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Total Synthesis of Dimethyl Sulfomycinamate

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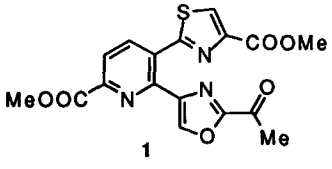
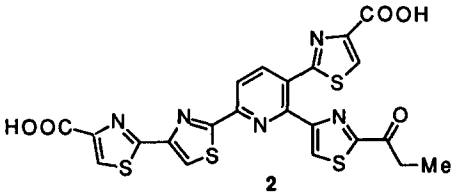
Abstract: The first total synthesis of dimethyl sulfomycinamate (1) is described. Highlights of the synthesis include a selective palladium-catalyzed coupling reaction on the bromotriflate **21**, and a condensation reaction to form the oxazole ring.

Sulfomycin I[1] is a novel thiopeptide antibiotic produced by a subspecies of *Streptomyces viridochromogenes*, which exhibits strong inhibitory activity against gram-positive bacteria. From the methanolysis products of sulfomycin I, dimethyl sulfomycinamate was isolated by a Japanese research group in 1978.[2] The structure was assigned as **1** by X-ray crystallography. Later, it was found that the same tris-heterocycle subunit is present in berninamycin A,[1] thioxamycin,[3] and A10255.[4] Because of the strong interest in thiopeptide antibiotics and the unique structure of **1**, we undertook its synthesis.



1

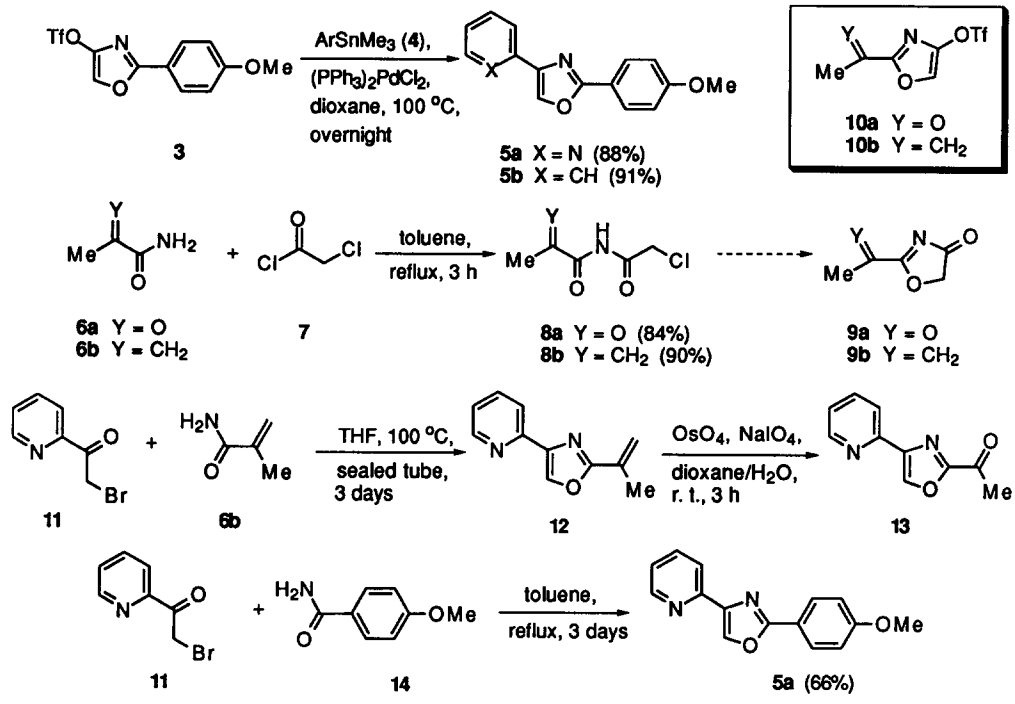


2

From the standpoint of synthetic strategy, we chose palladium-catalyzed cross-coupling reactions as the key transformations to form the biaryl bonds. In the earlier synthesis of micrococcinic acid (**2**)[5] achieved in this laboratory, the pyridine and thiazole units were assembled using a similar biaryl coupling strategy. At the outset of the present project, there were no examples of biaryl bond formation between oxazole and pyridine units, so the effort began with a model study to test the reactivity of oxazole triflate **3**[6] (Scheme I). Reaction of **3** with different arylstannanes **4**[7] under standard palladium-catalysis conditions[8] gave the corresponding coupled products **5** in good yield. To our knowledge, this was the first time that an oxazole triflate was either made or coupled with an arylstannane to form a biaryl bond. We then sought to apply this strategy to the synthesis of **1**. The reaction of amides **6a** and **6b** with chloroacetyl chloride (**7**) produced imides **8a** and **8b**. Unfortunately, however, neither **8a** nor **8b** could be cyclized to the corresponding oxazolones **9a** or **9b**, which could have served as precursors to the desired oxazole triflates **10**.

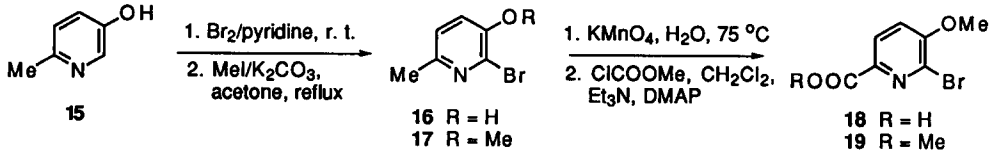
At this point, other possibilities for preparing the oxazole moiety were examined. Condensation[9, 10] of methacrylamide (**6b**) and 2-(α-bromoacetyl)pyridine (**11**)[11] was used as a model. To our delight, **6b** and **11** reacted smoothly to give the desired oxazole product **12** in 62% yield. Oxidative cleavage[12] of the olefin **12** using OsO_4 and $NaIO_4$ afforded acetyloxazole **13** in 86% yield. The regiochemical outcome of the reaction between **11** and **6b** was corroborated by the reaction of bromoketone **11** and amide **14** to give compound **5a**.

Scheme I: Model Study on the Oxazole Ring.[21]



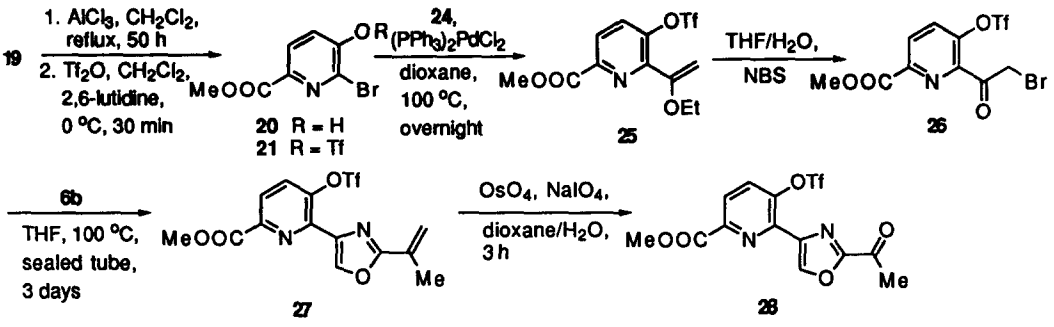
With a method for preparing the pyridyloxazole unit established, the actual synthesis of **1** was initiated. Starting from commercially available 3-hydroxy-6-methylpyridine (**15**) (Scheme II), bromination following a known procedure gave **16**[13] in 74% yield, and methylation of **16** in acetone with iodomethane and potassium carbonate provided methyl ether **17**[14] in 88% yield. Oxidation of the methyl group in **17** using aqueous $KMnO_4$ afforded acid **18**; esterification[15] of **18** gave methyl ester **19** in 63% yield from **17**.

Scheme II: Preparation of the Substituted Pyridine Ring.[21]

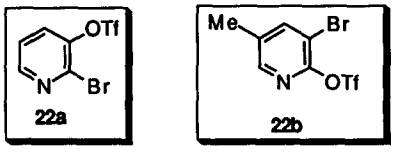


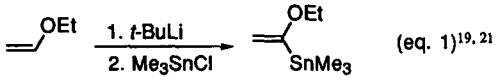
Selective cleavage of the methyl ether in **19** (Scheme III) in the presence of the methyl ester was achieved by using $AlCl_3$[16] in refluxing CH_2Cl_2 to give a 93% yield of hydroxypyridine **20**, which was converted to triflate **21** in 97% yield. In an independent study,[17] the reactivity of pyridines doubly substituted with bromine and triflate at the 2- and 3-positions was investigated. In particular, compounds **22a**[18a] and **22b**[18b] were made in order to test their reactivity toward palladium-catalyzed cross-coupling reactions. It was found that regardless of the leaving group, the 2-position was more reactive than the 3-

Scheme III: Synthesis of the Pyridyloxazole.[21]



position of the pyridine in both **22a** and **22b**. Accordingly, bromotriflate **21** was coupled with exactly one equivalent of vinylstannane **24**[19] (eq. 1) to give **25** in 97% yield. Reaction of **25** with NBS and water in THF



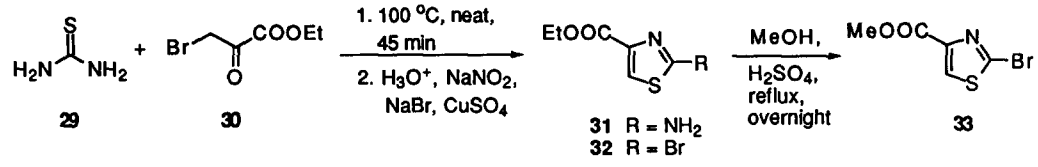


(eq. 1)[19, 21]

proceeded to give bromoketone **26** in high (95%) yield. Condensation of **26** with methacrylamide (**6b**) afforded oxazole **27** in 63% yield. Oxidative cleavage of the olefin **27** by OsO_4 and $NaIO_4$ furnished **28** in 89% yield, which was ready to couple with the thiazole moiety.

The thiazole synthesis (Scheme IV) started from the condensation of thiourea (**29**) and ethyl bromopyruvate (**30**), which afforded aminothiazole **31**; without purification, **31** was converted into bromothiazole **32** via diazotization in the presence of NaBr and $CuSO_4$. The yield of this two-step transformation is 75%. Transesterification in methanol with a catalytic amount of concentrated sulfuric acid gave methyl ester **33** in 89% yield.

Scheme IV: Synthesis of the Bromothiazole.[21]



In an effort to couple triflate **28** and bromothiazole **33**, we sought to convert one of them into the corresponding stannane. Extensive attempts to convert either **28** or **33** into an isolable stannane failed. Finally, we succeeded in coupling triflate **28** and bromothiazole **33** by treating a mixture of the two with bis(tributyltin), bis(triphenylphosphine)palladium(II) chloride and tetrakis(triphenylphosphine)palladium(0) in dioxane at 100 °C overnight. The reaction, which presumably proceeds by way of in situ generation and coupling of a stannane intermediate, gave the desired dimethyl sulfomycinamate (**1**) in 35% yield. Spectra of the synthetic product matched those of naturally derived material.[20]

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18. a) Synthesized by triflation[6] of commercially available 2-bromo-3-hydroxypyridine. b) Synthesized in three steps (NBS, CH_2Cl_2; 9 M H_2SO_4, $NaNO_2$; Tf_2O[6]) from 2-amino-5-methylpyridine.
19. For preparation of the *O*-methyl analog, see: Soderquist, J. A. and Hsu, J.; *Organometallics*, **1982**, *1*, 830.
20. We thank L. B. Crandall and M. H. Niedenthal of Lilly Research Laboratories for a sample of A10255B,[4] from which an authentic sample of **1** was prepared.

21. **Analytical data for selected new compounds** (unless otherwise indicated, $CDCl_3$ is the NMR solvent). **3**: white solid, mp 37.2-38.0 °C. ^1H NMR: 7.95 (2H, d); 7.63 (1H, s); 6.98 (2H, d); 3.85 (3H, s). **5a**: white solid, mp 131-132 °C. ^1H NMR: 8.60 (1H, d); 8.28 (1H, s); 8.07 (2H, d, *J*=9.0 Hz); 8.01 (1H, d); 7.78 (1H, t); 7.22 (1H, m); 7.00 (2H, d, *J*=9.0 Hz); 3.88 (3H, s). **5b**: white solid, mp 97.5-99.0 °C. ^1H NMR: 8.05 (2H, d, *J*=8.5 Hz); 7.92 (1H, s); 7.81 (2H, d, *J*=7.2 Hz); 7.25-7.42 (3H, m); 6.98 (2H, d, *J*=8.5 Hz); 3.86 (3H, s). **12**: white solid, mp 60.2-60.8 °C. ^1H NMR: 8.59 (1H, dd); 8.20 (1H, s); 7.93 (1H, dd); 7.77 (1H, m); 7.20 (1H, m); 6.02 (1H, d); 5.43 (1H, d); 2.24 (3H, d). **13**: ^1H NMR: 8.60 (1H, d); 8.42 (1H, s); 8.00 (1H, d); 7.80 (1H, t); 2.76 (3H, s). **18**: white solid, mp 142.2-143.6 °C. ^1H NMR (D_2O): 7.73 (1H, d); 7.22 (1H, d); 3.78 (3H, s). **19**: white solid, mp 143-144 °C. ^1H NMR: 8.11 (1H, d, *J*=8.7 Hz); 7.20 (1H, d, *J*=8.7 Hz); 4.00 (3H, s); 3.98 (3H, s). **20**: white solid, mp 190-200 °C. ^1H NMR: 8.07 (1H, d, *J*=8.0 Hz); 7.39 (1H, d, *J*=8.0 Hz); 6.03 (1H, br); 3.98 (3H, s). **21**: colorless crystal, mp 54.5-56.0 °C. ^1H NMR: 8.20 (1H, d, *J*=8.4 Hz); 7.75 (1H, d, *J*=8.4 Hz); 4.03 (3H, s). **24**: colorless liquid. ^1H NMR: 4.68 (1H, s); 4.08 (1H, s); 3.70 (2H, q); 1.25 (3H, t); 0.21 (9H, s). **25**: colorless oil. ^1H NMR: 8.16 (1H, d, *J*=8.4 Hz); 7.72 (1H, d, *J*=8.4 Hz); 5.06 (1H, d, *J*=3.0 Hz); 4.62 (1H, d, *J*=3.0 Hz); 3.98-4.03 (m, 5H); 1.42 (3H, t, *J*=7.2 Hz). **26**: colorless oil. ^1H NMR: 8.41 (1H, d); 7.88 (1H, d); 4.85 (2H, s); 4.05 (3H, s). **27**: white solid, mp 75.2-78.1 °C. ^1H NMR: 8.38 (1H, s); 8.14 (1H, d); 7.80 (1H, d); 6.07 (1H, s); 5.50 (1H, s); 4.00 (3H, s); 2.23 (3H, s). **28**: white solid, mp 100-101 °C. ^1H NMR: 8.62 (1H, s); 8.20 (1H, d, *J*= 8.7 Hz); 7.85 (1H, d, *J*=8.7 Hz); 4.04 (3H, s); 2.79 (3H, s). ^{13}C NMR: 185.7, 163.8, 157.7, 147.3, 145.1, 143.1, 143.0, 138.4, 131.7, 125.9, 120.2, 117.0, 53.2, 26.6. HRMS: Calc. for $C_{13}H_9N_2O_7SF_3$: 394.00826. Found: 394.00770. **32**: white solid, mp 68.5-69.2 °C. ^1H NMR: 8.13 (1H, s); 4.43 (2H, q); 1.41 (3H, t). **33**: white solid, mp 128.2-129.0 °C. ^1H NMR: 8.14 (1H, s); 3.96 (3H, s). Satisfactory combustion analyses were obtained for **5a**, **5b**, **12**, **18**, **19**, **20**, **32**, and **33**.

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