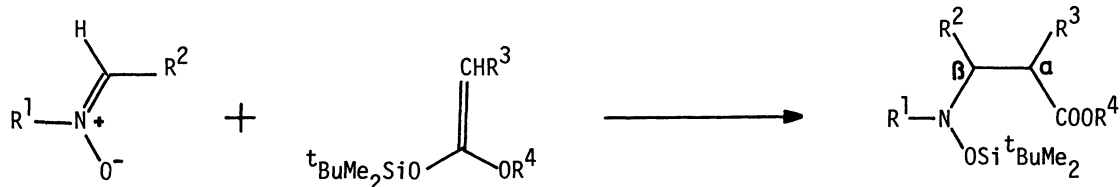


CARBON-CARBON BOND FORMING REACTION ASSISTED BY SILICON TRANSFER.
THE REACTION BETWEEN NITRONES AND KETENE SILYL ACETALS

Shuji TOMODA*, Yoshito TAKEUCHI, and Yujiro NOMURA
Department of Chemistry, College of General Education
The University of Tokyo, Komaba, Meguro-ku, Tokyo 153

Nitrones reacted with ketene silyl acetals at room temperature to afford β -siloxyamino esters in high yields. The stereochemistry of the products was assigned on the basis of NMR spectral data. A mechanism involving initial silicon transfer from ketene silyl acetals to nitrones has been proposed.

Nitrones¹⁾ are now widely recognized as versatile element in the syntheses of a variety of naturally occurring products such as alkaloids²⁾, β -lactams³⁾, amino sugars⁴⁾, and others.⁵⁾ These syntheses without exception rely on their remarkable nature to undergo 1,3-dipolar cycloaddition reactions,⁶⁾ which in general result in high regio- and stereospecificities. Herein we wish to report a new mode of reaction of nitrones with ketene silyl acetals.⁷⁾ This novel carbon-carbon bond forming reaction stems from the general observation that silicon atom possesses a high affinity toward oxygen. One may therefore reasonably expect facile silicon transfer from ketene silyl acetals (2) to nitrones (1) to provide β -siloxyamino esters (3), a masked form of β -amino esters, which serve as useful intermediates in the synthesis of biologically important compounds such as β -lactams.⁸⁾



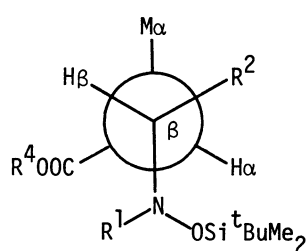
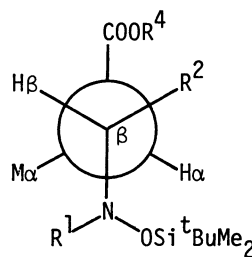
<u>1</u>	R ¹	R ²	<u>2</u>	R ³	R ⁴	<u>3</u>	R ¹	R ²	R ³	R ⁴
a	Ph	Ph	a	H	Me	aa	Ph	Ph	H	Me
b	Me	<i>p</i> -NO ₂ -C ₆ H ₄	b	Me	Me	ab	Ph	Ph	Me	Me
c	Me	<i>p</i> -Me-C ₆ H ₄	c	-CH ₂ CH ₂ -		ac	Ph	Ph	-CH ₂ CH ₂ -	
						ba	Me	<i>p</i> -NO ₂ -C ₆ H ₄	H	Me
						bc	Me	<i>p</i> -NO ₂ -C ₆ H ₄	-CH ₂ CH ₂ -	
						cc	Me	<i>p</i> -MeC ₆ H ₄	-CH ₂ CH ₂ -	

Indeed diphenyl nitronone (1a) smoothly reacted with 1-*t*-butyldimethylsiloxy-1-methoxyethylene (2a) at 25°C in acetonitrile to afford the β -siloxyamino ester (3aa) in 93% yield (entry 1 in the Table). The structure of 3aa was supported by combustion analysis (C, H, and N), NMR (¹³C and ¹H), and IR spectral data. A strong IR band at 1740 cm⁻¹ due to the methoxycarbonyl group unambiguously precluded the possibility of isoxazolidine structure which would have arisen from 1,3-dipolar cycloaddition reaction.⁷⁾ In addition to the ten aromatic protons (δ 7.20), the methoxy protons

(δ 3.52, s) and the *t*-butyldimethylsilyl group (δ 0.90(*t*-Bu), -0.03(Me), -0.40(Me)), the $^1\text{H-NMR}$ spectrum of 3aa indicated the benzylic proton (δ 4.76, dd, $J=7.8$ and 6.9 Hz) which is coupled to the two protons (δ 2.98, ddd, $J=13.2$, 7.8 , and 6.9 Hz) at the α position of the methoxycarbonyl. The $^{13}\text{C-NMR}$ spectrum also supported this structure; $\delta(\text{CDCl}_3)$ 171.95(s, C=O), 70.59(d, C_β), 51.36(q, OMe), 34.83(t, C_α), 26.17(q, *t*-BuSi), 17.99(s, *t*-BuSi), 4.93(q, SiMe), 5.53(q, SiMe) and seven degenerate aromatic peaks.

As shown in the Table, the reactions, in which there is a possibility of diastereomeric products, in fact provided approximately 7:3 stereoisomers in nearly all cases (entries 2-6, 8, and 9). Thus the reaction of 1a with a 8:2 stereoisomer mixture of 1-*t*-butyldimethylsilyloxy-1-methoxypropene (2b)⁹⁾ afforded a 76:24 mixture of 3ab in acetonitrile; comparable isomer ratio was also observed in *N,N*-dimethylformamide. In all cases studied here, stereoisomers (3ab, 3ac, 3bc, and 3cc) were chromatographically separated and their structures elucidated by combustion analysis, NMR (^{13}C and ^1H) and IR. In no cases were products arising from 1,3-dipolar cycloaddition isolated.

In order for this reaction to be useful in synthesis, stereochemical assignment of each diastereomeric pair (erythro or threo) must be made. This was inferred from the shielding effect of the aryl group at the β position (R^2) upon the methyl or methylene bonded to $\text{C}_\alpha(\text{M}_\alpha)$. Thus on the basis of the reasonable assumption that the most stable conformation of these diastereomers would be 3-T (threo) and 3-E (erythro) (Newman projection along $\text{C}_\beta\text{-C}_\alpha$ bond) shown below, one may recognize

3-T(Threo)3-E(Erythro)

that the shielding effect of R^2 on M_α would be greater in 3-T than in 3-E. It then follows that stereochemical assignment can be made by utilizing chemical shift difference of group M_α between 3-T and 3-E ($\Delta\delta$). For instance, in the case of 3ab, where $J(\text{H}_\alpha, \text{H}_\beta)=11.6$ and 11.0 Hz for the two isomers¹⁰⁾, the methyl proton absorptions (M_α) appear at δ 0.97 (major) and 1.68 (minor). The unusually high chemical shift for the major isomer as well as a significant chemical shift difference ($\Delta\delta(^1\text{H})=0.71$) necessarily leads to the assignment of the major isomer as 3-T. Comparable magnitude of $\Delta\delta(^{13}\text{C})=0.78$ was observed for the corresponding ^{13}C chemical shifts, further supporting this assignment. On the other hand, in the cases of 3ac, 3ab, and 3cc, which involve 2c as a ketene acetal component, $\Delta\delta(^1\text{H})$'s are 0.38, 0.42 and 0.34 with δ 's of minor isomers being higher field; the minor isomer should therefore be assigned structure 3-T. In all these three cases involving 2c, $^{13}\text{C-NMR}$ spectra exhibited the trend consistent with this assignment; $\Delta\delta(^{13}\text{C})=1.25$, 2.60 and 2.00 for 3ac, 3bc, and 3cc, respectively. It is interesting that the stereochemical consequence of the major isomer is reversed between the cases involving 2b and 2c.

The above stereochemical assignments for the diastereomers of 3ab, 3ac, 3bc, and 3cc are also supported by a marginal but yet definitive trend observed in ^{13}C chemical shifts of ester carbonyl groups. If the above assignments are correct, the minor isomer (3-E) of 3ab would show its carbonyl absorption at higher field than the corresponding major isomer due to the shielding effect of R^2 .

Table Synthesis and properties of β -siloxyamino esters (3)

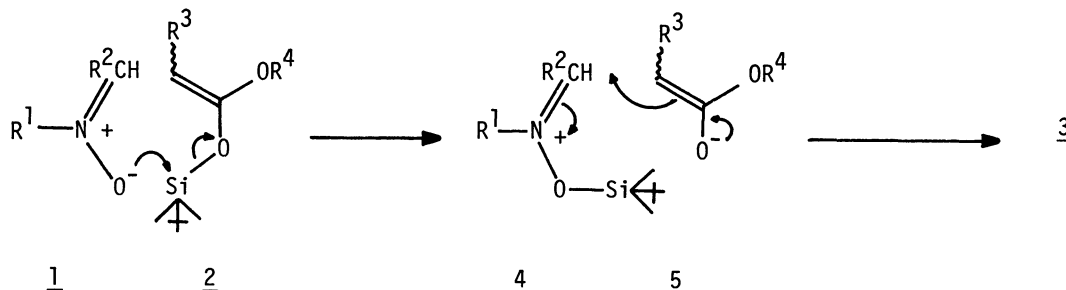
Entry	<u>1</u>	<u>2</u>	Conditions	Product	¹ H-NMR ^e		¹³ C-NMR ^e	
			(solvent ^a , °C, h)	(<u>3</u> ^b , %Yield, ratio ^c)	δ (M α) ^d	δ (M α) ^d	δ (C=O) ^f	
1	<u>1a</u>	<u>2a</u>	MeCN, 25, 24	<u>3aa</u> , 93, -	-	-	171.95	
2	<u>1a</u>	<u>2b</u>	MeCN, 25, 23	<u>3ab</u> , 88, 76:24	major	0.97	16.25	176.34
					minor	1.68	17.03	174.95
3	<u>1a</u>	<u>2b</u>	DMF, 25, 21	<u>3ab</u> , 90, 73:27	-	-	-	
4	<u>1a</u>	<u>2c</u>	MeCN, 25, 18	<u>3ac</u> , 83, 70:30	major	2.61	27.25	175.96
					minor	2.23	26.00	177.26
5	<u>1a</u>	<u>2c</u>	DMF, 25, 28	<u>3ac</u> , 87, 74:26	-	-	-	
6	<u>1a</u>	<u>2c</u>	THF, 80, 11	<u>3ac</u> , 63, 68:32	-	-	-	
7	<u>1b</u>	<u>2a</u>	MeCN, 25, 26	<u>3ba</u> , 81, -	-	-	171.35	
8	<u>1b</u>	<u>2c</u>	MeCN, 25, 25	<u>3bc</u> , 89, 63:37	major	2.58	27.16	175.81
					minor	2.16	24.56	176.84
9	<u>1c</u>	<u>2c</u>	MeCN, 25, 24	<u>3cc</u> , 94, 73:27	major	2.44	26.07	176.14
					minor	2.10	24.07	177.98

^aMeCN=Acetonitrile, DMF=N,N-Dimethylformamide, THF=Tetrahydrofuran. ^bThe two alphabetical suffixes for compound 3 refer to those of nitron (1) and ketene silyl acetal (2) in this order. ^cDetermined by proton NMR integration of a crude product. ^dM α refers to methylene or methyl group at C α (see text and Newman projection depicted in the previous page). ^eObtained in CDCl₃ as solvent with tetramethylsilane as an internal standard. ^f δ Values for ester carbonyl.

On the other hand, the carbonyl absorptions of the major isomers(3-E) of 3ac, 3bc, and 3cc would show up at higher field than those of minor ones for the same reason. This seems exactly what is observed in ¹³C-NMR spectra as shown in the Table; $\Delta\delta(^{13}\text{C})=1.39$ for 3ab, 1.30 for 3bc and 1.84 for 3cc. It should be noted here that the carbonyl absorptions of all minor isomers of 3ac, 3bc and 3cc appear at lower field than those of major isomers, whereas that of the minor isomer of 3ab appears at higher field than that of the corresponding major isomer in complete agreement with the aforementioned discussion.

It is clear that the new carbon-carbon bond forming reaction is greatly facilitated by silicon-oxygen affinity compared with ordinary 1,3-dipolar cycloaddition reaction; the former requires much milder reaction conditions(room temperature, about 24 h) than the latter(usually above 100°C, 10-24 h).⁷⁾ This implies that the activation energy required for the carbon-carbon bond formation may be reduced to a significant extent by the transfer of the silyl group to the nitron oxygen highly activated as a nucleophile. Since the concerted ene-type reaction involving 8π seven-

membered cyclic transition state is symmetry-forbidden,¹¹⁾ a stepwise mechanism may be more likely. An attractive two step mechanism is illustrated in the following scheme; initial silicon transfer from ketene silyl acetal (2) to nitron (1) would generate an N-siloxyiminium ion (4) and an ester enolate (5) which would then rapidly combine to form product 3.



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