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Amination of Chiral β-Silylated Silyl Ketene Acetals by (Ethoxycarbonyl)nitrene

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Abstract: The reaction of β-silylated silyl ketene acetals with (ethoxycarbonyl)nitrene, generated by photolysis of N_3CO_2Et, produces β-silylated *N*-(ethoxycarbonyl)-α-amino esters. The prevailing attack of the electrophile was always *anti* to the β-silyl group in the substrates containing variously substituted chiral β-carbon atoms. © 1997 Elsevier Science Ltd.

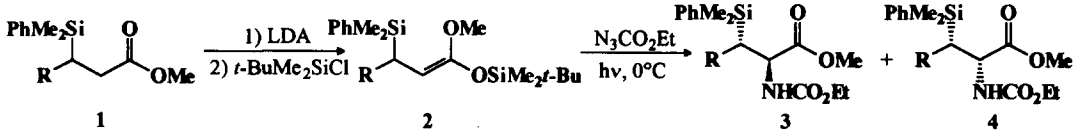
In recent years we reported that (Ethoxycarbonyl)nitrene reacts with silyl ketene acetals to produce *N*-(ethoxycarbonyl)-α-amino esters.[1] The interest on this class of compounds, precursors of biologically and pharmacologically active molecules, encouraged us to develop a stereoselective introduction of the amino group in silyl ketene acetals. In the presence of a resident chiral β-carbon it was possible to obtain good diastereoselectivity and to improve it with the contemporary use of a chiral auxiliary.[2]

The behaviour of silyl ketene acetals bearing a dimethylphenylsilyl group on the chiral β-carbon in reactions with several carbon electrophiles was recently studied by Fleming and co-workers[3]. They always obtained an attack *anti* to the dimethylphenylsilyl group, synthesising alkyl derivatives in high yields and with good stereoselectivity.

The lack of studies in the use of β-silylated silyl ketene acetals with nitrogen electrophiles urged us to analyse their behaviour in reactions with (ethoxycarbonyl)nitrene in order to obtain different β-silylated *N*-(ethoxycarbonyl)-α-amino esters, precursors of β-hydroxy-α-amino acids. For this purpose we considered compounds **2a-e**, carrying different groups on the chiral β carbon atom to investigate whether the dimethylphenylsilyl group has any effect on stereoselectivity of the amination reaction with (ethoxycarbonyl)nitrene.

All substrates were prepared from the β-silyl esters **1a-e**, derived from the corresponding α,β-unsaturated compounds[4] according to the method described by Fleming[5] to obtain the β-silylated *E*-trimethylsilyl ketene acetals, using *t*-$BuMe_2SiCl$ instead of Me_3SiCl.

The reactions of **2a-e** with (ethoxycarbonyl)nitrene, generated by photolysis of ethyl azidoformate (N_3CO_2Et),[6] produced the β-silylated *N*-(ethoxycarbonyl)-α-amino esters *anti* **3a-e** and *syn* **4a-e** which were isolated by flash chromatography with the yields and diastereomeric ratios reported in Table.



1 2 3 4

Table. Reactions of N_3CO_2Et with β-silylated Silyl Ketene Acetals.

substrate	R	ratio 3 : 4	yield, %[a]
2a	Me	76 : 24	37
2b	Ph	81 : 19	38
2c	heptyl	66 : 34	44
2d	cyclohexyl	62 : 38	36
2e	*tert*-butyl	58 : 42	39

a. The yields refer to the starting β-silyl esters.

All the major diastereomers were separated with more than 90% purity.[7] On the basis of the ^{1}H NMR we think that the ratio of the diastereomers derivatives is always in favour of the products **3**, derived from the attack *anti* to the dimethylphenylsilyl group. The stereoselectivity decreased with the increase of the steric bulk of the substituents.

This confirms the prevailing steric effect of alkylsilyl group in this kind of reactions and is in agreement with the results obtained by Fleming with an analogous series of β-silylated lithium enolates in reactions of methylation.[5]

Efforts to extend the use of this procedure are still in progress and enclose the conversion of the dimethylphenylsilyl into hydroxy group[8] in order to obtain highly functionalized *N*-protected α-amino esters.

General procedure: A solution of ethyl azidoformate (1 ml) (CAUTION! It is toxic and can decompose explosively at 160°C) and silyl ketene acetal **2** (3.5 mmol), syntesised from the β-silyl ester **1**, LDA and *t*-$BuMe_2SiCl$ according to the reported procedure,[5] directly used in dry pentane after filtration through celite and concentration to 8 ml, was photolysed at 0°C in an argon atmosphere, in a quartz vessel, using a medium pressure Hanovia PCR lamp (100 W) until the complete disappearance of the $\nu_{C=C}$ in the IR spectrum. After removal of the solvent *in vacuo*, the crude reaction mixture was chromatographed on silica gel (flash chromatography, hexane : ethyl acetate = 95 : 5) giving the pure diastereomers **3** and **4** in the reported yields and diastereomeric ratios.

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7. As representative example: **3a**: **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.52-7.30 (5H, m, Ph), 4.92 (1H, d, *J* = 10 Hz, N*H*), 4.53 (1H, dd, *J* = 4 and 10 Hz, C*H*NH), 4.08 (2H, q, OCH_2), 3.63 (3H, s, OCH_3), 1.60 (1H, m, SiC*H*), 1.18 (3H, t, CH_3CH_2), 0.87 (3H, d, CH_3CH), 0.34 (3H, s, $SiCH_3$), 0.32 (3H, s, $SiCH_3$). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 172.98 (*C*O), 156.02 (*C*O), 137.71 (*C* Ph), 135.83 (*C*H Ph), 129.14 (*C*H Ph), 127.84 (*C*H Ph), 60.95 (OCH_2), 56.24 (*C*HNH), 51.76 (OCH_3), 30.85 (SiCH), 14.62 (CH_3), 14.50 (CH_3),-4.15 ($SiCH_3$), -4.20 ($SiCH_3$). **IR:** (CCl_4) cm^{-1} 3420 (ν_{NH}), 1720 ($\nu_{C=O}$);. **4a**: **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.52-7.28 (5H, m, Ph), 5.11 (1H, d, *J* = 9 Hz, N*H*), 4.39 (1H, dd, *J* = 6.5, 9 Hz, C*H*NH), 4.04 (2H, q, OCH_2), 3.57 (3H, s, OCH_3), 1.62 (1H, m, SiC*H*), 1.14 (3H, t, CH_3CH_2), 0.93 (3H, d, CH_3CH), 0.33 (3H, s, $SiCH_3$), 0.30 (3H, s, $SiCH_3$), **IR:** (CCl_4) cm^{-1} 3420 (ν_{NH}), 1720 ($\nu_{C=O}$);.
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