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Remote steric effects in the Sakurai reaction

Michael D. Groaning and A. I. Meyers *

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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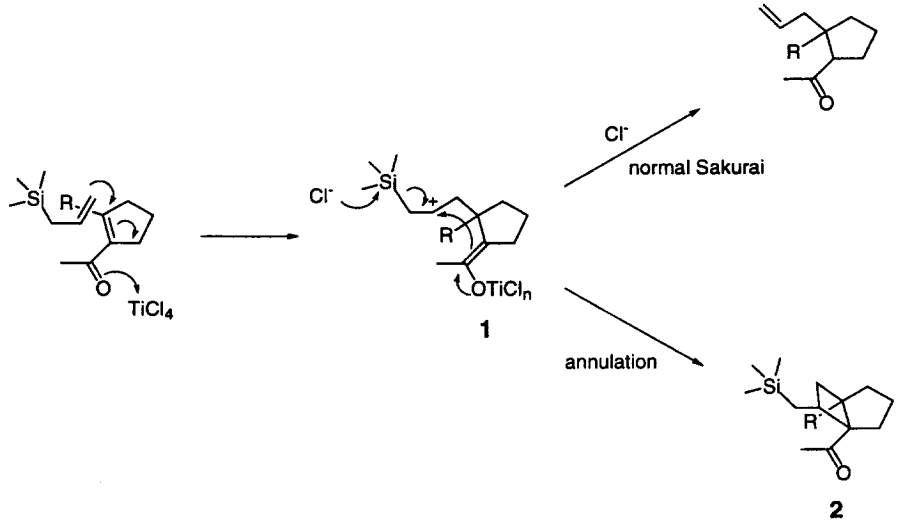
Abstract

A remote steric effect in the Sakurai addition to unsaturated esters containing small to large alkyl groups has been detected which leads to either cyclobutane or allyl adducts.

The Sakurai reaction has become a fundamental synthetic process in organic chemistry.[1] Shortly after its introduction, Santelli[2] observed a minor by-product (ca. 18%) resulting from the intramolecular reaction of the titanium enolate with the silicon stabilized β carbenium ion **1** (Scheme 1). The structure of the by-product was assigned as a trimethylsilylmethylcyclobutane based on spectroscopic data.



Scheme 1.

This cyclobutane by-product was later reported by several other groups[3] until the assignment was challenged in 1990. Additionally, Danheiser[4] demonstrated that there was a steric dependence on

* Corresponding author.

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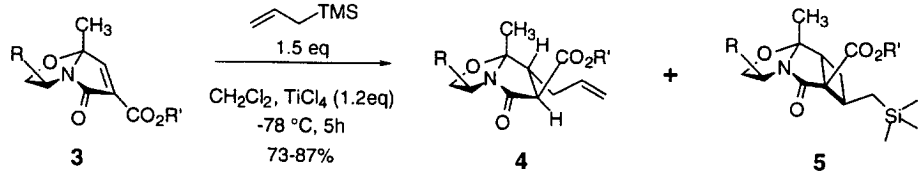
the Sakurai/annulation ratio with allyltriisopropylsilane giving the annulation product predominately whereas allyltrimethylsilane gave the expected Sakurai product. Our earlier studies in this area involved the addition of allyltriisopropylsilane to α,β-unsaturated bicyclic lactams **3** to obtain silylcyclobutanes and silylcyclopentanes.[5] During that study we found that the reaction produced silylcyclobutanes as the kinetic product and upon warming gave the more thermodynamically stable silylcyclopentane. Thus, it appeared that the duality in the reaction occured only when allyltriisopropylsilane was employed, but only normal Sakurai products were observed when allyltrimethylsilane was utilized.

Herein, we report an interesting and unexpected remote steric effect involved in the addition of allytrimethylsilane to α-carboalkoxy α,β-unsaturated bicyclic lactams **3a–c**. During our studies of allylsilane additions to the bicyclic lactam **3** it was observed that at low temperatures (i.e. –78°C) the allyltrimethylsilane was producing only the cyclobutane **5**. This cyclobutane was only appearing in substrates where the α-alkoxycarbonyl group was large (Scheme 2). In order to investigate this steric effect, a series of alkoxycarbonyl bicyclic lactams **3a–c** were subjected to identical Sakurai conditions and the products were isolated as illustrated (Scheme 2).

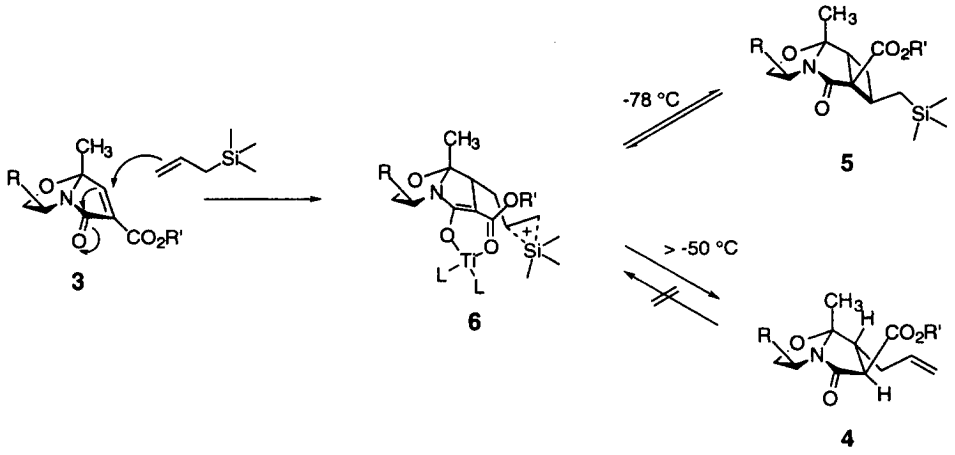


R	R'	4(%)	5(%)
3a *i*-Pr	Me	>95	<5
3b Ph	*i*-Pr	33	67
3c Ph	*t*-Bu	<5	>95

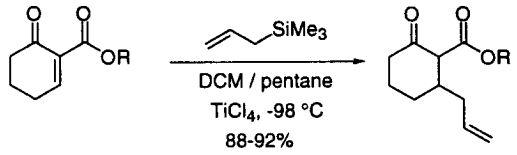
Scheme 2.

It should be noted that all three esters **3a–c** provide the normal Sakurai product **4** upon warming above –50°C. It appears the siliranium ion intermediate **6** (Scheme 3) is in close proximity to the titanium enolate, minimizing charge separation, and intermolecular nucleophilic attack by Cl^- is inhibited by the bulky ester substituent. As a result, the annulation product **5** predominates but the cyclobutane adduct was seen to revert to the siliranium intermediate **6** upon warming and in the presence of $TiCl_4$. When the reaction temperature rises above –50°C, the process irreversibly produces the normal Sakurai product **4**.

To further probe the generality of this duality in mechanism, alkyl 6-oxo-1-cyclohexane carboxylates **7a–b** were subjected to the Sakurai reaction conditions.[6] The increased electrophilicity of the β-carbon upon addition of the α-ester resulted in a large increase in the reaction rate. As observed in the bicyclic lactam series, the smaller α-methoxycarbonyl provided the Sakurai product **8a** exclusively. When the larger *t*-butoxycarbonyl **7b** was submitted to the same reaction conditions at –78°C, the starting material was consumed in 10 min providing only the allyl transfer product **8b**. The cyclohexenone and allylsilane were dissolved in a 1:1 mixture of DCM:pentane, cooled to –98°C and subjected to the same conditions. Again, the reaction was completed within 15 min and provided **8b** exclusively (Eq. 1). It is conceivable that in the more complex environment of the bicyclic lactams, **3**, the steric inhibition to chloride ion attack is more important, while in the simpler cyclohexenone systems the chloride ion is not prevented from attack on silicon by remote alkyl groups on the ester group.[7]



Scheme 3.



(1)

7a = CH_3 **8a = CH_3**
7b = *t*-Bu **8b = *t*-Bu**

In summary, we have observed a novel remote steric effect in the addition of allylsilanes to α,β-unsaturated bicyclic lactam systems. With careful control of the reaction conditions and substrate size, it is possible to exploit the dual reactivity of allylsilanes. Our continuing studies of allylsilane reactivity and their application toward the construction of optically pure carbocycles and heterocycles will be published in due course.

Acknowledgements

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6. Synthesis of **7a** and **7b** was accomplished using the literature procedure: Kato, M.; Kamat, V. P.; Koshikoshi, A. *Synthesis* **1988**, 699.
7. Experimental. General procedure: to a flame dried round bottomed flask was added dichloromethane and cooled to −78°C. The bicyclic lactam was added followed by 1.5 equivalents of allyltrimethylsilane. The solution was stirred for ca. 15 min prior to the addition of 1.2 equivalents of $TiCl_4$. The reaction was stirred at −78°C for 5 h then quenched by the addition of

aq. NH_4Cl. The layers were separated, the aqueous layer was washed with dichloromethane, the combined organic layers were dried over Na_2SO_4 and concentrated to an oil under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and GC to determine the ratio of Sakurai vs cyclobutane products. Column chromatography (20% Et_2O in hexane) provided the products as colorless oils/solids (**5a**, 73%; **5b**, 84%; **5c**, 87%). **5c** colorless solid, mp=99–101°C; $[\alpha]_D$=24 (c=1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.02 (s, 9H), 0.75 (app. t, J=11 Hz, 2H), 1.15 (dd, J=3, 8 Hz, 1H), 1.51 (s, 9H), 1.51 (s, 3H), 1.63 (ddd, J=9, 7, 3 Hz, 1H), 2.48 (ddd, J=9, 6, 3 Hz, 1H), 2.78 (ddd, J=7, 6, 3 Hz, 1H), 3.38 (app. t, J=7 Hz, 1H), 4.25 (dd, J=9, 8 Hz, 1H), 4.81 (app. t, J=8 Hz, 1H), 5.2 (app. t, J=9 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 0.84, 19.48, 23.99, 24.89, 28.22, 37.46, 43.77, 57.45, 75.13, 82.04, 125.64, 127.53, 128.76, 139.60, 174.34; IR (film) 1711 cm^{-1}.