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Tetrabutylammonium triphenyldifluorosilicate (TBAT) initiated intramolecular addition of allylsilanes to 2,3-dihydro-4-pyridones. A novel route for the stereoselective construction of indolizidine systems

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Abstract—A general and preparatively simple access to multisubstituted indolizidines has been developed. The key step involves the fluoride ion induced intramolecular reaction of 2,3-dihydro-4-pyridones with allylsilane located in the side-chain.

Allylsilanes have been applied as nucleophilic components in the formation of carbon–carbon bonds.[1] The reactions of allylsilanes with conjugated enones (Sakurai reaction) in the presence of Lewis acids lead to the formation of δ,ε-enones.[2] Examples of both inter- and intramolecular Sakurai reactions have been reported.[3] These allylation reactions generally require stoichiometric or greater amounts of Lewis acids to obtain an acceptable yield of products. A catalytic version of this reaction is possible when $InCl_3$ (10 mol%) in the presence of TMSCl is used.[4] Reactions of allylsilanes with enones can be also carried out in a 1,4-fashion in the presence of fluoride ions.[5]

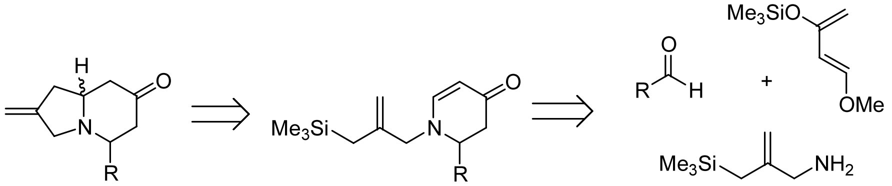
Numerous natural products contain an azabicyclic skeleton as a structural element.[6] Indolizidine alkaloids belong to this class of compounds. As they often exhibit marked pharmacological activity and because new members of this class of compounds continue to be discovered in Nature, the stereoselective synthesis of indolizidines is of great importance.

In this article, we describe a fluoride ion induced intramolecular reaction between the allylsilyl functional group and 2,3-dihydro-4-pyridones, as a key reaction within a proposed general approach to a variety of indolizidines (Scheme 1).

The key allylsilane amine **2**[7] can be obtained more effectively, in three steps, starting from allyl alcohol **1**[8] using known methods[9] in 82% overall yield (Scheme 2).

The aldimine **3** obtained from amine **2** and benzaldehyde reacted smoothly with Danishefsky's diene in the presence of a catalytic amount of $Yb(OTf)_3$ to afford the 2,3-dihydro-4-pyridone **4** in good yield (Scheme 3). Not surprisingly, the five-membered ring product **5** was not detected.[10]

Many imines, in particular those derived from aliphatic aldehydes are not particularly stable. It appeared desirable, from the synthetic point of view, to generate the



Scheme 1.

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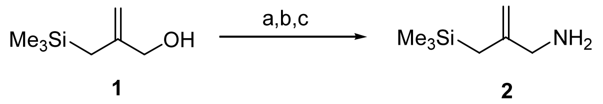
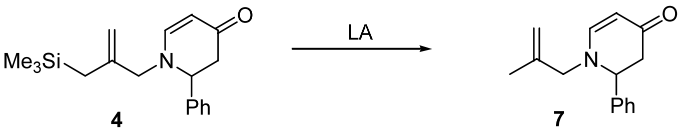


Scheme 2. *Reagents and conditions*: (a) TsCl, $(C_2H_5)_3N$, 0°C, 3 h; (b) NaN_3, DMF, rt, 2 h; (c) PPh_3, THF/H_2O, 20 h, rt.



Scheme 4.

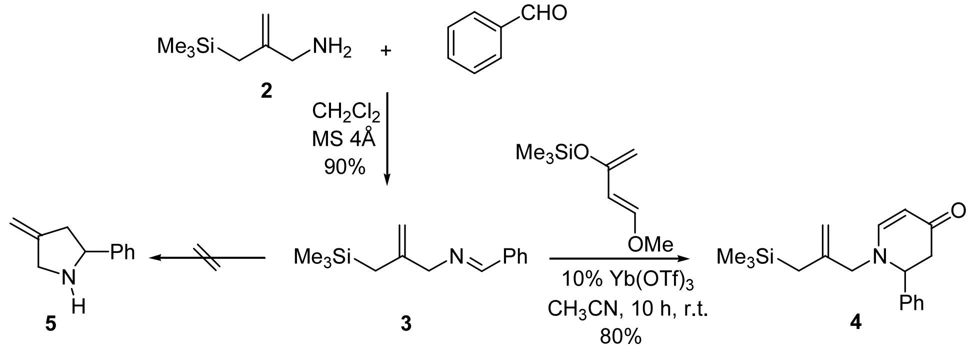
intermediate aldimines in situ and allow them to react with the appropriate diene under one-pot reaction conditions. Recently, Kobayashi[11] has reported that a catalytic amount of $Yb(OTf)_3$ (15–20%) effectively mediates the aza-Diels–Alder reaction between Danishefsky's diene and aldimines generated in situ from aliphatic aldehydes and *p*-anisidine. Also, Akiyama[12] reported that in the presence of montmorillonite K10, a three component aza-Diels–Alder reaction can be performed effectively.

We studied the three-component synthesis of the dihydro-4-pyridone derivatives by a one-pot aza-Diels–Alder reaction. As shown (Table 1), the one-pot reaction afforded the corresponding adducts **6** in good yield.[13]

The average yield of the cyclo-condensation reactions was comparable to that obtained from analogous reactions with isolated aldimines. The respective dihydro-4-pyridones were obtained using a wide range of aldehydes, including aromatic, olefinic and heteroaromatic aldehydes, even in the presence of water (entry 9).

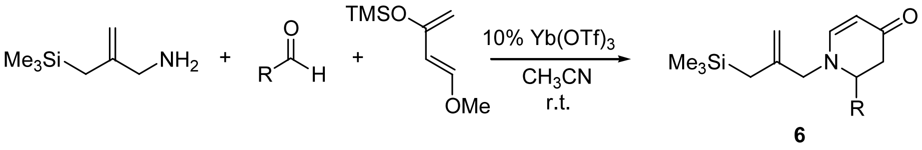
The 4-pyridones thus obtained were subjected to a Lewis acid mediated intramolecular Sakurai reaction. Unfortunately, numerous attempts using $TiCl_4$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $EtAlCl_2$, $InCl_3$/TMSCl all failed to promote the intramolecular conjugated addition and resulted only in the protodesilylation product **7** (Scheme 4).

We also examined various fluoride ion sources as promoters of the Sakurai reaction. The use of anhydrous Bu_4NF in the DMF/HMPT (3:1) mixture[5b] afforded the expected indolizidines in 20% yield, along with a significant amount of desilylated product. Other fluoride ion sources such as CsF or TASF failed to promote the cyclization at all. However, the use of the soluble, anhydrous, non-hygroscopic tetra-



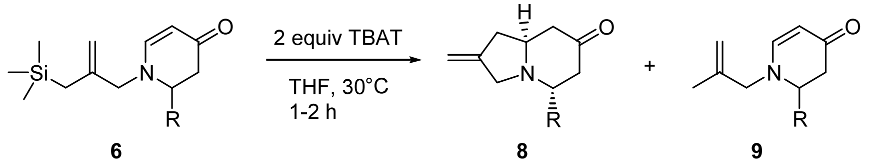
Scheme 3.

Table 1. Results of the three-component aza-Diels–Alder reaction

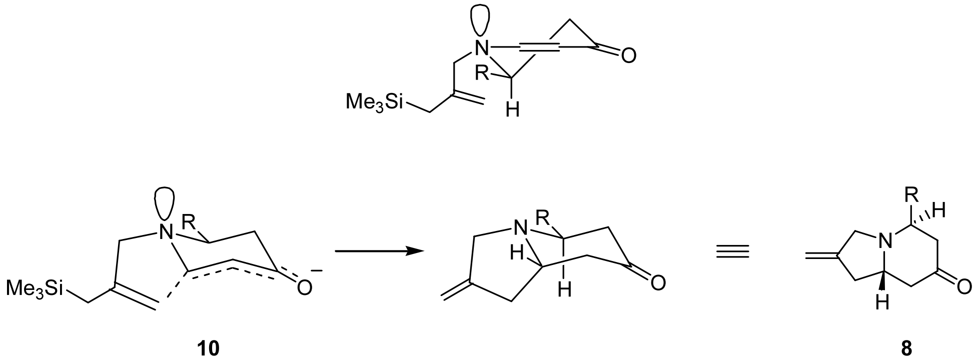


Entry	R	Solvent	Yield of **6**, %
1	C_6H_5	CH_3CN	96
2	4-$MeOC_6H_4$	CH_3CN	85
3	2-Pyridyl	CH_3CN	80
4	$BnOCH_2$	CH_3CN	70
5	$CH_3CH_2CH_2$	CH_3CN	78
6	$(CH_3)_2CH$	CH_3CN	70
7	$(CH_3)_3C$	CH_3CN	56
8	$CH_3(CH_2)_8$	CH_3CN	68
9	$(CH_3O)_2CH$	CH_3CN/H_2O	60

Table 2. TBAT initiated intramolecular addition of allylsilane to 2,3-dihydro-4-pyridones



Entry	R	Yield of **8**, %	Yield of **9**, %
1	Ph	81	0
2	4-MeOC$_6$H$_4$	70	0
3	2-Pyridyl	82	0
4	BnOCH$_2$	63	7
5	CH$_3$CH$_2$CH$_2$	84	8
6	(CH$_3$)$_2$CH	59	0
7	(CH$_3$)$_3$C	56	5
8	CH$_3$(CH$_2$)$_8$	77	0
9	(CH$_3$O)$_2$CH	67	0



Scheme 5.

butylammonium triphenyldifluorosilicate (TBAT)[14] as the fluoride source (2 equiv.) gave much better results (Table 2).[15]

For all entries in Table 2, treatment of the 2-substituted 2,3-dihydro-4-pyridones with 2 equiv. of TBAT in THF at 30°C led to the desired indolizidines in good yields as a single detectable diastereomer, as estimated from the ^{1}H and ^{13}C NMR data.[16] The relative stereochemistry at C5 and C9 was established with the aid of NOE experiments. The stereochemical outcome observed in these cyclizations is rationalized in Scheme 5.

We suggest that the reaction proceeds through the transition state **10** where the bulky substituent R is located in the equatorial position, while the nitrogen electron pair is in the axial orientation. The nucleophilic terminal of the double bond enters exclusively *anti* to the R substituent to provide compound **8** with the *trans* orientation between the C5 and C9 protons.

In conclusion, we have demonstrated a general and efficient stereospecific synthesis of indolizidines. Work is currently in progress to apply this methodology to the diastereo- and enantioselective synthesis of indolizidines.

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13. The typical experimental procedure for the ytterbium triflate mediated reaction: The aldehyde (0.2 mmol), amine 2 (0.2 mmol) and Danishefsky's diene (0.22 mmol) were dissolved in MeCN (5 mL) at rt and $Yb(OTf)_3$ (0.02 mmol, 10 mol%) was added in one portion. The reaction mixture was stirred for 10–15 h, then water was added and the product was extracted with CH_2Cl_2 (10 mL×3). After usual work-up, the crude material obtained was chromatographed on silica gel to give the final product. Representative data for 2-phenyl-1-(2-trimethylsilanylmethyl-allyl)-2,3-dihydro-1*H*-pyridin-4-one (Table 1, entry 1): ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.25 (m, 5H), 7.13 (d, 1H, $J=7.6$ Hz), 5.03 (d, 1H, $J=7.6$ Hz), 4.79 (m, 2H), 4.62 (m, 1H), 3.52 (m, 2H), 2.94 (dd, 1H, $J=16.5$ and 7.3), 2.68 (dd, 1H, $J=16.5$ and 7.1), 1.44 (s, 2H), −0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.1, 154.2, 142.2, 138.7, 128.9, 128.2, 126.9, 110.7, 98.2, 60.8, 59.4, 43.5, 23.6, −1.5; HRMS (ESI) calcd for $C_{18}H_{26}NOSi$ $(M+H^+)$ 300.1778, found 300.1791.
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15. Typical experimental procedure for TBAT mediated cyclocondensation: The 2,3-dihydro-4-pyridones (0.1 mmol) and TBAT (0.2 mmol) were dissolved in THF (5 mL). After 10 min, the reaction turned orange, and after 1 h, the reaction was complete. The THF was removed under reduced pressure, the residue was redissolved in 10 mL of 1:1 Et_2O/EtOAc, and filtered. The filtrate was concentrated, and the crude material obtained was purified by column chromatography to give the desired product. Representative data for 2-methylene-5-phenyl-hexahydro-indolizin-7-one (Table 2, entry 1): ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 4.90 (m, 2H), 4.33 (dd, 1H, $J=6.3$ and 4.3 Hz), 3.47 (dd, 1H, $J=13.7$ and 1.4 Hz), 3.20 (m, 1H), 3.13 (ddd, 1H, $J=13.7$, 2.3 and 1.0 Hz), 2.88 (ddd, 1H, $J=15.3$, 6.3 and 1.0 Hz), 2.73 (ddd, 1H, $J=15.3$, 4.3 and 1.6 Hz), 2.67 (ddd, 1H, $J=14.9$, 3.9 and 1.6 Hz), 2.60 (m, 1H), 2.44 (ddd, 1H, $J=14.9$, 9.9 and 0.8 Hz), 2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 209.4, 146.0, 138.3, 128.4, 128.2, 127.6, 106.2, 60.1, 55.3, 55.2, 46.0, 45.2, 38.4; HRMS (EI) calcd for $C_{15}H_{17}NO$ 227.13101, found 227.13189.
16. All new compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy and by HRMS analysis.