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Development of a Scalable and Safer Synthesis of Diazeniumdiolates

Yong-Li Zhong, Daniel J. Muzzio, Mark Weisel, Li Zhang, Guy R. Humphrey, Kevin M. Maloney, and Kevin R Campos

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ABSTRACT: Although diazeniumdiolates (DAZDs) and the synthetic methods to access DAZDs were

discovered over 50 years ago, the current methodology is not safe, has a limited substrate scope, and is not amenable to large scale production. For example, a recent investigation utilizing the standard methodology to prepare DAZDs resulted in two unexpected explosions, highlighting the need for safer and more practical chemistry. Recently, we have reported a general, scalable, safer, and high yielding methodology adaptable to large scale synthesis of diazeniumdiolates in water using a calcium hydroxide base. Herein, we report the full account for the development of the reaction. The merit of this strategy is evidenced by the highly efficient and safer preparation of a key DAZD intermediate, on the kilogram scale, needed for the preparation of MK-8150 (1), a novel O-alkylated diazeniumdiolate NO donor under investigation as a potent and significant blood-pressure lowering drug candidate.

KEYWORDS: NO-donors, nitric oxide, nitrous oxide, diazeniumdiolate calcium salts, MK-8150

INTRODUCTION

Nitric oxide (NO) is a signaling molecule and plays a key role for all living systems.¹⁻⁷ Many pathological and physiological processes are implicated due to the NO deficiency.⁸⁻¹³ Diazeniumdiolate (DAZD)-based NO-donors, which are able to release two equivalents of nitric oxide under either physiological or metabolized conditions, indicate the bioactivity for the treatment of cardiovascular diseases.¹⁴⁻²² Seeking to further optimize the pharmacokinetic profile, medicinal chemists at Merck & Co., Inc., Kenilworth, NJ, USA, have discovered MK-8150 (1),²³⁻²⁴ a novel *O*-alkylated diazeniumdiolate NO donor, as a potent and significant blood-pressure lowering

drug candidate in humans. As shown in Figure 1, DAZD (2) is a key intermediate for the synthesis of 1. We have previous reported a novel and scalable synthesis of the intermediate and the application to the preparation of $1.^{25}$ Herein, we report the full account of the development of the reaction.



Figure 1. Structure and synthetic analysis of MK-8150 (1). High energy compound DAZD (2) is a key synthetic intermediate for the preparation of 1.

As shown in Figure 2, the medicinal chemistry route for the preparation of DAZD employing sodium methoxide in methanol and NO gas at 250 psi, gave desired product **A** in 9-19% yield with 50-60 wt% purity.²⁶⁻²⁷ During optimization, two unexpected explosions occurred in a 500-mL autoclave reactor (during venting) due to the rapid depressurization of high-pressure nitric oxide (NO) from the headspace through Teflon-lined steel-braided tubing to the atmospheric pressure.²⁸ The magnitude of the energy released in these events was substantial as shown from the damage of the high pressure hose. The explosive energy of the event caused the stainless-steel braided Teflon hose to break apart in not just one but multiple places (Figure 2). Fortunately, no one was injured in the events and damage was contained within the appropriate barricaded hood. Similarly, Drago reported an explosion over 50 years ago when aniline DAZD was attempted to be prepared through the reaction of aniline with NO in ether at high pressure.²⁹ The heat generated melted the high pressure tubing used in their system.



Figure 2. The medicinal chemistry route afforded low yield and low purity of the DAZD sodium salt. Two unexpected violent explosions occurred in a 500-mL autoclave reactor. The pictures of destroyed equipment: On the left, the ruptured valve metal bellows. In contrast, a new pristine bellows is shown in middle photo. On the far right, the metal braided hose ruptured by the reaction. Normal working pressure for the hose is 2500 psi and maximum burst pressure is 10,000 psi. The multiple breaks in the hose demonstrate this was a detonation and not merely an over-pressure event.

RESULTS AND DISCUSSION

According to a previous report by Muzzio and coworkers,²⁸ the cause of the explosions was likely due to the large amount of nitrous oxide (N_2O) formed during the reaction. While venting the gas at the end of reaction, the methanol vapor and nitrous oxide rushing through the Teflon-lined tubing created optimal conditions to create brush static electricity of sufficient energy to ignite the highly combustible vapor. It is well documented that N_2O is

a strong oxidizing reagent, similar to hydrogen peroxide, and much stronger than oxygen gas.³⁰ Thus, the

minimization of N₂O formation during the reaction will be a key factor for safe preparation of DAZD. After careful analysis of the reaction mechanism for DAZD formation, we summarized the possible side reactions in which formation of nitrous oxide could occur as shown in Figure 3. The reaction of NO with carbanions in the presence of sodium methoxide to prepare carbon-bound DAZDs was discovered over 100 years ago,³¹ however, the side reaction of NO with sodium methoxide to generate sodium formate and potentially hazardous nitrous oxide was just recently identified by Hrabie (Figure 3, equation-2).32 The NO gas can undergo a relatively quick disproportionation reaction that can lead to significant N₂O and NO₂ production in a short period of time. It is estimated 0.5 mol% of this impurity mixture is formed every 10 days under typical commercial pressures (450-500 Schoenfisch and coworkers discovered that nitrosamines could form competitively with DAZDs in psi).³³ anaerobic reactions of NO with polyamines, which could lead to the formation of nitrous oxide.³⁴ Thus, tertbutylamine could be oxidized to nitrosamines and nitrous oxide (Figure 3, equation-1). NO is also an oxidant that could oxidize methanol solvent in the presence of a base, leading to the formation of nitrous oxide (Figure 3, equation-3). In addition, base/acid swings and hydrolysis of sodium methoxide to sodium hydroxide in the presence of water is certain (Figure 3, equation-4 to 6). Lastly, sodium hydroxide can react with NO, leading to the formation of nitrous oxide and sodium nitrite (Figure 3, equation-7).



Figure 3. Problems with diazeniumdiolate scale up by the medicinal chemistry route.

As stated above, several challenges remain for scaling up the preparation of DAZD by the literature reported chemistry. Recently, we have reported a general, scalable, safer, and high yielding methodology adaptable to large scale synthesis of diazeniumdiolates in water using a calcium hydroxide base.²⁵ To gain an understanding of the reaction, we initially conducted control experiments in the absence of the starting material organic amines. Three experiments were performed in 1.76 N NaOMe/MeOH, 1.76 N NaOH/water, and a slurry of Ca(OH)₂ (equal to 1.76 N ⁻OH) in water. All reactions were run under 250 psi NO gas at 20-25 °C. As expected, all the three control experiments showed the generation of N₂O during the agitation of the basic solution under the pressure of NO (Figure 4) but with dramatically different rates. In the NaOH/water system, N2O was rapidly generated and reached the unsafe zone, over the limited fraction N₂O/NO (0.25), associated with hydrogen or flammable organic solvents/compounds³⁵⁻³⁶ within ~ 450 min after the reaction started. After 1300 min reaction time, the fraction N₂O/NO reached 0.659 and the reaction was depressurized and terminated (Figure 4, a). In the NaOMe/MeOH solution, the generation of N₂O was slower than in the NaOH/water system. It required around ~ 2500 min to reach the unsafe zone. However, the fraction N₂O/NO got as far as 1.15 after 8500 min. The fraction N₂O/NO increased impressively to 2.38 after depressurizing the reaction to 5 psi (Figure 4,

b). Formation of N_2O was much slower from the slurry of $Ca(OH)_2$ in water, which generated only around 0.012
fraction of N ₂ O/NO after stirring 10000 min (Figure 4, c). The plot clearly showed that the Ca(OH) ₂ /water reaction
system didn't build up dangerous levels of N_2O gas. These results were consistent with the analysis of the anion
concentration of nitrite (NO ₂ ⁻) and formate (HCO ₂ ⁻) in the reaction mixture by ion chromatography (IC). 70.9 mol%
and 22.8 mol% of nitrite were generated in the reaction of NaOH/water and NaOMe/MeOH, respectively.
Furthermore, large amounts of the formate (10.4 mol%) were detected in the NaOMe/MeOH reaction system. As
expected, the Ca(OH) ₂ /water reaction system generated very low level of nitrite (< 3 mol%). Therefore, the
$Ca(OH)_2$ water system should be the safest out of the methods we explored for the production of DAZD, based
on our understanding of combustion for the N_2O/NO system. It was noteworthy to note that the fraction of
N_2O/NO in the headspace dramatically increased after depressurizing from 250 psi to 5 psi (Figure 4, b) This was
likely due to the higher solubility of N_2O than NO in solvents under high pressure. This finding clearly explained
the two previous unexpected explosions that occurred during the rapid depressurization (venting) of high-
pressure nitric oxide (NO).





Figure 4. Plots of the ratio of N₂O to NO sampled from the headspace of high pressure NO reaction systems over time: Background control reaction (without organic amines) for N₂O generation from the bases and solvents with NO gas. **a**, 0.422 g NaOH (10.6 mmol) in degassed deionized (D.I.) water (6 mL) in a 15 mL reactor was agitated with NO gas (250 psi) at 20 °C. **b**, 0.600 g NaOMe (95%, 10.6 mmol) in MeOH (6 mL) in a 15 mL reactor was agitated with NO gas (250 psi) at 20 °C. **c**, 0.412 g Ca(OH)₂ (95%, equal to 10.6 mmol ⁻OH) in degassed D.I. water in a 15 mL reactor was agitated with NO gas (250 psi) at 20 °C. **c**, 0.412 g Ca(OH)₂ (95%, equal to 10.6 mmol ⁻OH) in degassed D.I.

Finally, *N*-(*tert*-butyl)allylamine was converted to the corresponding DAZD calcium salt **5** under 250 psi of nitric oxide in 95% isolated yield (Scheme 1). Monitoring the fraction of N₂O/NO in the headspace of the real reaction, we found that the fraction of N₂O/NO in the headspace was less than 0.015 after the end of the reaction and less than 0.03 after depressurizing from 250 psi to 5 psi (Figure 5, **b**). Both these numbers are well below the safety guideline limit of 0.25 in the headspace. It clearly showed that the DAZD calcium salt formation didn't build up dangerous levels of N₂O gas. Analysis of the aqueous solution in the reaction mixture by IC showed the concentrations of nitrite and formate were 3.0 mol% and 0.29 mol%, respectively. The stability tests for the ACS Paragon Plus Environment

ending reaction mixture were conducted in 20 °C, 50 °C and 95 °C, respectively. We found that there were no pressure building up both at 20 °C and 50 °C after agitation for 10 days. It suggested that the reaction mixture is stable at \leq 50 °C. However, we observed 13 psi net pressure increase after agitation at 95 °C over 168 h, which corresponded to around 7.1% of calcium *t*-butyl allyl DAZD salt **5** decomposition. The preparation of **5** was successfully carried out in multiple batches on multiple kilogram scale and was achieved in 95% isolated yield and high purity by direct isolation from the reaction batch.

Scheme 1. Preparation of DAZD Calcium salt 5

 $\begin{array}{c} H \\ H \\ N \\ \end{array} \qquad \begin{array}{c} H \\ Ca(OH)_{2}, \text{ water} \\ \hline 20 \ ^{\circ}C, \ 160 \ h \\ 95\% \end{array} \qquad \begin{array}{c} \bigcirc \\ N \\ \textcircled{} \\ \end{array} \qquad \begin{array}{c} \bigcirc \\ O \\ O \\ \end{array} \qquad \begin{array}{c} \bigcirc \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} \bigcirc \\ O \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} \bigcirc \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} \bigcirc \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array} \qquad \begin{array}{c} O \\ O \\ O \\ \end{array} \end{array}$ 95%



Figure 5. Plots of the ratio of N₂O to NO sampled from the headspace of high pressure NO reaction systems over time: Comparison of the Ca(OH)₂/water reaction system with or without the organic amine substrate. a, 0.412 g Ca(OH)₂ (95%, equal to 10.6 mmol ⁻OH) in degassed D.I. water (6 mL) in a 15 mL reactor was agitated with NO gas (250 psi) at 20 °C. b, 0.412 g Ca(OH)₂ (95%, equal to 10.6 mmol ⁻OH) and 1.03 g *tert*-butylallylamine (8.80

mmol) in degassed D.I. water (6 mL) in a 15 mL reactor was agitated with NO gas (250 psi) at 20 °C.

DSC data showed that the dried calcium *t*-butyl allyl DAZD salt **5** is stable below 110 °C and has no exothermic decomposition below 200 °C (Figure 6) and is not shock sensitive by drop weight testing (impact 300 kg/cm, 6 of 6 negative). It does undergo a large endothermic decomposition at ~150 °C. Although not specifically studied, this decomposition is probably associated with a large gas release from the decomposition of DAZD. On

the other hand, sodium salt 6 showed a thermal profile with the main exotherm being ~ 418 joule/gram initiating at





Figure 6. DSC data for the DAZD calcium salt 5 and sodium salt 6.

With key intermediate **5** in hand, a robust process for the synthesis of MK-8150 (**1**) was developed and was achieved in high purity (> 99.5 LCAP) and 85.6% isolated yield to MK-8150 (1) in two steps from **3a** and **5**.²⁵



Figure 7. Application of DAZD calcium 4 for the successful synthesis of MK-8150 (1) in kilogram-scale.

CONCLUSION

A practical, efficient, and safer methodology for the synthesis of diazeniumdiolate calcium salt 5 was

developed. This novel synthetic method has demonstrated several advantages over previous methods such as

significantly improved yields, and easy isolation. The isolated diazeniumdiolate calcium salt has no exothermic decomposition below 200°C, and is not shock sensitive, which is convenient for handling. More significantly, the use of less soluble Ca(OH)₂ as a base and water as solvent resulted in the controlled release of hydroxide to suppress the formation of hazardous nitrous oxide, which was identified as a key factor in causing previous explosions for the preparation of diazeniumdiolate using literature method. Additional safeguards were employed by backfilling the vent line with an insert gas at reaction pressure prior to venting the reaction. Also re-configured the control system to perform a much slower reaction vent at the end of the reaction. Monitoring the fraction of N_2O/NO in the headspace of the real reaction through FT-IR, we detected that the fraction of N_2O/NO in the headspace is less than 0.015 after the end of the reaction and less than 0.03 after venting. Both these numbers are far below the safety guideline limit 0.175 in the headspace, a significant improvement over traditional methodology that has been used for the past 50 years. Based on the safety data, the preparation of 5 was successfully carried out in multiple batches on multiple kilograms scale and was achieved in 95% isolated yield and high purity by direct isolation to support the MK-8150 NO-donor program at Merck & Co., Inc., Kenilworth, NJ, USA. It is worthwhile to mention that anyone who uses this chemistry does so at their own risk and need to generate their own safety data.

EXPERIMENTAL SECTION

General Information. Nuclear magnetic resonance (NMR) spectra were recorded for ¹H NMR at 500 MHz or 400 MHz, for ¹³C NMR at 125 MHz or 100 MHz. Chemical shifts were reported in ppm (δ), and coupling constants were reported in Hz. ¹H resonances were relative to the residual deuterated solvent peaks for CDCl₃ (7.26 ppm), CD₃OD (3.34 ppm), D₂O (4.79 ppm), or DMSO-d₆ (2.54 ppm). ¹³C resonances were reported relative ACS Paragon Plus Environment to the residual deuterated solvent peaks for CDCl₃ (77.0 ppm), CD₃OD (49.8 ppm), or DMSO-d₆ (39.5 ppm). ¹⁹F resonances were relative to CFCl₃ (δ = 0.0 ppm). Splitting patterns for ¹H NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), broad singlet (br s) or m (multiplet). HPLC analysis was performed on either (method 1) a Zorbax Eclipse Plus C₁₈ 50 mm x 4.6 mm, 1.8 µm, standard gradient: 10% B to 95% B (A = 0.1% H₃PO₄, B = acetonitrile), 1 min hold, 2 min post, 1.5 mL/min, UV at 210 nm, 30 °C, 8 min run time or (method 2) XBridge C₁₈ 15 cm x 4.6 mm, 3.5 µm, gradient: 5% B to 90% B (A = 10 mM trimethylammonium hydroxide and adjust the pH with H_3PO_4 to 10.5, B = acetonitrile), 2 min hold, 5 min post, 1.0 mL/min, UV at 210 nm, 25 °C, 16 min run time. Ion chromatography (IC) was performed on a Dionex IonPac AG194 x 250 mm (anion exchange) analytical column with IonPac4 x 50 mm guard column, mobile phase A with 100% de-ionized water, gradient: 5 mM potassium hydroxide to 25 mM, 5 min hold, 2 min post, 1.0 mLmin (isocratic from mobile phase A), column temperature 30 °C, suppressor ASRS 300_4mm, P/N#064554, conductivity detector cell temperature 35 °C, suppressor_current 62 mA. High resolution mass spectrometry (HRMS) data were obtained using electrospray ionization technique either in positive or negative mode (ESI+ or ESI-). Melting points were measured in open capillaries and are uncorrected. Water content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF coulometer. Room temperature (rt) is defined as 20-25 °C. The fraction of N₂O/NO was measured in Matrix MG01 FT-IR spectrometer. The wavenumbers (vmax) of N₂O and NO are 2100-2300 cm⁻¹ and 1800-1950 cm⁻¹, respectively. Differential Scanning Calorimetry (DSC) data were collected using DSC Q2000 V24.4 Build 116.

All reagents were of commercial grade and were used without further purification unless noted otherwise. All solvents were purchased from Sigma Aldrich or Fisher Scientific as anhydrous and used without further

 purification unless otherwise noted. Acetonitrile and water (HPLC grade) were purchased from Fisher Scientific.

For reactions run in water (H₂O), deionized and degassed water was used unless stated otherwise.

General Procedure of the Reactions and Results of IC Analysis for Figures 4 and 5. All reactions in Figures 4 and 5 were run in an Endeavor Stirred Reactor.

Experiment in Figure 4: a, To a 15 mL Endeavor stirred reactor was charged NaOH (0.422 g, 10.6 mmol) and degassed deionized (D.I.) water (6 mL). The reaction mixture was depressurized and pressurized with nitrogen 3 times, with nitric oxide 3 times and then was pressurized with nitric oxide to 250 psi ± 2.5 psi while maintaining the temperature at 20 °C. Each gas sample was taken 4 psi from the headspace of high pressure NO reaction systems over time and diluted with nitrogen to 50 psi. The fraction of N₂O/NO was obtained by FT-IR. After stirring for 1300 min, the vessel was slowly depressure and then purged with nitrogen. The resulting mixture was a homogenous solution. The concentration of formate, nitrite and nitrate in the solution (diluted by 10000X) was analyzed by IC.

Experiment in Figure 4: b, To a 15 mL endeavor stirred reactor was charged NaOMe (0.600 g, 95 wt%, 10.6 mmol) and methanol (6 mL). The reaction mixture was depressurized and pressurized with nitrogen 3 times, with nitric oxide 3 times and then was pressurized with nitric oxide to 250 psi ± 2.5 psi while maintaining the temperature at 20 °C. Each gas sample was taken 4 psi from the headspace of high pressure NO reaction systems over time and diluted with nitrogen to 50 psi. The fraction of N₂O/NO was obtained by FT-IR. After stirring for 8500 min, the vessel was slowly depressure and then purged with nitrogen. The resulting mixture was a homogenous solution. The methanol solution was concentrated to dry and the resulting solid was dissolved in

D.I. water (6 mL). The concentration of formate, nitrite and nitrate in the solution (diluted by 1000X) was analyzed

by IC.

Experiment in Figure 4: c, To a 15 mL endeavor stirred reactor was charged $Ca(OH)_2$ (0.412 g, 95%, equal to 10.6 mmol OH⁻) and degassed D.I. water (6 mL). The reaction mixture was depressurized and pressurized with nitrogen 3 times, with nitric oxide 3 times and then was pressurized with nitric oxide to 250 psi ± 2.5 psi while maintaining the temperature at 20 °C. Each gas sample was taken 4 psi from the headspace of high pressure NO reaction systems over time and diluted with nitrogen to 50 psi. The fraction of N₂O/NO was obtained by FT-IR. After stirring for 10000 min, the vessel was slowly depressure and then purged with nitrogen. The resulting mixture was a light slurry. The solid [Ca(OH)₂] was filtered off through solka flock bed. The concentration of formate, nitrite and nitrate in the filtrate (diluted by 500X) was analyzed by IC.

Experiment in Figure 5: b, To a 15 mL endeavor stirred reactor was charged Ca(OH)₂ (0.412 g, 95%, equal to 10.6 mmol OH), *tert*-butylallylamine (1.03 g, 8.80 mmol) and degassed D.I. water (6 mL). The reaction mixture was depressurized and pressurized with nitrogen 3 times, with nitric oxide 3 times and then was pressurized with nitric oxide to 250 psi \pm 2.5 psi while maintaining the temperature at 20 °C. Each gas sample was taken 4 psi from the headspace of high pressure NO reaction systems over time and diluted with nitrogen to 50 psi. The fraction of N₂O/NO was obtained by FT-IR. After stirring for 10000 min, the vessel was slowly depressure and then purged with nitrogen. The resulting mixture was a slurry. The solid (compound 30, typical 95% yield) was filtered off. The concentration of formate, nitrite and nitrate in the filtrate (diluted by 250X) was analyzed by IC.

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Reaction	Formate (HCO ₂ -)	Nitrite (NO ₂ -) conc.	Nitrate (NO ₃ -) conc.
	conc. mg/mL (mol%)	mg/mL (mol%)	mg/mL (mol%)
1	0.01 (0.012)	1.77 (2.2)	0.11 (0.10)
2	0.23 (0.29)	2.42 (3.0)	0.17 (0.16)
3	8.25 (10.4)	18.51 (22.8)	0.21 (0.19)
4	0.01 (0.012)	57.63 (70.9)	1.7 (1.6)

Figure 8. IC analysis of the aqueous solution of the reactions

Experiment in Figure 6 for DSC data collection: a) for DAZD calcium salt 5, compound 5 (4.10 mg, 90

wt%) was charged to a 40 µL of tantalum-lined pressure-tight crucibles and was run at a scan rate of 5K/min. b)

for DAZD sodium salt 6, compound 5 (5.80 mg, 70 wt%) was charged to a 40 µL of tantalum-lined pressure-tight

crucibles and was run at a scan rate of 5K/min.

Calcium 1(3-Allyl-3-(*tert*-Butyl))Diazen-1-lum-1,2-Diolate (5).25



To 100 L vessel-1 was charged degassed deionized water (50 L), tert-butylallyl amine (99 wt%, 5.000 kg, 43.73 mol) and Ca(OH)₂ (96 wt%, 2.000 kg, 25.91 mol) while maintaining the batch temperature at 20-30 °C. The batch in vessel-1 was purged with nitrogen for 3 times and was transferred to a 100 L autoclave (vessel-2). The vessel-1 was rinsed with degassed deionized water (25 L), which was transferred to vessel-2. The batch in vessel-2 was purged with nitric oxide for 3 times and then was pressurized with nitric oxide to 250 psi while maintaining the temperature at 20-30 °C. The reaction mixture was stirred while maintaining the NO pressure at 250 ± 40 psi until no further nitric oxide consumption was detected. The batch was cooled to 10-25 °C. The vessel-2 was vented slowly over 2-4 h, then purged with nitrogen. The batch in vessel-2 was transferred to a filter pot for filtration. The vessel-2 was rinsed with 0.01 M Ca(OH)₂ aqueous solution (15 L x 2). The rinsed solutions were transferred to the filter pot. The solid in filter pot was washed with 0.01 M Ca(OH)₂ (10 L x 1), dried under vacuum with nitrogen sweep at 30-40 °C. The desired product 30 was obtained in 8.050 kg (95% yield), m.p. 150 °C (decompose). IR (KBr) v_{max} 2974, 1603, 1481, 1416, 1392, 1376, 1361, 1236, 1185, 1079, 1002, 983, 947, 925 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 5.81 (ddt, J = 17.2, 10.2, 6.4 Hz, 1H), 5.25 (d, J = 17.2, 1.7 Hz, 1H), 5.06 (m, 1H), 3.71 (d, J = 17.2, 1.7 Hz, 1H), 5.06 (m, 2.1), 3.71 (d, J = 1.2), 3.71 (d, J = 6.4 Hz, 2H), 1.28 (s, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 136.1, 119.4, 60.8, 50.8, 28.1; HRMS (ESI-TOF): [M + OH] calcd for C₁₄H₂₉CaN₆O₅401.1825, found 401.1810.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:

e 19 of	24 Organic Process Research & Development
	Experimental ignition tests and results, experimental stability tests of reaction mixture and results and ¹ H
	and ¹³ C NMR spectra of 5 (PDF).
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