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Urea nitrate and nitrourea: powerful and regioselective aromatic nitration agents

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Abstract—Urea nitrate (UN) and nitrourea (NU), easily prepared from urea and nitric acid, convert deactivated aromatic compounds to the corresponding nitrated derivatives with a high yield and a high regioselectivity under very mild conditions. The performance of the two reagents is quite similar indicating that NU is an intermediate in the UN nitration process.

Urea nitrate (UN) is mostly known as a nitrogeneous fertilizer.[1,2] It is also a powerful explosive[3] and can be prepared by mixing nitric acid with an aqueous solution of urea under cooling.[4,5] Prior literature only sporadically discloses the application of urea nitrate as a nitration agent for aromatic compounds but no systematic synthetic or mechanistic studies were reported. We report here the results of a methodological study of this reaction with a particular emphasis on the role of the assumed intermediate in these reactions, nitrourea (NU) and the pronounced regioselectivity of these two reagents.

Majumdar and Kudav have applied urea nitrate in sulfuric acid for the dinitration of anisole and diphenyl ether and the mono (*meta*) nitration of acetophenone and methyl benzoate.[6] Nabar and Kudav used urea nitrate in polyphosphoric acid[7] for the nitration of bromobenzene, anisole and acetophenone. In a later study, Kudav et al.[8] described the regioselective *para* nitration of anilines using urea nitrate in sulfuric acid. Intriguingly, when the *para* position was blocked, nitration took place at the *meta* position. Mundla[9] had applied the same reagent for the efficient regioselective *ortho* nitration of *para* halonitrobenzenes. In a more recent study, Nagarajan et al.[10] described the synthesis of nitrocarbazole using an identical technique.

The main conclusion from reviewing these studies is that there is a clear distinction in regioselectivity in the nitration of monosubstituted benzenes with UN/H_2SO_4 in comparison with the classical mixed-acid procedures, the former resulting in significantly higher *p*/*o* ratios. Consequently, we can safely argue that the nitration mechanism with UN is fundamentally different from that of mixed acids. It is thus unlikely that UN is simply a source of nitrate ions,which are converted to nitric acid upon dissolution in sulfuric acid. Alternatively, we suggest that UN can be initially dehydrated to NU[11] Eq. 1, which then functions as the actual nitrating agent.

$$(H_2N)_2C = OH^+NO_3^- \rightarrow H_2NCONHNO_2 + H_2O \quad (1)$$

NU can directly generate nitronium ions via, for example, protonation and decomposition Eq. 2

$$NH_2CONHNO_2 + H^+ \rightarrow NH_2CONH_2 + NO_2^+ \quad (2)$$

UN was prepared from urea and nitric acid according to Shead.[12] NU was prepared by a slight modification of the procedure described by Davis and Blanchard[11] as follows: 10 g (81 mmol) of UN was added with stirring in 1 g batches over a period of 20 min to a 100 ml flask containing 35 ml of concentrated sulfuric acid maintained in an ice bath. After complete dissolution, the mixture was poured into 50 g of crushed ice. The product was separated by filtration. After drying at room temperature under vacuum, 6.8 g (80% yield) of NU was obtained with a mp of 157–9 °C (98% purity).

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Table 1. Nitration of deactivated benzenes with UN and with NU

Run	Substrate	Product of UN nitration	Total yield (%) (isolated)	Product of NU nitration	Total yield (%) (isolated)
1	Nitrobenzene	1,3-Dinitrobenzene (91%), 1,2-dinitrobenzene (9%)	93	1,3-Dinitrobenzene (93%), 1,2-dinitrobenzene (7%)	68
2	Benzonitrile	3-Nitrobenzamide (78%),[a] 3-nitrobenzonitrile (10%), 2-nitrobenzonitrile (12%)	85	3-Nitrobenzonitrile (86%), 2-nitrobenzonitrile (14%)	90
3	Benzoic acid	3-Nitrobenzoic acid	97	3-Nitrobenzoic acid	71
4	*m*-Toluic acid	3-Methyl-6-nitrobenzoic acid (58%), 3-methyl-2-nitrobenzoic acid (22%), 3-methyl-4-nitrobenzoic acid (12%)	94	3-Methyl-6-nitrobenzoic acid (74%), 3-methyl-2-nitrobenzoic acid (23%), 3-methyl-4-nitrobenzoic acid (3%)	75
5	*o*-Anisic acid	2-Methoxy-5-nitrobenzoic acid[b]	93	2-Methoxy-5-nitrobenzoic acid[b]	100
6	*p*-Nitrotoluene	2,4-Dinitrotoluene	99	2,4-Dinitrotoluene	99
7	*o*-Nitrotoluene	2,4-Dinitrotoluene (70%), 2,6-dinitrotoluene (30%)	98	2,4-Dinitrotoluene (70%), 2,6-dinitrotoluene (30%)	98

[a] Formed by hydrolysis of the initially obtained, 3-nitrobenzonitrile.

[b] Structure determined by ^{1}H NMR.

Both UN and NU were applied to the nitration of several deactivated and moderately deactivated benzene derivatives. In a typical nitration procedure, solid UN (20 mmol) was added in small portions over a period of 30 min to a stirred solution of an aromatic substrate (10 mmol) in concentrated sulfuric acid (10 ml) maintained at 0 °C. The temperature was then raised to 25 °C and stirring was continued for an additional 24 h. The final solution was poured onto crushed ice (100 g) and extracted twice with 50 ml of chloroform. The combined extract was washed once with 50 ml of 10% sodium carbonate solution and once with 50 ml deionized water. After drying over magnesium sulfate, the solvent was evaporated to produce a thick oil which spontaneously crystallized after several hours. The crystals were dried under vacuum. The product structure was confirmed based on GC and MS analysis (comparison with an authentic sample).

An identical procedure was used with NU in place of UN.

Table 1 summarizes the nitration experiments of deactivated aromatic compounds using UN and NU. It was noticed that only one nitro group was introduced, regardless of the molar ratio between reagent and substrate (up to a ratio of 4:1). The enhanced regioselectivity of nitration with UN over the classical mixed-acid procedure was best demonstrated by the products obtained with benzoic acid as a substrate. While the latter process produced a mixture of 3-nitrobenzoic acid (79%), 2-nitrobenzoic acid (20%) and 4-nitrobenzoic acid (1%),[13] nitration with UN produced only 3-nitrobenzoic acid in a nearly quantitative yield (Table 1). Similarly, the nitration of 4-nitrotoluene produced, with 99% selectivity, the preferred isomer 2,4-dinitrotoluene while classical batch nitration with mixed-acids yields 80:20 molar ratio of 2,4-dinitrotolune and 2,6-dinitrotoluene.[14] UN and NU nitrations of nitrobenzene were also (though marginally) more chemo- and regio-selective in comparison with the traditional method, which is known to form 10% of 1,2-dinitrobenzene along with 2% of 1,4-dinitrobenzene and 2% of 4-nitrophenol.[14] The latter was not detected at all in our product mixture. Strongly deactivated substrates such as 1,4-dinitrobenzene, *o*-phthalic acid and pyridine did not undergo nitration using either UN or NU even when the mixture was heated above 60 °C.

We conclude that NU and UN are a unique category of novel nitration agents that are remarkably active and regioselective in the aromatic nitration of moderately deactivated substrates. The nature and isomer distribution of the nitrated products clearly implies a mechanism involving electrophilic aromatic substitution.

Caution: UN and NU are both potential explosives and must be handled with care, similarly to ammonium nitrate.[15]

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