Tetrahedron Vol 44, No 1, pp 187 to 193, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

REACTIVITY, REGIOCHEMISTRY, AND STEREOCHEMISTRY OF A CYCLIC NITRONE AND ITS α-KETO DERIVATIVE IN 1, 3-DIPOLAR CYCLOADDITION REACTIONS

SK. ASROF ALI* and MOHAMMED I. M. WAZEER

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

(*Received in UK 12 October 1987*)

Abstract - Rate constants for the cycloadditions of 3,4,5,6-tetrahydropyridine 1-oxide (1), and 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide (2) to several mono- and disubstituted alkenes have been determined at 36°C by ^{1}H NMR Spectroscopy. Small solvent effect on the rate constant indicate the concerted nature of the reaction. It is found that nitrone 2 reacts slower than 1 because of the presence of bond opposition strain in the transition state for the former nitrone. Addition rates are influenced by the dipole moments of the nitrones. Reactivity of these addition reactions usually follows the prediction of frontier orbital approximation. Both the nitrones exhibit very similar regiochemical and stereochemical properties. Significant secondary orbital interaction is observed with several electron deficient alkenes. However, maleic anhydride is found to undergo addition predominantly via exo mode of attack.

INTRODUCTION

The use of 1,3-dipolar cycloaddition reactions of nitrones in organic synthesis has developed quite rapidly in recent years.[1] This reaction is indeed the best chemical template for constructing isoxazolidines.[2] The highly regioselective and stereoselective nature of this reaction has made it specially attractive in incorporating multiple stereocenters in a single step. The regiochemical and stereochemical aspects of intermolecular[3,4] and intramolecular[5] additions involving both cyclic[6] and acyclic nitrones and their reactivities have been explored in some detail. The cyclic nitrone 3,4,5,6-tetrahydropyridine 1-oxide (1) has been found to be very reactive[7] and its addition[1a,3c] to alkenes could be used as a key step in the synthesis of natural products containing piperidine rings which are widespread in nature. However, while the use of the functionally modified nitrone, 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide (2), offers a great synthetic potential, the details of its addition have been examined only to a limited extent.[7]

A detailed knowledge of dipolar cycloadditions of the cyclic α-ketonitrone 2 is of both theoretical and practical importance. It offers an unique opportunity to study the effect of the α-keto group on regiochemical, stereochemical, and reactivity phenomena. Hence we undertook a systematic kinetic study of the additions of nitrone 1 and its α-keto derivative 2 onto several mono- and disubstituted alkenes, using high field proton NMR technique. We also compared the regio- and stereochemistry of the addition of 2 with that of the parent nitrone 1.[6]

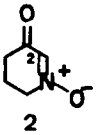
RESULTS AND DISCUSSION

Kinetic results obtained for the cycloaddition of nitrones 1 and 2 with different alkenes in $CDCl_3$ at 36°C are shown in Table 1. All reactions were carried out under conditions that would reflect kinetic rather than thermodynamic factors. Cycloadditions were monitored by proton NMR technique as described before.[7] The ^{1}H NMR signals of 2-H of nitrones and olefinic-protons of alkenes and

in some cases 2-H of cycloadducts were free of overlapping signals. Thus, the ratio of the concentration of nitrone and alkene was determined from time to time and second-order rate constants were obtained by linear regression analysis. The cycloaddition products, nitrones and alkenes are all stable under the mild reaction conditions. At 36°C the regio- and stereoisomers are not interconvertible.

Table 1

Rate constants (k_2) for the cycloaddition reactions at 36°C in deuterochloroform

Alkene	$k_2 \times 10^5$/l mol^{-1} s^{-1}	
	 1	 2
Maleic anhydride	27,400	12.4
Dimethyl fumarate	3,370	15.0
Methyl acrylate	340	14.9[a]
Dimethyl maleate	209	1.54
Methyl methacrylate	105	15.8
Methyl crotonate	22.6	0.727
Hex-1-ene[b]	-	0.589
Allyl alcohol	1.82	1.41
Styrene	7.56	1.80
Ethyl vinyl ether[b]	8.10	1.84

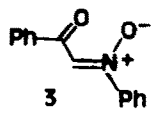
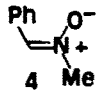
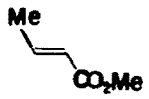
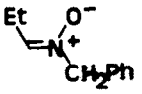
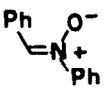
[a] k_2 is 23.3×10^{-5} and 50.2×10^{-5} l mol^{-1} s^{-1} in methanol and toluene respectively

[b] From ref.[7]

According to Sustmann's classification[8], nitrone cycloaddition is a type II process, where both HOMO - LUMO interactions contribute to the stabilization of the transition state.[4,9-12] Both electron-rich and electron-deficient alkenes should undergo additions faster than normal alkenes.[4] This is evident from table 1. Electron-rich ethyl vinyl ether reacts faster than allyl alcohol or hex-1-ene. However , vastly increased rates of cycloaddition of 1 are observed with electron-deficient alkenes. This rate acceleration is less drastic with nitrone 2. This is presumably due to the presence of the electron withdrawing keto group in nitrone 2, which is more likely to have less negative charges on terminal atoms. Thus,the presence of the keto function in 2 decrease its nucleophilicity. A diminished rate of addition of dimethyl maleate in comparison to dimethyl fumarate and maleic anhydride is observed in our study. A similar trend is reported for the rate of the addition of acyclic nitrones.[13] The α-keto nitrones 2 and 3 react with maleic anhydride and dimethyl fumarate nearly equally fast, whereas the rate ratio is 8 for 1 and 14 for 4 (see Table 2).

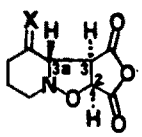
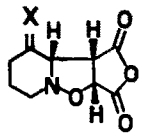
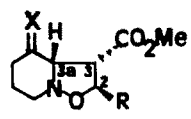
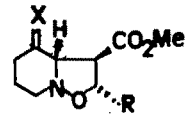
For methyl crotonate it is reported[14] that acyclic ketonitrone 3 undergoes addition much faster than other acyclic nitrones 4,5,6 having no α-keto group. However, in our study it is indeed surprising to observe the opposite trend. As is evident from Table 1, cyclic nitrone 1 shows a much faster rate than the cyclic ketonitrone 2 in the addition onto several electron-deficient and electron rich alkenes examined here. Several factors may contribute to this anomaly. In acyclic nitrones E $\rightleftarrows$ Z isomerization[15] prior to cycloaddition sometimes complicates the reactivity and stereochemical phenomena. The Z isomer is more stable than the E isomer, however, it is the latter isomer that undergoes addition faster than the former due to steric reason. Cyclic nitrones which exist only in E form, because of structural constraints, undergo addition faster than their acyclic counterparts. However, ketonitrone 2 reacts much slower than nitrone 1. This decreased rate of addition can be attributed to the introduction of destabilizing strain in the transition state

Table 2. Rate Constants (k_2) for some nitrone-alkene cycloadditions.

		Rate constant, $k_2 \times 10^5$/1 $mol^{-1}s^{-1}$			
 3	temp 25°C($CHCl_3$)	Dimethyl maleate	Dimethyl fumarate	Maleic anhydride	Ref. 13
		37.2	184	200	
 4	85°C(toluene)	Diethyl maleate	Diethyl fumarate	Maleic anhydride	14
		24.7	72.5	1010	
		 4	 5	6	3
	100°C(toluene)	10.7	43	55.4	6200	14

where the dipole is about to change its hybridization from sp^2 to sp^3. This change in hybridization introduces severe bond opposition strain[7] in the transition state similar to that present in a cyclohexanone system. The ratio of maximum and minimum rate constants for the addition of nitrone 2 with methyl acrylate in nonpolar and polar solvents at 36°C is 3.4 (See Table 1). The ketonitrone 2 reacts faster in methanol than in chloroform, however, the reverse is the case with nitrone 1.[7] Similar trend is observed with acyclic nitrones.[13,14] This opposite dependence of rates on solvent polarity may be attributed to the differences in the dipole moments of 1 and 2. Nitrone 1 should have substantial dipole moment whereas the partial moments in 2 may cancel each other. The small solvent effect observed in our studies is indeed a reflection of the concerted nature of the cycloaddition reaction.[13,14,16]

Next we focussed our attention to identify and characterize the various addition products. Addition of nitrones to monosubstituted and unsymmetrical disubstituted alkenes can lead to the formation of four diastereomeric adducts via four different isomeric transition states. The addition of nitrone 2 to maleic anhydride afforded a mixture of cycloadducts 7a, 8a in a ratio of 70:30, respectively. The ^1H NMR spectrum of the major isomer 7a displayed the C(3)H as doublet ($J_{2,3}$ 7.4 Hz) at δ4.53 and C(2)H also as a doublet ($J_{2,3}$ 7.4 Hz) at δ4.94. The C(3)H signal collapsed into a singlet upon irradiation of the C(2)H signal. The zero coupling constant observed for $J_{3,3a}$ thus indicates an approximate dihedral angle of 90° between the protons at C(3) and C(3a).

X = O	7a	8a	9a,b	10a,b
$X = H_2$	7b	8b	11a,b	12a,b

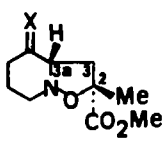
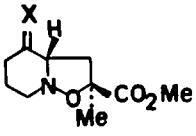
a, R = CO_2Me;
b, R = Me;

7a/8a, 70:30
7b/8b, 81:19

9a/10a, 63:37; 9b/10b, 100:-0
11a/12a, 60:40; 11b/12b, 90:10

Inspection of molecular model also substantiates the above reasoning for assigning the major isomer with exo orientation of the anhydride functionality. Steric encumbrance thus overrides the favourable secondary orbital interaction inherent in the endo mode of attack.

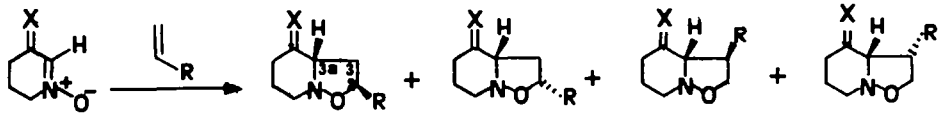
The reaction of nitrone 2 with dimethyl fumarate gave a mixture of adducts 9a, 10a in a ratio of 63:37 respectively. Similar ratio was observed in the addition of nitrone 1 with dimethyl fumarate.[6] The major isomer probably has the stereochemistry as depicted in 9a with carbomethoxy group having endo orientation at C(3). This is based on the cis $J_{3,3a}$ value of 7.0 Hz observed for the major isomer 9a. For the cycloadducts obtained from addition of nitrone 1 and several trans -1,2-disubstituted alkenes, cis $J_{3,3a}$ and trans $J_{3,3a}$ values are found to be in the range of 8 - 8.5 Hz and 10 - 10.5 Hz, respectively.[6]

X = O	13a	14a	13a/14a, 96:4
X = H_2	13b	14b.	13b/14b, 96:4

Addition of methyl crotonate to nitrone 2 afforded 9b as the sole product with carbomethoxy group in the endo orientation. Precedent literature has amply demonstrated the significant tendency of carbomethoxy group to manifest secondary orbital interaction in nitrone - crotonate cycloadditions.[17] The coupling constant ($J_{3,3a}$ 8.8 Hz) is also supportive of the stereochemistry depicted in 9b. In the nitrone 2 - dimethyl maleate reaction equivalent amounts of reactants were consumed. However, we were unable to isolate any normal cycloadducts, which presumably decomposed or rearranged to other products. The reaction of methyl methyacrylate with 2 afforded a mixture of adducts 13a, 14a in a ratio of 96:4, respectively. It is safe to assume the carbomethoxy group to be in endo orientation in the major isomer 13a. Nitrone 1 and methyl methacrylate also gave a similar adduct ratio.[6]

The results for the nitrone-monosubstituted alkene reaction are presented in Table 3. Ethyl vinyl ether underwent regioselective addition to nitrone 2 to give 15a and 16a in 92:8 ratio respectively, as determined by the integration of the 2-H. Methyl acrylate, acrylonitrile, styrene, and allyl alcohol appear to react with 2 smoothly at room temperature. While the additions of styrene and allyl alcohol are regieselective, methyl acrylate and acrylonitrile afforded a mixture of four possible isomers in each case. The addition of styrene to nitrone 2 presumably gave a



X = O , 2	15	16	17	18
X = H_2, 1	19	20	21	22

a, R = OEt; b, R = Ph; c, R = CH_2OH; d, R = CO_2Me; e, R = CN

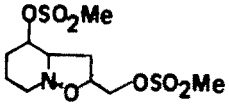
single adduct 15b or 16b. The ^1H NMR displayed a double doublet at δ 5.25 and a triplet at δ 3.95 due to C(2)H and C(3a)H, respectively. Treatment with $Eu(DPM)_3$ shift reagent did not reveal the presence of minor isomer if any. The methyl acrylate adducts were an approximate 58:29:6:7 mixture of 15d - 18d (see experimental). We were unable to assign the stereochemistry. An attempt to convert dimesylates 23,24 (obtained from 15d - 18d by lithium aluminum hydride reduction followed by mesylation) into compounds[3d] with known stereochemistry using Super - Hydride[18] induced SN^2

Table 3. Regioselectivity and Stereochemistry of the additions of nitrone(1) and (2) with several monosubstituted alkenes at 20°C

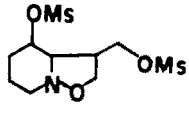
Nitrone	alkene	isomer ratio
2	ethyl vinyl ether	15a : 16a 92 : 8
1	ethyl vinyl ether	19a : 20a 93 : 7
2	styrene	15b or 16b 100 : 0
1	styrene	19b : 20b 78 : 22
2	methyl acrylate	(15d + 16d) : (17d + 18d) 87 : 13
1	methyl acrylate	19d : 20d :21d: 22d 69 : 15 : 10 : 6
2	acrylonitrile	(15e + 16e) : (17e + 18e) 79 : 21
1	acrylonitrile	19e : 20e :21e: 22d 61 : 20 : 13 : 6

The isomer ratios for 15d/16d (or 16d/15d) and 17d/18d (or 18d/17d) were 58 : 29 and 7:6, respectively. The isomer ratios for 15e/16e (or 16e/15e) and 17e/18e (or 18e/17e) were 59:20 and 14:7 respectively.

displacement of the mesylate function by hydride ion at 75°C (sealed tube) was unsuccessful. Even though the primary mesylate function was cleaved cleanly at C-O bond, the secondary mesylate was cleaved at O-S bond. The acrylonitrile adducts were also a mixture of four isomers 15e - 18e in an approximate ratio of 59:20:14:7 as determined by the ^{1}H NMR analysis of the signals due to C(2)H of 2-substituted isomers 15e, 16e and C(3a)H of 3-substituted isomers 17e, 18e (see experimental). The unstable nature of the allyl alcohol adducts 15c,16c and failure to convert the corresponding dimesylates 23 into known compounds[3d] did not allow us to carry out stereochemical analysis.[19]



23



24

EXPERIMENTAL

Liquid alkenes were distilled and maleic anhydride and dimethyl fumarate were recrystallized before use. Nitrone 1 and ketonitrone 2 were prepared as described in the literature.[20] All melting points are uncorrected. Elemental analyses were performed on a Carlo-Erba Elemental analyser 1106. I. R. Spectra were run on a Perkin Elmer 237B spectrometer and are reported in wave numbers (cm-1). 70 ev E. I mass spectra were recorded on a Ribermag GC-MS system, R-10-10, with quadrupole mass filter and Riber 400 acquisition system. TLC cards, silica gel, aluminium backed plates (Fluka AG, layer thickness 0.2 mm) were used to monitor the reaction progress. Reagent grade dichloromethane was passed through active alumina before use. The NMR spectra for the kinetic runs were recorded on a Varian XL 200 nmr spectrometer operating at a proton frequency of 200 MHz and in the pulse Fourier transform mode. Flip angle of 20°, digital resolution of 0.15 Hz, and four transients were employed in all measurements. The absolute intensity mode was used to measure integrals of interested peaks. Spectra at different times for the kinetic runs were obtained by arraying the preaquisition delay times. The temperature in the probe was controlled by the standard Varian equipment and was accurate to ±0.5°C. The temperature was calibrated by standard chemical shift of methanol. Deuterated chloroform (99.95% isotope purity) with TMS as internal standard was used. In some kinetic runs 100% isotopically pure deuterochloroform was used to avoid interference from residual $CHCl_3$ proton signal. For analysis of the cycloadducts, the proton NMR spectra were recorded on a Bruker AC 80 spectrometer, operating at a proton frequency of 80 MHz. Cycloaddition reactions were carried out under nitrogen.

Kinetics of Cycloaddition Reaction: Kinetic runs were studied by NMR technique as described before.[7] The cyclic nitrone 1 was prepared from 1.01g N-hydroxypiperidine (10 mmol) and the solution of the nitrone 1 in 50 ml dichloromethane was kept in the freezer(-20°C). The nitrone solution was stable for weeks in the freezer without any detectable formation of nitrone dimer. A suitable volume of nitrone solution was transferred to a vial and CH_2Cl_2 was completely removed by blowing N_2 at 0°C and the residue was dissolved in 1 ml $CDCl_3$. In an NMR tube, purged with N_2, was taken a known amount of alkene and was cooled in a salt ice bath (-15°C). The nitrone in $CDCl_3$ was transferred to the NMR tube which was then sealed immediately. The mixture was then mixed thoroughly and inserted into the NMR probe which was kept at constant temperature throughout the kinetic measurements. The initial concentration of the nitrone was determined by NMR integration and using the known concentration of the alkene. The volume of the reaction mixture was taken as the average of the volumes at the beginning and end of the kinetic runs. The ratio of the concentrations of nitrone and alkene was determined from time to time by integration of signals due to 2-H of the nitrone and the olefinic protons of the alkene. Kinetic runs for ketonitrone 2 and alkene (both of which could be weighed accurately) addition reactions were executed in a

similar way.

Concentration of nitrone 1 was judiciously kept low in certain slow reactions in order to avoid nitrone dimer formation. In cases where signals due to 2-H nitrone and alkene protons overlap, the help of other proton signals of the nitrone and cycloadducts were sought to determine the concentration ratio of the reactants. The second order rate constants were determined by linear regression analysis of the data and was reproducible within 3-10%.

The initial concentrations, written in parenthesis, of nitrone 1 and alkenes were as follows: nitrone (0.268 M) - methyl crotonate (0.711 M); nitrone (0.727 M) - methyl methacrylate (0.579M); nitrone (0.0693 M) - dimethyl fumarate (0.0570 M); nitrone (0.0625 M) - maleic anhydride (0.0527M); nitrone (0.402 M) - dimethyl maleate (0.252 M); nitrone (0.214 M) - styrene (0.857 M); nitrone (0.220 M) - allyl alcohol (1.65 M). Concentrations of the ketonitrone was kept around 0.500 M and that of alkene were in the range of 1.00 - 1.50 M. The additions were followed upto 40-90% chemical conversion.

Cycloadducts from the Addition Reaction of α-Ketonitrone 2 and Several Alkenes: In a typical addition reaction 1 mmol of 2 was treated with 1 ml of liquid alkene and the reaction was continued at room temperature under N_2, until the tlc (silica gel/ethyl acetate) experiment indicates the absence of ketonitrone. Removal of the excess volatile alkene in vacuo afforded cycloadducts in quantitative yield. However, for non volatile alkenes like maleic anhydride, dimethyl fumarate and dimethyl maleate, 1.5 mmol of the alkene in each case was treated with 1 mmol of ketonitrone dissolved in minimum quantity of dichloromethane and the reaction was continued until the reaction was almost complete as indicated by tlc analysis. Most of the cycloadducts are unstable at room temperature. The presence of α-aminoketone moiety, presumably, imparts the instability in such cycloadducts.

Reaction of Ketonitrone 2 with Maleic Anhydride : The ^1H spectrum of the crude cycloaddition products revealed the presence of two isomers 7a, 8a in a ratio of 70:30. The major isomer was obtained as white crystals after crystallization from dichloromethane - ether, m.p. 105° (dec), m/z 211 (M+ 3.1%); ν_{max} (KBr) 2990, 2925, 2907, 1867, 1790, 1777, 1727, 1447, 1267, 1227, 1095, 1037, and 932 cm^{-1}; (Found:C,50.89; H,4.19; N,6.51. $C_9H_{17}NO_4S$ requires C,51.19; H,4.30; N,6.63%); δ_H 2.20 -2.90 (3H, m), 3.25 - 4.00 (3H,m), 4.30 (1H, s), 4.53 (1H, d, J 7.4Hz) and 4.94 (1H,d,J 7.4Hz) The spectrum of the crude mixture displayed a minor doublet at 5.07 (J=7.8 Hz) which collapsed into a singlet on irradiation of signals around δ 4.0. We were unable to isolate minor isomer 8a from mother liquor as it darkened gradually due to extensive decomposition of the minor isomer.

Isomers of trans-Dimethyl hexahydro-4-oxo-2H-isoxazolo[2,3-a]pyridine-2-3-dicarboxylate (9a,10a): Addition reaction afforded a crude mixture of adducts. The major isomer was crystallized out from dichloromethane - ether , m.p. 109-110°C; m/z 257 (M+ 10.8%); Anal. Found: C,50.95; H,5.74; N,5.55. $C_{11}H_{15}NO_6$ requires C,51.36; H,5.88; N,5.45. ν_{max} 2995, 2930, 1725(br), 1413, 1340, 1190, 1175, 1043, 950, 750, 710 cm^{-1}; δ_H 1.98-2.70 (3H,m), 3.00-3.95 (4H,m), 3.79 (3H, s), 3.83 (3H, s) 4.24 (1H, d, J 7.0 Hz), and 4.91 (1H, d, J 6.3 Hz). The ^1H NMR spectrum of the crude mixture displayed a minor doublet for the C-2H of the minor isomer at 4.80 (d, J 6.0 Hz). The ratio of the isomers was found to be 63:37 by NMR integration of the C-2H protons. We were unable to isolate the minor isomer from mother liquor as it darkened gradually.

Methyl hexahydro-2-methyl-4-oxo-2H-isoxazolo[2,3-a]pyridine-3-carboxylate (9b) : The cycloadduct , obtained as yellow oil, gradually darkened at room temperature. m/z 213 (M+ 9.4%) ν_{max} (neat) 2920, 1730, 1710, 1255, 1199 cm^{-1}; δ_H 1.38 (3H, d, J 6.2 Hz), 1.70 - 2.80 (4H, m), 3.05-3.65 (3H, m, including a ^1H dd, J 7.1 and 8.8 Hz at 3.23), 3.73 (3 H, s), 4.09 (1H, d J 8.8 Hz), and 4.53 (1H, dq, J 6.2 and 7.1 Hz).

Isomers of methyl hexahydro-4-oxo-2-methyl-isoxazolo[2,3-a]pyridine-2-carboxylate (13a, 14a): The mixture of cycloadducts was obtained as a light yellow oil. m/z 213 (M+ 21.1%); ν_{max} (neat) 3022, 2898, 1732(br), 1447, 1292, 1202, 1112, 985, 902, 822 cm^{-1}; δ_H 1.44, 1.52 (3H, major and minor s in a ratio of 96:4), 1.71 - 2.64 (5H, m), 2.75 - 3.69 (4H, m), and 3.74 (s, 3H)

Isomers of Hexahydro - 2 - ethoxy -4-oxo-2H-isoxazolo[2,3-a]pyridine (15a-16a): The cycloadducts were obtained as a colorless oil. m/z 185 (M+ 69.9%); ν_{max} (neat) 2924, 1710, 1435, 1080, 978, 880 cm^{-1}; δ_H 1.21 (3H, t, J 7.0 Hz), 1.60 - 2.75 (5H, m), 2.90-4.00 (6H, m) and a major dd at δ 5.05 (J 2.6 and 6.4 Hz) and a minor dd at δ 5.20 (J 3.4 and 5.2 Hz) integrate for one proton in a ratio of 92:8.

Hexahydro-2-phenyl-4-oxo-2H-isoxazolo [2,3a]pyridine (15b or 16b): The cycloadduct was obtained as colorless needles, m.p. 65-66°C (ether). The product decomposes within days at room temperature. However, it is stable inside freezer. m/z 217 (M+ 31.2%); ν_{max} 2915, 1715, 1455, 1323, 1244, 1108, 775, 710 cm^{-1}; δ_H 1.85-2.70 (5H, m), 3.00-3.60 (3H, m), 3.95 (1H,t, J 7.0 Hz), 5.25 (1H, dd, J 5.8 and 9.0 Hz) and 7.4 (5H, m).

Isomers of Hexahydro-2-hydroxymethyl-4-oxo-2H-isoxazolo[2,3-a]pyridine. (15c, 16c): The cycloadducts were obtained as a light brown oil which gradually darkens further even under N_2. m/z 171 (M+37.6%); ν_{max} (neat) 3340, 2910, 1710, 740 cm^{-1}; δ_H 1.70 - 2.95 (7H, m), 3.17-3.95 (5H,m) and 4.20 (1H,m).

Isomers of methyl hexahydro-4-oxo-2H-isoxazolo[2,3-a]pyridine-2 and -3-carboxylate (15d - 18d): The mixture of cycloadducts was obtained as a light yellow oil which could not be purified because of extensive decomposition during silica gel chromatography. The mixture of adducts darkens gradually in open air. m/z 199 (M+ 20.9%) ν_{max}(neat) 2924, 1735, 1700, 1435, 768 cm^{-1}; δ_H 1.70-3.50 (8H, m), 3.60-3.85 (4H, m), and 3.90-4.65 (m, 1H). The above is an approximate description of the NMR data. There are four different methyl singlets at 3.76, 3.74, 3.71 and 3.67 in a ratio of 58 : 29 : 6 : 7 respectively. There are minor signals in the δ 3.9-4.3 due to 3-substituted minor regiomers. The degenerate dd for 2-substituted major isomers appeared at δ 4.50 which shifted downfield on treatment with $Eu(DPM)_3$ shift reagent. The major dd (J 5.4 and 9.0 Hz) shifted more downfield than the minor dd (J 6.5 and 9.0 Hz). The ratio was found to be 2:1.

Isomers of Hexahydro-4-oxo-2H-isoxazolo[2,3-a]Pyridine-2 and-3-carbonitrile (15e-18e): The mixture of cycloadducts was obtained as a faint yellow oil which gradually darkens at room temperature due to decomposition; m/z 166 (7.5%); ν_{max} (neat) 2920, 2233, 1712, 1450, 1325, 1165, 1115,

1020 cm^{-1}; δ_H 1.69 - 4.22 (m, 9H), 4.33 (two overlapping doublets , J 6.0 Hz for the major,J 7.5Hz for the minor, integrating for 3/14 of a proton due to the signal for the bridgehead protons of the minor isomer in an approximate ratio of 2:1) , 4.7 (degenerate dd integrating for 11/14 of a proton for C-2H of major isomers. Treatment with Eu(DPM)$_3$ shift reagent shifted the signal downfield. Minor dd, J 5.6, 9.0 Hz shifted downfield more than major dd, J 4.0, 9.0 Hz. The ratio was found to be 3:1. Thus the four isomers were present in an approximate ratio of 59:20:14: 7.

ACKNLOWLEDGEMENTS

Financial support provided by the King Fahd University of Petroleum and Minerals, Dhahran is gratefully acknowledged. We thank Mr. M. Saleem for recording mass spectra.

REFERENCES AND NOTES

1. (a) J. J. Tufariello, *Accs. Chem. Res., 12,* 396 (1979). (b) H. Ida, C. Kibyasi, *Yuki Gosei Kagakio Kyokaishi, 41,* 652 (1983). (c) J. P. Freeman, *Chem. Rev., 83,* 241 (1984). (d) J. J. Tufariello, 1,3[one,three] - *Dipolar Cycloaddit. Chem. 2,*83 (1984). (e) N. Subramanian, *Org. Prep. Proc. Int., 17,* 23 (1985).

2. J. Hamer, A. Macaluso, *Chem. Rev., 64,* 473 (1964).

3. (a) R. Huisgen, *Angew. Chem. Int. Engli., 2,* 565, 633 (1963). (b) D. St. Black, R. F. Crozier, V. C. Davis, *Synthesis, 7,* 205 (1975). (c) J. J. Tufariello, Sk. A. Ali, *Tetrahedron Lett.,* 4647 (1978). (d) Sk. A. Ali, P. A. Senaratne, C. R. Illig, H. Meckler and J. J. Tufariello, *Tetrahedron Lett.,* 4167 (1979).

4. R. Huisgen, *J. Org. Chem, 41,* 403 (1976), and references cited therein.

5. (a)N. A. Lebel, G. M. J. Sensacruk, L. A. Spurlock, *J. Am. Chem. Soc., 84,* 4360 (1962). (b) W. Oppolzer, M. Petrzilka *J. Am. Chem. Soc., 98,* 6722 (1976) (c) J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, Sk. A. Ali, *J. Am. Chem. Soc., 101,* 2435 (1978). (d) A. Padwa, *1,3[one, three]- Dipolar Cycloaddit. Chem., 2,* 277 (1984).

6. Sk. A. Ali, M. I. M. Wazeer, *J. Chem. Soc., Perkin Trans. 1,* in press.

7. Sk. A. Ali, M. I. M. Wazeer, *J. Chem. Soc. Perkin. Trans. 2,* 1789 (1986).

8. R. Sustmann, *Pure Appl. Chem., 40,* 569 (1974).

9. K. Fukui, *Accs. Chem. Res., 4,* 57 (1971).

10. K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, J. K. George, *J. Am. Chem. Soc.,95,* 7287 (1973).

11. (a) K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc., 95,* 7301 (1973). (b) K. N. Houk, J. Sims, *ibid, 95,* 5798 (1973).

12. P. G. De Benedetti, S. Quartieri, A. Rastelli , M. De Amici, C. De Micheli, R. Gandolfi, P. Gariboldi, *J. Chem. Soc., Perkin Trans. 2,* 95 (1982).

13. Y. Yoshimura, J. Osugi, M. Nakahara, *J. Am. Chem. Soc., 105,* 5414 (1983).

14. R. Huisgen, H. Seidl, I. Bruning, *Chem. Ber.,102,* 1102 (1969)

15. (a) L. W. Boyle, M. J. Peagram, G. H. Whitham, *J. Chem. Soc. B,* 1728 (1971). (b) A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez, G. S. K. Wong, *J. Org. Chem., 49,* 276 (1984).

16. R. Gompper, *Angew. Chem., Int. Ed. Engl., 8,* 312 (1969).

17. (a) M. Joucla, F. Tonnard, D. Gree, J. Hamelin, *J. Chem. Res. (M),* 2901 (1978). (b) J. J. Tufariello, G. G. Lee, P. A. Senaratne, M. A. Al-Nuri, *Tetrahedron Lett.,* 4359 (1979).

18. S. Krishnamurthy, H. C. Brown, *J. Org. Chem., 41,* 3064 (1976).

19. The configurations of most of the nitrone (1)-alkene addition products[6] were confirmed by conversion of the adducts into compounds of known stereochemistry. However conversions of ketonitrone (2) adducts 15-18 into 19-22 of known configurations[6] were not successful either by the Super-Hydride reduction method as described in the Results and Discussion or by application of a variant of Wolff-Kishner method using tosylhydrazone derivatives. The difficulties in reducing the keto group to alkane presumably arises from the presence of leaving group (amino) in the α position. For a review, see 'Modern Synthetic Reactions' by H.O. House, 2nd Ed., The Benzamin/Cummings Publishing Company, P.228.

20. V. M. Clark, B. Sklarz, A. Todd, *J. Chem. Soc.,* 2123 (1959).