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Synthesis of Pyrrolizidine Alkaloids via Rhodium-Catalyzed Silylformylation and Amidocarbonylation

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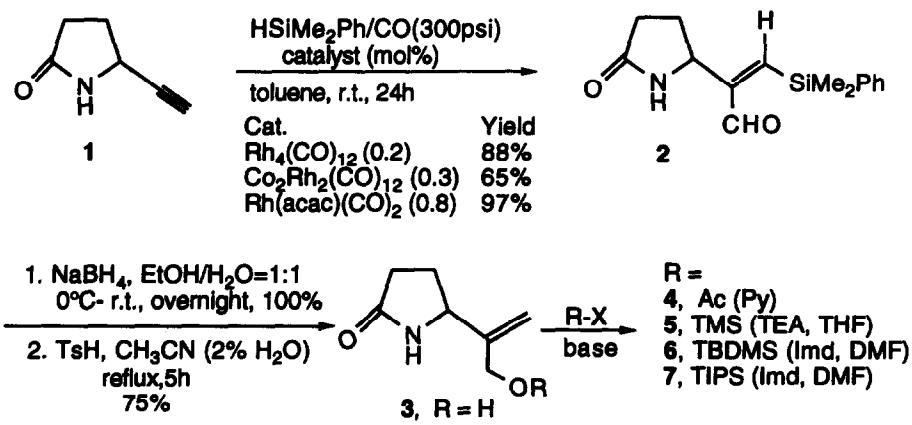
Abstract: *Rhodium-catalyzed silylformylation and amidocarbonylation are applied to the syntheses of pyrrolizidine alkaloids, (±)-isoretronecanol and (±)-trachelanthamidine, from 5-ethynyl-2-pyrrolidinone.*

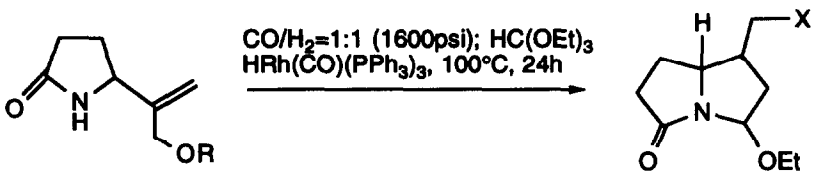
Recently, transition metal catalyzed silylformylation has been developed[1] and mechanistic detail of the reaction has been investigated.[2] The synthetic utility of this reaction arises from its ability to convert alkynes into (*Z*)-1-formyl-2-silylalkenes stereo- and regioselctively in excellent chemical yield.[3] We applied silylformation to the synthesis of precursors of pyrrolizidine alkaloids. Construction of the basic skeleton of pyrrolizidine alkaloids, aza[3.3.0]octane ring system, can be achieved by using rhodium catalyzed amidocarbonylation.[4] We report here the synthesis of (±)-isoretronecanol and (±)-trachelanthamidine from 5-ethynyl-2-pyrrolidinone (**1**) via silylformylation followed by amidocarbonylation.

Silylformylation of 5-ethynyl-2-pyrrolidinone[5] (**1**) was carried out with a catalytic amount of $Rh_4(CO)_{12}$, $Co_2Rh_2(CO)_{12}$, or $Rh(acac)(CO)_2$ under 300 psi of carbon monoxide in toluene at ambient temperature to afford (*Z*)-5-[(2-dimethylphenylsilyl-1-formyl)ethenyl]pyrrolidinone (**2**) as only product in 65-97% yield.[6] Among the catalysts employed, $Rh(acac)(CO)_2$ gave the best yield. The reduction of formyl group in **2** with sodium borohydride followed by desilylation with *p*-toluenesulfinic acid in wet acetonitrile[7] gave 5-(1-hydroxymethylethenyl)-2-pyrrolidinone (**3**) in 75% yield.



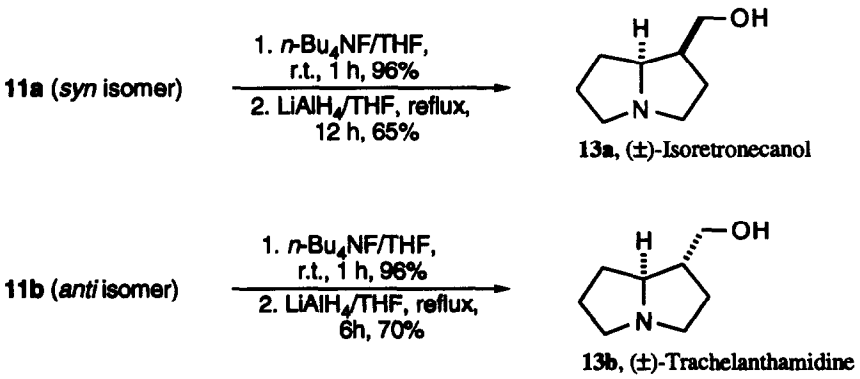
Attempted amidocarbonylation of **3** by using $HRh(CO)(PPh_3)_3$ as a catalyst did not proceed cleanly probably due to side reactions of reactive intermediates bearing hydroxyl group. Therefore, the hydroxyl group was protected by acetyl (Ac), trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), or triisopropylsilyl (TIPS) group.

The amidocarbonylation of **4** gave a diastereomer mixture of the desired product **8** and deacetoxylation product **9** (**8** / **9** = 5 / 2) with the *syn/anti* selectivity of 2 for both products. The TMS group in **5** was cleaved during the reaction to give **10** in 42% yield with the *syn/anti* ratio of 2. The TBDMS and TIPS groups in **6** and **7** survived during the reaction to give **11**[8] and **12**, respectively, in good yields with the *syn/anti* ratio of 2.

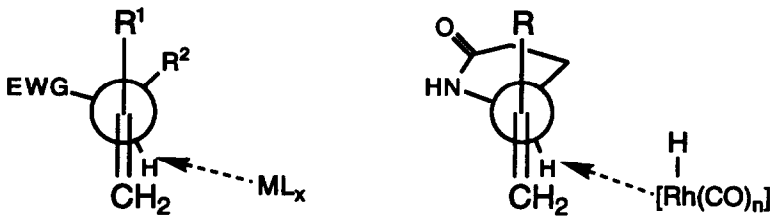


Starting Material,	Product;	X= (yield, *syn/anti*)
4,	**8**,	OAc (37%, 2/1), **9**, H (14%, 2/1)
5,	**10**,	OH (42%, 2/1)
6,	**11**,	OTBDMS (72%, 2/1)
7,	**12**,	OTIPS (68%, 2/1)

The diastereoisomers (*syn/anti*) of **11** were separated by preparative HPLC (silica gel, 3% 2-propanol in hexanes). Both diastereoisomers, **11a** and **11b**, were successfully converted to pyrrolizidine alkaloids, (±)-isoretronecanol (**13a**) and (±)-trachelanthamidine (**13b**), respectively, through removal of TBDMS group with tetrabutylammonium fluoride followed by LAH reduction of the amidal and amido groups in 67% yield.[9]



The observed *syn/anti* selectivity in the amidocarbonylation stays same in all cases, which suggests that the *syn/anti* selectivity does not depend upon the steric and electronic effects of hydroxy protecting groups. In addition, thermodynamically less stable *syn* isomer was obtained as the major product. The results can be accommodated by taking into account the stereoelectronic effects in allyl alcohol derivatives proposed for rhodium-mediated hydroboration reactions,[10] viz., the substrate alkene approaches to a rhodium catalyst with the face *anti* to an electron-withdrawing group (EWG). This model predicts *syn* isomer as the major product in the amidocarbonylation of **4**, **5**, **6**, and **7**.



Acknowledgment: This research was supported by grants from National Institute of Health (NIGMS) and National Science Foundation. A generous support from Mitsubishi Kasei Corp. is also gratefully acknowledged.

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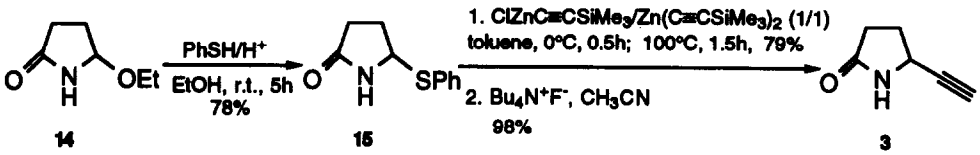
5. The starting material, **1**, was prepared from 5-ethoxy-2-pyrrolidinone (**14**) in three steps. Acid promoted amido-nucleophilic substitution with thiophenol gave 5-phenylthio-2-pyrrolidinone (**15**) in 78% yield. Amidoalkynylation of **15** with (2-trimethylsilyl)ethynylzinc reagent[11] followed by desilylation using tetrabutylammonium fluoride gave **1** in 76% yield.



6. **2**: m.p. 69-70°C; IR ($CHCl_3$) 3220, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.53 (s, 6H), 1.68-1.75 (m, 1H), 2.31 (t, J = 8.0 Hz, 2H), 2.46-2.55 (m, 1H), 4.62-4.66 (m, 1H), 6.42 (br.s, NH), 7.10 (s, 1H), 7.35-7.50 (m, 5H), 9.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.43, 28.08, 29.41, 53.56, 60.27, 128.27, 129.72, 133.43, 146.84, 155.96, 179.81, 192.01. Anal. Calcd. for $C_{15}H_{19}NO_2Si$: C, 65.91; H, 7.01; N, 5.13. Found: C, 65.80; H, 6.97; N, 4.92.

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8. **13**: IR (neat) 1682, 1086 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ [0.035 (s), 0.043 (s)] (6H), [0.88 (s), 0.89 (s)] (9H), [1.180 (t, J = 7.1 Hz), 1.184 (t, J = 7.1 Hz)] (3H), 1.56-2.12 (m, 4H), 2.30-2.48 (m, 2H), 2.56-2.69 (m, 1H), 3.48-3.73 (m, 4H), [3.88 (q, J = 7.3 Hz), 4.24 (q, J = 7.4 Hz)] (1H), 5.14-5.22 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ -5.60, -5.53, 15.01, 15.58, 18.13, 21.09, 25.78, 25.92, 33.69, 33.88, 37.44, 41.00, 48.79, 61.50, 62.56, 63.94, 64.28, 64.45, 83.92, 83.98, 176.25, 176.57; Anal. Calcd. for $C_{16}H_{31}NO_3Si$: C, 61.30; H, 9.97; N, 4.47. Found: C, 61.13; H, 9.90; N, 4.48.
13a: ^1H NMR (300 MHz, $CDCl_3$) δ 0.031 (s, 6H), 0.87 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H), 1.97-2.14 (m, 4H), 2.46-2.64 (m, 2H), 2.67-2.73 (m, 1H), 3.48-3.67 (m, 4H), 4.28 (q, J = 7.6 Hz, 1H), 5.19 (dd, J = 3.3, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.58, 14.94, 18.18, 21.41, 25.84, 34.06, 37.56, 40.85, 61.95, 62.60, 64.30, 83.85, 177.68. **13b**: ^1H NMR (300 MHz, $CDCl_3$) δ .043 (s, 6H), 089 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H), 1.61-1.72 (m, 1H), 1.77-1.97 (m, 2H), 2.30-2.48 (m, 3H), 2.56-2.69 (m, 1H), 3.50-3.75 (m, 4H), 3.86 (q, J = 7.3 Hz, 1H), 5.20 (dd, J = 4.5, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.49, 15.04, 18.16, 25.84, 26.00, 33.68, 37.52, 48.84, 63.86, 64.22, 64.51, 84.05, 176.57.

9. Spectral data (^1H NMR, ^{13}C NMR, and MS) of the pyrrolizidine alkaloids matched with the literature values; (a) Keck, G. E.; Cressman, N. K.; Enholm, E. J., *J. Org. Chem.*, **1989**, *54*, 4345, (b) Kunec, E. K.; Robins, D. J., *J. Chem. Soc. Perkin Trans. I*, **1989**, 1437, (c) Mori, M.; Kanda, N.; Oda, I.; Ban, Y., *Tetrahedron*, **1985**, *41*, 5465, (d) Pinnick, H. W.; Chang, Y., *J. Org. Chem.*, **1978**, *43*, 4662.

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