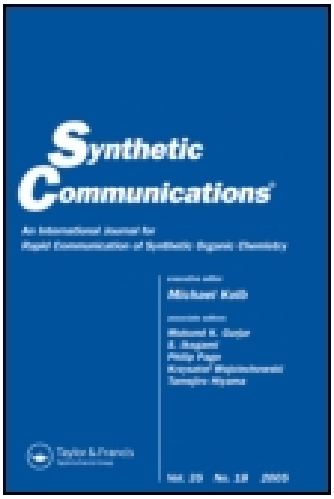

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APPLICATION OF [3 + 2]-CYCLOADDITION IN THE SYNTHESIS OF VALDECOXIB

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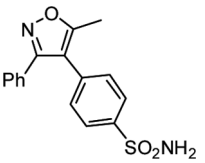
GRAPHICAL ABSTRACT



Valdecoxib **1**

Abstract *A large scale synthesis of valdecoxib* ***1*** *is described. Our work features potential application of [3 + 2]-dipolar cycloaddition involving enamine and in situ–generated nitrile oxide derivatives.*

Keywords Chlorination; cycloaddition; enamine; NSAID; sulfonation

INTRODUCTION

Valdecoxib **1** (Fig. 1) is a nonsteroidal anti-inflammatory drug (NSAID), which acts as an inhibitor of cyclooxygenase-2 (COX-2), although in practice it is used for the treatment of rheumatoid arthritis, osteoarthritis, and dysmenorrhea.[1–3] Several synthetic procedures for valdecoxib **1** are known. Apart from utilizing dipolar cycloaddition, most of the synthetic methods involve either industrially nonviable reagents such as butyl lithium,[4,5] lithium diisopropylamide,[6] diethyl chlorophosphate, and hexamethylphospharamide[7] or commercially unavailable materials,[8] and a few of them suffer from lack of regioselectivity.[7,9]

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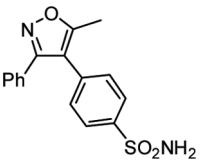


Valdecoxib **1**

Figure 1. Structure of valdecoxib **1**.

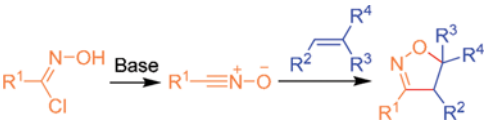


Figure 2. Example of in situ–generated nitrile oxide and its cycloaddition with olefin. (Figure is provided in color online.)

[3 + 2]-Cycloaddition of nitrile oxide with olefinic compounds is of synthetic importance because the derivatives of isoxazoline are versatile intermediates for the synthesis of bifunctional compounds of pharmaceutical relevance.[10] Traditionally, the synthesis of nitrile oxides involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate,[11] alkali hypochlorite,[12] *N*-chlorosuccinamide (NCS) in dimethylformamide followed by base treatment,[13] chloramine-T (CAT),[14] iodobenzene dichloride,[15] 1-chlorobenzotriazole,[16] or mercuric acetate[17] as well as the reaction of nitro compounds with an aryl isocyanate as presented in Fig. 2.[18]

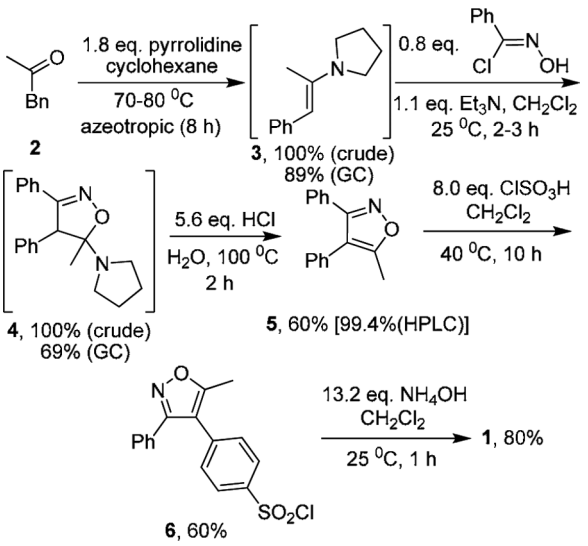
Based on the mechanistic pathway of cycloaddition as shown in Fig. 1 and the reports on the application of enamine as an olefin equivalent in such reactions,[19,20] we designed a novel synthetic route that allows us to access valdecoxib **1** efficiently.

Herein, we report the synthesis of valdecoxib **1** that involves [3 + 2]-dipolar cycloaddition, aromatization, and chlorosulfonation followed by sulfamidation.

RESULTS AND DISCUSSION

Required enamine **3** (olefin equivalent) was synthesized by employing phenylacetone **2** with pyrrolidine in cyclohexane. The Safety of the process was ascertained by conducting calorimetric experiments. Thereafter, enamine **3** was reacted with benzonitrile oxide that was generated in situ from chlorobenzaldoxime[20] to provide diarylisoxazole derivative **5**. Safety concerns about in situ–generated nitrile oxide or its precursor were addressed by conducting reaction calorimetric experiments following the literature protocol.[21] The desired chlorobenzaldoxime was prepared by adopting the reported procedure.[13] Chlorosulfonation on **5** using chlorosulfonic acid in dichloromethane followed by treatment with aqueous ammonia furnished the desired valdecoxib **1** as shown in Scheme 1.

During the synthesis of **5**, we encountered two intermediates, **3** and **4**. While intermediate **4** found to be quite stable (to make process robust, it was not isolated), intermediate **3** was in equilibrium with the corresponding tautomer **7**. As a result,



Scheme 1. Novel approach to the synthesis of valdecoxib **1**.

20% [by gas chromatography (GC)] of **7** was found to take part in cycloaddition to afford cycloadduct **8** as an impurity [by high-performance liquid chromatography (HPLC)] (Fig. 3) along with the desired product **4**.

After acid-mediated aromatization of the mixture of **4** and **8**, we were able to isolate the desired isoxazole derivative **5** with 60% yield. Aromatized side product **9** (Fig. 4) originated from **8** and was separated by crystallization in isopropanol.

Chlorosulfonation of **5** afforded the corresponding chlorosulfonated intermediate **6** in 60% yield. We observed poor yield (60%) of **6**, and to find mass balance we isolated at least two side products **10** (10% by HPLC) and **11** (15% by HPLC). Additionally, we were also able to isolate chlorosulfonated side product of **9** as an impurity **12**. Removal of these two side products by crystallization using cyclohexane led to the poor yield of **6**. Because of poor stability of chlorosulfonated impurities, without characterization, we converted them to corresponding sulfamidated moieties (**13**, **14**, and **15**) (Fig. 5).

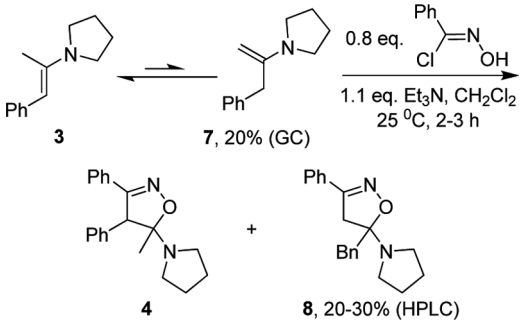


Figure 3. Existence of tautomer **7** and corresponding cycloadduct **8**.

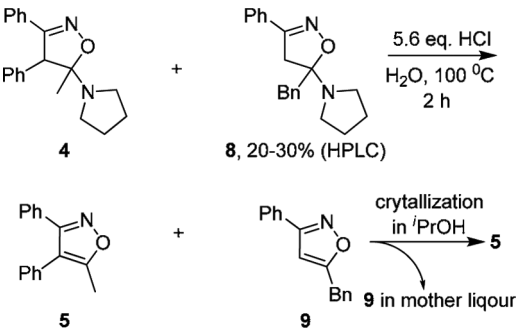


Figure 4. Aromatization and removal of **9**.

In the final step, aqueous ammonia was used. There are a few more impurities (**16** and **17**) formed as a result of the reaction of **6** with water and **1** respectively as shown in Fig. 6.

After addressing impurity-related deficiencies and intensive process development, we realized that the developed novel synthetic route can be carried out on a multi-kilogram scale in the concurrent pilot plant scale.

CONCLUSION

We have developed an enamine directed [3 + 2]-dipolar cycloaddition process using commercially available inexpensive raw materials for the synthesis of

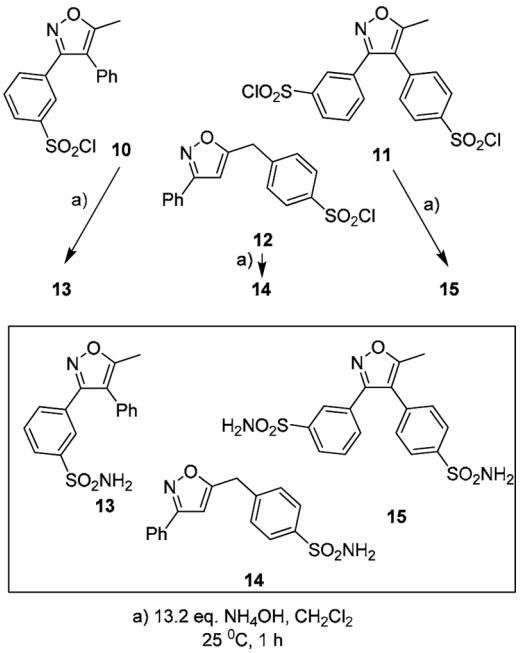


Figure 5. Structures of impurities **10–15**.

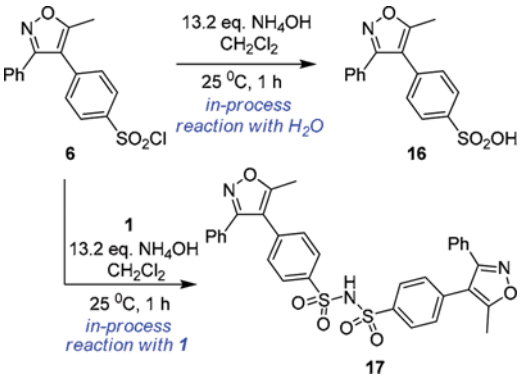


Figure 6. In-process impurities **16** and **17**. (Figure is provided in color online.)

valdecoxib **1**. This process is more advantageous than the reported processes and was successfully implemented on a multi-kilogram scale in the plant.

EXPERIMENTAL

The ^{1}H NMR spectra were measured in $CDCl_3$, dimethylsulfoxide (DMSO-d_6), mixture of $CDCl_3$ and DMSO-d_6, and mixture of $CDCl_3$ and CD_3CN using 200-MHz and 400-MHz Fourier transform (FT)NMR spectrometers. The chemical shifts are reported in δ ppm relative to tetramethylsilane (TMS). The FT-IR spectra were recorded in the solid state as KBr dispersion using a FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on a liquid chromatography–mass spectometry (LC-MS) spectrometer. The solvents and reagents were used without further purification.

Synthesis of Compound 3

A solution of phenylacetone (45.2 kg, 336.9 mol, 1.0 equiv), pyrrolidine (42.5 kg, 597.6 mol, 1.8 equiv), and cyclohexane (370 L) was heated to azeotropic reflux (70–80 °C) for 8 h. Thereafter, cyclohexane and excess pyrrolidine were removed from the reaction mixture under reduced pressure at below 50 °C to provide the title compound **3** [the residue was directly used in the next step without further isolation (63.1 kg; crude yield was considered to be 100%), 89% (GC)].

Synthesis of Compound 4

A solution of chlorobenzaldoxime (61.6 kg, 395.9 mol, 0.8 equiv) and dichloromethane (95 L) was added to a stirring solution of compound **3** (63.0 kg, 469.5 mol, 1.0 equiv), triethylamine (53 kg, 523.8 mol, 1.1 equiv), and dichloromethane (575.0 L) at 5–10 °C. The temperature of reaction mixture was raised to 25–35 °C, and it was stirred for 2–3 h. Subsequently, water (360 L) was added to the reaction mixture, and it was stirred for 30 min. The organic layer was separated and concentrated at 50–55 °C under atmospheric pressure to provide the title compound **4** [residue was

directly used in next step without further isolation (121.3 kg; crude yield was considered to be 100%), 70% (GC)].

Synthesis of Compound 5

Concentrated hydrochloric acid (226 L, 2197.2 mol, 5.6 equiv) was added to a stirring mixture of water (480 L) and compound **4** (121.3 kg, 395.9 mol, 1.0 equiv) at 40–50 °C. The resulting reaction mixture was heated, and the distillate was collected until the temperature reached to 98–102 °C. The mixture was stirred for 1.5–2.5 h at 98–102 deg;C. Thereafter, the reaction mixture was cooled to 25–35 °C, and the product was extracted with dichloromethane (2 × 220 L). The combined organic layers were washed with water (145 L) and concentrated under atmospheric pressure at 45–50 °C followed by reduced pressure at 45–50 °C. Isopropyl alcohol (35 L) was added to the residue and distilled off under vacuum at 45–50 °C. Subsequently, an additional quantity of isopropyl alcohol (75 L) was added and maintained for 15–30 min at 45–50 °C. The resulting reaction mixture was cooled to 0–5 °C and stirred for 45–60 min. The precipitated solid was filtered and washed with chilled isopropyl alcohol (3.15 L). The wet compound was charged into isopropyl alcohol (75 L), heated to 55–60 °C until the clear solution was obtained, cooled to 0–5 °C, and stirred for 50–60 min. The precipitated solid was filtered, washed with chilled isopropyl alcohol (3.2 L), and dried under vacuum at 40–45 °C to obtain 24 kg (60%) of isoxazole derivative **5** with 99.4% purity by HPLC. Mass: m/z 236 ($M^+ + H$); IR (KBr, cm^{-1}): 3051 (aromatic C−H stretching), 2928 (aliphatic C−H stretching), 1619 and 1598 (aromatic C=C stretching), 1416 and 1240 (aliphatic C−H bending), 779 and 768 (aromatic C−H bending); ^{1}H NMR (200 MHz, $CDCl_3$+ CD_3CN): 2.4 (s, 3H), 7.0–7.5 (m, 10H).

Synthesis of Compound 6

A solution of compound **5** (25 Kg, 106.2 mol, 1.0 equiv) in dichloromethane (50 L) was added to a stirring solution of chlorosulfonic acid (98 Kg, 841.0 mol, 8.0 equiv) and dichloromethane (75 L) at 0–10 °C. The reaction mixture was heated to reflux, stirred for 9–11 h, cooled to 25–35 °C, and quenched into chilled water (175 L) below 10 °C. Thereafter, the temperature of the reaction mixture was raised to 25–35 °C, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 62.5 L). The combined organic layers were washed with water (3 × 190 L) and concentrated under atmospheric pressure below 60 °C. Cyclohexane (250 L) was added and heated to reflux for 15–30 min. Water (75 L) was added to the reaction mixture and again heated to reflux for 15–30 min. The organic layer was separated, cooled to 25–35 °C, and stirred for 45 min. The precipitated solid was filtered and washed with cyclohexane (22 L). Recrystallization employing cyclohexane was repeated twice and dried under vacuum at 50–55 °C to obtain 21.3 kg (60%) of compound **6** with 98.7% purity by HPLC. Mass: m/z 334 ($M^+ + H$); IR (KBr, cm^{-1}): 3091 and 3064 (aromatic C−H stretching), 1626 (C=N stretching), 1591 and 1492 (aromatic C=C stretching), 1464 and 1396 (aliphatic C−H bending), 1383 and 1191 (O=S=O asymmetric and symmetric stretching), 782 and 755 (aromatic C−H bending); ^{1}H NMR (200 MHz, $CDCl_3 + CD_3CN$): 2.53 (s, 3H),

7.2–7.6 (m, 5H), 7.45 (d, *J* 8.6 Hz, 2H), 8.03 (d, *J* 8.6 Hz, 2H); ^{13}C NMR (200 MHz, DMSO-d_6): 11.3, 114.9, 126.0, 128.1, 128.7, 128.8, 129.0, 129.7, 130.0, 147.2, 160.6, 167.1.

Synthesis of Valdecoxib 1

Charcoal (1 kg) was added to a stirring solution of compound **6** (20 kg, 59.9 mol, 1.0 equiv) in dichloromethane (120 L) and stirred for 30–45 min. Thereafter, the charcoal was filtered and washed with dichloromethane (40 L). To the combined filtrate was added 15% aqueous ammonia (90 L, 794.1 mol, 13.2 equiv) at 20–30 °C for 1–1.5 h. Subsequently, dichloromethane was distilled off from the reaction mixture below 45 °C under atmospheric pressure, cooled to 5–10 °C, and stirred for 30–45 min. The precipitated solid was filtered and washed with water (20 L). The wet compound was charged into water (100 L) and stirred for 45–60 min and thereafter the solid was filtered and washed with water (20 L). The wet compound was dried under vacuum at 80–85 °C to afford the 15 kg (80%) of title compound **1** with 99.92% purity by HPLC. Mass: m/z 315 ($M^+ + H$); IR (KBr, cm^{-1}): 3378 and 3251 (N−H stretching), 2927 (aliphatic C−H stretching), 1622 (C=N stretching), 1595 and 1564 (aromatic C=C stretching), 1466 and 1392 (aliphatic C−H bending), 1334 and 1151 (O=S=O asymmetric and symmetric stretching), 785 (aromatic C−H bending); ^{1}H NMR (400 MHz, DMSO-d_6): 2.47 (s, 3H), 7.3–7.5 (m, 5H), 7.41 (d, *J* 8.2 Hz, 2H), 7.84 (d, *J* 8.2 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): 11.3, 114.2, 126.1, 128.2, 128.4, 128.8, 129.7, 130.0, 133.3, 143.3, 160.7, 167.6; Anal. calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.92; S, 10.19. Found: C, 60.89; H, 4.35; N, 8.98; S, 10.21.

Synthesis of Impurity 9

A solution of **3** (100 g, 0.745 mol, 1.0 equiv) and pyrrolidine (88 g, 1.239 mol, 1.7 equiv) in cyclohexane (740 mL) was heated for azeotropic reflux until water collection stoped. The resulting reaction mass was concentrated under reduced pressure below 70 °C. Dichloromethane (1000 mL) and triethylamine (116 g, 1.146 mol) were charged at 25–35 °C. To the resulting reaction mixture was added a solution of chlorobenzaldoxime (125 g, 0.803 mol) in dichloromethane (200 mL) and stirred at 25–35 °C for 3 h. Subsequently, the reaction mixture was quenched with water (750 mL), and layers were separated. The product was extracted with dichloromethane (200 mL) from the aqueous layer. The combined organic layers were concentrated under reduced pressure below 55 °C. Thereafter, concentrated hydrochloric acid (350 mL) and water (700 mL) were charged to the reaction mixture, which was heated to 85–90 °C under distillation mode, and the dichloromethane was collected. The resulting reaction mixture was refluxed for 3 h at 100 °C and cooled to 25–35 °C. Thereafter, dichloromethane (450 mL) was added to the reaction mixture at 25–35 °C, and layers were separated. The product was extracted with dichloromethane (200 mL) from the aqueous phase. The combined organic layers were concentrated under reduced pressure below 50 °C. After cooling the reaction mixture at 25–35 °C, isopropyl alcohol (100 mL) was charged, and the solid (compound **5**)was filtered. The obtained mother liquor was concentrated below 60 °C

under reduced pressure, charged with acetone (200 mL) at 25–35 °C, and stirred for 1 h. The solid was filtered and dried at 40–45 °C to obtain 26 g (15%) of compound **9** with 98.5% purity (HPLC). MS: m/z 236 ($M^+ + H$); IR (KBr, cm^{-1}): 2919 (aliphatic C−H stretching), 1598 and 1578 (aromatic C=C stretching); ^{1}H NMR (200 MHz, $CDCl_3$): 4.1 (s, 2H), 6.3 (s, 1H), 7.2–7.8 (m, 10H).

Synthesis of Impurity 13

A solution of **5** (100 g, 0.425 mol, 1.0 equiv) in dichloromethane (100 mL) was added to a solution of chlorosulfonic acid (396.2 g, 3.400 mol, 8.0 equiv) in dichloromethane (400 mL) at 0–10 °C. The reaction mixture was refluxed for 7–8 h. The resulting reaction mixture was quenched with water (1000 mL) below 10 °C. The organic layers were separated, and the product was extracted from the aqueous layer with dichloromethane (2 × 500 mL). The combined organic layers were concentrated below 45 °C under reduced pressure. Thereafter, cyclohexane (1000 mL) was added to the residue at 25–35 °C and stirred for complete solid isolation. The precipitated solid (compound **6**) was filtered, and the filtrate was concentrated at below 60 °C under reduced pressure to obtain **10** (not isolated) along with some quantity of **6** (not quantified). Aqueous ammonia (15%, ~650 mL 5.735 mol, 13.2 equiv) was added to a solution of **10** (crude) and **6** in dichloromethane (1000 mL) at 25–35 °C. The resulting reaction mixture was stirred for 1 h at 25–35 °C. The layers were separated, and the product was extracted from the aqueous layer with dichloromethane (2 × 200 mL). The combined layers were concentrated under reduced pressure below 45 °C, and dichloromethane (100 mL) was added at 25–35 °C and thereafter cooled to 10–15 °C. After stirring for 1 h, the precipitated solid (**1**) was filtered. The filtrate was concentrated, and the crystallization was repeated twice using dichloromethane to remove **1** completely. The filtrate free from **1** was taken and concentrated below 45 °C under reduced pressure. Ethyl acetate was added to the resulting residue, heated to reflux for 30 min followed by cooling to 0–5 °C, and stirred for 1 h. The precipitated solid was filtered and dried at 80–85 °C to provide 13.5 g (10%) of compound **13** with 96.0% purity (HPLC); MS: m/z 315 ($M^+ + H$); IR (KBr, cm^{-1}): 3337 and 3247 (N−H stretching), 1334 and 1165 (O=S=O asymmetric and symmetric stretching); ^{1}H NMR (200 MHz, $CD_3CN + CDCl_3$): 2.48 (s, 3H), 7.37 (m, 5H), 7.43 (d, J 7.8 Hz, 1H), 7.52 (t, J8.0, 7.8 Hz, 1H), 7.74 (s, 1H), 7.87 (d, J7.8 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): 11.2, 114.9, 125.1, 126.0, 126.5, 128.0, 128.3, 129.0, 129.2, 130.0, 147.5, 148.8, 160.6, 167.0.

Synthesis of Impurity 14

A solution of **9** (20 g, 0.085 mol, 1.0 equiv) in dichloromethane (50 mL) was added to a solution of chlorosulfonic acid (79.2 g, 0.680 mol, 8.0 equiv) in dichloromethane (50 mL) at 0–5 °C. The reaction mixture was stirred at 40 °C for 3–5 h and quenched with water (140 mL) below 10 °C. The layers were separated, and the product was extracted with dichloromethane (2 × 50 mL) from the aqueous layer. Thereafter, aqueous ammonia solution (15%, 130 mL 1.147 mol, 13.5 equiv) was added to the organic layer at 25–35 °C and stirred for 1–2 h. The precipitated solid was filtered and washed with water (40 mL) and dichloromethane (20 mL) successively. The wet

solid was dried at 80–85 °C to afford 16 g (60%) of compound **14** with 99.5% (HPLC); MS: m/z 315 ($M^+ + H$); IR (KBr, cm^{-1}): 3363 and 3271 (N−H stretching), 1342 and 1158 (O=S=O asymmetric and symmetric stretching); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.27 (s, 2H), 6.33 (s, 1H), 7.20–7.80 (m, 5H), 7.52 (d, $J = 8.4$ Hz, 2H), 8.02 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): 31.8, 100.4, 126.0, 126.5, 128.5, 129.0, 129.2, 130.1, 140.3, 142.7, 161.9, 171.7.

Synthesis of Impurity 15

A solution of **5** (20 g, 0.085 mol, 1.0 equiv) in dichloromethane (40 mL) was added to a stirring solution of chlorosulfonic acid (347 g, 2.978 mol, 35.0 equiv) and dichloromethane (400 mL) at 0–10 °C. The reaction mixture was refluxed for 7–8 h. The resulting reaction mixture was quenched with water (900 mL) below 10 °C. The layers were separated, and the product was extracted from the aqueous layer with dichloromethane (2 × 100 mL). Aqueous ammonia (15%, 260 mL, 2.294 mol, 27.0 equiv) was added to the combined organic layer at 25–35 °C and stirred for 1 h. The precipitated solid was filtered and dried at 80–85 °C to provide 23.5 g (70%) of compound **15**. Purity by HPLC 97.0%; MS: m/z 394 ($M^+ + H$); IR (KBr, cm^{-1}): 3322 and 3241 (N−H stretching), 1346 and 1161 (O=S=O asymmetric and symmetric stretching); ^{1}H NMR (400 MHz, DMSO-d_6): 2.45 (s, 3H), 7.36 (d, J 8.4 Hz, 1H), 7.45 (d, J 8.4 Hz, 2H), 7.58 (t, J 8.0, 7.6 Hz, 1H), 7.86 (d, J 8.4 Hz, 2H), 7.90 (d, J 8.0 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): 11.4, 114.2, 125.1, 126.1, 126.8, 129.0, 129.4, 129.9, 131.2, 132.6, 143.4, 144.8, 159.6, 168.1.

Synthesis of Impurity 16

A mixture of **6** (20 g, 0.060 mol, 1.0 equiv), water (65 mL), and THF(280 mL) was heated to reflux and maintained for 24 h. The solvent was distilled off completely from the reaction mixture below 80 °C under reduced pressure. The reaction mixture was cooled to 25–35 °C, charged with toluene (200 mL), and stirred for 1 h. The solid was filtered and dried at 50–55 °C to obtain 18.5 g (98.4%) of compound **16**. Purity by HPLC 99.7%; MS: m/z 316 ($M^+ + H$); IR (KBr, cm^{-1}): 3063 (O−H stretching), 1396 and 1176 (O=S=O asymmetric and symmetric stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.35–7.45 (m, 5H), 7.64 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): 11.3, 114.9, 126.0, 128.1, 128.7, 128.8, 129.0, 129.6, 129.9, 147.4, 160.6, 167.1.

Synthesis of Impurity 17

A mixture of **1** (10 g, 0.032 mol, 1.0 equiv), **6** (16 g, 0.048 mol, 1.5 equiv), and pyridine (50 mL) was heated to 110–115 °C and stirred for 9 h. The reaction mixture was concentrated under reduced pressure at 95 °C. The resulted solid was recrystallized from isopropyl alcohol (300 mL), and the wet compound was again recrystallized from the mixture of water (100 mL) and acetone (100 mL). The wet solid was dried at 80–85 °C to afford 12.5 g (64%) of compound **17** with 98.0% purity (HPLC); MS: m/z 612 ($M^+ + H$); IR (KBr, cm^{-1}): 3339 (N−H, stretching), 1369 and 1165 (O=S=O asymmetric and symmetric stretching); ^{1}H NMR (400 MHz,

$CDCl_3$ +DMSO-d_6): δ 2.5 (s, 6H), 7.32 (d, $J = 8.2$ Hz, 4H), 7.36–7.45 (m, 10H), 7.95 (d, $J = 8.2$ Hz, 4H); ^{13}C NMR (400 MHz, DMSO-d_6): 11.3, 114.5, 126.5, 128.1, 128.5, 128.8, 129.0, 129.7, 131.5, 145.5, 160.7, 167.3.

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