the three cations. There is in addition a significant shift in the λ_{max} of the cation, increased conjugation of the aryl ring and the benzopyrylium ion leading to a bathochromic shift. This observation is important since the parameter being measured here is a property of the cation only (and its excited state).

Acknowledgment. The continued financial support of the Natural Engineering and Research Council of Canada is gratefully acknowledged.

Appendix. Kinetic Analysis. The Formation of the 4'-Methoxy-3-methylflavylium Ion from Neutral Solutions

The kinetic system is defined as

$$ZC \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} B2 \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} F^+ \qquad (A1)$$

and the boundary conditions that at zero time, $[F^+] = 0$ and $[ZC]/[B2] = k_2/k_{-2}$, the following expression can be derived[15] for the flavylium ion absorbance

$$\frac{A_\infty - A}{A_\infty} = C_1 e^{-C_2 t} + (1 - C_1) e^{-C_3 t} \qquad (A2)$$

where A_∞ is the final absorbance value in the solution in question and

$$C_1 = \frac{\dfrac{k_1k_2 + k_1k_{-2} + k_{-1}k_{-2}}{k_2 + k_{-2}} - C_2}{C_3 - C_2} \qquad (A3)$$

$$C_2, C_3 = \tfrac{1}{2}\{(k_1 + k_{-1} + k_2 + k_{-2}) \pm \sqrt{(k_1 + k_{-1} + k_2 + k_{-2})^2 - 4(k_1k_2 + k_1k_{-2} + k_{-1}k_{-2})}\}$$

The experimental absorbance:time curves were fit by using nonlinear least squares to provide values of C_1, C_2, and C_3 at each pH. These provide three equations in the constants k_1, k_2, k_{-1}, and k_{-2}.

$$\frac{k_1k_2 + k_1k_{-2} + k_{-1}k_{-2}}{k_2 + k_{-2}} = C_1(C_3 - C_2) + C_2 \qquad (A5)$$

$$k_1 + k_{-1} + k_2 + k_{-2} = C_2 + C_3 \qquad (A6)$$

$$k_1k_2 + k_1k_{-2} + k_{-1}k_{-2} = C_2C_3 \qquad (A7)$$

A fourth equation is available using the observed acidity constant

$$\frac{k_{-1}k_{-2}}{k_1k_2 + k_1k_{-2} + k_{-1}k_{-2}} = \frac{[H^+]}{[H^+] + K_{obsd}{}^a(F^+)} \qquad (A8)$$

Algebraic manipulation of these four equations provides the four individual constants.

(15) Bernasconi, C. F. "Relaxation Kinetics"; Academic Press: New York, 1976.

Metalation of Isoxazolyloxazolines, a Facile Route to Functionally Complex Isoxazoles: Utility, Scope, and Comparison to Dianion Methodology

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2-(5'-Alkylisoxazol-4'-yl)-Δ^2-oxazoline was metalated at the C-5' alkyl group, and the lithio anion was quenched with a variety of electrophiles. Alkyl halides, aldehydes, and acylpyridinium salts were used as electrophiles. The lithio anion was oxygenated with MOOPH or *N*-(phenylsulfonyl)oxaziridene. The isoxazolyloxazoline system was converted to the isoxazolyl carboxylic acid, aldehyde, ketone, and chiral oxazoline. The isoxazolyloxazoline was formed, metalated, and deprotected in synthetically useful yields and represents a facile entry into functionally complex isoxazoles. To determine the necessity of the oxazoline protection/deprotection scheme, dianions of isoxazole-4-carboxylic acids were studied. The dianion method was found to be more efficient for simple alkyl halides, but limited in scope.

Isoxazoles continue to be of interest both for their synthetic utility and intrinsic biological activity.[1] In the course of related studies[2] we desired a facile entry into derivatives containing a carbonyl functional equivalent in the C-4 position of the isoxazole ring. We have examined the use of the oxazoline protecting group[3] for the carboxyl group, and herein report in full on the utility, scope, and limitations of this approach.[4] We have also examined the formation and utility of dianions of isoxazole-4-carboxylic acids to weigh the relative merit of the use of the oxazoline protecting group.

The metalation of simple alkylisoxazoles, termed "lateral" metalation by Micetich,[5] is a useful synthetic

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(2) (a) Natale, N. R. *Tetrahedron Lett.* **1982**, 5009. (b) Natale, N. R.; Quincy, D. A. *Synth. Commun.* **1983**, *13*, 817.

(3) (a) For a recent review on oxazoline chemistry see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Eng.* **1976**, *15*, 270.

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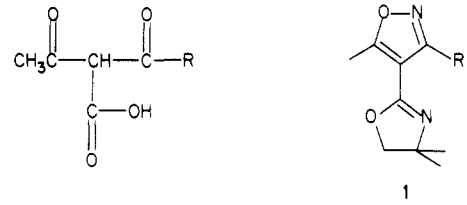
Table I. Metalation and Electrophilic Quenching of 1 To Produce 2

entry	R	E_1	method[a]	yield,[b] %	mp (bp, mmHg)	formula	MS, m/z (M^+ rel int)[f]
a	Me	DOMe	B	82–89	76–78	$C_{10}H_{13}DN_2O_2$[h]	195 (22)
b	Me	MeI	A	92	(88, 0.4)	$C_{11}H_{16}N_2O_2$[i]	208 (75)
c	Me	MeI	B	78–86		same product as above	
d	Me	$PhCH_2Br$	A	49 (50)	(148, 0.25)	$C_{17}H_{20}N_2O_2$[i]	284 (13)
e	Me	$PhCH_2Br$	B	91		same product as above	
f	Me	*n*-octyl bromide	A or B	82	[g]	$C_{18}H_{30}N_2O_2$[i]	306 (12)
g	Me	PhCHO	B	97	[g]	$C_{17}H_{20}N_2O_3$[i]	283 (0.5)
							194 (100)
							CI, 301 (M + 1, 71)
h	Et	MeI	B	74	[g]	$C_{12}H_{18}N_2O_2$[i]	222 (100)
i	Ph	DOMe	B	72	43–46	$C_{15}H_{15}DN_2O_2$[h]	
j	Ph	MeI	A	36 (40)	(114, 0.2)	$C_{16}H_{18}N_2O_2$[i]	270 (66)
k	Ph	MeI	B	86–92		same product as above	
l	Ph	MeI	C	ca. 89[c]		same product as above	
m	Ph	o-$BrC_6H_4CH_2Br$	B	98	(160, 0.25)	$C_{22}H_{21}N_2O_2Br$[i]	426 (19)
							424 (19)
n	Ph	5[e]	B	67	[g]	$C_{26}H_{25}N_3O_3$[i]	427 (21)
o	Me	5[e]	B	72 (85)	96–98	$C_{21}H_{23}N_3O_3$[i]	365 (27)
p	Me	MOOPH	B	32–53 (49–64)	52–54	$C_{10}H_{14}N_2O_3$	210 (43)
q	Ph	Me_3SiCl	B	73 (ca. 97[d])	[g]	$C_{18}H_{24}N_2O_2Si$	255 (15)
							CI, 329 (M + 1, 79)
r	Ph	2,6-$Cl_2C_6H_3CH_2Cl$	B	89	(170, 0.25)	$C_{22}H_{20}N_2O_2Cl_2$[i]	418 (9)
							416 (50)
							414 (75)
s	Ph	$Cl(CH_2)_3Br$	B	61	(146–8, 0.25)	$C_{18}H_{21}N_2O_2Cl$[i]	334 (11)
							332 (31)
t	Ph	PhCHO	B	81	146–8	$C_{22}H_{22}N_2O_3$[i]	362 (0.9)
u	Ph	o-ClC_6H_4CHO	B	50	134–6	$C_{22}H_{21}N_2O_3Cl$[i]	CI, 399 (7)
							397 (21)
v	Ph	2,5-$(MeO)_2C_6H_3CHO$	B	77	[g]	$C_{24}H_{26}N_2O_5$[i]	423 (0.8)
w	Ph	4-CNC_6H_4CHO	B	40	[g]	$C_{23}H_{21}N_3O_2$	387 (11.6)
x	Ph	4-BrC_6H_4CHO	B	66	132–4	$C_{22}H_{21}N_2O_3Br$[i]	442 (0.5)
							440 (0.6)
y	Ph	o-$NO_2C_6H_4CHO$	B	50	131–3	$C_{22}H_{21}N_3O_5$[i]	407 (1.9)
z	Ph	3-PyrCHO	B	66	135–6	$C_{21}H_{21}N_3O_3$[i]	363 (1.7)

[a] Method A, LDA, −5 °C, 30 min. Method B, *n*-BuLi, −78 °C, 2 h. Method C, $NaNH_2$ (excess), −78 °C, 4 h, MeI (excess). [b] Yield of purified product isolated by column or radial chromatography and/or distillation (value in parentheses is the yield based on recovered starting material). [c] GC–MS indicated C-5′ isopropyl as the major product. The C-5′ isopropyl to ethyl to *tert*-butyl ratio was 4:1:trace. [d] GC–MSCI indicated C-5′ bis(Me_3Si) as a minor product. [e] **5** = 4-chloromethyl-5-methyl-3-phenylisoxazole. [f] EI (70 EV) unless otherwise noted. [g] Purified by radial chromatography. [h] See Table III. [i] Satisfactory combustion analytical data ±0.3% were provided for these compounds.

method. The scope of this methodology has been reviewed by Kashima,[6] and recently, factors influencing regiocontrol have been surveyed by Micetich[7] (vide infra). Introduction of electron-withdrawing substituents at the C-4 position, however, has been observed to lead to Michael addition at the C-5 ring position of the isoxazole.[8]

The use of oxazolines to direct heteroatom facilitated metalation reactions is a useful tool in synthesis, yet studies in the presence of other heterocyclic systems are few. Oxazolines have been used to direct metalation on thiophenes[9] and 4-oxazolinylpyridines.[10,11] In the case of 3-oxazolinylpyridines, hindered nonnucleophilic bases can effect deprotonation.[11,12] Alkyl- and aryllithium reagents, however, attack the pyridine ring.[11–14] The isoxazolyloxazoline system represents a protected form of a 2,4-dioxobutane-3-carboxylic acid, a fundamental and potentially



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useful building block. Selective base catalyzed approaches to elaboration of the unprotected synthon would encounter difficulties arising from the presence of two additional acidic protons, and complications from nucleophilic attack and decarboxylation.

The formation, metalation, quenching, and deprotection of the isoxazolyloxazoline is accomplished with astounding ease, and represents a versatile, selective, and facile route to isoxazole derivatives.

The isoxazolyloxazolines (**1**) used for this study are easily available from the corresponding isoxazolecarboxylic acids. Deprotonation was effected with either lithium diisopropylamide (LDA, −5 °C, 30 min, Method A), *n*-BuLi (−78 °C, 2 h, Method B), or $NaNH_2$ (−78 °C, Method C). Treatment with methanol-*d* gave clean deuterium incorporation in the C-5′ position to produce **2** (Table I, entries a and i, and Table III). Primary iodides (entries b, c, j, and k) and bromides (entries d and e) and 4-(chloromethyl)isoxazole (**5**) (entries n and o) all are suitable as

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(10) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227.
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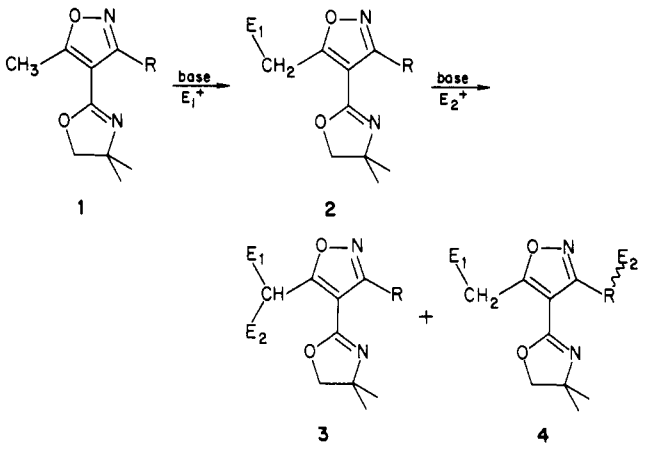
(13) (a) Meyers, A. I.; Natale, N. R.; Wettlaufer, D.; Clardy, J. C.; Rafii, S. *Tetrahedron Lett.* **1981**, 5123. (b) Meyers, A. I.; Natale, N. R. *Heterocycles* **1982**, *18*, 13.
(14) (a) Giam, C. S.; Hauck, A. E. *J. Chem. Soc., Chem. Commun.* **1978**, 615. (b) Hauck, A. E.; Giam, C. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2070. (c) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 56. (d) Dubey, S. K.; Knaus, E. E.; Giam, C. S. *Heterocycles* **1984**, *22*, 1091.

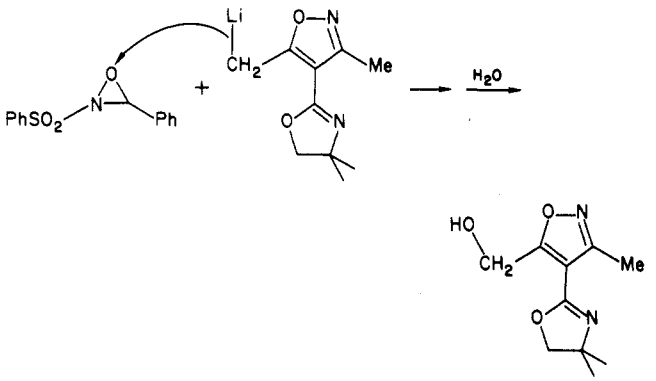
Table II. Subsequent Metalation of 2b, 2j, and 2n

Entry	R	E_1	E_2	yield, %	product	formula	MS, m/z (M^+, rel int)
aa	Me	Me	D	85	(3) 95, (4) 5	$C_{11}H_{15}DN_2O_2$[a]	
bb	Me	Me	Me	73	(3)	$C_{12}H_{18}N_2O_2$[b]	
cc	Me	CH_2Ph	Me	70	(3)	$C_{18}N_{22}O_2N_2$[b]	
dd	Ph	Me	D	97	(3)	$C_{16}H_{17}DN_2O_2$[a]	
ee	Ph	Me	Me	93	(3)	$C_{17}H_{20}N_2O_2$[b]	284 (84)
ff	Ph	Me	CH_2Ph	74	(3)	$C_{23}H_{24}N_2O_2$[b]	360 (43)
gg	Ph	5	5	89	(3)	$C_{37}H_{34}N_4O_4$[b]	598 (50.3)

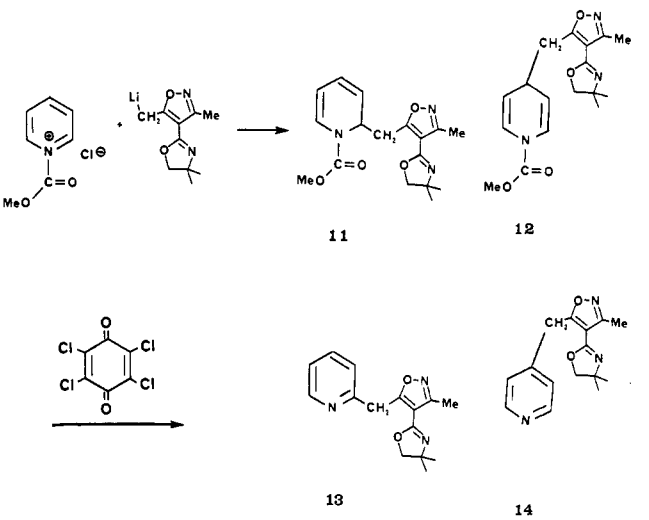
[a] See Table III. [b] See Table I, footnote *i*.



electrophiles. In some cases where method A gives unsatisfactory results, method B succeeds (entry d vs. e and j vs. k). Addition to aldehydes proceeded smoothly (entry g) and tolerated several functional groups, as entries t to z illustrate. Several of the aldehyde adducts (**2t**, **2u**, **2v**, **2x**, **2z**) showed nonequivalent signals in the ^1H NMR for the oxazoline *gem*-dimethyls resulting from hindered rotation about the ring junction. The aldehyde adducts, after crystalization, appear to be single diastereomers. To determine the relative stereochemical relationship of the chiral center at C-5′ and the stereogenic, chirotopic ring juncture, a single crystal X-ray analysis was undertaken



Scheme I



of product **2u**. The major diastereomer was observed to be the *RS*/*SR* diastereomer with a 47° dihedral angle between the heterocyclic rings.[15]

Oxidation with molybdenumoxodiperoxy pyridine HMPA complex (MOOPH, entry p) gave moderate isolated, purified yields of the alcohol (E = OH). We have also found that the *N*-(phenylsulfonyl)oxaziridene developed by Davis[16] gave comparable results. However, the *N*-(phenylsulfonyl)oxaziridene was found to be a more convenient reagent system.

In our hands, reaction of aryl nitriles, *N*-benzylimines, and pyridines with the lithio anion from (1) gave only recovered starting material. Acylpyridinium salts, however, undergo rapid reaction. The conditions of choice were found to be those of Comins.[17] The carbomethoxypyridinium salt gave a mixture of 1,2-addition (**11**) and 1,4-addition (**12**) (Scheme I).[24] Oxidation with tetrachlorobenzoquinone provided the corresponding pyridines (**13** and **14**).

Excess base in the presence of excess electrophile produced minor amounts of products from incorporation of more than one electrophile (entry q). With Method C, in fact, the double substitution product (**3**) was obtained as

(15) Hope, H.; Nichols, B. G. *Acta Crystallogr.* **1981**, *B37*, 158. A referee pointed out that nonequivalence of the *gem*-dimethyl protons would also be observed even if the rings were in the same plane in solution, due to the chiral center at C-5′. The X-ray study was performed according to Hope, and details will be presented elsewhere. An ORTEP of the major diastereomer **2u** is included in the supplementary material.

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(17) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, 3297. (c) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1984**, *49*, 3392. (d) Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151. (e) Comins, D. L.; Smith, R. K.; Stroud, E. D., *Heterocycles*, **1984**, *22*, 339.

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(20) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, *10*, 17.

(21) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676.

(22) Lutomski, K. A.; Meyers, A. I. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, Chapter 3.

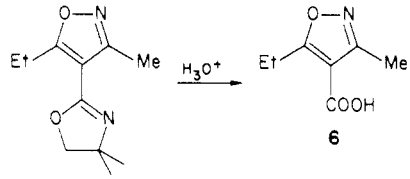
(23) Mislow, E.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

(24) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

79% of the reaction mixture (entry l). Thus, it is important that the organolithium reagent be carefully titrated before use.[18]

It occurred to us that this tactic could be used for sequential incorporation of different groups.[6,7,19] Thus, subsequent metalations under thermodynamic conditions gave rise to predominant C-5′ substitution (Table II). Only traces of C-3′ substituted product **4** were detected. The product **3** can be obtained, free of the C-3′ substance **4**, by simple radial chromatography. Alkyl groups are readily incorporated in useful yield.

Deprotection of the product isoxazolyloxazolines can be effected with surprising ease. Thus, the oxazoline moiety was cleanly removed with aqueous acid (3 N aqueous HCl, reflux, overnight) to give the isoxazole-4-carboxylic acid **6b** from **2b** in 62% yield. Similar results were obtained with **2k**, and **6k** was obtained in 64% yield.



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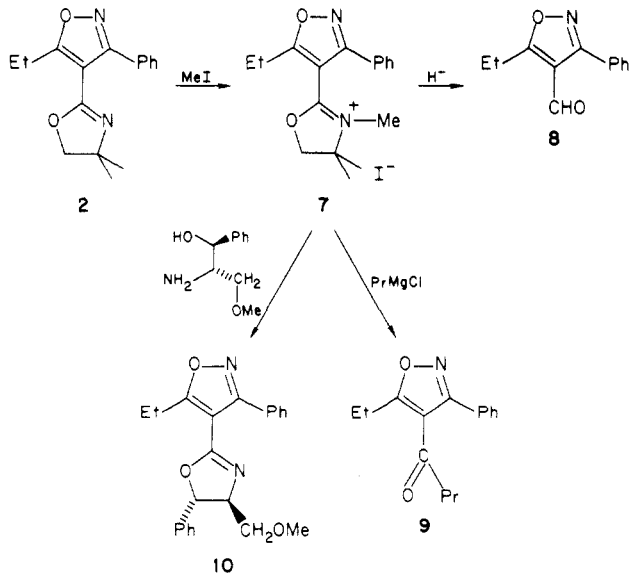
The above result indicates that the oxazoline nonbonded pair of electrons is significantly more basic than that of the isoxazole. To illustrate this further, isoxazolyloxazoline (**2k**, E = CH_3, R = Ph) was treated with iodomethane in nitromethane at 70 °C. The product oxazoline methiodide (**7**) was obtained as a crystaline solid in 60–70% yield. The methiodide (**7**) is a useful precursor for the synthesis of a variety of functionalized isoxazoles from **2**. Reduction of **7** with potassium tri-*sec*-butyl borohydride (K-Selectride, Aldrich),[20] followed by aqueous workup affords the isoxazole aldehyde **8**. Treatment of **7** with propyl magnesium chloride[21] in THF, followed by aqueous workup gave the ketone **9**. Refluxing of **7** with the Meyers reagent[22] in dichloroethane produced the chiral isoxazolyloxazoline (**10**).



2 7 8 9 10

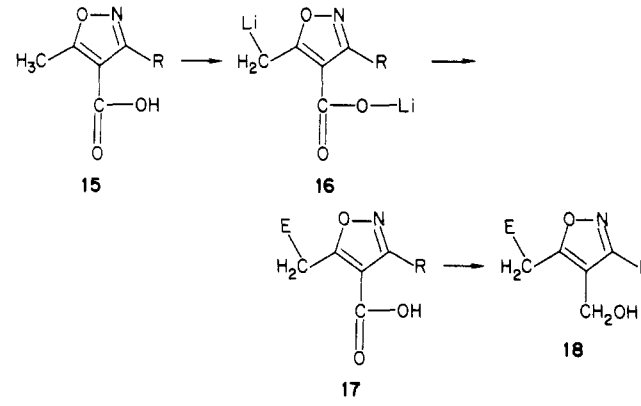
The versatility of isoxazolyloxazoline (**1**) as a precursor to more complex isoxazole derivatives has now been demonstrated. The isoxazolyloxazoline (**10**) has potential for intramolecular transfer of chirality across a chirotopic and stereogenic ring juncture.[23]

In order to weigh the necessity of the oxazoline protection/deprotection sequence, we examined the generation of dianions from isoxazole-4-carboxylic acids. Although the metalation of simple 3,5-dimethylisoxazole has been developed into a useful tool in organic synthesis,[5-7] dianion studies on more complex isoxazoles are less common.[25] Stork has utilized the dianion of 4-(carboxy methyl)-5-methylisoxazolone in the synthesis of tetracycline.[25a] Dianions of isoxazolyl secondary carboxamides have been described in the patent literature.[25c-e] Recently, Oster and Harris have generated dianions of 3-hydroxy-5-methylisoxazole and applied this to the synthesis of muscimol.[25b] A useful dianion approach to isoxazoles involves open chain dianions of syn-1,4-dilithio-oximes which are acylated and cyclized.[26] We have found that dianions (**16**)[27] of isoxazolyl-4-carboxylic acids (**15**) can be quenched

Table III. Deuterium Incorporation Studies on Isoxazolyloxazolines and Dianions of Isoxazole-4-carboxylic Acids

starting material	product	^{1}H NMR	^{2}H NMR
1, R = Me	**2a**	2.5, t, 2 H	2.5[a]
2b, E = Me; R = Me	**3aa**	2.9, qt, 1 H	2.9[b,c]
1, R = Ph	**2i**	2.5, t, 2 H	2.5
2k, E = Me; R = Ph	**3dd**	3.05, qt, 1 H	
15a, R = Me	**17a**, E = D	2.5, t, 2 H	2.5
15e, R = Ph	**17e**, E = D	2.6, t, 2 H	2.6
17a, R = E = Me	**20**, E′ = D	3.1, qt, 1 H	3.1[c]

[a] 93–94% deuterium by mass spectrometry. [b] Contains ca. 5% C-3′ deuterium by ^{2}H NMR. [c] Kinetic metalation conditions produced complete C-5 deuteration with no detectable C-3 deuterium.



15 16 17 18

with electrophiles, and the products (**17**) are obtained with good regioselectivity in synthetically useful yields.

Treatment of 3,5-dimethylisoxazole-4-carboxylic acid (**15**, *R* = Me)[28] with two equivalents of *n*-butyllithium at −78 °C in tetrahydrofuran, followed by treatment with deuteriomethanol gave complete monodeuterium incorporation via mass spectrometry and ^{1}H NMR (triplet for the C-5 methyl). More significantly, the decoupled ^{2}H NMR shows only a *single peak* at δ 2.5. Other electrophiles are readily incorporated in synthetically useful yields (Table IV).

This method now allows facile entry into functionally complex isoxazole-4-carboxylic acid derivatives from a common intermediate, without recourse to protecting-

(25) (a) Stork, G.; Hagedorn, A. A., III *J. Am. Chem. Soc.* **1978**, *100*, 3609. (b) Oster, T. A., Harris, T. M. *J. Org. Chem.* **1983**, *48*, 4307, and cited references. (c) Nadelson, J. British Patent 1 563 388, 1980; *Chem. Abstr.* **1981**, *94*, 156910y. (d) Nadelson, J. U.S. 4 124 714; *Chem. Abstr.* **1979**, *90*; 87293c. (e) Denzer, M.; Smith, J. A. U.S. Patent 4 113 727; *Chem. Abstr.* **1979**, *90*; 103936x.

(26) (a) Hoskin, D. H.; Olofson, R. A. *J. Org. Chem.* **1982**, *47*, 5222. (b) Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015. (c) Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1806.

(27) For a review on dianions, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.

(28) Stork, G.; McMurry, J. *J. Am. Chem. Soc.* **1967**, *89*, 5463.

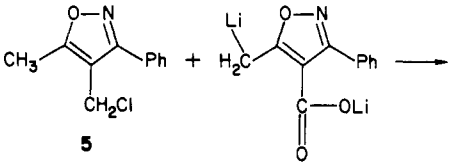
Table IV. Formation and Utility of Dianions of Isoxazole-4-carboxylic Acids[a]

entry	starting material	R	E	E_1	carboxylic acid product	yield, %	alcohol product	yield, %	bp, mmHg	formula	MS, m/z (rel. int.)
a	15	Me	D	H	17	83	see Table III				
b	15	Me	Me	H	17	91	18	77	90, 0.3	$C_7H_{11}NO_2$[b]	141 (47)
c	15	Me	CH_2Ph	H	17	88	18	70	100, 0.25	$C_{13}H_{15}NO_2$[b]	217 (1)
d	15	Me	n-C_8H_{17}	H	17	69	18	65	120, 0.6	$C_{14}H_{25}NO_2$[b]	239 (9)
e	15	Ph	D	H	17	99	see Table III				
f	15	Ph	Me	H	17	81	18	70	120, 0.25	$C_{12}H_{13}NO_2$[b]	203 (52)
g	17	Me	Me	Me	20	92	21	79	91, 0.25	$C_8H_{13}NO_2$[b]	155 (23)
h	17	Ph	Me	Me	20	89	21	45	130, 0.25	$C_{13}H_{15}NO_2$	217 (28)

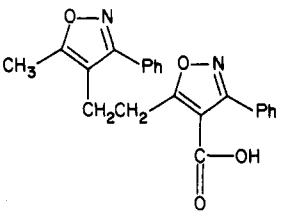
[a] ^1H NMR, ^{13}C NMR, and IR data are in supplementary material. [b] See Table I, footnote *i*.

group strategies. The products **17** were reduced with lithium aluminum hydride to the alcohols **18** to facilitate full characterization.

In light of the usefulness of isoxazoles as ligands for several metals,[29] we have examined the use of 4-chloromethyl-3-phenyl-5-methylisoxazole (**5**) as an electrophile. Quenching of the dianion (**16**, R = Ph) with 1 equiv of electrophile, followed by the usual workup (vide infra), gave the desired product (**19**) in 53% yield.

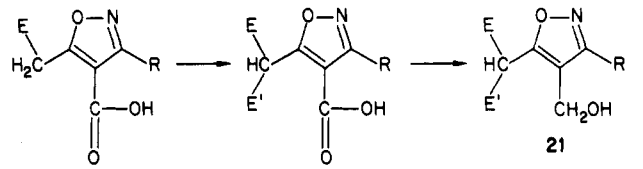


5 **16**



19

When base in excess of 2 equiv was used, products arising from incorporation of more than one electrophile were observed. The product **17** (E = R = Me) was examined for subsequent metalation behavior. We observed that the metalation/quenching protocol produced **20** (E = E′ = Me), the 5-isopropyl derivative, in 83% yield. In a similar manner **17** (E = Me, R = Ph) was used to prepare **20** (E = E′ = Me, R = Ph) by metalation, followed by treatment with methyl iodide. The resulting carboxylic acids (**20**) were reduced with LAH to the alcohols (**21**).

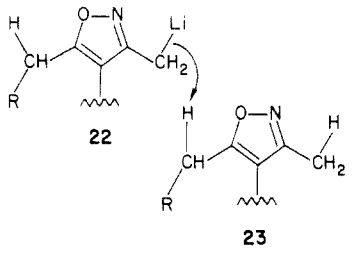


17 **20** **21**

In summary, the dianions of alkylisoxazole-4-carboxylic acids (**16**) can be quenched with alkyl halides to produce monoalkylation (**17**) and dialkylation (**20**) products, with a high degree of selectivity.

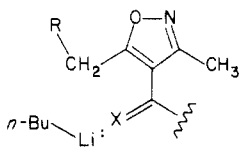
The regiochemistry of lateral metalation of alkylisoxazoles has been examined by several groups. Kashima[6] and Micetich[7] have observed that sequential electrophilic incorporation was selective for C-5. Micetich has attributed this to prior chelation of the alkyl lithium. Brunelle[19] has reported that, using kinetic conditions, C-3 metalation can be obtained. Thus, for the isoxazolyloxazolines and isoxazole-4-carboxylic acid dianions two possibilities appeared likely. (i) Kinetic deprotonation at C-3 (**22**) may be followed by equilibration to C-5 (**23**). Alternatively, (ii) the C-4 substituent may adopt a conformation, in or close to conjugation with the isoxazole C-4–C-5 double bond, which reinforces C-5 lateral deprotonation (**24**). Kinetic studies to date on both systems indicate predominant C-5 metalation (Table III); therefore, presently we favor the second explanation.

(29) Reference 1, p 169, and cited references. The use of isoxazole rings in elegant synthetic approaches to vitamin B-12 has also appeared: Stevens, R. V.; Chang, J. H.; Lapalme, R.; Schow, S.; Schlageter, M. G.; Shapiro, R.; Weller, H. N. *J. Am. Chem. Soc.* **1983**, *105*, 7719.



22

23



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We continue to explore, the metalation chemistry of functionalized isoxazoles, and will report on our progress in due course.

Experimental Section

Mass spectra were measured on a VG 7070 GC/MS with Model 11/250 data system. The following abbreviations are used: electron impact, EI; chemical ionization, CI; fast atom bombardment, FAB. ^1H NMR were obtained on a Varian EM-360 or JEOL FX-90Q NMR spectrometers and are reported in ppm downfield from tetramethylsilane internal standard. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. ^2H and ^{13}C NMR were obtained on the JEOL. IR spectra were obtained on an Infracord Spectrophotometer as neat liquids or melts on NaCl plates unless otherwise noted and are reported in cm^{-1}. Combustion analyses were performed by Guelph Chemical Laboratories, Ltd. Preparative thin-layer chromatography (PTLC) was performed on a Harrison Associates Chromatotron, using silica gel unless otherwise specified. For reactions under inert atmosphere, the inert gas (Ar or N_2) was passed over activated catalyst R3-11 followed by indicator Drierite. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All chromatography solvents (hexane, CH_2Cl_2, $CHCl_3$, EtOAc, MeOH) were distilled. Organolithium reagents were titrated using the procedure of Ronald.[18]

4,4-Dimethyl-2-(3′,5′-dimethylisoxazol-4′-yl)-Δ^2-oxazoline (1, R = Me). 3,5-Dimethylisoxazole-4-carboxylic acid (36.9 g, 0.26 mole) was treated with thionyl chloride (100 mL) at room temperature. After stirring overnight the excess thionyl chloride was concentrated in vacuo and the resulting amber oil dissolved in chloroform (50 mL) and placed in an additional funnel. The solution of isoxazolyl acid chloride was added dropwise to a cold (0 °C) solution of 2-amino-2-methyl-1-propanol (75 mL) in chloroform (150 mL). The reaction mixture was allowed to come to room temperature overnight, after which time it was poured over ice. The layers were separated and the aqueous layer extracted with chloroform (500 mL in five portions). The combined chloroform layers were washed with water and dried over anhydrous sodium sulfate. Filtration and concentration gave an oil which crystallized on standing: NMR 5.5 (br s, 2 H), 4.0 (s, 2 H), 2.6 (s, 3 H), 2.4 (s, 3 H), 1.4 (s, 6 H); mass spectrum EI, m/z 181 (M − 31); CI, m/z 213 (M + 1).

The amide was dissolved in chloroform (400 mL) and cooled to 0 °C. Thionyl chloride (20 mL) in chloroform (80 mL) was added dropwise over 40 min. The solution was allowed to warm to room temperature overnight. The reaction mixture was poured over ice and 6 N aqueous sodium hydroxide, the layers were separated, and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined chloroform layers were washed with water (2 × 50 mL), 1 N HCl (50 mL), and water (50 mL) and dried over anhydrous sodium sulfate. Filtration, concentration, and distillation on the Kugelrohr apparatus gave isoxazolyloxazoline (1, R = Me) as a white solid, 29.8 g (59% overall), mp 76–78: mass spectrum, m/z (% relative intensity) 194 (26), 179 (100); ^1H NMR 3.93 (s, 2 H), 2.53 (s, 3 H), 2.36 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR 171.3, 159.3, 155.7, 105.7, 78.0, 67.1, 28.2, 12.7, 11.5; IR 2940, 1640, 1610, 1430, 735. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26. Found: C, 62.14; H, 7.05.

4,4-Dimethyl-2-(5′-methyl-3′-phenylisoxazol-4′-yl)-Δ^2-oxazoline (1, R = Ph) was prepared to similar manner. The solution was filtered, concentrated, and Kugelrohr-distilled to give 1 (R = Ph) in 81% yield, as an oil which crystallized on standing, mp 43–46: TLC (SiO_2, EtOAc/$CHCl_3$, 1:1) R_f 0.49; ^1H NMR 7.5 (m, 2 H), 7.2 (m, 3 H), 3.9 (s, 2 H), 2.5 (s, 3 H), 1.3 (s, 6 H); ^{13}C NMR 171.98, 160.6, 154.8, 129.4, 128.9, 128.1, 127.3, 104.5, 77.6, 27.4, 11.9; IR 3100, 3000, 1680, 1615, 1460, 778, 697; mass spectrum, EI, m/z (% relative intensity) 256 (4), 255 (13), 241 (8), 86 (65), 84 (100); CI, 257 (M + 1) (48), 185 (21), 104 (100). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29. Found: C, 70.41; H, 6.16.

1, R = Et, was prepared in a similar manner to the isoxazolyloxazolines described above in 68% overall yield: ^1H NMR 3.9 (s, 2 H), 2.7 (q, 2 H), 2.5 (s, 3 H), 1.3 (s, 6 H), 1.2 (t, 3 H); IR 2985, 1680, 1650, 1470, 1050, 796; mass spectrum, m/z (% relative intensity) 208 (34), 193 (84), 180 (24), 165 (100). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74. Found: C, 63.01; H, 7.52.

General Metalation Procedure. Method A. Preparation of 2b (R = Me, E = Me). A 100-mL round-bottom flask was charged with 1 (R = Me) (465 mg, 2.39 mmol) and freshly distilled THF (50 mL) and cooled to −5 °C under an Ar atmosphere. Lithium diisopropylamide (2.5 mmol) in THF (15 mL) was added dropwise. After 30 min iodomethane (0.25 mL) was added, and the reaction was allowed to warm to room temperature overnight. The THF was concentrated, and the residue chromatographed on silica gel ($CHCl_3$). The product (**2b**) was obtained as an oil (456.9 mg, 92%): ^1H NMR 4.0 (s, 2 H), 3.1 (q, 2 H), 2.4 (s, 3 H), 1.3 (s, 6 H), 1.2 (t, 3 H); IR 2990, 1670, 1460, 1050; mass spectrum, m/z (% relative intensity) 208 (75), 193 (100). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74. Found: C, 63.27; H, 7.73.

Method B. Preparation of 2k (R = Ph, E = Me). A dry 100-mL round-bottom flask was charged with isoxazolyloxazoline (1, R = Ph) (996.6 mg, 3.89 mmol) and THF (50 mL) and cooled to −78 °C under an inert atmosphere. A solution of *n*-BuLi in hexane (1.8 M, 2.4 mL, 4.3 mmol) was added via syringe dropwise over 5 min. After 2 h at −78 °C, iodomethane (0.3 mL, 4.6 mmol) was added. The reaction was allowed to warm to room temperature overnight, after which time the THF was concentrated. The reaction mixture was chromatographed on silica gel ($CHCl_3$), and the residue flash distilled on a Kugelrohr apparatus (bp 114 °C/0.2 mmHg). The product (**2k**) was obtained as an oil (963.5 mg, 92%). ^1H NMR 7.5–7.7 (m, 2 H), 7.3–7.4 (m, 3 H), 3.9 (s, 2 H), 3.1 (q, 2 H), 1.32 (s, 6 H), 1.34 (t, 3 H); IR 3090, 2990, 1670, 1610, 1460, 1450, 1040, 777, 749, 695; mass spectrum, m/z (% relative intensity) 270 (66), 269 (100), 255 (62), 199 (33), 171 (14), 143 (20), 108 (44). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71. Found: C, 71.40; H, 6.77.

5-Ethyl-3-phenylisoxazole-4-carboxylic Acid (6k). A solution of **2k** (E = Me, R = Ph) (681 mg, 2.5 mmol) was warmed to reflux in 20 mL of 3 N aqueous HCl overnight. The solution was then cooled and the carboxylic acid (**6k**) crystallized as a white solid (351 mg, 64% mp 147–9): ^1H NMR δ 7.2–7.5 (m, 5 H), 3.25 (q, 2 H), 1.3 (t, 3 H); IR 3030 (sh), 2940, 2600 (br), 1690, 1580, 1480, 1330, 1165, 790, 710; mass spectrum, m/z 217 (relative intensity 73.6), 188 (100), 172 (14), 144 (66.2), 116 (14), 93 (18.6), 77 (81.3), 57 (47.7). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.26; H, 5.49; N, 6.22.

Methiodide Salt (7). A solution of **2k** (E = Me, R = Ph) (4.5 g, 16 mmol), iodomethane (3.5 mL), and nitromethane (ca. 150 mL) was warmed to 70 °C overnight. The excess iodomethane and nitromethane solvent was then concentrated in vacuo, and the resulting oil was triturated in ethyl acetate (50 mL) which produced a yellow solid. The yellow solid was dissolved in acetonitrile and precipitated by the addition of ethyl ether. This process was repeated, and the methiodide salt (**7**) was obtained as a white solid, mp 159–164 dec (4.2 g, 61%): ^1H NMR δ 7.3 (br s, 5 H), 4.9 (s, 2 H), 3.25 (q, 2 H, J = 8 Hz), 2.4 (s, 3 H), 1.5 (s, 6 H), 1.3 (t, 3 H), J = 8 Hz); IR 3021, 1661, 1555, 1451, 1372, 1155, 1038, 918, 820, 776, 695, 675; mass spectrum, FAB, m/z 411 (M − 1, 0.4% relative intensity), 285 (100, M − I). Anal. Calcd for $C_{17}H_{21}N_2O_2I$: C, 49.53; H, 5.13; N, 6.80. Found: C, 49.3; H, 5.23; N, 6.81.

5-Ethyl-3-phenylisoxazole-4-carboxaldehyde (8). A slurry of methiodide salt **7** (954 mg, 2.3 mmol) in THF (20 mL) was stirred at room temperature. K-Selectride (2.3 mL) was added via syringe dropwise over 10 min, and the mixture stirred at room temperature overnight. Sufficient aqueous HCl (3 N) was added to adjust the pH to acidic, and after stirring for 2 h the solvent was concentrated in vacuo. The residue was treated with a solution of 4 mL of THF, 2.5 mL of 10% aqueous NaOH, and 1.5 mL of 30% H_2O_2. After 30 min the reaction mixture was extracted with methylene chloride (3 × 30 mL), and the combined organic

extracts were washed with brine and dried over anhydrous Na_2SO_4. Filtration and concentration provided aldehyde (**8**) (231 mg, 50%): ^1H NMR δ 9.7 (s, 2 H), 7.2–7.5 (m, 5 H), 3.1 (q, 2 H), 1.3 (t, 3 H); IR 3049, 1698, 1590, 1572, 1471, 801, 767, 693; mass spectrum, m/z 201 (35% relative intensity), 172 (39), 144 (100), 116 (23), 103 (54). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51: N, 6.96. Found: C, 71.75; H, 5.78; N, 6.93.

1-(5-Ethyl-3-phenylisoxazol-4-yl)-1-butanone (9). A slurry of methiodide salt **7** (750 mg, 1.8 mmol) in THF (30 mL) was stirred at room temperature, and 2 mL of propylmagnesium bromide (2 M in ethyl ether) was added dropwise via syringe. After stirring at ambient temperature overnight, the reaction was quenched with ice water (200 mL), the pH adjusted to acidic by the addition of 1.5 N aqueous HCl, and the solution washed with hexane (which was discarded). The aqueous layer was rendered alkaline with aqueous NaOH, and extracted with ether (3 × 30 mL). The ether extracts were concentrated, treated with oxalic acid, and refluxed for 0.5 h. The reaction mixture was allowed to cool, extracted with ether (3 × 30 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration provided the ketone **9** (240 mg, 55%): ^1H NMR δ 7.2 (s, 5 H), 2.9 (q, 2 H), 2.2 (t, 2 H), 1.1–1.6 (m, 5 H), 0.7 (t, 3 H); IR 3096, 1686, 1443, 1410, 1253, 1091, 1017, 786, 714, 643. The ketone (**9**) was further characterized as its tosylhydrazone, mp 201–203: mass spectrum, CI, m/z 412 (5% relative intensity), 396 (14), 228 (30), 125 (100), 91 (90.2). Anal. Calcd for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 64.31; H, 6.45; N, 10.18.

Chiral Isoxazolyloxazoline (10). Methiodide salt **7** (991 mg, 2.4 mmol) and (+)-(1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol (Meyers' reagent) (558 mg, 3 mmol) were refluxed overnight in dichloroethane (30 mL). The mixture was cooled, the solvent concentrated, and the residue dissolved in water and extracted with methylene chloride (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate. Filtration, concentration, and radial chromatography provided the chiral isoxazolyloxazoline (**10**) (160 mg, 18%), bp 155–160 °C/0.15 mmHg: ^1H NMR δ 7.5–7.8 (m, 2 H), 7.2–7.4 (m, 3 H), 7.2 (s, 5 H), 5.4 (d, 1 H), 4.3 (m, 1 H), 3.6 (m, 2 H), 3.4 (s, 3 H), 3.2 (q, 2 H), 1.3 (t, 3 H); IR 3021, 1678, 1610, 1458, 1122, 1076, 1031, 978, 950, 901, 734, 680; mass spectrum, EI, m/z 363 (2.1% relative intensity), 362 (8), 361 (9), 318 (21.9), 317 (100), 261 (15.1), 144 (11.8), 119 (26), 91 (25.8), 77 (10.3), 57 (32.6), 45 (18); CI, 363 (M + 1 67.9), 361 (12), 318 (22.8), 317 (100), 261 (13.4), 199 (25), 144 (19.5), 119 (19.6), 91 (29.1), 77 (13), 57 (28.1).

General Dianion Procedure. A solution of 3,5-dimethylisoxazole-4-carboxylic acid (705 mg, 5 mmol) in freshly distilled THF (50 mL) was cooled to −78 °C under inert atmosphere. *n*-Butyllithium (1.8 M in hexane) was added dropwise via syringe. On the addition of the second equivalent of *n*-butyllithium (total 6 mL, 1.8 M, 10.8 mmol) formation of a yellow slurry was observed. The slurry was stirred *vigorously* for 2 h at −78 °C. The electrophile was then introduced via syringe, i.e., methyl iodide (1 mL). The reaction mixture was stirred at −78 °C for 40 min, and methanol was added (5 mL). The reaction mixture was allowed to warm to room temperature, at which time the resulting clear solution was concentrated in vacuo. The residue was dissolved in water (50 mL) and washed with methylene chloride (which was discarded). The solution was cooled to 0 °C and the pH adjusted to 2 with concentrated hydrochloric acid. The resulting precipitate was extracted with methylene chloride (3 × 15 mL), and the combined extracts were dried over anhydrous magnesium sulfate. After filtration and removal of the solvent in vacuo, the resulting product was sublimed (140 °C/0.25 mmHg). The substituted isoxazole acid **17** (R = CH_3, E = CH_3) was obtained as a solid, 707 mg, mp 122–4 °C (91%): ^1H NMR 7.3–7.6 (m, 5 H), 3.2 (q, 2 H), 1.3 (t, 3 H).

After purification, the carboxylic acids **17** and **20** were reduced with lithium aluminum hydride as previously described[2b] to the substituted isoxazole alcohols **18** and **21**, respectively, and fully characterized.

Acknowledgment. We thank the M. J. Murdock Charitable Trust of Research Corporation, BRSG S07 RR 07170 awarded by the Biomedical Research Support Grant Program (Division of Research Resources, National Institutes of Health), and Shell Development for financial support. We are also grateful to the National Science Foundation for a departmental instrument grant (GC–MS).

Registry No. **1a**, 93599-35-0; **1h**, 93599-36-1; **1i**, 93599-37-2; **2** (R = Me, E_1 = Li), 99298-96-1; **2a**, 99298-68-7; **2b**, 93599-39-4; **2d**, 93599-40-7; **2f**, 93599-41-8; (±)-**2g**, 99298-69-8; **2h**, 93599-43-0; **2i**, 99298-70-1; **2j**, 93599-45-2; **2m**, 99298-71-2; **2n**, 99298-72-3; **2o**, 99298-80-3; **2p**, 93599-47-4; **2q**, 93599-48-5; **2r**, 93599-49-6; **2s**, 93599-50-9; (±)-**2t**, 99298-73-4; (±)-**2u**, 99298-74-5; (±)-**2v**, 99298-75-6; (±)-**2w**, 99298-76-7; (±)-**2x**, 99298-77-8; (±)-**2y**, 99298-78-9; (±)-**2z**, 99298-79-0; (±)-**3aa**, 99298-81-4; **3bb**, 99298-82-5; (±)-**3cc**, 99298-83-6; (±)-**3dd**, 99298-84-7; **3ee**, 99298-85-8; (±)-**3ff**, 99298-86-9; **3gg**, 99298-87-0; **4aa**, 93599-52-1; **5**, 18718-83-7; **6k**, 91569-55-0; **7**, 99298-92-7; **8**, 99298-93-8; **9**, 99298-94-9; **10**, 99298-95-0; (±)-**11**, 99298-97-2; **12**, 99298-98-3; **13**, 99298-99-4; **14**, 99299-00-0; **15a**, 2510-36-3; **15a** (acid chloride), 31301-45-8; **15a** (1-hydroxy-2-methylisopropylamide), 99298-88-1; **15h**, 17147-85-2; **15h** (acid chloride), 99298-90-5; **15h** (1-hydroxy-2-methylisopropylamide), 99298-91-6; **15i**, 1136-45-4; **15i** (acid chloride), 16883-16-2; **15i** (1-hydroxy-2-methylisopropylamide), 99298-89-2; **17** (R = Me, E = D), 99299-01-1; **17** (R = Me, E = Me), 69083-54-1; **17** (R = Me, E = CH_2Ph), 99299-02-2; **17** (R = Me, E = n-C_8H_{17}), 99299-03-3; **17** (R = Ph, E = D), 99299-04-4; **18** (R = Me, E = Me), 60148-44-9; **18** (R = Me, E = CH_2Ph), 99299-05-5; **18** (R = Me, E = n-C_8H_{17}), 99299-06-6; **18** (R = Ph, E = Me), 99299-07-7; **20** (R = Me, E = Me, E_1 = Me), 90087-36-8; **20** (R = Ph, E = Me, E_1 = Me), 92029-28-2; **21** (R = Me, E = Me, E_1 = Me), 99299-08-8; **21** (R = Ph, E = Me, E_1 = Me), 99299-09-9; MOOPH, 23319-63-3; $HOCH_2CMe_2NH_2$, 124-68-5; (1*S*,2*S*)-HOCH(Ph)CH(CH_2OMe)NH_2, 51594-34-4; n-$C_8H_{17}Br$, 111-83-1; PhCHO, 100-52-7; o-$BrC_6H_4CH_2Br$, 3433-80-5; Me_3SiCl, 75-77-4; 2,6-$Cl_2C_6H_3CH_2Cl$, 2014-83-7; $Cl(CH_2)_3Br$, 109-70-6; o-ClC_6H_4CHO, 89-98-5; 2,5-$(MeO)_2C_6H_3CHO$, 93-02-7; 4-NCC_6H_4CHO, 105-07-7; 4-BrC_6H_4CHO, 1122-91-4; 2-$O_2NC_6H_4CHO$, 552-89-6; 3-pyridyl aldehyde, 500-22-1; carbomethoxypyridinium chloride, 86950-96-1.

Supplementary Material Available: ^1H, ^{13}C NMR, IR, and complete mass spectra for compounds in Tables I, II, and IV, and atomic coordinates, ORTEP, thermal parameters, bond lengths, bond angles, anisotropic thermal parameters and H coordinates for compound **2u** (E = o-$ClC_6H_4CH(OH)$–, R = Ph) (15 pages). Ordering information is given on any current masthead page.