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Base- and acid-catalyzed intramolecular oxy-Michael reaction for the synthesis of tetrahydrofuran ring

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On the celebration of Tetrahedron Prize 2014, this paper is dedicated to Professor Jiro Tsuji for his great contribution on Pd-chemistry

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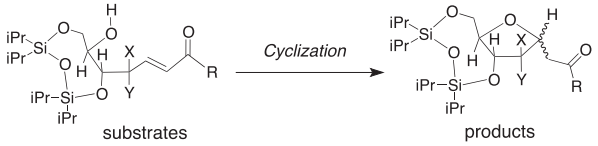
ABSTRACT

Base- and acid-catalyzed intramolecular oxy-Michael reactions are reported. Three ε-hydroxy α,β-unsaturated ketones **1**, **2**, and **3** and one ester **4** were cyclized in 5-*exo*-*trigonal* fashion to afford 2,5-disubstituted tetrahydrofurans in good yields. The substituent at the γ-hydroxy group and its stereochemistry influenced the stereoselectivity of the THF products. The precursor **2** bearing an (*R*)-γ-hydroxy group gave 2,5-*trans*-**6** exclusively. In contrast, **3**, bearing an (*S*)-γ-hydroxy group, gave only 2,5-*cis*-**7** under acidic conditions but gave a mixture of 2,5-*trans* and 2,5-*cis* isomers of **7** under basic conditions. On the other hand, in the absence of a hydroxyl group at the γ-position, the cyclization conducted under both basic and acidic reaction conditions provided a mixture of 2,5-*trans*- and 2,5-*cis* isomers of **5** and **8**.

1. Introduction

Oxa-heterocycles are an important unit in heterocyclic chemistry and the synthesis of oxa-cyclic ring has been well investigated.[1] Tetrahydrofuran (THF) rings exist widely as a core component in natural products[2] as well as in biologically active compounds[3] including C-nucleosides. A number of synthetic methods for 2,5-substituted THF compounds by ring forming reactions have been reported, e.g., cascade reaction of epoxides,[4a–c] oxidative ring formation to alkenes,[4d,e] halolactonization,[4f,g] radical cyclization,[4h–j] CH-insertion,[4k] and oxy-palladation.[4l] The oxy-Michael reaction is a powerful method to form oxa-heterocycles not only for tetrahydropyran (THP) rings[5] but also for THF rings. In fact, the 2,5-substituted THF ring unit has been synthesized by this method.[6] However the method has been employed mainly for α,β-unsaturated esters but poorly for α,β-unsaturated ketones. The reaction has been used limitedly for the γ-substituted α,β-unsaturated esters,[7] and only a few reaction for the γ-hydroxy α,β-unsaturated ester have been reported so far.[7h] We have been interested in the oxy-Michael reaction with ε-hydroxy-α,β-unsaturated ketones including γ-hydroxy derivatives for the synthesis of the 5-acetonyl-THF ring and its stereochemical course of the reactions. In this paper, we report the oxy-Michael reaction of four substrates **1**–**4** and the investigation of their stereochemistry (Scheme 1).



1 X = Y = H, R = CH_3
2 X = OH, Y = H, R = CH_3
3 X = H, Y = OH, R = CH_3
4 X = Y = H, R = OCH_3

5 X = Y = H, R = CH_3
6 X = OH, Y = H, R = CH_3
7 X = H, Y = OH, R = CH_3
8 X = Y = H, R = OCH_3

Scheme 1. Precursors of oxy-Michael reaction and synthesis of 2,5-disubstituted THF compounds.

2. Results and discussion

The precursors of the oxy-Michael reaction **1**, **2**, **3** and **4** were prepared from 2-deoxy-D-ribose, D-arabinose and D-ribose in 2 steps.[8] First, we treated compound **1** with 20 mol % of *t*-BuOK in THF at room temperature. The two diastereomeric isomers of 2,5-*trans*-**5** and 2,5-*cis*-**5** were obtained with 82% yield in a ratio of 2:3

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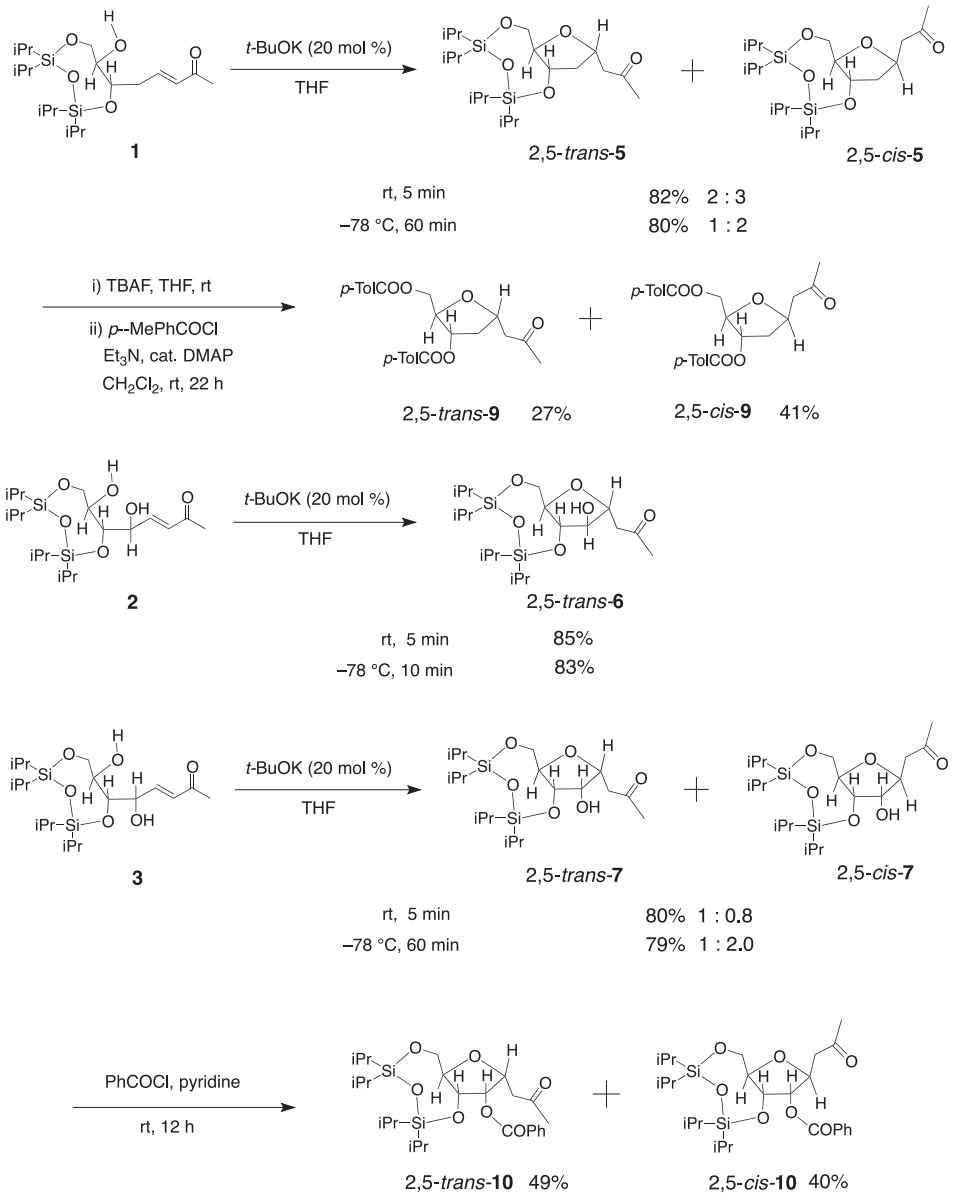
(Scheme 2). Unfortunately they were not separable by chromatography. They were derivatized to a mixture of di-*O*-toluoyl derivatives 2,5-*trans*-**9** and 2,5-*cis*-**9** with 47% yield in two steps i) removal of cyclic silyl ether with TBAF and ii) toluoylation with toluoyl chloride. After this conversion, they were separable by HPLC to give the polar 2,5-*trans*-**9** and the less polar 2,5-*cis*-**9**. The major isomer was identified to be 2,5-*cis*-**9** and the minor isomer 2,5-*trans*-**9** determined by the NOESY experiments.[9] When the reaction was conducted at −78 °C, a mixture of 2,5-*trans*-**5** and 2,5-*cis*-**5** was obtained in 80% yield and the selectivity of *cis* isomer increased little to be 1:2.

79% yield. Their stereochemistries were determined after the conversion to the corresponding benzoates. A 1:2 mixture of 2,5-*trans*-**7** and 2,5-*cis*-**7** was acylated with benzoyl chloride to give a mixture of 2,5-*trans*-**10** and 2,5-*cis*-**10** in the same ratio. They were separable and their NOESY spectra supported their relative structures.[9]

According to the oxy-Michael reactions for α,β-unsaturated esters in literature,[6] the 2,5-*trans* isomer was usually formed predominantly. However the reaction of the α,β-unsaturated ketone in the present cases, favored the production of the 2,5-*cis* isomer as opposed to the 2,5-*trans* isomer. When the γ-substituent was



Scheme 2. Oxy-Michael reaction of **1**, **2**, **3** and transformation to **9** and **10**.

Interestingly, the reaction of **2** under the same conditions afforded a single stereoisomer either at room temperature or at −78 °C, which was assigned to be 2,5-*trans*-**6**.[9] These chemical yields were excellent in 85% and 83%, respectively. On the other hand, the reaction of **3** gave a mixture of 2,5-*trans*-**7** and 2,5-*cis*-**7** in a ratio of 1:0.8 at room temperature in 80% yield. However, when the reaction was conducted at −78 °C, 2,5-*cis*-**7** produced favorably in a ratio of 1:2.0 with present, the stereochemistry of the product was not simple. We examined other reaction conditions using either basic or acidic catalysts. The results are shown in Table 1.

The effect of temperature on the reaction rate was evaluated but little difference in the selectivity was observed (entries 1–3) except the case at 78 °C (entry 4). The chemical yields were not much affected by the nature of the solvent (*t*-BuOH and toluene) used in the reaction (entries 5 and 6). The reactions in DMSO and