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Synthesis of Dimethyl Sulfomycinamate

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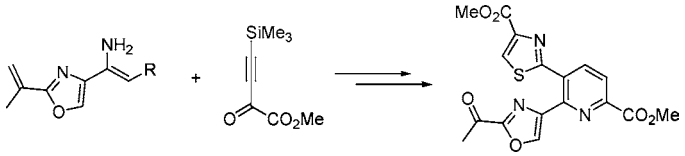
ABSTRACT

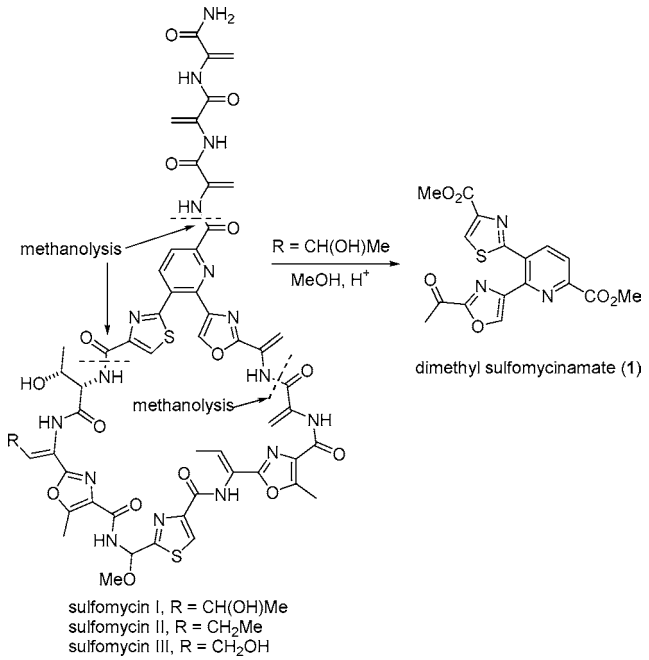


Dimethyl sulfomycinamate, the oxazole–thiazole–pyridine product generated in the methanolysis of the thiopeptide antibiotic sulfomycin I, is prepared in 13 steps and 8% overall yield by the Bohlmann–Rahtz heteroannulation of 1-(oxazol-4-yl)enamines and methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate.

The sulfomycins are members of the thiopeptide family of antibiotics, isolated from *Streptomyces viridochromogenes*. These cyclic peptides are characterized by a common oxazole−thiazole−pyridine central heterocyclic core, and their large number of heterocyclic and dehydroamino acids. The structure of sulfomycin I, isolated from subspecies *Sulfomycini* ATCC 29776,[1] was identified by combined spectroscopic techniques.[2] It is distinct from sulfomycins II and III, isolated from subspecies MCRL-0368, only in the nature of the side chain located on an 2-(2-aminoalkenyl)oxazole residue in the peptide backbone.[3] Instrumental in the structure elucidation process was the use of chemical degradation to isolate and identify various heterocyclic fragments.

When sulfomycin I was heated at reflux in methanol in the presence of Amberlyst 15 ion-exchange resin for 20 h, dimethyl sulfomycinamate (**1**) was produced, whose structure was determined by X-ray crystallography (Scheme 1).[4] The oxazole−thiazole−pyridine heterocyclic domain of dimethyl sulfomycinamate and the sulfomycins is common to many other members of the thiopeptide antibiotics, including A10255,[5] the berninamycins,[2,6,7] geninthiocin,[8] methylsulfomycin,[9] promoinducin,[10] the promothiocins,[11] radamycin,[12] thioactin,[13] thiotipin,[14] and thioxamycin.[15]

Scheme 1. Methanolysis of Sulfomycin I



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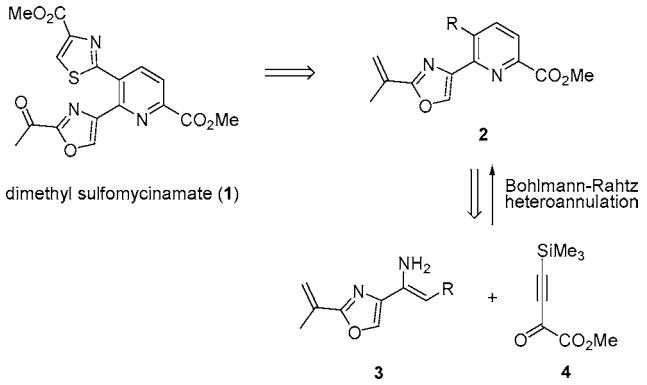
Prior to our work in this area Kelly et al had already described an elegant synthesis of dimethyl sulfomycinamate that used palladium-catalyzed coupling reactions for target construction.[16] Our new approach, which will be discussed shortly, complements this earlier work. It avoids the use of palladium catalysts and constructs the heterocyclic components from acyclic precursors.

Our synthetic plan for accessing dimethyl sulfomycinamate (**1**) hoped to establish pyridine **2** by the Bohlmann−Rahtz reaction[17] of methyl oxobutynoate **4** with a suitable enamine **3**, already bearing the thiazole substituent (−R) (Scheme 2).

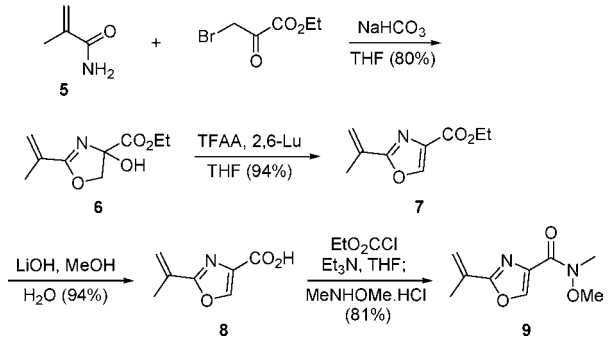
Scheme 2. Dimethyl Sulfomycinamate (**1**) Disconnective Scheme



We have previously developed mild methods for affecting this transformation and have demonstrated their utility for constructing the pyridine core of a range of thiopeptide targets.[18]

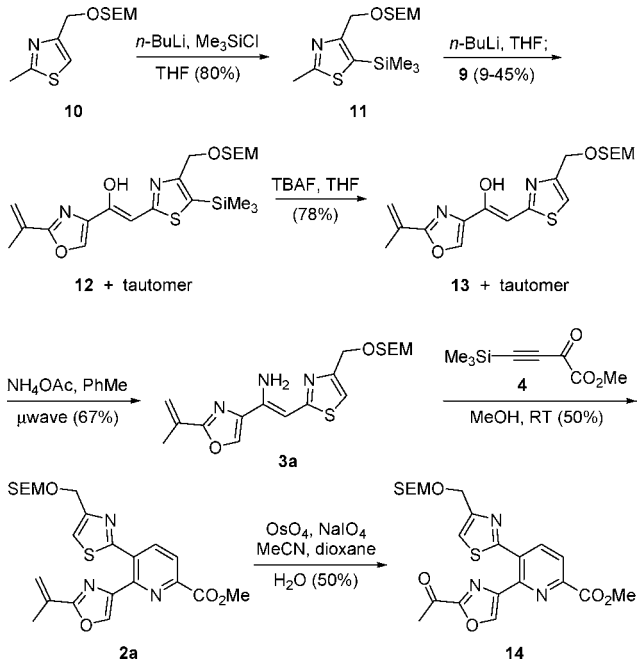
Starting from 2-methacrylamide (**5**), oxazole **7** was produced in excellent yield via a two-step modified Hantzsch reaction with ethyl bromopyruvate. Hydrolysis with lithium hydroxide in methanol−water and subsequent generation of the Weinreb amide **9** was accomplished by reacting acid **8** with ethyl chloroformate and treating the mixed anhydride with *N*-methoxymethylamine hydrochloride (Scheme 3).

Scheme 3. Synthesis of 2-(2-Propenyl)oxazoles **7**, **8**, and **9**



Readily available 2-methyl-4-[2-(trimethylsilyl)ethoxymethoxymethyl]thiazole (**10**)[19] was deprotonated with *n*-butyllithium and reacted with chlorotrimethylsilane to provide 5-(trimethylsilyl)thiazole **11** in 80% yield. This then permitted lithiation at the 2-methyl substituent (Scheme 4).

Scheme 4. Synthesis of Oxazole−Thiazole−Pyridine Domain **14**



Subsequent reaction of **11** with *n*-butyllithium and condensation with Weinreb amide **9** provided Claisen condensation product **12** as a mixture of tautomers. Although successful, the efficiency of this transformation proved to be highly unreliable and varied with scale. Moreover all efforts to improve the reaction through the use of alternative conditions failed to increase the yield of enol **12** above 45%.

Subsequent reaction of **12** with tetrabutylammonium fluoride protodesilylated the 5-position and gave thiazole **13** in good yield. Conventional attempts to form enamine **3a**

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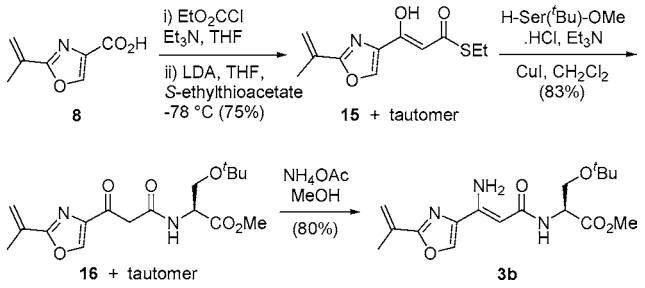
(19) Produced by the reduction of ethyl 2-methylthiazole-4-carboxylate with $LiAlH_4$ followed by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl).

according to the method of Baraldi failed,[20] but microwave irradiation of enol **13** at 120 °C in the presence of ammonium acetate generated 1-(4-oxazolyl)-2-(2-thiazolyl)enamine **3a** as a single (enamine) tautomer in 67% yield after only 30 min. Submitting enamine **3a** to the key pyridine-forming reaction involved stirring a solution of the precursor with methyl oxobutynoate **4**[21] in methanol; this generated pyridine **2a** directly in 50% yield, with no trace of the aminodienone intermediate usually produced under these conditions.[17] Efforts to improve the efficiency of the heteroannulation by using acid-catalyzed conditions[18] failed; these difficulties are attributed to the acid sensitivity of the methylidene group. Degradation of this function by treatment with osmium tetroxide in the presence of sodium periodate liberated the desired acetyl moiety and established sulfomycinamate analogue **14** with orthogonal protection suitable for subsequent elaboration. Our efforts confirmed that a Bohlmann−Rahtz approach to the target degradation product **1** did have some potential.

We now sought to access pyridine **2** by a strategy that avoided the capricious Claisen condensation. To this end, the enamine **3b** was employed in the Bohlmann−Rahtz heteroannulation. This contained a *tert*-butoxy serine residue that would later serve as the thiazole ring precursor (−R in Scheme 2), and would circumvent problems experienced in the acidic workup of reactions involving Weinreb amide **9**.

2-(2-Propenyl)oxazole-4-carboxylic acid **8** was activated by mixed anhydride methodology and reacted with the lithium enolate of *S*-ethyl thioacetate according to the procedure of Olsen[22] to give the homologated product **15**, in equilibrium with the corresponding keto form, in good yield. Reaction with *O-tert*-butyl-L-serine methyl ester hydrochloride in dichloromethane in the presence of copper(I) iodide and triethylamine generated amide **16** as a mixture of tautomers (Scheme 5). A solution of the keto−enol

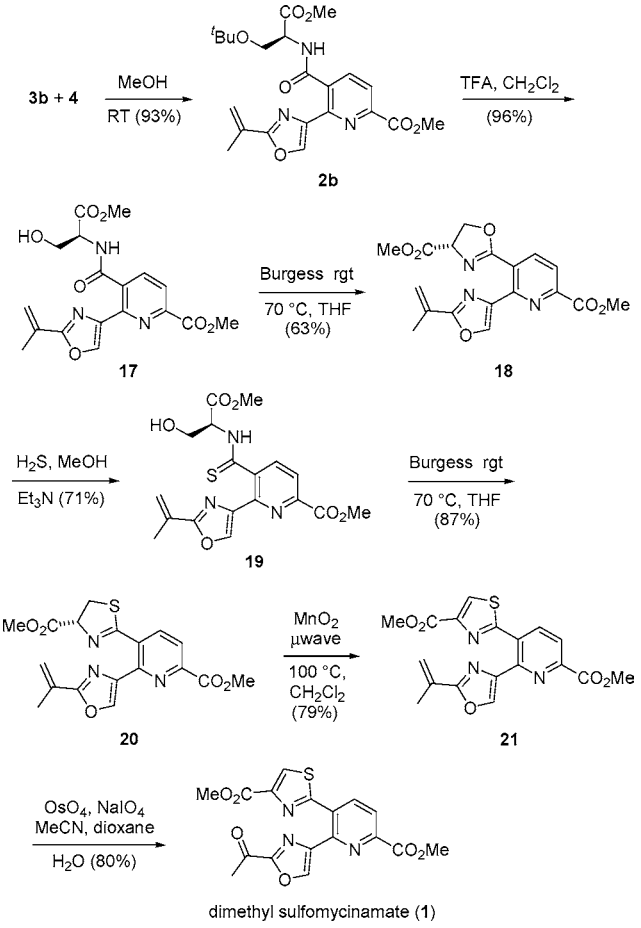
Scheme 5. Synthesis of Enamine **3b**



mixture in methanol was heated at reflux overnight in the presence of ammonium acetate to give enamine **3b** as a single tautomer.

With **3b** in hand the key Bohlmann−Rahtz reaction was now affected by stirring a solution of enamine **3b** and methyl oxobutynoate **4** in methanol at room temperature. The desired Michael addition and spontaneous cyclodehydration occurred readily to give pyridine **2b** in excellent yield (93%), as a single regioisomer (Scheme 6).

Scheme 6. Synthesis of Dimethyl Sulfomycinamate (**1**)



Once again, the highly facile nature of this reaction was surprising. Conditions that normally only promote the initial Michael addition (methanol, room temperature)[21] were sufficient in this instance to give the target heterocycle.

Deprotection under acidic conditions gave alcohol **17** (Scheme 6). Subsequent cyclization to the oxazoline **18** with Burgess reagent was followed by thionation with hydrogen sulfide in methanol−triethylamine, to give thioamide **19**. Cyclization of **19** with Burgess reagent at 70 °C and oxidation of **20** to the thiazole **21** was then accomplished by microwave irradiation at 100 °C in dichloromethane in the presence of activated manganese dioxide. Finally, reaction of **21** with osmium tetroxide/sodium periodate cleaved the alkene unit to give dimethyl sulfomycinamate (**1**), mp 159−161 °C (lit.[4] mp 160.5−161.0 °C), whose spectroscopic properties were in agreement with literature data.[4,16]

In conclusion, this paper demonstrates that the Bohlmann−Rahtz heteroannulation reaction provides a route to the sulfomycin degradation product dimethyl sulfomycinamate

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(**1**) that complements the cross-coupling methodology of Kelly.[16] The reaction of ethyl oxobutynoate **4** with enamines in this process is particularly facile and can tolerate acid-sensitive functionality to give pyridines in excellent yield and with total regiocontrol.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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