Tetrahedron Letters,Vol.23,No.30,pp 3011-3014,1982 0040-4039/82/303011-04$03.00/0
Printed in Great Britain

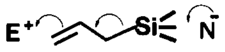
Unexpected Regiochemistry in the Reaction of Some γ-Trimethylsilylated 3-Dialkylamino-crotonate Esters with Carbonyl Electrophiles.

T.H. Chan* and G.J. Kang,

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6.

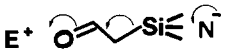
Summary: 4-Trimethylsilyl-3-dialkylaminocrotonate esters (4) react with a number of carbonyl electrophiles and titanium tetrachloride to give products with substitution at γ-position. A dynamic equilibrium of 4 and its O-silyl isomer 16 is proposed to explain the regiochemistry.

Much of the recent interest in the use of allylsilanes (1) and enol silyl ethers (2) in organic synthesis are due, to a large extent, the regiospecific nature of their reactions with electrophiles[1,2]. On the other hand, α-trimethylsilylcarbonyl compounds (3) are in general less reactive towards electrophiles than the isomeric enol silyl ethers (2). It was therefore surprising to us when we found that some γ-trimethylsilylated 3-dialkylaminocrotonate esters (4) reacted with a number of carbon electrophiles to give substitution products 5 at the γ-position instead of the α-position (equation 1). The regiochemistry is the more puzzling since the presence of the 3-amino group should favor reaction at the α-site as well.

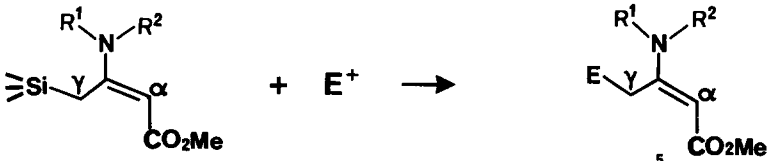


1

2



3

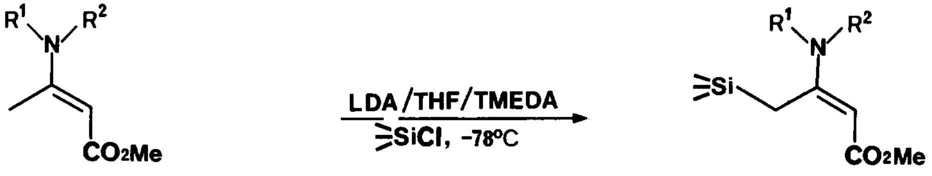


4 5 (1)

a: $R^1R^2 = -(CH_2)_4-$

b: $R^1R^2 = -(CH_2CH_2OCH_2CH_2)-$

Compounds 4 were prepared by the following procedures: To a solution of lithium diisopropylamide (24 mmol) in 50 ml THF containing tetramethylethylenediamine (3.2 ml) at -78°, methyl 3-dialkylaminocrotonate (6, 20 mmol) was added. The mixture was stirred for 0.5 h, and then quenched with trimethylchlorosilane. Work up by the usual procedure gave 4 in 90% yield of > 95% purity by ^{1}H NMR. They could be distilled in vacuo without decomposition.



6

4

That 4 was the result of C-silylation and not O-silylation was evident from spectroscopic analysis. Thus, in the infrared spectra of both 4a and b, the carbonyl absorption at 1670 cm^{-1} was very strong. In the ^{1}H NMR, there was only one vinyl proton. ^{13}C NMR showed two olefinic carbons and one carbonyl carbon. Furthermore, 4 exist as one geometrical isomer[3]. By noting the similarity of the ^{1}H and ^{13}C NMR between 4 and 6 which is known to have the E geometry[4], 4 is assigned to have the E geometry as well.

When 4 was reacted with benzaldehyde and equivalent amount of titanium tetrachloride in CH_2Cl_2, compound 7 was obtained in moderate yield[5]. (See Table).

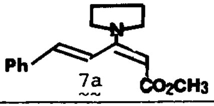
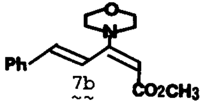
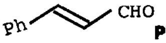
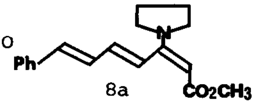
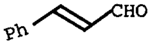
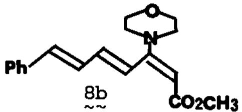
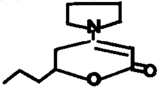
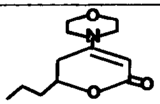
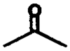
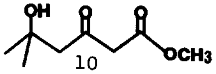
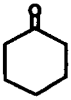
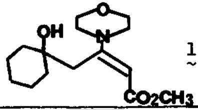
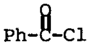
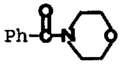
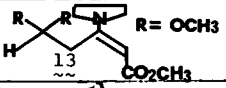
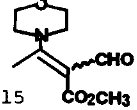
Condensation of 4 with cinnamaldehyde under similar conditions gave the poly-unsaturated esters 8 in good yields. Only one geometrical isomer of 8 was obtained, and was assigned to be 2E,4E,6E- from the ^{1}H NMR spectra.

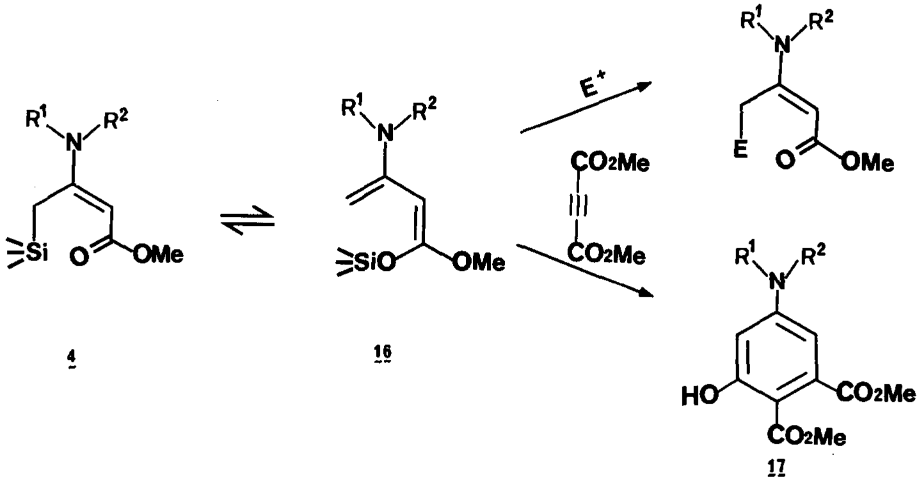
With butanal, condensation reaction gave the δ-lactone 9 in place of olefinic products.

There are however differences in the reactivity between 4a and 4b. It seems that the morpholino- compound 4b is more reactive than the pyrrolidino-compound 4a. Thus, with the less reactive ketone electrophiles, only 4b gave the corresponding substitution products 10 and 11. On the other hand, with the more reactive electrophiles such as benzoyl chloride or trimethyl orthoformate, 4a reacted under titanium tetrachloride activation to give 12 and 13 respectively as a result of reactions at γ-position. Benzoyl chloride reacted with 4b and $TiCl_4$ to give the benzamide 14 as the only identifiable product in 61% yield. Under identical conditions, 4b and trimethyl formate gave product 15, the only example of α-reaction. It seems that enamine reactivity finally manifests itself on reaction with the more reactive electrophiles in the case of 4b.

It remains to explain the regiochemistry observed in equation 1. In view of the E-geometry of 4 and the known ease of 1,5-migration of silyl group[6], a reasonable pathway may be that 4 exists as a dynamic equilibrium of $4 \rightleftharpoons 16$ but with 16 present only in minor concentration. In reactions with electrophiles (E^+) however, 16 selectively reacted to give the γ-product. In support of this explanation, when a mixture of 4a and dimethyl acetylenedicarboxylate was heated in benzene, the diene 16 was indeed trapped as the Diels-Alder adduct 17 which was isolated in 57% yield as a crystalline compound, m.p. 128-130°C.

Table: Reaction of methyl 4-trimethylsilyl-3-dialkylaminocrotonate with carbonyl electrophiles.

Comp. 4	Electrophile E^+	Product	% Yield isolated	^{1}H nmr ($CDCl_3$)
4a	PhCHO	 7a	68	1.95(m,4H), 3.33(m,4H), 3.60(s,3H), 4.60(s,1H), 6.66(d,J = 17 Hz,1H), 7.2-7.6(m,6H).
4b	PhCHO	 7b	60	307(m,4H), 3.56(s,3H), 3.70(m,4H), 4.84(s,1H), 6.75(d, J=16 Hz,1H), 7.1-7.5(m,6H).
4a		 8a	81	1.93(m,4H), 3.33(m,4H), 3.60(s,3H), 4.57(s,1H), 6.54(d, J=16 Hz,1H), 6.50(dd, J=16 and 6 Hz,1H), 6.86(d, J=16 Hz,1H), 6.84(dd, J=16 and 6 Hz,1H), 7.12-7.34(m,5H).
4b		 8b	83	3.10(m,4H), 3.63(s,3H), 3.73(m,4H), 4.90(s,1H), 6.62(d, J=16 Hz,1H), 6.63(dd, J=16 and 6 Hz,1H), 6.90(dd, J=16 and 6 Hz,1H), 6.97(d, J=16 Hz,1H), 7.16-7.38(m,5H).
4a	$CH_3CH_2CH_2CHO$	 9a	53	0.73-1.77(m,7H), 1.93(m,4H), 2.40(d, J=8 Hz,2H), 3.27(m,4H), 4.2(m,1H), 4.53(s,1H).
4b	$CH_3CH_2CH_2CHO$	 9b	49	0.8-1.9(m,7H), 2.40(d, J=7 Hz,2H), 3.23(m,4H), 3.77(m,4H), 4.33(m,1H), 4.87(s,1H).
4b		 10	44	1.30(s,6H), 2.73(s,2H), 3.23(b,1H), 3.50(s,2H), 3.73(s,3H).
4b		 11	56	1.57(m,10H), 3.07(s,2H), 3.23(m,4H), 3.50(b,1H), 3.68(s,3H), 3.77(m,4H), 5.03(s,1H).
4a	 $\mathrm{Ph\overset{\overset{O}{\|}}{C}Cl}$	 12	44	1.93(m,4H), 3.30(m,4H), 4.87(d, J=2 Hz, 1H) 6.20(d, J=2 Hz,1H), 7.17-7.8(m,5H).
4b	 $\mathrm{Ph{-}\overset{\overset{O}{\|}}{C}{-}Cl}$	 14	61	
4a	HC(OMe)$_3$	 13	64	1.90(m,4H), 3.20(d, J=6 Hz,2H), 3.40(s,6H), 3.60(s,3H), 4.47(s,1H), 4.63(t, J=6 Hz,1H).
4b	HC(OMe)$_3$	 15	50	2.23(s,3H), 3.30(m,4H), 3.70(s,3H), 3.63 (m,4H), 7.57(s,1H). Ir(film): 1690 and 1640 cm^{-1}.



The unexpected regiochemistry has therefore a rational basis. It is also clear that 4, with its array of reactive functional groups, can be quite useful as synthetic intermediates. We shall report on this application in organic synthesis in due course.

Acknowledgement:

We thank NSERC of Canada and the Ministry of Education, Government of Quebec for financial support. G.J.K. also thanks the Government of the Peoples' Republic of China for a scholarship.

References and Footnotes

1. T.H. Chan and I. Fleming, Synthesis, 761 (1979).
2. J.K. Rasmussen, Synthesis 91 (1977).
3. Spectroscopic data of 4a: Ir(film, cm^{-1}) 1665, 1545; ^{1}H Nmr (CDCl$_3$,δ) 0.1 (s,9H), 1.93(m,4H), 2.73(s,2H), 3.30(m,4H), 3.60(s,3H), 4.47(s,1H); 4b: Ir(film, cm^{-1}) 1675, 1560; ^{1}H Nmr (CDCl$_3$,δ) 0.1(s,9H), 2.73(2,2H), 3.20(m,4H), 3.60(s,3H), 3.73(m,4H), 4.73(s,1H); ^{13}C Nmr (CDCl$_3$,δ) -0.9, 19.5, 47.1, 50.2, 66.6, 86.2, 165.7, 169.5.
4. A.G. Sanchez and J. Bellanato, J. Chem. Soc. Perkin II, 1561 (1975).
5. Experimental procedure: To a mixture of benzaldehyde (1 mmol) and titanium tetrachloride (1 mmol) in 3 ml of CH$_2$Cl$_2$ at -78° was added 4 (1 mmol). The mixture was stirred for 3 hrs at -78°, then overnight at room temperature. Concentrated aqueous sodium bicarbonate solution was added. The organic layer was dried (MgSO$_4$), filtered and evaporated to give product 7 which could be purified by column chromatography on silica gel.
6. I.K. Kuznezowa, K. Rühlmann and Gründemann, J. Organometal. Chem., 47, 53 (1973).

(Received in USA 24 March 1982)