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Unexpected Prins cyclization: iron-promoted cyclization/hydration of alkynyl-dimethyl acetals

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ABSTRACT

Unexpected products containing acyl-substituted unsaturated seven-membered carbocycle were synthesized by $FeCl_3$-promoted intramolecular Prins cyclization of alkynyl-dimethylacetals in good yields. It is remarkable that the synthesized 7-exocyclic vinyl cations generated as a result of Prins-type cyclization were trapped by H_2O (no halogen ion) in CH_2Cl_2 to give the corresponding enol derivatives. Those enol derivatives underwent enol-keto tautomerism and then eliminated one molecule of MeOH to give the corresponding acyl-substituted unsaturated seven-membered carbocycle.

The Prins reaction is an important carbon–carbon bond forming reaction consisting in the acid-catalyzed condensation of aldehydes with alkenes.[1] Today the relevance of this reaction as substrates and acid-catalyst has led to the study and application of many variations.[2] Acid catalysts, such as Lewis acids, organic acids, and supported catalysts have been reported to assist both Prins acyclic reaction and Prins cyclization. Alkynyl and allenyl group-attached acetals, ketone, and oxocarbenium ions (generated from aldehydes and alcohols) have been described as substrates in the Prins reaction. The Lewis acid-promoted reactions of alkynyl–aldehyde or acetals (LA $\geqslant$ 1.0 equiv and with halogen) usually gave rise to the halogen products which formed as the result of vinyl cation intermediate-trapping by halogen ion (Scheme 1).[2,3] However, Lewis acid promoted-cyclization reactions of alkynes, using other nucleophilic reagents such as H_2O to capture the vinyl cation intermediates, have received less attention.[3e] In this Letter, we report an intramolecular Prins cyclization for the synthesis of acyl-substituted unsaturated seven-membered carbocycle. The reaction features use of H_2O to capture the vinyl cation intermediates, and employment of inexpensive, environmentally friendly, and stable $FeCl_3$ as catalyst.

We recently found a new cascade process to synthesize spiro[4.5]decane derivatives with high diastereoselectivity by using $FeCl_3$ promoted Prins cyclization of 2-(5,5-dimethoxypentyl)-1-substituted cyclopentanols (Scheme 1).[4] Of late, we explored the use of this cascade reaction to generate spiro[4.4]nonane derivatives. However, when $m = 0$, treating compound **1** with $FeCl_3$ provided acyl-substituted unsaturated seven-membered carbocycle **3** in moderate yields (Scheme 1).

To our knowledge, only one example[5] has been reported on the synthesis of acyl-substituted products by TMSOTf promoted Prins-type cyclization of terminal-substituted alkynyl alcohols with various aldehydes. Moreover, bicyclo[5.3.0]decane skeletons are also ubiquitous in nature, occurring in a wide range of biologically active substances, such as Bisanhydrolactarorufin A[6] and Frondosin B.[7] Therefore, there has been much interest in the development of methods for synthesis of these subunits from α-hydroxy alkynyl acetals.

Firstly, we started our investigation by treating alkynyl-dimethyl acetals **1a** with $FeCl_3$ (0.3 equiv) in CH_2Cl_2 at 0 °C (Table 1, entry 1). Acyl-substituted unsaturated seven-membered carbocycle **3a** was obtained in 36% yield and **1a** was recovered in 16% yield. Increasing the amount of $FeCl_3$ to 1.0 equiv (entry 2) led to the complete conversion within 30 min. and **3a** was obtained in 46% yield with complete conversion of **1a**. However, when alkynyl-dimethyl acetals **1a** was treated with $FeCl_3$ (1.0 equiv) in the presence of 4 Å molecule sieve in CH_2Cl_2 at 0 °C, lower yield was obtained (Table 1, entry 3). We speculated that H_2O might play a role in the reaction. Therefore, 2.0 equiv of H_2O was added and the yield of **3a** was increased to 50% (entry 4).When the amount of H_2O was increased to 3.0 equiv, **3a** was obtained in 79% yield (entry 5). However, further raising the amount of H_2O to 4.0 equiv, it did not lead to further improvement (entry 6). These results confirmed that H_2O (3.0 equiv) was essential to induce this cyclization reaction. Other iron salt catalysts were used to study the reaction (entries 7 and 8). $FeCl_2$ would not improve the yield of **3a** and

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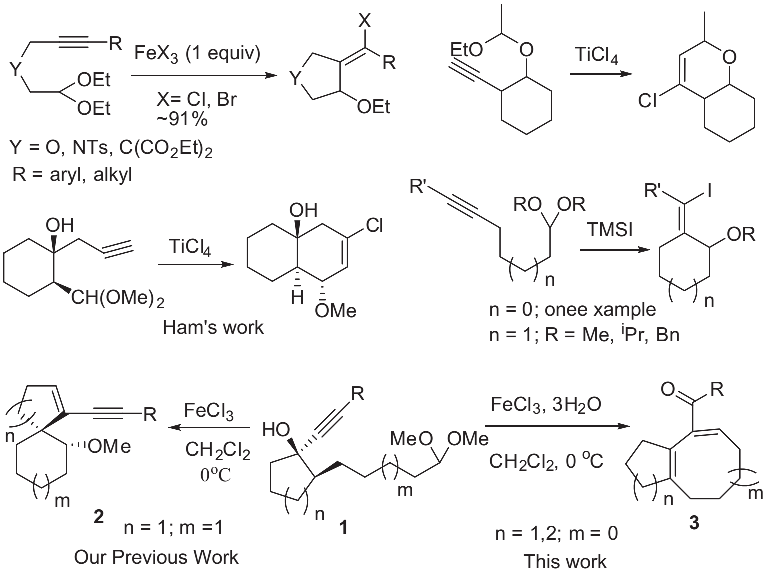
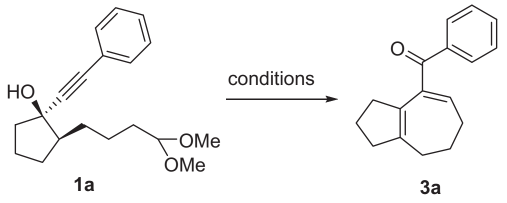


Scheme 1. Lewis acid promoted Prins cyclization of alkynyl acetals.

Table 1
Optimization of intramolecular Prins cyclization conditions[a]



Entry	Cat./equiv	Solvent	H_2O/equiv	Temp (°C)	Time (min)	Yield[c] (%)
1	$FeCl_3$/0.3	CH_2Cl_2	–	0	50	36
2	$FeCl_3$/1.0	CH_2Cl_2	–	0	30	46
3	$FeCl_3$/1.0	CH_2Cl_2[b]	–	0	60	37
4	$FeCl_3$/1.0	CH_2Cl_2	2	0	30	50
5	**$FeCl_3$/1.0**	**CH_2Cl_2**	**3**	**0**	**30**	**79**
6	$FeCl_3$/1.0	CH_2Cl_2	4	0	30	61
7	$FeCl_2$/1.0	CH_2Cl_2	3	0	60	32
8	$Fe_2(SO_4)_3$/1.0	CH_2Cl_2	3	rt	120	–
9	TMSOTf/1.0	CH_2Cl_2	3	−23	20	73
10	$TiCl_4$/1.0	CH_2Cl_2	3	−78	20	32
11	$SnCl_4$/1.0	CH_2Cl_2	3	−78	30	16
12	$FeCl_3{\cdot}6H_2O$/1.0	CH_2Cl_2	–	0	40	Trace
13	AgOTf/0.1	CH_2Cl_2	3	0	40	–
14	$ZnBr_2$/1.0	CH_2Cl_2	3	0	60	–
15	$CuCl_2$/1.0	CH_2Cl_2	3	rt	120	–
16	TsOH/1.0	CH_2Cl_2	3	0	120	–
17	$FeCl_3$/1.0	THF	3	0	60	–
18	$FeCl_3$/1.0	MeCN	3	0	60	–

[a] Reactions were conducted with 0.2 mmol of **3a**, in 5 mL of solvent.
[b] 4 Å molecule sieve was added in reaction.
[c] Isolated yield.

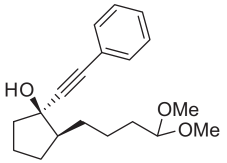
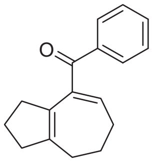
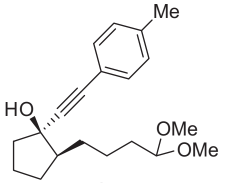
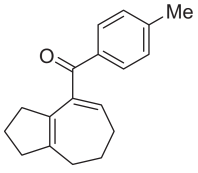
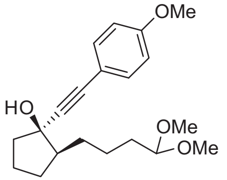
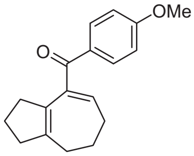
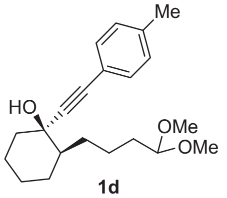
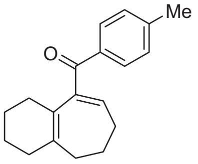
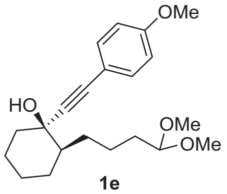
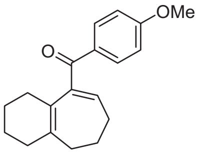
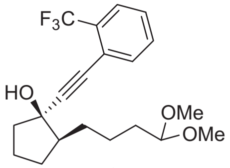
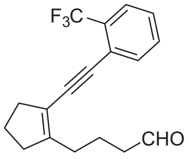
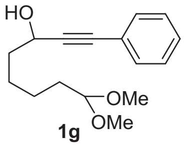
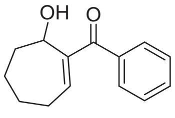
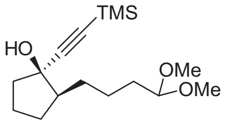
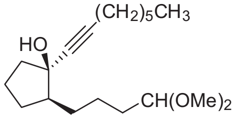
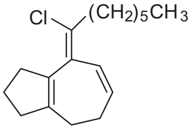
$Fe_2(SO_4)_3$ was inactive. And then, the effects of other Lewis and Brønsted acids were investigated (entries 9–16). Use of TMSOTf failed to improve the yield of **3a** (entry 7). $TiCl_4$, $SnCl_4$, and $FeCl_3{\cdot}6H_2O$ showed low catalytic activity while AgOTf, $ZnBr_2$, $CuCl_2$, and TsOH were inactive. When THF or MeCN was employed as solvents, no desired product was observed (Table 1, entries 17 and 18). Thus, the optimized cyclization conditions were found to be using 1.0 equiv of **1a**, 1.0 equiv of $FeCl_3$ and 3.0 equiv of H_2O in CH_2Cl_2 at 0 °C for 30 min.

To explore the scope of the Prins cyclization, a variety of alkynyl-dimethyl acetals **1** were examined under the optimized conditions. And the results were summarized in Table 2. Electron-donating substituents at *para*-position of the aryl group did not obviously affect the yields of the desired products (entries 1–3). The reactions of substrates containing six-member rings were also investigated. As expected, the corresponding α,β-unsaturated keto bicyclo[5.4.0]hendecanes **3d** and **3e** were obtained in good yields (entries 4 and 5).

When substrate containing an electron-withdrawing group at *ortho*-position of the aryl ring was used, no cyclized product was observed (entry 6); instead, aldehyde **3f** was detected as a major product. It was probable that the 2-trifluoromethyl on aryl group reduced the electron density of the carbon–carbon triple bond to prevent it from attacking the oxonium ion, which was generated from acetal in the presence of $FeCl_3$. Additionally, acetal **1g** with a linker chain was examined; the desired product **3g** was obtained in 10% yield. When trimethylsilanealkynyl **1h** was used, the starting material decomposed and no product was observed under the optimized conditions. Additionally, when the alkyne was attached to an alkyl group instead of an aryl ring (entry 9), the chlorovinyl bicarbocycles **3i** was obtained in 39% yield as the main product.

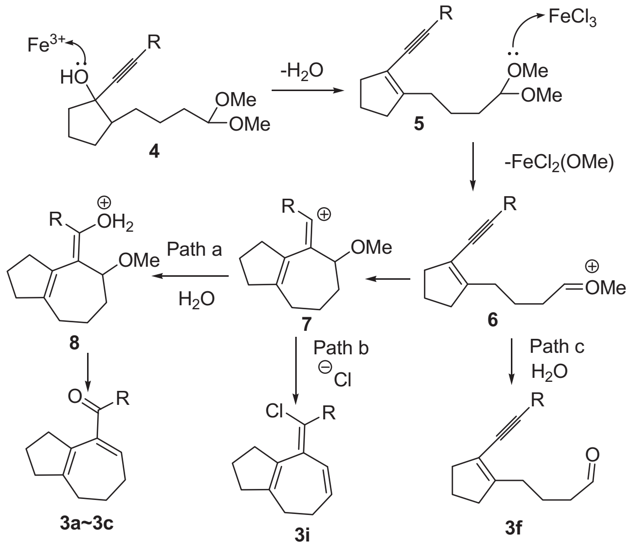
Based on these results, a reaction mechanism is proposed as shown in Scheme 2. The reaction was initiated by eliminating one molecule of H_2O from **4** in the presence of $FeCl_3$,[8] giving rise to **5**. The compound **5** was transformed by the action of $FeCl_3$ to the oxonium ion intermediate **6** with Denmark[9] and Yu's[3h] work as literature precedents. Nucleophilic attack of C–C triple bond on the cation center in **6** would lead to the formation of **7**. It was noted that when the C–C double bond was also present in **6**, the attack on the cation center at double bond seemed more easily than at triple bond, since the relative rate for Prins cyclization is in the order of alkene > alkyne.[3b,4] In our cases, however, the products containing bicyclo[5.3.0]decane or bicyclo[5.4.0]hendecane formed more easily than that the spiro[4.4]decane derivatives. When R was the electron-rich aryl group, the H_2O attacks the vinyl cation intermediate **7** to give enol derivatives (path a). Those enol derivatives then underwent enol-keto tautomerism and eliminated one molecule of MeOH to give the corresponding acyl-substituted unsaturated seven-membered carbocycles. If R was aryl group attached to an

Table 2
The scope of the synthesis of acyl-substituted unsaturated seven-membered carbocycles by $FeCl_3$-promoted intramolecular Prins cyclization[a]

Entry	Substrates **1**	Products **3**	Yield (%)[b]
1	 **1a**	 **3a**	79
2	 **1b**	 **3b**	72
3	 **1c**	 **3c**	72
4	 **1d**	 **3d**	81
5	 **1e**	 **3e**	77
6	 **1f**	 **3f**	48
7	 **1g**	 **3g**	10
8	 **1h**	Decompose	
9	 **1i**	 **3i**	39

[a] Optimized conditions: **1** (0.2 mmol), $FeCl_3$ (1.0 equiv), H_2O (3.0 equiv), CH_2Cl_2 (5 ml), 0 °C, 30–40 min.

[b] Isolated yield.



Scheme 2. A plausible mechanism for the formation of products.

electron-withdrawing group, the oxonium ion was attacked by neither double bond nor triple bond. H_2O attacked the oxonium ion to give aldehyde **3f**. When R was an alkyl group, the Cl^- attacked the vinyl cation intermediate **7** to give the halogen product **3i**.

In conclusion, a new strategy is developed for the synthesis of the acyl-substituted unsaturated seven-membered carbocycle by employing the $FeCl_3$-promoted intramolecular Prins cyclization. This is convenient, economical, and environmentally friendly. The process would serve as a good complement to the existing methodologies and its mild reaction condition must be useful in the synthesis of nature products with such skeletons. Efforts toward this goal are in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.035.

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