A simple oxime–nitrone isomerisation and intramolecular nitrone-cycloaddition reaction of 3-(alk-2-enylamino)propionaldehyde oximes

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3-(Alk-2-enylamino)-2,2-dimethylpropionaldehyde oximes **3** underwent thermally induced 1,3-dipolar cycloaddition under mild conditions leading to isoxazolo[4,3-*c*]pyridine derivatives **4**. The methyl groups at the 2-position and the alkenylamino nitrogen in oximes **3** should facilitate the cycloaddition due to restriction of the conformational flexibility of the reaction sites and promotion of the isomerisation to NH-nitrone intermediate, respectively.

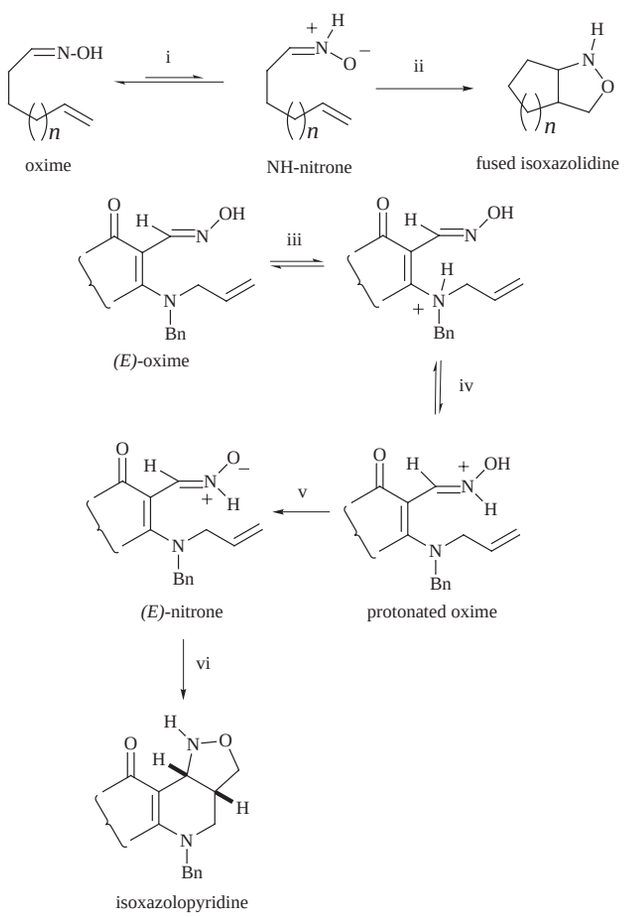
Introduction

The nitrone cycloaddition reaction with olefins and acetylenes can accomplish the regio- and stereo-selective preparation of isoxazolidines and isoxazolines, which have a labile N–O bond easily cleaved under reductive conditions. These sequences have been utilised as a key step for the synthesis of highly functionalised targets such as biologically active natural products.[1]

Since a new concept in the isomerisation of oximes to nitrones through a thermal 1,2-hydrogen shift was proposed by Grigg *et al.*[2] and the existence of the resultant NH-nitrone was elucidated by its forming intramolecular cycloaddition products (named the intramolecular oxime olefin cyclo-addition; IOOC) (Scheme 1), extensive investigations on the synthesis of highly functionalised isoxazolidine derivatives have been developed by many groups.[3] Nevertheless, only a few reports on further mechanistic elucidation of the oxime–nitrone isomerisation have been found; we have demonstrated that a simple oxime–nitrone isomerisation takes place in the oximes of heterocyclic aldehydes bearing an *N*-(alk-2-enyl)-*N*-benzyl-amino moiety at the adjacent position.[4] The alkenylbenzyl-amino nitrogen in the oximes could play a role as an intra-molecular catalyst in the isomerisation of oxime to NH-nitrone (Scheme 1).

The nitrone structure is the less stable tautomer in the equilibrium between oxime and nitrone and no examples of the isolation or detection of the resultant NH-nitrones have been reported; these were only trapped as intramolecular cycloaddition products. Sammes and co-workers disclosed that sterically bulky groups adjacent to the nitrone dipole and the dipolarophile moieties could facilitate the rate of cycloaddition due to restriction of the conformational space of the dipole and dipolarophile (buttress effect).[5] More recently, Heaney's group have demonstrated that thermal reaction of ω-alkenyloximes gives the fused isoxazolidines *via* IOOC and the cyclic nitrone *via* 1,3-azaprotio cyclotransfer (APT),[6] respectively (Scheme 2).[7] The reaction features depended mainly both on the length of the tether linking the oxime and the dipolarophile and on the configuration of the oximes.

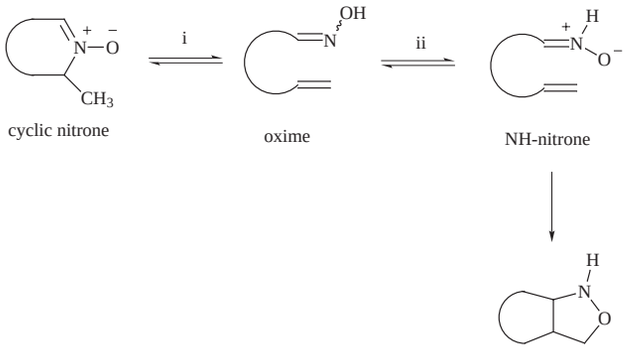
In the course of our study, we examined the thermal reaction of acyclic aldehyde oximes with more conformational flexi-bility, in which similar catalytic assistance by proton transfer is expected.



Scheme 1 *Reactions*: i, 1,2-hydrogen shift; ii, intramolecular cycloaddition; iii, protonation; iv, proton transfer; v, deprotonation; vi, intramolecular cycloaddition in an *endo* approach.

Results and discussion

In order to elucidate the controlling factors in the oxime–nitrone isomerisation process, we prepared 3-(*N*-allyl-*N*-benzyl-amino)propionaldehyde oxime **1a** as a prototype in this study to compare with 3-(*N*-allylanilino)- **1b**, 3-(*N*-allyl-*N*-cyclohexyl-amino)- **1c** and 3-(*N*,*N*-diallylamino)propionaldehyde oxime **1d**



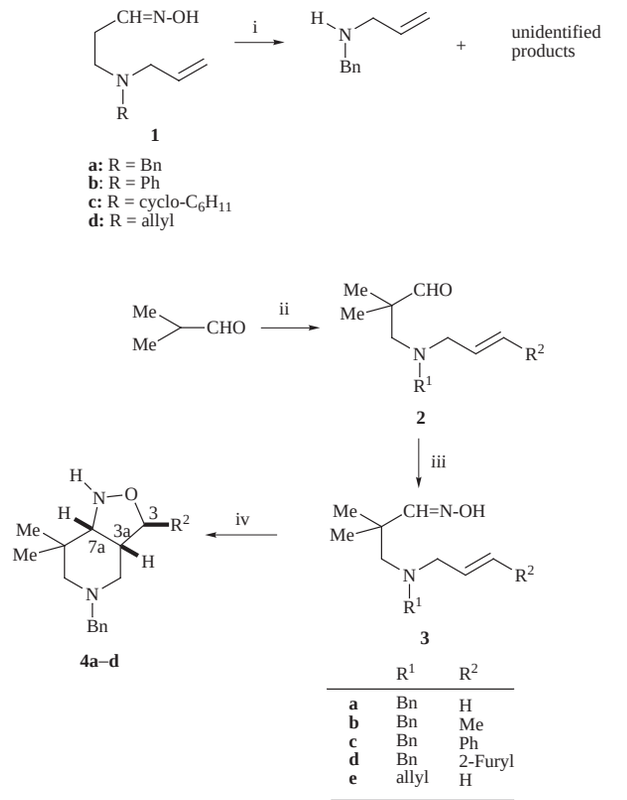
Scheme 2 *Reactions*: i, APT; ii, 1,2-H shift.

reported by Hassner's group. They demonstrated that oximes **1b**,**c** failed to undergo an IOOC leading to the corresponding isoxazolidine fused to a piperidine ring on heating even at 130 °C.[8a] On the other hand, they also communicated that the reaction of oxime **1d** in toluene at 180 °C in a sealed tube gave a nitrone–cycloadduct and a tricyclic product.[8b] However, details of the reaction (yield and structural confirmation) have not yet been reported to our best knowledge.

The reaction of oxime **1a** in ethanol or benzene under reflux gave an inseparable mixture of products along with *N*-allylbenzylamine (in 30–40% yield), which was probably formed by a retro-Michael addition of oxime **1a**. Some efforts to obtain the IOOC product under thermal (except for utilising the sealed-tube method) or catalytic conditions were made, unsuccessfully. Oxime **1a** was not particularly stable; on storage in deuteriochloroform at rt for 1 day or on silica gel chromatography oxime **1a** underwent partial decomposition to give a mixture of unidentified products along with *N*-allylbenzylamine. We suggest, however, that the structural and/or electronic modification of oxime **1a** should provide better results. To improve the stability of the starting oxime and to restrict the conformational flexibility of both reaction sites, 3-[*N*-(alk-2-enyl)amino]-2,2-dimethylpropionaldehyde oximes **3** were prepared and allowed to react. Mannich reaction of isobutyraldehyde with *N*-(alk-2-enyl)benzylamines or diallylamine gave the corresponding 3-[*N*-(alk-2-enyl)amino]propionaldehydes **2** in moderate to good yields. Usual treatment of aldehydes **2** with hydroxylamine in methanol at rt gave the desired oximes **3a**–**d** in good yields. Oximes **3a**–**d** were obtained as single isomers whereas oxime **3e**, on the other hand, was obtained as a mixture of (*E*)- and (*Z*)-isomers,[9] in some runs, which could not be separated on silica gel chromatography (Scheme 3). However, the (*Z*)-isomer in deuteriochloroform solution was changed to the (*E*)-isomer on storage overnight at rt. This means that the configuration of oximes **3** must not be taken into consideration for their reactivity due to the easy interconversion between (*E*)- and (*Z*)-isomers.

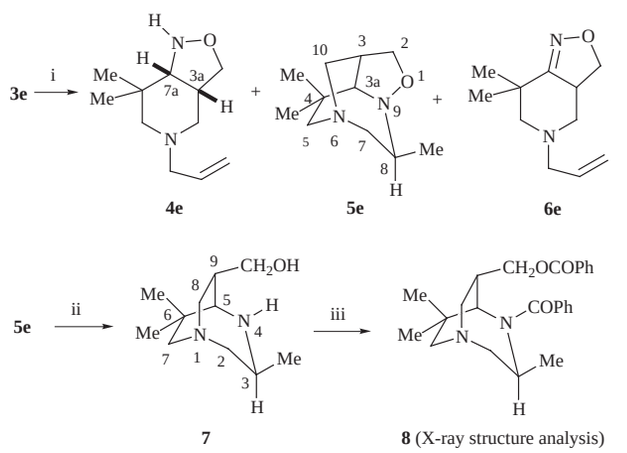
The reaction of oxime **3a** in ethanol under reflux for 72 h gave nitrone-cycloadduct **4a** and unchanged oxime **3a** in 66% yield and 28% recovery, respectively. Similar reaction of oxime **3a** at an elevated temperature [in refluxing butan-1-ol (BuOH) for 12 h] gave bicycle **4a** in 78% yield. The thermal reaction of oximes **3b**–**d** with more reactive olefinic dipolarophiles gave also nitrone-cycloadducts **4b**–**d** in quantitative yields (Table 1). The stereochemistry between 3a-H and 7a-H in cycloadducts **4a**–**d** was deduced to be *cis* (J = 4.0–5.3 Hz) and that between 3-H and 3a-H in adducts **4b**–**d** was *trans* (J = 1.0–2.0 Hz) on the basis of the coupling constants compared with those of related fused isoxazolidines.[10]

The reaction of oxime **3e** in BuOH under reflux for 12 h gave nitrone-cycloadduct **4e** (93%) and another type of product **5e** (trace) (Scheme 4). The ratio of products **4e** to **5e** depended on the solvent utilised, and the reaction in toluene under reflux gave an almost 1:1 mixture of products **4e** and **5e**. In some cases isoxazolopyridine derivative **6e**, formed by partial dehy-



	R^1	R^2
a	Bn	H
b	Bn	Me
c	Bn	Ph
d	Bn	2-Furyl
e	allyl	H

Scheme 3 *Reagents and conditions*: i, under thermal or catalytic conditions; ii, amines (0.77 equiv.), paraformaldehyde (1.0 equiv.), HCl (1.2 equiv.), EtOH, reflux, 6–12 h; iii, $H_2NOH{\cdot}HCl$ (1.0 equiv.), NaOAc (2.0 equiv.), MeOH, rt, 6–12 h; iv, EtOH or BuOH, reflux, 5–72 h.



Scheme 4 *Reagents and conditions*: i, in refluxing solvents; ii, Zn (15 equiv.), 1:1 water–AcOH, 80 °C, 3 days; iii, Et_3N (4.0 equiv.), DMAP (1.0 equiv.), PhCOCl (1.5 equiv.), THF, rt, 8 h.

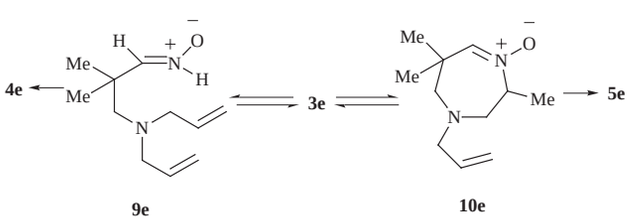
Table 1 Thermal reaction of oximes **3**

Run	Oxime	Solvent	Time (t/h)	Products/Yield (%)[a]
1	**3a**	EtOH	72	**4a**/66, **3a**/28
2	**3a**	BuOH	12	**4a**/78
3	**3b**	BuOH	8	**4b**/96
4	**3c**	EtOH	36	**4c**/quant.
5	**3c**	BuOH	8	**4c**/quant.
6	**3d**	BuOH	5	**4d**/quant.
7	**3e**	BuOH	12	**4e**/93, **5e**/trace
8	**3e**	1,4-dioxane	144	**4e**/66, **5e**/24, **6e**/trace, **3e**/5
9	**3e**	toluene	48	**4e**/51, **5e**/49
10	**3e**	MeCN	110	**4e**/43, **5e**/trace, **6e**/4, **3e**/50

[a] Based on isolated products.

drogenation of adduct **4e**, was also obtained. The structure of **5e** was deduced to be 4,4,8-trimethylperhydro-3,6-methano-isoxazolo[2,3-*d*][1,4]diazepine on the basis of its analytical and spectroscopic data; its molecular formula showed it to be an isomer of compound **4e**. In the ^{13}C NMR spectra of tricycle **5e**, including DEPT measurement, eleven sp^3-carbon signals, three methyl (δ = 15.2, 27.5, and 31.8), four methylene (δ = 54.5, 58.1, 60.9, and 79.2), three methine (δ = 40.6, 55.2, and 70.2) and one quaternary carbon (δ = 29.9), were observed, while no signals were shown in the sp^2-carbon region. Its ^1H–^{13}C and ^1H–^1H COSY spectra elucidated three sets of alignments: methyl (δ = 1.17; 8-Me)–methine (δ = 3.34; 8-H)–methylene protons (δ = 2.66 and 3.08; 7-H), methine (δ = 3.28; 3a-H)–methine (δ = 2.84; 3-H) and methylene (δ = 3.83 and 4.27; 2-H)–methine (δ = 2.84; 3-H)–methylene protons (δ ~2.84 and 3.14; 10-H). However, further structural confirmation of compound **5e** could not be accomplished, because the signals assigned to methylene protons 5-H overlapped with those of 3-H and one of 10-H. The N–O bond of compound **5e** was selectively cleaved with zinc–acetic acid to afford amino alcohol **7** in 72% yield, which was benzoylated by usual procedures to give dibenzoylated product **8** in 77% yield (Scheme 4). The structure of product **8** was unambiguously confirmed by its single-crystal X-ray analysis.[11]

The formation of compound **5e** from oxime **3e** is explained by tandem reactions[12] as follows; APT reaction of oxime **3e** gives cyclic nitrone **10e**, and intramolecular nitrone–olefin cycloaddition reaction of nitrone **10e** furnishes tricylic product **5e**. The existence of the equilibrium between oxime and cyclic nitrone forms in ω-alkenyloximes was also proposed by Heaney's group.[7] So, final products **4e** and **5e** were exposed to more severe conditions (in xylene under reflux for 20 h) and were recovered unchanged almost quantitatively. This implies that the existence of the cycloreversion of isomers **4e** and **5e** leading to the intermediary NH-nitrone **9e** and cyclic nitrone **10e**, respectively, can be ruled out and that the existence of the equilibria among oxime **3e** and nitrones **9e** and **10e** is plausible. We suggest that the solvents utilised might have affected these equilibria (Scheme 5), but the exact effects of the solvents on the reaction features are still unclear.

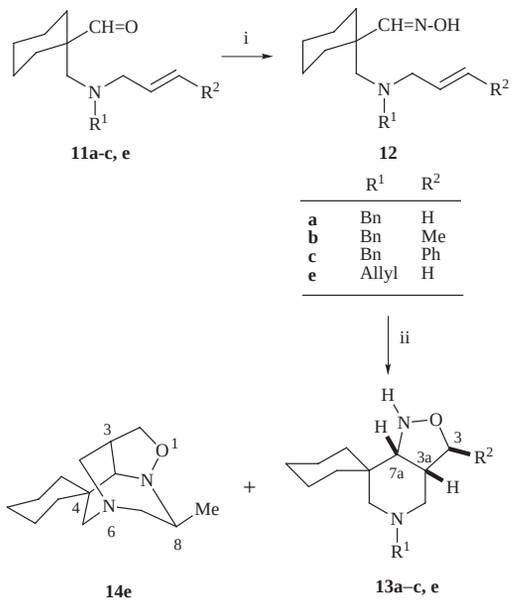


Scheme 5

In order to elucidate the effect of the substituent at the 2-position, aldehyde oximes **12a**–**c** and **12e** were prepared similarly to oximes **3**. Similar reaction of oximes **12a**–**c** gave *cis*-fused nitrone-cycloadducts **13a**–**c** in excellent yields. Also, oxime **12e** gave nitrone-cycloadduct **13e** and the isoxazolo-diazepine **14e** (Scheme 6 and Table 2). Although the IOOC reaction of oximes **12** was carried out more easily (with shorter reaction periods) than that of oximes **3**, an expected apparent acceleration of the reaction rate could not be observed.

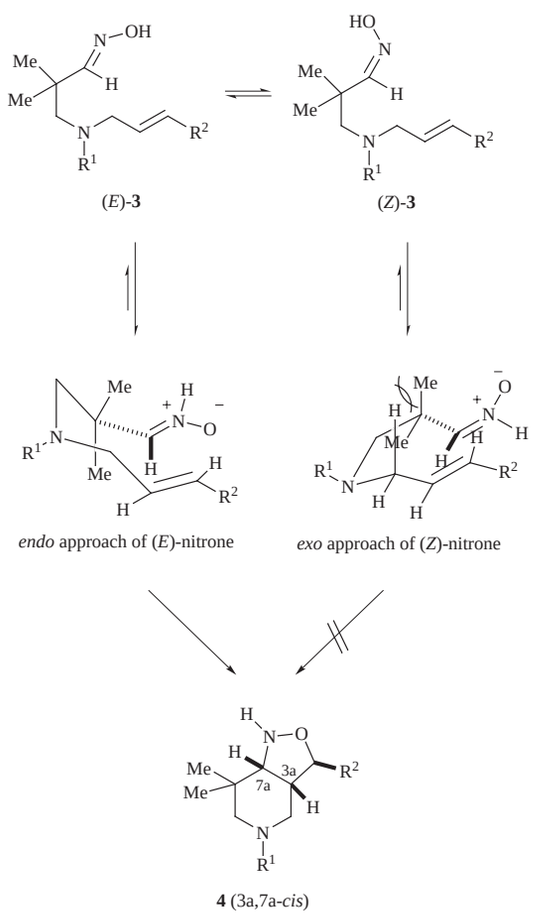
The formation of *cis*-fused nitrone-cycloadducts **4** and **13** is explained on the basis of the transition-state geometries. From considerations utilising Dreiding models, the substituents at the 2-position of oximes **3** and **12** were revealed to be essential. These suggested that the *endo*-transition state of the (*E*)-nitrone leading to *cis*-fused products **4** and **13** was only possible due to the less serious non-bonding interaction between the substituent at the 2-position and the allylic proton (Scheme 7).

Finally, the role of the alkenylamino nitrogen in the oxime–nitrone isomerisation was examined; two other oximes, **3f** and



	R^1	R^2
a	Bn	H
b	Bn	Me
c	Bn	Ph
e	Allyl	H

Scheme 6 *Reagents and conditions*: i, $H_2NOH{\cdot}HCl$ (1.0 equiv.), NaOAc (2.0 equiv.), MeOH, rt, 6–12 h; ii, in refluxing solvents.



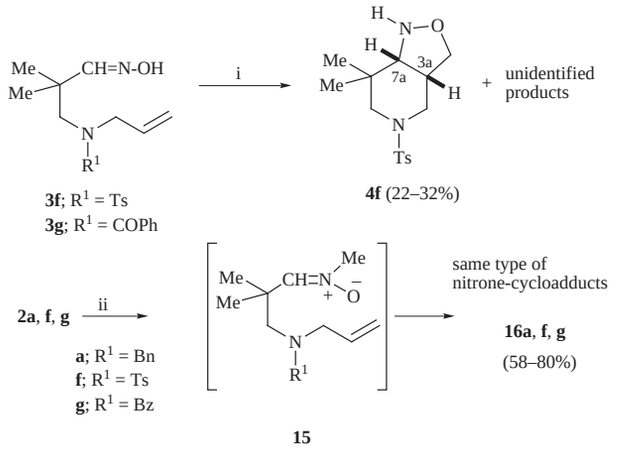
Scheme 7

Table 2 Thermal reaction of oximes **12**

Run	Oxime	Solvent	Time (*t*/h)	Products/Yield (%)[a]
1[b]	**12a**	EtOH	72	**13a**/68
2[b]	**12a**	BuOH	12	**13a**/65
3	**12b**	BuOH	4	**13b**/quant.
4	**12c**	BuOH	3	**13c**/quant.
5	**12e**	BuOH	12	**13e**/80, **14e**/trace
6	**12e**	toluene	36	**13e**/66, **14e**/23

[a] Based on isolated products. [b] Unidentified products were also formed.

3g, bearing an electron-withdrawing group on the nitrogen were prepared and allowed to react. On heating *N*-tosyl oxime **3f** in BuOH or toluene for 12–30 h gave nitrone-cycloadduct **4f** (22–32%) along with a mixture of unidentified products (Scheme 8). On the other hand, similar reaction of *N*-benzoyl



Scheme 8 *Reagents and conditions*: BuOH or toluene, reflux, 12–30 h; ii, MeNHOH·HCl (2.0 equiv.), Et_3N (2.4 equiv.), acetonitrile or EtOH, reflux, 3–12 h.

oxime **3g** gave only an inseparable mixture of products. These findings are sharply contrasted to the cycloaddition reactions of the corresponding *N*-methyl nitrones **15**, generated by the condensation of aldehydes **2a**, **2f** and **2g** with *N*-methylhydroxylamine in refluxing acetonitrile or EtOH, in which the same type of intramolecular cycloadduct **16** was formed.[13] Although an apparent effect of the substituents on the akenylamino nitrogen on the reactivity of the cycloaddition could not be observed, somehow better results in yields of the cycloadducts were obtained for substrates **2f** and **2g** compared with **2a** (Scheme 8). This means that the electron-withdrawing or amido nature of the substituents in intermediates **15f** and **15g** does not affect the cycloaddition step. Although we suggest that the electron-withdrawing substituents on the amino nitrogen affect the oxime–nitrone isomerisation step, details of the lower reactivity of oximes **3f** and **3g** for IOOC are still obscure. Further investigations on the mechanistic aspects are in progress and the details will be reported elsewhere.

In conclusion, we have reported a simple oxime–nitrone isomerisation of 3-(alk-2-enylamino)propionaldehyde oximes and intramolecular nitrone cycloaddition reaction (IOOC), in which the oximes bear appropriate substituents on the 2-position to restrict the conformational flexibility.

Experimental

General

Mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IR-Report-100 spectrophotometer from samples as KBr pellets or NaCl discs. ^{1}H NMR and ^{13}C NMR spectra were measured on JEOL EX-270 (270 MHz for ^{1}H and 67.8 MHz for ^{13}C) spectrometers for samples in deuteriochloroform solutions. Tetramethylsilane was used as internal standard and *J*-values are given in Hz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; and ov, overlapping with each other. Mass spectra were determined on a JEOL JMS-SX102A spectrometer. Elemental analyses were performed on a Yanagimoto MT-5 CHN analyser. All non-aqueous reactions were run under a positive pressure of argon or nitrogen. All solvents were dried by standard methods before use. The progress of reactions was monitored by TLC (Silica Gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or Silica Gel 60 (230–400 mesh, Merck). Ether refers to diethyl ether.

Preparation of oximes 3 and 12. Preparation of 3-(*N*-allyl-*N*-benzylamino)-2,2-dimethylpropionaldehyde 2a. Typical procedures

A solution of isobutyraldehyde (2.36 ml, 26 mmol), *N*-allylbenzylamine (2.9 g, 20 mmol), paraformaldehyde (0.78 g, 26 mmol) and conc. hydrochloric acid (2.7 ml, 30 mmol) in EtOH (14 ml) was heated under reflux for 8 h. The EtOH was evaporated off and the residue was treated with 5% NaOH aq. and extracted with ether (2 × 30 ml). The combined ethereal layer was washed with brine and dried over anhydrous magnesium sulfate. The ether was evaporated off and the residue was subjected to silica gel column chromatography to afford compound **2a** (3.3 g, 55%) with hexane–ethyl acetate (4 : 1).

In some cases, additional paraformaldehyde (50% of the quantity initially used) was added to the reaction mixture during the reaction. Similar Mannich reaction of cyclohexanecarbaldehyde with the secondary amines gave 1-(alk-2-enylaminomethyl)cyclohexanecarbaldehydes **11**. The desired aldehydes **2** and **11** were obtained in 38–82% yield along with their acetals. Similar reaction of isobutyraldehyde with paraformaldehyde and benzylamine oxalate[14] in EtOH gave 3-benzylamino-2,2-dimethylpropionaldehyde in 34% yield. The reaction of the 3-benzylamino aldehyde with toluene-*p*-sulfonyl chloride (1.0 equiv.) and benzoyl chloride (1.0 equiv.) in the presence of DMAP (0.2 equiv.) and triethylamine (1.5 equiv.) in THF gave aldehydes **2f** and **2g** in 86 and 81% yield, respectively. The structure of aldehydes **2** and **11** was elucidated by their ^{1}H NMR spectroscopic data, and they were used for the preparation of oximes without further purification.

Preparation of 3-(*N*-allyl-*N*-benzylamino)-2,2-dimethylpropionaldehyde oxime 3a. Typical procedures

A mixture of aldehyde **2a** (1.68 g, 7.3 mmol), hydroxylamine hydrochloride (0.47 g, 7.3 mmol), and sodium acetate (1.23 g, 15.0 mmol) in MeOH (10 ml) was stirred at rt for 6 h. The MeOH was removed under reduced pressure and the residue was treated with 10% aq. $NaHCO_3$ and extracted with ethyl acetate (2 × 15 ml). The organic layer was washed successively with brine (2 × 10 ml) and water (10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated off and the residue was subjected to column chromatography on silica gel to afford oxime **3a** (1.45 g, 81%) with hexane–ethyl acetate (9 : 1).

3-(*N*-Allyl-*N*-benzylamino)-2,2-dimethylpropionaldehyde oxime 3a. *Oil* (Found: C, 72.6; H, 9.2; N, 10.8. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00; N, 11.37%); ν_{max}(NaCl)/cm^{-1} 3250 (OH); δ_H 1.07 (6 H, s, 2-Me_2), 2.51 (2 H, s, 3-H), 3.04 (2 H, d, *J* = 6.6 Hz, $>$NCH_2CH=), 3.62 (2 H, s, $>$NCH_2Ph), 5.11 (2 H, ov, CH=CH_2), 5.85 (1 H, m, C*H*=CH_2), 7.25–7.36 (6 H, ov, Ph and 1-H) and 8.01 (1 H, br s, OH); *m*/*z* (EI) 246.1700 ($C_{15}H_{22}N_2O$ requires *M*, 246.1733).

3-[*N*-Benzyl-*N*-(*E*)-but-2-enylamino]-2,2-dimethylpropionaldehyde oxime 3b. *Oil* (Found: C, 73.5; H, 9.4; N, 10.7. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29; N, 10.76%); ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.06 (6 H, s, 2-Me_2), 1.68 (3 H, d, *J* = 4.6 Hz, =CH*Me*), 2.48 (2 H, s, 3-H_2), 2.96 (2 H, d, *J* = 4.0 Hz, $>$NCH_2CH=), 3.60 (2 H, s, $>$NCH_2Ph), 5.41–5.59 (2 H, ov, C*H*=C*H*), 7.20–7.36 (6 H, ov, Ph and 1-H) and 7.78 (1 H, br s, OH).

3-[*N*-Benzyl-*N*-(*E*)-cinnamylamino]-2,2-dimethylpropionaldehyde oxime 3c. *Oil* (Found: C, 77.8; H, 8.4; N, 8.45. $C_{21}H_{26}N_2O$ requires C, 78.22; H, 8.13; N, 8.69%); ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.09 (6 H, s, 2-Me_2), 2.57 (2 H, s, 3-H_2), 3.20 (2 H,

d, J = 6.6 Hz, $>$NCH_2CH=), 3.68 (2 H, s, $>$NCH_2Ph), 6.24 (1 H, td, J = 6.6 and 16.2 Hz, CH=CHPh), 6.43 (1 H, d, J = 16.2 Hz, CH=CHPh) and 7.19–7.39 (12 H, ov, 2 × Ph, OH and 1-H).

3-[*N*-Benzyl-*N*-(*E*)-3-(2-furyl)prop-2-enylamino]-2,2-dimethylpropionaldehyde oxime 3d. *Oil* (Found: C, 72.85; H, 7.9; N, 8.9. $C_{19}H_{24}N_2O_2$ requires C, 73.04; H, 7.74; N, 8.9%); ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.08 (6 H, s, 2-Me$_2$), 2.55 (2 H, s, 3-H), 3.18 (2 H, d, J = 5.9 Hz, $>$NCH_2CH=), 3.66 (2 H, s, $>$NCH_2Ph), 6.12–6.36 (4 H, ov, CH=CH and furyl 3- and 4-H), 7.19–7.37 (7 H, ov, Ph, furyl 5-H, and 1-H) and 7.96 (1 H, br s, OH).

3-(*N*,*N*-Diallylamino)-2,2-dimethylpropionaldehyde oxime 3e. *Oil*: ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.07 (6 H, s, 2-Me$_2$), 2.43 (2 H, s, 3-H), 3.10 (4 H, ov, $>$NCH_2CH=), 5.14 (4 H, ov, CH=CH_2), 5.81 (2 H, ov, CH=CH$_2$), 7.56 (1 H, s, 1-H) and 9.25 (1 H, br s, OH); m/z (EI) (M^+) 196.1564 ($C_{11}H_{20}N_2O$ requires M, 196.1576).

3-(*N*-Allyl-*N*-tosylamino)-2,2-dimethylpropionaldehyde oxime 3f. *Oil* (Found: C, 57.9; H, 7.3; N, 8.7. $C_{15}H_{22}N_2O_3S$ requires C, 58.04; H, 7.15; N, 9.02%); ν_{max}(NaCl)/cm^{-1} 3300 (OH), 1340 and 1160 (SO$_2$); δ_H 1.17 (6 H, s, 2-Me$_2$), 2.43 (3 H, s, tosyl Me), 3.22 (2 H, s, 3-H$_2$), 3.84 (2 H, d, J = 6.3 Hz, $>$NCH_2CH=), 5.11 (1 H, dd, J = 1.3 and 16.2 Hz, CH=CHH), 5.13 (1 H, dd, J = 1.3 and 10.6 Hz, CH=CHH), 5.32 (1 H, m, CH=CH$_2$), 7.30 (2 H, br d, J = 8.3 Hz, ArH), 7.36 (1 H, s, 1-H), 7.70 (2 H, br d, J = 8.3 Hz, ArH) and 7.76 (1 H, br s, OH).

3-(*N*-Allyl-*N*-benzoylamino)-2,2-dimethylpropionaldehyde oxime 3g. *Prisms* from hexane–benzene; mp 104–105 °C (Found: 69.1; H, 7.9; N, 10.6. $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%); ν_{max}(KBr)/cm^{-1} 3300 (OH) and 1600 (CO); δ_H 1.22 (6 H, s, 2-Me$_2$), 3.56 (2 H, s, 3-H$_2$), 3.90 (2 H, d, J = 4.3 Hz, $>$NCH_2CH=), 5.08 (1 H, d, J = 17.2 Hz, CH=CHH), 5.17 (1 H, d, J = 10.2 Hz, CH=CHH), 5.53–5.63 (1 H, m, CH=CH$_2$), 7.36 (5 H, s, Ph), 7.46 (1 H, s, 1-H) and 7.72 (1 H, s, OH).

1-(*N*-Allyl-*N*-benzylaminomethyl)cyclohexanecarbaldehyde oxime 12a. *Pale yellow oil*; ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.20–1.80 (10 H, ov, cyclohexyl H), 2.53 (2 H, s, 1′-H$_2$), 3.02 (2 H, d, J = 6.6 Hz, $>$NCH_2CH=), 3.61 (2 H, s, $>$NCH_2Ph), 5.05–5.13 (2 H, ov, CH=CH_2), 5.84 (1 H, m, CH=CH$_2$), 7.19–7.36 (6 H, ov, Ph and CH=NOH) and 8.15 (1 H, br s, OH); m/z (EI) (M^+) 286.2051 ($C_{18}H_{26}N_2O$ requires M, 286.2045).

1-[*N*-Benzyl-*N*-(*E*)-but-2-enylaminomethyl]cyclohexanecarbaldehyde oxime 12b. *Oil* (Found: C, 75.6; H, 9.3; N, 9.1. $C_{19}H_{28}N_2O$ requires C, 75.95; H, 9.39; N, 9.33%); ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.17–1.80 (10 H, ov, cyclohexyl H), 1.68 (3 H, d, J = 4.0 Hz, =CHMe), 2.51 (2 H, s, 1′-H$_2$), 2.94 (2 H, d, J = 3.6 Hz, $>$NCH_2CH=), 3.60 (2 H, s, $>$NCH_2Ph), 5.46–5.56 (2 H, ov, CH=CH), 7.18–7.35 (6 H, ov, Ph and CH=NOH) and 8.07 (1 H, br s, OH).

1-[*N*-Benzyl-*N*-(*E*)-cinnamylaminomethyl]cyclohexanecarbaldehyde oxime 12c. *Prisms* from hexane; mp 94–95 °C (Found: C, 79.5; H, 8.5; N, 7.7. $C_{24}H_{30}N_2O$ requires C, 79.51; H, 8.34; N, 7.73%); ν_{max}(NaCl)/cm^{-1} 3220 (OH); δ_H 1.18–1.83 (10 H, ov, cyclohexyl H), 2.59 (2 H, s, 1′-H$_2$), 3.18 (2 H, d, J = 6.3 Hz, $>$NCH_2CH=), 3.67 (2 H, s, $>$NCH_2Ph), 6.23 (1 H, td, J = 6.3 and 15.8 Hz, CH=CHPh), 6.41 (1 H, d, J = 15.8 Hz, CH=CHPh) and 7.18–7.39 (11 H, ov, 2 × Ph and CH=NOH) and 7.51 (1 H, s, OH).

1-(*N*,*N*-Diallylaminomethyl)cyclohexanecarbaldehyde oxime 12e. *Pale yellow oil* (Found: 70.8; H, 10.5; N, 11.4. $C_{14}H_{24}N_2O$ requires C, 71.14; H, 10.24; N, 11.85%); ν_{max}(NaCl)/cm^{-1} 3300 (OH); δ_H 1.18–1.80 (10 H, ov, cyclohexyl H), 2.44 (2 H, s, 1′-H$_2$), 3.08 (4 H, d, J = 6.3 Hz, $>$NCH_2CH=), 5.08–5.16 (4 H, ov, CH=CH_2), 5.74–5.89 (2 H, m, CH=CH$_2$), 7.26 (1 H, s, CH=NOH) and 8.19 (1 H, br s, OH); m/z (EI) (M^+) 236.1880 ($C_{14}H_{24}N_2O$ requires M, 236.1889).

Thermal reaction of oximes 3 and 12. Reaction of oxime 3a in BuOH. Typical procedure

A solution of oxime **3a** (0.240 g, 1.0 mmol) in BuOH (8 ml) was heated under reflux for 12 h and was then evaporated. The residue was subjected to silica gel column chromatography to afford nitrone-cycloadduct **4a** (0.187 g, 78%) with hexane–ethyl acetate (3 : 1).

5-Benzyl-7,7-dimethylperhydroisoxazolo[4,3-*c*]pyridine 4a. *Oil* (Found: C, 72.8; H, 9.0; N, 11.3. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00; N, 11.37%); ν_{max}(NaCl)/cm^{-1} 3200 (NH); δ_H 0.93 and 1.21 (each 3 H, each s, 7-Me$_2$), 1.93 (1 H, d, J = 11.9 Hz, 6-H), 2.00 (1 H, d, J = 9.9 Hz, 4-H), 2.30 (1 H, d, J = 11.9 Hz, 6-H), 2.70–2.81 (2 H, ov, 3a- and 4-H), 3.05 (1 H, d, J = 4.6 Hz, 7a-H), 3.42 and 3.51 (each 1 H, each d, J = 13.3 Hz, $>$NCH_2Ph), 3.62 (1 H, dd, J = 1.0 and 7.3 Hz, 3-H), 3.89 (1 H, dd, J = 5.6 and 7.3 Hz, 3-H), 4.8–5.2 (1 H, br, NH) and 7.23–7.33 (5 H, ov, Ph); δ_C 25.4 and 28.1 (7-Me$_2$), 31.9 (7-C), 40.4 (3a-C), 53.5 (4-C), 60.4 (6-C), 62.5 ($>$NCH_2Ph), 66.0 (7a-C), 72.7 (3-C) and 126.8, 128.1, 128.5 and 138.6 (Ph C).

5-Benzyl-3,7,7-trimethylperhydroisoxazolo[4,3-*c*]pyridine 4b. *Oil* (Found: C, 73.7; H, 9.2; N, 10.55. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29; N, 10.76%); ν_{max}(NaCl)/cm^{-1} 3400 (NH); δ_H 0.94 (3 H, s, 7-Me), 1.18 (3 H, d, J = 6.3 Hz, 3-Me), 1.19 (3 H, s, 7-Me), 1.92 (1 H, d, J = 11.6 Hz, 6-H), 1.98 (1 H, t, J = 11.6 Hz, 4-H), 2.28 (1 H, dd, J = 1.7 and 11.6 Hz, 6-H), 2.37 (1 H, ddd, J = 1.3, 4.9 and 11.6 Hz, 3a-H), 2.74 (1 H, ddd, J = 1.7, 6.3 and 11.6 Hz, 4-H), 3.11 (1 H, d, J = 4.9 Hz, 7a-H), 3.43 and 3.50 (each 1 H, each d, J = 13.5 Hz, $>$NCH_2Ph), 3.89 (1 H, dq, J = 1.3 and 6.3 Hz, 3-H), 5.3–6.0 (1 H, br, NH) and 7.25–7.33 (5 H, ov, Ph); δ_C 21.0 and 28.3 (7-Me$_2$), 25.4 (3-Me), 31.9 (7-C), 46.3 (3a-C), 53.9 (4-C), 61.0 (6-C), 62.6 ($>$NCH_2Ph), 65.1 (7a-C), 80.3 (3-C) and 126.9, 128.2, 128.6, and 138.6 (Ph C).

5-Benzyl-7,7-dimethyl-3-phenylperhydroisoxazolo[4,3-*c*]pyridine 4c. *Needles* from hexane; mp 84–86 °C (Found: C, 78.0; H, 8.3; N, 8.7. $C_{21}H_{26}N_2O$ requires C, 78.22; H, 8.13; N, 8.69%); ν_{max}(KBr)/cm^{-1} 3180 (NH); δ_H 0.97 and 1.12 (each 3 H, each s, 7-Me$_2$), 2.02 (1 H, d, J = 11.9 Hz, 6-H), 2.19 (1 H, dd, J = 8.9 and 10.9 Hz, 4-H), 2.30 (1 H, d, J = 11.9 Hz, 6-H), 2.70 (1 H, dddd, J = 2.0, 5.3, 6.3 and 8.9 Hz, 3a-H), 2.93 (1 H, dd, J = 6.3 and 10.9 Hz, 4-H), 3.18 (1 H, d, J = 5.3 Hz, 7a-H), 3.47 and 3.57 (each 1 H, each d, J = 13.4 Hz, $>$NCH_2Ph), 4.81 (1 H, d, J = 2.0 Hz, 3-H), 5.5–6.4 (1 H, br, NH) and 7.22–7.36 (10 H, ov, Ph); δ_C 25.4 and 28.4 (7-Me$_2$), 32.1 (7-C), 48.8 (3a-C), 54.1 (4-C), 60.9 (6-C), 62.6 ($>$NCH_2Ph), 64.5 (7a-C), 85.3 (3-C) and 125.4, 126.9, 127.3, 128.2, 128.3, 128.6, 138.6 and 142.1 (Ph C).

5-Benzyl-3-(2-furyl)-7,7-dimethylperhydroisoxazolo[4,3-*c*]-pyridine 4d. *Oil* (Found: C, 72.6; H, 8.1; N, 8.9. $C_{19}H_{24}N_2O_2$ requires C, 73.04; H, 7.74; N, 8.97%); ν_{max}(NaCl)/cm^{-1} 3200 (NH); δ_H 0.98 and 1.19 (each 3 H, each s, 7-Me$_2$), 2.04 (1 H, d, J = 11.5 Hz, 6-H), 2.15 (1 H, t, J = 11.9 Hz, 4-H), 2.28 (1 H, d, J = 11.5 Hz, 6-H), 2.79–2.93 (2 H, ov, 3a- and 4-H), 3.36 (1 H, d, J = 5.0 Hz, 7a-H), 3.50 (2 H, s, $>$NCH_2Ph), 3.2–4.0 (1 H, br, NH), 4.73 (1 H, d, J = 2.0 Hz, 3-H), 6.24 (1 H, d, J = 3.3 Hz, furyl 3-H), 6.30 (1 H, dd, J = 2.0 and 3.3 Hz, furyl 4-H) and 7.22–7.36 (6 H, ov, Ph and furyl 5-H); δ_C 25.3 and 28.3 (7-Me$_2$), 32.4 (7-C), 45.5 (3a-C), 53.4 (4-C), 61.3 (6-C), 62.6 ($>$NCH_2Ph), 65.9 (7a-C), 79.0 (3-C), 107.3, 110.1, 142.4 and 163.8 (furyl C) and 127.0, 128.2, 128.6 and 138.6 (Ph C); m/z (EI) (M^+) 312.1843 ($C_{19}H_{24}N_2O_2$ requires M, 312.1838).

7,7-Dimethyl-5-tosylperhydroisoxazolo[4,3-*c*]pyridine 4f. *Prisms* from hexane; mp 165–167 °C (Found: C, 58.0; H, 7.0; N, 9.2. $C_{15}H_{22}N_2O_3S$ requires C, 58.04; H, 7.15; N, 9.02%); ν_{max}(KBr)/cm^{-1} 3220 (NH), 1325 and 1150 (SO_2); δ_H 0.95 and 1.22 (each 3 H, each s, 7-Me_2), 2.27 (1 H, br t, J = 11.8 Hz, 4-H), 2.29 (1 H, d, J = 13.5 Hz, 6-H), 2.44 (3 H, s, tosyl Me), 2.87 (1 H, m, 3a-H), 3.17 (1 H, d, J = 4.0 Hz, 7a-H), 3.19 (1 H, dd, J = 1.7 and 13.5 Hz, 6-H), 3.64 (1 H, d, J = 4.9 Hz, 3-H), 3.69 (1 H, ddd, J = 1.7, 6.6 and 11.8 Hz, 4-H), 3.89 (1 H, dd, J = 4.9 and 8.2 Hz, 3-H), 5.3–6.0 (1 H, br, NH) and 7.32 and 7.62 (each 2 H, d, each br d, J = 8.3 Hz, tosyl H); δ_C 21.5 (tosyl Me), 24.7 and 26.7 (7-Me_2), 32.5 (7-C), 40.0 (3a-C), 44.9 (4-C), 51.8 (6-C), 65.0 (7a-C), 71.9 (3-C) and 127.5, 129.8, 133.2 and 143.7 (Ar C).

A similar reaction of oxime **3e** in toluene under reflux for 12 h and usual chromatographic purification gave nitrone-cycloadduct **4e** and isoxazolopyridine **6e** with hexane–ethyl acetate (3 : 1), and isoxazolodiazepine **5e** with ethyl acetate–MeOH (20 : 1), respectively.

5-Allyl-7,7-dimethylperhydroisoxazolo[4,3-*c*]pyridine 4e. *Plates* from hexane; mp 71–72 °C (Found: C, 67.1; H, 10.3; N, 14.2. $C_{11}H_{20}N_2O$ requires C, 67.05; H, 10.29; N, 14.26%); ν_{max}(KBr)/cm^{-1} 3190 (NH); δ_H 0.96 and 1.19 (each 3 H, each s, 7-Me_2), 1.86 (1 H, d, J = 11.5 Hz, 6-H), 1.93 (1 H, br t, J = 13.5 Hz, 4-H), 2.35 (1 H, d, J = 11.5 Hz, 6-H), 2.71–2.80 (2 H, ov, 3a- and 4-H), 2.91–3.02 (2 H, ov, >NCH_2CH=), 3.04 (1 H, d, J = 4.3 Hz, 7a-H), 3.64 (1 H, dd, J = 1.3 and 7.3 Hz, 3-H), 3.91 (1 H, dd, J = 5.3 and 7.3 Hz, 3-H), 5.11–5.23 (2 H, ov, CH=CH_2), 5.81 (1 H, m, CH=CH_2) and 5.1–5.9 (1 H, br, NH); δ_C 25.7 and 28.4 (7-Me_2), 31.9 (7-C), 40.4 (3a-C), 53.7 (4-C), 60.5 (6-C), 61.5 (>NCH$_2$CH=), 66.1 (7a-C), 72.9 (3-C), 117.5 (CH=CH$_2$) and 135.3 (CH=CH$_2$).

4,4,8-Trimethylperhydro-3,6-methanoisoxazolo[2,3-*d*][1,4]-diazepine 5e. *Oil* (Found: C, 64.6; H, 10.1; N, 13.6. $C_{11}H_{20}N_2O$·1/2 H_2O requires C, 64.36; H, 10.31; N, 13.65%); δ_H 1.15 and 1.22 (each 3 H, each s, 4-Me_2), 1.17 (3 H, d, J = 6.9 Hz, 8-Me), 2.66 (1 H, dd, J = 11.9 and 14.5 Hz, 7-H), 2.73–2.86 (4 H, ov, 3-H, 5-H_2 and 10-H), 3.08 (1 H, dd, J = 5.3 and 14.5 Hz, 7-H), 3.14 (1 H, dd, J = 7.2 and 7.4 Hz, 10-H), 3.28 (1 H, d, J = 6.6 Hz, 3a-H), 3.34 (1 H, m, 8-H), 3.83 (1 H, dd, J = 3.0 and 7.6 Hz, 2-H) and 4.27 (1 H, dd, J = 7.6 and 8.3 Hz, 2-H); δ_C 15.2 (8-Me), 27.5 and 31.8 (4-Me_2), 29.9 (4-C), 40.6 (3-C), 54.5 (10-C), 55.2 (8-C), 58.1 (5-C), 60.9 (7-C), 70.2 (3a-C) and 79.2 (2-C); *m*/*z* (EI) (M^+) 196.1588 ($C_{11}H_{20}N_2O$ requires *M*, 196.1576).

5-Allyl-7,7-dimethyl-3,3a,4,5,6,7-hexahydroisoxazolo[4,3-*c*]-pyridine 6e. *Pale yellow oil* (Found: C, 67.5; H, 9.8; N, 14.0. $C_{11}H_{18}N_2O$ requires C, 68.00; H, 9.34; N, 14.42%); δ_H 1.24 and 1.29 (each 3 H, each s, 7-Me_2), 1.91 (1 H, d, J = 11.2 Hz, 6-H), 1.95 (1 H, br t, J = 10.6 Hz, 4-H), 2.67 (1 H, dd, J = 2.0 and 11.2 Hz, 6-H), 2.96–3.11 (2 H, ov, >NCH_2CH=), 3.24 (1 H, ddd, J = 2.0, 6.3 and 10.6 Hz, 4-H), 3.57 (1 H, m, 3a-H), 3.76 (1 H, dd, J = 7.9 and 10.6 Hz, 3-H), 4.44 (1 H, dd, J = 7.9 and 10.6 Hz, 3-H), 5.14–5.23 (2 H, ov, CH=CH_2) and 5.82 (1 H, m, CH=CH$_2$); *m*/*z* (EI) (M^+) 194.1422 ($C_{11}H_{18}N_2O$ requires *M*, 194.1425).

Reductive cleavage of N–O bond of tricycle 5e leading to amino alcohol 7

A mixture of tricycle **5e** (0.116 g, 0.59 mmol) and activated zinc (0.58 g, 15 equiv.) in 50% aq. AcOH (30 ml) was heated at 80 °C for 3 days. The reaction mixture was basified with ammonium hydroxide and extracted with dichloromethane (3 × 15 ml). The combined extract was evaporated and the residue was subjected to silica gel column chromatography to afford amino alcohol **7** (0.084 g, 72%) with ethyl acetate–MeOH (1 : 2).

9-(Hydroxymethyl)-3,6,6-trimethyl-1,4-diazabicyclo[3.2.2]-nonane 7. *Prisms* from hexane–ethanol; mp 95–97 °C (Found: C, 66.4; H, 11.3; N, 14.1. $C_{11}H_{22}N_2O$ requires C, 66.62; H, 11.18; N, 14.13%); ν_{max}(KBr)/cm^{-1} 3230 (OH and NH); δ_H 0.97 (3 H, d, J = 6.3 Hz, 3-Me), 1.00 and 1.17 (each 3 H, each s, 6-Me_2), 2.00 (1 H, m, 9-H), 2.66–2.82 (4 H, ov, 2-H_2, 7- and 8-H), 2.98–3.11 (3 H, ov, 5-, 7- and 8-H), 3.0–4.6 (2 H, br, NH and OH), 3.25 (1 H, m, 3-H), 3.65 (1 H, dd, J = 4.0 and 11.2 Hz, CHHOH) and 3.93 (1 H, dd, J = 1.7 and 11.2 Hz, CHHOH); δ_C 19.9, 26.2, 31.2, 34.5, 36.3, 47.8, 51.0, 58.5, 62.6, 63.5 and 66.6.

Benzoylation of amino alcohol 7 leading to dibenzoylated product 8

To a solution of amino alcohol **7** (0.048 g, 0.24 mmol), triethylamine (0.135 ml, 4.0 equiv.) and DMAP (0.029 g, 1.0 equiv.) in THF (3 ml) was added benzoyl chloride (0.083 ml, 0.72 mmol) and the resultant mixture was stirred at rt for 8 h. The solvent was evaporated off and the residue was extracted with dichloromethane (3 × 10 ml). The combined organic layer was dried over magnesium sulfate and the solvent was evaporated off. The residue was subjected to silica gel column chromatography to afford compound **8** (0.041 g, 77%) with ethyl acetate–MeOH (5 : 1).

4-Benzoyl-9-benzoyloxymethyl-3,6,6-trimethyl-1,4-diaza-bicyclo[3.2.2]nonane 8. *Prisms* from hexane–EtOH; mp 152–153 °C (Found: C, 73.5; H, 7.5; N, 6.9. $C_{25}H_{30}N_2O_3$ requires C, 73.86; H, 7.44; N, 6.89%); δ_H 0.90 and 1.15 (each 3 H, each s, 6-Me_2), 1.47 (3 H, d, J = 6.3 Hz, 3-Me), 2.50 (1 H, m, 9-H), 2.56 (1 H, d, J = 14.5 Hz, 7-H), 2.76 (1 H, dd, J = 2.3 and 14.5 Hz, 7-H), 2.98 (1 H, ddd, J = 2.3, 6.9 and 14.9 Hz, 2-H) 3.12 (1 H, dd, J = 4.3 and 15.2 Hz, 8-H), 3.18 (1 H, dd, J = 8.3 and 15.2 Hz, 2-H), 3.46 (1 H, dd, J = 10.0 and 14.9 Hz, 8-H), 4.00 (1 H, br, 3-H), 4.45–4.61 (3 H, ov, CH_2OH and 5-H) and 7.28, 7.45, 7.58 and 7.96 (total 10 H, Ph).

The structure of compound **8** was confirmed by an X-ray single-crystal structural analysis (see below).

The reaction of oximes **12a**–**c** also gave nitrone-cycloadducts **13a**–**c** and a similar reaction of oxime **12e** in toluene under reflux gave nitrone-cycloadduct **13e** and the isoxazolodiazepine **14e**.

5-Benzylperhydroisoxazolo[4,3-*c*]pyridine-7-spirocyclohexane 13a. *Prisms* from hexane; mp 77–79 °C (Found: C, 75.2; H, 9.3; N, 9.7. $C_{18}H_{26}N_2O$ requires C, 75.48; H, 9.15; N, 9.78%); ν_{max}(KBr)/cm^{-1} 3400 (NH); δ_H 1.12–1.75 (10 H, ov, cyclohexyl H), 1.82 (1 H, d, J = 11.9 Hz, 6-H), 2.00 (1 H, br t, J = 13.2 Hz, 4-H), 2.53 (1 H, d, J = 11.9 Hz, 6-H), 2.70–2.81 (2 H, ov, 3a- and 4-H), 3.24 (1 H, d, J = 4.3 Hz, 7a-H), 3.40 and 3.52 (each 1 H, each d, J = 13.5 Hz, >NCH_2Ph), 3.60 (1 H, dd, J = 1.3 and 7.3 Hz, 3-H), 3.89 (1 H, dd, J = 5.3 and 7.3 Hz, 3-H), 5.3–5.8 (1 H, br, NH) and 7.21–7.33 (5 H, ov, Ph); δ_C 21.2, 21.4, 26.1, 34.4 and 35.3 (cyclohexyl C), 34.6 (7-C), 39.8 (3a-C), 54.3 (4-C), 58.5 (6-C), 62.8 (8-C), 63.9 (7a-C), 72.9 (3-C) and 127.0, 128.6, 128.6 and 138.7 (Ph C).

5-Benzyl-3-methylperhydroisoxazolo[4,3-*c*]pyridine-7-spiro-cyclohexane 13b. *Prisms* from hexane; mp 75–77 °C (Found: C, 75.5; H, 9.8; N, 9.1. $C_{19}H_{28}N_2O$ requires C, 75.95; H, 9.39; N, 9.33%); ν_{max}(KBr)/cm^{-1} 3200 (NH); δ_H 1.19 (3 H, d, J = 6.3 Hz, 3-Me), 1.12–1.69 (10 H, ov, cyclohexyl H), 1.82 (1 H, d, J = 11.9 Hz, 6-H), 2.00 (1 H, t, J = 11.2 Hz, 4-H), 2.35 (1 H, m, 3a-H), 2.52 (1 H, dd, J = 2.0 and 11.9 Hz, 6-H), 2.75 (1 H, ddd, J = 2.0, 6.3 and 11.2 Hz, 4-H), 3.29 (1 H, d, J = 5.0 Hz, 7a-H), 3.40 and 3.51 (each 1 H, each d, J = 13.5 Hz, >NCH_2Ph), 3.87 (1 H, dq, J = 1.3 and 6.3 Hz, 3-H), 5.4–6.0 (1 H, br, NH) and 7.21–7.32 (5 H, ov, Ph); δ_C 21.3, 21.5, 26.4, 34.5 and 35.6 (cyclohexyl C), 21.6 (3-Me), 34.7 (7-C), 46.1 (3a-C), 54.9 (4-C), 59.3 (6-C), 63.1 (>NCH$_2$Ph), 63.2 (7a-C), 80.7 (3-C) and 127.3,

128.9 × 2 and 139.1 (Ph C); *m/z* (EI) (M^+) 300.2202 ($C_{19}H_{28}N_2O$ requires *M*, 300.2202).

5-Benzyl-3-phenylperhydroisoxazolo[4,3-*c*]pyridine-7-spirocyclohexane 13c. *Oil* (Found: C, 79.05; H, 8.8; N, 7.6. $C_{24}H_{30}N_2O$ requires C, 79.51; H, 8.34; N, 7.73%); ν_{max}(NaCl)/cm^{-1} 3200 (NH); δ_H 1.23–1.76 (10 H, ov, cyclohexyl H), 1.93 (1 H, d, *J* = 11.9 Hz, 6-H), 2.23 (1 H, dd, *J* = 10.6 and 11.2 Hz, 4-H), 2.55 (1 H, *J* = 11.9 Hz, 6-H), 2.69 (1 H, m, 3a-H), 2.94 (1 H, dd, *J* = 6.3 and 10.6 Hz, 4-H), 3.1–3.7 (1 H, br, NH), 3.33 (1 H, d, *J* = 5.0 Hz, 7a-H), 3.44 and 3.58 (each 1 H, each d, *J* = 13.2 Hz, >NC*H*$_2$Ph), 4.78 (1 H, d, *J* = 1.7 Hz, 3-H) and 7.22–7.33 (10 H, ov, Ph); δ_C 21.2, 21.3, 26.1, 34.2 and 35.1 (cyclohexyl C), 34.7 (7-C), 48.1 (3a-C), 54.9 (6-C), 58.3 (4-C), 62.7 (>*C*H$_2$Ph), 62.8 (7a-C), 85.6 (3-C) and 127.0, 127.3, 128.2, 128.3, 128.4, 128.6, 138.6 and 142.2 (Ph C); *m/z* (EI) (M^+) 362.2327 ($C_{24}H_{30}N_2O$ requires *M*, 362.2358).

5-Allylperhydroisoxazolo[4,3-*c*]pyridine-7-spirocyclohexane 13e. *Plates* from hexane; mp 84–86 °C (Found: C, 71.0; H, 10.55, N, 11.8. $C_{14}H_{24}N_2O$ requires C, 71.14; H, 10.24; N, 11.86%); ν_{max}(KBr)/cm^{-1} 3180 (NH); δ_H 1.19–1.77 (10 H, ov, cyclohexyl H), 1.74 (1 H, d, *J* = 12.2 Hz, 6-H), 1.97 (1 H, t, *J* = 13.5 Hz, 4-H), 2.62 (1 H, d, *J* = 12.2 Hz, 6-H), 2.72–2.81 (2 H, ov, 3a- and 4-H), 2.87 (1 H, br dd, *J* = 6.7 and 13.5 Hz, >C*H*HCH=), 3.02 (1 H, dd, *J* = 5.9 and 13.5 Hz, >CH-*H*CH=), 3.23 (1 H, d, *J* = 4.3 Hz, 7a-H), 3.62 (1 H, dd, *J* = 1.0 and 7.3 Hz, 3-H), 3.91 (1 H, dd, *J* = 5.3 and 7.3 Hz, 3-H), 5.12–5.23 (2 H, ov, CH=C*H*$_2$), 5.0–5.9 (1 H, br, NH) and 5.82 (1 H, m, C*H*=CH$_2$); δ_C 21.4, 21.6, 26.4, 34.7 and 35.5 (cyclohexyl C), 34.6 (7-C), 40.0 (3a-C), 54.6 (4-C), 58.5 (6-C), 61.8 (>*C*H$_2$CH=), 64.0 (7a-C), 73.1 (3-C), 117.7 (CH=*C*H$_2$) and 135.5 (*C*H=CH$_2$).

8-Methylperhydro-3,6-methanoisoxazolo[2,3-*d*][1,4]diazepine-4-spirocyclohexane 14e. *Oil* (Found: C, 68.0; H, 10.0; N, 11.25. $C_{14}H_{24}N_2O{\cdot}1/2H_2O$ requires C, 68.52; H, 10.27; N, 11.42%); δ_H 1.15 (3 H, d, *J* = 6.3 Hz, 8-Me), 1.23–1.81 (10 H, ov, cyclohexyl H), 2.63 (1 H, t, *J* = 14.2 Hz, 5-H), 2.61–2.77 (4 H, ov, 3-, 7- and 10-H), 2.88 (1 H, d, *J* = 14.5 Hz, 10-H), 3.09 (1 H, t, *J* = 13.5 Hz, 7-H), 3.09 (1 H, d, *J* = 14.2 Hz, 5-H), 3.30 (1 H, m, 8-H), 3.38 (1 H, d, *J* = 6.9 Hz, 3a-H), 3.81 (1 H, dd, *J* = 2.6 and 7.9 Hz, 2-H) and 4.25 (1 H, t, *J* = 7.9 Hz, 2-H); δ_C 15.2 (8-Me), 21.9, 22.1, 25.8, 36.2 and 38.6 (cyclohexyl C), 32.9 (4-C), 40.1 (3-C), 55.0 (7-C), 55.2 (8-C), 55.3 (10-C), 61.0 (5-C), 69.2 (3a-C) and 79.2 (2-C); *m/z* (EI) (M^+) 236.1874 ($C_{14}H_{24}N_2O$ requires *M*, 236.1889).

X-Ray single-crystal structure analysis of dibenzoylated compound 8

Single crystals of compound **8** were obtained from hexane–EtOH as prisms. A crystal of approximate dimensions 0.180 × 0.340 × 0.940 mm was used for data collection. All measurements were made on a Rigaku AFC5S diffractometer by employing graphite-monochromated Mo-Kα radiation. The unit-cell dimensions were obtained by least-square analysis of 24 reflections within the range 20.7 < 2θ < 23.9°.

Crystal data for compound 8. Crystal system: monoclinic; space group: $P2_1/c$ (#14); cell constants: a = 8.36(1) Å, b = 16.383(6) Å, c = 16.111(7) Å, V = 2162(3) Å^3; β = 101.50(6)°; Z = 4; D_c = 1.249 g cm^{-3}. The ω–2θ scan technique to a maximum 2θ-value of 55° was used. Scans of (1.52 + 0.30 tan θ)° were made at a speed of 32° min^{-1}. A total of 5483 observed reflections (unique: 5139; R_{int} = 0.064) were collected. All calculations were performed using TEXAN program.[15] Atoms other than hydrogen were refined anisotropically. The structures were solved by direct methods (SIR)[16] and refined by least-squares to R 0.076 (R_w 0.074).

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