Intramolecular 1,3-dipolar cycloaddition at the periphery of heterocyclic systems. Part 1. Facile oxime–nitrone isomerisation at the periphery of pyran and 1-benzopyran

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4-(Alk-2-enylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oximes **5** underwent thermally induced 1,3-dipolar cycloaddition under mild conditions giving isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridine derivatives **6** in good yields. The features of the oxime–nitrone isomerisation and nitrone–olefin cycloaddition are discussed.

Since a new concept for the generation of nitrone intermediates was proposed by Grigg and co-workers,[1] the oxime–nitrone isomerisation and nitrone–olefin cycloaddition reactions have provided a versatile approach for the stereoselective synthesis of isoxazolidines. Therein, the thermal 1,2-hydrogen shift from oxygen to nitrogen in the oxime function is suggested to be a key step; an unassisted proton shift affords N-unsubstituted (or N-protonated) nitrone intermediates (Scheme 1). The resultant nitrone intermediates could be trapped only intramolecularly to give fused isoxazolidine derivatives.[2] Because of the predominant existence of the oxime isomer in the oxime–nitrone equilibrium, elevated reaction temperatures were needed to accomplish the cycloaddition reactions. Above all, harsher reaction conditions were required for the formation of the isoxazolidines fused by a six-membered ring; in toluene at 110 °C for 20 h for 1,3,3a,3b-tetrahydro-4*H*-[1]benzopyrano-[4,3-*c*]isoxazole †·[2a] from 2-allyloxybenzaldehyde oxime, and in toluene at 180 °C in a sealed tube for 10 h for 1,1a,3,3a,4,5,6,7,8,8a-decahydro-1*H*-pyrrolo[1,2-*a*]isoxazolo-[3,4-*c*]pyridine[2e] from 1-(but-3-enyl)pyrrolidine-2-carbaldehyde oxime.

In this paper, we report that a facile oxime–nitrone isomerisation takes place in the 4-(alk-2-enylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oxime system. The mechanistic elucidation of the oxime–nitrone isomerisation and stereoselective synthesis of fused isoxazolidines using the isomerisation will be also detailed.

Results and discussion

Reaction of 4-(alk-2-enylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehydes with hydroxylamines

In order to obtain information on the intramolecular nitrone cycloaddition at the periphery of 2-oxo-2*H*-1-benzopyran, we examined the reaction of 4-(allylbenzylamino)-2-oxo-2*H*-1-benzopyran-3-carbaldehyde **1a** with *N*-methylhydroxylamine hydrochloride **2** in ethanol at room temperature, which after 12 h gave the cycloadduct **3a** in 75% yield. Similar reactions of 4-[benzyl(*trans*-but-2-enyl)amino]- **1b** and 4-[benzyl(*trans*-cinnamyl)amino]-2-oxo-2*H*-1-benzopyran-3-carbaldehyde **1c** with **2** gave the corresponding adducts **3b**, **c** in good yields (Scheme 2).

† Recently, Orlek *et al.* described that 2-allyloxybenzaldehyde oxime did not undergo intramolecular cycloaddition under the conditions reported by Oppolzer and Keller.[2a] They reported that the restriction of the conformational space of dipole and dipolarophile in the above system was crucial.[3]

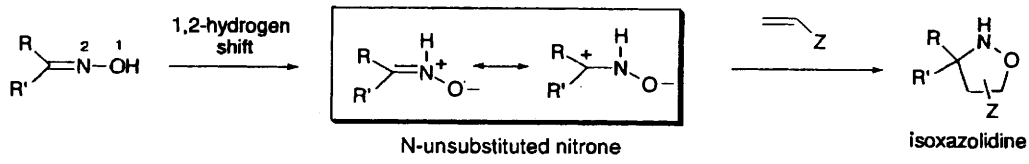
Table 1 Reaction of aldehyde **1** with hydroxylamine hydrochloride **4** in ethanol

Run	Aldehyde	Temp.	Time (*t*/h)	Products (% yield[a])
1	**1a**	rt	2	**5a** (74), **6a** (trace)
2	**1a**	rt	30	**5a** (12), **6a** (85)
3	**1a**	reflux	6	**6a** (92)
4[b]	**1b**	rt	1	**5b** (54), **6b** (trace)
5	**1b**	reflux	1	**6b** (61)
6	**1c**	rt	7	**6c** (48)
7	**1d**	rt	3	**6d** (55)
8	**1e**	rt	3	**6e** (66)
9	**1f**	rt	10	**6f** (59)

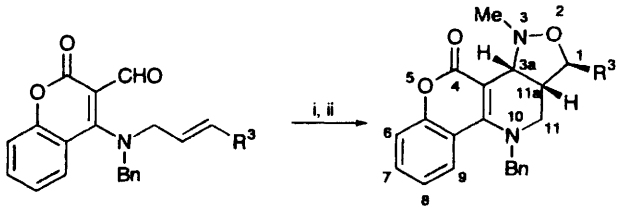
[a] Isolated yield. [b] Et_3N (3.0 equiv.) was added to the reaction mixture to obtain free hydroxylamine *in situ*.

The stereochemistry of the isoxazolidine rings in products **3** was determined to be 3,4-*cis* and 4,5-*trans* from the coupling constants and by comparison with those of similar systems reported by Oppolzer.[2a] This suggested that the resultant nitrone with *Z*-configuration[4] reacted with the olefinic dipolarophile component in an *exo*-approaching manner.

Our next concern was focused on the behaviour of the oximes of aldehydes **1**; the reaction of aldehyde **1a** with hydroxylamine hydrochloride **4** (1.4 equiv.) in ethanol at room temperature for 1 h, followed by neutralisation with aqueous sodium hydrogen carbonate gave the oxime **5a** and a trace amount of **6a**. The structure of **6a** was deduced to be 1,3a,4,5,11,11b-hexahydro-3*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-11-one from its spectroscopic data. Prolonged reaction time at the same temperature or heating the ethanol solution of **5a** afforded **6a** as a major product. These results indicate that product **6a** is a secondary product from the oxime **5a** and suggest that a nitrone, formed through a 1,2-hydrogen shift in **5a**, is a key intermediate for the formation of **6a**. To elucidate the utility of this isoxazolidine synthesis, similar reactions of aldehydes **1b** and **1c** were examined; oxime **5b** and/or isoxazolo[1]benzopyranopyridine **6b** and **6c** were formed depending on the conditions. The reaction of 4-(alk-2-enylamino)-6-methyl-2-oxo-2*H*-pyran-3-carbaldehydes **1d–f** with **4** gave only 3*H*-isoxazolo[3,4-*c*]pyrano[3,4-*e*]pyridin-9-ones **6d–f** in fair to good yields (Scheme 3, Table 1). Efforts to isolate oximes **5d–f** failed. These results reveal that the oxime–nitrone isomerisation followed by intramolecular cycloaddition proceeds in extremely mild conditions. The stereochemistry on the isoxazolidine rings was also assigned to be 3,4-*cis* (*J* 5.1–6.6 Hz) and 4,5-*trans* (*J* 1.8–2.6 Hz) compared with those of the *N*-methyl analogues **3a–c**. This suggests that the N-unsubstituted



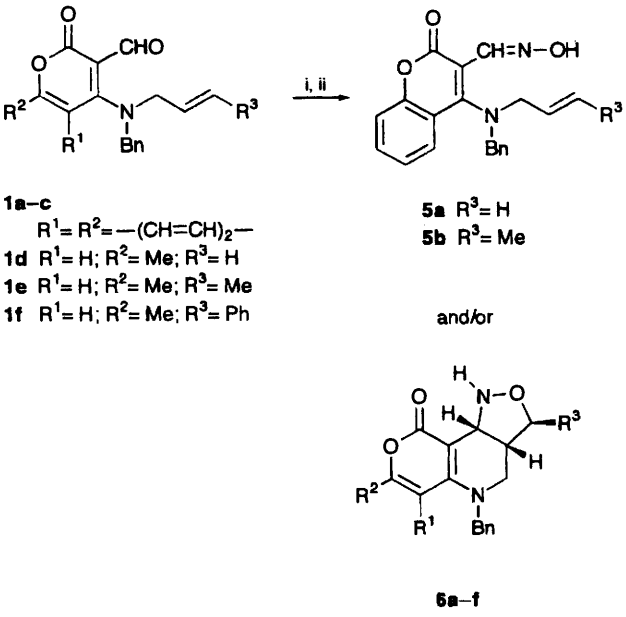
Scheme 1 Oxime–nitrone isomerisation through 1,2-hydrogen shift



1a R^3= H
1b R^3= Me
1c R^3= Ph

3a R^3= H
3b R^3= Me
3c R^3= Ph

Scheme 2 *Reagents and conditions:* i, MeNHOH·HCl **2**, EtOH, rt; ii, 5% aq. $NaHCO_3$



1a–c R^1= R^2= —(CH=CH)$_2$—
1d R^1= H; R^2= Me; R^3= H
1e R^1= H; R^2= Me; R^3= Me
1f R^1= H; R^2= Me; R^3= Ph

5a R^3= H
5b R^3= Me

and/or

6a–f

Scheme 3 *Reagents and conditions:* i, NH_2OH·HCl **4**, EtOH, rt–reflux, 1–30 h; ii, 5% aq. $NaHCO_3$

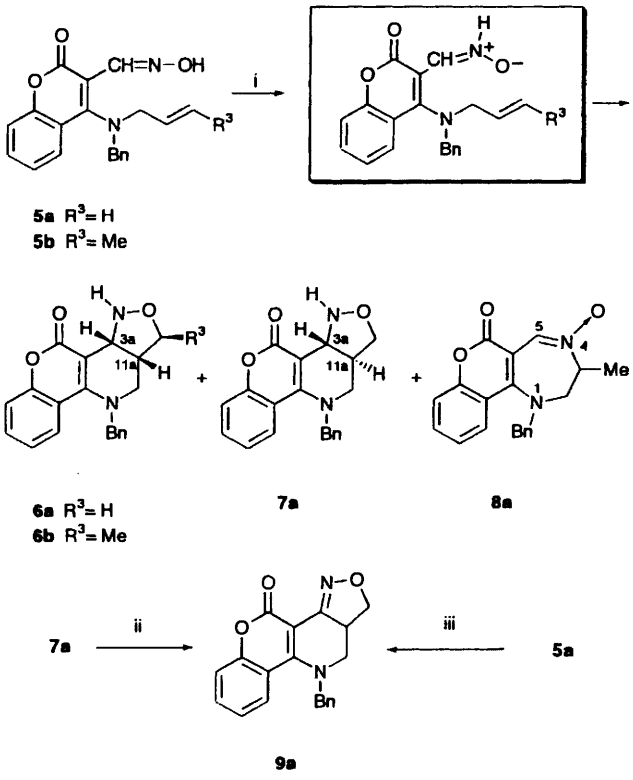
nitrones with *Z*-configuration also react with the olefin moieties in an *exo*-approaching manner or that the (*E*)-nitrones do in an *endo*-approaching one.

Oxime–nitrone isomerisation at the periphery of 1-benzopyran

Although many reports on the fused isoxazolidine synthesis utilising oxime–nitrone isomerisation have been found,[2] no mechanistic discussions could be found.[1a,5] In a previous paper, Shimizu *et al.* proposed an alternative route for the isoxazolidine synthesis from oxime and olefin.[6] According to the pathway proposed, under acidic conditions oximes were protonated to give cationic dipoles (RR'C$^+$–NH–OH), which underwent similar [3 + 2] cycloadditions‡ with olefinic dipolarophiles.

Therefore, we examined the oxime–nitrone isomerisation using the oximes isolated. Their reaction was found to be

‡ The cycloaddition of cationic dipoles formed from hydrazones or oximes was symbolised as [3$^+$ + 2] cycloadditions.[6]



5a R^3= H
5b R^3= Me

6a R^3= H
6b R^3= Me

7a

8a

9a

Scheme 4 *Reagents and conditions:* i, heating in some solvents; ii, $CDCl_3$, rt, 1 d; EtOH, reflux, 2 h; or column chromatography on silica gel; iii, NEt_3 (2.0 equiv.), CH_2Cl_2–10% aq. NaOCl, 0 °C, 1 h

dependent on the type of solvent used; refluxing **5a** in ethanol for 2 h or heating **5b** at 50 °C in ethanol for 3 h gave **6a** and **6b** in quantitative yields, respectively. Refluxing **5a** in benzene and acetonitrile or heating **5a** in dioxane at 80 °C gave two other products **7a** and **8a**, along with the major product **6a** (Scheme 4, Table 2). The ratio of the products obtained depended slightly on the polarity of the solvent used; on increasing the polarity the formation of products **7a** and **8a** was depressed. The structure of **7a** was determined to be the [3 + 2] cycloadduct with a *trans*-fused isoxazolidine ring from investigation of its coupling constant ($J_{3a,11a}$ 10.2 Hz).[2a] On the other hand, product **8a** was assigned to be 1-benzyl-3-methyl-6-oxo-1,2,3,6-tetrahydro[1]benzopyrano[4,3-*e*][1,4]diazepine 4-oxide, also from its spectroscopic data ($\delta_{CH=N}$ 8.37). A similar transformation of oximes to *N*-oxides, another type of nitrone, was found in the literature.[7] *trans*-Fused isoxazolidine **7a** was not very stable; when it was left in deuteriochloroform at room temperature for 1 day, or when it was heated in ethanol solution under reflux for 1 h, or when chromatographed on silica gel it was converted into 1,4,5,11-tetrahydro-3*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-11-one **9a**, which was also formed by the treatment of oxime **5a** with aqueous sodium hypochlorite, through a nitrile oxide cycloaddition reaction.

Finally, we examined the rates of the oxime–nitrone isomerisation in several solvents using an HPLC method (see Experimental section). In all cases the rates of the

Table 2 Thermal reaction of oximes **5a** and **5b**

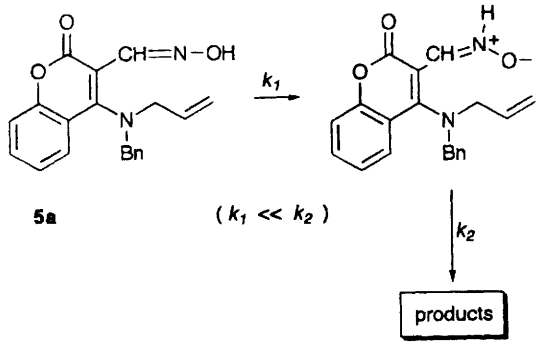
Run	Oxime	Solvent	Temp. (°C)	Time (*t*/h)	Products (% yield[a])
1	**5a**	benzene	reflux	8	**6a** (63), **7a** (8), **8a** (3)
2	**5a**	dioxane	80	11	**6a** (55), **7a** (7), **8a** (trace)
3	**5a**	MeCN	reflux	6	**6a** (78), **7a** (3), **8a** (trace)
4	**5a**	EtOH	reflux	4	**6a** (quant.)
5	**5b**	EtOH	50	3	**6b** (quant.)

[a] Isolated yield.

Table 3 Rate constants for the conversion of oxime **5a**

Temp. (°C)	Solvent	PTSA (equiv.)	$k \times 10^5$ (s^{-1})	Activation enthalpy (kcal mol^{-1})[a]	Activation entropy (cal mol^{-1} K^{-1})[a]
61.2	dioxane	—	1.02	20.8	−16.2
66.0	dioxane	—	1.86		
80.1	dioxane	—	5.78		
87.2	dioxane	—	12.36		
				Relative rate	
66.0	dioxane	—	1.86	1.0	
66.0	DMF	—	3.12	1.7	
66.0	butan-1-ol	—	12.1	6.6	
66.0	dioxane	0.59	1.96	1.1	
66.0	dioxane	2.00	3.58	1.9	
66.0	dioxane	*b*	2.01	1.1	

[a] 1 cal = 4.184 J. [b] NEt_3 (10.0 equiv.) was added to the solution.



disappearance of oxime **5a** were first-order with respect to the oxime concentrations. The activation energy for the conversion of oxime **5a** into isoxazolidine **6a** in dioxane was estimated to be 21.5 kcal mol^{-1} from the Arrhenius plot. The activation enthalpy and entropy for the conversion at 61.2 °C was estimated to be 20.8 kcal mol^{-1} and −16.2 cal mol^{-1} K^{-1}, respectively (Table 3). The effects of the solvents used on the rates of the conversion of **5a** were also examined (Table 3). Replacing dioxane with DMF as a solvent resulted in a small increase of the reaction rate, but a similar conversion in butan-1-ol was considerably accelerated (6.6 times faster than in dioxane). Addition of toluene-*p*-sulfonic acid (PTSA) to the dioxane solution of **5a** did not cause a remarkable increase in reaction rate (Table 3). In early nitrone chemistry, Huisgen *et al.* reported that the activation enthalphy for the intermolecular reaction of *N*-methyl-*C*-phenyl-nitrone with ethyl *trans*-but-2-enoate at 85.5 °C was 17.0 kcal mol^{-1}.[8] As expected, polar solvents depressed the rates of the 1,3-dipolar cycloaddition; the constants at 85.0 °C in the reaction of *N*-methyl *C*-phenyl nitrone and ethyl acrylate were 2.77×10^4 (dm^3 mol^{-1} s^{-1}) in dioxane, 1.64×10^4 in DMF, and 0.86×10^4 in ethanol, respectively.[8] From these results, the value of 21.5 kcal mol^{-1} should correspond to the activation energy for the oxime–nitrone isomerisation, and the intermediacy of cationic dipoles[6] was ruled out in our systems. Shimizu *et al.* also reported that 2-allyloxynaphthalene-1-carbaldehyde oxime did not undergo isomerisation to the corresponding nitrone in refluxing ethanol under neutral conditions.[6] Although the exact details of the facile oxime–nitrone isomerisation and successive nitrone cycloaddition in our case are still obscure, plausible explanations can be given; the alkenylamino nitrogen and/or carbonyl groups in the oximes could play a role as intramolecular catalyst in the hydrogen shift,§ or the restricted conformations of the dipole and dipolarophile could enhance the cycloaddition reaction rates.

While we have no evidence on the effects of the alcoholic solvents on the reaction, the following interpretation is proposed; solvation by alcoholic solvents during the isomerisation and cycloaddition steps might provide stabilisation of the nitrone intermediate and the restriction of the approach of the dipole and dipolarophile.

Further investigations on the reaction mechanism and scope of the oxime–nitrone isomerisation are in progress in our laboratory.

Experimental

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. ^1H and ^{13}C NMR spectra were measured on JEOL GSX-400 and/or 270 spectrometers in deuteriochloroform solutions, unless otherwise stated. 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 signals. Mass spectra were determined on a JEOL JMS-021G-2 or JMS-D spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. All non-aqueous reactions were

§ We wish to acknowledge the referees for this paper, who pointed this out.

run under a positive pressure of argon. 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). The aldehydes **1a–c** are known compounds[9] and **1d–f** were obtained similarly from 4-chloro-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde and the corresponding amines in 37–76%.

4-[Allyl(benzyl)amino]-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde 1d: yellow oil (Found: C, 72.5; H, 6.1; N, 4.7. $C_{17}H_{17}NO_3$ requires C, 72.06; H, 6.05; N, 4.94%); δ_H(270 MHz) 2.09 (3 H, s, Me), 4.02 (2 H, d, *J* 6, CH_2), 4.71 (2 H, s, CH_2Ph), 5.13–5.33 (2 H, ov, $=CH_2$), 4.86 (1 H, m, CH=), 6.23 (1 H, s, 5-H), 7.38 (5 H, Ph) and 10.09 (1 H, s, CHO).

4-[Benzyl(*trans*-but-2-enyl)amino]-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde 1e: yellow oil (Found: C, 73.0; H, 6.2; N, 4.45. $C_{18}H_{19}NO_3$ requires C, 72.70; H, 6.44; N, 4.71%); δ_H(270 MHz) 1.64 (3 H, d, *J* 4, Me), 2.11 (3 H, s, 6-Me), 3.88 (2 H, d, *J* 4, CH_2), 4.59 (2 H, s, CH_2Ph), 5.44 (2 H, ov, CH=CH), 6.01 (1 H, s, 5-H), 7.34 (9 H, ov, Ph) and 9.62 (1 H, s, CHO).

4-[Benzyl(*trans*-cinnamyl)amino]-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde 1f: yellow oil (Found: C, 77.2; H, 5.5; N, 4.0. $C_{23}H_{21}NO_3$ requires C, 76.86; H, 5.89; N, 3.90%); δ_H(270 MHz) 2.04 (3 H, s, Me), 4.00 (2 H, d, *J* 6.0, CH_2), 4.54 (2 H, s, CH_2Ph), 5.85–6.37 (3 H, ov, 5-H and CH=CH), 7.07 (10 H, Ph) and 9.70 (1 H, s, CHO).

Reaction of aldehyde 1a with *N*-methylhydroxylamine

General procedure. A solution of aldehyde **1a** (0.10 g, 0.31 mmol) and *N*-methylhydroxylamine hydrochloride **2** (0.12 g, 1.5 mmol) in ethanol (5 cm^3) was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and the residue treated with 5% aqueous sodium hydrogen carbonate (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The organic layer was evaporated to give a residue, which was subjected to column chromatography on silica gel eluting with ethyl acetate–hexane (1:1) to afford compound **3a** (0.081 g, 74%). Similarly, products **3b** and **3c** were obtained in 81 and 63% yields respectively.

(3a*R,11a*R**)-10-Benzyl-3-methyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-4-one 3a**, yellow plates from hexane–benzene, mp 210–220 °C (Found: 72.6; H, 5.8; N, 7.9. $C_{21}H_{20}N_2O_3$ requires C, 72.39; H, 5.79; N, 8.04%); ν_{max}/cm^{-1} 1690 (CO); δ_H(270 MHz) 2.36 (1 H, m, 11a-H), 2.99 (3 H, s, 3-Me), 3.20 (1 H, dd, *J* 4.8 and 13.2, 11-H), 3.42 (1 H, t, *J* 13.2, 11-H), 3.57 (1 H, dd, *J* 1.8 and 8.4, 1-H), 3.74 (1 H, d, *J* 5.5, 3a-H), 4.25 (1 H, dd, *J* 6.2 and 8.4, 1-H), 4.61 and 4.89 (each 1 H, each d, *J* 16.9, CH_2Ph), 7.10 (1 H, dd, *J* 7.3 and 8.4, 8-H), 7.27–7.49 (7 H, ov, 6- and 7-H and Ph) and 7.59 (1 H, d, *J* 8.4, 9-H); δ_C(68 MHz) 35.3 (Me), 45.2 (C-11a), 49.2 (C-11), 58.3 (CH_2Ph), 62.2 (C-3a), 68.4 (C-1), 101.4 (C-3b), 115.6 (C-9a), 117.7 (C-6), 123.5 (C-8), 124.9 (C-9), 126.7, 128.0, 129.2, 136.5 (ArC), 131.5 (C-7), 153.2 (C-5a), 155.9 (C-9b) and 162.2 (C-4); *m*/*z* 348 (M^+).

(1*S,3a*R**,11a*R**)-10-Benzyl-1,3-dimethyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]-pyridin-4-one 3b**, colourless prisms from hexane–benzene, mp 229–230 °C (Found: C, 73.3; H, 6.15; N, 7.9. $C_{22}H_{22}N_2O_3$ requires C, 72.91; H, 6.12; N, 7.73%); ν_{max}/cm^{-1} 1690 (CO); δ_H(270 MHz) 1.30 (3 H, d, *J* 6.2, 1-Me), 1.86 (1 H, m, 11a-H), 2.92 (3 H, s, 3-Me), 3.19 (1 H, dd, *J* 4.4 and 12.5, 11-H), 3.50 (1 H, t, *J* 12.5, 11-H), 3.76–3.84 (2 H, ov, 1- and 3a-H), 4.59 and 4.92 (each 1 H, each d, *J* 16.9, CH_2Ph), 7.09 (1 H, dd, *J* 7.3 and 8.1, 8-H), 7.26–7.50 (7 H, ov, 6- and 7-H and Ph) and 7.57 (1 H, d, *J* 8.1, 9-H); δ_C(68 MHz) 20.8 (1-Me), 41.2 (3-Me), 45.0 (C-11a), 49.2 (C-11), 58.5 (CH_2Ph), 61.5 (C-3a), 76.3 (C-1), 99.6 (C-3b), 115.5 (C-9a), 117.8 (C-6), 123.5 (C-8), 124.9 (C-9), 126.9, 128.0, 129.2, 136.4 (ArC), 131.6 (C-7), 153.3 (C-5a), 156.3 (C-9b) and 162.2 (C-4); *m*/*z* 362 (M^+).

(1*R,3a*R**,11a*R**)-10-Benzyl-3-methyl-1-phenyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]-pyridin-4-one 3c**, colourless prisms from hexane–benzene, mp 233–235 °C (Found: C, 76.3; H, 5.75; N, 6.2. $C_{27}H_{24}N_2O_3$ requires C, 76.39; H, 5.70; N, 6.60%); ν_{max}/cm^{-1} 1690 (CO); δ_H(270 MHz) 2.20 (1 H, m, 11a-H), 3.50 (3 H, s, Me), 3.34 (1 H, dd, *J* 4.8 and 12.5, 11-H), 3.68 (1 H, t, *J* 12.5, 11-H), 4.20 (1 H, d, *J* 5.1, 3a-H), 4.62 (1 H, d, *J* 2.6, 1-H), 4.49 and 4.96 (each 1 H, each d, *J* 17.2, CH_2Ph), 7.09 (1 H, dd, *J* 6.9 and 8.0, 8-H), 7.25–7.50 (12 H, ov, 6- and 7-H and Ph) and 7.57 (1 H, d, *J* 8.0, 9-H); δ_C(68 MHz) 42.9 (Me), 44.7 (C-11a), 49.7 (C-11), 58.5 (CH_2Ph), 62.0 (C-3a), 82.5 (C-1), 99.5 (C-3b), 115.5 (C-9a), 117.8 (C-6), 123.5 (C-8), 124.9 (C-9), 126.6, 128.0, 128.6, 129.2, 131.7, 136.3, 140.5 (ArC), 153.2 (C-5a), 156.5 (C-9b) and 162.2 (C-4); *m*/*z* 424 (M^+).

Reaction of aldehyde 1a with hydroxylamine

General procedure. A solution of aldehyde **1a** (0.10 g, 0.32 mmol) and hydroxylamine hydrochloride **4** (0.03 g, 0.45 mmol) in ethanol (5 cm^3) was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue treated with 5% aqueous sodium hydrogen carbonate (30 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The organic layer was evaporated to give a residue, which was subjected to column chromatography on silica gel eluting with ethyl acetate–hexane (2:1) to afford compounds **5a** (0.078 g, 74%) and **6a** (trace). Similarly, reaction of **1a** and **4** in ethanol under reflux for 6 h gave only **6a** in excellent yield.

4-[Allyl(benzyl)amino]-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oxime 5a, pale yellow crystals, mp 162–163 °C (Found: C, 72.1; H, 5.5; N, 8.2. $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3260 (OH) and 1700 (CO); δ_H(270 MHz) 3.86 (2 H, d, *J* 6.7, CH_2CH=), 4.46 (2 H, s, CH_2Ph), 5.22 (1 H, dd, *J* 1.3 and 17.2, $=CH_2$), 5.30 (1 H, dd, *J* 1.3 and 10.2, $=CH_2$), 5.83 (1 H, m, CH=), 7.18–7.38 (7 H, ov, 6- and 8-H and Ph), 7.54 (1 H, dd, *J* 7.2 and 8.6, 7-H), 7.68 (1 H, d, *J* 8.2, 5-H), 8.05 (1 H, s, CH=N) and 9.14 (1 H, br s, OH); δ_C(68 MHz) 55.8 (CH_2Ph), 56.9 (NCH_2CH=), 108.8 (C-3), 117.6 ($=CH_2$), 118.7 (C-4a), 119.9 (C-8), 123.9 (C-6), 125.9 (C-5), 128.0, 128.6, 128.8 and 137.0 (ArC), 132.1 (C-7), 133.2 (CH=), 144.5 (CH=N), 153.4 (C-8a), 159.3 (C-4) and 160.3 (C-2); *m*/*z* 334 (M^+).

(3a*R,11a*R**)-10-Benzyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-4-one 6a**, yellow plates from hexane–benzene, mp 179–180 °C (Found: C, 72.0; H, 5.6; N, 8.3. $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3280 (NH) and 1695 (CO); δ_H(270 MHz) 2.50 (1 H, m, 11a-H), 3.09 (1 H, dd, *J* 12.8 and 13.5, 11-H), 3.25 (1 H, dd, *J* 5.1 and 13.5, 11-H), 3.58 (1 H, dd, *J* 2.6 and 8.4, 1-H), 4.17 (1 H, dd, *J* 6.6 and 8.4, 1-H), 4.26 (1 H, d, *J* 6.6, 3a-H), 4.55 and 4.89 (each 1 H, each d, *J* 16.5, CH_2Ph), 7.13 (1 H, dd, *J* 7.3 and 8.4, 8-H), 7.26–7.51 (7 H, ov, 6- and 7-H and Ph) and 7.62 (1 H, d, *J* 8.4, 9-H); δ_C(68 MHz) 35.6 (C-11a), 48.6 (C-11), 54.9 (C-3a), 57.4 (CH_2Ph), 71.6 (C-1), 104.0 (C-3b), 115.7 (C-9a), 117.9 (C-6), 123.7 (C-8), 124.5 (C-9), 126.8, 128.0, 129.2 and 136.4 (ArC), 131.5 (C-7), 153.2 (C-5a), 155.2 (C-9b) and 162.5 (C-4); *m*/*z* 334 (M^+).

4-{Benzyl[(*E*)-but-2-enyl]amino}-2-oxo-2*H*-1-benzopyran-3-carbaldehyde oxime 5b, yellow needles from hexane–benzene, mp 132–133 °C (Found: C, 72.7; H, 5.8; N, 8.05. $C_{21}H_{20}N_2O_3$ requires C, 72.39; H, 5.79; N, 8.04%); ν_{max}/cm^{-1} 3280 (OH) and 1710 (CO); δ_H(270 MHz) 1.75 (3 H, d, *J* 6.3, Me), 3.80 (2 H, d, *J* 6.6, CH_2CH=), 4.47 (2 H, s, CH_2Ph), 5.47 (1 H, td, *J* 6.6 and 12.5, CH=), 5.65 (1 H, qd, *J* 6.3 and 12.5, CH=), 7.16–7.38 (7 H, ov, 6- and 8-H and Ph), 7.53 (1 H, dd, *J* 7.2 and 8.6, 7-H), 7.67 (1 H, d, *J* 8.2, 5-H), 8.03 (1 H, s, CH=N) and 9.15 (1 H, br s, OH); *m*/*z* 348 (M^+).

(1*S,3a*R**,11a*R**)-10-Benzyl-1-methyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-4-one 6b**, yellow crystals from hexane–benzene, mp 68–70 °C (Found: C, 72.0; H, 6.1; N, 7.7. $C_{21}H_{20}N_2O_3$ requires C, 72.39; H, 5.79; N, 8.04%); ν_{max}/cm^{-1} 3220 (NH) and 1700 (CO); δ_H(270 MHz) 1.32 (3 H, d, *J* 6.3, Me), 2.04 (1 H, m, 11a-H), 3.11 (1 H, t, *J* 13.2, 11-H), 3.26 (1 H, dd, *J* 4.9 and 13.2, 11-H), 3.82 (1 H, dq, *J* 3.0 and 6.3, 1-H), 4.32 (1 H, d, *J* 6.6, 3a-H), 4.52 and 4.90 (each 1 H, each d, *J* 16.8, C*H*$_2$Ph), 6.32 (1 H, br s, NH), 7.12 (1 H, dd, *J* 7.9 and 8.2, 8-H), 7.27–7.50 (7 H, ov, 6- and 7-H and Ph) and 7.60 (1 H, d, *J* 8.2, 9-H); δ_C(68 MHz) 19.5 (Me), 42.2 (C-11a), 48.4 (C-11), 54.8 (C-3a), 57.4 (*C*H$_2$Ph), 78.9 (C-1), 103.3 (C-3b), 115.7 (C-9a), 117.9 (C-6), 123.7 (C-8), 124.5 (C-9), 126.8, 128.0, 129.2 and 136.5 (ArC), 131.5 (C-7), 153.2 (C-5a), 155.4 (C-9b) and 162.5 (C-4); *m*/*z* 348 (M$^+$).

(1*R,3a*R**,11a*R**)-10-Benzyl-31-phenyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-4-one 6c**, yellow crystals from hexane–benzene, mp 270–272 °C (Found: C, 76.4; H, 5.6; N, 6.7. $C_{26}H_{21}N_2O_3$ requires C, 76.08; H, 5.40; N, 6.83%); ν_{max}/cm^{-1} 3400 (NH) and 1710 (CO); δ_H(270 MHz) 2.43 (1 H, m, 11a-H), 3.30 (1 H, t, *J* 13.5, 11-H), 3.41 (1 H, dd, *J* 5.6 and 13.5, 11-H), 4.48 (1 H, d, *J* 4.6, 3a-H), 4.66 (1 H, d, *J* 3.3, 1-H), 4.46 and 4.93 (each 1 H, each d, *J* 16.8, C*H*$_2$Ph), 7.13 (1 H, t, *J* 8.2, 8-H), 7.26-7.52 (12 H, ov, 6- and 7-H and Ph) and 7.61 (1 H, d, *J* 8.2, 9-H); δ_C(68 MHz) 43.8 (C-11a), 48.7 (C-11), 55.3 (C-3a), 57.3 (*C*H$_2$Ph), 84.7 (C-1), 103.3 (C-3b), 115.7 (C-9a), 118.0 (C-6), 123.8 (C-8), 124.4 (C-9), 126.3, 126.7, 128.0, 128.2, 128.7, 129.2, 136.4 and 139.8 (ArC), 131.6 (C-7), 153.2 (C-5a), 155.4 (C-9b) and 162.5 (C-4).

(3a*R,9b*R**)-5-Benzyl-7-methyl-3,3a,4,5,9,9b-hexahydro-1*H*-isoxazolo[3,4-*d*]pyrano[4,3-*b*]pyridin-9-one 6d**, yellow plates from hexane–benzene, mp 144–145 °C (Found: 68.4; H, 6.1; N, 9.3. $C_{17}H_{18}N_2O_3$ requires C, 68.44; H, 6.08; N, 9.39%); ν_{max}/cm^{-1} 3200 (NH) and 1690 (CO); δ_H(270 MHz) 2.16 (3 H, s, Me), 2.65 (1 H, m, 3a-H), 3.20 (1 H, t, *J* 12.9, 4-H), 3.27 (1 H, dd, *J* 5.9 and 12.9, 4-H), 3.62 (1 H, dd, *J* 2.6 and 7.9, 3-H), 4.13 (1 H, dd, *J* 6.6 and 7.9, 3-H), 4.30 (1 H, d, *J* 5.9, 9b-H), 4.58 (2 H, s, C*H*$_2$Ph), 5.85 (1 H, s, 6-H) and 7.14–7.41 (5 H, ov, Ph); δ_C(68 MHz) 20.3 (Me), 37.8 (C-3a), 48.4 (C-4), 54.0 (C-9b), 54.4 (*C*H$_2$Ph), 71.5 (C-3), 89.5 (C-9a), 95.1 (C-6), 126.3, 128.0, 129.1, 135.8 (ArC), 154.4 (C-5a), 161.2 (C-7) and 164.3 (C-9); *m*/*z* 298 (M$^+$).

(3*S,3a*R**,9b*R**)-5-Benzyl-3,7-dimethyl-3,3a,4,5,9,9b-hexahydro-1*H*-isoxazolo[3,4-*d*]pyrano[4,3-*b*]pyridin-9-one 6e**, yellow plates from hexane–benzene, mp 145–146 °C (Found: C, 69.1; H, 6.6; N, 8.9. $C_{18}H_{29}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97%); δ_H(270 MHz) 1.30 (3 H, d, *J* 6.3, 3-Me), 2.15 (3 H, s, 7-Me), 2.20 (1 H, m, 3a-H), 3.21 (1 H, t, *J* 12.8, 4-H), 3.28 (1 H, dd, *J* 12.8 and 6.3, 4-H), 3.85 (1 H, dq, *J* 3.0 and 6.3, 9b-H), 4.58 (2 H, s, C*H*$_2$Ph), 5.83 (1 H, s, 6-H) and 7.14–7.40 (5 H, ov, Ph); δ_C(68 MHz) 19.6 (3-Me), 20.3 (7-Me), 44.2 (C-3a), 48.1 (C-4), 53.6 (C-9b), 54.6 (*C*H$_2$Ph), 78.8 (C-3), 89.0 (C-9a), 95.1 (C-6), 126.2, 127.9, 129.0, 135.7 (ArC), 154.4 (C-5a), 161.2 (C-7) and 164.2 (C-9); *m*/*z* 312 (M$^+$).

(3*R,3a*R**,9b*R**)-5-Benzyl-7-methyl-3-phenyl-3,3a,4,5,9,9b-hexahydro-1*H*-isoxazolo[3,4-*d*]pyrano[4,3-*b*]pyridin-9-one 6f**, yellow crystals, mp 92–95 °C (Found: C, 73.4, H, 6.25; N, 7.3. $C_{23}H_{22}N_2O_3$ requires C, 73.78; H, 5.92; N, 7.48%); ν_{max}/cm^{-1} 3200 (NH) and 1680 (CO); δ_H(270 MHz) 2.17 (3 H, s, Me), 2.59 (1 H, m, 3a-H), 3.33–3.49 (2 H, ov, 4-H), 4.53 (1 H, d, *J* 6.3, 9b-H), 4.54 and 4.65 (each 1 H, each d, *J* 16.8, C*H*$_2$Ph), 4.70 (1 H, d, *J* 3.3, 3-H), 5.85 (1 H, s, 6-H) and 7.15–7.42 (10 H, ov, Ph); δ_C(68 MHz) 20.4 (Me), 46.4 (C-3a), 48.3 (C-4), 54.2 (C-9b), 54.6 (*C*H$_2$Ph), 84.5 (C-3), 89.3 (C-9a), 95.3 (C-6), 126.2, 126.5, 128.1, 128.7, 129.2, 135.8 and 140.1 (ArC), 154.5 (C-5a), 161.5 (C-7) and 164.3 (C-9); *m*/*z* 374 (M$^+$).

Isomerisation of oxime 5a to nitrone and its cycloaddition reaction

General procedure. A solution of **5a** (0.167 g, 0.5 mmol) in dry benzene (8 cm^3) was heated under reflux for 8 h. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel to give **6a** (0.100 g, 63%) (eluting with ethyl acetate) and **7a** (0.014 g, 8%) and **8a** (0.005 g, 3%) (eluting with ethyl acetate–methanol 10 : 1).

(3a*R,11a*S**)-10-Benzyl-3,3a,4,10,11,11a-hexahydro-1*H*-isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridin-4-one 7a**, yellow crystals; mp 115–117 °C (Found: 72.0; H, 5.6; N, 8.3. $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3200 (br, NH) and 1680 (CO); δ_H(270 MHz) 2.77 (1 H, m, 11a-H), 3.23 (1 H, t, *J* 12.2, 11-H), 3.63 (1 H, dd, *J* 6.6 and 10.9, 1-H), 3.69 (1 H, dd, *J* 3.9 and 12.2, 11-H), 4.07 (1 H, d, *J* 10.2, 3a-H), 4.18 (1 H, t, *J* 6.6, 1-H), 4.62 and 5.09 (each 1 H, each d, *J* 17.2, C*H*$_2$Ph), 7.09 (1 H, br t, *J* 8.0, 8-H), 7.26–7.50 (7 H, ov, 6- and 7-H and Ph) and 7.60 (1 H, d, *J* 8.2, 9-H); δ_C(68 MHz) 45.9 (C-11a), 50.5 (C-11), 58.9 (*C*H$_2$Ph), 59.2 (C-3a), 68.2 (C-1), 101.0 (C-3b), 115.2 (C-9a), 118.2 (C-6), 123.4 (C-8), 124.3 (C-9), 126.5, 128.1, 129.3 and 136.0 (ArC), 131.4 (C-7), 153.7 (C-5a), 154.2 (C-9b) and 160.0 (C-4); *m*/*z* 334 (M$^+$).

1-Benzyl-3-methyl-6-oxo-1,2,3,6-tetrahydro[1]benzo[4,3-*e*][1,4]diazepine 4-oxide 8a, yellow prisms from hexane–ethyl acetate, mp 112–114 °C (Found: C, 72.0; H, 5.55; N, 8.55. $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38%); δ_H(270 MHz) 1.52 (3 H, d, *J* 6.9, Me), 3.46 (1 H, dd, *J* 7.2 and 14.8, 2-H), 3.72 (1 H, dd, *J* 1.6 and 14.8, 2-H), 4.14 (1 H, m, 3-H), 4.71 and 5.03 (each 1 H, each d, *J* 16.8, C*H*$_2$Ph), 7.15 (1 H, m, 10-H), 7.26–7.54 (7 H, ov, 8- and 9-H and Ph), 7.74 (1 H, d, *J* 8.2, 11-H) and 8.37 (1 H, s, 5-H); δ_C(68 MHz) 15.6 (Me), 55.2 (*C*H$_2$Ph), 59.4 (C-2), 66.9 (C-3), 101.2 (C-5a), 116.1 (C-11a), 118.0 (C-8), 124.1 (C-10), 124.9 (C-11), 127.1, 128.6, 129.5 and 134.8 (ArC), 132.3 (C-9), 132.9 (C-5), 152.2 (C-7a), 154.6 (C-11b) and 160.8 (C-6).

Dehydrogenation of 7a to 9a

A solution of **7a** (0.055 g, 0.16 mmol) in ethanol (5 cm^3) was heated under reflux for 2 h. Evaporation of the solvent and usual work-up gave **9a** (0.052 g, 95%). Compound **9a** was also obtained in 74% yield by the treatment of **5a** (0.17 g, 0.5 mmol) and triethylamine (0.14 cm^3, 1.0 mmol) in dichloromethane (10 cm^3) with 10% aqueous sodium hypochlorite (5 cm^3) at 0 °C for 1 h, followed by column separation.

10-Benzyl-4,10,11,11a-tetrahydro-1*H*-isoxazolo[3,4-*d*][1]-benzopyrano[4,3-*b*]pyridin-4-one 9a, yellow needles from methanol, mp 278–280 °C (Found: C, 72.1; H, 4.7; N, 8.05. $C_{20}H_{16}N_2O_3$ requires C, 72.28; H, 4.85; N, 8.43%); δ_H(270 MHz, [$^2H_6$]DMSO) 3.47 (1 H, t, *J* 12.8, 11-H), 3.66–3.75 (2 H, ov, 1- and 11-H), 3.87 (1 H, m, 11a-H), 4.47 (1 H, dd, *J* 7.9 and 9.3, 1-H), 4.82 and 4.98 (each 1 H, each d, *J* 16.5, C*H*$_2$Ph) and 7.14–7.63 (9 H, ov, Ph); δ_C(68 MHz, [$^2H_6$]DMSO) 44.3 (C-11a), 52.2 (C-11), 58.7 (*C*H$_2$Ph), 70.3 (C-1), 93.1 (C-3b), 114.5 (C-9a), 117.6 (C-6), 123.5 (C-8), 125.1, 126.5, 129.0 and 136.3 (ArC), 127.7 (C-9), 132.7 (C-7), 151.6 (C-5a), 153.1 (C-3a), 155.7 (C-9b) and 156.5 (C-4); *m*/*z* 332 (M$^+$).

Kinetic studies

General procedure. A solution of the oxime **5a** in *o*-dichlorobenzene (0.1 cm^3) and dioxane (15 cm^3) was placed in a test tube. The tube was sealed under nitrogen and placed in one neck of a two-necked flask. A condenser was placed on the other neck and the flask was filled with a solvent with appropriate bp, such as chloroform (bp 61.2 °C), THF (bp 66.0 °C), benzene (bp 80.1 °C), and trichloroethylene (bp 87.2 °C) until the solvent was just touching the bottom of the test tube. The outer flask was placed in a thermostatic oil bath and heated to keep the solvent refluxing. At appropriate

intervals an aliquot of the *o*-dichlorobenzene–dioxane solution (0.05 cm^3) was withdrawn with a micro syringe through a septum. The collected sample was immediately cooled in an ice–salt bath to stop the reaction and was analysed by HPLC.

HPLC measurements were performed with a Hitachi L-6200 instrument using a UV detector (Hitachi L-4000; 254 nm) and a Wakosil-II 5C18 HG (id 4.6 mm × 150 mm) column. The flow rate of the elution (acetonitrile–water 1:1) was 1.0 cm^3 min^{-1}. The rate of disappearance of the oxime **5a** was determined with an integrator (Hitachi D-2500) using *o*-dichlorobenzene as internal standard. All rates of conversion of **5a** under several conditions (temperature, solvent and additive) were first-order with respect to the oxime concentration. The rate constants are summarized in Table 3.

References

1 R. Grigg, H. Q. N. Gunaratne and J. Kemp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 41; R. Grigg, M. Jordan, A. Tangthongkum, F. W. B. Einstein and T. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1984, 47. Also see: R. Grigg, *Chem. Soc. Rev.*, 1987, **16**, 89.

2 (*a*) W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1970, 1117; (*b*) R. Grigg and S. Thianpantangul, *J. Chem. Soc., Perkin Trans. 1*, 1984, 653; (*c*) M. H. Norman and C. H. Heathcock, *J. Org. Chem.*, 1987, **52**, 226; (*d*) K. K. S. Murthy and A. Hassner, *Tetrahedron Lett.*, 1987, **28**, 97; A. Padwa, U. Chiacchio, D. C. Dean, A. M. Schoffstall, A. Hassner and K. S. K. Murthy, *Tetrahedron Lett.*, 1988, **29**, 4169; A. Hassner, R. Maurya and E. Mesko, *Tetrahedron Lett.*, 1988, **29**, 5313; A. Hassner and R. Maurya, *Tetrahedron Lett.*, 1989, **30**, 5803; A. Hassner, K. S. K. Murthy, A. Padwa, U. Chiacchio, D. C. Dean and A. M. Schoffstall, *J. Org. Chem.*, 1989, **54**, 5277; A. Hassner, R. Maurya, O. Friedman, H. E. Gottlieb, A. Padwa and D. Austin, *J. Org. Chem.*, 1993, **58**, 4539; A. Hassner, E. Falb, A. Nudelman, A. Albeck and H. E. Gottlieb, *Tetrahedron Lett.*, 1994, **35**, 2397; (*e*) A. Hassner and R. Maurya, *Tetrahedron Lett.*, 1989, **30**, 2289; A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775;

3 B. S. Orlek, P. G. Sammes and D. J. Weller, *J. Chem. Soc., Chem. Commun.*, 1993, 1412.

4 J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Chapter 9, pp. 87–89, Wiley-Interscience, New York, 1984; K. B. G. Torssell, in *Nitrile Oxides, Nitrones and Nitronate in Organic Synthesis*, pp. 75–78, VCH Publishers, Inc., Weinheim 1988; E. Breuer, in *Nitrones, Nitronates and Nitroxides*, eds. S. Patai and Z. Rappoport, pp. 149–152 and 251–252, John Wiley and Sons, Chichester 1989.

5 P. D. Adeney, W. J. Bouma, L. Radom and W. R. Rodwell, *J. Am. Chem. Soc.*, 1980, **102**, 4069.

6 T. Shimizu, Y. Hayashi and K. Teramura, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 397.

7 R. Bishop, P. R. Brooks and S. C. Hawkins, *Synthesis*, 1988, 997; A. B. Holmes, A. L. Smith, S. F. Williams, L. R. Hughes, Z. Lidert and C. Swithenbank, *J. Org. Chem.*, 1991, **56**, 1393; R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929; R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1993, 372; A. Hassner, S. Singh, R. Sharma and R. Maurya, *Tetrahedron*, 1993, **49**, 2317.

8 R. Huisgen, H. Seidl and I. Brüning, *Chem. Ber.*, 1969, **102**, 1102.

9 Y. Kuroki, R. Akao, T. Inazumi and M. Noguchi, *Tetrahedron*, 1994, **50**, 1063.

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