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# Practical Synthesis of Triethylammonium (*Z*)-2-[2-(Boc-amino)thiazol-4-yl]-2-(trityloxyimino)acetate, the Side Chain of Cefmatilen

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**Abstract:**

**A practical synthesis of triethylammonium (*Z*)-2-[2-(*N*-*tert*-butoxycarbonylamino)thiazol-4-yl]-2-(triphenylmethyloxyimino)acetate (1) which is the C-7 side chain of cefmatilen, a new cephalosporin antibiotic, is described. The conditions were optimized to control the impurity and to increase the yield. Selective acetylation of oxime group before *tert*-butoxycarbonylation reduced the amount of $Boc_2O$. Compound 1 was synthesized from compound 6 by this improved process in 80% overall yield (12% higher than that for the medicinal process) via a four-reaction sequence (95% per reaction).**

## Introduction

(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetyl group is significantly useful as a C-7 side chain for cephalosporin antibiotics, for instance, cefdinir,[1] cefdaloxime,[2] and cefmatilen,[3] since this side chain gives a broad antibacterial spectrum and some oral activity. Cefmatilen, which was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan, is a new oral cephalosporin antibiotic.[3] In our previous report,[4] a practical large-scale synthesis of cefmatilen hydrochloride hydrate (**5**) from three starting materials (triethylammonium (*Z*)-2-[2-(*N*-*tert*-butoxycarbonylamino)thiazol-4-yl]-2-(triphenylmethyloxyimino)acetate (**1**) as the C-7 side chain, diphenylmethyl (−)-(6*R*,7*R*)-7-amino-8-oxo-3-methanesulfonyloxy-5-thia-1-azabibicyclo[4.2.0]oct-2-ene-2-carboxylate hydrochloride (**2**) as the cephem part, and 4-(acetylthiomethylthio)-1*H*-1,2,3-triazole (**3**) as the C-3 side chain) in good yield was described as shown in Scheme 1.

As shown in Scheme 2, a medicinal process for the synthesis of aminothiazolyl acetate **11** was described in our previous report.[3b] Oxime ester **6** was *tert*-butoxycarbonylated to give a mixture of di-Boc-protected ester **7** and tri-Boc-protected ester **8**. Hydrolysis of the mixture by aqueous HCl afforded mono-Boc-protected ester **9**. Hydrolysis of ester **9** with NaOH in EtOH followed by neutralization gave carboxylic acid **10** in 75% of overall yield from ester **6**. Protection with trityl chloride (TrCl) gave carboxylic acid **11** in 91% yield (68% overall yield from ester **6**). There were the following four problems in the medicinal process: (1) The yield was still low. (2) Excess $Boc_2O$ (2.6−3.5 equiv) was used as a reagent. (3) Haloalkane was used as a solvent. It is difficult to recover $CH_2Cl_2$ completely, mainly due to its low boiling point. Unless $CH_2Cl_2$ can be 100% recovered, its use should be avoided due to the effect on environment. (4) Carboxylic acid **11** contained impurity **13** (1−2%) which had an ethoxycarbonyl group instead of Boc (Scheme 3). A bulk drug of compound **5** which was produced from compound **1** containing impurity **13** contained ethoxycarbonylated cefmatilen **14** (ca. 1%) as an impurity. To improve the quality and the yield of compound **1**, to reduce the cost, and to make the process more environmentally suitable, we developed an improved process as shown in Scheme 4. In this contribution,[4a] an optimized practical process for the synthesis of compound **1** is described briefly.

## Results and Discussion

In the medicinal process (Scheme 2), since oxime ester **6** can be *tert*-butoxycarbonylated at three positions to give a mixture of di-Boc-protected ester **7** and tri-Boc-protected ester **8**, excess $Boc_2O$ was necessary (2.6−3.6 equiv) for the reaction completion. To reduce the amount of $Boc_2O$, the oxime group should be selectively protected before the *tert*-butoxycarbonylation. According to two examples for the protection of oxime ester **6** with TrCl, which were independently reported by Kamachi[5] and Wollmann,[2c] the selectivity (*O*-tritylester/*N*,*O*-ditritylester = 4:1[5] and 9:1[2c]) and yield (81%)[2c] were not satisfied. Since acetic anhydride ($Ac_2O$)

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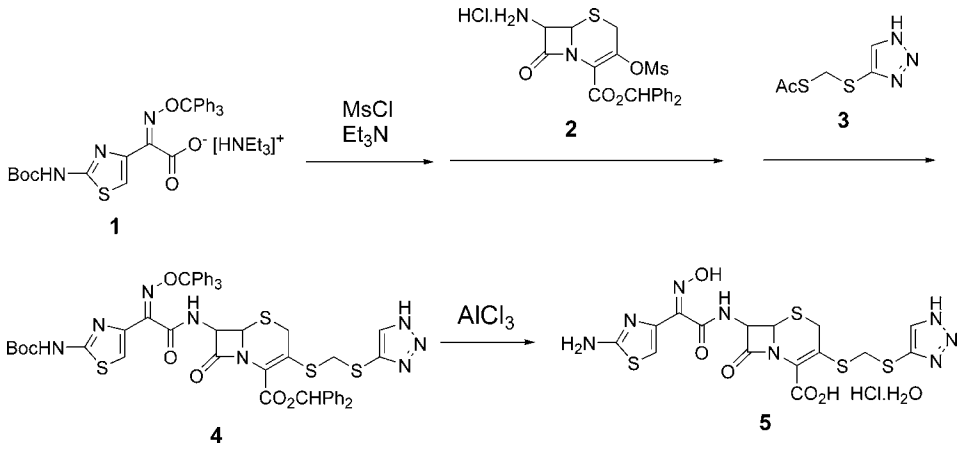
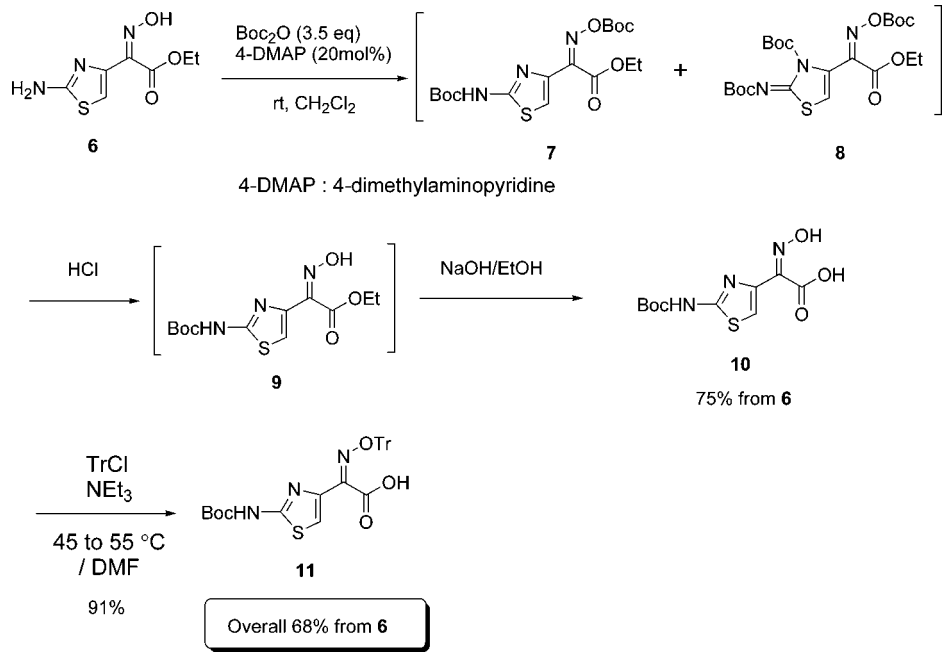
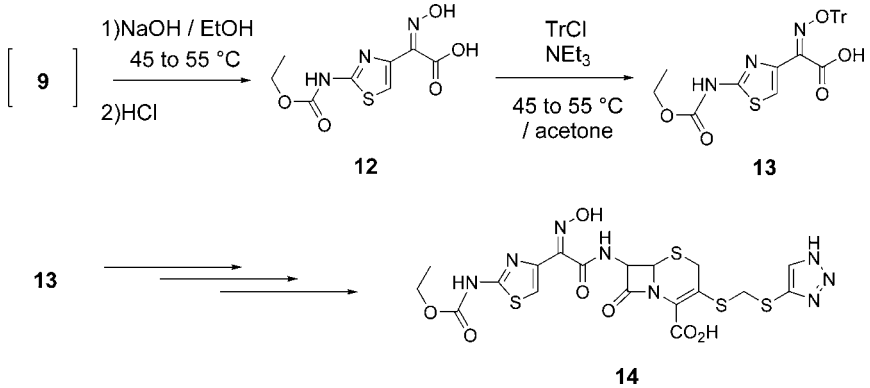
***Scheme 1***




***Scheme 2.*** **Medicinal process**




***Scheme 3.*** **Formation of impurity 14**




is cheaper than $Boc_2O$, we then tried selective acetylation of oxime ester **6** with $Ac_2O$. The reaction conditions for the selective acetylation to give acetoxyimine **15** were investigated. The representative results are summarized in Table 1. When no 4-DMAP was used as a catalyst (Table 1, entry 1), the conversion was 58% and diacetylation occurred to give acetoxyimine **19** (Scheme 5). The ratio of acetoxyimines **15** and **19** was 65:35. Interestingly, the selective acetylation in acetone in the presence of 4-DMAP (0.005−0.05 equiv) as a catalyst afforded acetoxyimine **15** as a single product (the selectivity = 100%) in 96% isolated yield (Table 1, entries 2−5). As expected, the amount of $Boc_2O$ was successfully reduced by the new route including the selective acetylation of the oxime group.

***Scheme 4.*** **Improved process**

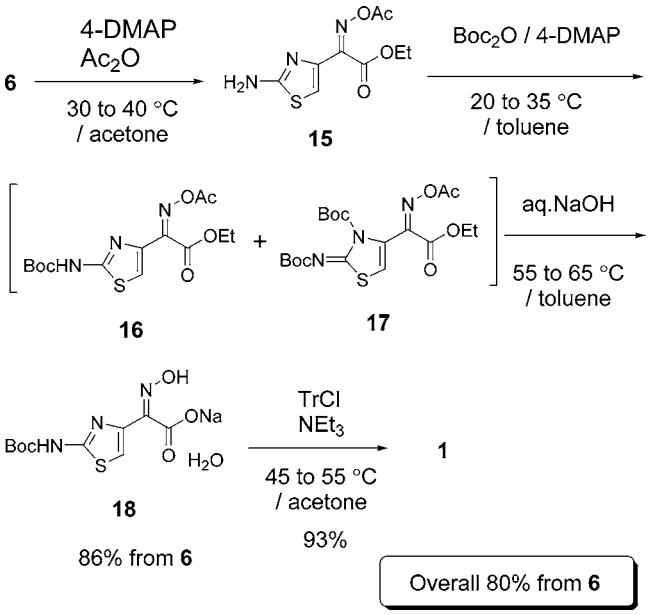
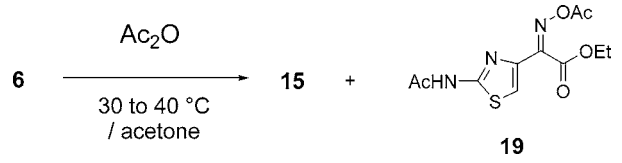



***Table 1.*** **Formation of compound 15 by acetylation of compound 6**[a]

| entry | 4-DMAP, equiv | conversion,[b] % | product ratio[b] of **15:19** | isolated yield, % |
|---|---|---|---|---|
| 1 | 0 | 58 | 65:35 | not isolated |
| 2 | 0.005 | 99 | 100:0 | 96 |
| 3 | 0.01 | 99 | 100:0 | 96 |
| 4 | 0.02 | 99 | 100:0 | 96 |
| 5 | 0.05 | 99 | 100:0 | 96 |

[a] Similar conditions described in the Experimental Section. [b] Determined by HPLC.

***Scheme 5***




$CH_2Cl_2$ was removed from the process by employing toluene as a reaction solvent for the *tert*-butoxycarbonylation of acetoxyimine **15** and the hydrolysis of esters **16** and **17**.

The reaction conditions for the *tert*-butoxycarbonylation of acetoxyimine **15** to afford a mixture of mono-Boc-protected ester **16** and di-Boc-protected ester **17** were investigated. The representative results are summarized in Table 2. When 4-DMAP (0.10 equiv) was used as a catalyst (Table 2, entry 1), the conversion (94%) and isolated yield (91%) were not satisfied. When more than 0.15 equiv of 4-DMAP was used (Table 2, entries 2−6), the reaction was completed and the isolated yields were not lower than 95%.

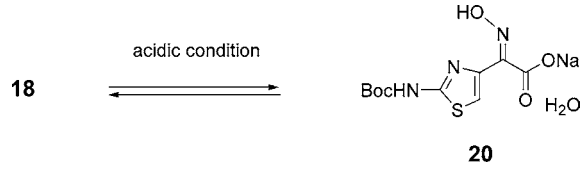
We then developed an improved process as shown in Scheme 4. Selective acetylation of oxime ester **6** with $Ac_2O$ (1.1 equiv) in the presence of 4-DMAP (0.01 equiv) in acetone gave acetoxyimine **15**. *tert*-Butoxycarbonylation of acetoxyimine **15** with $Boc_2O$ (1.6 equiv) in the presence of 4-DMAP (0.2 equiv) in toluene gave a mixture of mono-Boc-protected ester **16** and di-Boc-protected ester **17**. Hydrolysis of the mixture by aqueous NaOH afforded mono-Boc-protected salt **18** in 86% of overall yield from ester **6**. Protection with TrCl gave triethylammonium carboxylate **1** in 93% yield (80% overall yield via a four-reaction sequence from ester **6**; 95% per reaction). The overall yield was 12% higher than that for the medicinal process.

***Table 2.*** **Formation of compounds 16 and 17 from compound 15**[a]

| entry | 4-DMAP, equiv | conversion,[b] % | formation yield,[b,c] % | others,[b] % |
|---|---|---|---|---|
| 1 | 0.10 | 94 | 91 | 3 |
| 2 | 0.15 | 99 | 95 | 4 |
| 3 | 0.17 | 99 | 95 | 4 |
| 4 | 0.19 | 100 | 95 | 4 |
| 5 | 0.29 | 100 | 96 | 4 |
| 6 | 0.39 | 100 | 97 | 4 |

[a] Similar conditions described in the Experimental Section. [b] Determined by HPLC. [c] Sum of compounds **16** and **17**.

***Scheme 6***




Compound **1** produced by the improved process did not contain any ethoxycarbonylated impurities. The side reaction to form ethoxycarbonylated byproduct during the hydrolysis of esters **16** and **17** was prevented by changing a reaction solvent from dry homogeneous conditions in ethanol into aqueous biphasic conditions in toluene/aqueous NaOH.

Isomerization of compound **18** under acidic conditions to give isomer **20** was observed in a crystallizing system (Scheme 6). To reduce the amount of isomer **20** formed, crystallization by addition of an alkaline aqueous solution of compound **18** into acidic aqueous acetone should be carried out below 25 °C.

The new process is more practical, efficient, and environmentally friendly than the medicinal process because of well-controlled impurities, higher yield, and no use of haloalkane. This process is amenable to large-scale production.

## Conclusions

We described a practical synthesis of compound **1**, which is the C-7 side chain of cefmatilen, a new cephalosporin antibiotic. The conditions were optimized to control the impurity and to increase the yield. Compound **1** was synthesized from compound **6** in an overall yield of 80% (12% higher than that for the medicinal process) via a four-reaction sequence (95% per reaction).

## Experimental Section

**Materials and Instrumentations.** Ethyl (*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate (**6**) was commercially available. The HPLC analysis was carried out on a COSMOSIL column (150 mm × 4.6 mm). The mobile phase

was at a flow rate of 1 mL/min, and a UV detector (245 nm) was used. NMR experiments were conducted by using a MERCURY 300 NMR spectrometer (Varian). IR spectra were obtained on a MAGNA 560 FT-IR spectrophotometer (Nicolet).

**Impurities Isolated from the Previous Process. (*Z*)-2-[2-(*N*-Ethoxycarbonylamino)thiazol-4-yl]-2-(hydroxyimino)acetic Acid (12).** Colorless crystalline powder. Mp 172−173 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.24 (t, 3H, $J$ = 7.5 Hz, Me), 2.51 (q, 2H, $J$ = 7.5 Hz, −$CH_2$−), 7.39 (s, 1H, 5-position of thiazole ring), 11.95 (s, 1H, −NH−). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 14.4, 61.7, 111.8, 142.0, 147.5, 154.0, 160.1, 164.4. IR (KBr): 1738, 1308, 1267 cm$^{-1}$. MS $m/z$ 260 $[M+H]^+$. Anal. Calcd for $C_8H_9N_3O_5S$: C, 37.06; H, 3.50; N, 16.21; S, 12.37. Found: C, 37.34; H, 3.43; N, 16.38; S, 12.38.

**(*Z*)-2-[2-(*N*-Ethoxycarbonylamino)thiazol-4-yl]-2-(triphenylmethyloxyimino)acetic Acid (13).** Colorless crystalline powder. Mp 148 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.22 (t, 3H, $J$ = 7.0 Hz, Me), 2.50 (s, 4.18 (q, 2H, $J$ = 7.0 Hz, −$CH_2$−), 7.27−7.35 (m, 15H, Ph and 5-position of thiazole ring), 12.00 (s, 1H, −NH−). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 14.2, 61.7, 90.8, 114.2, 127.3, 127.4, 127.7, 128.5, 140.7, 143.5, 148.5, 153.9, 160.5, 164.1. IR (KBr): 1727, 1559, 1447, 1236 cm$^{-1}$. MS $m/z$ 500 $[M-H]^-$. Water (KF) 1.51%. Anal. Calcd for $C_{27}H_{23}N_3O_5S\cdot 0.4H_2O$: C, 63.74; H, 4.55; N, 8.26; S, 6.30. Found: C, 63.94; H, 4.67; N, 8.30; S, 6.17.

**Sodium (*E*)-2-[2-(*N*-*tert*-Butoxycarbonylamino)thiazol-4-yl]-2-(hydroxyimino)acetate (20).** $^1$H NMR (300 MHz, $D_2O$) $\delta$ 1.53 (s, 9H, Me), 7.83 (s, 1H, 5-position of thiazole ring). $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 30.1, 86.7, 122.2, 140.9, 152.9, 156.8, 162.3, 173.0. MS $m/z$ 310 $[M+H]^+$, 332 $[M+Na]^+$. Anal. Calcd for $C_{10}H_{12}N_3O_5SNa$: C, 38.83; H, 3.92; N, 13.59; S, 10.37. Found: C, 38.54; H, 3.89; N, 13.38; S, 10.27.

**Improved Process (Scheme 4). Ethyl (*Z*)-2-(2-Aminothiazol-4-yl)-2-acetoxyiminoacetate (15).** A mixture of ethyl ester **6** (27.0 g, 125 mmol), acetone (46 g), 4-DMAP (0.16 g, 1.3 mmol), and acetic anhydride (14.1 g, 138 mmol) was warmed to 30 °C and stirred at 35 °C for 90 min or more until the content of ester **6** was less than 2.0% (by HPLC). The pH of the reaction mixture was adjusted to 5−6 with aqueous 3% sodium hydroxide (about 168 g) at 0 °C. The resulted slurry was stirred for 1 h at 0 °C. The precipitate was collected and rinsed with water (167 g) to give compound **15** (about 36.6 g) as a wet crystalline product. This was used in the next step without drying. A small amount of sample was dried for determining spectral data: Mp 87 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.40 (t, 3H, $J$ = 7.1 Hz, Me), 2.17 (s, 3H, Ac), 4.45 (q, 6H, $J$ = 7.1 Hz, −$CH_2$−), 6.78 (s, 1H, 5-position of thiazole ring), 7.56 (brs, 1H, −$NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 19.4, 62.5, 114.2, 140.4, 151.2, 161.3, 167.5, 170.2. IR (KBr): 3442, 1771, 1731, 1619, 1534,1286, 1203 cm$^{-1}$. MS $m/z$ 258 $[M+H]^+$. Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.02; H, 4.31; N, 16.33; S, 12.46. Found: C, 41.80; H, 4.33; N, 16.21; S, 12.49.

**Sodium (*Z*)-2-[2-(*N*-*tert*-Butoxycarbonylamino)thiazol-4-yl]-2-(hydroxyimino)acetate Monohydrate (18).** Compound **15** (about 36.6 g) as a wet crystal was dissolved in acetone (50 g) and toluene (296 g). The solution was distilled under reduced pressure at 40 to 55 °C to give the concentrate (about 190 mL) whose water content was less than 0.07%. A solution of $Boc_2O$ (44.9 g, 206 mmol) in toluene (54 g) and 4-DMAP (2.96 g, 24.2 mmol) was added to the solution of compound **15** at 20 to 35 °C. The mixture was warmed to 60 °C and stirred for 4 h and then cooled to 20 °C. Aqueous 20% NaOH (143 g) was added to the reaction mixture. The mixture was warmed to 60 °C and stirred for 4 h or more until the content of each compound **7**, **9**, **16**, and **17** was less than 0.1% (by HPLC). The layers were separated. Organic layer was back extracted with water (17 g). The aqueous layers were combined and added to a mixture of acetone (179 g) and aqueous 18% hydrochloric acid (99.5 g) at 15 to 20 °C. The pH of the mixture was adjusted to 6.0 with 48% sodium hydroxide. The resulted slurry was cooled to 0 °C and stirred for 30 min. The precipitate was collected and rinsed with chilled aqueous 70%(w/w) acetone (168 g) and dried to give compound **18** (35.3 g, 86% from ester **6**) as a slightly yellow crystalline powder. Mp ca. 194 °C dec; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.50 (s, 9H, Me), 7.76 (s, 1H, 5-position of thiazole ring), 11.31 (s, 1H, −NH−), 17.67 (s, 1H, −OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 27.9, 81.4, 113.0, 145.1, 147.1, 152.6, 159.0, 164.9. IR (KBr): 3595, 3194, 1715, 1609, 1565, 1401, 1252, 1158 cm$^{-1}$. MS $m/z$ 288 $[M+H]^+$. Water (KF) 4.67%. Anal. Calcd for $C_{10}H_{14}N_3O_6SNa$: C, 36.70; H, 4.31; N, 12.84; S, 9.80; Na, 7.02. Found: C, 36.61; H, 4.19; N, 12.69; S, 9.55; Na, 7.25.

**Triethylammonium (*Z*)-2-[2-(*N*-*tert*-Butoxycarbonylamino)thiazol-4-yl]-2-(triphenylmethyloxyimino)acetate (1).** Triethylamine (10.9 g, 108 mmol) and trityl chloride (30.0 g, 108 mmol) were added to the mixture of compound **18** (32.0 g, 97.8 mmol) and acetone (100 g) at 25 °C. The mixture was warmed to 50 °C and stirred for 3 h. After the completion of the reaction (by HPLC), the reaction mixture was cooled to 15 °C, diluted with ethyl acetate (173 g) and water (150 g), and then cooled to 10 °C. The pH of the mixture was adjusted to 1.2−1.7 with 33% sulfuric acid at 10 °C. The layers were separated. The organic layer was washed with water (64 g). Triethylamine (15.8 g, 156 mmol) was added to the organic extract and stirred for 5 min. The resulted slurry was distilled under reduced pressure to give a concentrate (160 mL). Ethyl acetate (230 g) was added to the concentrate, and the mixture was distilled under reduced pressure to give a concentrate (160 mL). Ethyl acetate (173 g) was added to the concentrate, and the mixture was distilled under reduced pressure to give the concentrate (160 mL) whose water content was less than 0.1%. The inside of the vessel was washed with ethyl acetate (18 g). The resulted slurry was stirred for 30 min at 25 °C. The precipitate was collected and rinsed with ethyl acetate (140 g) and dried to give compound **1** (57.4 g, 93%) as a colorless crystalline powder. Mp 171−173 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.16 (t, 9H, $J$ = 7.5 Hz, Me), 1.44 (s, 9H, Me), 3.00 (q,

6H, $J = 7.5$ Hz, $-CH_2-$), 7.29 (s, 1H, 5-position of thiazole ring), 7.04−7.37 (m, 15H, Ph), 11.60 (s, 1H, −NH−). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 8.48, 27.8, 44.9, 81.0, 89.2, 113.8, 126.8, 127.4, 128.8, 143.7, 144.7, 152.9, 154.3, 159.6, 166.1. IR (KBr): 1709, 1604, 1557, 1160 $cm^{-1}$. MS *m*/*z* 528 $[M-H]^-$. Water (KF) 0.79%. Anal. Calcd for $C_{35}H_{42}N_4O_5S \cdot 0.3H_2O$: C, 66.08; H, 6.75; N, 8.81; S, 5.04. Found: C, 66.05; H, 6.75; N, 8.90; S, 5.10.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