THE NITRATION OF SOME PHENYL-SUBSTITUTED N-HETEROCYCLES

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Abstract - The nitration of 3-methyl-1-phenylpyrazole using nitric acid and sulphuric acid at 0°C gives the p-nitrophenyl isomer as the only isolated mono nitro-product and 3-methyl-4-nitro-1-p-nitrophenylpyrazole as the dinitro-product. 3-Methyl-4-phenylpyrazole gives 3-methyl-4-p-nitrophenylpyrazole with the second nitration also occurring in the phenyl ring to give 3-methyl-4-(2',4'-dinitrophenyl)pyrazole.

2-Phenylimidazole nitrates under these conditions to give first 2-p-nitrophenyl-imidazole and then 4-nitro-2-p-nitrophenylimidazole whilst 4-phenylimidazole gives 4-nitro-5-p-nitrophenylimidazole readily even when the amount of nitric acid is limited to one equivalent and only traces of a mono nitro-product are found. 2-Phenylimidazoline gives solely the m-nitrophenyl isomer under the same conditions.

The mixed acid nitration at 0°C of 4-phenylmorpholine gives 4-m-nitrophenyl- and 4-p-nitrophenylmorpholine in the ratio of about 5:1.

INTRODUCTION

Extensive studies have been carried out on the directing properties of substituents on the *benzene ring in relation to electrophilic* substitution of the aromatic ring and of such electrophilic substitutions nitration seems to have been the most widely studied reaction[1,2]. A number of workers have used the nitration of heterocyclic compounds synthetically but comparatively little systematic work seems to have been carried out using heterocycles as the substituents on the benzene ring. For example in the 1980 review of aromatic nitration[2] less than four pages out of 350 are devoted to the nitration of phenyl heteroaromatics. Katritzky and co-workers have carried out excellent work, including kinetic studies, of some heteroaromatic systems (see for example ref.3 and refs. therein).

The nitration of phenyl N-heterocycles is of particular interest not only because of the importance of N-heterocycles in medicinal chemistry and agricultural chemistry but also because of the ability of the N-heterocyclic system to act as either an electron-releasing or as an electron-attracting substituent. One can thus observe ortho:para and meta direction in attack

upon the phenyl ring as well as substitution in the heteroaromatic ring. There are striking differences in directing effects and in ortho:para:meta ratios as the heterocyclic substituent is changed and the position of substitution is reagent dependent. Nitration reactions using nitric acid in acetic anhydride are further complicated since not only is acetoxylation and adduct formation a complicating reaction accompanying nitration, but nitronium ions can attack one position and then migrate[4,5].

We have been interested in the nitration of phenyl-N-heterocycles and have reported some of our results in this area[6,7]. This work has included the interesting observation of the production of ortho and meta nitrophenyl products, but no para nitrophenyl product, in the case of some 2- and 4-phenylpyrimidines (see also ref.8). Cohen-Fernandes and Habraken have also reported a case of predominant ortho substitution in the phenyl ring in the nitration of 1-methyl-4-phenylpyrazole[9].

We report here further results of nitration reactions of N-heterocycles.

RESULTS AND DISCUSSION

We have used two standard methods for nitration studies. In the first method the compound is nitrated at 0°C in mixed acid (concentrated sulphuric acid, d 1.80:nitric acid, d 1.50) and in the second method nitric acid in acetic anhydride is used as the nitration agent.

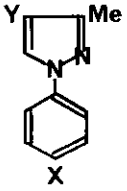
The nitration of phenylpyrazoles has been reported[10] to take place first in the para position of the phenyl ring and then in the 4-position of the pyrazole ring. We have confirmed this in the case of 3-methyl-1-phenylpyrazole (1a) which gives the p-nitrophenyl product (1b) as the only isolable product with one equivalent of nitric acid[11], and 3-methyl-4-nitro-1-p-nitrophenylpyrazole (1c) together with (1b) with excess nitric acid. Under similar conditions 3-methyl-4-phenylpyrazole (2a) gives first the p-nitrophenyl product (2b) and then the second nitration also occurs in the phenyl ring to give the 2',4'-dinitrophenyl product (2c). No ortho or meta isomers were isolated in either case. Casoni[12] has reported the mixed acid nitration of (1b) to give (1c) and there is a report[13], with no details, of the nitration of (2a) to give (2b).

The nitration of 2-phenylimidazole (3a) using one equivalent of nitric acid in sulphuric acid gave the p-nitrophenyl isomer (3b) as the only isolated product of mononitration and the use of excess nitric acid gave 4-nitro-2-p-nitrophenylimidazole (3c) as the only isomer which was isolated.

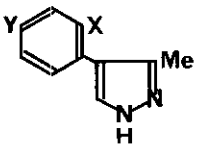
The nitration of 2-phenylimidazole has been reported[14] to be carried out by heating the nitrate salt of the base with concentrated sulphuric acid to 100°C to give the three nitrophenyl isomers in the following yields para:50%, ortho:1.5%, meta:0.2%. However, we did not observe the other isomers under our conditions and recovered the p-nitro isomer only in >96% yield.

The nitration of 4-phenylimidazole (4a) is a very much less satisfactory reaction. The use of excess nitric acid in sulphuric acid gave >90% recovered yield of 5-nitro-4-p-nitrophenylimidazole (4c) and no other products were seen on tlc. The use of one molar equivalent of nitric acid still gave the dinitro product as the predominant one with the recovery of some unchanged 4-phenylimidazole and with only a very small quantity of mono substituted product. We have so far failed to achieve a satisfactory separation of this minor product from the dinitrophenyl product. Our initial studies have shown that it may be the 4-p-nitrophenyl product and we hope to confirm this by extending tlc and hplc separation studies. However it is interesting to note the apparently ready second nitration in this case compared to that of 2-phenylimidazole. 4-Phenylimidazole nitrate has been reported[15] to give 69% of the para isomer and 25% of the ortho isomer when heated to 100°C in concentration sulphuric acid. We have obtained these two compounds by this method. The difference in the product distribution in these two methods is striking and we have not rationalised these results yet.

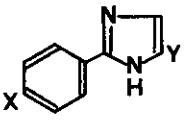
The nitration of 2-phenyl-2-imidazoline (5a) using mixed acid at 0°C gave the m-nitrophenyl product (5b) exclusively, >95% being isolated. Thus the change from the aromatic imidazole to the non-aromatic imidazoline results in a complete change from para to meta substitution in the benzene ring. The treatment of 2-phenyl-2-imidazoline nitrate with concentrated sulphuric acid at 100°C has also been reported[16] to give 2-m-nitrophenyl-2-imidazoline (isolated as the hydrochloride salt).



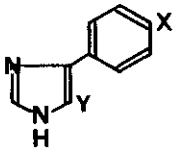
(1) (a) X = Y = H
(b) X = NO_2, Y = H
(c) X = Y = NO_2



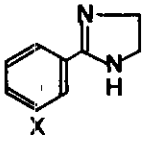
(2) (a) X = Y = H
(b) X = H, Y = NO_2
(c) X = Y = NO_2



(3) (a) X = Y = H
(b) X = NO_2, Y = H
(c) X = Y = NO_2

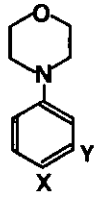


(4) (a) X = Y = H
(b) X = NO_2, Y = H
(c) X = Y = NO_2



(5) (a) X = H
(b) X = NO_2

(6) $PhCONCH_2CH_2NHAc$ (Ac)



(7) (a) X = Y = H
(b) X = H, Y = NO_2
(c) X = NO_2, Y = H

We have found that the phenylimidazoles do not nitrate at 0°C using nitric acid and acetic anhydride but 4-phenylimidazole gave an almost quantitative yield of 1-acetyl-4-phenylimidazole. This product was not obtained by reaction with acetic anhydride alone at 0°C but has previously[17] been obtained by refluxing 4-phenylimidazole in acetic anhydride. 2-Phenyl-2-imidazole likewise failed to undergo nitration in acetic anhydride at 0°C and gave as the only isolable product (50%) N,N'-diacetyl-N-benzoyl-1,2-diaminoethane (6). This compound has been obtained by the acetylation of 2-phenyl-2-imidazoline using acetic anhydride and pyridine.[18]

Although we have found that 4-phenylpyrimidine gives the ortho and meta isomers on mixed acid nitration[6], and also that 3-methyl-2-phenylpyridine gives a quantitative yield of the m-nitrophenyl product[7] whereas 2-phenylpyridine is reported[19,20] to give ortho:meta:para in yields of 9:39:52% we have found that N-phenylmorpholine (7a) gives the meta:para products (7b,c) in the ratio of about 5:1 under similar nitration conditions.

In our present studies we have thus observed only meta or para products in the nitration of phenyl N-heterocycles and have observed nothing similar to the case of the phenylpyrimidines[6,7,8] in which ortho and meta orientation is seen. The size of the heterocyclic substituent obviously inhibits ortho attack but it is still difficult to predict and to rationalise whether meta or para direction will result. However some advances have been made in this area[3]. We hope to continue to investigate thoroughly the products of nitration of simple phenyl substituted N-heterocycles to characterise and quantify the products completely and to rationalise the observed results.

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EXPERIMENTAL

^{1}H-Nmr spectra were recorded on a Perkin Elmer R32 90MHz spectrometer. Spectra were run in d_6 dimethyl sulphoxide or in $CDCl_3$ using Me_4Si as standard. Melting points are uncorrected. TLC investigations were carried out using Kieselgel plastic backed plates with fluorescent indicator using a range of eluants.

Standard Nitration Conditions

(A) The phenyl compound (∿ 1.00g) was dissolved in sulphuric acid (d,1.80,4-5ml), cooled to 0°C in an ice-bath, and then a mixture of nitric acid (d,1.5, excess or 1.0 mole equivalent) in sulphuric acid (d,1.80, 2-5ml) was added. The reaction was allowed to stand at 0°C for >2h and then poured into ice-water. Any product which was formed was collected, washed, then dried. The filtrate was then adjusted to pH9, any further solid collected, and the clear solution was

extracted with methylene dichloride. Any residue left after drying the extract (anhydrous sodium sulphate) and evaporating to dryness was also investigated.

(B) The above method was followed but using acetic anhydride in place of sulphuric acid.

By using the above procedures the following compounds were obtained pure:

3-Methyl-1-*p*-nitrophenylpyrazole (1b), mp 169-171°C (lit.[21] 170°C). δ(d_6DMSO) 2.30(s,Me)6.45(d,4-H) 8.57(d,5-H)8.04 and 8.30(2d,C_6H_4) Found: C,59.2; H,4.5; N,21.0%. $C_{10}H_9N_3O_2$ requires C,59.1; H,4.4; N,20.7%

3-Methyl-4-*p*-nitrophenylpyrazole (2b), mp 182-184°C (lit.[13] 181-182°C). δ(d_6DMSO) 2.55(s,Me)7.80 and 8.25 (2d,C_6H_4) 8.29(s,5-H). Found: C,59.2; H,4.4; N,20.8%. $C_{10}H_9N_3O_2$ requires C,59.1; H,4.4; N,20.7%

3-Methyl-4-(2',4'-dinitrophenyl)pyrazole (2c), mp 164-168°C. δ(d_6DMSO) 2.24(s,Me)7.75(s,5-H)7.81 (d,6'-H)8.50(dd,5'-H)8.89(d,3'-H) Found: C,48.2; H,3.3; N,22.8%. $C_{10}H_8N_4O_4$ requires C,48.4; H,3.2; N,22.6%.

2-*p*-Nitrophenylimidazole (3b), mp 309-312°C (lit.[14] 310-315°C). δ(d_6DMSO) 7.30(s,4,5-H)8.30(m,C_6H_4). Found: C,57.3; H,3.7; N,22.7%. $C_9H_7N_3O_2$ requires C,57.1; H,3.7; N,22.7%.

4-Nitro-2-*p*-nitrophenylimidazole (3c), mp 289-292°C (lit.[22] 290-291°C). δ(d_6DMSO) 8.30(m,C_6H_4) 8.60(s,5-H). Found: C,46.2; H,2.8; N,23.8%. $C_9H_6N_4O_2$ requires C,46.2; H,2.6; N,23.9%.

5-nitro-4-*p*-nitrophenylimidazole (4c), mp 292-295°C (lit.[15] 293°C). δ(d_6DMSO) 7.95 and 8.36 (2d,C_6H_4) 8.0(s,2-H). Found: C,46.1; H,2.4; N,23.5%. $C_9H_6N_4O_2$ requires C,46.2; H,2.6; N,23.9%.

2-*m*-Nitrophenyl-2-imidazoline (5b) (as nitrate salt), mp 137-141°C. δ($CDCl_3$) 3.55(bt,4,5-Hs)7.80 (t,5'-H)8.25 and 8.40(2bd,4' and 6'-Hs)8.70(t,2'-H). Found: C,42.8; H,4.0; N,22.4%. $C_9H_9N_3O_2 \cdot HNO_3$ requires C,42.5; H,4.0; N,22.1%.

N-*m*-Nitrophenylmorpholine (7b), mp 106.5°C. δ($CDCl_3$)3.21 and 3.88(m,aliphatic CH_2)7.15(bd,6'-H) 7.39(t,5'-H)7.68(bd,4'-H)7.70(d,2'-H). Found: C,57.6; H,5.7; N,13.2%. $C_{10}H_{12}N_2O_3$ requires C,57.7; H,5.8; N,13.5%.

N-*p*-Nitrophenylmorpholine (7c), mp 149-150°C (lit.[23] 149-150°C). δ(d_6DMSO) 3.40 and 3.80 (m, aliphatic CH_2) 6.98 and 8.05 (2d,C_6H_4). Found: C,57.9; H,5.9; N,13.3%. $C_{10}H_{12}N_2O_3$ requires C,57.7; H,5.8; N,13.5%.

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