

## Aromatic Nitration with Nitric Acid/Trifluoromethanesulfonic Anhydride<sup>1</sup>

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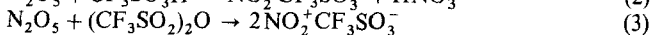
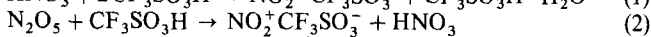
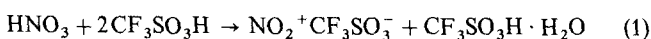
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Received October 18, 1991; revised 31 March 1992

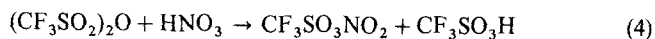
Nitric acid/trifluoromethanesulfonic (triflic) anhydride was shown to be a highly effective electrophilic nitrating agent. A series of aromatics were nitrated under mild conditions in high yields. Similar results were also obtained when using nitric acid/trifluoromethanesulfonic acid/phosphorus pentoxide as nitrating agent in nitroethane or nitromethane solution. The <sup>15</sup>N NMR spectrum of <sup>15</sup>N enriched nitric acid in triflic anhydride was studied and compared with that of other nitrating reagents. The data indicate the predominantly covalent nature of trifluoromethanesulfonyl nitrate formed in the systems.

Electrophilic aromatic nitration is one of the most extensively studied organic reactions. The reactive electrophile in these nitrations is usually the nitronium ion, NO<sub>2</sub><sup>+</sup>. Indeed stable nitronium salts, such as nitronium tetrafluoroborate, nitronium antimony pentafluoride, and nitronium hexafluorophosphate were prepared and used extensively as nitrating agents.<sup>2,3</sup>

Nitronium tetrafluoroborate and nitronium hexafluoroantimonate are poorly soluble even in polar solvents such as nitromethane and tetramethylene sulfone, and thus their reactions must be carried out under heterogeneous conditions. Although this difficulty is overcome by the highly soluble nitronium hexafluorophosphate, the use of this reagent is somewhat limited by the availability of phosphorus pentafluoride. Coon and co-workers<sup>4</sup> showed that nitronium triflate is an excellent nitrating agent and has a high solubility in typical organic solvents. Thus nitration can be effected dichloromethane, fluorotrichloromethane, carbon tetrachloride, and pentane. Reaction temperatures ranging from -110 °C to 30 °C were used in these nitrations. Nitronium triflate was prepared from two equivalents of triflic acid and one equivalent of nitric acid according to eq. 1. The crystalline compound was characterized by elemental analysis and Raman spectroscopy. It can also be prepared from dinitrogen pentoxide and triflic acid,<sup>5</sup> (eq. 2), or triflic anhydride (eq. 3).<sup>6</sup> Moodie and co-workers<sup>7</sup> studied the kinetics of nitration using the reagent in nitric acid, and concluded that the reaction proceeds through the usual nitronium ion mechanism.



We report now that highly effective nitration can be achieved using nitric acid and trifluoromethanesulfonic anhydride. The nitrating reagent obtained contains triflic acid as byproduct (eq. 4) which catalyzes subsequent electrophilic nitration of aromatics.

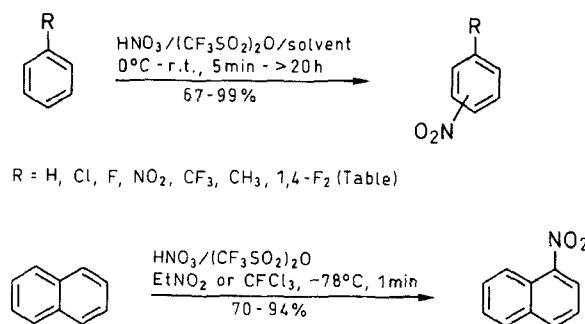


Further, it was also found that triflic anhydride can be replaced by triflic acid and phosphorous pentoxide,

allowing in situ preparation of triflic anhydride (and probably some nitrogen pentoxide).

Nitric acid and triflic anhydride formed a clear, colorless homogeneous solution in nitroethane, which nitrated toluene and benzene at 0 °C in near quantitative yields. A two layered system resulted in nitromethane solvent, but it also showed excellent nitrating ability.

Although nitromethane is widely used as a solvent in Friedel-Crafts chemistry, it has several disadvantages: a) it is difficult to purify and generally contains nitrile impurities (≈ 5%), b) its relatively high melting point (-29 °C) limits low temperature chemistry, and c) it is potentially explosive in strong acids. Nitroethane, on the other hand, is generally free of nitrile impurities, can be easily purified, has a much lower melting point (-90 °C), and is less acid sensitive. Added to that, the present reagent system gives homogeneous solutions in nitroethane, as opposed to nitromethane. The reactions carried out in fluorotrichloromethane as solvent were, however, much slower compared to those in nitromethane or nitroethane. Thus, nitroethane is considered to be the preferred solvent in these nitrations.



Using the described systems a series of aromatics were nitrated under mild conditions (Table 1). Even deactivated aromatics, such as nitrobenzene, halogenated aromatics, and benzotrifluoride undergo efficient nitration. Whereas the nitration system is highly reactive, it is significant to note its high regioselectivity in the nitration of toluene and other substrates. Naphthalene at -78 °C gives α-nitronaphthalene (α:β = 99.7:0.3) almost exclusively. This is the highest α:β ratio yet reported for the nitration of naphthalene. Nitration with typical nitronium salts, such as nitronium tetrafluoroborate gives an α:β isomer ratio of 10.<sup>7b</sup>

It was of interest to compare the nature of the nitrating agent in the present nitrations with previously studied nitronium salts or nitrates. Competitive nitrations of toluene and benzene were frequently used to find the relative reactivity of nitronium compounds.<sup>8</sup> Typically preformed nitronium salts are very reactive, and lack

**Table 1.** Nitration of Aromatics with Nitric Acid/Trifluoromethanesulfonic Anhydride

Substrate	Solvent	Reaction Conditions Temp. (°C)/Time	Yield <sup>a</sup> (%)	Isomer Distribution (%) <sup>b</sup>			Product	bp (°C)/Torr or mp (°C) found reported	
				2-nitro	3-nitro	4-nitro			
benzene	MeNO <sub>2</sub>	0/5 min	80				nitrobenzene	95/4.5	210–211/760 <sup>9</sup>
	EtNO <sub>2</sub>	0/5 min	82						
toluene	MeNO <sub>2</sub>	0/5 min	73	55.5	4.4	40.1	2-, 3-, and 4-nitrotoluene	125–130/6.5 <sup>f</sup>	–
	EtNO <sub>2</sub>	0/5 min	70	60.9	3.6	35.5			
naphthalene	EtNO <sub>2</sub>	– 78/1 min	94				1-nitronaphthalene	59 <sup>c, d</sup>	59–60 <sup>9</sup>
	CFCl <sub>3</sub>	– 78/1 min	70						
chlorobenzene	EtNO <sub>2</sub>	0/30 min	86	25.0		75.0	2-, and 4-nitrochlorobenzene	115–118/3.5 <sup>f</sup>	–
	CFCl <sub>3</sub>	r. t./> 12 h	92	29.0		71.0			
fluorobenzene	EtNO <sub>2</sub>	0/5 min	84	9.0		91.0	2-, and 4-nitrofluorobenzene	95–97/4.5 <sup>f</sup>	–
	CFCl <sub>3</sub>	0/3 h	90	15.0		85.0			
1,4-difluorobenzene	EtNO <sub>2</sub>	r. t./15 min	88				2,5-difluoronitrobenzene	105–106/2 <sup>e</sup>	206.5/760 <sup>9</sup>
	CFCl <sub>3</sub>	r. t./4 h	99						
nitrobenzene	EtNO <sub>2</sub>	r. t./4 h	76	0.3	96.0	3.7	1,3-dinitrobenzene	87 <sup>d</sup>	88–90
	CFCl <sub>3</sub>	r. t./20 h	67	< 0.5	99.0	< 0.5			
trifluoromethylbenzene	EtNO <sub>2</sub>	r. t./4 h	87	8.9	90.0	1.1	2-, 3-, and 4-trifluoromethyl-nitrobenzene	109–110/110 <sup>f</sup>	–
	CFCl <sub>3</sub>	r. t./> 20 h	92	8.0	92.0	0.0			

<sup>a</sup> Yield of isolated product.<sup>b</sup> Isomer composition determined by GC or <sup>19</sup>F NMR before the isolation of the products by distillation or crystallization.<sup>c</sup> 1-, and 2-nitronaphthalenes were formed in a ratio of 99.7 : 0.3.<sup>d</sup> The major isomer was obtained free of the regioisomers by crystallization.<sup>e</sup> 2,5-Difluoronitrobenzene was the only product observed.<sup>f</sup> Boiling point of the isomer mixture.<sup>9</sup> Handbook of Fine Chemicals, Aldrich, 1992–1993.**Table 2.** <sup>15</sup>N NMR Chemical Shifts for Some Nitrating Systems

Method of Preparation <sup>a</sup>	Chemical Shift <sup>b</sup>
HNO <sub>3</sub> + Na <sup>15</sup> NO <sub>3</sub> + CF <sub>3</sub> SO <sub>3</sub> H <sup>c</sup>	249.0
Na <sup>15</sup> NO <sub>3</sub> + CF <sub>3</sub> SO <sub>3</sub> H <sup>d</sup>	248.8
HNO <sub>3</sub> + Na <sup>15</sup> NO <sub>3</sub> + CF <sub>3</sub> CO <sub>2</sub> H	308.9
HNO <sub>3</sub> + Na <sup>15</sup> NO <sub>3</sub> + (CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> O	336.6

<sup>a</sup> The nitrating agents were prepared in nitroethane solvent, unless otherwise noted.<sup>b</sup> Chemical shift ( $\delta$  <sup>15</sup>N values) are from NH<sub>3</sub> ( $\delta$  = 0).<sup>c</sup> More than 5 equivalents of triflic acid was used.<sup>d</sup> Observed in neat triflic acid.

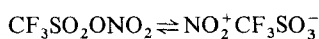
substrate selectivity in the nitration of toluene and benzene. Relative  $k_i/k_b$  reactivities frequently were found to be less than 2. On the other hand, covalent nitrates, such as trifluoroacetyl nitrate, and acetyl nitrate are milder nitrating reagents, and exhibit higher  $k_i/k_b$  ratios. The  $k_i/k_b$  ratio observed for nitric acid/acetic acid (45°C),<sup>9</sup> nitric acid/nitromethane<sup>10</sup> and trifluoroacetyl nitrate<sup>11</sup> were 24, 21 and 28, respectively.

When a tenfold excess of equimolar amounts of benzene and toluene were nitrated with nitric acid-trifluoromethanesulfonic anhydride in nitroethane solution a  $k_i/k_b$  ratio of 36 was obtained.

Table 1 shows that the nitration using nitric acid/trifluoromethanesulfonic anhydride closely resembles the nitration reaction mediated by acyl nitrates. The observed isomer distribution of the nitration of toluene (61% ortho, 4% meta, 35% para) is very similar to that observed in typical electrophilic nitrations with NO<sub>2</sub><sup>+</sup> acting as the *de facto* nitrating agent.

We also probed the nature of the intermediate species by <sup>15</sup>N NMR spectroscopy. The data are summarized in Table 2. The <sup>15</sup>N-labeled nitronium triflate was prepared by dissolving <sup>15</sup>N-labeled sodium nitrate in excess triflic acid, or by Coon's procedure<sup>4</sup> in nitroethane. Both solutions exhibited nearly identical <sup>15</sup>N NMR chemical shifts ( $\delta^{15}\text{N} = 249$ ). This value is in close agreement with that of nitronium tetrafluoroborate ( $\delta^{15}\text{N} = 251$ ).<sup>12</sup> A sample of <sup>15</sup>N-labeled nitronium trifluoroacetate was prepared by adding a mixture of nitric acid and <sup>15</sup>N-labeled sodium nitrate to trifluoroacetic acid in nitroethane. The resulting clear solution showed an <sup>15</sup>N NMR absorption at  $\delta^{15}\text{N} = 308.9$ , considerably deshielded from that of the nitronium species.

<sup>15</sup>N-Enriched reagent prepared from equimolar amounts of nitric acid and triflic anhydride containing <sup>15</sup>N-labeled sodium nitrate on the other hand, gave in nitroethane a <sup>15</sup>N signal at  $\delta^{15}\text{N} = 336.6$  slightly deshielded from that of trifluoroacetyl nitrate, but considerably deshielded from that of ionic nitronium species. The slight deshielding with respect to trifluoroacetyl nitrate is expected based on the higher electronegativity of the trifluoromethanesulfonyl group compared to the trifluoroacetyl group, but the system essentially seems to be covalent in nature, with only very limited dissociation equilibrium, if any.



The nitrating ability of trifluoromethanesulfonyl nitrate (CF<sub>3</sub>SO<sub>2</sub>ONO<sub>2</sub>) is enhanced by trifluoromethanesulfonic acid formed in the system which allows protolytic cleavage of the O–NO<sub>2</sub> bond.

All aromatic substrates, their *o*-, *m*-, and *p*-nitro derivatives, and HNO<sub>3</sub> (fuming, > 90%; ACS reagent) were obtained from Aldrich, and used as received. EtNO<sub>2</sub> (W.R. Grace) was stirred over, and distilled from anhydrous MgSO<sub>4</sub>. MeNO<sub>2</sub> was purified as described previously.<sup>14</sup> Trifluoromethanesulfonic anhydride was prepared according to the reported procedure<sup>13</sup> by stirring trifluoromethanesulfonic acid with P<sub>2</sub>O<sub>5</sub>, followed by distillation. The resulting anhydride was distilled twice from P<sub>2</sub>O<sub>5</sub>. All the reactions were carried out under N<sub>2</sub> atmosphere, unless otherwise mentioned.

Melting points were determined on a Mettler FP1 melting point apparatus. GC analyses were done on a Varian model 3700 gas chromatograph equipped with a Hewlett-Packard 3390A integrator, using a DB wax column (30 m × 0.25 mm i.d.; film thickness = 0.25 μ). GC/MS analyses were carried out on a Finnigan Mat Inco-50 mass spectrometer, equipped with a Varian 3400 gas chromatograph using the above column. <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were recorded on a Varian VXR-200 instrument, using CDCl<sub>3</sub> as a solvent. The chemical shifts were referenced to internal TMS for <sup>13</sup>C, <sup>1</sup>H, and internal CFCl<sub>3</sub> for <sup>19</sup>F spectra. <sup>15</sup>N NMR spectra (at 20.28 MHz on VXR-200 instrument) were recorded in nitroethane solvent, using internal capillary solution of D<sub>2</sub>O, as the lock solvent. The chemical shifts are referenced from Na<sup>15</sup>NO<sub>3</sub> (δ = 376.53, precalibrated from δ (NH<sub>3</sub>) at 0.0). A spectral width of 10000 Hz, an acquisition time of 0.75 sec, and a pulse width of 6.0 μsec were used. Typically 200 to 2000 scans were required to obtain a reasonable signal to noise ratio.

#### Nitration of Aromatics with Nitric Acid/Trifluoromethanesulfonic Anhydride; General Procedure:

Fuming HNO<sub>3</sub> (0.72 g, 11.4 mmol, 1.1 eq) was added to trifluoromethanesulfonic anhydride (2.93 g, 10.4 mmol), and the mixture was dissolved separately in MeNO<sub>2</sub>, EtNO<sub>2</sub> or CFCl<sub>3</sub>. Clear, homogeneous solution resulted in EtNO<sub>2</sub>; in the case of MeNO<sub>2</sub> and CFCl<sub>3</sub>, heterogeneous suspensions were obtained. The arene (10.4 mmol) dissolved in the same solvent (2 mL) was added dropwise to the mixture, and stirred under N<sub>2</sub> atmosphere during the reaction times indicated in Table 1 [in the case of benzene and toluene, addition was carried out at -78°C (dry ice-acetone) and warmed to 0°C]. After quenching with ice water (20 mL) the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL), the combined extracts were washed with sat. NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), and the solvent was rotary evaporated. The composition of the regioisomeric product nitroarenes was determined by GC, GC/MS and/or <sup>19</sup>F NMR. The liquid nitroarenes (Table 1) were obtained by distillation at reduced pressure. Nitronaphthalene and 1,3-dinitrobenzene were obtained as crystalline solids by cooling their EtOH solutions to -78°C, followed by filtration through a Buchner funnel. The products were identified by comparing their GC retention times, mass spectra, <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR with those of authentic samples.

#### Nitration of nitrobenzene with Nitric Acid/Triflic Acid/Phosphorus Pentoxide:

Fuming HNO<sub>3</sub> (0.36 g, 5.7 mmol) and CF<sub>3</sub>SO<sub>3</sub>H (1.71 g, 11.4 mmol) were dissolved in (2 mL) of EtNO<sub>2</sub>. P<sub>2</sub>O<sub>5</sub> (2.43 g, 17.1 mmol) was added to the contents and the mixture was stirred at r. t. for 10 min. Nitrobenzene (0.7 g, 5.7 mmol) dissolved in (1 mL) of EtNO<sub>2</sub> was added to the contents and stirred for 5 min. Excess P<sub>2</sub>O<sub>5</sub> was destroyed by the dropwise addition of ice-cold water, and worked up as described above. A GC analysis (uncalibrated) showed that the 1,3-dinitrobenzene was formed in 91% yield, the remainder being the unreacted nitrobenzene. (At a column temperature of 200°C, nitrobenzene and 1,3-dinitrobenzene had retention times of 1.82 and 2.24 min, respectively.) A similar experiment without the use of P<sub>2</sub>O<sub>5</sub> resulted in 61% completion of the reaction.

#### Competitive Nitration of Toluene and Benzene:

Fuming HNO<sub>3</sub> (5.4 mmol) and trifluoromethanesulfonic anhydride (1.52 g, 5.4 mmol) were added to (5 mL) of EtNO<sub>2</sub> to form a clear colorless solution. The solution was cooled to 0°C, and then slowly added to the precooled solution of toluene (2.48 g, 27 mmol) and benzene (2.11 g, 27 mmol) in EtNO<sub>2</sub> (5 mL). The mixture was stirred for 5 min, then quenched with 50 mL of ice water, extracted with

Et<sub>2</sub>O (2 × 25 mL), washed with sat. NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), and the combined filtrates were analyzed by GC. The retention times of nitrobenzene, *o*-, *m*-, and *p*-nitrotoluenes were 2.74, 3.53, 4.05, and 4.34 min respectively at a column temperature of 120°C. Nitrotoluenes and nitrobenzene were formed in a ratio of 32.7:1 (after correcting for GC response factors, i.e., nitrobenzene/nitrotoluene = 1/1.2) which corresponded to  $k_t/k_b = 36$ .  $k_t/k_b$  was obtained by using the equation,  $k_t/k_b = (\log T_o - \log T_i)/(\log B_o - \log B_i)$ , where  $T_i$  and  $B_i$  are the remaining concentrations of toluene and benzene, respectively, and  $T_o$  and  $B_o$  are the initial concentrations of toluene and benzene, respectively.

#### <sup>15</sup>N NMR Spectroscopic Study of Nitrating Systems:

Authentic samples of nitronium NO<sub>2</sub><sup>+</sup>OTf<sup>-</sup> were prepared by two independent methods: a) Na<sup>15</sup>NO<sub>3</sub> (50 mg) was dissolved in CF<sub>3</sub>SO<sub>3</sub>H (2 mL), and the mixture was warmed gently using a heat gun. The resulting viscous liquid showed a <sup>15</sup>N absorption of δ<sup>15</sup>N = 248.8, and b) fuming HNO<sub>3</sub> (0.18 g, 2.9 mmol) and CF<sub>3</sub>SO<sub>3</sub>H (about 2.5 g > 5 eq), and Na<sup>15</sup>NO<sub>3</sub> (50 mg) were dissolved in EtNO<sub>2</sub> (1 mL). The resulting clear solution gave <sup>15</sup>N NMR spectra with δ<sup>15</sup>N = 249.0. Using only 2 equivalents of triflic acid did not result in any discernible <sup>15</sup>N signals.

Trifluoroacetyl nitrate was prepared by dissolving fuming HNO<sub>3</sub> (0.18 g, 2.9 mmol), Na<sup>15</sup>NO<sub>3</sub> (50 mg), and CF<sub>3</sub>CO<sub>2</sub>H (0.66 g, 5.8 mmol) in (1 mL) of nitroethane. The resulting solution has an <sup>15</sup>N absorption at δ = 308.9.

Trifluoromethanesulfonyl nitrate was prepared by dissolving fuming HNO<sub>3</sub> (0.18 g, 2.9 mmol), trifluoromethanesulfonic anhydride (0.82 g, 2.9 mmol), and Na<sup>15</sup>NO<sub>2</sub> (50 mg), in EtNO<sub>2</sub> (1 mL), and the resulting solution showed <sup>15</sup>N absorption at δ = 336.6.

Support of our work by the Office of Naval Research is gratefully acknowledged. The W.R. Grace Company is thanked for a gift of nitroethane.

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