Pergamon

Tetrahedron 56 (2000) 7229–7236

TETRAHEDRON

Synthesis and Cycloaddition Reactions of 2,3,4,5-Tetrahydropyrazine 1-Oxide

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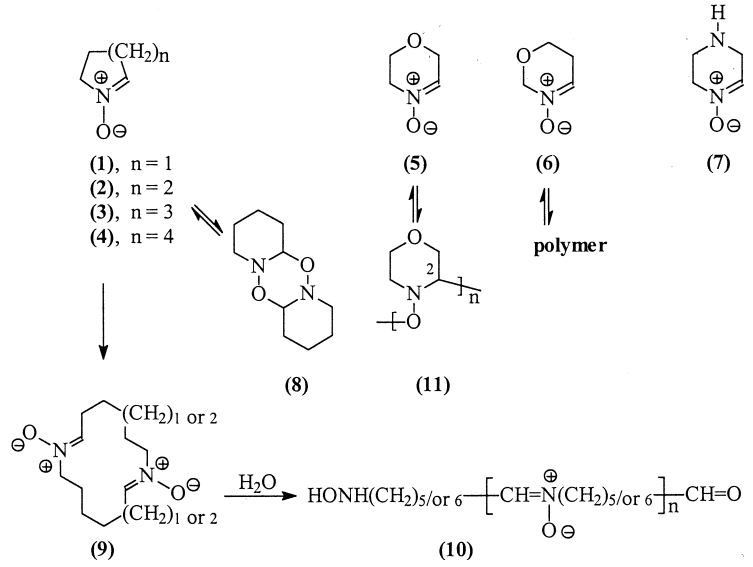
Received 4 April 2000; revised 31 May 2000; accepted 15 June 2000

Abstract—The stereochemistry and reactivity of the cycloaddition reactions of a heterocyclic nitrone, 2,3,4,5,-tetrahydropyrazine 1-oxide, have been studied. The heterocyclic nitrone is found to be more reactive than its carbocyclic counterpart. The nitrone underwent regio- and stereo-selective cycloaddition reaction with several alkenes to afford bicyclic isoxazolidines efficiently. Barriers to nitrogen inversion in the cycloadducts have been determined. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Nitrone functionality has become an important chemical tool in organic synthesis.[1] 1,3-Dipolar cycloadditions of cyclic nitrones have found widespread use in the synthesis of natural products.[2] Regio-, stereo-chemical and reactivity phenomena associated with the addition reactions of several parent carbo-(**1**–**4**)[3–6] and hetero-cyclic nitrones[7,8] (**5** and **6**) with a variety of alkenes has been studied in some detail (Scheme 1). The behaviour of concentrated solutions of the cyclic nitrones is quite puzzling; while the nitrone (**1**) is stable, the nitrone **(2)** dimerizes to **8** and the nitrones **3** and **4** polymerize[5,6,9,10] to **10** via the dimers **9**. The hetero-cyclic nitrone **5**, however, polymerises[7,11] to **11** with a repeating skeletal of –C–N–O– unit. The concentrated solution of the nitrone **6**, on the other hand, gave polymeric product of intractable structure.[8] Reason for this puzzling difference is not well understood (Scheme 1). However, all these cyclic nitrones undergo cycloaddition reactions with a variety of dienophiles to give cycloadducts with remarkable



Scheme 1.

Keywords: cycloadditions; nitrones; regiochemistry; stereochemistry.

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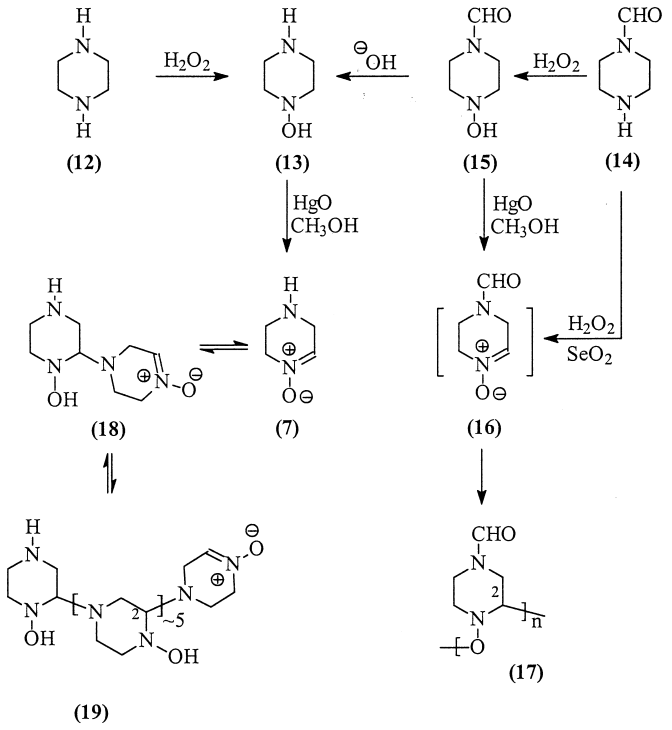
PII: S0040-4020(00)00574-3



Scheme 2.

regio- and stereoselectivity.[3–8] Usually a dilute solution of the nitrone in the presence of excess alkene ensures the suppression of the polymerisation process and affords the cycloadducts in excellent yields.

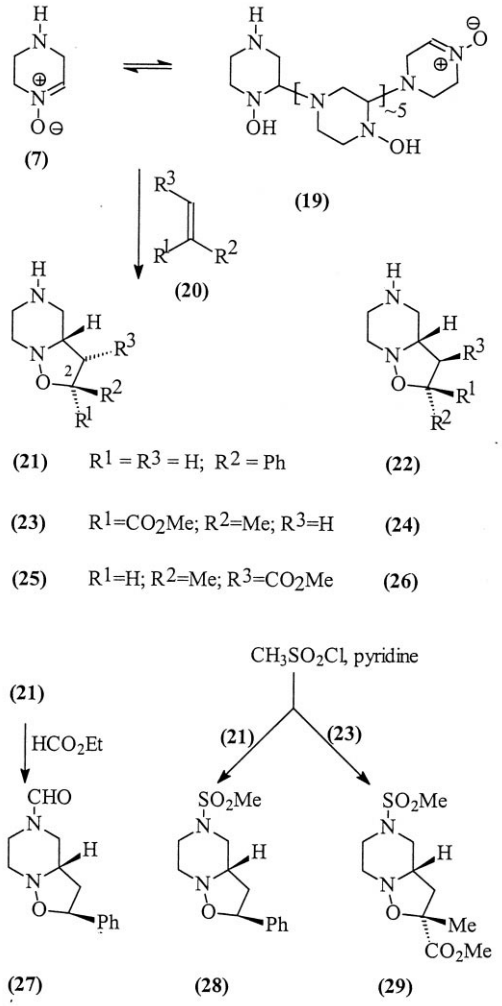
To the best of our knowledge, the synthesis of the interesting heterocyclic nitrone **7**, containing the ring skeleton of biologically important piperazine moiety, and its cycloaddition reactions are not reported to date (Schemes 1 and 2). Herein we report the synthesis, cycloaddition and reactivity of the nitrone **7** with some alkenes. We also examined the slow nitrogen inversion process in some of the cycloadducts, the 6–5 fused isoxazolidines, to determine the stereochemistry of the ring fusion in the bicyclic system.

Results and Discussion

The preparation of the nitrone **7** from piperazine (**12**) requires selective oxidation of one of the two identical amine groups and as such an efficient synthesis demands the selective protection of one of the amine groups (Scheme 2). Commercially available monoprotected derivative, *N*-formylpiperazine (**14**), is an attractive starting material, since the *N*-formyl group could be readily removed either by acid or by basic hydrolysis.

It was supposed at the outset that, while the preparation of the nitrone **16** from **14** would be a trivial matter, the synthesis of the corresponding free amine, the piperazine-nitrone **7**, might pose a problem (Scheme 2). However, repeated attempts to prepare the nitrone **16** either by the SeO_2 mediated[12] oxidation of the monoprotected amine **14** using H_2O_2 or via mercury(II) oxide oxidation of the corresponding hydroxylamine (**15**) ended in failure. Each time an intractable mixture of polymeric materials was obtained. The mercury(II) oxide oxidation of the hydroxylamine **15**, prepared using a modified procedure (see Experimental), was unsuccessful at the usual temperature of 0°C. However, the oxidation proceeded at 20°C as indicated by the formation of the greyish mercury salts. The ^{1}H NMR spectra of the oxidation products revealed the presence of at least fifteen singlets around δ 8.0 ppm attributed to NCHO proton signal. Several signals of low intensities appeared around δ 7.35 attributed to the C(2) H signals of the nitrone **16** or its related materials. The situation did not improve even when a dilute solution (0.05 M) of the hydroxylamine was oxidised. The polymer **17**, like **11**, presumably, have a repeated skeletal of –C–N–O– unit as shown in **17**. The C(2) H (i.e. CHNO) signals of the polymers **11**[7] and **17** appeared at δ 4.65 and 4.55 ppm, respectively. The polymer **17** was shown to be not in equilibrium with the monomeric nitrone **16** since it failed to undergo cycloaddition reaction with a variety of alkenes (namely styrene and methyl methacrylate). The polymer **11**, on the other hand, is reported[7] to give the adduct of the nitrone **5** with alkene, thus demonstrating the equilibration between the nitrone **5** and its polymer **11** (Scheme 1).

Next we pursued the preparation of the unprotected piperazine nitrone **7**. Presence of two basic nitrogen required the selective oxidation of one of the nitrogens. The *N*-hydroxypiperazine (**13**) was prepared from piperazine (**12**) using the procedure of Thesing and Meyer[13] for the oxidation of secondary amines and by deformylation of the hydroxylamine **15**. Both, the hydroxylamines **13** and **15** are prepared for the first time. Mercury(II) oxide oxidation of **13** in CD_3OD afforded the nitrone **7**, which upon removal of the solvent gave an amorphous polymeric material, which was found to be insoluble in many organic solvents including



Scheme 3.

methanol but was readily soluble in water. The ^{1}H NMR spectrum revealed broad envelope in 2.3–4.0 ppm range and multiple of signals of low intensities around δ 7.3–8.5 range. The oxidation of the hydroxylamine **13** in $CDCl_3$ was unsuccessful as it afforded a sticky insoluble material during oxidation. A 0.4 M solution of the nitrone **7** in CD_3OD revealed the presence of two C(2)H signals at δ 7.36 and 7.31 in a respective ratio of 80:20. However, the nitrone, prepared in very dilute solution (0.05 M), displayed the signals at δ 7.36 and 7.31 in a ratio of 90:10, respectively. While the signal at δ 7.36 was attributed to the C(2)H of **7**, the signal at δ 7.31 presumably belongs to the C(2)H of one of the end rings of the dimeric **18** and oligomeric materials **19** (Scheme 2). The next downfield signal at δ 3.77 was attributed to the NCHN proton, thus indicating the polymeric material to have a repeated skeletal as shown in **19** as a result of intermolecular nucleophilic addition of the secondary amine to the nitrone moiety. Absence of signal around δ 4.65 (for OCHN proton) precluded the presence of the repeated skeletal of –C–N–O– in the polymer **19**. The nature of the species present in the nitrone solution was revealed during the kinetic runs involving the addition reaction of methyl methacrylate (vide infra).

Unlike many other nitrone–alkene cycloaddition reactions, the kinetics of the nitrone (**7**)–alkene cycloaddition reactions were complicated due to presence of the oligomeric materials in equilibrium with the nitrone. The ratio of the concentrations of the nitrone and the alkene(methyl methacrylate), determined from time to time by the integration of proton signals at δ 7.35, 7.31 (for the nitrones) and the alkene protons, did not give a straight line fit for the second order kinetics. The problem stemmed from the fact that the signals around δ 7.3 did not represent the actual concentration of the nitrone. When several of the kinetic runs using excess methyl methacrylate was allowed to consume the nitrone completely (both the signals at δ 7.35 and 7.31 disappeared completely), then the ratio of the cycloaddion products and the remaining excess alkene helped to determine the initial concentration of the nitrone from the known concentration of the alkene. It was found that C(2)H signals around δ 7.3 ppm represented about 58±2% of the monomeric nitrone and one of the end rings of the oligomers; almost 40% represented the $(n-1)$ units of the oligormers (**19**). Thus the actual concentration of the nitrone at any time was calculated by multiplying the C(2)H intensities by a factor of 100/58. The excellent correlation obtained in the calculation of second order rate constants by linear regression analysis, indicated that the kinetics of the nitrone–oligomer equilibration is faster than that of the cycloaddition reaction (Scheme 3). The kinetic results obtained for the cycloaddition in CD_3OD are shown in Table 1. Low activation energies and large negative entropy of activation reflect the concerted nature of the nitrone cycloaddition reaction. For the sake of comparison, the relative rate of cycloaddition of the nitrone **2** and **7** with methyl methacrylate was carried out. The nitrone **7** was found to be twice as reactive as the nitrone **2**.[14] Kinetic study of the cycloaddition reaction of various cyclic nitrones are carried out usually in $CDCl_3$. However, the nitrone under study cannot be prepared in $CDCl_3$ and as such the cycloaddition was examined in CD_3OD. The morpholine nitrone **5** is reported to undergo addition reaction with methyl methacrylate at 36°C in $CDCl_3$ faster than the nitrone **2** by a factor of 4.[7,14] The incorporation of heteroatom (O or N) in the 4-position is thus found to increase the rate of addition

Table 1. Rate constants and activation parameters for cycloaddition reactions of the nitrone **7** with methyl methacrylate in CD_3OD

Nitrone	Temperature (°C)	k_2 (10^{-5} dm^3 mol^{-1} s^{-1}	E_a(kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})
7	16	23.7				
	26	44.3	48.3	45.8	92.4	−156
2	36	87				
	26	21.4[a]				

[a] Value obtained from the relative rates of addition of methyl methacrylate onto nitrones **2** and **7**.

Table 2. Stereochemistry of cycloaddition of the nitrone **7** with alkenes (**20**)

Alkene (**20**)	% Composition of adducts[a]		Isolated yield(%)
Styrene	(**21**) 100	(**22**)~0	73
Methyl methacrylate	(**23**) 96	(**24**) 4	86
Methyl crotonate	(**25**) 93	(**26**) 7	75

[a] Compounds are written in parentheses.

reaction. At this stage we are unable to provide a rationale for this rate differences.

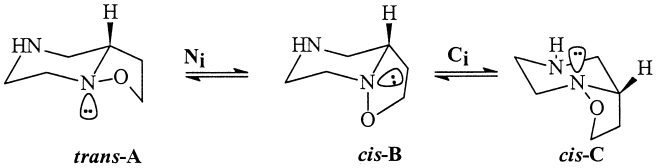
Next we pursued the regio- and stereo-chemistry associated with the addition reaction of the nitrone **7** with some common alkenes (**20**) (Scheme 3). The stereochemical details along with isolated yields are given in Table 2. The addition of styrene, methyl methacrylate and methyl crotonate were found to be regiospecific as well as highly stereoselective. The ^{1}H NMR assignments are consistent with the regiochemistry as shown in Scheme 3. For instance, the chemical shift of δ 5 ppm for the C(2)H of the styrene adduct **21** confirms the presence of phenyl at C(2); for the alternate regiochemistry, the C(2)H should appear around δ 4 ppm. Based on precedent literature[3,4,7,8] the major adduct was assigned the stereochemistry as depicted in **21**, **23** and **25** with *exo*-orientation of the phenyl and methyl group obtained via sterically favoured *exo*-mode of attack. The favourable secondary orbital interaction in the transition state involving *endo*-oriented methoxycarbonyl group dictates the stereoselection in the addition reaction of methyl methacrylate and methyl crotonate. We were concerned at the beginning that the amine functionality in **7** may undergo Michael addition to methacrylate and crotonate. We were gratified to find out that no such addition took place. The presence of the secondary amine (NH) group in the cycloadducts was confirmed by its conversion to *N*-formyl and *N*-methanesulfonyl drivatives by treatment with ethyl formate (**21→27**) and methane-sulfonyl chloride (**21→28**; **23→29**) (Scheme 3).

Finally, we decided to investigate the stereochemistry of the ring junction of the cycloaddition products. The cycloadducts can, in principle, exist in three different conformations as depicted in Scheme 4. The *cis* pair **B** and **C** is in rapid equilibrium by chair inversion ($\mathbf{C_i}$) and one of the *cis* conformers **B** is converted to the *trans* invertomer **A** by a relatively slow nitrogen inversion process ($\mathbf{N_i}$). The ^{1}H and ^{13}C NMR spectra, even at room temperature, showed the presence of two invertomers in each of the cycloadducts studied. The benzylic C(2)H of the adduct **21** appeared as a pair of signals at δ 5.04 and 5.41. The presence of the adjacent heteroatom oxygen slows the lone pair inversion[15,16] in the nitrogen to such an extent that the presence of two interconverting isomers can be identified by NMR spectroscopy, which offers a convenient way to measure the nitrogen inversion barrier[17] as well as the relative stability of the *cis* and *trans* invertomers.

The ^{13}C NMR spectra of the compounds investigated showed broadened peaks at ambient temperature. On lowering the temperature, the spectral lines sharpened and showed the presence of two distinct isomers in these compounds. The ^{13}C chemical shifts were assigned on the basis of the data on the corresponding adducts of nitrones **2** and **5**. The major and minor invertomers were assigned based on the integration of relevant peaks. The ^{13}C chemical shifts are shown in Table 3. We have shown in our earlier studies[17,18] on the adducts of **2** and **5**, that the carbons of the *cis* isomer are more shielded than the corresponding carbons of the *trans* isomer, except for the C-2 carbon, which is generally less shielded in the *cis* isomer. The axial oxygen substituent of the six-membered ring in the *cis* conformer **B** will have γ-*gauche* interactions with C-5 and C-7, whereas the other axial substituent CH_2 (or CHX) of the *cis* isomer **C** will have γ-*gauche* interactions[19] with C-6 and C-8. This provides further evidence that the *cis* isomer is a fast equilibrating pair of conformers **B** and **C** as the carbons C-5 to C-8 are shielded in the *cis* isomer. Assignment of *cis* and *trans* conformation to the adducts were further confirmed by ^{1}H NMR, where the *endo*-oriented hydrogen at C(2) in the *trans* invertomer is known[7] to resonate at higher field than the *cis* invertomer.

Obtaining accurate exchange rate constants by fitting NMR band shapes is well known to be fraught with difficulties,[20] and considerable errors result in the thermodynamic parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ if the Eyring plots are used within a limited temperature range. In fact many errors are systematic in nature, and those resulting for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are often mutually compensatory so that $\Delta G^{\ddagger}$ is better defined near coalescence. Although the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were obtained we attach little significance to them for the reasons stated above, and they are not reported in this paper. The $\Delta G^{\ddagger}$ values, obtained from Eyring plots, are given in Table 4, along with the ratio of *cis*/*trans* populations.

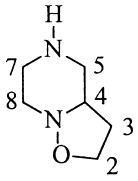
While the styrene adducts **21**, **27**, **28** with *exo*-oriented phenyl groups tend to favour the *cis* conformation, the adducts **23** (or **25**) having *endo*-oriented group at C(2) (or C(3)) presumably experiences unfavourable steric hindrance in the *cis* invertomer and as such favours the *trans* isomer. For the sake of comparison the ratio of *trans* to *cis* invertomer populations for various bicyclic systems obtained by nitrone–styrene cycloaddition reactions are given in Scheme 5. Geometric constraints prevent *cis*–*trans* interconversion by nitrogen inversion in **34** and it remains exclusively as the *cis* isomer.[17] For hydrindane,



trans-**A** *cis*-**B** *cis*-**C**

Scheme 4.

Table 3. ^{13}C NMR chemical shifts (in ppm relative to internal TMS at −25°C) of cycloadducts



		C-2	C-3	C-4	C-5	C-7	C-8	Other[a]
21	Major(*cis*)	78.37	38.87	58.78	43.94	42.32	49.33	*i*- 142.56, *o*- 128.49, *m*- 126.15, *p*- 127.60
	Minor(*trans*)	77.54	40.54	65.67	48.87	44.21	55.44	*i*- 141.03, *o*- 128.49, *m*- 126.76, *p*- 127.93
23	Major (*trans*)	79.72	42.33	66.49	48.80	44.24	56.41	CO_2Me- 175.31, 52.52; Me- 24.44
	Minor (*cis*)	83.72	39.27	59.65	44.64	44.08	51.37	CO_2Me- 175.31, 52.52; Me- 25.88
25	Major (*trans*)	74.48	55.78	68.70	47.06	44.23	56.70	CO_2Me- 171.48, 51.92; Me- 19.31
	Minor (*cis*)	74.80	52.20	62.10	43.26	42.55	56.42	CO_2Me- 172.63, 50.30; Me- 20.38
28	Major (*cis*)	78.76	38.90	59.12	44.25	42.19	49.12	*i*- 141.98, *o*- 128.64, *m*- 126.06, *p*- 127.85
	Minor (*trans*)	77.28	39.58	64.83	48.89	44.35	53.52	*i*- 140.06, *o*- 128.64, *m*- 126.72, *p*- 128.39
29	Major (*trans*)	81.06	41.37	64.47	48.63	44.14	53.38	CO_2Me- 174.95, 52.86; Me- 24.11, 35.41
	Minor (*cis*)	83.21	40.38	58.65	43.92	42.33	52.92	CO_2Me- 174.09, 49.49; Me- 25.74, 34.37

[a] *i*, *o*, *m* and *p* refer to *ipso*, *ortho*, *meta* and *para* carbons of the phenyl group, respectively.

the carbocyclic counter part of the compounds under study, a ΔG_0 value of around 1.06 kJ mol^{-1} at 25°C favours the *trans* isomer.[21] Incorporation of heteroatoms in the six-membered ring increases the amount of the *cis* invertomer; in the case of the adduct **33** it even becomes the sole invertomer. Incorporation of additional heteroatoms in the six-membered ring shortens the two C–X bond lengths and its overall dimension becomes closer to that of the 5/5 system (**34**). The presence of the heteroatoms also removes some potentially destabilising 1,3-diaxial interaction in the *cis* invertomers (Scheme 4). These could be the plausible reasons for the increase in the *cis*/*trans* ratio in these systems.

The cycloaddition products are obtained from piperazine based nitrone **7** for the first time. The study does indeed pave the way to incorporate and elaborate the biologically important piperazine moiety in an efficient way.

Table 4. Free energies of activation for nitrogen inversion (*trans*→*cis* isomerization at 298 K) and *cis*/*trans* isomer ratio in the adducts

Compound	$\Delta G^{\ddagger}$(kJ mol^{-1})	*Cis*/*trans*[a]
21	65.3	55:45
23	66.0	30:70
25	67.6	26:74
27	65.1	58:42
28	65.1	68:32
29	64.7	36:64

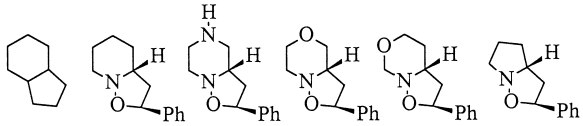
[a] At 253 K.

Experimental

Elemental analyses were performed on a Fisons Instruments Elemental Analyser 1108. All mps are uncorrected. IR spectra were recorded on a Nicolet 5 DXB FTIR, and are reported in wave numbers (cm^{-1}). Mass spectra at 70 eV E.I. were recorded on a Ribermag GC-MS system, R-10-10, with quadrupole mass filter and a Riber 400 acquisition system. Silica gel chromatography separations were performed with silica gel 100 (Fluka Chemie AG.).

The variable temperature ^{1}H and ^{13}C spectra were recorded on a JEOL Lambda 500 NMR spectrometer operating at 500.00 and 125.65 MHz respectively. The compounds were studied as 75 mg cm^{-3} solutions in $CDCl_3$ with TMS as internal standard. The ^{13}C NMR spectra were obtained with wide band proton decoupling and using DEPT technique to determine multiplicities of signals. The temperature control was achieved using the Lambda 500 temperature controller and calibrated using standard chemical shifts of methanol and glycol for low and high temperatures, respectively.

For compound **23**, two ring carbon resonances were utilised for exchange studies. The simulation of exchange affected spectra were carried out using a computer program[22] AXEX, corresponding to a two non-coupled sites exchange with unequal populations. The rate constant obtained at each temperature was an average of two calculated values. For



Scheme 5.

compound **29** the C(3) methyl resonance singlet and for compound **27** the aldehyde proton singlets were utilised for the exchange studies. The program AXEX was used for simulation of the exchange broadened spectra in both cases. For compound **21** and **28**, the C(2)H proton signal, which appeared as quartets, was used for the exchange studies. Simulation of spectra were carried out using a modified two-site exchange program reported earlier.[18]

1-Hydroxypiperazine (13). To a stirred powdered piperazine **(12)** (10.0 g, 116 mmol) at 0°C was added H_2O_2 (30%, 16 g, 141 mmol) over a period of 10 min, and the reaction mixture was kept around 10°C during the addition. After the removal of the ice bath the temperature of the reaction mixture started to increase and as soon as it crossed 45°C, the reaction flask was immersed in the ice-water bath. The temperature still kept on increasing with a mild explosion the exothermic reaction was complete (ca. 30 min). The yellow reaction mixture was saturated with anhydrous K_2CO_3 and washed with methanol (3×50 cm^3). After removal of the solvent the residual liquid was chromatographed using 1:1 mixture of CH_2Cl_2/MeOH to give the hydroxylamine **13** as a white solid (2.9 g, 24.5%). An analytical sample was prepared by crystallisation from MeOH/ether. Mp 128–129°C (Found: C, 46.9; H, 9.7; N, 27.2. $C_4H_{10}N_2O$ requires C, 47.03; H, 9.87; N, 27.43%); ν_{max} (KBr)/cm^{-1} 3177, 3083, 2949, 2924, 2861, 2831, 2784, 2751, 1509, 1467, 1452, 1373, 1360, 1272, 1261, 1180, 1168, 1111, 1012, 994, 957, 866, 852, 830, 790, 636 and 618; δ_H($CDCl_3$) 2.56 (2H, app t, J=9.6 Hz), 2.82 (2H, app t, J=12.3 Hz), 3.05 (2H, app d, J=13.2 Hz), 3.19 (2H, app d, J=11.0 Hz); δ_C ($CDCl_3$) 45.33, 59.36; *m/z*: 103 (M^++1, 48.5%), 102 (M^+, 9.8%), 85 (M^+−OH, 100%).

4-Formyl-1-hydroxypiperazine (15). To a solution of 1-formylpiperazine (**14**) (10.0 g, 87.7 mmol) and SeO_2 (0.437 g, 4.0 mmol) in methanol (250 cm^3) was added 30% H_2O_2 (13.1 g, 115 mmol) dropwise (ca. 10 min) under N_2. The resulting mixture was stirred under N_2 for 40 h. After the removal of the solvent and water the residual thick syrup was chromatographed using 80:20 CH_2Cl_2/MeOH mixture as the eluant to give the hydroxylamine (4.2 g, 37%) as a faint yellow solid. An analytical sample was obtained by crystallizing from acetone–ether. Mp 117–118°C (Found: C, 45.9; H, 7.65; N, 21.3. $C_5H_{10}N_2O_2$ requires C, 46.14; H, 7.74; N, 21.53%); ν_{max} (KBr)/cm^{-1} 3200, 2995, 2957, 2920, 2883, 2827, 1655, 1463, 1444, 1400, 1277, 1243, 1205, 1133, 1037, 1014, 964, 741, 674, 600; δ_H($CDCl_3$) 2.63(2H, m), 3.04 (1H, app t, J=10.5 Hz), 3.27 (3H, m), 3.66 (1H, app d, J=12.9 Hz), 4.23 (1H, app d, J=13.5 Hz), 7.75 (1H, br, OH), 8.02 (1H, s); δ_C ($CDCl_3$) 37.93, 43.60, 56.67, 57.67, 160.70, 77.12; *m/z*: 131 (M^++1, 63.7), 130 (M^+, 9.9%), 113 (5.9%), 103 (10.7%, 85 (100%).

Interconversion of the hydroxylamines 13 and 15

A mixture of **13** (100 mg) and ethyl formate (0.5 cm^3) was heated at 50°C for 12 h and TLC experiment (silica, ether:-methanol(saturated with NH_3), 1:1) indicated completion of the reaction. After removal of the solvent the resulting product was found to be identical in every respect to the **15**, prepared before.

To a solution of NaOH (1.6 g, 40 mmol) in H_2O (10 cm^3) was added 4-formyl-1-hydroxypiperazine **15** (3.90 g, 30 mmol) and the mixture was stirred under N_2 at 20°C for 36 h or until the TLC experiment indicated the completion of the reaction. After neutralising the excess NaOH with acetic acid the reaction mixture was saturated with K_2CO_3 and extracted with 3:1 $CHCl_3$/MeOH mixture (6×25 cm^3). The combined organic layer was dried (Na_2SO_4), concentrated and residual semisolid was purified by chromatography as before to give the **13** (2.74 g, 80%). The deformylation reaction was also successful by hydrolysis in 10% HCl solution (overnight, 20°C).

The preparation of the nitrone 7

A solution of the hydroxylamine **13** (4.6 mg, 0.045 mmol) in CD_3OD (0.52 g) was oxidised with HgO (30 mg) under stirring at 0°C under N_2 for a period of 2 h. The mixture was centrifuged and ^{1}H NMR of the clear solution was taken. δ_H 3.15 (2H, t, J=5.5 Hz), 3.65 (2H, app td, J=2.5, 5.5 Hz), 3.70 (2H, m), 7.35 (1H, m). The spectrum was virtually free of signal attributed to the oligomers. However, spectra taken after 24 and 72 h showed the presence of considerable amount of polymer along with 60% of the original nitrone in each time. The end group nitronic proton C(2)H of the polymeric material appeared at 7.31 ppm. The ratio of the C(2)H signals at 7.35 and 7.31 was found to be 90:10, respectively. Careful integration revealed the presence of the nitrone **7** and its oligomer in a respective ratio of 55:45. The oligomers were found to contain an average of seven monomer units. The oligomer proton signals appeared in the range 2.5–3.0 ppm and around 3.77 ppm.

Using the above procedure, the hydroxylamine **13** (102 mg, 1.0 mmol) in methanol (2 cm^3) was oxidised by yellow HgO (0.659 mg, 3.0 mmol) at 20°C for 3 h. After centrifuging, the clear solution was passed through glass wool. The removal of solvent gave a cream coloured powder, which was found to be insoluble in common organic solvents including MeOH, but readily dissolved in D_2O. The ^{1}H NMR spectrum revealed the presence of intractable mixture of polymeric materials along with minor amount (~5%) of the nitrone **7**.

Attempted oxidation of 15 using HgO

To a solution of the hydroxylamine **15** (130 mg, 1.00 mmol) in CD_3OD (1.5 cm^3) at 0°C under N_2 was added yellow HgO (0.650 g, 3.0 mmol) and the reaction mixture was stirred at 0°C for 1 h. The TLC (silica, ethyl ether/methanol (saturated with NH_3) 1:1) experiment indicated that no oxidation had happened and the colour of the yellow HgO did not change to greyish salt usual for HgO oxidation process. The reaction mixture was then stirred at 20°C for 4 h during which the greyish mercury salt appeared. The TLC experiment indicated multiple spots and ^{1}H NMR indicated the presence of at least 15 signals around 8.0 ppm attributed to the NCHO proton. The above oxidation mixture was divided into two parts and reacted with styrene (0.5 cm^3) and methyl methacrylate (0.5 cm^3) at 70°C for 5 h. The ^{1}H NMR spectrum was very complicated and failed to show the presence of any appreciable quantity of the anticipated cycloadducts.

At very dilute concentration, the oxidation of the hydroxylamine (4.2 mg) and CD_3OD (0.54 g) and HgO (30 mg) at 20°C for 2 h, again afforded an intractable mixture of products, the ^1H NMR of which showed 10 signals around 8.0 ppm due to the NCHO proton.

Kinetic study

The nitrone **7** for the kinetic runs was prepared in CD_3OD in the usual way as described (vide supra). The concentration of the nitrone was determined using known concentration of the alkene by ^1H NMR integration as described in the text. The concentrations of the nitrone and methyl methacrylate were kept around 0.35 and 0.5 M, respectively. The kinetic runs were followed up to 40–60% conversions and the rate constants were found to be reproducible within 5–7%.

Relative rates of addition reaction of the nitrone **2** and **7** with methyl methacrylate was determined in the following way. In an NMR tube was taken methyl methacrylate (30.0 mg, 0.30 mmol). A solution (~1 cm^3) of approximately 1:1 ratio of the nitrone **2** and **7** in CD_3OD (~0.5 M), was quickly introduced into the NMR tube containing methyl methacrylate at −5°C. An immediate ^1H NMR spectrum revealed no noticeable cycloaddition reaction. The NMR tube was then kept at a constant temperature (26°C) bath for 24 h, and then the ^1H NMR revealed the absence of any methyl methacrylate. The integration of several signals of the initial spectrum revealed the initial amounts of the nitrone **2**, **7** and methyl methacrylate as 0.27, 0.25 and 0.30 mmol (known), respectively. At the end of the reaction the amount of unreacted nitrones **2** and **7** was found to be 0.148 and 0.072 mmol, respectively. The signals of the C(2) methyl groups of the cycloaddition products (e.g. **23** from **7** and corresponding known[3] product from nitrone **2**) were examined carefully and analysed to reveal the presence of nitrone **2**- and nitrone **7**-adducts in 0.122 and 0.178 mmol quantities, respectively. Using Ingold and Shaw equation,[23] the relative rate, k_7/k_2 was found to be 2.07.

2-Phenylperhydro[1,2]oxazolo[2,3-*a*]pyrazine (21). To a solution of the hydroxylamine **13** (0.510 g, 5.0 mmol) in methanol (40 cm^3) was added yellow HgO (3.25 g, 10.15 mmol) at 0°C and stirred under N_2 for 3 h or until the oxidation was complete as indicated by the absence of the hydroxylamine in the TLC experiment (silica, 1:1 ether/MeOH (saturated with NH_3)). After filtering through a bed of $MgSO_4$, styrene (5 cm^3) was added to the nitrone solution and was stirred under N_2 at 50°C for 24 h. After removal of the solvent and excess styrene by blowing a gentle stream of N_2, the residual liquid was purified by chromatography using a 4:1 mixture of ether/methanol to give the adduct **21** as a pale yellow liquid (0.745 g, 73%). (Found: C, 70.7; H, 8.1; N, 13.6. $C_{12}H_{16}N_2O$ requires C, 70.55; H, 7.90; N, 13.72%); ν_{max} (neat)/cm^{-1} 3312, 3031, 2951, 2918, 2848, 1494, 1453, 1361, 1310, 1272, 1154, 1132, 1105, 1029, 1004, 965, 761, 701 cm^{-1}; δ_H($CDCl_3$, 200 MHz, +8.5°C) 2.00–3.80 (9H, m), 5.04 (0.45H, dd, *J*=4.0, 9.0 Hz), 4.69 (1H, br), 5.41 (0.55H, dd, *J*=4.0, 10.0 Hz), 7.40 (5H, m), The ^1H NMR spectra of the crude and purified product failed to detect the presence of the minor isomer **22**.

Methyl 2-methylperhydro[1,2]oxazolo[2,3-*a*]pyrazine-2-carboxylate (23 and 24). The nitrone was prepared by oxidation of the hydroxylamine (200 mg, 1.9 mmol) by HgO (1.00 g, 4.6 mmol) in methanol (5 cm^3) for 1 h at 20°C. The reaction mixture was then passed through a bed of $MgSO_4$ on top of glass wool in a pipette. The nitrone solution was treated with methyl methacrylate(2 cm^3) and the reaction was complete after 4 h at 20°C as indicated by the TLC experiment (1:1 ether/methanol (saturated with NH_3)). After removal of the solvent and excess alkene the residual liquid was purified by chromatography using 4:1 CH_2Cl_2/methanol mixture as the eluant to give the adduct (**23**) as a faint yellow liquid (0.335 g, 85.5%) (major/minor 96:4). (Found: C, 53.8; H, 7.95; N, 14.1. $C_9H_{16}N_2O_3$ requires C, 53.98; H, 8.06; N, 13.99%); ν_{max} (neat)/cm^{-1} 3319, 2955, 2837, 1743, 1442, 1308, 1255, 1212, 1131, 986, 917, 734; δ_H ($CDCl_3$, 20°C) 1.50 (3H, s), 2.00–3.65 (10H, complex m), 3.78 (3H, s). A minor singlet at δ 1.60 indicate the presence of the minor isomer **24** in a 96:4 ratio. At −20°C, the presence of two invertomers of the major isomer **23** is shown by the presence of singlets at δ 1.53(0.70×3H), 1.55 (0.30×3H), 3.80 (0.70×3H) and 3.82 (0.30×3H).

Methyl 2-methylperhydro[1,2]oxazolo[2,3-*a*]pyrazine-3-carboxylate (25 and 26). A solution of the nitrone **7** (prepared by mercury(II) oxide oxidation of 1.0 mmol of the hydoxylamine **13**) and *trans*-methylcrotonate (1 cm^3) in methanol (10 cm^3) was heated under N_2 at 50°C for 3 h. After removal of the solvent and excess alkene the residual liquid was chromatographed using 5% methanol in CH_2Cl_2 as the eluent to give the inseparable mixture of the adducts **25** and **26** as a colourless liquid (150 mg, 75%) (Found: C, 54.2; H, 8.15; N, 14.2. $C_9H_{16}N_2O_3$ requires C, 53.98; H, 8.06; N, 13.99%); ν_{max} (neat)/cm^{-1} 3320, 2954, 2840, 1734, 1440, 1380, 1264, 1200, 1122, 1042, 910, 790. δ_H($CDCl_3$, 0°C) 1.35 (3H, d, *J*=6.0 Hz), 1.93 (1H, br, s), 2.40–3.79 (8H, m), 3.72 (3H, s, two closely spaced singlets in a 3:1 ratio of peak heights), 4.52 (0.74H, quint, *J*=6.0 Hz), 4.92 (0.26H, quint, *J*=6.0 Hz). The methyl doublets for major and minor invertomers remained degenerate even at −50°C. The non-overlapping signals attributed to the minor isomer **26** were observed at δ 1.40 (3H, d, *J*=6.0 Hz), 4.37 (1H, quint, *J*=6.0 Hz). The major and minor adducts were found to be in the ratio of 93:7 as determined by integration of several relevant signals.

2-Phenyl-5-formylperhydro[1,2]oxazolo[2,3-*a*]pyrazine (27). A solution of **21** (204 g, 1.0 mmol) in ethyl formate (1 cm^3) was heated in a closed vessel at 50°C for 24 h or until the reaction was complete as indicated by the TLC experiment (silica, MeOH/ether 1:1). After the removal of ethyl formate the residual product was purified by chromatography using 10:1 ether/methanol mixture as the eluant to give the compound **27** (195 mg, 84%) as colourless crystals, mp 83–84°C (ether–MeOH) (Found: C, 67.0; H, 6.8; N, 11.9. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); ν_{max} (KBr)/cm^{-1} 2971, 2930, 2862, 1674, 1438, 1378, 1276, 1250, 1190, 1034, 772, 702; δ_H($CDCl_3$, −40°C) 2.29 (1H, m), 2.47–2.80 (2H, m), 2.95–4.77 (6H, m) 5.13 (0.42H, m), 5.39 (0.58H, m), 7.35 (5H, m), 8.10 (0.26H, s), 8.11 (0.17H,s), 8.14(0.25H,s), 8.18 (0.32H, s);

2-Phenyl-5-methansulfonylperhydro[1,2]oxazolo[2,3-*a*]-

pyrazine (28). To a solution of the adduct (**21**) (204 mg, 1.0 mmol) in CH_2Cl_2 (2 cm^3) was added at 0°C under N_2, pyridine (240 mg, 3 mmol) followed by methanesulfonyl chloride (160 mg, 1.4 mmol). After stirring at 0°C for 30 min a saturated solution of K_2CO_3 (3 cm^3) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3×5 cm^3). The organic layer was dried ($MgSO_4$), concentrated and the residual solid (230 mg, 82%) was crystallised from ether/methanol mixture to give **28** as colourless needles; mp 117–118°C. (Found: C, 55.1; H, 6.3; N, 9.85. $C_{13}H_{18}N_2O_3S$ requires C, 55.30; H, 6.42; N, 9.92%); ν_{max} (KBr)/cm^{-1} 3026, 2912, 2858, 1456, 1324, 1276, 1156, 970, 942, 796, 758, 696; δ_H($CDCl_3$, 20°C) 2.35 (1H, m), 2.84 (3H, s and 1H, m), 3.15–4.10 (7H, m), 5.13 (0.32H,m), 5.34 (0.68H, m), 7.35 (5H, m). At −20°C, the two isomers can be seen as indicated by the following signals: 2.87 (0.68×3H,s), 2.90 (0.32×3H,s), 5.15(0.32H, dd, *J*=4.5, 9.5 Hz), 5.38 (0.68H, dd, *J*=5.0, 9.3 Hz).

Methyl 2-methyl-5-methanesulfonylperhydro[1,2]oxazolo[2,3-*a*]pyrazine-2- carboxylate (29). The compound **23** is sulfonylated using procedure as described above. The crude reaction product was purified using 10:1 ether/methanol mixture as the eluant to give **29** as a colourless liquid (70% yield). (Found: C, 42.9; H, 6.35; N, 9.9. $C_{10}H_{18}N_2O_5S$ requires C, 43.15; H, 6.52; N, 10.06%); ν_{max} (neat)/cm^{-1} 2955, 2847, 1743, 1453, 1340, 1273, 1228, 1198, 1147, 966, 942, 787; δ_H($CDCl_3$, 20°C) 1.53 (3H, s), 2.20–4.00 (9H, complex m), 2.81 (3H, s), 3.79 (3H, s). At 0°C, all the methyl signals were split into two singlets indicating the presence of two invertomers in a ratio of 64:36: δ 1.54 (maj), 1.56 (min); 2.82 (min), 2.83 (maj); 3.79 (maj), 3.81 (min).

Acknowledgements

Facilities provided by the King Fahd University of Petroleum and Minerals are gratefully acknowledged.

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