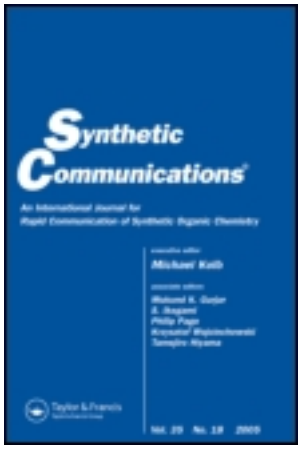

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PRACTICAL PREPARATION OF TRIMETHOPRIM: A CLASSICAL ANTIBACTERIAL AGENT

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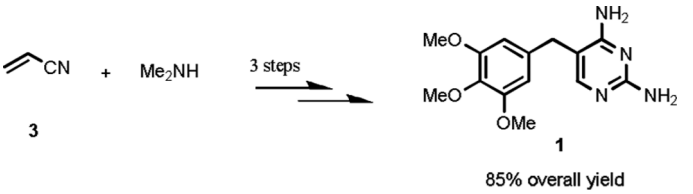
GRAPHICAL ABSTRACT



Abstract *An efficient, simple, and mild preparation of the classical antibacterial agent trimethoprim (**1**) was achieved in 85% overall yield from 3,4,5-trimethoxybenzaldehyde (**2**). First, the addition of propenenitrile (**3**) with dimethylamine almost quantitatively afforded 3-dimethylaminopropanenitrile (**7**). Then, by condensation of **7** with **2** as well as the continuous replacement of 3-dimethylamino group with aniline in situ, the key intermediate 3-anilino-2-(3,4,5-trimethoxybenzyl)propenenitrile (**9**) was obtained in an excellent yield of 91% with a one-pot procedure. Finally, the cyclization of **9** with guanidine nitrate furnished **1** in yields as good as 95% in the presence of the excessive sodium methoxide.*

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Keywords Antibacterial agent; highly effective preparation; trimethoprim; 3,4,5-trimethoxybenzaldehyde

INTRODUCTION

Trimethoprim (**1**) is a classical antibacterial agent that serves as a potent and selective inhibitor of bacterial dihydrofolate reductase. It is used solely, or acts as a potentiator in combination with sylfamethoxazole, to treat a wide range of bacterial infections in humans and poultry.[1] In recent decades, antibacterial agent

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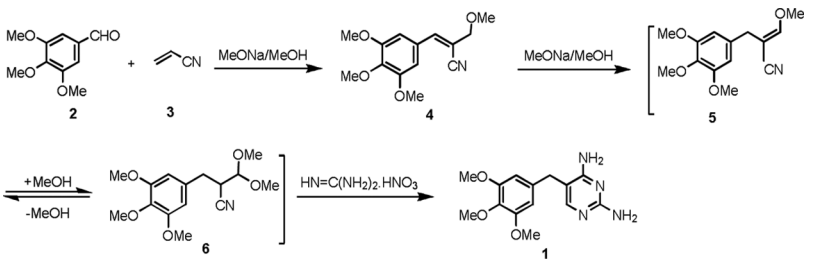
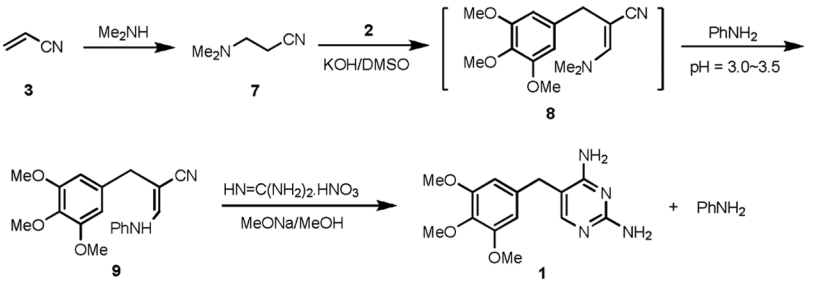


Scheme 1. Route to **1**.

1 has been embodied in the pharmacopoeias of many countries in the world. In China, more than 3,000 tons of **1** were output in 2010 for the global market, which shows an increasing demand because of **1**'s antimicrobial and antimalarial applications. So far, antibacterial agent **1** has been regarded as the most mature dihydrofolate reductase inhibitor in clinical application.

Based on the previously known synthesis involving a base-catalyzed 1,3-prototropic rearrangement to form enol ether/acetal intermediates (**5**/**6**) along the route shown in Scheme 1,[1–3] an improved manufacturing process of **1** was carried out with an unsatisfactory yield of 65% or less from 3,4,5-trimethoxybenzaldehyde (**2**), a relatively expensive material.[4] Because of the limitation of the reactivity of **5** and **6** in the manufacturing process, it is very difficult to further increase the yield of **1**. The previous patents, which we named the "Cresswell approach,"[5,6] displayed a superior synthesis of **1** using a powerful cyclization of 3-anilino-2-(3,4,5-trimethoxybenzyl)-propenenitrile (**9**) and guanidine.

In pursuit of greater yield and lower cost, we re-examined the Cresswell approach to develop a practical preparation of **1** (Scheme 2). In this report, we describe a highly efficient preparation of **1**, taking advantage of the crucial cyclization of **9** and guanidine. By means of dimethylamine and aniline as assistant reagents, the key intermediate **9** was effectively prepared via the condensation of 3-dimethylaminopropanenitrile (**7**) and **2**, followed by substituting 3-dimethylamino group with aniline in situ with a convenient one-pot procedure. Besides, the addition reaction of propenenitrile (**3**) and dimethylamine was achieved to afford **7** in nearly quantitative yield.



Scheme 2. Practical route to preparing **1**.

RESULTS AND DISCUSSION

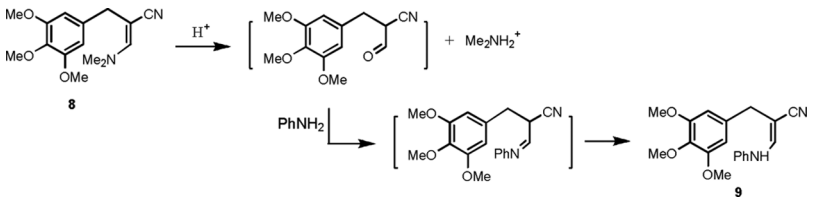
In comparison with the excellent cyclization capability of **9** with guanidine,[5,6] we noticed that the analog 3-dimethylamino-2-(3,4,5-trimethoxy-benzyl)propenenitrile (**8**) does not possess a corresponding cyclization capability because of its aliphatic amino-substituted pattern. It has been proved that the condensation of **8** with guanidine was extremely sluggish to give **1**.[1,6] Therefore, we had to exclude **8** as a proper cyclization substrate to directly prepare **1**. Further, direct formation of **9** from 3-anilinopropanenitrile and **2** requires stoichiometric potassium *tert*-butoxide as a condensing agent,[5,6] leading to an unsatisfactory yield and a relatively high cost. In addition, the reported preparation of 3-anilinopropanenitrile was considered unpractical and uneconomical owing to the relatively poor yield[7] or the use of expensive organometallic catalyst.[8] Thus, the Cresswell approach prompted us to investigate its improvement.

The Cresswell approach[5,6] has clearly revealed that 3-morpholinopropanenitrile is absolutely qualified for the condensation with the aldehyde **2** in excellent yield. We reasonably presumed that aliphatic amino-3-substituted propanenitrile **7**, as the most inexpensive alternative to 3-morpholinopropanenitrile, should similarly possess a prominent capability to form **8** in the condensation of **7** with **2**. Moreover, we wished to efficiently perform an acid-mediated substitution of aniline for the dimethylamino group of **8** in situ to achieve the key intermediate **9**. Thus, it would lead to accomplishing a one-pot procedure for synthesis of **9** using quite inexpensive dimethylamine as an assistant reagent.

Compared with Scheme 1, antibacterial agent **1** was prepared in an overall yield as high as 85% from **2** with the improved synthesis (Scheme 2).Because of the intrinsically high reactivity for the addition reaction of **3** and dimethylamine,[9] we could readily perform this Michael addition, preparing **7** in aqueous media with nearly quantitative yield. At the reaction end, sodium hydroxide should be added to further promote its thorough completion and simultaneously to partition the solution into two phases. Practically, it is unnecessary to employ *N*-donor ligand[10] or $InCl_3$[11] as catalyst in the addition reaction.

In the presence of the catalytic amount of potassium hydroxide and methanol, the aldehyde **2** reacted entirely with an excess of **7** via a base-catalyzed 1,3-prototropic isomerization to form **8** in the solvent dimethylsulfoxide (DMSO). Subsequently, after adjusting pH to 3.0–3.5 with inorganic acid for the reaction solution, an acid-mediated substitution of aniline for the dimethylamino group in situ was smoothly administrated to afford **9** in an isolated yield of 91% with a one-pot procedure. The use of the catalytic amount of potassium hydroxide would profitably lead to an economical consumption of inorganic acid. Here, an intrinsic hydrolysis–condensation sequence (Scheme 3) was implicated in the substitution. In the course of the substitution, the hydrolysis of enamine **8** brought about the steady dimethylammonium ion and the corresponding aldehyde under acidic conditions. Meantime, the aldehyde underwent a condensation with aniline ultimately to result in the insoluble and more stable enamine **9**, which comprises a steadily π–π–p–Π conjugated structure.

An Indian patent reported that enamine **9** could be synthesized in 91% yield from **2** in the presence of the catalysts potassium methoxide and PEG-600 in



Scheme 3. Intrinsic hydrolysis–condensation sequence leading to **9**.

methanol.[12] We attempted to reproduce the process to prepare **9** with a one-pot procedure, but **9** was obtained only in ca. 80–83% yields. Actually, we found that DMSO acts as an important factor to efficiently facilitate the formation of **8**.

Finally, in the presence of the excessive sodium methoxide, the treatment of **9** with guanidine nitrate gave **1** in 95% yield under reflux for 10 h and synchronously released the assistant reagent aniline. Understandably, the solvents and the assistant reagents would be recovered and reused through appropriate separation engineering during large-scale production.

In conclusion, we have accomplished an improved and practical preparation of **1** using dimethylamine and aniline as assistant reagents. The preparation, which features good yield, cost efficiency, convenient manipulation, and better feasibility, will meet the demands in industrial manufacture of this classic drug.

EXPERIMENTAL

Melting points were determined by capillary method without correction. NMR spectra were recorded on Bruker AV400 in $CDCl_3$ or DMSO-d_6 as indicated in parentheses and chemical shifts were expressed in δ ppm relative to tetramethylsilane (TMS). Mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) were carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel plates (HF254), and TLC visualizations were performed with I_2 vapor and ultraviolet (UV) light. All solvents and reagents were obtained from commercial sources and used without further purification.

Preparation of 3-Dimethylaminopropanenitrile (7)[10]

Propenenitrile **3** (53.1 g, 1.0 mol) was added dropwise under vigorous stirring to a 40 mass % aqueous solution of dimethylamine (118.3 g, 1.05 mol) for 5 h to control the temperature within the range of 18–20 °C with an external ice bath, and then the solution was stirred further for 0.5 h. To this solution ca. 30 g solid sodium hydroxide to dissolve the mixture was added for demixing. The top organic layer was separated and distilled to provide **7** as colorless oil. Yield: 96.1 g, 98%; bp 110–113 °C / 29–31 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 2.58 (t, $J = 7.2$ Hz, Hz, 2H, CH_2), 2.45 (t, $J = 7.2$ Hz, 2H, CH_2), 2.24 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 118.7, 54.5, 44.9, 16.2; ESI-MS (m/z): 99.1 ($M + H^+$).

Preparation of 3-Anilino-2-(3,4,5-trimethoxybenzyl)propenenitrile (9)

A mixture of DMSO (400 mL), methanol (40 mL), solid potassium hydroxide (8.3 g, 95% purity, 0.14 mol), and **7** (88.3 g, 0.90 mol) was heated to 35 °C. The solution of 2 (117.7 g, 0.60 mol) in DMSO (100 mL) was slowly added to the mixture, and then the reaction solution was heated to 40–45 °C. After vigorous stirring for 5 h at the same temperature, the solution was cooled to 30 °C and aniline (56.8 g, 0.61 mol) was added. A dilute hydrochloric acid (2 N) was added slowly to the mixture, which was vigorously stirred for 1 h under reflux and properly adjusted to maintain pH 3.0–3.5. Finally, the resulting mixture was cooled to ambient temperature. After the addition of water (200 mL), the mixture was cooled once again to 5 °C. The product was collected by filtration and dried in vacuo to give **9** as a yellowy solid. Yield: 177.1 g, 91%; mp 138–142 °C (lit.[5] mp 132–133 °C). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.63 (s, 1H, =CH), 7.27 (t, $J = 8.0$ Hz, 2H, Ar), 7.19 (d, $J = 8.0$ Hz, 2H, Ar), 6.92 (t, $J = 8.0$ Hz, Hz, 1H, Ar), 6.58 (s, 2H, Ar), 3.77 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ: 153.3, 142.9, 142.0, 136.6, 136.0, 129.7, 121.8, 119.9, 115.6, 106.0, 80.8, 60.5, 56.3, 37.1; ESI-MS (m/z): 325.2 (M $+H^+$), 347.1 (M $+Na^+$), 363.1 (M $+K^+$). HRMS (ESI): calculated for ($C_{19}H_{20}N_2O_3$ $+H^+$), 325.1552; m/z found, 325.1557; calculated for ($C_{19}H_{20}N_2O_3$ $+Na^+$), 347.1372; m/z found, 347.1382; calculated for ($C_{19}H_{20}N_2O_3$ $+K^+$), 363.1111; m/z found, 363.1122.

Preparation of Trimethoprim (1)[1]

Guanidine nitrate (97.7 g, 0.80 mol) was added to a solution of sodium methoxide freshly prepared from clean sodium (24.1 g, 1.05 mol) and methanol (500 mL). The solution was heated to reflux for 0.5 h to free guanidine and then cooled to 30 °C. Subsequently, compound **9** (162.2 g, 0.50 mol) was added to the solution and the mixture was stirred under reflux for 10 h. The solvent methanol (ca. 250 mL) was boiled off and the mixture was cooled to 5 °C. The resulting crystal was collected by filtration, and further concentration of the filtrate gave the second crop of the crystal. The combined product was washed with water (2×300 mL) and cold acetone (2×150 mL) in turn to give **1** as a off-white solid. Yield: 137.8 g, 95%; mp 200–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm), δ: 7.53 (s, 1H, pyrimidine), 6.55 (s, 2H, Ar), 6.10 (s, 2H, NH_2), 5.70 (s, 2H, NH_2), 3.73 (s, 6H, OCH_3), 3.62 (s, 3H, OCH_3), 3.54 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ: 162.63, 162.59, 156.1, 153.2, 136.289, 136.280, 106.323, 106.248, 60.4, 56.3, 33.4; ESI-MS (m/z): 291.1 (M $+H^+$).

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