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Propellants, Explosives, Pyrotechnics

RESEARCH ARTICLE

Synthesis of nitroxyethylnitramine (NENA) plasticizers and dinitroxydiethylnitramine (DINA) in continuous flow

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Abstract

Nitroxyethylnitramines (NENAs) and dinitroxydiethylnitramine (DINA) are useful energetic plasticizer components in propellants and explosives. However, their synthesis at large scale can be delicate because it involves two dissimilar nitration reactions: nitrate ester formation and halide-catalyzed nitramine formation. Consequently, these preparations, and particularly when conducted in a single-stage/pot operation, are problematic with respect to issues such as process safety (heat transfer, temperature control), product purity, replicability and operability. Herein, we briefly review procedures for preparation of NENAs and/or DINA and then report on our own work on continuous flow synthesis of this family of nitramine-nitrate ester compounds. We find them to be particularly suited for flow synthesis. Our studies are first and foremost distinguished from previous ones by focusing on the use of acetyl chloride as a metal-free, convenient chloride catalyst and the application of glacial acetic acid as a salt-forming secondary amine solvent, thus facilitating pumping of the amino alcohols and preventing local exotherms. We have also incorporated post-reaction simmering of the final flow effluent to enhance product purities by removal of nitroso impurities.

KEYWORDS
DINA, energetic plasticizers, flow synthesis, NENA, nitration

1 | INTRODUCTION

During the Second World War, in September 1942, the research group of George F Wright (1904–1976) at the University of Toronto, Canada, made the unexpected discovery of a chloride-catalyzed nitration of secondary amines when a sample of dinitroxydiethylammonium nitrate was dried in a desiccator over calcium chloride and subsequently reacted with acetic anhydride to give dinitroxydiethylnitramine (DINA). Samples of the same nitrate intermediate dried in an air draft did not provide satisfactory yields. The discovery made possible the

Abbreviations: Ac, acetic; Bu, butyl; DINA, dinitroxydiethylnitramine; eq, equivalent; Et, ethyl; *J*, coupling constant; m, multiplet (in NMR); Me, methyl; NDRC, National Defense Research Committee; NENA, nitroxyethylnitramine; NMR, nuclear magnetic resonance; q, quartet (in NMR); r.t., room temperature; s, singlet (in NMR); t, triplet (in NMR); t_1, residence time in Reactor 1; t_2, residence time in Reactor 2; T_1, temperature in Reactor 1; T_2, temperature in Reactor 2; V_1, volume of Reactor 1; V_2, volume of Reactor 2.

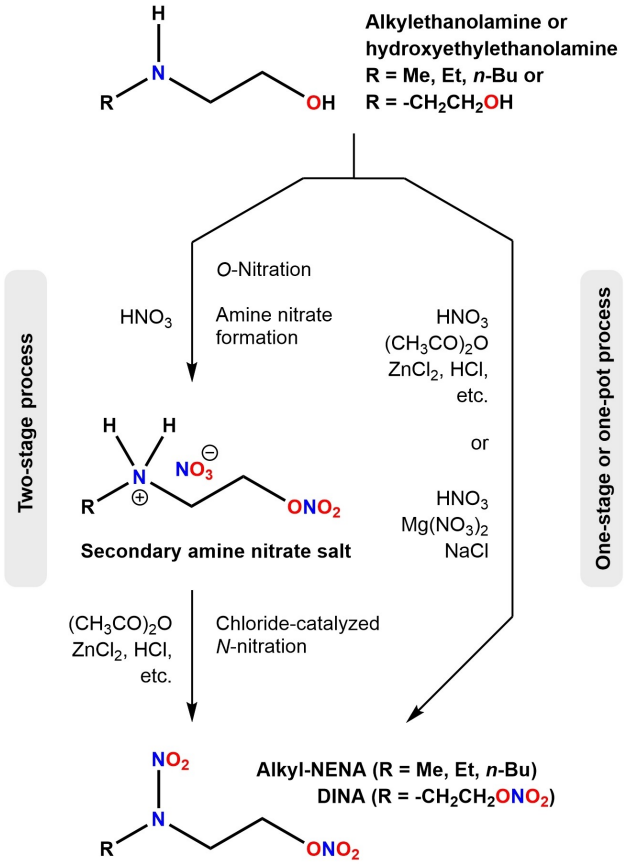
preparation of DINA from diethanolamine, nitric acid, acetic anhydride and a trace of an ionic chloride [1–3]. Use of bromide catalysis was also found effective [4].

Owing to the growing importance of flashless gun propellants during nighttime naval engagements in the Pacific, the US Navy tasked the newly established National Defense Research Committee (NDRC) with developing new flashless powders in late 1942 [3]. Because of the hazards of nitroglycerine volatilization and low mechanical strength of triple-base (Cordite N) flashless propellant, the development resulted in a new powder named Albanite. The formulation contained 20.0 parts nitrocellulose (12.6% N), 19.5 parts DINA, 55.0 parts nitroguanidine, 4.0 parts dibutyl phthalate, 1.5 parts ethyl centralite and some potassium sulfate, depending on weapon type [3]. DINA is less volatile than nitroglycerine and has a decent plasticizing action on nitrocellulose. The Albanite name was apparently derived from the propellant's white color [3].

Development work on the Albanite propellants led to synthesis of many new nitramine-nitrate esters, including the liquid *N*-alkyl-*N*-(2-nitroxyethyl)nitramine (alkyl-NENA) plasticizers first synthesized at Cornell University by Alfred Theodore Blomquist (1906–1977) and coworkers [5]. Blomquist expanded on Wright's work and made improvements in the synthesis of both DINA and NENAs [6]. In particular, the purification and stabilization of DINA necessitated improvements [7].

At first, there were two methods of preparing DINA or the NENAs: the "two-stage" or the "one-stage" process. The two-stage method entailed preparation and isolation of the secondary amine nitrate salt of the nitrate ester (diester in the case of DINA), followed by treatment of the isolated nitrate with acetic anhydride and a small amount of the chloride catalyst [1, 2]. In the one-stage method, the secondary amine was treated simultaneously with nitrating agent, acetic anhydride and a small amount of the appropriate chloride catalyst [1, 2]. Both procedures involved two steps: nitric acid esterification of the hydroxyl group(s) and conversion of the secondary amine to a nitramine (see Scheme 1). Concerning the chloride catalyst, use of zinc chloride or a small amount of the proper hydrochloride salt of the relevant secondary amine was preferred.

A recurrent problem in the synthesis of DINA and NENAs according to either method above was the charring and ignition that could occur when the amine contacted concentrated nitric acid [2]. Moreover, the one-stage modification was somewhat difficult to regulate thermally, as heat was evolved from both of the reactions occurring in the mixture. The two-stage method involved isolation of a dangerous intermediate in solid form and excessive use of nitric acid [6]. As a result, a



SCHEME 1 Reported syntheses of NENAs and DINA.

modified two-stage method was developed by Blomquist, where the secondary amine nitrate salt was kept as a solution in anhydrous nitric acid. The liquid nitrate salt solution was then fed into acetic anhydride, in the presence of the selected chloride catalyst [6]. In spite of Blomquist's two-stage, liquid-feed preparation, apparently only the one-stage method was evaluated on a pilot scale (with hydrogen chloride as catalyst) [3]. A pilot plant by DuPont for making DINA, to be used in Albanite, was started in April 1944 and continued in operation until the end of the war [3].

In the post-war era, development of NENA and DINA syntheses has continued to evolve. Production of NENA plasticizers, at commercial scales, has been dominated by the continuous process developed in the late 1990s by the company Dyno in Norway (currently Chemring Nobel) [8]. The *N*-alkylethanolamine is first reacted with nitric acid (below the liquid acid surface) and then with acetic anhydride and zinc chloride catalyst, all handled in a fully continuous process using specially designed equipment and work-up [8].

Unlike preparation of alkyl-NENAs, production of DINA is dominated by batchwise operations [9–12]. A procedure of importance in China and Russia is distinct from the methods above. Here, diethanolamine is first

added to a nitrating and dehydrating medium composed of magnesium nitrate dissolved in nitric acid (prepared from MgO and HNO_3) to achieve *O*-nitration. Sodium chloride is then added as a catalyst and the temperature is raised to facilitate *N*-nitration to DINA. This process is carried out as a one-pot preparation without intermediate purification [9–12]. However, the method is apparently plagued by poor thermal control. In 2017, a severe fire and explosion occurred in China, reportedly due to overheating taking place during post-processing of a DINA reaction mixture [12].

Flow synthesis is particularly suited for the preparation of NENAs and DINA because temperature control and efficient heat transfer is of such paramount significance. The firm Nitrochemie Aschau GmbH has recently patented syntheses of NENAs and DINA that use miniaturized continuous flow reactors [13]. In this process, nitric acid is cooled in a microreactor and fed into a second microreactor together with the secondary amine. After a short residence time, acetic anhydride with chloride catalyst is introduced. The flow system is operated at overpressure, and the reaction mixture is quenched by inflow of an aqueous solution. In the patent examples included, the process has been used for preparation of ethyl-NENA and liquid mixtures of methyl-NENA and ethyl-NENA, but not for DINA [13].

Among the alkyl-NENAs, butyl-NENA is by far the most important in commercial terms [14–18]. Direct, chloride-free nitration of 2-(butylamino)ethanol to butyl-NENA by application of specialized nitrating agents (dinitrogen pentoxide, *N*-nitropyridinium nitrate, thionyl nitrate) has been reported [17, 18]. However, the use of such agents at pilot plant or industrial scales is difficult and, probably, prohibitively expensive.

Below, we report on our work on preparation of alkyl-NENAs and DINA in continuous flow. Our studies are first and foremost distinguished from previous ones by focusing on the use of acetyl chloride as a metal-free, convenient catalyst and the use of glacial acetic acid as secondary amine solvent to facilitate pumping and improve temperature control. We also incorporate post-reaction simmering of the flow effluent to achieve enhanced product purities. Our methods do not need precooling of nitric acid and operates at intermediate reaction temperatures (room temperature to 60 °C).

We have primarily developed our methodology through preparation of butyl-NENA in continuous flow, due to the low sensitivity of this energetic plasticizer, and then extended it successfully to DINA. We have also used the methodology in mature form to prepare methyl-NENA and ethyl-NENA, the two components used in making the MEN-42 eutectic plasticizer mixture (58% methyl-NENA, 42% ethyl-NENA) [19]. We have made such mixtures either by making each component separately and then combining the two or by the direct co-nitration of the two relevant amino alcohols.

2 | EXPERIMENTAL SECTION

2.1 | Chemicals

2-(Butylamino)ethanol (98%), 2-(Ethylamino)ethanol (98%), 2-(Methylamino)ethanol (98%), Diethanolamine (98%), nitric acid (≥90%), glacial acetic acid (≥99%), acetic anhydride (≥98.5%) and acetyl chloride (≥99%) were obtained from Sigma Aldrich/Merck Life Science or VWR and used without further purification.

2.2 | Instruments and analysis

All flow syntheses were carried out using a Syrris Asia Flow Chemistry System, controlled by laptop computer (via the Asia manager software) and fitted with the following modules: Two syringe pumps (each having two separate pumping channels and equipped with two different set of syringes, providing a flowrate range of 1–250 $\mu L \cdot min^{-1}$ with 50/100 μL syringes for the first pump and 5–1250 $\mu L \cdot min^{-1}$ with 250/500 μL syringes for the second), pressurized input store and pressure controller. These modules were coupled to coiled reactor systems made from Bohlender™ PTFE tubing (ID 0.5 mm, OD 1.6 mm, wall thickness 0.55 mm). Tube reactor volumes were 0.5, 1.0, 2.0 and 4.0 mL. The tube reactors were fitted with connection systems as described in the Syrris manual, consisting of PTFE seal, 316 stainless steel ferrule and a compact fitting. The flow setup used T-connectors made from ETFE material and acquired from Dolomite Microfluidics. An overview of our flow system is given in Figure 1.

^{1}H NMR and ^{13}C NMR spectra were acquired with a Bruker Avance III 600 MHz NMR spectrometer (5 mm broadband probe). Data acquisition and data processing was performed with TopSpin 3.6 software. Chemical shifts (δ) are reported in parts per million. They are referenced to tetramethylsilane (TMS) using the solvent ($CDCl_3$) as internal reference (7.26 ppm).

FTIR spectra were collected on a Nicolet iS10 spectrometer equipped with a ZnSe crystal for ATR measurements. The resolution was 4 cm^{-1}, and each spectrum was based on 32 scans.

LC-ESI-Q-TOF-MS data were recorded using a Dionex Ultimate 3000 Rapid Separation LC (RSLC) coupled with a Bruker Daltonics micrOTOF-Q III mass spectrometer. Please see the Supporting Information for additional information on instruments and analysis.

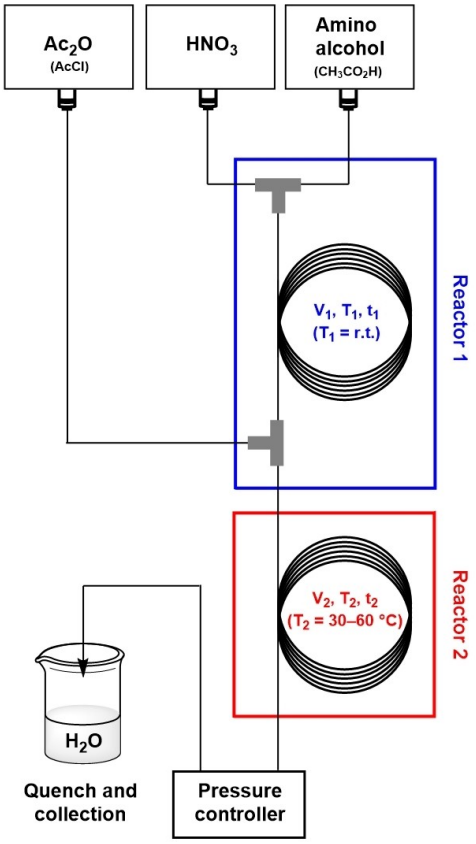


FIGURE 1 Experimental setup of flow chemistry system (please see experimental section for details).

2.3 | General procedure for preparation of NENAs and DINA in continuous flow

Prior to experiments in the flow chemistry system, the target compounds were prepared once in batch under comparable reaction conditions, in order to ensure that no intermediate or reaction product would precipitate inside the tube reactors, which may lead to clogging. This is particularly important in the case of DINA and methyl-NENA, these being solids at room temperature.

Before flow synthesis experiments, the system was conditioned using glacial acetic acid, and a leak test was performed according to the recommended procedure set by Syrris. If the leak test was passed, the glacial acetic acid was replaced by the relevant reagent solutions and cooling/heating baths were set to the value required by the experiment.

Two reagent flows, one consisting of nitric acid and the other containing the relevant amino alcohol, were pumped into Reactor 1 via a T-connector. For DINA and methyl-NENA, the amino alcohol was first diluted with glacial acetic acid (a solution made by dropping the amino alcohol dropwise into acetic acid under cooling from an ice/water bath). Reactor 1 was placed in a water bath held at room temperature (r.t.), helping to dissipate the heat of reaction. A second T-connector was used to combine the exit flow from Reactor 1 with the third reagent flow, consisting of acetic anhydride and chloride catalyst. The combined flow entered Reactor 2, which was kept in a water bath set to a specific temperature (however, the first part of Reactor 2 was placed in the water bath held at room temperature). The flow effluent from the second reactor then passed the pressure controller and was collected in an aqueous quenching bath kept under vigorous stirring. All reagent solutions in the pressurized input store, except for the nitric acid, was placed under 1 bar pressure. The different reaction products necessitated individual workup procedures. These are specified in the sections below. Following flow experiments, the system was thoroughly flushed with glacial acetic acid, followed by isopropanol.

2.4 | Preparation of butyl-NENA

Butyl-NENA was prepared from 2-(butylamino)ethanol in accordance with the general procedure given above, with no solvent needed for the amino alcohol. The final flow effluent was collected in a glass beaker containing water under agitation, giving a biphasic system with colorless butyl-NENA making up the bottom layer. The mixture was heated to 60 °C in a water bath and kept at this temperature for 30 min under vigorous stirring. The simmered mixture was allowed to cool to room temperature, transferred to a separatory funnel and extracted with ethyl acetate (10 mL). The organic phase was separated, washed with aqueous K_2CO_3 (5 wt%, 10 mL) and saturated brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Butyl-NENA was obtained as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 4.75$ (t, 2H, $^3J = 5.0$ Hz), 4.04 (t, 2H, $^3J = 5.0$ Hz), 3.78 (t, 2H, $^3J = 7.6$ Hz), 1.67 (m, 2H), 1.37 (m, 2H), 0.96 (t, 3H, $^3J = 7.4$ Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 69.1$, 52.9, 49.0, 28.6, 19.8, 13.5 ppm.

2.5 | Preparation of ethyl-NENA

Ethyl-NENA was prepared from 2-(ethylamino)ethanol in accordance with the general procedure, carried out as for butyl-NENA. Ethyl-NENA was obtained as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 4.76$ (t, 2H, $^3J = 5.0$ Hz), 4.04 (t, 2H, $^3J = 5.0$ Hz), 3.84 (q, 2H, $^3J = 7.1$ Hz), 1.29 (t, 3H, $^3J = 7.1$ Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 69.1$, 48.7, 48.2, 11.5 ppm.

2.6 | Preparation of methyl-NENA

Methyl-NENA was made from 2-(methylamino)ethanol in accordance with the general procedure, using glacial acetic acid as solvent to give a reagent solution of 2-(methylamino)ethanol in acetic acid (2.07 M). Upon collection of the final flow effluent in water under stirring, a homogeneous and colorless solution was obtained. The solution was heated to 60 °C under vigorous stirring for 30 min. The simmered solution was allowed to cool to room temperature, transferred to a separatory funnel together with aqueous K_2CO_3 (5 wt%, 10 mL) and ethyl acetate (15 mL). The organic phase was separated, washed with aqueous K_2CO_3 (5 wt%, 10 mL) and saturated brine (8 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Methyl-NENA was obtained as a colorless oil that crystallized upon storage. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.75 (t, 2H, ^3J = 5.0 Hz), 4.11 (t, 2H, ^3J = 5.0 Hz), 3.47 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 69.1, 50.3, 40.2 ppm.

2.7 | Preparation of DINA

DINA was made from diethanolamine in accordance with the general procedure, using glacial acetic acid as solvent to give a reagent solution of diethanolamine in acetic acid (2.71 M). Upon collection of the final flow effluent in water under stirring, DINA was found either to precipitate directly as a solid material or to form droplets that would later solidify. Either way, the mixture was heated to 60 °C under vigorous stirring for 30 min. The simmered solution was allowed to cool to room temperature, giving solidification of the DINA. The product was collected by vacuum filtration, rinsed with water and dried in air. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.76 (t, 4H, ^3J = 5.0 Hz), 4.13 (t, 4H, ^3J = 5.0 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 68.9, 50.2 ppm.

2.8 | Preparation of methyl-/ethyl-NENA (MEN) plasticizer mixtures by co-nitration

As an alternative to making the components separately and then mixing the two, mixtures of methyl-NENA and ethyl-NENA were also prepared directly from mixtures of 2-(methylamino)ethanol and 2-(ethylamino)ethanol in accordance with the general procedure, carried out as for butyl-NENA but with a slightly modified work-up. Two amine mixtures were used as starting materials: 60:40 and 56.8:43.2 mixtures of 2-(methylamino)ethanol to 2-(ethylamino)ethanol, respectively (ratios by weight).

The two mixtures were first co-nitrated as for butyl-NENA. The final flow effluent was collected in a glass beaker containing water under agitation, giving a colorless biphasic system. The mixture was heated to 60 °C in a water bath and kept at this temperature for 30 min under vigorous stirring. The simmered mixture was allowed to cool to room temperature, transferred to a separatory funnel and mixed with aqueous K_2CO_3 (5 wt%, 5 mL) and ethyl acetate (15 mL). The organic phase was separated, washed with aqueous K_2CO_3 (5 wt%, 5 mL) and saturated brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The methyl-/ethyl-NENA mixtures were obtained as colorless oils. The molar ratio of methyl- to ethyl-NENA in the samples were measured by ^{1}H NMR analysis by using the ratios of the integrated peaks (that is, methyl signal in methyl-NENA at 3.47 ppm and methyl signal in ethyl-NENA at 1.29 ppm).

2.9 | Preparation of the *O*-acetyl nitramine impurity 2-(Butylnitramino)ethyl acetate

A round bottom flask containing CF_3CO_2H (12 mL) was placed in an ice/water bath, and 2-(butylamino)ethanol (1.556 g, 13.27 mmol) was added under stirring over a period of 5 min. Following 5 min of additional stirring, acetyl chloride (1.75 mL, 24.61 mmol) was dropwise over a period of 10 min. The ice/water bath was then removed and the mixture was allowed to reach room temperature and stirred at this temperature for 3 h, giving a colorless solution. The solution was added dropwise into diethyl ether (150 mL), forming a white suspension. The suspension was stirred for 15 min, and the solid was collected by vacuum filtration, washed with diethyl ether (50 mL) and dried under reduced pressure to give 2-(butylamino)ethyl acetate hydrochloride as a white solid (2.105 g, 81% yield). This salt is hygroscopic and should be used in the next step as soon as possible. The convenient synthesis methodology used for this work is the chemoselective *O*-acylation of amino alcohols [20]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.76 (s, 2H), 4.49 (t, 2H, ^3J = 5.2 Hz), 3.25 (m, 2H), 3.01 (m, 2H), 2.17 (s, 3H), 1.87 (m, 2H), 1.42 (m, 2H), 0.95 (t, 3H, ^3J = 7.3 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.8, 58.8, 46.6, 45.9, 27.6, 21.0, 20.0, 13.5 ppm. IR (ATR): 2961, 2874, 2783, 2734, 2548, 2483, 2452, 2417, 1747, 1736, 1244, 1230, 1048 cm^{-1}. HRMS (ESI): calculated for $C_8H_{18}NO_2Cl$ [M−Cl] 160.1332, found 160.1347.

2-(Butylamino)ethyl acetate hydrochloride salt (0.177 g, 0.90 mmol), prepared as described above, was placed in a round bottom flask, and CH_2Cl_2 (1.0 mL) and

acetic anhydride (0.20 mL) were added. The heterogeneous mixture was cooled in an ice/water bath and nitric acid (≥90%, 0.16 mL, 3.4 mmol) was added dropwise, giving a yellow and homogeneous solution. While under cooling from the ice/water bath, the mixture was stirred for 4.5 h. It was then quenched in ice/water (~20 mL) and stirred vigorously for 5 min, diluted with ethyl acetate (30 mL) and transferred to a separatory funnel. The organic phase was separated, washed with aqueous $NaHCO_3$ (2.5 wt.%, 2×10 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to furnish 2-(butylnitramino)ethyl acetate as a colorless oil (0.127 g, 69% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.34 (t, 2H, ^3J = 5.3 Hz), 3.98 (t, 2H, ^3J = 5.3 Hz), 3.76 (t, 2H, ^3J = 7.5 Hz), 2.07 (s, 3H), 1.67 (m, 2H), 1.36 (m, 2H), 0.96 (t, 3H, ^3J = 7.3 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.6, 60.7, 52.5, 50.4, 28.6, 20.7, 19.9, 13.7 ppm. IR (ATR): 2961, 2875, 1741, 1509, 1281, 1222, 1032 cm^{-1}. HRMS (ESI): calculated for $C_8H_{16}N_2O_4$ [M + H] 205.1183, found 205.1198.

3 | RESULTS AND DISCUSSION

3.1 | Synthesis of butyl-NENA

The experimental setup of our flow chemistry system is shown in Figure 1 (see also the experimental section). We opted for a two-stage flow process. First, a flow of the appropriate amino alcohol was reacted with a flow of nitric acid in a tube reactor submerged in a water bath held at room temperature. The output flow was then mixed with a flow of acetic anhydride (Ac_2O), containing the chloride catalyst, and led into a second tube reactor kept in a heated water bath (30–60 °C). As such, the chemical pathway of our synthesis follows that of the two-stage process shown in Scheme 1.

Due to the relative insensitivity of butyl-NENA, we started out our flow synthesis experiments by using 2-(butylamino)ethanol as substrate, an amino alcohol that can be pumped directly into the first tube reactor in a facile manner, without the need of any solvent. The choice of chloride catalyst for the *N*-nitration in the second tube reactor is essential. At first, we made use of anhydrous $ZnCl_2$, but as contamination of waste streams with inorganic heavy metals is problematic, we transitioned to the use of acetyl chloride (AcCl). Wright listed acetyl chloride as a potential chloride catalyst [2]. Blomquist later advocated its use as a convenient catalyst (because of its liquid condition) [6]. It is an acetyl chemical having much in common with acetic anhydride, the key reagent of the process.

As the starting point for our flow experiments, we applied reagent ratios, of nitric acid and anhydride, as previously reported for continuous synthesis of butyl-NENA (2.8 eq HNO_3 and 2.8 eq Ac_2O) [8], but we used 10 mol% AcCl (relative to amino alcohol) as the catalyst. We then varied the temperature of Reactor 2. The results are presented in Table 1. The final flow effluent was collected in water and simmered at 60 °C for 30 min (under vigorous stirring) in order to destroy labile nitrosamine byproduct(s) [1–3, 7].

^{1}H NMR analysis of the resulting butyl-NENA showed only one impurity to be present at detectable levels. This was believed to be the *O*-acetyl nitramine analogue of butyl-NENA. We confirmed our suspicions through separate synthesis and ^{1}H NMR analysis of that compound. We determined its level in butyl-NENA through NMR analysis by integrating the methylene signal at δ = 4.75 ppm in butyl-NENA and the methylene signal at δ = 4.34 ppm in the *O*-acetyl nitramine impurity. For other alkyl-NENAs and DINA, we have used NMR analysis of corresponding signals.

As is evident from Table 1, temperatures of 40–60 °C in Reactor 2 (T_2) gave high yields (~85%) of butyl-NENA, while lower temperatures affected yields negatively. However, impurity levels, as measured by the content of the *O*-acetyl nitramine byproduct in the butyl-NENA, were significantly lowered at the reduced temperatures. For relevant comparison, we analyzed a commercial sample of butyl-NENA obtained from Chemring Nobel and found it to contain 0.48 mol% of the *O*-acetyl nitramine byproduct.

We then probed the reaction stoichiometry by keeping the temperature of Reactor 2 (T_2) at 40 °C and varying the applied amounts of nitric acid (Table 2) or acetic anhydride (Table 3). In these two flow series, the volumes of Reactor 1 (V_1) and Reactor 2 (V_2) were kept the same, and the residence time in Reactor 2 (t_2) was kept constant at 6 min. As a result, residence time in Reactor 1 (t_1) will vary somewhat from experiment to

TABLE 1 Flow synthesis of butyl-NENA, emphasizing the effect of temperature in Reactor 2 (T_2) on yield and purity (keeping HNO_3, Ac_2O and AcCl constant).[a]

Entry	T_2 [°C]	Yield [%]	Impurity level [mol%][b]
1	60	85	2.63
2	40	84	1.67
3	35	64	0.52
4	30	46	0.45

[a] HNO_3 (2.8 eq), Ac_2O (2.8 eq), AcCl (10 mol%), Reactor 1 (V_1 = 2.0 mL, T_1 = r.t., t_1 = 6 min), Reactor 2 (V_2 = 2.0 mL, t_2 = 3 min).
[b] 2-(butylnitramino)ethyl acetate content by ^{1}H NMR.

TABLE 2 Flow synthesis of butyl-NENA, emphasizing the effect of nitric acid use in Reactor 1 on yield and purity (keeping T_2, Ac_2O and AcCl constant).[a]

Entry	HNO_3 [eq]	Yield [%]	Impurity level [mol%][b]
1	2.5	85	3.29
2	2.8	86	1.43
3	3.0	77	0.94
4	3.2	74	0.58
5	3.4	77	0.58
6	3.6	57	0.29
7	4.0	36	0.24

[a] Ac_2O (2.8 eq), AcCl (10 mol%), Reactor 1 (V_1 = 1.0 mL, T_1 = r.t., t_1 = 329–371 s), Reactor 2 (V_2 = 2.0 mL, T_2 = 40 °C, t_2 = 6 min).
[b] 2-(butylnitramino)ethyl acetate content by ^{1}H NMR.

TABLE 3 Flow synthesis of butyl-NENA, emphasizing the effect of acetic anhydride use on yield and purity (keeping T_2, HNO_3 and AcCl constant).[a]

Entry	Ac_2O [eq]	Yield [%]	Impurity level [mol%][b]
1	1.8	47	6.69
2	2.6	75	1.53
3	2.8	86	1.43
4	3.0	82	1.63
5	3.8	82	2.12

[a] HNO_3 (2.8 eq), AcCl (10 mol%), Reactor 1 (V_1 = 1.0 mL, T_1 = r.t., t_1 = 296–425 s), Reactor 2 (V_2 = 2.0 mL, T_2 = 40 °C, t_2 = 6 min).
[b] 2-(butylnitramino)ethyl acetate content by ^{1}H NMR.

experiment. Reactor 1 was held at room temperature (T_1 = r.t.) throughout these experimental series.

Application of nitric acid in the range of 2.8–3.4 eq had modest effect with respect to product yields, but the purity level was notably improved (Table 2). Use of more than 3.4 eq nitric acid proved detrimental to product yields. Concerning acetic anhydride use, application of 2.8 eq was found optimal, both with respect to product yields and with respect to the purity of the butyl-NENA product (Table 3).

We also explored the effect of the catalyst in a separate experimental series (Table 4), varying the amount of acetyl chloride in the range of 10 to 1 mol% (relative to the amino alcohol). We found the product yields of butyl-NENA to drop at the reduced catalyst loadings, and hardly any yield at all could be obtained when using 1 mol% acetyl chloride (Table 4). At this low catalyst level, the purity of the butyl-NENA was found to be unacceptable. The main impurity was now thought to be the mono-nitrated product 2-(butylamino)ethyl nitrate, but that has not been proven by separate synthesis.

TABLE 4 Flow synthesis of butyl-NENA, emphasizing the effect of acetyl chloride catalyst on yield and purity (keeping T_2, HNO_3 and Ac_2O constant).[a]

Entry	AcCl [mol%]	Yield [%]	Impurity level [mol%][b]
1	10.0	86	1.43
2	5.0	67	0.84
3	2.5	54	0.74
4	1.0	13	36.6[c]

[a] HNO_3 (2.8 eq), Ac_2O (2.8 eq), Reactor 1 (V_1 = 1.0 mL, T_1 = r.t., t_1 = 6 min), Reactor 2 (V_2 = 2.0 mL, T_2 = 40 °C, t_2 = 6 min).
[b] 2-(butylnitramino)ethyl acetate content by ^{1}H NMR.
[c] The main impurity is probably 2-(butylamino)ethyl nitrate (not proven).

3.2 | Synthesis of alkyl-NENAs and DINA

Having established useful reagent stoichiometries and reactor conditions on the basis of our flow experiments targeting butyl-NENA, we proceeded to extend our flow procedures to include synthesis of ethyl-NENA, methyl-NENA and DINA.

We first incorporated ethyl-NENA, as this is an oily liquid bearing much resemblance to butyl-NENA. Moreover, the 2-(ethylamino)ethanol starting material can be pumped efficiently without solvent. Virtually identical flow conditions to those used for butyl-NENA gave ethyl-NENA (Table 5). Surprisingly, the purity of the obtained ethyl-NENA, relative to our butyl-NENA, was significantly improved. The presence of what we believe to be 2-(ethylnitramino)ethyl acetate in our ethyl-NENA was about half of that of the analogous impurity in butyl-NENA. We have not been able to identify any particular reason for this, but we note that of all our intended target molecules, ethyl-NENA was the one that was easiest to obtain in high purity.

Unlike ethyl- and butyl-NENA, methyl-NENA is a solid material at ambient temperatures. Additionally, 2-(methylamino)ethanol was found to react particularly vigorously with nitric acid. If pumped into Reactor 1 in neat condition, bubbles could form in the tube reactor system. We therefore pumped it as a solution in glacial acetic acid, in effect making the amine acetate salt the substrate. The use of acetic acid as a salt-forming solvent for amines, in the synthesis of nitramines, was introduced by Wright during the Second World War [21]. Originally, Wright had used glacial acetic acid as solvent for hexamine in an adaptation of Bachmann's synthesis of RDX, thereby opening up for the industrial all-liquid-feeds process for preparation of RDX by the Tennessee Eastman Corporation at Holston [21–23]. Shortly thereafter, Wright applied the methodology for his chloride-

TABLE 5 Flow synthesis of alkyl-NENAs and DINA using optimized reaction conditions.[a]

Product	HNO_3 [eq]	Ac_2O [eq]	T_2 [°C]	t_2 [min]	Yield [%]	Impurity [mol%][c]
Me-NENA[b]	2.8	2.8	35	6	84	1.88
Et-NENA	3.0	2.8	35	6	82	0.68
Bu-NENA	2.8	2.8	40	6	86	1.43
DINA[b]	3.8	3.8	35	3	89	2.44

[a] AcCl (10 mol%). For Me-NENA and DINA: Reactor 1 (V_1 = 0.5 mL, T_1 = r.t., t_1 = 149–257 s) and Reactor 2 (V_2 = 1.0 mL). For Et-NENA and Bu-NENA: Reactor 1 (V_1 = 1.0 mL, T_1 = r.t., t_1 = 257–360 s) and Reactor 2 (V_2 = 2.0 mL).
[b] Glacial acetic acid used as solvent.
[c] Content of *O*-acetyl nitramine by ^{1}H NMR.

catalyzed conversion of secondary amines to nitramines, such as in the synthesis of DINA [2]. As adapted by us, 2-(methylamino)ethanol was dissolved in about five times its volume of glacial acetic acid when making methyl-NENA, and diethanolamine was dissolved in about 2.5 times its volume when making DINA.

By use of this method, we found that we could achieve both excellent thermal control and improved practicality in the synthesis of methyl-NENA in flow by pumping 2-(methylamino)ethanol as acetate solution in glacial acetic acid. Apart from the glacial acetic acid, reaction conditions (stoichiometry and temperatures) were quite similar to those applied for butyl-NENA and ethyl-NENA (Table 5). There are minor variations of a few degrees in Reactor 2 and the amount of applied nitric acid in Reactor 1 in the flow procedures for the various NENAs. Moreover, when we used acetic acid as amine solvent, smaller tube reactors were applied in order to lower the total pressure in the flow system.

We now extended our flow preparatory method to synthesis of DINA. In that case, the diethanolamine starting material is a viscous liquid, so use of glacial acetic acid as a solvent was undertaken first and foremost with the purpose of reducing viscosity and facilitating pumping. Besides that, reaction conditions, as they were applied for flow synthesis of alkyl-NENAs could be transferred more or less directly to DINA, except that the reaction stoichiometry, which must be adjusted accordingly, as diethanolamine contains one amino group and two hydroxyl groups. As shown in Table 5, the amount of nitric acid must be increased from 2.8–3.0 eq to 3.8 eq for DINA, relative to the alkyl-NENAs. The applied quantity of acetic anhydride had to be increased by one equivalent (2.8 to 3.8 eq). We found that the residence time in Reactor 2 (t_2) could be reduced from 6 to 3 min for DINA compared to the alkyl-NENAs. This might be coupled to the fact that all the alkyl-NENAs need, in a relative sense, more *N*-nitration compared to DINA. Alkyl-NENAs contain one nitramine group per nitrate ester group while DINA contain one nitramine group per two nitrate ester groups. The relative kinetic rates for catalyzed *N*-nitration versus *O*-nitration have not been investigated by us.

3.3 | Synthesis of methyl-/ethyl-NENA (MEN) plasticizer mixtures by co-nitration

After having successfully synthesized DINA and all three of the most relevant alkyl-NENAs using our flow chemistry system, we finally addressed the synthesis of methyl-/ethyl-NENA (MEN) plasticizer mixtures by direct co-nitration of the two relevant amino alcohols, as a convenient alternative to making each component separately and then mixing the two. Two such mixtures of methyl- and ethylamino alcohols were co-nitrated under conditions analogous to those for butyl-NENA (but using a slightly modified work-up). The results of these experiments are shown in Table 6.

Our flow experiments showed that the product ratios of methyl- to ethyl-NENA corresponded relatively closely to the applied ratios of amine starting materials, although there occurred a slight enrichment of ethyl to methyl derivatives during the co-nitrations (compared to the ratios in starting materials). Accordingly, a 60:40 mixture of methyl- to ethylamino alcohol by weight, corresponding to a molar ratio of 1.78, gave rise to a 61:39 to 60:40 mixture of methyl- to ethyl-NENA, corresponding to a molar ratio of around 1.63 to 1.70. A 56.8:43.2 amine mixture by weight, having a molar ratio of 1.56, during co-nitration gave rise to a 57:43 mixture of methyl- to ethyl-NENA, having a molar ratio of 1.43. This MEN-43 mixture has a composition very close to the 1.50 molar ratio in MEN-42. One should note, however, that these ratios have been determined by ^{1}H NMR analysis, and there are slight variations of numbers depending on the exact choice of integration of NMR signals (please see the experimental section for details on our selection).

Comparable co-nitrations to our own in making MEN plasticizer mixtures in continuous flow reactors

TABLE 6 Flow synthesis of methyl-/ethyl-NENA (MEN) plasticizer mixtures by direct co-nitration.[a]

Entry	Amine ratio[b]	T_2 [°C]	t_2 [min]	Yield [%]	Impurity [mol%][c]	Product ratio[b]
1	60.0 : 40.0	35	6	76	0.50	61.0 : 39.0
2	60.0 : 40.0	40	6	92	0.59	60.0 : 40.0
3	56.8 : 43.2	40	6	80	0.84	57.0 : 43.0
4	56.8 : 43.2	40	3	76	0.39	57.0 : 43.0

[a] HNO_3 (2.8 eq), Ac_2O (2.8 eq), AcCl (10 mol%).
[b] Ratios by weight. Product ratios were determined by calculating from the molar ratios obtained by ^{1}H NMR.
[c] Content of *O*-acetyl nitramine by ^{1}H NMR (combined integrations for methyl- and ethyl-NENA relative to the combined integration of *O*-acetyl nitramine impurities).

have apparently given a somewhat higher attrition of the methyl relative to the ethyl derivative, with a 60:40 amine mixture (1.78 molar ratio) resulting in MEN-42 (1.50 molar ratio) [13].

4 | CONCLUSION

In summary, we have devised a flow chemistry setup capable of making alkyl-NENAs and DINA in a safe and controllable manner. This flow system comprised two coiled tube reactors in succession, where the first reactor was maintained at room temperature and the second at 35–40 °C. A flow of amino alcohol, either neat or as amine acetate solution in glacial acetic acid, was reacted with a flow of nitric acid in the first reactor. Immediately downstream, the exit flow was combined with a flow of acetic anhydride-acetic chloride mixture and led into the second reactor. Following a residence time there of a few minutes, the flow effluent was led into a beaker holding water and simmered for 30 min at 60 °C. By adjusting the temperature of the second reactor and the reagent ratios, alkyl-NENAs or DINA having excellent purity could be obtained in high yields – in a reproducible manner and without the possibility of thermal runaways. We find the possibility of making all the three most relevant alkyl-NENAs and DINA with the same setup of flow chemistry equipment and essentially the same reaction conditions to be highly convenient and an improvement in safety relative to the use of batch procedures. Moreover, our procedure was also successful in making liquid MEN plasticizer mixtures by direct co-nitration of the two relevant amino alcohols, with only minor changes in the ratios of methyl- to ethyl derivatives during the operation.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data may be requested via the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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