CHEMISTRY LETTERS, pp. 957-960, 1985.

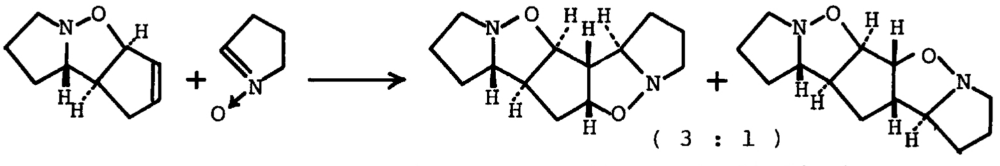
THE REGIOSELECTIVE EFFECT OF THE ALLYLIC SILICON OR OXYGEN ATOM IN 1,3-DIPOLAR CYCLOADDITION OF NITRONES

Satomi NIWAYAMA, Shigeyuki DAN, Yoshinobu INOUYE, and Hiroshi KAKISAWA*
Department of Chemistry, University of Tsukuba,
Sakura-mura, Niihari-gun, Ibaraki 305

1,3-Dipolar cycloaddition of nitrones on several allyl silanes, allyl ethers, and allyl alcohol was investigated. The silicon atom in dipolarophiles controlled the regioselectivity in favor for 5-(silylmethyl)isoxazolidines, while the oxygen atom for 4-(alkoxymethyl)isoxazolidines.

The 1,3-dipolar cycloaddition of nitrones has been widely used for the construction of various natural products.[1,2] The reaction is generally highly regio- and/or stereoselective and the N–O bond of the isoxazolidine ring formed can be effectively cleaved under mild conditions. The regioselectivity is of interest in both synthetic and theoretical aspects and is well documented in the reactions with mono- or di-substituted dipolarophiles which possess polar substituent(s) attached on the C–C double bond.[3-7]

On the contrary, 1,2-dialkyl substituted olefins had been rarely used as dipolarophiles until 1978, when McAlduff, Caramella, and Houk reported the cycloaddition of benzonitrile oxide to 3-substituted cyclopentenes and found that the regioselectivity was reversed depending on the electron donating or withdrawing nature of the substituents.[8] On the other hand, we found previously that, in the nitrone cycloaddition, the allylic oxygen atom seemed to affect the regioselectivity in favor of formation of 4-(alkoxymethyl)isoxazolidine as shown below.[9]



These results prompted us to investigate the effect of allylic heteroatoms on the regioselectivity of 1,3-dipolar cycloaddition of nitrones. In the present communication, we wish to report preliminarily the marked effect of the allylic silicon and oxygen atoms.

The reactions were conducted with a mixture of nitrone and excess dipolarophile at room temperature or at elevated temperature in a sealed tube. The products were separated by column chromatography or recrystallization and characterized by ^{1}H NMR spectra.[10)] The results are shown in Table 1.

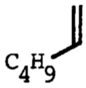
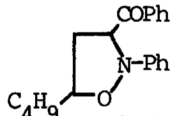
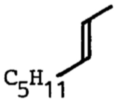
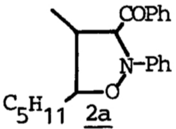
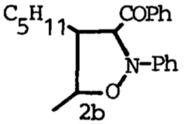
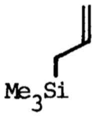
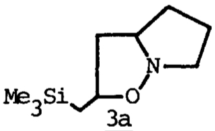
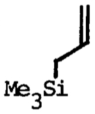
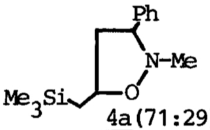
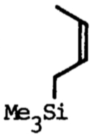
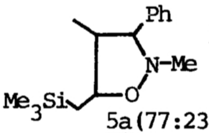
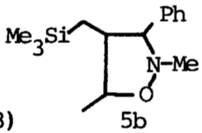
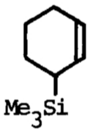
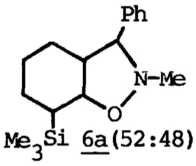
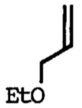
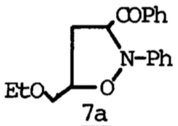
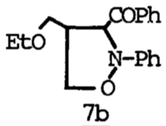
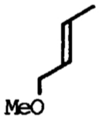
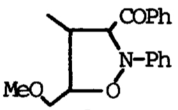
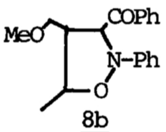
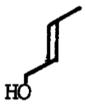
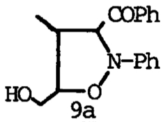
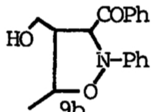
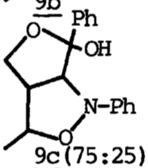
At first, we followed the reaction of a terminal alkene, 1-hexene,[11)] and confirmed regioselective production of 5-butylisoxazolidine 1a in 70% yield(run 1). None of regioisomers were detected but a very minute amount of stereoisomer 1a' was isolated by preparative TLC.[12)] In the case of (E)-2-octene (run 2), two regioisomers 2a and 2b were obtained almost in equal amount, as expected from the similar electronic nature of both alkyl substituents.

The effect of the allylic silicon atom was investigated in runs 3 - 6. The reactions with allyltrimethylsilane showed the same regioselectivity as the run 1 and 5-(trimethylsilylmethyl)isoxazolidines 3a and 4a were isolated in moderate yield, respectively (runs 3 and 4). Regioselective effect of the silicon atom became clear when 1-trimethylsilyl-(Z)-2-butene was used as dipolarophile (run 5). The allylic silyl group remarkably controls the selectivity to afford 5-(trimehtylsilylmethyl)isoxazolidine 5a. This tendency is kept in the reaction with 3-trimethylsilylcyclohexene, though the yield was low (run 6).

On the other hand, the allylic oxygen atom was found to affect in opposite direction (runs 7 - 9). The reaction with 3-ethoxypropene proceeded in similar yield as that of the run 1, but gave clearly two regioisomers 7a and 7b (run 7). The formation of 7b may be due to the presence of the allylic oxygen atom. Reversed regioselective effect of the oxygen atom compared with the silicon atom was further confirmed by the reaction with 1-methoxy-(E)-2-butene (run 8): 4-(methoxymethyl)isoxazolidine 8b was mainly obtained. The allylic hydroxyl group also showed regioselectivity in favor of producing 4-(hydroxymethyl)isoxazolidines (9b + 9c). The slight decrease in regioselectivity in the run 9 compared with the run 8 can be partially attributed to the hydrogen bonding of the hydroxyl group to the O←N of the nitrone so as to locate both components to give 9a.

The present results show that the allylic silicon and oxygen atoms affect the regioselectivity of 1,3-dipolar cycloaddition of nitrones in opposite direction. Further works on fundamental aspects are now in progress.

Table 1. Cycloaddition of Nitrones with Some Allylsilanes, Allyl Ethers, or Related Dipolarophiles

Run	Dipolarophile	Nitrone $R_1CH=N(O)R_2$		Conditions	Yield/%	Products[a]	Regioisomeric ratio (a/b)
1		PhCO	Ph	r.t. (43h) benzene	70	 1a(>97:<3)	100/0
2		PhCO	Ph	r.t. (70h) benzene	64	 2a  2b	47/53
3		$-CH_2CH_2CH_2-$		110°C (12h) benzene	63	 3a	100/0
4		Ph	Me	165°C (12h)	70	 4a(71:29)	100/0
5		Ph	Me	190°C (24h) benzene	31	 5a(77:23)  5b	98/2
6		Ph	Me	190°C (24h)	15	 6a(52:48)	100/0
7		PhCO	Ph	r.t. (41h) benzene	71	 7a  7b	91/9
8		PhCO	Ph	r.t. (40h) benzene	90	 8a  8b	6/94
9		PhCO	Ph	r.t. (36h) benzene	94	 9a  9b  9c(75:25)	28/72[b]

a) Stereoisomeric ratio is shown in parentheses. b) 9a/(9b + 9c).

The authors wish to thank Doctor Noboru Nakayama of Nippon Roche Research Center for measurements of high-resolution mass spectra.

References

1) J. J. Tufariello, Acc. Chem. Soc., 12, 396(1979).

2) H. Iida and C. Kibayashi, Yuki Gosei Kagaku, 41, 652(1983).

3) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, J. Am. Chem. Soc., 95, 7287(1973).

4) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, J. Am. Chem. Soc., 95, 7301(1973).

5) J. Sims and K. N. Houk, J. Am. Chem. Soc., 95, 5798(1973).

6) R. Huisgen, J. Org. Chem., 41, 403(1976).

7) P. DeShong and J. M. Leginus, J. Org. Chem., 49, 3421(1984); P. DeShong, C. M. Dicken, R. R. Staib, A. J. Freyer, and S. M. Weinreb, J. Org. Chem., 47, 4397 (1982); M. Joucla and J. Hamelin, J. Chem. Res. (M), 1978, 3535; M. Joucla, D. Grée, and J. Hamelin, Tetrahedron, 29, 2315(1973); A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez, and G. S. K. Wong, J. Org. Chem., 49, 276(1984).

8) E. J. McAlduff, P. Caramella, and K. N. Houk, J. Am. Chem. Soc., 100, 105 (1978).

9) H. Oinuma and H. Kakisawa, unpublished results.

10) Satisfactory elemental analyses or exact mass spectra were obtained for the new compounds. The regiochemistry was easily determined from the ^{1}H NMR specta. For example, 1a: δ($CDCl_3$, 90MHz)= 0.92(diffuse t, 3H), 1.2-1.9(m,6H), 2.45(ddd, 1H,J=11.5, 8.6, 6.0 Hz), 2.59(ddd, 1H, J=11.5, 8.2, 6.5 Hz), 4.14 (ddt, 1H, J=8.6, 6.5, 5.4 Hz), and 5.01(dd, 1H, J=8.2, 6.0 Hz).

11) R. Huisgen, H. Hauk, H. Seidl, and M. Burger, Chem. Ber., 102, 1117(1969).

12) Only one stereoisomer was generally obtained in the reactions of 1-pyrroline N-oxide or C-benzoyl-N-phenylnitrone, while considerable amount of streoisomers were detected in those of N-methyl-C-phenylnitrone.

(Received April 17, 1985)