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Synthesis of 1-Alkoxy-4-nitronaphthalenes in a Novel Nitration of Naphthalene

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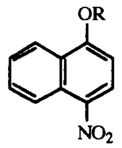
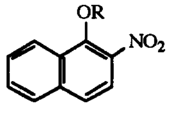
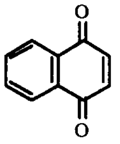
Abstract: A new nitration of naphthalene affords as major products 1,4-disubstituted naphthalenes and as minor products 1,2-disubstituted naphthalenes. By use of ceric ammonium nitrate suspended on silica gel, or in homogeneous solution, nitration of naphthalene in the presence of alcohols, sodium- or tetrabutyl ammonium- nitrite and acid gives alkoxynitronaphthalenes. A preparation of 1-nitronaphthalene is described under heterogeneous conditions.

Conventional mixed acid procedures for nitration of aromatic substrates pose extensive environmental difficulties and there is a need to find more acceptable alternatives. One strategy has been the use of zeolites[1], which whilst offering many advantages, has limitations[2]. Alternatives might be the use of reagents suspended on inert supports[3]. Nitric acid[4] and ceric ammonium nitrate[5] have both been used adsorbed on silica gel, and sulfuric acid[6] has also, as catalyst, been supported on silica gel. We[7] have previously successfully used the Wolf and Lamb techniques devised[8] by Patchornik *et al*, in which two highly reactive species are immobilized separately on independent supports. The use of two or more reagents supported on independent supports has recently been further investigated[9] but these concepts have not been applied to nitrations. Here we describe how initial study of the application of Wolf and Lamb procedures to the nitration of naphthalene has led first to simple nitration to give 1-nitronaphthalene under heterogeneous conditions, and then how further developments have permitted effective routes to be devised to afford disubstituted naphthalenes from naphthalene under homogeneous conditions.

The potential advantages of effecting nitrations using nitric and sulfuric acids suspended independently on solid supports are obvious. Work up by simple filtration and evaporation of the inert solvent can lead to rapid and efficient isolation of the products and recycling of the nitric and sulfuric acids. We find that much of the potential is realised when naphthalene is nitrated by the acids supported on silica gel in a suspension in dichloromethane at room temperature. Although reaction is a little slow (4 hours), 1-nitronaphthalene is readily isolated in 98% yield. In the absence of sulfuric acid naphthalene is recovered unchanged. In Wolf and Lamb procedures Patchornik *et al* [8] were aware of the chain sequence involving substrates generating intermediates at one reagent site, migrating, after transformation, through the solution to the second suspended reagent and finally reacting at the second site. We wondered if we might use similar concepts in order to accelerate our otherwise efficient nitration of naphthalene. In our first approach we investigated the replacement of nitric acid by ceric ammonium nitrate and the consequence of adding tetrabutyl ammonium nitrite, which is soluble in dichloromethane. When well dried ceric ammonium nitrate on silica gel, sulfuric acid supported on silica gel and naphthalene were stirred at room temperature in dichloromethane in the presence of tetrabutyl ammonium nitrite 1-nitronaphthalene was rapidly formed and could be isolated in 81% yield. These experiments show that suspension of both the nitrating agent and sulfuric acid on silica gel permits very efficient nitrations. However in the course of our studies we found that the reaction pathway could be diverted to afford disubstituted naphthalenes and the report of these discoveries constitutes the remainder of this paper.

TABLE

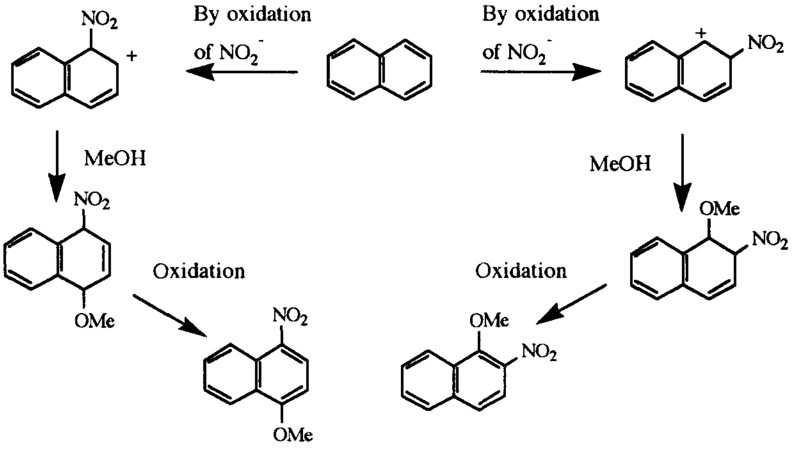
Nitration of Naphthalene by Ceric Ammonium Nitrate, Sulfuric Acid and Added Nitrites in Alcohols

Alcohol	Reagents	Conversion (%)	Product distribution (%)		
					
Methanol	CAN (8 eq) Bu_4NNO_2 (1eq) H_2SO_4 (5 eq)	100	70	15	10
Methanol	CAN (5 eq) $NaNO_2$ (2 eq) H_2SO_4 (5 eq)	92	49	16	11
Ethanol	CAN (8 eq) Bu_4NNO_2 (1 eq) H_2SO_4 (5 eq)	85	74	14	6
n-Propanol	CAN (8 eq) Bu_4NNO_2 (1 eq) H_2SO_4 (5 eq)	69	55	12	10
n-Butanol	CAN (8 eq) Bu_4NNO_2 (1eq) H_2SO_4 (5 eq)	61	59	15	10
i-Propanol	CAN (8 eq) Bu_4NNO_2 (1eq) H_2SO_4 (5 eq)	53	68	16	16

We chose to prepare the supported ceric ammonium nitrate on silica gel by evaporation of a solution in methanol of the reagent in the presence of silica gel. We quickly found that traces of methanol in the subsequent nitration reactions diverted the reaction pathway. Traces of 1,4-naphthoquinone were observed as a product, but more surprisingly 1-methoxy-4-nitronaphthalene (**1**) was isolated in 10-20% yield. By variation of the conditions the yield of the disubstituted naphthalene (**1**) could be raised above 50% using these heterogeneous conditions. As no direct procedure to permit synthesis of 1-alkoxy-4-nitronaphthalenes from naphthalene has been previously reported and the reaction course was unclear, we decided to investigate the reaction further under homogeneous conditions. By reaction of ceric ammonium nitrate (8 mol equiv) in excess methanol in the presence of sulfuric acid (5 mol equiv), naphthalene (1 equiv) and tetrabutyl ammonium nitrite (1 mol equiv), work up and chromatography of the products afforded 1-methoxy-4-nitronaphthalene and 1-methoxy-2-nitronaphthalene in 70% and 15% yields respectively. In the Table the products of nitration of naphthalene in the presence of a variety of alcohols are reported. Two conclusions can be drawn. First the direct preparation of 1-alkoxy-4-nitronaphthalenes from naphthalene can be achieved in yields justifying further interest in this unique transformation. Such nitro compounds have been used[10] as intermediates in the synthesis of pharmacologically interesting compounds, e.g. anti-tumor agents. The second point to note is the unusual product distribution. In conventional nitrations the ratio of attack at the 1-position to that at the 2-position is typically[11, 12] between 10 and 20. Here the ratio is below 5: hence an unusual nitration mechanism is operative.

The isolation of the two series of disubstituted naphthalenes, 1-alkoxy-4-nitronaphthalenes and 1-alkoxy-2-

nitronaphthalenes might be explained by one of three distinct mechanistic sequences. These are (1) a route by SET in which the naphthalene is oxidized by cerium salts to give a cation radical which is then trapped by the alcohol to give intermediate alkoxynaphthalenes, which are then nitrated to afford the products; (2) a classical nitration by the nitronium ion, addition of the alcohol to give a disubstituted dihydronaphthalene and finally oxidation by cerium salts to give the observed products; and (3) a route similar to the classical nitration, but deviating at an early stage by featuring an initial attack on naphthalene, possibly by the NO_2 radical or NO_2 complexed to a cerium species, followed by oxidation leading to the same intermediates postulated in the second mechanism. We have evidence which eliminates the first two mechanistic scenarios but is consistent with the third mechanism. The first mechanism involving initial formation of the naphthalene cation radical has good precedent as the oxidation of aromatics to cation radicals by ceric ammonium nitrate has been reported[13] and the electrochemical oxidation of naphthalene[14] in the presence of nitrite ion has given nitronaphthalenes via the cation radical. However the first mechanism is simply eliminated by the observation that 1-methoxynaphthalene and 2-methoxynaphthalene fail to give, under our same reaction conditions, good yields of the products observed in our nitration of naphthalene. Also in the electrochemical study[14] the ratio of 1-nitronaphthalene: 2-nitronaphthalene was greater than 50. The ratio of attack at the 1- and 2-positions in naphthalene has been used as a criterion of the mechanism of substitution. Olah *et al* [11] first recognised the importance of this ratio and Suzuki and Mori[12] have recently tabulated ratios for reaction of naphthalene under a variety of conditions. Under conditions where nitration by attack of a nitronium ion on naphthalene occurs, the expected ratio of attack at the 1- and 2-positions is between 10 and 20, and thus our observed yields of 70% of the 1-methoxy-4-nitronaphthalene and 15% of 1-methoxy-2-nitronaphthalene, are not consistent with a classical nitration mechanism. The ratio of 5, which we observed, is found when naphthalene is attacked by a radical species. All electrophilic substitutions and nitrations proceeding by SET[15] give substantially higher ratios (10-65). Our results are consistent with the mechanism shown in the Scheme with initial attack by NO_2 as a radical or complexed with ceric ion. A number of recent observations support this scheme. Nitrations of naphthalene with nitrogen dioxide in carbon tetrachloride or dichloromethane are characterized by a low (4-8) ratio of attack at the 1- and 2-positions and are recognised[16] to occur *via* a radical mechanism. Nitrations have recently been reported[2,17] where the presence of ferric[17] and lanthanide[2] salts have led to catalysis. Indeed catalysis of nitrations with nitric acid by ceric ion[18] has been previously recognised. In our study, the nature of the species initially reacting with naphthalene is unclear. However the product ratio is consistent with a radical or metal complexed species. Finally, our proposal, that the naphthalene products arise via the intermediacy of dihydronaphthalenes receives good



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support from recent publications. Nitration of naphthalene has been shown[19,20] to give dihydronaphthalenes as 1,4-adducts. Furthermore the observation that nitration of naphthalene in carbon tetrachloride gives 1,3-dinitronaphthalene and 2,3-dinitronaphthalene as minor products has been interpreted[16] as evidence of an addition elimination mechanism. In our own study the conversion of the dihydronaphthalenes to naphthalenes may well proceed by an analogous addition elimination sequence. Although details of our proposed route require further clarification, our observations reveal a surprisingly efficient direct route from naphthalene to disubstituted naphthalenes. These results emphasize both the role of supported reagent techniques and add to the developing importance of the role of metal ions to facilitate nitrations. If such sequences can be generalised, the potential in the synthesis of polysubstituted aromatics is considerable.

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