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Synthesis and Prior Misidentification of 4-*tert*-Butyl-2,6-dinitrobenzaldehyde

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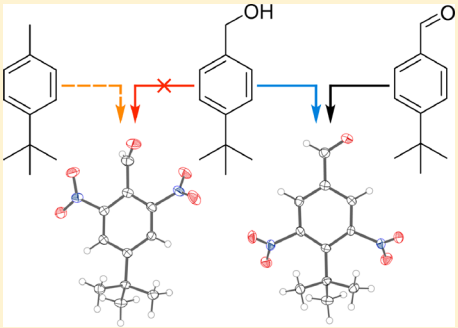
Supporting Information

ABSTRACT: Substituted 2,6-dinitrobenzaldehydes are valuable synthetic precursors and have been prepared by several methods. We report here that one reported synthetic method actually forms the 3,5-dinitro isomer, 4-*tert*-butyl-3,5-dinitrobenzaldehyde, instead of the claimed 2,6-isomer, 4-*tert*-butyl-2,6-dinitrobenzaldehyde. Improved syntheses for the large-scale preparation of both compounds and their single-crystal X-ray structures are described.



Substituted 2,6-dinitrobenzaldehydes are useful reagents for the preparation of dyes, pigments, and macrocycles such as porphyrins and corroles.[1−6] In particular, 2,6-dinitrobenzaldehydes are used in the synthesis of tetrakis-5,10,15,20-(2′,6′-dinitrophenyl)porphyrins, precursor molecules for bis-picket fence porphyrin derivatives.[4] The acid-catalyzed condensation of 2,6-dinitrobenzaldehyde or related derivatives with pyrrole produces substituted 2′,6′-dinitrophenylporphyrins but typically only in low yields, ranging from 0.5 to 9%. The highest yields are for the tetrakis-5,10,15,20-(4′-*tert*-butyl-2′,6′-dinitrophenyl)porphyrin, a common derivative.[3] In order to make reasonable amounts of this porphyrin target (>100 mg), its synthesis requires sizable amounts of 4-*tert*-butyl-2,6-dinitrobenzaldehyde, the starting benzaldehyde precursor.

The synthesis of 4-*tert*-butyl-2,6-dinitrobenzaldehyde (**1**) has been reported using two different routes (Methods A and C in Scheme 1).[3,6] Method A reported what seemed to be the most direct synthesis, a one-pot nitration and oxidation of 4-*tert*-butylbenzylalcohol.[6] This synthesis was stated to be "noteworthy since it occurs with concomitant chemoselective oxidation of the benzylic alcohol to the corresponding aldehyde and represents the by far most practical route" to this common precursor.[6] Following this preparation, we obtained a product in similar yields, which had ^{1}H NMR and ^{13}C NMR spectra identical to the reported spectra (Figures S1 and S2). Slow evaporation of this product from ethyl acetate yielded crystals suitable for single-crystal X-ray diffraction. The single-crystal data revealed that the product of this reaction was not **1** but was instead the isomeric 3,5-dinitro compound, 4-*tert*-butyl-3,5-dinitrobenzaldehyde (**2**) (Figure 1, right; Scheme 1, Method A). Presumably the hot HNO_3/H_2SO_4 oxidation of the benzyl alcohol proceeds by initial formation of 4-*tert*-butylbenzaldehyde, which directs nitration to positions *meta* to the aldehyde. Consistent with this possible intermediate formation, we report the synthesis of the 3,5-dinitro isomer, product **2**, in much higher yields (>95%) from the nitration of 4-*tert*-butylbenzaldehyde (Scheme 1, Method B; procedure in the Experimental Section). After a literature search of articles citing ref 6, we believe that this incorrect assignment may have led to a synthesis and misidentification of what is actually tetrakis-5,10,15,20-(4′-*tert*-butyl-3′,5′-dinitrophenyl)porphyrin.[7]

An earlier paper by Rose et al. reported a three-step preparation of the target 2,6-dinitro isomer **1** from 4-*tert*-butyltoluene (Scheme 1, Method C).[3] Following this procedure, including chromatography and recrystallization, we obtained a product with ^{1}H NMR and ^{13}C NMR spectra (Figures S3 and S4) that were identical to those reported in ref 3. Crystals were obtained from ethyl acetate/ethanol mixtures, and single-crystal X-ray diffraction showed that the product of this reaction was correctly assigned as 4-*tert*-butyl-2,6-dinitrobenzaldehyde (**1**) (Figure 1, left). The ^{1}H NMR and ^{13}C NMR spectra for **1** and **2** are quite distinct, as are the solid-state structures.

It is unfortunate that the apparently scalable Method A does not produce the desired compound **1**. Although Method C is suitable for the synthesis of **1** in small quantities, it does not scale well to larger amounts. After three steps, the overall yield of **1** is only 41% from 4-*tert*-butyltoluene, and the synthesis requires stoichiometric amounts of chromium reagents and multiple chromatography columns. We are pleased to report an improved route to **1**, starting from inexpensive 4-*tert*-butyltoluene, that can be done on much larger scales and without the need for chromatography or chromium reagents.

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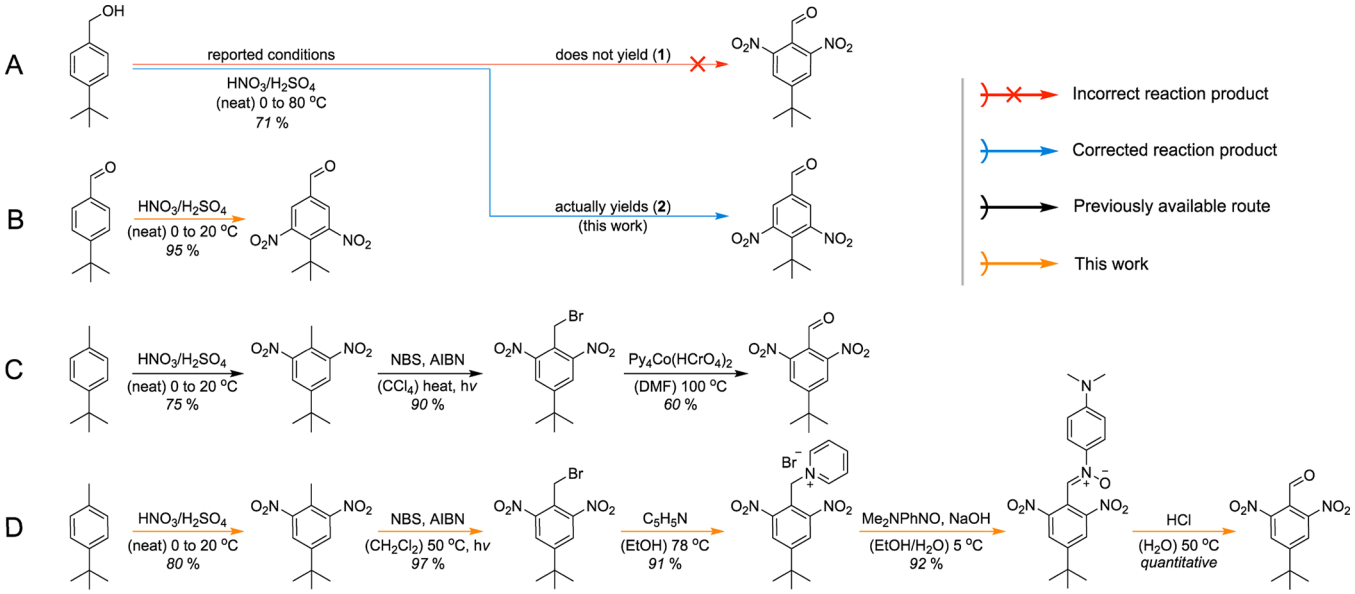
Scheme 1. Preparations of 4-*tert*-Butyl-2,6-dinitrobenzaldehyde and 4-*tert*-Butyl-3,5-dinitrobenzaldehyde[a]



[a]Incorrect previous report (red), corrected reaction product (blue), previously available route (black), and new—chromium and column-free—procedures (gold) are shown. Method A: reported synthesis in ref 6; actually yields **2** (this work). Method B: high yield synthesis of **2** (this work). Method C: previously reported synthesis of **1** requiring chromium reagents and chromatography purification from ref 3. Method D: high yield, high-throughput synthesis of **1** (this work).

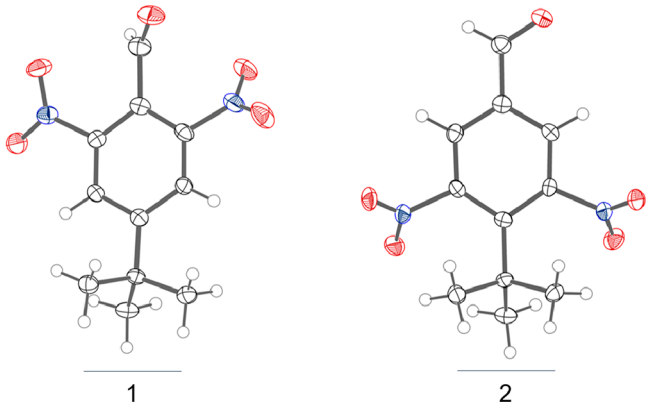


Figure 1. Thermal ellipsoid plots (50% probability level) of X-ray structures for 4-*tert*-butyl-2,6-dinitrobenzaldehyde and 4-*tert*-butyl-3,5-dinitrobenzaldehyde. The unit cell of **1** contained two chemically identical, crystallographically distinct molecules of **1** ($Z' = 2$); only one molecule is shown for clarity.

Our synthesis of **1** (Method D, Scheme 1) was adapted from the reported syntheses of other *ortho*-substituted aldehydes, including 2,6-dinitrobenzaldehyde.[8,9] First, 4-*tert*-butyl-2,6-dinitrotoluene was prepared by nitration of 4-*tert*-butyltoluene. The synthesis of this compound has been reported in several articles[3,6,10,11] and we have found no reports of hazards such as being explosive or forming explosive species. Bromination using *N*-bromosuccinimide yielded 4-*tert*-butyl-2,6-dinitrobenzyl bromide. Heating 4-*tert*-butyl-2,6-dinitrobenzyl bromide with pyridine in ethanol resulted in the precipitation of 4-*tert*-butyl-2,6-dinitrobenzylpyridinium bromide as a white, crystalline solid. Base-catalyzed condensation of the pyridinium salt with *N*,*N*′-dimethyl-4-nitrosoaniline generated the *N*-(4-dimethylaminophenyl)-α-(4-*tert*-butyl-2,6-dinitrophenyl)-nitrone, which precipitated as an orange solid from cold ethanol/water. Acid-catalyzed hydrolysis of the nitrone precipitated **1** as a yellow solid from acidic water. The ^{1}H NMR and ^{13}C NMR data for all of the intermediates are reported in the Supporting Information (Figures S5−S12). Although this synthesis has more steps, it gives **1** in 65% overall yield (starting from 1 mol of the parent toluene) and requires only recrystallization and solubility differences for purification (Method D, Scheme 1). An alternative synthesis via direct oxidation of the benzyl bromide intermediate using DMSO/Et_3N was briefly explored. Whereas this gave **1** in fewer steps than the method detailed here, it was not pursued because it required chromatography to separate the unreacted benzyl bromide and was therefore less attractive at a large scale.

In summary, we report here that a published method[6] yields 4-*tert*-butyl-3,5-dinitrobenzaldehyde (**2**) rather than the claimed 2,6-dinitro isomer, 4-*tert*-butyl-2,6-dinitrobenzaldehyde (**1**). As the 2,6-isomer is a valuable synthetic intermediate, we have developed an improved synthesis without the need for chromatography or chromium reagents. This synthesis has been scaled to yield more than 150 g of **1** with an overall yield of 65%. We also report a convenient synthesis of **2**. The ^{1}H NMR and ^{13}C NMR spectra and the X-ray crystal structures of both isomers are reported.

EXPERIMENTAL SECTION

Instrumentation. ^{1}H NMR spectra were recorded on an Agilent 500 MHz spectrometer and were referenced to proteo solvent impurities. High-resolution mass spectrometry was performed using a Waters Xevo G2-XS QToF mass spectrometer. Gas chromatography/mass spectrometry was performed using an Agilent 6890N/5973 mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Ledgewood, NJ.

Materials. Potassium nitrate (Sigma-Aldrich, ReagentPlus, >99%), sulfuric acid (J.T. Baker, 98%), 4-*tert*-butylbenzylalcohol (Sigma-Aldrich, 95%), 4-*tert*-butylbenzaldehyde (Sigma-Aldrich, 97%), 4-*tert*-butyltoluene (Sigma-Aldrich, 95%), *N*-bromosuccinimide (Sigma-Aldrich, ReagentPlus, 99%), 2,2′-azobis(2-methylpropionitrile)

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(Sigma-Aldrich, 98%), pyridine (Sigma-Aldrich, 99.8%), *N*,*N*-dimethyl-4-nitrosoaniline (Sigma-Aldrich, 97%), aqueous hydrochloric acid (Macron, 36−38 wt %), sodium chloride (Sigma-Aldrich, >99%), sodium bicarbonate (Sigma-Aldrich, >99%), sodium hydroxide (Macon, 95%), chloroform (Sigma-Aldrich, 99.8%), ethyl acetate (Sigma-Aldrich, 99.8%), absolute ethanol (Decon Laboratories, 200 proof), diethylether (Sigma-Aldrich, 99%), and acetone (Sigma-Aldrich, 99.8%) were all used as received. Dichloromethane was degassed with argon and dried using a Pure Process Technology solvent system prior to use.

Single-Crystal X-ray Diffraction Methods. Low-temperature diffraction data (ω scans) were collected on a Rigaku SCX mini-diffractometer coupled to a Rigaku Mercury275R CCD with Mo Kα radiation (λ = 0.71073 Å). The diffraction images were processed and scaled using Rigaku Oxford diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structures were solved with SHELXT and were refined against F^2 on all data by full-matrix least-squares with SHELXL.[1] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in both models at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms to which they are linked (1.5 times for methyl groups). For **2**, the data set was refined as a two-component twin. The fractional volume contribution of the minor twin component was freely refined to a converged value of 0.3850(19). For **1**, the data set yielded a unit cell containing two chemically identical, crystallographically distinct molecules.

The full numbering scheme of compounds **1** and **2** can be found in the full details of the X-ray structure determinations (CIFs), which are included as Supporting Information. CCDC number 1923128 (**1**) and 1923129 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Mixed Acid Preparation for Nitration Reactions. ***Caution:*** *Fuming nitric acid* (FNA) is a corrosive strong acid and a strong oxidant; concentrated sulfuric acid is a corrosive strong acid, and the mixture of the two is considered a stronger acid and oxidant. All of these materials are highly hazardous and should be handled with substantial caution with emphasis on appropriate specialized personal protective equipment (PPE). Our laboratory's standard operating procedure (SOP) for FNA and the mixed acid are included as Supporting Information. FNA (+98%) was freshly prepared immediately before use via distillation of HNO_3 at 80 °C from a mixture of potassium nitrate and concentrated sulfuric acid, prepared as described in the SOP. FNA (1 part by volume, for instance, 50 mL) was cooled to 5 °C in an ice bath before concentrated sulfuric acid (1.4 parts by volume, for instance, 70 mL) was slowly added. Upon addition, the mixed acid warmed to 15 °C. The mixed acid solution was cooled to 5 °C before being used immediately for nitration reactions.

Improved Synthesis of 4-*tert*-Butyl-3,5-dinitrobenzaldehyde (2). Approximately 120 mL of the mixed H_2SO_4/HNO_3 acid (see preparation above) was prepared in a 500 mL round-bottom flask with a large stir bar and was cooled to 5 °C with an ice bath. [**Caution:** hazardous! See above and SOP in Supporting Information.] Above the round-bottom was suspended a dropping funnel filled with 4-*tert*-butylbenzaldehyde (25 mL, 0.149 mmol). The benzaldehyde was added dropwise to the stirring solution, and the flow rate was adjusted such that the reaction temperature did not increase above 15 °C. After complete addition, the solution was yellow/orange and the reaction flask was allowed to warm to room temperature before being gently heated to 40 °C for 1−2 h. During this time, some off-white precipitate formed. The reaction was then quenched by *carefully* pouring the entire reaction into a large amount of crushed ice (ca. 500 mL). The precipitated product was filtered off and washed with excess water. The dilute acidic filtrate was neutralized and added to the aqueous waste. After being air-dried, the crude yellow solid (crude yield by weight = 36 g, 97%) was dissolved in chloroform and filtered through Celite to remove any overoxidized 4-*tert*-butyl-2,6-dinitrobenzoic acid (the white solid formed during synthesis). The filtrate was collected and removed with a rotary evaporator to dryness. The collected solid was then recrystallized from boiling ethyl acetate to yield pale yellow crystals (Figure S18). After being filtered and air-dried, 29 g of crystals were collected (80% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 9.99 (s, 1H, C*H*O), 7.99 (s, 2H, Ar-*H*), 1.49 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (ppm) = 187.0, 153.7, 141.1, 135.3, 126.6, 38.2, 30.0. Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.13; H, 4.65; N, 10.95. MS (EI) m/z = 252.1 ([M]$^+$), 237.1 ([M]$^+$ − CH_3).

4-*tert*-Butyl-2,6-dinitrotoluene. This synthesis was adapted from the literature.[4] Approximately 240 mL of the mixed H_2SO_4/HNO_3 acid (see preparation above) was prepared in a 1 L round-bottom flask with a large stir bar and was cooled to 5 °C with an ice bath. [**Caution:** hazardous! See above and SOP in Supporting Information.] Above the round-bottom was suspended a dropping funnel filled with 4-*tert*-butyltoluene (173 mL, 1.0 mol). The 4-*tert*-butyltoluene was added dropwise to the stirring solution over the course of 3 h such that the temperature of the reaction stayed between 5 and 10 °C. The yellow product formed and floated to the reaction surface during the addition. After complete addition, the reaction flask was allowed to warm to room temperature and was stirred for another 12 h. The reaction was quenched by *carefully* pouring the reaction mixture into 500 mL of crushed ice. After filtration, the collected yellow solid was washed with excess water. The dilute acidic filtrate was neutralized and added to the aqueous waste. The damp solid was then recrystallized from boiling EtOH (approximately 750 mL). Upon being cooled, large yellow crystals formed (Figure S13). The solution was cooled at 0 °C overnight before the crystals were filtered and washed with cold EtOH. After being dried, the isolated yield was 190 g of flaky crystalline solid (80% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.97 (s, 2H, Ar-*H*), 2.52 (s, 3H, CH_3), 1.37 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (ppm) = 152.2, 151.6, 124.7, 124.1, 35.3, 30.8, 14.5. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.42; H, 5.78; N, 11.68. MS (EI): m/z = 238.1 ([M]$^+$), 223.1 ([M]$^+$ − CH_3).

4-*tert*-Butyl-2,6-dinitrobenzyl bromide. To a 3 L three-necked round-bottom flask were added a large stir bar, 4-*tert*-butyl-2,6-dinitrotoluene (190 g, 0.798 mol, 1 equiv), *N*-bromosuccinimide (170 g, 0.998 mol, 1.25 equiv), and AIBN (1.5 g, 0.009 mol, 0.01 equiv). Two of the three ports were stoppered, and 1.5 L of dry dichloromethane was added to the solids. The solution was sparged with N_2 for 20 min before a condenser was attached to the third port and the reaction was heated to a gentle reflux (45−50 °C). A white LED light (14 V dc, 0.7 A from Digi-Key) was clamped a few inches away from the flask, and the reaction was loosely shrouded in aluminum foil. At the 12, 48, 74, and 82 h marks, additional NBS (20 g, 0.117 mL, 0.15 equiv) and AIBN (0.5 g, 0.0045 mol, 0.005 equiv) were added. The solid additions were made by funneling the NBS/AIBN through an opened port under gently flowing N_2 only after the reaction was cooled to room temperature. After 4 days, the reaction was nearly complete (>98% conversion based on the ratio of product to starting material by ^{1}H NMR). The solvent was removed using a rotary evaporator to yield a damp solid. The solid was resuspended in chloroform and filtered to remove the bulk of the succinimide. The filtrate was separated with saturated Na_2CO_3 solution to remove residual succinimide before being dried with $MgSO_4$ and filtered. The solvent was removed, and the product was recrystallized from hot diethyl ether to yield extremely large pale-yellow crystals (5−7 g apiece, Figure S14). Isolated yield was 235.5 g of large yellow crystals and 13.2 g of noncrystalline powder with matching ^{1}H NMR spectra (97.7%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.04 (s, 2H, Ar-*H*), 4.84 (s, 2H, CH_2Br), 1.37 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (ppm) = 155.3, 150.1, 125.9, 123.6, 35.7, 30.7, 20.4. Anal. Calcd for $C_{11}H_{13}BrN_2O_4$: C, 41.7; H, 4.1; N, 8.8. Found: C, 41.69; H, 4.01; N, 8.71. MS (EI): m/z = 301.0 ([M]$^+$ − CH_3), 237.1 ([M]$^+$ − Br), parent ion not observed.

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4-*tert*-Butyl-2,6-dinitrobenzylpyridinium bromide. The crude 4-*tert*-butyl-2,6-dinitrobenzyl bromide (246 g, 0.778 mol, 1 equiv) was added to a 2 L beaker. The solid was dissolved in 1 L of EtOH (200 proof) and was heated to 78 °C with stirring. Pyridine (130 mL, 1.55 mol, 2 equiv) was added dropwise to the stirring solution, which darkened and eventually precipitated flocculent white crystals (Figure S15). After complete addition, the solution was stirred for an additional hour at reflux before an additional hour of stirring at room temperature. The crystals were filtered and washed with EtOH and acetone. After being dried, the first crop of crystals weighed 258 g. The filtrate was pumped to a solid using a rotary evaporator and was repeatedly recrystallized from EtOH to yield an additional 25 g of off-white solid with ^{1}H NMR that matched the crystalline material (total solid collected: 283.0 g, 91.3% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) = 9.06 (d, J = 6.0 Hz, 2H, 2,6-py-*H*), 8.72 (t, J = 7.8 Hz, 1H, 4-py-*H*), 8.53 (s, 2H, Ar-*H*), 8.21 (t, J = 7.1 Hz, 2H, 3,5-py-*H*), 6.14 (s, 2H, Ar−CH_2-py), 1.41 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (DMSO-d_6, 500 MHz): δ (ppm) = 157.9, 152.0, 146.7, 144.5, 128.5, 127.6, 116.5, 56.0, 36.2, 30.5. Anal. Calcd for $C_{16}H_{18}N_3O_4Br$: C, 48.50; H, 4.58; N, 10.60. Found: C, 48.31; H, 4.32; N, 10.38. HRMS (ESI/Q-TOF) m/z: [M − Br]$^+$ calcd for $C_{16}H_{18}N_3O_4^+$ 316.1297; found 316.1296.

***N*-(4-Dimethylaminophenyl)-α-(4-*tert*-butyl-2,6-dinitrophenyl)nitrone.** To a large Erlenmeyer flask was added approximately 1/3 of the dry 4-*tert*-butyl-2,6-dinitrobenzylpyridinium bromide (85.4 g, 0.215 mol, 1 equiv) and *N*,*N*-dimethyl-4-nitrosoaniline (40.0 g, 0.266 mol, 1.24 equiv). The solids were suspended in 1.0 L of ethanol (200 proof), and the solution was cooled to 5 °C with an ice bath. An addition funnel was suspended above the reaction and was filled with 600 mL of 1 N sodium hydroxide solution. With vigorous stirring, the NaOH solution was added dropwise such that the temperature was kept between 5 and 10 °C. After complete addition, the solution was stirred for another 2 h before being diluted with 1 L of ice water. The nitrone precipitated as an orange solid (Figure S16), which was filtered and washed with excess water. This procedure was repeated until nearly all of the benzylpyridinium bromide was used (279.3 g, 0.714 mol). All of the orange solids were collected and dried in a vacuum oven at 50 °C until reaching a constant mass (2−3 days). After being dried, the yield was 257.7 g of orange powder (92.4% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.44 (s, 1H, Ar−C*H*=N), 8.30 (s, 2H, Ar-*H*), 7.67 (d, J = 9.1 Hz, 2H), 6.67 (d, J = 9.1 Hz, 2H), 3.04 (s, 6H, N(CH_3)$_2$), 1.42 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (ppm) = 155.3, 152.1, 149.6, 136.8, 126.1, 122.8, 122.5, 117.8, 111.4, 40.5, 35.9, 30.9. Anal. Calcd for $C_{19}H_{22}N_4O_5$: C, 59.06; H, 5.74; N, 14.50. Found: C, 58.92; H, 5.56; N, 14.34. HRMS (ESI/Q-TOF) m/z: [M + H$^+$] calcd for $C_{19}H_{23}N_4O_5^+$ 387.1668; found 387.1682.

4-*tert*-Butyl-2,6-dinitrobenzaldehyde (1). In a large beaker, nearly all of the *N*-(4-dimethylaminophenyl)-α-(4-*tert*-butyl-2,6-dinitrophenyl)nitrone (257.2 g) was suspended in 2 L of water. Concentrated sulfuric acid (400 mL) was added slowly, and the solution was warmed to approximately 50 °C. The suspension was stirred for 30 min, during which time the solution color lightened to a pale yellow-brown. The suspension was filtered, and the collected solid was washed with excess water. After being dried, 164 g of pale-yellow powder was collected (98% yield). The solid could be recrystallized from hot ethanol or from mixtures of ethanol/ethyl acetate to yield golden flake-like crystals (Figure S18). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 10.57 (s, 1H, C*H*O), 8.45 (s, 2H, Ar-*H*), 1.45 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ (ppm) = 186.2, 157.1 147.7, 129.0, 126.8, 36.1, 30.9. Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.13; H, 4.61; N, 10.94. MS (EI) m/z = 252.1 ([M]$^+$), 237.1 ([M]$^+$ − CH_3).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01737.

Copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

X-ray data for compound **1** (CIF)

X-ray data for compound **2** (CIF)

Standard operating procedures for working with concentrated nitric and sulfuric acids, with emphasis on safety precautions (PDF)

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Notes

The authors declare no competing financial interest.

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