

Flow Electrochemistry for the *N*-Nitrosation of Secondary Amines

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Abstract: A flow electrochemical method towards the synthesis of *N*-nitroso compounds from secondary amines using cheap and readily available sodium nitrite has been developed. Sodium nitrite dissolved in aqueous acetonitrile made additional electrolytes unnecessary. This mild and straightforward approach made the use of acids or other harsh and

toxic chemicals redundant. This procedure was applied to an assortment of cyclic and acyclic secondary amines (27 examples) resulting in yields of *N*-nitrosamines as high as 99%. To demonstrate the practicality of the process, scaled-up reactions were performed. Finally, selected products could be purified by using an in-line acidic extraction.

Introduction

N-Nitrosamines (N–NO) are a class of compounds known for their toxic,^[1] carcinogenic,^[2–4] and mutagenic^[5,6] properties. *N*-Nitrosamines are relatively stable and can persist for prolonged times in the environment, resulting in the pollution of, *inter alia*, water, the atmosphere, soil, food, agricultural pesticides and herbicides, and medicinal drugs.^[7] The first *N*-nitrosamine, namely *N*-nitrosodiethylamine, was discovered by Geuther in 1863 by the reaction of diethylamine hydrochloride and sodium nitrite.^[8] Despite their harmful properties, such compounds can be profoundly beneficial. For example, *N*-nitrosamines have practical applications in the pharmaceutical and biological industries as nitric oxide (NO) donors.^[9,10] Moreover, *N*-nitrosamines are useful intermediates in organic synthesis, as they can be transformed into other useful functionalities, such as diazo compounds,^[11] hydrazines,^[12,13] and *N*-nitramines.^[14–16]

Typically, a compound containing an electrophilic nitrosonium ion [(NO⁺)], that is, a nitrosating agent, is required to access *N*-nitrosamines. The most conventional route towards the formation of *N*-nitrosamines is the use of sodium nitrite in combination with a strong acid.^[17–21] Sodium nitrite under acidic conditions forms nitrous acid (HNO₂) *in situ*, which is the active species responsible for the nitrosation. Sodium nitrite can also be combined with a Brønsted acid,^[22,23] formaldehyde,^[24] a Lewis

acid,^[25,26] acetic anhydride,^[27] oxone,^[28] or *N*-chlorosuccinimide^[29] to allow secondary amines to be successfully nitrosated. Throughout the years, a diverse range of nitrosating agents have been developed, such as alkyl nitrites,^[30–32] dinitrogen trioxide (N₂O₃), dinitrogen tetroxide (N₂O₄),^[29,33–37] nitric oxide (NO) in the presence of oxygen,^[35,38] nitrosyl halides,^[25,26,39,40] and nitrosonium tetrafluoroborate (NOBF₄).^[41] These reagents can be particularly hazardous and are not environmentally friendly, difficult to handle and store, and thus the development of alternative routes is an attractive goal. This is especially desired if the molecule contains a group sensitive to any of the additives such as acid-labile groups.

Electrochemistry is a promising alternative to the above-mentioned processes as the use of toxic redox reagents can be eliminated and be replaced with electrons, a much greener and cheaper redox reagent. Flow chemistry in combination with electrochemistry is a great tool, as any short-lived intermediates generated from the electrolysis of chemicals can readily react with substrates due to the proximity of the electrodes. Additionally, multistep syntheses can be easily integrated into the system, products can be purified in-line, and reactions are easily scalable.^[42] Several batch electrochemical processes towards the *N*-nitrosation of secondary amines have already been developed. The first electrochemical approach towards the synthesis of *N*-nitrosamines was performed by Masui and co-workers using sodium nitrite as the nitrosating source (Scheme 1).^[43] Lu *et al.* used Fe(NO₃)₃·9H₂O as a source of nitrate responsible for the *N*-nitrosation under electrochemical conditions.^[44] Unfortunately, high temperatures of 70 °C were required for this reaction. Another electrochemical approach was described by Gao and co-workers, who used potassium nitrite as the nitrosating source (Scheme 1).^[45] They also investigated sodium nitrite, a much cheaper source of nitrite ions, but this led to unacceptable yields. The latter two approaches require inert conditions for the reaction to proceed successfully. Additionally, all above methods suffer from the very low solubility of the nitrite salts in the organic reaction solvents, which must be addressed for developing suitable flow conditions.

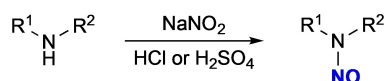
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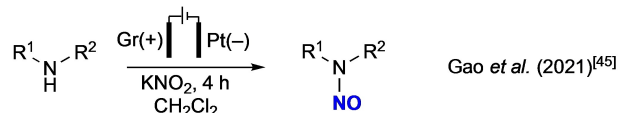
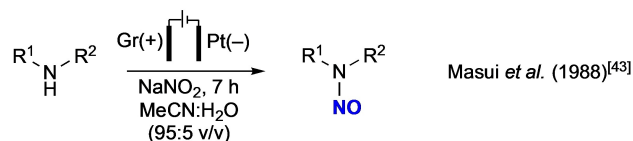
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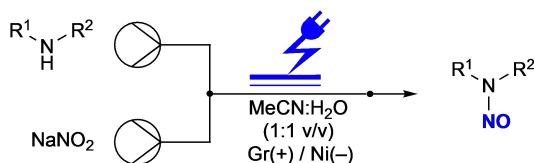
Conventional method



Batch electrochemistry



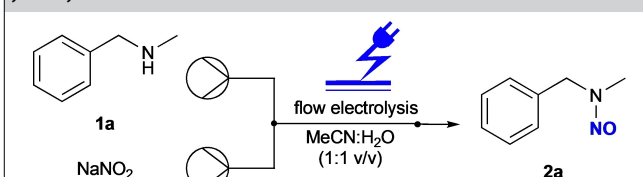
Flow electrochemistry: This work

Scheme 1. Synthesis of *N*-nitrosamines.

Herein, we report the development of an acid- and oxidant-free, continuous-flow electrochemical process towards the synthesis of *N*-nitrosamines from secondary amines. In this strategy, a one-electron anodic oxidation of the nitrite ion provides NO_2^\cdot radicals, which dimerise and exist in equilibrium with dinitrogen tetroxide (N_2O_4),^[46–48] a known nitrosating agent for secondary amines under neutral or alkaline aqueous conditions and in organic media.^[33,35]

Results and Discussion

The flow electrochemical experiments were carried out at ambient temperatures in an undivided, commercially available flow electrochemical reactor.^[49] Constant current conditions were applied and a 500 μm FEP spacer was used to separate the electrodes, creating a channel with a 0.6 mL volume inside the reactor with an active surface area of 12 cm^2 for each electrode. *N*-Methylbenzylamine **1a** was employed as the substrate for the determination of the optimal conditions required for the electrolysis towards *N*-nitrosamine **2a** (Table 1). NaNO_2 was selected to be the source of nitrite ions as it is significantly cheaper than KNO_2 (NaNO_2 : £7.4/mol;^[50] KNO_2 : £90.2/mol^[51]). As nitrite salts are insoluble in organic solvents, water must be used as the medium to dissolve the sodium nitrite, while the secondary amine was dissolved in acetonitrile owing to its miscibility with water. Due to the sufficient conductivity of the nitrite salt solutions and the small interelectrode distance, there was no need to add a supporting electrolyte. Using platinum as the cathode and graphite as the anode, an applied charge of 2 F mol^{-1} and a flow rate of

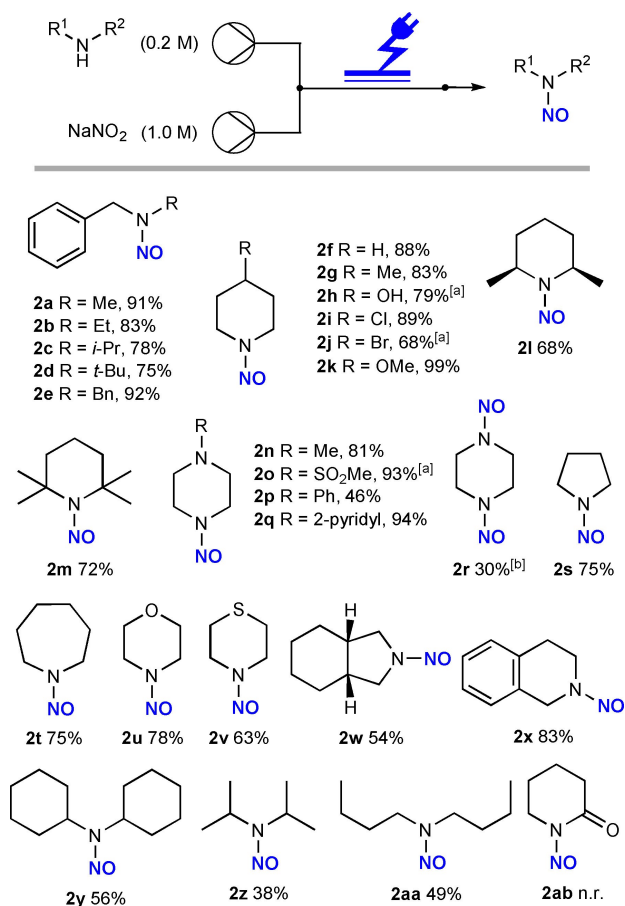
Table 1. Optimisation studies for the *N*-nitrosation of *N*-methylbenzylamine **1a**.^[a]


	[1a] ₀ [M]	[NaNO_2] ₀ [M]	Cathode material	Flow rate [mL min^{-1}]	Charge [F mol^{-1}]	Current [mA]	2a [%]
1 ^[b]	0.14	0.17	Pt	0.05	2.0	14	15
2	0.14	0.71	Pt	0.05	1.75	50	88
3	0.14	0.71	SS ^[c]	0.05	1.75	50	73
4	0.14	0.71	Cu	0.05	1.75	50	67
5	0.14	0.71	Gr ^[d]	0.05	1.75	50	25
6	0.14	0.71	Ni	0.05	1.75	50	88
7	0.2	1.0	Ni	0.05	1.75	70	81
8	0.2	1.0	Ni	0.05	1.25	50	89
9	0.2	1.0	Ni	0.075	1.25	75	81
10	0.2	1.0	Ni	0.1	1.25	100	78
11	0.3	1.5	Ni	0.05	1.25	75	70
12	0.4	2.0	Ni	0.05	1.25	100	65

[a] Standard reaction conditions: undivided flow cell, Gr anode (active surface area: 12 cm^2), Ni cathode, interelectrode distance: 0.5 mm, **1a** (1 equiv.) in MeCN, NaNO_2 (5 equiv.) in H_2O . Yield determined by $^1\text{H NMR}$ using 1,3,5-trimethoxybenzene as internal standard. [b] 1.2 equiv. NaNO_2 . [c] Stainless steel. [d] Graphite.

0.05 mL min^{-1} gave the desired product **2a** in 15% yield (Table 1, entry 1). Using an excess NaNO_2 (5 equiv.) as shown in the recent batch reactions allowed the reaction to proceed efficiently.^[45] This led to a dramatic increase in the yield (88%, Table 1, entry 2). Changing the cathode material from platinum to nickel did not decrease the yield (Table 1, entry 6). Other cathodic materials were investigated and provided **2a** in 73% (SS), 67% (Cu), and 25% (Gr) yield, respectively (Table 1, entries 3–5). Because Ni is considerably cheaper than Pt, Ni was chosen for the subsequent work. An increase in the concentrations of **1a** and NaNO_2 from 0.14 and 0.71 M to 0.2 and 1.0 M led to **2a** being formed in 81% yield, showing a slight decrease (Table 1, entry 7). However, at the increased concentrations, reducing the amount of charge applied from 1.75 to 1.25 F mol^{-1} increased the yield of **2a** slightly to 89% (Table 1, entry 8). Increased flow rates while keeping the charge applied constant at 1.25 F mol^{-1} , hence resulting in higher charge densities, led to a decrease in the observed yield (Table 1, entries 9 and 10). Finally, starting with even higher initial concentrations of **1a** and NaNO_2 unfortunately resulted in a decrease in the formation of **2a** (Table 1, entries 11 and 12).

With the optimised conditions in hand, the versatility of the procedure for converting cyclic and acyclic aliphatic secondary amines to their corresponding *N*-nitrosamines (Scheme 2) was explored. Starting with *N*-methylbenzylamine and increasing the steric bulk to *N*-ethyl, *N*-isopropyl, and *N*-*tert*-butyl resulted in good to excellent yields of the product, although the yield slightly decreased with increased steric bulk (**2a–2d**). Dibenzylamine produced the product **2e** with a very good yield of 92%. The method was also efficient for piperidine and its 4-substituted derivatives, as the products were obtained in yields



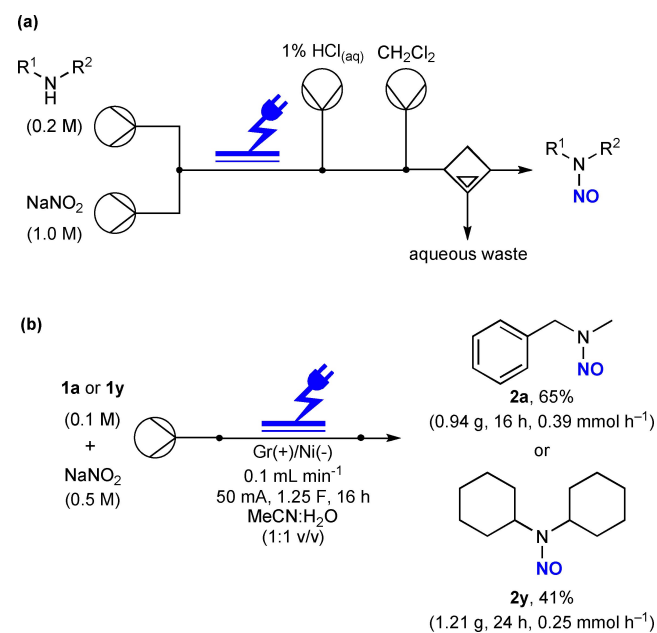
Scheme 2. Substrate scope for the electrochemical synthesis of *N*-nitrosamines from aliphatic secondary amine derivatives in flow. Standard reaction conditions: undivided flow cell, Gr anode (active surface area: 12 cm²), Ni cathode, amine (0.2 M) in MeCN, sodium nitrite (1.0 M) in H₂O, combined flow rate of 0.05 mL min⁻¹, constant current of 50 mA. Isolated yields. [a] Amine and NaNO₂ solutions combined into one syringe to account for the poor solubility of the amine in MeCN only. [b] H₂O as a solvent, constant current of 100 mA.

ranging from 68 to 99% (2f–2k). Also, *cis*-2,6-dimethylpiperidine and 2,2,6,6-tetramethylpiperidine provided products 2l and 2m in 68% and 72% yield, respectively. *N*-Substituted piperazine derivatives were nitrosated successfully and products 2n, 2o, and 2q were obtained in good to excellent yields, apart from 1-phenylpiperazine, which gave the product 2p in only moderate yield of 46%. Piperazine was dinitrosated in 30% yield (2r), however, for this reaction the solvent had to be changed to water only due to the formation of a biphasic system in the standard solvent system. Pyrrolidine and azepane were employed as other cyclic amines, affording the products in good yields of 75% (2s and 2t). Morpholine and thiomorpholine furnished the nitrosated products in 78 and 63% yield, respectively (2u and 2v). Fused bicyclic ring compounds such as *cis*-octahydroisoindole and 1,2,3,4-tetrahydroisoquinoline provided the products in 54 and 83% yield, respectively (2w and 2x). Furthermore, several acyclic, symmetrical aliphatic amines such as dicyclohexylamine, diisopropylamine, and dibutylamine yielded the *N*-nitrosated amines in

poor to moderate yields (2y–2aa). Unfortunately, secondary cyclic amides, such as δ -valerolactam (1ab), were not nitrosated successfully under the given conditions, even at elevated temperatures of 80 °C. Finally, tributylamine resulted in trace amount of *N*-nitrosamine 2aa, due to dealkylative nitrosation of tertiary amines being significantly slower than that of the corresponding secondary amine in aqueous media (see the Supporting Information).^[52] Due to the hindered rotation around the N–N bond resulting from its partial double bond character, the ¹H NMR spectra of all *N*-nitrosamines show the presence of configurational isomers.^[53]

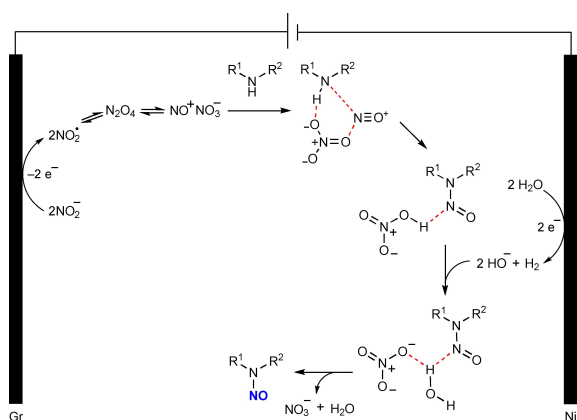
Interestingly, several of the synthesised products did not require purification by column chromatography, and an in-line purification method was devised based on an acidic work-up protocol (Scheme 3a). This was achieved by including a commercially available in-line liquid-liquid extractor.^[54] Here, 1% aqueous HCl is pumped into the system to make sure any unreacted starting material, excess NaNO₂, and species resulting from the electrolysis of NaNO₂ will be extracted into the aqueous phase. Subsequently, dichloromethane is added to extract the *N*-nitrosamine, and the two different solvent streams are passed into a phase separator. The products that were able to be purified using the in-line system were 2a, 2f, 2g, 2h, 2i, 2k, 2l, 2n, 2o, and 2u. To demonstrate the scalability of the procedure, *N*-methylbenzylamine 1a and dicyclohexylamine 1y were subjected to the reaction procedure with doubled flow rate to achieve a higher productivity (Scheme 3b). The products 2a and 2y were obtained in 65 and 41% yield, respectively, after 16 and 24 h of reaction time.

To investigate the reaction mechanism, several mechanistic experiments were carried out. Cyclic voltammetry (CV) experiments were performed on both *N*-methylbenzylamine 1a and NaNO₂ solutions, and the voltammograms showed the oxida-



Scheme 3. a) In-line purification system for the *N*-nitrosation of secondary amines. b) Scaled-up experiments.

tion peaks to be 1.3 and 0.7 V (vs Ag/AgNO₃), respectively (see Figure S1 in the Supporting Information). The oxidation peak of NaNO₂ in the reaction mixture was seen at a lower oxidation potential of 0.4 V (vs Ag/AgNO₃). These results, in combination



Scheme 4. Proposed reaction mechanism.

with past literature reports^[45–48] allowed to propose a possible reaction mechanism (Scheme 4). Initially, NO₂⁻ anions undergo a one electron oxidation to the NO₂[•] radical. This species can dimerise to form N₂O₄, which is in equilibrium with a NO⁺ cation and NO₃⁻ anion in solution. The NO⁺ cation and NO₃⁻ anion interact with the amine, which is followed by the introduction of a hydroxide anion, generated from the reduction of water at the cathode. This resulting intermediate allows the formation of the desired *N*-nitrosamines, with the release of one water molecule and a nitrate anion. Previously, it was shown that 5 equivalents of the nitrite source are necessary for the reaction to proceed efficiently. This is due to the fact that the NO₂[•] radicals formed not only dimerise, but can also form various other species under the electrochemical conditions.^[46–48]

For further investigations of the mechanism, a series of density functional theory (DFT) calculations at the SMD/ωB97X-D/def2tzvp//B3LYP-D3/6-31G(d) level were studied with **1e** as the model substrate. The DFT results, presented in Figure 1, show that the reaction starts with three possible pathways for the formation of different forms of the NO₂ dimer: symmetric

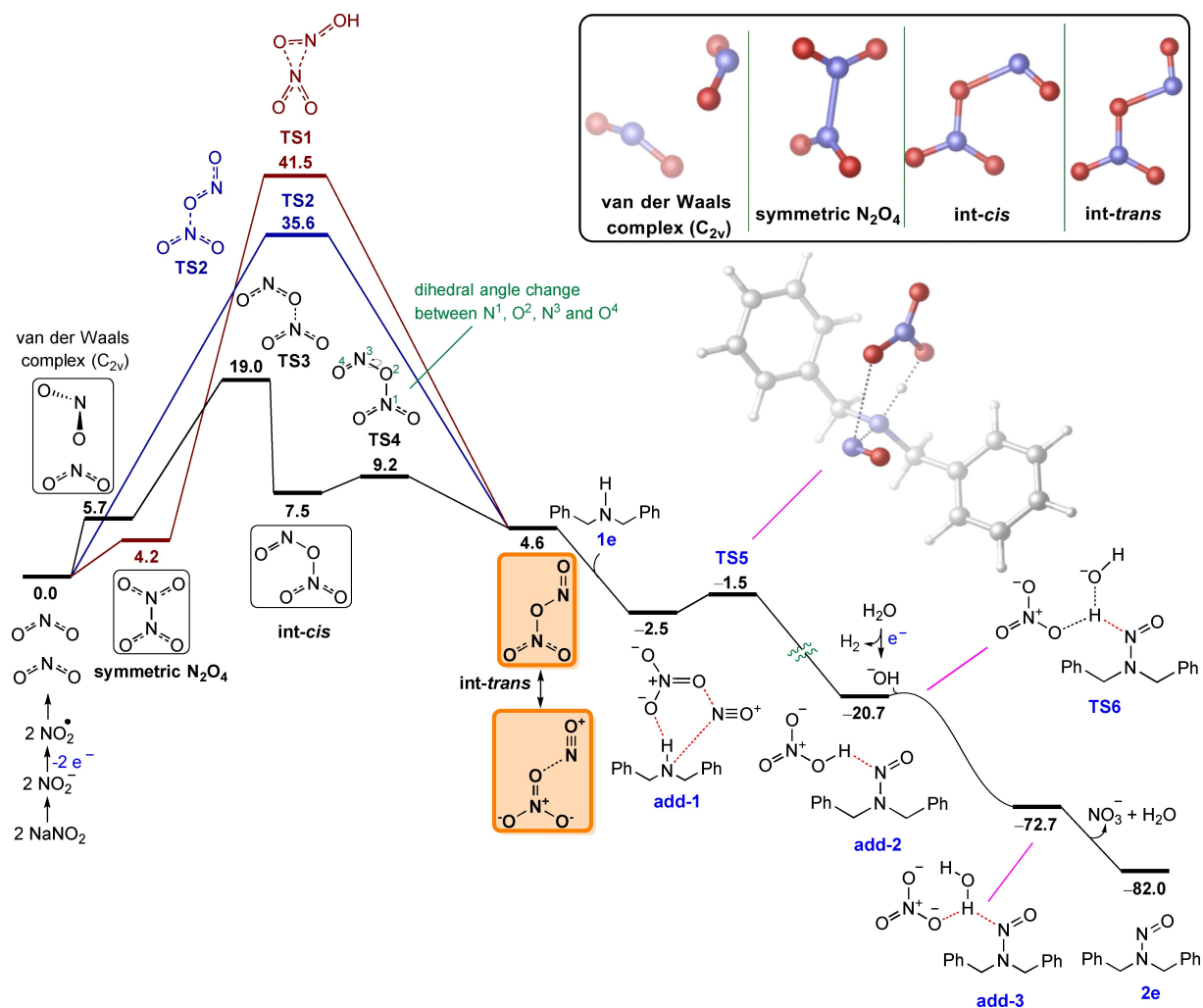


Figure 1. DFT reaction pathway for the formation of *N*-nitrosamine compound **2e** from the reaction of dinitrogen tetroxide and secondary amine **1e** computed at the SMD/ωB97X-D/def2tzvp//B3LYP-D3/6-31G(d) level of theory. The relative free energies are given in kcal mol⁻¹.

N_2O_4 , *int-trans*, and *int-cis*, from two monomers of NO_2 . The activation barrier for the formation of *int-cis* is $19.0 \text{ kcal mol}^{-1}$, while that for *int-trans* is $35.6 \text{ kcal mol}^{-1}$. However, attempts to locate the transition structure for symmetric N_2O_4 were unsuccessful. The activation barrier for symmetric N_2O_4 isomerising to *int-trans* was calculated to be $37.3 \text{ kcal mol}^{-1}$, making it an unlikely process in the NO_2 isomerisation. Thus, it is more favourable to first form *int-cis* and then convert it to *int-trans* where the activation barrier is $1.7 \text{ kcal mol}^{-1}$ (TS4). These results align with the report by Goddard and Liu on the interconversion between the three isomers of dinitrogen tetroxide in chemical processes.^[55]

After the formation of *int-trans*, the intermolecular *N*-nitrosation of the secondary amine **1 e** will progress by forming adduct **add-1**. The subsequent generation of adduct **add-2** occurs through transition structure TS5, which has an energy barrier of $1.0 \text{ kcal mol}^{-1}$. Subsequently, the formation of **add-3** occurred without encountering any energy barrier. The presence of the hydroxide ion generated from the reduction of water at the cathode facilitated the deprotonation of **add-3**, leading to the production of the final product *N*-nitrosamine **2 e**. This conversion proceeded through an exergonic process with a relative free energy of $-82.0 \text{ kcal mol}^{-1}$, resulting in the release of NO_3^- and H_2O .

Conclusions

In conclusion, a new continuous-flow electrochemical method has been developed to access *N*-nitrosamines from their corresponding secondary amines by using sodium nitrite as the nitrosating source. This is a non-hazardous, straightforward, and simple to set-up approach that avoids the use of any additional supporting electrolyte or other toxic reagents. Additionally, ambient temperatures and less hazardous solvents were employed for these reactions, thus harsh reaction conditions could be avoided. This method allowed the synthesis of a diverse scope of *N*-nitrosamines in good to excellent yields. One such reaction demonstrated the di-nitrosation of a substrate. Furthermore, great functional group tolerance was observed, and some of the products could be purified by using an in-line acidic extraction. This method proved to be easily scalable, an invaluable asset intrinsic of continuous-flow chemistry, demonstrating great applicability in both academic and industrial settings.

Experimental Section

General procedure for the flow electrochemical *N*-nitrosation of secondary amines: the electrolysis was performed in an undivided cell using a Vapourtec Ion electrochemical reactor^[49] (FEP spacer = 0.5 mm, reactor volume = 0.6 mL), employing a graphite electrode as the anode and a nickel electrode as the cathode (active surface area = 12 cm^2 for each electrode). A solution of secondary amine (0.2 M, 1 equiv.) in acetonitrile and sodium nitrite (1.0 M, 5 equiv.) in distilled water were pumped with a flow rate of $0.025 \text{ mL min}^{-1}$ (combined flow rate of 0.05 mL min^{-1}) into the electrochemical

reactor and were electrolysed under constant current conditions (50 mA, 1.25 F mol^{-1}). 1.5 reactor volumes were disposed to ensure a steady state of the system had been reached. After collection for a known period, the reaction mixture was treated with 1% $\text{HCl}_{(\text{aq})}$ and the aqueous phase was extracted with dichloromethane ($3 \times 25 \text{ mL}$). The organic layers were combined, dried over MgSO_4 , filtered, and the solvent was removed *in vacuo* to yield the crude product. The crude product was purified by column chromatography.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: density functional calculations · environmental chemistry · flow electrochemistry · in-line purification · *N*-nitrosation

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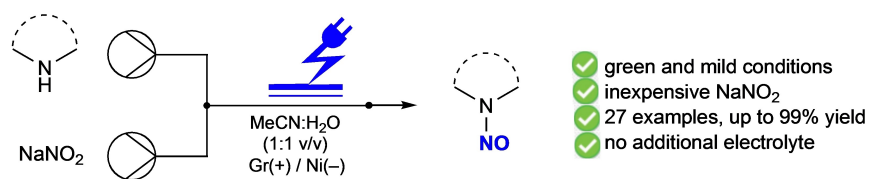
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RESEARCH ARTICLE



Go with the flow: *N*-Nitroso compounds have been synthesised from secondary amines by using sodium nitrite in an electrochemical flow setup. A 1:1 mixture of acetonitrile and water was used for this reaction, making this a mild

approach avoiding the use of additional supporting electrolytes. *N*-Nitrosamines could be obtained in yields up to 99%, and several compounds could be purified with an in-line acidic extraction.

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Flow Electrochemistry for the *N*-Nitrosation of Secondary Amines

