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AN INTERMOLECULAR [4+3] CYCLOADDITION REACTION USING 3-HYDROXY-2-PYRONE DERIVATIVES WITH AN OXYALLYL CATION

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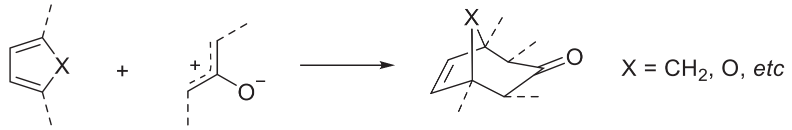
This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

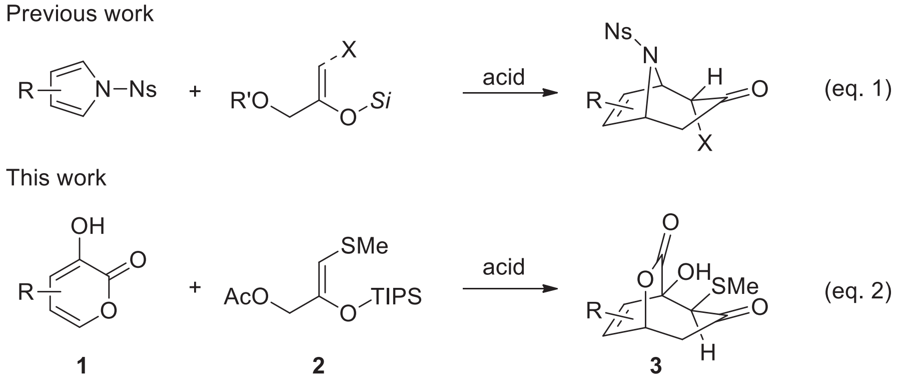
Abstract – An intermolecular [4+3] cycloaddition reaction using 3-hydroxy-2-pyrone derivatives with (2-silyloxy)allyl acetate was developed under Brønsted acid conditions to yield highly functionalized seven-membered carbocycles. The transformations of the cycloadducts are described.

Naturally-occurring seven-membered carbocycles are widely found in terpenoids and alkaloids. These compounds have been attractive as a synthetic target.[1] One of the most powerful tools for the construction of seven-membered carbocycles is the [4+3] cycloaddition reaction using 1,3-dienes and various oxyallyl cations (Scheme 1).[2] Much effort have been devoted during last two decades to investigate novel three-carbon units, e.g., allenamides,[3] epoxy enol silanes,[4] furfuryl alcohols,[5] 4-silyloxypentadienals,[6] 2-silyloxyacroleins,[7] and α-tosyloxy ketones;[8] however, the four-carbon units used in these studies were limited to acyclic 1,3-dienes or five-membered cyclic 1,3-dienes such as 1,3-cyclopentadiene and furan. Therefore, the investigation of a novel four-carbon unit is an essential task to expand the utility of the [4+3] cycloaddition reaction. The synergetic effect can provide powerful synthetic strategies for complex natural products.

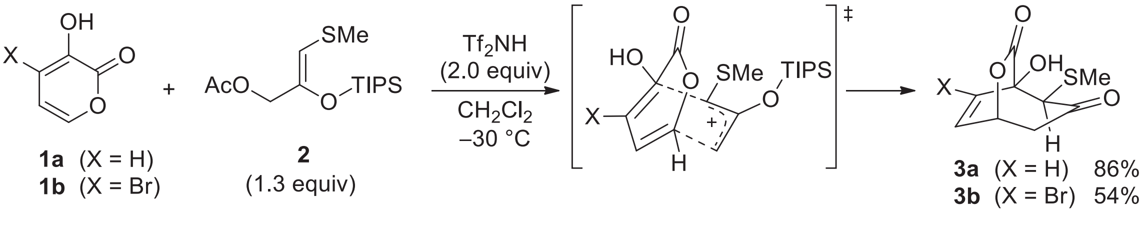


Scheme 1. [4+3] Cycloaddition reaction of 1,3-dienes and oxyallyl cations

In this context, we reported the acid-catalyzed inter-/intramolecular [4+3] cycloaddition reaction using *N*-nosyl pyrroles[9] with various (2-silyloxy)allyl cations (eq. 1). This cycloaddition reaction provided an 8-azabicyclo[3.2.1]oct-6-ene skeleton, which enables easy access to various natural products,[10] including tropane alkaloids. Recently, we found that 3-hydroxy-2-pyrone derivatives were good substrates as cyclic 1,3-dienes for the intermolecular Diels-Alder reaction, in terms of reactivity and selectivity, in our total synthesis of (−)-*iso*-A82775C.[11] Therefore, we focused on the investigation of an intermolecular [4+3] cycloaddition reaction using 3-hydroxy-2-pyrone derivatives **1** as a four-carbon unit[12] and (2-silyloxy)allyl acetate **2**[13] as the three-carbon unit (eq. 2). The cycloadduct **3** possesses the array of functionality in the bicyclic framework, providing a platform for the synthesis of complex natural products. We herein report; (i) the stereoselective intermolecular [4+3] cycloaddition of 2-pyrones and the oxyallyl cation prepared *in situ* from **2**, and (ii) the representative transformations of the obtained cycloadducts.



We firstly examined the intermolecular [4+3] cycloaddition reaction using 3-hydroxy-2-pyrone (**1a**) and (*Z*)-3-acetoxy-1-(methylthio)-2-(triisopropylsilyloxy)-1-propene (**2**) in the presence of Brønsted or Lewis acids. After several experiments, we found that the treatment of **1a** with **2** (1.3 equiv) and Tf_2NH (2.0 equiv) in CH_2Cl_2 at −30 °C afforded cycloadduct **3a** in 86% yield, as a single diastereomer (Scheme 2).



Scheme 2. Initial attempts for the intermolecular [4+3] cycloaddition reaction using 3-hydroxy-2-pyrones

X-Ray crystallographic analysis confirmed the stereochemistry of **3a** (Figure 1).[14] It is noteworthy that this reaction shows perfect regio- and stereoselectivity,[15] even though the intermolecular version of [4+3] cycloaddition generally shows less regioselectivity.

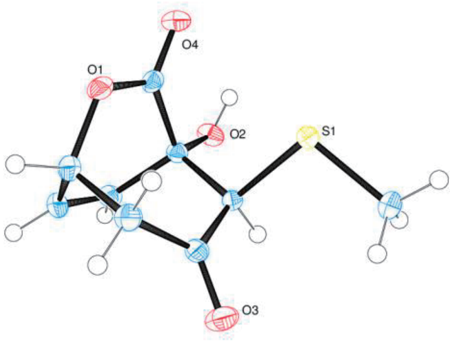
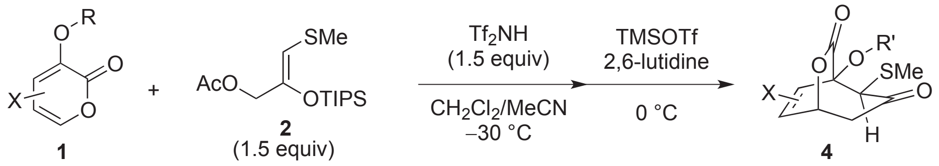
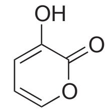
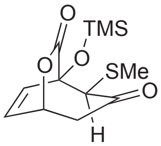
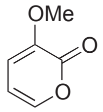
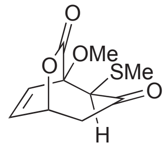
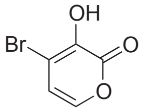
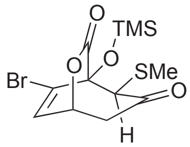
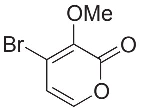
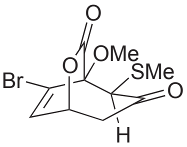
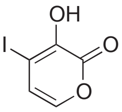
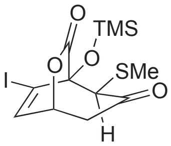
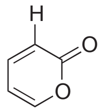
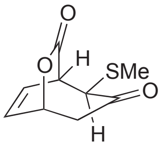
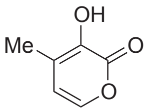
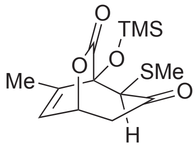
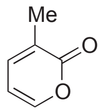
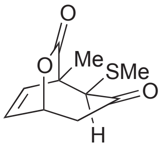
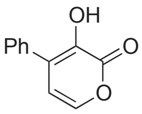
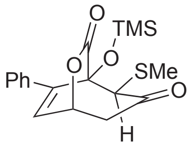
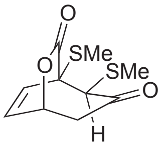


Figure 1. ORTEP drawing of cycloadduct **3a**

Next, we attempted the cycloaddition reaction of di-substituted 2-pyrones, such as **1b**, and acetate **2**. Using the same condition provided the desired cycloadduct **3b** as the sole product in crude mixture; however, **3b** was obtained in 54% yield after purification. It was found that **3b** is slightly unstable, probably due to the *retro*-aldol type ring-opening reaction. Thus, the *in situ* TMS-protection protocol[16] was employed to investigate the [4+3] cycloaddition using 3-hydroxy-2-pyrone derivatives **1a-f** (Table 1). Using this protocol for the reaction of **1a** and **1b** with **2** increased the yield of cycloadducts **4a** and **4b** (entries 1 and 2). The reaction using 4-iodo derivative **1c** and **2** proceeded smoothly to give cycloadduct **4c** in 85% yield (entry 3). Alkyl-substituted 3-hydroxy-2-pyrone **1d** was also a good substrate for this cycloaddition, providing **4d** in 77% yield (entry 4). On the other hand, using phenyl-substituted 3-hydroxy-2-pyrone **1e** (entry 5) resulted in a decrease in the yield to 54%, probably due to steric effect. Next, we investigated the substituents at C3 position. The cycloaddition reaction using 3-methoxy-2-pyrone (**1f**) and **2** afforded cycloadduct **4f** in 81% yield; however, the use of 4-bromo-3-methoxy-2-pyrone (**1g**) did not result in a reaction.[17] Moreover, the less electron-rich 2-pyrones **1h**, and **1i** did not react, and sulfide **1j** was decomposed in this condition.

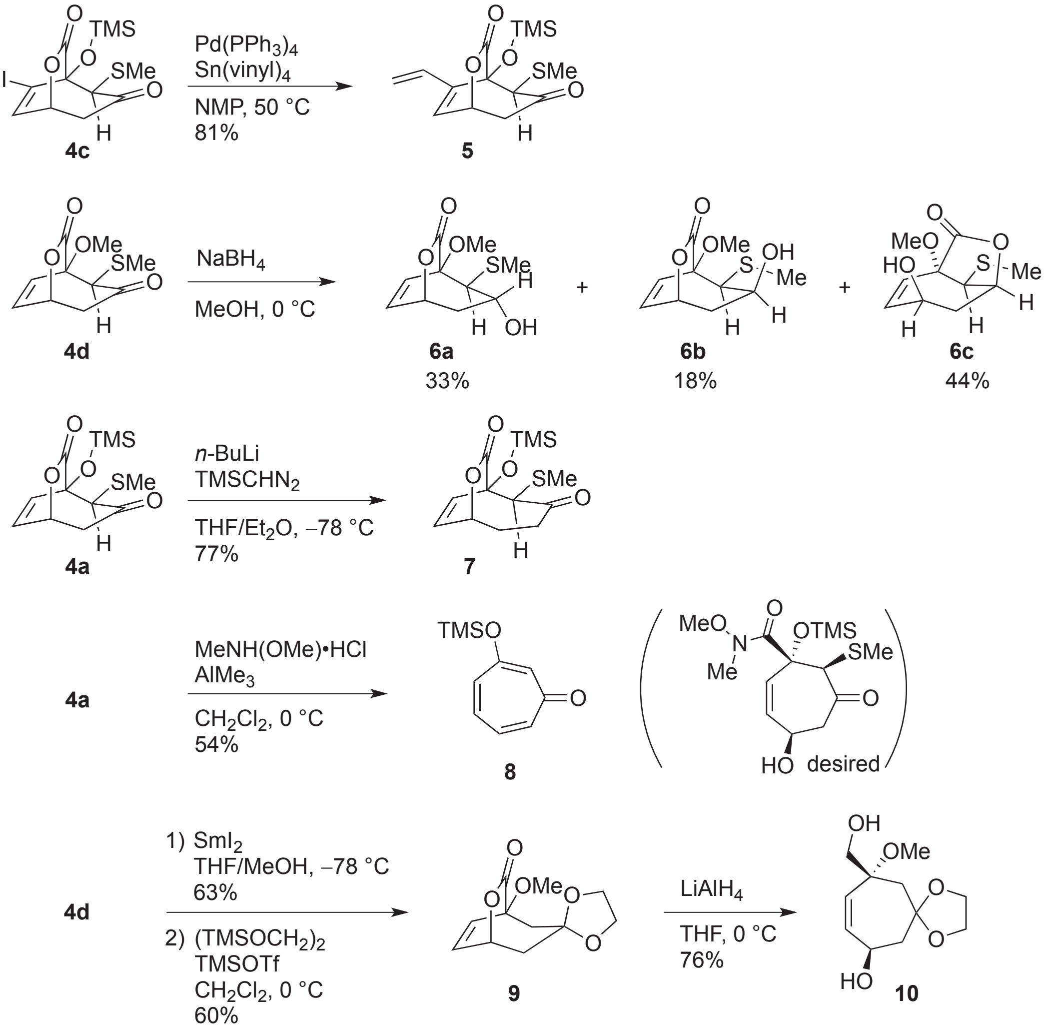
Table 1. Investigation of the intermolecular [4+3] cycloaddition reaction using 2-pyrones



entry	2-pyrone	product	yield (%)	entry	2-pyrone	product	yield (%)
1	 **1a**	 **4a**	92	6[a]	 **1f**	 **4f**	81
2	 **1b**	 **4b**	94	7[a]	 **1g**	 **4g**	-
3	 **1c**	 **4c**	85	8[a]	 **1h**	 **4h**	-
4	 **1d**	 **4d**	77	9[a]	 **1i**	 **4i**	-
5	 **1e**	 **4e**	54	10[a]	 **1j**	 **4j**	-

[a] Reaction was carried out without TMS-protection.

We next focused on the transformation of the cycloadducts, i.e., 6-oxabicyclo[3.2.2]non-8-ene-3,7-diones, the reactivities of which are unknown (Scheme 3). Although the structure of the cycloadducts contains an allylic ester moiety, oxidative addition in the presence of Pd catalysts did not occur in the Tsuji-Trost-type conditions. Hence, Stille coupling of vinyl iodide **4c** with tetravinyltin, in the presence of $Pd(PPh_3)_4$, successfully proceeded to give conjugated diene **5**. Nucleophilic addition reaction to ketone using $NaBH_4$ gave a mixture of alcohols **6a-6c** because of less selectivity, and translactonization. The treatment of **4a** with lithium trimethylsilyldiazomethane at −78 °C provided the eight-membered compound **7**[18] in 77% yield via a nucleophilic addition to ketone and a subsequent Tiffeneau-Demjanov reaction.[19] Unexpectedly, cleavage of the lactone ring proved troublesome. Standard conditions (alkaline saponification, Weinreb amide formation, transesterification using DMAP, etc.) gave tropone **8**. We assumed that the aromatization reaction was accelerated by the elimination of the methylthio group and the deprotonation of the α-hydrogen of ketone. Indeed, the treatment of lactone **9**, prepared in 2 steps from **4d**, with $LiAlH_4$ resulted in the cleavage of the lactone ring to give diol **10**.



Scheme 3. Several transformations of the obtained cycloadducts

In conclusion, we achieved stereoselective intermolecular [4+3] cycloaddition using 3-hydroxy-2-pyrone derivatives. Moreover, we demonstrated several transformations of the obtained cycloadducts. Further examinations of the inter-/intramolecular [4+3] cycloaddition reactions of 2-pyrones with other three-carbon units are currently underway.

ACKNOWLEDGEMENTS

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12. To the best of our knowledge, there are only two reports of the [4+3] cycloaddition reaction using 2-pyrones: (a) B. M. Trost and S. Schmeider, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 213; (b) B. M. Trost and M. C. Matelich, *J. Am. Chem. Soc.*, 1991, **113**, 9007. Their Pd-catalyzed [4+3] cycloaddition using 2-trimethylsilylmethylallyl acetate as a three-carbon unite gave seven-membered carbocycles via a stepwise mechanism; however the reaction using a 3-substituted pyrone was favored a [3+2] cycloaddition reaction.
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14. CCDC1864564 (for **3a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via

www.ccdc.cam.ac.uk/data_request/cif.

15. Interestingly, the cycloaddition using pyrones shows as *exo* selectivity, whereas the *endo* approaches were favored in our previous studies (see, ref. 9). The mechanistic studies to clarify the selectivity remain to be investigated.
16. General procedure for [4+3] cycloaddition reaction: To a solution of 2-pyrone **1** (0.20 mmol) and acetate **2** (0.30 mmol) in MeCN (1.0 mL) was added a solution of Tf_2NH (0.30 mmol) in CH_2Cl_2 (1.0 mL) at −30 °C. The mixture was stirred for 30 min at the same temperature. After completion of the reaction (by monitoring TLC), 2,6-lutidine (1.2 mmol) and TMSOTf (0.70 mmol) were added to the reaction mixture and the mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with MeOH (0.55 mmol) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Hexane/AcOEt = 3/1 as eluent) to give cycloadduct **4** as a solid.
17. We postulated that due to the steric repulsion of Me group with Br and carbonyl groups, Me group shields vertical surfaces of **1g**.
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