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AN EFFICIENT METHOD FOR THE SYNTHESIS OF 3-MERCAPTO-1-(1,3-THIAZOLIN-2-YL)AZETIDINE USEFUL FOR THE PENDANT MOIETY OF ORAL CARBAPENEM, L-084

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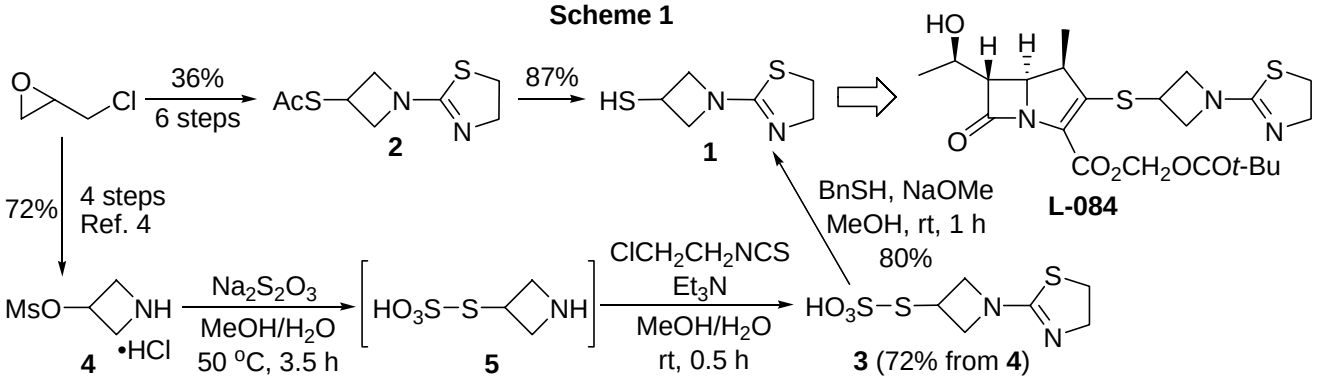
Abstract – An efficient method for the synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (**1**) is described. This thiol synthesis was achieved in 3 steps from readily available 3-methanesulfonyloxyazetidine *via* key intermediates, Bunte salts (**3** and **5**). The final step was enabled to proceed under mild conditions using the benzylthiol-mediated cleavage of the S-S bond in the Bunte salt (**3**).

3-Mercapto-1-(1,3-thiazolin-2-yl)azetidine (**1**)[1] is exploited as the C-2 substituent of the oral carbapenem antibiotic L-084, which is now in the clinical stage. L-084 shows a strong antimicrobial activity against Gram-positive and Gram-negative bacteria and also exhibits a significant pharmacokinetic profile especially in humans.[2] In the course of our synthetic study of L-084 on a large scale, we required a practical and economical process for **1** (Scheme 1). The compound (**1**) was previously prepared from an oily precursor, 3-acetylthio-1-(1,3-thiazolin-2-yl)azetidine (**2**), obtained by adopting a roundabout synthetic way from epichlorohydrin (31% total yield, 7 steps).[2] In order to establish a new route for **1**, we designed a precursor (**3**) (Bunte salt) that was protected with a sulfonate group instead of an acetyl group. Although it has been known since 1874 that the Bunte salt[3] bearing a thiosulfonate function was easily prepared at low cost using sodium thiosulfate, there have been few applications utilizing this functionalized intermediate in organic synthesis.

We first carried out the preparation of **3** in two steps from 3-methanesulfonyloxyazetidine hydrochloride (**4**)[4] which was synthesized according to the literature method. Compound (**4**) was reacted with sodium thiosulfate at 50 °C in a mixture of methanol and water to afford **5**[5] in 52% yield. At the next step, the

Bunte salt (**3**)[6] was obtained in 71% yield from the reaction of **5** and chloroethylisothiocyanate in the presence of triethylamine in a mixture of methanol and water. While this stepwise method can be used to prepare the desired compound (**3**), we envisioned that this synthesis could be achieved in the mixed solvents in a one-pot manner. As described in the following procedure, crystalline compound (**3**) was obtained in 72% yield from **4** without isolation of **5** (Scheme 1). The mixture of **4** (1.72 g, 10 mmol), sodium thiosulfate (1.58 g, 10 mmol), methanol (2 ml) and water (8 ml) was stirred at 50 °C for 3.5 h, and cooled to room temperature. To the reaction mixture were added chloroethylisothiocyanate (1.21 g, 10 mmol) and triethylamine (1.39 ml, 10 mmol) at room temperature. After stirring for 0.5 h, 2-propanol (10 ml) was added to the mixture, and the resulting precipitate was filtered and dried *in vacuo* to give **3** (gross 2.36 g, 77% purity, net 7.2 mmol). According to the sequential addition protocol, we successfully prepared the key intermediate (**3**) on a multi-kilogram scale with good reproducibility.

Scheme 1



The conversion of **3** to **1** was first tried by hydrolysis.[7] Although thiol (**1**) was obtained in 76% yield by treatment under a severe acidic condition (conc. HCl, 60 °C), disulfide (**6**) was concomitantly formed in 14% yield, and the removal of **6** from the crude product was found to be difficult.[4c] Because the formation of **6** could not be suppressed under any acidic conditions, we investigated Swan's method[8] in detail to obtain **1** selectively. The reduction method[9] of the Bunte salt ($RSSO_3H$) with thiol (R'SH), called Swan's method, has not been widely applied in organic synthesis because of its moderate chemoselectivity due to a disproportionation (Scheme 2).[10] Thus, we wished to optimize this reaction condition by screening thiols (R'SH). As shown in Table 1, we evaluated four kinds of thiols, methanethiol,[8b] hydroxyethanethiol,[9c] benzenethiol, and benzylthiol, by comparing the yields of **1**. The best result was

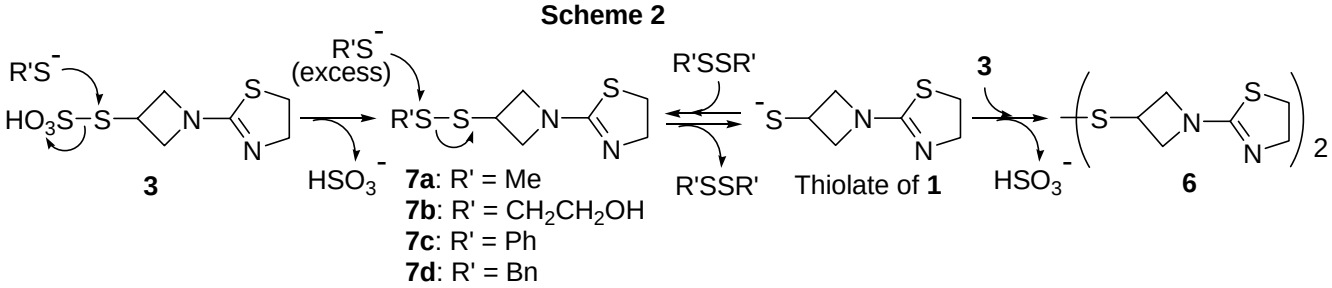
Table 1. Reduction of **3** with various thiols and thiolate[a]

Entry	Reagents (equiv.)	NaOMe (equiv.)[b]	Solvent	Time (min)	Yield (%)[c]
1	MeSNa (4)	-	H_2O	60	74 (-)
2	$HOCH_2CH_2SH$ (2.1)	2.1	MeOH	20	53 (-)
3	PhSH (3.2)	3.2	MeOH	60	22 (-)
4	BnSH (3.2)	3.2	MeOH	60	88 (80)

[a]All reactions were performed at rt. A trace amount compound (**6**) was ditected in all cases.
[b]28% Methanol solution. [c]HPLC yields of **1** after working up. Isolated yields are in parentheses.

obtained with the use of benzylthiol (80% isolated yield as a hydrochloride salt). Sodium methylthiolate also showed a high yield, but it failed to isolate **1**·HCl as crystals. The typical procedure in order to obtain **1** is as follows: To the mixture of benzylthiol (0.94 ml, 8 mmol) and 28% NaOMe (1.53 g, 8 mmol) in methanol (3.5 ml) was added **3** (gross 0.83 g, 77% purity, net 2.5 mmol) at room temperature, and the mixture was stirred for 1 h. After the reaction was quenched with 2 M HCl aq (6.5 ml), the aqueous layer was washed with $CHCl_3$ and concentrated to dryness under reduced pressure. The crude product was stirred in methanol, and the precipitate was removed by filtration. The filtrate was concentrated and crystallized (CH_3CN-THF) to give the hydrochloride salt of **1** (0.42 g, 80%).

Scheme 2



We then extensively surveyed the reaction of **3** checking several thiols (R'SH) for 24 h on the basis of the HPLC analysis.[11] When benzylthiol was allowed to react with **3**, heterodisulfide (**7d**)[12] was obtained in low yields (3~8%) throughout 24 h, probably due to the occurrence of a small reverse reaction of **1** to **7d**. On the other hand, heterodisulfides (**7a-c**)[12] gradually increased to 19, 56 and 61% yields at 24 h, respectively, accompanying the decrease in **1**. Regarding the formation of **6**, we found only its trace amount in each reaction.[13] We ascertained that the reaction using benzylthiol must be efficient for the further scale-up production of **1**.

In summary, an improved method for the synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (**1**), an important intermediate for the synthesis of L-084, has been developed. We established a practical method for the synthesis of **1** utilizing a novel and mild deprotection procedure of the Bunte salt (**3**), which was prepared economically and conveniently in a one-pot manner. The new method not only shortened the synthesis but also improved the overall yield of **1**, compared to the original method.

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5. Data for **5**: colorless crystals (from CH_3OH-H_2O), mp 225 °C (decomp.); IR (KBr) 3230, 1556, 1308, 1193, 1029 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.19-4.27 (m, 2H), 4.44-4.54 (m, 3H); HRMS (FAB) calcd for $C_3H_8NO_3S_2$ 169.9946 (MW+H), found *m/z* 169.9932 (M^++H).
6. Data for **3**: colorless crystals (from CH_3OH-H_2O), mp 218 °C (decmp.); IR (KBr) 3129, 3041, 1656, 1453, 1242, 1205, 1024 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.65 (t, *J* = 7.5 Hz, 2H), 4.00 (t, *J* = 7.5 Hz, 2H), 4.43-4.56 (m, 3H), 4.70 (dd, *J* = 8.4, 9.3 Hz, 2H); HRMS (FAB) calcd for $C_6H_{11}N_2O_3S_3$ 254.9932 (MW+H), found *m/z* 254.9953 (M^++H).
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11. HPLC conditions: Ultron VX-octyl 4.6 x 250 mm, 0.01 M sodium dodecyl sulfate (pH 2.2):MeCN = 1:1, 216 nm, rt, 1.4 ml/min.
12. Compounds (**7a-d**) were isolated as oils from each reaction mixture. Data for **7a**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.36 (m, 2H), 3.87-3.92 (m, 1H), 3.99-4.05 (m, 4H), 4.29 (m, 2H); EI-MS *m/z* 220 (M^+). Data for **7b**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (dt, *J* = 5.9, 9.0 Hz, 2H), 3.36 (t, *J* = 7.7 Hz, 2H), 3.84-3.90 (m, 2H), 3.91-3.96 (m, 1H), 3.99-4.04 (m, 4H), 4.31 (t, *J* = 7.7 Hz, 2H); EI-MS *m/z* 251 (M^++H). Data for **7c**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.33-3.38 (m, 2H), 3.83-4.04 (m, 5H), 4.22-4.32 (m, 2H), 7.20-7.54 (m, 5H); EI-MS *m/z* 282 (M^+). Data for **7d**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (t, *J* = 7.5 Hz, 2H), 3.39-3.46 (m, 1H), 3.81 (dd, *J* = 5.6, 8.7 Hz, 2H), 3.92 (s, 2H), 4.00 (t, *J* = 7.5 Hz, 2H), 4.07 (dd, *J* = 8.4, 8.7 Hz, 2H), 7.26-7.35 (m, 5H); EI-MS *m/z* 296 (M^+).
13. The Bunte salt (**3**) was reacted with **1**·HCl in the presence of NaOMe (2 equiv.) to afford **6** in 73% isolated yield. However, it was observed that only a trace amount of **6** was formed in the reaction shown in Scheme 2.