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New Routes to N-Alkylated Cyclic Sulfamidates

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BOC- and dibenzosuberyl-protected chiral and hindered cyclic sulfamidates ([1,2,3]-oxathiazolidine-2,2-dioxides) were synthesized and subsequently deprotected using trifluoroacetic acid. The resulting crystalline sulfamidates were then used in several alkylation reactions involving benzyl bromide and alcohols in a versatile route to cyclic sulfamidates with differing *N*-alkyl substituents.

Introduction

In general, cyclic sulfamidates ([1,2,3]-oxathiazolidine-2,2-dioxides) are reactive alkylating reagents which can be used to convert amino alcohols into a diverse set of substituted amines and amino acids.[1,2] Their use is limited, however, as each substrate must be uniquely synthesized from its corresponding amino alcohol under conditions (e.g., treatment with $SOCl_2$ and RuO_4) that are incompatible with many sensitive molecules.

Cyclic sulfamidates have played an integral part in our development of subtype-selective β-adrenergic ligands for noninvasive, in-vivo imaging of the heart using positron emission tomography (PET).[3,4] In the interest of improving our β-adrenergic ligand syntheses, we sought a route to N-deprotected cyclic sulfamidates which could then be reacted with the ligand precursor in a convergent manner with the aim to eliminate several steps in the ligand synthesis with ^{18}F. This would be a strategic advantage, given the 110 min half-life of fluorine-18. We describe here the syntheses of two cyclic sulfamidates, (*R*)-4-methyl- (**15**) and 4,4-dimethyl- (**16**) oxathiazolidine-2,2-dioxides, produced from sulfamidates with easily removed N-protecting groups (BOC and dibenzosuberyl[5] (Sub)). We have used **15** and **16** in alkylation reactions with benzyl bromide, and 3-phenylpropanol as examples of general syntheses with conditions that may be applied to a variety of substrates in convergent syntheses of cyclic sulfamidates previously not accessible via conventional procedures.

Results and Discussion

Cyclic Sulfamidate Syntheses. The cyclic sulfamidites ([1,2,3]-oxathiazolidine-2-oxides), which are precursors to the sulfamidates, are typically prepared from N-protected amino alcohols and $SOCl_2$ in low polarity solvents at low temperature.[2,4] Attempts to synthesize carbamate-protected sulfamidites **5** and **7** in CH_2Cl_2, however, resulted in only fair yields (40−50%) and required high dilution conditions (ca. 5 mM of **1** or **2**, see Supporting Information) for success. The acyclic sulfite diesters **6** and **8** were the side products of these reactions, and their relative amounts increased in more concentrated reactions. A change of solvent to CH_3CN permitted higher concentrations to be used (ca. 0.48 M) and only limited amounts of **6** or **8** (Scheme 1) were produced. The carbamate nitrogens of **1** and **2** are expected to be less nucleophilic than their *N*-alkyl counterparts, and it appears that the more polar nature of CH_3CN facilitates the nucleophilic reactions of the carbamates **1** and **2**.

An optimized synthesis of the N-BOC sulfamidites (**5**, **7**) was developed using amino alcohol (**1**) as a model amino alcohol substrate. Best results were obtained by rapid addition of **1**, as a solution in CH_3CN, to a cold (−40 °C) solution of $SOCl_2$ (2.5 equiv) in CH_3CN, and then adding pyridine (5 equiv) to neutralize HCl produced in the reaction (Scheme 1). Pyridinium hydrochloride was conveniently removed by precipitation with EtOAc and subsequent filtration. The product was simply purified by filtration over silica, and it was convenient to use this isolated sulfamidite directly in the subsequent RuO_4 oxidation.

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(1) Some recent examples include: Lyle, T. A.; Magill, C. A.; Pitzenberger, S. M. *J. Am. Chem. Soc.* **1987**, *109*, 7890−7891. Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4584−4586. Stiasny, H. C. *Synthesis* **1996**, 259−264. Aguilera, B.; Fernandez-Mayoralas, A.; Jaramillo, C. *Tetrahedron* **1997**, *53*, 5863−5876. Zubovics, A.; Toldy, L.; Varro, A.; Rabloczky, G.; Kürthy, M.; Dvortsak, P.; Jerkovich, G.; Tomori, E. *Eur. J. Med. Chem.* **1986**, *21*, 370−378. Kim, B. M.; So, S. M. *Tetrahedron Lett.* **1998**, *39*, 5381−5384. Ok, D.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **1999**, *40*, 3831−3834. Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421−1429. Atfani, M.; Wei, L.; Lubell, W. D. *Org. Lett.* **2001**, *3*, 2965−2968. Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94−104.

(2) For a review of cyclic sulfates and sulfamidates, see Lohray, B. B.; Bhushan, V. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1997; Vol. 68, pp 89−180.

(3) Posakony, J. J.; Tewson, T. J. *J. Labelled Compd. Radiopharm.* **1999**, *42*, S527−529.

(4) Posakony, J. J.; Tewson, T. J. *Synthesis*, in press.

(5) Pless, J. *Helv. Chim. Acta* **1976**, *59*, 499−512.

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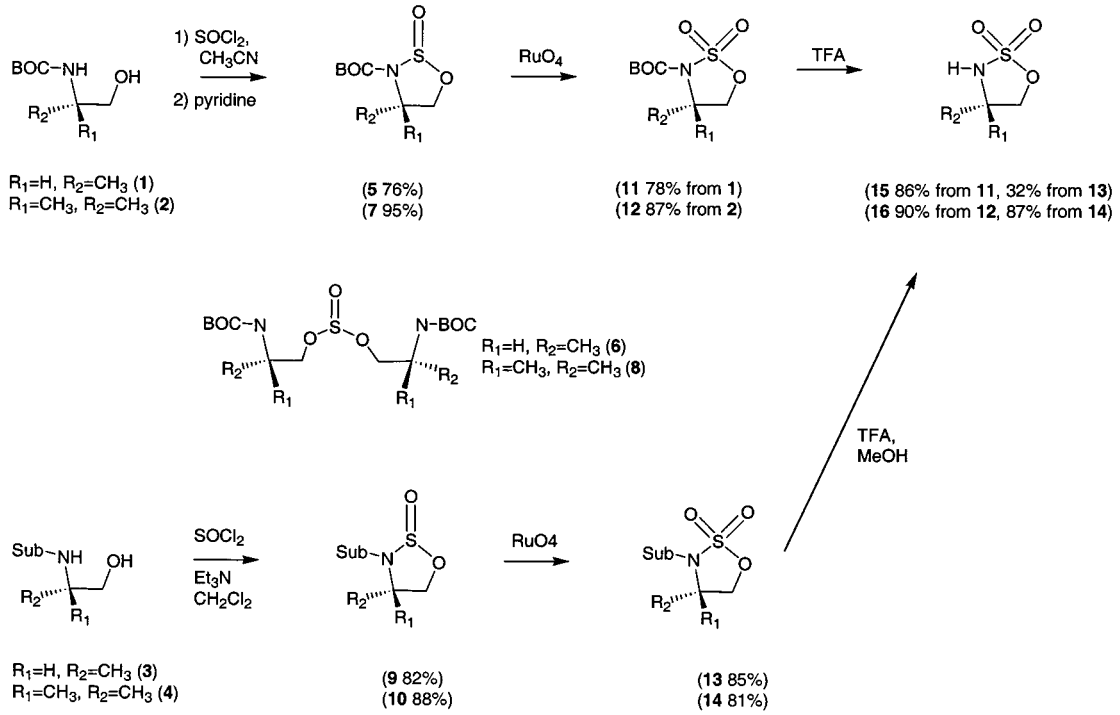
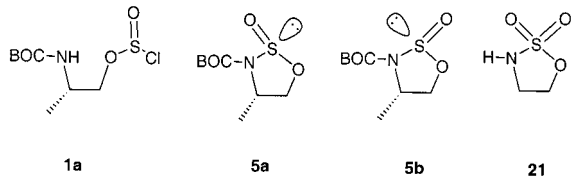
SCHEME 1



Under these conditions, the chlorosulfite ester of **1** (**1a**) is the expected initial product of the reaction, which would be converted to **5** after adding pyridine. The presence of **1a** was indicated by TLC which showed an intermediate product (tentatively assigned as **1a** or a hydrolysis product thereof on the TLC plate) and a trace of **5** before pyridine addition. After adding pyridine, large quantities of **5** were observed, whereas the intermediate was absent. Sulfite **6** was present both before and after the pyridine addition. Using less $SOCl_2$ or conducting the reaction at rt led to increased production of unwanted **6**.



1a **5a** **5b** **21**

We determined the overall yields of compounds **5** and **6**, and **7** and **8**, using small-scale reactions. Compounds **5** and **6** (from **1**) were isolated in 76% and 9% yields, respectively, after chromatographic purification. In contrast, amino alcohol **2** yielded **7** in 95% yield, and no **8** was isolated. In the synthesis of **5**, two products (assigned as **5a** and **5b**) were separated by repeated column chromatography. As expected for diastereomeric sulfamidites,[6] compounds **5a** and **5b** exhibited identical mass spectra, but different ^1H NMR spectra, and each yielded **11** when treated with RuO_4. Interestingly, the synthesis of **5** in CH_2Cl_2 afforded exclusively **5a** (41% yield, Supporting Information). The RuO_4 oxidations of the crude sulfamidites **5** and **7** yielded sulfamidates **11** and **12** in 78 and 87% overall yields, respectively.

The dibenzosuberyl-protected sulfamidates **13** and **14** were synthesized from the corresponding protected amino alcohols **3** and **4** under the same conditions used for our previous synthesis of *N*-benzyl cyclic sulfamidates.[4] The overall yields of **13** and **14** were approximately 70%.

Sulfamidate Deprotection. The utility of N-deprotected cyclic sulfamidates as general reagents is dictated largely by their accessibility. In our hands, attempts at synthesizing these unprotected sulfamidates using unprotected amino alcohols with conventional cyclic sulfamidite/sulfamidate procedures were unsuccessful. Thus, it encouraged us to develop a strategy to prepare cyclic sulfamidates with protecting groups that are easily removed by acid, such as BOC and dibenzosuberyl[5] (Sub). The trityl group was also investigated, but proved to be incompatible with RuO_4.

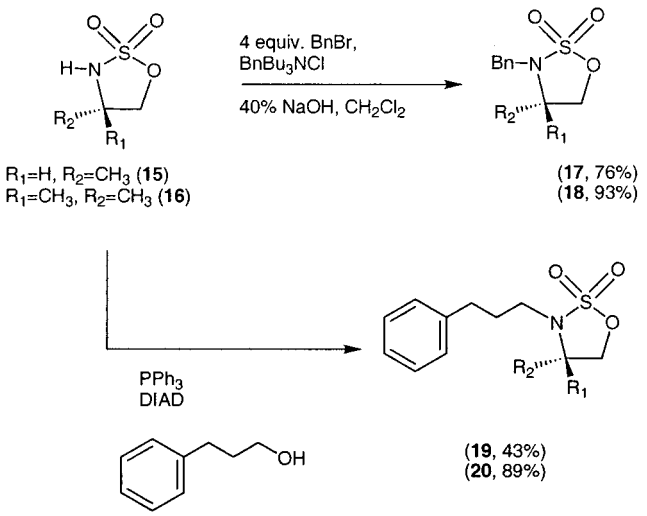
There are only a few reported examples of unprotected cyclic sulfamidates, one being [1,2,3]-oxathiazolidine-2,2-dioxide (**21**) described by Corral et al.; however, few details were provided.[6] Espino et al. recently described the preparation of unprotected cyclic sulfamidates via Rh-catalyzed oxidative cyclization of sulfamate esters, a method that holds great promise for the synthesis of a variety of cyclic sulfamidates.[7] However, that method appears unsuitable for the preparation of **15** and **16**, in part because of the bias to form oxathiazinanes (six-membered cyclic sulfamidates) and a lack of enantioselectivity given an achiral starting alcohol, a necessary precursor to **15**.

Deprotection of the BOC- and Sub-protected sulfamidates was readily accomplished at rt with an excess of TFA in CH_2Cl_2 (Scheme 1). Starting from **11** and **12**, sulfamidates **15** and **16** were isolated in 86−90% yield.

(6) Corral, C.; Lissavetzky, J.; Manzanares, I.; Darias, V.; Expósito-Orta, M. A.; Conde, J. A. M.; Sánchez-Mateo, C. C. *Bioorg. Med. Chem.* **1999**, *7*, 1349−1359.

(7) Espino, C. G.; When, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936.

SCHEME 2



Addition of TFA to a solution of **13** (or **14**) in CH_2Cl_2 yielded an orange/red solution, presumably due to the presence of the dibenzosuberyl cation, and TLC indicated the presence of **15** (or **16**) along with materials with higher R_f values. If the solvent was removed from this orange/red solution, **13** (or **14**) reformed, suggesting an equilibrium between the free sulfamidate and **13** (or **14**). This unwanted process was minimized by adding MeOH and then base after solvent evaporation. It appears that the dibenzosuberyl cation was captured by MeOH and 5-methoxydibenzosuberane was formed. Sulfamidate **15** was then isolated by chromatography in 32% yield (55% yield of recovered **13**). In contrast, **16** was isolated in high yield (87%) without resorting to chromatography.

Alkylation Reactions. The challenges inherent in the alkylation of sulfamidates **15** or **16** are not insignificant, because the products of these reactions are themselves potent electrophiles. The unprotected cyclic sulfamidates (N−H forms) are relatively poor electrophiles compared to their N-substituted counterparts.[7] In addition, deprotonated **15** and **16** are also quite resistant to nucleophilic attack, as shown by the stability of these sulfamidates in aqueous NaOH (Experimental Section). Thus, we sought conditions mild enough to preserve the N-alkylated products but under which the sulfamidate would be deprotonated and, as such, be able to act as a nucleophile (Scheme 2).

Good results were obtained in phase-transfer-catalyzed reactions. Sulfamidates **15** and **16** reacted with an excess (4 equiv) of benzyl bromide under optimized conditions (5 mol % $BnBu_3NCl$ and aqueous NaOH) to provide the N-benzylated products, **17** and **18**[4] in 76 and 93% yields, respectively. TLC analysis of the organic and aqueous phases revealed that the sulfamidate (**15** or **16**) was transferred to the aqueous phase within minutes of addition, presumably present as its deprotonated anion. The yields were lower when less than 4 equiv of benzyl bromide was used.

When these same phase-transfer catalyzed conditions were applied to the less reactive 1-bromo-3-phenylpropane or 3-phenylpropyl methanesulfonate,[8] no reaction was observed even after several days of stirring, apart from a gradual loss of the starting sulfamidate. These phase transfer-catalyzed conditions appear to be limited to very reactive alkylating reagents such as benzyl bromide.

Other attempts to deprotonate and alkylate sulfamidate **15** with alkyl bromides, iodides and mesylates in DMF or DMSO were also unsuccessful. ^{1}H NMR experiments demonstrated upfield shifts for sulfamidate CH and CH_2 signals and loss of the N−H signal when **15** was treated with DBU. This was consistent with the formation of the anion of **15** in solution. Sulfamidate **15** could also be deprotonated by KO-*t*-Bu, aqueous K_2CO_3, and lithium bis-trimethylsilylamide, whereas Et_3N did not induce such changes in the ^{1}H NMR spectra.

Deprotonated **15** reacted with benzyl bromide to form **17** in ∼50% yield, but no alkylation occurred when deprotonated **15** was mixed with 1-bromo-3-phenylpropane, 3-phenylpropyl methanesulfonate, or 1-iodo-2-phenylethane. By ^{1}H NMR, the alkyl halide/mesylate signals remained unchanged, but a gradual loss of deprotonated **15** was observed.

The Mitsunobu reaction proved more useful for N-alkylating **15** and **17**. For example, 3-phenylpropanol and **15** and **16** yielded the 3-(3-phenylpropyl)-substituted sulfamidates **19** and **20**, in 43 and 89% yields, respectively. The most favorable conditions used an excess of diisopropyl azodicarboxylate (DIAD), PPh_3 and the alcohol (1.6 equiv each) in CH_3CN or THF.

To investigate the relatively low yield of **19**, several control reactions were conducted and monitored by ^{1}H NMR and TLC. The sulfamidates **15** and **17** (a model substrate for **19**) were not inherently sensitive to PPh_3 or DIAD, as shown by experiments in CD_3CN over a period of 30 min. However, when DIAD (1 equiv) was added portionwise to a solution of PPh_3 and sulfamidate **15** in CD_3CN, ^{1}H NMR and TLC indicated that **15** was being consumed and the quality of the ^{1}H NMR spectrum deteriorated. Similar results were obtained when PPh_3 was added to a solution of **17** and DIAD. Thus, the low yield of **19** was presumably a result of **15** and/or **19** reacting with the PPh_3/DIAD adduct formed in-situ to form ring-opened products. In contrast, the reactive carbon centers on sulfamidates **16** and **20** are less accessible, and this may have curtailed unwanted side-reactions.

Conclusion

Routes to *N*-alkyl cyclic sulfamidates were developed that should be applicable to the synthesis of previously inaccessible cyclic sulfamidates. Cyclic sulfamidates with BOC- and dibenzosuberyl protecting groups were synthesized in good overall yield from their corresponding amino alcohols. These protecting groups were conveniently removed from these sulfamidate derivatives using TFA and sulfamidates **15** and **16** were isolated as stable, crystalline compounds. A phase transfer-catalyzed alkylation of **15** and **16** was developed, but this was useful only with benzyl bromide. The Mitsunobu reaction was a practical alternative for alkylation of **15** and **16** with a primary alcohol to yield **19** and **20**.

Experimental Section

Low resolution mass spectrometry was performed using electrospray ionization. ^{1}H NMR coupling constants are rounded

(8) Weibull, B. *Acta Chem. Scand.* **1995**, *49*, 207−216.

to the nearest 0.5 Hz. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Prior to elemental analysis, samples were dried under high vacuum at 40−50 °C. Flash column chromatography was performed using silica gel (Merck, grade 9385, 230−400 mesh). Analytical TLC was performed using silica gel Analtech GF plates (0.25 mm); preparative TLC was performed using silica gel Analtech GF plates (1 mm). Product visualization on TLC was performed using UV light or by spraying the plate with a sulfuric acid reagent solution (1:1 v/v MeOH/concentrated H_2SO_4 or 0.25 g $K_2Cr_2O_7$ in 7 M H_2SO_4) followed by heating. Unless otherwise noted, reagents were purchased from Aldrich Chemical Co. Solvents were ACS reagent grade or better and anhydrous solvents (Aldrich) were used as received unless otherwise indicated. CH_3CN and pyridine were dried by storing over activated, crushed 3 Å molecular sieves.

2-((*tert*-Butyloxycarbonyl)amino)-2-methylpropan-1-ol (2). Reaction conditions described by Caputo et al.,[9] used to synthesize other BOC-amino alcohols, were adapted to synthesize **2**. Briefly, Et_3N (1.4 mL, 10 mmol) and 2-methyl-2-aminopropan-1-ol (1 mL, 10 mmol) were dissolved in dry THF (30 mL), and the mixture was cooled to 0 °C. BOC_2O (2.3 g, 10 mmol) was added, and then the cooling bath was removed. After stirring for 90 min at rt, the solvent was removed. Water (50 mL) was added to the residue, and the mixture was extracted with EtOAc (100 mL). The organic extract was dried (Na_2SO_4), and the solvent was removed. The product was recrystallized from EtOAc/heptane to yield 1.55 g (8.2 mmol, 82%): mp 59.5−60.5 °C (lit.[10] 57−60 °C); R_f = 0.65 (CH_2Cl_2:acetone 20:1); MS *m*/*z*: 190.3 (100, M + H), 134.2 (M + H − C_4H_8); ^{1}H NMR (CD_3CN) 1.20 (s, 6H), 1.41 (s, 9H), 3.44 (s br, 3H), 5.15 (s br, 1H). Anal. Calcd for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.40. Found: C, 57.02; H, 10.30; N, 7.21.

(*R*)-2-((5-dibenzosuberyl)amino)propan-1-ol (3). A solution of 5-chlorodibenzosuberane (0.59 g, 2.6 mmol) in dry CH_3CN (10 mL) was added dropwise over 30 min to a solution of (*R*)-2-aminopropan-1-ol (0.2 mL, 2.6 mmol) and Et_3N (0.37 mL, 2.7 mmol) in dry CH_3CN (15 mL). After the addition was complete, the solution was stirred for 30 min, and then the solvent was removed. The resulting product residue was chromatographed on silica gel (1:1 hexanes:EtOAc) to yield two products. The more mobile product (R_f = 0.76; 0.19 g, 16%) was identified as the *O*- and *N*-bis(dibenzosuberyl)-protected amino alcohol and was discarded. Compound **3** (R_f = 0.5, 0.4 g, 58%) was isolated as a colorless oil which solidified over several days: mp 69.5−70.5 °C; MS *m*/*z*: 268.1 (10, M + 1), 193 (100, $C_{15}H_{13}^+$); ^{1}H NMR ($CDCl_3$) 1.11 (d, J = 6.5 Hz, 3H), 2.0 (s br, 2H), 2.7 (m, 1H), 2.9−3.1 (m, 2H), ABX spin system (3.2 (dd, 1H), 3.45 (dd, 1H), 3.85 (m, 1H), J_{AB} = 10.5 Hz, J_{AX} = 4 Hz, J_{BX} = 7 Hz), 3.55 (m, 1H), 4.95 (s, 1H), 7.1−7.3 (m, 8H). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.85; H, 7.92; N, 5.24. Found: C, 80.71; H, 8.07; N, 5.24.

2-((5-Dibenzosuberyl)amino)-2-methylpropan-1-ol (4). The synthetic procedure for preparing **3** was applied to 2-amino-2-methylpropan-1-ol, but chromatography was performed using hexanes/EtOAc (3:2) to afford **4** (70%) as a colorless oil: MS *m*/*z*: 193 (100, $C_{15}H_{13}^+$), 282.1 (15, M + 1); ^{1}H NMR ($CDCl_3$) 1.09 (s, 6H), 1.6 (s br, 2H), 2.95 (s br, 2H), 3.17 (s, 2H), 3.8 (s br, 2H), 5.0 (s br, 1H), 7.1−7.3 (m, 8H). Compound **4** was used without further purification to synthesize **10**.

(*R*)-3-(*tert*-Butyloxycarbonyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (5). A solution of $SOCl_2$ (10.4 mL, 143 mmol) in dry CH_3CN (70 mL) under Ar was cooled to −40 °C, and then (*R*)-2-((*N*-*tert*-butyloxycarbonyl)amino)propan-1-ol[9] (**1**, 10 g, 57 mmol) in dry CH_3CN (50 mL) was added dropwise over 12 min. TLC indicated a new product (R_f = 0.3; 10:1 CH_2Cl_2:acetone) and a trace of **5**. Dry pyridine (23 mL) was then added, and TLC indicated larger quantities of **5** (R_f = 0.7). The mixture was then allowed to warm to room temperature. The solvent volume was reduced to ca. 75 mL, EtOAc (100 mL) was added, the resulting precipitate was filtered off, and the filtrate was concentrated to a residual oil. This material was filtered through a plug of silica (4 cm × 6 cm dia.), eluting with EtOAc/hexanes (1:1, 400 mL). Solvent removal afforded crude **5** as an oil (11.8 g) which also contained a small amount of the corresponding sulfite **6**. Crude **5** was used directly in the RuO_4 oxidation, described below.

Small scale (× 0.1) reactions were performed and the products isolated by chromatography on silica (50:1 to 20:1 CH_2Cl_2:acetone) to accurately determine the yields of **5** and **6** in these reactions. Sulfite **6** (0.21 g, 9.3%) was isolated as a white solid and then recrystallized from CH_2Cl_2:hexanes for analysis: mp 97−98 °C; R_f = 0.25 (50:1 CH_2Cl_2:acetone); MS *m*/*z*: 397.1 (5, M + 1), 419.1 (100, M + 1); ^{1}H NMR ($CDCl_3$) 1.20 and 1.21 (two d, J = 6.5 Hz, 6H), 1.45 (s, 18H), 3.9−4.1 (m, 6H), 4.7 (s br, 2H). Anal. Calcd for $C_{16}H_{32}N_2O_7S$: C, 48.46; H, 8.14; N, 7.06. Found: C, 48.39; H, 8.26; N, 7.06. Sulfamidite **5** (0.955 g, 76%) was isolated as an oily mixture of **5a** and **5b** (1.45:1 ratio), which were later separated by repeated chromatography (100:1 CH_2Cl_2:acetone, R_f = 0.39 and 0.45, respectively). **5a** and **5b**: MS *m*/*z*: 244 (25, M + Na), 239 (100, M + NH_4), 222 (20, M + H), 197.9 (20, M + K − C_4H_8), 183 (20, M + Na − C_4H_8), 165.9 (M + H − C_4H_8). **5a**: ^{1}H NMR ($CDCl_3$) 1.28 (d, J = 6.5 Hz, 3H), 1.52 (s, 9H), 4.30 (m, 2H), 5.03 (dd, J_1=9 Hz, J_2=5.5 Hz, 1H). Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.44; H, 6.84; N, 6.33. Found: C, 43.51; H, 7.11; N, 6.35. **5b**: ^{1}H NMR ($CDCl_3$) 1.48 (d, J = 6 Hz, 3H), 1.51 (s, 9H), 4.05 (m, 1H), 4.66 (dd, J_1=J_2=9 Hz), 4.76 (dd, J_1=9 Hz, J_2=7 Hz). Anal. Found: C, 43.39; H, 7.06; N, 6.29.

3-(*tert*-Butyloxycarbonyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2-oxide (7). Sulfamidate **7** was synthesized with the same procedure used to prepare **5**. When carried out using 6 g of **2** (31.7 mmol), 7.1 g of crude **7** was isolated, which contained only a trace of **8** by TLC. This crude product was used directly in the RuO_4 oxidation step to prepare (**12**). The reaction was also carried out using 1 g (5.3 mmol) of **2** which yielded pure **7** (1.18 g, 95%) as an oil after column chromatography: R_f = 0.75, CH_2Cl_2:acetone 50:1; MS *m*/*z*: 274.1 (10, M + K), 258.1 (100, M + Na), 253.1 (M + NH_4), 236.1 (M + H), 180.1 (40, M + H − C_4H_8); ^{1}H NMR ($CDCl_3$) 1.40 (s, 3H), 1.515 (s, 9H), 1.59 (s, 3H), 4.33 (d, 1H, J = 9 Hz), 4.81 (d, 1H, J = 9 Hz). Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.94; H, 7.28; N, 5.95. Found: C, 46.01; H, 7.52; N, 5.91.

(*R*)-3-(5-Dibenzosuberyl)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (9). Sulfamidite **9** was synthesized using the same conditions described for the *N*-benzyl sulfamidites.[4] The product was purified by flash chromatography (EtOAc:hexanes 1:1) to afford pure **9** (82%) as a colorless oil which solidified over several days: mp 105−111 °C; MS *m*/*z*: 193.1 (75, $C_{15}H_{13}^+$), 336.1 (100, M + Na); ^{1}H NMR ($CDCl_3$): 0.71 (d), 1.26 (d), 2.8 (m), 3.0 (m), 3.4 (m), 3.7 (m), 3.95 (m), 4.1 (m), 4.2 (m), 4.55 (d), 5.05 (dd), 5.17 (two s). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.87; H, 6.30; N, 4.46.

3-(5-Dibenzosuberyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2-oxide (10). Sulfamidite **10** was synthesized using the same conditions described for the *N*-benzyl sulfamidites[4] and was purified by filtration through a plug of silica, eluted with ether. Compound **10** was isolated in 88% yield: mp 110−139 °C; MS *m*/*z*: 193 (100, $C_{15}H_{13}^+$), 350.1 (15, M + Na), 366.1 (10, M + K); ^{1}H NMR ($CDCl_3$) 1.01 (s, 3H), 1.27 (s, 3H), 2.9 (m, 2H), 3.85 (m, 1H), 4.05 (m, 1H), 4.23 (d, J = 8.5 Hz, 2H), 4.77 (d, J = 8.5 Hz, 2H), 5.34 (s, 1H), 7.1−7.3 (m, 8H). Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.88; H, 6.74; N, 4.19.

RuO_4 Oxidations. The RuO_4 oxidations were carried out using the procedures described for *N*-benzyl sulfamidates.[4,11]

(9) Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron* **1995**, *51*, 12337−12350.

(10) Seki, T.; Nakao, T.; Masuda, T.; Hasumi, K.; Gotanda, K.; Ishimori, T.; Honma, S.; Minami, N.; Shibata, K.; Yasuda, K. *Chem. Pharm. Bull.* **1996**, *44*, 2061−2069.

(11) White, G. J.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 3177−3178.

However, in synthesizing the dibenzosuberyl-protected sulfamidates (**11** and **12**), a 2.5:1 CH_3CN/H_2O solvent mixture was used.

3-(*tert*-Butyloxycarbonyl)-(*R*)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (11). RuO_4 oxidation of crude **5** (11.8 g) afforded **11** (10.5 g, 78% from **1**): mp 120−121 °C; MS *m*/*z*: 255 (80, M + NH_4), 198.9 (100, M + NH_4 − C_4H_8); $[\alpha]^{23}_{589}$ = 9.45 (*c* 1.06, MeOH); ^{1}H NMR ($CDCl_3$) 1.53 (d, 3H, J = 6 Hz), 1.58 (s, 9H), ABC spin system (4.19 (dd, 1H) 4.41 (m, 1H), 4.67 (dd, 1 H), J_{AB} = 9 Hz, J_{AC} = 6 Hz, J_{BC} = 3 Hz). Anal. Calcd for $C_8H_{15}NO_5S$: C, 40.49; H, 6.37; N, 5.90. Found: C, 40.62; H, 6.54; N, 5.89.

3-(*tert*-Butyloxycarbonyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (12). Oxidation of crude **7** afforded **12** in 87% yield: mp 101−102 °C; MS *m*/*z*: 290.2 (100, M + Na), 218.1 (60, M + Na − C_4H_8); ^{1}H NMR (CD_3CN) 1.536 (s, 9H), 1.54 (s, 6H), 4.35 (s, 2H). Anal. Calcd $C_9H_{17}NO_5S$: C, 43.01; H, 6.82; N, 5.57. Found: C, 42.86; H, 7.01; N, 5.35.

(*R*)-3-(5-Dibenzosuberyl)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (13). Sulfamidate **13** was purified by column chromatography (1:1 EtOAc:hexanes) and subsequently recrystallized from CH_2Cl_2/hexanes to afford a colorless solid (85%): mp 173.5−175 °C; MS *m*/*z*: 347.1 (M + NH_4), 352.1 (M + Na); ^{1}H NMR ($CDCl_3$) 1.09 (d, J = 6.5 Hz, 3H), 2.85 (m, 1H), 3.05 (m, 1H), 3.65 (m, 2H), AMX spin system (4.03 (dd, 1H), 4.15 (m, 1H), 4.57 (dd, 1H), J_{AM} = 8.4 Hz, J_{AX} = 3 Hz, J_{MX} = 6.3 Hz), 5.20 (s, 1H), 7.1−7.3 (m, 8H). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.41; H, 5.93; N, 4.17.

3-(5-Dibenzosuberyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (14). Purification of **14** was achieved by filtration through a silica plug using 1:1 CH_2Cl_2:Et_2O followed by solvent removal and recrystallization from CH_2Cl_2:hexanes. Yield was 81% of a colorless solid: mp 185−187.5 °C; MS *m*/*z*: 193 (100, $C_{15}H_{13}^+$), 361.1 (15, M + NH_4), 366.1 (10, M + Na), 382.1 (40, M + K); ^{1}H NMR ($CDCl_3$) 1.16 (s, 6H), 2.93 (m, 2H), 3.96 (m, 2H), 4.11 (s, 4H), 5.24 (s, 1H), 7.1−7.4 (m, 8H). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.19; H, 6.28; N, 4.02.

Sulfamidate Deprotection. (*R*)-4-Methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (15). From 11: Sulfamidate **11** (3 g, 12.6 mmol) was dissolved in CH_2Cl_2 (20 mL), and TFA (4.9 mL, 5 equiv) was added. The mixture was stirred for 30 min and then the solvent evaporated under reduced pressure. The residual oil was treated with Et_3N (typically <5 drops), until the mixture tested basic. The mixture was then filtered through a plug of silica using EtOAc:hexanes (1:1, 300 mL). The solvent was removed from the filtrate to afford 1.72 g of an oil, and **15** (1.48 g, 86%) was crystallized from this mixture using CH_2Cl_2:hexanes: mp 40.5−42 °C; R_f = 0.5 (1:1 EtOAc/hexanes); MS *m*/*z*: 159.9 (M + Na); ^{1}H NMR (CD_3CN) 1.33 (d, J = 6.5 Hz, 3H), AMX spin system (4.05 (m, 1H), 4.11 (dd, 1H), 4.63 (dd, 1H), J_{AM} = 8 Hz, J_{AX} = 8 Hz, J_{MX} = 6 Hz), 5.5 (s br, 1H). Anal. Calcd for $C_3H_7NSO_2$: C, 26.28; H, 5.15; N, 10.21. Found: C, 26.27; H, 5.35; N, 10.12.

When 1 equiv of DBU was added to a solution of **15** in CD_3CN, the sulfamidate resonances shifted upfield with loss of the N−H signal: 1.20 (d, J = 6.5 Hz, 3H), AMX spin system (3.57 (dd, 1H), 3.85 (m, 1H), 4.30 (dd, 1H), J_{AM} = 8 Hz, J_{AX} = 7 Hz, J_{MX} = 6.5 Hz). Similar shifts were observed when an excess of NaOH was added to a solution of **15** in D_2O, and the sulfamidate anion thus formed was stable over several hours in solution. No such chemical shift changes were observed when 1 equiv of Et_3N was added to a solution of **15** in CD_3DN.

From 13: TFA (0.4 mL. 5 mmol) was added to a solution of sulfamidate **13** (0.165 g, 0.5 mmol) in CH_2Cl_2 (2−3 mL) at which point the solution changed from colorless to a clear orange/red color. Tlc analysis (silica/CH_2Cl_2) of this solution showed **15** (R_f = 0.2), a trace of **13** (R_f = 0.55) and at least three other UV-absorbing products (R_fs = 0.75 to 0.95). After stirring for 5 min, MeOH (2 mL) was added and the solution turned colorless. TLC then indicated a new UV-absorbing product (R_f = 0.8) as the main product. The solvent was removed, and the light orange residue (the color likely due to reformed dibenzosuberyl cation) was purified by column chromatography (1:1 EtOAc:hexanes) to afford **15** (22 mg, 32%); dibenzosuberyl sulfamidate **13** (92 mg, 0.28 mmol) was also recovered from the reaction mixture. If the solvent was removed before MeOH was added, the mixture's color was lost and **13** was regenerated as the main product according to TLC.

4,4-Dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (16). The procedure used to prepare BOC-sulfamidate **11** was applied to BOC-sulfamidate **12** to afford **16** (90%): mp 105.5−108 °C; MS *m*/*z*: 174.0 (100, M + Na); ^{1}H NMR (CD_3CN) 1.41 (s, 6H), 4.31 (s, 2H), 5.6 (s br, 1H). Anal. Calcd for $C_4H_9NSO_2$: C, 31.79; H, 6.00; N, 9.26. Found: C, 31.86; H, 6.21; N, 9.21.

From 14: The same procedure for deprotecting the dibenzosuberyl sulfamidate (**13**) was applied to **14**. After MeOH addition and subsequent solvent removal, **16** was crystallized from the mixture using EtOAc:hexanes (87%).

Alkylation Reactions. (*R*)-3-Benzyl-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (17). Phase Transfer Catalysis. A solution of 40 wt % NaOH (1.5 mL) was added to a solution of **15** (0.2 g, 1.5 mmol), benzyl bromide (0.7 mL, 4 equiv), and benzyltributylammonium chloride (23 mg, 5 mol %) in CH_2Cl_2 (5 mL). The mixture was rapidly stirred for 5 h at rt. During this period, TLC indicated a gradual decrease of **15** in the aqueous phase and an increase of **17** in the organic phase. Removal of the solvent from the organic phase and purification of the crude product by preparative TLC (CH_2Cl_2) afforded **17** (0.25 g, 76%); this sample had characterization data identical to **17** synthesized from *N*-benzyl-2-aminopropan-1-ol.[4]

Deprotonation Using KO-*t*-Bu. Freshly sublimed KO-*t*-Bu (0.1 g, 0.9 mmol) was added to a solution of **15** (0.125 g, 0.9 mmol) in dry THF (2.5 mL) at −10 °C under Ar, and the solution was stirred for 5 min. Then, benzyl bromide (0.11 mL, 1.8 mmol) and dry CH_3CN (2 mL) were added, and the solution was stirred for 3 h while allowing the solution to gradually warm to room temperature. EtOAc was added, the mixture was filtered, and the solvent was subsequently removed from the filtrate. The product was purified by preparative TLC (CH_2Cl_2) to yield **17** (0.11 g, 54%).

3-Benzyl-4,4-dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (18). The same procedure used for **17**, above, was applied to sulfamidite **16** (0.227 g, 1.5 mmol) to afford **18** (0.34 g, 93%). This material was identical to **18** synthesized from *N*-benzyl-2-amino-2-methylpropan-1-ol.[4]

3-(Phenylpropyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (19). A solution of DIAD (0.32 mL, 1.6 mmol) in dry CH_3CN (5 mL) was added in 4 portions to a solution of PPh_3 (0.43 g, 1.6 mmol), 3-phenyl-1-propanol (0.215 mL, 1.6 mmol), and **15** (0.137 g, 1 mmol) in dry CH_3CN (15 mL). Each DIAD portion was added dropwise at 15 min intervals with each addition lasting 3−5 min. Fifteen minutes after the last addition, the solvent was removed, and the mixture was chromatographed on silica/CH_2Cl_2 to afford 0.11 g of **19** (R_f = 0.41, 43%) as a colorless oil: MS *m*/*z*: 256.0 (M + H, 50), 278 (M + Na, 45), 294 (M + K, 100); ^{1}H NMR ($CDCl_3$) 1.27 (d, J = 6 Hz, 3H), 2.04 (m, 2H), 2.73 (m, 2H), 3.02 (m, 1H), 3.13 (m, 1H), ABC spin system (3.68 (m, 1H), 4.1 (dd, 1H), 4.53 (dd, 1H), J_{AB} = 8 Hz, J_{AC} = 6.5 Hz, J_{BC} = 8.5 Hz), 7.2−7.35 (m, 5H). Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.46; H, 6.71; N, 5.48. Found: C, 56.51; H, 6.88; N, 5.54. More rapid addition of the DIAD solution resulted in substantially lower yields.

3-(Phenylpropyl)-4,4-dimethyl-[1,2,3]-oxathiazolidine-2,2-dioxide (20). The same conditions used to synthesize **19** were applied to **16** (0.23 g, 1.5 mmol) to afford **20** (0.36 g, 89%) as a colorless oil: MS *m*/*z*: 270.1 (M + H, 100), 287.1 (M + NH_4, 15), 292.1 (M + Na, 100); ^{1}H NMR ($CDCl_3$) 1.30 (s, 6H), 2.07 (m, 2H), 2.74 (t, J = 8 Hz, 2H), 3.03 (t, J = 7 Hz, 2H),

4.25 (s, 2H), 7.2 (m, 5H). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.91; H, 7.25; N, 5.31.

^{1}H NMR Experiments. To investigate the low yield of **19**, combinations of PPh_3 (26 mg, 0.1 mmol), sulfamidate **15** (14 mg, 0.1 mmol), sulfamidate **17** (23 mg, 0.1 mmol), and/or DIAD (20 μL, 0.1 mmol) were used in several experiments (A−F) carried out in CD_3CN (ca. 1 mL). The solutions were monitored by ^{1}H NMR and TLC for any reaction. The following combinations were used: (Experiment A) PPh_3/**15**; (B) PPh_3/**17**; (C) DIAD/**15**; (D) DIAD/**17**; (E) DIAD was added in 4 equal portions, 15 min apart to a solution of PPh_3/**15**; (F) PPh_3 was added to a solution of DIAD/**17**.

In experiments A−D, no significant reaction was observed over 30 min. In experiment E, the first addition of DIAD resulted in the loss of the N−H signal and an upfield shift (~0.5 ppm) of the sulfamidate CH_2 signals (4.1 and 4.6 ppm) occurred. The relative integration (to the solvent peak) of the CH_2 signals was smaller, and the quality of the rest of the spectrum had deteriorated, suggesting a number of products. By the fourth addition, the relative integration of the sulfamidate CH_2 signals had decreased by 50%, the CH_3 doublet (1.3 ppm) was surrounded by broad peaks, and TLC suggested that less **15** was present. In combination F, the PPh_3 was added all at once to the DIAD/**17** mixture; results similar to combination E were observed.

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Supporting Information Available: High dilution conditions used for the synthesis of sulfamidites **5** and **7** which yielded sulfite esters **6** and **8**; the characterization details of **6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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