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2-*tert*-Butoxy-3-phenylcyclopropanone acetal, a stable precursor of lithiated 2-phenylcyclopropenone acetal

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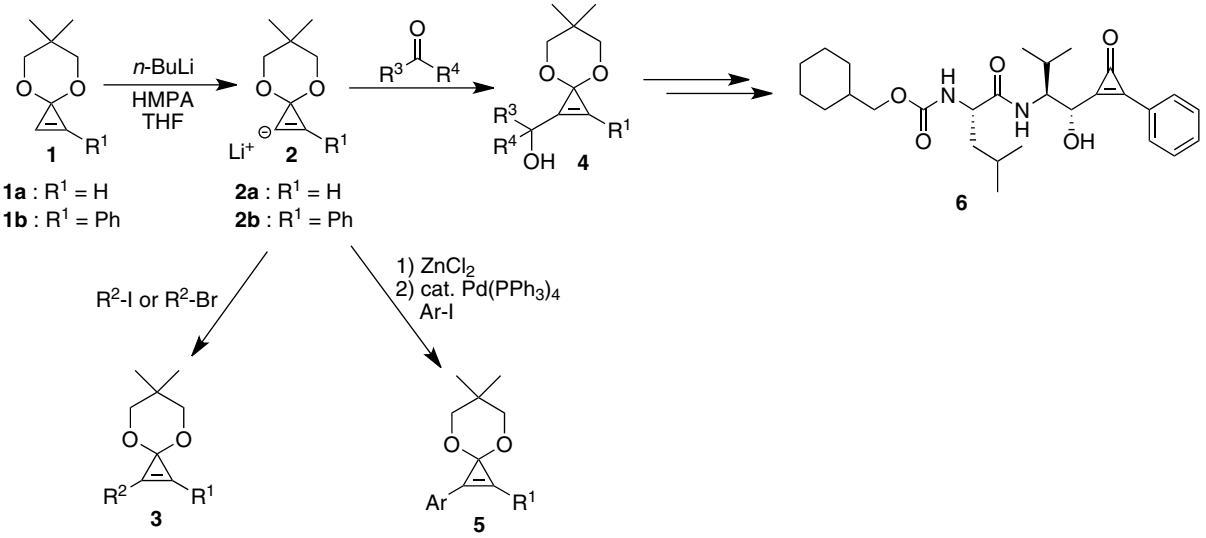
Abstract—2-*tert*-Butoxy-3-phenylcyclopropanone acetal **8** was found to be a stable precursor of lithiated cyclopropenone acetal. Acetal **8** was used in the practical synthesis of cysteine proteinase inhibitors; isolated yield of the key intermediate **14** was better than the one by the previous method.

Lithiated cyclopropenone acetal **2** is a very useful intermediate, and many reactions have been reported so far. For example, reaction with alkyl halides or carbonyl compounds gave the alkylated derivative **3**[1] or adduct **4**,[1,2] and transmetalation to the zinc salt followed by coupling reaction with aryl iodides in the presence of palladium catalyst afforded the arylated derivative **5**.[1] Cyclopropenone acetals obtained by these reactions were used as key intermediates for biologically active compounds containing a cyclopropenone moiety, for example, antimicrobial penitricin derivatives,[3] cysteine proteinase inhibitors,[4,5] or factor XIIIa inhibitor alutacenoic acid derivatives[6] (Scheme 1).

It is reported that intermediate **2** was prepared by treatment of cyclopropenone acetal **1** with *n*-BuLi in the presence of HMPA or TMEDA.[1] However, there is a serious problem in the synthesis of the starting material



Scheme 1. Preparation and reactions of the lithiated cyclopropenone acetal **2**.

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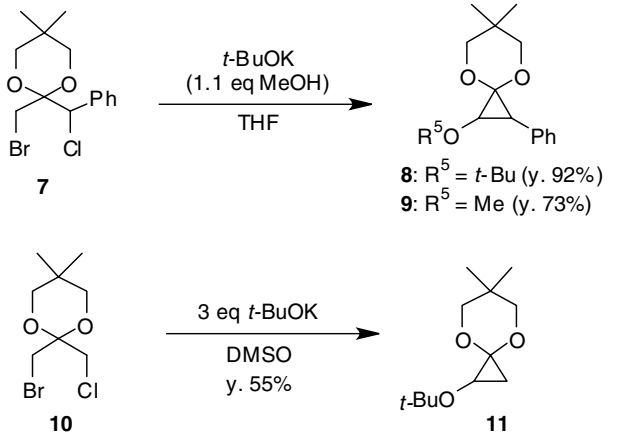
1 because it is thermally unstable. According to the evaluation by a differential scanning calorimeter (DSC), cyclopropenone 2,2-dimethyl-1,3-propanediyl acetal **1a** started the generation of heat below 50 °C, and the peak temperature of that was 136 °C. The calorific value of the exothermic peak was 752 J/g[7]—which suggests that a violent explosion of **1a** would occur by even mild heating. 2-Phenylcyclopropenone 2,2-dimethyl-1,3-propanediyl acetal **1b**, which is the key intermediate for cysteine proteinase inhibitor **6**, was slightly more stable than **1a**; the starting and peak temperature of the generation of heat were 87 °C and 126 °C, respectively, and the calorific value of the exothermic peak was 514 J/g. These results suggest that it is necessary to conduct experiments carefully, especially at the isolation, purification, and drying steps in the synthesis of cyclopropenone acetal **1**.

During our continuous study of practical synthesis of cysteine proteinase inhibitors, we have found that 2-*tert*-butoxy-3-phenylcyclopropanone acetal **8** could be prepared from 2-bromomethyl-2-(chlorophenylmethyl)-5,5-dimethyl-1,3-dioxane **7** via 2-phenylcyclopropenone acetal **1b**.[8] Although the *tert*-butoxy group is not a good leaving group, it would be possible to generate cyclopropenone acetal **1b** from **8** by elimination of the *tert*-butoxy group by treatment with a strong base. We will report herein a thermally stable precursor of lithiated 2-phenylcyclopropenone acetal **2b**.

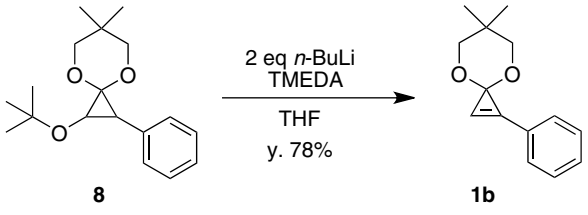
2-*tert*-Butoxy-3-phenylcyclopropanone acetal **8** was easily prepared even in a large scale from dihalide **7** by treatment with 2.5 equiv of *t*-BuOK in THF at room temperature in excellent yield via successive reactions of deprotonation at the benzylic position, cyclization to produce the cyclopropane ring, dehydrochlorination to produce the cyclopropenone acetal **1b**, and addition of *tert*-butoxide anion.[8,9] Compound **8** is more stable and much less explosive than compound **1b**; the starting and peak temperature of the generation of heat were 106 °C and 138 °C, respectively, and the calorific value of the exothermic peak was 64.3 J/g. 2-Methoxy-3-phenylcyclopropanone acetal **9** was also prepared in a similar manner in the presence of 1.1 equiv of methanol in 73% yield. 2-*tert*-Butoxycyclopropanone acetal **11** was prepared from 2-bromomethyl-2-chloromethyl-5,5-dimethyl-1,3-dioxane **10** by treatment with *t*-BuOK in DMSO in 55% yield[10,11] (Scheme 2).



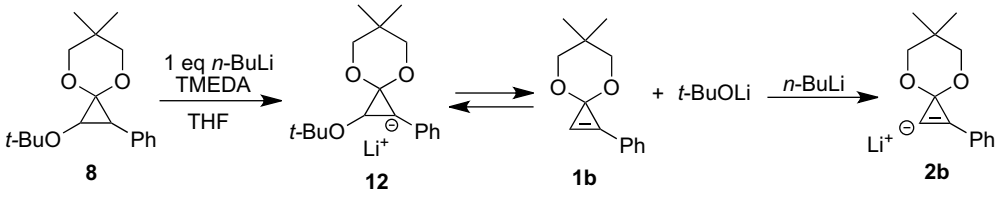
Scheme 2. Synthesis of 2-alkoxycyclopropanone acetals.

Treatment of cyclopropanone acetal **8** with 1 equiv of strong base such as *n*-BuLi would give cyclopropenone acetal **1b** via deprotonation of the benzylic position followed by elimination of the *tert*-butoxy group. However, in this reaction mixture lithium *tert*-butoxide exists as the side product, which would add to acetal **1b** to regenerate intermediate **12** as shown in Scheme 3. Thus this reaction is reversible, and quenching by water would give a mixture of **8** and **1b** whose ratio would depend on the reaction condition. In order to overcome this equilibrium, addition of one more equivalent of strong base such as *n*-BuLi would be effective because formation of lithiated cyclopropenone acetal **2b** would lead shift of this equilibrium to the right side.

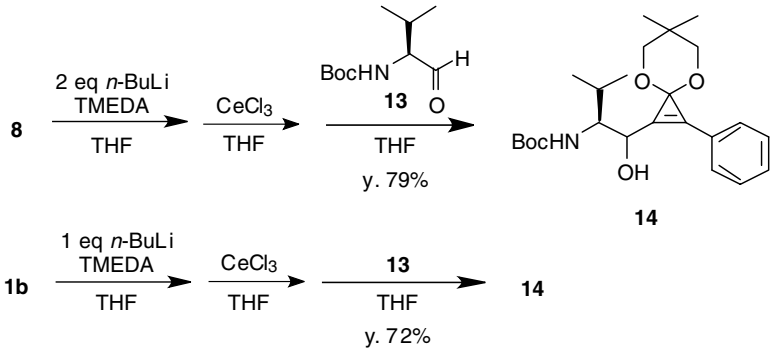
Reaction of acetal **8** with 2 equiv of *n*-BuLi at −60 °C followed by quenching by the addition of water afforded cyclopropenone acetal **1b**[12] as we had expected. However, it took long time to complete the reaction because the deprotonation or elimination step was slow. Thus we investigated reaction conditions and found that it needed at least 2 h to produce lithiated cyclopropenone acetal **2b** completely. This intermediate was thermally very unstable; it decomposed at −50 °C. Isolated yield of **1b** after reacting acetal **8** with 2 equiv of *n*-BuLi at −60 °C for 2 h was 78%.[13] Reaction of methoxy deriva-



Scheme 4. Synthesis of the cyclopropenone acetal **1b**.



Scheme 3. Generation of the lithiated 2-phenylcyclopropenenone acetal **2b**.



Scheme 5. Synthesis of the key intermediate **14**.

tive **9** with 2 equiv of *n*-BuLi also afforded cyclopropenone acetal **1b** in 80% yield. However, all attempts to generate lithiated cyclopropenone acetal **2a** from acetal **11** were unsuccessful (Scheme 4).

We applied this reaction to the practical synthesis of cysteine proteinase inhibitors. After generating lithiated cyclopropenone acetal **2b**, a THF suspension of anhydrous cerium chloride, which was prepared by dehydration of $CeCl_3{\cdot}7H_2O$,[14] was added at −78 °C. (*S*)-Boc-Valinal **13** was then added, and the resulting mixture was stirred for 3.5 h at that temperature. Work-up and purification by column chromatography afforded the key intermediate **14** whose isolated yield was 79%.[15] This yield was better than the one by the previous method (72%) in which thermally unstable cyclopropenone acetal **1b** was used as the starting compound[4b] (Scheme 5).

In conclusion, 2-*tert*-butoxy-3-phenylcyclopropanone acetal **8** was found to be a stable precursor of lithiated cyclopropenone acetal **2b**. Acetal **8** was used in the practical synthesis of cysteine proteinase inhibitors; isolated yield of the key intermediate **14** was better than the one by the previous method.

Acknowledgment

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7. Thermal stability of compounds was evaluated by a Seiko DSC-20 instrument. For each compound, a 1 mg of sample was placed in a sealed Ag pressure-resistant cell under nitrogen. The sample was then heated from room temperature to 450 °C at a rate of 10 °C/min.
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9. *2-tert-Butoxy-3-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl acetal* **8**. To a solution of 2-bromomethyl-2-(chlorophenylmethyl)-5,5-dimethyl-1,3-dioxane **7**[8] (185.1 g) in THF (750 mL), *t*-BuOK (155.4 g) was added slowly at 0 °C. The resulting solution was then stirred overnight at room temperature, and THF (about 350 mL) was removed in vacuo. After addition of water to the residue, the water layer was extracted with *n*-heptane three times. Combined extracts were washed with saturated NaCl solution and dried over anhydrous sodium sulfate. After filtration of the drying agent, the filtrate was evaporated to give crude solids (164.1 g), which was dissolved in 2-propanol (300 mL) by heating. After this resulting solution was cooled to 0 °C, water (350 mL) was added slowly. The precipitates formed were filtered and washed with 2-propanol–water mixture (1:1) to afford the desired compound (147.8 g, 92%). Spectroscopic properties were identical with reported ones.[8]
10. No reactions proceeded in THF.
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12. No reaction proceeded by treatment with triethylamine or DBU.
13. *2-Phenylcyclopropenone 2,2-dimethyl-1,3-propanediyl acetal* **1b**. To a solution of acetal **8** (1.00 g) in THF (10 mL), TMEDA (1.03 mL) was added at −60 °C. *n*-BuLi (1.61 mol/L solution in *n*-hexane, 4.29 mL) was then added at −60 °C in 5 min, and the resulting solution was stirred at that temperature for 2 h. After 4:1 mixture of THF–water (3 mL) was added at −60 °C, the reaction mixture was warmed to room temperature, and anhydrous Na_2SO_4 was added. Subsequently, solids in this solution were filtered by Celite, and the filtrate was evaporated to give the crude mixture (894 mg). Purification by column chromatography (*n*-hexane/AcOEt = 20/1) afforded the desired compound (579 mg, 78%). Spectroscopic properties were identical with reported ones.[8]
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15. *2-((2S)-2-tert-Butoxycarbonylamino-1-hydroxy-3-methylbutyl)-3-phenylcyclopropenone 2,2-dimethyl-1,3-propanediyl acetal* **14**. Acetal **8** (996 mg) was dissolved in THF (10 mL), and TMEDA (0.97 mL) was added. The resulting solution was then cooled to −78 °C, and *n*-BuLi (1.63 mol/L solution in *n*-hexane, 3.98 mL) was added in 5 min. After stirring for 1.5 h at that temperature, a cooled suspension of anhydrous $CeCl_3$, which was prepared from $CeCl_3{\cdot}7H_2O$ (1.92 g) by drying in vacuo at 140 °C for 3.5 h, in THF (20 mL) was slowly added, and the resulting suspension was stirred for 50 min at −78 °C. Subsequently, (*S*)-*N*-*tert*-butoxycarbonylvalinal **13** (293 mg) in THF (5 mL) was added in 10 min, and the resulting mixture was stirred at −78 °C for 3.5 h. The reaction mixture was then quenched by addition of 4:1 mixture of THF–water (3 mL) at −78 °C, and it was warmed to room temperature. Subsequently, anhydrous Na_2SO_4 was added to the resulting suspension; solids were filtered by Celite and were washed well with ethyl acetate. Evaporation of the filtrate afforded the crude mixture (1.44 g), which was purified by column chromatography (*n*-hexane/ethyl acetate = 4/1) to give the desired compound (484 mg, 79% yield base on aldehyde **13**). Spectroscopic properties were identical with reported ones.[4b]