Steric acceleration of intramolecular oxime and hydrazone cycloadditions

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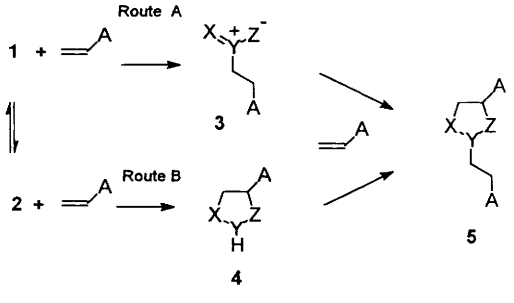
Selected conformational constraints, achieved by the incorporation of *ortho*-substituents in 2-substituted 1-allyloxybenzenes, where the substituent is a 1,3-dipole or its tautomeric precursor, as in oximes, can be employed to accelerate the 1,3-dipolar cycloaddition process. Some evidence that hydrazones preferentially react with the alkene group by prior oxidation to the corresponding nitrilimine species is presented.

The ability to optimise the spatial orientation of reactant molecules to favour their mutual approach and reaction is an attractive prospect. In nature, enzymes achieve their characteristically impressive reaction efficiencies both by the sequestration of the respective reactant molecules in close proximity[1,2] prior to reaction and by limiting the molecular freedom of the reactants such that the key interacting orbitals are 'steered' along a discrete reaction path.[3] In recent work we have described the steric acceleration of intramolecular 1,3-dipolar cycloadditions of azides[4] and 3-oxidopyridinium betaines.[5] In the former case reaction rates may be greatly enhanced and, in the latter case, reactions that otherwise do not occur can be promoted. This paper describes some intramolecular 1,3-dipolar cycloaddition reactions of certain oximes and hydrazones that illustrate such steric control by the incorporation of buttressing groups. The conformational mobility of the reactive moieties is sufficiently impeded to promote their mutual approach and intramolecular reaction.

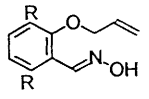
Oximes and hydrazones belong to a group of compounds that can undergo a 1,2-prototropic shift to generate a 1,3-dipolar species, as in the equilibrium **1** ⇌ **2** [eqn. (1)]. With

$$X = Y - ZH \rightleftharpoons X = Y^{+}H - Z^{-} \qquad (1)$$
1 **2**

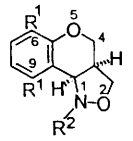
activated (conjugated) dipolarophiles, studies on the reactions of the species **2** may be masked by a competing sequence of reactions where the tautomer **1** initially undergoes a Michael reaction to form another 1,3-dipolar species, **3** (Scheme 1), followed by cycloaddition with a further molecule of the dipolarophile to give the product **5**.[6] Since the product **5** may



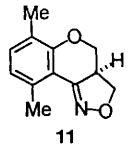
Scheme 1



6 R = H
7 R = Me



8 $R^1 = R^2 = H$
9 R^1 = Me, R^2 = H
10 R^1 = Me, R^2 = COMe



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also be formed from the tautomer **2** by an initial 1,3-dipolar cycloaddition, to give **4**, which may then undergo Michael addition to give the same product(s) **5**,[7] a dichotomy arises and considerable efforts have been made to distinguish between the major pathways, route A or B.

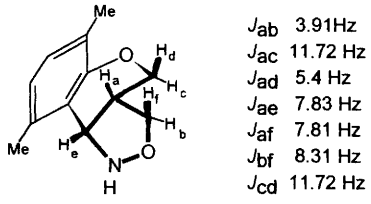
One approach to help unravel this dichotomy has been to use unactivated dipolarophiles, *e.g.* simple olefins. However, the unfavourable orbital interactions in such reactions generally preclude the use of intermolecular reactions and chemists have resorted to intramolecular examples.[8] This area seemed ideal in order to test our success at using steric buttressing to enhance reaction rates.

The oxime **6**, readily obtained from salicylaldehyde, has been reported by Oppolzer and Keller to give low yields of the isoxazolidine cycloadduct **8** by heating in toluene at 110 °C for 20 h,[9] whilst both Grigg *et al.* [10] and ourselves showed no change after extensive heating at temperatures ranging from 80 to 140 °C. In complete contrast, the 3,6-dimethyl-substituted oxime **7** was completely converted into the single isoxazolidine **9** when heated in benzene at 80 °C for 48 h. No evidence for any competing reactions, such as Claisen rearrangements[11] could be observed. The ^{1}H NMR spectrum of **9** showed loss of the allylic group and the presence of the tightly coupled ring protons. The *cis*-fusion between the isoxazolidine ring and the pyran system was indicated by the coupling constant of 7.8 Hz

between the ring protons H_a and H_e. Inspection of molecular models indicated two possible conformations of the benzopyran ring but the coupling constants between H_a and H_c and H_d indicated that the preferred conformation of the pyran ring is a half-chair with H_c and H_a in an antiperiplanar relationship (J 11.72 Hz), see Fig. 1 [12]

Recently, Grigg's group, in following up earlier work of Shimizu,[13] has reported similar steric effects either when using the naphthalene-1-carbaldehyde oxime **12**, which reacts cleanly to give the cycloadduct **14**, whereas its isomer **13** is relatively inert, or systems using the buttressing effect of an *o*-methoxy group.[14]

The isoxazolidine **9** could be acetylated, with acetic anhydride in pyridine, to produce the acetamide **10**. Furthermore, dehydrogenation, by use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), gave the dihydroisoxazole **11**. None of the dihydroisoxazole **11** was detected in the thermal cyclisation products from the oxime **7**.

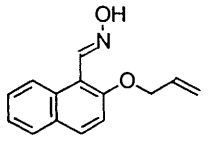


J_{ab} 3.91Hz
J_{ac} 11.72 Hz
J_{ad} 5.4 Hz
J_{ae} 7.83 Hz
J_{af} 7.81 Hz
J_{bf} 8.31 Hz
J_{cd} 11.72 Hz

Fig. 1 Observed ^1H–^1H coupling constants in **9**

Compound **11** could also be obtained, in modest yield, by initial oxidation of the starting oxime **7** with DDQ at room temperature. Presumably this reaction involves initial oxidation of the oxime to the nitrile oxide, followed by a rapid, intramolecular cycloaddition. A higher yield of the dihydroisoxazole **11** was obtained by the normal oxidation of the oxime **7** using *N*-chlorosuccinimide followed by treatment with triethylamine.[15,16]

Having illustrated the steric buttressing by the adjacent methyl groups in the oxime **7**, attention was turned to the corresponding acceleration of cycloadditions with hydrazones. Examples of these reacting smoothly *via* their prototropic tautomers are sketchy. Hydrazones were first reported by Hesse to undergo 1,3-dipolar-like cycloadditions to multiple bonds under acidic conditions[17] and these have been confirmed by Shimizu *et al.*[18] and LeFevre *et al.*[19] It was suggested that the protonated forms of the hydrazones are involved as no cycloaddition products were observed after refluxing in ethanol in the absence of the acid. In contrast, Grigg has reported[20] that when the phenylhydrazone **15** is heated at 140 °C for 6 days it undergoes a low (18%) conversion into a cyclic hydrazone product **21** and this was assumed to be a result of initial



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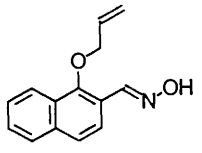

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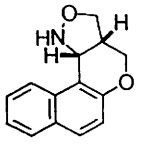

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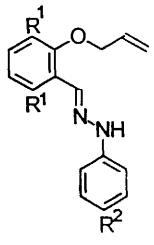
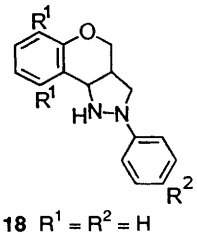
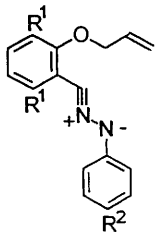


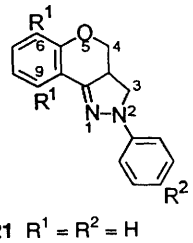
15 $R^1 = R^2 = H$
16 $R^1 = H$, $R^2 = NO_2$
17 $R^1 = Me$, $R^2 = NO_2$



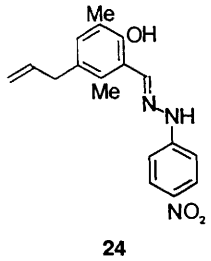
18 $R^1 = R^2 = H$
19 $R^1 = H$, $R^2 = NO_2$
20 $R^1 = Me$, $R^2 = NO_2$



25 $R^1 = H$, $R^2 = NO_2$
26 $R^1 = Me$, $R^2 = NO_2$



21 $R^1 = R^2 = H$
22 $R^1 = H$, $R^2 = NO_2$
23 $R^1 = Me$, $R^2 = NO_2$



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cycloaddition with formation of the 1,3-dipolar adduct **18** followed by its rapid aerial oxidation; in this case none of the initial cycloadduct **18** was actually isolated.

We have re-investigated the latter reaction, using, instead, the less readily oxidised 4-nitrophenylhydrazone **16**. It was considered that the presence of the nitro group would also make the hydrazone N–H group more acidic and hence more readily able to undergo tautomerism of the type **1** ⇌ **2**. Heating of the hydrazone **16** at 140 °C under nitrogen for 2 days led to its gradual degradation with the formation of a complex array of products. None of the expected cycloadduct **19**, or its oxidised product **22**, could be isolated. The sterically hindered hydrazone **17** was then prepared and heated under identical conditions. In this case a much cleaner reaction ensued with the formation of two new products. The minor product, isolated in 30% yield, proved to be the oxidised benzopyran cycloadduct **23**, although, again, none of the presumed intermediate **20** was detected. The major product, isolated in 50% yield, was found to be the Claisen rearrangement product **24**.

The formation of the cycloadduct **23** attests to the power of the buttressing effect of the two aromatic methyl groups but the fact that the Claisen rearrangement competes supports the existing evidence that cycloaddition of the hydrazone tautomer to unactivated olefin bonds is not electronically favourable.

The relatively low yields of cycloaddition observed and the fact that none of the expected hydrazine cycloadduct was isolated but only the oxidised product, prompted concern that an alternative process was involved, *viz.* that aerial oxidation to the nitrile imine *preceded* cycloaddition, since nitrile imines are known, active 1,3-dipolar species.[21] Furthermore hydrazones, in particular unsubstituted phenylhydrazones, are known to be readily oxidised.[17,22]

In order to explore this possibility, the hydrazones **16** and **17** were oxidised *at room temperature* and their reactions observed. Of several oxidants examined, either DDQ (as a mimic for aerial dehydrogenation) or *N*-chlorosuccinimide (NCS), followed by treatment with triethylamine, proved to be acceptable. With the use of 1 equivalent of DDQ in dry toluene under nitrogen at room temperature for 16 h, the buttressed hydrazone **17** disappeared to give, in 30% isolated yield, the cycloadduct **23**; use of NCS improved the yield to 77%. In contrast, the unbuttressed hydrazone **16**, with DDQ, did not produce any of the corresponding cycloadduct **22**, whilst use of NCS afforded a low yield (16%) of this.[23] The mild conditions used for this oxidation supports prior oxidation to the nitrile imines **25** and **26** but that, whereas buttressing in the intermediate **26** holds this in the correct orientation for intramolecular cycloaddition, the absence of these groups in the intermediate **25** allows other reaction paths to predominate.

The results of the DDQ and NCS oxidations strongly support the hypothesis that oxidation precedes cycloaddition and that, for the hydrazones, cycloaddition across the isolated olefinic bond, by the pathway involving initial tautomerism to the 1,3-dipole (see Scheme 1,), followed by rapid oxidation, is less likely.

The results from both the oxime and hydrazone series illustrate the powerful effect of buttresses as a useful tool in aiding cycloadditions.

Experimental

Mps were obtained on a Kofler hot-stage apparatus and are uncorrected. Mass spectra were obtained on an AEI MS902 spectrometer, infrared spectra on a PE 1420 spectrophotometer as either thin films or KBr discs. ^{1}H NMR spectra were obtained on either a JEOL FX200 or a Varian CFT20 instrument using $CDCl_3$ solutions with tetramethylsilane as internal reference unless otherwise indicated. Coupling constants are given in Hz. High resolution ^{1}H NMR studies were conducted by the SERC High Resolution NMR Service, University of Warwick and accurate mass and FAB measurements were conducted by the SERC Mass Spectrometry Service, University of Swansea. Microanalytical determinations were carried out by MEDAC Ltd, Brunel University. All solvents were distilled before use using literature procedures.[24] Thin layer chromatography was carried out on 0.25 mm GF60A silica gel plates and column chromatography utilised Kieselgel 60. Solvent ratios are in volumes prior to mixing. Generally, reaction solvents were removed, after drying over anhydrous sodium sulfate, under reduced pressure using a rotary evaporator. Light petroleum refers to the fraction of boiling range 40–60 °C. Ether refers to diethyl ether.

2-Allyloxy-3,6-dimethylbenzaldehyde oxime 7

2-Allyloxy-3,6-dimethylbenzaldehyde[5] (0.5 g, 2.6 mmol) was added to aqueous ethanolic hydroxylamine hydrochloride (0.29 g, 4.17 mmol in 10 cm^3) and then sodium hydroxide (0.53 g, 13 mmol) was added with stirring. The solution was heated to reflux for 15 min and then allowed to cool and poured into water (50 cm^3). The mixture was acidified with conc. HCl (2 cm^3) and then extracted with dichloromethane (2 × 50 cm^3). The organic extract was dried and the solvent removed under reduced pressure to give a yellow oil. Column chromatography, using dichloromethane as eluent, afforded the *title compound* as yellow crystals (0.31 g, 57%) mp 50 °C; δ_H(80 MHz) 2.24 (3 H, s), 2.41 (3 H, s), 4.23–4.33 (2 H, m), 5.43–5.48 (2 H, m), 5.82–6.23 (1 H, m), 6.84 (1 H, d, *J* 7.4), 7.05 (1 H, d, *J* 7.4), 8.43 (1 H, s) and 8.51 (1 H, br s); *m/z* 205 (M^+) (Found: C, 70.2; H, 7.3; N, 6.6. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%).

2-Allyloxybenzaldehyde oxime[15] 6

This was prepared as above to afford the known oxime **6** as a colourless oil (50%) (Found: C, 67.3; H, 6.3; N, 7.7. Calc. for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9%).

Attempted formation of 1,3a,4,9b-tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole 8

The oxime (50 mg) was dissolved in [$^2H_6$] benzene in a sealed 2.5 mm NMR tube after careful degassing. The solution was heated at 80 °C for several days and the reaction was monitored by ^{1}H NMR spectroscopy. After 5 days little reaction was observed. After work-up (preparative TLC) the major compound isolated (40 mg, 80%) was unchanged starting material. None of the title compound[15] was observed.

6,9-Dimethyl-1,3a,4,9b-tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]-isoxazole 9

The oxime **7** (50 mg) was dissolved in [$^2H_6$]benzene (1 cm^3) and the solution sealed *in vacuo* in a 2.5 mm NMR tube. The solution was heated at 80 °C and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. After 48 h all the starting material had disappeared. Following work-up by preparative TLC (using chloroform as solvent) the *title cycloadduct* was isolated as pale yellow crystals (45 mg, 90%), mp 80–81 °C; δ_H(200 MHz) 2.18 (3 H, s), 2.42 (3 H, s), 2.93 (H_a, m), 3.68 (H_b, dd, *J* 8.31, 3.91), 3.71 (H_c, t, *J* 11.72), 4.20 (H_d, dd, *J* 11.72, 5.4), 4.32 (H_e, br d, *J* 7.83), 4.34 (H_f, dd, *J* 8.31, 7.81), 5.00 (H_g, br s), 6.72 (H_h, d, *J* 7.6) and 7.00 (H_i, d, *J* 7.6) (Found: M^+, 205.1103; C, 69.5; H, 7.2; N, 6.45%. $C_{12}H_{15}NO_2$ requires M^+, 205.1103; C, 70.2; H, 7.4; N, 6.8%).

The cycloadduct was further characterised as its N-*acetyl derivative* **10**, prepared by acetylation with acetic anhydride and pyridine at room temperature for 12 h. The acetyl derivative was isolated by extraction into chloroform and then separation by preparative TLC, using chloroform as solvent. The acetyl derivative was isolated as a pale yellow oil (67%); δ_H(200 MHz)

2.15 (3 H, s), 2.32 (3 H, s) 3.06–3.19 (1 H, m), 4.02 (1 H, dd, *J* 11.72, 2.44), 4.13 (1 H, dd, *J* 9.77, 7.81), 4.25 (1 H, dd, *J* 11.72, 1.95), 4.29 (1 H, dd, *J* 7.81, 5.13), 5.86 (1 H, d, *J* 8.31), 6.72 (1 H, d, *J* 7.81) and 6.95 (1 H, d, *J* 7.81) (Found: M^+, 247.1208; $C_{14}H_{17}NO_3$ requires M^+, 247.1208).

Dehydrogenation of the isoxazolidine 9

The isoxazolidine (140 mg, 0.68 mmol) in toluene (6 cm^3) was stirred with DDQ (160 mg, 1.1 equiv.) at room temperature for 16 h. During this time a dark red precipitate formed. The mixture was filtered, the solids washed with some toluene and the filtrate evaporated to dryness and then chromatographed through silica gel using 1:1 $CHCl_3$–light petroleum as eluent. The major fraction obtained was the 6,9-*dimethyl*-3a,4-*dihydro*-3H-[1]*benzopyran*[4,3-c]*isoxazole* **11** as a pale yellow solid (20 mg, 14%), mp 84 °C; δ_H 2.18 (3 H, s), 2.55 (3 H, s), 3.81–4.13 (3 H, m), 4.62–4.74 (2 H, m), 6.76 (1 H, d, *J* 7.81) and 7.07 (1 H, d, *J* 7.81) [Found: M^+, 203.094. $C_{12}H_{13}NO_3$ requires M^+, 203.094(6)].

Dehydrogenation of the oxime 7

(a) With DDO. The dimethylbenzaldehyde oxime (2.0 g, 9.7 mmol) was dissolved in toluene (50 cm^3) with DDQ (2.21 g, 1 equiv.) and the solution stirred for 2 days at room temperature. The precipitate was removed by filtration and the solvent removed from the filtrate to give a brown gum. The product was chromatographed through silica gel, using 1:1 chloroform–light petroleum as eluent, to give the dihydroisoxazole **11** (0.1 g, 5%), the properties of which were identical with those described above.

(b) With NCS. The dimethylbenzaldehyde oxime (0.31 g, 1.5 mmol) was dissolved in carbon tetrachloride (5 cm^3) with NCS (0.2 g, 1 equiv.) and the solution stirred at room temperature for 4 h. The product mixture was filtered and triethylamine (0.15 g, 1 equiv.) was added to it. The solution was stirred at room temperature overnight and then washed with water, dried and evaporated to a small bulk. The product was chromatographed through silica gel, using 1:1 chloroform–light petroleum as solvent, to afford the dihydrooxazole **11** as a yellow crystalline solid (0.12 g, 40%), mp and mixed mp 84 °C

Formation of phenylhydrazones

To 4-nitrophenylhydrazine (0.46 g, 3 mmol) in absolute ethanol (30 cm^3) was added glacial acetic acid (0.1 cm^3) and the mixture was warmed to produce a clear solution before addition of the aromatic aldehyde. The solution was heated at reflux for 30 min, cooled and the crystalline precipitate collected by filtration before one further recrystallisation from ethanol, to give the hydrazone.

2-Allyloxybenzaldehyde 4-nitrophenylhydrazone 16. Red crystals (77%), mp 207 °C (lit.,[18] 213–215 °C); δ_H(200 MHz) 4.64–4.68 (2 H, m), 5.26–5.57 (2 H, m) 6.03–6.22 (1 H, m), 6.99–7.08 (2 H, m), 7.27 (2 H, d, *J* 9.46), 7.34–7.92 (2 H, m), 8.05 (1 H, br s), 8.16 (2 H, d, *J* 9.46) and 8.47 (1 H, s); *m/z* 297 (M^+) (Found: C, 64.6; H, 5.0; N, 14.0. $C_{16}H_{15}N_3O_3$ requires C, 64.65; H, 5.05; N, 14.1%).

2-Allyloxy-3,6-dimethylbenzaldehyde 4-nitrophenylhydrazone 17. Red crystals (60%), mp 166 °C; δ_H(200 MHz) 2.28 (3 H, s), 2.63 (3 H, s), 4.25–4.42 (2 H, m), 5.28–5.52 (2 H, m), 6.04–6.18 (1 H, m), 6.96 (1 H, d, *J* 7.81), 7.05 (1 H, d, *J* 7.81), 7.07 (2 H, d, *J* 9.27), 8.06 (1 H, br s), 8.19 (2 H, d, *J* 9.27) and 8.35 (1 H, s); *m/z* 325 (M^+) (Found: C, 66.2; H, 5.5; N, 12.7. $C_{18}H_{19}N_3O_3$ requires C, 66.45; H, 5.8; N, 12.9%).

6,9-Dimethyl-2-(4-nitrophenyl)-2,3,3a,4-tetrahydro[1]benzopyrano[4,3-*c*]pyrazole 23

The hydrazone **17** (50 mg, 0.15 mmol) was heated in xylene (5 cm^3) under an atmosphere of nitrogen for 48 h. The solvent was removed under reduced pressure and the resultant red residue purified by preparative TLC ($CHCl_3$) to afford two main bands. The less polar product proved to be the *title cycloadduct*, isolated as a red solid (15 mg, 30%), mp 206–207 °C; δ_H(200 MHz) 2.19 (3 H, s), 2.65 (3 H, s), 3.45 (1 H, dd, *J* 9.76, 10.74), 3.78–3.98 (1 H, m), 4.13 (1 H, dd, *J* 9.77, 12.45), 4.22 (1 H, dd, *J* 9.77, 10.74), 4.78 (1 H, dd, *J* 5.37, 9.76), 6.77 (1 H, d, *J* 7.81), 7.02 (2 H, d, *J* 9.28), 7.06 (1 H, d, *J* 7.81) and 8.20 (2 H, d, *J* 9.28) [Found: M^+, 323.1270. $C_{18}H_{17}N_3O_3$ requires M^+, 323.1269(9)].

The more polar band was found to be 5-*allyl*-2-*hydroxy*-3,6-*dimethylbenzaldehyde* 4-*nitrophenylhydrazone* **24**, isolated as a red crystalline solid (25 mg, 50%), mp 188 °C; ν_{max}/cm^{-1} 3150; δ_H(200 MHz) 2.27 (3 H, s), 2.31 (3 H, s), 3.31–3.36 (2 H, m), 4.76–5.08 (2 H, m), 5.84–6.00 (1 H, m), 6.98 (1 H, s), 7.00 (2 H, dd, *J* 9.28), 7.95 (1 H, br s), 8.21 (2 H, d, *J* 9.28) and 8.41 (1 H, s) (Found: M^+, 325.1476. $C_{18}H_{19}N_3O_3$ requires M^+, 325.1426).

DDQ Oxidation of hydrazones

(a) Oxidation of hydrazone 17. The hydrazone (46 mg, 0.14 mmol), dissolved in dry toluene (10 cm^3) with DDQ (52 mg, 0.23 mmol), was stirred at room temperature, under dry nitrogen, for 16 h. The precipitated solids were removed by filtration and the solvent removed under reduced pressure to produce a red oil which was separated by preparative TLC. The less polar product was the cycloadduct **23** (15 mg, 33%), the properties of which (TLC and MS) were identical with those described above. The major compound was recovered starting material (30 mg, 65%).

(b) Oxidation of the unsubstituted hydrazone 16. Under similar conditions and scale as described above for the hydrazone **17**, DDQ oxidation resulted in the formation of complex mixtures and none of the required dihydro-2*H*-pyrazole **22** was isolated.

N-Chlorosuccinimide oxidation of hydrazones

(a) Oxidation of hydrazone 17. The hydrazone (0.6 g, 2.0 mmol) in carbon tetrachloride (50 cm^3) and NCS (0.27 g, 2.0 mmol) was stirred at room temperature overnight and then the precipitated solids were filtered off and triethylamine (0.2 g, 2 mmol) was added to it. The solution was stirred at room temperature overnight, washed with water, dried and the solvent removed under reduced pressure. The residue was chromatographed through silica gel, using 1:1 chloroform–light petroleum as solvent. The major product isolated was the dihydro-2*H*-pyrazole **23** (0.46 g, 77%), mp and mixed mp 207 °C, the properties of which were identical with those of the material described above.

(b) Oxidation of hydrazone 16. The hydrazone (0.23 g, 0.8 mmol) was dissolved in carbon tetrachloride (50 cm^3) and dichloromethane (30 cm^3) with NCS (0.14 g, 1.0 mmol) and stirred for 16 h at room temperature. The mixture was filtered and triethylamine (0.15 g, 1.5 mmol) was added to the filtrate and stirred for a further 16 h. The solution was worked up as previously to afford 2-(4-*nitrophenyl*)-2,3,3a,4-*tetrahydro*[1]*benzopyrano*[4,3-c]*pyrazole* **22** (40 mg, 17%), as a brown amorphous solid, δ_H 3.39 (1 H, m), 3.74–3.97 (1 H, m), 4.06–4.23 (2 H, m), 4.67–4.87 (1 H, m) and 6.89–8.45 (8 H, m) [Found: $M^{\cdot+}$ 295.0957. $C_{16}H_{13}N_3O_3$ requires M^+, 295.0956(9)].

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