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Improved Nitrations Using Metal Nitrate–Sulfuric Acid Systems

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Abstract—Procedures for efficient mono- and di-nitration of aromatic substrates have been developed using ceric ammonium nitrate suspended in dichloromethane in the presence of 2 equiv. of sulfuric acid. By suspending the sulfuric acid on silica gel following nitration, products are easily isolated by filtration and evaporation of solvent. In these nitrations ceric ammonium nitrate can be replaced by other metal nitrates, for example potassium- or tetrabutylammonium-nitrate. In contrast the nitration of naphthalene by ceric ammonium nitrate in the presence of methanol and sulfuric acid affords a mixture of 1,4- and 1,2-methoxynitronaphthalenes, but these nitrations cannot be achieved using potassium or tetrabutylammonium nitrate. The mechanism of this nitration/oxidation is discussed. © 2000 Elsevier Science Ltd. All rights reserved.

The serious effluent problems, created by nitration processes based on mixed nitric and sulfuric acids, have stimulated the search for alternative procedures. Recently a number of different methods have been examined. Some are based on homogeneous procedures in solution. Others depend upon reactions involving heterogeneous conditions. Nitrations in solution based on dinitrogen pentoxide, a powerful nitrating agent, can be efficient. For example pyridines[1] can be readily nitrated. However whether in direct use of dinitrogen pentoxide, or by Kyodai nitrations[2] using other nitrogen oxides, reactions require the handling of ozone or other explosive materials. The use of metal nitrates has received much study. Recently a vanadium nitrate $VO(NO_3)_3$ has proved to be useful[3] in nitration of simple aromatics. However this nitrate must be prepared from dinitrogen pentoxide. Earlier iron,[4,5] copper,[5] chromium[6] and cerium[7] nitrates have been studied but have failed to be generally useful. New analyses of the possible catalytic role in nitrations of metal nitrates and other metal salts have been made. First the catalytic role of ytterbium triflate[8] in nitrations of aromatics using nitric acid has been indicated. Then the greater efficiency of hafnium and zirconium triflates[9] was demonstrated. Finally a detailed analysis favours[10] a promotion in such nitrations by an accentuation of the Bronsted acidity of nitric acid, leading to a higher concentration of the nitrating species, the nitronium ion.

Alongside these recent developments designed to improve nitrations in solution, there have been major studies using solid supported reagents. Iron and copper nitrates on clay[11] proved to be efficient reagents for the nitration of phenols and stimulated the search for other nitration procedures. Nitric acid has been used[12] adsorbed on silica gel. Sulfuric acid, acting as a catalyst, has also been adsorbed[13] on silica gel. Chawla and Mittal[14] have described the nitration of alkoxynaphthalenes using ceric ammonium nitrate adsorbed on silica gel, and a recent study[15] extends this methodology to methoxybenzenes. Aside from the interest in designing clean and efficient nitration procedures, a further stimulus to the use of supported reagents is the possibility of influencing the regiochemical outcome of nitrations. Thus acyl nitrates[16] on silica gel and on clays can lead to interesting regioselectivites. The two goals of promoting nitrations and influencing regioselectivity have also led to procedures using zeolites.[17]

We[18] have recently reported the use of sulfuric acid and nitric acid separately suspended on silica gel to permit the efficient nitration of naphthalene. In an extension of the study we found that nitrations also proceeded efficiently when the nitric acid was replaced by ceric ammonium nitrate. Thus in the absence of added alcohols, 1-nitronaphthalene was isolated in high yield. In the presence of alcohol the reaction course was diverted to afford 1-alkoxy-4-nitronaphthalenes as major products. In our present paper we report novel nitration procedures based on extensions to the methodology described in our preliminary paper. Here we report the first use of ceric ammonium nitrate and silica gel supported on sulfuric acid for the nitration of monosubstituted benzenes in dichloromethane. By carrying out nitrations in dichloromethane, with a variety of nitrating agents and different amounts of added sulfuric acid, efficient procedures for mono- or di-nitration of

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Keywords: ceric ammonium nitrate; naphthalene; nitration; silica gel.

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Table 1. Nitration of simple aromatic substrates with a nitrate–H_2SO_4 system

Substrate (**1**)	Time (h)	Yield of nitrated product (**2**) %	*ortho–para* ratio
X=CH_3	12	95	56:44
X=CH_3	4	95	57:43
X=CH_3	1	73	56:44
X=CH_3	4	75[a]	53:47
X=H	12	95	–
X=H	4	94	–
X=Cl	4	89	37:63
X=Cl	1	77	36:64
X=Cl	4	73[a]	34:66
X=Br	4	91	46:54
X=^{t}Bu	4	82	11:89

[a] Using KNO_3 in place of ceric ammonium nitrate.

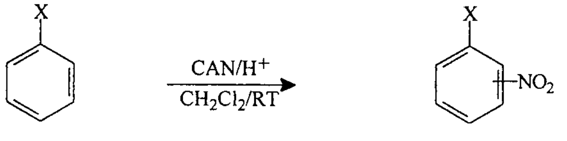
substituted benzenes have been developed. Finally we report evidence concerning the mechanism of nitration of different aromatics with ceric ammonium nitrate and compare our observations with other recent analyses of catalysed nitrations.

In our first paper[18] we described a variety of nitration products of naphthalene. Having established that the Wolf and Lamb[19] procedures of Patchornik et al. could be modified to permit the nitration of naphthalene by independently supporting sulfuric acid and, nitric acid or ceric ammonium nitrate, on silica gel we wanted to generalise the applicability of these methods. First we established that naphthalene can be efficiently nitrated in either dichloromethane or 1,2-dichloroethane solution with ceric ammonium nitrate present as a suspension. The convenience of using ceric ammonium nitrate suspended in chlorinated solvents is illustrated by the nitration of various substituted benzenes (Eq. (1)) shown in Table 1. Reaction of 1 equiv. of substrate with 1 equiv. of CAN in the presence of 2 equiv. of concentrated sulfuric acid in dichloromethane as solvent furnishes nitrated products at room temperature in short times as illustrated in Table 1. Hence it can be shown that this procedure provides an efficient protocol for mononitration of simple aromatic compounds. By comparison with the earlier reported[14,15] nitrations using CAN these results first extend the use of CAN to the nitration of aromatics other than electron rich alkoxybenzenes or alkoxynaphthalenes and second they establish a new methodology of direct suspension of the reagent in chlorinated solvents. The above results are obtained using sulfuric acid directly added to the dichloromethane solution and this procedure requires an aqueous work up of the reaction mixture. An alternative described below depends upon the addition of sulfuric acid suspended on silica gel and permits a simplified work up procedure. The *ortho–para* ratios are in accord[20] with ratios observed in mixed acid nitrations proceeding via nitronium ion mechanisms. Hence it seems probable that these CAN nitrations involve reaction with sulfuric acid to generate nitronium ions. Therefore the use of other metal nitrates might be expected to lead to similar nitration procedures. Nitration of toluene and chlorobenzene with potassium nitrate and sulfuric acid in dichloromethane indeed led to the corresponding nitrated products in 75 and 73% yields, respectively (Table 1). Potassium nitrate has been shown[21] in literature examples to be an effective nitrating agent. However the solvent in these examples is sulfuric acid. In our studies the acid component is present in 2:1 ratio of acid to substrate with dichloromethane as the solvent. Clearly our protocol has the advantages of requiring much less acid and offering a simplified work up procedure.

Table 2. Nitration of aromatic substrates using CAN and silica-supported H_2SO_4

Substrate (**1**)	Yield[a] of nitrated product (**2**) (%)	*ortho–para* ratio
X=H	92	–
X=CH_3	95	51:49
X=Cl	97	24:76
X=Br	99	42:58
X=^{t}Bu	99	20:80

[a] Reactions carried out using 10 equiv. of H^+-silica to substrate.

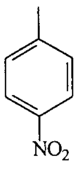


(1) **(2)** (1)

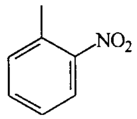
The sulfuric acid may also be suspended on silica gel. As a consequence longer reaction times (typically overnight, 12 h) are required (Table 2). However, isolation of products is extremely facile. Minor changes in *ortho–para* ratios are observed relative to results in Table 1. These changes may reflect a minor influence of the silica gel.

A further extension beyond the successful nitration of these relatively activated aromatic substrates is to use suspended

Table 3. Nitration of deactivated aromatic compounds



(3)



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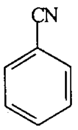


(5)

Entry	Substrate	H_2SO_4 (equiv.)	Nitrated Pdts yield (%)
1	(**3**)	2	0
2	(**3**)	5	94
3	(**3**)	5[a]	98
4	(**3**)	5[b]	95
5	(**4**)	5	98[c]
6	(**5**)	5	75[d]
7	(**3**)	10[e]	0

[a] KNO_3 in place of CAN.

[b] Bu_4NNO_3 in place of CAN.

[c] 2,4-dinitro–2,6-dinitro (71:29) products.

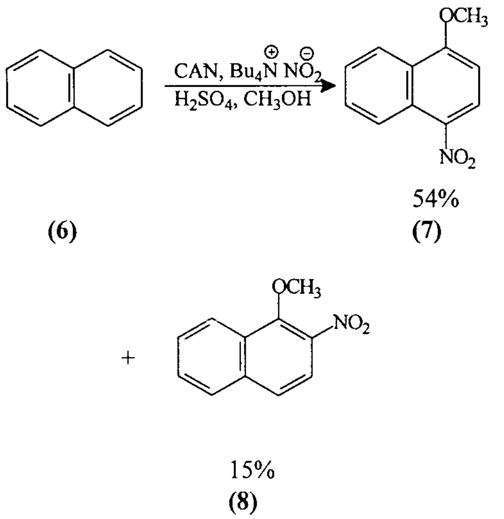
[d] *ortho–meta* (20:80) products, based on unreacted starting material.

[e] H_2SO_4-silica.

metal nitrates in the nitration of deactivated aromatics. Accordingly we have developed an efficient procedure proceeding at room temperature involving use of 1 equiv. of CAN suspended in dichloromethane in the presence of 5 equiv. of sulfuric acid. As described in Table 3, nitration to afford products from deactivated benzenes is efficient. Not only can nitrations be achieved in dichloromethane using CAN, but potassium nitrate or tetrabutyl ammonium nitrate can also be used, for example using *para*-nitrotoluene (**3**) as substrate, 2,4-dinitrotoluene is obtained in 98 and 95% yield, respectively (Table 3, entries 3 and 4).

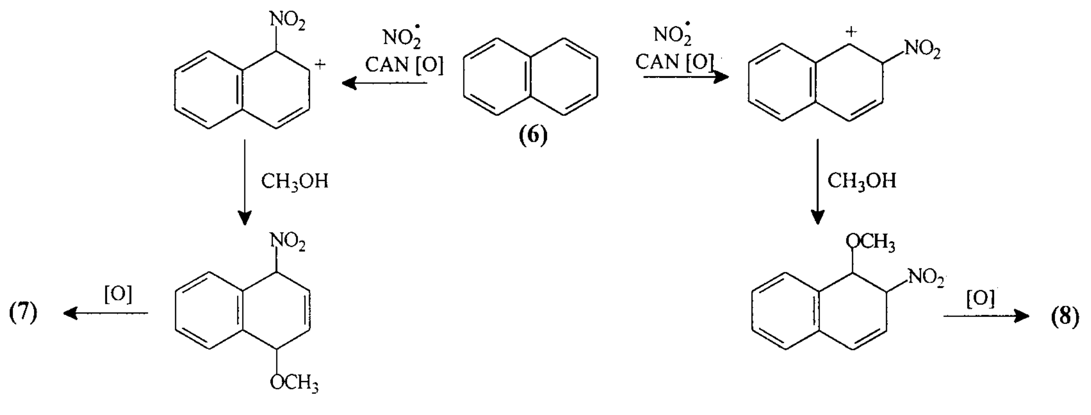
In contrast to the dinitration of the more activated aromatic substrates, with deactivated substrates, for example *para*-nitrotoluene (**3**), further nitration using supported silica gel does not proceed. However these very simple procedures establish that the use of suspended nitrate salts in dichloromethane is applicable to a good range of substituted benzenes, and a slight increase in acid component is able to bring about reaction of a deactivated substrate (Table 3, compare entries 1 and 2). The use of such cheap reagents with few problems in work up may be compared with other recently described nitration methods. Reactions with a vanadium nitrate,[3] or with the ytterbium,[8] hafnium[9] and zirconium[9] triflates offer little advantage relative to the mild and economical conditions described in this paper.

The observation of significant catalysis of aromatic nitrations from added metal salts raises the question of the mechanism of our CAN nitrations of substituted benzenes. Our observation of *ortho–para* ratios characteristic of nitronium ion nitrations, and the similarity of the outcome of reactions conducted with potassium nitrate or tetrabutyl ammonium nitrate strongly suggest the absence of any special catalytic effect associated with the ceric ion. If the ceric ion is promoting reaction in a manner analogous to ytterbium or hafnium, the effect is minor. In contrast, we can report unusual mechanistic features of the reaction of CAN with naphthalene (**6**) in the presence of methanol or ethanol. In the presence of sulfuric acid and tetrabutyl ammonium nitrite, nitration gives 1-methoxy-4-nitronaphthalene (**7**) and 1-methoxy-2-nitronaphthalene (**8**) in 54 and 15%, respectively (Eq. (2)).



(2)

In addition to the surprising formation of these two products, we can report the further observations that replacement of CAN with other metal nitrates (potassium nitrate or copper nitrate) affords no products of nitration, naphthalene is recovered. Of further interest is the role of the tetrabutyl ammonium nitrite. Removal of the nitrite species from the mixtures halted progress of the reaction, indicating it plays an essential part in the procedure. These preliminary observations establish that, in contrast to the nitration of the simple aromatic substrates outlined earlier in this paper, formation of these disubstituted naphthalenes follows a reaction path likely to be one other than through the classical nitronium ion mechanism. This is further substantiated by the ratio of α–β nitration. The ratio of α to β attack has been used[22] as an effective indicator of the mechanism of nitration of naphthalene. Conventional nitronium ion attack always leads to a high α–β ratio (typically >20). In contrast, the anomalous α–β ratio (3 to 4) observed in the formation of (**7**) and (**8**) adds weight to our hypothesis that the mechanism is not consistent with an initial nitronium ion attack. Alternative mechanisms might include a SET process in which naphthalene is oxidised to a cation



Scheme 1.

radical by CAN and quenched by methanol to give methoxynaphthalenes which are then nitrated. Control experiments establish methoxynaphthalenes are not intermediates; 1- and 2-methoxynaphthalene do not give the products (**7**) and (**8**) or other products in significant yield. Thus a SET mechanism leading to these intermediates can be rejected. In addition, SET processes are associated with high α–β ratios (~35:65), which is not the outcome in our case.

Finally a third possible mechanism might proceed via an attack of naphthalene on the NO_2 radical. Such nitrations are known and are characterised by unusually low α–β ratios. CAN is a powerful oxidising agent. Hence oxidation of nitrite ion to give a radical species able to react with naphthalene, and then to further oxidise the cyclohexadienyl radical to give a cyclohexadienyl cation trapped by methanol is not unexpected (Scheme 1). Clearly such a reaction sequence would not be possible with potassium nitrate or tetrabutylammonium nitrate. Therefore in contrast to the earlier nitrations of substituted benzenes with CAN, the nitration of naphthalene in the presence of added tetrabutylammonium nitrite requires a different pathway. The differing pathways establish that CAN and other metal nitrates can be used in improved nitration procedures.

Experimental

Melting points were determined in a capillary tube using an Electrothermal melting point apparatus, and are uncorrected. Mass spectra were recorded using a Thermoquest Trace MS with Trace GC instrument. Infra-red spectra were recorded on a Perkin–Elmer 298 spectrometer, as solutions in dichloromethane. ^{1}H Nuclear magnetic resonance spectra were recorded in $CDCl_3$, using a Bruker 300 MHz spectrometer, with residual protic solvent $CHCl_3$ (δ_H=7.26 ppm) as internal reference or tetramethylsilane as internal reference. Coupling constants are measured in Hertz (Hz). ^{13}C NMR spectra were recorded at 68 MHz using a Joel spectrometer, and are reported as position (δ_C) using tetramethylsilane as reference. Short flash column chromatography was carried out on Kiesel gel 60G silica gel (Merck) in a glass column using solvents as stated. Thin layer chromatography was performed on silica gel (Merck) mounted on aluminium cards. All substrates were used as purchased from Aldrich without further purification.

Silica gel supported sulfuric acid

Silica gel (20 g) was soaked with a 50% solution of sulfuric acid (25 mL) and evaporated under reduced pressure to afford a white free flowing powder. The powder was stored in an air tight vessel until used. For this reagent, 0.24 g of material contained 1 mmol of sulfuric acid.

Silica gel supported ceric ammonium nitrate (CAN)

Dichloromethane (10 mL) was added to a solution of ceric ammonium nitrate (2 g, 3.65 mmol) in methanol (15 mL) followed by silica gel (10 g). The resulting slurry was efficiently shaken and the solvent removed under reduced pressure. The product was dried on a rotary evaporator to afford a free flowing yellow powder. For this reagent, 3.2 g of powder contained 1 mmol of CAN.

Nitration of simple aromatic substrates

General procedure for nitrations involving CAN. To CAN (1 equiv.) in dichloromethane (6 mL) was added the substrate (1 equiv.) followed by concentrated sulfuric acid (2 equiv.) at room temperature. The resulting mixture was allowed to stir at room temperature for up to 18 h. The product was extracted into dichloromethane and the organic phase washed with saturated sodium bicarbonate solution followed by distilled water. The crude product was dried ($MgSO_4$), filtered and the solvent evaporated to yield the nitrated material which was thus analysed by NMR. The results are summarised in Tables 1 and 2.

General procedure for nitrations involving potassium nitrate. Reactions were performed according to the general procedure outlined for the nitrations involving CAN, except that CAN was replaced by potassium nitrate. The results are summarised in Table 1.

General procedure for nitrations using silica supported sulfuric acid and CAN. To CAN (1 equiv.) suspended in dichloromethane (20 mL) was added the substrate (1 equiv.) followed by silica supported sulfuric acid (10 equiv.) at room temperature. The resulting mixture was allowed to stir at room temperature for up to 18 h. The silica supported sulfuric acid was then filtered off through a sintered funnel and the resultant solution was washed with saturated sodium bicarbonate solution followed by distilled water. The organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo to afford the nitrated material which was thus analysed by NMR. The results are summarised in Table 2.

Nitration of deactivated aromatics

Reactions were performed according to the general procedure outlined above for CAN, using CAN, potassium nitrate and tetrabutyl ammonium nitrate. Also 5 equiv. of sulfuric acid were used. The results are summarised in Table 3.

Nitration of naphthalene with silica gel supported ceric ammonium nitrate (CAN) and silica gel supported sulfuric acid in the presence of tetrabutyl ammonium nitrite

Silica gel supported sulfuric acid (1.2 g, 5 mmol) was added to a slurry of CAN–silica gel (16.9 g, 5 mmol) in dichloromethane (30 mL) at room temperature to give a yellow mixture. Tetrabutyl ammonium nitrite (0.29 g, 1 mmol) was added to the slurry followed by the dropwise addition of naphthalene (0.13 g, 1 mmol) in dichloromethane (1 mL). The reaction was allowed to stir for 2 h. The silica gel was removed by vacuum filtration, the resulting filtrate was washed with water (2×200 mL), dried over anhydrous magnesium sulfate and the solvent removed in vacuo. The crude material was purified by column chromatography on silica gel using petroleum ether–ethyl acetate (95:5) as eluant to yield 1-nitronaphthalene (0.14 g, 81%) as a bright yellow crystalline solid, mp 53–55°C (Lit[23] 58–59°C).

Procedure for the reaction of naphthalene with CAN and tetrabutyl ammonium nitrite in the presence of sulfuric acid using methanol as solvent

To CAN (8 mmol) in methanol (20 mL) was added tetrabutyl ammonium nitrite (1 mmol) followed by naphthalene (1 mmol). To this was added concentrated sulfuric acid (5 mmol) and the resulting mixture was allowed to stir at room temperature for approximately 18 h. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (1×100 mL) and the products extracted into dichloromethane (2×100 mL). The combined organic extracts were washed with distilled water (1×100 mL), dried over anhydrous magnesium sulfate and the solvent evaporated. The resulting crude mixture was purified by column chromatography on silica gel using petroleum spirit–ethyl acetate (9:1) as eluant. Column chromatography yielded the following two products.

1-Methoxy-2-nitronaphthalene (8). (30 mg, 15%) as a pale yellow solid, mp 76–77°C (Lit[24] 80°C); δ_H 4.16 (3H, s, OCH_3), 7.60–7.75 (2H, m), 7.65 (1H, d, J=9.6 Hz), 7.85–7.95 (1H, m), 7.90 (1H, d, J=9.6 Hz), 8.30–8.35 (1H, m); δ_C 63.8 (OCH_3), 121.1, 124.3, 124.5, 127.7, 128.4, 128.7 (q), 129.6, 136.6 (q), 139.2 (q), 151.8 (q); ν_{max} (CH_2Cl_2)/cm^{-1} 3072, 3043, 1587, 1527, 1416, 1351, 1274, 1248, 1085; m/z 203 (M^+, 61), 173 (28), 127 (100), 114 (79); Found M^+=203.0578, $C_{11}H_9NO_3$ requires 203.05824.

1-Methoxy-4-nitronaphthalene (7). (109 mg, 54%) as a yellow solid, mp 81–83°C (Lit[25] 85°C); δ_H 4.00 (3H, s, OCH_3), 6.69 (1H, d, J=8.8 Hz, 2-H), 7.48 (1H, ddd, J=1.48, 7.0, 8.5 Hz 7-H), 7.65 (1H, ddd, J=1.5, 7.0, 8.5 Hz 6-H), 8.25 (1H, d, J=8.8 Hz, 8-H), 8.29 (1H, d, J=8.8 Hz, 3-H), 8.68 (1H, d, J=8.8 Hz, 5-H); δ_C 56.4 (OCH_3), 102.0, 122.9; 123.6, 125.7 (q), 126.7, 127.0 (q), 127.4, 130.2, 139.3 (q), 160.7 (q); ν_{max} (CH_2Cl_2)/cm^{-1} 3051, 1629, 1573, 1513, 1402, 1425, 1323, 1272, 1127, 1102; m/z 203 (M^+, 42), 187 (12), 173 (32), 157 (26), 114 (100); Found M^+=203.05824, $C_{11}H_9NO_3$ requires 203.05824.

Procedure for the reaction of naphthalene with CAN and tetrabutyl ammonium nitrite in the presence of sulfuric acid using dichloromethane as solvent

To CAN (8 mmol) in dichloromethane (20 mL) was added tetrabutyl ammonium nitrite (1 mmol) followed by naphthalene (1 mmol). To this was added concentrated sulfuric acid (5 mmol) and the resulting mixture was allowed to stir at room temperature for approximately 18 h. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (1×100 mL) and the products extracted into dichloromethane (2×100 mL). The combined organic extracts were washed with distilled water (1×100 mL), dried over anhydrous magnesium sulfate and the solvent evaporated. The resulting crude mixture was purified by column chromatography on silica gel using petroleum spirit–ethyl acetate (9:1) as eluant.

Column chromatography yielded 1-nitronaphthalene (105 mg, 61%) as a yellow solid, identical to an authentic sample.

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