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A new route to 2-substituted perimidines based on nitrile oxide chemistry

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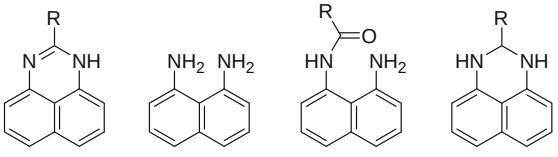
ABSTRACT

A new route to perimidines has been developed which involves reaction of a nitrile oxide with 1,8-diaminonaphthalene. Benzonitrile oxide, generated by dehydrochlorination of benzohydroximoyl chloride, and 1,8-diaminonaphthalene afforded 2-phenylperimidine. 2-Pyranosylperimidines were prepared by the same approach from pyranosyl hydroximoyl chlorides.

Perimidines (1*H*-benzo[*d*,*e*]quinazolines) (**1**) are unusual among azines in that the lone pair of a pyrrole-like nitrogen participates in the π-system of the molecule, and there is a transfer of electron density from the heterocycle to the naphthalene ring.[1] These *peri*-naphtho-fused pyrimidines therefore have the characteristics of both π-deficient and π-excessive systems.[2] They have long been used in dyestuffs[1] and in the manufacture of polyester fibres,[1] and more recently as a source of a novel carbene ligand.[3] Their biological activity has also attracted attention, for example, their potential to act as anti-fungal, anti-microbial, anti-ulcer and anti-tumour agents.[1,4,5]

Most synthetic routes[1] to 2-substituted perimidines are based on the reactions of 1,8-diaminonaphthalene (**2**, DAN) with various carbonyl compounds. Carboxylic acids,[6,7] acyl halides and anhydrides afford the mono-amide derivatives **3**, and these undergo acid-catalysed cyclisation to **1**. The corresponding reaction with aldehydes affords 2,3-dihydroperimidines **4**, which are readily dehydrogenated to **1**.[8,9] Although a wide range of 2-alkyl, aryl and heterocycle-substituted perimidines have been prepared by these approaches, there have been no examples bearing carbohydrate groups so far.



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

It has previously been shown[10–12] that the reactions of nitrile oxides with 1,2-diaminobenzene can be used to prepare 2-substituted benzimidazoles. In view of the *peri*-arrangement of the two amino groups in DAN, we reasoned that DAN and nitrile oxides should react similarly, and thus provide a new synthetic approach to 2-substituted perimidines. To test this hypothesis we attempted to prepare the known 2-phenylperimidine (**1**, R = Ph)[1,13] by reaction of DAN with benzonitrile oxide (**5**, R = Ph). As nitrile oxides are prone to dimerise to furoxans (1,2,5-oxadiazole *N*-oxides),[14] the benzonitrile oxide was generated in situ by dehydrochlorination of benzohydroximoyl chloride (**6**, R = Ph). A solution of PhCCl=NOH (1.3 mmol) and DAN (2.5 mmol) in dry EtOH was heated at reflux for 5 h. After cooling and addition of CH_2Cl_2, the reaction mixture was worked up by washing with aq K_2CO_3 and then with 4% aq $CuSO_4$, followed by chromatography; washing with aq $CuSO_4$ was found to be an effective means of removing excess DAN. The product was identified as 2-phenylperimidine (**1** R = Ph, 68%) by comparison of its physical and spectroscopic properties with those reported in the literature.[13,15] The reaction is believed to involve initial dehydrochlorination of the hydroximoyl chloride by DAN acting as a base to generate the nitrile oxide **5**, then nucleophilic addition of one of the amino groups of a second molecule of DAN to the nitrile oxide to form the mono-amidoxime **7**, followed by cyclisation with loss of hydroxylamine, as illustrated in Scheme 1.

Having established that 2-phenylperimidine could be prepared by reaction of DAN with benzonitrile oxide, the same approach was investigated using pyranosyl nitrile oxides as a route to 2-pyranosylperimidines. We have previously described a method for the synthesis of pyranosyl hydroximoyl chlorides and shown that they are an efficient source of pyranosyl nitrile oxides.[16,17] The same

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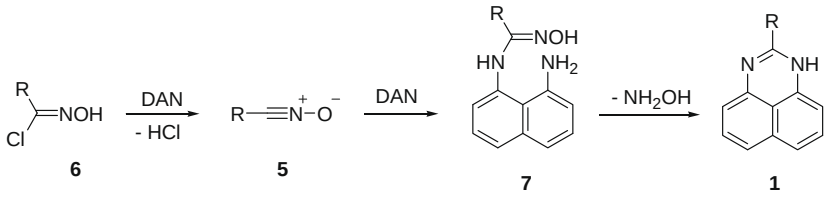
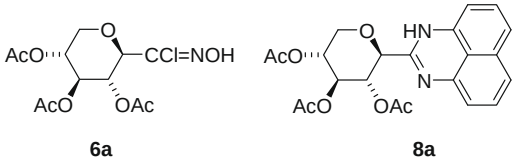
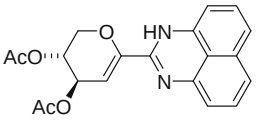


Scheme 1.

method was therefore used in the present work. In a typical experiment, a solution of D-xylose-derived hydroximoyl chloride **6a** (0.6 mmol) and DAN (1.5 mmol) in dry EtOH was heated at reflux for 5 h. Work-up of the reaction mixture as described above for **1** (R = Ph) afforded two products (Table 1, entry 1). The more polar product (silica/Et_2O, R_f = 0.27) was identified from its spectroscopic properties[18] as the target D-xylopyranosyl-perimidine **8a** (16%). In the ^1H and ^{13}C NMR spectra there were, in addition to the expected peaks associated with the tri-*O*-acetylxylopyranosyl substituent, characteristic signals for the carbons and hydrogens of the perimidine moiety;[9] in particular the δ_C values for C-2 (154.0 ppm), C-3a (145.8), C-9a (139.4) and C-9b (123.6). The less polar product (R_f = 0.35) was assigned the corresponding glycal structure **9a** (43%).[19] In contrast to **8a**, in this case only two acetate groups were detected in the NMR spectra [δ_H 2.12, 2.10 (Me); δ_C 171.0, 170.9 (C=O) and 22.3, 22.2 (Me)] and, in addition to the perimidine signals, there were distinctive ^{13}C peaks for the glycal carbons C-1′ and C-2′ at 149.2 and 99.9 ppm, respectively. In order to minimise the formation of the glycal the reaction was repeated under less forcing conditions (room temperature, 15 h). Under these conditions the major product was the target pyranosyl-perimidine **8a** (60%) with only traces of **9a** being detected (Table 1, entry 2). The formation of **9a** is attributed to facile base-catalysed elimination of acetic acid at C-1′/C-2′ of the xylopyranosyl ring yielding the glycal in which the alkene unit is conjugated to the perimidine.



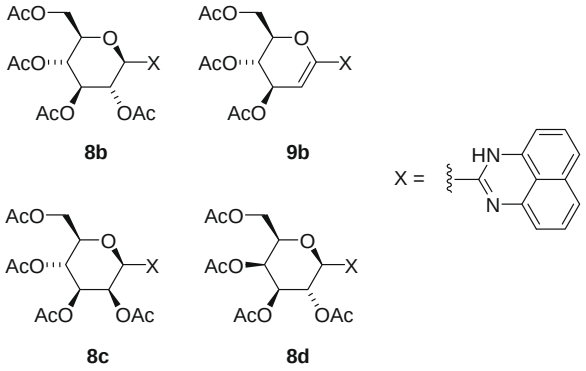


Similar results were obtained with the reaction of hydroximoyl chlorides **6b–d** prepared from D-glucose, D-mannose and D-galactose, respectively (Table 1). DAN and D-glucose-derived hydroximoyl chloride **6b**, at room temperature afforded the pyranosyl-perimidine **8b**[20] (65%), together with traces of the glycal **9b**, and in EtOH at reflux, compound **9b** was the major product (Table 1, entries 3 and 4). D-Galactopyranosyl-perimidine **8d** (69%) was prepared similarly from DAN and **6d** (Table 1, entry 7). The corresponding reaction at room temperature in the D-mannose series also yielded the expected mannopyranosyl-perimidine **8c** (55%), but in ethanol at reflux the proportion of the glycal-perimidine increased to **9b**:**8c** = 8.5:1 (Table 1, entries 5 and 6), consistent with the more favourable arrangement for the elimination of AcOH.

Table 1
Formation of perimidines **8** and **9**

Entry	RCCl=NOH	Conditions[a]	Pyranosyl-perimidine	Glycal-perimidine[b]
1	D-Xyl (**6a**)	A	**8a** (16%)	**9a** (43%)
2	D-Xyl (**6a**)	B	**8a** (60%)	**9a** (trace)
3	D-Glc (**6b**)	A	**8b** (16%)	**9b** (34%)
4	D-Glc (**6b**)	B	**8b** (65%)	**9b** (trace)
5	D-Man (**6c**)	A	**8c** (4%)	**9b** (34%)
6	D-Man (**6c**)	B	**8c** (55%)	**9b** (trace)
7	D-Gal (**6d**)	B	**8d** (69%)	—

[a] A: 5 h, reflux; B: 15 h, room temperature.
[b] 2-(2-Deoxy-1-enopyranosyl)perimidines.



In conclusion, a new and efficient route to 2-substituted perimidines has been established, based on the cyclocondensation of 1,8-diaminonaphthalene with nitrile oxides. This approach is particularly suited for the synthesis of 2-pyranosyl-perimidines from pyranosyl nitrile oxides, which can readily be generated from the corresponding hydroximoyl chlorides.

Acknowledgement

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15. Orange crystals (68%); mp 187–188 °C (lit[13] 187–188 °C); δ_H (360 MHz, $CDCl_3$); 6.65 (2H, br s, 9-H, 4-H), 7.14–7.26 (4H, m, ArH), 7.47–7.55 (3H, m, ArH), 7.85–7.90 (2H, m, ArH); δ_C (93 MHz, $CDCl_3$); 120.9, 122.9, 127.2, 129.4, 129.9, 132.2, 135.01, 136.4 (C-6a), 153.7 (C-2); *m/z* (EI) 244 (M^+); HRMS (EI) found: M^++1 244.10036, $C_{17}H_{12}N_2$ requires: M^++H 244.10005.
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18. 2-(2′,3′,4′-Tri-*O*-acetyl-D-xylopyranosyl)perimidine (**8a**).Yellow/green solid (60%); mp 169–170 °C; $[\alpha]_D^{20}$ −40 (*c* 0.2, $CHCl_3$); δ_H (360 MHz, CD_3SOCD_3); 1.93, 2.03, 2.05 (9H, s, $COCH_3$), 3.67 (1H, dd, *J* = 10.9, 11.0 Hz, 5′a-H), 4.10 (1H, dd, *J* = 5.5, 11.0 Hz, 5′e-H), 4.24 (1H, d, *J* = 9.7 Hz, 1′-H), 5.02 (1H, m, 4′-H), 5.24 (1H, dd, *J* = 9.6, 9.7 Hz, 2′-H), 5.41 (1H, dd, *J* = 9.5, 9.6 Hz, 3′-H), 6.42 (1H, dd, *J* = 0.9, 7.2 Hz, 9-H), 6.54 (1H, dd, *J* = 1.1, 7.5 Hz, 4-H), 6.99–7.17 (4H, m, H-5, H-6, H-7, H-8), 10.48 (1H, br s, NH); δ_C (93 MHz, CD_3SOCD_3); 21.8, 21.9, 22.0 ($COCH_3$), 66.8 (C-5′), 69.8, 71.2, 73.6, 78.8 (C-1′–C-4′), 104.1 (C-9), 115.0 (C-4), 119.2 (C-7), 121.1 (C-6), 123.6 (C-9b), 129.5 (C-8), 130.3 (C-5), 136.6 (C-6a), 139.4 (C-9a), 145.8 (C-3a), 154.0 (C-2), 170.7, 171.1, 171.2 ($COCH_3$); *m/z* (FAB) 427 (M^+ +1); HRMS (FAB) found: M^++1 427.15109, $C_{22}H_{22}N_2O_7$ requires: M^++H 427.15053.
19. 2-(3′,4′-Di-*O*-acetyl-D-*threo*-pento-1-enopyranosyl)perimidine (**9a**).Orange solid (43%); mp 148–149 °C; $[\alpha]_D^{20}$ −113 (*c* 0.15, $CHCl_3$); δ_H (360 MHz, CD_3SOCD_3); 2.10, 2.12 (6H, s, $COCH_3$) 4.14 (1H, m, 5′a-H), 4.48 (1H, m, 5′b-H), 5.04 (1H, m, 3′-H), 5.12 (1H, m, 4′-H), 6.02 (1H, d, *J* = 5.1 Hz, 2′-H), 6.58 (1H, dd, *J* = 0.9, 7.2 Hz, 9-H), 6.60 (1H, dd, *J* = 1.1, 7.5 Hz, 4-H), 7.47–7.51 (4H, m, H-5, H-6, H-7, H-8), 10.49 (1H, br s, NH); δ_C (93 MHz, $CD_3S(O)CD_3$); 22.2, 22.3 ($COCH_3$), 64.5, 66.2, 67.6 (C-3′–C-5′), 99.9 (C-2′), 104.7 (C-9), 115.2 (C-4), 119.5 (C-7), 121.0 (C-6), 123.8 (C-9b), 129.5 (C-8), 130.4 (C-5), 136.6 (C-6a), 139.2 (C-9a), 145.9 (C-3a), 149.2 (C-1′), 150.1 (C-2), 170.9, 171.0 ($COCH_3$); *m/z* (FAB) 367 (M^+ +1); HRMS (FAB) found: M^++1 367.12985, $C_{20}H_{18}N_2O_5$ requires: M^++H 367.12940.
20. The structure of compound **8b** has been confirmed by X-ray crystallography (Moggach, S. unpublished observations).