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A Convenient and Safer Synthesis of Diaminoglyoxime

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Supporting Information

ABSTRACT: A new procedure for the synthesis and isolation of diaminoglyoxime (DAG) is described. A previous procedure involved treating glyoxal with 2 equiv each of hydroxylammonium chloride and sodium hydroxide to form glyoxime, followed by further treatment of this intermediate with two additional equivalents of hydroxylammonium chloride and sodium hydroxide at 95 °C to form DAG. Two recrystallizations were needed to obtain the desired product in pure form. Another previous procedure employed glyoxal in the presence of 4 equiv each of hydroxylammonium chloride and sodium hydroxide at 95 °C to form DAG. Though this latter procedure gives product after a few hours, yields do not exceed 40%, and the reaction is prone to thermal runaway. Furthermore, the use of decolorizing carbon and recrystallization of the crude solid are necessary to obtain a pure product. The new disclosed procedure involves treating a preheated aqueous hydroxylamine solution (50 wt %, 10 equiv) with aqueous glyoxal (40 wt %), followed by heating at 95 °C for 72−96 h. The reaction is cooled to room temperature and then to 0−5 °C to obtain DAG in pure form, without recrystallization or decolorizing carbon in 77−80% yield. The exothermic nature of the reaction is also minimized by this updated process.

INTRODUCTION

Diaminoglyoxime (DAG) is a popular intermediate for the synthesis of a multitude of energetic materials. This includes not only materials stemming from the *bis*-1,2,4-oxadiazole ring system[1] but also the many compounds derived from diaminofurazan (DAF).[2,3] Some representative molecules that fall into these two classes of materials are summarized in Figure 1.

Though DAG has been synthesized by numerous methods, the most popular methods to-date are via a two-step synthesis[4] or a one-step synthesis.[5] In the two-step procedure, as summarized in Scheme 1, glyoxal is first converted to glyoxime (**1**) upon exposure to 2 equiv of hydroxylammonium chloride and 2 equiv of aqueous sodium hydroxide. Following recrystallization, **1** is then treated with these same reaction conditions, plus exposure to heating for several hours to provide crude DAG (**2**). Crude DAG is recrystallized from boiling water to afford DAG as a yellow crystalline solid. The overall yield for the two-step procedure is 44%.

In the one-step procedure (Scheme 2), DAG is obtained as a crude material by heating an aqueous solution of glyoxal, 4 equiv of hydroxylammonium chloride, and 4 equiv of sodium hydroxide for several hours. After isolation of the yellow, crystalline material, the crude product is redissolved in hot water, treated with decolorizing carbon, and filtered hot to obtain pure DAG as a white, crystalline solid. While convenient as a one-step procedure that provides pure material in a matter of a few hours, this method is prone to thermal runaway, and the yields are typically a maximum of ca. 40%.

Given the aforementioned yield and lengthy processing issues, the development of a simpler process that yields DAG in a higher yield would provide a significant benefit to the energetic materials community. Such a high yielding and simple process to obtain DAG from glyoxal is given in Scheme 3. In this procedure, an excess of 50% aqueous hydroxylamine is heated to 95 °C with stirring, and a 40% aqueous solution of glyoxal is then added dropwise over an hour. Following addition, the flask is fitted with a reflux condenser, and the reaction mixture is stirred for 72−96 h. Following this time, the reaction mixture is slowly cooled to room temperature with stirring and is then further cooled to 0−5 °C with stirring. Filtration of the resulting white crystalline solid affords the product in a greatly improved yield of 77−80%. Treatment with decolorizing carbon and further recrystallizations are not necessary to obtain a pure product.

Optimization of the new, all aqueous procedure focused initially on the protocols of previous reports using hydroxylammonium salts in the one-pot formation of DAG from glyoxal.[6] The glyoxal solution was added to aqueous hydroxylamine (5 molar equiv) in such a manner to keep the reaction below 5 °C. Halfway through the addition, glyoxime precipitated, and following the addition, the mixture was warmed to 20 °C. The thick white precipitate was then heated in one of two manners: heating rate controlled by the temperature of the reaction (T_r) over 10 min, or ramping the temperature of the heating jacket (T_j) immediately to 95−100 °C. During the initial temperature ramp, the reaction was heterogeneous and the slope of T_r vs time steadily climbed at ∼5 °C/min, but at approximately 75 °C, the solids went into solution and the rate of T_r increase doubled. In trials where T_r was used to ramp temperature, the heating rate of the jacket was immediately reduced by the control software to limit the reaction temperature rate during this event. The reaction temperature would plateau just around the input temperature and no thermal runaway would occur.[7] When T_j was used to control the reaction heating, the same pattern of dissolution

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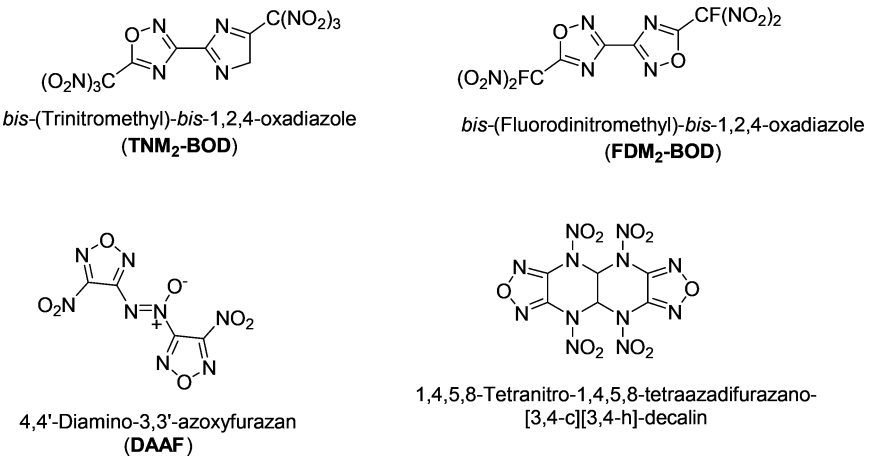
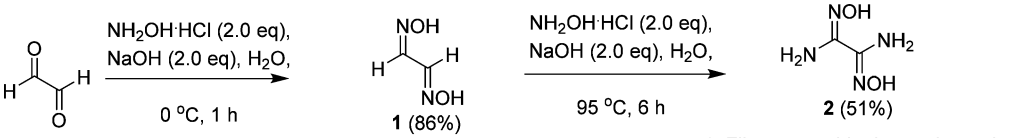


Figure 1. Energetic materials obtained from the DAG intermediate.

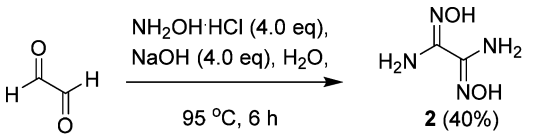
Scheme 1. Previous Two-Step Synthesis of Diaminoglyoxime



1. Filter to provide crude product
2. Recrystallize from hot H_2O
3. Filter to give the pure product

1. Filter to provide the crude product
2. Recrystallize from hot H_2O
3. Filtered tp give the product (yellow crystalline solid)

Scheme 2. Previous One-Step Synthesis of Diaminoglyoxime

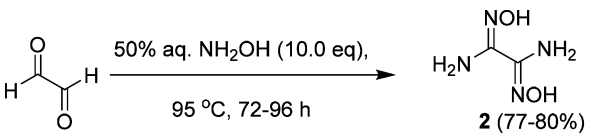


1. Filter to provide the crude product
2. Redissolve in hot H_2O
3. Treat with decolorizing carbon
4. Filter while hot to remove decolorizing carbon and to give the pure product upon cooling (white, crystalline solid)

and heating rate increase was observed while the reaction temperature exceeded the T_r input and gradually reduced to the input temperature. There were no runaway reactions observed in any case where only aqueous reagents were used. At this point, it was determined that more than 5 equiv of hydroxylamine were necessary to drive the reaction to completion due to significant discoloration in the final material, and the presence of impurities inseparable by recrystallization. In some cases, where only 5 equiv of hydroxylamine were used, discoloration was not observed, but the recovered material had a significantly depressed melting/decomposition point, much closer to that of diaminoglyoxime. Resubmission of this material to heating in additional aqueous hydroxylamine led to a pure, colorless DAG material.

By adding the glyoxal over a period of 30 min to the preheated aqueous hydroxylamine (T_r = 90 °C), there is no precipitation/dissolution of intermediates, and the bulk of the reaction heat is evolved instantaneously as each drop is consumed, minimizing the number of molecules reacting at any given moment. Thus, the likelihood of thermal runaway is mitigated in this procedure by minimizing the presence of reactive species during dissolution and subsequent conversion of glyoxime to DAG. Heat flow calorimetery[8] (HFC) was used to quantitate heat evolution during the glyoxal addition step. The HFC experiment revealed a heat release of −93.5 kJ/mol over the glyoxal addition period (30 min), and immediately following the addition, the reaction temperature quickly returned to the input temperature. Heating was controlled by maintaining the jacket temperature between 95 and 100 °C, which translated to approximately 90−95 °C in reaction temperature. This new method has been performed reprodu-

Scheme 3. New One-Step Procedure for the Synthesis of Diaminoglyoxime



1. Cool slowly to room temperature with stirring
2. Cool to 0-5 °C with stirring
3. Filter to obtain the pure product

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cibly multiple times on the 81 g scale and was then subsequently scaled-up successfully at the 250 g scale.

EXPERIMENTAL SECTION

Chemicals and solvents were used as received from Sigma-Aldrich. ^{1}H NMR spectra were recorded using an Anastazi 90 MHz instrument. The chemical shifts quoted in ppm in the text refer to typical standard tetramethylsilane (^{1}H) in $CDCl_3$ as the solvent. Infrared spectra were measured with a Bruker Alpha-P FTIR instrument. Decomposition temperatures were measured at a heating rate of 5 °C/min using a TA Instruments Q10 DSC instrument.

81 g Scale. A 1 L round-bottom flask equipped with a stir bar was charged with aqueous hydroxylamine (50 wt %, 569 mL, 8.62 mol) and was immersed in an oil bath. The oil bath was heated to 95 °C, the aqueous hydroxylamine was stirred for 30 min, and glyoxal (40 wt %, 125 mL, 0.862 mol) was added via a pressure-equalizing addition funnel over 30 min. Following the addition, the reaction was allowed to stir for 72−96 h. The reaction mixture was removed from the oil bath and was slowly cooled to 20 °C with stirring, during which time a white solid appeared. The reaction mixture was immersed into an ice bath and was cooled to 0−5 °C, followed by stirring for 1 h. The white solid was collected by Buchner filtration, rinsed with minimal cold water, and vacuum-dried overnight to afford 81.3 g (80%) of **2** as a white, crystalline solid; mp = 210.75 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 9.73 (s, 2H), 5.17 (s, 4H); IR (neat) cm^{-1} 3646.82 (m), 3361.46 (s), 1641.62 (m),1569.84 (s); T_m = 210.75 °C; T_{peak} = 223.71 °C.

250 g. A 2 L glass jacketed reactor with an overhead stirrer was charged with aqueous hydroxylamine (50 wt %, 1.69 L, 27.5 mol), and the jacket was heated to 100 °C. Once the process solution temperature stabilized (~85 °C), glyoxal (40 wt %, 315 mL, 2.74 mol) was added over 1.5 h. Following the addition, the reaction was allowed to stir for 4 d and was then cooled to 20 °C over 20 h with stirring at 40 rpm. Prior to filtering, the reactor was cooled to 0−5 °C over 3 h, followed by stirring for three additional hours. Following filtration, the isolated crystals, identified as DAG (**2**), were rinsed with minimal cold water and vacuum-dried overnight (240 g, 74% yield). An additional 9.5 g (3%) of **2** were recovered from the mother liquor upon sitting.

The thermostat, dosing pump, and stirrer were controlled with a Mettler Toledo RX-10, which allowed for a preprogrammed reaction sequence and overtemperature control (automatic cooling if reaction temperature reached a predetermined set point).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00329.

Synthetic procedure of **2**, its ^{1}H NMR, IR, and DSC trace (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

NaOH = sodium hydroxide; NH_2OH = hydroxylamine; $NH_2OH{\cdot}HCl$ = hydroxylamine hydrochloride; DAG = diaminoglyoxime

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(6) An EasyMax 102 or 402 synthesis workstation with iControl 5.4 software (Mettler Toledo) was used to follow and control the reaction conditions.
(7) The authors experienced thermal runaway with the hydroxylammonium salt procedures when heat was not actively controlled/removed during the initial heating ramp following dissolution of the glyoxime.
(8) A Mettler-Toledo HFCal accessory was used for calorimeter measurements of the glyoxal addition at elevated temperature in the EasyMax 102.

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