

A REINVESTIGATION OF NITRATION OF PHENOLS WITH METAL NITRATES UNDER NON-AQUEOUS AND APROTIC CONDITIONS[☆]

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ABSTRACT: Nitration of phenol and various 4-substituted phenols with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in different anhydrous organic solvents are investigated. High selectivity ratio of para vs ortho isomers has been observed. Mono- and dinitro compounds from phenol and 4-substituted phenols by choosing the proper solvents and reaction conditions, are also obtained with high selectivity in excellent yields. Rate enhancement for mononitration of phenols in the presence of LiClO_4 with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ is observed.

KEY WORDS: Nitration, Metal nitrates, Mononitration, Dinitration, Phenol.

INTRODUCTION

Synthetic methodology is important and investigation for the new reagents, reaction conditions, efficiency and selectivity of the method is of interest in organic synthesis. Nitration of aromatic rings is one of the old classical organic reactions which most organic chemists have closed its file. Many practical problems are remained unsolved and reinvestigation of the reactions and improvement of the yields of one product versus another eg., 4-nitrotoluene vs 2-nitrotoluene, or 4-nitrophenol vs 2-nitrophenol is important from environmental consideration, and production of 2-nitroestrone versus 4-nitroestrone is important from pharmaceutical points of views [1,2].

A survey of the literature indicates the lack of entire selectivity of nitration of phenol and gives 67% of ortho isomer versus 33% of para isomer [1]. It is pointed out by different investigators that the yields and the regioselectivity of the reactions are dependent on the nature of the solvents [1-3b], the nitrating agents, reaction conditions, and so on [1-3]. Nitration of aromatic rings of different aromatic compounds has been performed by $\text{NaNO}_2/\text{HNO}_3$ / an aromatic solvent [3], $\text{HNO}_3/\text{H}_2\text{SO}_4$ [4,5], N-nitropyrazole/ $\text{BF}_3 \cdot \text{ET}_2\text{O}/\text{CH}_2\text{Cl}_2$ [6], via nitroso compounds and their subsequent oxidation to nitro compounds with HNO_3 [7], metallic nitrates in protic solvents [8-10],

[☆] Dedicated to Professor Abbas Shafiee on the occasion of his 60th birthday.

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$\text{NaNO}_3/\text{H}_2\text{SO}_4/\text{NaNO}_2$ [11], $\text{NaNO}_3/\text{HCl}/\text{La}(\text{NO}_3)_3/\text{Et}_2\text{O} \cdot \text{H}_2\text{O}$ [12], $\text{AgNO}_3/\text{BF}_3/\text{CH}_3\text{CN}$ [13], graphite nitrate [14], tetranitromethane [14], clay supported nitrates [1,2,15], impregnated alumina and silica with N_2O_4 [1,16]. AcONO_2 [17], BzONO_2 [18,19] and TfONO_2 [20] serve as nitronium delivery sources. Some of these methods require strong acidic media and some of them proceed in aqueous media which usually produce messy reaction mixtures [11b,21] and make the work up a tedious process. Some of them suffer from long reaction times (20 hours) and some other do not give reproducible results [1]. e.g. clayfen which is a useful reagent for the nitration, suffers from being unstable and the preparation and storage of the reagent need precautions. The reaction times are usually long (20 hours) and the reagent is strongly acidic in nature [2].

EXPERIMENTAL

Chemicals were purchased from *Fluka*, *Aldrich*, *Merck* and *Riedel-Dehaen AG* Chemical Companies. All the solvents must be completely dried and redistilled. Commercial silica gel plates 60 F₂₅₄ were used to monitor the progress of reactions. Column chromatography was carried out using silica gel 60. Yields refer to isolated pure products after column chromatography. Products were characterized by comparison with authentic samples (mp, IR and NMR spectra).

General procedure for nitration of phenol

To a solution of phenol (2 mmol) in an appropriate solvent (4 mL), the metal nitrate was added (the molar ratio of the metal nitrate to the substrate was optimized on the basis of formation of mono- or dinitrated products, Tables 1-5 and 8). The mixture was stirred vigorously at room temperature or under reflux conditions. The progress of the reaction was monitored by TLC. The reaction mixture was pre-sorbed on silica gel (5 g) and the resulting mixture was applied on a silica gel column and eluted with petroleum ether/acetone (9:1) for the separation of mononitrated products and petroleum ether/EtOAc (3:1) for the separation of dinitrated products.

Mononitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$

as a typical procedure

A mixture of phenol (188 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (482 mg, 2 mmol) in acetone (4 mL) was stirred vigorously at room temperature for 6 hours and after column chromatography on silica gel with petroleum ether/acetone (95/5) 2-nitrophenol, 77 mg, 28%, mp 46 °C, (lit. [10] mp 44 °C) and 4-nitrophenol, 154 mg, 56%, mp 112-113 °C (lit. [10] mp 114 °C) and benzoquinone, 11 mg, 5%, mp 113-114 °C, (lit. [5] mp 115 °C) were isolated.

Dinitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as a typical procedure

Phenol (188 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (1.446 g, 6 mmol) were added to EtOAc (4 mL) and the mixture was stirred vigorously under reflux conditions for 0.4 hours. Column chromatography on a short column of silica gel with petroleum ether/EtOAc (3:1) gave 2,4-dinitrophenol as pale yellow crystals, 328 mg, 90%, mp 112-113 °C, (lit. [10] mp 113 °C).

Preparation of silica gel supported $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$

$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (10 g) and silica gel (100 g) were mixed together in acetone (500 mL) and the mixture was stirred magnetically at room temperature for 24 hours. Evaporation of the solvent and drying the solid material under vacuum resulted a pale blue solid.

Mononitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$ as a typical procedure

Phenol (188 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$ (2 mmol, 2.482 g) in acetone (4 mL) were stirred vigorously at reflux condition for 0.25 hours. 2-Nitrophenol, 111 mg, 40%, mp 46 °C (lit. [10] mp 44 °C), 4-nitrophenol, 146 mg, 54%, mp 112-113 °C (lit. [10] mp 114 °C) and benzoquinone, 12 mg, 4%, mp 113-114 °C (lit. [5] mp 115 °C) were separated and purified by column chromatography on silica gel with petroleum ether/acetone (95/5).

Dinitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$ as a typical procedure

A mixture of phenol (188 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$ (6 mmol, 7.446 g) in ethyl-

acetate (12 mL) was prepared. The mixture was stirred vigorously under reflux condition for 3 hours. After column chromatography on silica gel using petroleum ether/EtOAc (3:1) as eluent, 2,4-dinitrophenol was obtained as pale yellow crystals, 250 mg, 94%, mp 112-113 °C, (lit. [10] mp 113 °C).

General procedure for nitration of 4-substituted phenols

To a solution of the phenolic compound (2 mmol) in an appropriate solvent (4 mL) metal nitrate was added (The molar ratio of metal nitrate to the substrate was optimized on the basis of the required conditions for mono- or dinitration reactions, Table 9). The mixture was stirred vigorously at room temperature or under reflux conditions. The progress of the reaction was monitored by TLC. The reaction mixture was presorbed on silica gel (5 g) and the resulting mixture was applied on a silica gel column and eluted with petroleum ether: acetone (9:1) for the separation of mononitrated products and petroleum-ether/EtOAc (3:1) for the separation of dinitrated products.

Mononitration of 4-chlorophenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as a typical procedure

A mixture of 4-chlorophenol (257 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (482 mg, 2 mmol) in acetone (4 mL) was prepared. The mixture was stirred vigorously under reflux conditions for 0.28 hours. After column chromatography on silica gel with petroleum ether:acetone (9:1) 4-chloro-2-nitrophenol was obtained as yellow needle crystals, 328 mg, 95%, mp 89 °C (lit. [10] mp 91 °C).

Dinitration of 4-chlorophenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as a typical procedure

4-Chlorophenol (257 mg, 2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (1.45 g, 6 mmol) were mixed together in EtOAc (4 mL). The mixture was stirred vigorously under reflux conditions for 1 hour. After column chromatography on silica gel using petroleum-ether/EtOAc (3:1) as eluent, 4-chloro-2,6-dinitrophenol was obtained as pale yellow crystals, (420 mg, 97%), mp 78-79 °C. (lit. [23] mp 81 °C).

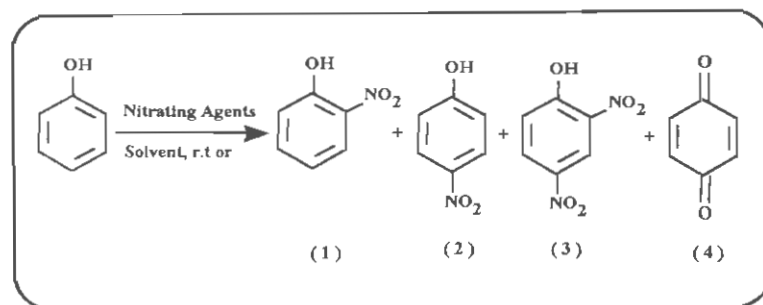
Mononitration of phenol with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$

under solid phase conditions as a typical procedure

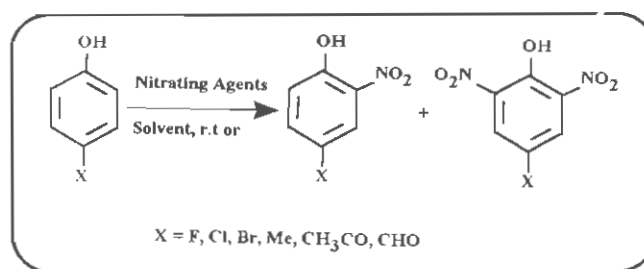
A mixture of phenol (188 mg, 2 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (808 mg, 2 mmol) was prepared and was allowed to stand at room temperature for 4 hours. The resulting mixture was dissolved in acetone (2 mL) and was presorbed on silica gel (5 g). The resulting silica gel mixture was applied on a silica gel column and eluted with petroleum ether/acetone (95/5) to afford 2-nitrophenol, 92 mg, 33%, mp 45 °C (lit. [10] mp 44 °C), and 4-nitrophenol, 173 mg, 63%, mp 113-114 °C (lit. [10] mp 114 °C).

RESULTS AND DISCUSSION

Nitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in EtOH is reported [10]. We have tried this reaction and have found that the results are not reproducible and the reagent does not nitrate phenol in EtOH. The other investigators have also reached more or less to this conclusion [1]. In the report [10] the authors have also concluded that the nitration of phenol with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in CHCl_3 results a total yield of para and ortho isomers equal to 79% with the ortho/para ratio equal to 1.7. We have reinvestigated this reaction and have found that the total yield of the two isomers does not exceed 49% and the ratio of ortho/para isomers is equal to 0.8%. The mononitration of *p*-cresol with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in EtOH is also reported to yield 2-nitrocresol in 83% [10]. We have tried this reaction under the same reaction conditions but the isolated yield of the product does not exceed 40%. $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ is believed to be the best nitrating agent in EtOH for nitration of phenol with para selectivity (76%) with a total yield of para and ortho isomers equal to 100% [1,10]. We have reinvestigated this reaction as reported in the literature [10]. Surprisingly, we have found that the para isomer formation does not exceed 56% with the total yield of the two isomers equal to 93%. These contrary not reproducible results and also the importance of the nitration reactions prompted us to reinvestigate the nitration of phenol (Scheme 1) and 4-substituted phenols (Scheme 2) with the three formerly reported reagents; $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ [10] but under new reaction conditions and also to investigate



Scheme 1



Scheme 2

the nitrating properties of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ supported on SiO_2 and in the presence of LiClO_4 and β -cyclodextrins, and also saturated solution of fructose, glucose and sucrose in acetone.

In this study we report that $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ is able to nitrate phenol (Scheme 1) in dry solvents such as; acetone, EtOAc, Et_2O , CHCl_3 , THF and HOAc. We have recognized that acetone is a good solvent for this purpose in which the lowest ratio of ortho/para isomers equal to 0.5 is observed with the total yield of the two isomers equal to 77-84%. Et_2O is also a suitable solvent and the total yield of the two isomers is increased to 91%, but the ratio of ortho/para isomers increases to 1.06. The results and the reaction conditions are tabulated in Table 1.

The ratios of the products do not alter by changing the molar ratios of the substrates towards $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (0.33-1). Except in EtOH, in which the reaction does not work and in Et_2O that the ratio of ortho/para isomer is >1 , in the other solvents this ratio is in the range of 0.5-0.81 which is either equal or smaller than is reported by clayfen nitration of phenols [1b]. Except in CHCl_3 , in which the total yield of the isomers drop to 49%; in the other solvents, total yields 75-95% have been obtained by this reagent. Silica gel supported $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$

has been also studied as a new nitrating agent for nitration of phenol in dry solvents such as; acetone, EtOAc, CHCl_3 , Et_2O , THF, HOAc and EtOH at room temperature or under reflux conditions. Except in EtOH, in the other solvents acceleration of the formation of ortho isomer is observed. The best total yield of the two isomers (97%) is obtained in Et_2O at room temperature with ortho/para ratio equal to 0.86 but the best ortho/para ratio 0.77-0.81 is obtained in acetone with the total yield equal to 85-92%. The advantage of the silica supported reagent is the easy work up of the reaction mixture and the high rate of the reactions. The results and the reaction conditions are summarized in Table 2.

$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in the presence of 0.5 molar solution of LiClO_4 in the solvents under our investigation, enhances the rate of mononitration of phenol but does not affect the ortho/para ratio of the isomers (Table 3). Addition of cyclodextrine and other carbohydrates such as glucose, fructose and sucrose to the reaction mixture do not effect the ortho/para ratio of the two isomers.

Nitration of phenol by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ has been reported by different research groups [1,2,10]. We have reinvestigated this reaction in dry solvents such as acetone, EtOAc, HOAc, Et_2O , THF and EtOH and

Table 1: Mononitration of phenol (see Scheme 1) with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$

Solvent	Reaction conditions			Products distribution ^a			Total yield	Ortho
	Reflux (h)	RT (h)	Subst. Reagent	(1) %	(2) %	(4) %	(1+2) %	Para
Acetone	0.66	6	1	26-28	51-56	5-6	77-84	0.51-0.5
Acetone	—	5	0.33	27	54	7	81	0.5
EtOAc	—	2	1	31	52	4	83	0.6
HOAc	—	0.25	2	31	50	3	81	0.62
CHCl_3	0.4	—	1	22	27	4	49	0.81
Et_2O	—	48	1	no reaction				
Et_2O	8	—	1	47	44	0	91	1.06
THF	—	24	1	29	36	5	65	0.8
THF	—	20	0.33	41	54	2	95	0.76
EtOH	48	48	1	no reaction				

a : Isolated yields by column chromatography.

Table 2: Mononitration of phenol (see Scheme 1) with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{Si}_2\text{O}$.

Solvent	Reaction conditions			Products distribution ^a			Total yield	Ortho
	Reflux (h)	RT (h)	Subst. Reagent	(1) %	(2) %	(4) %	(1+2) %	Para
Acetone	0.16	4	1	38-40	47-52	3-4	85-92	0.77-0.81
EtOAc	0.1	4	1	42-45	46-47	7-8	88-92	0.9-0.96
HOAc	—	0.16	2	43	42	13	85	1
HCCl_3	—	1.5	1	34	43	8	77	0.79
Et_2O	—	1	1	45	52	3	97	0.86
THF	—	5.5	1	31	42	12	73	0.74
EtOH	24	24	1	a polymeric mass				

a : Isolated yields by column chromatography.

also in the absence of solvent at room temperature. THF and HOAc are found to be suitable solvents for this purpose. In THF a total yield of the two isomers equal to 93% is obtained with ortho/para ratio equal to 0.75. In HOAc a total yield equal to 82% with the ortho/para ratio equal to 0.6 are observed. Surprisingly, we have found that $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ is able to nitrate phenol in solid phase by mixing the substrate with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ powder in 1:1 molar ratio at room temperature. The reaction mixture

thaws as the reaction proceeds to completion in 4 hours. The yield of the product is excellent (96%) and the ratio of ortho/para isomers is 0.52. Whereas, for clayfen this ratio is 0.81 with the total yield of 90.5% and the reaction proceeds about 20 hours. This is a promising results for our solid phase reaction method. We may also conclude that $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in the above mentioned solvents works better than its clay supported analogue; clayfen [1,2,15]. In our opinion, this method is advantageous over clayfen

Table 3: Mononitration of phenol (Scheme) with $\text{Cu}(\text{NO}_2)_2 \cdot 3\text{H}_2\text{O}$ in the presence of LiClO_4 .

Solvent	Reaction conditions			Products distribution ^a			Total yield	Ortho
	Reflux ^b (h)	Subst. Reagent	Molarity of LiClO_4^c	(1) %	(2) %	(4) %	(1+2) %	Para
Acetone	6	1	0	27	60	5	87	0.45
Acetone	3.5	1	0.5	43	42	2	85	1.02
Acetone	1.5	1	2.5	10	23	1	33	0.43
Et_2O	48	1	2.5	10	23	1	33	0.43
Et_2O	8(34 °C)	1	0	47	44	2	91	1.06
Et_2O	immediately	1	2.5	21	52	5	73	0.40
Et_2O	0.08	1	0.5	36	47	1	83	0.76
Et_2O	1	1	5.5	0	14	0	14	0
THF	8	1	0	29	36	5	65	0.80
THF	6	1	0.5	35	45	2	80	0.77
EtOAc	2	1	0	31	52	4	83	0.59
EtOAc	0.16	1	0.5	45	45	1	90	1

a : Isolated yields by column chromatography.

b : The time which was required for the complete consumption of phenol during the reactions.

c : Reaction rates were accelerated in the presence of LiClO_4 , but production of undesired coupling products of phenol were observed which affects the yield of the nitrated phenol.

Table 4: Mononitration of phenol (see Scheme 1) with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$.

Solvent	Reaction conditions			Products distribution ^a			Total yield	Ortho
	Reflux (h)	RT (h)	Subst. Reagent	(1) %	(2) %	(4) %	(1+2) %	Para
Acetone	—	0.75	1	42	41	5	83	1.02
EtOAc	—	1.75	1	42	46	1	88	1.1
HOAc	—	0.25	1	31	51	2	82	0.6
Et_2O	—	1	1	22	29	4	51	0.76
Et_2O	—	3.5	2	47	46	3	93	1.02
THF	—	5.5	2	40	50	1	90	0.8
THF	—	1.2	1	40	53	5	93	0.75
EtOH	—	18	1	34	43	1	77	0.79
CHCl_3	—	7	1	40	47	1	87	0.85
— ^b	—	4	1	33	63	1	96	0.52

a : Isolated yields by column chromatography.

b : Solid phase reaction.

with respect to the following facts; a) stability of the reagent, b) much shorter reaction times and c) lower ortho/para ratios. The results and the reaction conditions are tabulated in Table 4.

Nitration of phenol with $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ is also

reinvestigated in different solvents such as acetone, EtOAc, THF, CHCl_3 , Et_2O and EtOH under various reaction conditions. It is found that excellent total yields equal to 93-100% with ortho/para ratio equal to 0.61-0.8 are observed in acetone, EtOAc, THF and

EtOH. Solid phase reaction with this reagent is very sluggish and only 20% of the two isomers are isolated after 20 hours. The results are shown in Table 5.

In all the above mentioned methods, benzoquinone (4) is the side product of the reactions and has been isolated in 1-12% yields (Table 1-5). A competitive reaction is performed between phenol and anisol by the above mentioned methods. We have ob-

served that phenol nitration is proceeded smoothly with high yields, whereas anisol is remained intact in the reaction mixtures.

For comparison and showing the advantages and disadvantages of the methods with those reported in the literature, some of the results are summarized in Tables 6 and 7.

High yields selective formation of mononitrated

Table 5: Mononitration of phenol (see Scheme 1) with $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$.

Solvent	Reaction conditions			Products distribution ^a			Total yield	Ortho
	Reflux (h)	RT (h)	Subst. Reagent	(1) %	(2) %	(4) %	(1+2) %	Para
Acetone	—	14	1	39	59	1	98	0.66
Acetone	0.5	—	2	44	55	1	99	0.80
EtOAc	—	24	1	9	17	—	26	0.53
EtOAc	0.16	—	2	42	58	0	100	0.72
THF	—	24	1	37	60	1	97	0.61
THF	1	—	2	42	52	1	94	0.80
CHCl_3	—	24	1	4	17	—	21	0.23
CHCl_3	1	—	1	37	42	—	79	0.88
CHCl_3	1.5	—	2	32	43	—	75	0.74
Et_2O	—	24	1	nor reaction				
Et_2O	8.5	—	1	31	42	0	73	0.74
EtOH	65 °C(1)	—	1	36	56	2	93	0.64

a : Isolated yields by column chromatography.

Table 6: Distribution of products of nitration of phenol by different methods.

	Method					Our methods				
	Classical procedures[5]	Kagan et al.[12]	Gaud et al.[25]	Thompson et al.[11]	Laszlo et al.[1b,2] (clayfen)	Yield ^a				
						A	B	C	D	E
Ortho %	36	55	39	55.7	40.5	28	40	33	40	39
Para %	25	26	26	41.3	50	56	52	63	53	59
Overall yield %	61	81	65	97	90.5	84	92	96	93	98
Starting material %	—	7	8	—	—	0	0	0	0	0
Ortho/Para	1.44	2.1	1.5	1.34	0.81	0.5	0.77	0.52	0.75	0.66

a : Isolated yield after column chromatography. A) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{acetone}$. B) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2/\text{acetone}$.

C) Solid phase reaction with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$. D) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{THF}$, E) $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{acetone}$.

Table 7: Comparison of the results with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in THF and solid phase $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (our observation) with those reported by $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in THF[1b], $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ in PhMe[1b] and clayfen[1b] in THF.

	$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$				Clayfen[1b]
	THF (Our observation)	THF (Reported)[1b]	Solid phase	PhMe (Reported)[1b]	
Ortho %	40	35	33	23	40.5
Para %	53	33	63	28	50
Overall yield %	93	68	96	51	90.5
Starting material %	0	<10	0	15	0
Ortho/Para	0.75	1.1	0.52	0.82	0.81

Table 8: Dinitration of phenol (see Scheme 1) with the nitrating agents.

Reagent	Solvent	Reaction conditions		(3) ^a
		Reflux (h)	Subst. Reagent	
$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$	EtOAc	0.41	0.33	90
$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$	EtOAc	3	0.33	94
$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	EtOAc	3	0.33	94
$\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	EtOAc	5	0.25	94

a: Isolated yields by column chromatography.

phenols versus dinitrated ones and vice versa is an achievement for the synthesis of chemically useful compounds. Dinitration of phenols by metal nitrates has not been reported before. We have investigated these reactions with the nitrates under our studies. We have found that they proceed very well with absolute selectivities and with excellent yields in many cases. The selectivity is easily achieved by controlling the reaction temperature and the nature of the solvents. The reaction conditions and the yields of the products are shown in Tables 8 and 9 (Schemes 1 and 2).

The results of selective mono- and dinitration of various 4-substituted phenols are shown in Table 9.

Comparison of the results of the methods under our investigations with some of those reported in the literature are shown in Table 10.

To the best of our knowledge dinitration of 4-substituted phenols with nitrates has not been reported in the literature. This reaction has also been

studied with the above mentioned reagents. We have found that dinitration of various 4-substituted phenols (Table 9, Scheme 2) may be achieved very easily in EtOAc and acetone under reflux conditions with high selectivity and high yields. We have not been successful in dinitration of 4-carbonyl (CH_3CO and CHO) substituted phenols.

CONCLUSIONS

In this study we have reinvestigated the nitration of phenol and 4-substituted phenols with metal nitrates in dry organic solvents and also under solid phase conditions. Our results show that these reactions are very sensitive towards reaction conditions and also the nature of the substituents and the nitrants. The experiments, under our investigations, show that unsupported $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ is more effective than clayfen in solution and in solid phase conditions and also from other points of views e.g.

time of reactions, yields of the products and handling of the reagent. Metal nitrates are also very useful reagents for the dinitration of phenol and 4-substituted phenols which has not been reported before. Silica gel supported $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ also shows a

good rate enhancement for the nitration of phenol and 4-substituted phenols with high yields. An advantage of this method is the ease of work up and the clean isolation of the product(s) from the reaction mixture.

Table 9: Mono- and dinitration of 4-substituted phenols (see Scheme 2) with the nitrating agents.

Reagent ^a	Solvent	X	Reaction conditions			Nitrated products(%)	
			Reflux (h)	RT (h)	Subst. Reagent	Mono ^b	Di
A	Acetone	F	0.25	5.5	1	91-93	0
A	EtOAc	F	1	—	0.33	0	98
A	Acetone	Cl	0.28	10	1	92-95	0
A	EtOAc	Cl	1	—	0.33	0	97
A	Acetone	Br	0.16	8	1	96-97	0
A	EtOAc	Br	1	—	0.2	0	97
A	Acetone	CH ₃	0.4	12	1	62-74	0
A	Acetone	CH ₃	0.86	—	2	62	0
A	EtOAc	CH ₃	—	1.66	1	67	0
A	EtOAc	CH ₃	0.25	—	0.33	0	75
A	Acetone	CH ₃ CO	—	2.5	1:1	97	0
A	Acetone	CHO	—	7	1:1	92	0
B	Acetone	F	0.08	3 ^a	1	97-100	0
B	Acetone	F	6	—	0.33	0	98
B	Acetone	Cl	— ^b	3	1	97	0
B	EtOAc	Cl	3.5	—	0.33	0	97
B	Acetone	Br	— ^b	3	1	95	0
B	EtOAc	Br	8	—	0.2	0	98
B	Acetone	CH ₃	0.08	10	1	65-70	0
B	EtOAc	CH ₃	0.75	—	0.33	0	75
B	Acetone	CH ₃ CO	1.25	—	1	96	0
B	Acetone	CHO	2	—	1	93	0
C	Acetone	F	— ^b	0.5	2	78	0
C	Acetone	F	— ^b	0.33	1	41	0
C	Acetone	F	2.66	—	0.33	0	63
C	EtOAc	F	1	—	0.33	0	85
C	Acetone	Cl	— ^b	1.5	1	100	0
C	EtOAc	Cl	3.5	—	0.33	0	100
C	Acetone	Br	—	1.25	1	100	0
C	EtOAc	Br	3	—	0.2	0	97
C	Acetone	CH ₃	— ^b	0.16	2.5	92	0
C	Ethanol	CH ₃	— ^b	(35°C)3	1	40+ unidentified compounds	0

Table 9 : Continued

Reagent ^a	Solvent	X	Reaction conditions			Nitrated products(%)	
			Reflux (h)	RT (h)	Subst. Reagent	Mono ^b	Di
C	Ethanol	CH ₃	— ^b	0.16	2.5	57+unidentified compounds	0
C	EtOAc	CH ₃	0.4	—	0.33	0	84
C	Acetone	CH ₃ CO	1.33	—	1	97	0
C	Acetone	CHO	1.5	—	1	93	0
D	—	Cl	—	0.05	2	46	0
D	—	Cl	—	0.16	1	91	0
D	—	Br	—	0.66	1	66	0
D	—	CH ₃	—	0.05	1	47	0
D	—	CH ₃ CO	—	48	no reaction		
D	—	CHO	—	48	no reaction		
E	Acetone	F	0.25	—	2	93	0
E	EtOAc	F	2.5	—	0.33	0	91
E	Acetone	Cl	1	—	2	94	0
E	EtOAc	Cl	0.75	—	0.2	0	93
E	Acetone	Br	1	—	2	85	0
E	EtOAc	Br	1	—	0.2	0	86
E	Acetone	CH ₃	0.25	—	2	85	0
E	EtOAc	CH ₃	0.25	—	0.33	0	88
E	Acetone	CHO	1.5	—	1	96	0
E	Acetone	CH ₃ CO	4	—	1	97	0

a : (A) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, (B) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2$, (C) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, (D) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ solid phase, (E) $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$

b : Mononitrated compound is produced cleanly at room temperature as the sole product.

Table 10: Comparison of mononitration of 4-substituted phenols (see Scheme 2) by our methods with those reported by the other investigators.

	Our methods(yield %) ^a					Other methods(yield %)	
	(A)	(B)	(C)	(D)	Clayfen[1b,2]	$\text{NaNO}_3/\text{La}(\text{NO}_3)_3$ [12]	$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ [10]
F	91-93	89	97-100	78	69	—	—
Cl	92-95	97	97	100	88	—	88
Br	96	95	95	100	—	—	64
CH ₃	62-74	28	65-70	92	58	77.5	83
COCH ₃	97	98	96	97	—	—	91
CHO	92	95	93	93	93	—	—

a : (A) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{acetone}$, (B) $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{acetone}$, (C) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}/\text{SiO}_2/\text{acetone}$, (D) $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{acetone}$.

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