



Microwave Assisted Catalytic Regio-selective Nitration of Resorcinol and Substituted Phenols

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Abstract Nitration of the organic compounds has been an important area of research with great industrial significance. Nitration of the aromatic substrates is a widely investigated reaction and has been of great industrial significance in industry and organic synthesis. In the present studies, solid phase microwave nitration of various substituted phenols and resorcinol has been investigated. Moreover, regioselective nitration of resorcinol and substituted phenols was optimized using different nitrating agents. The results showed that $\text{Cu}(\text{NO}_3)_2$ proved the most effective nitrating salt with the maximum yield of 26% and the most ineffective nitrating salt was KNO_3 with 5.4% yield. As far as microwave assisted nitration of substituted phenols using NaNO_3 /oxalic acid is concerned the maximum yield of 29% as 2-chloro-6-nitro phenol from 2-chloro phenol was obtained in the reaction. It was concluded from the current investigation that although microwave assisted nitration is more hazard free regioselective method of nitration, the low yield of the product is a concern and need further investigation to optimize the process for better yield and standardization.

Keywords Nitration, Microwave, Regioselective, Resorcinol, Nitrating agents

Introduction

Nitration of organic compounds has long been an important and attractive area of the research having a large body of literature available [1-6]. Nitration of aromatic substrates widely explored reactions and is of great industrial and synthetic importance. Several nitro-aromatics are being used as feedstock for pharmaceutical, dyes, agrochemicals and natural products synthesis. The introduction of the Nitro group to toluene gives nitrotoluene which can be nitrated to dinitrotoluenes. Consequently, further nitration of the dinitrotoluenes to yield trinitrotoluene (TNT). Toluene diisocyanate (TDI), feedstock for the polyurethanes is yielded from the conversion of dinitrotoluene. Moreover, dyestuffs and pharmaceuticals can be prepared by the reduction of nitro anisole to its corresponding amine used as an intermediate. A similar process can be performed with nitrochlorobenzene [7].

Nitrosubstituted aromatic compounds are important for the industrial production of a wide variety of essential chemical intermediates, high value commercial compounds such as p-nitrochlorobenzene and end products, including high energy explosives such as 2,4,6-trinitrotoluene (TNT) [7]. Nitrosubstituted aromatic compounds used as additives in plastics and rubbers and as an intermediate in dyestuffs and pharmaceuticals.

A reaction where one direction of the chemical bond creation or breaking took place, preferably over all other possible directions is known as regioselective reaction. The term was originally restricted to the addition reactions of unsymmetrical reagents to unsymmetrical alkenes. Earlier, the term regiospecificity was proposed for complete



regioselectivity. The terminology is not normally suggested because of inconsistency with the terms stereoselectivity and stereospecificity [8].

Phenols are aromatic rings containing -OH group which is an electron donating substituent, so the commercial nitration of phenols normally give rise to a mixture of predominantly ortho- and para- nitrated products, usually following statistical distribution. Similarly, in substituted phenols, due to the same ortho-para directing effect of -OH group, the formation of a single isomer does not occur normally, but if either of the positions is blocked by substitution then regioselective nitration does occur. However, methods have been developed for the regioselective nitration of phenols and substituted phenols [7- 9].

Resorcinol is a substituted Phenol in which a second hydroxyl group is substituted at position three. As both the substituents in resorcinol are electron donating group so substitution in resorcinol will readily occur at position 2, 4 and 6. Nitration of Resorcinol is not widely explored reaction. As resorcinol has electron donating groups so substitution reaction, i.e. nitration of resorcinol will give rise to a mixture of 2 and 4 or 6 substituted resorcinol. Nitration of resorcinol using nitrating mixture produces a relatively high concentration of 2-Nitroresorcinol. But this process has obvious disadvantages because it needs the use of concentrated nitric acid and sulfuric acid causing too much acid waste. These reagents create serious environmental issues and the treatment and disposal of 'used' acids are expensive. Additionally, another serious issue with this nitration concerns the regioselectivity (*i.e.* the product distribution in terms of the ortho:meta:para isomer ratio). However, no general method is available for the synthesis of 4-Nitroresorcinol. Therefore, attempts are required for its synthesis and for such methods which do not involve drawbacks of the commercialization process, i.e. the process should be selective, inexpensive, produce high yield and does not involve environmental hazards and byproducts. Sulfuric acid as solid plays an important role in the commercial manufacturing process, assisting in the nitronium species formation. Therefore, reduction in the spent acid generated during the reaction, increased selectivity of the product, may be achieved by the use of solid catalyst.

Material and Methods

Catalytic regioselective nitration of resorcinol and various substituted phenols, following microwave assisted nitration, was carried out. The various materials and instruments used during the experimental work are given below. Also the various procedures which have been followed are discussed below.

Materials and Instruments used in Experimental Work

All the reagents and solvents were obtained from commercial suppliers and were used after purification according to standard laboratory procedures. e.g., recrystallization, distillation and drying agents [10] etc. wherever needed. Monitoring of reactions and Rf values were carried out using Merck 60 F₂₅₄ silica gel, aluminum supported precoated silica gel TLC plates, and Visualization with UV light (254-365nm). Melting points were measured using Gallenkamp melting point apparatus in open capillaries. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker 300MHz in DMSO and CDCl₃ as solvent, using TMS as an internal standard IR-spectra were recorded using FTIR-8201PC, Shimadzu, while UV spectra were taken using Shimadzu UV spectrophotometer. Microwave oven used was GermanPool TM WP80020 microwave oven 800W, 2450 MHz. All the products were purified on flash. Silica column using 20% ethyl acetate/Hexane as eluting solvents.

Procedures used in Experimental Work

The 2-Nitroresocinol was prepared by commercial method while 4-nitroresorcinol (Fig. 1) and the other nitro substituted phenols were synthesized in microwave oven. The nitration of resorcinol was done by both commercial method and microwave method in order to see the difference in selectivity and other differences between the two methods.

Metal Nitrates used in the reactions

NaNO₃, KNO₃, AgNO₃, Ca(NO₃)₂, Sr(NO₃)₂, Cu(NO₃)₂, CO(NO₃)₂ and Bi(NO₃)₃, respectively.



Synthesis of 2-Nitroresorcinol

A volume of 8.7 ml of concentrated nitric acid was placed in a 250 ml round bottom flask and 10 ml of concentrated sulfuric acid was added in portions with shaking. The mixture was kept cool during the addition by immersing the flask in cold water. Resorcinol weighing 3.2 gms was introduced into the flask with shaking to ensure thorough mixing. After addition of resorcinol a reflux condenser was fitted to the flask and heated it in a water bath maintained at 60 °C for 40-45 minutes. The flask was removed from the bath and shake it vigorously to ensure good mixing. The content of the flask was poured into about 250 ml of cold water in a beaker. The mixture was stirred well in order to wash out as much acid as possible from nitroresorcinol and allowed to stand. The 2-nitroresorcinol was separated from the aqueous layer by separatory funnel. The 2-nitroresorcinol obtained was recrystallized from ethanol to give an orange-red color crystals having melting point of 90-92 °C and yield 34%.

Synthesis of 4-Nitroresorcinol

Synthesis of 4-Nitroresorcinol was done under different catalytic conditions, using oxalic acid as catalyst and changing the metal nitrates, following the same procedure of microwave irradiation. So the general procedure and the effect of various metal nitrates are discussed below.

General Method of Synthesis

A suitable nitrating agent (metal nitrate salt), oxalic acid (catalyst) and resorcinol were thoroughly grounded for 2-3 minutes. The combined mixture was then irradiated under microwave irradiation for 1-30 minutes, after completion of reactions as monitored by TLC, the reaction mixture was then chromatogramed on Silica gel column to obtain the target 4-Nitroresorcinol as a pure single isomer. Recrystallized from CCl₄ m.p. 118 - 120°C.

Synthesis of Nitro-substituted Phenols

General Method

- Oxalic acid and sodium nitrate in equimolar ratio (1.2mmol) were taken in an agate mortar, were thoroughly grounded and then mixed with phenol (1 mmol) to form homogenous mixture. The combined mixture was then irradiated under microwave irradiations for a few minutes, after completion of reaction as monitored by TLC; the reaction was then chromatogramed on Silica gel column to obtain the target nitrated product.

Results and Discussion

Effect of Various Metal Nitrates on Product Yield

The effect of various nitrating salts in the presence of a catalyst on the yield of 4-nitroresorcinol has been shown in Table 1. The results showed that maximum yield, 26 % of 4-nitroresorcinol (Fig. 1) was obtained while using Cu(NO₃)₂ as nitrating salt, followed by 12.8, 9.3, 8.6, 7.2, 7.1, 6.3 and 5.4% for Sr(NO₃)₂, Bi(NO₃)₂, NaNO₃, Ag(NO₃)₂, Ca(NO₃)₂ Co(NO₃)₂ and KNO₃, respectively (Table 1, Fig. 3).

Table 1: Microwave assisted nitration under different catalytic conditions

Phenol	Nitrating Salt	Catalyst	Time (min)	Product
Resorcinol 1 mmol	NaNO ₃ 2.5 mmol	(CO ₂ H) ₂ 2.5 mmol	2	4-Nitroresorcinol
	KNO ₃ 2.5 mmol	(CO ₂ H) ₂ 2.5 mmol	2	
	AgNO ₃ 3.5 mmol	(CO ₂ H) ₂ 3 mmol	1	
	Ca (NO ₃) ₂ 2 mmol	(CO ₂ H) ₂ 2 mmol	1	
	Sr(NO ₃) ₂ 2.5 mmol	(CO ₂ H) ₂ 2.5 mmol	1	
	Cu(NO ₃) ₂ 2 mmol	(CO ₂ H) ₂ 2 mmol	1/2	
	Co(NO ₃) ₂ 2.5 mmol	(CO ₂ H) ₂ 2.5 mmol	1/2	
	Bi(NO ₃) ₃ 3 mmol	(CO ₂ H) ₂ 3 mmol	30	



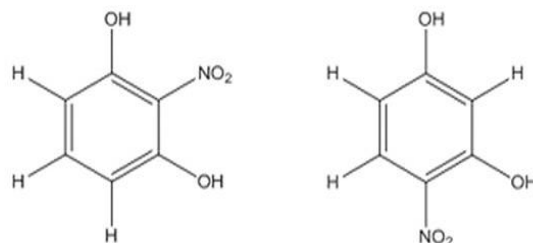


Figure 1: Chemical structure of 2-nitroresorcinol (left) and 4-nitroresorcinol (right)

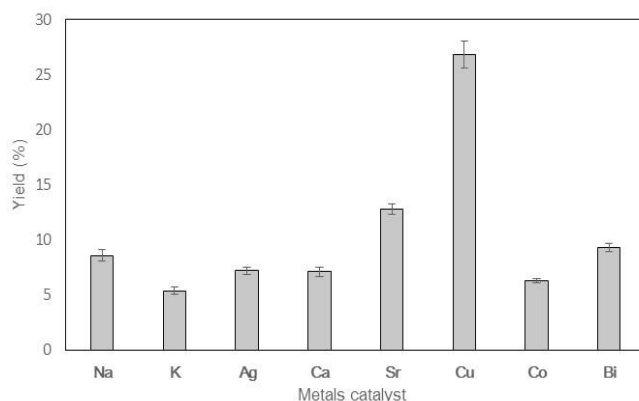


Figure 2: Yield of 4-Nitroresorcinol with different metals used as a catalyst

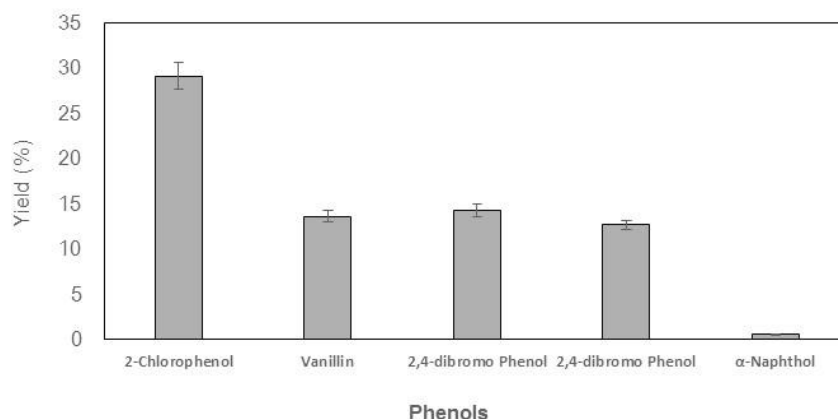


Figure 3: Percent yield of different nitro substituted phenols using NaNO_3 as a nitrating salt

Synthesis of Nitro-substituted Phenols

Synthesis of different nitro-substituted phenols were synthesized using oxalic acid and NaNO_3 with different phenols and their yields have been shown in Table 2. The results showed that maximum yield, 29% of 2-chloro-6-nitrophenol was obtained from 2-chlorophenol while using NaNO_3 as nitrating salt, followed by 14.3, 13.6, 12.7 and 0.54 was obtained for 2,4-dibromo phenol, vanillin, 2,3-dibromo phenol and α -Naphthol, respectively (Table 2, Fig. 4).

We have optimized suitable reaction conditions for the efficient conversion of resorcinol selectively to 4-nitroresorcinol using selected metal nitrates, including NaNO_3 , KNO_3 , AgNO_3 , $\text{Ca}(\text{NO}_3)_2$, $\text{Sr}(\text{NO}_3)_2$, $\text{Cu}(\text{NO}_3)_3$, $\text{Co}(\text{NO}_3)_2$, and $\text{Bi}(\text{NO}_3)_3$ as nitrating agents and Oxalic-acid as catalyst in the present studies. Next we have Optimized stoichiometric ratio for the complete conversion of starting material into product since we failed to get the target compound as single product using an equimolar ratio of resorcinol, and always unreacted resorcinol was found along with the product. Increasing the ratio of metals as nitrating agents without increasing the ratio of the catalyst again resulted in the incomplete conversion of resorcinol into product, also any difference in the ratio of



nitrating agent and catalyst did not give full conversion. In this thus the best stoichiometric ratio found were resorcinol (1 mmol), metal nitrates (2-3.5 mmol) and oxalic acid (2-3.5 mmol) as given in the Table 1. In search of improving yield, amazingly we observed no significant increase in the yield and 26.8% was the maximum yield obtained in our present studies. Among the metal nitrate, $(\text{CuNO}_3)_2$ gave the highest yield. A suitable mechanism has been proposed. The possible mechanism believed to be involved the initial activation of metal nitrate by oxalic acid followed by the electrophilic attack on the resorcinol (Fig 4).

Table 2: Microwave assisted nitration of substituted phenols using NaNO_3 .

Phenols	Structure	Product	M.P (°C)
2-Chlorophenol		2-Chloro-6-nitrophenol	58-60
Vanillin		4-Hydroxy-3-methoxy-5-nitrobenzaldehyde	152-154
2,4-dibromo Phenol		2-4-dibromo-5-nitro phenol	124-126
2,3-dibromo Phenol		2-3-dibromo-5-nitro phenol	98-100
α -Naphthol		2-nitro-1-naphthol	178-180

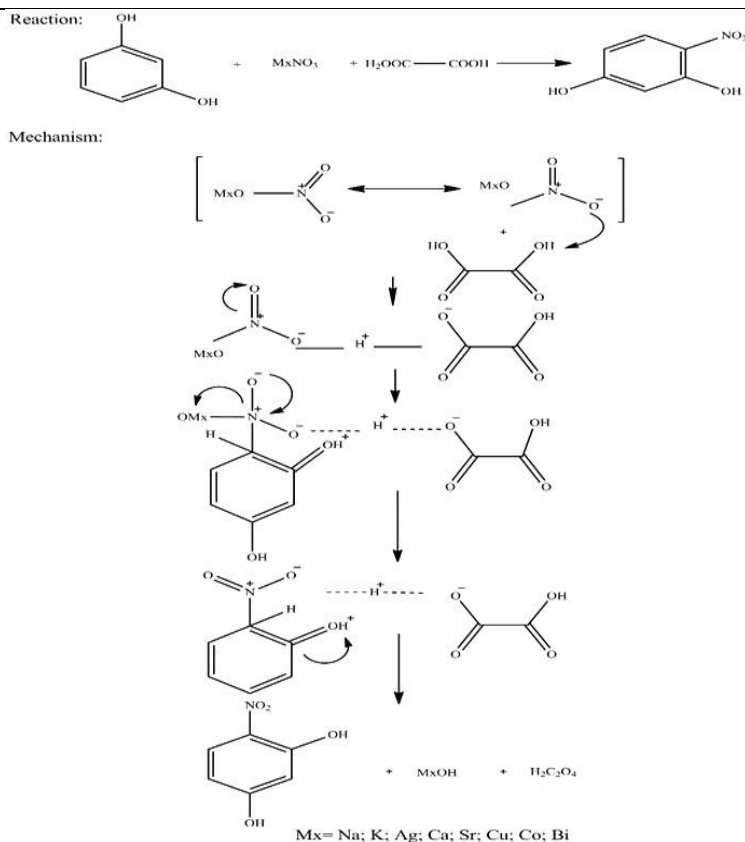


Figure 4: Proposed mechanism for the oxalic acid catalyzed regioselective nitration of resorcinols

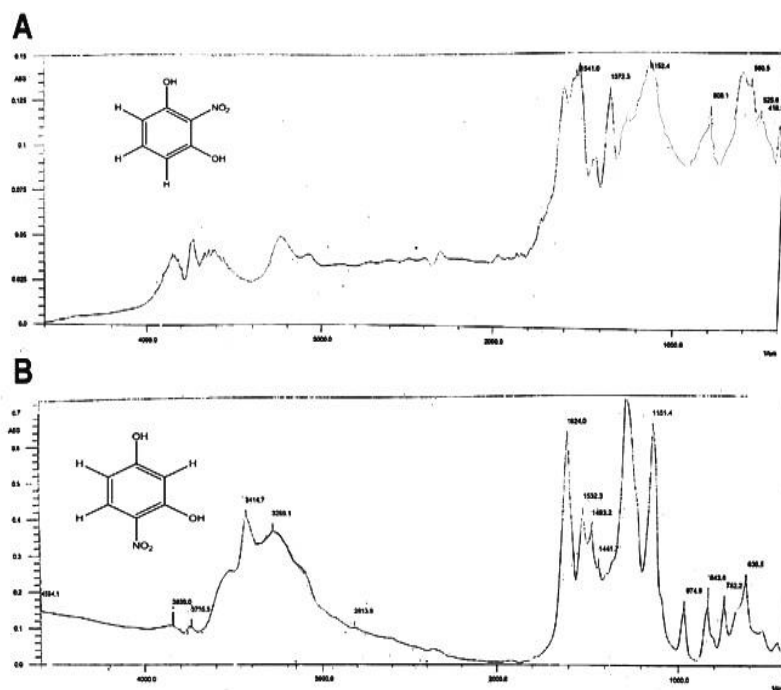


Figure 5: IR spectra of 2-nitroresorcinol (A) and 4-nitroresorcinol (B)

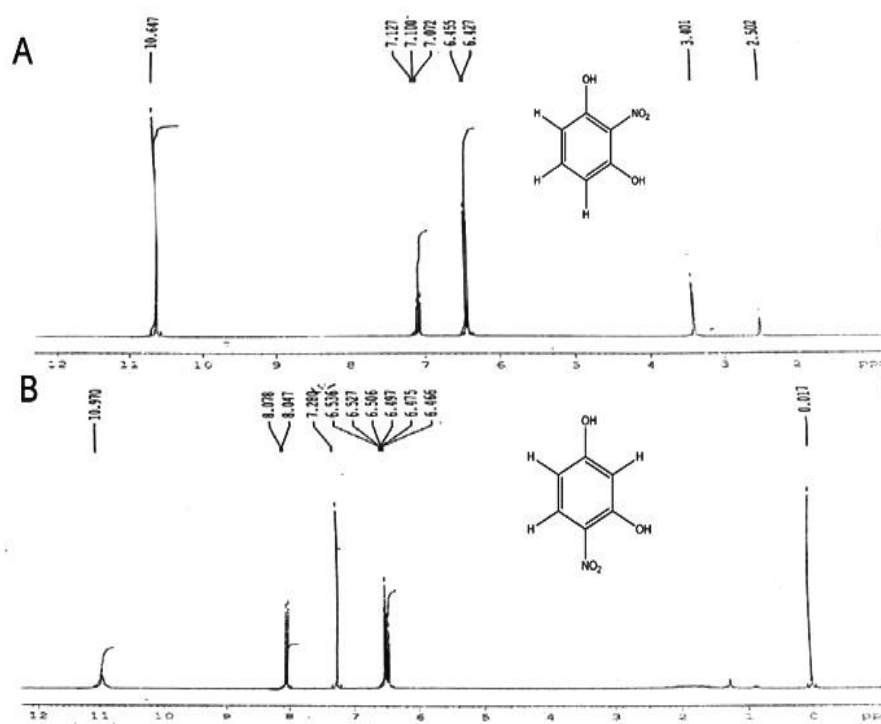


Figure 6: ¹H NMR spectra of 2-nitroresorcinol (A) and 4-nitroresorcinol (B)

Microwave assisted synthesis has got much attention of synthetic chemists and the number of publications has significantly risen since the mid of 1990s [11]. Microwave technology not only provide convenient and efficient



way of heating reaction, but also considerably increase the rate of reaction and yield as well. Environmental and economic interests have attracted chemists around the globe to explore simple, efficient and cheaper synthetic methodologies using microwave synthetic approaches. Literature methods reported for the nitration of aromatic substances are associated with drawbacks such as the use of hazardous reagents and solvents and the need of larger reaction time as well.

Nitrophenol as precursors has great utility for dyes, pharmaceuticals and agrochemicals industry [3,5,12-13]. Conventionally, procedure for the nitration of Phenols involves the mixture of concentrated sulfuric acid and nitric acid [14-16]. The use of acid mixture for nitration produce large amount of acid waste which requires neutralization before disposal. Another problem include, over nitration, oxidation and poor selectivity are also related problems. In fact, the yield of direct nitration never surpasses 60%. A number of nitrating agents such as concentrated nitric acid and metal triflate in conjunction with HNO₃, peroxyxynitrite nitrogen oxide, and several metal nitrates/nitrites have been reported. In certain cases the reaction is performed in microemulsions and costly media such as ionic liquids.

In the present study we have reported regioselective nitration of resorcinol to 4-nitroresorcinol using an oxalic acid catalyst and different nitrating salts, we also extended our studies to the regioselective nitration of various substituted phenols using NaNO₃, oxalic acid as a nitrating mixture under microwave irradiations using the substrate and nitrating mixture in the ratio of 1:12. In this study all the substituted phenols give the corresponding substituted nitrophenols but again in less % yield and we found, that structure of the substrate affects the percent yield. Thus 2-chlorophenol gave the highest yield (29.1%) while yield decreased in vanillin, 2,4-dibromophenol and minimum yield was observed in α -Naphthol (Table 2, Fig. 4). Further, both the regioisomers resulted in 2,4-dibromophenol under the conditions used and no regioselectivity was observed using NaNO₃/ Oxalic acid as nitrating mixture. It was therefore noticed.

On the other hand selectivity in the organic synthesis is of much concerned to synthetic chemists most of the published literature does not emphasize on the selective nitration of resorcinol and in the same way very limited literature is available on the catalytic nitration of resorcinol. We have therefore attempted and investigated a regioselective nitration for the synthesis of 4-nitroresorcinol under microwave irradiation in a short time compared to the conventional thermal methods. The structural characterization was accomplished by IR and ¹H-NMR data. ¹H-NMR was found more helpful to differentiate between 2-nitroresorcinol and 4-nitroresorcinol (Fig. 5 A&B; Fig. 6 A&B).

A number of industrial processes use nitration of aromatic compounds for the manufacturing of colorants, explosives, drugs and agriculture based compounds [3,5, 12-13]. Conventionally, nitration of aromatic compounds requires sulfuric acid and nitric acid in a mixture [2]. Unfortunately, these procedures have several disadvantages, for example, creation of unwanted dinitro compounds and substrate over oxidation [17-19]. Moreover, the acid mixture used in nitration of organic compounds is highly corrosive, toxic and hazardous to the environment [15-16, 20]. To avoid such problems microwave assisted nitration along with other safe methods have been used [11].

Conclusion

Based on the results of the current investigations, it was concluded that, however the microwave assisted nitration is the safest method of nitration, the low yield of the desired product is a challenge and need further investigations to improve the methodology for enhancement of product yield.

References

1. Ingold, K. (1969). In *Structure and Mechanism in Organic Chemistry*, 2nd ed, Cornell University Press, Ithaca, NY, p. 794.
2. Olah, G. A. and Kuhn, S. J. (1964). In *Friedel-Crafts and Related Reactions*; Wiley-Interscience: New York, p. 1393.
3. Olah, G. A., Malhotra R. and Narang, S. C. (1989). In *Nitration Methods and Mechanism*, VCH: New York, p. 5.



4. Hoggett, J. G., Moodie, R .B., Penton J. R. and Schofield, K. (1971). In *Nitration and Aromatic Reactivity*, Cambridge University Press, London, p. 163.
5. Schofield, K. (1980). In *Aromatic Nitration*; Cambridge University Press: Cambridge, p. 8.
6. Malysheva, L .V., Paukshtis, E .A. and Ione, K .G. (1995). *Nitration of Aromatics by Nitrogen Oxides on Zeolite Catalysts: Comparison of Reaction in the Gas Phase and Solutions*, *Catal. Rev. Sci. Eng.*, 37, 179-226.
7. Jayasuriya, K. and Damavarapu, R. (1999). Regioselective Nitration of Aromatic Compounds by Dinitrogen Pentoxide and the Reaction Products Thereof, US Patent. 5977418 A.
8. McNaught A.D. and Wilkinson, A. (1997). In *IUPAC Compendium of Chemical Terminology*, 2nd Edition, Blackwell Scientific Publications, Oxford, UK, p.1160.
9. Sunajadevi K .R. and Sugunan, S. (2005). Sulfated Titania Mediated Regioselective Nitration of Phenol in Solid State, *Catalytic Communications*, 6: 611-616.
10. Vogel, A. I., Furnis, B. S., Hannaford, A. J., Smith, P. W. G. and Tatchell, A. R. (1989). In *Text book of Practical organic chemistry*, 5th ed, Longman Scientific & Technical, New York, p. 395.
11. Bose, K., Ganguly, S. N., Manhas, M. S., Srirajan, V., Bhattacharjee, A., Rumthao, S. and Sharma, A. H. (2004). Microwave Assisted Synthesis of an Unusual Dinitro Phytochemical, *Tetrahedron Lett.*, 45: 1179-1181.
12. Conlon, D. A., Lynch, J. E., Hartner, F. W., Reamer, R. A. and Volante, R. P. (1996). Nitrous Acid-catalyzed Nitration of 4-bromo-2,5-dichlorophenol. Observation of an Unusually Facile Rearrangement of a 4-bromo-2-nitrophenol During Nitration, *J. Org. Chem.*, 61: 6425-6429.
13. Tamiri, T., Rozin, R., Lemberger, N. and Almog, J. Urea (2009). Nitrate, an Exceptionally Easy-to-make Improvised Explosive: Studies Towards Trace Characterization, *Anal. Bioanal. Chem.*, 395: 421-428.
14. Laszlo, P. (1986). Catalysis of Organic Reactions by Inorganic Solids, *Acc. Chem. Res.*, 19: 121-127.
15. Cornelis, A., Laszlo P. and Pennetreau, P. (1984). Nitration of Phenols by Clay-supported ferric nitrate, *Bull. Soc. Chim. Belg.*, 93: 961-972.
16. Poirier, J. M. and Vottero, C. (1989). Mononitration de Phenols par des Nitrates Metalliques, *Tetrahedron*, 45: 1415-1422.
17. Firouzabadi, H., Iranpoor, N. and Zolfigol, M. A. (1998). Dinitrogen Tetroxide Complexes of Iron(III) and Copper(II) Nitrates as Versatile Reagents for Organic Synthesis. Efficient Oxidative Deprotection of Silyl or Tetrahydropyranyl Ethers, Acetals, and Thioacetals, *Bull. Chem. Soc. Jpn.*, 71: 2169-2173.
18. Firouzabadi, H., Iranpoor, N. and Zolfigol, M. A. (1998). Dinitrogen Tetroxide Complexes of Iron (III) and Copper (II) Nitrates as New Versatile Reagents for Organic Synthesis. Efficient and Selective Oxidation of Sulfides to Corresponding Sulfoxides under Mild Conditions, *Synth. Commun.*, 28: 3301-3311.
19. Firouzabadi, H., Iranpoor, N. and Zolfigol, M. A (1998). Selective and Efficient Transformation of Thioethers to Sulfoxides and Catalytic Conversions of Thiols to the Disulfides with Hydrated Iron(III) and Copper(II) Nitrates in Aprotic Organic Solvents under Solvent- Free Conditions, *Synth. Commun.*, 28: 1179-1187.
20. Cornelis, A. and Laszlo, P. (1994). Molding Clays into Efficient Catalysts, *Synlett.*, 3: 155-161.

