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ANOMALOUS METALATION BEHAVIOR IN 1,3-OXAZOLES. ALKYLATION OF 2-METHYL-4-CARBOXYOXAZOLES VIA THE CORNFORTH INTERMEDIATE†

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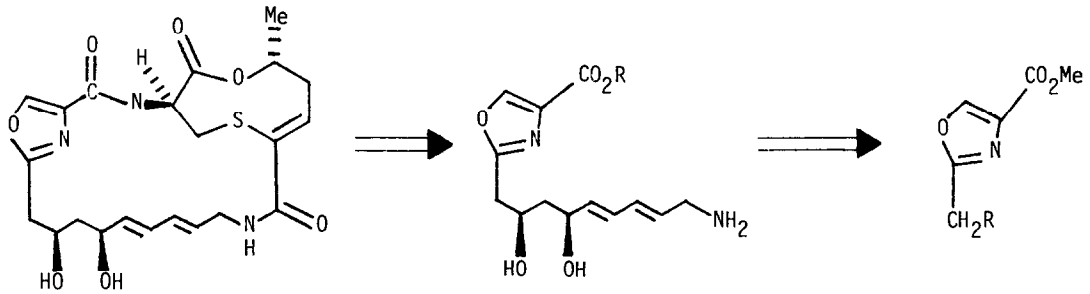
SUMMARY: Metalation of the methyl group in the title compound is accomplished through the open chain Cornforth precursor. This technique is necessary due to the preferred metalation of the 5-H proton in oxazoles.

In the course of a synthetic program aimed at the total synthesis of Griseoviridin 1, a convergent scheme involving three key features of the molecule were addressed: a) synthesis of the 9-membered lactone in 1;[2] b) stereoselective routes to E,E-diene allylic amines as in 2[2], and c) elaboration of the 2-methyl group in 1,3-oxazoles as in 3 (R=H). What appeared to

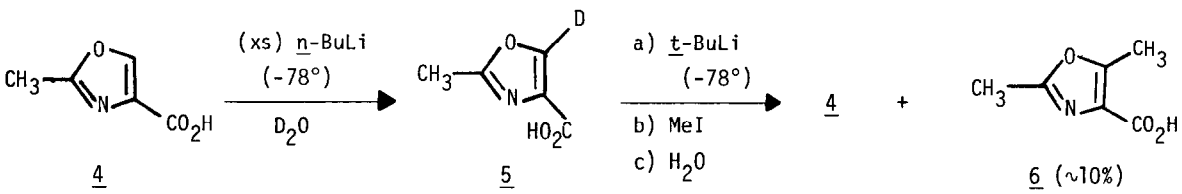


1 2 3 R = H, Li

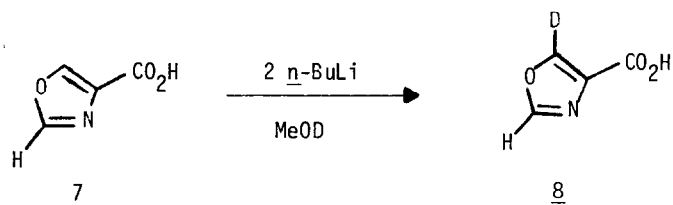
be routine metalation of 3 (R=H) to its lithio salt 3 (R=Li) followed by alkylation to precursors of 2, actually required a major detour and provided a novel route to elaborated oxazoles.

Attempts to metalate 4[3] as the acid or ester at the 2-methyl group gave, after D_2O quench, only the 5-D oxazole 5 (92% D). These results did not change regardless of the number of equivalent of n-BuLi employed. With LDA as the base, no deuterium incorporation was observed suggesting that this base was inappropriate for anion formation. Treatment of 5 with n-butyllithium and water quench showed no reaction; the isotope effect inhibiting D-abstraction with

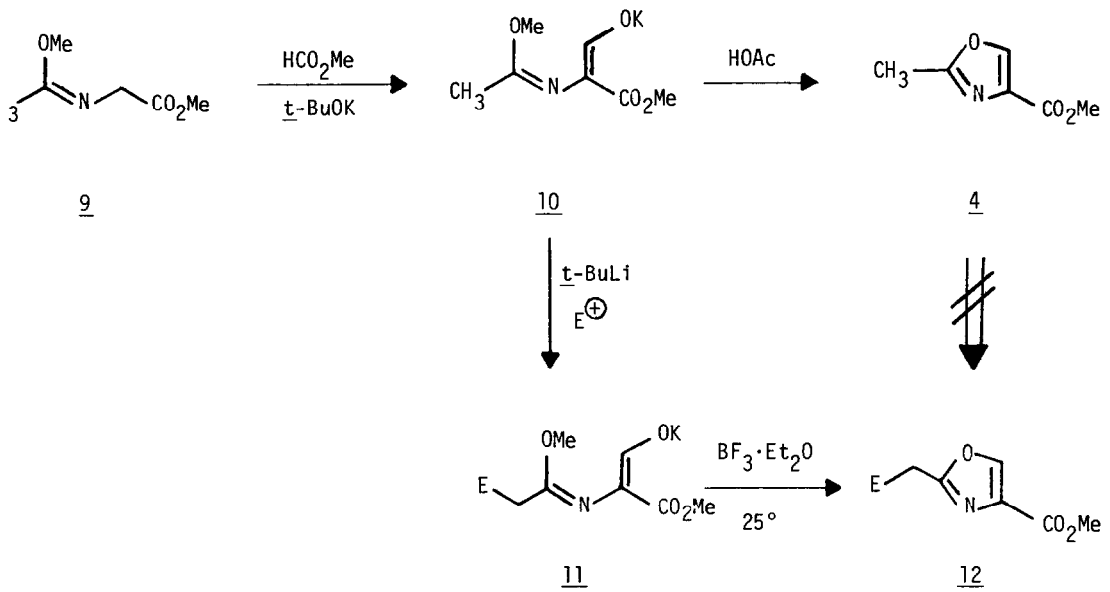
this base. However, when 5 was metalated with t-butyllithium, only the deuterium was abstracted as evidenced by methyl iodide quench, followed by aqueous workup. The products were ~90% 4 and ~10% 6, the latter completely protonated suggesting the poor nucleophilicity of the 5-lithio oxazole. In an effort to determine if the 5-position was kinetically favored while the 2-methyl group would form the thermodynamic anion 3 (R=Li), 2-methyl oxazole ester 3 was stirred for 96 h

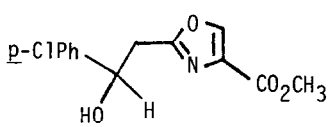
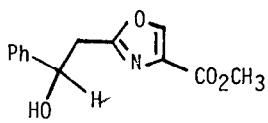
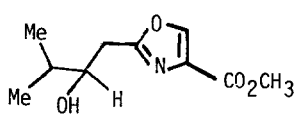
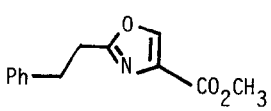


with MeOD-MeO$^-$. To our surprise only 5 (Me ester) containing 99% D at the 5-position was obtained with no visible deuterium incorporation in the 2-methyl group.[4] The failure of 2-methyl-4-carboxyoxazoles 4 to metalate at the methyl group is in contrast to the recently reported study[5,9] which described smooth deprotonations of 2,4,5-trisubstituted oxazoles with LDA and n-BuLi. In a related study, Schollkopf showed[6] that various 2-H oxazoles metalate at the 2-position. We, therefore, examined oxazole 7 and after treatment with 2 equiv of n-BuLi (-78°, THF) and MeOD, found the 5-D derivative 8 as the only product. Thus, the presence of



the 4-carboxy group strongly activates the adjacent ring proton toward removal by strong bases. In the absence of the carboxyl substituent, metalation of the 2-H or 2-methyl group proceeds with ease. Failure to elaborate the methyl group in 3 or 4 required a novel approach to introduce various 2-substituents in carboxyl-containing oxazoles, a moiety present in many natural products.[5] The solution to this problem lay in the Cornforth oxazole synthesis[3] (9→10→4) which passes through the useful intermediate 10.[7] It was reasoned that metalation of 10, followed by addition of an electrophile to 11 would eliminate the regio chemical problems in metalation. Acid catalyzed ring closure to 12 would then show that metalation-alkylation of 10 is tantamount to direct metalation of 4. That this was indeed feasible is seen from the examples of electrophiles introduced[8] and now opens a route to elaboration of carboxy-containing oxazoles necessary for the griseoviridin synthesis.



$E^{\oplus}$	12	% Yield (from 10)	(Mp)[a]
p-ClC_6H_4CHO		56	100-101°
PhCHO		51	91.5-92.0°
Me_2CHCHO		45	oil
$PhCH_2Br$		38	64-66°

a) All oxazoles gave satisfactory C, H, N analyses.

REFERENCES AND NOTES

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3. J. W. Cornforth and R. H. Cornforth, J. Chem. Soc., 96 (1947).
4. Oxazole carboxylic esters were reported to be unstable to alkaline conditions necessary for D-exchange; D. J. Brown and P. B. Gosh, J. Chem. Soc. (B), 270 (1969).
5. B. H. Lipshutz and R. W. Hungate, J. Org. Chem., 46, 1410 (1981).
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7. In the Cornforth synthesis (Ref. 3) the ethyl esters of 9, 10, and 11 were employed along with potassium ethoxide. It was found in this study that KOBu-t in THF (-10°) was superior for the formation of 10. The latter is precipitated from solution with ether, filtered under argon, dried in vacuo and used immediately. NMR (DMSO-d_6) 1.61 (s, 3), 3.35 (s, 3), 3.53 (s, 3), 8.62 (s, 1).
8. Metalation, alkylation, and cyclization of 10 to 12 was performed by dissolving n grams of 10 in 10n ml diglyme (Na, 55°/12 mm), followed by 5n ml of THF and cooling to -78°. To avoid precipitation of 10, an additional 25 n ml THF was added and the solution cooled further to -98° (MeOH-liq N_2). Addition of 1.0 equiv t-BuLi (pentane) was followed by stirring (1 h) and 1.0 equiv of electrophile at -98°. For benzyl bromide stirring was continued at -78° overnight; for aldehydes, reaction was complete in 20 min at -98°. To the cold solution was added 2.05 equiv $BF_3 \cdot Et_2O$ (HOAc at reflux for 10 min for benzyl bromide) and stirred for 5 min at -98° followed by warming to ambient overnight. One ml of sat. $NaHCO_3$ was added and the solvents removed in vacuo. Addition of aqueous $NaHCO_3$ to the residue was followed by ether extraction, drying (K_2CO_3) and concentration. The crude products 12 were purified by prep. TLC (acetone:hexane, 1:2).
9. After this manuscript was completed, another report [H. H. Wasserman, et al., Tet. Letters, 1737 (1981)] described metalation of 2-methyl-4,5-diphenyl oxazoles.

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† This paper is dedicated to the occasion of the 60th birthday of Professor Harry H. Wasserman.

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