Thermal fragmentation of 1,2,5- and 1,2,4-oxadiazoles

William R. Mitchell and R. Michael Paton*

School of Chemistry, The University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, UK
E-mail: R.M.Paton@ed.ac.uk

Abstract

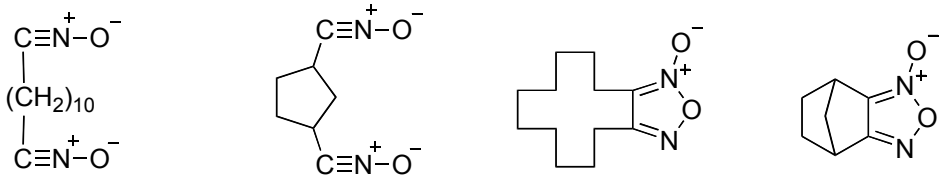
Thermolysis of 3,4-diphenyl-1,2,5-oxadiazole (diphenylfurazan) in tetradec-1-ene at 245 ºC afforded 5-dodecyl-3-phenyl-2-isoxazoline resulting from cycloaddition of benzonitrile oxide to the alkene. Similarly, the tetramethylene and decamethylene furazans **13** and **15** in 4-methoxybenzonitrile at 240 ºC fragmented to ω-cyanoalkanonitrile oxides, which were trapped as their 1,2,4-oxadiazole cycloadducts **17** and **19**, respectively. The flash vacuum pyrolysis (FVP, 550-650 ºC) technique was used to investigate the process in more detail using a range of mono and bicyclic furazans. In all cases the 1,2,5-oxadiazole ring cleaved cleanly at O(1)–N(2) and C(3)–C(4) to nitrile and nitrile oxide fragments. The nitrile oxides were trapped in high yield (81-100%) as their isoxazoline cycloadducts by reaction with hex-1-ene. The tetramethylene furazan **13** was converted into 4-cyanobutyl isocyanate by FVP and reaction of the condensate with sulfur dioxide. 3,5-Diphenyl-1,2,4-oxadiazole showed greater thermal stability under similar conditions (FVP, 600 ºC), but at higher temperatures (700-800 ºC) phenyl isocyanate was formed and trapped as its methyl urethane derivative. Attempts to trap the putative benzonitrile oxide intermediate were unsuccessful.

Keywords: 1,2,5-Oxadiazoles, flash vacuum pyrolysis, nitrile oxides, 1,3-dipolar cycloaddition, isocyanates, 1,2,4-oxadiazoles

Introduction

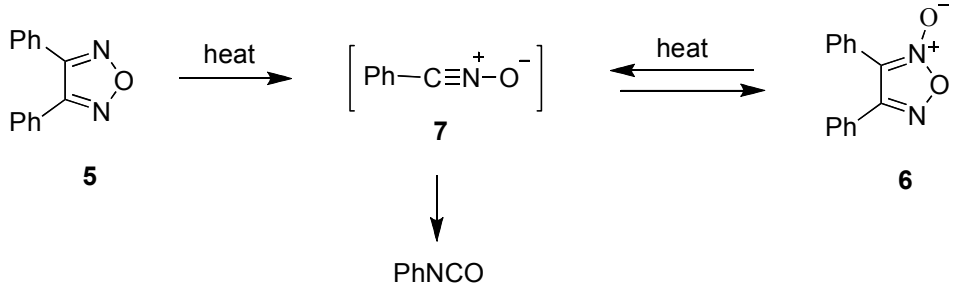
The thermal fragmentation of furoxans (1,2,5-oxadiazole *N*-oxides), involving cleavage at O(1)–N(2) and C(3)–C(4), has proved to be an effective method for the generation of nitrile oxides, and the process has therefore been investigated in some detail.[1-7] It is particularly useful for bis(nitrile oxides) for which alternative approaches are often less successful. For example, dodecane(dinitrile oxide) **1** and cyclopentane-1,3-bis(carbonitrile oxide) **2** can be generated from the readily accessible cyclododecane-furoxan **3** and the norbornane-furoxan **4**,

respectively.[2,3a,3d,3e,7] In contrast, less attention has been paid to the corresponding furazans (1,2,5-oxadiazoles).



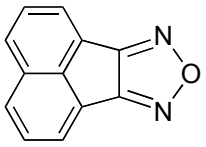
1 **2** **3** **4**

The earliest reports concerning the thermolytic cleavage of a furazan ring date from 1888 when it was noted that heating diphenylfurazan **5** at >200 ºC afforded benzonitrile together with some phenyl isocyanate.[8,9] Similar formation of phenyl isocyanate from the thermolysis of diphenylfuroxan **6**[10,11] suggested a common pathway with the known benzonitrile oxide **7** as intermediate (Scheme 1). Boulton and Mathur[12] later observed that fusion of the oxadiazole to a five-membered ring lowers the temperature required for ring opening; thus acenaphtho[1,2-*c*]furazan **8** at 72 ºC afforded the nitrile oxide **9**, which could be trapped with phenylacetylene as its 1,3-dipolar cycloadduct **10**. Similarly, Tsuge *et al.* found that strained thianorbornane-fused furazans, *e.g.* **11**, undergo cleavage to nitrile and nitrile oxide fragments under mild conditions.[13] Photolytic ring cleavage to nitrile oxide and nitrile has also been established for furazans and benzofurazans,[14-16] and kinetic studies have been performed on the gas phase thermolysis of furazans.[17] 3,5-Diaryl-1,2,4-oxadiazoles have long been known for their thermal stability. For example, 3,5-diphenyl-1,2,4-oxadiazole can be distilled at 296 ºC;[18] however, as found for the isomeric furazan **5**, on prolonged heating, partial decomposition leads to phenyl isocyanate and benzonitrile.[19,20] We now report the results of an investigation into the fragmentation of a range of furazans and of 3,5-diphenyl-1,2,4-oxadiazole using both solution phase and flash vacuum pyrolysis (FVP) techniques.



5 **7** **6**

Scheme 1



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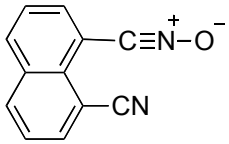

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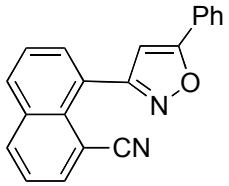

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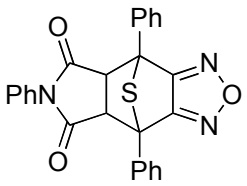

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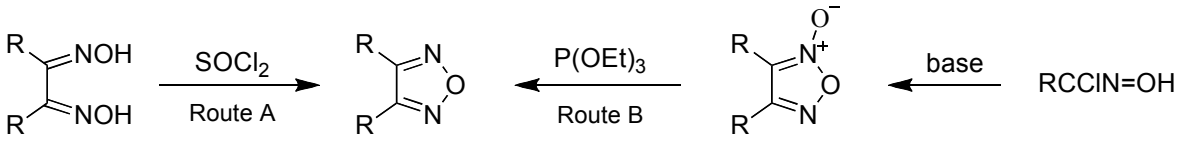
Results and Discussion

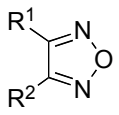
The furazans under investigation were prepared, as illustrated in Scheme 2, either by dehydration of the corresponding glyoxime using thionyl chloride after the method of Boulton and Mathur,[12] or by deoxygenation of the furoxan with triethyl phosphite as described by Mukaiyama *et al*.[21] Of the two synthetic approaches, deoxygenation of furoxans (Route B) is a more general method, whereas dehydration of glyoximes (Route A) is restricted to those glyoximes that do not undergo Beckmann rearrangement to the 1,2,4-oxadiazole. In the present context Route A was used successfully to prepare 3,4-dimethylfurazan **12** (52%) and the tetramethylenefurazan **13** (53%). In contrast, an attempt to prepare 3,4-diphenylfurazan **5** by this approach afforded not **5** but 3,5-diphenyl-1,2,4-oxadiazole in 85% yield. If the furoxan is readily available, as was the case for the present investigation, Route B is the method of choice with deoxygenation taking place in excellent yield (usually >90%), whereas Route A normally gave *ca.* 50% yield of the furazan The products were identified from their analytical and spectroscopic properties. In particular, they showed ^{13}C NMR signals at 149-154 ppm, characteristic for C(3) and C(4) of the oxadiazole ring.[22]



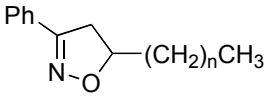
Scheme 2

As the role of benzonitrile oxide in the original thermolysis of furazan **5** (Scheme 1) had not been firmly established,[8,9] we repeated the experiment in the presence of a dipolarophile in an attempt to trap it as its cycloadduct. A similar approach had been successful for trapping the same nitrile oxide formed on fragmentation of the corresponding furoxan **6** using tetradec-1-ene as the dipolarophile.[3a] Thus a solution of diphenylfurazan **5** was heated in tetradec-1-ene at reflux (245 ºC) for 6 hours, and from the reaction mixture was isolated in 75% yield 5-dodecyl-3-phenyl-2-isoxazoline **14**, which was identified by comparison with an authentic sample prepared from benzohydroximoyl chloride and tetradec-1-ene. HPLC analysis of the reaction mixture gave the 2-isoxazoline **14** (83%) together with unreacted **5** (15%). The formation of

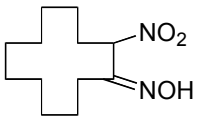
cycloadduct **14** in high yield (98% based on consumed **5**) shows that the 1,2,5-oxadiazole ring cleaves cleanly at O(1)–N(2) and C(3)–C(4). Under identical conditions the corresponding furoxan **6** was consumed in 2 hours, whereas the furazan reaction was incomplete even after 6 hours, suggesting that the furazan has greater thermal stability.[3a]



5 $R^1 = R^2 = Ph$
12 $R^1 = R^2 = Me$
13 $R^1R^2 = (CH_2)_4$
15 $R^1R^2 = (CH_2)_{10}$
21 $R^1 = R^2 = 4\text{-}MeOC_6H_4$
22 $R^1 = R^2 = 4\text{-}MeC_6H_4$
23 $R^1 = Ph$, $R^2 = Me$
24 $R^1 = Ph$, $R^2 = 4\text{-}ClC_6H_4$
25 $R^1 = Ph$, $R^2 = 4\text{-}MeC_6H_4$



14 n = 11
20 n = 3



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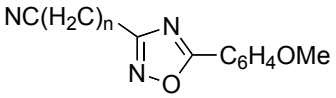
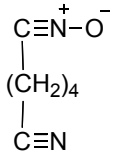


17 n = 4
19 n = 10



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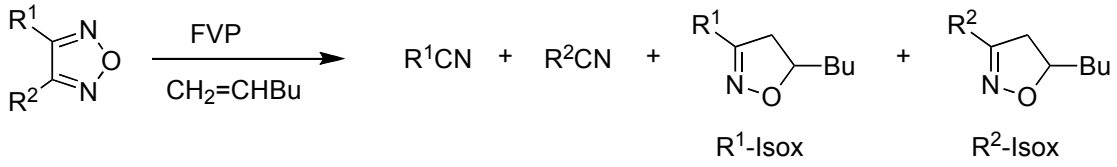
dipolarophile. The product mixture was worked up by removal of excess hexene and then vacuum distillation to afford benzonitrile (1.65 mmol, 92%). From the residue was obtained by sublimation 5-butyl-3-phenyl-2-isoxazoline **20** (96%), which was identified by comparison with an authentic sample.[3a] Similar results were obtained for the pyrolyses of the di-(4-methoxyphenyl)-, di-(4-tolyl)-, and dimethyl-furazans **21**, **22**, **12**. The results, which are summarised in Table 1, show that all the furazans afford nitriles and nitrile oxide cycloadducts **23**-**25** in high yield.

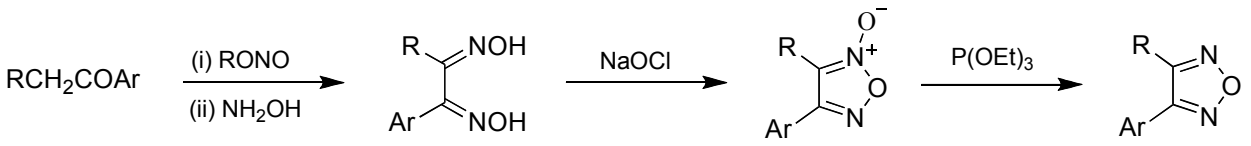
Table 1. 2-Isoxazolines and nitriles from FVP[a] of furazans



Entry	Furazan	R^1	R^2	Oven Temp./ºC	Product yields/% R^1Isox / R^2Isox	R^1CN / R^2CN
1	**5**	Ph	Ph	600	**20** (96)	92
2	**21**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	550	**23** (93)	96
3	**22**	4-MeC_6H_4	4-MeC_6H_4	600	**24** (96)	93
4	**12**	Me	Me	600	**25** (81)	91[b]
5[b]	**26**	Ph	Me	650	**20** (65) / **25** (35)	35 / -[c]
6[b]	**27**	Ph	4-ClC_6H_4	600	**20** (47) / **29** (47)	49 / 51
7[b]	**28**	Ph	4-$MeOC_6H_4$	600	**20** (40) / **23** (47)	52 / 43

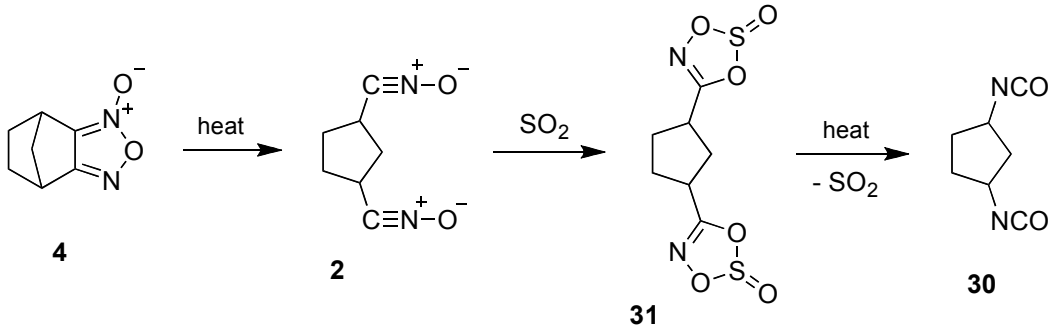
[a] at 10^{-3} mmHg; [b] Yields determined by GC; [c] not determined.

In order to gain some insight into the mode of fragmentation of the heterocyclic ring three asymmetrically-substituted furazans **26-28** were investigated. These were prepared *via* the glyoxime and furoxan as outlined in Scheme 3. For such furazans there are two possible fragmentation pathways involving cleavage at C(3)–C(4) and at either O(1)–N(2) or O(1)–N(5). In all three cases FVP afforded mixtures of 2-isoxazolines and nitriles that were analysed by GC (Table 1, entries 5-7). For the 3-methyl-4-phenyl compound **26**, the observed ratio (65:35) of 3-phenyl- to 3-methyl-isoxazolines **20**, **25** shows that the major pathway involves ring cleavage at O(1)–N(2) and C(3)–C(4), rather than O(1)–N(5) and C(3)–C(4). For **27** and **28** the ratio of products is more finely balanced, with only a slight preference for formation of 4-methoxybenzonitrile oxide rather than benzonitrile oxide in the case of **28**. Although these results are limited in scope, it is noted that fragmentation favours the more 'stable' nitrile oxide. Acetonitrile oxide is known to have a much shorter lifetime than benzonitrile oxide,[26] and it has also been reported that 4-methoxybenzonitrile oxide is longer lived that benzonitrile oxide, an effect attributed to the electron-donating methoxy substituent.[27]



Scheme 3

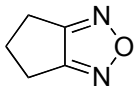
We have previously established that ring-strained bicyclic furoxans can be converted into diisocyanates in good yield in the presence of sulfur dioxide. For example, the diisocyanate **30** was prepared from the norbornane furoxan **4** by heating in toluene saturated with SO_2.[3e] The process is believed to involve fragmentation to the dinitrile oxide **2**, which undergoes 1,3-dipolar cycloaddition to the SO_2 to form the bis-dioxathiazolone **31**. Thermal fragmentation of **31** with extrusion of SO_2 then affords the diisocyanate **31**, as illustrated in Scheme 4. The sulfur dioxide thus plays a key role by effecting the nitrile oxide to isocyanate conversion at temperatures lower than those normally required, and also by minimising competing polymerisation of the intermediate dinitrile oxide.[3e] The conversion of unstrained furoxans to isocyanates was also achieved by using FVP and reacting the condensate with sulfur dioxide. For example, using this approach phenyl isocyanate (93%) was prepared from diphenylfuroxan **6**.[3c]



4 **2** **31** **30**

Scheme 4

The corresponding reaction for bicyclic furazans has the potential to produce ω-cyanoalkyl isocyantes. Indeed, we have previously found that heating the strained trimethylenefurazan **32** in the presence of sulfur dioxide generated 3-cyanopropyl isocyanate **33**, which could be trapped by aniline as its urea adduct **34**.[28] To extend the scope of this reaction we examined the tetramethylene compound **13** as an example of an unstrained bicyclic furazan. Furazan **13** was therefore subjected to FVP at 600 ºC and the pyrolysate condensed onto sulfur dioxide. Addition of toluene and heating the resulting solution at reflux afforded 4-cyanobutyl isocyanate **35**, which was converted into the urea **36** by treatment with aniline. The reaction presumably proceeds *via* 5-cyanopentanonitrile oxide **18** and the dioxathiazolone **37**, which on heating affords the isocyanate with expulsion of SO_2.



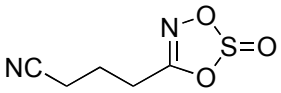
32

$NC(CH_2)_nNCO$

33 n = 3
35 n = 4

$NC(CH_2)_nNHCONHPh$

34 n = 3
36 n = 4



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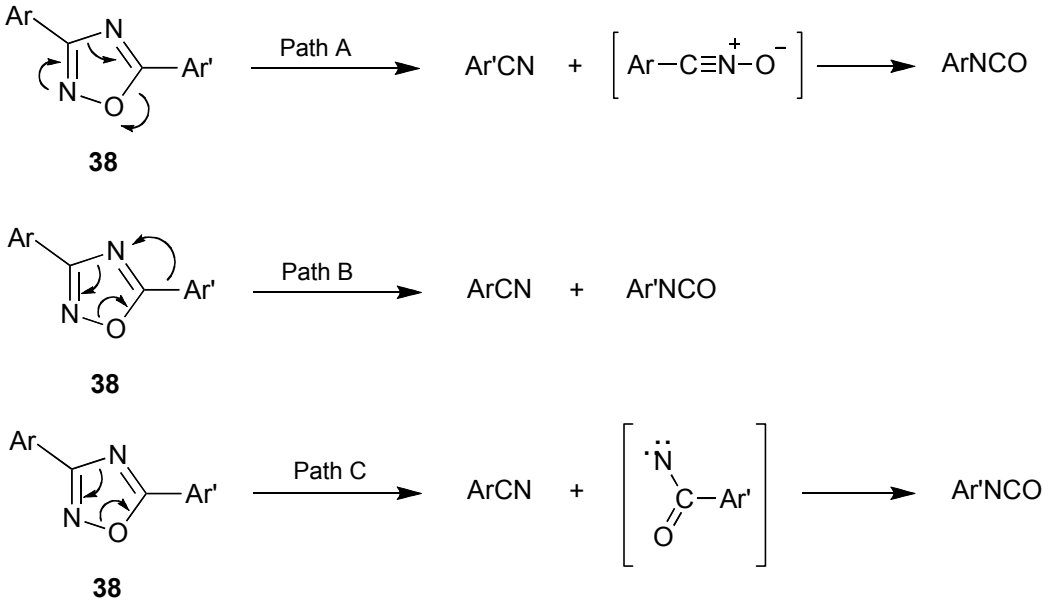
The early literature suggests that 3,5-aryl-1,2,4-oxadiazoles are more stable than the corresponding furazans,[18-20] but that at temperatures in excess of 300 ºC decomposition leads to nitriles and isocyanates. Three possible decomposition pathways are illustrated in Scheme 5: Path A, a retro-1,3-dipolar cycloaddition to nitrile and nitrile oxide fragments involving cleavage at O(1)–C(5) and C(3)–N(4), followed by the known[26] nitrile oxide to isocyanate rearrangement; Path B, a one-step process involving cleavage at O(1)–N(2) and C(3)–N(4) with concomitant migration of the aryl group at C(5) to N(4); and Path C, a two-step pathway involving fragmentation to the nitrile and an acylnitrene intermediate that rearranges to the isocyanate. Cotter and Knight[19] found only benzonitrile and phenyl isocyanate, together with unreacted starting material, when they heated 3,5-diphenyl-1,2,4-oxadiazole **38a** at 340 ºC in an evacuated sealed ampoule, and they proposed the one-step mechnism (Path B) to explain the results. On the other hand, Ainsworth[20] found that thermolysis of the unsymmetrically-substituted analogue 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole **38b** afforded 4-chlorophenyl isocyanate and 4-methoxybenzonitrile, rather than 4-methoxyphenyl isocyanate and 4-chlorobenzonitrile; and he interpreted these results in terms of the nitrile oxide intermediate (Path A). Mass spectrometry studies have shown that electron impact-induced fragmentation of **38** also proceeds *via* Path A.[29] It was anticipated that by using the FVP technique which had successfully been applied to diphenylfuroxan **6** and diphenylfurazan **5**, it might prove possible to isolate the putative benzonitrile oxide intermediate **7** formed on fragmentation of the 1,2,4-oxadiazole analogue **38a.**

3,5-Diphenyl-1,2,4-oxadiazole **38a** was prepared in good yield (85%) by thionyl chloride-induced Beckmann rearrangement of benzil dioxime. Heating a solution of the oxadiazole **38a** in excess tetradec-1-ene at 251 ºC yielded only recovered starting material and none of the isoxazoline cycloadduct **14** could be detected, thus confirming its greater thermal stability of **38a** compared with the furazan **5**. Similarly, FVP of **38a** at 600 ºC onto hex-1-ene resulted only in recovered starting material (97%). At 700 ºC some decomposition did take place with 54% of **38a** being recovered, but the isoxazoline **20** that would have been formed from benzonitrile oxide could not be detected in the product mixture. It had previously been established[30] that FVP of diphenylfuroxan **6** at 700 ºC afforded benzonitrile oxide **7** in very high yield (95%), thus demonstrating that the benzonitrile oxide to phenyl isocyanate rearrangement is slow under these conditions. The involvement of benzonitrile oxide as an intermediate in the formation of phenyl isocyanate from oxadiazole **38a** therefore remains unproven. FVP of **38a** at 800 ºC onto methanol was carried out in an attempt to trap benzoylnitrene, but failed to produce any *N*-benzoyl-*O*-methylhydroxylamine that would have resulted from O–H bond insertion; the only product isolated was the phenyl isocyanate-derived urethane ($PhNHCO_2Me$).



Scheme 5. [**a**, Ar = Ar′ = Ph; **b**, Ar = 4-ClC_6H_4, Ar′ = 4-$MeOC_6H_4$].

In conclusion, these results show that the fragmentation of furazans to nitrile oxides and nitriles does not depend on special features such as ring strain or bulky substituents, and that using the FVP technique gives excellent yields of cleavage products (87-100%). It is also noteworthy that by using FVP a wider range of furazans and dipolarophiles can be used compared with liquid-phase reactions. Bicyclic furazans afford ω-cyanoalkyl nitrile oxides, which can be trapped as their 1,3-dipolar cycloadducts and using sulfur dioxide as the dipolarophile provides access to ω-cyanoalkyl isocyanates. Attempts to trap benzonitrile oxide from the decomposition of 3,5-diphenyl-1,2,4-oxadiazole were not successful.

Experimental Section

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra (^1H at 100 or 360 MHz, ^{13}C at 20 or 93 MHz) were recorded on solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard and using Brucker WH360, Varian XL100 or Varian CFT-20 spectrometers. Mass spectra were obtained on an AEI M902 instrument and reaction mixtures analysed using a VG Micromass 12 mass spectrometer/gas chromatograph. A Perkin Elmer 157G spectrophotometer was used to record IR spectra. For qualitative and quantitative GC investigations were carried using Pye 104 and Perkin-Elmer F11 instruments, using SE30 as stationary phase. HPLC analyses were performed using either Spherisorb silica, Spherisorb alumina, or ODS-Hypersil supplied by Shandon-Southern Ltd.

Preparation of furazans

The furazans were prepared by one of the following two methods:

Method 1. Dehydration of the glyoxime after the method of Boulton and Mathur,[12] as illustrated below for 3,4-tetramethylenefurazan **13**.

Method 2. Deoxygenation of the corresponding furoxan using triethyl phosphite after the method of Mukaiyama *et al*.[21] as illustrated below for 3,4-bis(4-methoxyphenyl)furazan **21**.

3,4-Tetramethylenefurazan (4,5,6,7-tetrahydrobenzofurazan) (13). This compound was prepared by Method 1 from the glyoxime. Thionyl chloride (4.2 g, 40 mmol) was added to a suspension of cyclohexane-1,2-dione dioxime (5.0 g, 40 mmol) in dry dichloromethane (50 ml) and the mixture stirred for 24 h. The reaction mixture was then poured onto crushed ice and extracted with dichloromethane, dried over $MgSO_4$, and the solvent removed *in vacuo* to leave a red oil. Chromatography (alumina, CH_2Cl_2) afforded 3,4-tetramethylenefurazan **13** (2.28 g, 53%) as colourless platelets (from pentane); mp 18-19 °C (lit.[23] 20.5 °C); IR (film): ν 1588 cm^{-1} (C=N); ^{13}C NMR ($CDCl_3$): δ 151.6 (furazan ring C), 22.2, 20.2 (CH_2); MS (EI): *m/z* (%) 124 (M^+, 86), 107 (36), 97 (39), 94 (46), 70 (64), 67 (96), 41 (100).

3,4-Dimethylfurazan (12). This compound was prepared from dimethylglyoxime by Method 1, as described above for compound **13**. The product was collected as a colourless oil (52%); bp 56 °C/18 mmHg (lit.[31] 154-159 °C/760 mmHg); IR (film): ν 1590 cm^{-1} (C=N); ^{13}C NMR ($CDCl_3$): δ 151.6 (furazan ring C), 8.0 (CH_3); MS (EI): *m/z* 98 (M^+), 57 ($MeCNO^+$).

3,4-Bis(4-methoxyphenyl)furazan (21). This compound was prepared by Method 2 from the furoxan. A mixture of 3,4-bis(4-methoxyphenyl)furoxan[32] (1.2 g, 3.82 mmol) and triethyl phosphite (10 ml) was heated at 160-170 °C under nitrogen for 12 h. The excess $P(OEt)_3$ and the triethyl phosphate formed during the reaction were removed by vacuum distillation to leave the product as a white solid. The furazan **21** (1.0 g, 93%) was isolated as white crystals (from EtOH); mp 125-127 °C; IR (Nujol): ν 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 6.8-7.6 (m, 8H, ArH), 3.81 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 152.4 (furazan ring C), 161.0, 130.5, 117.9, 114.2 (ArC), 55.1 (OCH_3); MS (EI): *m/z*(%) 282 (M^+,100), 252 (40), 149 (55, $MeOC_6H_4CNO^+$), 126 (17), 119 (15), 106 (10). Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.1; H, 5.0; N, 9.9% Found: C, 67.9; H, 4.9; N, 9.9%

3,4-Diphenylfurazan (5). This compound was prepared from the furoxan by Method 2, as described above for compound **21**. The product was collected as a white crystalline solid (from MeOH) (90%); mp 95-97 °C (lit.[8] 98 °C); ^{13}C NMR ($CDCl_3$): δ 153.1 (furazan ring C), 130.4, 128.9, 128.5, 127.7 (ArC).

3,4-Decamethylenefurazan (15). This compound was prepared from the furoxan by Method 2, as described above for compound **21**. After heating under reflux for 12 h, the solution was cooled and poured onto ice, a few drops of 2M aq HCl added and the mixture allowed to stand for 12 h. The mixture was extracted with hexane, dried ($MgSO_4$) and the solvent evaporated to leave a colourless oil. Chromatography (alumina, hexane) afforded a solid which was further purified by vacuum distillation to yield the product was as a white solid (79%); mp 43-44 °C;

^{13}C NMR ($CDCl_3$): δ 154.7 (furazan ring C), 26.9, 25.3, 24.7, 23.3, 20.1 (CH_2). Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.2; H, 9.6; N, 13.4% Found: C, 69.2; H, 9.9; N, 13.2%

3,4-Bis(4-methylphenyl)furazan (22). This compound was prepared from the furoxan by Method 2, as described above for compound **21**. The product was collected as a white crystalline solid (from EtOH) (60%); mp 92-94 °C; ^{1}H NMR ($CDCl_3$): δ 7.1-7.6 (m, 8H, ArH), 2.38 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 152.8 (furazan ring C), 140.4, 129.4, 128.5, 122.8 (ArC), 21.2 (CH_3); MS (EI): *m/z* (%) 250 (M^+,100), 222 (74), 133 (89, $MeC_6H_4CNO^+$), 103 (46), 77 (31). Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2% Found: C, 76.8; H, 5.7; N, 11.2%

3-Methyl-4-phenylfurazan (26). This compound was prepared from phenylacetone *via* methylphenylglyoxime and 3-methyl-4-phenylfuroxan as outlined in Scheme 3. α-Acetylbenzaldoxime (23.0 g, 140 mmol), prepared from phenylacetone and pentyl nitrite,[33] was dissolved in a solution of sodium hydroxide (11.2 g, 280 mmol) in water (100 ml). Hydroxylamine hydrochloride (20.0 g, 290 mmol) was added slowly and the mixture heated on a steam bath for 1 h. On cooling methylphenylglyoxime (15.6 g, 63%) precipitated and was recrystallised from ethanol, mp 236-239 °C (lit.[34] 238-239 °C). Using the method of Ponzio[34] the glyoxime was oxidised to a mixture of methylphenylfuroxans, from which was isolated by crystallisation 3-methyl-4-phenylfuroxan as a white crystalline solid (from EtOH) (41%); mp 91-92 °C (lit.[34] 96 °C); ^{1}H NMR ($CDCl_3$): δ 7.4-7.6 (m, 5H ArH), 2.31 (s, 3H CH_3); ^{13}C NMR ($CDCl_3$): δ 156.6, 130.7 (furoxan ring C), 128.9. 127.0, 126.3, 111.8 (ArC), 8.8 (CH_3). Heating for 24 h with triethyl phosphite, as described above for compound **21**, afforded 3-methyl-4-phenylfurazan **26**, which was purified by chromatography (alumina, hexane) and vacuum distillation to afford a colourless oil (94%); bp 65 °C/0.1 mmHg (lit.[35] 145 °C/16 mmHg); IR (film): ν 1590 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 7.3-7.7 (m, 5H, ArH), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 153.6, 149.4 (furazan ring C), 130.2, 128.9, 127.8, 125.9 (ArC), 9.4 (CH_3).

3-(4-Chlorophenyl)-4-phenylfurazan (27). This compound was prepared from 4-chlorobenzyl phenyl ketone *via* 4-chlorobenzil-α-oxime, 4-chlorobenzil dioxime and (4-chlorophenyl)-phenylfuroxans as outlined in Scheme 3. 4-Chlorobenzyl phenyl ketone[36] (10.0 g, 43.3 mmol) was added to a cooled solution of sodium (1.0 g, 43.3 mmol) in dry ethanol (500 ml) and the temperature maintained at 0 °C. Pentyl nitrite (5.1 g, 43.4 mmol) was added over 1.5 h and the mixture allowed to stand for 2 days. The solvent was removed under reduced pressure, the residue dissolved in water (250 ml), and the resulting precipitate collected by filtration. The brown solid was taken up in diethyl ether and precipitated from hexane to give 4-chlorobenzil-α-oxime (from EtOH/H_2O) (6.0 g, 53%). The 4-chlorobenzil monooxime (4.0 g, 16 mmol) was dissolved in a solution of sodium hydroxide (1.0 g, 25 mmol) in water (50 ml). Hydroxylamine hydrochloride (2.2 g, 50 mmol) was added slowly, the mixture heated on a steam bath for 1 h and allowed to stand for 60 h. The resulting white solid was collected by filtration and the filtrate concentrated to afford a second crop of product, thus yielding 4-chlorobenzil dioxime (3.5 g, 82%). The glyoxime (2.0 g, 7.3 mmol) was then added to a solution of sodium hydroxide (1.0 g, 25 mmol) in water (50 ml) and the mixture cooled to -10 °C. Toluene (20 ml) was added, followed by 10% aq. sodium hypochlorite and the mixture stirred 16 h. The organic layer was

separated, dried ($CaCl_2$), and the solvent removed *in vacuo* to leave a mixture of 3-(4-chlorophenyl)-4-phenylfuroxan/4-(4-chlorophenyl)-3-phenylfuroxan (1.8 g, 91%), which were isolated as yellow crystals from MeOH/H_2O. Heating for 12 h with triethyl phosphite, as described above for compound **21**, afforded 3-(4-chlorophenyl)-4-phenylfurazan **27**, which was purified by recrystallisation from EtOH/H_2O to afford white needless (1.3 g, 92%); mp 94-96 °C (lit.[22a] 98 °C); IR (film): ν 1600 cm^{-1} (C=N); ^{13}C NMR ($CDCl_3$): δ 152.8, 152.0 (furazan ring C), 136.7, 136.5, 130.0, 129.1, 128.7, 125.2, 124.2 (ArC); MS (EI): *m/z* (%) 258 (M^+, 14), 256 (M^+, 100), 226 (60), 153 (18, ClC_6H_4CNO), 123 (11), 118 (11), 89 (20), 63 (10).

3-(4-Methoxyphenyl)-4-phenylfurazan (28). This compound was prepared from 4-methoxybenzyl phenyl ketone *via* 4-methoxybenzil-7-oxime, 4-methoxybenzil dioxime and (4-methoxy-phenyl)phenylfuroxans as outlined in Scheme 3, using the procedures described above for 3-(4-chlorophenyl)-4-phenylfurazan **27**. The product (92%) was isolated as white crystals, mp 78-79 °C (lit.[37] 84 °C); ^{13}C NMR ($CDCl_3$): δ 152.8, 152.6 (furazan ring C), 161.5, 130.1, 129,6 129.1, 128.7, 125.9, 117.7, 114.3 (ArC), 55.2 (OCH_3); MS (EI): *m/z* (%) 252 (M^+, 100), 149 ($MeOC_6H_4CNO^+$).

Preparation of 5-butyl-3-(4-methoxyphenyl)-2-isoxazoline (23). 4-Methoxybenzo-hydroximoyl chloride (2.0 g, 10.8 mmol) was added to a mixture of hex-1-ene (10 ml) and dry xylene (70 ml), and the mixture heated at reflux (~ 140 °C). After 48 h evolution of HCl had ceased and the solvent and excess hexene were removed *in vacuo* to leave the product (2.4 g, 95%) as a brown solid, which was dissolved in chloroform and treated with activated charcoal. Evaporation of the solvent afforded 5-butyl-3-(4-methoxyphenyl)-2-isoxazoline **23** as white platelets (from EtOH/H_2O); mp 82-84 °C; IR (Nujol): ν 1598, 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.60 (d, J = 10 Hz, 2H, ArH), 6.89 (d, J 10 = Hz, 2H, ArH), 4.65 (m, 1H, H-5), 3.80 (s, 1H, OCH_3), 3.35 (dd, $J_{4a,4b}$ = 16, $J_{4a,5}$ = 10 Hz, 1H, H-4a), 2.90 (dd, $J_{4,b4a}$ = 16, $J_{4b,5}$ = 8 Hz, 1H, H-4b), 0.8-1.9 (m, 9H, CH_2/CH_3); ^{13}C NMR ($CDCl_3$): δ 155.8 (C-3), 160.7, 127.8, 122.3, 113.8 (ArC), 81.0 (C-5), 55.1 (OCH_3), 40.0 (C-4), 34.8, 27.5, 22.3 (CH_2), 13.8 (CH_3). Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0% Found: C, 71.9; H, 8.3; N, 6.9%

Liquid-phase thermolysis of furazans

Thermolysis of 3,4-diphenylfurazan (5) in tetradec-1-ene. A mixture of 3,4-diphenylfurazan **5** (0.22 g, 0.90 mmol) and tetradec-1-ene (15 ml) was heated at reflux (251 °C), under dry nitrogen, in the presence of *o*-terphenyl as an internal standard, and the reaction mixture monitored by HPLC. After 6 h it became evident the product (isoxazoline **14**) had begun to decompose and the reaction was stopped at this point. The excess tetradecene was removed by vacuum distillation (95 °C/0.5 mm Hg). Chromatography of the residue afforded 5-dodecyl-3-phenyl-2-isoxazoline **14** as a white crystalline solid (0.21 g, 75%); mp and mixed mp 69-70 °C (lit.[3a] 69-70 °C). HPLC analysis of the reaction mixture of a repeated experiment under the same conditions gave 5-dodecyl-3-phenyl-2-isoxazoline **14** (83%) and unreacted furazan **5** (15%).

Thermolysis of 3,4-tetramethylenefurazan (13) in 4-methoxybenzonitrile. 3,4-Tetramethylenefurazan **13** (300 mg, 2.34 mmol) and 4-methoxybenzonitrile (1.50 g, 11.28

mmol) were heated at reflux (240 °C) under dry nitrogen for 2 h, by which time TLC (silica, toluene) showed that all the furazan had been consumed. The excess 4-methoxybenzonitrile was removed by vacuum distillation and the residue purified by chromatography (silica, CH_2Cl_2) and treatment with activated charcoal to afford 3-(4-cyanobutyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole **17** (430 mg, 72%) as a white solid; recyrstallisation from chloroform-pentane yielded white needles, mp 65-67 °C; ^{1}H NMR ($CDCl_3$): δ 6.9-8.0 (m, 4H, ArH), 3.87 (s, 3H, OCH_3), 2.84 (t, J = 6 Hz, 2H, CH_2), 2.42 (t, J = 6 Hz, 2H, CH_2), 1.6-2.2 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$): δ 175.3, 169.9 (oxadiazole ring C), 163.0, 129.8, 119.1, 114.4 (ArC), 116.6 (CN), 53.0 (OCH_3), 25.7, 25.0, 24.6, 16.7 (CH_2). Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.4; H, 5.8; N, 16.3% Found: C, 65.7; H, 5.9; N, 16.3%

Thermolysis of 3,4-decamethylenefurazan (15) in 4-methoxybenzonitrile. 3,4-Decamethylenefurazan **13** (210 mg, 0.94 mmol) and 4-methoxybenzonitrile (1.0 g, 9.26 mmol) were heated at reflux (240 °C) under dry nitrogen for 3 h, by which time TLC (silica, CH_2Cl_2) showed that all the furazan had been consumed. The excess 4-methoxybenzonitrile was removed by vacuum distillation and the residue purified by chromatography (silica, CH_2Cl_2) to afford the 3-(10-cyanodecyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole **19** (210 mg, 67%) as a white solid; recyrstallisation from diethyl ether-hexane yielded white platelets; mp 74-75 °C; ^{1}H NMR ($CDCl_3$): δ 6.9-8.1 (m,, 4H, ArH), 3.85 (s, 3H, OCH_3), 2.78 (t, J = 6 Hz, 2H, CH_2), 2.28 (t, J = 6 Hz, 2H, CH_2), 1.2-2.2 (m, 16H, CH_2); ^{13}C NMR ($CDCl_3$): δ 175.3, 171.0 (oxadiazole ring C), 162.9, 129.8, 119.6, 114.4 (ArC), 116.8 (CN), 53.3 (OCH_3), 29.1, 28.9, 28.5, 26.9, 26.0, 25.2, 16.9 (CH_2). Anal. Calcd. for $C_{20}H_{27}N_3O_2$: C, 70.4; H, 7.9; N, 12.3% Found: C, 70.5; H, 8.0; N, 12.2%

Flash vacuum pyrolysis (FVP) of furazans

General procedure

The furazan was volatalised under rotary pump pressure through an electrically-heated silica tube (36 x 2.0 cm), arranged horizontally and packed with 6 cm lengths of silica tube (7 mm o.d., 5 mm i.d.). The pyrolysate was condensed into a cold trap (*ca.* –196 °C) containing an excess of the dipolarophile, and a further layer of the dipolarophile was then added. The reaction mixture was allowed to warm to room temperature under a nitrogen atmosphere and the entire pyrolysate dissolved in solvent and removed from the trap. The results are summarised in Table 1.

FVP of 3,4-diphenylfurazan (5). 3,4-Diphenylfurazan **5** (400 mg, 1.8 mmol) was pyrolysed at 600 °C, the pyrolysate condensed onto hex-1-ene (4.0 g, 48 mmol) and the reaction mixture allowed to warm to room temperature under dry nitrogen. The excess hexene was removed *in vacuo* and the residue vacuum distilled to give a colourless liquid, benzonitrile (170 mg, 92%), bp 40 °C/0.05 mmHg (lit.[38] 191 °C/760 mmHg); the IR spectrum was indistinguishable from that of an authentic sample. Sublimation of the residue (75 °C at 0.05 mmHg) afforded 5-butyl-3-phenyl-2-isoxazoline **20** (350 mg, 96%); mp 40-41 °C (lit.[39] 41 °C); ^{1}H NMR ($CDCl_3$): δ 7.2-7.7 (m, 5H, ArH), 4.75 (m, 1H, H-5), 3.38 (dd, $J_{4a,4b}$ = 16, $J_{4ab,5}$ 10 Hz, 1H, H-4a), 2.93 (dd, $J_{4b,4a}$ = 16, $J_{4b,5}$ = 8 Hz, 1H, H-4b), 0.8-1.9 (m, 9H, CH_2/CH_3); ^{13}C NMR ($CDCl_3$): δ 156.1 (C-3), 129.6,

128.4, 126.3 (ArC), 81.2 (C-5), 39.7 (C-3), 34.8, 27.4, 22.3 (CH_2), 13.7 (CH_3). Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9% Found: C, 76.7; H, 8.4; N, 6.7%

FVP of 3,4-bis(4-methoxyphenyl)furazan (21). 3,4-Bis(4-methoxyphenyl)furazan **21** (300 mg, 1.1 mmol) was pyrolysed at 550 °C, the pyrolysate condensed onto hex-1-ene (5 ml) and the reaction mixture allowed to warm to room temperature under dry nitrogen. The excess hex-1-ene was removed *in vacuo* and the residue vacuum distilled to give 4-methoxybenzonitrile (140 mg, 96%); bp 95 °C/0.6 mmHg, mp and mixed mp 60-61 °C (lit.[38] 60-61 °C); chromatography (alumina, diethyl ether/hexane) of the residue afforded 5-butyl-3-(4-methoxyphenyl-2-isoxazoline **23** (230 mg, 93%); mp and mixed mp 84-85 °C. The IR and NMR spectra were indistinguishable from those of an authentic sample, *vide supra*.

FVP of 3,4-bis(4-methylphenyl)furazan (22). 3,4-Bis(4-methylphenyl)furazan **22** (300 mg, 1.2 mmol) was pyrolysed at 600 °C, the pyrolysate condensed onto hex-1-ene (5 ml) and the reaction mixture allowed to warm to room temperature under dry nitrogen. The excess hexene was removed *in vacuo* and the residue vacuum distilled to give 4-methylbenzonitrile (130 mg, 93%); mp and mixed mp 26-27 °C (lit.[38] 26-28 °C); chromatography (alumina, diethyl ether/hexane) of the residue afforded 5-butyl-3-(4-methylphenyl)-2-isoxazoline **24** (260 mg, 96%) as white platelets, mp 42-44 °C; ^{1}H NMR ($CDCl_3$): δ 7.42 (d, J = 10 Hz, 2H, ArH), 7.08 (d, J = 10 Hz, 2H, ArH), 4.65 (m, 1H, H-5), 3.24 (dd, $J_{4a,4b}$ = 16, $J_{4a,5}$ 10 Hz, 1H, H-4a), 2.78 (dd, $J_{4,b4a}$ 16, $J_{4b,5}$ = 8 Hz, 1H, H-4b), 2.33 (s, 3H, CH_3), 0.6-1.8 (m, 9H, CH_2/CH_3); ^{13}C NMR ($CDCl_3$): δ 156.2 (C-3), 139.9, 129.2, 127.0, 126.4 (ArC), 81.1 (C-5), 39.9 (C-4), 34.9, 27.5, 22.4 (CH_2), 21.2, 13.8 (CH_3). Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.8; N, 6.5% Found: C, 77.3; H, 8.7; N, 6.4%

FVP of 3,4-dimethylfurazan (12). 3,4-Dimethylfurazan **12** (500 mg, 5.12 mmol) was pyrolysed at 600 °C, the pyrolysate condensed onto hex-1-ene and the reaction mixture allowed to warm to room temperature under dry nitrogen. GC analysis on 10% of the reaction mixture, using freshly distilled propanonitrile as internal standard, showed the presence of acetonitrile (74%). The excess hexene was removed *in vacuo* and the residue vacuum distilled to give unreacted furazan **12** (90 mg, 18%) and 5-butyl-3-methyl-2-isoxazoline **25** (430 mg, 66%); bp 62 °C/0.05 mmHg; ^{1}H NMR ($CDCl_3$): δ 4.4-4.6 (m, 1H, H-5), 2.94 (ddq, $J_{4a,4b}$ = 16.8, $J_{4a,5}$ = 10.2, $J_{4a,Me}$ = 1.0 Hz, 1H, H-4a), 2.52 (ddq, $J_{4b,4a}$ = 16.8, $J_{4b,5}$ = 8.2, $J_{4b,Me}$ = 1.0 Hz, 1H, H-4b), 1.96 (t, $J_{Me,4ab}$ = 1.0 Hz, 3H, Me), 1.3-1.7 (m, 6H, CH_2), 0.88 (t, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.5 (C-3), 79.8 (C-5), 41.6 (C-4), 34.8, 27.4, 22.2 (CH_2), 13.6, 12.1 (CH_3); HRMS (EI): Calcd. for $C_8H_{15}NO$: M 141.115358. Found: m/z 141.114942.

FVP of 3-methyl-4-phenylfurazan (26). 3-Methyl-4-phenylfurazan **26** (530 mg, 2.68 mmol) was pyrolysed at 650 °C, the pyrolysate condensed onto hex-1-ene, and the reaction mixture allowed to warm to room temperature under dry nitrogen. GC analysis using 4-methylbenzonitrile as internal standard gave benzonitrile (0.94 mmol, 35%), 5-butyl-3-methyl-2-isoxazoline **25** (0.94 mmol, 35%) and 5-butyl-3-phenyl-2-isoxazoline **20** (1.17 mmol, 65%). Acetonitrile was not detected under the GC conditions used.

FVP of 3-(4-chlorophenyl)-4-phenylfurazan (27). 3-(4-Chlorophenyl)-4-phenylfurazan **27** (210 mg, 0.84 mmol) was pyrolysed at 600 °C, the pyrolysate condensed onto hex-1-ene and the

reaction mixture allowed to warm to room temperature under dry nitrogen. GC analysis using diphenyl ether as internal standard gave benzonitrile (0.41 mmol, 49%), 4-chlorobenzonitrile (0.43 mmol, 51%), 5-butyl-3-phenyl-2-isoxazoline **20** (0.39 mmol, 47%), and 5-butyl-3-(4-chlorophenyl)-2-isoxazoline **29** (0.39 mmol, 47%).

FVP of 3-(4-methoxyphenyl)-4-phenylfurazan (28). 3-(4-Methoxyphenyl)-4-phenylfurazan **28** (220 mg, 0.88 mmol) was pyrolysed at 600 °C, the pyrolysate condensed onto hex-1-ene and the reaction mixture allowed to warm to room temperature under dry nitrogen. GC analysis using diphenyl ether as internal standard gave benzonitrile (0.46 mmol, 52%), 4-methoxybenzonitrile (0.38 mmol, 43%), 5-butyl-3-phenyl-2-isoxazoline **20** (0.35 mmol, 40%), and 5-butyl-3-(4-methoxyphenyl)-2-isoxazoline **23** (0.41 mmol, 47%).

FVP of 3,4-tetramethylenefurazan (13). 3,4-Tetramethylenefurazan **13** (430 mg, 4.3 mmol) was pyrolysed at 650 °C, the pyrolysate condensed onto an excess of dry sulfur dioxide. Dry toluene was added and the mixture allowed to warm to room temperature under dry nitrogen. After heating at reflux for 3 h, the solution was concentrated and the presence of 4-cyanobutyl isocyanate **35** established by IR spectroscopy [ν (toluene) 2265, 2160 cm^{-1} (N=C=O)]. An excess of freshly distilled aniline was added and the mixture heated at reflux for a further 30 min. The solvent and unreacted aniline were removed *in vacuo* and the resulting brown solid treated with activated charcoal to afford *N*-(4-cyanobutyl)-*N′*-phenyl urea **36** (from toluene) (450 mg, 45%); mp 130-132 °C; HRMS (EI): Calcd. for $C_{12}H_{15}N_3O$: *M* 217.121505. Found: *m/z* 217.122252.

Preparation of 3,5-Diphenyl-1,2,4-oxadiazole (34a). Benzil dioxime (5.0 g, 20 mmol) was suspended in dry dichloromethane (30 ml) and thionyl chloride (2.4 g, 20 mmol) added slowly. The mixture was stirred at room temperature for 60 h and then poured onto ice and extracted with dichloromethane. Concentration of the solution afforded a yellow solid, which was purified by chromatography (alumina, Et_2O/hexane) to give **34a** (3.8 g, 85%) as white needles (from ethanol); mp 97-98 °C, (lit.[40] 108 °C); ^{13}C NMR ($CDCl_3$): δ 175.6, 168.9 (oxadiazole ring C), 132.6, 131.1, 129.0, 128.8, 128.1, 127.5, 127.0, 124.3 (ArC); MS (EI): *m/z* (%) 222 (M^+, 100), 119 ($PhCNO^+$).

Thermolysis of 3,5-diphenyl-1,2,4-oxadiazole (38a) in tetradec-1-ene. A mixture of 3,5-diphenyl-1,2,4-oxadiazole **38a** (0.50 g, 2.25 mmol) and tetradec-1-ene (15 ml) was heated at reflux (251 °C) under dry nitrogen for 12h. TLC analysis (alumina, Et_2O/hexane) established that no benzonitrile or isoxazoline **14** were present in the reaction mixture; the only identifiable component was unreacted starting material.

FVP of of 3,5-diphenyl-1,2,4-oxadiazole (38a). 3,5-Diphenyl-1,2,4-oxadiazole **38a** (700 mg, 3.15 mmol) was pyrolysed at 600 °C, the products being condensed onto hex-1-ene, as described above for furazans. HPLC analysis indicated only the presence of the starting material. The excess hexene was evaporated to leave a solid that was identified as 3,5-diphenyl-1,2,4-oxadiazole **38a**, mp and mixed mp 107-108 °C (lit.[40] 108 °C). The IR spectrum was

indistinguishable from that of an authentic sample. A repeat experiment carried out at 700 °C afforded a multicomponent mixture from which the starting material was isolated in 54% yield. 3,5-Diphenyl-1,2,4-oxadiazole **38a** (500 mg, 2.25 mmol) was also pyrolysed at 800 °C, the products being condensed onto dry methanol. HPLC analysis indicated a complex mixture of at least 10 products and that all the starting material had been consumed. By using authentic samples of methyl phenylcarbamate ($PhNHCO_2Me$) and *N*-benzoyl-*O*-methylhydroxylamine (PhCONHOMe), the expected products from the reaction of methanol with phenyl isocyanate and benzoylnitrene, it was established that the phenyl isocyanate-derived product was present in the reaction mixture; there was no evidence for the nitrene-derived methylhydroxylamine. GC-MS analysis showed that the main components were benzonitrile (*m/z* 103, M^+), methyl phenylcarbamate (*m/z* 151, M^+) and biphenyl (*m/z* 154, M^+).

Acknowledgements

We are grateful to the EPSRC for research and maintenance (W.R.M.) grants. Our thanks are due to H. McNab for valuable discussions and access to FVP facilities.

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