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β-Destabilizing Effect of Silicon in Regioselective Hydroxymethylation of β-Silylcycloalkanone Enol Acetates by Electrochemical Method

Jih Ru Hwu,[*,†,‡] Shwu-Chen Tsay,[†] Lung Ching Lin,[§] and Lu Lin Chueh[§]

Organosilicon and Synthesis Laboratory
Institute of Chemistry, Academia Sinica
Nankang, Taipei, Taiwan 11529, Republic of China
Department of Chemistry, National Tsing Hua University
Hsinchu, Taiwan 30043, Republic of China
Department of Chemistry, National Taiwan University
Taipei, Taiwan 10671, Republic of China

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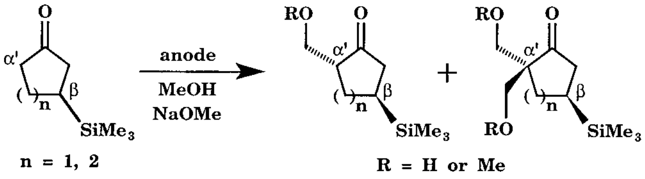
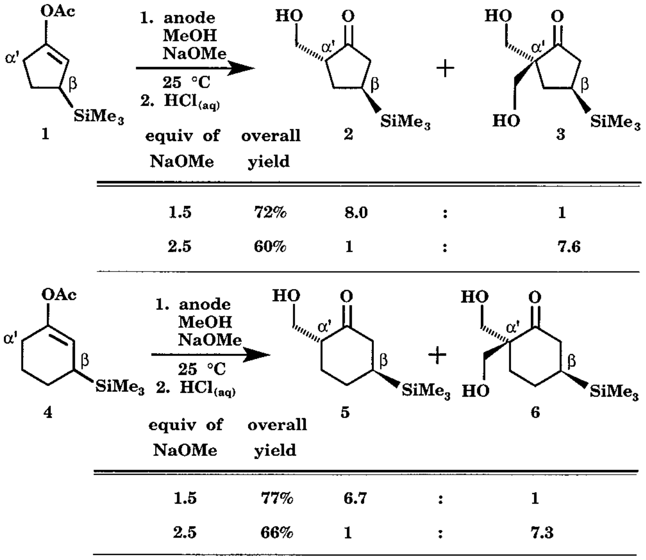
The β-stabilizing effect of silicon is widely utilized in control of reactions involving carbocationic intermediates.[1a,2] In contrast, very few experimental and theoretical works have been reported on the application of the β-destabilizing effect of silicon.[1b] Fleming et al.[3] reported a pioneering reaction, in which the directing effect of a β-silyl group is detectable on base-catalyzed enolization of an unsymmetrical ketone. The effect appears to be largely steric in origin. The electronic effect resulting from a silyl group, however, could be in a different extent under electrochemical conditions. For example, a β-silyl group can destablize the highly dissociated anions to a greater extent than those tightly associated with a metal cation. Its recent application in electrochemical processes includes the silicon-directed aldol condensation.[4] Although this new reaction offers good regioselectivity, it often provides a mixture of products containing mono- and bis-hydroxymethyl groups in comparable yields (Scheme 1). It may also produce a complicated mixture containing hydroxymethylated and methoxymethylated ketones.

We considered to develop an electrochemical reaction[5−9] by using a β-Me$_3$Si group to destabilize the allylic anion of an enol acetate. The sequential hydroxymethylation[10] would then occur at the α' position with high regioselectivity. Our goal is to allow this reaction to produce predominantly a mono- or bis-hydroxymethylated product in an appealing yield under control conditions.

Scheme 1



Scheme 2



equiv of NaOMe	overall yield	2	:	3
1.5	72%	8.0	:	1
2.5	60%	1	:	7.6

equiv of NaOMe	overall yield	5	:	6
1.5	77%	6.7	:	1
2.5	66%	1	:	7.3

To obtain hydroxymethylated ketones, we used enol acetates as the substrates in the electrochemical reactions (see Scheme 2). Electricity of 2.0−4.0 F/mol at a constant current of 0.10 A (0.20 A/cm^2, terminal voltage 20 V) was passed through an anhydrous methanolic solution (25 mL) in an undivided cell equipped with two platinum electrodes. This solution contained 3-(trimethylsilyl)cyclopentan-1-one enol acetate (**1**, 50.0 mmol) and 1.5 equiv of NaOMe (75.0 mmol). After enol acetate **1** was consumed completely at room temperature in 2.0 h, the reaction mixture was worked up with 0.50 N aqueous HCl (30 mL), and then the aqueous solution was extracted with ether. Purification of the crude products by use of silica gel column chromatography with a mixture of CHCl$_3$ and hexanes (1:1 in volume) as the eluant gave pure mono-hydroxymethylated ketone **2** in 64% yield. The byproduct **3** bearing two hydroxymethyl groups was isolated in 8% yield only. The ratio was 8.0:1 for **2**/**3**.

After testing numerous combinations, we found the optimum conditions for the generation of bis-hydroxymethylated product **3** as the major product in good yields. Performance of the electrochemical reactions under the same conditions by increment of the stoichiometric amount of NaOMe to 2.5 equiv (i.e., 125 mmol) gave **3** in 53% yield upon isolation. The mono-hydroxymethylated **2** was generated as the byproduct in 7% yield only.

In these electrochemical reactions, methanol was the source of the hydroxymethylation agent; sodium methoxide functioned as a supporting electrolyte and a base. Use of different cations Li$^+$ and K$^+$ to replace Na$^+$ in the reaction media led to similar yields and ratios of the same products ($\pm$6% difference). Results from our previous works indicate that replacement of NaOMe and methanol with glacial acetic acid and tetraethylammonium *p*-toluenesulfonate generates the 3-trimethylsilyl-2-cyclopenten-1-one exclusively through anodic oxidation.[11] On the other hand, we found that addition of THF, DMF, or DMSO as the cosolvent of methanol provided the same type and distributions of the products (i.e., hydroxymethylated ketones **2** and **3**). Nevertheless, the overall yields were significant lower ($<$45%). These results indicate that the solvent effect was minimal on the regioselectivity although it affected efficiency of the electrochemical transformation. Furthermore, these electrochemical reactions were monitored

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[*] To whom correspondence should be addressed. Fax: 886-22-788-1337. E-mail: jrhwu@chem.sinica.edu.tw.

[†] Academia Sinica.

[‡] National Tsing Hua University.

[§] National Taiwan University.

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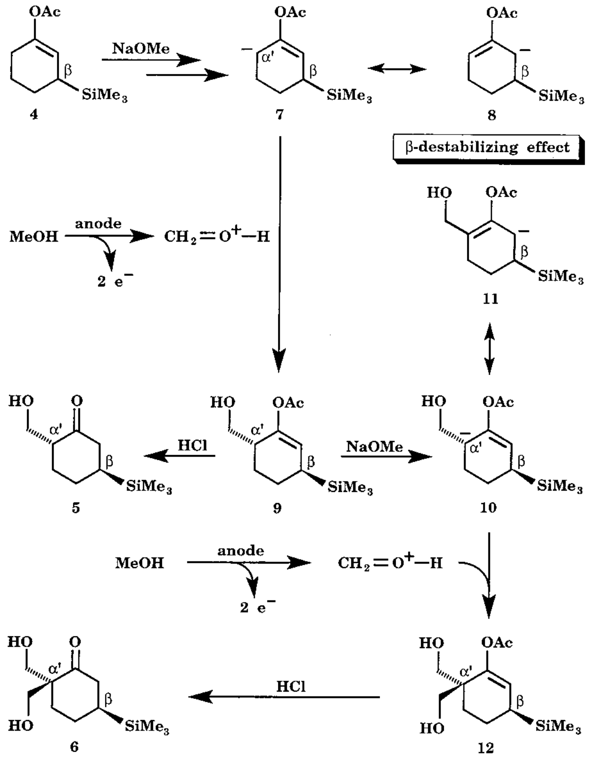
Scheme 3



by TLC and often stopped in 2.0 h. An extended period of reaction time did not lead to the hydroxymethylated products in higher yields.

The newly developed method was applicable to a substrate with six-membered ring. We treated 3-(trimethylsilyl)cyclohexan-1-one enol acetate (**4**) with 1.5 equiv of NaOMe under the same electrochemical conditions described before to generate hydroxyl ketone **5** in 67% yield (see Scheme 2). The ratio was 6.7:1 for this major product **5** to the byproduct **6** bearing two hydroxymethyl groups. Similarly, use of an excess of NaOMe (i.e., 2.5 equiv) led **4** to **6** as the major product in 58% yield. The ratio of **5**/**6** was changed to 1:7.3.

Spectroscopic methods including ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry were used for identification of products **2**, **3**, **5**, and **6**.[4] The hydroxymethyl substituents attached at the α′ position were unambiguously confirmed by the crystals of **6** (mp 110−112 °C), of which the molecular framework has been determined by single-crystal X-ray diffraction analysis.[4]

The mechanism depicted in Scheme 3, as exemplified by the conversions of **4** → **5** and **4** → **6**, can account for the results from the electrochemical hydroxymethylations of *β*-silylcycloalkanone enol acetates. The transformation is initiated by deprotonation of **4** with NaOMe. The resultant canonical form **7**[12] overwhelms form **8** because of the silicon *β*-destabilizing effect. Around the anode, the dissociated *β*-silyl enolate ions react with $CH_2{=}O^+H$, which is generated from the solvent MeOH through electrochemical oxidation,[13] to produce hydroxymethylated enol acetate **9**. Hydrolysis of **9** under acidic conditions affords the α′-monohydroxymethyl ketone **5**. The first step of the entire mechanism is the equilibrium process **4** + $^-$OMe → **7** + MeOH. Although this equilibrium disfavors the formation of the intermediate **7**, it could strongly couple with the $CH_2{=}O^+H$ species generated in situ. After its concentration decreases, the Le Chatelier's principle is applied to the system and drives the reaction to product **5** as shown in Scheme 3.

Repetition of the deprotonation, anodic hydroxymethylation, and hydrolysis can lead **9** to bis-hydroxymethylated ketone **6** via intermediates **10** and **12**. The carbanion center is trisubstituted in **10**, yet it is disubstituted in **11**. Carbanion **11** was again a disfavored form because of the *β*-destabilizing effect resulting from silicon. We found that the second hydroxymethylation occurred exclusively at the α′ position of **10** to give the intermediate **12**. On the other hand, one may consider the possibility that the products (i.e., **2**, **3**, **5**, and **6**) come from hydroxymethylations of *β*-silylcycloalkanone enolates, which could be generated from the saponification of enol acetates **1** and **4** by NaOMe. We believe that this process is not responsible for the results shown in Scheme 2. Our previous results indicate that the enolate ion resulting from deprotonation of the corresponding cyclohexanone (the same as that from de-acetylation of **4**) gives a mixture of **5** and **6** in a ratio of 1:1.2.[4] In a sharp contrast, application of the newly developed procedure gave the same mixture of **5** and **6** in a ratio of 6.7:1.

In a control experiment, we applied the same electrochemical conditions to 3-(*i*-propyl)cyclohexan-1-one enol acetate in the presence of NaOMe (2.5 equiv). After 2.0 h at room temperature, a hydroxymethylation took place at the α (i.e., C-2), instead of the α′, position exclusively to afford 2,2-dihydroxymethyl-3-(*i*-propyl)cyclohexan-1-one[4] as the major product in 45% yield. The isopropyl and the trimethylsilyl groups often display comparable steric influence,[14−18] but the former one does not exert the *β*-destabilizing effect. Thus, the remarkable contrast between 3-(trimethylsilyl)cyclohexan-1-one enol acetate (**4**) and 3-(*i*-propyl)cyclohexan-1-one enol acetate in their hydroxymethylation orientation is believed to come from the electronic effect of the *β*-silicon.[19]

In conclusion, regioselective hydroxymethylation of *β*-(trimethylsilyl)-cycloalkanone enol acetates with methanol was accomplished electrochemically under basic conditions with NaOMe. The silyl group exhibited a profound destabilizing effect on dissociated *β*-allylic anions **8** and **11**; thus, the hydroxymethylation proceeded at the α′ position of **7** and **10**. Both of the desired mono- and bis-α′-hydroxymethylated cycloalkanones can be produced as the major products in 53−67% yields by control of the quantity of the applied base NaOMe. This new reaction exhibits a successful application of the *β*-destabilizing effect of silicon to organic synthesis.

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Supporting Information Available: Synthetic procedures and spectroscopic data for **2**, **3**, **5**, and **6**, as well as computational results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Formation of carbanion **7** may go through deprotonation of **4** with NaOMe at the acetyl group initially, which is followed by an intramolecular proton abstraction from an allylic position. This possibility is supported by the results from the experiment involving use of the corresponding enol benzoate as the substrate. It did not lead to the hydroxymethylated products in a significant amount under the same electrochemical conditions.

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