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SYNTHESIS OF TRINITROAROMATICS USING ALTERNATIVE MIXED ACID NITRATION CONDITIONS

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Conditions for the mild and efficient nitration of phloroglucinol (1,3,5-trihydroxybenzene), 5-methoxyresorcinol, 3,5-dimethoxyphenol, and 1,3,5-trimethoxybenzene have been developed. Yields of the trinitro derivatives are excellent (~90%) for systems having one or more hydroxyl groups, and in the case of 1,3,5-trimethoxybenzene, the trinitro analog was obtained in 62% yield. The optimum nitration conditions utilize sulfuric acid (94–98%) and an inorganic nitrate salt.

Keywords**:** Dimethoxypicric acid; methoxystyphnic acid; nitration; trimethoxy-trinitrobenzene; trinitrophloroglucinol

INTRODUCTION

A fundamental challenge in preparing highly nitrated aromatic species is overcoming the inherent ring deactivation caused by incorporation of two or more nitro groups. Thus, although mono- and dinitrations of aromatics are generally facile, trinitrations are comparatively more difficult. Trinitrations typically necessitate more vigorous reaction conditions than mono- or dinitrations and as a result promote oxidative decomposition of starting materials, intermediates, and products that lead to poor chemical yields.[1,2a–c] A number of nitration strategies have been reported,[3,4] but few have been exploited to efficiently trinitrate aromatics.

Sulfuric acid solutions of nitrate salts ($NaNO_3$, KNO_3) were once widely used as nitrating agents but eventually lost popularity in favor of mixed acids as nitric acid became more readily available.[5a] Examples of nitroaromatics synthesized from sulfuric acid or oleum solutions of potassium nitrate include dinitroquinoline,[6] 1,3,5-tribromo-2,4,6-trinitrobenzene,[7] 1,3,5-trichloro-2,4,6-trinitrobenzene,[7] 1,5-dibromo-2,4-dinitrobenzene,[8] and 1,3-dibromo-2,4,6-trinitrobenzene.[8] More recently, Lu and coworkers reported the preparation of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20) using superacid solutions of potassium, sodium, or ammonium nitrate.[9] Kinetic studies have also been conducted on nitrations of anthraquinone with nitrate salts of various cations in sulfuric acid.[10]

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Polynitroaromatic compounds are renowned for their utility in the field of energetic materials.[1,5a,5b] Nitrated phenols and phenolic ethers are of particular interest because they serve as synthetic intermediates to a diverse range of explosives.[1,5,11–14] Phloroglucinol (PG) has been converted to trinitrophloroglucinol (**1**) by mixed acid nitration,[15,16] nitration with N_2O_5 in sulfuric acid,[12] oxidation of the trinitroso intermediate,[17] and nitration of the corresponding triacetate followed by –OH restoration via hydrolysis.[12] To the best of our knowledge, 3-methoxystyphnic acid (**2**) has not been reported, but its parent compound, styphnic acid, prepared by sulfonation and ensuing nitration of resorcinol, is well known.[5a] Tribromotrinitrobenzene[18] and pentanitrophenol[19,20] have both been converted to 3,5-dimethoxypicric (DMP) acid (**3**) by treatment with sodium methoxide. Nitration of 1,3,5-trimethoxybenzene (TMB) has been thoroughly investigated by Bellamy and coworkers, who obtained moderate yields of 1,3,5-trimethoxy-2,4,6-trinitrobenzene (**4**) using N_2O_5 in acetonitrile with sulfuric acid as a catalyst.[21]

Herein, we present a means of synthesizing four trinitroaromatic compounds in moderate to excellent yields employing a mild nitration mixture of sulfuric acid (94–98%) and an inorganic nitrate salt, XNO_3, where $X = NH_4^+$, Na^+, K^+. The aromatic starting materials are PG, 5-methoxyresorcinol (MR), DMP, and TMB.

RESULTS AND DISCUSSION

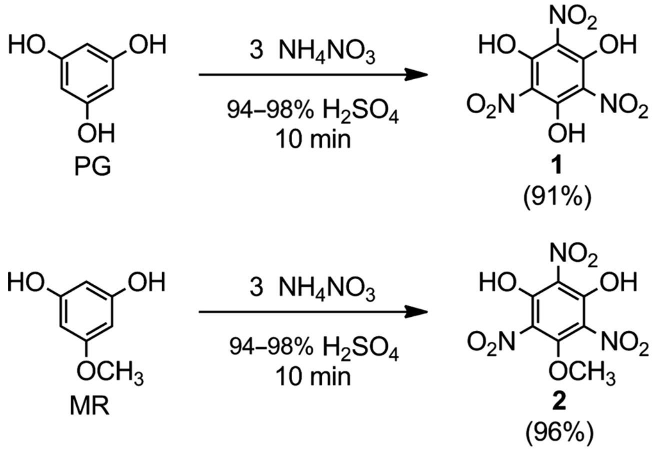
The combination of a nitrate salt in sulfuric acid is derived from the common mixed acid nitrating reagent. However, the additional equilibrium between the nitrate anion and nitric acid distinguishes this reagent from mixed acid (Eq. 1).

$$NO_3^- \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} HNO_3 \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} NO_2^+ + H_2O \qquad (1)$$

The initial equilibrium is assumed to mediate the nitration reaction by controlling the amount of nitric acid and subsequent nitronium ions available for nucleophilic attack by the aromatic substrate.

The nitrate salt in sulfuric acid has several advantages over mixed acid nitrations: (1) nitrate salts are more economical, have a longer shelf life, and are less hazardous than nitric acid; (2) a minimal temperature increase is observed upon mixing nitrate salts with sulfuric acid compared to the considerable exotherm encountered when adding nitric acid to sulfuric acid; (3) heating nitrate salt / sulfuric acid reactions does not generate visible NO_x gases; and (4) sulfuric acid is partially neutralized with the nitrate salt as the reaction proceeds, aiding in the disposal of spent acid. Furthermore, the in situ generation of nitric acid limits the amount of oxidant available in solution to compete with the nitration reaction.

We evaluated the efficacy of the three nitrate salts individually dissolved in sulfuric acid (94–98%) as nitrating agents for the four aromatic starting materials. The choice of nitrate salt had little observed effect on chemical yield and purity of **1** and **2**. PG and MR were both converted to their trinitro counterparts in comparable yields and purities with all three nitrate salts in 10 min. Ultimately, ammonium nitrate was the preferred salt because of its rapid dissolution in sulfuric acid and consistently excellent yields of **1** (91% yield) and **2** (96% yield) (Scheme 1).



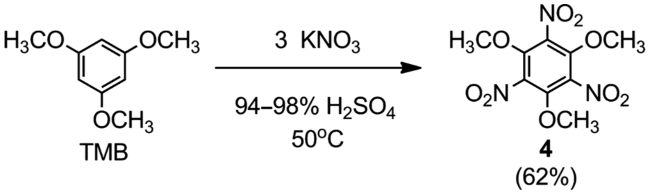
Scheme 1. Preparation of **1** (top) and **2** (bottom).

The identity of the starting nitrate salt had a more pronounced effect on the nitrations of DMP and TMB. DMP was most favorably converted to **3** (85% yield) in 20 min using sodium nitrate (Scheme 2). When potassium nitrate was used, reactions took approximately 15 min and afforded **3** in good yield and purity. Ammonium nitrate successfully converted DMP to **3** in only 10 min, but the reactions frequently yielded a crude product that was tan or brown in color, although nearly identical by NMR spectroscopy to the yellow material recovered from the sodium and potassium nitrate reactions.

The best conditions for the synthesis of **4** (62% yield) from TMB included 3 molar equivalents of potassium nitrate with heating to 50 °C (Scheme 3). Three molar equivalents of ammonium nitrate at 45 °C also produced good-quality **4**, but yields were slightly better with potassium nitrate. Four molar equivalents of sodium nitrate were necessary to obtain similar results at 40 °C for 30 min. Heating to 65 °C with 3 molar equivalents of sodium nitrate gave a 52% yield of **4**. A summary of observed nitration results for all four starting materials is shown in Table 1.

Mixtures of ice and water were used to quench the nitration reactions, and the amounts of each played an important role in yield and product appearance. Compounds **1**, **2**, and **3** are water soluble so the sulfuric acid reaction solvent was used

Scheme 2. Preparation of **3**.



Scheme 3. Preparation of **4**.

Table 1. Summary of nitration results

Reaction	XNO_3[a] (X^+)	Reaction time[c] (min)	Yield (%)
PG → **1**	NH_4	10	91
	K	10	89
	Na	10	88
MR → **2**	NH_4	10	96
	K	10	90
	Na	10	90
DMP → **3**	NH_4	10	80
	K	15	83
	Na	20	85
TMB → **4**	NH_4	heated to 40 °C	61
	K	heated to 50 °C	62
	Na	heated to 65 °C	52
	Na[b]	30 @ 40 °C	60

[a] 3 mol. equivalents based on starting aromatic unless noted otherwise.

[b] 4 mol. equivalents based on TMB.

[c] For TMB→4, ramp rates are ~5 °C/min. Reactions quenched at indicated temperature.

to keep the pH low enough to promote precipitation upon quenching. A point of diminishing returns was reached if too much ice or water was used (>5.75 mM **1** in H_2O, >60 mM **2** and **3** in H_2O) to recover **1**, **2**, and **3** as significant portions of product would remain dissolved. Compound **4** is insoluble in water, so the volume used for quenching the reactions was less influential and not investigated further. Compounds **1** and **2** precipitated out of solution as the nitration reaction proceeded but were still added to ice to aid in product filtration and isolation. Compound **3** was most sensitive to the amount of ice and water used for product recovery. It was determined that 75 g of ice mixed with 75 g of water was ideal for quenching the reactions starting with 250 mg of DMP. Lesser amounts of ice/water tended to produce tan- or brown-colored product as opposed to yellow, although the NMR spectra did not always reflect appreciable purity differences in such cases. The variations in product color were more apparent when ammonium nitrate was used as the nitro source instead of sodium or potassium nitrates, particularly in the synthesis of **3**. Moderate success at purifying brown-colored product was achieved by flash chromatography with ethyl acetate and silica gel.

CONCLUSION

The straightforward synthesis of a series of four trinitrophenol/ether derivatives employing a stoichiometric amount of ammonium, potassium, or sodium nitrate in sulfuric acid has been described. The choice of the nitrate salt had minimal effects on the nitrations of aromatics with two or three hydroxyl groups but had a marked impact on the nitrations of aromatics with one or no hydroxyl groups. This nitration strategy displays clear advantages over the more popular mixed acid nitration approach.

EXPERIMENTAL

General

Warning: Nitrated aromatics, including those described here, are potentially explosive. Extreme caution should be exercised when handling these compounds. Minimize exposure of these materials to impact, friction, heat, and electrostatic discharge.

Sulfuric acid (94–98%) was purchased from VWR International. Phloroglucinol dihydrate, 5-methoxyresorcinol, 3,5-dimethoxyphenol, 1,3,5-trinitrobenzene, ammonium nitrate, sodium nitrate, and potassium nitrate were purchased from Aldrich Chemical Company and used as received. CD_2Cl_2 and $CDCl_3$ were obtained from Cambridge Isotopes Laboratories. Water was purified in-house using a typical double-distillation apparatus. ^1H and ^{13}C NMR data were collected on a Jeol Eclipse +400-MHz spectrometer; the chemical shifts are reported in δ (ppm) relative to residual solvent peaks ($CDCl_3$ δ ^1H 7.25, ^{13}C 77.00; CD_2Cl_2 δ ^1H 5.31, ^{13}C 53.08). Melting points are uncorrected and were determined using the standard open capillary method. Elemental analyses were performed on a Perkin-Elmer model 2400 series II CHNS/O analyzer.

Synthesis and Characterization

2,4,6-Trinitrophloroglucinol monohydrate (1). A round-bottom flask was charged with sulfuric acid (94–98%, 30 mL) and chilled to approximately 5 °C. Ammonium nitrate (1.48 g, 18.48 mmol) was added with stirring at a rate such that the temperature did not exceed 10 °C. Once the solution temperature returned to 5 °C, phloroglucinol dihydrate (PGDH; 1.00 g, 6.16 mmol) was added at a rate such that the temperature did not exceed 10 °C. Vigorous stirring was maintained to visibly prevent concentrating the solid in the center vortex. After PGDH addition was complete and the associated exotherm began to subside, the cooling bath was removed and the reaction was stirred for an additional 10 min. The heterogeneous yellow mixture was added in one portion to crushed ice (100 g) and was stirred gently until all the ice had melted. The precipitate was isolated by vacuum filtration, washed with cold 10% HCl, and air dried to afford 2,4,6-trinitrophloroglucinol monohydrate (1.57 g, 91%) as a yellow solid. Melting point and ^1H and ^{13}C NMR spectra matched those previously reported.[11]

5-Methoxystyphnic acid (2). Similar to **1**, ammonium nitrate (1.72 g, 21.48 mmol) and MR (1.00 g, 7.14 mmol) were used in the reaction. The precipitate was isolated by vacuum filtration, washed with cold 10% HCl, and air dried to afford 5-methoxystyphnic acid (1.89 g, 96%) as a light yellow solid, mp = 165–167 °C (decomp.): ^{1}H NMR (CD_2Cl_2) δ 4.09 (s, 3H, CH_3), 11.37 (s, 2H, OH); ^{13}C NMR (CD_2Cl_2) δ 61.99, 118.34, 126.20, 151.22, 152.02. Elemental analysis calculated for $C_7H_5N_3O_9$: C, 30.56; H, 1.83; N, 15.27. Found: C, 30.12; H, 1.54; N, 14.83.

3,5-Dimethoxypicric acid (3). A round-bottom flask was charged with sulfuric acid (94–98%, 10 mL) and chilled to approximately 5 °C. Sodium nitrate (410 mg, 4.82 mmol) was added with stirring at a rate such that the temperature did not exceed 10 °C. Once the solution temperature returned to 5 °C, DMP (250 mg, 1.62 mmol) was added at a rate such that the temperature did not exceed 10 °C. Vigorous stirring was maintained to visibly prevent concentrating the solid in the center vortex. After DMP addition was complete and the associated exotherm began to subside, the cooling bath was removed and the reaction was stirred for an additional 20 min. The dark red solution was added in one portion to a mixture of ice (75 g) and water (75 g) and was stirred gently until all the ice had melted. The precipitate was isolated by vacuum filtration, washed with cold 10% HCl, and air dried to afford 3,5-dimethoxypicric acid (400 mg, 85%) as a light yellow solid, mp = 75–76 °C: ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 6H, CH_3), 11.25 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 63.83, 127.53, 133.47, 150.57, 150.79. Elemental analysis calculated for $C_8H_7N_3O_9$: C, 33.23; H, 2.44; N, 14.53. Found: C, 33.25; H, 2.17; N, 14.37.

1,3,5-Trimethoxy-2,4,6-trinitrobenzene (4). A round-bottom flask was charged with sulfuric acid (94–98%, 10 mL) and chilled to approximately 5 °C in an ice bath. Potassium nitrate (452 mg, 4.47 mmol) was added with stirring at a rate such that the temperature did not exceed 10 °C. After addition was complete and the temperature returned to 5 °C, TMB (250 mg, 1.49 mmol) was added at a rate such that the temperature did not exceed 10 °C. Vigorous stirring was maintained to visibly prevent concentrating the solid in the center vortex. After TMB addition was complete and the associated exotherm began to subside, the reaction was warmed (5 °C/min) to 50 °C. The dark red solution was added in one portion to crushed ice (60 g) and stirred gently until all the ice had melted. The precipitate was isolated by vacuum filtration, washed with distilled water, and air dried to yield 1,3,5-trimethoxy-2,4,6-trinitrobenzene (280 mg, 62%) as a light yellow solid. Melting point and ^{1}H and ^{13}C NMR spectra matched those previously reported.[21]

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