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A FACILE SYNTHESIS OF FUNCTIONALLY COMPLEX ISOXAZOLE DERIVATIVES

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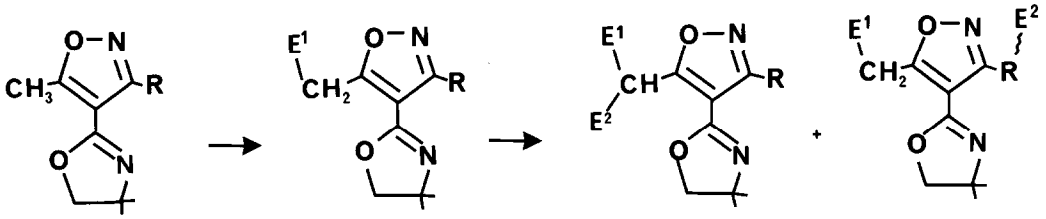
Summary: Metalation of 2(4'-Isoxazolyl)-Δ^2-oxazolines takes place initially and selectively on the C-5'-alkyl group. Subsequent metalation also proceeds at this position. Selective deprotection of the oxazoline was accomplished without disturbing the isoxazole ring.

Isoxazoles are 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 Δ^2-oxazoline as a protecting group for the carbonyl functional group, and herein report on the utility of this approach.



1 **2** **3** **4**

The starting materials for this study, 2-(4'-Isoxazolyl-)-Δ^2-oxazolines (1) are easily prepared from the corresponding isoxazole carboxylic acids.[4] Deprotonation was effected with either LDA (-5°C, 30 min, method A), n-BuLi (-78°C, 2 h, method B), or $NaNH_2$ (-78°, method C). Treatment of the THF solution with methanol-d gave clean deuterium incorporation in the C-5' position.[5,6] Primary iodides (Table I entries b,c,j,k) and bromides (entry f), benzyl bromides (entries d,e) and heterobenzyl-chlorides (entries n and o) all are suitable as electrophiles. In some cases where method A gives unsatisfactory results, method B succeeds (entry d vs. e and j vs k). Addition to an aldehyde proceeded smoothly (entry g). Oxidation with molybdenumoxodiperoxy pyridine HMPA complex (MOOPH, entry p) gave moderate isolated, purified yields of the alcohol (E=OH).

Table I. Metalation and electrophilic quenching of (1) to produce (2).

Entry	R	E'	Method[a]	Yield[b]
a	CH_3	D-OMe	B	82-89[c+d]
b	CH_3	CH_3-I	A	92[c]
c	CH_3	CH_3-I	B	78-86[c+d]
d	CH_3	$PhCH_2$-Br	A	49[d][50]
e	CH_3	$PhCH_2$-Br	B	91[c+d]
f	CH_3	n-C_8H_{17}-Br	A or B	82[c]
g	CH_3	PhCHO	B	97[c]
h	CH_2CH_3	CH_3-I	B	74[d]
i	Ph	D-OMe	B	72[d]
j	Ph	CH_3-I	A	36[d][40]
k	Ph	CH_3-I	B	86-92[c+d]
l	Ph	CH_3-I	C	ca 89[d+e]
m	Ph	o-Br$PhCH_2$-Br	B	98[c+d]
n	Ph	5[g]	B	67[c]
o	CH_3	5[g]	B	72[c+d][85]
p	CH_3	MOOPh	B	32-53[c][49-64]
q	Ph	TMS-Cl	B	ca 97[d+f]
r	Ph	2,6-diCl$PhCH_2$-Cl	B	89[c]
s	Ph	Cl$(CH_2)_3$-Br	B	61[d]

[a] Method A, LDA, -5°C, 30 min. Method B, BuLi, -78°C, 2h. Method C, $NaNH_2$, -78°C, 4 h (excess), CH_3I (excess).

[b] Yield of isolated purified product.

[c] Isolated by column or radial chromatography.

[d] Distillation. [Value in brackets is yield based on recovered starting material.]

[e] GC-MS indicated C-5'-isopropyl as the major product. The C-5' isopropyl to ethyl to t-butyl ratio was 4:1:trace.

[f] GC-MS-CI indicated C-5'-bis-TMS as a minor product.

[g] 5 = 4-chloromethyl-5-methyl-3-phenyl-isoxazole.

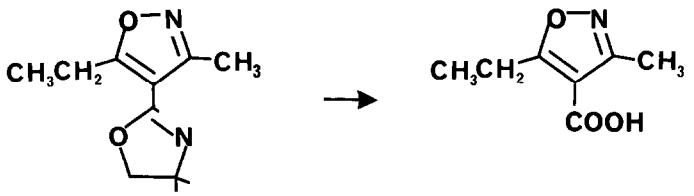
Table II. Subsequent metalation of (2b) and (2j).

Entry	R	E	E'	% yield	Product
aa	CH_3	CH_3	D	85	(3)95,(4)5
bb	CH_3	CH_3	CH_3	73	(3)
cc	Ph	CH_3	D	97	(3)
dd	Ph	CH_3	CH_3	93	(3)
ee	Ph	CH_3	CH_2Ph	74	(3)
ff	Ph	5	5	89	(3)

Excess base in the presence of excess electrophile produced minor amounts of products from incorporation of more than one electrophile (entries l and q). Thus it is important that the organolithium reagent be carefully titrated immediately before use.[7] It occured to us that this tactic could be used to our advantage.

Thus, subsequent metalation[8] under thermodynamic conditions gives rise to predominant C-5' metalation (Table II). Only traces of C-3' substituted product (4) were detected. The product (3) can be obtained, free of the C-3' substance, by simple radial chromatography. Alkyl groups are readily incorporated in useful yields.

Deprotection of the product isoxazole-oxazolines was effected with surprising ease. Thus, the oxazoline was cleanly removed with aqueous acid (3 N aq. HCl, reflux, overnight) to give the isoxazole-4-carboxylic acid (6) from (2b) in 62% yield.



2b **6**

We are exploring a systematic study of the synthetic utility of this and related systems.

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References

1. a) For a review on isoxazoles, see Wakefield, B. J.; Wright, D. J. Adv. Heterocycl. Chem. 1979, 25, 147.
b) For a recent report of isoxazole metalation see Oster, T. A.; Harris, T. M. J. Org. Chem. 1983, 48, 4307.
c) For an excellent review on heteroatom facilitated metalation, see Gschwend, H. W.; Rodriguez, H. R. Org. React. (N.Y.) 1979, 26, 1. Heteroatom facilitated metalation of alkyl groups has seen recent application:
d) Mills, R. J.; Snieckus, V. J. Org. Chem. 1983, 48, 1565.
e) Comins, D. L.; Brown, J. D. J. Org. Chem., 1984, 49, 1078.
2. a) Natale, N.R. Tetrahedron Lett. 1982, 5009.
b) Natale, N.R. and Quincy D. A. Synth. Commun., 1983, 13, 817.
3. Meyers, A. I., Mihelich, E. D. Angew. Chem. Int. Ed. Engl., 1976, 15, 270.
4. Prepared using the method of Meyers: Meyers, A. I., Gabel, R. A., J. Org. Chem., 1982, 47, 2633. For example, overall yield of (1, R=Ph) from the commerically available carboxylic acid was 80% after purification.
5. Deuterium incorporation was studied by means of ^{1}H-, ^{2}H-NMR and mass spectrometry.
6. A list of pertinent data and experimental detail has been supplied to the editor. This supplementary material can be obtained from the author. Full experimental details will be published shortly.
7. Winkle, M. R., Lansinger, J. J., Ronald, R. C., J. Chem. Soc., Chem. Commun. 1980, 87.
8. There are conflicting reports on the regiochemistry of simple 3,5-dialkylisoxazole metalation:
a) Brunnelle, D. J. Tetrahedron Lett., 1981, 3699.
b) Kashima, C.; Yamamoto, Y.; Tsuda, Y. Heterocycles, 1977, 6, 805.

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