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$GaCl_3$-Promoted Ethenylation of Silylated *β*-Dicarbonyl Compound with Silylethyne. Synthesis of Ethenylmalonate

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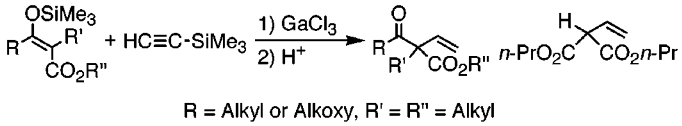
ABSTRACT



In the presence of $GaCl_3$, silyl enol ethers derived from α-substituted *β*-ketoesters or malonates are ethenylated at the α-carbon atom with trimethylsilylethyne in high yields. Ethenylmalonates can also be synthesized by this method.

Ethenylation reaction of *β*-dicarbonyl compounds is not well developed in organic synthesis. Reported methods include a stepwise ethenylation of α-substituted *β*-ketoesters using phenyl vinyl sulfoxide,[1] and a one-step method for an α-substituted malonate which reacts with ethyne at 150−180 °C under 15 atm.[2] These methods are of limited scope in terms of the active methylene compounds applicable. Another limitation is that they provide only ethenylated products not possessing the α-proton. It is expected that such compounds can readily isomerize to the thermodynamically stable conjugated carbonyl compounds. In this regard, it is interesting that two syntheses of ethenylmalonate possessing the α-proton were reported,[3,4] although we could not reproduce either synthesis. Previously, we developed the ethenylation reaction of the ketone silyl enol ether with trimethylsilylethyne in the presence of $GaCl_3$.[5] Described here is the ethenylation of silyl enol ethers derived from α-substituted *β*-ketoesters and malonates. A notable aspect of this method is that it can be applied to the synthesis of ethenylmalonates possessing the acidic α-proton.

To a mixture of trimethylsilylethyne (1.0 mmol), a *β*-ketoester silyl enol ether[6] (0.5 mmol), and *tert*-butyl

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[1] Koppel, G. A.; Kinnick, M. D. *J. Chem. Soc., Chem. Commun*. **1975**, 473. Also see, Oishi, T.; Takechi, H.; Ban, Y. *Tetrahedron Lett*. **1974**, *43*, 3757.

[2] Seefelder, M. *Liebigs Ann. Chem*. **1962**, *652*, 107.

[3] Torgashina, Z. I.; Naumchuk. A. L. *J. Gen. Chem., USSR* **1956**, *26*, 3353. The reaction could not be reproduced in our hands. We obtained only diethyl 2,4-di(ethoxycarbonyl)-3-methylpentanedioate, which may be formed by the conjugate addition of malonate to ethylidenemalonate.

[4] Adelman, R. L. U.S. 2,550,439; *Chem. Abstr*. **1951**, *45*, 8035. The reaction was also not reproducible, and the only product obtained was ethylidenemalonate.

[5] Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc*. **1999**, *121*, 4074.

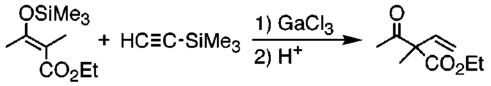
[6] (*E*)-Stereochemistry of the silyl enol ether is determined by NOE experiment.

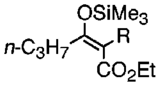
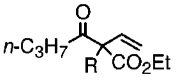
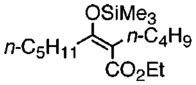
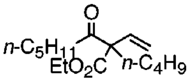
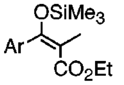
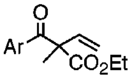
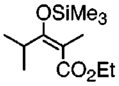
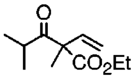
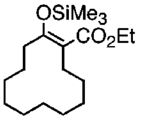
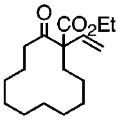
[7] Typical procedures for the ethenylation of malonate: Under an argon atmosphere, a solution of $GaCl_3$ (1.0 M, 6 mmol) in methylcyclohexane (6 mL) was added to a mixture of dipropyl malonate silyl enol ether (130 mg, 0.5 mmol) and trimethylsilylethyne (0.42 mL, 3 mmol) in methylcyclohexane (2 mL) at room temperature. After the mixture was stirred at the temperature for 5 min, THF (4 mL) was added to dissolve the insoluble materials. The mixture was cooled to −20 °C, and 12 M hydrochloric acid (10 mL) was added. After 30 min at −20 °C, water was added, and the acid layer was removed. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by neutral silica gel column chromatography (Kanto Chemical Co., Inc. 37561-79, hexane: ethyl acetate = 150−50:1) at −78 °C to give dipropyl ethenylmalonate (45 mg, 42%), which was accompanied by dipropyl (2-silylethenyl)malonate (17 mg, 12%). Dipropyl ethenylmalonate: ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (6H, t, $J = 7.8$ Hz), 1.67 (4H, sixtet, $J = 7.2$ Hz), 4.05 (1H, d, $J = 8.8$ Hz), 4.12 (4H, m), 5.29 (1H, d, $J = 16.0$ Hz), 5.32 (1H, d, $J = 10.4$ Hz), 6.07 (1H, ddd, $J = 16.0, 10.4, 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 22.0, 56.6, 67.2, 120.1, 129.8, 167.8. IR (neat) 1737, 1643 cm^{-1}. MS (EI) m/z 214 (M^+, 1%), 86 ($M^+ - 128$, 100%). HRMS Calcd for $C_{11}H_{18}O_4$: 214.1205. Found: 214.1198.

10.1021/ol015583b CCC: $20.00

alcohol (0.25 mmol) in methylcyclohexane was added $GaCl_3$ (2.0 mmol) in methylcyclohexane at 0 °C. After 15 s at the temperature, THF and 6 M sulfuric acid were added, and an α-ethenyl-β-ketoester was obtained in a high yield (Table 1). A small amount of α-silylethenyl-β-ketoester formed could be desilylated by the acid workup of the crude product. The carbon−carbon bond formation is very rapid at 0 °C and is completed within 15 s. The yield of the product increases in the presence of a small amount of *tert*-butyl alcohol. The organogallium compound generated in this reaction is insoluble in the nonpolar solvent, and THF is added to form a homogeneous solution. A broad scope of this method is shown by the reactions of acyclic and cyclic β-ketoester derivatives with (*E*)-stereochemistry.[6] In contrast, (*Z*)-silyl enol ether, for example that derived from 2-ethoxycarbonylcyclohexanone, is less reactive, and the ethenyl product is obtained in less than 20% yield. An attempted ethenylation of a ketoester lacking the α-substituent, ethyl 3-trimethylsiloxy-2-hexenoate, gives only the ethylidene product in 56% yield. The mechanism of the ethenylation involves carbogallation at the carbon−carbon triple bond, and the acid workup with 12 M DCl in D_2O gives the ethenylated β-ketoester-d_2 (Scheme 1).

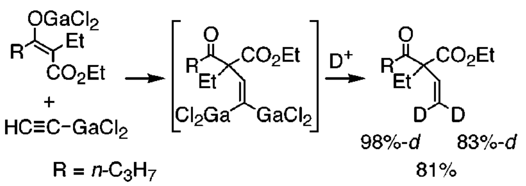
Table 1. Ethenylation of Silylated β-Ketoester with Silylethyne[a]



substrate	product	yield/%
		
R = Me		74 37[b]
R = Et		84
R = n-C_3H_7		85 83[c]
		92
		
Ar = C_6H_5		55
Ar = p-MeC_6H_4		72
Ar = p-FC_6H_4		65
		67
		88

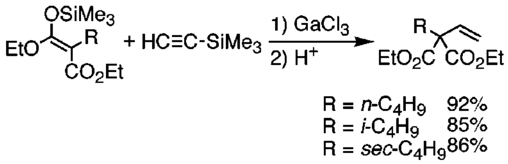
[a] See Supporting Information for typical procedures. [b] The reaction was carried out without *t*-BuOH. [c] The reaction was carried out in 5 mmol scale.

Scheme 1

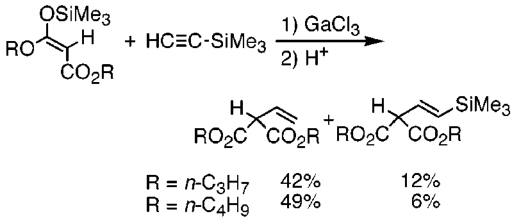


Ethenylation reaction of silyl enol ethers derived from alkylmalonates also takes place with trimethylsilylethyne at room temperature in 5 min (Scheme 2). Notably, the reaction of dipropyl malonate gives dipropyl ethenylmalonate in 42% yield, which is accompanied by dipropyl α-silylethenylmalonate (12%) (Scheme 3).[7] Careful quenching of the reaction at −20 °C and isolation by neutral silica gel column chromatography at −78 °C suppress the formation of the conjugated product in less than 3% yield. The ethenylmalonate exhibits the acidic α-proton at δ 4.05 by ^1H NMR. The compound is relatively insensitive to acid, and no isomerization is observed when treated with 2 M sulfuric acid in THF or 1% acetic acid in hexane at room temperature for 1 h. In contrast, rapid isomerization to the conjugate enoate takes place under basic conditions, even in 1% triethylamine−hexane at room temperature within 5 min.

Scheme 2



Scheme 3



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Supporting Information Available: Spectroscopic data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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