1.02 (s, 3H, $C(CH_3)$), 0.96 (s, 3H, $C(CH_3)$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 151.8 ($C_2H_2N_3$), 144.5 ($C_2H_2N_3$), 139.9 (C_6H_4), 131.8 (C_6H_4), 130.4 (C_6H_4), 128.6 (C_6H_4), 82.7 ($CHCOH(CH_2)$), 54.1 ($C_2H_2N_3CH_2$), 47.2 ($CH_2C(CH_3)$), 46.6 (CH_2CHCOH), 38.4 ($ClC_6H_4CH_2$), 36.1 ($CHCH_2CH_2$), 27.5 (CH_2CH_2C), 25.4 ($C(CH_3)$), 22.2 ($C(CH_3)$).

Results and discussion

A short synthetic sequence is always beneficial for synthesis of a target molecule. Our newly developed process for synthesis of metconazole requires only four steps (Scheme 2), being shorter than previously reported routes (Scheme 1). Firstly, easily available starting materials, cyclopentone and *p*-chlorobenzaldehyde, are used to synthesize (*E*)-2-(4-chlorobenzylidene)cyclopentan-1-one (**1**) via aldol condensation. Although several methods have been reported for synthesis of intermediate **1** [10–18], the reaction conditions (ultrasound, nano-microsphere or costly reagents) are not suitable for large-scale synthesis. To overcome this problem, the cheap organocatalyst L-proline and commonly used solvent EtOH were applied to obtain the desired α-monosubstituted product **1** with high yield and selectivity. Additionally, the L-proline can be easily recovered and reused without loss of activity. Moreover, the product (*E*)-2-(4-chlorobenzylidene)cyclopentan-1-one (**1**) can be easily separated and directly used without further purification due to the high conversion. Dimethylation of intermediate **1** has only been mentioned in a European patent. The reported procedure uses a flow system under very high reaction temperature, giving unsatisfactory product yield [19]. Conversely, our synthetic route utilizes conventional alkylation. After careful screening of solvents and bases, intermediate (*E*)-5-(4-chlorobenzylidene)-2,2-dimethylcyclopentan-1-one (**2**) could be obtained in moderate yield by using *t*-AmONa as base and THF as solvent. In subsequent hydrogenation reaction, the Pd/C catalyst, which is the most commonly used catalyst for reduction of α,β-unsaturated ketones, showed poor selectivity between alkenyl and carbonyl groups. After testing several other metal catalysts, $RuCl_3$ was found to be the best candidate, giving the desired product **3** with high yield and good selectivity. Using a BiphPHOX-Ir catalyst developed in our laboratory [3–6, 9], asymmetric hydrogenation of α,β-unsaturated ketone **2** was also realized to obtain the chiral ketone **3** in complete yield with excellent enantioselectivity (96% ee). Finally, the key intermediate 5-(4-chlorobenzyl)-2,2-dimethylcyclopentan-1-one (**3**) was transformed into the target molecule via one-pot triazolation instead of the traditional two-step method.

Conclusions

A short and simple synthetic route was developed for preparation of the important antiseptic metconazole. The target compound was obtained in total yield of 27% over four steps. Each step in this pathway is easy to operate and provides

satisfactory yield. After further optimization, this process has potential for use on industrial scale.

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