



Synthesis and Characterization of Related Substances of Torasemide

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Abstract

Keywords

- torasemide
- loop diuretic
- related substances
- synthesis
- process development

Torasemide, a pyridine-3-sulfonylurea derivative, is a high-efficiency loop diuretic. During the process development of torasemide, five process-related substances, which have been specified in the pharmacopeia, would be produced. In this study, all these related substances, including compounds A–E, were synthesized via simple procedures and subsequently characterized by ¹H nuclear magnetic resonance (NMR), ¹³C NMR, and mass spectrometry. Particularly, a simple synthetic method for compound A has not been found in previous literature. It is worth noting that other related substances could be prepared from compound B in one or two steps. The availability of these related substances could allow for quality control in the process of torasemide.

Introduction

The presence of impurities in a drug substance can have a significant impact on the quality and safety of the drug product. The risk for patients' health caused by the presence of small molecular impurities in active pharmaceutical ingredients (APIs) has become an increasing concern of pharmaceutical companies, regulatory authorities, patients, and doctors.^{1–3} Therefore, the synthesis and characterization of related substances can provide the required information for drug registration application and references for optimizing reaction conditions to obtain pharmaceuticals with a better quality.⁴ In the synthesis of related substances and relevant analogues of APIs, key intermediates containing synthetic building blocks and privilege scaffolds usually play a significant role.^{5,6} Moreover, some related substances might be discovered to exhibit other biological activities and pharmacological actions based on the drug repositioning strategy. Therefore,

the research on the synthesis of the related substances is of great importance.

Torasemide (► **Fig. 1**), chemically known as *N*-(isopropyl-carbamoyl)-4-(*m*-tolylamino) pyridine-3-sulfonamide and approved in Belgium in 1993 and in China in 2003, is a highly potent, selective, long-acting, and orally bioavailable loop diuretic for the treatment of hypertension and edema caused by congestive heart failure, kidney or liver disease.^{7–10} It occupies most of the market share of high-potency diuretics due to its strong diuretic effect, high bioavailability, long-lasting effect, and good safety.⁷

The synthesis and identification of process-related substances play a vital role in the process of quality control. There are five related substances of torasemide (**A**, **B**, **C**, **D**, and **E**) described in USP (the United States Pharmacopoeia), ChP (Chinese Pharmacopoeia), and EP (European Pharmacopoeia), among which compound **B** is the key intermediate in most synthetic routes and also the raw material in the final

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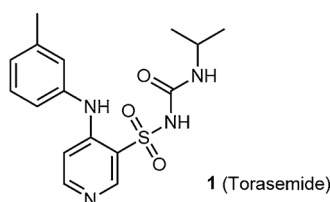


Fig. 1 Structure of torasemide.

step for the synthesis of torasemide.^{11–16} To the best of our knowledge, the synthesis of compound **A** has not been found in previous literature. Although the syntheses of compounds **C** and **D** (Scheme 1) have been revealed in patents,¹³ the raw materials *N*-ethyl-1*H*-imidazole-1-carboxamide and *N*-butyl-1*H*-imidazole-1-carboxamide are not readily available commercially. The synthesis of compound **E** has been documented in the literature.¹⁷ Nevertheless, ethyl chloroformate is restrictive due to its high toxicity. The details are shown in Scheme 1.

To meet the requirements of research and development and quality control, herein, the process of the universal intermediate (compound **B**) and the synthesis of the related compounds **A**, **C**, **D**, and **E** of torasemide were studied. All of them were successfully synthesized and confirmed by ¹H nuclear magnetic resonance (NMR), ¹³C NMR, and (high-resolution) mass spectrometry. Compound **B** was synthesized from 4-hydroxypyridine (**2**) via sulfonation, chlorination, amination, and nucleophilic substitution. Compound **A** was obtained from **B** via cyclization. The compounds **C** and **D** were synthesized from **B** via substitution reaction. Compound **E** was prepared from **B** via substitution reaction. The synthetic routes are shown in Scheme 2.

Results and Discussion

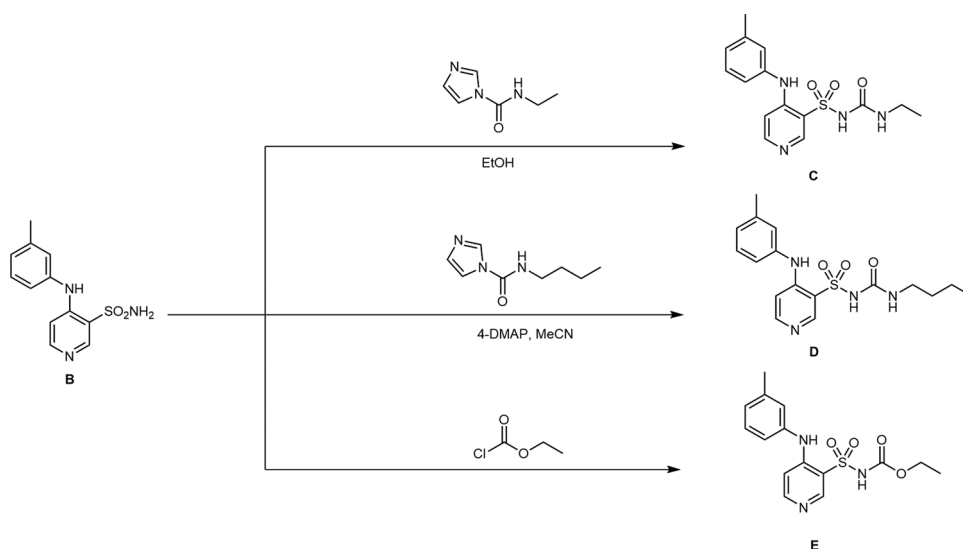
Compound **B** was prepared following the previously reported procedure.¹⁴ However, the synthesis of intermediate **3** involves a complicated work-up procedure with a low

yield, including dilution with ice water, neutralization with calcium carbonate, alkalization with barium hydroxide, ion exchange with ion exchange resin, and crystallization with acetone. Considering that intermediate **3** has low solubility in ethanol, the synthetic process was optimized: the reaction solution was poured into industrial alcohol in ice water bath, filtered, and dried to give intermediate **3**. The work-up procedure is much simpler and the yield is higher than the previously reported procedure.

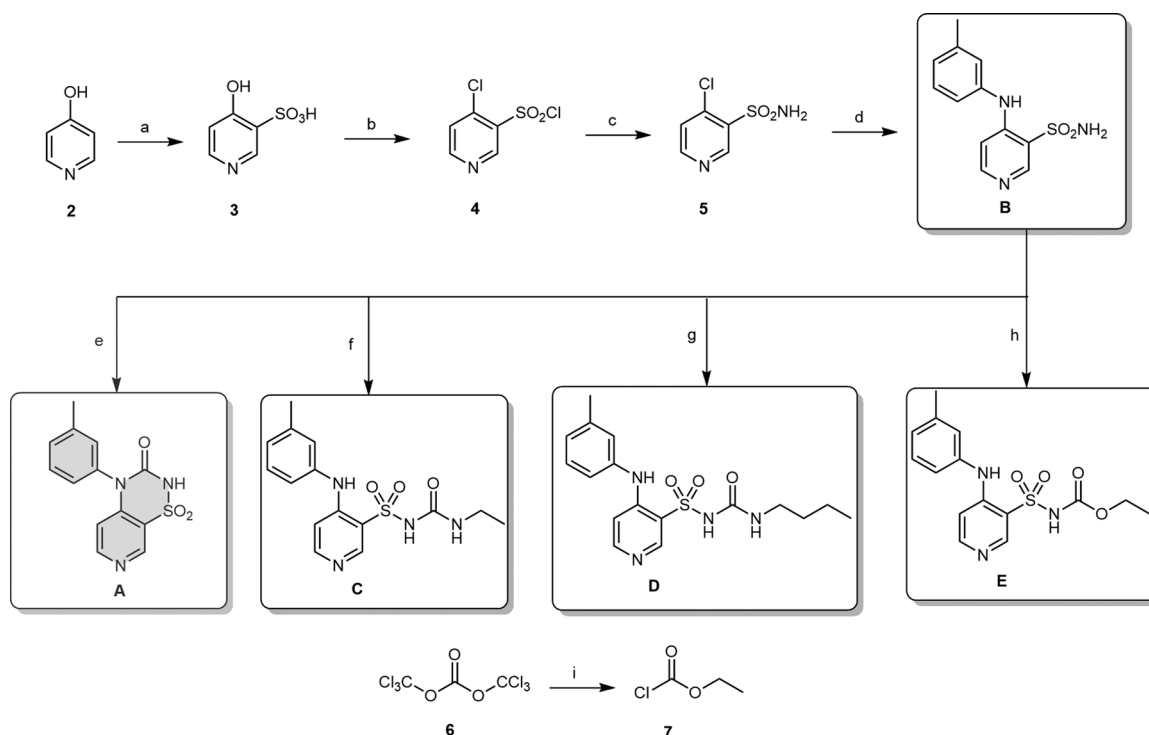
Based on a similar synthetic method,^{18,19} the synthetic route of compound **A** is designed as Scheme 2. A safer triphosgene was used to replace phosgene to generate compound **A** due to the risk of phosgene. With respect to the preparation of compounds **C** and **D**, *N*-ethyl-1*H*-imidazole-1-carboxamide and *N*-butyl-1*H*-imidazole-1-carboxamide used in the literature are not readily available commercially.¹⁴ The idea of using *N,N*-carbonyldiimidazole (CDI) and isopropylamine as raw materials to give torasemide is provided in the literature.¹⁸ Considering that the structures of compounds **C** and **D** are slightly different from torasemide only in the alkyl chain, their synthesis can be completed by referring to the method with commercially available reagents.¹⁶ Compound **D** was prepared from compound **B**, CDI, and *n*-butylamine in the presence of Et₃N in CH₂Cl₂. Using the same strategy, compound **C** was synthesized from compound **B**, CDI, and ethylamine hydrochloride in the presence of Et₃N in CH₃CN. Compound **E** was obtained following the previously reported procedure,¹⁷ in which ethyl chloroformate was synthesized following the reported synthetic method.²⁰

Conclusion

In this study, the process-related substances of torasemide were successfully synthesized via simple procedures and characterized. Compound **B** was obtained from 4-hydroxypyridine within four steps, and the other compounds **A**, **C**, **D**, and **E** could be synthesized from compound **B** in one or two steps. The methods are suitable for the synthesis of reference



Scheme 1 Synthesis of compounds (**C**), (**D**), and (**E**) reported in the literature.



Scheme 2 Synthesis of compounds (A–E). Reagents and conditions: (a) fuming sulfuric acid, HgSO_4 , 190°C , 10 hours; (b) PCl_5 , POCl_3 , 120°C , 5 hours; (c) $\text{NH}_3 \cdot \text{H}_2\text{O}$, r.t., 30 minutes; (d) *m*-toluidine, *n*-propanol, 105°C , 2 hours; (e) triphosgene, Et_3N , CH_2Cl_2 , 0°C , 6 hours; (f) CDI, CH_3CN , Et_3N , ethylamine hydrochloride, 85°C , 4 hours; (g) CDI, CH_2Cl_2 , Et_3N , *n*-butylamine, 35°C , 2 hours; (h) CH_2Cl_2 , Et_3N , **7**, 0°C , 4 hours. (i) CH_2Cl_2 , EtOH, r.t., 2 hours.

substances for the quality control of torasemide. Significantly, the synthetic method for compound **A** has been reported for the first time. This study provides required information for drug registration application and references for optimizing reaction conditions to obtain premium pharmaceuticals.

Experimental Section

Chemistry

All solvents and reagents were obtained from commercially available sources and used without further purification. Melting points were measured on a SGW X-4A microscopic melting-point apparatus (Shanghai Jingke Leici Co., Ltd., China). The ^1H NMR and ^{13}C NMR spectra were recorded on a AVANCE NEO 400 NMR spectrometer (Bruker Co., Switzerland) at 400 MHz in $\text{DMSO}-d_6$. The solvent used was $\text{DMSO}-d_6$. The ^1H NMR chemical shift values were reported as δ ppm relative to tetramethylsilane and the ^{13}C NMR chemical shift values were reported as δ ppm relative to $\text{DMSO}-d_6$. Mass spectra were obtained on a Quattro Micromass instrument (Waters Corporation, United Kingdom) using electrospray ionization (ESI) techniques. High-resolution mass spectra were recorded on a Waters SYNAPT G1 HDMS instrument (Waters Corporation, United Kingdom).

4-Hydroxypyridine-3-sulfonic Acid (**3**)

To a three-necked round-bottom flask equipped with a reflux condenser and a thermometer was added fuming sulfuric acid (20% SO_3 , 120 mL) and mercury sulfate (1.90 g, 6.4 mmol). The mixture was stirred in an ice bath for 20 minutes, and then 4-hydroxypyridine (38.04 g, 0.4 mol) was added

portion-wise at a temperature below 25°C . The resulting mixture was slowly heated to 190°C and stirred at this temperature for 10 hours. The resulting mixture was cooled to room temperature and then slowly poured into industrial ethanol (360 mL). The resulting slurry was stirred for 1 hour in an ice bath and then filtered. The filter cake was added to industrial alcohol (200 mL) and stirred for another 1 hour in an ice bath. The slurry was filtered, and the filter cake was dried under vacuum at 60°C for 12 hours to afford the desired 4-hydroxypyridine-3-sulfonic acid (49.58 g) as a white solid in 70.84% yield. The crude product **3** was carried on to the next step without further purification.

4-Chloropyridine-3-sulfonamide (**5**)

To a three-necked round-bottom flask equipped with a reflux condenser and thermometer was successively added **3** (17.50 g, 0.1 mol), phosphorus pentachloride (52.06 g, 0.25 mol), and phosphorus oxychloride (23 mL, 0.25 mol). The resulting mixture was slowly heated to 120°C and stirred at this temperature for 5 hours. The reaction solution was concentrated under reduced pressure. Next, toluene (100 mL \times 3) was added to the residue and concentrated under reduced pressure for three times to give 4-hydroxypyridine-3-sulfonyl chloride (**4**) as a light green oil. The 1,4-dioxane was added to the above oil and stirred for 10 minutes in an ice bath. The mixture was added dropwise for 30 minutes to concentrated ammonia (60 mL) in an ice bath and the reaction solution turned pale yellow. After stirring in an ice bath for 30 minutes, the resulting mixture was concentrated under reduced pressure to obtain the crude as a yellow solid, followed by adding ice water

(30 mL) to the crude. After stirring at 20 to 25°C for 20 minutes, the resulting precipitate was filtered. The solid was dried under vacuum at 45°C for 6 hours to afford the desired 4-chloropyridine-3-sulfonamide (**5**) (12.94 g) as a pale yellow solid in two-step total yield of 67.42%. Compound **5** was used directly in the next step without further purification.

4-(*m*-Tolylamino)pyridine-3-sulfonamide (Compound B)

To a three-necked round-bottom flask equipped with a reflux condenser and a thermometer was successively added **5** (9.60 g, 0.05 mol), *n*-propanol (100 mL), and *m*-toluidine (6.5 mL, 0.06 mol). The mixture was allowed to warm to 105°C and stirred for 2 hours. The resulting mixture was cooled to room temperature and then concentrated under reduced pressure to give the crude as a yellow solid. The crude was dissolved with 2 mol/L sodium hydroxide solution (80 mL) and water (150 mL) at room temperature. Next, the mixture was adjusted to pH 6 to 7 with 3 mol/L hydrochloric acid. The resulting precipitate was filtered, washed with ice water, and dried to give compound **B** (12.21 g) as an off-white solid in a yield of 92.86%. mp: 162–164°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.25 (d, *J* = 5.9 Hz, 1H), 8.06 (s, 1H), 7.76 (s, 2H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.15–7.03 (m, 3H), 6.99 (d, *J* = 5.9 Hz, 1H), 2.33 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.68, 149.07, 147.33, 139.20, 138.12, 129.42, 126.03, 124.12, 123.02, 120.61, 107.85, 20.90. HR-MS (ESI) (*m/z*) calcd. for C₁₂H₁₃N₃O₂S [M + H]⁺ 264.0728, found 264.0793.

4-(*m*-Tolyl)-2H-pyrido[4,3-*e*][1,2,4]thiadiazin-3(4H)-one-1,1-dioxide (Compound A)

To a stirred solution of **5** (1.05 g, 4 mmol) and triethylamine (1.1 mL, 8 mmol) in dichloromethane was slowly added triphosgene (0.40 g, 1.34 mmol) in an ice bath. After the mixture being stirred for 6 hours in an ice bath, the solvent was evaporated under reduced pressure and the residue was dissolved with 1 mol/L sodium hydroxide solution (5 mL). The resulting mixture was filtered, and the filtrate was adjusted to pH 6 to 7 with 3 mol/L hydrochloric acid. The resulting precipitate was filtered, washed with ice water, and dried to give compound **A** as a white solid in 63.12% yield. mp: 168–170°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 8.39 (d, *J* = 6.9 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.14–7.00 (m, 2H), 6.51 (d, *J* = 6.9 Hz, 1H), 2.37 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.48, 149.23, 146.67, 142.64, 139.32, 138.46, 129.59, 129.54, 128.70, 126.14, 121.01, 109.93, 20.74. ESI-MS (*m/z*) calcd. for C₁₃H₁₁N₃O₃S [M + H]⁺ 290.0521, found 290.00.

N-(Ethylcarbamoyl)-4-(*m*-tolylamino)pyridine-3-sulfonamide (Compound C)

Compound **B** (1.05 g, 4 mmol), CDI (0.78 g, 4.8 mmol), and triethylamine (1.1 mL, 8 mmol) were successively added to acetonitrile (10 mL) and then the mixture was stirred at room temperature. Upon completion of the reaction (monitored by thin layer chromatography [TLC]), ethylamine hydrochloride

(0.97 g, 12 mmol) was added. The resulting mixture was heated to 85°C and stirred for 4 hours. The solvent was evaporated under reduced pressure and the residue was dissolved with 1 mol/L sodium hydroxide solution (5 mL). The resulting mixture was filtered, and the filtrate was adjusted to pH 6 to 7 with 3 mol/L hydrochloric acid. The resulting precipitate was filtered, washed with ice water, and dried to give compound **C** as a white solid in a yield of 82.17%. mp: 151–153°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.66 (s, 1H), 8.23 (d, *J* = 6.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.21–6.91 (m, 4H), 6.72 (s, 1H), 3.10–2.86 (m, 2H), 2.33 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 153.44, 151.19, 149.30, 148.89, 139.34, 137.78, 129.55, 126.42, 124.02, 120.90, 120.56, 107.92, 34.27, 20.90, 14.93. HR-MS (ESI) (*m/z*) calcd. for C₁₅H₁₈N₄O₃S [M + H]⁺ 335.1100, found 335.1174.

N-(Butylcarbamoyl)-4-(*m*-tolylamino)pyridine-3-sulfonamide (Compound D)

Compound **B** (1.05 g, 4 mmol), CDI (0.78 g, 4.8 mmol), and triethylamine (1.1 mL, 8 mmol) were successively added to dichloromethane (10 mL) and then the mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), *n*-butylamine (0.58 g, 8 mmol) was added. The resulting mixture was warmed to 35°C and stirred for 2 hours. The solvent was evaporated under reduced pressure and the residue was dissolved with 1 mol/L sodium hydroxide solution (5 mL). The resulting mixture was filtered, and the filtrate was adjusted to pH 6 to 7 with 3 mol/L hydrochloric acid. The resulting precipitate was filtered, washed with ice water, and dried to give compound **D** as a white solid in a yield of 69.24%. mp: 163–164°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.66 (s, 1H), 8.23 (d, *J* = 5.9 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 3H), 7.00 (d, *J* = 6.2 Hz, 1H), 6.69 (d, *J* = 6.7 Hz, 1H), 2.98 (q, *J* = 6.6 Hz, 2H), 2.33 (s, 3H), 1.39–1.27 (m, 2H), 1.20 (h, *J* = 7.2 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 153.36, 151.22, 149.31, 148.88, 139.32, 137.75, 129.54, 126.46, 124.07, 121.55, 120.63, 107.93, 38.97, 31.38, 20.88, 19.35, 13.58. HR-MS (ESI) (*m/z*) calcd. for C₁₇H₂₂N₄O₃S [M + H]⁺ 363.1413, found 363.1784.

Ethyl Chloroformate

To a stirred solution of **6** (2.97 g, 0.01 mol) in dry dichloromethane (30 mL) was added anhydrous ethanol (1.8 mL, 0.03 mol) in an ice bath. A solution of triethylamine (4.2 mL, 0.03 mol) in dry dichloromethane (10 mL) was added dropwise to the mixture at the temperature below 10°C. The mixture was stirred and slowly warmed to room temperature for 2 hours. The mixture was washed with water (40 mL × 3), and then the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give the corresponding compound **7**. The reaction mixture was used as such in the next step without further treatment.

N-(Ethylcarbamoyl)-4-(*m*-tolylamino)pyridine-3-sulfonamide (Compound E)

Compound **B** (1.05 g, 4 mmol), triethylamine (1.1 mL, 8 mmol), and **7** (0.86 g, 8 mmol) were successively added to

dichloromethane (10 mL) in an ice bath. After the mixture being stirred for 4 hours in ice bath, the solvent was evaporated under reduced pressure and the residue was dissolved with 1 mol/L sodium hydroxide solution (5 mL). The resulting mixture was filtered, and the filtrate was adjusted to pH 6 to 7 with 3 mol/L hydrochloric acid. The resulting precipitate was filtered, washed with ice water, and dried to give compound **E** as a light yellow solid in 46.17% yield. mp: 171–173°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.53 (s, 1H), 8.65 (s, 1H), 8.24 (d, $J=6.9$ Hz, 1H), 7.40 (t, $J=7.6$ Hz, 1H), 7.22–7.06 (m, 4H), 3.90 (q, $J=7.1$ Hz, 2H), 2.35 (s, 3H), 1.09 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 156.98, 151.33, 144.40, 143.49, 139.71, 136.52, 129.80, 127.60, 124.45, 123.67, 121.02, 107.98, 60.33, 20.83, 14.39. HR-MS (ESI) (m/z) calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 336.0940, found 336.0991.

Supporting Information

The ^1H NMR, ^{13}C NMR, or MS spectra of compounds **A**, **B**, **C**, **D**, and **E** can be seen in the Supporting Information (**► Figs. S1–S12 [online only]**).

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Conflicts of Interests

The authors declare no conflicts of interests.

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