

An Improved Procedure for the Reduction of 2,4-Dinitrobenzaldehyde to 2,4-Diaminobenzaldehyde with Iron and Acetic Acid under Dose-Controlled Conditions

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To fulfill a need for gram to kilogram quantities of 2,4-diaminobenzaldehyde (**2**) a safe and operationally simple procedure to reduce 2,4-dinitrobenzaldehyde (**1**) to 2,4-diaminobenzaldehyde (**2**) was developed. The reduction of **1** to **2** with iron powder and aqueous HCl in ethanol at 95 °C has been described.¹ Due to the highly energetic nature of **1** as shown by DSC² (Figure 2) and its impact sensitivity,³ a more thorough study was undertaken to adapt this process for safe scale-up.

Attempts to scale the published procedure¹ gave tarry solids that were difficult to granulate and contained significant quantities of iron. Chromatography was required to purify the material, and the isolated yields were typically less than 50%. Further investigations led to a procedure employing an acetic acid/ethyl acetate/water mixture and a reaction temperature below 50 °C. High temperatures were not required, and the product was cleaner. It was noted that the decomposition/polymerization of **2** is catalyzed by strong acid. Subsequent product isolations were conducted in base (aqueous NaOH)-washed glassware. An extractive work-up with ethyl acetate and treatment of the extracts with activated carbon (Darco G60) (10% w/w relative to **1**) were effective at removing the iron salts from the crude product. After partial concentration, the desired product could then be precipitated into hexanes to give good quality material (>95% by HPLC, NMR) in good yields (70–80%). This isolation protocol also minimizes any polymerization due to the presence of the diamine and aldehyde functionality.

In attempts to optimize the loading level of reagents, initial difficulties were encountered in reproducing our own results. It was observed that the reduction could be accomplished with as little as 2.5 equiv (mol/mol) of iron and 3.5 equiv of acetic acid for each nitro group if it was run open to the air. (Literature stoichiometry⁴ is 3 equiv of iron and 6 equiv of acid per nitro group.) In a second experiment, under nitrogen, no reaction was observed even with efficient stirring at reflux overnight. When the reactor was opened to the air and the mixture transferred to a second container, the mixture self-heated and proceeded quite quickly to give almost complete

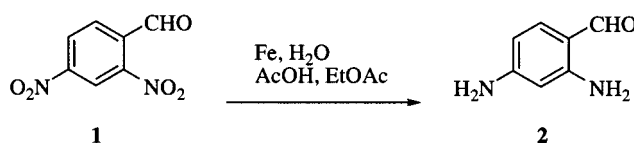


Figure 1.

reduction within 1 h. How oxygen acts to activate the iron surface and allow the reaction to occur is currently unclear.

To obtain a reproducible procedure for reactions under a nitrogen atmosphere, the iron powder was activated by the addition of 1 equiv of acetic acid to the iron/water mixture, prior to the addition of a solution of **1**. The use of 4 equiv of iron and 6.5 equiv of acetic acid per nitro group was the preferred stoichiometry.

The reaction energy can be effectively controlled by the rate of addition of **1**, as a solution in ethyl acetate/acetic acid, to a slurry of iron powder in water. Ideally **1** was added at such a rate as to maintain the temperature below 50 °C. Under these conditions, the kinetics are fast enough to maintain dose rate control of the reaction exotherm and limit the accumulation of **1** in the reaction mixture. Therefore, there is a lower probability of thermal runaway, thus reducing the overall risk of the process. An online monitoring tool, such as in situ FTIR, is recommended to ensure that **1** does not accumulate.

DSC analysis of the product **2** shows no apparent energy release between ambient temperature and 350 °C. Furthermore, DSC analysis of samples of the reaction mixture throughout the addition also show no energy release. TLC analysis of these samples showed only **2** and led to the conclusion that under these reaction conditions there is no accumulation of **1** and the reduction intermediates.

Heat Flow Calorimetry Results and Discussion

Reaction calorimetry was performed using a Mettler-Toledo RC-1e reaction calorimeter equipped with a 1-L SV01 reactor. The reactor was initially charged with iron powder and water held isothermally at 50 °C. Automated doses (linear) of 0.5 equiv of acetic acid, then a solution of **1** in ethyl acetate and acetic acid were completed. Heat flow was monitored to give Figure 3 and the accompanying table.

Figure 3 illustrates the heat flow associated with each dose in W/L throughout this process and clearly shows, along with the TLC and DSC profiling noted previously, that the reaction is dose rate-controlled (2-h addition) and there is

(1) Merlic, Craig A.; Motamed, Soheil; Quinn, Bruce J. *Org. Chem.* **1995**, *60*, 3365–3369.

(2) DSC Result of isolated solid: Exothermic decomposition near 218 °C liberating 2669 J/g of energy. DSC Result of 1:1 w/w in ethyl acetate: Exothermic decomposition near 219 °C liberating 477 J/g of energy.

(3) BAM Fallhammer Test: Impact sensitive above 56 J.

(4) Owsley, D. C.; Bloomfield, J. J. *Synthesis* **1977**, 118–120.

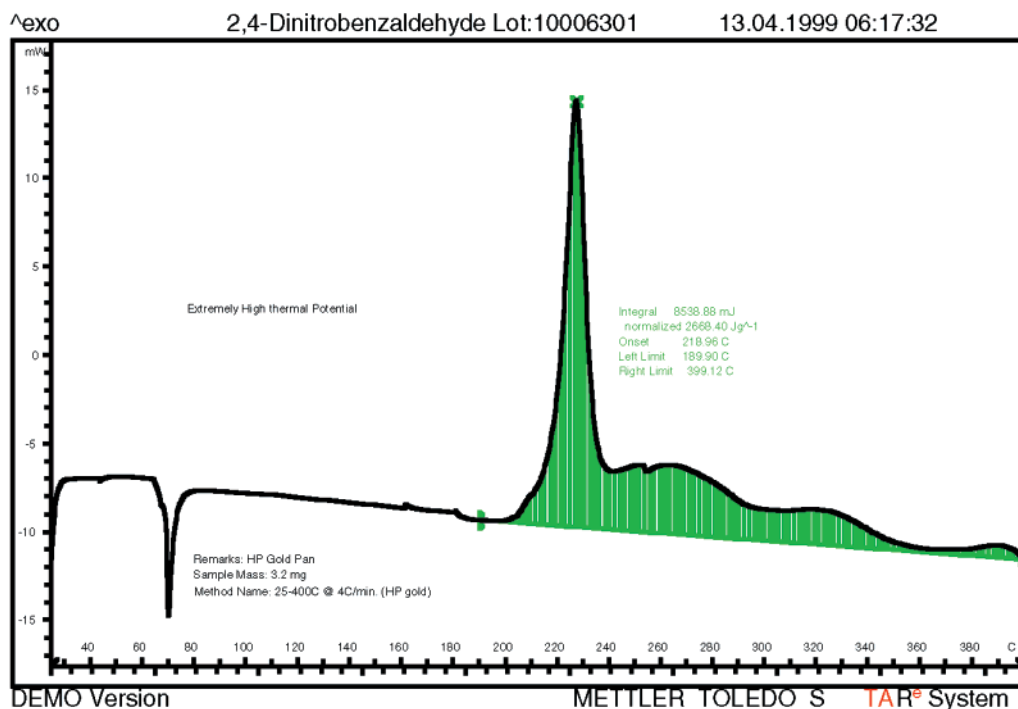
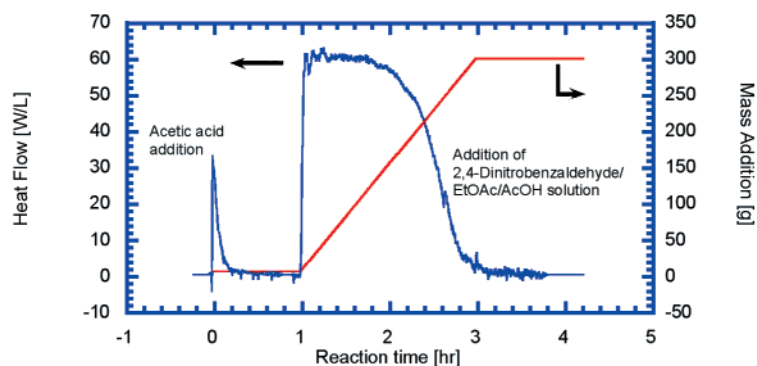


Figure 2.



Operation	Heat Liberated	$\Delta T_{\text{adiabatic}}$	Max. Heat Flow
Dosing of 0.5 equiv. AcOH	12 kcal/mole of AcOH	3.8°C	32 W/L
Dosing of EtOAc/AcOH/ 2,4-Dinitrobenzaldehyde solution	253 kcal/mole of 2,4-DNB	64.1°C	60 W/L

Figure 3.

no accumulation of reaction intermediates. A slower rate of addition would reduce the cooling load needed to maintain isothermal reaction conditions at 50 °C.

Experimental Section

2,4-Diaminobenzaldehyde, 2. To a nitrogen purged 5-L, 4-neck flask fitted with a condenser, mechanical stirrer, addition funnel, and temperature probe was added 325 mesh iron dust (220 g, 3.9 mol), water (800 mL), and acetic acid (5 mL). Over the next hour, some frothing occurred and the temperature rose to 28 °C. In a separate container, 2,4-dinitrobenzaldehyde (97 g, 0.49 mol) was dissolved in 1:1

acetic acid/ethyl acetate (800 mL). A portion of the aldehyde solution (5 mL) was added to the iron mixture, which led to a dissipation of the frothing. The reaction mixture was warmed to 35 °C with heat from a steam bath. The steam was turned off, and the dinitrobenzaldehyde solution was added at a rate to maintain the temperature below 50 °C. The addition was complete after 6 h. The reaction mixture was diluted with water (1 L), and Celite (100 g) was added. The reaction mixture was stirred an additional 3 h while the temperature dropped to 25 °C. The solids were filtered off, and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3 × 400 mL). The combined

extracts were used to wash the solids from the initial filtration. The filtered organics were washed with water (400 mL) and saturated aqueous NaHCO_3 (3×400 mL). The organics were dried over anhydrous MgSO_4 and Darco G-60 (10 g). After filtration, the organics were concentrated in vacuo to a slurry and diluted with 1 L of hexanes. The precipitated solids were collected by suction filtration and dried in air to give 2,4-diaminobenzaldehyde (48 g, 71%) as a light yellow solid.

Mp 151 °C. ^1H MNR (acetone- d_6) δ 5.48 (br s, 2H), 5.94 (d, 1H $J = 1.9$ Hz), 6.08 (dd, 1H, $J = 2.0, 8.6$ Hz), 6.75 (br s, 2H), 7.20 (d, 1H, $J = 8.6$ Hz), 9.51 (s, 1H). ^{13}C NMR (acetone- d_6) 189.8, 155.0, 153.4, 137.8, 111.6, 104.8, 96.9. Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}$: C, 61.75; H, 5.92; N, 20.58; Found C, 61.69; H, 5.98; N, 20.39.

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