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Citation

Published Version
doi:10.3987/COM-02-9480

Citable link
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SYNTHETIC STUDIES TOWARD HENNOXAZOLE A. USE OF A SELECTIVE BISOXAZOLE ALKYlation AS THE KEY FRAGMENT COUPLING

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Abstract – A model system for side chain fragment coupling to the core of hennoxazole A is investigated. Lateral metallation of a C_{13}-TBS-protected bisoxazole, using lithium diethylamide, allows for selective and efficient alkylation at C_{15}.

INTRODUCTION

Marine natural products containing the oxazole nucleus have drawn considerable attention recently (Figure 1). Synthetic studies of complex molecules containing isolated 2,4-disubstituted oxazole units such as the phorboxazoles,\(^1\) bisoxazoles such as the hennoxazoles\(^2\) and diazonamides,\(^3\) and trisoxazoles such as the ulapualides,\(^4\) have contributed methods for the assembly of these systems and have resulted in several total syntheses. The development of relatively mild oxazole-forming reaction sequences\(^5\) has

Figure 1. Oxazole-Containing Marine Natural Products
made the late-stage creation of these ring systems a common strategy—with cleavage of an oxazole ring frequently serving as the key disconnection back to major coupling fragments. Approaches involving end game functionalization of intact oxazole rings, however, provide the opportunity to use relatively simple oxazoles as starting materials and then efficiently carry these, practically inert, heterocycles through a variety of synthetic transformations. In consideration of these issues, our synthesis plan for hennoxazole A (1, Scheme 1) involves late-stage construction of the C15–C16 bond by metallation of a relatively elaborate bisoxazole (2) at the C15-methyl position, followed alkylation with an allylic halide C16–C25 side chain fragment (3).

**Scheme 1. Retrosynthetic Analysis for Hennoxazole A**

Synthetically useful lateral metallations of some 2-methyl-oxazole and -thiazole systems have been reported. If these rings are unsubstituted at C5, however, competitive deprotonation of the C5-ring hydrogen is frequently observed (Scheme 2). In fact, Williams has shown that bisoxazole 4 is lithiated with n-BuLi exclusively at the C5'-ring position, suggesting that alkylation of 2 at C15 may be problematic if R = H. Despite this result, previous work confronting a similar problem in the synthesis of phorboxazole, demonstrated that the regioselectivity of some oxazole deprotonations can be altered by the use of lithium diethylamide. As elaborated in the preceding communication, deprotonation of

**Scheme 2. Oxazole and Bisoxazole Alkylations**
2-methyl-4-phenyloxazole (6) using n-BuLi at –78 °C followed by alkylation with methyl iodide gives a 14:86 ratio of products (7:8) favoring ring methylation, while the use of LiNEt₂ leads to alkylation solely at the C₇-methyl site. This reversal of regioselectivity is thought to arise from the ability of diethylamine to mediate the low-temperature equilibration of a kinetic mixture of otherwise noninterconverting lithiated intermediates (9 and 10).¹⁵

Herein we report our results on a model fragment coupling for hennoxazole A using lithium diethylamide.

RESULTS AND DISCUSSION
To test the viability of our key side chain coupling strategy, we first prepared bisoxazole (13) as a model substrate (Scheme 3). Bisoxazole ester (11)¹⁶ was reduced with DIBAL-H in CH₂Cl₂ at low temperature to give aldehyde (12)¹⁷ in quantitative yield. Dimethyl acetal (13) was then generated under Noyori conditions¹⁸ in 93% yield. In results consistent with Williams’ studies of 4,¹² treatment of bisoxazole (13) with n-BuLi led to deprotonation exclusively at the C₁₃ ring position (hennoxazole numbering), with no deprotonation occurring at the C₁₅-methyl group. For this substrate, replacing the base with LDA or LiNEt₂ did not alter the regioselectivity, suggesting that deprotonation at C₁₃ is both kinetically and thermodynamically favored.¹⁹ Attempts to alkylate the dianion of 13 were not fruitful. To circumvent this dilemma, we chose to block C₁₃ with a silyl protecting group.²⁰ Although TMS and TES groups were found to be too labile under these metallation conditions, the TBS group proved to be suitable. Treatment of 13 with n-BuLi followed by addition of TBSOTf led to C₁₃-protected bisoxazole (15) in 96% yield.

Scheme 3. Preparation of a Hennoxazole Model System

To model our key coupling step, we treated protected bisoxazole (15) with several different strong bases and quenched with MeI (Scheme 4). Gratifyingly, alkylation occurred at the desired C₁₅ site, with LiNEt₂ providing the best results. It is interesting to note that n-BuLi and LDA both gave poor conversion and small amounts of product 17—methylated at both at the C₁₅-methyl and C₁₀-ring positions—at the
expense of starting material conversion. No significant monomethylation at C_{10} was observed. We speculate that this result could potentially arise from rate differences of the C_{10}^- and C_{15}^- anions with respect to alkylation and intermolecular proton exchange. Chelation of lithium between C_{10} and an oxygen atom of the C_{8}-dimethyl acetal could decrease the reactivity at this center and lead to the observed product mixtures. To better mimic the reactivity of the actual side chain fragment (3), we also alkylated 15 with allyl iodide and prenyl bromide, both of which gave excellent results with LiNEt_2. Finally, treatment of alkylated products (18) and (19) with TBAF demonstrated that the oxazole could be cleanly deprotected under mild conditions. 

**Scheme 4. Hennoxazole Side Chain Alkylation Model Studies**

**CONCLUSION**

Selective alkylation of a C_8–C_{15} model for the bisoxazole portion of hennoxazole A is possible using lithium diethylamide when the C_{13}-position is blocked. Thus, modification of our initial retrosynthetic analysis (Scheme 1) to include a silyl protecting group at C_{13} (R = TBS) should provide a successful fragment coupling approach to hennoxazole A. Further reports on this synthesis will be forthcoming.

**ACKNOWLEDGEMENTS**

We thank the ACS Petroleum Research Fund (PRF-36453-GB1) and Williams College for financial support. A Pfizer Summer Undergraduate Research Fellowship for EPB is also gratefully acknowledged.

**REFERENCES AND NOTES**


7. For a review of the uses of oxazoles as protected carboxylate equivalents see: H. H. Wasserman, K. E. McCarthy, and K. S. Prowse, Chem. Rev., 1986, 86, 845. See also: references 5b and 5c.


15. The carbanion of 9 may be delocalized into the C=N π system.

16. Known ester (11) was prepared in 5 steps following literature procedures. See reference 6b. See

17. Aldehyde (12) has been reported, but no preparation conditions are given: D. R. Williams, D. A. Brooks, J. L. Moore, and A. O. Stewart, *Tetrahedron Lett.*, 1996, 37, 983. See reference 23 for spectral data.


19. Williams carried out semiempirical calculations also suggesting that the ring-lithiated intermediate was thermodynamically favored due to chelation with the adjacent oxazole nitrogen (reference 12).


21. Product identities and ratios were determined using a combination of ¹H NMR and GCMS analysis. All isolated yields are following silica gel chromatography. Spectral data for 12–15 and 19–21 are given in reference 23.

22. Representative Bisoxazole Alkylation Procedure using LiNEt₂: To a solution of diethylamine (22 µL, 0.213 mmol) in THF (1 mL) at −78 °C under Ar was added n-butyllithium (133 µL of a 1.5 M hexane solution, 0.199 mmol) dropwise. After stirring at −78 °C for 5 min, warming to 0 °C for 10 min, and re-cooling to −78 °C, this solution was added via canula to a solution of bisoxazole (15) (48.0 mg, 0.142 mmol) in THF (1 mL). The resulting bright red solution was stirred at −78 °C for 30 min. Allyl iodide (14.3 µL, 0.156 mmol) was added dropwise and the color faded to a light orange. After 15 min, the reaction was quenched with sat. aq. NaHCO₃ (2 mL) and warmed to rt. The resulting mixture was partitioned between CH₂Cl₂ (10 mL) and sat. aq. NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL), the combined organics were dried over a 1:1 mixture of K₂CO₃ and Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel deactivated with 2.5% Et₃N) eluting with 1:4 Et₂O:hexanes to afford the allylated product (18, 47.0 mg, 88%) as a colorless oil; ¹H NMR (CDCl₃) δ 7.68 (d, J = 0.9 Hz, 1H), 5.84 (ddt, J = 17.1, 10.3, 6.5 Hz, 1H), 5.45 (d, J = 0.6 Hz, 1H), 5.06 (dd, J = 17.1, 1.6 Hz, 1H) 4.99 (dd, J = 10.2, 1.3 Hz, 1H), 3.36 (s, 6H), 2.94 (t, J = 7.9 Hz, 2H), 2.55 (dt, J = 7.1, 7.8 Hz, 2H), 0.93 (s, 9H), 0.376 (s, 6H) ppm.; ¹³C NMR (CDCl₃) δ 168.1, 156.8, 155.0, 139.8, 139.1, 136.7, 136.5, 116.1, 98.8, 53.0, 31.2, 27.7, 26.7, 17.8, −5.7 ppm.; IR (neat) 3124, 1686, 1295, 1206 cm⁻¹; Anal. Calcd for C₁₉H₃₀N₂O₄Si: C, 60.29; H, 7.99; N, 7.40. Found: C, 60.56; H, 8.02; N, 7.37.

23. Spectral data for other new compounds are as follows:

12: ¹H-NMR (CDCl₃, 300 MHz) δ 10.0 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 2.57 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 184.3, 163.3, 156.6, 143.7, 141.7, 139.6, 129.7, 98.6, 53.1, 14.0 ppm.; IR (neat) 3124, 1686, 1295, 1206 cm⁻¹; Anal. Calcd for C₁₉H₃₀N₂O₄Si: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.08; H, 3.45; N, 15.70.

13: ¹H-NMR (CDCl₃, 300 MHz) δ 8.08 (s, 1H), 7.64 (s, 1H), 5.38 (s, 1H), 3.30 (s, 6H), 2.45 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 162.8, 155.7, 139.7, 138.5, 137.0, 130.6, 98.6, 53.1, 14.0
ppm.; IR (neat) 3119, 1636, 1530, 1106, 1058, 984 cm⁻¹; Anal. Calcd for C₁₀H₁₂N₂O₄: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.68; H, 5.41; N, 12.41.

14: ¹H-NMR (CDCl₃, 300 MHz) δ 7.66 (d, J = 0.8 Hz, 1H), 5.43 (s, J = 0.8 Hz, 1H), 3.35 (s, 6H), 2.60 (s, 3H), 2.43 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 160.3, 156.7, 149.9, 139.5, 136.4, 125.2, 98.7, 53.0, 13.8, 11.7 ppm.; IR (neat) 2937, 1593, 1197, 1097, 1055, 980 cm⁻¹; Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.57; H, 5.97; N, 11.66.

15: ¹H-NMR (CDCl₃, 300 MHz) δ 7.69 (d, J = 0.9 Hz), 5.45 (d, J = 0.9 Hz), 3.37 (s, 6H), 2.53 (s, 3H), 0.94 (s, 9H), 0.38 (s, 6H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 165.3, 156.8, 155.0, 139.9, 139.2, 136.7, 98.8, 53.0, 26.7, 17.8, 14.0, –5.7 ppm.; IR (neat) 2929, 1611, 1114, 1101, 1061 cm⁻¹; Anal. Calcd for C₁₆H₂₆N₂O₄Si: C, 56.78; H, 7.74; N, 8.28. Found: C, 56.98; H, 7.67; N, 8.29.

19: ¹H-NMR (CDCl₃, 300 MHz) δ 7.68 (d, J = 0.9 Hz, 1H), 5.45 (d, J = 0.9 Hz, 1H), 5.13 (t, J = 7.1 Hz, 1H), 3.36 (s, 3H), 2.85 (t, J = 7.3 Hz, 2H), 2.4 (dt, J = 7.4, 7.4 Hz, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 0.93 (s, 9H), 0.37 (s, 6H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 168.5, 156.9, 154.8, 139.8, 139.1, 136.7, 133.6, 122.4, 98.8, 52.9, 28.5, 26.6, 25.9, 17.82, 17.79, –5.7 ppm.; IR (neat) 2954, 2930, 1469, 1251, 1104, 1062, 843, 124 cm⁻¹; Anal. Calcd for C₂₁H₃₄N₂O₄Si: C, 62.03; H, 8.43; N, 6.89. Found: C, 62.17; H, 8.56; N, 6.94.

20: ¹H-NMR (CDCl₃, 300 MHz) δ 8.17 (s, 1H), 7.71 (d, J = 1.0 Hz, 1H), 5.84 (ddt, J = 17.1, 10.3, 6.5 Hz, 1H), 5.47 (d, J = 1.0, 1H), 5.08 (ddt, J = 17.1, 3.2, 1.6 Hz, 1H), 5.02 (ddt, J = 10.2, 2.8, 1.2 Hz, 1H), 3.38 (s, 3H), 2.93 (t, J = 7.2 Hz, 2H), 2.58 (dt, J = 6.6, 6.6 Hz, 2H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 165.6, 155.8, 139.8, 138.5, 137.1, 136.3, 130.5, 116.4, 98.6, 53.1, 30.1, 27.8 ppm.; IR (neat) 2939, 1103, 1059, 984, 916 cm⁻¹; Anal. Calcd for C₁₃H₁₆N₂O₄: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.94; H, 6.16; N, 10.46.

21: ¹H-NMR (CDCl₃, 300 MHz) δ 8.16 (s 1H), 7.70 (d, J = 0.9 Hz, 1H), 5.46 (d, J = 0.8 Hz, 1H), 5.11 (t, J = 7.1 Hz, 1H), 3.74 (s, 6H), 2.83 (t, J = 7.3 Hz, 2H), 2.48 (dt, J = 7.4, 6.8 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 166.0, 155.8, 139.7, 138.4, 137.0, 133.9, 130.4, 122.0, 98.6, 53.0, 28.5, 25.8, 25.7, 17.8 ppm.; IR (neat) 2933, 1103, 1059, 984 cm⁻¹; Anal. Calcd for C₁₃H₂₀N₂O₄: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.38; H, 7.06; N, 9.36.