

## Introduction

The electrophilic nitration of aromatic compounds is a highly valuable synthetic process<sup>1</sup>. Nitroaromatics are used in large quantities in a wide variety of industries including pharmaceuticals, high energy materials/explosives, agrochemicals, dyes, and perfumes. In addition to their direct applications they serve gateway chemicals to amines, hydroxylamines, aldehydes, carboxylic acids, and as indirect starting materials to heterocycles<sup>2</sup>. As a prominent example, acetaminophen or paracetamol, the API in the drug Tylenol, is produced via the reduction and subsequent acylation of *p*-nitrophenol<sup>3</sup>. Traditionally, nitration methods use highly acidic and corrosive mixed acid systems which present a number of drawbacks including poor yields, low regioselectivity, and limited functional group tolerance<sup>4</sup>. Additionally, these methods are corrosive, hazardous, and waste-producing. As a consequence, there is a need for effective and environmentally benign methods for electrophilic aromatic nitrations. Especially because, according to earlier data, 10<sup>8</sup> tons of nitro-aromatics are produced worldwide every year<sup>5</sup>. The volume of the industrial production of chemicals, pharmaceuticals, agrochemicals, or consumer goods is directly related to the chemical industry where chemical processes are carried out on a multibillion ton scale worldwide. Hence, even a 10% cut of hazardous waste means a tremendous decrease in the total amount of waste to treat. In this work, the major aim was to develop reaction protocols that are more environmentally benign while also considering safety issues. The reactions were carried out in dilute aqueous nitric acid, and a broad range of experimental variables, such as acid concentration, temperature, time, and activation method, were investigated.

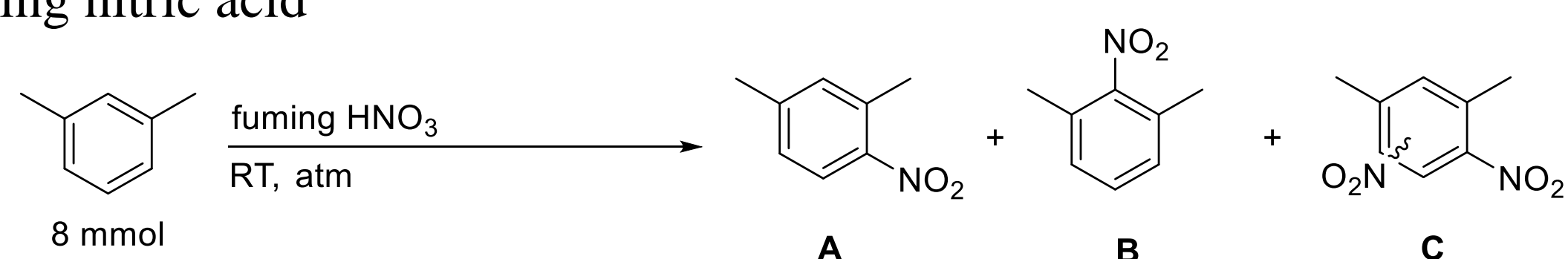
## Methods

Several alternative activation methods were tested including conventional stirring, ultrasounds, microwaves, and high hydrostatic pressure. Nitrations using aqueous 15.8M HNO<sub>3</sub> and non-polar hydrocarbons are a two-phase system which is likely limited by mass transfer over the phase boundary. Thus, we hypothesized ultrasonication, known for its mixing efficiency, would increase the reaction rate compared to conventional stirring. Microwaves were used for deactivated aromatics that did not produce sufficient yields under other conditions. Nitrations under high hydrostatic pressure were also tested.

## Results

### Initial Investigations

**Table 1.** Effects of reaction conditions on the nitration of *m*-xylene using fuming nitric acid

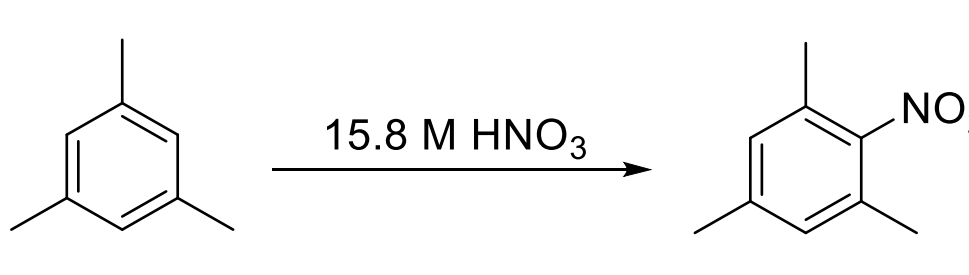


Entry	fuming HNO <sub>3</sub> (mmol) <sup>a</sup>	Additive/catalyst	time (min)	A (%) <sup>b</sup>	B (%) <sup>b</sup>	C (%) <sup>b</sup>
1	12.01	K-10 (0.5 g)	103	75	9	16
2	18.01	K-10 (0.5 g)	100	74	9	13
3	24.01	K-10 (0.5 g)	90	64	12	24
4	48.02	K-10 (0.5 g)	90	36	6	58
5	12.01	-	15	92	8	0
6	12.01	-	90	85	12	3
7	18.01	-	15	94	6	0
8	18.01	-	90	85	8	7
9	24.01	-	15	87	13	0
10	24.01	-	90	91	9	0
11	48.02	-	15	37	5	58
12	48.02	-	90	39	5	56

<sup>a</sup> calculated based on literature fuming HNO<sub>3</sub> density of 1.513 g/mL. <sup>b</sup> GC yields

### Optimization

**Table 2.** Effect of reaction conditions on the nitration of mesitylene.

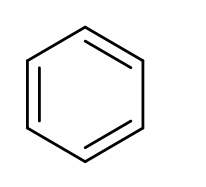
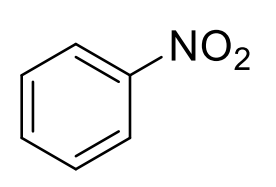
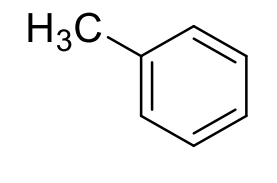
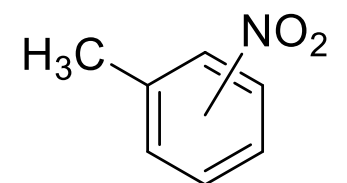
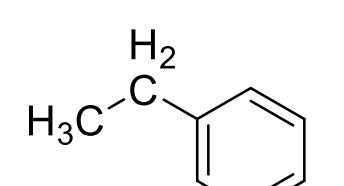
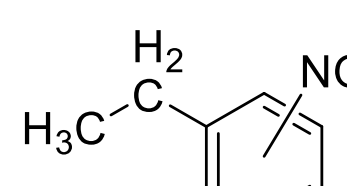
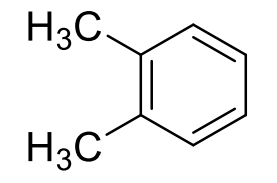
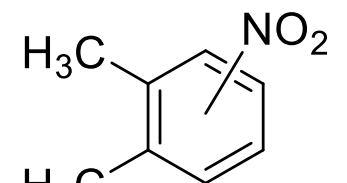
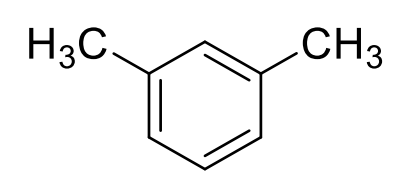
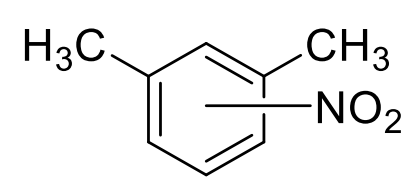
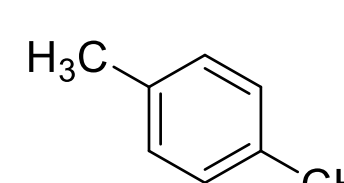
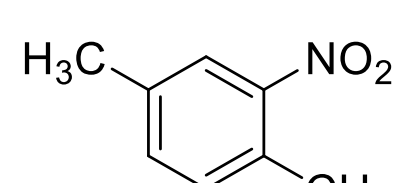
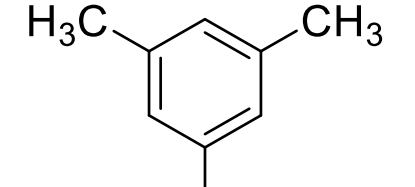
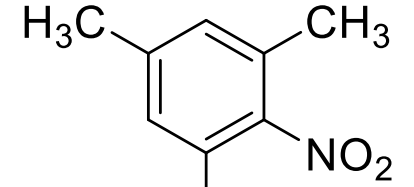
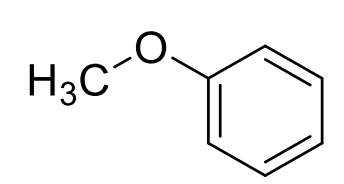
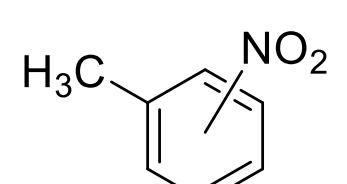
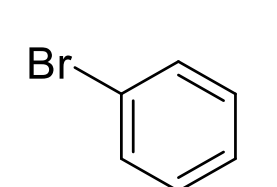
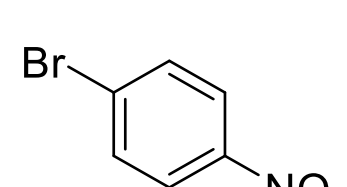
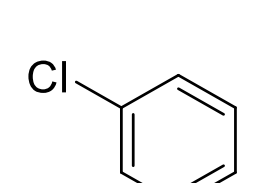
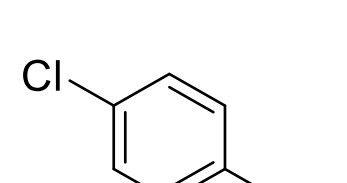
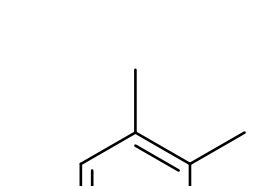
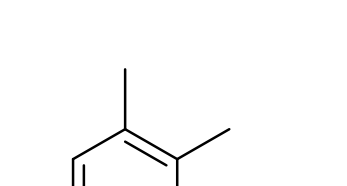


Entry	HNO <sub>3</sub> (mL)	mesitylene (mL)	molar ratio HNO <sub>3</sub> /Mes	conditions	time (min)	yield % <sup>a</sup>
1	5.0	0.5	22	ultrasounds, rt	30	34
2	5.0	0.5	22	ultrasounds, rt	40	91
3	5.0	0.5	22	ultrasounds, rt	50	94
4	5.0	0.5	22	ultrasounds, rt	90	100
5	5.0	0.5	22	conventional stirring, rt	60	97
6	6.0	0.5	26.3	ultrasounds, rt	60	96
7	6.0	0.5	26.3	conventional stirring, rt	60	97
8	3.5	0.5	15.4	ultrasounds, rt	60	95
9	3.5	0.5	15.4	conventional stirring, rt	60	90
10	2.5	0.5	11.0	ultrasounds, rt	60	100
11	2.5	0.5	11.0	conventional stirring, rt	60	100
12	2.0	0.5	8.8	ultrasounds, rt	60	2
13	2.0	0.5	8.8	conventional stirring, rt	60	88
14	1.5	0.5	6.6	ultrasounds, rt	60	2
15	1.5	0.5	6.6	conventional stirring, rt	60	26
16	1.0	0.5	4.4	ultrasounds, rt	60	3
17	1.0	0.5	4.4	conventional stirring, rt	60	3
18	0.5	0.5	2.2	ultrasounds, rt	60	1
19	0.5	0.5	2.2	conventional stirring, rt	60	4

<sup>a</sup>GC yield

### Scope

**Table 3.** Nitration of aromatics with co-acid-free aqueous nitric acid.

entry	substrate (S)	molar ratio HNO <sub>3</sub> /S	conditions	product	yield % <sup>a</sup>
1		11	stirring, rt, 2.6 mL HNO <sub>3</sub> /0.4 mL benzene, 90 min		66
2		11	ultrasounds, rt, 2.6 mL HNO <sub>3</sub> /0.4 mL toluene, 120 min		100 ( <i>o/m/p</i> : 53/4/43)
3		11	ultrasounds, rt, 2.6 mL HNO <sub>3</sub> /0.4 mL toluene, 120 min		74 ( <i>o/m/p</i> : 39/7/54)
4		10	stirring, rt, 2.6 mL HNO <sub>3</sub> /0.45 mL <i>o</i> -xylene, 90 min		60 (3/4-NO <sub>2</sub> : 31/69)
5		11	stirring, rt, 2.6 mL HNO <sub>3</sub> /0.45 mL <i>m</i> -xylene, 90 min		88 (2/4-NO <sub>2</sub> : 23/77)
6		11	ultrasounds, rt, 2.6 mL HNO <sub>3</sub> /0.45 mL <i>p</i> -xylene, 120 min		71
7		11	stirring, rt, 2.5 mL HNO <sub>3</sub> /0.5 mL mesitylene, 60 min		100
8		11	ultrasounds, rt, 2.6 mL HNO <sub>3</sub> /0.4 mL anisole, 120 min		95 ( <i>o/m/p</i> : 19/0/81)
9		11	microwaves, 50 °C, 2.6 mL HNO <sub>3</sub> /0.4 mL bromobenzene, 30 min		93 ( <i>o/m/p</i> : 2/0/98)
10		11	microwaves, 50 °C, 2.6 mL HNO <sub>3</sub> /0.4 mL chlorobenzene, 30 min		18 ( <i>o/m/p</i> : 33/0/67)
11		11	ultrasounds, rt, 2 mL HNO <sub>3</sub> /0.3858 g 1,2,4,5-tetramethylbenzene, 120 min		42

<sup>a</sup>GC yield

## Conclusions

It can be concluded that aqueous dilute nitric acid can be applied for the nitration of various aromatic compounds in moderate to excellent yields and often high selectivities. Notably, these conditions prevent the undesired double nitration of substrates, which sets it apart from fuming nitric acid-driven reactions or other processes involving strong co-acids. Additionally, the use of commercially available diluted nitric acid (15.8 M) provides several benefits including improved safety and significantly reduced waste production. Our results suggest that scaling up this nitration protocol for industrial purposes warrants further consideration.