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O-SILYLATED KETENE ACETAL CHEMISTRY[1]; β-(ALKOXYCARBONYL)METHYL O-SILYL ENOLATES, USEFUL SYNTHONS FOR α-SUBSTITUTED-β-(ALKOXYCARBONYL)METHYLALKANONES

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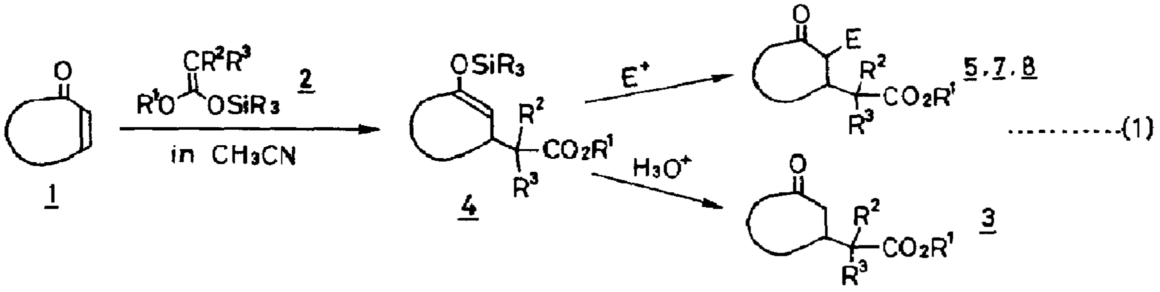
Summary: Conjugate addition of O-silylated ketene acetals 2 to α,β-unsaturated carbonyl compounds 1 in acetonitrile gave quantitative yields of the correspondin β-(alkoxycarbonyl)methyl O-silyl enolates 4. Site specific electrophilic substitutions of 4 yielded the corresponding α-substituted β-(alkoxycarbonyl)-methylalkanones 5, 7, and 8.

We report here a new effective procedure for the regiospecific assembly of α-substituted β-(alkoxycarbonyl)methylalkanones 5, 7, and 8 through β-(alkoxycarbonyl)methyl O-silyl enolates 4. The procedure is illustrated in Scheme 1.



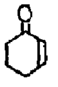
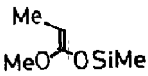
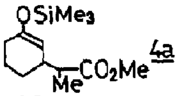
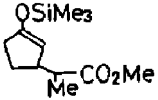
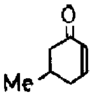
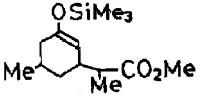
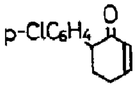
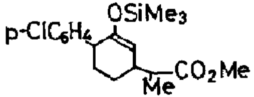
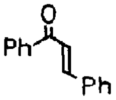
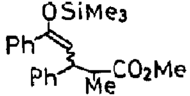
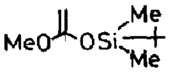
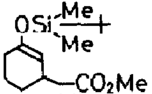
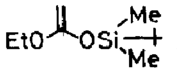
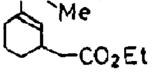
It involves the conjugate addition of O-silylated ketene acetals 2 to α,β-unsaturated carbonyl compounds 1, followed by reaction with electrophile to the O-silylated adducts 4.

Preparation of β-(Alkoxycarbonyl)methyl O-Silyl Enolates 4

The Michael addition of O-silylated ketene acetals 2 with α,β-unsaturated carbonyl compounds 1 was known not to proceed.[2] Recently, Mukaiyama and co-workers have succeeded in reacting the acetals 2 with 1 by an activation method using titanium tetrachloride,[3,4] which gives β-(alkoxycarbonyl)methylalkanones 3. We now found that the use of acetonitrile as a solvent can greatly enhance the reactivity of 2 toward 1 without any catalyst to give almost quantitative yields of the corresponding O-silylated Michael adducts 4[5] in place of their hydrolyzed ketones 3. The success of these procedures depends crucially on the use of acetonitrile as a solvent. Thus, when the reaction was performed in other solvents such as ether, tetrahydrofuran, benzene, carbon tetrachloride, and methylene chloride, no satisfactory addition occurred.

A typical experimental procedure for the preparation of β-(alkoxycarbonyl)-methyl O-silyl enolates 4 is as follows (entry 1). To a stirred solution of cyclohexenone (1a, 12.5 mmol) in dry acetonitrile (11 ml) was added ketene methyl trimethylsilyl acetal (2a, 12.5 mmol). After stirring at 55° for 2h, a small amount of 2a (0.2 mmol) was added every 30 min for 1.5h to complete the reaction. The reaction mixture was concentrated *in vacuo* and distilled to give the pure O-silyl enolate 4a [b.p. 140-145°/2.7 mmHg, δ (CCl_4) ppm: 0.17 (s, 9H, Me_3Si), 1.08 (d, 3H, CH_3CH), 0.83-2.70 (m, 8H, $CH_2\times3$ and $CH\times2$), 3.59 (s, 3H, OCH_3), and 4.58 (d, 1H, CH=), ν_{max} (CCl_4) 1740 and 1660 cm^{-1}, m/e 256 (M^+), *Anal.* Calcd for $C_{13}H_{24}O_3Si$: C, 60.88; H, 9.45. Found: C, 61.02; H, 9.60]. Hydrolysis of 4a by the treatment with HCl-ether gave methyl 2-(3-oxocyclohexyl)propionate 3a, which was identified with an authentic specimen.[6]

In a similar manner, several β-(alkoxycarbonyl)methyl O-silyl enolates 4 were obtained[7] in excellent yields by the reaction of O-silylated ketene acetals 2[8] and α,β-unsaturated carbonyl compounds 1. All these O-silyl enolate structures assigned to the products 4 are consistent with their IR, NMR, and Mass spectral data. A characteristic ^1H-NMR resonance at δ 4.38-5.4 of vinyl proton of an O-

Entry	Enone (1)	Ketene acetal (2)	Product[a] (4)	Reaction Conditions	Yield[b] (%)	$\nu_{max}(CCl_4)$ cm^{-1}
1	 1a	 2a	 4a	55°, 4h	96	1735, 1660
2				55°, 4h	98	1735, 1640
3				55°, 5h	96	1740, 1665
4				55°,22h	99	1740, 1660
5				55°, 8h	99	1740, 1645
6		 2b		55°,12h	90	1740, 1665
7		 2c		55°,12h	90	1730, 1660

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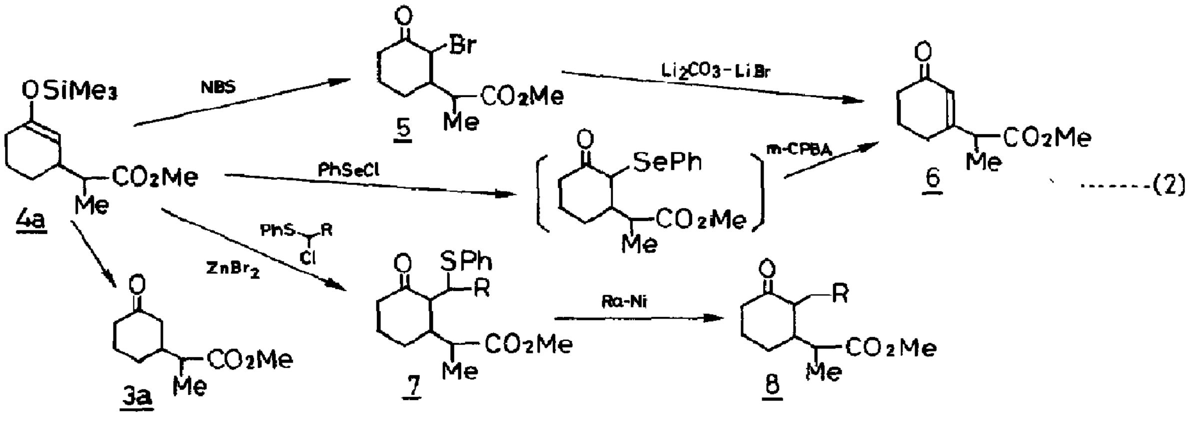
a) All these products gave satisfactory microanalyses: C ±0.37%; H ±0.29%.
b) The purity of the products was checked by G.L.C. and T.L.C.

silyl enolate and an IR absorption at 1730-1740 cm^{-1} of an ester moiety were observed. The results are summarized in the Table. These ketene acetals are found to be valuable equivalents of ester enolates in the Michael reaction.

Introduction of α-Substituent to the β-(Alkoxycarbonyl)methyl O-Silyl Enolates 4

Site specific attack of electrophile on the α-position of β-(alkoxycarbonyl)methyl O-silyl enolates 4 was established as outlined in Scheme 2. Strongly active electrophile[9] such as N-bromosuccinic imide (NBS) or phenylselen chloride readily reacts with 4a at room temperature for a short time in a normal solvent without catalyst. In the case of weakly active electrophile, anhydrous Lewis acid is required as shown in the α-alkylation of 4a.



……(2)

Treatment of 4a (11 mmol) in dry acetonitrile (11 ml) with NBS (11.4 mmol) at room temperature for 15 min under argon gave a 66% yield of methyl 2-(2-bromo-3-oxocyclohexyl)propionate 5 [a mixture of cis/trans (4/5), ν_{max} (CCl$_4$) 1730 cm^{-} cis-5: m/e 263 (M$^+$), trans-5: m/e 263 (M$^+$)], which was converted into methyl 2-(3-oxocyclohexenyl)propionate 6 [67% yield from cis-5, 68% yield from trans-5, ν_{max} (CCl$_4$) 1630, 1675, 1740 cm^{-1}, δ (CCl$_4$) ppm, 1.31 (d, 3H, J 7, CHC$\underline{H}_3$), 1.50-2.50 (m, 6H, CH$_2$×3), 3.23 (q, 1H, J 7, C$\underline{H}$CH$_3$), 3.62 (s, 3H, OCH$_3$), and 5.74 (s, 1H, CH=), m/e 182 (M$^+$), *Anal.* Calcd for C$_{10}$H$_{14}$O$_3$: C, 65.92; H, 7.74. Found: C, 65.54 H, 7.87] by the treatment with Li$_2$CO$_3$-LiBr in DMF (21 ml) at 100° for 5h. The same enone 6 was obtained by a similar reaction involving site-specific α-phenylselenylation of 4a (1.36 mmol) with PhSeCl (1.36 mmol) in methylene chloride (5 ml) at room temperature for 15 min followed by oxidative syn-elimination using m-chloroperbenzoic acid (2.7 mmol) in methylene chloride (15 ml). The over-all yield of 6 from 4a was 51%.

Introduction of primary alkyl group to the α-position of 4a was successful with the Lewis acid-prompted phenylthioalkylation using α-chloroalkylphenylsulfide, followed by the Raney-nickel desulfurization.[10] A catalytic amount of powdered anhydrous ZnBr$_2$ (ca. 20 mg) was added to a solution of α-chloroethylphenylsulfide (4.9 mmol) and 4a (3.7 mmol) in dry methylene chloride (7 ml).

The mixture was stirred at 15° for 30 min and concentrated *in vacuo* to give the crude α-phenylthioethyl ketone 7 [R=CH_3, a mixture of cis and trans isomers,[11] ν_{max} (CCl_4) 1740 and 1710 cm^{-1}, m/e 321 (M^+)], which was submitted to the reductive desulfurization with W-2 Raney-nickel in ethanol at room temperature for 30 min, followed by purification with column chromatography on silica gel (benzene:ethyl acetate=10:1 as eluents) to give methyl 2-(2-ethyl-3-oxocyclohexyl)propionate 8 [R=CH_3, a mixture of cis and trans isomers,[11] 41% over-all yield from 4a, ν_{max} (CCl_4) 1735 and 1705 cm^{-1}, m/e 212 (M^+), *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.51. Found: C, 67.82; H, 9.69].

References and Notes

1 For a previous paper in this series, see: Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, *Tetrahedron Lett.*, 1979, 4311.

2 The aldol condensation of O-silylated ketene acetals 2 with carbonyl compounds was also known not to proceed except for aromatic aldehydes. Only aromatic aldehydes can react with 2 under vigorous conditions (at 150° for 18h), giving moderate yields of the products; P.L. Creger, *Tetrahedron Lett.*, 1972, 79.

3 K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, 1975, 989.

4 K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, 1976, 163.

5 The Michael adducts could be trapped by the intermolecular transfer of the mobile trialkylsilyl substituent since the reaction was performed in the absence of Lewis acid.

6 D.K. Banerjee and P.S. Halwe, *J. Ind. Chem. Soc.*, 37, 669 (1960).

7 Following two approaches (i and ii) were examined for the preparation of 4a but failed: i) A conjugate addition of the lithio methyl propionate to cyclohexenone 1a at room temperature followed by the treatment with trimethylsilyl chloride [cf. A conjugate addition of alkyl group and subsequent silylation was reported: J.W. Patterson, Jr. and J.H. Fried, *J. Org. Chem.*, 39, 2506 (1974)] and ii) Direct silylation of the ketoester 3a into its O-silyl enolate 4a by the House's methods using LDA/trimethylsilyl chloride and triethylamine/DMF/trimethylsilyl chloride [H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, *J. Org. Chem.*, 34, 2324 (1969)].

8 The ketene acetals 2b and 2c were obtained in 72 and 71% yields, respectively according to the previously reported methods [C. Ainsworth, F. Chen, and Y.N. Kuo, *J. Organometal. Chem.*, 46, 59 (1972), M.W. Rathke and D.F. Sullivan, *Synth. Commun.*, 3, 67 (1973)]: 2b; b.p. 76-76.5°/24 mmHg, ν_{max} (CCl_4) 1645 cm^{-1}, δ (CCl_4) ppm 0,14 (s, 6H, Me_2Si), 0.93 (s, 9H, t-Bu), 2.95 (d, 1H, J 2.5, CH=), 3.10 (d, 1H, J 2.5, CH=), and 3.49 (s, 3H, OCH_3), m/e 188 (M^+). 2c; b.p. 67-68°/10 mmHg, ν_{max} (CCl_4) 1645 cm^{-1}, δ (CCl_4) ppm 0.16 (s, 6H, Me_2Si), 0.93 (s, 9H, t-Bu), 1.30 (t, 3H, J 7, CH_2CH_3), 2.92 (d, 1H, J 2.5, CH=), 3.08 (d, 1H, J 2.5, CH=), and 3.68 (q, 2H, OCH_2), m/e 202 (M^+).

9 The reaction of O-silyl enolates with strongly active electrophile such as PhSCl, PhSeBr or NBS in a normal solvent in the absence of catalyst has been reported; reaction with PhSCl; S, Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc. Chem. Commun.*, 1972, 946, reaction with PhSeBr; I. Ryu, S. Murai, I. Niwa, N. Sonoda, *Synthesis*, 1977, 874, reaction with NBS; R.H. Reuss and A. Hassner, *J. Org. Chem.*, 39, 1785 (1974).

10 I. Paterson and I. Fleming, *Tetrahedron Lett.*, 1979, 995, and references cited therein.

11 All efforts to separate the mixture failed.

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