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Ortho-Selective Nitration of Acetanilides with Nitrogen Dioxide in the Presence of Ozone

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Abstract: *In the presence of ozone, nitrogen dioxide rapidly reacts with acetanilides ortho-selectively at low temperatures, giving a high proportion of ortho-nitro derivatives in good yields.*

Aromatic 1,2-diamines are important as the synthetic intermediates for a variety of pharmaceuticals, agricultural drugs, and dyestuffs. This type of compounds is usually prepared by the reduction of 1,2-nitroamines, which in turn are obtained from the nitration of acetanilides followed by hydrolysis or from the ammonolysis of 1,2-chloronitroarenes. The latter route lacks generality and is highly dependent on the availability of starting materials.

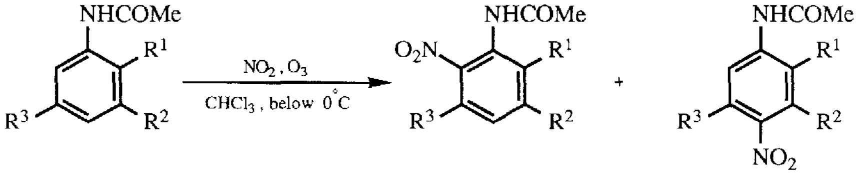
We have recently observed that lower oxides of nitrogen are activated in the presence of ozone to enter easily into nonactivated aromatic nuclei as the nitro group, giving the corresponding nitro compounds in good to moderate yields.[1]

When this interesting reaction was applied to acetanilides, we were surprised to observe a high proportion of *ortho*-substitution (Table 1). The *ortho*/*para*-ratios of nitroacetanilides obtained were mostly higher than the ones found in the classical nitric acid/acetic anhydride system.[2,3] The reaction was clean and no resinous substances were formed.

The general procedure was as follows: A solution of acetanilide (**1**, 10 mmol) in a polychlorinated hydrocarbon (50 ml) was vigorously stirred below 0°C, while streams of ozonized oxygen or air and nitrogen dioxide were slowly introduced from separate inlet tubes just over the surface of the liquid mixture.[4] Within 1 to 3 h,[5] the reaction ran to completion at mononitration stage and was quenched by the addition of aqueous sodium hydrogencarbonate. The organic phase was separated and worked up as usual to obtain nitroacetanilides **2** and **3**.

Dichloromethane and chloroform were the solvents of choice. The reaction occurred more quickly in the former solvent, while the degree of the positional selectivity was higher in the latter solvent. In carbon tetrachloride and tetrachloroethylene, the *ortho*-selectivity decreased. No *meta*-substitution was observed. When ozonized oxygen was replaced by ozonized air, the reaction became slower and interestingly enough the *ortho*/*para*-ratios of the products somewhat decreased. In the absence of ozone, the nitration was quite sluggish and the nitro group entered almost exclusively into the *para*-position when the conversion was low. Prolonged contact only led to a complicated mixture of products.

Scheme 1



1 **2** **3**

		R^1	R^2	R^3
a	:	H	H	H
b	:	Me	H	H
c	:	H	Me	H
d	:	Me	Me	H
e	:	Me	H	Me
f	:	H	Me	Me
g	:	H	Cl	H
h	:	NO_2	H	H

The hydrogen atom of the amide group in **1** often plays an important role in determining the proportion of *ortho*-isomer. Thus, when N-methylacetanilide (**4**) is subjected to nitration, it undergoes complete *para*-substitution both in mixed acid and in nitric acid/acetic anhydride.[6] In our case, however, a high *ortho*-selectivity (*ortho*/*para*-ratio, 3.3) was manifested irrespective of the absence of the amide hydrogen atom in **4**.[7] An exception to the enhanced *ortho*-reactivity was observed in the reaction of 2-nitroacetanilide, which mainly led to 2,4-dinitro compound rather than 2,6-dinitro isomer (2,4-/2,6-ratio, 2.2-2.5) . Relative decrease in *ortho*-reactivity may be understood on steric rather than electronic basis, brought by a special interaction between the amide hydrogen atom and nitro group in close proximity.

Nitration of anilides has a history of controversy over the way in which the nitro group enters into aromatic nucleus, and the problem apparently remains unsettled yet.[2,3,6] Nitrations with nitric acid in acetic anhydride give the *ortho*/*para*-isomer ratios greater than unity (up to 9), whereas nitrations with mixed acid show the *ortho*/*para*-ratios in the range 0.01-0.8.

Nitrogen dioxide is known to react with ozone instantaneously to form dinitrogen pentoxide and nitrogen trioxide.[8] Then the present nitration may be expected to proceed via two different types of reaction pathways; one is the electrophilic nitration with dinitrogen pentoxide,[9] a process which has long been known to lead to a high proportion of *ortho*-substitution. Another is the charge-transfer nitration[10] where nitrogen trioxide oxidizes anilide to a radical cation, which is captured by nitrogen dioxide to form some sort of precursor leading to the final products. There is a possibility that both mechanisms operate in parallel.

Table 1. Nitration of acetanilides with nitrogen dioxide / ozone

Anilide **1**	Solvent	Reaction time (h)	Yield of nitro-anilides (%)[a]	Ratio of **2**/**3**
a	CH_2Cl_2	2.5	98	3.6
a	$CHCl_3$	2.5	99	4.4
b	$CHCl_3$	2.0	93	1.6
c	$CHCl_3$	2.0	99	3.2[b]
d	$CHCl_3$	1.5	81	4.4
e	$CHCl_3$	1.5	96	2.8
f	$CHCl_3$	1.5	78	2.2
g	$CHCl_3$	3.0	96	3.5[c]
h	$CHCl_3$	2.0	20	0.46[d]

a Yields based on **1** were not optimized. The conversion was almost complete expect for entry h, and hence the difference from 100% corresponds roughly to the extent of polynitration.

b Ratio of *ortho*/*para*-substitutions. Mononitration product was composed of 2-nitro (21%), 4-nitro (24%) and 6-nitro (55%) isomers.

c Ratio of *ortho*/*para*-substitutions. Mononitration product was composed of 2-nitro (17%), 4-nitro (22%) and 6-nitro(61%) isomers. Determinations with modern instruments failed to confirm the very high *ortho*/*para*-value (9.0) claimed by canadian chemists.[3]

d Determined at 20% conversion.

Phenolic ethers and benzylic ethers are known to exhibit a similar high *ortho*-reactivity when nitrated with nitric acid in acetic anhydride.[11] It would be worthy to mention herein that the enhancement of *ortho*-substitution was not so prominent in the nitration of these ethers with the nitrogen dioxide/ozone system.[7]

The present *non-acid* procedure for aromatic nitration is especially attractive for a large-scale preparation of aromatic 1,2-nitroamines, since the classical procedure based on nitric acid /acetic anhydride system needs careful control of the exothermic reaction because of the explosive nature of acetyl nitrate generated *in situ*.[12] Additional advantage is the use of recoverable polychlorohydrocarbons as the solvent, in place of expensive acetic anhydride which is destroyed after the reaction.

REFERENCES AND NOTES

1. H. Suzuki, T. Murashima, K. Shimizu and K. Tsukamoto, *Chem. Lett.*, **1991**, 817.
2. R.O.C. Norman and G.K. Radda, *J. Chem. Soc.*, **1961**, 3030; R.B. Moodie, P.N. Thomas and K. Schofield, *J. Chem. Soc. Perkin Trans. 2*, **1977**, 1693; Z. Daszkiewicz and J.B. Kyziol, *J. prakt. Chem.*, **1988**, *330*, 44.
3. B.M. Lynch, C.M. Chen and Y.-Y. Wigfield, *Can. J. Chem.*, **1968**, *46*, 1141.
4. When both gases were introduced into the solution as fine bubbles, there resulted extensive polynitration. The reaction was carried out in the presence of excess nitrogen dioxide, using a three-necked 50 ml flask in order to minimize the open space in the reaction vessel.
5. Reaction time is dependent on the efficiency of the ozone generator. An apparatus (Nippon Ozone Co. Ltd., type ON-1-2) was used for the generation of ozone.
6. S.R. Hartshorn, R.B. Moodie and K. Shofield, *J. Chem. Soc., (B)*, **1971**, 2454.
7. To be published.
8. O.R. Wulf, F. Daniels and S. Karrer, *J. Am. Chem. Soc.*, **1922**, *44*, 2398; E.J. Jones and O.Wulf, *J. Chem. Phys.*, **1939**, *3*, 873.
9. K. Shofield, '*Aromatic Nitration*,' Cambridge University Press, London, 1980.
10. L. Eberson and F.Radner, *Acc. Chem. Res.*, **1987**, *20*, 53.
11. J.R. Knowles and R.O.C. Norman, *J. Chem. Soc.*, **1961**, 2938, 3888.
12. W. König, *Angew. Chem.*, **1955**, *67*, 157.

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