

Mild, Efficient and Selective Nitration of Anilides, Non-Activated and Moderately Activated Aromatic Compounds with Ammonium Molybdate and Nitric Acid as a New Nitrating Agent

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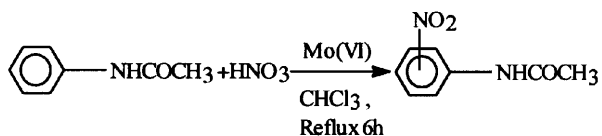
Ammonium molybdate [Mo(VI)] is operationally simple, environmentally safe and inexpensive reagent. Regioselective nitration of anilides, non-activated and moderately activated aromatic compounds could be afforded by employing ammonium molybdate and nitric acid as mild and effective nitrating agent. This procedure works efficiently under reflux conditions to prepare mononitroderivatives of anilides, non-activated and moderately activated aromatic compounds in good to excellent yield with high regioselectivity.

Recent development in the areas such as DOM methodology¹ has sparked a renaissance in the field of aromatic chemistry, due to a high demand for multifunctional aromatic substrates and the inadequacies of existing techniques. In particular, the nitration of aromatic rings has received considerable attention due to unsolved problems pertaining to regioselectivity, over nitration and competitive oxidation of substrates.^{2,3}

Nitro compounds have found their use in many industrial applications,⁴ specially, the para isomers are more commercially desirable products. Therefore, there is an intense need to develop a novel catalyst to facilitate aromatic nitrations.

Ammonium molybdate [(NH₄)₆ Mo₇O₂₄·4H₂O or Mo(VI)] is operationally simple, environmentally safe and readily available inexpensive reagent which is found to have many uses as a mild and selective agent in organic synthesis.⁵ A perusal of literature depicts that ammonium molybdate could be conveniently used in conjunction with other substances for effective oxidations.⁶ It could be used as a catalyst for the oxidation of alcohols⁷ in the presence of H₂O₂ and also for regioselective bromination reactions.⁸

As our efforts were to get nitrated anilides with good regioselectivity, it was found that ammonium molybdate and nitric acid can act as a good reagent system. Anilides are compounds used as intermediates in the production of pharmaceuticals and dyes.⁹ For instance, Paracetamol^R is widely used as antipyretic drug. It is reported that anilides in general and acetanilides in particular act as cell growth inhibitors in metabolic activities.



Nitration of anilides in presence of ammonium molybdate, proceeds rapidly affording high yields of the corresponding mononitro derivatives with high regioselectivity. When the reaction is conducted in absence of ammonium molybdate, the

reaction did not proceed even under reflux conditions for a prolonged period. Thus, it is assumed that ammonium molybdate with nitric acid forms a proper species for nitration. Progress of the reaction is monitored by a visible change in the colour of reaction mixture and also from TLC during the course of reaction. After completion of the reaction as indicated by TLC the reaction mixture is filtered, washed with water and worked up as usual to give the nitrated products. The results are summarized in Table 1. To check the regioselectivity of the reaction, the reaction is carried out with different substituted anilides (entries 2 and 4), which afforded only ortho nitrated products in excellent ortho selectivity. It shows that nitration is selective. The reaction first takes place at para position then at ortho position. The reaction appeared to follow the ortho/para rules. It is also observed that in any case dinitration did not take place. To prove the generality of the reaction, the reaction is carried out with some non-activated and moderately activated aromatic compounds. Under similar conditions, chlorobenzene, toluene and ethylbenzene (entries 14, 15 and 16), were smoothly nitrated selectively giving the respective nitration products in good yields. However, benzene failed to be nitrated under the condition employed. The ammonium molybdate catalyzed nitration of naphthalene, anthracene, α -naphthol, β -naphthol, 2-aminoanthracene and 1-naphthaldehyde which proved to be quite satisfactory, giving the nitration products in nearly quantitative yields (80-95%). The regioselectivity was higher compared with those observed for classical nitration. The nitration of activated aromatics such as phenols giving good nitrating products in less time. The results of the nitration of phenols and activated aromatic compounds have been communicated elsewhere.¹⁰

Table 1. Regioselective nitration of anilides non-activated and moderately activated aromatic compounds with ammonium molybdate/nitric acid

Entry No.	Substrate	Reaction Time/h	Yield / %	
			Para	Ortho
1.	Acetanilide	6	99	-
2.	4-Methyl acetanilide	6	-	92
3.	2-Chloro acetanilide	6	100	-
4.	4-Chloro acetanilide	6	-	99
5.	3-Nitro acetanilide	6	65	29
6.	4-Fluoro acetanilide	6	-	96
7.	4-Bromo acetanilide	6	-	94
8.	4-Nitro acetanilide	6	-	97
9.	4-Hydroxy acetanilide	6	-	87
10.	Benzanilide	6	86	12
11.	2-Chloro benzanilide	6	86	-
12.	4-Chloro benzanilide	6	-	92
13.	4-Nitro benzanilide	6	-	88
14.	Chlorobenzene	6	82	16
15.	Toluene	6	74	20
16.	Ethylbenzene	6	83	12

In order to shed light on the reaction mechanism, the kinetic work is under investigation to prove the exact path of the reaction and the formation of intermediate. However, it is believed that nitration is taking place via the formation of nitronium ion bound molybdenum species. It is also believed that the mechanism is similar to that of the literature reports.¹¹ The reaction with 0.25 equivalent or 0.5 equivalent of ammonium molybdate is very slow. Therefore, reaction is carried out at 1:1:1 molar ratio. The nitrated products were characterized by comparison of their spectral (IR, UV, ¹H-NMR, HPLC and TLC) and physical data with authentic samples.

The results clearly indicate that the direct nitration of anilides, non-activated and moderately activated aromatic compounds can be achieved successfully by employing ammonium molybdate and nitric acid as nitrating agent.

In conclusion, the present method of nitration of anilides, non-activated and moderately activated aromatic compounds using ammonium molybdate as catalyst with high regioselectivity offers the advantages such as, environmentally safe, readily available inexpensive reagents and mild reaction conditions with simple work up. Thus, it is believed that the present method is to be a major step forwarded in the area of clean technology for aromatic nitration.

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- Nitration of Anilides: Dissolve the anilide (1 mmol) in CHCl₃ and add ammonium molybdate (1.235 gms, 1 mmol), 70% HNO₃ (0.063 ml, 1 mmol) and reflux for 6 hr. Check the TLC for completion of the reaction. Filter the reaction mixture, wash it with water, separate the organic layer, then dry it over with sodium sulphate (Na₂SO₄), evaporate under vacuum, purify with column chromatography using chloroform : methanol (9.9 : 0.1) as eluent to get pure product.