

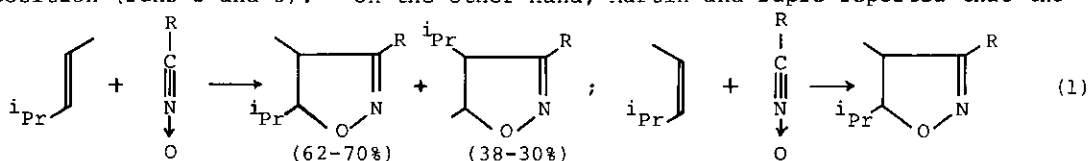
REGIOSELECTIVE EFFECTS OF THE ALLYLIC HETEROATOMS IN 1,3-DIPOLAR
CYCLOADDITION OF NITRONES TO SEVERAL ALLYL DERIVATIVES [#]

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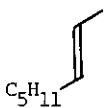
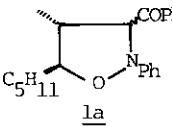
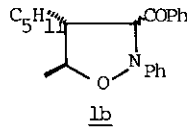
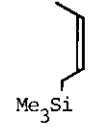
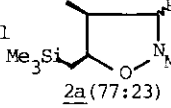
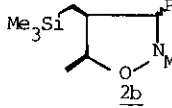
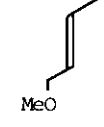
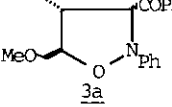
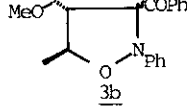
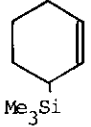
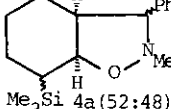
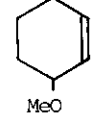
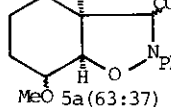
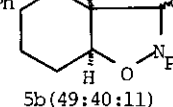
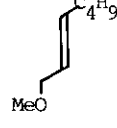
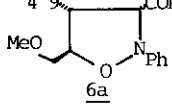
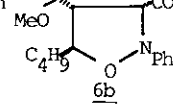
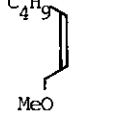
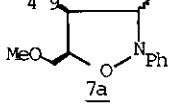
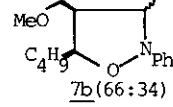
Abstract - Further evidences that the allylic oxygen atom affects
the regioselectivity in 1,3-dipolar cycloaddition of nitrones
highly toward to produce 4-alkoxymethylisoxazolidines were
presented. The selectivity was unaffected by the geometry of
dipolarophiles.

Attainment of high regioselectivity in cycloaddition is one of the challenging
problems in synthetic organic chemistry. The 1,3-dipolar cycloaddition of nitrones
has been successfully employed in natural product syntheses during the last decade.¹
In these syntheses, mono- or disubstituted olefins, in which a polar substituent
directly attaches to the double bond, were used as the dipolarophiles to gain high
regioselectivity. On the contrary, the addition to a 1,2-dialkyl substituted
olefin showed, as expected, no recognizable selectivity (Table 1, run 1).²
In 1974, Caramella and Cellerino reported the cycloadditions of benzonitrile oxide
to 3-substituted cyclopentenes and found that the regioselectivity was affected by
the electron-donating or -withdrawing nature of the substituents.³ The phenomena
were explained as that the effect of the allylic substituent is due to the π -orbital
deformation caused by the substituent.⁴ In the course of our synthetic studies on
natural products, we noticed that the regioselectivity in the cycloaddition of
nitronone was also affected by the allylic heteroatoms and found that quite reverse
selectivity was observed when silicon or oxygen atom was placed at the allylic
position (runs 2 and 3).² On the other hand, Martin and Dupre reported that the



[#]Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

Table 1. Cycloaddition of Nitrones

Run	Dipolarophile	Nitronne $R_1CH=N(O)R_2$	Conditions	Yield (%)	Products ^a	Ratio (a/b)	Ref
1		PhCO	Ph r.t. (70h) benzene	64	 	47/53	2
2		Ph	Me 190°C (24h) benzene	31	 	98/2	2
3		PhCO	Ph r.t. (40h) benzene	90	 	6/94	2
4		Ph	Me 190°C (24h)	15		100/0	2
5		PhCO	Ph 80°C (1.5h) benzene	13	 	30/70	
6		PhCO	Ph r.t. (4d) benzene	67	 	6/94	
7		PhCO	Ph 80°C (8h) benzene	44	 	4/96	

^aAll isomers were separated and characterized. For those having the same regio-structure but the different stereochemistry, stereoisomeric ratios are shown in parentheses.

regioselectivity was, in some cases, affected by the geometry of a dipolarophile as shown in equation (1).⁵ They explained as in (Z)-olefin the transition state being restricted by the steric repulsion of both components to give only one regioisomer. As our results shown above being limited to the special dipolarophiles — i.e., (Z)-olefin was used in run 2, while (E)-olefin in run 3 —, two series of 1,3-dipolar cycloaddition of C-benzoyl-N-phenylnitronne is reported here in order to clarify whether the reverse regioselectivity in runs 2 and 3 depends on the existence of the allylic heteroatom or the geometry of the olefin.

The reactions were conducted with either excess of the nitron or dipolarophile under the conditions shown in Table 1. The products were separated by chromatography or recrystallization and characterized by ^1H nmr spectra. The addition to 3-trimethylsilylcyclohexene (run 4) had been reported previously.² The selectivity lied so far to produce the 5-trimethylsilylmethylisoxazolidine. When 3-methoxycyclohexene was used (run 5), five isoxazolidines were isolated and characterized.⁶ Of those, three have the same regioisomeric structure. The selectivity was again similar to that of acyclic dipolarophile (run 3) and reversed to that of 3-trimethylsilylcyclohexene exhibiting no effect of the geometry of a dipolarophile. As the yields were low due to the poor reactivity of cyclohexene system⁷ and steric environment at both allylic positions was slight different, the reactions with acyclic geometrical isomers, 1-methoxy-2E- and 2Z-heptenes, were investigated (runs 6 and 7). In both cases, the major regioisomer(s) was a 4-methoxymethylisoxazolidine 6b (or 7b) and the regioisomeric ratios were essentially the same; thus it led to the conclusion that in 1,3-dipolar cycloaddition of nitron to the dipolarophile having a heteroatom at the allylic position the regioselectivity is controlled by the heteroatom and leads to give 4-alkoxymethylisoxazolidines when the heteroatom is oxygen, while 5-isomer when it is silicon.

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