Metalation Studies of Trisubstituted Oxazoles†

Bruce H. Lipshutz*[1] and Randall W. Hungate

Department of Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106

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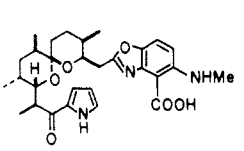
Metalation studies of trisubstituted oxazoles have been completed as part of a program designed to prepare novel heterocyclophanes. Proton abstraction of 2,4,5-trimethyloxazole at C-2 could be effected by using LDA/THF at −78 °C, while 2,4-dimethyl-5-phenyloxazole, 2,5-dimethyl-5-phenyloxazole, and 2-methyl-4,5-diphenyloxazole required *n*-BuLi in THF at −100 °C. All gave good to excellent yields of coupling product with a variety of electrophiles, including aldehydes, ketones, enones, alkyl halides, silyl chlorides, epoxides, and organometallic species.

As a part of a program aimed at preparing new [*m.n*]-heterocyclophanes containing an oxazole, imidazole, or isoxazole moiety in addition to a phenyl ring, we have initially chosen to examine the functionalization of trisubstituted oxazoles. These aromatic systems have found considerable utility as latent functional group equivalents.[2] Furthermore, a number of interesting and biologically active natural products containing the oxazole nucleus, as exemplified by conglobatin,[3a] berninamycin A,[3b] calcinomycin (A-23187, 1),[4] and griseoviridin, 2,[5] have been reported and are currently the object of intensive synthetic endeavors. An early report[6] had shown that 2-methyl-4,5-diphenyloxazole was susceptible to condensation with carbonyl compounds, employing sodamide in liquid ammonia, affording products in fair yields. In an effort to examine the scope of oxazole metalations, we now report the results from our far more extensive study in this area, demonstrating the variety of electrophiles which can partake in coupling reactions with lithiated oxazoles.



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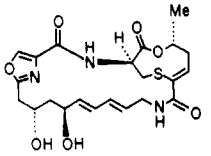

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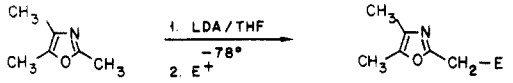
Initial work centered on the simple system, 2,4,5-trimethyloxazole, 3.[7] Addition of 3 to a solution of LDA (1.05 equiv) in THF (0.5 M) at −78° C for 20 min produced an orange, homogeneous reaction mixture. Addition of an electrophile at this temperature followed by quenching (with pH 7 phosphate buffer) and warming to room temperature led to derivatized materials 4[8] in good yields. Table I provides a representative sampling of the electrophiles used. Condensation with aldehydes and ketones, as expected, occurred readily at −78 °C, while alkylations with activated halides or an epoxide required somewhat higher temperatures.



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Extending this simple procedure to other trisubstituted systems, however, led to less satisfactory results. Hence, we investigated different conditions for effecting proton abstraction. Fortunately, an efficient general procedure was found wherein *slow addition* of 1.05 equiv of *n*-BuLi in THF (0.1 M) at −100 °C is employed. Thus, 2-

Table I. Reactions of 2,4,5-Trimethyloxazole with Electrophiles

Substrate	Electrophile	Product (%)[a]
3	CHO	(89)
3	O	(95)
3	Cl[b]	(92)
3	Br[c,d]	(70)
3	CHO	(73)
3	CHO[e] Fe	(57)
3	Ph, O[b]	(72)

[a] All yields refer to isolated, chromatographically pure materials. [b] Reaction was warmed to 0° for 1.5 − 3 h. [c] Prepared as described by P.R. Tavssig, G.B. Miller, and P.W. Storms, J. Org. Chem., 30, 3122 (1965). [d] Reaction was warmed to room temperature for ca. 1 h. [e] Commercially available from the Aldrich Chemical Company.

† Dedicated to Professor Harry H. Wasserman on the occasion of his 60th birthday.

(1) American Cancer Society, Junior Faculty Fellow, 1981-1983.

(2) See, for example; Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748; Jacobi, P. A.; Ueng, S.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2043; Kozikowski A. P.; Ames, A. *Ibid.* **1980**, *45*, 2548; Kozikowski, A. P.; Hansan, N. M. *Ibid.* **1977**, *42*, 2039; Wasserman, H. H.; Floyd, M. B. *Tetrahedron, Suppl.*, **1966**, *7*, 441; Wasserman, H. H.; Vinick, F. J.; Chang, Y. C. *J. Am. Chem. Soc.* **1972**, *94*, 7180; Wasserman, H. H.; Lenz, G. *Heterocycles* **1976**, *5*, 409; Wasserman, H. H.; Druckrey, E. *J. Am. Chem. Soc.* **1968**, *90*, 2440; Reddy, G. S.; Bhatt, M. V. *Tetrahedron Lett.* **1980**, *21*,3627.

(3) (a) Westley, J. W.; Liu, C.-M; Evans, R. H.; Blount, J. F. *J. Antibiot.* **1979**, *32*, 874. (b) Liesch, J. M.; Rinehart, K. L. *J. Am. Chem. Soc.* **1977**, *99*, 1645.

(4) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789; Grieco, P. A.; Kanai, K.; Williams, E. *Heterocycles* **1979**, *12*, 1623.

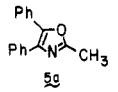
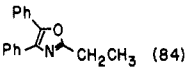
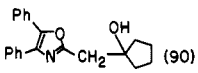
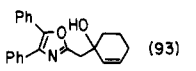
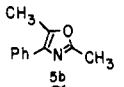
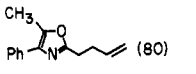
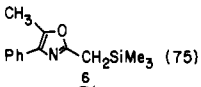
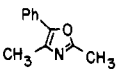
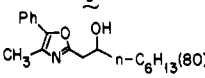
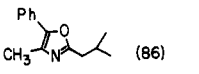
(5) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.

(6) Dryanska, V.; Ivanov, K. *God. Sofii. Univ., Khim. Fak.* **1968**, *63*, 105; *Chem. Abstr.* **1972**, *76*, 126844*r*.

(7) Prepared by the method of Davidson, Weiss, and Jelling (*J. Org. Chem.* **1937**, *2*, 328); sold commercially by the Aldrich Chemical Company, Milwaukee, WI.

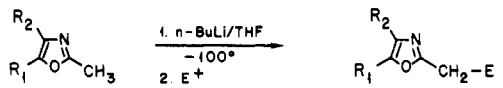
0022-3263/81/1946-1410$01.25/0

Table II. Reactions of 2,4,5-Trisubstituted Oxazoles

Substrate	Electrophile	Product (%)[a]
 5a	CH_3I [b]	 (84)
5a	 [c]	 (90)
5a		 (93)
 5b		 (80)
5b	Me_3SiCl	 6 (75)
 5c	$n-C_6H_{13}CHO$	 (80)
5c	 [b]	 (86)

[a] Yields based on isolated, chromatographically pure products. [b] Reaction quenched at −78° and warmed slowly to rt. [c] Literature yield is 45%; see Ref. 6.

methyl-4,5-diphenyloxazole (**3**)[10] 2,4-dimethyl-5-phenyloxazole (**5b**),[11] and 2,5-dimethyl-4-phenyloxazole (**5c**),[11]



5a, $R_1 = R_2 = Ph$
5b, $R_1 = Ph$, $R_2 = CH_3$
5c, $R_1 = CH_3$, $R_2 = Ph$

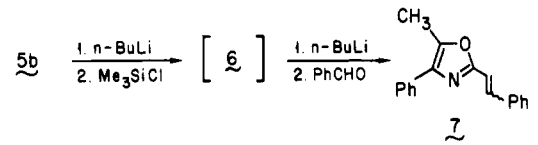
following metalation, warming to −78 °C and addition of an electrophile, gave good to excellent yields of C-2-substituted products. Notably, the secondary halide 2-iodopropane reacted cleanly, although only to the extent of 70% conversion, while cyclopentanone gave an excellent yield (90%) of condensation product, returning 6% unreacted oxazole from ketone enolization. Quenching a 2-methyloxazole anion with cyclohexenone formed only the product of 1,2-addition. Chlorotrimethylsilane trapping of the oxazole anion led to the clean formation of the expected product (by TLC); however, rapid silica gel chromatography afforded some recovered starting material, thus decreasing the overall yield. This is, however, a quite useful compound, since not only is proton abstraction from the methylene group in **6** (see Table II) facilitated by silicon substitution, but condensation with carbonyl compounds (e.g., benzaldehyde) leads directly to substituted vinyloxazoles via a Peterson olefination-like sequence. Compounds of this type may serve as Michael acceptors in cyclophane synthesis. These general observations are summarized in Table II.

(8) Metalation on the methyl group at the 2-position was apparent from previous work[6] and NMR analysis of the derivatized materials. This result was expected based on numerous calculations indicating C-2 to contain the greatest density of positive charge relative to C-4 and C-5 in oxazoles.[9a] Furthermore, only the 2-methyl group undergoes condensation in the case of 2,5-dimethyloxazole.[9b]

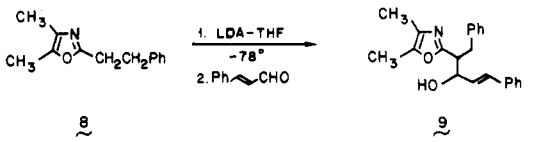
(9) (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, 389. (b) French Patent No. M. 2583, 1964; *Chem. Abstr.* **1964**, *61*, 13319.

(10) Japp, F. R.; Murray, T. S. *J. Chem. Soc.* **1893**, *63*, 469.

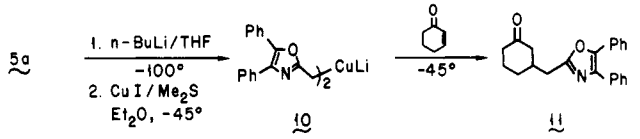
(11) Bredereck, H.; Gomper, R.; Reich, F. *Chem. Ber.* **1960**, *93*, 1389.



To further extend the value of these sequences the effectiveness of remetalation of oxazole 8 was investigated. Treatment of 8 with LDA in the usual fashion (vide supra) and quenching with cinnamaldehyde afforded **9** in ca. 60% yield as a ca. 1:1 mixture of diastereomers.[12]



Finally, clean formation of lithiated 2-methyloxazoles, using *n*-BuLi at low temperatures, has enabled us, in a preliminary study, to investigate the formation of homocuprate **10** via metalation and subsequent reaction with (0.5 equiv) CuI in the presence of 2 equiv of dimethyl sulfide at −45 °C. Addition of cyclohexenone (0.25 equiv) at −78 °C followed by stirring at −45 °C for 30 min afforded adduct **11** in >80% yield.[10]



In conclusion, we have shown that 4,5-disubstituted-2-alkyloxazoles will undergo efficient side-chain metalation and can be used as nucleophiles in subsequent processes. Multiple proton abstractions from 2-methyl-substituted systems have been demonstrated, leading to more complex derivatives. Incorporation of these observations en route to cyclophanes of varied structures is actively underway. Extension of these metalation procedures to the formation of various heteroaromatic Gilman reagents is also under investigation, the details of which will be reported in due course.

Experimental Section

NMR spectra were recorded on a Varian T-60 or Varian FT-80 spectrophotometer in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise specified. Infrared spectra were measured by using a Perkin-Elmer 283 or 337 grating spectrophotomer in $CHCl_3$ solution. Mass spectral data were recorded at 70 eV, using either an AEI-MS 902 or ZAB-2F spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. THF was distilled from benzophenone ketyl. All reactions were conducted under a blanket of argon, with all liquid transfers done using syringe and/or canula techniques.

Usual workup procedures consisted of extraction with CH_2Cl_2 or Et_2O (3 × 25 mL) and washing the combined extracts successively with sodium bicarbonate (saturated) and saturated brine solution followed by drying over anhydrous sodium sulfate, potassium carbonate, or magnesium sulfate, filtration, and concentration in vacuo. Column chromatography was performed with silica gel 60 (Merck, 70–230 mesh). Merck precoated silica gel plates were used for TLC monitoring of reactions, with chromatograms being developed with phosphomolybdic acid and heat.

General Procedures for Preparation of 2-Substituted-4,5-Dimethyloxazoles, 4. To a solution of lithium diisopropylamide (1.1 equiv, prepared from *n*-BuLi, 2.37 M in hexane,

(12) This was determined by using a 2 ft × 2 mm 2% OV-101 plus 0.2% Carbowax 20 M on Chromosorb W with a Hewlett-Packard Model 5992A GC/MS unit.

and diisopropylamine in THF at −78 to 0 °C recooled to −78 °C) under argon was added 2,4,5-trimethyloxazole (3), dropwise via syringe. After the orange solution was stirred for 20 min at this temperature, 1.1 equiv of electrophile (dried in an Abderhalden or freshly distilled) was added. In the case of aldehydes and ketones, the reaction was further stirred for 5 min and quenched with pH 7 phosphate buffer. Other electrophiles were allowed to slowly warm to 0 °C, where the temperature was maintained for 1.5 h. The resulting bright yellow solution was quenched with pH 7 phosphate buffer and extracted several times with dichloromethane. After a standard washing with water and brine and drying over $MgSO_4$, a residue was obtained which was chromatographed on silica gel to afford the product in yields of 57–95%.

2-(β-Naphthylethyl)-4,5-dimethyloxazole: 70%; R_f (Et_2O/pentane, 1/1) 0.57; ^1H NMR δ 2.06 (3 H, s), 2.19 (3 H, s), 3.11 (4 H, m), 7.51 (7 H, m); IR ($CHCl_3$) 3050, 3010, 1610, 1590, 1575, 1520, 1451 cm^{-1}; mass spectrum; *m/e* (relative intensity) 251 (38, M^+), 141 (100), 115 (16), 110 (19), 43 (11).

2-Propyl-(3-hydroxyl-3-phenyl)-4,5-dimethyloxazole: 72%; R_f (Et_2O) 0.31; ^1H NMR δ 2.77 (2 H, t, J = 8 Hz), 3.89 (1 H, br s), 4.77 (1 H, t, J = 7 Hz), 7.34 (5 H, s); IR (neat) 3360, 1605, 1590, 1550, 1460, 1440 cm^{-1}; mass spectrum, *m/e* (relative intensity) 214 (16), 188 (10), 126 (16), 125 (46), 112 (100), 105 (26), 18 (29).

1-(2,4,5-Trimethyl-2-oxazolyl)-cyclohexan-1-ol: 95%; R_f (Et_2O) 0.36; ^1H NMR δ 1.50 (10 H, br s), 1.96 and 2.00 (3 H, s), 2.17 and 2.19 (3 H, s), 2.78 (2 H, s) 3.50 (1 H, s); IR ($CHCl_3$) 3400, 1567, 1150 cm^{-1}; mass spectrum, *m/e* (relative intensity) 209 (<1, M^+), 111 (100), 81 (12).

4,5-Dimethyl-2-(β-phenylethyl)oxazole: R_f (Et_2O/pentane, 1/1) 0.31; ^1H NMR δ 2.02 and 2.07 (3 H, s), 2.19 (3 H, s), 3.01 (4 H, m), 7.25 (5 H, s); IR (neat) 3020, 1601, 1585, 1560, 1500, 1445 cm^{-1}; mass spectrum, *m/e* (relative intensity) 201 (72, M^+), 124 (12), 110 (100), 91 (30).

2-Ethyl-(2-hydroxyl-2-phenyl)-4,5-dimethyloxazole: 72%; R_f (Et_2O) 0.34; ^1H NMR δ 2.00 and 2.02 (3 H, s), 2.15 and 2.17 (3 H, s), 2.98 (2 H, d, J = 6 Hz), 4.15 (1 H, br s), 5.09 (1 H, t, J = 6 Hz), 6.30 (5 H, m); IR ($CHCl_3$) 3325, 1595, 1587, 1575, 1505, 1450 cm^{-1}; mass spectrum, *m/e* (relative intensity) 198 (77), 115 (71), 111 (100), 77 (58), 28 (90).

2-[2-(2-Furyl)-2-hydroxylethyl]-4,5-dimethyloxazole: 73%; R_f (Et_2O) 0.32; ^1H NMR δ 1.97 and 2.00 (3 H, s), 2.10 (3 H, s), 3.12 (2 H, d, J = 7 Hz), 4.10–4.47 (1 H, br s), 5.12 (1 H, t, J = 7 Hz), 6.24 (2 H, m), 7.32 (1 H, m); IR ($CHCl_3$) 3280, 1655, 1572 cm^{-1}; mass spectrum, *m/e* (relative intensity) 189 (14), 148 (10), 111 (100), 97 (42), 28 (33).

1-[2-(4,5-Dimethyl-2-oxazolyl)-1-hydroxyethyl]ferrocene: 57%; R_f (Et_2O) 0.38; ^1H NMR δ 2.02 (3 H, s), 2.15 (3 H, s), 2.98 (2 H, d, J = 6 Hz), 3.25 (1 H, br s), 4.23 (10 H, s), 4.82 (1 H, t, J = 6 Hz); IR ($CHCl_3$) 3240, 1660, 1580 cm^{-1}; mass spectrum, *m/e* (relative intensity) 325 (7, M^+), 307 (35), 242 (100), 171 (59), 111 (61), 41 (65).

3-Hydroxyl-4-(4,5-dimethyl-2-oxazolyl)-1,5-diphenylpent-1-ene, 9: 60%; R_f (Et_2O) 0.46; ^1H NMR δ 2.00 (3 H, s), 2.13 (3 H, s), 3.15 (3 H, m), 3.95 (1 H, m), 4.50 (1 H, m), 6.60 (2 H, m), 7.25 (10 H, m); IR ($CHCl_3$) 3280, 1600, 1560, 1550, 1495, 1450 cm^{-1}; mass spectrum, *m/e* (relative intensity) [less polar component (retention time 8.3 min)] 333.4 (11, M^+), 315.3 (7), 202.5 (40), 201.6 (100), 200.6 (42), 133.3 (45), 124.4 (64), 115.2 (86), 110.1 (80), 103.4 (48) 77.1 (55), 43.3 (26); mass spectrum, *m/e* (relative intensity) [more polar component (retention time 8.5 min)] 333.4 (9, M^+), 315.3 (20), 156.6 (59), 132.2 (65), 131.3 (100), 104.4 (60), 77.1 (67).

Typical Procedure for Metalation and Reaction of Trisubstituted Oxazoles with *n*-BuLi. 2-Ethyl-4,5-diphenyloxazole. A solution of **5** (92.5 mg, 0.394 mmol) in THF (3.9 mL) was cooled to −100 °C (pentane, liquid N_2) and *n*-BuLi (0.18 mL, 0.398 mmol) was slowly added over 20 min. The resulting deep orange-red solution was brought to −78 °C whereupon addition of excess CH_3I and warming to room temperature dissipated the deep color. Quenching with phosphate buffer (pH 7) and workup, followed by silica gel chromatography (2/1 pentane–Et_2O), yielded 82.2 mg (84%) of a clear oil; R_f (Et_2O) 0.68; ^1H NMR δ 1.35 (3 H, t, J = 6 Hz), 2.81 (2 H, q, J = 7, 8 Hz), 7.35 (10 H, m); IR (neat) 1570 cm^{-1}; mass spectrum, *m/e* (relative intensity) 249 (100, M^+), 206 (46), 165 (88), 117 (29), 103 (25), 105 (29), 28 (75).

1-(2-Methyl-4,5-diphenyl-2-oxazolyl)cyclopentan-1-ol: 90%; R_f (Et_2O) 0.56; white solid; mp 102.7–104 °C; ^1H NMR (CCl_4) δ 1.25–2.13 (8 H, m), 3.03 (2 H, s), 3.53–3.83 (1 H, br s), 7.0–7.8 (10 H, m); IR ($CHCl_3$) 3300, 1560 cm^{-1}; mass spectrum, *m/e* (relative intensity) 319 (5, M^+), 301 (38), 235 (100), 207 (13), 165 (59), 104 (19).

1-(2-Methyl-4,5-diphenyl-2-oxazolyl)cyclohex-2-en-1-ol: 93% clear oil; R_f (Et_2O/pentane, 1/1) 0.22; ^1H NMR δ 1.42–2.22 (6 H, m), 3.05 (2 H, s), 3.57–3.92 (1 H, br s), 5.58–5.95 (2 H, m), 6.91–7.77 (10 H, m); IR ($CHCl_3$) 3380, 1560 cm^{-1}; mass spectrum, *m/e* (relative intensity) 313 (19), 285 (9), 235 (100), 165 (58), 104 (22), 97 (28), 77 (33), 68 (44).

2-(3-Butenyl)-4-methyl-5-phenyloxazole: 80%; light yellow oil; R_f (Et_2O) 0.60; ^1H NMR δ 2.35 (3 H, s), 2.40–2.90 (4 H, m), 5.06 (2 H, m), 5.87 (1 H, m), 7.40 (5 H, m); IR (neat) 1640, 1560 cm^{-1}; mass spectrum, *m/e* (relative intensity) 214 (8, M^+), 213 (54), 172 (41), 122 (26), 105 (49), 102 (100), 75 (53), 58 (17).

2-[(Trimethylsilyl)methyl]-4-methyl-5-phenyloxazole, 6: 75%; clear oil; R_f (Et_2O/pentane, 1/1) 0.64; ^1H NMR ($CDCl_3$ with CH_2Cl_2 as internal standard) δ 0.20 (9 H, s), 2.30 (2 H, s), 2.40 (3 H, s), 7.25–7.66 (5 H, m); IR (neat) 1555, 1250 cm^{-1}; mass spectrum, *m/e* (relative intensity) 246 (55, M^+), 187 (17), 72 (100), 28 (17).

1-(5-Phenyl-4-methyl-2-oxazolyl)octan-2-ol: 77%; white solid; mp 75–76.3 °C; R_f (Et_2O) 0.62; ^1H NMR (CCl_4) δ 1.03–1.64 (14 H, m), 2.49 (3 H, s), 2.64 (2 H, d, J = 3 Hz), 2.75 (1 H, s); IR (KBr) 3300, 1580 cm^{-1}; mass spectrum, *m/e* (relative intensity) 287 (4, M^+), 173 (100), 55 (16).

2-Isobutyl-4-phenyl-5-methyloxazole: 86%; R_f (Et_2O) 0.69; ^1H NMR δ 1.03 (6 H, d, J = 7 Hz), 2.09 (1 H, m), 2.49 (3 H, s), 2.58 (2 H, d, J = 7 Hz), 7.47 (5 H, m); IR (neat) 1570 cm^{-1}; mass spectrum, *m/e* (relative intensity) 215 (53, M^+), 200 (18), 173 (100), 172 (42), 129 (23), 106 (80), 78 (61).

3-(2-Methyl-4,5-diphenyloxazolyl)cyclohexan-1-one, 11. A solution of **5** (119.0 mg, 0.50 mmol) in 5.0 mL of THF was cooled to −100 °C (pentane, liquid N_2) and *n*-BuLi (0.23 mL, 0.50 mmol) was slowly added over 25 min. The resulting deep orange red solution was brought to −78 °C and transferred via cannula into CuI (50.9 mg, 0.267 mmol) and dimethyl sulfide (39.1 μL, 0.53 mmol) which was in 1 mL of Et_2O. Final washing of the oxazole anion with 1 mL of Et_2O brought the concentration of cuprate to ca 0.04 M. The resulting heterogeneous reaction mixture was brought to −45 °C (cyclohexanone/CO_2) for 15 min where a clear homogeneous orange solution formed. Recooling back to −78 °C was followed by adding cyclohex-2-en-1-one (6.3 μL, 0.063 mmol) and stirring at this temperature for 7 h. After the solution was quenched at −78 °C [90% NH_4Cl (saturated) + 10% NH_4OH (concentrated)], workup and chromatography on silica gel (2/1 pentane/Et_2O), 17.5 mg of the 1,4-addition product (85%) was obtained: R_f (20% acetone/hexane) 0.18; ^1H NMR δ 1.69–2.64 (9 H, m), 2.80 (2 H, d , J = 6 Hz), 7.35 (10 H, m); IR (neat) 1725, 1560 cm^{-1}; mass spectrum, *m/e* (relative intensity) 331 (9, M^+), 235 (100), 165 (47), 103 (47), 86 (51), 84 (79), 59 (54), 42 (64), 28 (62).

2-(2-Phenylvinyl)-4-methyl-5-phenyloxazole, 7. A solution of **6** (77.3 mg, 0.44 mmol) in 4.4 mL of THF was cooled to −100 °C under Ar and *n*-BuLi (0.205 mL, 0.445 mmol) was added slowly over 20 min. The deep yellow solution was warmed to −78 °C and transferred via cannula to a solution of chlorotrimethylsilane (57.1 μL, 0.445 mmol) in 0.4 mL of THF. The silylated oxazole (by TLC) was subsequently treated with 1 equiv of *n*-BuLi (at −78 °C) and stirred for 30 min to generate a deep green solution. Quenching with benzaldehyde (43.3 μL, 0.445 mmol) immediately dissipated the color. The reaction was further stirred for 2 min followed by the addition of pH 7 buffer. Usual workup and chromatography over silica gel (2:1 pentane/Et_2O) afforded 66.5 mg (56%) of the desired product as a pale yellow oil in a ca. 1:1 mixture of isomers. Less polar *Z* isomer: R_f (3:1 pentane/Et_2O) 0.14; ^1H NMR δ 2.47 (3 H, s), 6.77 (2 H, dd, J = 13, 18 Hz), 7.40 (10 H, m). More polar *E* isomer: R_f (3:1 pentane/Et_2O) 0.19; ^1H NMR δ 2.48 (3 H, s), 6.96 (1 H, d of dd, J = 17 Hz), 7.50 (11 H, m); IR ($CHCl_3$, mixture of *E* and *Z*) 1630, 1600, 1585, 1500, 1450 cm^{-1}; mass spectrum; *m/e* (relative intensity) 261 (<1, M^+), 173 (100), 144 (18), 104 (71), 28 (63).

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Registry No. 3, 20662-84-4; **5a**, 14224-99-8; **5b**, 20662-92-4; **5c**, 23012-31-9; **6**, 76346-79-7; **7** (*E*), 76346-80-0; **7** (*Z*), 76346-81-1; **8**, 76346-82-2; **9** (isomer 1), 76346-83-3; **9** (isomer 2), 76346-84-4; **11**, 76346-85-5; 2-(β-naphthylethyl)-4,5-dimethyloxazole, 76346-86-6; 2-(3-hydroxy-3-phenylpropyl)-4,5-dimethyloxazole, 76346-87-7; 1-(2,4,5-trimethyl-2-oxazolyl)cyclohexan-1-ol, 76346-88-8; 2-ethyl-(2-hydroxyl-2-phenyl)-4,5-dimethyloxazole, 76346-89-9; 2-[2-(2-furyl)-2-hydroxylethyl]-4,5-dimethyloxazole, 76346-90-2; 1-[2-(4,5-dimethyl-2-oxazolyl)-1-hydroxylethyl]ferrocene, 76346-70-8; 2-ethyl-4,5-diphenyloxazole, 53833-30-0; 1-(2-methyl-4,5-diphenyl-2-oxazolyl)cyclopentan-1-ol, 35491-02-2; 1-(2-methyl-4,5-diphenyl-2-oxazolyl)cyclohexen-2-en-1-ol, 76346-91-3; 2-(3-butenyl)-4-methyl-5-phenyloxazole, 76346-92-4; 1-(5-phenyl-4-methyl-2-oxazolyl)octan-2-ol, 76346-93-5; 2-isobutyl-4-phenyl-5-methyloxazole, 76346-94-6; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; (chloromethyl)-benzene, 100-44-7; 2-(bromomethyl)naphthalene, 939-26-4; 2-furancarboxaldehyde, 98-01-1; formylferrocene, 12093-10-6; phenyloxirane, 96-09-3; cyclopentanone, 120-92-3; 2-cyclohexen-1-one, 930-68-7; 3-bromo-1-propene, 106-95-6; chlorotrimethylsilane, 75-77-4; heptanal, 111-71-7; 2-iodopropane, 75-30-9; iodomethane, 74-88-4; cinnamaldehyde, 14371-10-9.

Chemistry of 2-Substituted Pyrimidines. Studies Directed toward the Synthesis of the Pyrimidine Moiety of Bleomycin

William K. Hagmann,[1] Fatima Z. Basha, Mitsunori Hashimoto, R. Bruce Frye, Shosuke Kojo, and Sidney M. Hecht*[2]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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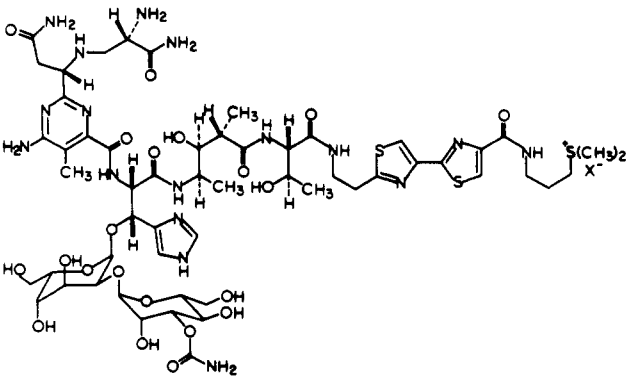
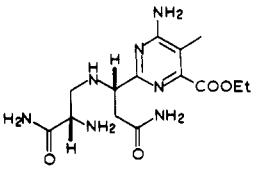
Synthetic approaches to 2-substituted pyrimidines have been studied in an effort to facilitate the preparation of the pyrimidine moiety of bleomycin (**2**). Ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (**4**) has been utilized as starting material; its conversion to the respective ethyl 2-(carboalkoxy)-5-methyl-4-oxopyrimidine-6-carboxylates provided electrophilic intermediates for attempted elaboration of the 2-substituent, while treatment of **4** with pyridine promoted the nucleophilic addition of the C-2 methyl group to chloral. Introduction of the requisite β-aminoalaninamide substituent was attempted in several ways, including conjugate addition reactions, the use of imine or enamine intermediates, and via nucleophilic halide displacement. Of particular interest were the use of 4-azidopyrimidines as synthetic intermediates leading to the required 4-aminopyrimidines and the solvent-dependent rearrangement of ethyl 3-azido-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (**46**) to ethyl 3-amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]acrylate (**47**) at ambient temperature.

The bleomycins are a family of structurally related antitumor antibiotics elaborated by the fungus *Streptomyces verticillus*.[3] Certain of the bleomycins are of considerable interest at present because of their clinical utility in the treatment of squamous cell carcinomas and malignant lymphomas.[4] As part of an effort to effect a convergent total synthesis of bleomycin A_2 (**1**),[5] we have recently prepared the pyrimidine moiety of bleomycin (**2**) blocked in a form suitable for reconstruction of the antibiotic.[6] Presently, we describe the chemistry of some 2-substituted pyrimidines, on the basis of which we were able to devise



1

a workable synthesis of an appropriate derivative of **2**.



2

In addition to solution of the stereochemical problem, successful construction of the requisite pyrimidine involved initial synthesis of a suitable 2-alkylpyrimidine and its conversion to a (pyrimidin-2-yl)propionamide, as well as introduction of the β-aminoalaninamide substituent. Particularly challenging was introduction of the amino group at C-4 of the pyrimidine and selective manipulation

(1) National Cancer Institute Postdoctoral Trainee, 1978-1979; National Cancer Institute Postdoctoral Fellow, 1979-1980.

(2) Alfred P. Sloan Fellow, 1975-1979; NIH Research Center Development Awardee, 1975-1980. Present Address: Department of Chemistry, University of Virginia, Charlottesville, VA 22901.

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