

THE NITRATION OF PHENYLPYRIMIDINES

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Abstract - The nitration of 4-phenylpyrimidine using nitric acid/sulphuric acid at 0° has been shown to give 4-o-nitrophenylpyrimidine and 4-m-nitrophenylpyrimidine in the ratio of 4:6. Under similar conditions 5-bromo-2-phenylpyrimidine has given 5-bromo-2-o-nitrophenyl and 5-bromo-2-m-nitrophenylpyrimidine in the ratio of 3:7 and 5-chloro-2-phenylpyrimidine has given the 2-o-nitrophenyl and the 2-m-nitrophenyl isomers in the ratio of 3.5:6.5.

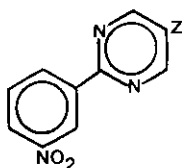
Extensive studies have been carried out on the directing properties of substituents on the benzene ring in relation to electrophilic substitution of the aromatic ring (for example see ref. 1). In general 'electron-releasing' groups are activating and are ortho and para directing whilst 'electron-attracting' groups are deactivating and are meta directing. However little systematic work has been carried out using heteroaromatic substituents such as pyridyl and pyrimidinyl systems. We have started a detailed study of the nitration of phenylpyrimidines and related compounds and this report describes our initial studies of such reactions. We intend to publish in full our findings on a number of systems at a later date.

Some non-quantitative nitrations of phenylpyrimidines have been reported, for example Lythgoe and Rayner² reported that the nitration of 2-phenylpyrimidine in nitric acid/sulphuric acid gave only one isolable product (74.6%) which they identified as the 2-m-nitro isomer 1a by independent synthesis. These workers also found that under the same conditions 4-phenylpyrimidine gave one isolable product (21.8%) which they thought to be the m-nitro isomer 2 but which they did not characterise.

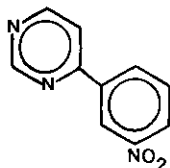
The nitration of 5-acetamido-2-phenylpyrimidine using nitric acid/sulphuric acid has been reported³ to give only one isolable product (30%) namely the 2-m-nitro isomer 1b and 5-nitro-2-phenylpyrimidine also gave the m-nitro isomer (49%) under similar conditions.

Lynch and Poon⁴ nitrated 4-phenylpyrimidine using three reagents - (a) mixed nitric and sulphuric

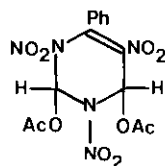
acids (b) nitric acid/trifluoroacetic anhydride and (c) nitric acid/acetic anhydride. They found that methods (a) and (b) gave excellent yields (> 90%) of 4-x-nitrophenylpyrimidines, method (a) giving the o and m-isomers in the ratio 2:3 and method (b) giving o, m and p-isomers in the ratio of 45:29:26. Method (c) gave 2,4-diacetoxy-1,3,5-trinitro-6-phenyl-1,2,3,4-tetrahydropyrimidine (3) as the only isolable product (40%).



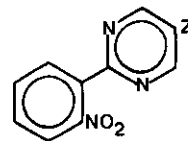
1 (a) Z=H (c) Z=Br
(b) Z=NHAc (d) Z=Cl



2



3



4 (a) Z=Br
(b) Z=Cl

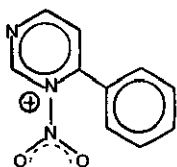
By using a method similar to that of Lynch and Poon (method a) we have obtained 97% yields of 4-x-nitrophenylpyrimidines. TLC, using two systems, and GLC has showed the presence of only two compounds. Fractional crystallisation and column chromatography both enabled pure samples to be obtained which were characterised as the 4-o and 4-m-nitrophenyl isomers. Quantitation of the product mixture was carried out by analysis of the ^1H nmr spectrum, by quantitative TLC (densitometry) and by GLC and a ratio of o:m-isomer of 2:3 was confirmed by each method.

In a similar way we have nitrated 5-bromo and 5-chloro-2-phenylpyrimidine and in each case have obtained only two products which we have characterised as the o-isomers 4a and 4b and the m-isomers 4c and 4d respectively. Quantitative analysis has shown that in the case of 5-bromo-2-phenylpyrimidine the ratio of o-nitrophenyl to m-nitrophenyl product is 3:7 and in the case of 5-chloro-2-phenylpyrimidine the ratio of o to m-nitrophenyl product is 3.5:6.5.

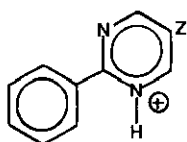
The nitration of 4-phenylpyrimidine in nitric acid/trifluoroacetic anhydride has provided some problems. The pyrimidine does not readily dissolve in trifluoroacetic anhydride at 0° and when some trifluoroacetic acid was added to aid dissolution and nitration was effected using nitric acid (d. 1.42) only the o and m-nitrophenyl isomers were obtained in the ratio of 2:3. A similar result was observed when nitric acid (d. 1.42) was added to a suspension of the pyrimidine in trifluoroacetic anhydride. When nitric acid (d. 1.50) was used TLC showed the presence of three products these being principally the o and m-nitro products (22:78) with a small quantity of a third which we believe to be the p-isomer. The presence of at least one product other than the o and m-isomer was confirmed by ^1H nmr and GLC analysis but we have not yet confirmed the presence of the p-nitro isomer. This result differs from that of Lynch and Poon.⁴

The nitration of 4-phenylpyrimidine using nitric acid in acetic anhydride gave one product in good yield similar to the product (3) described by Lynch and Poon.

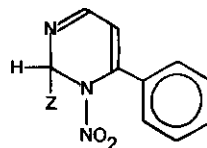
Several mechanisms can be proposed for the nitration of phenylpyrimidines. Lynch and Poon⁴ have proposed that the initial step in the case of 4-phenylpyrimidine is the formation of the N-nitronium species 5 which would be expected to undergo nitration at the m-position similar to the nitration of the benzyltrimethylammonium ion.⁵ If 5 dissociates into an ion-pair these workers have proposed that the most likely site of attack for the nitronium ion is the o-position. Using the analogy of the 4-pyrimidinyl substituent for the 2,4-dinitrophenyl substituent 4-phenylpyrimidine would be expected to undergo o and p-substitution similar to that observed for 2,4-nitrobiphenyl.⁶ However, the 2- or 4-pyrimidinyl substituent may also be considered to be analogous to the cyano group which is m-directing.



5



6


 7, Z=OAc, OCOCF₃

The product of nitration of nitronium species such as 5 (and that derived from a 2-phenylpyrimidine) or protonated species such as 6 would be expected to be the m-isomer. Our failure to observe significant quantities of p-isomer would argue against the nitration of the free base which might be o,p-directing and would support a mechanism for o-substitution such as that proposed by Lynch and Poon. However addition products such as 7 should be o,p-directing^{4,7} so that nitrations in acetic acid or trifluoroacetic acid might be expected to give different product ratios.

Our present studies show that 5-halogeno 2-phenylpyrimidines seem to give higher m:o ratios than 4-phenylpyrimidine and higher basicity tends to favour m-attack. We hope to be able to define precise reaction pathways for the nitration of phenylpyrimidines when we have completed a study of this system.

EXPERIMENTAL

All mp are uncorrected. ¹H nmr spectra were measured using a Perkin Elmer R32 90 MHz instrument, mass spectra were measured using an A.E.I. 902 instrument. TLC systems: silica gel G_{F254} using diethyl ether: dichloromethane (10:90 v/v), cellulose (with fluorescent indicator) using distilled water. GLC was carried out using a Perkin Elmer gas chromatograph (FID) and an OV-1 5% silicone column (3m) at 200^o.

Nitration of 4-phenylpyrimidine⁴ (a) 4-Phenylpyrimidine (1.00 g) was dissolved in sulphuric acid (d. 1.80, 3.3 ml) at 0^o then a mixture of nitric acid (d. 1.50, 1.6 ml) and sulphuric acid

(d. 1.80, 2.2 ml) cooled to 0° was added. The reaction mixture was allowed to stand for 2 hr then poured onto ice/water (~ 250 g). The products were recovered by dichloromethane extraction of the resulting suspension. The average yield of 4-x-nitrophenylpyrimidine products was 97%. Separation and recrystallisation (dichloromethane) gave 4-m-nitrophenylpyrimidine (mp. 122-124°, lit.⁴ 123°) τ (CDCl₃) 7.68 (t, 5¹-H) 7.77 (d, 5-H) 8.40 (superimposed d, 4¹, 6¹-H) 8.85 (d, 6-H) 8.93 (split s, 2¹-H) 9.3 (s, 2-H). M⁺ 201; 4-o-nitrophenylpyrimidine (mp 69-70°, lit.⁴ 67°) τ (CDCl₃) 7.47 (split d, 5-H) 7.57-7.65(m) 7.90-8.13(m) (nitrophenyl Hs) 8.82 (d, 6-H) 9.24 (s, 2-H). M⁺ 201.

5-Bromo-2-phenylpyrimidine⁸ was reacted similarly to give a mixture (92%) of 5-bromo-2-o-nitrophenylpyrimidine (mp 101-102°) τ (CDCl₃) 7.57-8.10 (m, nitrophenyl Hs) 8.85 (s, 4,6-H). M⁺ 281(279). C, 43.6; H, 2.7; N, 14.6% C₁₀H₆BrN₃O₂ requires C, 42.9; H, 2.2; N, 15.0%. 5-Bromo-2-m-nitrophenylpyrimidine (mp 169-170°) τ (CDCl₃) 7.62 (t, 5¹-H) 8.32 (broad d, 6¹-H) 8.82 (d, 4¹-H) 8.86 (s, 4,6-H) 9.25 (split s, 2¹-H). M⁺ 281(279). C, 43.3; H, 2.6; N, 14.3%. C₁₀H₆BrN₃O₂ requires C, 42.9; H, 2.2; N, 15.0%.

5-Chloro-2-phenylpyrimidine⁸ similarly gave a mixture (93%) of 5-chloro-2-o-nitrophenylpyrimidine (mp 104-105°) τ (CDCl₃) 7.55-8.10 (m, nitrophenyl Hs) 8.77 (s, 4,6-H). M⁺ 237(235). C, 51.1; H, 3.3; N, 16.9%. C₁₀H₆ClN₃O₂ requires C, 50.9; H, 2.6; N, 17.8%.

5-Chloro-2-m-nitrophenylpyrimidine (mp 168-170°, lit.² 172-173°) τ (CDCl₃) 7.75 (t, 5¹-H) 8.38 (broad d, 6¹-H) 8.75 (d, 4¹-H) overlapping with 8.80 (s, 4,6-H) 9.29 (split s, 2¹-H). M⁺ 237(235). C, 51.4; H, 2.9; N, 17.1%. Calc. for C₁₀H₆ClN₃O₂ C, 50.9; H, 2.6; N, 17.8%.

Nitration of 4-phenylpyrimidine⁴ (b) 4-Phenylpyrimidine (1.00 g) was suspended in trifluoroacetic anhydride (12 ml) at 0° then nitric acid (d. 1.42, 0.5 ml) was added. The reaction mixture was set aside for 160 hr then the solvent was removed under reduced pressure, the residue was adjusted to pH7 with dilute ammonia and then extracted with dichloromethane. Mononitro product (> 90%) was obtained shown by TLC to be the o and m-nitro isomers (ratio 2:3). In another experiment trifluoroacetic anhydride (5 ml) was added to dissolve the 4-phenylpyrimidine. Work up, as above, gave the o and m-nitro isomers (96%) in the ratio of 2:3. In further experiments addition of nitric acid (d. 1.50) to a suspension of 4-phenylpyrimidine in trifluoroacetic anhydride as above gave 85% of mononitrated product mixture which showed a small quantity of a third product by TLC and GLC.

The nitration of 4-phenylpyrimidine in acetic anhydride (Lynch and Poon⁴) gave a single crystalline product (mp. ex dichloromethane 140-144° lit.⁴ 147° ex methanol) τ (CDCl₃) 2.10, 2.16 (s, Ac-CH) 7.54 (m, phenyl Hs) 8.09 (s) 8.39 (s) (2 and 6-H).

REFERENCES

1. J.G. Hoggett, R.B. Moodie, J.R. Penton and K. Shofield, 'Nitration and aromatic reactivity', Cambridge University Press, Cambridge, 1971.
2. B. Lythogoe and L.S. Rayner, J. Chem. Soc., 1951, 2323.
3. M.P.L. Caton and J.F.W. McOmie, J. Chem. Soc. (C), 1968, 836.
4. B.M. Lynch and L. Poon, Can. J. Chem., 1967, 45, 1431.
5. C.K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd Ed., Cornell University Press, Ithaca, London, 1969.
6. H.C. Gull and E.E. Turner, J. Chem. Soc., 1929, 491.
7. R. Ettinger, Tetrahedron, 1964, 20, 1579.
8. F. Knuckell and L. Zumbusch, Ber., 1902, 35, 3164.

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