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Communication

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Development of a Safe and Efficient Two-Step Synthesis for Preparing 1-Bromoacetyl-3,3-dinitroazetidine, a Novel Clinical Anticancer Candidate

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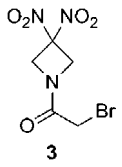
Supporting Information

ABSTRACT: An efficient process for synthesizing and isolating a new investigative anticancer agent, 1-bromoacetyl-3,3-dinitroazetidine, is described. The reaction entails a sequence of oxidative nitration followed by acylative dealkylation. The methods reported give 50−60-g batches of high-purity product without a designated purification step. The reaction conditions have been designed to mitigate the safety concerns associated with *gem*-dinitroazetidines. Some observations on the acylative dealkylation mechanism are discussed.

INTRODUCTION

Research into medicinal compounds derived from structures originating in the aerospace and defense industries that contain novel pharmacophores has resulted in the identification of 1-bromoacetyl-3,3-dinitroazetidine (ABDNAZ, **3**, Figure 1) as a promising lead molecule with intriguing biological activity.[1,2]



3

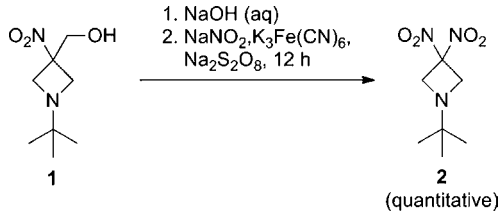
Figure 1. Structure of 1-bromoacetyl-3,3-dinitroazetidine (**3**).

gem-Dinitroazetidines can pose potential processing issues due to their inherent energetic nature; therefore, keen vigilance should be exercised when handling such materials. Gram quantities of **3** for initial anticancer screening were originally prepared by an unoptimized approach[1] that was not suitable for scale-up and failed to address specific hazards of the reaction intermediates and coproducts. The success of **3** in preclinical studies[2] prompted the need for a safe, reliable, and scalable synthesis to provide larger supplies of the active pharmaceutical ingredient (API) for further investigation and eventual clinical trials. Accordingly, we modified the synthesis to improve yield and purity, minimize steps and reagents, and mitigate hazards. The process development was guided by rigorous calorimetry and thermal evaluation of the reactions and intermediates. Herein, we report the safe and efficient synthesis of **3** which embodies the first of an encouraging new category of pharmaceutical candidates. The presently reported synthesis has been carried out at a scale that repeatedly affords 50−60-g batches of **3** (≥80% chemical yield) in only two steps. The procedure is expected to be adaptable to kilogram scale.[3]

RESULTS AND DISCUSSION

Synthesis of 1-*tert*-Butyl-3,3-dinitroazetidine (2) by Oxidative Nitration. Synthesis of 3,3-dinitroazetidines has been well-documented due mainly to the significance of 1,3,3-trinitroazetidine (TNAZ) to the field of energetic materials.[4−11] A convenient route to the azetidine moiety is by treatment of epichlorohydrin with a bulky primary amine.[8,12−14] The intermediate 1-alkylamino-3-chloro-2-propanols spontaneously cyclize to give the corresponding 1-alkyl-3-hydroxyazetidines (HCl salts).[12,13] These and similar species have been converted to their 3,3-dinitro analogues by a variety of methods.[5,6,8] 1-*tert*-Butyl-3,3-dinitroazetidine (**2**) has been prepared in 60% distilled yield by oxidative nitration of 1-*tert*-butyl-3-nitroazetidine[6] or of the hydrochloride salt of 1-*tert*-butyl-3-hydroxymethyl-3-nitroazetidine (**1**) in both methoxide[15] and hydroxide[9,16] solutions. The highest previously reported isolated yield of **2** was 83%.[9] We employed similar oxidative nitration conditions to convert **1** to **2** in excellent purity (≥99.5% relative purity by HPLC), (Scheme 1). By extending

Scheme 1. Preparation of 2



1 **2** (quantitative)

the reaction time to at least 12 h, compared to the literature report[9] of 1 h, we were able to increase the percent yield of **2** by 17%, giving essentially quantitative conversion of **1** to **2**. A comparative summary of results for the preparation of **2** is presented in Table 1.

In the preparation of **2**, **1** is first converted with aqueous alkali to its nitronate salt in situ via a retro-Henry[4] mechanism. The second nitro group is installed on the ring by catalytic oxidative nitration with $NaNO_2$ and $K_3Fe(CN)_6$;[17] stoichiometric $Na_2S_2O_8$ is used as a secondary oxidant[18] to regenerate

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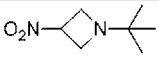
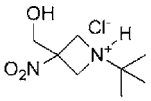
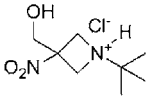
Table 1. Comparative summary of reaction results for the preparation of 2

Starting material	Duration of oxidative nitration[a] (h)	Yield of 2
	1	60%[6]
	1[b]	not reported[15]
	1	83%[9]
1	12	quantitative

[a]Reagents: 1. NaOH (aq); 2. $NaNO_2$, $K_3Fe(CN)_6$, $Na_2S_2O_8$. [b]NaOMe in MeOH was used as base instead of NaOH.

the active Fe^{III} ion from its reduced (Fe^{II}) state. Reagent ratios were modeled after the general conditions developed by Garver et al.[18] for oxidative nitration of nitronate salts. The reaction is performed relatively dilute to minimize the effect of exotherms. Initially, reagents are added at a reduced temperature (~10 °C) to absorb heat, but ultimately the reaction equilibrates to room temperature (~25 °C). A small temperature increase of the reaction solution is observed when the nitration mixture ($NaNO_2$ and $K_3Fe(CN)_6$) is added to the chilled nitronate solution. This arises from preliminary oxidative nitration that occurs due to the presence of the catalytic amount of Fe^{III} added. However, this reaction is limited by the molar equivalents of Fe^{III} available and thus quickly terminates until the secondary oxidant ($Na_2S_2O_8$) is introduced. The reaction mixture is brought back to ~10 °C for the addition of $Na_2S_2O_8$. Following an initial endotherm of dissolution, a brief exotherm occurs before thermal equilibrium is reached. For reactions starting with up to 100 g of **1**, both of the observed exotherms never exceeded 15 °C and were controllable with an ice−water bath.

The synthesis reaction of **2** was studied in a stirred reaction calorimeter to obtain quantifiable heat flow data to assess the magnitude of the exotherms.[19] Formation of the nitronate salt by addition of **1** to aqueous NaOH produced a very small exothermic enthalpy of solution, −11.1 kJ/kg of **1**. The exothermic enthalpy change observed by the addition of the oxidation mixture ($NaNO_2$ and $K_3Fe(CN)_6$) to the nitronate solution was also small, −3.57 kJ/kg of reactor contents. In this case, 'reactor contents' are the mass of everything in the reactor after the addition step in question.

Beginning with the addition of $Na_2S_2O_8$ to the reaction mixture held at 10 °C, the maximum exothermic heat flow for the synthesis is about 45 W/kg of reactor contents, and it declines below 15 W/kg of reactor contents after 40 min (~0.6 h) (Figure 2). While one should verify that a reaction vessel has enough heat transfer capability to remove this amount of heat flow, it is worth noting that the total exothermic enthalpy change over the 40-min period is only −50.38 kJ/kg of reactor contents. In the event of a total cooling failure and if the system were adiabatic, this amount of energy would only be enough to raise the temperature of the system by 12.0 °C, assuming that the reactor contents have the heat capacity of water (4.184 kJ/kg °C).

Figure 3 shows the heat flow curve after heating the mixture in Figure 2 to 25 °C. A small number of data points (about 10 min worth) are lost during heating and equilibration of the calorimeter at 25 °C. After heating to 25 °C the maximum exothermic heat flow is on the order of 30−35 W/kg of reactor contents, and it declines to zero after 2.7 h at 25 °C. The total integrated enthalpy of reaction for the 2.7 h period is only −40.15 kJ/kg of reactor contents. Therefore, a thermal runaway is impossible under these conditions, as the additional adiabatic temperature rise would be <10 °C.

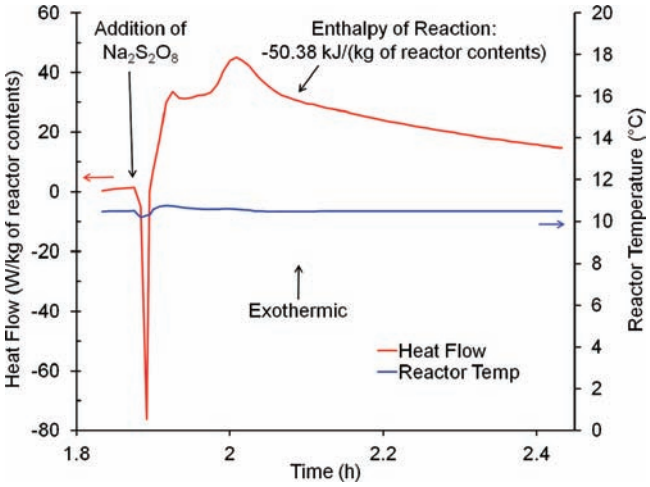


Figure 2. Reaction calorimeter heat flow curve for the synthesis of **2** following addition of secondary oxidant, $Na_2S_2O_8$.

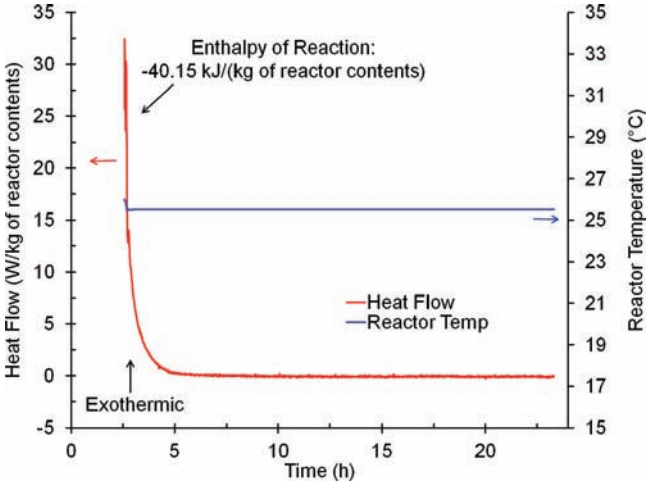


Figure 3. Reaction calorimeter heat flow curve for the synthesis of **2** after heating from 10 to 25 °C.

While the reaction calorimetry suggests conversion of **1** to **2** is complete at 2.7 h, we were interested in the result of the reaction left to stir for at least 12 h to examine the robustness of the product mixture. Reaction times ranging from 12 to 72 h provided essentially identical purities and yields of **2** which separates from the reaction mixture as a viscous yellow/orange liquid. The product is isolated by extraction with CH_2Cl_2. On the basis of a previous report[6] of an energetic degradation of **2** and our own accelerating rate calorimetry (ARC) data, it was critical to circumvent isolating **2** as neat material. We designed the subsequent acylative dealkylation reaction to be carried out in CH_2Cl_2 to avoid isolation of neat **2**. Our ARC analysis of pure **2** showed an initial, albeit low, exotherm near 75 °C and then a runaway exotherm near 115 °C. Differential scanning calorimetry (DSC, ramp rate = 20 °C/min) of **2** displayed an

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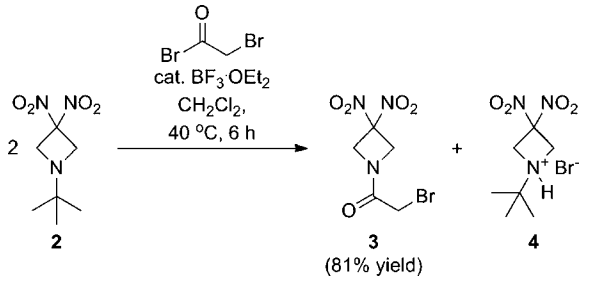
exotherm onset of 135 °C. These observations are consistent with the rapid decomposition of **2** near 120 °C noted by Archibald et al.[6] Dilution of **2** with CH_2Cl_2 substantially reduced the exothermic activity and shifted the initial exotherm to 135 °C when examined by ARC. While ARC data demonstrate that lower temperatures are preferred for storage, we have stored dried CH_2Cl_2 solutions of **2** up to 25 °C (ambient) for one month, and at 6−10 °C for 12 months without incident.

Synthesis of 1-Bromoacetyl-3,3-dinitroazetidine (3) by Acylative Dealkylation. Tertiary amines bearing a *tert*-butyl group undergo clean dealkylative substitutions by displacing gaseous isobutylene with NO_2^+,[6,20] chloroformates,[7,21] anhydrides,[22,23] and acid halides.[22,24] However, the reactivity of these electrophiles can vary depending on the nature of the *N*-nucleophile.[24,25] Dave and co-workers have described the generality of Lewis acid (BF_3·OEt_2)-catalyzed acylative dealkylations with various cyclic tertiary amines containing *tert*-butyl, and other, leaving groups.[22,23] The corresponding acetamide derivatives were obtained by acylation in excess neat acetic anhydride. Oxalyl chloride, also used neat and in large excess, was the only example of an acid halide employed as the acylating agent; reactivity at both carbonyls gave the corresponding dimeric oxamide.[22] Expanding on the use of acid halides as acylating agents, we converted **2** to **3** by treating the former with bromoacetyl bromide. After optimization, we found that 75 mol % (with respect to **2**)[26] of bromoacetyl bromide in the presence of catalytic BF_3·OEt_2 gave the best yields of **3** (81% yield) in refluxing CH_2Cl_2. Less than 75 mol % bromoacetyl bromide resulted in diminished yields of **3**. Greater than 75 mol % bromoacetyl bromide caused an increase in the level of bromoacetic acid (the hydrolysis product of bromoacetyl bromide) contamination and did not improve the yield of **3**. We opted to forego adding an acid (HBr) scavenger and simply adjusted the reaction stoichiometry to exploit half the molar equivalents of **2** as sacrificial base (Scheme 2). Thus, the bromoacetyl bromide is in 25% stoichiometric excess when added at 75 mol % of **2**.

Scheme 2. Preparation of 3



The production of **3** in solution was monitored using GC. After 6 h, the appearance of various brominated esters and alkanes indicated the termination point for the reaction in spite of unreacted starting material. Therefore, with isolated yields of pure **3** in the 80% range, the pursuit of superior yields via longer than 6 h reaction times was considered not worth the associated risk of added contamination.

The coproduct in the synthesis of **3**, 1-*tert*-butyl-3,3-dinitroazetidine hydrobromide (**4**), has low solubility in CH_2Cl_2; thus, its emergence as solid in the reaction vessel serves as a qualitative visual indicator of reaction progress. DSC analysis of **4** displays a sharp exotherm with a baseline departure near 170 °C and an extrapolated onset of 177 °C, with a significant amount of exothermic decomposition energy (2100−2300 J/g). In ARC, the initial exotherm for **4** is detected at a lower temperature (125 °C) than with DSC. Furthermore, dry solid **4** displays sensitivity in standard drop-weight testing.[27] By our internal methods (2 kg drop weight and approximately 25 mg of sample), **4** has a threshold impact sensitivity value of 6.9 cm. For comparison, by the same testing procedures, 2,4,6-trinitrotoluene (TNT) has a threshold impact sensitivity value of 41 cm. Initially, in single gram scale syntheses, precipitated **4** was removed by filtration. To mitigate the hazards of handling dry **4**, we explored aqueous extractions as an alternative to filtration. Dissolving energetic materials in solvents, especially water, significantly reduces, or altogether eliminates, related energetic decomposition hazards. We were pleased to discover that precipitated **4** was sufficiently soluble in water to be removed by dissolution, thus circumventing isolating the material as dry solid. Subsequent aqueous extractions of the organic phase effectively removed residual **4** dissolved in the CH_2Cl_2. The aqueous extractions also helped to remove the catalyst (BF_3·OEt_2) and consume unreacted bromoacetyl bromide by converting it to bromoacetic acid.

We assessed the effectiveness of the extraction step by analyzing samples of **3** isolated by evaporation of CH_2Cl_2 solutions washed with water or aqueous sodium bicarbonate (Table 2). We suspected that bicarbonate might aid in the removal of the bromoacetic acid. The results showed that bicarbonate did not remove impurities as well as distilled water alone, and that washing five times with water removed substantially more dissolved **4** than washing only three times but had little overall effect on the relative amounts of bromoacetic acid and **2**.

Table 2. Relative amounts (HPLC % peak area, total peak area = 100%) of impurities observed in 3 isolated from described washings of CH_2Cl_2 reaction solutions

wash	4[a]	bromoacetic acid	2	3
no wash	7.2	1.3	3.2	88.3
water × 3	2.2	1.6	1.8	94.4
water × 5	0.7	1.6	1.9	95.9
1% $NaCO_3H$ (aq)	1.2	2.2	2.8	93.8
0.1% $NaCO_3H$ (aq)	1.7	2.3	2.6	93.4

[a]Solid **4** was first removed by filtration for this study.

Acylative Dealkylation Mechanism Observations. In the bromoacetylation of **2** it is not immediately obvious when the N−C(*tert*-butyl) bond cleaves to liberate isobutylene. However, the indirect method of preparing 3,3-dinitroazetidine via a carbamate[7] signifies that **2** does not favor uncatalyzed discharge of isobutylene. Our work supports this premise specifically because neither 3,3-dinitroazetidine nor its HBr salt were detected in any component of the bromoacetylation reaction. These results are consistent with other reports[22,28] of BF_3-catalyzed acylations of tertiary amines and implies that loss of isobutylene from **2** occurs only after formation of the new N−C(acyl) bond and proceeds through a quaternary *N*-acyl-*N*,*N*,*N*-trialkylammonium intermediate (Scheme 3).

Isolation/Purification of 3. In the initial synthesis of **3**, crude product was isolated by complete evaporation of the solvent and other volatiles.[1] Using that process, marginal success at purification was achieved by washing/triturating the

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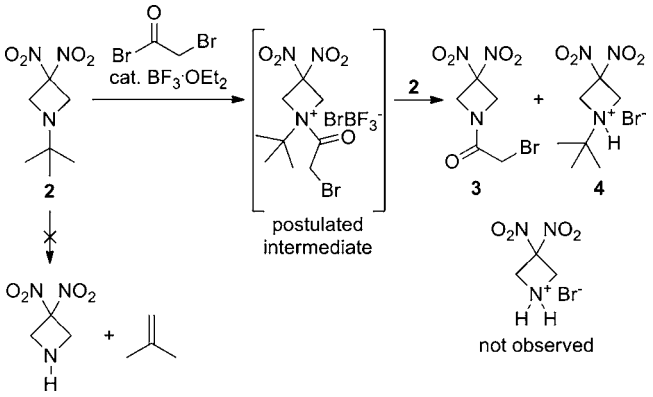
Scheme 3. Postulated reaction mechanism for the bromoacetylation of 2



product with Et_2O and then collecting the remaining solid by filtration. Compound **3** is not substantially soluble in Et_2O; thus, **2**, **4**, and bromoacetic acid were detectable in the final product at ~0.5% HPLC peak area each. We focused our attention on obtaining higher purity (>99%) **3** via conventional organic recrystallization solvents with only limited success. Instead, we were successful in isolating high-purity **3** directly from the reaction solution via antisolvent addition. Ethanol readily dissolved the major impurities (**2**, **4**, and bromoacetic acid) but did not appreciably dissolve **3** at ambient temperature. Isolation of pure **3** could be achieved efficiently by concentrating the CH_2Cl_2 reaction extract by half its initial volume followed by addition of EtOH. Removal of the remaining CH_2Cl_2 caused precipitation of **3** as a crystalline solid in >99.2% relative purity by HPLC after filtration. The amount of EtOH used for product precipitation was optimized at ~35% EtOH (v/v with respect to the CH_2Cl_2 solution of **3**) (Table 3).

Table 3. Effect of added EtOH concentration on the yield of isolated 3

% EtOH[a]	% yield of 3	purity of isolated 3
25	64	99.9
35	82	99.8
45	73	99.8

[a]With respect to the volume of CH_2Cl_2 solution of **3**.

In an effort to identify a method for reducing product particle size and combining multiple sub-batches of **3** into larger batch sizes, we developed a final solvent/antisolvent flash precipitation step. In this process, **3** is dissolved in EtOAc and then added rapidly to stirring heptane. Compound **3** immediately precipitates as a flocculent white solid that is filtered, rinsed with heptane, and air-dried. This step also aids in removing trace amounts of remaining CH_2Cl_2. We have successfully flash precipitated up to 160 g (three sub-batches) of **3**. The average recovery was 85%; however, the remaining 15% of product could be recovered and recycled. From a processing standpoint, the flocculent form of **3** is superior to the crystalline form obtained from EtOH, as the former has lower bulk density and particle size (~0.2 g/cm^3 and ~15 μm, respectively).

Compound **3** undergoes runaway self-heating at 125 °C as determined by ARC. DSC analysis of **3** shows a minor endotherm near 127 °C (melting point) followed by a substantial exotherm at 220 °C (onset = 247 °C). The magnitude of the exotherm is ~2400 J/g. Dried samples of **3** isolated from the final flash precipitation step showed no impact sensitivity up to the detection limit (80 cm) of our testing apparatus. Table 4 shows a combined summary of the lowest observed DSC and ARC exotherms for the nitroazetidines involved in the preparation of **3**. The DSC onset temperatures are 'extrapolated onset' temperatures, i.e. the intersections of a line drawn tangent to the steepest slope of the peak with the baseline. Exothermic departures from the DSC baseline are observed at lower temperatures, approximately 200, 100, 220, and 170 °C for compounds **1**–**4**, respectively.

Table 4. Lowest observed DSC and ARC exotherms for compounds 1–4

cmpd	lowest observed DSC exotherm onset temperature (°C)[a]	lowest observed ARC exotherm temperature (°C)
1	209	115
2	135	75
2 in CH_2Cl_2	–	135
3	247	125
4	177	125

[a]Ramp rate = 20 °C/min.

CONCLUSIONS

In summary we have described the safe and straightforward preparation of the novel API 1-bromoacetyl-3,3-dinitroazetidine, **3**. The synthesis is achieved in only two steps from commercially available starting materials and utilizes a minimal number of reagents. In the development process the percent yield of 1-*tert*-butyl-3,3-dinitroazetidine, **2**, was improved by 17% compared to that in previous reports of its preparation. The exothermic decomposition and sensitivity hazards associated with the synthesis have been mitigated by keeping intermediate **2** in solution (CH_2Cl_2) at all times, and by exploiting water extraction in place of filtration to remove the coproduct 1-*tert*-butyl-3,3-dinitroazetidine hydrobromide, **4**. The procedures provide high-purity API directly from the reaction solution. The final product is isolated by a flash precipitation technique that allows for the combination of sub-batches into larger batches. The bromoacetyl substituent of **3** presents a degree of reactivity at the α-carbon that is unavailable with the acetamide[22,23] functional group. This added functionality makes **3** susceptible to derivatization and thus a convenient building block to related species. The extent of this reactivity is currently under investigation.

EXPERIMENTAL SECTION

CAUTION: The flocculent form of **3** isolated by flash precipitation is exceptionally prone to dusting; therefore, adequate ventilation as well as a respirator or dust mask are recommended. Our calorimetry and thermal data indicate that compound **3** is safe to handle as a dry solid under typical ambient processing conditions (i.e., 20–30 °C) and that compounds **2** and **4** should be kept solvent wet or in solution. Nevertheless, *gem*-dinitroazetidines can undergo rapid decomposition and may be sensitive to heat, friction, impact, and electrostatic discharge. Handle with caution and appropriate safety equipment!

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General. 1-*tert*-Butyl-3-hydroxymethyl-3-nitroazetidine (**1**) was obtained from Parish Chemical Company (Vineyard, UT) in ≥98% purity.

1-*tert*-Butyl-3,3-dinitroazetidine (2). A solution of distilled water (1470 mL) and sodium hydroxide (71.2 g, 1780 mmol) at 20−25 °C was treated with **1** (97.6 g, 519 mmol) over a period of 1 min. The mixture was stirred at ambient conditions for 1−2 h. The nitronate solution was chilled to 10 °C, and a solution of potassium ferricyanide (17.2 g, 52 mmol) and sodium nitrite (143.2 g, 2075 mmol) in water (400 mL) was added. With the solution at 10−15 °C, sodium persulfate (173.2 g, 727 mmol) was introduced over a period of 2 min. The reaction temperature initially dropped and then increased by 10−15 °C. Once the exotherm began to subside, the reaction was warmed to 20−25 °C over 1 h and held for 16 h. The resulting orange/brown emulsion was extracted with CH_2Cl_2 (3 × 450 mL). The combined yellow/orange organic extracts were dried (Na_2SO_4) and then concentrated to ∼450 mL. For quantification and identification purposes, a small sample of the solution was brought to dryness in vacuo, yielding yellow/brown oil. (CAUTION: solvent-free compound may undergo rapid energetic decomposition if sufficiently heated![6]) Yields were consistently >99%,[29] spectral and analytical data matched those previously reported.[6]

1-Bromoacetyl-3,3-dinitroazetidine (3). Under a blanket of N_2, the CH_2Cl_2 solution of **2** (described earlier) was treated with $BF_3{\cdot}OEt_2$ (6.37 mL, 52 mmol) followed by bromoacetyl bromide (33.77 mL, 388 mmol). The N_2 purge was stopped, and the vessel sealed and fitted with a small pressure-release vent. The mixture was heated to a mild reflux and held for 6 h. Heating was stopped, and CH_2Cl_2 (1000 mL) and distilled water (800 mL) were added in that order. The two-phase system was stirred vigorously for 16 h. The aqueous phase was removed and the organic layer washed with additional distilled water (4 × 500 mL). The organic solution was dried (Na_2SO_4) and concentrated to approximately half its initial volume followed by addition of EtOH (250 mL). The remaining CH_2Cl_2 was removed at 25−30 °C, causing a precipitate to form. The slurry was chilled in an ice bath (30 min), and the solid was collected by filtration, rinsed with cold EtOH (5 × 150 mL), and air-dried to afford pure **3** (56.04 g, 81% yield[26]) as colorless crystals: mp 127−129 °C. IR (neat, cm^{-1}): 3013, 1677, 1586, 1567, 1446, 1368, 1338. ^1H NMR (400 MHz, acetone-d_6, δ): 4.0 (s, 2H, $-CH_2Br$), 4.9 (br s, 2H, ring $-CH_2-$), 5.3 (br s, 2H, ring $-CH_2-$); ^{13}C NMR (acetone-d_6, δ): 25.5, 58.5, 60.5, 107.6, 167.4. Anal. Calcd for $C_5H_6BrN_3O_5$: C, 22.41; H, 2.26; N, 15.68. Found: C, 22.52; H, 1.89; N, 15.60.

Flash Precipitation of 3. A quantity of **3** was dissolved in EtOAc (mass of **3** in grams × 6 = mL of EtOAc). This solution was rapidly added to a beaker of stirring (500 rpm) heptane (mass of **3** in grams × 18 = mL of heptane), immediately resulting in a white precipitate. The suspension was stirred for 5 min, and the solid was collected by vacuum filtration and rinsed with heptane. To ensure thorough solvent removal, air was pulled through the solid on the filter for 16 h. Analytical data matched that described previously for **3**.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of **2** and **3**; FT-IR spectrum of **3**; ARC, DSC, and reaction calorimetry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(3) Subsequent to the preparation of this article, RadioRx (see ref 2) employed a contracting organization to produce kilo quantities of **3** for clinical trials using the methods described here. Batch size = 6 kg of **1**; average yield of **3** = 85%.

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