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An efficient approach to the synthesis of 3-vinylidene tetrahydropyrans via Prins-type cyclization

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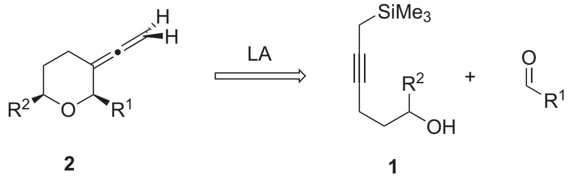
Abstract—Lewis acid-catalyzed intramolecular reactions of oxocarbenium ions with propargylsilanes are described. The results obtained indicate that trimethylsilyl trifluoromethanesulfonate (TMSOTf) efficiently catalyses cyclization leading to the corresponding 3-vinylidene tetrahydropyrans in high yield as single isomers.

Substituted tetrahydropyrans are common structural fragments of many natural products and biologically active compounds and many strategies for their synthesis have been reported.[1] A valuable approach to the preparation of tetrahydropyrans is a Prins-type cyclization in which a homoallylic alcohol and carbonyl compound in the presence of an acid catalyst forms the oxocarbenium cation, which subsequently undergoes an intramolecular reaction with the alkene.[2] Considerable effort has been directed towards improving the efficiency of the Prins cyclization, primarily by increasing the nucleophilicity of the alkene reagents. A number of previous reports documented the utility of allylsilanes,[3] vinylsilanes[4] and allenylmethylsilanes[5] as intramolecular traps for the oxocarbenium ions generated.

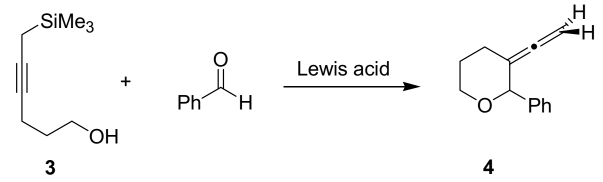
Herein, we report that propargylsilanes of type **1** that can also be used as substrates in Lewis acid promoted reactions with aldehydes, to yield the corresponding 3-vinylidene tetrahydropyrans **2** as shown in Scheme 1.

6-(Trimethylsilyl)-4-hexyn-1-ol **3**[6] was chosen as the substrate for our initial studies. It was efficiently prepared in three steps starting from 4-butyn-1-ol in 75% overall yield.



Scheme 1.

Table 1. Lewis acid mediated synthesis of 2-phenyl-3-vinylidene tetrahydropyran



Entry	Lewis acid	Conditions	Yield of **4** (%)
1	TMSOTf	1.5 equiv, Et_2O, −78 °C	90
2	$TiCl_4$	1.0 equiv, CH_2Cl_2, −78 °C	72
3	$BF_3{\cdot}Et_2O$	1.0 equiv, CH_2Cl_2, −78 °C	80
4	$InCl_3$	1.0 equiv, CH_2Cl_2, rt	53
5	$Yb(OTf)_3$	0.1 equiv, CH_3CN, rt	41

In order to test the feasibility of **3** as a precursor for a Prins cyclization, its reaction with benzaldehyde with a range of Lewis acids was investigated (Table 1).

Of the Lewis acids screened, TMSOTf (entry 1) was found to be the most promising candidate. The other Lewis acids generally did not exhibit activity

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Keywords: Propargylsilanes; Tetrahydropyrans; Prins cyclization.

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comparable to that of TMSOTf, furnishing the same product, but in lower yields (entries 2–5).

After establishing the optimized reaction conditions, the scope and limitations of this variant of the Prins cyclization were subsequently examined. Representative results are summarized in Table 2.

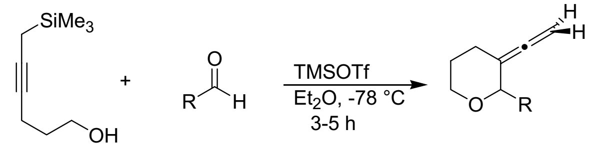
In most cases, good to excellent yields were obtained for the TMSOTf mediated reaction using a range of different aldehydes.[7] There were no significant differences in the yield of the reaction for the various benzaldehydes (entries 1–4). The aliphatic aldehydes also worked well, however, in those cases the products were obtained in somewhat decreased yields (entries 5–7). The lower yield can be attributed to the volatility of such compounds. Finally, an α,β-unsaturated aldehyde (entry 8) was also a suitable reaction partner but, in this case, afforded a 3-vinylidene tetrahydropyran in a modest yield only.

In order to investigate the synthesis of 2,6-disubstituted-3-vinylidene pyrans, we extended our studies to α-ethyl **6** and α-phenyl **7** substituted alcohols (Scheme 2).

These substrates were easily prepared in two steps using the literature methods[8] (oxidation using CrO_3/C_5H_5N followed by addition of the appropriate Grignard reagents) from **3** in 46% and 52% overall yields, respectively.

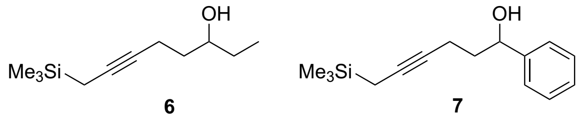
Reactions of **6** and **7** with representative aldehydes led to the 2,6-disubstituted-3-vinylidene tetrahydropyrans in good yields and with excellent stereoselectivity; only the respective 2,6-*cis* isomers were formed (Table 3).[9] The relative stereochemistry at C2 and C6 was easily established with the aid of NOE experiments. The H-2 and H-6 protons displayed a spin–spin interaction of about 7.0%. Careful examination of the crude reaction mixture did not show the presence of any 2,6-*trans* isomeric products.

Table 2. Synthesis of 2-substituted-3-vinylidene tetrahydropyrans



3 **5**

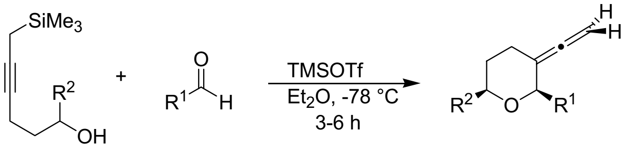
Entry	R	Yield of **5** (%)
1	Ph	90
2	p-MeC_6H_4	87
3	p-$MeOC_6H_4$	86
4	p-ClC_6H_4	87
5	$Ph(CH_2)_2$	93
6	n-C_6H_{13}	65
7	c-C_6H_{11}	76
8	PhCH=CH	42



6 **7**

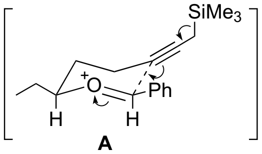
Scheme 2.

Table 3. Synthesis of 2,6-disubstituted-3-vinylidene tetrahydropyrans

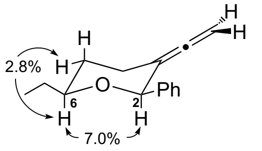


2

Entry	R^2	R^1	Yield of **2** (%)
1	C_2H_5	Ph	83
2	C_2H_5	p-MeC_6H_4	85
3	C_2H_5	p-$MeOC_6H_4$	90
4	C_2H_5	p-ClC_6H_4	85
5	C_2H_5	$Ph(CH_2)_2$	90
6	C_2H_5	$PhCH_2OCH_2$	76
7	Ph	Ph	92
8	Ph	p-$MeOC_6H_4$	82
9	Ph	p-ClC_6H_4	74
10	Ph	$Ph(CH_2)_2$	92
11	Ph	$PhCH_2OCH_2$	80
12	Ph	c-C_6H_{11}	72



A



We assume that the cyclization proceeds through the chair-like transition state **A**, where the aryl and alkyl substituents occupy the equatorial positions.

In conclusion, we have shown that propargylsilanes are excellent terminating groups for Prins cyclizations. The presented methodology provides an easy access to a variety of substituted tetrahydropyrans. The application of the developed procedure to the synthesis of functionalized tetrahydropyrans is currently underway in our laboratory.

Acknowledgement

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7. Typical experimental procedure for the trimethylsilyl trifluoromethanesulfonate mediated reaction: to a solution of propargylsilane (0.2 mmol) and aldehyde (0.4 mmol) in Et_2O (6 mL) at −78 °C, under argon, TMSOTf (0.4 mmol) was added dropwise. The reaction was stirred at −78 °C for 3–6 h. After completion of the reaction (TLC), the solution was allowed to warm to 0 °C, poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (2×10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (typically hexane–Et_2O, 95:5).
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9. Representative data for *syn*-6-ethyl-2-phenyl-3-vinylidene tetrahydropyran (Table 3, entry 1): ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 4.92 (m, 1H), 4.37 (m, 2H), 3.51 (m, 1H), 2.55 (ddd, $J = 2.5$, 4.8 and 13.7 Hz, 1H), 2.44 (m, 1H), 1.81 (m, 1H), 1.67 (m, 1H), 1.56 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 140.3, 127.5, 127.3, 127.1, 102.6, 80.0, 79.4, 76.1, 31.3, 29.1, 29.0, 9.8; IR (neat) cm^{-1} 1964, 1091; HRMS calcd for $C_{15}H_{18}O$: 214.1357. Found 214.1350.