Tetrahedron Letters, Vol.22, No.38, pp 3699 - 3702, 1981
Printed in Great Britain

0040-4039/81/383699-04$02.00/0

ISOXAZOLES AS β-DIKETONE SYNTHONS-SELECTIVE ANION FORMATION ON 3,5-DIALKYLISOXAZOLES

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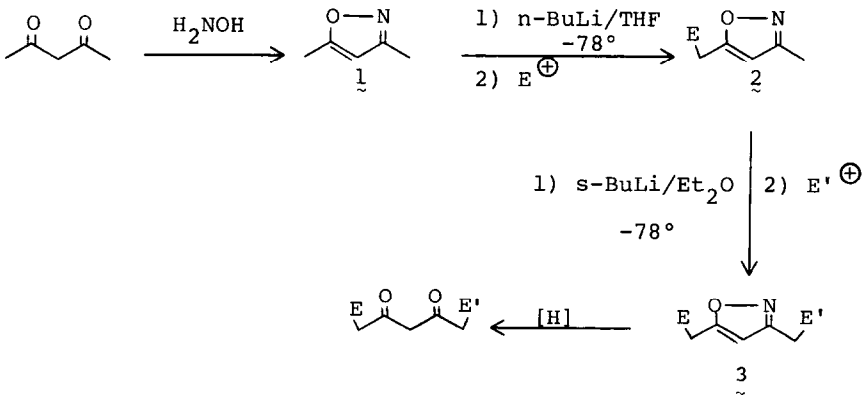
Summary: 3,5-Dimethylisoxazole can be metalated and alkylated regiospecifically. Alkylation occurs first on the 5-methyl group, and a second alkylation occurs on the 3-methyl group. This method permits specific synthesis of disubstituted isoxazoles, and of the corresponding β-diketones.

A recent report by Tischler and Weiler[1] on the alkylation of N-substituted isoxazolin-5-ones prompts us to report our results in a similar area. In connection with other studies, we required a number of substituted β-diketones. Use of dianion chemistry[2] was unattractive for a number of reasons: precipitation of the dianions occurred, yields were variable, and isolation and purification of the products were often tedious. We have thus investigated the use of isoxazoles and pyrazoles as synthons for the β-diketone functionality. Although the pyrazole did not prove suitable, the isoxazole proved to be an efficient replacement for the β-diketone in alkylation reactions. We have found, in fact, that 3,5-dimethyl isoxazole can be selectively alkylated first at the 5-position, and then at the 3-position, in sequential reactions. The unsymmetric substituted isoxazole may then be reduced to yield a new β-diketone (Equation 1).

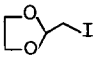


Several years ago, Micetich[3] and Kashima[4] reported that isoxazoles and pyrazoles could be metalated and their anions alkylated. Isoxazole 1 can be metalated by a variety of bases (n-BuLi, $LiN(iPr)_2$, $NaNH_2/NH_3$) at -78° in THF. Quenching with MeOD at low temperature yields at least 98% deuterium incorporation

at the 5-methyl group. The anion is stable for several hours at -78°, but decomposes upon warming to 0° for 1/2 hour (less than 25% yield of deuterated starting material is recovered). NMR studies utilizing Europium shift reagents[5] have verified that alkylation occurs only on the 5-methyl group: the 3-methyl singlet is shifted downfield farther than the 5-methylene group in 3-methyl-5-ethyl isoxazole prepared by alkylation with methyliodide. Results of reaction with various electrophiles are summaried in Table I.

Table I

Reaction of 3,5-Dimethyl Isoxazole Anion[a] with Various Electrophiles

Electrophile	Yield[b]
CH_3I	75 (70)
n-BuI	90
$CH_2=CHCH_2Br$	97 (44)
$PhCH_2Cl$	98 (70) (62)[c]
PhCHO	96 (22)
	95
	97 (18)
	87 (15)
Me_3SiCl	80
$I(CH_2)_{10}I$	78
	82

[a]Formed at -78° by addition of n-BuLi to a THF solution of 3,5-dimethyl isoxazole

[b]Yields in parentheses are from Reference 4a and b; anion formation with $NaNH_2$/liq. NH_3.

[c]Reference 3.

Kashima, et al[4] have reported that alkylation of 3,5-dimethylisoxazole using sodium amide/liquid ammonia yields only 5-alkylation, and that second and third alkylations occur only at the 5-methyl group. However, we have found that reaction of 5-alkylated isoxazoles 2 with s-BuLi or t-BuLi at -78° in THF or ether, followed by quenching with various electrophiles affords only 3-alkylation. For example, reaction of 3-methyl-5-pentyl-isoxazole with s-BuLi/ether at -78°, followed by addition of MeI, slow warming to 0° and quenching with NH_4Cl solution yields 92% of 3-ethyl-5-pentylisoxazole. The NMR spectrum clearly shows the 5-methylene group to be unchanged, while the 3-methyl singlet of the starting material (2.22 ppm) has become a quartet at 2.7 ppm. Results of other 3-alkylation reactions are shown in Table II. It is interesting to note that n-BuLi does not metalate 3-methyl-5-pentylisoxazole; reaction at -78° in THF followed by quenching with D_2O/THF gave no deuterium incorporation. A similar reaction using t-BuLi yielded the starting material with 97% deuteration at the 3-methyl position. Tanaka, et al[6] report anion formation at the 5-position of 3,5-diethyl-4-methylisoxazole, using lithium diisopropylamide; we observe no deprotonation in 1/2 hour at -78° using this base. The regioselectivity we observe is probably steric in origin; Tanaka's substrate has equal steric environments at the 3- and 5-positions, and Kashima[4] utilizes a sterically small base. We have seen no equilibration to the anion at the 5-position upon warming to 0° (although extensive decomposition occurs), hence it is difficult to comment on the relative thermodynamic stabilities of the 3-alkyl vs. 5-alkyl anions in our system.

Table II

Alkylation Reactions of 3-methyl-5-Alkylisoxazoles (2→3)

5-Substituent	Electrophile	Base	Yield
$n\text{-}C_5H_{11}$	MeI	t-BuLi	50
$n\text{-}C_5H_{11}$	MeI	s-BuLi	92
$n\text{-}C_5H_{11}$	$CH_2{=}CH\text{-}CH_2Br$	s-BuLi	80
$n\text{-}C_5H_{11}$		s-BuLi	80
$n\text{-}C_5H_{11}$	Me_3SiCl	s-BuLi	83
$n\text{-}C_5H_{11}$	PhCHO	t-BuLi	93
$PhCH_2CH_2$	$PhCH_2Cl$	s-BuLi	85
$PhCH_2CH_2$	n-BuI	s-BuLi	85
$PhCH_2CH_2$	Me_3SiCl	s-BuLi	90

The alkylated isoxazoles are stable and easily purified by column chromatography, distillation, or preparative vpc. Cleavage by catalytic hydrogenation to either the diketone or to the β-aminoenone can be achieved.[7] The β-aminoenones were isolated in high yield from reduction with W-2 Raney nickel, in ethanol at 15° or using platinum oxide;[4] acid hydrolysis in ethanol yields the β-diketones. Yields of 70-95% were obtained for the overall conversion of isoxazole to alkylated 1,3-diketone. Alternatively, the α,β-unsaturated ketones may readily be obtained.[8]

We are currently investigating alternative isoxazole cleavage reactions, as well as the selective formation of isoxazoles from ketones[9] and β-diketones, and their reactions.

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(Received in USA 6 May 1981)