CHEMISTRY LETTERS, pp. 735-736, 1986.

α-ACYLAMINORADICAL ANNELATION IN THE DIASTEREOSELECTIVE SYNTHESIS OF 1- AND 5-SUBSTITUTED TETRAHYDROPYRROLO[1,2-c]OXAZOLE AND 1-SUBSTITUTED PYRROLIZIDINE DERIVATIVES

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Diastereoselective synthesis of 1,8-trans-1-substituted and 5,8-trans-5-substituted tetrahydropyrrolo[1,2-c]oxazoles was achieved by an application of α-acylaminoradical cyclization at a silylated triple bond. The method was applied to an enantioselective synthesis of the 1,8-trans-oriented 1-oxygenated pyrrolizidine.

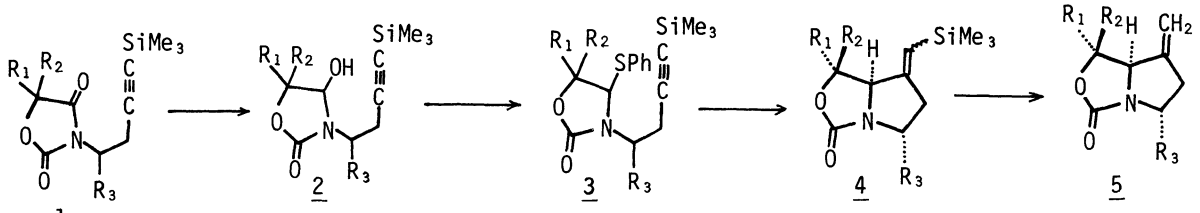
Radical cyclization is rapidly becoming an important method for the construction of bicyclic systems.[1,2] α-Acylaminoradical cyclization at an unsaturated component was also applied to a synthesis of N-heterocycles.[1] Our interest in the efficient synthesis of functionallized heterocyclic systems led us to develop an annelation of α-acylaminoradicals, reported as a highly regiospecific reaction,[2] for a diastereoselective synthesis of pyrrolidine and pyrrolizidine derivatives.

First, we prepared 4-phenylthiooxazolidin-2-ones (3a-e) and 2-phenylthiopyrrolidin-5-one (9) utilized for a generation of the corresponding α-acylaminoradical species. Reduction of 1a-e, obtained by condensation of 5-substituted oxazolidine-2,4-diones with silylated alcohols by Mitsunobu's method,[3,4] with $NaBH_4$ (methanol, 0 °C) afforded 2a-e, respectively. The imide (7), obtained by starting with (S)-malic acid through the imide (6),[5] was also reduced to 8. Conversion of 2a-e and 8 to 3a-e and 9, respectively, was carried out by an application of the modified Walker's method[6] (PhSSPh, n-Bu_3P, benzene, room temperature, 9 h).

Benzene solution of 3a-e (0.01 M solution) was heated in the presence of tri-n-butyltin hydride (1.3 equiv.) and AIBN by the usual way[1] to give the corresponding exo-cyclization products[7] as a mixture of E- and Z-isomers (4a, 75%; 4b, 70%; 4c, 32%; 4d, 74%; and 4e, 72% yield, respectively) as an oil in all cases. Desilylation of 4a-e with CF_3COOH-CH_2Cl_2 (1:2; room temperature, 9 h) gave quantitative yields of 5a-e as a single diastereomer, respectively, as an oil except 5a, mp 63-64 °C and 5d, mp 64-65 °C. The stereochemical assignments for 5a-c were based on the comparison of the ^1H NMR spectrum of 5a with that of 5d. The ^1H NMR spectrum of 5d showed two singlets at δ 1.27 and 1.54 due to two CH_3 groups at 1-position. The higher signal was attributable to the trans-oriented CH_3 in regard to 8-H owing to the shielding effect of 7-exo-double bond and the lower signal was assigned to the cis-oriented CH_3. The ^1H NMR spectrum of 5a showed only one doublet at δ 1.54 (J=6 Hz). These facts indicate that 1-H of 5a-c is trans-oriented in regard to 8-H. The magnitude of $J_{1,8}$(=4.5 Hz), clearly visible in the ^1H NMR spectra of 5a-c, would also support this assignment. The ^1H NMR spectra of

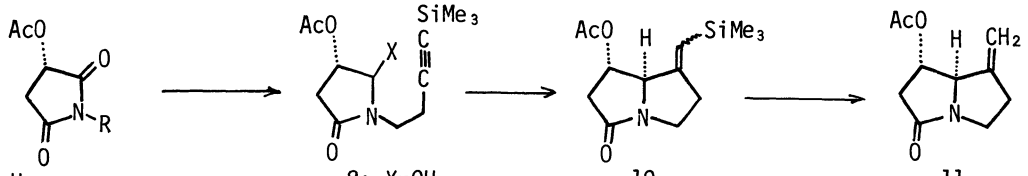
5a-e exhibited characteristic signals due to the trans-oriented 5-H in regard to 8-H at around δ 3.80-4.02; these signals were lower than those due to the cis-oriented 5-H, appeared at δ 2.90-3.18, because of the deshielding effect of carbonyl at 3-position. The ^{1}H NMR spectrum of 5e showed only lower signals due to 5-H at around δ 4.00. Based on these facts, 5-CH_3 (δ 1.22, d, J=7 Hz) of 5e was found to take cis relationship with 8-H. This radical cyclization was applied to the enantioselective synthesis of 11, which would be a useful precursor for an enantioselective synthesis of antitumor pyrrolizidine alkaloids such as hastanecine and retronecine.[8] Treatment of 9 with tri-n-butyltin hydride as above gave 10 as an oil of a 3:1 mixture of E- and Z-isomers in 60% yield. Desilylation of 10 afforded 11 as a single oily product in 95% yield, $[\alpha]_D^{23}$-36.4° (c 0.10, methanol).

Thus, these ring formations were found to proceed with remarkable diastereoselectivity in regard to the orientation of the substituent.



1 2 3 4 5

a: R_1=Me, R_2=R_3=H; b: R_1=Et, R_2=R_3=H; c: R_1=C_6H_5, R_2=R_3=H;
d: R_1=R_2=Me, R_3=H; e: R_1=R_2=H, R_3=Me



6: R=H
7: R=$CH_2CH_2C{\equiv}CSiMe_3$
8: X=OH
9: X=SPh
10
11

References

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7) Products were isolated by column chromatography on silica gel. Elution with hexane removed stannic compounds and further elution with benzene gave products.

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(Received February 12, 1986)