α,β- UNSATURATED LACTONE-NITRONE CYCLOADDITIONS. A ROUTE TO THE SYNTHESIS OF (±) -TUSSILAGIN

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ملخص

لقد أدى تفاعل النيترون (5) مع مركب اللاكتون الغير مشبع (6) الى فصل ناتج واحد فقط (7) . ان السيطرة الريجيوكيميائية العالية في هذه التفاعلات شجعت على اعطاء دفعة قوية في كشف جديد لتحضير النواتج الطبيعية . ان هذا البحث يتضمن وصف كامل لطريقة جديده مؤدية الى تحضير الناتج الطبيعي : توسيلاجن .

ABSTRACT

Reaction of nitrone (5) with α,β -unsaturated lactone (6) resulted in the isolation of a single adduct (7). The observed high regiochemical control has encouraged further explorations of natural product synthesis. A route to the synthesis of an interesting member of Pyrrolizidine-Alkaloid family; (±) -Tussilagin (1), has been described

INTRODUCTION

The development of the chemistry of 1,3- dipolar cycloaddition reactions of nitrones,[1,2] which began in the late fifties,[3] has recently had a significant impact on the synthesis of natural products.[4] Several recent studies have emphasized the use of nitrones in the synthesis of alkaloidal systems.[5-8]

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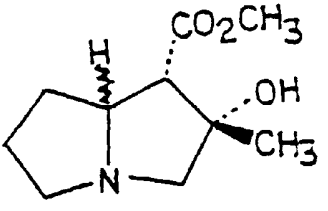
The additions of nitrones to a wide variety of dipolarophiles have been shown to have a high regiochemical control.[9] In the present research, the cycloaddition reaction of a five membered ring nitrone onto α,β -unsaturated lactone has shown to have a very high regiochemical control. It would seem likely that the presence of strongly attracting groups on the dipolarophile tends to favor a transition state where carbon-oxygen bond formation leads (Michael - like character).[10] The observed results have encouraged us to utilize a synthetic route to the synthesis of an elegant natural product; (±) -Tussilagin 1. Tussilagin is a naturally occuring compound which has antitumor properties. It is a member of Pyrrolizidine-Alkaloids family.[11,12] The structure of Tussilagin has been confirmed by x-ray crystallography and other methods of analysis.[11,12]



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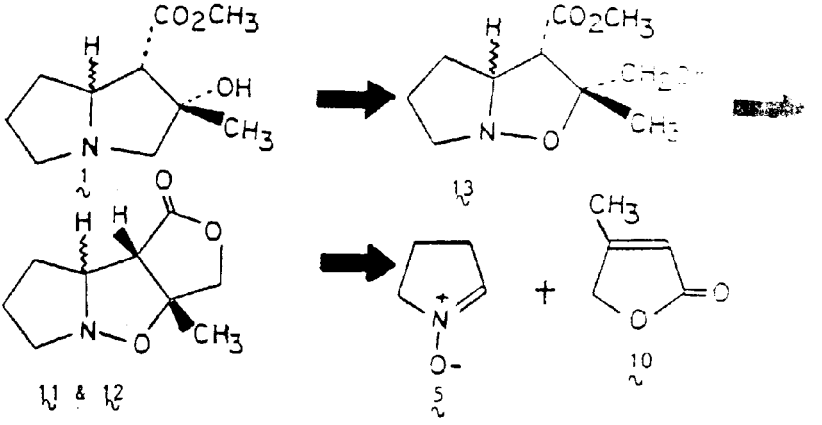
RESULTS AND DISCUSSION

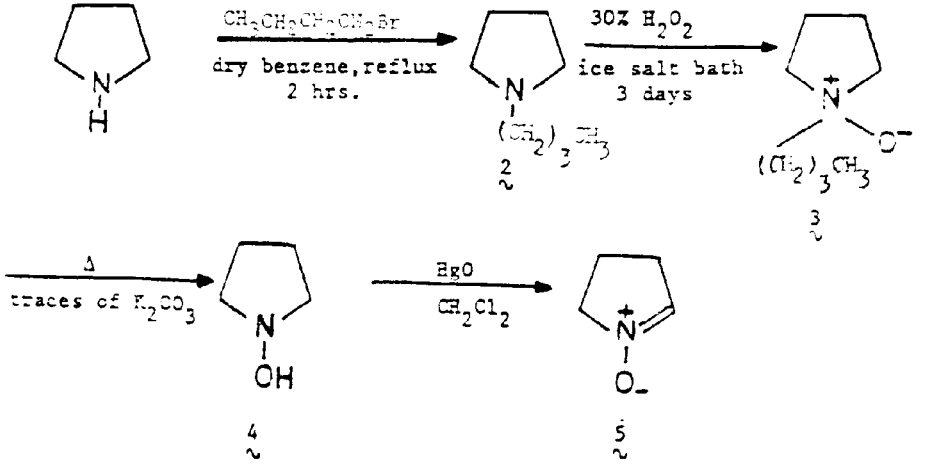
The retrosynthetic scheme led us to consider a 1,3-dipolar nitrone cycloaddition reaction using an unsaturated lactone as a new dipolarophile (Scheme I).

Scheme (I)



The nitrone, 1-pyrroline -1- oxide 5, was prepared in a four-step route as shown in Scheme II.

Scheme (II)

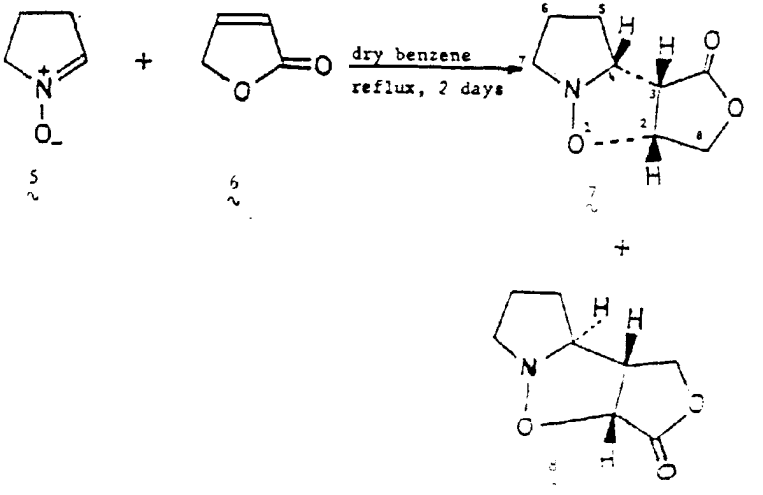


The reaction of pyrrolidine with n-butyl bromide was carried out under reflux for 2hours in dry benzene to afford n-butylpyrrolidine

2 in 85%yield as a colorless liquid.[13]Oxidation of compound 2 with a 30% aqueous hydrogen peroxide solution at room temperature for 3 days afforded the oxide 3 in 75% yield as a light yellow viscous oil. The nmr spectrum was difficult to interpret, as most of the signals are multiplets. The Cope reaction of oxide 3 afforded N - hydroxy-pyrrolidine 4 in 80% yield. The nmr spectrum exhibited a complex pattern at δ1.43 for the C-3 and the C-4 protons, a multiplet at δ3.10 for the C-2 and the C-5 protons. The deuterium exchangeable OH proton appeared at δ8.15. Nitrone 5 was prepared by a mercuric oxide oxidation[14] of the hydroxylamine 4. The nmr spectrum disclosed a multiplet at δ1.92 for the C-3 and the C-4 protons, a complex pattern at δ3.90 for the C-5 protons and a complex pattern at δ6.95 for the C-2 proton.

The cycloaddition reaction of nitrone 5 with α,β -unsaturated lactone 6 is shown in Scheme III.

Scheme (III)

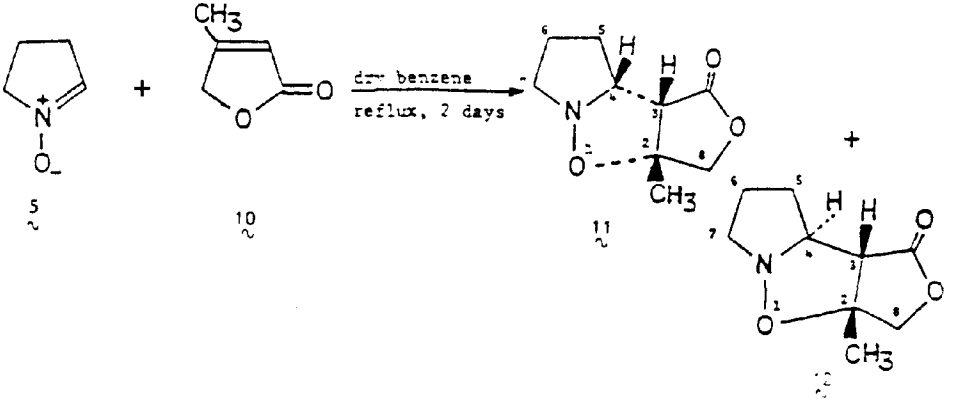


A single adduct 7 has only been isolated. On the basis of a spin decoupling experiment, it has been confirmed that no traces of adduct 8 has been detected.[19]

Isoxazolidine 7 (MS: M^+ 169) shows lactone carbonyl absorption in the region of 5.55 - 5.90 μ of the infrared. The NMR spectrum ($CDCl_3$,250 MHz) shows a complex pattern at δ1.75 for the C-5 protons, a complex pattern at δ2.1 for the C-6 protons, a multiplet at δ3.1 for the C-3 proton, a multiplet at δ3.5 for the C-7 protons, a triplet at δ3.5 for the C-7 protons, a triplet at δ3.9 (t,1,J= 2.0 Hz) for the C-4 proton, a complex pattern at δ4.45 for the C-8 protons, and a complex pattern at δ4.93 for the C-2 proton.

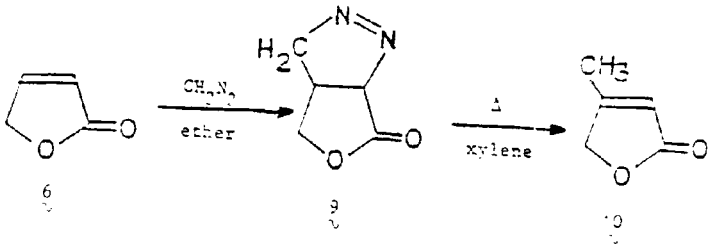
It would seem likely that the presence of strongly attracting groups on the dipolarophile tends to favor a transition state where carbon - oxygen bond formation leads (Michael - like character).[10] The high regiochemical control in this type of cycloaddition has prompted us to utilize a synthetic route as an approach to the synthesis of (±)-Tussilagin 1. The cycloaddition reaction of nitrone 5 with unsaturated lactone 10 is shown in Scheme IV.

Scheme (IV)

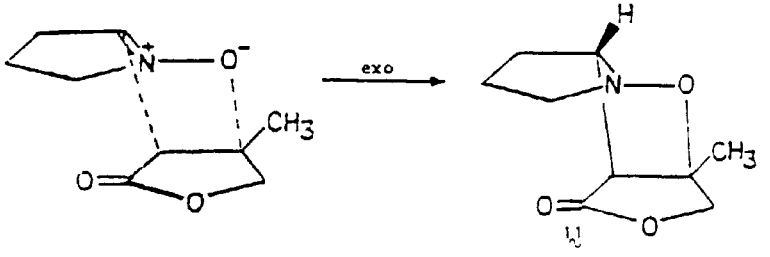


5 10 11 12

Scheme (V)



The Cycloaddition of a benzene solution of nitrone 5 and 4-methyl-2(5H)-furanone 10 [15] (Scheme V) at 100° for 2 days furnished a mixture of stereoisomers in 70% yield. The mixture, which contains exo/endo isomers in a ratio of 75/25 corresponds to exo-and endo-isoxazolidines, 11 and 12 respectively. As anticipated,[16,17] alkene - nitrone cycloadditions proceed via exo-transition state predominantly.



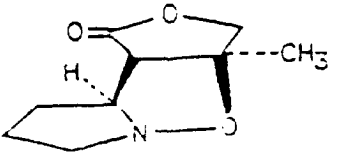
The mixture of stereoisomers was separated using column chromatography (silica gel,7:3 (v/v) methylene chloride/ ethyl acetate).

Isoxazolidine 11 (MS:M$^+$ 183) shows lactone carbonyl absorption in the 5.56 - 5.80μ region of the infrared. The NMR spectrum ($CDCl_3$, 250 MHz) shows a singlet at δ1.52 for the methyl protons, a complex pattern at δ1.75 for the C-5 protons, a complex pattern at δ2.15 for the C-6 protons, a multiplet at δ3.0 for the C-3 proton and for H_β of the C-7, a multiplet at δ3.42 for the H_α of the C-7, a triplet at δ3.73 (t,1,J = 2.5 Hz) for the C-4 proton, a doublet at δ 4.15 (d,1,J =3.0 Hz) for H_α of the C-8.

Isoxazolidine 12 (MS:M$^+$ 183) shows lactone carbonyl absorption in the region of 5.60 - 5.85μ region of the infrared. The NMR spectrum ($CDCl_3$, 250 MHz) shows a singlet at δ1.58 for methyl protons, a complex pattern at δ1.95 for the C-5 and the C-6 protons, a multiplet at δ 2.97 for the C-3 proton, a multiplet at δ3.3 for the C-7 protons, a multiplet at δ4.0 for the C-7 protons, a multiplet at δ4.0 for the C-4 proton, a doublet at δ4.08(d,1,J=2.5 Hz) for the H_β of the C-8, and a doublet at δ4.32 (d,1,J=2.5 Hz) for the H_α of the C-8.

The orientation of cis-isomer 11 and trans-isomer 12 was assigned on the basis of a spin decoupling experiments.

The structural models of isomers 11 and 12 show that structure 11 is less hindered than structure 12 .



12

Few steps toward the target molecule; (±)-Tussilagin 1, are being executed and will be reported in the next paper.

EXPERIMENTAL

The melting points, determined on a Mel-Temp capillary tube apparatus and boiling points, are reported in °C (uncorrected).

Infrared spectra (ir) have been determined on a Perkin - Elmer 1310 spectrometer and calibrated using the 6.238μ band of polystyrene; infrared data are reported in microns, where w,m , and s indicate the intensity of absorption as weak, medium, and strong respectively. Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker EM 250 (250 MHz) spectrometer using tetramethylsilane as an internal standard . Chemical shifts data are reported in parts per million (ppm) downfield from tetramethylsilane using the delta (δ) scale. Coupling constants (J) are given in hertz (Hz). Splitting patterns are designated s,d,dd,t,q, quint,m,and cp designate singlet, doublet, doublet of doublets, triplet, quartet, quintet, multiplet, and complex pattern, respectively. The integration numbers are shown in parentheses. Mass spectra were recorded on a Hitachi Perkin - Elmer RMU- 6E spectrometer with an ionization voltage of 70 volts and a current of 80 μA.

1-Pyrroline 1-oxide (5)

Using the modified procedure of Thesing and Sirrenberg,[14] compound 5 was prepared. To a vigorously stirred solution of N-hydroxyamine 4 [1.0 g, 11.0 mmol] in chloroform (100 ml) at 0°C was added yellow mercuric oxide (6.20g, 29 mmol). After stirring for two

hours , several spatulas full of anhydrous magnesium sulfate were added to the dark green suspension and stirring was continued for another hour. The cold suspension was filtered through a magnesium sulfate pad and the filtrate solution was used in subsequent reactions. Solvent removal in vacuo gave a light yellow oil (0.90 g, 92%) IR (neat) 3.23 (s), 3.38 (m), 6.33 (s), 6.90(m), 7.33(m), 8.19 (s), 8.61(w), 9.61 (m), 9.96 (m), 10.70(m), 12.80 (m), 14.50 (m), and 16.02 (m)μ; ^{1}H NMR (250 MHz, $CDCl_3$) δ1.60 - 2.90 (cp, 2H), 2.05 - 2.29 (cp,2H) 2.90-3.1 (cp, 2H), and δ6.94 (cp, 1H).

4-Methyl -2(5H)- furanone (10):

The procedure of Pelletier[15] was modified and used to prepare compound 10. The etheral solution of diazomethane (2.50g, 60 mmol) was added slowly to a stirred solution of the 2(5H)-furanone [18,19] (3.50g, 40 mmol) in THF at room temperature for a period of 15 - 30 min, and stirred at the same temperature for 1-8 hour. The crystalline adduct 10 was collected, yield (3.50g, 75%), m.p. 109 - 110°C, and the filtrate evaporated under reduced pressure. Compound 10 (2.50 g) in dioxane (25 ml) was heated in an oil bath at 120° C with stirring for 48 hours. After removal of solvent with a rotary evaporator, the yellow oil remaining was distilled to yield 1.5g (77%) of 10. Compound 10 showed: b.p. 112 - 113°/14 mm Hg;IR(neat): 5.60 (s), 5.62 (s), and 6.06(s)μ; ^{1}H NMR(250 MHz, $CDCl_3$), δ 2.15 (s, 3H), 4.62 (s, 2H), and δ5.83 (m, 1H).

Hexahydro -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole - 3- carboxylate Lactone (7):

A stirred solution of 0.9g (1.1 mmol) of 1-pyrroline 1-oxide 5,

0.9g (1.1 mmol) of 1-butenolide 6, and 50 ml of dry benzene was refluxed for 48 hours. Evaporation of benzene under reduced pressure left a brown solid. Recrystallization using petroleum ether/ dichloromethane (4:1) afforded white needles : 1.44g, 62% yield; m.p. 89 - 90°C; IR(KBr) 3.36 (m), 5.58 - 5.88(s), 7.25 (m), and 8.49 μ(s); ^{1}H NMR(250 MHz, $CDCl_3$) δ 1.52 - 2.40 (cp, 4H), 3.00 - 3.40 (cp, 3H), 3.90 (t, 1H), 4.34 - 4.50 (cp, 2H),and δ 4.88 - 4.94 (m, 1H).

Hexahydro -2- methyl -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole -3- carboxylate Lactone (11):

Hexahydro -2- methyl -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole -3- carboxylate Lactone(12):

A stirred solution of 0.50g (5.6 mmol) of 1-pyrroline-1-oxide 5, 0.80 g (8.2 mmol) of 4-methyl -2(5H)-furanone 10, and 50 ml of dry benzene was refluxed for 36 hours. Evaporation of benzene under reduced pressure left a brown oil which was subjected to column chromatography (silica gel, 3:7 (v/v) ethyl acetate/dichloromethane) to give two components in an approximate ratio of 75 : 25, corresponding to the exo-11 (mp 95-96 °C) and endo - 12 isomers respectively: IR $(KBr)_{exo}$ 3.38(m), 5.55 - 5.75(s), 6.85 (m), 7.25(m), and 7.70(m)μ; ^{1}H NMR(250 MHz, $CDCl_3$) δ 1.55 (s,3H), 1.65 - 1.90 (cp, 2H), 2.08 (cp, 2H), 2.9 - 3.1 (cp, 2H), 3.40 - 3.50 (cp, 1H), 3.73 (t, 1H), 4.15 (d, 1H) and δ 4.50 (d, 1H).

IR $(neat)_{endo}$ 3.40(s), 6.85(m), 7.27 (m), 7.88 (m), and 8.45 (s) μ; ^{1}H NMR(250 MHz, $CDCl_3$) δ1.58 (s, 3H), 1.72 - 2.0 (cp, 2H), 2.02 - 2.25 (cp, 2H) 2.92 - 3.08 (dd, 1H), 3.24 - 3.38 (cp, 2H), 4.0 - 4.12 (cp, 2H), and δ 4.35 (d, 1H).

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