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Aromatic nitration using nitroguanidine and EGDN

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ABSTRACT

Acid catalyzed nitration has been examined using a variety of novel nitration agents: guanidine nitrate (GN) and nitroguanidine (NQ) as well as the simple nitrate ester, ethylene glycol dinitrate (EGDN). Reactions with either activated or deactivated aromatic substrates proceed rapidly and in high yield. Regioselectivity was similar for all nitrating agents examined. The synthetic advantages of liquid EGDN include high solubility in organic solvents, strong nitration activity and ease of preparation.

1. Introduction

Mixed acid nitration is an inexpensive and universal nitration technique that proceeds rapidly and in excellent yield.[1] The actual nitrating agent is the NO_2^+ ion afforded by the ionization of nitric acid or nitrate salts and nitro compounds in concentrated mineral acid. The degree of nitration can be controlled by adequately relying on the strong deactivating nature of the nitro group. Major drawbacks, however, are harsh conditions and a lack of regioselectivity. Recent reports have utilized exotic nitrates and solvent conditions in attempts to yield a selective transformation.[2–6] Research has considered the nitration mechanism in terms of the intimate ion-pair and the sigma complex and in terms of an electrophilic versus charge transfer mechanism.[7,8] Such studies are important in aiding the design of nitrating agents, which show marked regioselectivity.

One of us (JA) recently reported the regioselective nitration of several aromatic compounds with urea nitrate and nitrourea.[9] Herein, we probe the generality of that work using guanidine nitrate (GN) and nitroguanidine (NQ) as well as the simple nitrate ester, ethylene glycol dinitrate (EGDN).

Guanidinium nitrate has been recently reported as the nitration agent in organic syntheses under acidic conditions.[10] The report claims high preference to the *para isomer*, however, toluene is mono-nitrated to give a 64:18 *ortho*:*para* ratio and the nitration of aniline yields a significant portion of *m*-nitroaniline alongside the *para*-nitro isomer.

2. Results

At room temperature, in concentrated acid, the nitration reactions proceed in excellent yield over short reaction times (Table 1). All the reagents—guanidinium nitrate (GN), nitroguanidine (NQ), urea nitrate (UN), nitrourea (NU), ammonium nitrate (AN), nitric acid, and ethylene glycol dinitrate (EGDN)—nitrated the arene rings in good yield (~90%) if sulfuric acid were present. The use of 1, 2 or 4 equiv of nitrating agent had no effect on the overall yield, and only slight differences were observed in the isomeric ratio of products.

Deactivated aromatic substrates—benzonitrile, benzoic acids, and nitrobenzene—could be nitrated only once under these conditions, while toluene produced dinitrotoluenes with all the reagents. The relative strengths of the nitrating reagents were similar for UN, NU, GN, and NQ. EDGN and AN appeared to be stronger nitration agents, producing appreciable amounts of 2,4,6-trinitrotoluene (TNT, Scheme 1) from 2,6-dinitrotoluene and, in the case of AN, producing 3,5-dinitro-*o*-toluic acid from *o*-toluic acid (Table 2).

While differences in selectivity were observed for different substrates (Table 2), we did not observe meaningful differences in regioselectivity among the nitrating reagents, which alludes to a common mechanism for all of them, namely, attack by nitronium (NO_2^+). Indeed, all the reagents (GN, NQ, UN, NU, AN, nitric acid, and EGDN) nitrated the aromatic substrates only in the presence of sulfuric acid. Attempts to carry out the reaction by suspending the reagents in the liquid substrate did not proceed at room temperature or with extended heating. No nitration was affected in acetic anhydride or acetic acid (80 °C) solvents. However, addition of a catalytic amount of sulfuric acid to a suspension of nitrating

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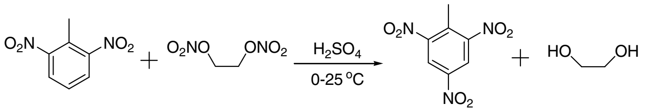
Table 1
Nitration reaction yields for various nitrating agents and mixed acids

Arene starting material	Yield by nitrating agent, %										
	EGDN	GN		NQ		UN		NU		AN	HNO_3
(Nitrate equiv)	1[a]	2	1	2	1	2	1	2	1	2	2
Nitrobenzene	93	94	89	91	84	93	47	94	80	81	94
Benzonitrile		78	83	75	83	76	84	85	88	82	
Benzoic acid		79	97	97	81		82		94		99
m-Toluic acid		84		85		99		89			
4(*p*)-NO_2 toluene	99	93	78	90	87	93	90	97	77	95	94
2(*o*)-NO_2 toluene	91	90		73		96					
o-Toluic acid		88		89						93	
Toluene[b]		94		98		78		98		90	

All yields represent direct extraction and workup to give solid products.

[a] EGDN can deliver 2 equiv nitrate per mole.

[b] 1 equiv toluene results liquid products (unrecovered), percent composition is reported in Table 2.



Scheme 1. Nitration of 2,6-dinitrotoluene to TNT with EGDN.

agent (UN, NU, GN, or NQ) in liquid arenes promoted nitration even at room temperature. (The nitration of carbazoles has been reported using acetic acid and urea nitrate but heating (70 °C) or a catalytic amount of sulfuric acid was often required.[11])

We have previously reported the thermal decomposition of UN and GN, sealed in the presence of substituted arenes (toluene, nitrobenzene), yielded nitration products.[12] Careful studies have shown that a mixture of nitrotoluene isomers are produce when toluene is used but only 1,3-dinitrobenzene appears as the nitration product of nitrobenzene. *meta*-Xylene, when heated to reflux in the presence of UN, gave a mixture of nitro-*m*-xylenes.

3. Discussion

The similarity in regioselectivity among the reactants reported herein is likely a result of the use of sulfuric acid catalyst. We assume the mechanism in all observed reactions proceeds via 'free' nitronium ion. It is reported that the action of sulfuric acid on GN converts it into NQ and then further dissociation of NQ into the nitronium ion.[10] This same reaction yields NU from the dehydration of UN.[9] The high conversion and rapid completion of the reactions reported in this work indicates rapid formation of NO_2^+.

Table 2
Nitration of various arenes with several nitrating agents

Substrate	Products	EGDN	Guanidine nitrate		Nitroguanidine		Urea nitrate		Nitrourea		AN	HNO_3
		1:1	2:1	1:1	2:1	1:1	2:1	1:1	2:1	1:1	2:1	2:1
Nitrobenzene	1,3-Dinitrobenzene	92	91	73	91	74	90	79	90	55	89	91
	1,2-Dinitrobenzene	8	7	24	7	24	8	19	10	21	9	7
	1,4-Dinitrobenzene		2		2		2				2	2
Benzonitrile	3-Nitrobenzamide[a]	100	91	79	91	92	96	91	100	63	96	
	3-Nitrobenzonitrile			15	<1	8	1	9		33		
	2-Nitrobenzonitrile		2		8		1				4	
	4-Nitrobenzonitrile		7	6						4		
	2-Nitrobenzamide[a]				>1		2					
Benzoic acid	3-Nitrobenzoic acid		100	100	100	100		100		100		100
m-Toluic acid	3-Me-6-Nitrobenzoic acid		54		48		45					
	3-Me-2-Nitrobenzoic acid		33		44		45					
	3-Me-4-Nitrobenzoic acid		13		9		5					
	Me-2,6-Dinitrobenzoic acid						5					
p-Nitrotoluene	2,4-Dinitrotoluene	100	100	100	100	100	100	100	100	100	91	89
	TNT										9	11
o-Nitrotoluene	2,4-Dinitrotoluene	66	67		68		81					
	2,6-Dinitrotoluene	22	33		32		19					
	TNT	12										
o-Toluicacid	2-Me-5-Nitrobenzoic acid		74		69							
	2-Me-3-Nitrobenzoic acid		26		22							
	3,5-Dinitro-*o*-toluic acid				9						100	
Toluene	2,6-Dinitrotoluene	17	10	3	13	7	17	11	9		10	19
	2,4-Dinitrotoluene	75	89	16	87	86	82	86	91		89	78
	3,4-Dinitrotoluene		1		2		1				1	
	2-Nitro toluene	2		42		4		3		59		
	3-Nitro toluene			2								
	4-Nitro toluene	6		38		2		1		41		2
	TNT											
2,4-DNT	TNT	1	<1		<1							
2,6-DNT	TNT	10	1		1		1				43	

Ratio mol:mol, (EGDN used 1:1 mol, 2 equiv nitrate).

[a] Benzamide products from the hydrolysis of nitrile product.

Reviewing the publications of researchers observing selective nitration, it appears that such success was based on tailoring the solvent system or substrate versus the nitrating agent. Nitrate salts of aromatic amines have been converted to their respective *para*-nitro compounds under mixed acid conditions. Product mixtures reported were similar to those produced by conventional methods, and the selectivity of this 'intramolecular nitration' was dictated by activating groups present on the ring.[13] However, changes in the solvent or acid catalyst did affect regioselectivity. Tsang suggested the high *ortho:para* ratio in the nitration of toluene may have resulted from the lack of a 'free' nitronium ion.[14] He speculated that a steric effect between polyphosphoric acid and the methyl substituent of toluene resulted in an intermediate complex which blocked the *ortho* position, leading to high *para*-selectivity. Olah used nitropyrazole to nitrate benzene/toluene mixtures. Varying the acid catalyst, large variations in substrate selectivity (nitrobenzene vs nitrotoluene) but no variations in positional selectivity (*ortho:para* ~1.4) were observed. This result was attributed to the varying ability of the acids to generate the nitrating species, and the rate and position of the nitration are determined in separate steps. Olah argued that the free nitronium ion was not generated; it would have produced an *ortho:para* ratio of ~2.[15] This argument may apply to the nitro-organic reagents used in this study.

Water content in the reaction mixture has been shown to be an important factor. Use of calcium sulfate (Drierite) to sequester water has been claimed to produce low *ortho:para* ratios in the nitration of arenes.[16] Many of the nitrating reagents employed in this study could be considered as 'dry' acids. Nitrourea, compared to urea nitrate (or NQ vs GN), has effectively one less mole of water to contribute to the reaction. Similarly, EGDN can be a water-free source of nitronium ion.

4. Conclusion

Similar regioselectivity is observed for a variety of nitrating reagents, both organic and inorganic. We interpret this as evidence of the action of free nitronium ion under acidic conditions. Indeed, nitration could not be affected without the presence of sulfuric acid. EGDN is a liquid with good solubility in organic solvents. These physical properties may make it synthetically useful, and its nitration strength is as good, or better, than many other nitrating species.

5. Experimental

Urea nitrate and nitrourea were synthesized by published methods.[17] Guanidine nitrate was purchased commercially and used to synthesize nitroguandine.[18] EGDN synthesis is readily available in the literature.[19,20]

> *EGDN has properties similar to nitroglycerine and is extremely sensitive. Synthesis, concentration, storage, and reactions should be performed with caution*.

The aromatic substrate (10 mmol) was dissolved in sulfuric acid (96%) and cooled to 0 °C in an ice bath. The nitrating agent was added slowly with rapid stirring. After addition and dissolution of nitrate, the solutions were allowed to stir in the ice bath for 30 min before being allowed to warm and stir at room temperature overnight. The solutions, which ranged in color from clear to dark orange, were poured over ice (100 mL) and then extracted twice with chloroform (2 × 50 mL) and the extracts washed with 10% sodium bicarbonate solution (50 mL) and distilled water (50 mL). For the benzoic acid derivatives, the carbonate was replaced with a second water wash. Immediately an aliquot of the extract was used for analysis. The solvent was then dried over magnesium sulfate, filtered, and the solvent evaporated to yield the solid products. (Similar reactions were prepared with acetic acid, acetic anhydride, or neat arene as the solvent. These did not promote nitration. In the final case, catalytic sulfuric acid resulted in nitration products as realized by GC/MS, but no quantification or workup was performed.)

Note: The fate of the urea and guanidine portion of the nitro-organic or nitrate salt is not been thoroughly examined. Attempts to recover the organic portion were met with some success. After completing the workup of a nitration performed with urea nitrate, the aqueous fraction was retained and processed as follows: Much of the water from the aqueous fraction was evaporated to yield 10 mL of an acidic mixture. The mixture was cooled to 0 °C and 4 mL of nitric acid was added. The reaction mixture was stirred for 1 h in an ice bath and then poured over 30 g of ice. The reaction mixture was cooled in the freezer overnight and then filtered to recover the precipitate which was determined to be nitrourea in ~50% yield.

Note: Several reactions were attempted using 2,3-dimethyl 2,3-dinitrobutane as the nitrating agent. Nitration was not promoted by this C–NO_2 compound in concentrated H_2SO_4.

Products were identified using a 5890 series II gas chromatograph with a 5971 mass selective detector (GC/MS) fitted with an Agilent Technologies HP-5MS column (30 m × 0.25 mm × 0.25 micron film). Helium was used as the carrier gas and held at a constant flow of 1 mL/min. The inlet was split with a 5 mL/min flow, and the temperature kept at 250 °C. The oven program was as follows: 50 °C initial ramped 20 °C/min to 150 °C then 5 °C/min to 220 °C and 20 °C/min to 250 °C with a 4 min hold. A solvent delay of 3 min was used. The detector was maintained at 300 °C and measured m/z 30–400. For identification, retention time and fragmentation pattern matching with known compounds was used alongside the NIST spectral database.

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