

# New Procedure for the Preparation of (Z)-2-(5-Amino-1,2,4-thiadiazole-3-yl)-2-trityloxyiminoacetic Acid

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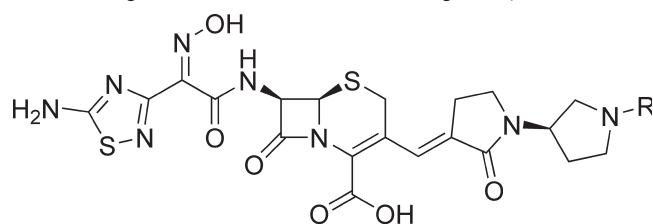
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## Supporting Information

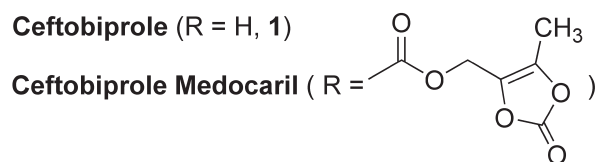
**ABSTRACT:** A novel and efficient procedure has been developed for the preparation of the C-7 side chain of ceftobiprole, (Z)-2-(5-amino-1,2,4-thiadiazole-3-yl)-2-trityloxyiminoacetic acid (**2**) from malononitrile (**9**) in a total yield of 19%. The key intermediate *N*-(3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)benzamide (**15b**) was synthesized for the first time in 76% yield by treatment of *N*-(3-aminoisoxazol-5-yl)acetamide (**13**) with benzoyl isothiocyanate. More importantly, (Z)-*N*-(3-(2-acetamido-2-oxo-1-(trityloxyimino)ethyl)-1,2,4-thiadiazol-5-yl)benzamide (**16b**) was prepared from **15b** with high stereoselectivity and good yield via successive oximation and protection of oxime hydroxy group. The process has a good prospect for industrial synthesis.

## INTRODUCTION

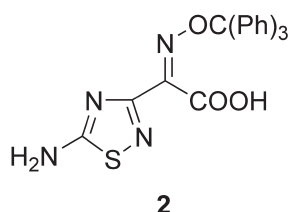
Ceftobiprole (Zeftera/Zevtera, **1**) is regarded as a new broad-spectrum fifth-generation cephalosporin antibiotic with high activity against a wide range of Gram-positive and Gram-negative pathogens, including several resistant species such as methicillin-resistant *Staphylococcus aureus* (MRSA),<sup>1,2</sup> penicillin-resistant *Streptococcus pneumoniae* (PRSP),<sup>1,2</sup> *Enterococcus faecalis*,<sup>2</sup> and *Pseudomonas aeruginosa*.<sup>2,3</sup> It was discovered and commercial produced by Basilea Pharmaceutical Company and developed by Johnson & Johnson Pharmaceutical Research and Development. Ceftobiprole (**1**) was approved in Canada in 2008 for the treatment of complicated skin and skin-structure infections under the trade name Zeftera.<sup>4,5</sup> The therapeutic activity of ceftobiprole medocartil, the water-soluble prodrug of ceftobiprole, was compared to that of vancomycin in a rat tissue cage model of chronic MRSA foreign-body infection.<sup>2,6</sup>



Ceftobiprole (R = H, **1**)



Ceftobiprole Medocartil (R = )



**2**

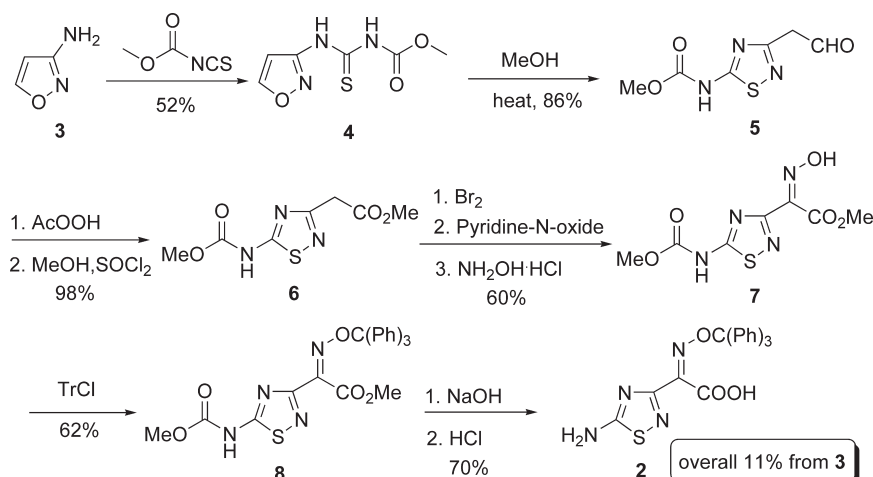
The C-7 side chain of ceftobiprole, (Z)-2-(5-amino-1,2,4-thiadiazole-3-yl)-2-trityloxyiminoacetic acid **2**, was proved to having a broad antibacterial spectrum. The original medicinal chemistry-based route of **2** is outlined in Scheme 1.<sup>7</sup> Commercially available 3-aminoisoxazole **3** was treated with methoxycarbonyl isothiocyanate in acetonitrile to give the thiourea derivative **4**, following by warming in methanol at 60 °C to afford the thiadiazolyl acetaldehyde **5**. Oxidation of **5** with peracetic acid provided the corresponding acetic acid, which was esterified with thionyl chloride and methanol to give methyl ester **6**. The hydroxyimino compound **7** was prepared from **6** through the corresponding keto ester in 60% yield via three-reaction sequence. Stereoselective protection of **7** with trityl chloride at 0 °C in the presence of triethylamine to give the Z-configuration of trityloxyimino methyl ester **8**, which was finally led to **2** by a base hydrolysis. However, there were the two following problems regarding Scheme 1 in the reported method, namely: (1) the overall yield of **2** was low (11% yield); (2) toxic and hazardous agents such as bromine and peracetic acid were used. Alternatively, the key intermediate **6** could be prepared from the 3-amino-5-methoxyisoxazole (**11**) directly through the skeletal rearrangement in several routes.<sup>8,9</sup> As shown in Scheme 2, the starting compound **11** was prepared from the malononitrile (**9**) through 3,3-dimethoxyacrylonitrile (**10**). Reaction of **11** with methoxycarbonyl isothiocyanate afforded **6** in 86% yield. Unfortunately, this route was impractical on a large scale due to its shortcomings such as low yield (38%) and harsh reaction conditions.

To improve the quality and the yield of product **2**, as well as to reduce the cost and make the process more environmentally suitable for a commercial production, we developed a new and efficient procedure for the preparation of **2** outlined in Scheme 3. Initially, an efficient one-pot synthesis of *N*-(3-aminoisoxazol-5-yl)acetamide (**13**) from malononitrile under mild conditions was described.<sup>10,11</sup> Important intermediates *N*-(3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)benzamide (**15b**) were prepared from compound **13** and benzoyl isothiocyanate through the skeletal rearrangement of thiourea intermediate

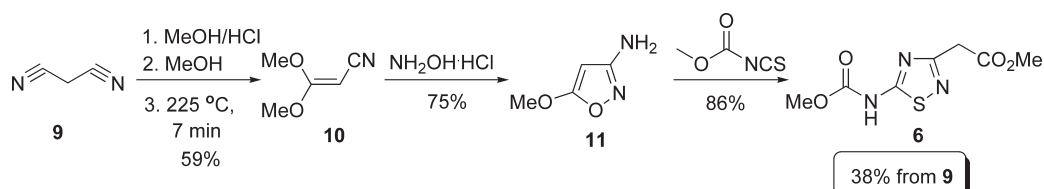
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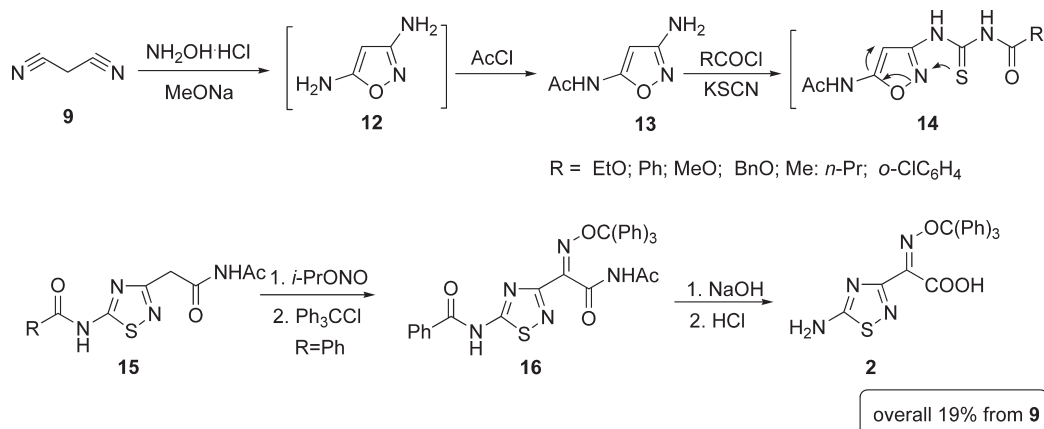
Scheme 1



Scheme 2



Scheme 3

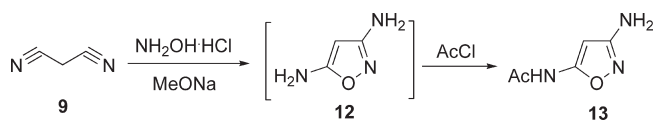


14 with good yield and purity.<sup>8,9,12</sup> The target compound 2 was formed and isolated as a white solid, and a purity of 98.5% was obtained by HPLC analysis after being recrystallized with ethanol. In this new procedure, up to 19% overall isolated yield was achieved from malononitrile.<sup>9</sup>

## RESULTS AND DISCUSSION

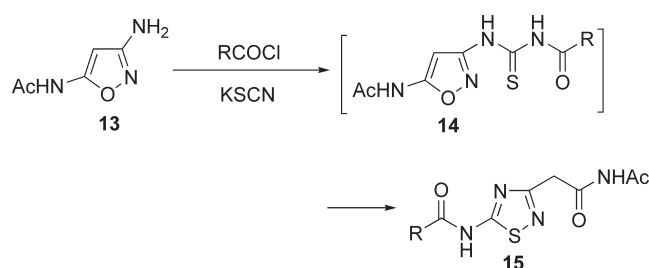
The starting *N*-(3-aminoisoxazol-5-yl)acetamide (13) was prepared from commercially available malononitrile (9) via two-reaction sequence in one pot. Thus, malononitrile was treated with hydroxylamine hydrochloride in the presence of sodium methoxide in methanol to afford 3,5-diamine-isoxazole (12),<sup>10</sup> which was subsequently converted into *N*-(3-aminoisoxazol-5-yl)acetamide (13)

with 71% yield through chemoselective acetylation of amino with 1.1 equiv of acetyl chloride at 5 °C.<sup>1</sup>



Then, how to efficiently convert compound 13 into 1,2,4-thiadiazoles 15 via a skeleton rearrangement of the thiourea intermediate 14 was one of our main tasks. Initially, treatment of compound 13 with ethoxycarbonyl isothiocyanate under various condition to afford ethyl 3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-ylcarbamate (15a) was investigated.<sup>8,9</sup> The results in Table 1 reveal that Lewis acids (zinc chloride) or bases (pyridine,

Table 1. Preparation of 15 from 13 under various conditions



entry	R	solvents	bases (equiv)	temp (°C)	time (h)	product 15 and yield <sup>a</sup> (%)
1	EtO	CH <sub>3</sub> CN	/	0	4	15a (55)
2	EtO	MeOH	/	0	5	15a (34)
3	EtO	CH <sub>3</sub> COCH <sub>3</sub>	/	0	5	15a (50)
4	EtO	EtOAc	/	0	4	15a (39)
5	EtO	CH <sub>3</sub> CN	/	25	3	15a (64)
6	EtO	CH <sub>3</sub> CN	/	40	3	15a (50)
7	EtO	CH <sub>3</sub> CN	/	70	2	15a (42)
8	EtO	CH <sub>3</sub> CN	pyridine (1.0)	25	4	15a (40)
9	EtO	CH <sub>3</sub> CN	Et <sub>3</sub> N (1.0)	25	4	15a (39)
10	EtO	CH <sub>3</sub> CN	TEMED <sup>b</sup> (1.0)	25	4	15a (41)
11	EtO	CH <sub>3</sub> CN	ZnCl <sub>2</sub> (1.0)	25	4	15a (30)
12	Ph	CH <sub>3</sub> CN	/	25	6	15b (76)
13	Ph	CH <sub>3</sub> CN	/	40	4	15b (70)
14	Ph	CH <sub>3</sub> CN	/	70	3	15b (63)
15	MeO	CH <sub>3</sub> CN	/	25	6	15c (66)
16	BnO	CH <sub>3</sub> CN	/	25	8	15d (60)
17	Me	CH <sub>3</sub> CN	/	25	8	15e (50)
18	<i>n</i> -Pr	CH <sub>3</sub> CN	/	25	10	15f (68)
19	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CN	/	25	6	15g (70)

<sup>a</sup> Isolated yields of 15 based on 13 (1.27 mol). <sup>b</sup> TEMED: *N,N,N',N'*-tetramethylethylenediamine.

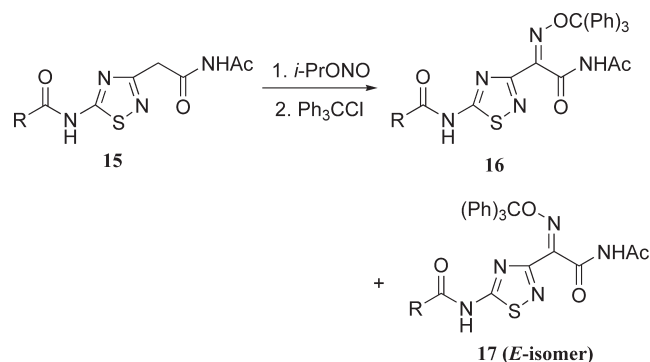
triethyl amine, and *N,N,N',N'*-tetramethylethylenediamine) could not increase the yields of 15a, and the highest yield was 64% under acid- or base-free condition (Table 1, entry 5). HPLC analysis revealed that the main byproduct was the unrearranged thiourea 14a, and the crude product was purified by recrystallization from acetone to yield a white crystalline. To improve the yield and product quality, other isothiocyanates instead of ethoxycarbonyl isothiocyanate were investigated for this reaction, and the results are summarized in Table 1. To our delight, when compound 13 was reacted with benzoyl isothiocyanate in acetonitrile at ambient temperature, the thiourea intermediate was nearly rearranged to the corresponding 1,2,4-thiadiazole 15b, and the product was isolated as yellow crystals with 76% yield (Table 1, entry 12).

With compounds 15 in hand, we then converted 15 into the corresponding trityloxyimino product 16. Treatment of 15a with isopropyl nitrite in THF containing conc. HCl to give the corresponding oxime compound, followed by addition of trityl chloride in the presences of triethylamine to give (*Z*)-configuration of trityloxyimino product 16. However, under various reaction conditions, the substrate 15a always brought out a mixture of the desired product 16a and its *E*-isomer 17a, which was isolated by silica gel chromatography (Table 2, entries 1–4). Low yield and cumbersome purification procedure of 16a led us to use other 1,2,4-thiadiazole to synthesize the *Z*-configuration of trityloxyimino product. Fortunately, it

was found that *N*-(3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)benzamide (15b) could be converted into the corresponding product 16b with the yield of 74% at room temperature under the similar condition, and only trace amount of *E*-isomer 17b was detected (less than 1%) by HPLC.

Finally, hydrolysis of the trityloxyimino product 16b to afford the target product 2 in a NaOH solution was investigated. Initially, the hydrolysis was carried out by using 20% NaOH (6 equiv) at 100 °C for 8 h; after acidification to pH = 3 with 10% HCl and filtration, the crude product was purified by recrystallization from ethanol to afford the desired product 2 in 29% yield (Table 3, entry 1). With respect to improving the yield of 2, various factors including the amount and concentration of NaOH and reaction temperature were carefully screened. Experimental results revealed that a higher concentration of NaOH (Table 3, entries 1–3) or a lower concentration of NaOH but longer reaction time (Table 3, entry 7) at high temperature easily led to the ring-opening of 1,2,4-thiadiazole to give some unknown side products, so that lower yields of 2 were obtained. The optimal condition was to carry out 16b with 5% NaOH (6 equiv) at 100 °C for 8 h (Table 3, entry 4) to give 2 with the isolated yield of 48% and a HPLC purity of 98.5%.

In summary, we have developed a new practical, efficient, and environmentally friendly process for the preparation of (*Z*)-2-(5-amino-1,2,4-thiadiazole-3-yl)-2-trityloxyiminoacetic acid 2 with a total yield of 19% from malononitrile. Several key intermediates

**Table 2.** Preparation of 16 from 15 under different conditions

entry	R	solvent	temp (°C)	time (h)	product 16/17 and yields <sup>a</sup> (%)	
					Z-isomer	E-isomer
1	EtO	THF	−20	7	16a (40)	17a (18)
2	EtO	THF	−10	6	16a (39)	17a (20)
3	EtO	THF	0	5	16a (40)	17a (21)
4	EtO	THF	25	4	16a (34)	17a (35)
5	EtO	THF	40	4	16a (30)	17a (47)
6	Ph	THF	0	5	16b (68)	—
7	Ph	THF	25	4	16b (74)	—

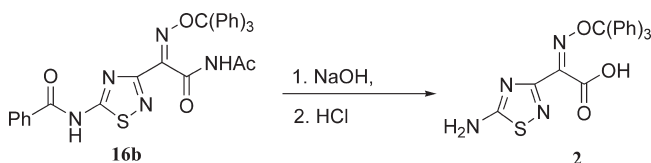
<sup>a</sup> Isolated yields based on 15.

such as *N*-(3-aminoisoxazol-5-yl)acetamide **13**, *N*-(3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)benzamide (**15b**), and (*Z*)-*N*-(3-(2-acetamido-2-oxo-1-(trityloxymino)ethyl)-1,2,4-thiadiazol-5-yl)benzamide (**16b**) were prepared with good yield and quality under mild conditions. For the well-controlled impurities, good yield, and no use of toxic and environmentally unfriendly reagents and solvents, this procedure is amenable to large-scale production.

## EXPERIMENTAL SECTION

**Materials and Instrument.** All solvents and reagents were purchased from commercial sources and were used without additional purification. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Avatar 370 instrument. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian (400 MHz) instruments in DMSO-*d*<sub>6</sub> with TMS as internal standard. Mass spectra were measured with a Finnigan Trace DSQ instrument. The HPLC analysis was performed on Agilent 1200 HPLC with DAD UV detector.

**Preparation of *N*-(3-Aminoisoxazol-5-yl)acetamide (**13**).** To a mixture of malononitrile (150 g, 2.27 mol) and hydroxylamine hydrochloride (156.6 g, 2.27 mol) in methanol (400 mL) was dropwise added a solution of sodium methoxide (240.3 g, 4.45 mol) in methanol (300 mL) at 5 °C over a period of 4 h. After stirring at the same temperature for 8 h, acetyl chloride (196.3 g, 2.50 mol) was dropwise added within 3 h. The reaction was stirred for 4 h further at the same temperature and condensed to one-third of the volume under vacuum. Then cold water (800 mL) was dropwise added, and the formed precipitates were filtered off, washed successively with water, and dried to

**Table 3.** Preparation of 2 from 16b under different conditions

entry	base (equiv)	temp (°C)	time (h)	yield <sup>a</sup> of product 2 (%)
1	20% NaOH (6)	100	8	29
2	10% NaOH (6)	100	8	34
3	8% NaOH (6)	100	8	36
4	5% NaOH (6)	100	8	48
5	5% NaOH (6)	80	12	40
6	5% NaOH (4)	100	12	30
7	2% NaOH (6)	100	12	28

<sup>a</sup> Isolated yields of 2 based on 16b.

afford **13** (226.6 g, 71% from **9**) as a pale-yellow solid. Mp 208.3–209.0 °C dec. IR (KBr): 3430, 3215, 1674, 1565, 1255 cm<sup>−1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 2.04 (s, 3H, CH<sub>3</sub>), 5.50 (s, 2H, −NH<sub>2</sub>), 5.68 (s, 1H, Ar-H), 11.15 (s, 1H, −NHCO−). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 23.0, 80.4, 159.0, 164.2, 166.3. MS (ESI): *m/z* (%) 140.3 [M − 1]<sup>−</sup>. HRMS (ESI) *m/z* calcd for C<sub>5</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: 141.0538; found: 141.0546. The HPLC analysis was performed on Agilent 1200 HPLC (Chromatographic column: Alltima C<sub>18</sub> 250 mm × 4.6 mm 5 μm) with DAD UV detector. Mobile phase was water/acetonitrile/40% Et<sub>3</sub>N solution = 94:4:1 with a flow rate of 1.0 mL/min. Detection wavelength was 230 nm, and injection volume was 20 μL.

**Preparation of Ethyl 3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl Carbamate (**15a**).** To a solution of potassium thiocyanate (135.8 g, 1.4 mol) in acetonitrile (350 mL) was dropwise added ethyl chloroformate (151.9 g 1.4 mol) at 5 °C over a period of 4 h. The mixture was stirred for 1 h further at room temperature. Then a solution of **13** (179.0 g, 1.27 mol) in acetonitrile (350 mL) was added, and the mixture was stirred at 25 °C for 3 h. Then the reaction mixture was cooled, and the formed solid was filtered. The crude product was recrystallized from acetone to give **15a** (221.8 g, 64% from **13**) as a white crystalline solid. Mp 167.4–168.5 °C dec. IR (KBr): 3453, 3302, 1710, 1566, 1242 cm<sup>−1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.27 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 2.16 (s, 3H, CH<sub>3</sub>), 3.98 (s, 2H, −CH<sub>2</sub>−), 4.28 (q, *J* = 7.2 Hz, 2H, −CH<sub>2</sub>−), 10.91 (s, 1H, −NHCOO−), 12.54 (s, 1H, −NHCOCH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 14.2, 24.8, 41.2, 62.7, 154.5, 165.2, 168.9, 171.1, 177.5. MS (ESI): *m/z* (%) 271.2 [M − 1]<sup>−</sup>. HRMS (ESI) *m/z* calcd for C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub>S: 272.0579 found: 272.0585.

***N*-(3-(2-Acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)benzamide (**15b**).** To a solution of potassium thiocyanate (160.5 g, 1.65 mol) in acetonitrile (420 mL) was dropwise added benzoyl chloride (231.8 g 1.65 mol) at 5 °C over a period of 5 h. The mixture was stirred for 3 h further at room temperature. Then a solution of **13** (179.0 g, 1.27 mol) in acetonitrile (350 mL) was added, and the mixture was stirred at 25 °C for 6 h. Then the reaction mixture was cooled, and the formed crystals were filtered, washed with ethanol, and dried to constant weight at 40 °C under high vacuum to give **15b** (293.42 g, 76% from **13**) as yellow crystals. Mp 178.2–178.9 °C dec. Chromatographic



purity by HPLC was shown to be 98%. IR (KBr): 3270, 3207, 1698, 1544, 1293  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.18 (s, 3H,  $\text{CH}_3$ ), 4.09 (s, 2H,  $-\text{CH}_2-$ ), 7.57 (t,  $J = 7.2$  Hz, 2H, ArH), 7.68 (t,  $J = 6.8$  Hz, 1H, ArH), 8.14 (d,  $J = 7.6$  Hz, 2H, ArH), 10.94 (s, 1H,  $-\text{NHCOPh}$ ), 13.49 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 24.9, 41.3, 128.5 (2C), 128.8 (2C), 130.5, 133.4, 164.7, 166.5, 169.0, 171.2, 176.0. MS (ESI):  $m/z$  (%) 305.1  $[\text{M} + 1]^+$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ : 304.0552; found: 304.0560. The HPLC analysis was performed on Agilent 1200 HPLC (Chromatographic column: XDB  $\text{C}_{18}$  150 mm  $\times$  4.6 mm 5  $\mu\text{m}$ ) with DAD UV detector. Mobile phase was 0.02 mol/L ammonium acetate water solution/acetonitrile = 20:80 with a flow rate of 1.0 mL/min. Detection wavelength was 226 nm, and injection volume was 20  $\mu\text{L}$ .

Similarly, compounds **15c–g** could be prepared from the corresponding isothiocyanates with satisfactory yield (Table 1)

**Methyl 3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-ylcarbamate (15c)**: 66% from **13**, yellow crystals. Mp 203.3–205.2  $^\circ\text{C}$  dec. IR (KBr): 3465, 3146, 1681, 1564, 1274  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.16 (s, 3H,  $\text{CH}_3$ ), 3.82 (s, 3H,  $\text{CH}_3$ ), 3.99 (s, 2H,  $-\text{CH}_2-$ ), 10.92 (s, 1H,  $-\text{NHCOO}-$ ), 12.61 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  24.9, 41.2, 53.7, 155.1, 165.3, 168.9, 171.2, 177.6. MS (ESI):  $m/z$  (%) 257.3  $[\text{M} - 1]^-$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_4\text{S}$ : 258.0423; found: 258.0426.

**Benzyl 3-(2-acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-ylcarbamate (15d)**: 60% from **13**, yellow crystals. Mp 178.5–179.0  $^\circ\text{C}$  dec. IR (KBr): 3445, 3270, 1756, 1526, 1230  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.16 (s, 3H,  $\text{CH}_3$ ), 4.00 (s, 2H,  $-\text{CH}_2-$ ), 5.30 (s, 2H,  $-\text{CH}_2-$ ), 7.37–7.46 (m, 5H, ArH), 10.92 (s, 1H,  $-\text{NHCOO}-$ ), 12.69 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 24.8, 41.2, 67.9, 128.3 (2C), 128.4, 128.5 (2C), 135.3, 154.5, 165.3, 168.8, 171.1, 177.4. MS (ESI):  $m/z$  (%) 333.1  $[\text{M} - 1]^-$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$ : 334.0736; found: 334.0742.

**2-(5-Acetamido-1,2,4-thiadiazol-3-yl)-N-acetylacetamide (15e)**: 50% from **13**, yellow solid. Mp 205.6–207.1  $^\circ\text{C}$  dec. IR (KBr): 3155, 3007, 1704, 1540, 1295  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.17 (s, 3H,  $\text{CH}_3$ ), 2.24 (s, 3H,  $\text{CH}_3$ ), 4.01 (s, 2H,  $-\text{CH}_2-$ ), 10.93 (s, 1H,  $-\text{NHCOCH}_3-$ ), 12.89 (br, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 22.1, 24.8, 41.3, 164.5, 168.9, 170.5, 171.1, 175.1. MS (ESI):  $m/z$  (%) 243.0  $[\text{M} + 1]^+$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_3\text{S}$ : 242.0474; found: 242.0479.

**N-(3-(2-Acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)butyramide (15f)**: 68% from **13**, yellow solid. Mp 134.9–135.8  $^\circ\text{C}$  dec. IR (KBr): 3217, 3157, 1679, 1282  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  0.91 (t,  $J = 7.4$  Hz, 3H,  $\text{CH}_3$ ), 1.65 (m, 2H,  $-\text{CH}_2-$ ), 2.17 (s, 3H,  $\text{CH}_3$ ), 2.51 (t,  $J = 7.2$  Hz, 2H,  $-\text{CH}_2-$ ), 4.01 (s, 2H,  $-\text{CH}_2-$ ), 10.92 (s, 1H,  $-\text{NHCOCH}_2-$ ), 12.92 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.4, 17.9, 24.8, 36.4, 41.2, 164.5, 169.0, 171.1, 173.2, 175.0. MS (ESI):  $m/z$  (%) 269.1  $[\text{M} - 1]^-$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_3\text{S}$ : 270.0787; found: 270.0781.

**N-(3-(2-Acetamido-2-oxoethyl)-1,2,4-thiadiazol-5-yl)-2-chlorobenzamide (15g)**: 70% from **13**, colorless crystals. Mp 93.8–95.0  $^\circ\text{C}$  dec. IR (KBr): 3540, 3214, 1687, 1550, 1295  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.15 (s, 3H,  $\text{CH}_3$ ), 4.05 (s, 2H,  $-\text{CH}_2-$ ), 7.44 (td,  $J_1 = 7.2$  Hz,  $J_2 = 1.6$  Hz, 1H, ArH), 7.51–7.57 (m, 2H, ArH), 7.66 (dd,  $J_1 = 7.2$  Hz,  $J_2 = 1.2$  Hz, 1H, ArH), 10.86 (s, 1H,  $-\text{NHCO}-$ ), 13.46 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$

NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  25.0, 41.3, 127.2, 129.6, 129.9, 130.4, 132.5, 132.6, 164.7, 166.2, 168.8, 170.9, 174.8. MS (ESI):  $m/z$  (%) 337.1  $[\text{M} - 1]^-$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}\text{ClN}_4\text{O}_3\text{S}$ : 338.0240; found: 338.0233.

**Preparation of (Z)-Ethyl 3-(2-acetamido-2-oxo-1-(trityloxyimino)ethyl)-1,2,4-thiadiazol-5-yl Carbamate (16a)**. To a solution of **15a** (54.4 g, 0.2 mol) and conc. HCl (4 mL, 0.04 mol) in THF (200 mL) was dropwise added isopropyl nitrite (21.4 g, 0.24 mol) at 0  $^\circ\text{C}$  within 1.5 h. The reaction mixture was stirred for further 3 h at the same temperature. Then the pH value of this mixture was adjusted to 10 with  $\text{Et}_3\text{N}$  (30.3 g, 0.3 mol), followed by addition of trityl chloride (78.0 g, 0.28 mol). After stirring at the same temperature for 2 h, the formed precipitate was filtered off and purified by column chromatography on silica gel with hexane/AcOEt (8:1) afford **16a** (43.7 g, 40%) as colorless crystals. Mp 260.7–262.5  $^\circ\text{C}$  dec. IR (KBr): 3458, 3301, 1685, 1524, 1242.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  1.29 (m, 3H,  $\text{CH}_3$ ), 2.05 (s, 3H,  $\text{CH}_3$ ), 4.32 (q,  $J = 7.2$  Hz, 2H,  $-\text{CH}_2-$ ), 7.28–7.35 (m, 15H, ArH), 10.70 (s, 1H,  $-\text{NHCOO}-$ ), 12.90 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 14.2, 24.3, 63.1, 92.7, 127.4 (3C), 127.8 (6C), 128.6 (6C), 143.3 (3C), 145.3, 154.9, 157.7, 162.3, 170.2, 177.5. MS (ESI):  $m/z$  (%) 566.2  $[\text{M} + \text{Na}]^+$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_5\text{S}$ : 543.1576; found: 543.1581.

**(E)-Ethyl 3-(2-Acetamido-2-oxo-1-(trityloxyimino)ethyl)-1,2,4-thiadiazol-5-yl carbamate (17a)**: 21% from **15a**, colorless crystal Mp 214.9–215.6  $^\circ\text{C}$  dec. IR (KBr): 3456, 3230, 1664, 1516, 1279  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  1.23 (m, 3H,  $\text{CH}_3$ ), 2.06 (s, 3H,  $\text{CH}_3$ ), 4.25 (q,  $J = 7.2$  Hz, 2H,  $-\text{CH}_2-$ ), 7.21–7.36 (m, 15H, ArH), 11.83 (s, 1H,  $-\text{NHCOO}-$ ), 12.83 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  14.2, 24.3, 63.1, 92.7, 127.4 (3C), 127.8 (6C), 128.6 (6C), 143.3 (3C), 145.3, 154.9, 157.7, 162.3, 170.2, 177.5. MS (ESI):  $m/z$  (%) 566.2  $[\text{M} + \text{Na}]^+$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_5\text{S}$ : 543.1576; found: 543.1584.

**Preparation of (Z)-N-(3-(2-Acetamido-2-oxo-1-(trityloxyimino)ethyl)-1,2,4-thiadiazol-5-yl)benzamide (16b)**. To a solution of **15b** (208 g, 0.68 mol) and conc. HCl (14 mL, 0.13 mol) in THF (800 mL) was dropwise added isopropyl nitrite (72.9 g, 0.82 mol) at 25  $^\circ\text{C}$  within 2 h. The reaction mixture was stirred for 3 h further at the same temperature. Then the pH value of this mixture was adjusted to 10 with  $\text{Et}_3\text{N}$  (103.0 g, 1.02 mol), followed by addition of trityl chloride (265.5 g, 0.95 mol). After stirring at the same temperature for 2.5 h, the formed precipitate was filtered off, washed with acetone, and dried to constant weight at 30  $^\circ\text{C}$  under high vacuum to afford **16b** as colorless crystals (290.2 g, 74%). Mp 227.4–228.6  $^\circ\text{C}$  dec. IR (KBr): 3458, 3228, 1688, 1539, 1289  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.08 (s, 3H,  $\text{CH}_3$ ), 7.26–7.37 (m, 15H, ArH), 7.59 (dd,  $J = 7.6$ , 7.6, 2H, ArH), 7.70 (dd,  $J = 7.6$ , 7.6, 1H, ArH), 8.17–8.20 (m, 2H, ArH), 10.73 (s, 1H,  $-\text{NHCOPh}$ ), 13.78 (s, 1H,  $-\text{NHCOCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 24.4, 92.6, 127.2 (3C), 127.6 (6C), 128.4 (6C), 128.5 (4C), 130.1, 133.3, 143.0 (3C), 145.2, 156.8, 161.9, 166.7, 169.9, 175.4. MS (ESI):  $m/z$  (%) 574.1  $[\text{M} - 1]^-$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{25}\text{N}_5\text{O}_4\text{S}$ : 575.1627; found: 574.1635. The HPLC analysis was performed on Agilent 1200 HPLC (Chromatographic column:  $\text{C}_{18}$  150 mm  $\times$  4.6 mm 5  $\mu\text{m}$ ) with DAD UV detector. Mobile phase was water/methanol/acetonitrile = 60:20:20 with a flow rate of 1.0 mL/min. Detection wavelength was 234 nm, and injection volume was 10  $\mu\text{L}$ .

**Preparation of (Z)-2-(5-Amino-1,2,4-thiadiazole-3-yl)-2-trityloxyiminoacetic Acid (2)**. A mixture of compound **16b**

(150 g, 0.26 mol) with NaOH (62.6 g, 1.57 mol) in water (1.25 L) was stirred for 8 h at 100 °C. After completion, the mixture was cooled to room temperature and acidified with 10% HCl to pH = 3. The formed crystals were filtered off and washed with water. Recrystallization from ethanol gave **2** as a white, cotton-wool-like solid (54.1 g, 48%). Mp 172.8–174.2 °C dec. IR (KBr): 3460, 3348, 1626, 1519 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.19–7.21 (m, 6H, ArH), 7.25–7.34 (m, 9H, ArH), 8.17 (s, 2H, –NH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 91.7, 127.3 (3C), 127.7 (6C), 128.3 (6C), 143.1 (3C), 146.1, 162.0, 162.5, 183.1 MS (ESI): *m/z* (%) 453.1 [M + Na<sup>+</sup>]<sup>+</sup>. HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>S: 430.1100 found: 430.1105. The HPLC analysis was performed on Agilent 1200 HPLC (Chromatographic column: Allima C<sub>18</sub> 150 mm × 4.6 mm 5 μm) with DAD UV detector. Mobile phase was water/acetonitrile/40% Et<sub>3</sub>N solution = 60:38:2 with a flow rate of 1.0 mL/min. Detection wavelength was 234 nm, and injection volume was 20 μL.

## ■ ASSOCIATED CONTENT

**S** Supporting Information. Proton NMR and mass spectra of compounds **13**, **15a–15 g**, **16a**, **16b**, **17a**, and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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