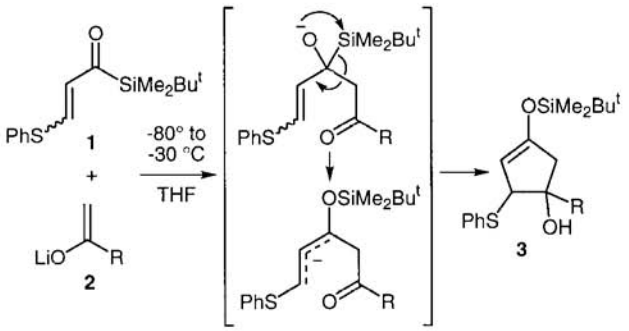
Synthesis of 4-Hydroxy-2-cyclopentenone Derivatives by [3 + 2] Annulation of β-Heteroatom-Substituted Acryloylsilanes and Lithium Enolate of Methyl Ketones

Kei Takeda,* Yasuhiro Ohtani, Emi Ando, Ken-ichi Fujimoto, Eiichi Yoshii, and Toru Koizumi
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194

(Received August 20, 1998; CL-980639)

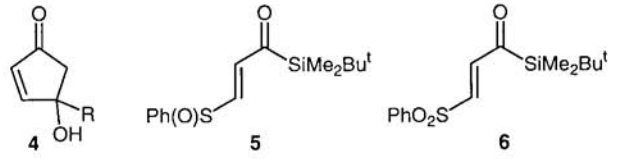
The [3 + 2] annulation using β-[2-(pyridyl)thio] and β,β-dichloro derivatives of acryloylsilane and the lithium enolate of methyl ketones successfully proceeded to afford 4-alkyl-4-hydroxy-3-(2-pyridylthio)cyclopentanone and 4-alkyl-3-chloro-4-hydroxy-2-cyclopentenone, respectively.

The construction of highly functionalized cyclopentenone derivatives has attracted a great deal of attention in recent years because the skeleton has been found in a variety of biologically important molecules. Earlier investigations[1-3] in our laboratory have shown that the [3 + 2] annulation employing a combination of (β-(phenylthio)acryloyl)silanes **1** and the lithium enolate of methyl ketones **2** provided an efficient route for the rapid construction of polyfunctionalized cyclopentenol derivatives **3**.

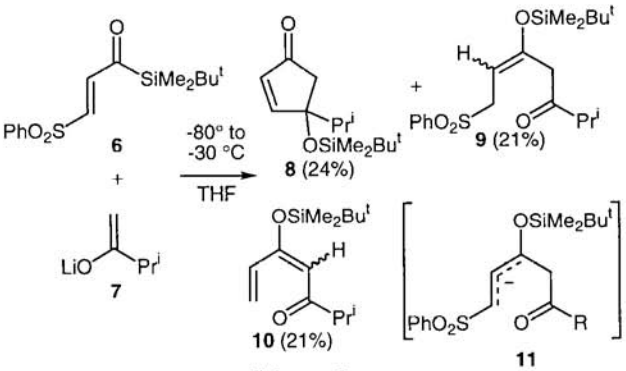


Scheme 1.

Although the cyclopentenols **3** resulting from the annulation are themselves useful structural entities because they contain potentially useful functionalities for further derivatization, the versatility of the annulation would be greatly enhanced if direct formation of 4-hydroxy-2-cyclopentenone derivative **4** from the annulation becomes possible. This prompted us to investigate the annulation using the acryloylsilane bearing a better leaving group than the phenylthio group as the β-substituent. First, we examined the reaction using the β-sulfinyl and β-sulfonyl derivatives, **5**[4] and **6**[4], which were prepared by the mCPBA oxidation of the phenylthio derivative **1**.

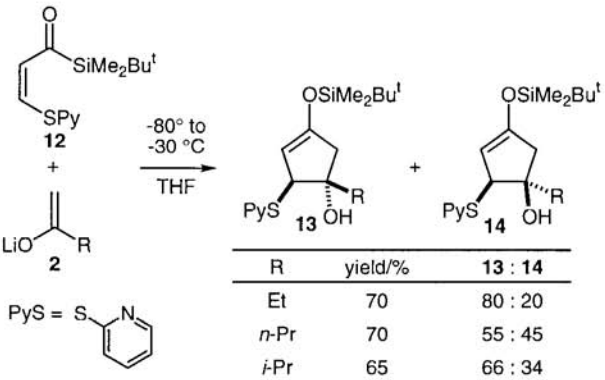


Although the sulfinyl derivative **5** afforded a complex mixture, the reaction of the sulfonyl derivative **6** produced the cyclopentenone **8** together with uncyclized products **9** and **10**. Compound **10** can be formed by the elimination of phenylsulfinate from the enolate of **9** which is generated by intramolecular and/or intermolecular proton abstraction involving the delocalized allylic anion intermediate **11**. The formation of **9** and **10** suggests that **11** is not reactive enough to cyclize in order to form **8** due to the carbanion stabilizing ability of the sulfonyl group and consequently undergoes the competing proton abstraction leading to **9** and **10**.



Scheme 2.

Next, we examined the reaction of acryloylsilane **12**[5] bearing the β-(2-pyridyl)thio group which has lithium chelating ability[6] and is more electron-withdrawing than the phenylthio group but less than the phenylsulfonyl group. When the reaction of **12** with the enolates **2** was conducted under the same conditions as those for **1**, diastereomeric cyclopentenols **13** and **14** rather than the cyclopentenol **4** were obtained as summarized in Scheme 3.

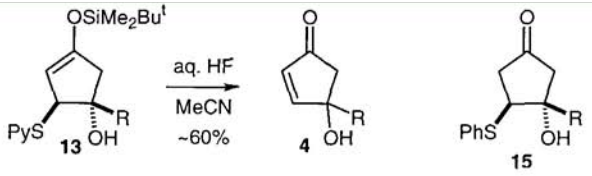


R	yield/%	13 : 14
Et	70	80 : 20
n-Pr	70	55 : 45
i-Pr	65	66 : 34
n-octyl	54	67 : 33

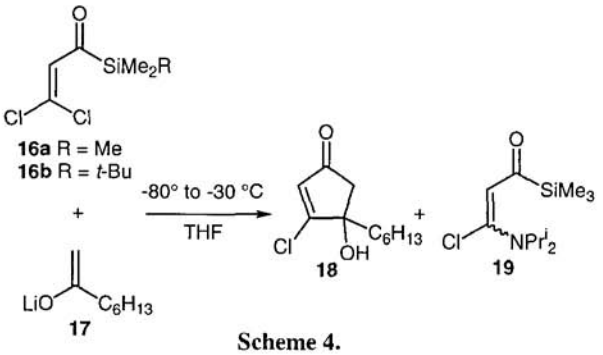
Scheme 3.

Treatment of **13** with aqueous HF in MeCN, however, afforded 2-cyclopentenone **4**, in contrast to the reaction of **3** under same conditions which provided the 3-(phenylthio)cyclopentanone derivatives **15**.[1]

We next turned to the use of (β,β-(dichloro)acryloyl)trimethylsilane (**16**), readily prepared according to the protocol of

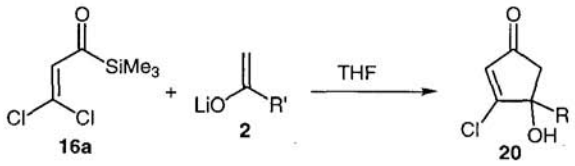


Cunico and Cui-ping[7,8] and expected it to give the 3-chloro-4-hydroxy-2-cyclopentenone derivative **18**, a potentially useful compound for further synthetic manipulation, during the annulation. We first attempted the reaction of **16a** with the lithium enolate of 2-octanone, generated from LDA, but 3-chloro-4-hexyl-4-hydroxy-2-cyclopentenone (**18**) was obtained in only 13% yield. The major side products were the enamine **19a** which can be formed by an addition-elimination reaction of the diisopropylamine to **16a**, and the aldol condensation products of the ketone. The aldol condensation can be attributed to the generation of the ketone by the enolate-mediated dehydrochlorination of **16a**.



Scheme 4.

Next, we examined the reaction under the amine-free conditions using mesityllithium as a base to prevent the formation of the side products. When **16a** was treated with lithium enolate **2** at -80° to -30° or 0 °C, 3-chloro-4-hydroxy-2-cyclopentenones **20** were obtained in moderate to good yields as shown in Scheme 5.[9]



R	conditions	yield/%
Et	-80° to 0 °C	43
i-Pr	-80° to -30 °C	65
i-Bu	-80° to 0 °C	62
t-Bu	-80° to -30 °C	70
hexyl	-80° to 0 °C	42
c-C_3H_5	-80° to -30 °C	48

Scheme 5.

Somewhat lower yields relative to the original annulation using **1**, especially in the normal chain ketones, might be attributed to the decomposition via the enolate-mediated dehydrochlorination. No enol silyl ether corresponding to **3**, even when *t*-butyldimethylsilyl derivatives **16b** was used, was detected. Slightly lower yields (39-53%) of **20** were obtained from the reaction of **16b**. The use of *β,β*-dibromo derivative resulted in a poor yield (~10%) of **20**.

In summary, we have demonstrated that the Brook rearrangement-mediated [3 + 2] annulation was successfully applied to the direct synthesis of the 3-chloro-4-hydroxy-2-cyclopentenone derivatives.

We thank the Grant-in-Aid for Scientific Research (No. 10671986 (K.T.)) from the Ministry of Education, Science, Sports and Culture, Japan, and the Hoan Sha Foundation for partial support of this research.

References and Notes

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4 These compounds were prepared by the mCPBA oxidation of (*Z*)-**1**. For the preparation of **1**, see: K. Takeda, A. Nakajima, M. Takeda, Y. Okamoto, T. Sato, E. Yoshii, T. Koizumi, and M. Shiro, *J. Am. Chem. Soc.*, **120**, 4947 (1998).
5 This compound was prepared using 2,2'-dipyridyldisulfide in a similar manner to that for **1**.
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9 General procedure for the [3 + 2] annulation using **16a**: Reaction of **16a** with Li enolate of 3,3-dimethyl-2-butanone. To a cooled (-80 °C) solution of 2-bromomesitylene (149 mg, 749 μmol) in THF (0.8 mL) was added *t*-BuLi (1.15M in pentane, 1.43 mL, 1.64 mmol). The solution was stirred at the same temperature for 20 min. To this mixture was added dropwise a solution of 3,3-dimethyl-2-butanone (94 μL, 749 μmol) in THF (1.5 mL). After being stirred at -80 °C for 30 min, the solution was added dropwise to a solution of (3,3-(dichloro)propanoyl)trimethylsilane (134.3 mg, 681 μmol) in THF (29 mL). The reaction mixture was allowed to warm to -30 °C over 30 min, and quenched using saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with Et_2O (30 mL x 2), and the combined organic phases were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residual oil was subjected to column chromatography (silica gel, 10 g; elution with 1:1 hexane-Et_2O) to give **20** (R = Et) (90 mg, 70%).