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INTRAMOLECULAR REACTIONS OF ACYCLIC N-ACYLIMINIUM IONS III[1,2] SILICON ASSISTED CYCLOCONDENSATION OF GLYOXYLIC ESTERS TO PROLINE AND PIPECOLIC ACID DERIVATIVES

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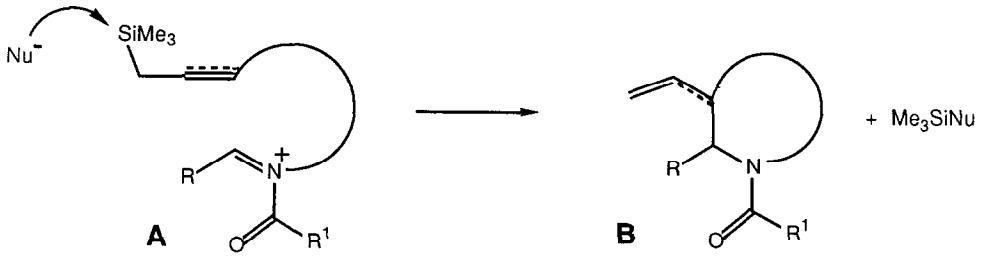
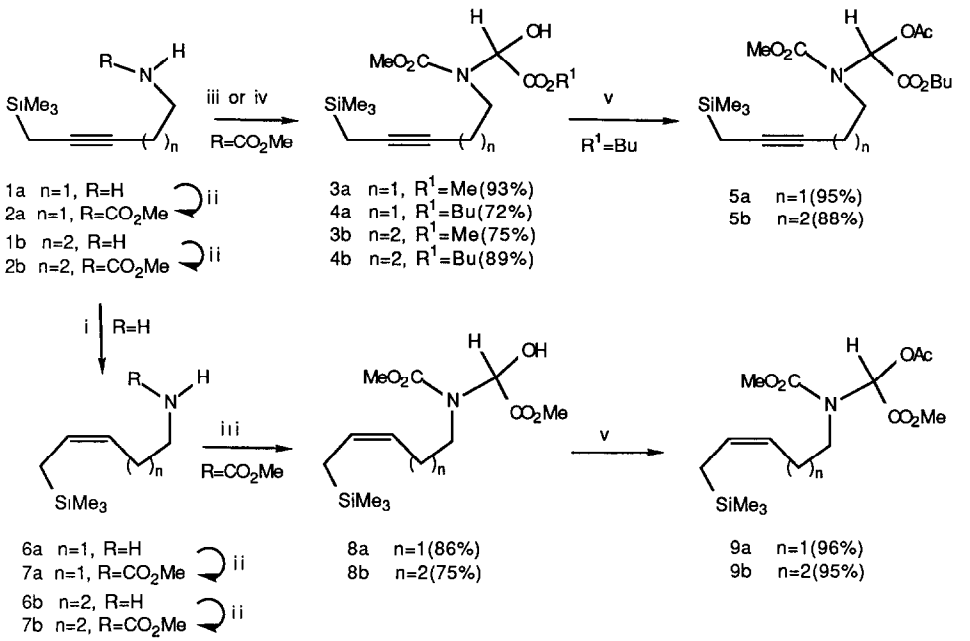
Abstract: Cyclizations of acyclic N-acyliminium ions, generated from the adducts of formaldehyde, n-butyl glyoxylate or methyl glyoxylate with amines containing an allyl or propargyl silane as terminator, lead to 3-ethenyl and 3-ethenylidene substituted pyrrolidines and piperidines, some of which are structurally related to proline and pipecolic acid.

The synthesis of natural and unnatural α-amino acids continues to attract considerable attention.[3,4] In this letter we wish to report the preparation of 3-substituted analogues of proline and pipecolic acid. These compounds may have interesting biological activity as irreversible enzyme inhibitors,[5,6] or be useful for the study of (oligo)-peptide conformations.[7] Our synthetic methodology is based on the recently reported cyclization reaction of acyclic N-acyliminium ions A (R=Ph) with allyl or propargyl silane as terminator to pyrrolidines and piperidines B.[1,2] However, generation of A through acylation of the corresponding imine is not a viable method in the case of R is CO_2R''. Therefore, a different technique to arrive at A was applied, which depends on the ready addition of secondary carbamates to reactive aldehydes.



The aliphatic primary amines 1a and 1b[1,2] served as starting materials for the syntheses of the precursors to the N-acyliminium intermediate A. These syntheses are detailed in Scheme 1 and require no further comment.

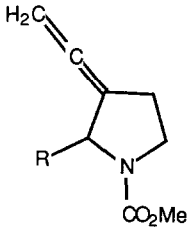
Formaldehyde was first studied as supplier of the electrophilic N-acyliminium carbon atom.[8] When the carbamates 2a, 2b, 7a, and 7b were stirred in formic acid and with 1.15 eq of paraformaldehyde for 17 h at room temperature, clean cyclization occurred to allenes[9,10] 10a (54%) and 10b (54%), and to olefins[9] 13a (58%) and 13b (51%). These results lead to the interesting conclusion that oxymethylation of nitrogen, N-acyliminium ion formation and ring closure proceed so facile, that protodesilylation does not seriously compete.



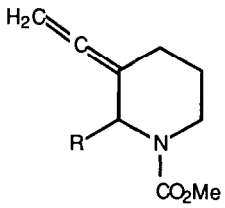
i) P_2Ni, H_2, $(CH_2NH_2)_2$, EtOH (ref 2). ii) $ClCO_2Me$, Et_3N, CH_2Cl_2. iii) MeO_2CCHO (ref 15),CH_2Cl_2. iv) BuO_2CCHO (ref 16), CH_2Cl_2. v) Ac_2O, DMAP(cat), pyridine.

We then turned our attention to the use of glyoxylic esters as reactive aldehydes.[11] We now chose a stepwise approach, which provided the possibility of investigating different cyclization conditions, i.e. a thermal method and Lewis acid catalysis, respectively. Thus, the N-hydroxyalkylated products 3a, 3b, 4a, 4b, 8a, and 8b were isolated and purified.

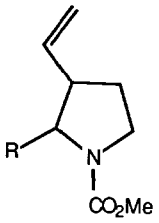
Treatment of 3a, 3b, 8a, and 8b with triethylamine (1.2 eq) and methanesulfonyl chloride (1.1 eq) in acetonitrile at room temperature furnished the corresponding mesylates. When these reaction mixtures were refluxed for 3 h,[12] cyclization occurred to the desired allenic and olefinic ester 11a, 11b, 14a, and 14b. Whereas the five-membered ring allene 11a[9,10] could be obtained pure in 42% yield, the six-membered ring allene 11b was isolated as an inseparable mixture with 2b. Probably, 2b arose from hydrolysis of the starting mesylate during workup. The olefins 14a[9] and 14b[9] were isolated in excellent yields of 88% and 79%, respectively, as inseparable isomer mixtures. The isomer ratio's were determined from their 250 MHz ^1H NMR spectra (DMSO-d_6) at 80°C, since spectra recorded at room temperature showed broad signals as a result of restricted rotation in the carbamate functionality. Product 14a exhibited for the hydrogen adjacent to the ester function two doublets at 4.03 ppm (J=5.9 Hz) and 4.35 ppm (J=8.5 Hz) in a ratio of 89:11. On the basis of these coupling constants[13] and analogy with our previous work,[2] we assume that the major product has the trans-configuration. Product 14b showed for the hydrogen adjacent to the ester function two doublets at 4.77 ppm (J=5.7 Hz) and 4.74 ppm (J=1.9 Hz) in a ratio of 55:45. The low field position and the rather small coupling constants point to an equatorial orientation of this hydrogen in both isomeric pyrrolidines. On the basis of recent literature,[14] indicating that for this hydrogen atom $^3J_{ee}$ is smaller than $^3J_{ea}$ we assume that the major product has the cis-configuration.



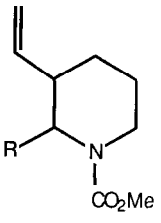
10a R=H
11a R=CO_2Me
12a R=CO_2Bu



10b R=H
11b R=CO_2Me
12b R=CO_2Bu



13a R=H
14a R=CO_2Me



13b R=H
14b R=CO_2Me

Lewis acidic cyclization conditions were applied to α-acetoxycarbamates 5a, 5b, 9a, and 9b. Cyclizations of 5a (4 eq Et_2AlCl) and 5b (4 eq BF_3OEt_2) were readily achieved during 2 h in CH_2Cl_2 at 0° → 20°C, to give pure allenes[9,10] 12a and 12b in yields of about 50%. Treatment of 9a and 9b with EtAlCl (4 eq, CH_2Cl_2, 0° → 20°C, 2 h) afforded the same olefins 14a and 14b as were obtained from the thermal cyclization reaction in yields of 78% and 75%, respectively. The trans:cis isomer ratio's from the Lewis acid induced reactions were 78:22 for 14a and 54:46 for 14b. Comparison of the results of the thermal and the Lewis acidic method for cyclization shows that both types of conditions furnish satisfactory to good yields of cyclization product. In the case of allyl silane cyclizations, the thermal method may be slightly preferred in terms of operational simplicity and yield.

In summary, we have developed a convenient route for the synthesis of 3-ethenyl and 3-ethenylidene substituted pyrrolidines and piperidines, which bear a carboxylic ester function at the 2-position. Hydrolysis of these products should afford interesting proline and pipecolic acid analogues. Currently, the intermolecular variant of the reaction described here is under study as well as the possibility of asymmetric induction.

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8. While this work was in progress related cyclization reactions using ordinary iminium ions were published: P.A. Grieco, W.F. Fobare, Tetrahedron Lett., 27, 5067 (1986).
9. Yields refer to purified (flash chromatography) products, which showed spectra (IR, ^{1}H NMR, ^{13}C NMR) and high resolution mass data in accord with their structure.[17]
10. The allenes were quite sensitive to air oxidation.
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17. Some selected data are:

10b: IR (liq.film): 1965 (C=C=C), 1695 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.68 (quintet, 2H, J=2.5 Hz, H_2C=C=), 3.99 (t, 2H, J=2.5 Hz, N-CH_2-C=), 3.80 (s, 3H, CO_2CH_3), 3.46 (t, 2H, J=5.5 Hz, NCH_2CH_2), 2.14-2.40 (m, 2H, $NCH_2CH_2CH_2$), 1.45-1.80 (m, 2H, NCH_2CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 203.3 (=C=), 155.6 (C=O), 95.4 (H_2C=C=C), 74.6 (H_2C=C=C), 52.4 (CH_3), 47.0 (=C-C-N), 44.0 (CH_2-CH_2-N), 28.5, 25.3.

11a: IR (liq.film): 1965 (C=C=C), 1745 (C=O), 1700 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.82-5.06 (m, 3H, H_2C=C=, N-CH-CO_2CH_3), 3.77 (s, 3H, NCO_2CH_3), 3.72 (s, 3H, CCO_2CH_3), 3.68 (m, 2H, NCH_2CH_2), 2.72 (m, 2H, NCH_2CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 201.8 and 201.7 (=C=), 170.9 (C-C=O), 155.1 and 154.6 (N-C=O), 99.4 and 98.5 (H_2C=C=C), 79.8 (H_2C=C=C), 60.9 and 60.5 (=C-C-N), 52.6 (CH_3), 52.2 (CH_3), 46.2 and 45.8 (NCH_2CH_2), 28.9 and 28.0 (NCH_2CH_2).

13a: IR (liq.film): 1690 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_2$): δ 5.61-6.15 (m, 1H, H_2C=CH), 5.00-5.28 (m, 2H, H_2C=CH), 3.75 (s, 3H, CO_2CH_3), 2.98-3.70 (m, 4H, CH_2NCH_2), 2.82 (m, 1H, =CH-CH), 1.48-2.24 (m, 2H, NCH_2CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.2 (C=O), 138.0 (HC=CH_2), 115.2 (HC=CH_2), 52.0 (CH_3), 50.7 and 50.3, 45.6 and 45.1, 42.6 and 41.7, 31.7 and 30.9.

14a: IR (liq.film): 1735 (C=O), 1695 cm^{-1} (C=O); ^{1}H NMR (250 MHz, DMSO-d_6), 80°C): trans isomer δ 5.83-5.97 (m, 1H, H_2C=CH-), 5.20-5.08 (m, 2H, H_2C=CH-), 4.03 (d, 1H, J=5.9 Hz, NCH), 3.69 (s, 3H, NCO_2CH_3), 3.61 (s, 3H, CCO_2CH_3), 3.35-3.58 (m, 2H, NCH_2), 2.88 (m, 1H, CH-CH=CH_2), 1.91-2.13 (m, 1H), NCH_2CH_2), 1.73-1.87 (m, 1H, NCH_2CH_2); characteristic signals of cis isomer: δ 5.22-5.71 (m, 1H, H_2C=CH-), 4.35 (d, 1H, J=8.5 Hz, NCH), 3.64 (s, 3H, NCO_2CH_3), 3.62 (s, 3H, CCO_2CH_3).

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