Synthesis of 4-hydroxylamino-1-azabuta-1,3-dienes and their cyclization to 2-substituted pyrazole 1-oxides

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2-Aromatic or 2-aliphatic substituted pyrazole 1-oxides with substituents at the 3-, 4- or 5-position have been prepared from β-dicarbonyl compounds or ketones. The β-dicarbonyl compounds were treated with *p*-toluidine to give 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium salts in which the *p*-tolylimino groups can be converted into alkylimino groups by treatment with an aliphatic amine. Subsequent deprotonation and treatment with *O*-*tert*-butyldimethylsilylhydroxylamine produced 4-arylamino- or 4-alkylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-diene. The tautomeric structure, the configuration and the conformation of the dienes were elucidated by ^{1}H and ^{13}C NMR spectroscopy. Oxidation of the alkylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-dienes with copper(II) ions led to cyclization with formation of pyrazole 1-oxides. These could also be prepared by oxidation of 3-amino oximes obtained from ketones through amino-alkylation at the α-position and treatment with hydroxyammonium chloride. If 1,5-diaryl-1,5-diazapenta-1,3-diene was treated with *O*-(*p*-tolylsulfonyl)hydroxylamine spontaneous cyclization occurred to give 1-(*p*-tolyl)pyrazole.

Preparation of pyrazole *N*-oxides

2-Substituted pyrazole 1-oxides like **7** are very useful for the regioselective introduction of electrophiles and nucleophiles at ring carbon atoms or at α-positions of carbon substituents in pyrazoles.[1-3] Pyrazole 1-oxides can also be used in the synthesis of 1-hydroxypyrazoles.[4] However, 2-substituted pyrazole 1-oxides like **7** are not yet generally accessible and despite recent improvements in methods for their preparation[1] there is a demand for a more effective approach.

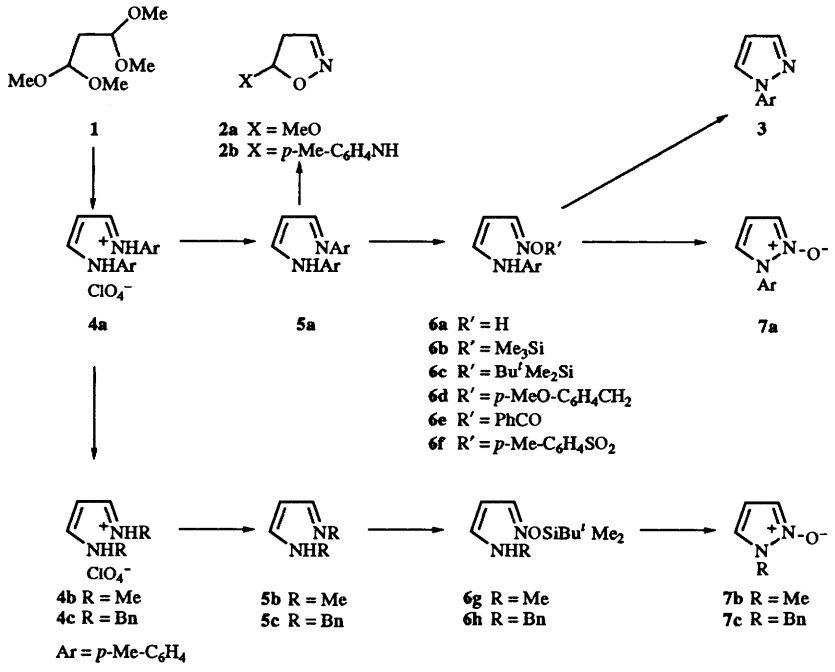
Pyrazole 1-oxides possessing alkyl or aryl groups at N-2 **7** have been prepared by (*i*) reduction of 2-hydroxypyrazole 1-oxides followed by N-alkylation,[5,6] (*ii*) cyclization of 1-imino-2-nitrosoalkenes,[7] and (*iii*) oxidation of 1-substituted pyrazoles[8] (Scheme 1). By the first method, only 3,5- and 3,4,5-substituted 2-hydroxypyrazole 1-oxides have been reported. The final alkylation to give 2-substituted pyrazole 1-oxides has only been successful for 1-hydroxyindazoles.[9] In contrast, the corresponding N-alkylation of 1-hydroxypyrazoles failed.[6] The second method seems to be limited to the preparation of 3,5-disubstituted pyrazole 1-oxides. The third method gives modest to poor yields, particularly if *N*-phenylpyrazoles are oxidized[1,6,8,10] and N-oxidation fails if electron attracting substituents are present in the pyrazole ring.[1]

2-Substituted 1,2,3-triazole 1-oxides can be prepared by oxidative cyclization of α-hydrazono oximes.[11,12] A de-aza analogue of this process leading to 2-substituted pyrazole 1-oxides like **7** is the cyclization of β-imino oximes which exist as the tautomeric α,β-unsaturated β-amino oxime form **6** (see below). To the best of our knowledge these compounds have not been described but they should be available by stepwise functionalization of 1,3-dicarbonyl compounds or appropriate derivatives.

However all attempts to monooximate propane-1,3-dial derivatives resulted in spontaneous cyclization with formation of 5-substituted 4,5-dihydroisoxazoles. Thus, treatment of malonaldehyde dimethyl acetal (1,1,3,3-tetramethoxypropane) **1** with hydroxylamine at various pHs gave 5-methoxy-4,5-dihydroisoxazole **2a** in high yield even if the hydroxylamine was added slowly at low temperature to a dilute solution of 1,1,3,3-tetramethoxypropane. Isoxazoles and 5-hydroxy-4,5-dihydroisoxazoles have been prepared by a similar condensation.[13] Similarly, the reaction between 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** and hydroxylamine gave 5-(*p*-tolylamino)-4,5-dihydroisoxazole **2b**. 1,5-Di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** was prepared in virtually quantitative yield from 1,1,3,3-tetramethoxypropane **1** which was treated with *p*-toluidine and perchloric acid to give 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a**[14] which was then deprotonated with potassium hydroxide. In order to avoid cyclization to the dihydroisoxazole the reaction with 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** was repeated replacing hydroxylamine with an O-protected derivative.

Treatment of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** with *O*-trimethylsilylhydroxylamine gave the desired 1-trimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6b** but it was too unstable to serve well in oxidative cyclization processes. The corresponding *O*-*tert*-butyldimethylsilylated amino oxime **6c** was more stable and could be cyclized to give 2-(*p*-tolyl)pyrazole 1-oxide **7a**. A variety of oxidants, for example copper(II) acetate, copper(II) chloride, potassium ferricyanide, magnesium dioxide, mercury(II) oxide, bromine and silver nitrate, were tried. The best reagent found was copper(II) sulfate in a mixture of acetonitrile and pyridine. In this way 2-(*p*-tolyl)pyrazole 1-oxide **7a** was obtained in 21% yield. The yield may appear modest but it should be compared with the yield of only 1% obtained by oxidation of 1-phenylpyrazole.[1] Furthermore, the β-dicarbonyl compounds (or simple ketones, see below) used as precursors are readily available and the total sequence can be run in two pots.

p-Methoxybenzyl-, benzoyl- and *p*-tolylsulfonyl-protected hydroxylamine were tested as alternatives to *O*-*tert*-butyldimethylsilylhydroxylamine. Treatment of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** with *O*-(*p*-methoxybenzyl)hydroxylamine gave a 98% yield of 1-(*p*-methoxybenzyloxy)-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6d** while similar treatment of *O*-benzoylhydroxylamine gave a complicated mixture. When 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** was treated with *O*-(*p*-tolylsulfonyl)hydroxylamine, 1-(*p*-tolylsulfonyloxy)-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6f**, the precursor for oxidative cyclization, could not be detected. Instead 1-(*p*-tolyl)pyrazole **3** was isolated in 33% yield. Two mechanisms may account for the formation of 1-(*p*-tolyl)pyrazole **3**. The azadiene **5a** may react



Scheme 1

with displacement of its *p*-tolylimine group to give of 1-(*p*-tolylsulfonyloxy)-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6f** which then cyclizes by nucleophilic attack of its enamine nitrogen atom at its oxime nitrogen atom with displacement of the *p*-tolylsulfonyloxy group. Alternatively, *O*-(*p*-tolylsulfonyl)-hydroxylamine N-aminates the enamine nitrogen atom of **5a** to give the corresponding enehydrazine which cyclizes by attack of its terminal hydrazine nitrogen at the imine carbon atom. Subsequent elimination of *p*-toluidine leads to the aromatic pyrazole **3**.

This new cyclization process to give 1-substituted pyrazoles from amines is complementary to other methods for the preparation of pyrazoles which usually use a hydrazine as the starting material.

Pyrazole 1-oxides with aliphatic substituents at the 2-position **7b**, **c** were prepared in high yield from 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** by dispacement of the aromatic amine by an aliphatic one. The resulting 1,5-dialkyl-1,5-diazapenta-1,3-dienium ion **4b**, **c** could not be deprotonated by treatment with potassium hydroxide. However, sodium hydride in dichloromethane solution worked well producing the 1,5-dialkyl-1,5-diazapenta-1,3-diene **5b**, **c**. When these were treated with *O*-*tert*-butyldimethylsilylhydroxylamine one amine was displaced and the 4-alkylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-dienes **6g**, **h** were formed and then cyclized to give the pyrazole 1-oxides **7b**, **c**.

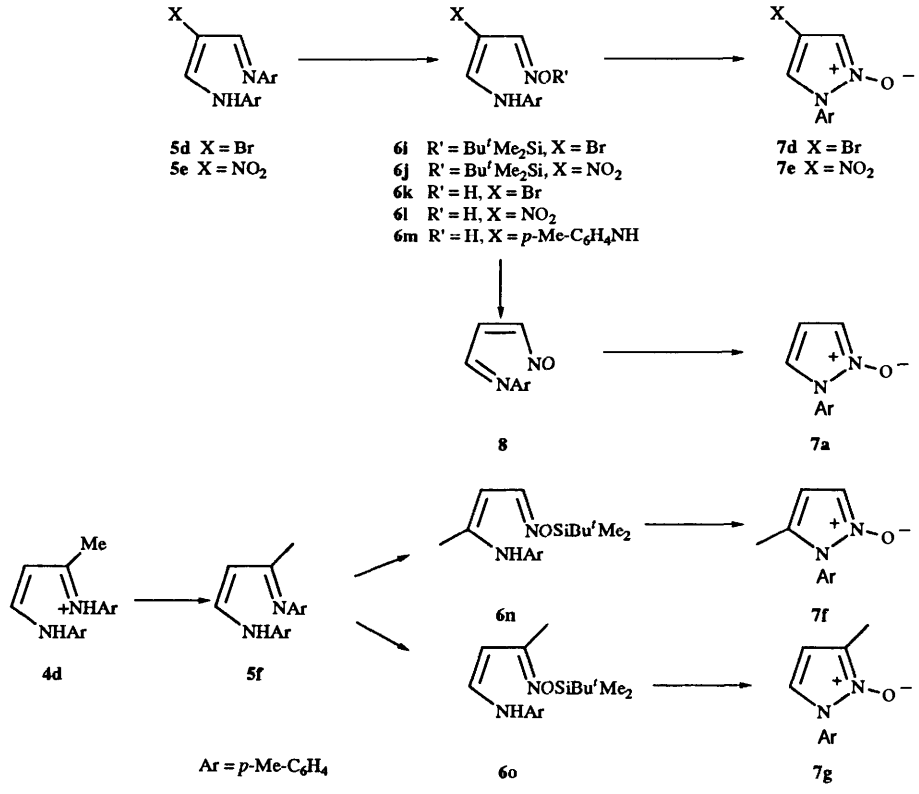
Analogously, 3-bromo-1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6i**, obtained in quantitative yield from bromomalonaldehyde by sequential reaction with *p*-toluidine and *O*-*tert*-butyldimethylsilylhydroxylamine, produced 16% of 4-bromo-2-(*p*-tolyl)pyrazole 1-oxide **7d** (Scheme 2). In addition, 34% of 2-(*p*-tolyl)pyrazole 1-oxide **7a** was isolated.

In separate experiments the bromopyrazole 1-oxide **7d** could not be converted into the pyrazole 1-oxide **7a** even with sodium sulfite as the reductant. Therefore it is suggested that pyrazole 1-oxide **7a** is formed by nonoxidative cyclization of the intermediate **8** formed by elimination of hydrogen bromide from **6k**. This mechanism was supported by the fact that **5d** upon treatment with hydroxylamine gave 27% of the pyrazole 1-oxide **7a**. In addition, a dihydroisoxazole assumed to be the 4-bromo derivative of **2b** on basis of its ^{1}H NMR spectrum was formed. The yield of the pyrazole 1-oxide **7a** dropped to 3% when its putative precursors **6k** and **8**, generated by treatment of compound **6i** with potassium fluoride in ethanol were used. When ethanol was replaced with pyridine in this experiment, no pyrazole 1-oxide **7a** could be detected.

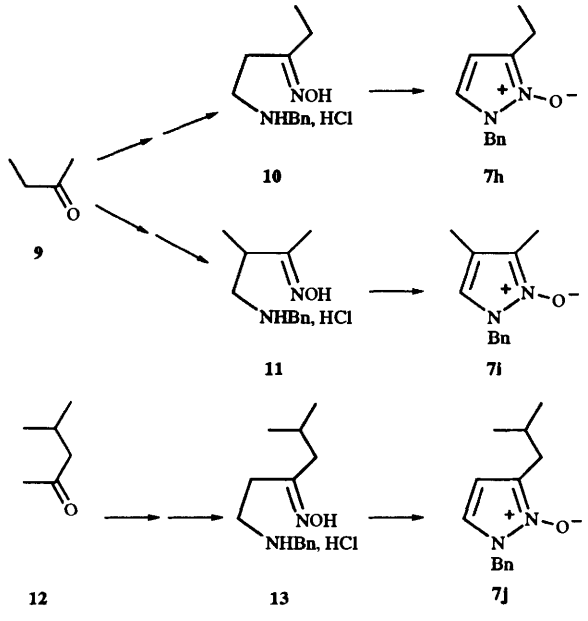
1-*tert*-Butyldimethylsilyloxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6j**, obtained in 75% yield from nitromalonaldehyde, failed to give 4-nitropyrazole 1-oxide **7e** upon oxidation. In the absence of *p*-toluidine a complicated mixture was formed containing 1-hydroxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6l** formed by desilylation of the oxime **6j**. If the oxidation was performed in the presence of toluidine then the nitro group of the oxime **6l** was displaced by the amine to give 1-hydroxy-3,4-bis-(*p*-tolylamino)-1-azabuta-1,3-diene **6m**. This compound was also formed under similar conditions when toluidine displaced the bromine of 3-bromo-1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6i**.

3- or 5-Substituted pyrazole 1-oxides **7f** and **7g** were prepared from alkan-3-ones, which may give rise to both **6n** and **6o** dependent on which imino group of the intermediate 2(4)-methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5f** is displaced by *O*-*tert*-butyldimethylsilylhydroxylamine. It was found that **5f** produced a 1.5:1 mixture of 2-(*p*-tolyl)-3-methyl- **7f** and -5-methyl-pyrazole 1-oxide **7g**. An NMR spectrum of the intermediate mixture of ene oximes **6n** and **6o** showed that these were formed in the ratio 1.9:1 indicating that the aldimine group of **5f** is more reactive than its ketimine group.

In a second approach 1,3-amino oximes **10**–**13** were subjected to oxidation. Due to the lack of a second double bond the 1,3-amino oximes are unable to cyclize to dihydroisoxazoles. Therefore protection of the oxime is unnecessary. The 1,3-amino oximes were prepared from simple ketones by aminoalkylation at the α-position. Subsequent treatment with hydroxyammonium chloride afforded a mixture of the *E* and *Z* oximes. In this case unsymmetric ketones may give rise to two isomeric pyrazole 1-oxides **7h** and **7i** (Scheme 3). Accordingly, butan-2-one **9** produced a 2.2:1 mixture of 2-benzyl-5-ethylpyrazole 1-oxide **7h** and 2-benzyl-4,5-dimethylpyrazole 1-oxide **7i**, indicating that aminoalkylation at the least



Scheme 2



Scheme 3

hindered α-position of the ketone **9** predominates. In fact, 4-methylpentan-2-one **12** produced 2-benzyl-5-isobutylpyrazole 1-oxide **7j** as the sole product under similar conditions.

By oxidation of the individual *E* and *Z* oximes or mixtures of these the *Z* isomer is oxidized much slower than the *E* isomer.

Configuration and conformation of intermediates

The 1,5-diazapenta-1,3-dienium perchlorates **4**, the 1,5-diazapenta-1,3-dienes **5** and the ene oximes **6** may exist in different tautomeric forms, configurations and conformations (Scheme 4). However, the complicated structural properties of these compounds could be unravelled through their ^1H and ^{13}C NMR (Tables 1–6).

In the 1,5-diazapenta-1,3-dienium perchlorates **4a** the π-electrons and the nitrogen lone pairs are all involved in extended conjugation. The three-bond proton–proton coupling constants between the vinylic protons are about 12 Hz (Table 1) indicating an all-*trans* configuration of the conjugated system (Scheme 1). With this configuration three conformations (**4-I–III**) are possible due to restricted rotation about the carbon–nitrogen bonds. When R = *p*-tolyl only isomer **4-I** is observed. This is the only one of the three conformers **4-I–III** in which conjugation is extended to both aromatic rings. In **4-II** and **4-III** steric interaction between the *o*-hydrogen of the phenyl group and 3-H of the diene will impede coplanarity, and hence conjugation, between the diene system and one or both benzene rings. When R = benzyl or methyl the steric interaction is reduced and all three conformers **4-I–III** are observed in the ^1H and the ^{13}C NMR spectra in the ratio 40:43:17 and 62:33:5, respectively. The rate of equilibration between **4-I**, **4-II** and **4-III** is low at room temperature. However, the signals from the conformers coalesce at 140 °C when R = benzyl and at 110 °C when R = methyl. One set of sharp signals is observed at 170 °C and 140 °C, respectively (Table 1, entries 5 and 9).

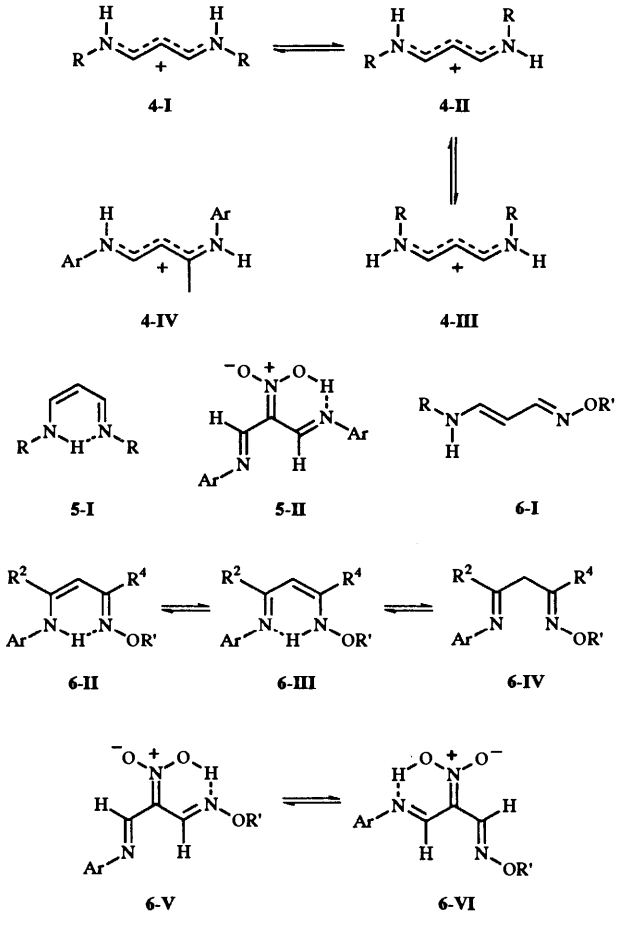
The 3-H of 2-methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4d** resonates at a higher field than 3-H of the parent 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a**. Most likely, the methyl group of **4d** disfavours the all-*trans* conformation **4-I** and the conformer **4-IV** becomes predominant. In this conformer steric interaction between the benzene ring and 3-H forces the benzene ring out of plane with the diene system bringing 3-H into the shielding cone of the benzene ring. This supports the previously reported suggestions.[15]

The 1,5-diazapenta-1,3-dienes **5** adopt a single conformation independent of the nature of R. The three-bond couplings

Table 1 ^{1}H NMR spectra of 1,5-diazapenta-1,3-dienium perchlorates **4** (δ, ppm; J, Hz; solvent, [$^2H_6$]DMSO)

Compound (configuration)	2-H	3-H	4-H	CH_3	CH_2	NH	$J_{2,3}$	$J_{3,4}$	$J_{NH,2-H}$	J_{NH,CH_2}
4a; Ar = *p*-tolyl	8.63 (dd)	6.12 (t)	8.63 (dd)	2.29 (s)	—	11.4	11.4	14.0		
4c (*E*,*E*)	8.02 (dd)	5.98 (t)	8.02 (dd)		4.63 (d)	9.94 (br s)	11.9	11.9	8.1	6.0
4c (*Z*,*E*)	8.16 (dd)	5.63 (t)	7.99 (dd)		4.61 (d)	10.19 (br s)	12.0	12.0	14.4	5.8
4c (*Z*,*Z*)	7.89 (dd)	5.73 (t)	7.89 (dd)		4.55 (d)	9.68 (br s)	12.0	12.0	8.1	6.1
4c [a]	7.90 (br s)	5.74 (t)	7.90 (br s)		4.56 (s)	9.0–9.6 (br s)	11.7	11.7		
4b (*E*,*E*)	7.83 (d)	5.48 (t)	7.83 (d)	2.92 (s)		9.28 (br s)	11.7	11.7		
4b (*Z*,*E*)	7.67 (dd)	5.35 (t)	7.67 (dd)	2.83 (s), 3.06 (s)		9.28 (br s)	12.0	12.0	5.7	
4b (*Z*,*Z*)				3.01 (s)						
4b [b]	7.77 (br s)	5.47 (t)	7.77 (br s)	2.98 (s)		8.6–9.2 (br s)	11.7	11.7		
5f·$HClO_4$; Ar = *p*-tolyl		5.77 (t)	8.57 (dd)	2.28 (s), 2.37 (s) 2-CH_3: 2.60 (s)			12.0	13.5		

[a] Temperature, 170 °C. [b] Temperature, 140 °C.



Scheme 4

between the vinylic protons are about 6 Hz (Table 3) indicating an all-*cis* configuration **5-I** of the conjugated system. Formation of hydrogen bonds accounts for the stabilization of this configuration. The structure of the nitro derivative **5e** presents its own characteristics. It has been described previously[16] that the diazapentadiene system derived from aniline adopts the structure **5-II**. In **5e** configuration **5-II** is further stabilized by an intramolecular hydrogen bond involving the nitro group. The presence of such a hydrogen bond is confirmed by the high chemical shift of 2-H (δ 9.01).

The O-substituted oximes **6** may exist in three tautomeric forms: an ene oxime form like **6-I** or **6-II**, an ene imine form like **6-III** or an imino oxime form like **6-IV**. The ene oxime form is expected to be preferred since oximes are more stable than imines. Accordingly, ^{1}H NMR spectra proved the ene oxime form **6-I** to be the only form present when derived from an aliphatic amine since the N-H proton couples with the α-protons of the *N*-methyl or *N*-benzyl protons of **6g**, **h**. The three-bond couplings are 9.5 and 13.8 Hz. The latter coupling signifies a *trans* configuration **6-I**. The former, although in the borderline, also suggests a *trans* configuration.

The ene oxime form seems also to be the only form present when derived from an aromatic amine. The imino oxime form can be excluded since the ^{1}H NMR spectra are devoid of CH_2-signals. By treatment of 2-methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5f** with *O*-*tert*-butyldimethylsilylhydroxylamine a 1.8:1 mixture of **6n** and **6o** was obtained. The structures of **6n** and **6o** were deduced from the subsequent oxidation of the mixture to give a 1.7:1 mixture of the *N*-oxides **7f** and **7g**. The structure of the *N*-oxides in turn was assigned through the coupling constants between their pyrazole protons which are 1.1 and 3.7 Hz, thus being characteristic of 4-H, 5-H couplings and 3-H, 4-H couplings, respectively, in pyrazole *N*-oxides.[1] Assuming that both isomers adopt the same tautomeric structure it most likely is the ene oxime form **6-II** since the *vic* H,H couplings are 5.7 and 8.4 Hz, respectively. This indicates *cis*-coupling through a double bond in compound **6o** and coupling through a single bond in compound **6n**.

The ^{1}H NMR spectra of the nitro substituted *O*-trialkylsilyl 3-amino oxime **6j** shows the presence of two very similar isomers. This may be explained if the nitro compound is present as a mixture of two tautomers **6-V** and **6-VI**, which both are stabilized by intramolecular hydrogen bonds. Only one isomer is observed in the ^{13}C NMR spectra. The coincidence of signals indicates that the rate of the tautomeric equilibration is equal to or faster than the time scale of the carbon spectrum but slower than that of the proton spectrum.

Experimental

General

Dichloromethane was dried over sodium hydride. Ethanol, pyridine and acetonitrile were distilled from magnesium,[17] potassium hydroxide[18] and phosphorus pentaoxide,[19] respectively. Unless otherwise stated, reactions were performed using syringe techniques and screw cap sealed reaction vessels[20] in an atmosphere of nitrogen dried over phosphorus pentaoxide. To dry solutions, magnesium sulfate was used unless otherwise

Table 2 ^{13}C NMR spectra of 1,5-diazapenta-1,3-dienium perchlorates **4** (δ, ppm; solvent, [$^2H_6$]DMSO)

Compound (configuration)	C-2	C-3	C-4	CH_3	CH_2	C-1′	C-2′	C-3′	C-4′
4a; Ar = *p*-tolyl	157.9	98.0	157.9	20.5	—	136.1	117.4	130.4	135.6
4c (*E,E*)	162.2	89.8	162.2		47.0	135.9	127.8 *	127.8 *	127.5
4c (*Z,E*)	160.7	91.3	165.9		52.9	136.5*, 135.9 *	128.8 *	128.7 *	
4c (*Z,Z*)	164.3	93.0	164.3		52.2		128.7 *		
4b (*E,E*)	162.4	88.7	162.4	30.2					
4b (*Z,E*)	166.3	90.1	160.7	35.5, 29.9					
4b (*Z,Z*)	164.6	92.1	164.6	35.1					
5f·$HClO_4$; Ar = *p*-tolyl	170.6	93.8	154.0	20.6, 20.4 2-CH_3: 18.2		136.3, 137.7	117.3, 125.2	130.2, 130.0	134.8, 133.8

* The assignments may have to be interchanged.

Table 3 ^1H NMR spectra of 1,5-diazapenta-1,3-dienes **5** (δ, ppm; *J* Hz; solvent, $CDCl_3$)

Compound	2-H	3-H	4-H	CH_3 or CH_2	NH	$J_{2,3}$	$J_{3,4}$
5a; Ar = *p*-tolyl	7.67 (d)	5.05 (t)	7.67 (d)	2.32 (s)		6	6
5c	7.26 (m)	4.93 (t)	7.26 (m)	CH_2: 4.35 (s)	6.30 (br s)	8.0	8.0
5b	7.28 (br s)	5.02 (br s)	7.28 (br s)	3.02 (s)	7.60 (br s)		
5d	7.80 (s)		7.80 (s)	2.33 (s)			
5e	9.01 (s)		9.01 (s)	2.34 (s)			
5f; Ar = *p*-tolyl		4.95 (d)	7.27 (d)	2.34 (s), 2.28 (s) 2-CH_3: 1.95 (s)			7.5

Table 4 ^{13}C NMR spectra of 1,5-diazapenta-1,3-dienes **5** (δ, ppm; solvent, $CDCl_3$)

Compound	C-2	C-3	C-4	CH_3	C-1′	C-2′	C-3′	C-4′
5a; Ar = *p*-tolyl	155.9	99.1	155.9	20.5	138.6	117.6	130.1	134.4
5e	148.6	124.1	148.6	20.9	141.3	119.1	130.1	136.3

Table 5 ^1H NMR spectra of 3-aminosilyl oximes **6** (δ, ppm; *J* Hz, solvent, $CDCl_3$)

Compound	2-H	3-H	4-H	CH_3 or CH_2	$J_{2,3}$	$J_{3,4}$	$J_{2,4}$	$J_{NH\text{-}CH_2}$	$J_{NH,2\text{-}H}$
6c; Ar = *p*-tolyl	7.83 (dd)	4.64 (dd)	7.01 (dd)	2.24 (s)	5.49	8.11	1.38		
6h	7.05 (dd)	5.76 (dd)	6.69 (dd)	CH_2: 4.17 (d)	9.5	13.8		5.3	7.7
6g	7.07 (d)	5.66 (dd)	6.75 (dd)	2.73 (d)	9.5	13.8		4.9	8.0
6i	7.88 (s)		7.12 (s)	2.30 (s)					
6j	8.94 (d), 8.89 (d)		8.85 (d), 8.86 (d)	2.36 (s) 2-CH_3: 1.94 (s)			2.4		
6n	7.79 (d)	4.49 (d)		2.28 (s) 4-CH_3: 2.01 (s)	5.7				
6o		4.65 (d)	*	2.36 (s)	8.4				

* The signal is hidden by the aromatic protons.

Table 6 ^{13}C NMR spectra of 3-aminosilyl oxime **6j** (δ, ppm; solvent $CDCl_3$)

Compound	C-2	C-3	C-4	CH_3	C-2′	C-3′	C-4′	$SiCH_3$	CCH_3
6j	150.3	121.1	141.4	21.0	117.3	130.8	136.2	−5.1	26.0

stated. Solvents were removed under reduced pressure by rotary evaporation. Filtration through silica gel was performed using silica gel Merck 60 (70–230 mesh). Flash chromatography was performed as described in ref. 21. All new compounds were colourless, unless otherwise stated. The purity of all compounds were confirmed using melting points, thin layer chromatography and ^1H and ^{13}C NMR spectra recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. *J* Values are given in Hz.

Reaction of 1,1,3,3-tetramethoxypropane with hydroxylamine

A solution of hydroxyammonium chloride (3.48 g, 50 mmol) in water (50 cm^3) was added to a solution of 1,1,3,3-tetramethoxypropane (8.20 cm^3, 50 mmol) in methanol (50 cm^3). After the mixture had been stirred for 24 h at room temperature, 5% aqueous sodium hydroxide was added until the reaction was neutralized. The reaction mixture was extracted with dichloromethane (3 × 50 cm^3), the combined extracts were dried and the solvent removed to afford 5-methoxy-4,5-dihydroisoxazole **2a** (2.3 g, 46%), bp 80 °C/0.1 mmHg (Found: C, 47.6; H, 6.3; N, 13.7. $C_4H_7NO_2$ requires C, 47.52; H, 6.98; N, 13.85%); ν(film)/cm^{-1} 1603, 1211, 1196 and 922; δ_H($CDCl_3$) 2.87 (1 H, dt, *J* 1.4, 14.6, 4-H), 3.07 (1 H, ddd, *J* 1.2, 5.5, 14.6, 4-H′), 3.45 (3 H, s, CH_3), 5.44 (1 H, dd, *J* 1.4, 5.5,

5-H) and 7.30 (1 H, d, *J* 1.2, 3-H); $\delta_C(CDCl_3)$ 41.84 (C-4), 55.10 (CH_3), 101.49 (C-5) and 146.38 (C-3).

1,5-Di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate 4a

In a round bottom flask, a mixture of 1,1,3,3-tetramethoxypropane (5.6 cm^3, 25 mmol), *p*-toluidine (5.35 g, 50 mmol) and ethanol (2.5 cm^3) was stirred and cooled at 0 °C. 60% Aqueous perchloric acid (5 cm^3) was added and the stirring was continued at 20 °C for 1 h. Filtration, afforded red 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** (6.06 g, 51%), mp 225–228 °C (diethyl ether–ethanol) (lit.,[14] 231–232 °C); ν(KBr)/(cm^{-1}), 3220, 1627, 1605, 1583, 1503, 1092 and 810.

1,5-Dimethyl-1,5-diazapenta-1,3-dienium perchlorate 4b

1,5-Di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** (3.51 g, 10 mmol) was added with efficient stirring to a 37% solution of methylamine in ethanol (9.4 cm^3, 75 mmol). The reaction mixture was stirred for 20 h, then the ethanol was removed and diethyl ether (75 cm^3) was added to it leading to the precipitation of orange 1,5-dimethyl-1,5-diazapenta-1,3-dienium perchlorate **4b** (1.85 g, 93%), mp 103–105 °C (ethanol–ethyl acetate) (Found: C, 30.3; H, 5.5; N, 13.7. $C_5H_{11}ClNO_4$ requires C, 30.24; H, 5.58; N, 14.1%); ν(KBr)/cm^{-1} 3330, 1618, 1222 and 1087.

1,5-Dibenzyl-1,5-diazapenta-1,3-dienium perchlorate 4c

Benzylamine (8.03 g, 75 mmol) was added to a suspension of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** (3.51 g, 10 mmol) in methanol (5 cm^3). The reaction mixture was stirred for 20 h, washed with diethyl ether (75 cm^3) and then the solvents were removed. 5% Aqueous perchloric acid (50 cm^3) was added to the residue and then the mixture was extracted with dichloromethane (2 × 20 cm^3). The combined organic extracts were dried and then the solvent was removed to afford the crude, orange 1,5-dibenzyl-1,5-diazapenta-1,3-dienium perchlorate **4c** (3.53 g, 44%), mp 112–114 °C (decomp. on recrystallization) (Found: C, 57.7; H, 5.4; N, 7.85. $C_{17}H_{19}ClN_2O_4$ requires C, 58.20; H, 5.46; N, 7.99%); ν(KBr)/cm^{-1} 3251, 1619, 1491, 1443, 1027, 754 and 697.

2-Methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate 4d

70% Aqueous perchloric acid (15 cm^3) was added with efficient stirring at 0 °C to a mixture of *p*-toluidine (16.1 g, 150 mmol), 1,1-dimethoxybutan-3-one (9.9 cm^3, 75 mmol) and ethanol (7.5 cm^3). The reaction mixture was stirred at 20 °C for 3 h and then filtered to afford yellow 2-methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4d** (15 g, 55%), mp 204–209 °C (ethanol) (Found: C, 59.4; H, 5.8; N, 7.8. $C_{18}H_{21}ClN_2O_4$ requires C, 59.26; H, 5.80; N, 7.68%); ν(KBr)/cm^{-1} 3285, 1636, 1611, 1586, 1557, 1508, 1092 and 810.

Preparation of dienes

1,5-Di-*p*-tolyl-1,5-diazapenta-1,3-diene 5a. To a solution of potassium hydroxide in methanol (0.75 mol dm^{-3}; 80 cm^3) cooled in an ice bath, 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** (9.86 g, 28 mmol) was added and the mixture was sitrred at 20 °C for 1 h. The mixture was cooled in an acetone–solid CO_2 bath to afford orange 1,5-di-*p*-tolyl-1,5-diazapenta-2,4-diene **5a** (5.84 g, 83%), mp 160–162 °C (ethanol–water) (lit.,[14] 164 °C); ν(KBr)/cm^{-1} 1637, 1605, 1589, 1505 and 810.

1,5-Dimethyl-1,5-diazapenta-1,3-diene 5b. Under nitrogen, a 55% suspension of sodium hydride in mineral oil (49 mg, 1.0 mmol) was washed with dry hexane (2 × 1 cm^3). A solution of 1,5-dimethyl-1,5-diazapenta-1,3-dienium perchlorate **4b** (199 mg, 1.0 mmol) in dry dichloromethane (5 cm^3) was added to it with stirring. Stirring was continued for 7 h and then the solvent was removed to afford yellow 1,5-dimethyl-1,5-diazapenta-1,3-diene **5b** (100 mg, 100%), mp 65–70 °C (decomp. on recrystallization).

1,5-Dibenzyl-1,5-diazapenta-1,3-diene 5c. Under nitrogen, a 60% suspension of sodium hydride in mineral oil (88 mg, 2.2 mmol) was washed with dry hexane (2 × 2 cm^3). A solution of crude 1,5-dibenzyl-1,5-diazapenta-1,3-dienium perchlorate **4c** (0.70 g, 2.2 mmol) in dry dichloromethane (10 cm^3) was added to the reaction mixture which was then stirred for 12 h, filtered and the solvent removed to afford yellow 1,5-dibenzyl-1,5-diazapenta-1,3-diene **5c** (0.5 g, 100%), mp 120–125 °C (decomp. on recrystallization); ν(KBr)/cm^{-1} 3426, 1613, 1493, 1450, 1290 and 820.

3-Bromo-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5d. A solution of bromomalonaldehyde[22] (1.5 g, 10 mmol) in ethanol (25 cm^3) was added during 15 min to a stirred solution of *p*-toluidine (2.14 g, 20 mmol) in ethanol (25 cm^3). Stirring was continued for 2 h, the solvent removed and the residue recrystallized from butanol to give yellow 3-bromo-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5d** (1.80 g, 55%), mp 167–170 °C (butanol) (Found: C, 62.1; H, 5.2; N, 8.0. $C_{17}H_{17}BrN_2$ requires C, 62.02; H, 5.20; N, 8.51%); ν(KBr)/cm^{-1} 3429, 3186, 1634, 1612, 1562, 1516, 816 and 802.

3-Nitro-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5e. Sodium nitromalonaldehyde monohydrate[23,24] (314 mg, 2.0 mmol), *p*-toluidine (428 mg, 4.0 mmol) and ethanol (4 cm^3) were stirred at 20 °C for 24 h. 37% Hydrochloric acid (0.17 cm^3) was added to the mixture and stirring was continued for 2 h. The solvent was removed and the residue recrystallized from ethanol to give orange 3-nitro-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5e** (177 mg, 30%), mp 156–158 °C (ethanol) (Found: C, 69.2; H, 5.8; N, 14.1. $C_{17}H_{17}N_3O_2$ requires C, 69.14; H, 5.80; N, 14.23%); ν(KBr)/cm^{-1} 3077, 1634, 1606, 1559, 1518, 1273, 820 and 805.

2-Methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5f. 2-Methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4d** (12 g, 33 mmol) was dissolved in a solution of potassium hydroxide in methanol (1 mol dm^{-3}; 66 cm^3). The methanol was removed and the residue was purified by ball tube distillation (180 °C, 0.05 mmHg) to give red 2-methyl-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5f** (6.5 g, 75%) (Found: C, 82.0; H, 7.3; N, 10.5. $C_{18}H_{20}N_2$ requires C, 81.78; H, 7.63; N, 10.60%); ν(KBr)/cm^{-1} 3268, 1643, 1591, 1509 and 802.

Reaction of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5a with hydroxylamine

A solution of potassium hydroxide in methanol (0.75 mol dm^{-3}; 6.7 cm^3) was added to a solution of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium perchlorate **4a** (1.75 g, 5 mmol) in methanol (10 cm^3). The mixture was stirred for 5 min at room temperature and then a solution of hydroxylamine (0.165 g, 5 mmol) in methanol (5 cm^3) was added to it and the stirring was continued for 3 h at room temperature. The reaction mixture was filtered and the filtrate was washed with methanol (50 cm^3). The solvent was removed and then the residue purified by column chromatography on silica gel (eluent, ethyl acetate–light petroleum, 1 : 4) to afford 5-(*p*-tolylamino)-4,5-dihydroisoxazole **2b** (0.43 g, 35%), mp 128–132 °C (tetrachloromethane) (Found: C, 68.1; H, 6.8; N, 15.8. $C_{10}H_{12}N_2O$ requires C, 68.16; H, 6.86; N, 15.90%). ν(KBr)/cm^{-1} 3299, 1616, 1588, 1524, 807 and 728; $\delta_H(CDCl_3)$ 2.25 (3 H, s, CH_3), 2.77 (1 H, ddd, *J* 1.9, 4.3, 18.4, 4-H), 3.3 (1 H, ddd, *J* 1.6, 9.1, 18.5, 4′-H), 5.99 (1 H, dd, *J* 4.2, 9, 5-H), 6.71, 6.75, 7.01, 7.05 (4 H, AA′BB′, C_6H_4) and 7.28 (1 H, br s, 3-H); $\delta_C(CDCl_3)$ 20.33 (CH_3), 40.47 (C-4), 84.78 (C-5), 114.91 (C-2′), 129.25 (C-4′), 129.70 (C-3′), 141.81 (C-1′) and 145.11 (C-3).

Reaction of 3-bromo-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5d with hydroxylamine

Hydroxyammonium chloride (0.18 g, 2.5 mmol) and sodium

hydrogen carbonate (0.21 g, 2.5 mmol) were stirred in methanol (2.7 cm^3) for 12 h. 3-Bromo-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5d** (0.823 g, 2.5 mmol) dissolved in methanol (5 cm^3) was then added to the mixture and stirring was continued for 48 h. The solvent was removed and the residue extracted with dichloromethane (2 × 10 cm^3), dried (magnesium sulfate) and then the solvent was removed to afford a crude product which was filtered through silica gel. Extraction with ethyl acetate afforded a complex mixture (0.184 g). The mixture was extracted with ethyl acetate–methanol (1:1), the solvents removed and the residue purified by preparative TLC (ethyl acetate–ethanol, 9:1) to afford 2-*p*-tolylpyrazole 1-oxide **7a**, identical with the compound described below.

Reaction of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene 5a with *O*-trimethylsilylhydroxylamine

A solution of *O*-trimethylsilylhydroxylamine[25] (26.3 mg, 0.25 mmol) in dichloromethane (0.5 cm^3) was added dropwise to a solution of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** (62.5 mg, 0.25 mmol) in dichloromethane (0.5 cm^3) with stirring. Stirring was continued for 24 h and then the solvent was removed to afford 72 mg of a mixture of *p*-toluidine and a 1.4:1 mixture (^{1}H NMR) of 5-(*p*-tolylamino)-4,5-dihydroisoxazole **2b** and 1-trimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6b**, $\delta_H(CDCl_3)$ 0.30 [9 H, s, $(CH_3)_3Si$], 2.26 (3 H, s, CH_3Ar), 4.66 (1 H, dd, *J* 5.4 and 8.2, 3-H), 6.79, 6.82, 7.02, 7.05 (4 H, AA'BB' pattern, C_6H_4), 7.09 (1 H, d, *J* 8.6, 4-H) and 7.83 (1 H, d, *J* 5.4, 2-H).

Reactions of 1,5-disubstituted 1,5-diazapenta-1,3-dienes with *O*-*tert*-butyldimethylsilylhydroxylamine

1-*tert*-Butyldimethylsilyloxy-4-methylamino-1-azabuta-1,3-diene 6g. Under nitrogen, a solution of *O*-*tert*-butyldimethylsilylhydroxylamine, mp 60–61 °C, prepared analogously to *O*-trimethylsilylhydroxylamine[25] in 81% yield (148 mg, 1.0 mmol) in dichloromethane (1 cm^3) was added to a solution of 1,5-dimethyl-1,5-diazapenta-1,3-diene **5b** (98 mg, 1.0 mmol) in dry dichloromethane (2 cm^3). The solution was stirred at 20 °C for 15 h and then the solvent was removed to afford 1-*tert*-butyldimethylsilyloxy-4-methylamino-1-azabuta-1,3-diene **6g** as an oil which was used without further purification, $\delta_H(CDCl_3)$ 0.18 [6 H, s, $(CH_3)_2Si$], 0.96 [9 H, s, $(CH_3)_3C$], 2.76 (3 H, d, *J* 4.9, CH_3N), 5.63 (1 H, dd, *J* 9.5 and 13.8, 3-H), 6.75 (1 H, dd, *J* 8.0 and 13.8, 4-H) and 7.07 (1 H, d, *J* 9.5, 2-H).

4-Benzylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-diene 6h. Similarly, 1,5-dibenzyl-1,5-diazapenta-1,3-diene **5c** (0.50 g, 2.0 mmol) produced 0.78 g of a mixture of 4-benzylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-diene **6h** and benzylamine which was used without further purification, $\delta_H(CDCl_3)$ 0.17 [6 H, s, $(CH_3)_2Si$], 0.93 [9 H, s, $(CH_3)_3C$], 4.17 (2 H, d, *J* 5.3, CH_2Ph), 5.76 (1 H, dd, *J* 9.5, 13.8, 3-H), 6.69 (1 H, dd, *J* 7.7, 13.8, 4-H), 7.05 (1 H, d, *J* 9.4, 2-H) and 7.27 (5 H, m, C_6H_5).

3-Bromo-1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene 6i. Similarly, 1,5-di-*p*-tolyl-3-bromo-1,5-diazapenta-1,3-diene **5d** (0.492 g, 1.5 mmol) afforded 0.55 g of a mixture (^{1}H NMR) of *p*-toluidine and 3-bromo-1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6i** as an oil, $\delta_H(CDCl_3)$ 0.2 [6 H, s, $(CH_3)_2Si$], 0.96 [9 H, s, $(CH_3)_3C$], 2.3 (3 H, s, CH_3Ar), 6.79, 6.83, 7.08. 7.12 (4 H, AA'BB', C_6H_4), 7.12 (1 H, s, 4-H) and 7.88 (1 H, s, 2-H). The mixture was used without further purification.

1-*tert*-Butyldimethylsilyloxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene 6j. A solution of *tert*-butyldimethylchlorosilane (75 mg, 0.5 mmol) in dry dichloromethane (0.5 cm^3) was added to a solution of 3-nitro-1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5e** (148 mg, 0.5 mmol) in dry dichloromethane (1 cm^3). After the mixture had been stirred for 3 h, a solution of *O*-*tert*-butyldimethylsilyl hydroxylamine (121 mg, 0.75 mmol) in dry dichloromethane (1 cm^3) was added to it and the stirring was continued for 15 h. The reaction mixture was washed with hydrochloric acid (1 mol dm^{-3}; 10 cm^3), dried and then the solvent was removed to afford 214 mg of a mixture of 1-*tert*-butyldimethylsilyloxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6j** and *p*-toluidine. Isomer **6-V**: $\delta_H(CDCl_3)$ 0.27 [6 H, s, $(CH_3)_2Si$], 0.99 [9 H, s, $(CH_3)_3C$], 2.36 (3 H, s, CH_3Ar), 7.04, 7.07, 7.22, 7.24 (4 H, AA'BB', C_6H_4), 8.86 (1 H, d, *J* 2.4, 4-H) and 8.89 (1 H, d, *J* 2.4, 2-H). Isomer **6-VI**: $\delta_H(CDCl_3)$ 0.27 [6 H, s, $(CH_3)_2Si$], 0.99 [9 H, s, $(CH_3)_3C$], 2.36 (3 H, s, CH_3Ar), 7.04, 7.07, 7.22, 7.24 (4 H, AA'BB', C_6H_4), 8.85 (1 H, d, *J* 2.4, 4-H) and 8.94 (1 H, d, *J* 2.4, 2-H); $\delta_C(CDCl_3)$ −5.1 [$(CH_3)_2Si$], 21.0 (CH_3Ar), 26.0 [$(CH_3)_3C$], 117.3 (C-2'), 121.1 (C-3), 130.8 (C-3'), 136.2 (C-4'), 141.4 (C-4) and 150.3 (C-2). The mixture was used without further purification.

1-*tert*-Butyldimethylsilyloxy-4-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene 6n and 1-*tert*-butyldimethylsilyloxy-2-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene 6o. Similarly, 1,5-di-*p*-tolyl-2-methyl-1,5-diazapenta-1,3-diene **5f** (0.53 g, 2.0 mmol) afforded 0.82 g of a 1.9:1 mixture of 1-*tert*-butyldimethylsilyloxy-4-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6n** and 1-*tert*-butyldimethylsilyloxy-2-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6o** and *p*-toluidine. For **6n**: $\delta_H(CDCl_3)$ 0.19 [6 H, s, $(CH_3)_2Si$], 0.95 [9 H, s, $(CH_3)_3C$], 2.01 (3 H, s, 4-CH_3), 2.28 (3 H, s, CH_3Ar), 4.49 (1 H, d, *J* 5.7, 3-H), 6.91, 6.93, 7.16, 7.19 (4 H, AA'BB', C_6H_4) and 7.79 (1 H, d, *J* 5.7, 2-H). For **6o**: $\delta_H(CDCl_3)$ 0.2 [6 H, s, $(CH_3)_2Si$], 0.95 [9 H, s, $(CH_3)_3C$], 1.94 (2-CH_3), 2.36 (3 H, s, CH_3Ar), 4.65 (1 H, d, *J* 8.4, 3-H) and 6.85, 6.88, 7.04, 7.08 (5 H, m, C_6H_4, 4-H). The mixture was used without further purification.

Reaction of compound 5a with *O*-(*p*-methoxybenzyl)hydroxylamine

Following the same procedure, extending the reaction time to 24 h, 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** (387 mg, 1.5 mmol) and *O*-(*p*-methoxybenzyl)hydroxylamine (187 mg, 1.0 mmol) afforded the crude product (545 mg). Column chromatography on silica gel (toluene–ethyl acetate, 9:1) afforded 0.45 g of a mixture of *p*-toluidine and 1-(*p*-methoxybenzyloxy)-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6d**, $\delta_H(CDCl_3)$ 2.28 (3 H), s, CH_3Ph), 3.80 (3 H, s, OCH_3), 4.61 (1 H, dd, *J* 5.6 and 8.1, 3-H), 5.04 (2 H, s, OCH_2), 6.71, 6.73, 7.04, 7.07 (4 H, AA'BB' pattern, NC_6H_4), 6.96 (1 H, dd, *J* 1.8 and 8.4, 4-H), 6.89, 6.93, 7.34, 7.38 (4 H, AA'BB' pattern, OC_6H_4) and 7.75 (1 H, dd, *J* 1.8 and 5.6, 2-H).

Reaction of compound 5a with *O*-benzoylhydroxylamine

Similarly, extending the reaction time to 24 h, *O*-benzoylhydroxylamine (137 mg, 1.0 mmol) and 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** (250 mg, 1.0 mmol) afforded a complex mixture (437 mg). Preparative TLC (toluene–ethyl acetate, 9:1) afforded *N*-(*p*-tolyl)benzamide (66 mg, 31%), mp 150–153 °C (lit.,[26] 158 °C); $\delta_H(CDCl_3)$ 2.34 (3 H, s, CH_3), 7.16, 7.19, 7.8–7.9 (4 H, m, C_6H_4), 7.4–7.6 (5 H, m, C_6H_5) and 7.76 (1 H, br s, NH). The next fraction contained unchanged starting material **5a** (65 mg, 26%).

Reaction of compound 5a with *O*-(*p*-tolylsulfonyl)hydroxylamine

A solution of *O*-(*p*-tolylsulfonyl)hydroxylamine in dry dichloromethane (1 mol dm^{-3}; 1 cm^3) was added to a solution of 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-diene **5a** (250 mg, 1.0 mmol) in dry dichloromethane (2 cm^3). During the addition a mild exothermic reaction took place with gas evolution, the red–yellow solution became red and a precipitate was formed. The reaction mixture was stirred at 20 °C for 24 h and then the solvent was removed to afford the crude product (430 mg),

which was purified by preparative TLC (toluene–ethyl acetate, 9:1) to afford 1-(*p*-tolyl)pyrazole **3** (52 mg, 33%) as a yellow oil, $\delta_H(CDCl_3)$ 2.38 (3 H, s, CH_3), 6.45 (1 H, dd, *J* 2.0, 2.2, 4-H), 7.23, 7.26, 7.56, 7.58 (4 H, AA'BB' pattern, C_6H_4), 7.71 (1 H, d, *J* 1.6, 5-H) and 7.88 (1 H, d, *J* 2.3, 3-H). The next fraction contained 1,5-di-*p*-tolyl-1,5-diazapenta-1,3-dienium toluene-*p*-sulfonate (43 mg, 10%), $\delta_H(CDCl_3)$ 2.20 (6 H, s, CH_3-tolyl), 2.35 (3 H, s, CH_3-tosyl), 6.77 (1 H, t, *J* 12.6, 3-H), 6.92, 6.95, 7.08, 7.11 (8 H, AA'BB' pattern, 2 × NC_6H_4), 7.20, 7.26, 7.90, 7.93 (4 H, AA'BB' pattern, SC_6H_4), 8.21 (2 H, t, *J* 12.6, 2-H and 4-H) and 11.51 (2 H, d, *J* 14.7, 2 × NH).

Oxidative cyclization

General procedure. A solution of the appropriate crude ene oxime **6** (1 mol equiv.) was dissolved in dry pyridine (1 cm^3) and dry acetonitrile (2 cm^3). Copper(II) sulfate (320 mg, 2.0 mmol) (dried at 130 °C for 5 h) was added to it and the mixture was heated to reflux for 0.5 h. After the mixture had been cooled to 20 °C, sulfuric acid (2 mol dm^{-3}) was added to pH *ca.* 3. Water (16 cm^3) was then added and the mixture extracted with dichloromethane (4 × 4 cm^3). The combined organic extracts were washed with aqueous NaOH (2 mol dm^{-3}; 4 cm^3) dried and then the solvent was removed to afford the crude product.

2-(*p*-Tolyl)pyrazole 1-oxide 7a. In this way, 1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6c** gave a crude product which was filtered through silica gel (20 g per g of crude product) and eluted with hexane–ethyl acetate (1:1) to remove silylated by-products. Subsequent elution with ethyl acetate–methanol (1:1) afforded the 2-(*p*-tolyl)pyrazole 1-oxide **7a** which was purified by preparative TLC (ethyl acetate–ethanol, 9:1) to give the pure product as a highly hygroscopic oil (21%). A correct microanalysis could not be obtained. ν(KBr)/cm^{-1} 1676, 1603, 1512, 1452, 1260, 1097, 1020 and 802; $\delta_H(CDCl_3)$ 2.42 (3 H, s, CH_3), 6.25 (1 H, dd, *J* 3.5 and 2.4, 4-H), 7.09 (1 H, d, *J* 3.5, 3-H), 7.30, 7.33, 7.42, 7.46 (4 H, AA'BB' pattern, C_6H_4) and 7.5 (1 H, d, *J* 2.4, 5-H); $\delta_C(CDCl_3)$ 21.2 (CH_3), 101.8 (C-4), 119.6, 119.8 (C-3, C-5), 125.8 (C-2'), 129.8 (C-3'), 131.2 (C-4') and 139.8 (C-1'); *m/z* 174.1595 (M^+, 44%), 158 (M − O, 100), 91 (C_7H_7, 85). $C_{10}H_{10}N_2O$ requires *M*, 174.0793.

2-Methylpyrazole 1-oxide 7b. Oxidation of 1-*tert*-butyldimethylsilyloxy-4-methylamino-1-azabuta-1,3-diene **6g** according to the general procedure followed by cooling to 20 °C, filtration, washing of the residue with hot dichloromethane (5 cm^3) and removal of the solvent gave a crude product which was filtered through silica gel. The crude product was extracted with hexane–ethyl acetate (1:1) to remove silylated by-products. Subsequent extraction with ethyl acetate–methanol (1:1) afforded 2-methylpyrazole 1-oxide **7b** (22 mg, 22%), identical with the material described previously;[1] ν(KBr)/cm^{-1} 1615, 1518 and 1088.

2-Benzylpyrazole 1-oxide 7c. Oxidation of 4-benzylamino-1-*tert*-butyldimethylsilyloxy-1-azabuta-1,3-diene **6h** according to the general procedure gave a crude product which was filtered through silica gel. The crude product was extracted with ethyl acetate–hexane (1:1) to remove silylated by-products. Subsequent extraction with ethyl acetate–hexane (1:1) afforded 2-benzylpyrazole 1-oxide **7c** (782 mg, 36%), identical with the compound described previously.[1] ν(KBr)/cm^{-1} 1629, 1601, 1583, 1499, 819, 789, 739 and 701.

4-Bromo-2-(*p*-tolyl)pyrazole 1-oxide 7d. Similar oxidation of 3-bromo-1-*tert*-butyldimethylsilyloxy-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6i** afforded a crude product which by flash chromatography (ethyl acetate–hexane, 1:1) afforded 16% of 4-bromo-(*p*-tolyl)pyrazole 1-oxide **7d** as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained. ν(KBr)/cm^{-1} 1602, 1511, 1260, 1094, 1020 and 800; $\delta_H(CDCl_3)$ 2.42 (3 H, s, CH_3), 7.10 (1 H, s, 3-H), 7.30, 7.34, 7.39, 7.43 (4 H, AA'BB' pattern, C_6H_4) and 7.31 (1 H, s, 5-H); $\delta_C(CDCl_3)$ 20.1 (CH_3), 88.3 (C-4), 118.3 (C-3), 119.3 (C-5), 124.7 (C-2'), 128.9 (C-3'), 129.4 (C-4') and 139.2 (C-1'); *m/z* 252.0893 and 254 (M^+ and M + 2, 33%); 236 and 238 (M − O and M + 2 − O, 35), 142 (55), 118 (75) and 91 (C_7H_7, 100). $C_{10}H_9BrN_2O$ requires *M*, 251.9898. The next fraction contained 34% of 2-(*p*-tolyl)pyrazole 1-oxide **7a**, identical with the material above.

Oxidation of 1-*tert*-butyldimethylsilyloxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene 6j. Following the general procedure but extending the reflux time to 24 h 1-*tert*-butyldimethylsilyloxy-3-nitro-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6j** (0.7 g) afforded 1-hydroxy-3,4-bis-(*p*-tolylamino)-1-azabuta-1,3-diene **6m** (90 mg, 15%), mp 143–145 °C (ethanol); ν(KBr)/cm^{-1} 3500, 2900, 1599, 1509, 1444, 1259, 1064 and 806; $\delta_H(CDCl_3)$ 2.31 (3 H, s, CH_3Ar), 2.33 (3 H, s, CH_3Ar), 6.97, 6.99, 7.14, 7.17 (4 H, AA'BB' pattern, C_6H_4), 7.10, 7.14, 7.40, 7.43 (4 H, AA'BB' pattern, C_6H_4), 8.16 (1 H, br s, 4-H) and 8.32 (1 H, br s, 2-H); $\delta_C(CDCl_3)$ 20.9 (CH_3), 119.3 (C-2'), 119.9 (C-3), 120.0 (C-2''), 129.6, 130.3 (C-3', C-3''), 134.0, 134.3, 134.5 (C-4', C-4'', C-1'), 135.3 (C-1''), 159.0 (C-4) and 162.6 (C-2).

3-Methyl-2-(*p*-tolyl)pyrazole 1-oxide 7f and 5-methyl-2-(*p*-tolyl)pyrazole 1-oxide 7g

Oxidation of a 1.9:1 mixture of 1-*tert*-butyldimethylsilyloxy-4-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6n** and 1-*tert*-butyldimethylsilyloxy-2-methyl-4-(*p*-tolylamino)-1-azabuta-1,3-diene **6o** gave a crude product which was flash chromatographed (ethanol–ethyl acetate, 1:4) to give 3-methyl-2-(*p*-tolyl)pyrazole 1-oxide **7f** (18%) as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained. ν(KBr)/cm^{-1} 1635, 1601, 1583, 1513, 801 and 760; $\delta_H(CDCl_3)$ 2.12 (3 H, s, 3-CH_3), 2.44 (3 H, s, CH_3Ar), 5.99 (1 H, d, *J* 1.1, 4-H), 7.23 (1 H, d, *J* 1.1, 5-H) and 7.24, 7.29, 7.34, 7.38 (4 H, AA'BB' pattern, C_6H_4); $\delta_C(CDCl_3)$ 12.6 (3-CH_3), 21.2 (CH_3Ar), 99.9 (C-4), 118.9 (C-5), 128.2 (C-2'), 129.4 (C-4'), 129.5 (C-3), 130.1 (C-3') and 140.5 (C-1'); *m/z* 188.1735 (M^+, 64%), 172 (M − O, 100), 171 (67), 132 (58) and 91 (C_7H_7, 94). $C_{11}H_{12}N_2O$ requires *M*, 188.0950. The next fraction contained 11% of 5-methyl-2-(*p*-tolyl)pyrazole 1-oxide **7g** as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained; ν(KBr)/cm^{-1} 1634, 1592, 1512, 817, 799, 770 and 759; $\delta_H(CDCl_3)$ 2.31 (3 H, s, 5-CH_3), 2.40 (3 H, s, CH_3Ph), 6.12 (1 H, d, *J* 3.7, 4-H), 7.04 (1 H, d, *J* 3.6, 3-H) and 7.27, 7.30, 7.41, 7.45 (4 H, AA'BB' pattern, C_6H_4); $\delta_C(CDCl_3)$ 10.7 (5-CH_3), 21.1 (CH_3Ar), 102.4 (C-4), 118.3 (C-3), 125.5 (C-2'), 128.2 (C-5), 129.6 (C-3'), 131.7 (C-4') and 139.1 (C-1'); *m/z* 188.1771 (M^+, 66%), 172 (M − O, 68), 118 (68) and 91 (C_7H_7, 100). $C_{11}H_{12}N_2O$ requires *M*, 188.0950.

2-Benzyl-5-isobutylpyrazole 1-oxide 7j

Copper(II) sulfate (800 mg, 5 mmol) (dried at 130 °C for 5 h) was added to a solution of 1-benzylamino-5-methylhexan-3-one oxime[27] **13** (as a 1.27:1 mixture of *E* and *Z* isomers) (224 mg, 1.0 mmol) in acetonitrile (2 cm^3) and pyridine (2.5 cm^3). The mixture was heated to reflux for 0.5 h. After cooling to 20 °C, sulfuric acid (2 mol dm^{-3}) was added to pH *ca.* 3. The reaction mixture was extracted with dichloromethane (4 × 5 cm^3) and the combined organic extracts were washed with aqueous NaOH (2 mol dm^{-3}; 4 cm^3). The solvent was removed to afford the crude product (92 mg) which was purified by filtration through silica gel (2 g). Extraction with hexane–ethyl acetate (1:1) (4 × 5 cm^3) followed by extraction with ethyl acetate–methanol (9:1) (3 × 10 cm^3) afforded 2-benzyl-5-isobutylpyrazole 1-oxide **7j** (18 mg, 8%) as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained. ν(KBr)/cm^{-1} 1673, 1524, 1499, 1453, 729 and 701; $\delta_H(CDCl_3)$ 0.97 [6 H, d, *J* 6.6, $(CH_3)_2CH$], 2.06 (1 H, m, *J* 6.6, CH), 2.58 (2

H, d, J 7.1, CH_2CH), 5.30 (2 H, s, CH_2Ph), 5.96 (1 H, d, J 3.7, 4-H), 6.78 (1 H, d, J 3.4, 3-H) and 7.33 (5 H, m, Ph); $\delta_C(CDCl_3)$ 22.1 (CH_3), 26.6 (CH), 33.5 (CH_2), 48.6 (CH_2Ar), 101.4 (C-4), 117.5 (C-3), 128.2 (C-3'), 128.7 (C-4', C-2'), 131.2 (C-5) and 134.4 (C-1'); m/z 230.2317 (M^+, 24%), 213 (M − OH, 16), 172 (14), 171 (15) and 91 (C_7H_7, 100). $C_{14}H_{18}N_2O$ requires M, 230.1419.

When the reaction time was extended to 6 h the yield of 2-benzyl-5-isobutylpyrazole 1-oxide **7j** increased to 16%. If a 1:3 mixture of E and Z isomers of **13** was used as the starting material then 10% of **7j** was isolated after 0.5 h reaction time. If only the E-isomer of **13** was used then **7j** was isolated in 18% yield.

2-Benzyl-5-ethylpyrazole 1-oxide 7h and 2-benzyl-4,5-dimethylpyrazole 1-oxide 7i

Using the above procedure and a reaction time of 6 h, a mixture of 4-benzylamino-3-methylbutan-2-one oxime **11** and 5-benzylaminopentan-3-one oxime **10** (0.62 g, 3.0 mmol) afforded a crude product which by column chromatography on silica gel (30 g, eluent, ethyl acetate) afforded 2-benzyl-5-ethylpyrazole 1-oxide **7h** (30 mg, 5%) as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained; ν(KBr)/cm^{-1} 1726, 1528, 1498, 1451, 1028, 798 and 700; $\delta_H(CDCl_3)$ 1.26 (3 H, t, J 7.8, CH_3), 2.74 (2 H, q, J 7.8, CH_2), 5.34 (2 H, s, $CH_2C_6H_5$), 6.04 (1 H, d, J 3, 4-H), 6.8 (1 H, d, J 3, 3-H) and 7.2–7.4 (5 H, m, C_6H_5); $\delta_C(CDCl_3)$ 11.28 (CH_3), 18.31 (CH_2), 49.38 ($CH_2C_6H_5$), 100.60 (C-4), 119.08 (C-3), 128.57 (C-4'), 128.62 (C-2'), 129.03 (C-3'), 134.39 (C-1') and 135.61 (C-5); m/z 202.1911 (M^+, 24%), 185 (M − OH, 17) and 91 (C_7H_7, 100). $C_{12}H_{14}N_2O$ requires M, 202.1106. The next fraction contained 2-benzyl-4,5-dimethylpyrazole 1-oxide **7i** (17 mg, 3%) as a colourless, highly hygroscopic oil. A correct microanalysis could not be obtained. ν(KBr)/cm^{-1} 1726, 1092, 1025, 799 and 701; $\delta_H(CDCl_3)$ 1.98 (3 H, s, 4-CH_3), 2 (3 H, s, 5-CH_3), 5.3 (2 H, s, $CH_2C_6H_5$), 6.7 (1 H, s, 3-H) and 7.2–7.4 (5 H, m, C_6H_5).

One-pot procedure for the preparation of pyrazole *N*-oxide

Under nitrogen, a 55% suspension of sodium hydride in mineral oil (49 mg, 1.1 mmol) and 1,5-dimethyl-1,5-diazapentadienium perchlorate **4b** (119 mg, 1.0 mmol) were washed with dry hexane (2 × 1 cm^3). Dichloromethane (5 cm^3) was added to the mixture with stirring and the stirring was continued at 20 °C for 7 h. The solid material was removed by filtration and *O*-*tert*-butyldimethylsilylhydroxylamine (148 mg, 1.0 mmol) was added to the filtrate. The mixture was stirred at 20 °C for 15 h and then the dichloromethane was removed under reduced pressure. The residue was dissolved in acetonitrile (2 cm^3) and pyridine (2.5 cm^3) and copper(II) sulfate (320 mg, 2.0 mmol) (dried at 130 °C for 5 h) were added to it. The mixture was heated to reflux for 0.5 h and then filtered. The residue was washed with hot dichloromethane (5 cm^3) and the solvents were removed to afford the crude product (526 mg) which was purified as above to give 2-methylpyrazole 1-oxide **7b** (36 mg, 36%), identical with the material described previously.

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