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SILICON-DIRECTED SELECTIVE GAMMA SUBSTITUTION OF AN α,β-UNSATURATED ESTER

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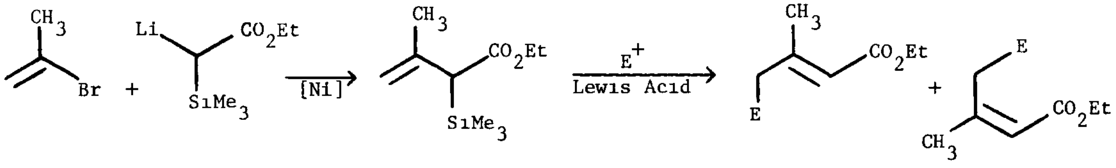
Abstract: Ethyl 3-methyl-2-trimethylsilyl-3-butenoate (3) undergoes reaction selectively at carbon 4, upon treatment with a Lewis acid and carbonyl compounds, acetals/ketals, acid chlorides, and chloromethyl phenyl sulfide. This overall conversion represents a highly selective gamma substitution on an α,β-unsaturated ester.

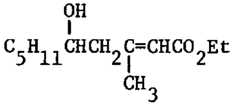
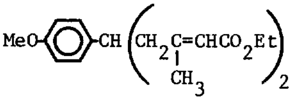
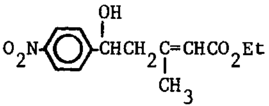
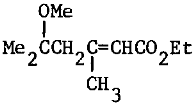
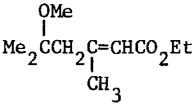
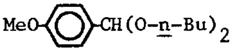
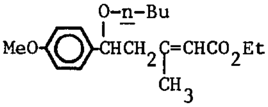
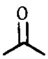
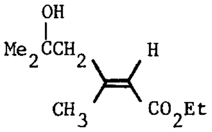
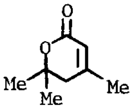
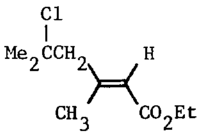
Lithium dienolates derived from α,β-unsaturated carbonyl compounds undergo alkylation predominantly at the α-carbon[1,2]. Because, in many cases, the gamma-substituted product would be more useful synthetically, numerous attempts have been made to derive a general method for gamma-selective alkylation of dienolates. We have demonstrated selective gamma-alkylation of copper dienolates of α,β-unsaturated esters[3] and acids[4], and Mukaiyama[5] and Fleming[6] have reported that O-silyl dienyl ethers derived from α,β-unsaturated carbonyl compounds undergo substitution with high gamma-selectivity, although α-substitution is observed in some cases. We felt that placement of a silyl group at the α-position of a β,γ-unsaturated ester might ensure that the attack of an electrophile would proceed with very high gamma-selectivity, because of the known gamma directing effect of allylsilanes. In this report, we describe the synthesis of ethyl 3-methyl-2-trimethylsilyl-3-butenoate (3) and report the clean gamma-selective substitution of this ester via Lewis acid-mediated reaction with electrophiles.

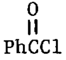
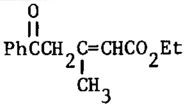
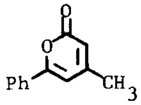
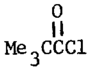
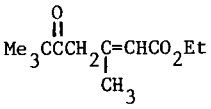
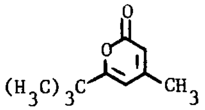
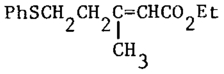


1 + 2 → 3 → 4E + 4Z

The silyl ester 3 was prepared via a nickel-catalyzed reaction of 2-bromopropene (1) with the lithium enolate of ethyl trimethylsilylacetate (2), according to the method of Rathke[7]. The product was obtained as a colorless oil in 62% yield after distillation (78° C at 44 Torr) ^{1}H NMR δ (CCl_4) 4.83-4.70 (m, 2H), 4.03 (q, J=7.2 Hz, 2H), 2.78 (s, 1H), 1.78 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 0.07 (s, 9H), IR (CCl_4) 1772, 1637, cm^{-1}; Mass spectrum (10 eV) $^m/e$ (rel. int.) 200 (M^+, 5). In contrast to the isomeric dienol silyl ether systems, the ester

Table 1. Reaction of Ethyl 2-Trimethylsilyl-3-Butenoate, **3**, With Various Electrophiles.[a]

	Electrophile	Promoter	Temp (°C) Time (h.)	Products (ratio)[b]	Yield (%) (crude, purified[c])
1	$C_5H_{11}CHO$	$TiCl_4$	−78°, 12 h., −30°, 3 h.	 $C_5H_{11}\overset{OH}{CH}CH_2\underset{CH_3}{C}=CHCO_2Et$ (E.Z = 92·8[d])	86, 22[e]
2		$TiCl_4$	−78°, 24 h.	 (E,E:E,Z = 82·18)	72, *[f]
3		$TiCl_4$	−78°, 16 h.	 (E = >95)[g]	89, 65
4	$Me_2C(OMe)_2$	$TiCl_4$	−78°, 22 h., 0°, 8 h.	 $Me_2\overset{OMe}{C}CH_2\underset{CH_3}{C}=CHCO_2Et$ (E:Z = 91:9)	∿100,[h] *[f]
5	$Me_2C(OMe)_2$	TMSOTf	−78°, 26 h.	 $Me_2\overset{OMe}{C}CH_2\underset{CH_3}{C}=CHCO_2Et$ (E Z = 86 14)	∿100, 83
6		TMSOTf	−78°, 2 h.	 (E·Z = 97.3)	∿100, 81
7		$TiCl_4$	r.t., 24 h.	 (76)  (10)  (14)	71, *[f]

	Electrophile	Promoter	Temp (°C) Time (h.)	Products (ratio)[b]		Yield (%) (crude, purified[c])
8	 $\overset{O}{\overset{\parallel}{PhCCl}}$	$TiCl_4$	r.t., 33 h.	 $PhC(=O)CH_2C(CH_3)=CHCO_2Et$	(28)[i]	∿100, 49
					(72)	
9	 Me_3CCCl (C=O)	$TiCl_4$	r.t., 23 h.	 $Me_3CC(=O)CH_2C(CH_3)=CHCO_2Et$	(82)[i]	86, 58
					(18)	
10	$PhSCH_2Cl$	$TiCl_4$	0°, 24 h.	 $PhSCH_2CH_2C(CH_3)=CHCO_2Et$ (E:Z = 44 56)		∿100, 52

a = In a typical procedure, 1.1 equivalents of an electrophile is added to a solution of $TiCl_4$ (0.181 mL, 1.65 mmol, 1.1 eq.) or TMSOTf (17 mg, 0.05 eq.) in 2 mL of CH_2Cl_2 at -78°C, followed by a solution of 3 (301 mg, 1.5 mmol, 1.0 eq.) in 2 mL of CH_2Cl_2. The reaction was stirred at -78°C for 15 minutes, then stirred under the conditions stated in the table. All new compounds exhibited ^1H NMR, IR, and MS consistent with the assigned structures and gave satisfactory elemental analysis. b = Determined by GLC. c = Sum of yields of all components after isolation by chromatography. d = The Z isomer was isolated as the dihydropyrone analogous to that obtained in entry 10 e = No attempt was made to maximize yield. f = Not determined. g = Only one isomer detected by NMR. h = Crude material contained s.m. and other unidentifiable components. i = Mixture of isomers containd a non-separable, unidentified component.

3 is quite stable and can be handled in an open atmosphere. To examine the scope of reaction of ester 3, a variety of electrophiles were allowed to react with 3 in the presence of titanium tetrachloride ($TiCl_4$)[8] or trimethylsilyl trifluoromethanesulfonate (TMSOTf).[9] The results are summarized in Table 1.

Facile, gamma-selective reaction of 3 was observed with aldehydes and ketones (entries 1-3 and 7) ketals and acetals (entries 4-6), acid chlorides (entries 8 and 9), and chloromethyl phenyl sulfide (entry 10). The ester 3 appears to have moderate reactivity, so reactions proceed at reasonable rates between -78°C and room temperature, and products could be isolated conveniently by preparative thin layer chromatography. In all cases, only products resulting from attack of the electrophile on the gamma carbon (4E and 4Z) were observed, no α-substituted products could be detected by GLC or ^1H NMR. Chloromethyl phenyl sulfide, an electrophile shown to give low γ α ratios when reacted with trimethylsilyl dienol ethers,[6,10] also gives clean gamma-selectivity with ester 3, albeit with lower stereoselectivity (entry 10, E Z ∿1 1) than is observed in most cases (entries 1-7, E Z ∿9 1).

The products isolated from the reactions of 3 with aldehydes, ketones, and acetals promoted by $TiCl_4$ appeared, in some cases, to arise from subsequent conversion of the initially-formed products (chlorination (entry 7) and bis-substitution (entry 2)[11]). In contrast, these further transformations were not observed with acetals and TMSOTf as catalyst. Products arising from the reaction of 3 with acid chlorides or aldehydes and ketones were often found partially cyclized to the δ-keto-α-pyrones (entries 8 and 9) or δ-hydroxy-dihydro-α-pyrones (entry 7), respectively. In the former case, the readily-enolizable δ-ketoenoates can be converted to the α-pyrones in high yield by treatment with NaOEt.

The method we have described provides a means for a highly regioselective, silicon-directed gamma-substitution of α,β-unsaturated esters, with high stereoselectivity for the E-isomer. Further investigations of the utility of this and other α-silyl-β,γ-unsaturated esters are currently underway.

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(10) Although Mukaiyama and Ishida[5] did not report any α-alkylated products from the reaction of acetals with silyl dienol ethers of aldehydes, Fleming[6] postulated that an electron-donating group on C-1 apparently increases reactivity at the α-carbon in order to explain the observance of α-products with O-silylated dienolates of ketones and esters. These observations serve to amplify the utility of our method, since no α-substitution was observed in any case with the ester 3.

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