Regiochemistry and mechanism of oxidation of *N*-benzyl-*N*-alkylhydroxylamines to nitrones

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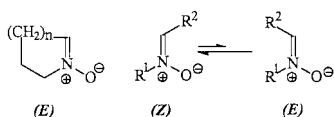Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

ABSTRACT: The oxidation of various *N*-(*o*-, *m*-, *p*-substituted benzyl)-*N*-alkylhydroxylamines and their dideuteriobenzyl (PhCD$_2$) counterparts was carried out using mercury(II) oxide and *p*-benzoquinone (*p*-BQ) as oxidants. An overwhelming preference for the formation of conjugated nitrones is observed in the oxidation of *N*-benzyl-*N*-isopropylhydroxylamines. Considerable intra- and intermolecular kinetic isotope effects and negative ρ values in the Hammet plots point towards a mechanistic pathway that involves electron transfer from nitrogen to the oxidant followed by hydrogen abstraction. The conformation of unstable (*E*)-nitrones, which readily isomerize to the more stable (*Z*)-nitrones, is deduced from ^{1}H NMR data. The $E \rightleftharpoons Z$ isomerization was found to be a bimolecular process. Copyright © 2000 John Wiley & Sons, Ltd.

INTRODUCTION

Nitrone functionality has become an important chemical tool in organic synthesis[1] and in spin trapping experiments to trap and identify reactive free radicals especially in biomedical fields.[2] Nitrones have been prepared by a variety of routes.[1,3–7] Whereas there are numerous reports on the preparation of nitrones by oxidation of symmetrical amines and hydroxylamines, studies of their unsymmetrical counterparts remain scarce,[1,7–10] apparently owing to the anticipation of regiochemical complications. While the widely used cyclic aldonitrones must remain in *E* geometry owing to structural constraints, their acyclic counterparts are involved in *E*⇌*Z* isomerization at higher temperature with equilibrium constant overwhelmingly favouring the more stable *Z* form[11] (Scheme 1). With rare exceptions,[12,13] it is the *Z* form which undergoes cycloaddition reactions, thus dictating the stereochemical outcome. The addition
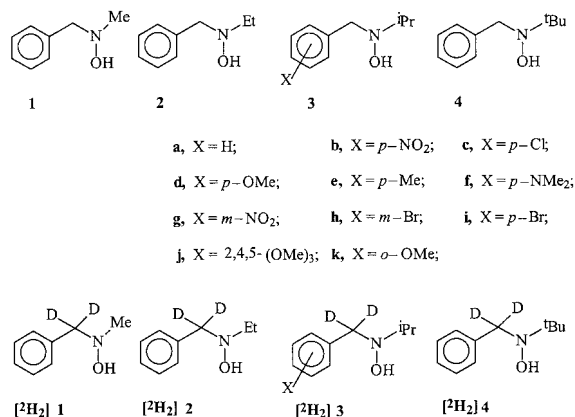
of the *E* isomer (which is expected to be much more reactive[12] than the *Z* form), on the other hand, would lead to cycloadducts with different stereochemistry. Oxidation of secondary hydroxylamines leads to the more stable (*Z*)-nitrones. In few cases, some unstable (*E*)-nitrones have been generated by irradiation of the *Z* isomers.[14] The mechanistic investigation of this widely used oxidation process has been studied to some extent.[10]

In our continuing studies[9,10] to investigate the regiochemistry and mechanism of oxidation of unsymmetrical secondary hydroxylamines to nitrones, we report here a systematic study of the oxidation of various *N*-benzyl-*N*-alkylhydroxylamines **1–4** and their deuterated counterparts [^{2}**H$_2$**]**1–4** using mercury(II) oxide and *p*-

a, X = H;   b, X = *p*−NO$_2$;   c, X = *p*−Cl;
d, X = *p*−OMe;   e, X = *p*−Me;   f, X = *p*−NMe$_2$;
g, X = *m*−NO$_2$;   h, X = *m*−Br;   i, X = *p*−Br;
j, X = 2,4,5-(OMe)$_3$;   k, X = *o*−OMe;
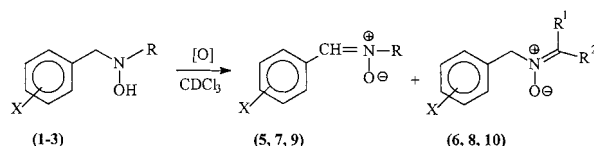

Scheme 2

Scheme 1

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Table 1. Composition of nitrones in the oxidation of hydroxylamines **1–3** with HgO at −10 to −20 °C and *p*-BQ at 20 °C

	Hydroxylamine			Composition[a] of nitrones					
No.	R	X	Oxidant					R^1	R^2
1	Me	H[b]	HgO	**5** (60)		**6**	(40)	H	H
			p-BQ	(65)			(35)		
2	Et	H	HgO	**7** (48)		**8**	(52)	H	Me
			p-BQ	(49)			(51)		
3a	iPr,	H	HgO	**9a** (95)		**10a**	(05)	Me	Me
			p-BQ	(95)			(05)		
3b	iPr,	*p*-NO$_2$	HgO	**9b** (98.5)		**10b**	(1.5)	Me	Me
3d	iPr,	*p*-OMe	HgO	**9d** (96)		**10d**	(04)	Me	Me
3g	iPr,	*m*-NO$_2$	HgO	**9b** (98.5)		**10b**	(1.5)	Me	Me
3j	iPr,	2,4,5-(OMe)$_3$	HgO	**9j** (96)		**10j**	(04)	Me	Me
3k	iPr,	*o*-OMe	HgO	**9d** (96)		**10d**	(04)	Me	Me

[a] Percentage compositions are given in parentheses.
[b] Taken from Ref. 10.

benzoquinone (*p*-BQ) as oxidants (Scheme 2). Efforts are being made to generate and study the unstable (*E*)-nitrones and subsequent $E \rightleftharpoons Z$ isomerization process.

RESULTS AND DISCUSSION

The regiochemistry of the oxidation of the *N*-benzyl-*N*-alkylhydroxylamines **1–3** with various substituents in the benzene ring of the hydroxylamine **3** is shown in Table 1. As is evident, the composition of the nitrones depends on the nature of the *N*-alkyl group but is somewhat independent of the nature of the oxidant, mercury(II) oxide or *p*-BQ. In the oxidation of the hydroxylamines **1** and **3**, both the oxidants afforded the conjugated nitrones as the major products. Allowing for the statistical correction for the number of equivalent abstractable α-protons, the benzyl C—H in **1** and **3a** is found to be 2.25 and 9.5 times, respectively, more reactive than the alkyl α-C—H. Surprisingly, the conjugated nitrone **7** is even formed as a minor isomer in the oxidation of *N*-benzyl-*N*-ethylhydroxylamines **2**. It is assumed that the conjugated nitrones do not equilibrate with their non-conjugated counterparts. A CDCl$_3$ solution of a pure sample of several nitrones (prepared independently) remained unchanged for weeks without equilibration to the regioisomeric nitrones. The formation of the non-conjuated nitrones **6** and **8** and conjugated nitrones **9** in considerable amounts implicates the involvement of the kinetic factor in a significant way in the abstraction of the hydrogen from sterically favoured positions.

Next we focussed our attention on determining the relative rate[10,15] (k_X/k_H) of oxidation of the hydroxyl-

amines **3** (X ≠ H) and **3a** (X = H), using HgO and *p*-BQ. As is evident from the Hammett plots (Figs. 1 and 2), the rate of oxidation increases with the electron donating ability of the substituents X. A good linear free energy relationship is obtained with ρ values of −0.404, −0.436 using HgO and *p*-BQ, respectively. The negative ρ values indicate the development of positive charge on the nitrogen in the transition states.

In order to shed more light on the oxidation process, hydroxylamines deuterated at the benzyl position were prepared (Scheme 3). As is evident from Table 2, with either oxidant the regiochemistry of the oxidation is either reversed or changed in favour of the non-conjugated nitrones. When a 1:1:1 mixture of a hydroxylamine (**1–4**), its corresponding dideuterated hydroxylamine ([²H₂]**1–4**) and HgO was allowed to react, the hydroxylamines **1–4** were found to react 1.34, 1.40, 3.35 and 7.00 times faster, respectively, than their deuterated counterparts [²H₂]**1–4**. Similar rate ratios are found in the
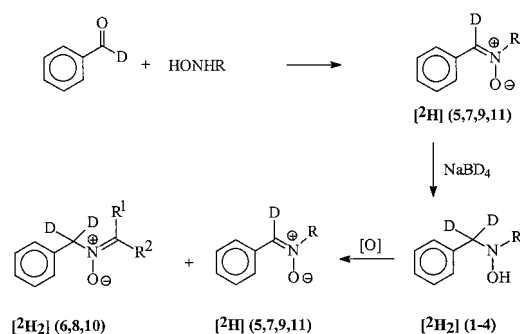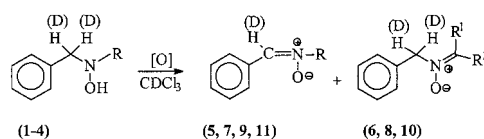

Scheme 3

Table 2. Regiochemistry and reactivity of hydroxylamines in oxidation using HgO (0 °C) and *p*-benzoquinone (*p*-BQ) (20 °C) in CDCl$_3$

		Composition of nitrones[b]				Rate ratio $k_{(1-4)}/k^2_{H2}$(**1–4**)	
Hydroxylamine[a]	Oxidant					HgO	*p*-BQ
PhCH$_2$N(OH)Me	HgO	**5**	(57)	**6**	(43)		
1	*p*-BQ	**5**	(65)	**6**	(35)	1.34	1.15
PhCD$_2$N(OH)Me	HgO	[^{2}H]**5**	(17)	[^{2}H$_2$]**6**	(83)		
[^{2}H$_2$]**1**	*p*-BQ	[^{2}H]**5**	(33)	[^{2}H$_2$]**6**	(67)		
PhCH$_2$N(OH)Et	HgO	**7**	(48)	**8**	(52)		
2	*p*-BQ	**7**	(49)	**8**	(51)	1.40	1.43
PhCD$_2$N(OH)Et	HgO	[^{2}H]**7**	(10)	[^{2}H$_2$]**8**	(90)		
[^{2}H$_2$]**2**	*p*-BQ	[^{2}H]**7**	(09)	^{2}H$_2$]**8**	(91)		
PhCD$_2$N(OH)^{i}Pr	HgO	**9a**	(95)	**10a**	(05)		
3a	*p*-BQ	**9a**	(95)	**10a**	(05)	3.35	4.39
PhCD$_2$N(OH)^{i}Pr	HgO	[^{2}H]**9a**	(68)	[^{2}H$_2$]**10**	(32)		
[^{2}H$_2$]**3a**	*p*-BQ	[^{2}H]**9a**	(63)	[^{2}H$_2$]**10**	(37)		
PhCH$_2$N(OH)^{t}Bu	HgO	**11**	(100)	—			
4	*p*-BQ	**11**	(100)	—		7.0	7.50
PhCD$_2$N(OH)^{t}Bu	HgO	[^{2}H]**11**	(100)	—			
[^{2}H$_2$]**4**	*p*-BQ	[^{2}H]**11**	(100)	—			

[a] Results for the oxidation of hydroxylamine **1** and [^{2}H$_2$]**1** were taken from Ref. 10 and that of **4** and [^{2}H$_2$]**4** from Ref. 9.
[b] Percentage compositions are given in parentheses.

oxidation using *p*-BQ. The values of the intra- and intermolecular kinetic isotope effects[16] are given in Table 3. The intramolecular kinetic isotope effects were calculated from the relative yields of the conjugated nitrone and its [^{2}H]-analogue obtained from the separate oxidation of the protio- (**1–4**) and deuterohydroxylamines ([^{2}H$_2$]**1–4**) (see Table 2). In the calculation it was assumed that the benzyl deuterons would only influence the rate of formation of the conjugated nitrones, have the rate of formation of the nonconjugated nitrones becomes an internal standard common to the oxidation of both hydroxylamines. The intermolecular kinetic isotope effects were determined using the relative yields of the products conjugated nitrone and its [^{2}H]-analogue obtained from the reaction involving direct competition of the protio- and deuterohydroxylamines for the oxidants (see Tables 2 and 3).

The oxidation using HgO at lower temperatures (−10 to −20 °C) afforded a mixture of (*E*)- and (*Z*)-nitrones in all cases except in the oxidation of the *test*-butyl derivative (**4**) (Table 4). In the oxidation of hydroxyl-amines **3** having electron-donating substituents, it is the *E* isomers which predominate. The *E* isomer equilibrates completely to the *Z* isomer. Proton NMR signals, given in Table 5, support the perpendicular and planar conforma-tion for the *E* and *Z* isomers, respectively. The *ortho* proton in the planar *Z* isomer is shifted downfield (*ca* 1 ppm) owing to the proximity of the negatively charged

oxygen atom of the nitrone group.[17–19] The downfield shift is more pronounced in the nitrones having an *ortho* substituent in which the C(6) H is located near the oxygen atom (e.g. in **9j** by 1.42 ppm and **9k** by 2.13 ppm). The two *ortho* protons in the other (*Z*)-nitrones appear at an

Table 3. Intramolecular[a] and intermolecular[b] kinetic isotpe effects from the separate and competitive oxidation, respectively, of PhCH$_2$N(OH)R (**1–4**) and PhCD$_2$N(OH)R [^{2}H$_2$](**1–4**)

Hydroxylamine	Oxidant	(k_H/k_D)intra[a]	(k_H/k_D)inter[b]
1 and [^{2}H$_2$]**1** (R = Me)	HgO	6.47	4.49
	p-BQ	3.77	2.27
2 and [^{2}H$_2$]**2** (R = Et)	HgO	8.31	6.72
	p-BQ	9.72	7.78
3a and [^{2}H$_2$]**3a** (R = ^{i}Pr)	HgO	8.94	4.68
	p-BQ	11.2	6.62
4 and [^{2}H$_2$]**4** (R = ^{t}Bu)	HgO	—	7.00
	p-BQ	—	7.50

[a] Calculated from the ratio of conjugated and non-conjugated nitrones in the separate oxidation of PhCH$_2$N(OH)R and PhCD$_2$N(OH)R (Table 3, e.g. k_H/k_D = [**5**]/[**6**] ÷ [^{2}H]**5**/[^{2}H$_2$]**6**).
[b] Calculated from the ratio of conjugated nitrones in the competitive oxidation of PhCH$_2$N(OH)R and PhCD$_2$N(OH)R (e.g. k_H/k_D = [**5**]/[^{2}H]**5**).

Table 4. Composition[a] of the nitrones in the oxidation of *N*-alkylhydroxylamines (**1–4**) with HgO in CDCl$_3$ at-10 to −20°C

(1-4)

(Z)- (5, 7, 9,11)   (E)- (5, 7, 9,11)
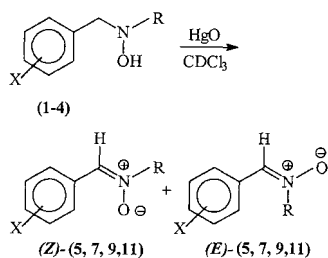
|	Hydroxylamine			
No.	R	X	Nitrone	Z:E[a]
1	Me	H	**5**	(55:45)
2	Et,	H	**7**	(62:38)
3a	^{i}Pr	H	**9a**	(45:55)
3b	^{i}Pr	*p*-NO$_2$	**9b**	(86:14)
3d	^{i}Pr	*p*-OMe	**9d**	(45:55)
3g	^{i}Pr	*m*-NO$_2$	**9g**	(90:10)
3j	^{i}Pr	2,4,5-(OMe)$_3$	**9j**	(39:61)
3k	^{i}Pr,	*o*-OMe	**9k**	(26:74)
4	^{t}Bu	H	**11**	(100:∼0)

[a] Percentage compositions are given in parentheses.

average position owing to the rotation of the phenyl group, thus resulting in a smaller difference (ca 1 ppm) in the chemical shift values of the (Z) and (E)-nitrones. The methine hydrogen (CH=N) in the E isomers, in most cases, is shifted downfield by 0.5–0.6 ppm (in comparison with the Z nitrones), indicating the *cis* relationship between the methine H and the negatively charged O, since an anisotropic effect of the neighbouring N—O

bond is known to deshield the proton.[17–20] However, in case of the nitrones **9j** and **9k**, the opposite trend is observed; the methine hydrogen (CH=N) of the (Z)-nitrones appears downfield owing to its proximity to the oxygen of the *o*-methoxy substituent. In order to avoid steric congestion between the aromatic *ortho* protons and the isopropyl group, the E isomer adopts the perpendicular conformation having the aromatic plane perpendicular to the plane of the nitrone functionality, whereas they are coplanar in the Z nitrones. The difference of ∼0.4 ppm between the chemical shifts of the methine proton of the *N*-CH(CH$_3$)$_2$ group was observed in the (E)- and (Z)-nitrones. While the shielding effect of the aromatic π-cloud in the non-coplanar (E)-nitrone is supposed to induce an upfield shift of the methine signal, conjugative electron withdrawal by the nitrone functionality from the aromatic ring in the planar Z form makes the nitrogen less electronegative, thereby resulting in an even greater upfield shift. Semi-empirical molecular orbital calculations[21] on the nitrone **5** predicted that the Z isomer with a coplanar arrangement is more stable than the E isomer with orthogonal geometry by 13–17 kJ mol^{-1}. Our experimental findings of an undetectable amount of E isomer after equilibration supports the calculation. It was calculated that the planar arrangement in the E isomer is destabilized by *ca* 126 kJ mol^{-1} in comparison with the orthogonal geometry.

The ease of oxidation of hydroxylamines **1–4** to the nitrones should reflect the ease of nitrogen inversion provided that the oxidation process, like nitrogen inversion,[22,23] involves a planar transition state in the rate-determining step with sp^2 character of nitrogen orbitals. Any crowding in the pyramidal ground state would be relieved in the transition state with an extended CNC bond angle (120°). The relative rates of oxidation of

Table 5. ^{1}H chemical shifts of (*E*)-and (*Z*)-nitrones **9** in CDCl$_3$ at −10°C

(E)-9   (Z)-9
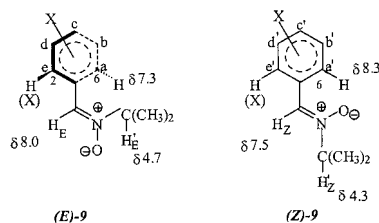
| Nitrone		E (ppm)			Z (ppm)		
9	X	Aromatic protons	H$_E$	H$'_E$	Aromatic protons	H$_Z$	H$'_Z$
a	H	7.34 (a, e)	7.87	4.73	8.26 (a′, e′)	7.40	4.22
b	*p*-NO$_2$	7.51 (a, e)	7.90	4.75	8.44 (a′, e′)	7.67	4.35
d	*p*-OMe	7.24 (a, e)	7.84	4.74	8.24 (a′, e′)	7.36	4.17
g	*m*-NO$_2$	—	7.90	4.70	8.64 (a′)	7.65	4.34
		8.19 (e)			9.15 (e′)		
j	2,4,5-(OMe)$_3$	7.73 (a)	7.73	4.52	9.15 (a′)	7.83	4.20
k	*o*-OMe	7.19 (a)	7.83	4.57	9.32 (a′)	7.92	4.24

Table 6. Relative rates of oxidation of various hydroxylamines using p-BQ and HgO in CDCl$_3$

Compound		$\Delta G^{\ddagger}_{273\ K}$ (kJ/mol^{-1})	Relative rate (k_R/k_{Me}) of oxidation using	
No.	R		p-BQ[a]	HgO[b]
1	Me	55.8	1.00	1.00
2	Et	55.3	1.35	0.902
3a	^{i}Pr	51.6	2.32	1.40
4	^{t}Bu	49.2	1.20	0.528

[a] At 20 °C.
[b] At 0 °C.

the hydroxylamines **1–4** by HgO and p-BQ along with the energy barrier for the nitrogen inversion process are listed in Table 6. It is evident that the rate of oxidation of **1** or **2** or **3a** using p-BQ (or HgO to a certain extent) parallels the rate of nitrogen inversion. In the oxidation using HgO, the *tert*-butylhydroxylamine **4** undergoes oxidation at slower rate in comparison with both the methyl **1** and *iso*propyl derivative **3a**, reflecting the complex interplay of the steric encounter in the approach of the oxidant toward **4** and its desire to relieve steric compression in the planar transition state.

The oxidation process can follow a pathway of single electron transfer (SET)[24,25] or a polar (S_N2) mechanism. Our experimental findings corroborate the mechanistic pathway as proposed earlier.[10] Approach to the conformer **A** by the oxidant will be energetically preferrable because of lesser steric hindrance (Scheme 4). SET followed by abstraction of hydrogen from the hydroxylaminium radical **C** would lead to the (E)-nitrone, whereas the conformer **B** would lead to the (Z)-nitrone. This *iso*propyl group can be accommodated into a *gauche* relationship with the phenyl group; steric congestion is relieved owing to the methine hydrogen pointing towards the phenyl ring. However, in case of the *tert*-butyl derivative which lacks an α-C—H, both the conformer, **A** and the intermediate **C** are energetically unfavourable,
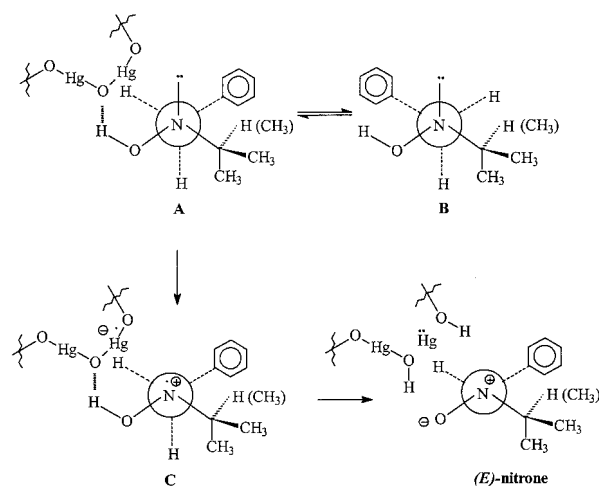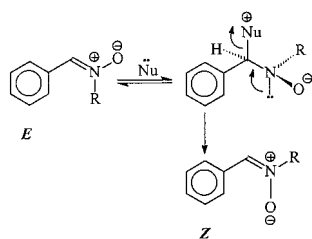

Scheme 4

thus inhibiting the formation of the (E)-nitrone. The negative ρ values suggest that the initial step in the oxidation is an one-electron transfer from the hydroxylamine to the oxidant followed by a product-determining deprotonation of the resulting hydroxylaminium radical. The deprotonation of a planar hydroxylamine cation radical requires overlap between the half-vacant nitrogen p-orbital and the incipient carbon radical p-orbital, thus giving rise to a stereoelectronic effect on the deprotonation step.[26] While the steric congestion makes the overlap of aminium p-orbital and the α-C—H bond of the isopropyl group difficult, the corresponding energetically favourable overlap involving the benzyl C—H dictates the overwhelming preference for the formation of the conjugated nitrones **9**. The large intra- and inter-molecular primary kinetic isotope effects suggest that α-C—H bond breakage is both rate-limiting and product-determining in these oxidations. Had the electron-transfer step been irreversible and rate-determining, there would be a small secondary intermolecular isotope effect (~1.3) for the electron-transfer step and a larger intramolecular

Table 7. Rate constants and thermodynamic parameters obtained for isomerization of (E)- to (Z)-nitrones

E	Temperature (°C)	$k/10^{-5}$ (s^{-1})	E_a (kJ/mol^{-1})	$\Delta H^{\ddagger}$ (kJ/mol^{-1})	$\Delta G^{\ddagger}_{273\ K}$ (kJ/mol^{-1})	$\Delta S^{\ddagger}$ (J/mol^{-1}K^{-1})
9a[a]	−10	1.28				
	0	4.23	72.5	70.2	89.5	−70.6
	10	13.3				
9k[a]	−10	0.788				
	0	2.55	71.1	68.9	90.9	−79.9
	10	7.83				
9a[b]	0	4.13				
5[b]	0	7.30				
9a[c]	−10	23.0				
9d[c]	−10	28.2				

[a] The mixture of the nitrones obtained from oxidation of a mixture of **3a** and **3k** was taken in the NMR tube for the kinetic study.
[b] The mixture of the nitrones obtained from oxidation of a mixture of **3a** and **1** was taken in the NMR tube for the kinetic study.
[c] The mixture of the nitrones obtained from oxidation of a mixture of **3a** and **3d** was taken in the NMR tube for the kinetic study.

Scheme 5

one for the proton transfer. In order to account for the negative ρ values (and hence positive charge on nitrogen) and large kinetic isotope effect, the most likely mechanism includes a rate-determining step that involves the concerted transfer of one electron from the hydroxylamine to the oxidant and concomitant cleavage of the α-C—H bond. While changing the R group in hydroxylamines from Me to ^tBu should decrease the energy requirement of the electron-transfer process (see above), the stereoelectronic effect dictates the α-C—H bond cleavage to follow the opposite trend. Combined energy requirements for the two steps determine the overall energy of activation, and hence no definite trend is observed in the kinetics of oxidation of the hydroxylamines **1–4** (Table 6).

The formation of a considerable amount of *E* isomer in the oxidation of hydroxylamines provided us with the opportunity to study the kinetics of $E \rightleftharpoons Z$ isomerization using NMR technique.[10,27] In a series of experiments a mixture of two hydroxylamines, **3a–3k**, **3a–l** and **3a–3d**, was oxidized with HgO in CDCl$_3$ (at -15 to $-20\,°C$, 2 h) and the rate constant for each first-order $E \rightleftharpoons Z$ isomerization process was determined by linear regression analysis with excellent correlation coefficients. The presence of two (*E*)-nitrones in the same NMR tube would enable them to experience almost similar effects (whatever those effects may be). Low values of E_a and $\Delta G^{\neq}$ and very large negative values of entropy of activation (Table 7) cast doubt on the validity of the assumption that the isomerization is an unimolecular process. In any unimolecular process the entropy of activation should be close to zero,[17,21] while second-order isomerization is expected to have high negative values of entropy of activation.[28] As is evident from Table 7, the rate constants are not reproducible; rate constants for the isomerization of the nitrone (*E*)-**9a** at -10 °C in two different runs were found to be 1.28×10^{-5} and $23.0 \times 10^{-5}\ s^{-1}$. The isomerization process was repeated many times and different values of rate constants were obtained.

Evidence presented so far indicates the isomerization to be a bimolecular process as previously reported[10] (Scheme 5). The slower isomerization of the nitrone (*E*)-**9k** could be attributed to the presence of *ortho* substituent which destabilizes the tetrahedral complex owing to steric crowding. Steric crowding could also be the reason

for slower isomerization of the *iso*propyl nitrone **9a** than its methyl counterpart **5**. As regards the nature of the nucleophilic species, it could be the unreacted hydroxylamine, the nitrone itself or any basic entity present during the oxidation with HgO.

A systematic study of the oxidation of *N*-benzyl-*N*-alkylhydroxylamines has been made. Efforts are currently under way to find ways to stabilize the (*E*)-nitrones and to study its cycloaddition reactions.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JEOL Lambda-500 and a Varian XL 200 NMR spectrometer, in CDCl$_3$ solutions using TMS as internal standard. Elemental analyses were performed on a Fisons Instruments Elemental Analyser 1108. All melting points are uncorrected. IR spectra were recorded a Nicolet 5 DXB FTIR instrument. Silica gel chromatographic separations were performed with flash silica gel (Baker Chemicals). The preparation of the hydroxylamine derivatives has been described in our previous papers.[22,23] The hydroxylamines deuterated at the benzyl position were prepared by using the same general procedure.[9,10] Condensation reactions always provided the (*Z*)-nitrones and using the known positions of the proton signals of the *Z* isomers, the non-overlapping chemical shifts of the (*E*)- and the non-conjugated nitrones were deduced from the spectra of their mixture. The condensation of the hydroxylamines RNHOH with PhCDO gave the nitrone [^{2}H](**7** and **9a**), which on reduction with NaBD$_4$ formed the required dideuriated hydroxylamines [^{2}H$_2$](**2** and **3a**). The kinetics of $E \rightleftharpoons Z$ isomerization were studied as described previously.[10]

N-[α,α−²H₂]Benzyl-*N*-ethylhydroxylamine, [²H₂]2.
Purified by chromatography using 4:1 hexane–diethyl ether as eluent. Colourless liquid. Found: C, 70.4; H, 9.8; N, 9.2. C$_9$H$_{11}$D$_2$NO requires C, 70.56; H, 9.85; N, 9.15%. ν_{max} (neat) (cm^{-1}), 3205, 3021, 2963, 2868, 2837, 2221, 2121, 2058, 1486, 1442, 1374, 1286, 1239, 1166, 1096, 1078, 1045, 1026, 985, 943, 884, 730, 691; $^{\delta}$H (CDCl$_3$, 20 °C), 1.12 (3 H, t, *J* 7.0 Hz), 2.70 (2 H, q, *J* 7.0 Hz), 6.70 (1 H, br, OH), 7.35 (5 H,m).

N-[α,α−²H₂]Benzyl-*N*-isopropylhydroxylamine, [²H₂]3a.
Purified by chromatography using 4:1 hexane–diethyl ether as eluent. Colourless needles, m.p. 78–80 °C (diethyl ether–hexane). Found: C, 71.7; H, 10.1; N, 9.4. C$_{10}$H$_{13}$D$_2$NO requires C, 71.83; H, 10.23; N, 8.38%. ν_{max} (KBr) (cm^{-1}), 3190, 3042, 2961, 2940, 2218, 2098, 1496, 1475, 1449, 1383, 1362, 1186, 1130, 1067, 1010, 960, 730, 703; $^{\delta}$H (CDCl$_3$, 20 °C), 1.16 (6 H, d, *J* 6.4 Hz), 2.98 (1 H, hept, *J* 6.4 Hz), 7.35 (5 H, s, 1 H, hydroxyl proton underneath).

General procedure for the preparation of the nitrones. To a solution of *N*-*iso*propylhydroxylamine (5.0 mmol) in ethanol (10 cm^3) was added the aldehyde (5.5 mmol). (Whereas the *N*-*iso*propylhydroxylamine was used as its free base, *N*-ethylhydroxylamine was introduced as its hydrochloride and the free base was liberated from its salt by adding 1.1 equiv. of sodium acetate in the reaction mixture.) The reaction mixture was stirred at 50–60 °C for 5 h and TLC (silica, diethyl ether) revealed the complete formation of the *N*-oxides (*Z*)-**9**. After removal of the ethanol the nitrones were recrystallized by using suitable solvents. In case of liquid nitrones chromatography purification (using hexane–diethyl ether as the eluent) was carried out in order to obtain analytical samples. For isolation of the *N*-oxide (*Z*)-**7**, the solvent ethanol was removed and the residual mixture was taken in dichloromethane (20 cm^3), and the organic layer was washed with saturated NaHCO$_3$ solution. The organic layer was dried and concentrated to give the nitrone as a liquid.

The ^{1}H NMR signals of the unstable (*E*)-nitrones were deduced from the spectra of the mixture of (*E*)- and (*Z*)-nitrones which were obtained from the oxidation of the corresponding hydroxylamines at low temperature (see below). The ^{1}H NMR signals of the minor regioisomeric nitrones were also deduced from the ^{1}H NMR spectra of the oxidized mixture.

*(Z)-N-Ethylbenzylideneamine N-oxide (**7**).* Found: C, 72.3, H, 7.4; N, 9.4. C$_9$H$_{11}$NO requires C, 72.45; H, 7.43; N, 9.39% $\nu_{\max}$ (neat) (cm^{-1}), 2980, 1582, 1446, 1164, 692; $^\delta$H (−10 °C), 1.58 (3 H, t, *J* 7.3 Hz), 4.00 (2 H, q, *J* 7.3 Hz), 7.40 (3 H, m, and 1 H, s at 7.42), 8.24 (2 H, d, *J* 7.7 Hz).

*(E)-N-Ethylbenzylideneamine N-oxide (**7**).* $^\delta$H (−10 °C), 1.56 (3 H, t, *J* 7.0 Hz), 4.05 (2 H, q, *J* 7.0 Hz), 7.26–7.58 (5 H, m), 7.97 (1 H, s).

*(Z)-N-Benzylethylideneamine N-oxide (**8**).* $^\delta$H (−10 °C), 2.01 (3 H, d, *J* 5.9 Hz), 4.90 (2 H, s), 6.72 (1 H, q, *J* 5.9 Hz), 7.42 (5 H, m).

*(Z)-N-Ethyl[α−²H]benzylideneamine N-oxide, [²H](**7**).* Found: C, 71.8, H, 7.9; N, 9.4. C$_9$H$_{10}$DNO requires C, 71.97; H, 8.04; N, 9.33%. $\nu_{\max}$. (neat) (cm^{-1}), 3053, 2968, 2932, 2842, 2263, 1569, 1494, 1444, 1377, 1335, 1250, 1195, 1115. 1073, 1029, 951, 897, 756, 689; $^\delta$H (−10 °C), 1.58 (3 H, t, *J* 7.3 Hz), 4.00 (2 H, q, *J* 7.3 Hz), 7.40 (3 H, m, and 1 H, s at 7.42), 8.24 (2 H, d, *J* 7.7 Hz).

*(Z)-N-Isopropylbenzylideneamine N-oxide (**9a**).* $^\delta$H (−10 °C) 1.51 (6 H, d, *J* 6.6 Hz), 4.22 (1 H, hept, *J* 6.6 Hz), 7.34 (3 H, m), 7.40 (1 H, s), 8.26 (2 H, d, *J* 7.9 Hz).

*(E)-N-Isopropylbenzylideneamine N-oxide (**9a**).* $^\delta$H (−10 °C) 1.45 (6 H, d, *J* 6.4 Hz), 4.73 (1 H, hept, *J* 6.4 Hz) 7.34 (5 H, m), 7.87 (1 H, s).

*(Z)-N-Isopropyl[α-²H]benzylideneamine N-oxide, [²**H**](**9a**).* Found: C, 72.9, H, 8.4; N, 8.35. C$_{10}$H$_{12}$DNO requires C, 73.14; H, 8.59; N, 8.53%. $\nu_{\max}$ (neat) (cm^{-1}), 3063, 2984, 2921, 2842, 2279, 1553, 1442, 1369, 1278, 1195, 1073, 1037, 948, 917, 769, 699; $^\delta$H (−10 °C), 1.51 (6 H, d, *J* 6.6 Hz), 4.22 (1 H, hept, *J* 6.6 Hz), 7.34 (3 H, m), 8.26 (2 H, d, *J* 7.9 Hz).

*N-Benzyl-1-methylethylideneamine N-oxide (**10a**).* $^\delta$H (−10 °C) 2.14 (3 H, s), 2.19 (3 H, s), 5.09 (2 H, s).

*(Z)-N-Isopropyl-4-nitrobenzylideneamine N-oxide (**9b**).* Yellow needles, m.p. 99–101 °C (diethyl ether–dichloromethane). Found: C, 57.6; H, 5.8; N, 13.5. C$_{10}$H$_{12}$N$_2$O$_3$ requires C, 57.68; H, 5.81; N, 13.46%. $\nu_{\max}$ (KBr) (cm^{-1}), 2978, 1614, 1352, 1150, 1094, 858; $^\delta$H (−10 °C), 1.55 (6 H, d, *J* 6.6 Hz), 4.35 (1 H, hept, *J* 6.6 Hz), 7.67 (1 H, s), 8.30 (2 H, d, *J* 8.4 Hz), 8.44 (2 H, d, *J* 8.6 Hz).

*(E)-N-Isopropyl-4-nitrobenzylideneamine N-oxide (**9b**).* $^\delta$H (−10 °C), 1.50 (6 H, d, *J* 6.4 Hz), 4.75 (1 H, hept, *J* 6.4 Hz), 7.51 (2 H, d, *J* 8.6 Hz), 7.90 (1 H, s), 8.35 (2 H, d, *J* 8.6 Hz).

*N-4-Nitrobenzyl 1-methylethylideneamine N-oxide (**10b**).* $^\delta$H (−10 °C), 2.21 (3 H, s), 2.25 (3 H, s), 5.20 (2 H, s).

*(Z)-N-Isopropyl-4-chlorobenzylideneamine N-oxide (**9c**).* White plates, m.p. 56–57.5 °C (diethyl ether–hexane). Found: C, 60.8; H, 6.0; N, 7.1. C$_{10}$H$_{12}$NOCl requires C, 60.76; H, 6.12; N, 7.09%. $\nu_{\max}$ (KBr) (cm^{-1}), 2978, 1578, 1454, 1308, 1150, 1086, 842; $^\delta$H (19 °C), 1.55 (6 H, d, *J* 7.0 Hz), 4.27 (1 H, hept), 7.45 (2 H, d, *J* 8.0 Hz), 7.49 (1 H, s), 8.30 (2 H, d, *J* 8.0 Hz).

*(Z)-N-Isopropyl-4-methoxybenzylideneamine N-oxide (**9d**).* Found: C, 68.3, H, 7.8; N, 7.2. C$_{11}$H$_{15}$NO$_2$ requires C, 68.37; H, 7.82; N, 7.25%. $\nu_{\max}$ (neat) (cm^{-1}), 2990, 1604, 1506, 1452, 1302, 1264, 1170, 1148, 1086, 1030, 842; $^\delta$H (−10 °C), 1.50 (6 H, d, *J* 6.6 Hz), 3.83 (3 H, s), 4.17 (1 H, hept, *J* 6.6 Hz), 6.93 (2 H, d, *J* 8.8 Hz), 7.36 (1 H, s), 8.24 (2 H, d, *J* 8.8 Hz).

*(E)-N-Isopropyl-4-methoxybenzylideneamine N-oxide (**9d**).* $^\delta$H (−10 °C), 1.46 (6 H, d, *J* 6.2 Hz), 3.83 (3 H, s), 4.74 (1 H, hept, *J* 6.2 Hz), 6.97 (2 H, d, *J* 8.6 Hz), 7.24 (2 H, d, *J* 8.6 Hz), 7.84 (1 H, s).

*N-4-Methoxybenzyl 1-methylethylideneamine N-oxide (**10d**).* $^\delta$H (−10 °C), 2.14 (3 H, s), 2.17 (3 H, s), 4.96 (2 H, s).
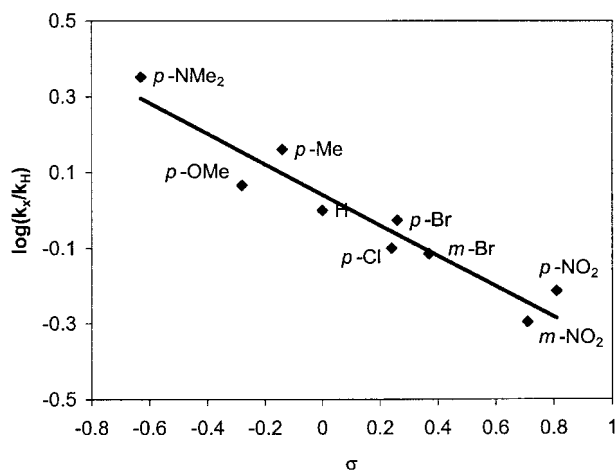
Figure 1. Hammett plot for the HgO oxidation of *N*-benzyl-*N*-isopropylhydroxylamins **(3)**

Figure 2. Hammett plot for the *p*-BQ oxidation of *N*-benzyl-*N*-isopropylhydroxylamins **(3)**

(Z)-N-Isopropyl-4-methylbenzylideneamine N-oxide (9e). White plates, m.p. 43–45 °C (diethyl ether–hexane). Found: C, 74.6; H, 8.5; N, 7.9. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%. ν_{max} (KBr) (cm^{-1}), 2977, 1570, 1446, 1308, 1150, 1084, 836; $^{\delta}$H (19 °C), 1.55 (6 H, d, *J* 7.0 Hz), 2.42 (3 H, s), 4.26 (1 H, hept), 7.30 (2 H, d, *J* 8.0 Hz), 7.48 (1 H, s), 8.24 (2 H, d, *J* 8.0 Hz).

(Z)-N-Isopropyl-4-dimethyaminobenzylideneamine N-oxide (9f). White crystals, m.p. 120–121.5 °C (diethyl ether). Found: C, 69.7; H, 8.8; N, 13.6. $C_{12}H_{18}NO_2$ requires C, 69.65; H, 8.80; N, 13.58%. ν_{max} (KBr) (cm^{-1}), 2978, 1060, 1522, 1366, 1304, 1166, 1084, 948, 840; $^{\delta}$H (19 °C), 1.54 (6 H, d, *J* 7.0 Hz), 3.16 (6 H, s), 4.19 (1 H, hept), 6.76 (2 H, d, *J* 9.0 Hz), 7.35 (1 H, s), 8.26 (2 H, d, *J* 9.0 Hz).

(Z)-N-Isopropyl-3-nitrobenzylideneamine N-oxide (9g). Yellow needles, m.p. 134–136 °C (diethyl ether–ethanol). Found: C, 57.7; H, 5.8; N, 13.5. $C_{10}H_{12}N_2O_3$ requires C, 57.68; H, 5.81; N, 13.46%. ν_{max} (KBr) (cm^{-1}), 2978, 1524, 1322, 1070, 678; $^{\delta}$H (−10 °C), 1.55 (6 H, d, *J* 6.6 Hz), 4.34 (1 H, hept, *J* 6.6 Hz), 7.63 (1 H, t, *J* 8.0 Hz), 7.65 (1 H, s) 8.27 (1 H, d, *J* 7.9 Hz), 8.65 (1 H, d, *J* 7.9 Hz), 9.15 (1 H, s).

(E)-N-Isopropyl-3-nitrobenzylideneamine N-oxide (9g). $^{\delta}$H (−10 °C), 1.51 (6 H, d, *J* 6.4 Hz), 4.70 (1 H, hept, *J* 6.4 Hz), 7.90 (1 H, s), 8.19 (1 H, s).

N-3-Nitrobenzyl 1-methylethylideneamine N-oxide (10g). $^{\delta}$H (−10 °C), 2.17 (3 H, s), 2.22 (3 H, s), 5.15 (2 H, s).

(Z)-N-Isopropyl-3-bromobenzylideneamine N-oxide (9h). White needles, m.p. 82–83 °C (diethyl ether–hexane). Found: C, 49.6; H, 5.1; N, 5.8. $C_{10}H_{12}NOBr$ requires C, 49.61; H, 5.00; N, 5.79%. ν_{max} (KBr) (cm^{-1}),
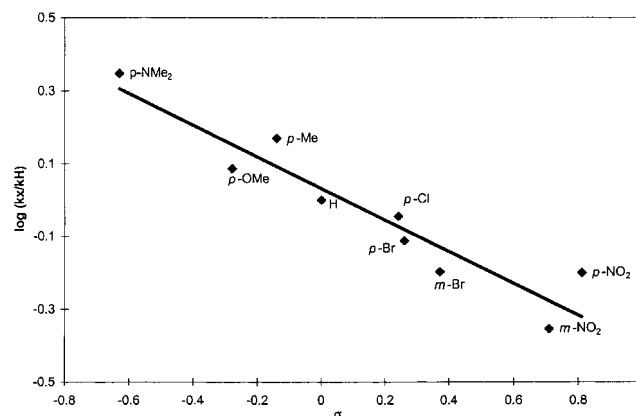
2988, 1570, 1462, 1326, 1152, 1092, 826, 766, 678; $^{\delta}$H (19 °C), 1.54 (6 H, d, *J* 7.0 Hz), 4.27 (1 H, hept), 7.34 (1 H, t, *J* 8.0 Hz), 7.48 (1 H, s), 7.70 (1 H, d, *J* 8.0 Hz), 8.11 (1 H, d, *J* 8.0 Hz), 8.68 (1 H, s).

(Z)-N-Isopropyl-4-bromobenzylideneamine N-oxide (9i). White crystals, m.p. 53–55 °C (diethyl ether–hexane). Found: C, 49.6; H, 5.1; N, 5.8. $C_{10}H_{12}NOBr$ requires C, 49.61; H, 5.00; N, 5.79%. ν_{max} (KBr) (cm^{-1}) 2958, 1578, 1458, 1320, 1154, 1092, 832; $^{\delta}$H (19 °C) 1.55 (6 H, d, *J* 7.0 Hz), 4.28 (1 H, hept), 7.50 (1 H, s), 7.62 (2 H, d, *J* 8.0 Hz), 8.23 (2 H, d, *J* 8.0 Hz).

(Z)-N-Isopropyl-2,4,5-trimethoxybenzylideneamine N-oxide (9j). Light brown crystals, m.p. 114–116 °C (diethyl ether–ethanol). Found: C, 61.7; H, 7.6; N, 5.5. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%. ν_{max} (KBr) (cm^{-1}) 2958, 1578, 1458, 1320, 1154, 1092, 832; $^{\delta}$H (−10 °C), 1.50 (6 H, d, *J* 6.6 Hz), 3.86 (3 H, s), 3.90 (6 H, s), 4.20 (1 H, hept, *J* 6.6 Hz), 6.49 (1 H, s), 7.83 (1 H, s), 9.15 (1 H, s).

(E)-N-Isopropyl-2,4,5-trimethoxybenzylideneamine N-oxide (9j). $^{\delta}$H (−10 °C), 1.42 (6 H, d, *J* 6.4 Hz), 3.82 (6 H, s), 3.84 (3 H, s), 4.52 (1 H, hept, *J* 6.4 Hz), 6.54 (1 H, s), 7.68 (1 H, s), 7.73 (1 H, s).

N-2,4,5-Trimethoxybenzyl 1-methylethylideneamine N-oxide (10j). $^{\delta}$H (−10 °C), 2.15 (3 H, s), 2.17 (3 H, s), 5.00 (2 H, s).

(Z)-N-Isopropyl-2-methoxybenzylideneamine N-oxide (9k). Found: C, 68.3, H, 7.8; N, 7.2. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%. ν_{max} (neat) (cm^{-1}), 2980, 2943, 1594, 1560, 1466, 1436, 1308, 1284, 1246, 1150, 1026, 766; $^{\delta}$H (−10 °C), 1.51 (6 H, d, *J* 6.6 Hz), 3.87 (3 H, s), 4.24 (1 H, hept, *J* 6.6 Hz), 6.87 (1 H, d, *J* 8.4 Hz), 7.02 (1 H, t, *J* 7.7 Hz), 7.35 (1 H, t, *J* 7.7 Hz), 7.92 (1 H, s), 9.32 (1 H, d, *J* 8.1 Hz).

(E)-N-Isopropyl-2-methoxybenzylideneamine   N-oxide (**9k**). $^\delta$H (−10 °C), 1.43 (6 H, d, *J* 6.4 Hz), 3.85 (3 H, s), 4.57 (1 H, hept, *J* 6.4 Hz), 6.96 (1 H, d, *J* 8.5 Hz), 7.03 (1 H, t, *J* 7.7 Hz), 7.19 (1 H, d, *J* 7.5 Hz), 7.41 (1 H, t, *J* 7.7 Hz), 7.83 (1 H, s).

N-2-Methoxybenzyl 1-methylethylideneamine N-oxide (**10k**). $^\delta$H (−10 °C), 2.14 (3 H, s), 2.19 (3 H, s), 5.07 (2 H, s).

General procedure for the determination of the relative rates of HgO oxidation of the hydroxylamines. To a solution of the hydroxylamine **3a** (0.15 mmol) and X-C$_6$H$_4$CH$_2$NOH^{i}Pr (**3**) (0.15 mmol) in CDCl$_3$ (2.0 cm^3) at 0 °C was added yellow HgO (40.0 mg, 0.185 mmol) and the mixture was stirred for 1 h or until the mercury salt turned greyish. The solution was passed through tightly packed glass-wool in a pipette to remove the mercury salts. Careful analysis of the ^{1}H spectrum helped to quantify each product and starting materials, by integration of several proton signals. After taking the spectra the contents of the NMR tube were quantitatively transferred into the reaction flask. Using the rate equation of Ingold and Shaw,[15] the relative rates were determined.

General procedure for the determination of the relative rates of *p*-BQ oxidation of the hydroxylamines. To a stirred solution of the hydroxylamine **3a** (0.15 mmol) and X-C$_6$H$_4$CH$_2$NOH^{1}Pr (**3**) (0.15 mmol) in CDCl$_3$ (1.0 cm^3) at 20 °C was added dropwise a solution of *p*-BQ (0.15 mmol) in 1 cm^3 of CDCl$_3$ over a period of 3–5 min. The solution immediately turned dark blue and after 10–20 min it became colourless with the separation of white crystals of hydroquinone. After passing through glass-wool (tightly packed in a pipette) to remove the hydroquinone, the reaction mixture was analysed by ^{1}H NMR spectroscopy and relative rates were determined as described above in the case of HgO oxidation.

General procedure for the determination of the E–Z composition of nitrones: HgO oxidation of the hydroxylamines. To a solution of hydroxylamine **3** (0.3 mmol) in CDCl$_3$ (0.2 cm^3) at −20 °C was added yellow HgO (1.0 mmol) and the mixture was stirred for 2 h. The solution was then passed through tightly packed glass-wool with a bed of MgSO$_4$ in a precooled pipette (to prevent rapid isomerization) to remove the mercury salts. The solution was collected into a base-washed precooled NMR tube. The NMR spectra at −10 °C revealed the composition of the isomers present (Table 4).

Acknowledgements

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