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Highly Selective $FeCl_3$-Catalyzed Cyclization of β-Sulfonamidoallenes or β-Allenols and Aldehydes

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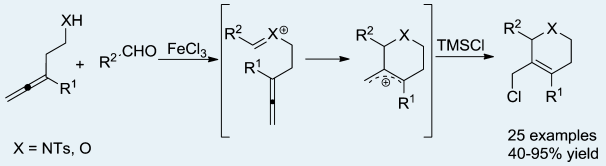
Supporting Information

ABSTRACT: A $FeCl_3$-catalyzed Prins cyclization reaction of β-sulfonamidoallenes or β-allenols with aldehydes has been developed for the synthesis of 3-chloromethyl-1,2,5,6-tetrahydro-1*H*-pyridine or 3-chloromethyl-5,6-dihydro-2*H*-pyran. The reaction is highly selective due to the stability of the allyl cation intermediate.

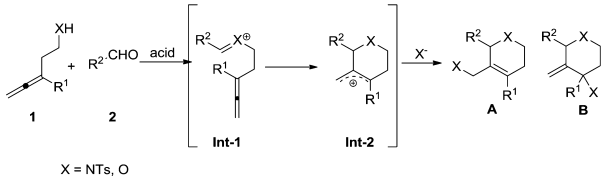


KEYWORDS: *β-sulfonamidoallenes, β-allenols, Prins cyclization, catalysis, 3-chloromethyl-1,2,5,6-tetrahydro-1H-pyridine, 3-chloromethyl-5,6-dihydro-2H-pyran*

Tetrahydropyridines and dihydropyran compounds, especially 3-chloromethyl-1,2,5,6-tetrahydropyridines and 3-chloromethyl-5,6-dihydro-2*H*-pyran derivatives, are important structural units of broad interest and have been extensively utilized as synthetic intermediates.[1−8] However, there are only scattered synthetic reports, such as by chlorination of the corresponding alcohols,[9−11] which indicated the challenge for synthesizing such compounds.[9−12]

During the last 20 years, cyclization reactions of allenes have been extensively developed as an efficient methodology for the synthesis of cyclic products.[13−22] On the other hand, Prins cyclization utilizing alkenes and alkynes as substrates has emerged as a powerful tool for the synthesis of heterocycles.[23−31] We envisioned that 3-chloromethyl-1,2,5,6-tetrahydropyridine derivatives may be efficiently constructed by using β-sulfonamidoallenes, aldehydes, and TMSCl in an atom-economic manner (X = NTs, Scheme 1). In principle, the

Scheme 1. Possible Reaction Pathways



reaction of β-sulfonamidoallenes or β-allenols with aldehydes under the catalysis of acid might provide intermediate **Int-1**.[27,28] Sequential cyclization and nucleophilic attack may provide products **A** and **B**. What is more interesting to us is the possibility of highly selective formation of **A**-type 3-chloromethyl-5,6-dihydropyran derivatives (X = O, Scheme 1).[32−37]

Herein, we report an efficient synthesis of 3-chloromethyl-1,2,5,6-tetrahydropyridine or 3-chloromethyl-5,6-dihydro-2*H*-pyran derivatives via $FeCl_3$-catalyzed cyclization reactions of β-sulfonamidoallenes[38] or β-allenols[39] in the presence of aldehydes and TMSCl under mild conditions.[40−42]

Our initial work began with *N*-(3,4-pentadienyl)-4-tolylsulfonamide **1a**, 4-chlorobenzaldehyde **2a**, and TMSCl under the catalysis of Fe(III). As a first try, we were happy to notice that the reaction of **1a** (1 equiv), **2a** (1.2 equiv), $FeCl_3$ (5 mol %), and TMSCl (1.5 equiv) in DCM with stirring at 30 °C for 10 h afforded the **A**-type cyclized product **3a** in 24% yield (Table 1, entry 1).[43] Increasing the amount of catalyst improved the yield greatly (Table 1, entries 2−3); however, applying 30 mol % of $FeCl_3$ decreased the yield of **3a** (Table 1, entry 4). Increasing the amount of **2a** did not help (Table 1, entry 5). Interestingly, when we reduced the amount of TMSCl, the reaction became higher yielding, with 1 equiv of TMSCl being the best (Table 1, entry 6). Studies on the solvent effect (Table 1, entries 7−9) revealed that DCM is the best. No product was obtained in the absence of $FeCl_3$ (Table 1, entry 10). Only a trace amount of product was afforded if TMSCl was not added (Table 1, entry 11). The reaction also did not happen if LiCl was used instead of TMSCl (Table 1, entry 12). Furthermore, $Fe(acac)_3$ and $FeSO_4·7H_2O$ were less efficient than $FeCl_3$ (Table 1, entries 13 and 14).

Having the optimized reaction conditions in hand, we next set out to examine the generality of this cyclization reaction of various substituted β-sulfonamidoallenes **1** with aldehydes. As for benzaldehyde **2b**, the corresponding product **3b** was obtained in 70% yield (Table 2, entry 1). The reactions were

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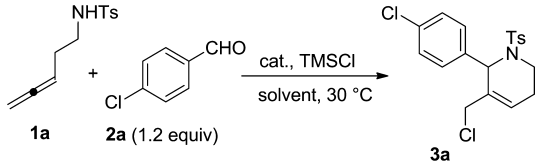
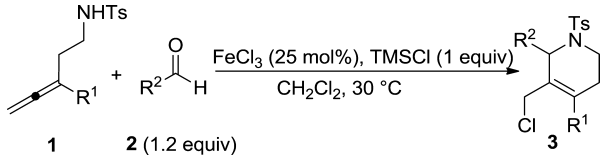
Table 1. Optimization of the Reaction Conditions for the Fe(III)-Catalyzed Prins Cyclization of 1a with 2a[a]



entry	cat. (mol %)	TMSCl (equiv)	solvent	t (h)	yield of **3a** (%)[b]
1	$FeCl_3$ (5)	1.5	DCM	10	24
2	$FeCl_3$ (10)	1.5	DCM	9	54
3	$FeCl_3$ (25)	1.5	DCM	8.5	70
4	$FeCl_3$ (30)	1.5	DCM	9	64
5[c]	$FeCl_3$ (25)	1.5	DCM	16	68
6	$FeCl_3$ (25)	1.0	DCM	8	78 (71[j])
7	$FeCl_3$ (25)	1.0	DCE	10	59
8	$FeCl_3$ (25)	1.0	toluene	10	15
9[d]	$FeCl_3$ (25)	1.0	THF	15.5	–
10[e]	–	1.0	DCM	16.5	–
11[f]	$FeCl_3$ (25)	–	DCM	16.5	6
12[g]	$FeCl_3$ (25)	–	DCM	23	–
13[h]	$Fe(acac)_3$	1.0	DCM	10	33
14[h,i]	$FeSO_4{\cdot}7H_2O$	1.0	DCM	12	–

[a]The reaction was conducted using **1a** (0.1 M), aldehyde (1.2 equiv), catalyst, and TMSCl in CH_2Cl_2 at 30 °C. [b]Determined by ^1H NMR analysis with 1,3,5-trimethyl benzene as the internal standard. [c]1.5 equiv of **2a** was applied. [d]The recovery of **1a** is 93%. [e]The recovery of **1a** is 94%. [f]The recovery of **1a** is 45%. [g]1.0 equiv of LiCl was used instead of TMSCl. The conversion of the reaction is 11%. [h]25 mol % catalyst was applied. [i]The recovery of **1a** is 84%. [j]Isolated yield.

Table 2. $FeCl_3$-Catalyzed Prins Cyclization of 1a with Aldehydes 2 under Standard Conditions[a]



entry	R^1	R^2	t (h)	yield of **3** (%)[b]
1	H (**1a**)	Ph (**2b**)	8	70 (**3b**)
2	H (**1a**)	4-BrC_6H_4 (**2c**)	8	68 (**3c**)
3	H (**1a**)	4-FC_6H_4 (**2d**)	9	52 (**3d**)
4	H (**1a**)	3-BrC_6H_4 (**2e**)	8	66 (**3e**)
5	H (**1a**)	3-$NO_2C_6H_4$ (**2f**)	8	66 (**3f**)
6	H (**1a**)	2-BrC_6H_4 (**2g**)	8	64 (**3g**)
7	H (**1a**)	2-ClC_6H_4 (**2h**)	8	65 (**3h**)
8[c]	H (**1a**)	H (**2i**)	8	40 (**3i**)
9[d]	H (**1a**)	n-C_3H_7 (**2j**)	19	71 (**3j**)
10[d]	H (**1a**)	i-C_3H_7 (**2k**)	10	64 (**3k**)
11	H (**1a**)	c-hexyl (**2l**)	10	61 (**3l**)
12	allyl (**1b**)	4-ClC_6H_4 (**2a**)	9.5	60 (**3m**)

[a]The reaction was carried out at 30 °C in CH_2Cl_2 using **1** (c = 0.1 M), aldehyde (1.2 equiv), $FeCl_3$ (25 mol %), and TMSCl (1.0 equiv) at the indicated time. [b]Yield of isolated product. [c]p-Formaldehyde was used. [d]$FeCl_3$ (30 mol %), aldehyde (2.0 equiv), and TMSCl (1.5 equiv) were used in this reaction.

also suitable when the phenyl ring in the aromatic aldehydes was substituted with $p/m/o$-Br (Table 2, entries 2, 4, and 6), p-F (Table 2, entry 3), m-NO_2 (Table 2, entry 5), or o-Cl (Table 2, entry 7). For aliphatic aldehydes, including paraformaldehyde (Table 2, entry 8), primary- (Table 2, entry 9), and secondary-alkyl aldehydes (Table 2, entries 10–11), the reaction also afforded the corresponding products in 40–71% yields. When *N*-(3-allyl-3,4-pentadienyl)-4-tolylsulfonamide, **1b**, was used as substrate, the corresponding product **3m** was obtained in 60% yield. The structure of the product was unambiguously established by the X-ray diffraction study of **3h** and **3k** (Figure 1).[44,45]

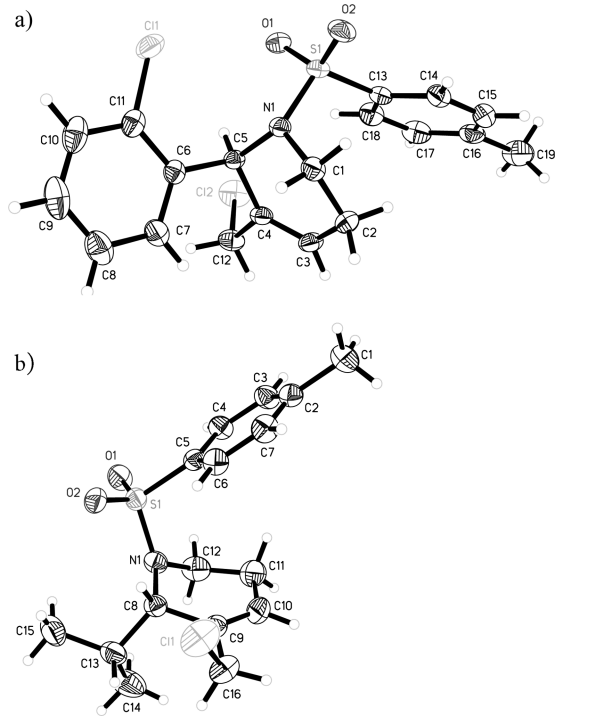
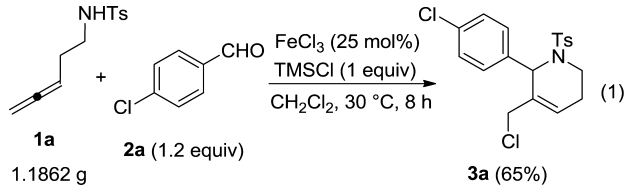


Figure 1. ORTEP drawings of (a) **3h** and (b) **3k**.

It is easy to conduct the reaction of **1a** and **2a** to afford **3a** in 65% yield in 1 g scale (eq 1).



Excitingly, when 3,4-pentadien-1-ol **4a** was applied as substrate, 3-chloromethyl-5,6-dihydro-2*H*-pyran derivative **5a** was also obtained in high yield and selectivity.[46,47] Only 5 mol % $FeCl_3$ was used at 40 °C due to the higher reactivity of β-allenol than β-sulfonamidoallene. As can be seen from Table 3, the cyclization of 3,4-pentadien-1-ol **4a** (R^1 = H) and various substituted aromatic aldehydes all proceeded smoothly to give the desired products **5** in excellent yields (Table 3, entries 1–9). Moreover, when R^1 was *n*-butyl or allyl, the corresponding products **5j** and **5k** were also formed in excellent yields (Table 3, entries 10 and 11). 3-Phenyl-3,4-pentadien-1-ol **4d** (R^1 = Ph) was also a suitable substrate for this reaction, although the yield was somewhat lower (Table 3, entry 12).

In conclusion, we have demonstrated a highly regioselective $FeCl_3$-catalyzed cyclization reaction of 3,4-allenyl amines or alcohols with aldehydes in the presence of TMSCl. This

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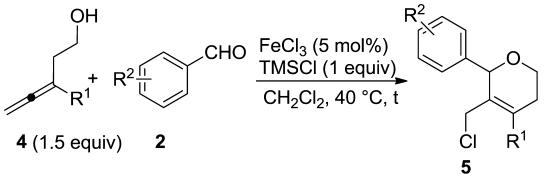
Table 3. $FeCl_3$-catalyzed Prins-cyclization of 4 with Aldehydes 2 under Standard Conditions[a]



4 (1.5 equiv) 2 5

entry	R^1	R^2	t (h)	yield of 5 (%)[b]
1	H (**4a**)	H (**2b**)	10	66 (**5a**)
2	H (**4a**)	4-^{i}Pr (**2m**)	10	75 (**5b**)
3	H (**4a**)	4-MeO (**2n**)	10	50 (**5c**)
4	H (**4a**)	4-Cl (**2a**)	10	78 (**5d**)
5	H (**4a**)	4-Br (**2c**)	10	85 (**5e**)
6	H (**4a**)	4-F (**2d**)	9.3	75 (**5f**)
7	H (**4a**)	4-CO_2Me (**2o**)	24	83 (**5g**)
8	H (**4a**)	3-Me (**2p**)	10	74 (**5h**)
9	H (**4a**)	2-Cl (**2h**)	10	72 (**5i**)
10[d]	n-C_4H_9 (**4b**)	4-Cl (**2a**)	2	95 (**5j**)
11[d]	allyl (**4c**)	4-Cl (**2a**)	2	94 (**5k**)
12[e]	Ph (**4d**)	4-Cl (**2a**)	3	76 (**5l**)

[a]Reaction conditions: 40 °C in CH_2Cl_2 using aldehyde **2** (c = 0.1 M), **4** (1.5 equiv), $FeCl_3$ (5 mol %), TMSCl (1.0 equiv) at indicated time. [b]Yield of isolated product. [c]$FeCl_3$ (10 mol %) and TMSCl (1.5 equiv) were used in this reaction. [d]$FeCl_3$ (10 mol %) and TMSCl (1.0 equiv) were used in this reaction. [e]$FeCl_3$ (10 mol %) and **4d** (2.0 equiv) were used in this reaction.

reaction produces 3-chloromethyl-1,2,5,6-tetrahydropyridine or 3-chloromethyl-5,6-dihydro-2*H*-pyran derivatives efficiently and highly selectively due to the high stability of the allyl cation intermediate. The combination of $FeCl_3$ and TMSCl work together to promote the condensation of the 3,4-allenyl amines or alcohols with aldehydes, while TMSCl also serves as the halide source.[40−42] In view of the easy availability of the starting materials and the catalyst, this methodology will be of great interest to the scientific community. Further studies on the scope and mechanism of the reaction as well as synthetic applications of the products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; characterization data; and copies of ^1H, ^{13}C, and ^{19}F NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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(44) Crystal data for **3h**. $C_{19}H_{19}Cl_2NO_2S$; MW = 396.31; triclinic; space group *P*-1; final *R* indices [$I > 2(I)$], $R_1 = 0.0409$, $wR_2 = 0.1115$; *R* indices (all data), $R_1 = 0.0479$, $wR_2 = 0.1175$; $a = 7.077(2)$ Å, $b = 7.792(2)$ Å, $c = 17.241(5)$ Å; $\alpha = 83.163(6)$ °, $\beta = 83.039(6)$°, $\gamma = 75.993(6)$°; $V = 911.7(5)$ Å^3; $T = 293(2)$ K; $Z = 2$; reflections collected/unique, 5582/3577 ($R_{int} = 0.0192$); number of observations [$I > 2(I)$], 3071; parameters, 227. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 914744).
(45) Crystal data for **3k**. $C_{16}H_{22}ClNO_2S$; MW = 327.86; orthorhombic; space group *Pbca*; final *R* indices [$I > 2(I)$], $R_1 = 0.0424$, $wR_2 = 0.1163$; *R* indices (all data) $R_1 = 0.0504$, $wR_2 = 0.1293$; $a = 14.8823(6)$ Å, $b = 15.0709(6)$ Å, $c = 15.0819(6)$ Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 3382.7(2)$ Å^3; $T = 296$ K; $Z = 8$; reflections collected/unique, 36842/2975 ($R_{int} = 0.0352$); number of observations [$I > 2(I)$], 2557; parameters, 191. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 913577).
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