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A Radical Approach to the Synthesis of (±)-Supinidine

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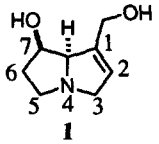
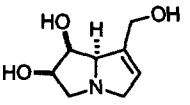
Key Words: radical cyclization; α-sulfonyl radical; (±)-supinidine; pyrrolizidine alkaloid; allylstannane

Abstract: Intramolecular addition of α-sulfonyl radicals to triple bonds followed by addition of tin radicals to the resulting allylsulfones gave pyrrolizidine skeletons. Subsequent manipulations led to a formal synthesis of (±)-supinidine.

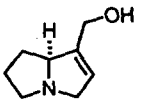
Pyrrolizidine alkaloids are an interesting class of compounds that exhibit a wide range of pharmacological activities.[1-5] A very common structural subunit of the necine bases features an allylic alcohol moiety such as shown in the most important necine, retronecine (**1**). The necine bases of this type differ in the degree and stereochemistry of hydroxylation especially at C-6 and C-7 as in crotanecine (**2**) and supinidine (**3**).[5] Coincide with our interest in free radical cyclization reaction[6] involving α-sulfur functionalities,[7,8] we felt that one might use this strategy in the construction of the allylic alcohol subunit. In this letter we wish to report the realization of this radical approach in the formal synthesis of (±)-supinidine (**3**), the most simple necine base of its class.



1
retronecine



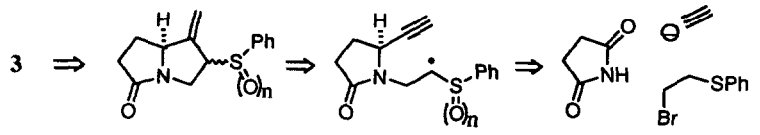
2
crotanecine



3
supinidine

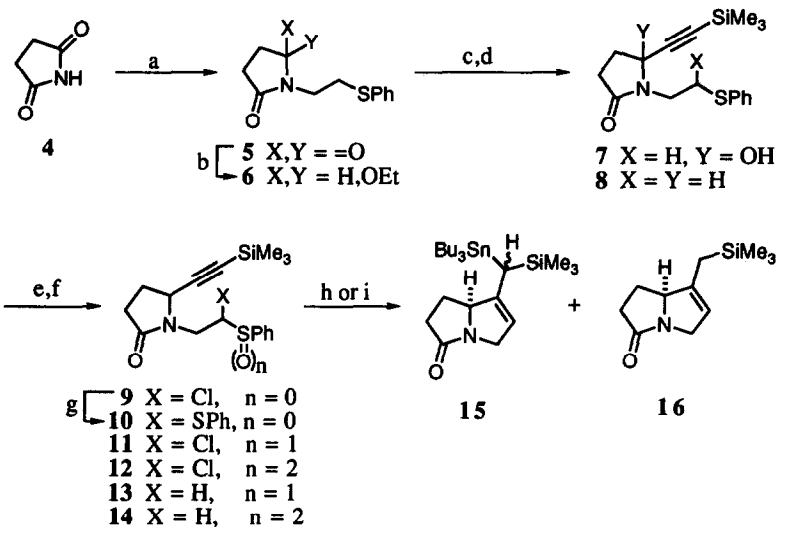
As shown in scheme I, our original plane involved a key radical cyclization reaction to construct the pyrrolizidine skeleton followed by an allylic sulfoxide rearrangement[9] to generate the desired allylic alcohol structure. Thus, alkylation of succinimide (**4**; scheme II) with 2-bromoethyl phenyl sulfide[10] gave the imide **5**

Scheme I



n = 0,1,2

Scheme II

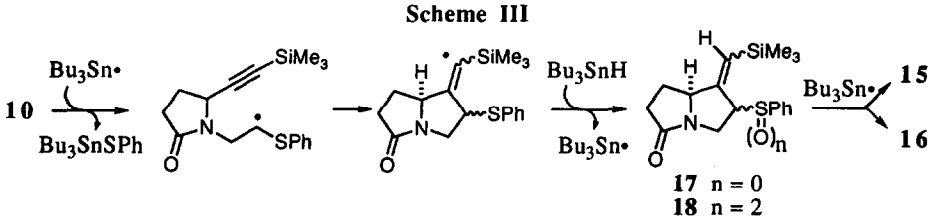


(a) NaH, DMF; $BrCH_2CH_2SPh$, room temp., 20 h (b) $NaBH_4$, H^+, EtOH (c) H-C≡C-$SiMe_3$ (1.5 equiv), *n*BuLi (1.5 equiv), -70 ° C, 70 min (d) $NaBH_3CN$, MeOH, pH 3, room temp., 1 h (e) NCS, CCl_4, room temp., 16 h (f) MCPBA (3.5 equiv), CH_2Cl_2, room temp., 4 h (g) PhSH, $ZnCl_2$, CCl_4, room temp., 15 min (h) Bu_3SnH (2.2 equiv), AIBN (0.1 equiv), PhH, 80 °C (i) Bu_3SnH (1.5 equiv), AIBN (0.1 equiv), PhH, 80 °C

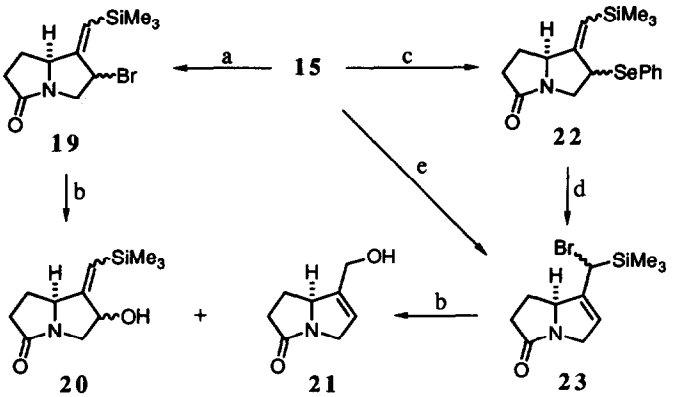
in 79% yield based on the bromide. Reduction of the imide **5** with sodium borohydride gave the lactam **6** with no problem.[11] However, attempted amidoalkylation[12-14] of **6** with trimethylsilylacetylene or bistrimethylsilylacetylene in the presence of a Lewis acid met with failure. Fortunately, trimethylsilyacetylide addition to **5**[15] followed by reduction of the resulting alcohol **7** with sodium cyanoborohydride produced the sulfide **8** in 59% yield with the recovery of 32% unreacted **5** (91% yield based on reacted **5**). Chlorination of **8** with *N*-chlorosuccinimide (NCS) followed by substitution of the Cl atom in the resulting chlorosulfide **9** with a thiophenoxy group gave the dithioacetal **10** in 95% yield.[7]

Radical cyclization carried out by the slow addition (4 h) of tributyltin hydride (0.4 M in benzene; 1.5 equiv) to a benzene solution of **10** (0.4 M) heated at 80 °C. Subsequent heating for another 18 h gave instead of the desired allylic sulfide **17**, the two pyrrolizidines **15** (28%) and **16** (29%). In addition was isolated the uncyclized reduction product **8** (16%) together with unreacted **10** (6%). The formation of **15** and **16** indicates that the initial cyclization proceeded as expected to give **17** (Scheme III). Further reduction of the allylic sulfide

Scheme III



Scheme IV



(a) PyHBr•Br_2, CH_2Cl_2, 0 °C, 4 h (b) NaOH, H_2O, 80 °C, 12 h (c) PhSeBr (1.5 equiv), CH_2Cl_2, -78 °C (d) PhSeBr (1.2 equiv), CH_2Cl_2, room temp., 1 h (e) PhSeBr (2.5 equiv), CH_2Cl_2, –78 °C → room temp.

moiety in **17** with tributyltin hydride gave **16**.[16,17] Addition of the tributyltin radical to the vinyl silane moiety in **17** followed by β-scission of the carbon-sulfur bond gave **15**.[18,19] This result indicates that the above mentioned two processes are competing with the formation of **17** from **10**. In contrast, the chlorosulfoxide **11** derived from **9** gave only **15** and **13** under the same reaction conditions.[8] Although the annoying over-reduction was eliminated, the extra chiral center in sulfoxide caused complication of structure identification and product isolation. We found that the reaction of chlorosulfone **12** derived from **9** (84%), with excess tributyltin hydride gave **15**[20] in 72% yield together with **14**.[8] With the lesser amount of the stannane the primary cyclization product **18** could be isolated along with **15**.

Since **15** can be obtained so easily, we decided to convert **15** to (±)-supinidine (**3**). Treatment of **15** with pyridinium bromide perbromide (scheme IV) gave **19** in 98% yield as a mixture of stereoisomers. Note that it is the allylstannane moiety that reacts and the chemoselectivity is excellent.[21] When **19** was subjected to hydrolytic condition the allylic alcohol **21**[17] was obtained directly in 42% yield along with 31% of **20**.[22] We believe that the formation of **21** involves a silicon directed S_N2' displacement[23] of the allylic bromide followed by Brook rearrangement[24] and desilylation of the resulting allyl silyl ether. Alternatively, treatment of **15** with 1.5 equivalent of phenylselenium bromide at –78 °C gave a 9/1 mixture of **22** and **23** in quantitative yield. Pure **22** reacted with phenylselenium bromide (1.2 equivalent) at room temperature to afford **23** in 97% yield.[25] More conveniently, one can perform this interesting transformation by direct reaction of **15** with 2.5 equivalent of phenylselenium bromide at –78 °C, and then warming up to room temperature to give **23** in quatitative yield as a 2/1 mixture of diastereomers. Under the same conditions for hydrolysis of **19**, the bromide **23** was converted to **21** in 59% yield.[25] Since **21** has been transformed to (±)-supinidine (**3**),[17] our method constitutes a formal synthesis of (±)-supinidine (**3**).

In summary, although the final synthesis deviated from our original plane, our method still provides an interesting entry to the synthesis of supinidine. Further application of this method directed to the synthesis of the more complicated necine bases is under way.

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19. For a review about the fragmentation process, see: Curran, D. P. *Synthesis* **1988**, 489.
20. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **15**: δ 0.02 (s, 9 H, $SiCH_3$), 0.86 (t, J = 7 Hz, 9 H, CH_3 of butyl), 1.20-1.55 (m, 19 H), 1.6-1.78 (m, 1 H, $COCH_2C\underline{H_2}$), 2.16-2.36 (m, 2 H, $COC\underline{H_2}C\underline{H_2}$), 2.55-2.75 (m, 1 H, $COC\underline{H_2}$), 3.68 (br d, J = 15 Hz, 1 H, $NC\underline{H_2}C$=), 4.35 (br d, J = 15 Hz, 2 H, $NC\underline{H_2}C$= and NCH), 5.07 (s, 1 H, =CH). All new compounds mentioned give satisfactory ^{1}H NMR, ^{13}C NMR, IR and HRMS.
21. This provide a rare case for direct comparison of the reactivity of allylsilane and allylstannane.
22. Alcohol **20** is a mixture of at least three diastereomers with a ratio of 2/3/5 determined by ^{1}H NMR integration of the signals at vinylic position.
23. For the silicon directing effect, please see: Fleming, I. in *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D.; Jones, D. N., Eds.; Pergamon Press: New York, 1979; Vol. 3, pp 546.
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25. Exploration of this new reaction is under way in our laboratory.

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