

## Selective Nitration of Phenol

Humayun Pervez, Liliias Rees, and Colin J. Suckling\*

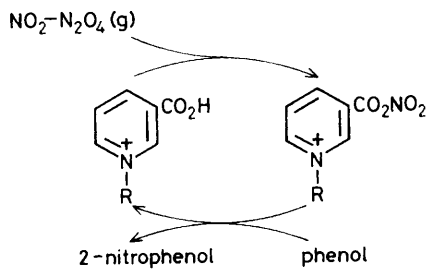
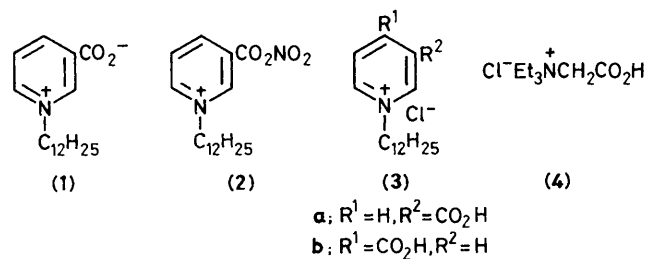
*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, U.K.*

Activated nitro derivatives of pyridinium salts have been shown to mediate in the highly selective *ortho* nitration of phenol in high yield.

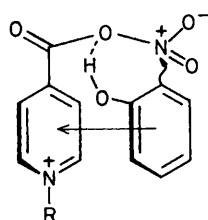
Biomimetic chemistry, as defined by Breslow,<sup>1</sup> is concerned with the imitation of natural chemistry to lead to useful new synthetic processes. In the course of our studies in this field on micelle-based systems for selective aromatic substitution,<sup>2-5</sup> we observed a strong donor-acceptor interaction between pyridinium salt head groups and phenolic substrates.<sup>2</sup> This communication describes the application of this interaction to the selective nitration of phenol.

Initially, the pyridinium carboxylate (**1**) was suspended in dry acetonitrile and treated with a solution of nitronium

tetrafluoroborate in acetonitrile until a solution was obtained. The product showed a carbonyl absorption in the i.r. spectrum at 1720–1730 cm<sup>-1</sup> in place of 1635 cm<sup>-1</sup> in the starting carboxylate, consistent with formation of the acyl nitrate (**2**). A solution of the acyl nitrate in acetonitrile rapidly nitrated phenol quantitatively and analysis of the products by g.c. showed that the products were 2-nitrophenol (95%) and 4-nitrophenol (5%). The closest analogy for such a selective nitration by an acyl nitrate comes from the work of Rees<sup>6</sup> who showed that biphenyl-2-carboxylic acid underwent nitration in



Scheme 1

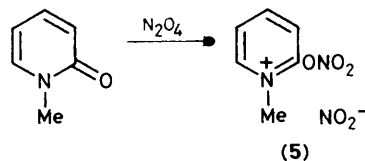


**Figure 1.** Hypothetical alignment of reactants leading to *ortho* nitration. Hydrogen bonding to C=O or  $NO_2$  could also be envisaged.

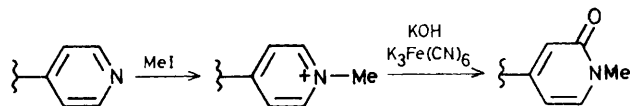
the 2'-position with  $N_2O_5$ . We also found that the product of passing  $NO_2-N_2O_4$  gas into a solution of a pyridinium carboxylic acid (**3a**) or (**3b**) was equally capable of mediating selective nitration of phenol. In this way, the expensive reagent nitronium tetrafluoroborate became unnecessary and the recovered pyridinium salt could be reused in further reactions (Scheme 1).

In order to establish the source of the selectivity of the reaction, we treated a number of carboxylate anions with nitronium tetrafluoroborate under the same conditions; no significant nitration was obtained with acetate, trifluoroacetate, 4-nitrobenzoate, salicylate, or with pyridine itself, although the nitro derivatives of the carrier molecules were detected by i.r. spectroscopy. Nitration of anisole by the acyl nitrate (**2**) was unselective and potassium phenoxide was nitrated slowly and unselectively. These observations demonstrate the importance of the *N*-alkyl pyridinium salt in promoting nitration. Further, the possibility that a hydrogen bond between phenol and the reagent (**2**) might control selectivity was suggested (Figure 1).<sup>7</sup>

Support for the hypothesis that the joint effects of hydrogen



Scheme 2



Scheme 3

bonding and donor-acceptor interaction between the pyridinium salt and phenol are necessary for selective nitration came from two observations. Firstly, both the carboxylic acids (**3a**) and (**3b**) promoted selective *ortho* nitration of phenol and secondly, the triethylammonium salt (**4**) afforded nitrated products but in diminished yield and selectivity. If such a hypothesis is correct, other pyridinium salts should be capable of acting as transfer agents. We therefore carried out this nitration experiment with *N*-methyl-2-pyridone (Scheme 2). After treatment with  $NO_2-N_2O_4$  gas in acetonitrile solution, the i.r. carbonyl absorption at  $1655\text{ cm}^{-1}$  was lost; addition of phenol to a solution of the transfer agent (**5**) once again led to highly selective *ortho* nitration of phenol (>98% yield). Further, an insoluble 2-pyridone derivative prepared from a 4-vinylpyridine-styrene-divinyl benzene copolymer (Scheme 3) was effective in selective nitration of phenol under analogous conditions using 1,2-dichloroethane as reaction medium, yielding a crystalline product that was 97% *o*-nitrophenol in 95% yield.

In these nitration reactions, which are thus highly selective and high yielding, molecular association and specific non-covalent interactions apparently control selectivity as in many enzyme-catalysed reactions. The simplicity of the reactants and the ease of separation of transfer agent and products makes the large scale application of processes of this type feasible.

We thank the Smith and Nephew Foundation for the endowment of a Royal Society Senior Research Fellowship (to C. J. S.) and Dr. D. C. Sherrington for supplying the copolymer.

Received, 23rd October 1984; Com. 1506

## References

- 1 R. Breslow, *Chem. Soc. Rev.*, 1972, **1**, 553.
- 2 C. J. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 661.
- 3 D. I. Robinson, D. C. Sherrington, and C. J. Suckling, *Tetrahedron*, 1984, **40**, 785.
- 4 C. A. Dewar, C. J. Suckling, and R. Higgins, *J. Chem. Res.*, 1979, (S) 336, (M) 3812.
- 5 S. O. Onyiriuka, C. J. Suckling, and A. A. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1103.
- 6 D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1962, 4579.
- 7 A. Guy, M. Lemaire, and J-P. Guette, *Tetrahedron*, 1982, **38**, 2339; 2347.