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SYNTHESIS, METALATION AND ELECTROPHILIC QUENCHING OF ALKYL-ISOXAZOLE-4-TERTIARY CARBOXAMIDES. A CRITICAL COMPARISON OF THREE ISOXAZOLE LATERAL METALATION METHODS

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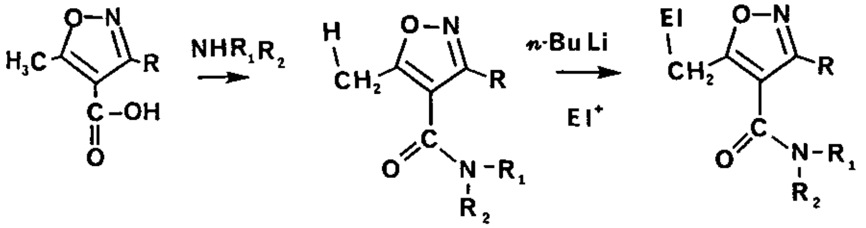
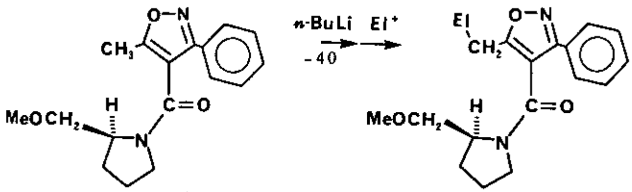
Abstract - Alkyl-isoxazole-4-tertiary carboxamides are easily formed from isoxazole-4-carboxylic acids. Lateral metalation and electrophilic quenching was accomplished regioselectively at C-5 in synthetically useful yields. The chief advantage of this method is in the preparation of chiral isoxazole-4-tertiary carboxamides. The scope and limitations of this methodology is critically compared to lateral metalation of isoxazole-4-oxazolines and isoxazole carboxylic acid dianions.

Isoxazoles continue to be of interest due to their utility as synthetic intermediates[1] as well as possessing a wealth of important biological activities.[2] The deprotonation of simple alkyl isoxazoles, termed lateral metalation by Micetich,[3] is a valuable synthetic method.[4] In the course of a systematic survey of isoxazole metalation,[5] we have extended our studies to isoxazole-4-tertiary carboxamides (2). The use of tertiary carboxamides to direct heteroatom facilitated metalation has been amply demonstrated by Beak and Sniekus.[6] A recent example of the utility of this methodology is the metalation of cubane tertiary carboxamide reported by Eaton.[7] There are several reasons for extending such studies to the isoxazole system. The tertiary carboxamides are available in direct fashion from the isoxazole carboxylic acids. The isoxazole-4-carboxylic acid chloride and two equivalents of inexpensive secondary amine produce the isoxazole-4-tertiary carboxamides (2) in high yield (Experimental Section, Method A and Table II). Direct coupling of the carboxylic acid (1) with one equivalent of amine with DCC proceeds readily (Method B). We have encountered difficulty preparing large amounts of chiral isoxazolyl-oxazolines,[8] and in contrast, the synthesis of isoxazole-4-tertiary carboxamides of prolinol derivatives proceeds readily by either method (Vide infra).



1 **2** **3**

The deprotonation of N,N-diisopropyl-3,5-dimethylisoxazole-4-carboxamide proceeds at -78°C, and incorporation of electrophiles was accomplished in synthetically attractive yields (Table I). A variety of aldehyde electrophiles were surveyed (Table I, entries 3 to 7), and the isoxazole anion shows selectivity in the presence of such normally reactive functional groups as cyano (entry 4), nitro (entry 5), pyridyl (entry 7), and furyl (entry 6) moieties. We attribute this moderated reactivity to resonance stabilization, since the lithio-anion of (2) can be considered to be a vinylogous imidate. The 3-phenyl-5-methylisoxazole carboxamide system, however, does not always readily metalate appreciably at -78°C after 2-3 h, and starting material was recovered for the diisopropyl, pyrrolidinyl and morpholinyl tertiary amides. At -40°C the metalation does proceed, and electrophiles can be incorporated in useful yield after isolation and purification (Table I, entries 8-16). The corresponding N,N-dibenzylamide does metalate at -78°C (Table I, entry 17). The synthesis of chiral amides from S-methoxymethyl prolinol[9] can be accomplished on a multi-gram scale in high yield. The 3-phenyl-5-methylchiral amide (4) was smoothly deprotonated at -40°C. Deuteromethanol and benzyl bromide have been used as electrophiles and produce the products (5) in reasonable yields.

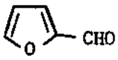
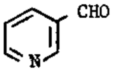


4 **5**

El	%
DOMe	97
$PhCH_2Br$	56

The isoxazole-tertiary amide system represents a useful alternative to the dianion and oxazoline methodology. A critical comparison of the three methods reveals that for simple alkyl halides the dianion methodology[5d] is most direct and proceeds directly without protection and deprotection complications. The widest scope is provided by the oxazoline system,[5a] since the metalation conditions are suitably mild to allow for a

Table I. Metalation and Electrophilic Quenching of Isoxazole Amides (2) to Produce (3).

Entry	R	R$_1$	R$_2$	El	Yield %	mp°C^a (bp)	^{1}H NMR	MS^b (% rel. intensity)
1	Me	iPr	iPr	DOMe	86	84-87	1.3(br,d,12H); 2.2(s,3H); 2.3(m,2H); 3.4-3.8(m,2H).	EI 225(7)
2	Me	iPr	iPr	MeI	55	63-65	1.0(t,3H); 3.1 ~3.7(m,2H); 1.15(br,d,12H); 2.0(s,3H); 2.45(q,2H).	EI 238(2.4)
3	Me	iPr	iPr	p-BrPhCHO	43	oil	0.7-1.8(br,d,12H); 2.15(s,3H); 2.9(d,2H); 3.2 ~3.9(m,2H); 4.6 5.1(m,1H); 6.9 ~ 7.4(m,4H).	EI^c 293(3.1) 291(3.0) M-(18+NiPr$_2$)
4	Me	iPr	iPr	p-NCPhCHO	48	R$_f$=0.3 Hex - EtOAc 1:1	0.5-1.7(m,12H); 2.0(s,3H); 2.85(d,2H); 3.1-3.8(m,2H); 4.7-5.4(m,2H); 6.9-7.6(m,4H).	EI 355(1.1)
5	Me	iPr	iPr	o-NO$_2$PhCHO	37	R$_f$=0.38 Hex - EtOAc 1:1	1.2 ~ 2.0(br,s,12H); 2.4(s,3H); 3.5(d,2H); 3.6-4.2(m,2H); 5.5-5.9(m,2H); 7.4-8.3(m,4H).	EI 375(0.9) 357(4.0) (M-18)
6	Me	iPr	iPr		70	R$_f$=0.37 Hex - EtOAc 1:1	1.2-2.2(m,12H); 2.6(s,3H); 3.45(d,2H); 3.6-4.3(m,2H); 4.6-5.5(m,2H); 6.4-6.6(s,2H); 7.5-7.7(s,1H).	EI 320(17.1)
7	Me	iPr	iPr		62	R$_f$=0.46 EtOAc= MeOH 1:1	1.0-1.8(m,12H); 2.3-2.4(s,3H); 3.05(d,2H); 3.2-4.0(m,2H); 5.1(t,1H); 5.8-6.2(m,1H); 7.0-7.4(m,1H); 7.5-7.8(m,1H); 8.2-8.6(m,2H).	EI 331(0.9) 231(14.6) (M-NiPr$_2$)
8	Ph	iPr	iPr	DOMe	88	88-89	0.9-1.7(br,d,6H); 1.5-2.1(br,d, 6H); 2.7-2.9(m, 2H); 3.5-4.2(m, 2H); 7.5-8.3(m,5H); ^{2}H 2.25,s.	EI 288(32.2)
9	Ph	iPr	iPr	MeI	70	103-105	0.2 ~ 0.9(br,s,6H);0.9-1.3(t,3H); 1.3-1.7(d,6H); 2.4 ~ 2.9(q,2H); 2.8 ~ 4.1(m,2H); 7.1-7.7(m,5H).	EI 300(21.0) CI 301(52.6)
10	Ph	iPr	iPr	P-BrPhCHO	40	158-161	0.4 ~ 1.0(br,d,6H); 1.4-1.8(br,d, 6H); 3.0 ~ 3.9(m,4H); 4.8 ~ 5.3(m, 2H); 7.1 ~ 7.8(m,9H).	EI 469(2.5) 471(2.8)
11	Ph	CH$_2$-CH$_2$-CH$_2$-CH$_2$		DOMe	90	128-130	1.4-1.9(m,4H); 2.3 ~ 2.4(m,2H); 2.75(t,2H); 3.2-3.5(t,2H); 7.2-7.7(m,5H).	CI 257(58.4) 258(42.5)
12	Ph	CH$_2$-CH$_2$-CH$_2$-CH$_2$		MeI	66	oil	1.25(t,3H); 1.4-2.2(m,4H); 2.9(q,2H); 2.8-3.2(t,2H); 3.55(t,2H); 7.3-7.9(m,5H).	EI 270(37.4) CI 271(100)

13	Ph	CH_2-CH_2-CH_2-CH_2	P-BrPhCHO	48	oil	1.3-1.9(m,4H); 2.5-2.8(t,2H); 3.15-3.35(d,2H); 3.4-3.7(t,2H); 5.0 - 5.4(m,2H); 7.3-8.0(m,9H).	EI 439(3.3) 441(3.1)
14	Ph	CH_2-CH_2-O-CH_2CH_2	D-OMe	91	102-105	2.3(t,2H); 2.8-3.3(br.s,4H); 3.3-3.8(br.s,4H); 7.2-7.7 (m,5H).	EI 273(19.5) CI 274(24.7)
15	Ph	CH_2-CH_2-O-CH_2CH_2	MeI	72	63-65	1.2 - 1.5(t,3H); 2.7-3.1(q,2H); 3.0-3.2(br,s,4H); 3.5 - 3.8(br,s, 4H); 7.4-7.7(m, 5H).	EI 286(7.5)
16	Ph	CH_2-CH_2-O-CH_2CH_2	P-BrPhCHO	60	138-140	2.7-3.0(br,s,4H); 3.0-3.3(d,2H); 3.4-3.8(br,s,4H); 4.7-5.1(m,2H); 7.1 - 7.9(m,4H).	EI 455(1.8) 457(1.6) (M-1)
17	Ph	CH_2PhCH_2-Ph	MeI	62	oil	1.1-1.4(t,3H); 2.5-3.0(q,2H); 4.0(s,2H); 4.5-4.7(m,2H);6.6-7.8(m,15H).	EI 396(26.5)

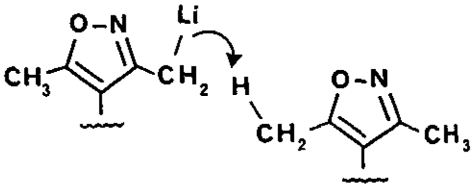
[a] All new compounds gave satisfactory combustion analyses.

[b] M^+ (or $M+1^+$ for CI) unless otherwise indicated.

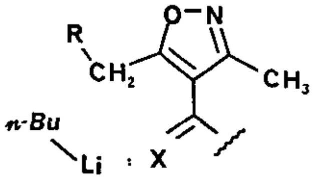
[c] Anal. calcd. for $C_{19}H_{25}N_2O_3Br$: C, 55.75; H, 6.16; N, 6.84. Found: C, 55.46; H, 6.27; N, 6.69.

wide range of electrophiles. The oxazoline is also a versatile precursor to other functional groups.[8] The amide system represents a compromise between the directness of the dianion approach and the broad scope of the oxazoline method. Since it requires only one step to form this protecting group, the preparation time and overall efficiency is superior to the oxazoline system. However, for the 3-phenyl-5-methylisoxazole-4-carboxamides the metalation is more sluggish[11] and the yields of the metalation step are generally slightly lower. For the preparation of chiral systems, however, the tertiary amide system appears to offer real advantages, since the preparation of chiral isoxazole oxazolines (in our hands) has not compared favorably.

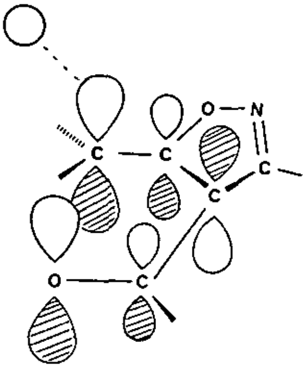
For the systems studied to date in our laboratories, C-5 metalation is indicated under both thermodynamic and kinetic conditions[13] for the dianion, oxazoline, and amide system. Thus the possibility of initial kinetic C-3 deprotonation followed by equilibration to C-5 seems unlikely.



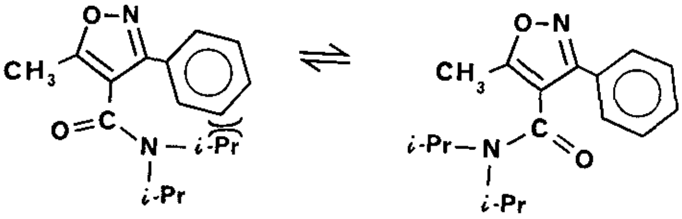
A second plausible possibility is that the -C=X double bond at C-4 adopts a cisoid conformer with the C-4/C-5 double bond of the isoxazole, thus reinforcing (or facilitating) C-5 deprotonation by chelation through the X lone pair.



A third possibility exists, in analogy to the stereoelectronic effects of enolate deprotonation/electrophile quenching proposed by Evans.[14] Thus, for a vinylogous enolate or imidate system, the π-HOMO assists deprotonation and/or electrophillic quenching via a secondary orbital symmetry effect.



For the 3-phenyl-systems the amide may be forced from the cisoid conformer by steric hindrance and chelation via the amide oxygen



cannot reinforce C-5 deprotonation. At higher temperature, chelation *via* the isoxazole oxygen appears to direct metalation, at a rate superior to proximity directed metalation on the aryl group.[15] Further synthetic and mechanistic studies are underway.

EXPERIMENTAL SECTION

Mass spectra were measured on a VG 7070 GC/MS with model 11/250 data system. ^1H NMR were obtained on a Varian EM-360 or JEOL FX-90Q spectrometers. ^2H and ^{13}C NMR were obtained on the JEOL. IR spectra were obtained on Digilab FTS-80 or Qualimatic FT-IR instruments as neat liquids on NaCl plates or, for solids, as KBr pellets. Combustion analyses were performed by MicAnal Organic Microanalysis, P.O. Box 41838, Tucson, Arizona. 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 BASF catalyst R3-11 followed by indicator Drierite. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. All chromatography solvents (hexane, CH_2Cl_2, $CHCl_3$, EtOAc, MeOH) were distilled before use. Organolithium reagents were titrated using the procedure of Ronald.[12] Commercially available reagents and/or literature compounds were purified immediately before use by recrystallization or distillation as appropriate.

Preparation of N,N-diisopropyl-3,5-dimethyl-isoxazole-4-tertiary carboxamide. Method A (Schotten-Baumann Reaction)

An addition funnel was charged with a solution of freshly distilled 3,5-dimethyl-isoxazole-4-carboxylic acid chloride (68 g, 0.426 mole) in methylene chloride (100 ml). This solution was added dropwise over 1 h at 0°C to a stirred solution of diisopropylamine (150 ml) in methylene chloride (250 ml) in a 1 L Morton flask. The resulting slurry was allowed to come to room temperature over twenty-four hours, and poured into 300 ml of aqueous 3N HCl. The layers were separated and the aqueous layer extracted with methylene chloride (2 x 100 ml). The combined organic extracts were washed with aqueous 3N HCl (2 x 100 ml), aqueous 3N NaOH (2 x 100 ml), brine (100 ml), and dried over anhydrous Mg SO_4. The solution was filtered and concentrated to give the crude amide as an off-white solid (96 g, 100%). The solid was sublimed at reduced pressure on a Kugelrohr apparatus (120°C/2mm Hg) to give a white solid (Table II, entry 1) (91.9 g, 96% yield). Anal. calcd. for $C_{12}H_{20}O_2N_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.31; H, 8.2; N, 12.58.

Method B. 3-Phenyl-5-methylisoxazole carboxylic acid (1.22 g, 6 mmol) was dissolved in THF (20 ml) in a 100 ml flask. A solution of dicyclohexyl carbodiimide (DCC) (1.1 eq) in methylene chloride (15 ml) was added. After stirring for 15 min at room temperature, pyrrolidine was added dropwise to the stirring solution (9.5 ml) and the mixture warmed to reflux for 8 h. The reaction mixture was cooled, chloroform added (30 ml), and the dicyclohexylurea filtered. The resulting solution was washed with aqueous 1.5 N HCl (80 ml), water (80 ml), and aqueous 1 N NaOH (80 ml). The organic layer was dried over anhydrous Na_2SO_4. Filtration and concentration gave the product as an oil which was purified by radial PTLC. The product so obtained crystallized on standing, mp 128-130°C (Table II, entry 4) (0.72 g, 47%). Anal. calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.21; N, 10.93. Found: C, 70.22; H, 6.16; N, 10.93.

General metalation procedure. N,N-diisopropyl-5-methyl-3-phenylisoxazole-4-carboxamide (0.93 g, 3.3 mmol) was dissolved in Tetrahydrofuran (50 ml) and cooled to -40°C. A solution of n-butyl lithium in hexanes (2.2 ml, 1.58 M, 3.476 mmol) was added dropwise by syringe. The solution was stirred at -40°C for 1.5 h, after which time methyl-iodide (4 ml) was added, and the reaction allowed to come slowly to room temperature over 8 h. The THF was removed, in vacuo, and the residue mixed with 50 ml of water, and extracted with methylene chloride (3 x 30 ml). After drying (Na_2SO_4) and filtration, the product was obtained as an amber oil, which was flashed down a short silica column to remove baseline impurities, and then chromatographed on silica using radial chromatography. The product (Table I, entry 9) crystallized on standing, mp 103-105°C (0.68 g, 70%). Anal. calcd. for $C_{18}H_{24}O_2N_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.04; H, 7.90; N, 9.28.

Table II. Data for Amide Starting Materials (2).

Entry	R	R_1	R_2	Method[a,b]	%	m.p.[c] (b.p., mm Hg)	^1H NMR	MS[d]
1	Me	iPr	iPr	A	96	84-87	1-1.5(br,d,12H); 2.15(s,3H); 2.25(s,3H); 3.2~3.9(m,2H).	CI 225(52.9)
2	Ph	iPr	iPr	A	70	88-90	0.6-0.85(d,6H); 1.35-1.6(d, 6H); 2.4(s,3H); 3.2-3.7(m, 2H); 7.25-7.8(m,5H).	CI 287(100)
3	Ph	$CH_2CH_2CH_2CH_2$		A	88	128-130	1.7~3.0(m,4H); 2.75(s,3H); 3.0-3.3(t,2H); 3.65-3.85(t, 2H); 7.4-8(m,5H).	CI 257(100)
4	Ph	$CH_2CH_2CH_2CH_2$		B	47	same as product above		
5	Ph	$CH_2CH_2-O-CH_2CH_2$		A	77	102-105	2.3(s,3H); 2.8-3.3(br,s,4H); 3.3-3.8(br,s,4H); 7.2-7.7(m, 5H).	CI 273(88.2)
6	Ph	$CH_2CH_2-O-CH_2CH_2$		B	56	same as product above		
7	Ph	CH_2Ph	CH_2Ph	A	69	(210,0.5)	2.4(s,3H); 4.0(s,2H); 4.7(s,2H); 6.7-6.9(m,2H); 7.0-7.4(10H); 7.5-7.7(3H).	EI 382(21)
8	Ph	$CH-CH_2CH_2CH_2$[e] CH_2OMe		A	60	(190,0.4)[f]	1.4-1.9(m,4H); 2.35(s,3H); 3.2-3.4(m,2H); 3.23(s,3H); 3.4-3.6(m,2H); 4.1(m,1H); 7.2-7.3(m,3H); 7.5-7.6(m,2H).	EI, $M+1^+$ 301(0.6) CI, $M+1^+$ 301(12.8)

[a] Method A : Schotten-Baumann reaction

[b] Method B : D.C.C.

[c] All new compounds gave satisfactory combustion analyses.

[d] M^+ (or $M+1^+$ for CI) unless otherwise noted.

[e] From (S) (+) - prolinol, prepared according to reference 9.

[f] $(\alpha)^{24}_{D}$ - 81.49° (EtOAc, c 10.16)

Table III. Combustion Analyses of Compounds in Table I.

Entry[a]	Formula	Anal. Calcd. (Found)		
		C	H	N
2	$C_{13}H_{22}N_2O_2$	65.52 (65.52)	9.30 (9.48)	11.75 (11.76)
3	$C_{19}H_{25}N_2O_3Br$	55.75 (55.46)	6.16 (6.27)	6.84 (6.69)
5	$C_{19}H_{25}N_3O_5$	60.79 (60.72)	6.71 (6.84)	11.19 (11.04)
6	$C_{17}H_{24}N_2O_4$	63.73 (63.24)	7.55 (7.58)	8.74 (8.57)
9	$C_{18}H_{24}N_2O_2$	72.04 (71.97)	7.90 (8.05)	9.28 (9.33)
10	$C_{24}H_{27}N_2O_3Br$	61.23 (61.15)	5.64 (5.77)	6.03 (5.94)
12	$C_{16}H_{18}N_2O_2$	70.08 (71.09)	6.59 (6.71)	10.31 (11.84)
13	$C_{22}H_{21}N_2O_3Br$	59.87 (59.72)	4.80 (4.91)	6.34 (6.02)
15	$C_{16}H_{18}N_2O_3$	66.88 (67.12)	6.20 (6.34)	9.69 (9.78)
16	$C_{22}H_{21}N_2O_4Br$	57.92 (57.78)	4.49 (4.63)	5.97 (6.13)
17	$C_{26}H_{24}N_2O_2$	78.76 (78.48)	6.10 (6.00)	7.07 (6.88)

[a] Entry numbers correspond to those in Table I.

Table IV. Combustion Analyses of Compounds in Table II.

Entry[a]	Formula	Anal. Calcd. (Found)		
		C	H	N
1	$C_{12}H_{20}N_2O_2$	64.31 (64.26)	8.92 (8.99)	12.58 (12.49)
2	$C_{17}H_{22}N_2O_2$	71.30 (71.56)	7.75 (7.93)	9.78 (9.37)
3	$C_{15}H_{16}N_2O_2$	70.22 (70.29)	6.16 (6.21)	10.92 (10.93)
5	$C_{15}H_{16}N_2O_3$	66.03 (66.16)	5.73 (5.92)	10.16 (10.17)
7	$C_{25}H_{22}N_2O_2$	78.51 (78.31)	5.80 (5.74)	7.32 (7.29)
8	$C_{17}H_{20}N_2O_3$	67.98 (67.24)	6.71 (6.39)	9.33 (8.74)

[a] Entry numbers correspond to those in Table II.

ACKNOWLEDGMENT

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REFERENCES

1. For a review see: B. J. Wakefield and D. J. Wright, Adv. Heterocycl. Chem., 1979, 25, 147.
2. For a recent example of isoxazoles with useful biological activity see: G. D. Diana, M. A. McKinlay, C. J. Brisson, E. S. Zalay, J. V. Miralles, and U. J. Salvador, J. Med. Chem., 1985, 28, 748.
3. R. G. Micetich, Can. J. Chem., 1970, 48, 2006.
4. (a) For a review of simple dialkyl isoxazole metalation see: C. Kashima, Y. Yamamoto, and Y. Tsuda, Heterocycles, 1977, 6, 805.
   (b) R. G. Micetich, C. C. Shaw, T. W. Hall, P. Spevak, and B. K. Bains, Heterocycles, 1985, 23, 585.
5. (a) N. R. Natale and C.-S. Niou, Tetrahedron Lett., 1984, 25, 3943.
   For earlier synthetic studies on isoxazoles, see:
   (b) N. R. Natale and D. A. Quincy, Synth. Commun., 1983, 13, 817.
   (c) N. R. Natale, Tetrahedron Lett., 1982, 5009.
   (d) Studies on isoxazole carboxylic acid dianions will appear: J. I. McKenna and N. R. Natale, J. Org. Chem., accepted pending revision.
6. P. Beak and V. Snieckus, Acc. Chem. Res., 1982, 15, 306.
7. P. E. Eaton and G. Castaldi, J. Am. Chem. Soc., 1985, 107, 724.
8. Preparation of chiral isoxazolyl-oxazolines proceeded in low yield (e.g., 20%), unpublished work with C.-S. Niou. For a review see:
   K. A. Lutomski and A. I. Meyers in "Asymmetric Synthesis" Vol. 3, J. D. Morrison , Ed., Academic Press: New York, 1984, p. 213.
9. D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Dauon, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H. A. Oei, and M. Schmidt, Helv. Chim. Acta, 1977, 60, 301.
10. M. Ohashi, H. Kamachi, H. Kakisawa, A. Tatematsu, H. Yoshizumi, H. Kauo, and H. Nakata, Org. Mass. Spectrom., 1969, 2, 195.

11. At higher temperature, isoxazoles with electron withdrawing substituents in the C-4 position may undergo Michael addition at C-5 of the isoxazole ring with alkyl lithium reagents. R. Pepino, A. Ricci, M. Taddei, and P. Tedeschi, *J. Organomet. Chem.*, 1982, **231**, 91.

12. M. R. Winkle, J. J. Lansinger, and R. C. Ronald, *J. Chem. Soc., Chem. Commun.*, 1980, 87.

13. In some cases, kinetic metalation conditions produce C-3 substitution, D. J. Brunelle, *Tetrahedron. Lett.*, 1981, 3699.

14. D. A. Evans in "Asymmetric Synthesis" Vol. 3, J. D. Morrison, Ed., Academic Press: New York, 1984, pp. 25-29, and references cited.

15. P. Beak, J. E. Hunter, and Y. M. Jun, *J. Am. Chem. Soc.*, 1983, **105**, 6350.

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