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Synthesis of Azepane Derivatives by Silyl-aza-Prins Cyclization of Allylsilyl Amines: Influence of the Catalyst in the Outcome of the Reaction

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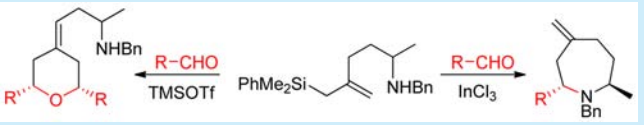
Supporting Information

ABSTRACT: The synthesis of seven-membered nitrogen heterocycles by silyl-aza-Prins cyclization is described. The process provides *trans*-azepanes in high yields and good to excellent diastereoselectivities. Moreover, the reaction outcome is dependent on the Lewis acid employed. Thus, while azepanes are selectively obtained when $InCl_3$ is used, the reaction in the presence of TMSOTf provides tetrahydropyran derivatives corresponding to a tandem Sakurai–Prins cyclization.



Functionalyzed azepanes are important structures present in several bioactive natural and unnatural products with medicinal and pharmaceutical properties. Their potential as glycosidase inhibitors[1] and their applications in the treatment of cancer,[2] diabetics,[3] and viral infections[4] has been reported. Examples of this type of compounds are the natural balanol,[5] a fungal metabolite isolated from *Verticillium balanolides* which is a potent PKC inhibitor, ophiocordin,[6] an antibiotic extracted from cultures of *Cordyceps ophioglossoides* which exhibit antifungal activity, and the unnatural (3*R*,4*R*,6*S*)-trihydroxyazepane, which has shown to be a potent inhibitor against (*R*)-mannosidase and (*R*)-fucosidase (Figure 1). Consequently, remarkable efforts have been made to develop efficient synthetic methods for these 7-membered azacycles.[7]

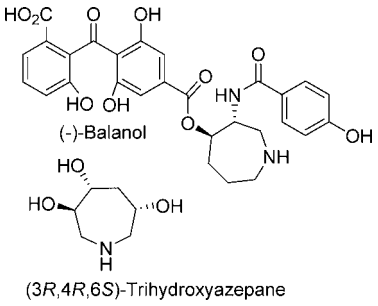
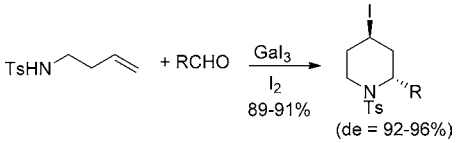


Figure 1. Azepane-containing bioactive products.

Prins cyclization has emerged as one of the most efficient approaches for the synthesis of heterocycles.[8] Typically, the reaction implies the acid-catalyzed addition of a homoallylic alcohol to an aldehyde to form an oxocarbenium ion, which undergoes 6-*endo* cyclization to afford the desired tetrahydropyran. This protocol has also been applied to the synthesis of 5- and 7-membered oxacycles.[9]

The extension of this methodology to the synthesis of nitrogen heterocycles, called aza-Prins cyclization, has been much less developed. Two different strategies have been described for this cyclization. One of them involves the reaction of two components such as a homoallylic amine and a carbonylic compound to give an iminium ion which readily undergoes intramolecular cyclization. This strategy has been used by Reddy[10] in the synthesis of 2,4-*trans*-piperidines. Thus, the reaction of *N*-tosylhomoallylamines with aldehydes, in the presence of gallium iodide, provides in high yield and excellent stereoselectivity the desired 4-iodopiperidines (Scheme 1).

Scheme 1. Synthesis of Piperidines by Aza-Prins Cyclization



In the alternative protocol, the iminium intermediate is formed in situ from a single precursor, generally an α-acetoxy-protected amine. For instance, Hanessian[11] has described an approach toward the total synthesis of natural oscillarin (marine metabolite with serine protease inhibitory activity) in which the key step is an aza-Prins cyclization of an α-acetoxypyrrolidine. The reaction involves the formation of an *N*-acyloxyiminium intermediate which undergoes 6-*endo* cyclization to provide the desired octahydroindole derivative (Scheme 2).

Although the aza-Prins cyclization has been frequently used to synthesize pyridine rings, to the best of our knowledge the synthesis of azepanes by Prins cyclization has never been reported.

In the course of our studies toward the synthesis of different sized carbo-[12,13] and heterocycles[14,15] from organosilanes, we became interested in the silyl-Prins cyclization. Using this

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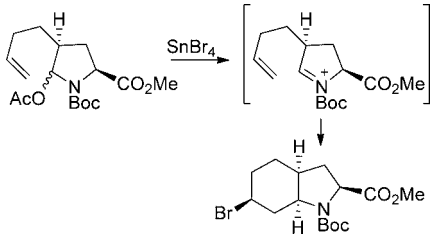
Scheme 2. Synthesis of Octahydroindoles by Aza-Prins Cyclization

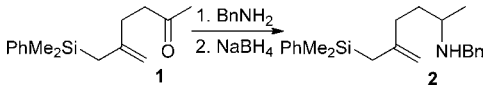


methodology, we have been able to synthesize oxepanes, dioxaspirodecanes, and oxocanes in a very efficient and stereoselective manner.

We herein present our results toward the synthesis of seven-membered nitrogen heterocycles using the silyl-aza-Prins cyclization.

The precursor allylsilyl amine was readily prepared in three steps. The reaction sequence implies the obtention of allylsilyl ketone **1** by silylcupration of allene and capture by but-3-en-2-one, followed by a reductive amination (Scheme 3).

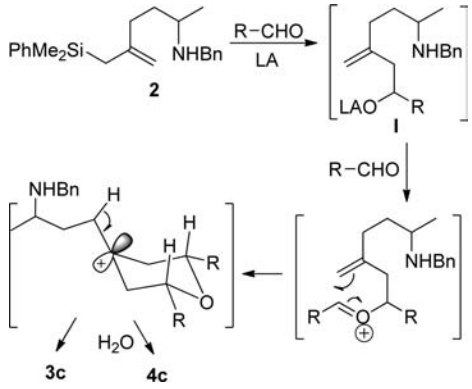
Scheme 3. Synthesis of Allylsilyl Amines



We chose the reaction between allylsilyl amine **2** and cinnamaldehyde as a model study to find the optimized conditions for this cyclization. The aza-Prins cyclization was studied using a variety of Lewis acids, as depicted in Table 1.

As shown, the reaction in the presence of $FeCl_3$, $SnCl_4$, $BF_3{\cdot}OEt_2$, or TFA proved to be ineffective, recovering the starting amine (Table 1, entries 1, 3, 4, and 5). The same reaction using TBAF, $TiCl_4$, or a mixture of $FeCl_3$ and TMSCl only provided the desilylated starting amine **5** (Table 1, entries 2, 6, and 7). With TMSOTf (1.2 equiv in DCM stabilized with EtOH) we obtained a mixture of three products which were tetrahydropyrans **3c** and **4c**, and the open-chain amine **6c** (Table 1, entry 8). Compound **6c** is the result of a Sakurai reaction between allylsilyl amine **2** and the intermediate acetal formed in situ by reaction of the aldehyde with EtOH. Compounds **3c** and **4c** are the products of a tandem Sakurai–Prins cyclization. Thus, reaction of allylsilane **2** with the aldehyde will give a homoallylic alkoxide **I** which readily undergoes condensation with another molecule of aldehyde to afford an intermediate oxocarbenium ion. The subsequent 6-*endo* Prins cyclization provides a tetrahydropiranyl cation which either undergoes elimination to give **3c** or addition of water to give **4c** (Scheme 4).

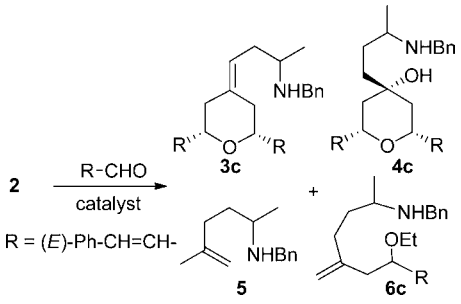
Scheme 4. Mechanism of Formation of Compounds 3 and 4



The same reaction in DCM free of EtOH provided a 9:1 mixture of tetrahydropyrans **3c** and **4c** in 78% yield (Table 1, entry 9). Increasing the amount of catalyst to 3 equiv gave the same result but in lower yield (Table 1, entry 10).

We next decided to explore the scope of this reaction using different aldehydes under the optimized conditions for the

Table 1. Prins Cyclization from Allylsilyl Amines



entry	catalyst	conditions	3c/4c/6c[a]	product (yield, %)
1	$FeCl_3$	rt, 720 h		nr[b]
2	$FeCl_3$, TMSCl	rt, 17 h		**5** (71)
3	$BF_3.OEt_2$	−78 °C, 1 h		nr[b]
4	TFA	−78 °C, 1 h		nr[b]
5	$SnCl_4$	−78 °C, 1 h		nr[b]
6	$TiCl_4$	−78 °C, 1 h		**5**[c] (65)
7	TBAF	MW		**5** (37)
8	TMSOTf	1.2 equiv of CH_2Cl_2/EtOH, −78 °C	18:2:80	**3c** + **4c** + **6c** (82)
9	TMSOTf	1.2 equiv of CH_2Cl_2 −78 °C, 1 h	90:10:0	**3c**+**4c** (78)
10	TMSOTf	3 equiv of CH_2Cl_2 −78 °C, 1 h	90:10:0	**3c** + **4c** (65)

[a]Determined by NMR analysis of the crude mixture. [b]No reaction. [c]From recovered starting amine.

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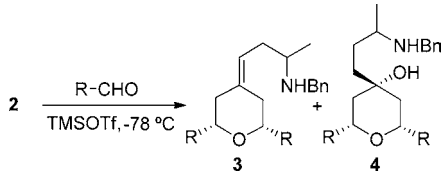
formation of tetrahydropyran derivatives (Table 1, entry 9). The results are shown in Table 2.

Table 2. Synthesis of Tetrahydropyran Derivatives from Allylsilyl Amines



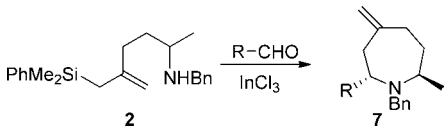
entry	R	3/4[a]	3 + 4 (yield, %)
1	4-MeOC$_6$H$_4$	91:9	**3a** + **4a** (81)
2	4-MeC$_6$H$_4$	93:7	**3b** + **4b** (77)
3	(*E*)-PhCH=CH	91:9	**3c** + **4c** (78)
4	(*E*)-MeCH=CH	90:10	**3d** + **4d** (76)
5	(*E*)-*n*-PrCH=CH	90:10	**3e** + **4e** (72)

[a]Determined by NMR analysis of the crude mixture.

As shown, the reaction is very selective toward the formation of **3**, although a small amount of compound **4** is always obtained.[16] Moreover, the cyclization is extremely stereoselective with the formation of a single diastereoisomer in each case. The stereochemical outcome of this process can be explained by a preferred chairlike transition state in which the bulky groups adopt the more stable pseudoequatorial position and the final nucleophilic attack of water occurs from the equatorial position.

We next decided to use $InCl_3$ as the Lewis acid since it has been reported to be an efficient catalyst for the aza-Prins cyclization of benzylic amines.[17] The reaction in DCM at room temperature did not provide the cyclic product but just the desilylated starting amine. Switching the solvent to acetonitrile and increasing the reaction temperature at reflux temperature provided the desired azepane derivative**7** in high yield. With these optimized conditions for the aza-Prins cyclization we extended the method to different aldehydes,[18] as shown in Table 3.

Table 3. Synthesis of Azepanes from Allylsilyl Amines



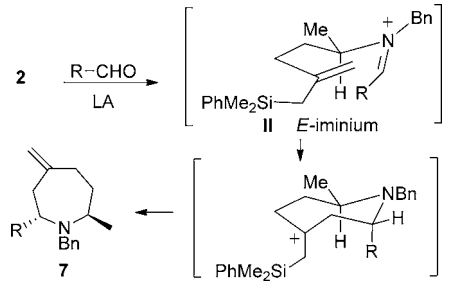
entry	R	7, *trans*/*cis*[a]	7 (yield, %)[b]
1	C$_6$H$_5$	86:14	**7a** (80)
2	4-MeOC$_6$H$_4$	91:9	**7b** (75)
3	4-MeC$_6$H$_4$	88:12	**7c** (82)
4	4-ClC$_6$H$_4$	80:20	**7d** (79)
5	4-BrC$_6$H$_4$	83:17	**7e** (78)
6	3-BrC$_6$H$_4$	80:20	**7f** (76)
7	(*E*)-PhCH=CH	82:18	**7g** (80)
8	(*E*)-*i*-BuCH=CPh	>95:5	**7h** (75)
9	(*E*)-Me-CH=CH		**7i**[c]
10	(*E*)-*n*-Pr-CH=CH		**7j**[c]

[a]Determined by NMR analysis of the crude mixture. [b]Isolated yield. [c]When crotonaldehyde or 2-hexenal were used the crude mixture showed high conversion of **2** to the azepane derivatives, whose identity could be corroborated by HRMS.[19] However, any attempt to purify and isolate them by chromatography was unsuccessful, probably due to their low boiling points.

The reaction is general both for arylic and vinylic aldehydes (Table 3). Moreover, the reaction leads to the corresponding *trans*-2,7-azepanes as the predominant or sole adducts. ^{1}H NMR and NOE experiments were used to establish the relative stereochemistry of azepanes **7** (see the SI). It is worth noting that the stereoselectivity of the cyclization is strongly dependent on the steric effects. Thus, when a very steric demanding aldehyde is used (Table 3, entry 8), a single diastereomeric *trans*-azepane **7h** is obtained.

The proposed mechanism for this silyl-aza-Prins cyclization implies the formation of a preferred *E*-iminium ion by condensation of **2** with the aldehyde. Further 7-*endo* cyclization will provide a stabilized carbocation β to silicon, which upon final elimination of the silyl group provides the azepane derivative (Scheme 5).

Scheme 5. Mechanistic Proposal for the Silyl-aza-Prins Cyclization



Theoretical calculations by Martin[20] and Milletti[21] have shown a greater stability of *E*-iminium ions (leading to the *trans*-isomers) versus the *Z* (leading to the *cis*-isomers). Following these conclusions, we can assume that in our case the most stable cation will be the *E*-iminium **II**, which selectively will provide the *trans*-azepane derivative. However, Dobbs[22] has recently noted that we can not rely on just the relative stability of intermediate iminium ions, since the Curtin–Hammett principle states that the product ratio is not solely dependent on the stability of intermediates but on the relative activation energies of their transition states.

In summary, we have developed a very efficient method for the synthesis of azepane derivatives by silyl-aza-Prins cyclization of allylsilyl amines. The reaction proceeds in high yield and with good to excellent diastereoselectivity toward the 2,7-*trans*-azepane. A survey of Lewis acids shows that $InCl_3$ is completely selective for the aza-Prins reaction. In contrast, when TMSOTf is used, a tandem Sakurai–silyl-Prins reaction leading to tetrahydropyran derivatives is observed. This catalyst-dependent chemoselectivity will be related to the most favorable of the two possible pathways (initial Sakurai reaction leading to intermediate **I** or aza-Prins cyclization). Thus, while we have shown that TMSOTf is able to promote Sakurai reactions,[15] TMSOTf has proven to be a poor catalyst for aza-Prins cyclizations.[23]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00538.

Experimental details, characterization data, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) We also tested the aza-Prins cyclization for the corresponding *N*-tosylamine ($InCl_3$, acetonitrile, reflux), but only the desilylated starting amine was obtained.

(19) **6i**: HRMS (ESI+) *m*/*z* calcd for $C_{18}H_{26}N$ ($[M + H]^+$) 256.2060, found 256.2058. **6j**: HRMS (ESI+) *m*/*z* calcd for $C_{20}H_{29}N$ ($[M+H]^+$) 284.2373, found 284.2376.

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