Facile Synthesis of Various 1-Azabicyclo[n.4.0]alkanes *via* Beckmann Rearrangement/Allylsilane Cyclization

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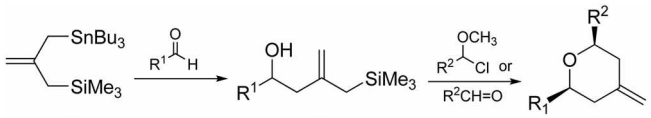
Received June 13, 2008

Key Words : Allylsilane. Beckmann rearrangement. 3-Stannyl-2-(silylmethyl)propene. *N*-Heterocycle

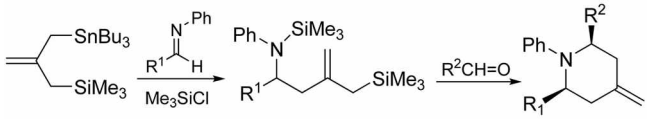
The carbon-carbon bond formation by the reaction of allylsilanes with electrophiles has been widely used in organic synthesis.[1] Particulary, intramolecular cyclization of allysilanes bearing an electrophilic terminus has an extensive application for the highly regio- and stereo-selective synthesis of various ring compounds.

The bismetallic reagent 3-stannyl-2-(silylmethyl)propene **1**[2] should be a versatile conjunctive reagent since the allylstannane and the allylsilane moieties of **1** could be manipulated sequentially and in a controlled manner.[3] Indeed, the allylstannane moiety of **1** selectively react with an aldehyde to yield hydroxy allylsilane **2**.[4] The reactions of **2** with either vinyl ethers or α-halo ethers give acetals which are subsequently cyclized to afford 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans **3**.[5]



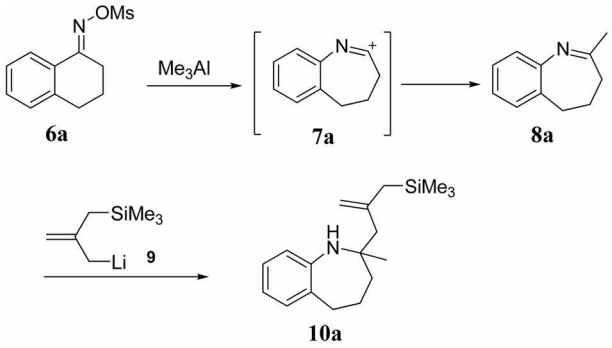
1 **2** **3**

Enantioselective synthesis of the tetrahydropyrans **3** was achieved by using the hydroxy allylsilanses **2** generated from the catalytic asymmetric allylation of **1** with aldehydes.[6] This annulation reaction enabled an efficient synthesis of the biologically active tetrahydropyran natural products.[7] Various 2,6-disubstituted 4-methylenepiperidines were also prepared in one-pot by the sequential reactions of aldimines with bismetallic reagent **1** followed by aldehydes.[8]



1 **4** **5**

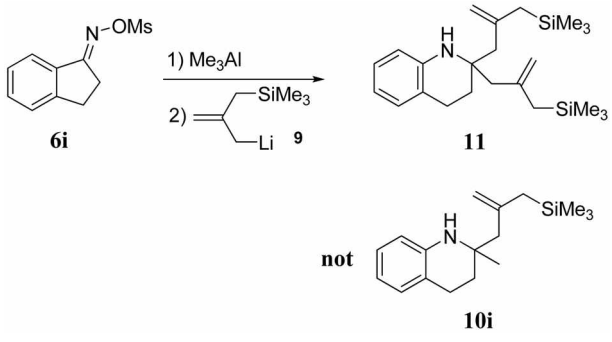
We described herein the synthesis of 1-azabicyclo[n.4.0]-alkanes using bismetallic reagent **1**. Reaction of α-tetralone oxime mesylate **6a** with 2 equivalents of trimethylaluminum resulted in the formation of cyclic ketimine **8a**. Methylation of intermediate iminocarbocation **7a**, which was generated from the organoaluminum-promoted Beckmann rearrangement[9] of oxime mesylate **6a**, with trimethylaluminum afforded cyclic imine **8a**. Allylation of cyclic ketimine **8a** with allyllithium **9** gave cyclic amino allylsilane **10a** in good yield.[10] 2-(Trimethylsilylmethyl)allyllithium **9** was generated by treating bismetallic reagent **1** with methyllithium.



6a **7a** **8a** **10a**

This easy and one-pot reaction has a wide generality. Other synthetic examples of this type are given in Table 1. It permits the introduction of an allylsilane moiety into a substrate with a simultaneous ring expansion.

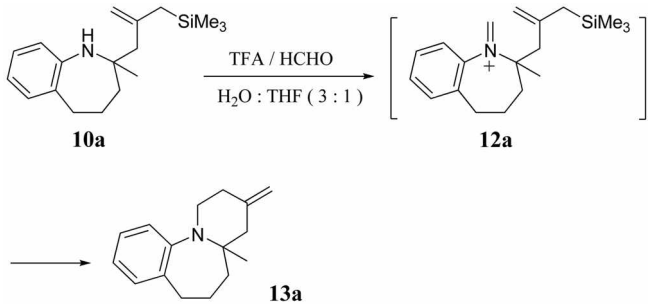
In the synthesis of ketimines **10a** and **10b**, rigorous regioselectivities were observed. The phenyl group anti to departing mesylate group migrated preferentially.[9] For some reasons, this process did not work for all the oxime mesylated tested. For example, reaction of 1-indanone oxime mesylate **6i** with trimethylaluminum and followed allyllithium **9** under standard reaction condition gave only diallylation product **11** in low yield.[11] Even with larger excess of trimethylaluminum (4 equiv) and after prolonged reaction time, the expected monoallylation product **10i** was not produced. It is not clear why such anormalous behavior was observed for 1-indanone oxime mesylate only.



6i **11** **10i**

Mannich cyclization of iminium-vinyl and allylsilanes is to provide an attractive method for the regio-controlled production of piperidines possessing either endo- or exo-

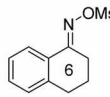
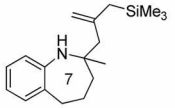
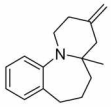
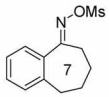
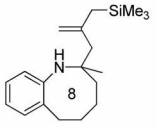
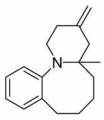
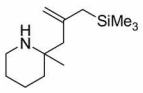
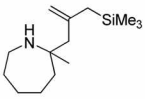
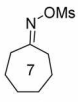
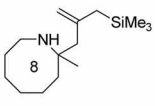
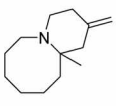
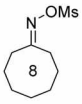
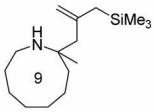
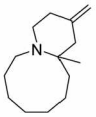
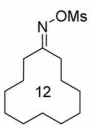
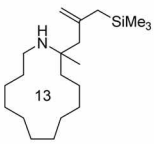
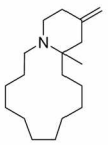
cyclic unsaturation.[12] Cyclic amino allylsilanes **10** as their trifluoroacetate salts were treated at 40-45 °C with 1.2 equiv. of formaldehyde in water:tetrahydrofuran (3:1) to give azabicyclic compounds **13**.[13]



10a **12a**

13a

Table 1. Synthesis of cyclic amino allylsilanes **10** and 1-azabicyclo[n.4.0]alkanes **13**

Entry	Oxime mesylate **6**	Amino allysilane **10**/Yield (%)		Azabicycle **13**/Yield (%)	
1	 **6a**	 **10a**	72	 **13a**	87
2	 **6b**	 **10b**	78	 **13b**	72
3	 **6c**	 **10c**	57	 **13c**	54
4	 **6d**	 **10d**	61	 **13d**	85
5	 **6e**	 **10e**	49	 **13e**	66
6	 **6f**	 **10f**	57	 **13f**	86
7	 **6g**	 **10g**	42	 **13g**	64

As shown be seen in Table 1. 1-azabicyclo[n.4.0]alkanes of various ring size (n = 4, 5, 6, 7 and 11) were obtained in good yields.

The present reaction sequence, organoaluminum-promoted Beckmann rearrangement of oxime mesylate, allylation reaction with 2-(trimethylsilylmethyl)allyllithium, and Mannich reaction, provides a versatile and useful synthetic method for 1-azabicylo[n.4.0]alkanes.

Acknowledgments. This work was supported for two years by Pusan National University Research Grant.

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10. **10a**: ^{1}H NMR δ 0.04 (9H, s), 1.06 (3H, s), 1.62-1.72 (4H, m), 1.63 (1H, d, J = 13.2 Hz), 1.74 (1H, d, J = 13.2 Hz), 2.08 (1H, d, J = 13.0 Hz), 2.23 (1H, d, 13.0 Hz), 2.74 (2H, t, J = 4.8 Hz), 3.74 (1H, brs), 4.74 (1H, s), 4.81 (1H, s), 6.67-6.98 (4H, m); ^{13}C NMR δ 1.5, 22.5, 25.5, 29.5, 35.5, 42.7, 50.6, 54.9, 111.9, 121.0, 121.2, 126.4, 129.9, 134.0, 144.3, 146.2; HRMS m/z 287.2080 ($C_{18}H_{29}NSi$ requires 287.2071).
11. **11**: ^{1}H NMR δ 0.00 (18H, s), 1.61 (4H, d, J = 13.2 Hz), 1.71 (4H, d, J = 13.2 Hz), 1.83 (2H, t, J = 6.8 Hz), 2.10 (4H, d, J = 13.4 Hz), 2.26 (4H, d, J = 13.4 Hz), 2.78 (2H, t, J = 9.8 Hz), 3.90 (1H, brs), 4.59 (2H,s), 4.71 (2H, s), 6.46-7.06 (4H, m); ^{13}C NMR δ −1.3, 23.7, 29.4, 30.4, 46.7, 54.0, 111.4, 114.7, 116.7, 120.4, 126.7, 129.2, 143.9, 144.0; HRMS m/z 385.2619 ($C_{23}H_{39}NSi_2$ requires 385.2623).
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13. **13a**. ^{1}H NMR δ 0.97 (3H, s), 1.26-1.42 (2H, m), 1.52-1.72 (1H, m), 1.80-1.99 (2H, m), 2.28-2.45 (2H, m), 2.48-2.74 (2H, m), 2.92-3.50 (3H, m), 4.75 (1H, s), 4.88 (1H, s), 6.88-7.28 (4H, m); ^{13}C NMR δ 19.2, 19.5, 30.3, 35.5, 37.7, 44.9, 46.8, 56.1, 109.6, 121.4, 122.5, 126.6, 128.2, 137.0, 145.6, 148.8; HRMS m/z 227.1681 ($C_{16}H_{21}N$ requires 227.1675).