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Efficient Hydrolysis of β-Aminosulfamic Acids Using a Lewis Acid and a Thiol for the Synthesis of 2,3-Diaminopropanoate Derivatives

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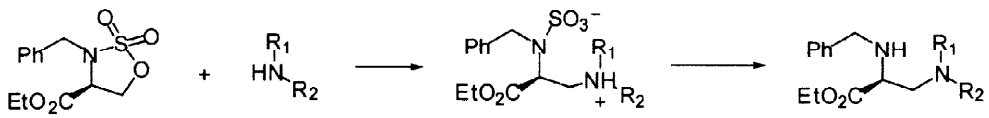
Abstract: New hydrolysis conditions for β-aminosulfamic acids produced from the opening of a cyclic sulfamidate with a variety of primary or secondary amines have been developed. This new hydrolysis method allowed us to use at most two equivalents of amine nucleophiles furnishing 2,3-diaminopropanoate derivatives in good to excellent yields.

Keywords: Amino acids and derivatives; Sulfamic acid and derivatives; Hydrolysis

Many natural and unnatural amino acid derivatives have been utilized for the construction of biologically active molecules.[1] From our continuing efforts in the development of novel enzyme inhibitors such as human immunodeficiency virus (HIV) protease inhibitors program,[2,3] we have been interested in the preparation of various optically active β-dialkylamine-substituted alanine derivatives as a natural amino acid surrogate. It has been known that treatment of alcohol-activated serine ester derivatives with amine nucleophiles tend to evoke elimination to yield α,β-unsaturated esters.[4] Quick review of the literature for the preparation of various 2,3-diaminopropanoate structures (**3**) revealed that opening of a cyclic sulfamidate[5] such as **1** derived from a serine ester with an amine nucleophile could serve as an attractive synthetic route (Eq. 1).[6,7] However, it was soon realized that the literature procedures called for large excesses of amine nucleophiles in order to furnish the diamine derivatives in an acceptable level of yields. Employment of excess amines would be undesirable in the cases where amine nucleophiles are not readily available. This prompted us to investigate the nucleophilic opening of the cyclic sulfamidates with various amines and particularly the subsequent hydrolysis of the intermediate β-aminosulfamic acid **2**. Herein we report a new, anhydrous method for the hydrolysis of β-aminosulfamic acids **2** through the use of a Lewis acid and a thiol, which allowed us to prepare β-aminoalanine derivatives (**3**) from the cyclic sulfamidate **1** in good to high yields using at most two equivalents of amines.



1 **2** **3** (1)

Preparation of the cyclic sulfamidate **1** was achieved from *N*-benzyl serine ethyl ester[8] according to the literature reported for a similar *tert*-butyl serine ester derivative.[6] Previously, ring opening of a cyclic sulfamidate prepared from the serine *tert*-butyl ester with pyrazole was investigated by Baldwin *et al.*[6] In this report, 5 equiv

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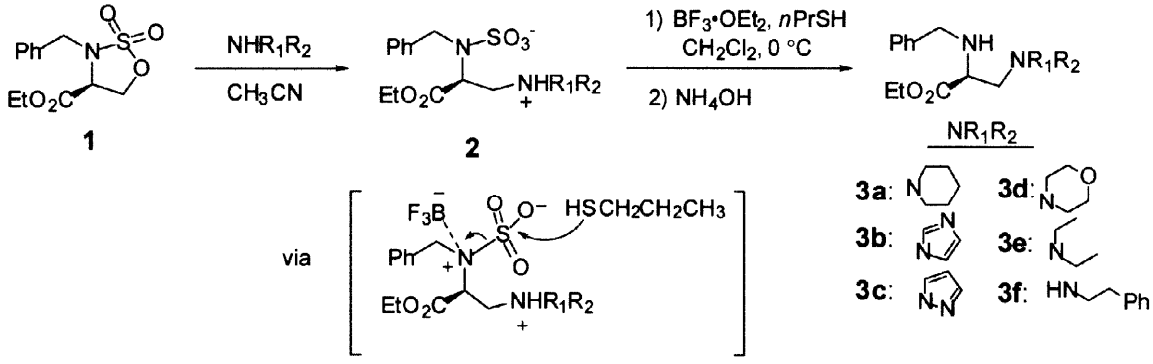
of pyrazole was employed to furnish 55% yield of the desired product. Alker *et al.* also carried out similar ring opening reactions of the cyclic sulfamidate derived from optically active 2-pyrrolidinemethanol with a variety of secondary amine nucleophiles in the presence of a catalytic amount of trifluoroacetic acid (TFA) in refluxing chloroform.[7,9] However, the Alker's conditions required a large excess of secondary amines to afford moderate to good yields of desired products. Our investigation of the opening reaction of the cyclic sulfamidate **1** with varying amounts of piperidine revealed that even with as low as 1.2 equiv of piperidine the initial ring opening reaction was virtually complete either in DMF or in acetonitrile at ambient temperature. The progress of the reaction was monitored through HPLC analysis (Vydac^{TM} C_{18} column, water:acetonitrile, 95:5 to 5:95, 1.0 mL/min gradient elution). This observation invariably relates the moderate yields and the need for large excess of amines to the hydrolysis step of the resulting sulfamic acid **2**. Indeed, when we carried out the hydrolysis of the sulfamic acid **2** under Alker's conditions, we found that the yield of the hydrolysis depended upon the amount of piperidine used in the ring opening reaction as shown in Table 1. When 1.0 equiv of piperidine was employed, almost no desired diamine was obtained. An appreciable level of yields were observed when the amount of piperidine was raised to 5-10 equiv (Table 1). This appears to indicate that the excess amine is required for the efficient hydrolysis.[10] When the TFA/chloroform hydrolysis conditions were applied to reactions involving primary amines and weakly nucleophilic amines with **1**, reactions were very sluggish. When acetonitrile or THF were tried as solvents in the reactions employing 5 equiv of piperidine, 33% and 35% yields of **3a**, respectively, were obtained showing no significant improvement over TFA/chloroform conditions.

Table 1. Yields of **3a** upon reaction with varying amounts of piperidine in TFA/chloroform[a]

Amount of piperidine	1.0 equiv	2.5 equiv	5.0 equiv	10.0 equiv
Isolated yield of **3a**	trace	18%	40%	52%

[a]The amount of TFA is usually a drop in mmol scale reactions.

Scheme 1.



For the hydrolysis of sulfamic acids such as **2** in aqueous acids, which is generally believed to proceed through an A2 mechanism,[11] the S–N bond cleavage has to occur through the nucleophilic attack of water molecule at the sulfur atom. Hydrolysis of sulfamic acids using aqueous mineral acids such as hydrochloric acid and sulfuric acid has been reported for simple sulfamidates.[9,11,12] However, in our case the reactions in aqueous mineral acids produced several products presumably due to instability of the ester functionality under the reaction conditions. A clue for milder anhydrous hydrolysis conditions came from facile deprotection method for benzyl ethers reported by E. Fujita *et al.*[13] Aliphatic and aromatic benzyl ethers have been readily cleaved to alcohols

upon treatment with boron trifluoride etherate and a thiol. This observation led us to suggest that a combination of a Lewis acid and a thiol could serve as an ideal system for the hydrolysis of β-aminosulfamic acids: the Lewis acid could activate the sulfamic acid through coordination from the nitrogen atom, and the thiol would serve as an excellent nucleophile for the sulfur atom, thus facilitating the cleavage of the sulfur-nitrogen bond[14] (Scheme 1). Indeed when we employed BF_3•OEt_2 and thiophenol for the hydrolysis of the sulfamidate **2**, 65% of the desired product **3a** was obtained after treatment with ammonium hydroxide. Later thiophenol was replaced by the more volatile 1-propanethiol, which provided almost the same result.

Table 2. Products with various amine nucleophiles using BF_3•OEt_2/nPrSH conditions.[a]

Entry	Nucleophile[b] (HNR_1R_2)	Coupling Conditions	Product diamines[c]	Product $[\alpha]_D$	Isolated Yields
1	piperidine	25 °C, 3.5 h	**3a**	$[\alpha]_D^{28}$ -38.1 (*c* 0.95, $CHCl_3$)	68%
2	imidazole	60 °C, 7.5 h	**3b**	$[\alpha]_D^{29}$ -21.0 (*c* 0.95, $CHCl_3$)	80%
3	pyrazole	60 °C, 6 h	**3c**	$[\alpha]_D^{28}$ -21.2 (*c* 0.75, $CHCl_3$)	83%
4	morpholine	25 °C, 4 h	**3d**	$[\alpha]_D^{26}$ -39.7 (*c* 0.50, $CHCl_3$)	65%
5	diethylamine	25 °C, 4 h	**3e**	$[\alpha]_D^{28}$ -43.5 (*c* 1.10, $CHCl_3$)	57%
6	2-phenylethylamine	25 °C, 4.5 h	**3f**	$[\alpha]_D^{29}$ -4.7 (*c* 1.04, $CHCl_3$)	52%

[a]A representative procedure for the preparation of diamine **3a** is as follows: To a solution of sulfamidate **1** (150 mg, 0.53 mmol) in dry acetonitrile (1.0 mL) was added piperidine (62 μL, 1.06 mmol) and the mixture was stirred for 3.5 h at room temperature, then solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (1.5 mL) and BF_3•OEt_2 (201 μL, 1.59 mmol) was added at 0 °C under nitrogen. Stirring was continued for 30 min and 1-propanethiol (144 μL, 1.59 mmol) was added. After the addition, the ice-bath was removed and stirring was continued for 1 h while the reaction mixture was allowed to warm to room temperature. Excess NH_4OH was added and the mixture was stirred for 0.5 h. Drying over anhydrous $MgSO_4$, filtration, concentration *in vacuo* followed by column chromatography of the crude product gave 100 mg (68%) of a pale yellow oil. [b]In all cases, two equiv of the amine was used for optimum yields. [c]All the spectral data including ^1H and ^{13}C NMR, infrared and high resolution mass spectra agreed with the indicated structures.

With this new protocol in hand, we have carried out hydrolyses of various β-aminosulfamic acids derived from the reaction of the sulfamidate **1** with a variety of primary and secondary amines. As seen in Table 2, weak nucleophiles such as imidazole and pyrazole required elevated temperature for the ring opening reaction and high yields of the diamines **3b** and **3c** were obtained after hydrolysis (entries 2 and 3, respectively). In the cases where cyclic or acyclic secondary amines were employed (entries 1, 4, and 5), the products were obtained in good yields. In order to check the stereochemical integrity of the process,[15] the secondary amine portions of two representative products, **3a** and **3c**, were derivatized with (*R*)-Mosher acid chloride[16] and (-)-menthyl chloroformate, respectively, and the ^1H NMR spectra of the resulting derivatives were compared with those of 1:1 diastereomeric mixtures prepared from (±)-**3a** and (±)-**3c**. The comparison in both cases indicated that *no apparent racemization occurred in the course of both the ring opening and the hydrolysis*. Optical rotation values of all products are listed in Table 2.

In conclusion, we have discovered mild anhydrous conditions for the hydrolysis of β-aminosulfamic acids

by employing a combination of a Lewis acid and a thiol. This new procedure allowed us to carry out coupling of various amine nucleophiles with the cyclic sulfamidate **1** furnishing good to excellent yields of 2,3-diaminopropanoate derivatives without employing excess amines. Further studies on the scope of this new method and the application to the building block synthesis for enzyme inhibitors are in progress and the results will be reported in due course.

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