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A convenient allylsilane-*N*-acyliminium route toward 5-alkylindolizidines. Diastereoselective synthesis of (±)-indolizidine 167B

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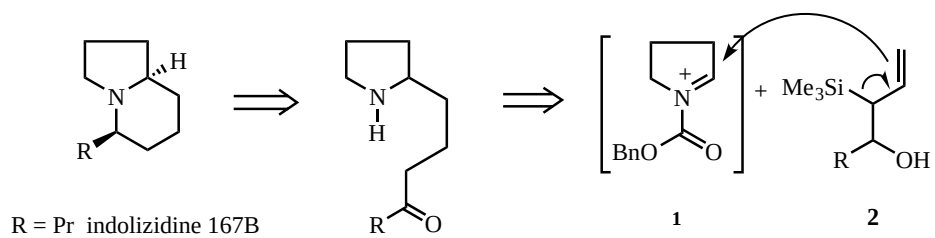
Abstract—A highly diastereoselective synthesis of 5-alkylindolizidines is described via an intermolecular addition of the allylsilyl functional group of homoallylic alcohols with an *N*-acyliminium ion derived from pyrrolidin-2-one.

Indolizidines constitute a very important class of compounds as they occur in a large number of natural products and display a variety of physiological activities. Indolizidines alkaloids have been isolated from the skin extracts of neotropical frogs of the family Dendrobates.[1,2] Most of them are monosubstituted by an alkyl chain in the 5-position or disubstituted in the 3,5- or 5,8-positions. These compounds serve as a defence against predation. Some of them are non-competitive blockers of nicotinic receptor channels. Accordingly, novel strategies for the stereoselective synthesis of indolizidine ring systems continue to receive considerable attention.[3]

The allylsilyl functional group is a weak carbon nucleophile extensively used for trapping *N*-acyliminium ions, thus providing an exceptionally useful method for carbon–carbon bond formation in both intermolecular and intramolecular cases.[4] We have applied the intramolecular methodology toward the synthesis of quinolizidine and indolizidine alkaloids.[5–7] In this article, we describe an intermolecular reaction between the allylsilyl functional group of homoallylic alcohols and the acyliminium ion coming from pyrrolidin-2-one as the key reaction for a new, general and flexible entry to a variety of 5-substituted indolizidines (Scheme 1). To highlight the method, this synthetic strategy was applied to the synthesis of indolizidine alkaloid (±)-167B.

Hydroxyallylsilanes **2** were synthesised as described[8] (Scheme 2) by reaction of the reagent prepared from allyltrimethylsilane, *sec*-butyllithium and titanium tetraisopropoxide with aldehydes. Compounds **2b**, **2d** and **2e** were obtained as a single diastereomer in 54, 76 and 67% yields, respectively, and their spectroscopic data were in agreement with literature;[8–10] compounds **2a** (88% yield) and **2c** (64% yield) were identified by comparison of their spectroscopic data with those of known compounds.



R = Pr indolizidine 167B

1 2

Scheme 1.

Keywords: silicon and compounds; iminium salts; alkaloids; indolizidines.

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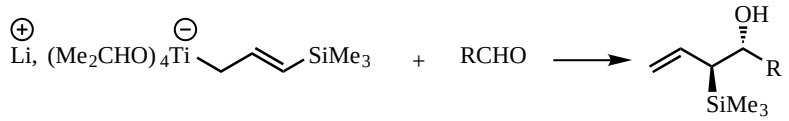


2a R = Me
2b R = Pr
2c R = Bu
2d R = Hex
2e R = Ph

Scheme 2.

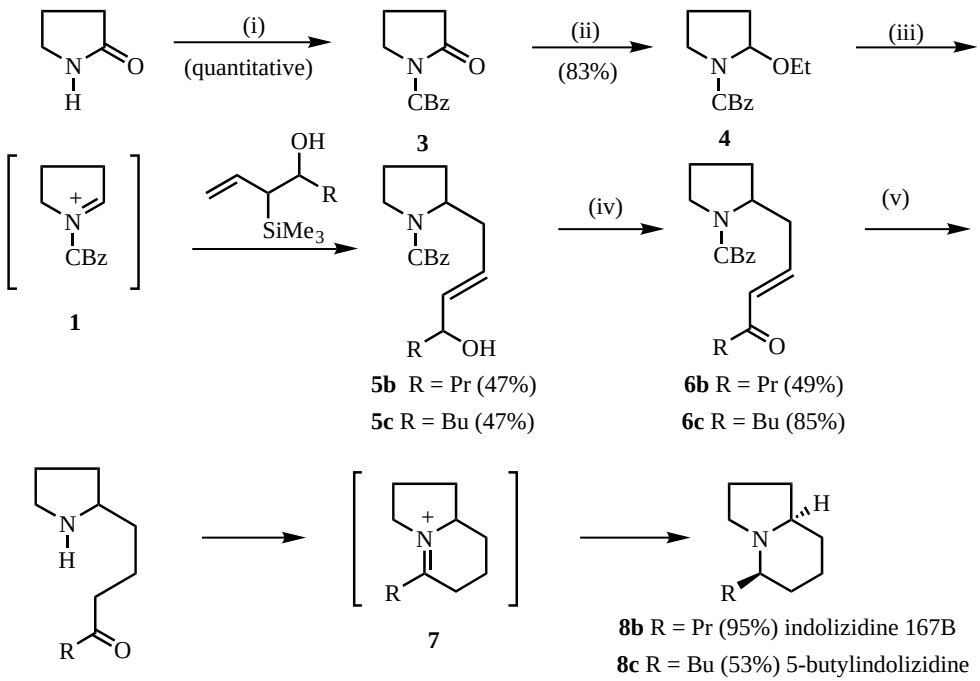
The synthesis of indolizidines **8b** and **8c** was carried out as shown in Scheme 3.

N-Benzyloxycarbonylpyrrolidin-2-one **3** was prepared as described.[11] Reduction of **3** with excess $NaBH_4$ in ethanol in acidic medium afforded ethoxycarbamate **4** in 83% yield.

The key-step of the synthesis is the intermolecular addition of the allylsilyl functional group of alcohols **2** on the acyliminium ion derived from ethoxycarbamate **4**. Treatment of a mixture of ethoxycarbamate **4** and hydroxyallylsilane **2b** (1.1 equiv.) with 1 equiv. of stannic chloride at low temperature resulted in the formation of **5b** in 47% yield,[12] via the acyliminium ion intermediate **1**. In the same way, hydroxyallylsilane **2c** was also reacted with ethoxycarbamate **4** and stannic chloride to give **5c** in 47% yield. These compounds were obtained as a single diastereomer as shown by their ^1H NMR spectra. Thus, the allylation reaction is diastereoselective. In the ^{13}C NMR spectra of **5b** and **5c**, two separate NMR signals are observed for each carbon nucleus because of hindered rotation due to the partial C–N double bond character of the carbamate group.

Subsequent oxidation of alcohols **5b** and **5c** with pyridinium dichromate (PDC) in CH_2Cl_2 afforded α,β-ethylenic ketones **6b** and **6c** in 49 and 85% yields, respectively. The ^1H NMR spectrum showed these compounds to have an *E* configuration for the double bond ($J = 15.9$ Hz).

Catalytic hydrogenation (H_2 over Pd/C in methanol) of ketones **6b** and **6c** induced simultaneously hydrogenolysis of the CBz group, reduction of the double bond of the side chain and reduction of the iminium ion intermediate **7** to give indolizidines **8b** and **8c**, respectively.



Scheme 3. (i) *n*-BuLi, THF then $PhCH_2OCOCl$; (ii) $NaBH_4$, H_2SO_4, EtOH; (iii) $SnCl_4$, CH_2Cl_2, −78°C; (iv) PDC, CH_2Cl_2; (v) H_2/Pd/C, MeOH.

This reaction proceeded with excellent diastereoselectivity, as only one diastereomer of **8b** and **8c** was detected in the crude reaction mixture. This result is in agreement with literature.[3h] Indolizidine **8b** was identified by comparison of its ^{1}H and ^{13}C NMR spectra with those reported for (−)-indolizidine 167B.

In conclusion, we have developed a concise method for the synthesis of 5-substituted indolizidines, starting from readily available materials. The synthesis of (±)-indolizidine 167B has been achieved in five steps and 18% overall yield from pyrrolidin-2-one. Work is currently in progress to apply this methodology to the enantioselective synthesis of indolizidine natural products.

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12. Typical experimental procedure for preparation of **5**: To a solution of *N*-benzyloxycarbonyl-2-ethoxypyrrolidone **4** (8 mmol) in dry CH_2Cl_2 (150 ml) cooled at −78°C under Ar was added $SnCl_4$ ($c=1$ M, 8 mmol). The temperature was then raised to −20°C and 3-trimethylsilylhept-1-ene-4-ol (8.8 mmol) was added. The reaction mixture was stirred at this temperature for 1.5 h and was then quenched with saturated sodium hydrogen carbonate. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (hexane/ethyl acetate, 7:3) to afford the product as a colourless liquid.
    Representative spectroscopic data for compound **5b**: ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H), 1.25–1.30 (m, 4H), 1.70–1.95 (m, 4H), 2.17 and 2.42 (m, 1H), 2.17 and 2.51 (m, 1H), 3.40 (m, 2H), 3.90 (m, 1H), 4.04 (m, 1H), 5.15 (m, 2H), 5.43–5.65 (m, 2H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.0, 18.6, 22.9 and 23.6, 29.7 and 30.1, 36.6 and 37.3, 39.4, 46.5 and 46.8, 56.8 and 57.4, 66.5 and 66.7, 72.5, 127.4, 127.8, 127.9, 128.4, 135.9, 136.1, 137.1, 154.9. Anal. calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.72; H, 8.32; N, 4.72.