Tetrahedron Letters,Vol.26,No.26,pp 3155-3158,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

INTRAMOLECULAR REACTIONS OF ACYCLIC N-ACYLIMINIUM IONS II

ALLYL SILANES AS NUCLEOPHILES

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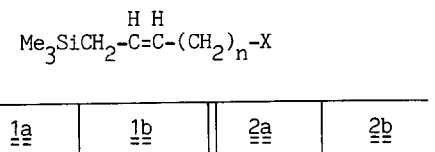
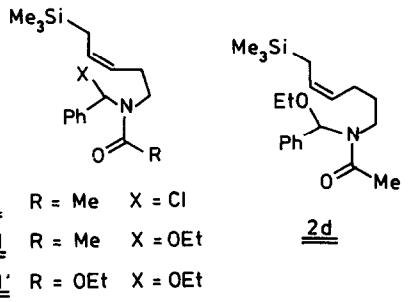
Abstract: Intramolecular reactions of acyclic N-acyliminium ions with allyl silanes, induced by protic or Lewis acid, lead to 3-vinylpyrrolidines or 3-vinylpiperidines.

In the preceding communication we have described intramolecular reactions of acyclic N-acyliminium ions with propargyl silanes[1]. In this paper we disclose our results on the use of allyl silanes as nucleophiles. There are some scattered reports in the literature on intramolecular electrophilic addition of acyclic N-acyliminium ions to simple olefins[2], but detailed studies on scope and stereo- and regiochemistry are lacking. The intermolecular reaction between acyclic N-acyliminium ions and olefins is well-known, and shows the features of a pericyclic [4+2] cycloaddition reaction[3,4].

The Z-allyl silanes 1a and 2a served as starting materials and were synthesized from their acetylenic analogues[1] by catalytic hydrogenation using the Brown nickel catalyst[5] in 80-85% yield. The amines 1a and 2a were converted into the imines 1b and 2b in quantitative yields through reaction with a slight excess of benzaldehyde in toluene and azeotropic removal of the water in vacuo. In order to make suitable N-acyliminium precursors, imines 1b and 2b were treated, successively, with 1.2 eq of acetyl chloride (producing an α-chloroamide e.g. 1c), 1.5 eq of triethylamine, and 5 eq of ethanol[1,6], to give after flash chromatography the ethoxy amides 1d and 2d in yields of 28% and 90%, respectively. The ^{1}H NMR spectra[7] indicated that these amides were a 2.5:1 mixture of rotamers, determined by integration of the singlets from the benzylic protons (7.05 ppm for the major and 6.04 ppm for the minor rotamer in both 1d and 2d). Treatment of 1b with diethyl pyrocarbonate[1] (1.2 eq, 66 h, 70°C, EtOH) led to ethoxy carbamate 1d' in 89% yield. The ^{1}H NMR spectrum[7] of 1d' showed the benzylic proton as a broad singlet at 6.6 ppm.



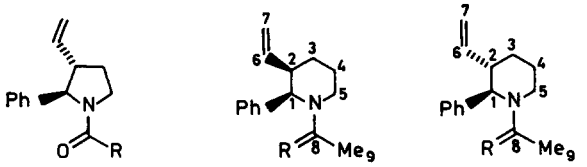
	1a	1b	2a	2b
X	NH_2	N=CHPh	NH_2	N=CHPh
n	2	2	3	3



1c R = Me X = Cl
1d R = Me X = OEt
1d' R = OEt X = OEt

2d

Cyclizations were first attempted by simply stirring the N-acyliminium ion precursors 1d, 1d' and 2d in formic acid at r.t. In this manner 2d gave after 16 h a 2:1 isomer mixture of cyclization products $2e^{cis}$ and $2e^{tr}$ in 60% yield. The isomers could easily be separated by flash chromatography. The stereochemistry could not be assigned at this stage, since the ^1H NMR spectra were complex as a result of hindered rotation. The individual isomers were, therefore, reduced to the corresponding N-ethyl compounds 2f[8] in over 85% yield using $LiAlH_4$ in refluxing THF. Most diagnostic in the ^1H NMR spectra of these amines was the coupling constant between H_1 and H_2, namely 9.9 Hz in the major and 3.4 Hz in the minor isomer. A magnitude of 9.9 Hz points to an axial coupling, which signifies that the major product of cyclization is $2e^{tr}$

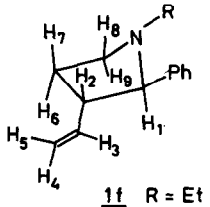


1e R = Me
1e' R = OEt

$2e^{cis}$ R = O $2e^{tr}$
$2f^{cis}$ R = H_2 $2f^{tr}$

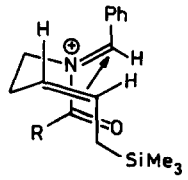
Dissolution of 1d' in formic acid and stirring for 17 h at r.t. led to 81% yield (after flash chromatography) of a single cyclization product 1e'[9]. The same single product was obtained, when the ring closure was brought about using the Lewis acids $SnCl_4$ (1.5 eq, CH_2Cl_2, 2 h, r.t., 73% yield) and Et_2AlCl (3 eq, CH_2Cl_2, 2 h, 0°→r.t., 69%). To determine its stereochemistry 1e' was reduced with $LiAlH_4$ in refluxing THF to the N-methylpyrrolidine 1f' in 78% yield[10]. Its ^1H NMR spectrum was analyzed in detail by measuring a J-resolved spectrum[10]. The NOE-difference technique was used to establish the trans stereochemistry for 1f', namely irradiation of H_1 gave rise to a NOE effect for H_3 and H_9.

Attempts to cyclize ethoxyamide 1d in good yield were in vain. The reasons for this failure and for the low yield in the synthesis of 1d (vide supra) are unclear. It was found, however, that the α-chloroamide 1c, which is an intermediate in the synthesis of 1d, could be cyclized in situ using Et_2AlCl (3 eq, CH_2Cl_2, 2 h, 0°→r.t.) as Lewis acid, in 69% yield overall from 1a after flash chromatography. The product 1e[11] was an approximately 4:1 mixture of rotamers, but a single stereoisomer, as was proved by reduction using $LiAlH_4$ in refluxing THF to a clean N-ethyl compound 1f[12] in 61% yield. The ^1H NMR spectrum of 1f was very similar to that of 1f' and in the same manner as described for 1f' the stereochemistry of 1f was established to be trans.



1f R = Et

1f' R = Me



Figure

The high stereoselectivity which attends the cyclizations to pyrrolidine systems can be rationalized as follows. The most stable conformation of the intermediate π-complex[13] is as shown in the Figure and based on the arguments: a) the six atoms participating in ring formation are arranged in a chair type conformation; b) the most stable N-acyliminium structure is the planar S-cis conformation[4,14]; c) the most stable imininium geometry is the E-form (phenyl group quasi-axial; a quasi-equatorial phenyl group would have serious steric interaction with the carbonyl oxygen). Ring closure of the structure shown in the Figure leads to products with the phenyl and the vinyl group trans, which were the observed products.

In summary, acyclic N-acyliminium ions react well as electrophiles in intramolecular reactions with allyl silanes. The reaction constitutes an expedient method for the synthesis of pyrrolidines[15] and piperidines[16] with a 3-vinyl substituent. Scope and possible applications in natural product synthesis are currently explored. It may be noted in this respect that kainic[17] and domoic acid[18] are 3-vinylpyrrolidines and that cinchona alkaloids[19] contain the 3-vinylpiperidine moiety.

ACKNOWLEDGEMENT: Thanks are due to Miss Karen H. Melching and Miss Johanna M. Zonjee for preliminary experiments, and Mr. C. Kruk and his staff for NMR measurements.

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7. All ^{1}H NMR data reported in this paper were determined at 250 MHz in $CDCl_3$ as solvent (Me_4Si at 0 ppm), unless otherwise indicated.
8. 2f^{tr}(major isomer): ^{1}H NMR[7]: δ 7.24 (m, Ph), 5.36 (m, H_6), 4.65 (m, H_7), 3.11 (br d, 9.7 Hz, H_{5eq}), 2.77 (d, 9.9 Hz, H_1), 2.46 (dq, H_8), 2.27 (m, H_2), 2.07 (m, H_{5ax}), 1.99 (dq, H_8'), 1.7-1.9 (m, H_4, H_{3eq}), 1.29 (m, H_{3ax}), 0.85 (t, H_9); ^{13}C NMR (63 MHz, $CDCl_3$): δ 142.8 (s), 128.5 (d), 127.9 (d), 126.8 (d) (phenyl carbons), 140.8 (C_6), 114.1 (C_7), 73.0 (C_1), 52.0 (C_2), 48.6 (C_8), 48.1 (C_5), 31.0 (C_3), 25.2 (C_4), 10.5 (C_9).
   2f^{cis}(minor isomer): ^{1}H NMR[7]: δ 7.21 (m, Ph), 6.21 (m, H_6), 4.79 (m, H_7), 4.59 (m, H_7'), 3.36 (d, 3.4 Hz, H_1), 3.18 (m, H_{5eq}), 2.59 (dq, H_8), 2.36 (m, H_2), 2.16 (m, H_{5ax}), 1.99 (dq, H_8'), 1.89 (m, H_{3eq}), 1.65-1.85 (m, H_{4ax}, H_{3ax}), 1.55 (m, H_{4eq}); ^{13}C NMR (63 MHz): δ 142.5 (s), 128.7 (d), 127.6 (d), 126.4 (d) (phenyl carbons), 139.3 (C_6), 115.2 (C_7), 71.2 (C_1), 52.6 (C_2), 49.2 (C_8), 46.6 (C_5), 31.5 (C_3), 21.6 (C_4), 11.0 (C_9).
   It is assumed that the phenyl group occupies an equatorial and the vinyl group an axial orientation in 2f^{cis}.
9. IR (neat liq): 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz): δ 7.2-7.5 (m, 5H), 5.7-6.1 (m, 1H), 4.9-5.2 (m, 2H), 4.57 (br d, 6 Hz, 1H), 3.5-4.3 (m, 4H), 2.72 (m, 1H), 1.5-2.3 (m, 2H), 0.9-1.4 (br, 3H), some signals broad due to hindered rotation.
10. IR (neat liq): 1640 cm^{-1}; ^{1}H NMR[7]: δ 7.15-7.35 (m, Ph), 5.74 (m, H_3), 4.87 (m, H_4), 4.77 (m, H_5), 3.26 (m, H_8), 2.76 (d, 9.0 Hz, H_1), 2.65 (m, H_2), 2.37 (m, H_9), 2.22 (m, H_7), 2.13 (s, Me), 1.69 (m, H_6).
11. IR (neat liq): 1640 cm^{-1}: ^{13}C NMR (63 MHz, $CDCl_3$, major rotamer): δ 170.4 (s, C_7), 138.1 (d, C_5), 142.5 (s), 128.9 (d, 2C), 127.5 (d), 125.6 (d, 2C)(phenyl carbons), 116.0 (t, C_6), 67.8 (d, C_1), 53.7 (d, C_2), 46.1 (t, C_4), 28.6 (t, C_3), 22.4 (q, Me).
12. IR (neat liq): 1640 cm^{-1}; ^{1}H NMR[7]: δ 7.2-7.4 (m, 5H, Ph), 5.76 (m, H3), 4.75-4.92 (m, H_4, H_5), 3.41 (m, H_8), 2.95 (d, 9.1 Hz, H_1), 2.5-2.75 (m, H_2, 1H of Et), 1.9-2.4 (m, H_9, H_7, 1H of Et), 1.74 (m, H_6), 1.03 (t, 7 Hz, Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 141.6 (s), 139.7 (d), 128.2 (d, 2C), 128.0 (d, 2C), 127.2 (d), 114.8 (t), 76.0 (d), 52.1 (t), 51.9 (d), 48.0 (t), 28.9 (t), 13.2 (q).
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(Received in UK 7 May 1985)