(12) UK Patent Application (19) GB (11) 2626410 (13) A

(43) Date of A Publication 24.07.2024

(21) Application No: 2317757.9

(22) Date of Filing: 21.11.2023

(30) Priority Data:
(31) 2300801 (32) 19.01.2023 (33) GB

(71) Applicant(s):
BAE Systems plc
6 Carlton Gardens, LONDON, SW1Y 5AD,
United Kingdom

(72) Inventor(s):
Matthew Paul Didsbury
Rebecca Elizabeth Stevens
Rojan Ali
Thomas Writh

(74) Agent and/or Address for Service:
BAE Systems plc
PO Box 87, Group IP Department, Warwick House,
Farnborough Aerospace Centre, FARNBOROUGH,
Hampshire, GU14 6YU, United Kingdom

(51) INT CL:
C07B 43/02 (2006.01) *C07C 241/00* (2006.01)
C07C 243/06 (2006.01) *C07D 209/44* (2006.01)
C07D 211/98 (2006.01) *C07D 213/74* (2006.01)
C07D 217/08 (2006.01) *C07D 295/30* (2006.01)
C25B 3/09 (2021.01) *C25B 3/20* (2021.01)
C25B 3/23 (2021.01)

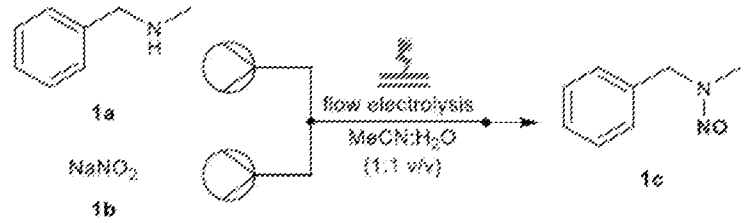
(56) Documents Cited:
WO 2000/052011 A2 CN 111235593 A
US 20190284131 A1
Chemistry - A European Journal, vol. 29, no. 32, 2023, Ali et al., "Flow Electrochemistry for the N-Nitrosation of Secondary Amines.", Article Number e202300957
Advanced Synthesis & Catalysis, vol. 362, no. 22, 2020, Zhao et al., "Electrochemical Nonacidic N-Nitrosation/N-Nitration of Secondary Amines through a Biradical Coupling Reaction", pages 5036-5043
Reaction Chemistry & Engineering, vol. 6, no. 10, Diab et al., "Flow synthesis kinetics for lomustine, an anti-cancer active pharmaceutical ingredient", pages 1819-1828
Chemical and Pharmaceutical Bulletin, vol. 34, no. 8, 1986, Ohmori et al., "Electrochemical Oxidation of N-nitrosopiperidines: Dual Pathways for N-Nitramine Formation", pages 3079-3086
Chemical and Pharmaceutical Bulletin, vol. 33, no. 7, 1985, Masui et al., "Electrochemical Oxidation of N-Nitrosodialkylamines: Mechanism of N-Nitramine and beta-ketonitrosamine Formation", pages 2721-2730
Journal of Electroanalytical Chemistry, vol. 389, no. 1/2, 1995, Gorski & Cox, "Oxidation of N-nitrosamines at a ruthenium-based modified electrode in aqueous solution", pages 123-128

(58) Field of Search:
INT CL **C07B, C07C, C07D, C25B**
Other: **WPI, EPODOC, INTERNET, CAS ONLINE, XPESP, XPSPRNG, SEARCH-PATENT, SEARCH-NPL**

(54) Title of the Invention: **Flow synthesis**
Abstract Title: **Electrochemical flow synthesis of N-nitrosamines**

(57) A method of electrochemical continuous flow synthesis of N-nitrosamines by nitrosylation of amines is provided, the method comprising the steps of (i) preparing input flow reagent A comprising an amine of Formula (I) as defined herein in a first solvent,; (ii) preparing input flow reagent B a nitrite salt in an aqueous solution; (iii) causing the input flow reagent A and B to enter a continuous electrochemical flow reactor provided with electrodes for electrolysis, at a flow rate, to provide a reaction solution comprising a N-nitrosamine of Formula II as defined herein. The formation of N-nitroso-N-methybenzylamine from N-methylbenzylamine with sodium nitrite is exemplified. Piperazine, pyrrolidine, azepane, morpholine and thiomorpholine can all be used as the amine in the electrochemical flow nitrosylation reaction. A method of electrochemical continuous flow nitrosylation of amines for the synthesis of N-nitrosamines is provided. A method of synthesising N-nitramines by electrochemical continuous flow comprising the steps of (xv) selecting an N-nitrosamine in a first solvent; (xvi) causing the N-nitrosamine to be subject to continuous flow electrochemical oxidation to form a N-nitramine is provided. The N-nitramine formed may be an energetic material such as RDX, HMX or CL20.

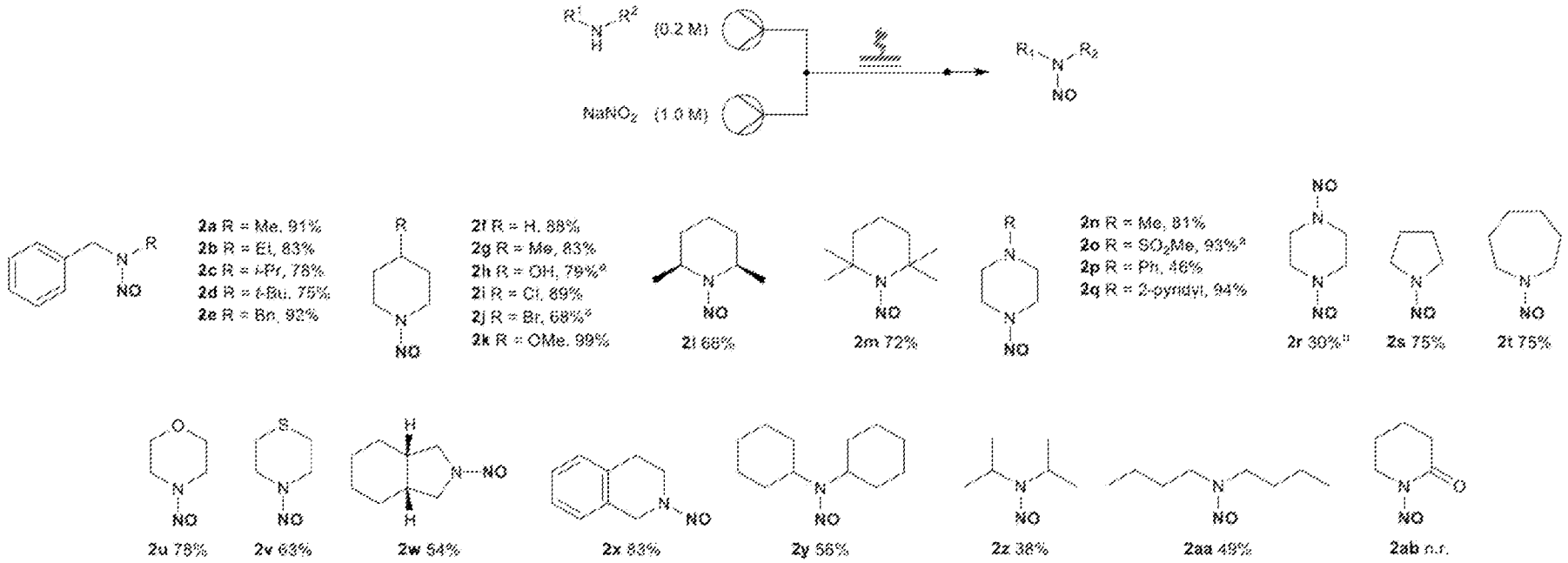
GB 2626410 A



Entry	$[\mathbf{1a}]_0$ (M)	$[\mathbf{1b}]_0$ (M)	Cathode	Flow rate (mL. min^{-1})	Charge (F)	Current (mA)	Yield **1c** (%)
1[a]	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	0.05	1.75	50	73
4	0.14	0.71	Cu	0.05	1.75	50	67
5	0.14	0.71	Gr	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

*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, **1b** (5 equiv.) in H_2O. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [a] 1.2 equiv. of **1b**.*

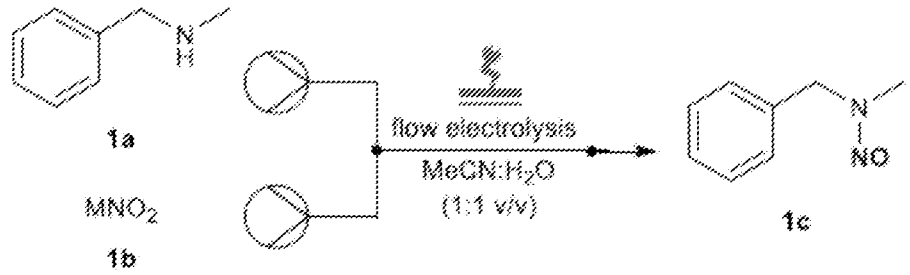
Fig 1



Standard reaction conditions: undivided flow cell, Gr anode (active surface area: 12 cm^2), Ni cathode, amine (0.2 M) in MeCN, sodium nitrite (1.0 M) in H_2O, combined flow rate of 0.05 mL min^{-1}, constant current 50 mA, isolated yields. **a** Amine and $NaNO_2$ solutions combined into one syringe due to account for poor solubility of the amine in MeCN only. **b** H_2O as a solvent.

Fig 2

Optimisation of salt

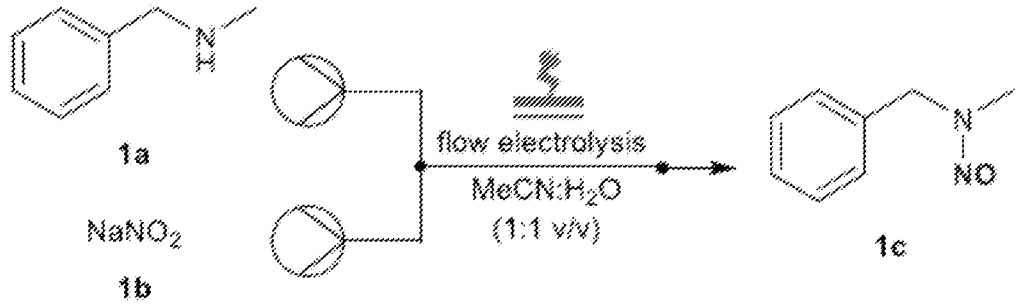


Entry	Salt	Yield (%)[b]
1[c]	$^{n}Bu_4NNO_2$	4
2	KNO_2	27
3	$NaNO_2$	26

a Standard reaction conditions: undivided flow cell, BDD anode (active surface area: 12 cm^2), Pt cathode, interelectrode distance: 0.5 mm, **1a** (0.14 M, 1 equiv.) in MeCN, **1b** (0.34 M, 2.4 equiv.) in H_2O, combined flow rate: 0.05 mL min^{-1}, constant current: 17 mA, charge: 1.25 F. **b** Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. **c** MeCN:H_2O (1:0 v/v).

Fig 3

Optimisation of equivalent of $NaNO_2$

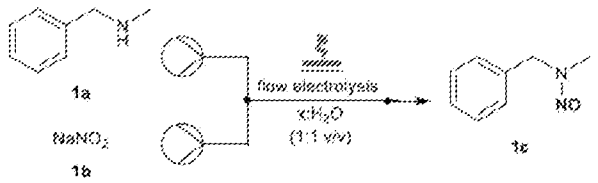


Entry	Equiv. of **1b**	$[1b]_0$ (M)	Charge (F)	Yield (%)[b]
1	1.2	0.17	5.10	13
2	2	0.28	3.10	21
3	3	0.43	2.05	31
4	4	0.57	1.55	34
5	5	0.71	1.25	40

a Standard reaction conditions: undivided flow cell, BDD anode (active surface area: 12 cm^2), Pt cathode, interelectrode distance: 0.5 mm, **1a** (0.14 M, 1 equiv.) in MeCN, **1b** (x M, y equiv.) in H_2O, combined flow rate: 0.05 mL min^{-1}, constant current: 35 mA. **b** Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Fig 4

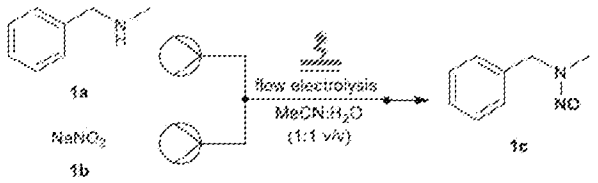
Optimisation of solvent composition



Entry	x	Yield (%)[a]
1	MeOH	19
2	MeCN	40

a Standard reaction conditions: undivided flow cell, BDD anode (active surface area: 12 cm^2), Pt cathode, interelectrode distance: 0.5 mm, **1a** (0.14 M, 1 equiv.) in x, **1b** (0.71 M, 5 equiv.) in H_2O, combined flow rate: 0.05 mL min^{-1}, constant current: 35 mA, charge: 1.25 F. **b** Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Optimisation of anodic material



Entry	Anode	Current (mA)	Charge (F)	Yield (%)[a]
1	BDD	35	1.25	40
2	Gr	50	1.75	88

a Standard reaction conditions: undivided flow cell, x anode (active surface area: 12 cm^2), Pt cathode, interelectrode distance: 0.5 mm, **1a** (0.14 M, 1 equiv.) in MeCN, **1b** (0.71 M, 5 equiv.) in H_2O, combined flow rate: 0.05 mL min^{-1}. **b** Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Fig 5

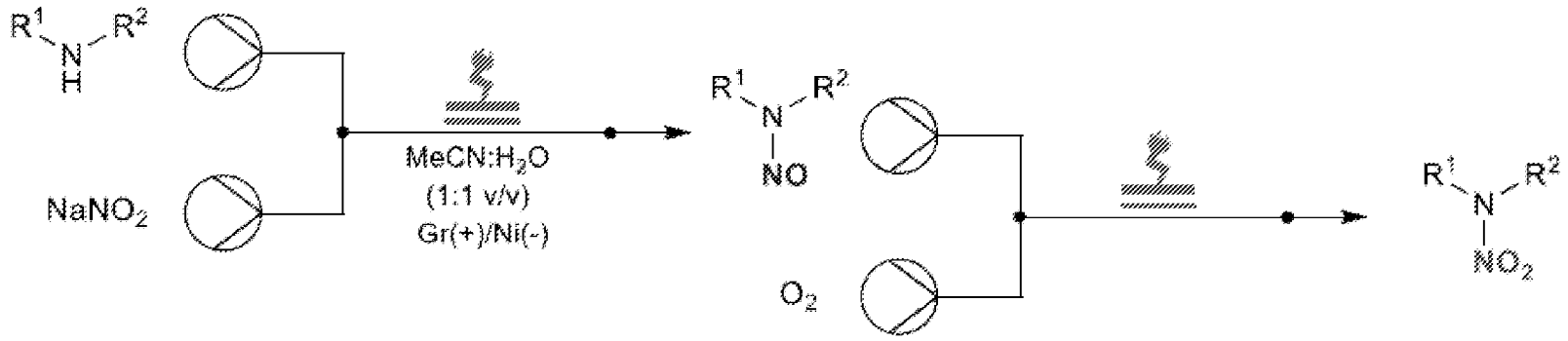

R1
N
R2
H
NaNO2
MeCN:H2O
(1:1 v/v)
Gr(+)/Ni(-)
R1
N
R2
NO
O2
R1
N
R2
NO2

Fig 6

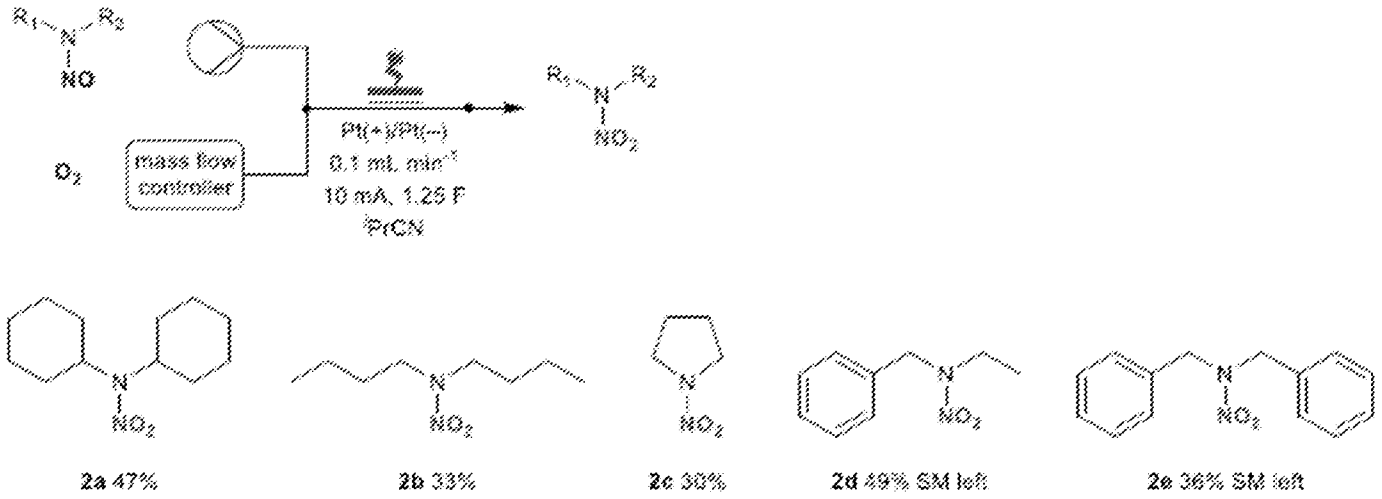

NO
O2
mass flow controller
Pt(+)/Pt(−)
0.1 mL min−1
10 mA, 1.25 F
iPrCN
NO2
2a 47%
2b 33%
2c 30%
2d 49% SM left
2e 36% SM left

Fig 7

FLOW SYNTHESIS

FIELD

The present invention relates to compound synthesis, and specifically relates to electrochemical flow synthesis nitrosylation for the synthesis of N-nitrosamines and subsequent oxidation to N-nitramines.

BACKGROUND

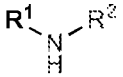
The formation of explosive compounds typically involves the use of batch synthesis to form large quantities of explosive material, which presents a significant explosion hazard.

SUMMARY

Before the present invention is described in further detail, it is to be understood that the invention is not limited to the particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims

According to the first aspect of the present invention, there is provided a method of electrochemical continuous flow nitrosylation of amines for the synthesis of *N*-nitrosamines, comprising the steps of:

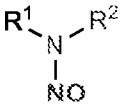
i). preparing input flow reagent A in a first solvent, comprising the amine compound of Formula (I),

Formula I 

wherein R^1 and R^2 are independently selected from H, alkyl, aryl, phenyl, cycloakyl, heterocyclic, heterocyclic aromatic, or together form heterocyclic, heterocyclic aromatic;

ii). preparing input flow reagent B, a nitrite salt in aqueous solution;

iii). causing the input flow reagents A and B to enter a continuous electrochemical flow reactor provided with electrodes for electrolysis, at a flow rate, to furnish a reaction solution comprising a *N-Nitrosamines* of Formula II.



Formula II

The nitrite salt may be any suitable nitrite salt, such as, for example tetrabutylammonium nitrite, group I metal nitrites, group II metal nitrites, preferably group I metal nitrites, such as KNO_2 or $NaNO_2$, more preferably $NaNO_2$.

The conditions are an acid-free, oxidant-free, electrolyte-free, continuous flow electrochemical strategy for the synthesis of *N*-nitrosamines from their corresponding primary or secondary amines.

The first solvent may be any suitable solvent in which the amine of Formula I is soluble, preferably a polar organic solvent, more preferably the solvent may be MeCN or MeOH.

The anode may be selected from any suitable anode, such as for example boron doped diamond (BDD) or graphite.

The cathode may be any inert metal, preferably platinum.

The reaction may be worked up by step iv) the reaction solution may be washed with dilute acid, such as for example $HCl_{(aq)}$. The products ie Formula II may be purified by any known purification means, such as, for example an in-line acidic extraction, chromatography or crystallisation.

The input flow reagent A, an amine compound of Formula (I) may be present in a 0.01M to 5M solution in the first solvent.

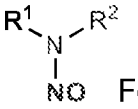
The input flow reagent B the nitrite salt in aqueous solution may be present in a 0.01M to 5M solution.

Preferably the concentration of the nitrite salt in aqueous solution may be at least double the concentration of the amine compound of Formula (I).

Preferably, Formula II R^1 and R^2 may be selected to form an N-Nitrosamines comprising at least two N-Nitrosamines groups. This allows the preparation of energetic material precursors, for highly nitrated nitramines.

According to a further aspect of the invention there is provided a method of synthesising *N*- nitramines by electrochemical continuous flow comprising the steps of

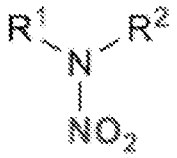
v) forming an *N-Nitrosamines* of Formula II,



Formula II

by any method or more preferably by a method as defined hereinbefore;

vi) causing the compound of Formula II to be subjected to continuous flow electrochemical oxidation to form a N-nitramine compound of Formula III,



Formula III;

wherein R1 and R2 are as hereinbefore defined.

Preferably, Formula III R^1 and R^2 are selected to form an energetic material N-nitramine comprising at least two N-nitramine groups, such as for example RDX (cyclo-1,2,3-trimethylene-2,4,6-trinitramine, Hexogen), HMX (cyclo-1,3,5,7-tetramethylene-2,4,6,8-tetranitramine, Octogen, NTO (3-nitro-1,2,4-triazol-5-one) or CL-20 (2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane).

Nitramine compounds are those containing at least one N-NO_2 group. Heteroalicyclic nitramines bear a ring containing N-NO_2 groups. Such ring or rings may contain for example from two to ten carbon atoms and from two to ten ring nitrogen atoms.

The electrochemical oxidation is more green and environmentally friendly, in line with the development direction of green chemical synthesis.

The continuous flow chemical oxidation may be carried out by any known process (1)Dissolving and mixing the compound of Formula II;

(2)The reaction solution is pumped into a microchannel reaction device equipped with electrodes for electrolysis reaction, and the reaction product is collected to obtain a solution comprising the compound represented by Formula III;

Common anions for the oxidation used as supporting electrolyte may be perchlorates, hexafluorophosphates, tetrafluoroborates or nitrites, since they have high discharge potential (the potential at which the anion will be oxidised at the electrode). As for the cation, their choice becomes more important when a cathodic reduction will be performed. The cationic parts may be tetraalkylammonium ions, lithium, sodium and magnesium ions.

Preferably, in step (2), the microchannel reaction device provided with electrodes includes a syringe pump, a microchannel reactor, a negative electrode sheet, a positive electrode sheet, and a receiver; wherein, both sides of the microchannel reactor are respectively provided with cathodes. The sheet and the anode sheet; the injection pump, the microchannel reactor and the receiver are connected in series; the connection is a pipeline connection.

Further preferably, the positive electrode sheet may be a carbon sheet electrode, and the negative electrode sheet may be a platinum-plated electrode.

According to a further aspect of the invention there is provided a method of electrochemical continuous flow nitrosylation of amines for the synthesis of N-nitrosamines, comprising the steps of:

xi). preparing input flow reagent A in a first solvent;

xii). preparing input flow reagent B a nitrite salt in aqueous solution;

xiii). causing the input flow reagents A and B to enter a continuous electrochemical flow reactor provided with electrodes for electrolysis, at a flow rate, to furnish a reaction solution comprising a *N*-nitrosamine.

According to a further aspect of the invention there is provided a method of synthesising N-nitramines by electrochemical continuous flow comprising the steps of:

xv) selecting an *N*-Nitrosamine in a first solvent;

xvi) causing the *N*-Nitrosamine in a first solvent to be subjected to continuous flow electrochemical oxidation to form a N-nitramine.

Experimental

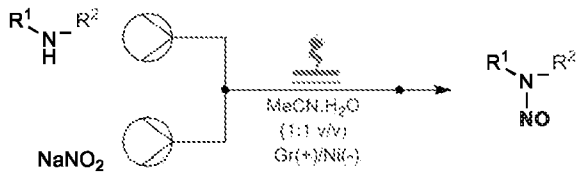
General

All chemicals were purchased from Acros Organics, Alfa Aesar, Apollo Scientific Ltd, Fisher Scientific Ltd, Scientific Laboratory Supplies Ltd, Merck KGaA, Fluorochem Ltd, and Sigma- Aldrich. All purchased chemicals were used without further purification. Deuterated solvents for NMR analysis were purchased from Sigma-Aldrich. Reference electrode kit was purchased from Osilla Ltd. Room temperature (rt) stands for 20-25 °C. Thin layer chromatography (TLC) experiments were performed on aluminum plates coated with silica (TLC Silica gel 60 F_{254}) purchased from Merck, and visualised by UV light. Column chromatography was carried out using silica gel (technical grade, pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size) purchased from Sigma-Aldrich, or by flash column chromatography on a Biotage® Isolera™ Four system using Biotage® SNAP Ultra 25 g, or 50 g, or Biotage® Sfär Silica D 25 g, or 50 g cartridges.

Electrolysis:

Flow electrochemical experiments were performed using a stand-alone Vapourtec Ion Electrochemical Reactor or integrated Vapourtec Ion Electrochemical Reactor for heated experiments, with an Aim-TTi EX354RD Dual Power Supply from Thurlby Thandar Instruments Ltd. Chemyx Fusion 100 Touch Syringe Pumps were used in the flow set-ups. Electrode materials employed were Graphite (Gr), Platinum (Pt), Nickel (Ni), Stainless Steel (SS), and Copper (Cu) purchased from Goodfellow and Boron Doped Diamond (BDD) purchased from Vapourtec. The electrodes (5 x 5 cm^2) were separated by a 0.5 mm FEP spacer or a 1.0 mm PTFE spacer resulting in a reactor volume of 0.6 mL or 1.2 mL, respectively with an exposed electrode surface area of 12 cm^2.

General Flow Electrolysis Procedure A:



The electrolysis was performed in an undivided cell using a Vapourtec Ion Electrochemical Reactor[1] (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 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). The first one and a half reactor volumes were disposed to ensure a steady state of the system had been reached. After collection for a known period of time, the

reaction mixture was treated with 1% $HCl_{(aq)}$ and the aqueous phase was extracted with dichloromethane (3 x 25 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.

Procedure **A** was adapted in certain cases by combining both solutions into one syringe to overcome solubility issues. Note: the combined solutions in the syringe are pumped with a flow rate of 0.05 mL min^{-1}.

Procedure **A** was adapted for piperazine by employing a water only system to avoid the formation of a biphasic system, by using sodium nitrite (2.0 M, 10 equiv.) in water and electrolysing the substrates under constant current conditions (100 mA, 1.25 F).

N-nitrosylation

The **N**-nitrosylation flow electrochemical experiments were carried out at ambient temperatures in an undivided, commercially available flow electrochemical reactor. Constant current conditions were applied and a 500 µm FEP spacer was used to separate the electrodes, creating a channel with a reactor volume of 0.6 mL, and an active surface area of 12 cm^2 for each electrode. *N*-Methylbenzylamine (**1a**) was the substrate employed for the purpose of reaction optimisation required for the electrolysis towards *N*-nitrosamine **1c** (Fig 1). Sodium nitrite was selected to be the source of nitrite ions as it is significantly cheaper than potassium nitrite. Since nitrite salts are insoluble in organic solvents, water must be utilised as the medium to dissolve the sodium nitrite, while the secondary amine was dissolved in an organic solvent miscible with water such as acetonitrile. The use of additional supporting electrolytes could be omitted due to not only the conductivity of the nitrite salts in solution, but also the small interelectrode distance.

Initially, equipping the reactor with Pt as the cathode, Gr as the anode, using 1.2 equiv. of $NaNO_2$, an applied charge of 2 F, a flow rate of

0.05 mL min^{-1} gave the desired product **1c** in 15% yield (Fig 1, entry 1).

Next, changing the nature of the cathode material from Pt to cheaper Ni did not decrease the yield (Fig 1, entry 6). Other cathodic materials were tested and gave rise to 73% (SS), 67% (Cu), and 25% (Gr) yields (Fig 1, entries 3–5). Since Ni is considerably cheaper than Pt, Ni was selected as the cathodic material.

An increase in the initial concentration of **1a** and **1b** from 0.14 M and 0.71 M to 0.2 M and 1.0 M led to **1c** being formed in 81% yield, showing a slight decrease (Fig 1, entry 9). However, at the increased concentrations, reducing the amount of charge applied from 1.75 F to 1.25 F increased the yield of **1c** to 89% (Fig 1, entry 10).

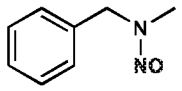
Turning to fig 2, with the optimum conditions in hand, the procedure was applied to converting various cyclic and acyclic aliphatic secondary amines to their corresponding *N*- nitrosamines (Figure 2). Starting with *N*-methylbenzylamine and increasing the steric bulk to *N*-ethyl, *N*-isopropyl, and N-*tert*-butyl resulted in good to excellent yields of the product, although the yield decreased with increased steric bulk (**2a**-**2d**). Dibenzylamine produced the product with an outstanding yield of 92% (**2e**). The method was also efficient for piperidine and its 4-substituted derivatives, as the products were obtained in yields ranging from 68% to 99% (**2f**–**2k**). Also, *cis*-2,6-dimethylpiperidine and 2,2,6,6-tetramethylpiperidine gave products **2l** and **2m** in 68% and 72% yields, respectively. Mono *N*-substituted piperazine derivatives were nitrosated successfully at the other nitrogen atom and products were obtained in good to excellent yields (**2n**, **2o** and **2q**), apart from 1-phenylpiperazine, which gave the product **2p** in only moderate yields of 46%. Piperazine was dinitrosated in poor yields of 30% (**2r**), however this reaction was performed with water as the only solvent, due to the formation of a biphasic system in the standard solvent system. Pyrrolidine and azepane were employed as amines in a five-membered and seven-membered ring system, affording the products in good yields of 75% (**2s** and **2t**). Morpholine and thiomorpholine furnished the

nitrosated products in 78% and 63%, 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%, respectively (**2w** and **2x**). Moreover, several acyclic, symmetrical aliphatic amines such as dicyclohexylamine, diisopropylamine, and dibutylamine yielded the *N*-nitrosated amines in poor to moderate yields (**2y**-**2aa**).

Characterisation of the Products

A selection of characterization data is provided below.

***N*-nitroso-*N*-methylbenzylamine (2a)**



Prepared according to the general procedure **A** from *N*-methylbenzylamine (54.5 mg, 58.0 µL, 0.45 mmol) over 1.5 h. The product was obtained as a yellow oil (61.7 mg, 0.41 mmol, 91%).

^{1}H NMR (500 MHz, CDCl3): δ 7.41-7.26 (m, 4.60H), 7.14-7.13 (m, 0.46H), 5.31 (s, 1.55H),

4.81 (s, 0.44H), 3.69 (s, 0.66H), 2.95 (s, 2.34H).

^{13}C NMR (126 MHz, CDCl3): δ 134.5, 133.8, 129.2, 129.0, 128.7, 128.5, 128.2, 128.1, 57.8,

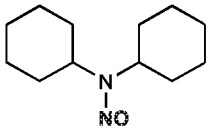
48.0, 38.6, 31.1.

HRMS (CI): *m/z* $[M+H]^+$ calcd for C8H11ON2 151.08659, found 151.0865.

Two configurational isomers, produced from the restricted rotation around the N-N partial double bond, were observed in the NMR spectra, with a ratio of 2:7.

NMR data is identical to the literature data

***N*-nitrosodicyclohexylamine (2y)**



Prepared according to the general procedure **A** from dicyclohexylamine (217.6 mg, 1.20 mmol) over 4 h. The crude product was purified by column chromatography on silica gel (DCM:cyclohexane = 3:7) to give **2y** as yellow crystals (140.9 mg, 0.67 mmol, 56%).

^{1}H NMR (500 MHz, CDCl3): δ 4.87 (tt, *J* = 11.7, 3.7 Hz, 1H), 3.71 (tt, *J* = 11.0, 4.5 Hz, 1H),

1.96-1.57 (m, 12H), 1.47-1.20 (m, 7H), 1.14 (qt, *J* = 12.9, 3.6 Hz, 1H).

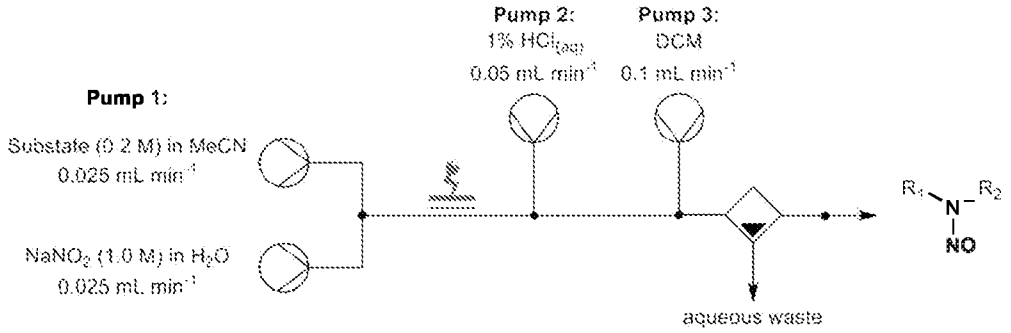
^{13}C NMR (126 MHz, CDCl3): δ 58.7, 52.3, 34.5, 29.5, 26.2, 25.6, 25.5, 25.4.

HRMS (CI): *m/z* $[M]^+$ calcd for C12H22ON2 210.17266, found 210.1727.

NMR data is identical to the literature data

In-line purification

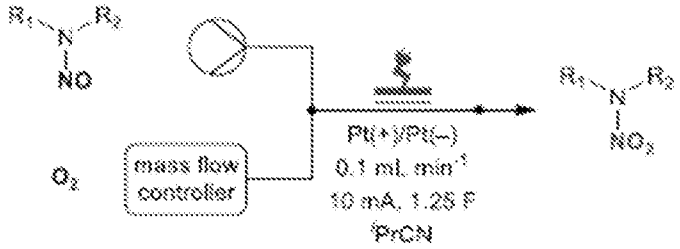
General Flow Electrolysis Procedure B:



This procedure is analogous to the above procedure **A**, except for a second pump connected *via* a T-piece, employed to protonate any remaining starting material and take up excess $NaNO_2$ and its intermediates, and a third pump connected *via* another T-piece, utilised for extraction of the product into the organic layer, where the layers are separated at the in-line liquid-liquid separator. After collection for a known period of time, the solvent was removed *in vacuo* to yield the pure product.

An in-line purification method was devised which is based on acidic work-up. This was achieved by including a commercially available in-line liquid-liquid extractor. A 1% $HCl_{(aq)}$ is pumped into the system to make sure any unreacted starting material, excess $NaNO_2$, and species resulting from the electrolysis of $NaNO_2$ will reside in the aqueous phase. Subsequently, dichloromethane was used to extract the *N*-nitrosamine from the aqueous phase, before the two different solvent streams are separated at the extractor.

Nitrosyl to nitro conversion- single step synthesis



Entry	Flow rate liquid (mL min^{-1})	Flow rate O_2 (mL min^{-1})	Back-pressure (bar)	Voltage (V)	Yield **1a** (%)	Yield **2a** (%)[b]
1	0.2	0.2	0	3.07-3.12	53	26
2	0.2	0.2	1	2.96-2.98	52	25
3	0.2	0.2	2	2.90-2.91	51	26

Table 1 **a** Standard reaction conditions: undivided flow cell, Pt anode (active surface area: 12 cm2), Pt cathode, interelectrode distance: 0.5 mm, current: 16 mA, charge: 1 F mol-1, 1a (0.05 M, 1 equiv.), nBu4NClO4 (0.1 M) in MeCN.

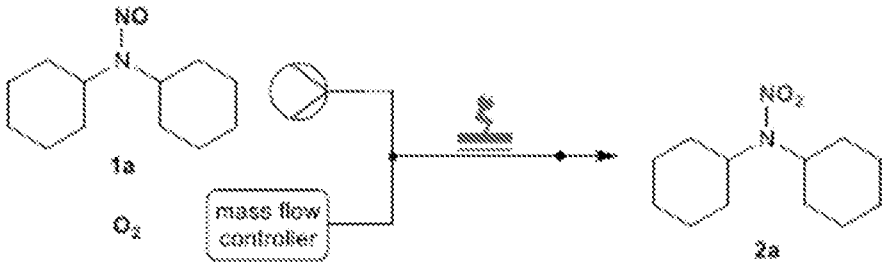
b Yield determined by GC-FID using benzonitrile as internal standard

The use of very low flow rates of 0.05 mL min-1, 1 bar of back-pressure cannot be achieved. Similarly, with 0.01 mL min-1, 2 bar of back-pressure cannot be achieved. Thus, 0.2 mL min-1 was used as the flow rate to investigate the effect of back-pressure on the system. As can be seen from Table 1, the effect of back pressure had little effect on the yield% of 2a. Preferably there is no back pressure regulator.

The effect of different anodic and cathodic materials were tested for their efficiencies and the results can be seen below in Table 2. Changing the anode from platinum (entry 1) to glassy carbon (GC) (entry 2) and graphite (entry 3) showed that despite the higher yields of product obtained for Pt and GC as the anode, there is less decomposition observed when using Gr. Therefore, graphite is a preferable anodic material. Moreover, changing the cathode from platinum to

nickel (entry 4), copper (entry 5), and stainless steel (entry 6) showed that platinum, nickel and copper resulted in similar yields of product and reactant.

The metal cathode may be chosen such that it can efficiently allow O_2 to chemisorb to the surface. The energy for this process should be around -0.5 to -2 eV which can be achieved by numerous metals. Platinum, gold, and silver are further suitable metals for the cathode.



Entry	Anode	Cathode	Voltage (V)	Yield **1a** (%)	Yield **2a** (%)[b]
1	Pt	Pt	3.02-3.09	54	25
2	GC	Pt	2.91-3.01	51	27
3	Gr	Pt	2.91-3.00	78	11
4	Gr	Ni	3.72-3.92	76	13
5	Gr	Cu	3.02-3.10	83	11
6	Gr	SS	3.40-3.44	69	15

Table 2

a Standard reaction conditions: undivided flow cell, x anode (active surface area: 12 cm_2), x cathode, interelectrode distance: 0.5 mm, current: 16 mA, charge: 1 F mol_{-1}, flow rate liquid: 0.2 mL min_{-1}, flow rate O_2: 0.2 mL min_{-1}, **1a** (0.05 M, 1 equiv.), $_nBu_4NClO_4$ (0.1 M) in MeCN.

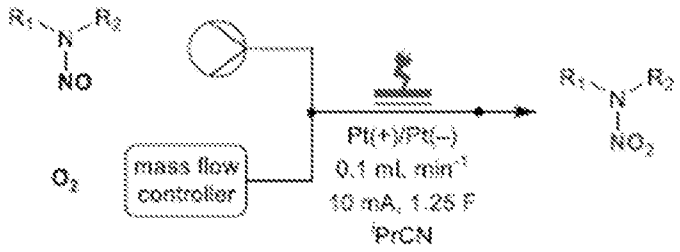
b Yield determined by GC-FID using benzonitrile as internal standard.

The increase in flow rate of the O_2 was examined. Flowing through O_2 at double and quadruple the flow rate of the liquid was also performed, to see whether an excess flow of oxygen gas will allow for more conversion of the starting material However, the yield of starting material and product in all cases was similar, indicating that flowing excess amount of gas has no impact on the results- this is beneficial as it is more cost effective to reduce the gas flow.

The applied charge was varied from 1 F mol-1 to 2 F mol-1 in increments of 0.25 F mol-1. It was observed that the best results were obtained with an applied charge of 1.25 F mol-1 resulting in 21% yield of the product with 55% of the starting material left unreacted. Higher charge applied results in slightly higher yields, with more decomposition observed, thus showing to be incompatible with the system.

Finally, the concentration of the solution was lowered from 0.05M to 0.025M to see whether this change will allow for more conversion of the starting material to occur, and whether decomposition will be less likely. However, several experiments were carried out for both concentrations and the results were nearly identical showing that this change had no impact on the results obtained.

The reaction scheme below was repeated to achieve compounds 2a-e, as described in Figure 7 below.



BRIEF DESCRIPTION OF THE FIGURES

Embodiments of the invention will now be described by way of example only with reference to the figures, in which:

Figure 1 shows the table of results for *N*-nitroso-*N*-methylbenzylamine

Figure 2 shows the table of example synthesised N- nitrosamines;

Figure 3 shows optimisation of the nitrite salt;

Figure 4 shows the optimisation of the $NaNO_2$;

Figure 5 shows .optimisation of solvent and anodic materials

Figure 6 shows the synthesis of N-nitramines in a multistep synthesis.

Figure 7 shows synthesised N- nitrosamines.

DETAILED DESCRIPTION

Figures 1 and 2 have been discussed in the Experimental.

Turning to Fig 3, shows the different yields of varying nitrite salts, conveniently low cost sodium nitrite provided excellent yields in comparison to other nitrites. However, other nitrites, particularly metal nitrites will provide similar results.

Turning to Fig 4, shows that increasing the concentration of sodium nitrite increased the yield.

Turning to Fig 5 alternative polar solvents will work, but MeCN which has a low hazard is highly suitable for large scale manufacture.

Alternative carbon based electrodes provide results, graphite provides the best yield in comparative studies.

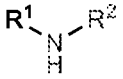
Turning to figure 6 there is provided the two step pathway for the conversion of amines to nitramines, for the synthesis of energetic materials.

Turning to figure 7 there is provided the electrochemical oxidation of nitrosylated amines to corresponding nitramines.

CLAIMS

1. A method of electrochemical continuous flow nitrosylation of amines for the synthesis of N-nitrosamines, comprising the steps of:

i). preparing input flow reagent A in a first solvent, comprising the amine compound of Formula (I),

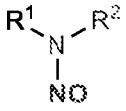


Formula I

wherein R^1 and R^2 are independently selected from H, alkyl, aryl, phenyl, cycloakyl, heterocyclic, heterocyclic aromatic, or together form heterocyclic, heterocyclic aromatic;

ii). preparing input flow reagent B a nitrite salt in aqueous solution;

iii). causing the input flow reagents A and B to enter a continuous electrochemical flow reactor provided with electrodes for electrolysis, at a flow rate, to furnish a reaction solution comprising a *N*-nitrosamine of Formula II;



Formula II.

2. The method according to claim 1, wherein the nitrite salt is tetrabutylammonium nitrite, group I metal nitrite, group II metal nitrite.

3. The method according to claim 1 or claim 2, wherein the first solvent is a polar organic solvent.

4 The method according to claim 3 wherein the solvent is MeCN or MeOH.

5. The method according to any one of the preceding claims, wherein the anode is BDD or graphite and the cathode is platinum.

6. The method according to any one of the preceding claims wherein step iv) the reaction solution is washed with dilute acid.

7. The method according to any one of the preceding claims wherein the amine compound of Formula (I) is present in a 0.01M to 5M solution.

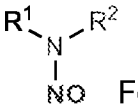
8. The method according to any one of the preceding claims wherein the nitrite salt in aqueous solution is present in a 0.01M to 5M solution.

9. The method according to any one of the preceding claims wherein the concentration of the nitrite salt in aqueous solution is at least double the concentration of the amine compound of Formula (I).

10. The method according to any one of the preceding claims wherein Formula II R^1 and R^2 form an N-Nitrosamine heterocycle comprising at least two N-nitrosamine groups.

11. A method of synthesising N-nitramines by electrochemical continuous flow comprising the steps of

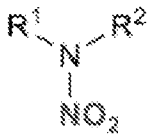
v) forming an *N*-Nitrosamine of Formula II;



Formula II

by a method as claimed in any one of the preceding claims:

vi) causing the compound of Formula II to be subjected to continuous flow electrochemical oxidation to form a N-nitramine compound of Formula III,



Formula III.

wherein R^1 and R^2 are independently selected from H, alkyl, aryl, phenyl, cycloakyl, heterocyclic, heterocyclic aromatic, or together form heterocyclic, heterocyclic aromatic.

12. The method according to claims wherein Formula III R^1 and R^2 form an energetic material N-nitramine comprising at least two N-nitramine groups.

13. The method according to claim 12 wherein energetic material is RDX, HMX, or CL20.

14. A method of electrochemical continuous flow nitrosylation of amines for the synthesis of N-nitrosamines, comprising the steps of:

xi). preparing input flow reagent A in a first solvent;

xii). preparing input flow reagent B a nitrite salt in aqueous solution;

xiii). causing the input flow reagents A and B to enter a continuous electrochemical flow reactor provided with electrodes for electrolysis, at a flow rate, to furnish a reaction solution comprising a *N*-nitrosamine.

15. A method of synthesising N-nitramines by electrochemical continuous flow comprising the steps of:

xv) selecting an *N*-Nitrosamine in a first solvent;

xvi) causing the *N*-Nitrosamine in a first solvent to be subjected to continuous flow electrochemical oxidation to form a N-nitramine.

Intellectual Property Office

Application No:	GB2317757.9	**Examiner:**	Dr Alistair Longshaw
Claims searched:	1-10 and 14	**Date of search:**	18 April 2024

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	Chemistry - A European Journal, vol. 29, no. 32, 2023, Ali et al., "Flow Electrochemistry for the N-Nitrosation of Secondary Amines.", Article Number e202300957 - See whole document
A	-	Advanced Synthesis & Catalysis, vol. 362, no. 22, 2020, Zhao et al., "Electrochemical Nonacidic N-Nitrosation/N-Nitration of Secondary Amines through a Biradical Coupling Reaction", pages 5036-5043 - See whole document, especially Tables 1 and 2
A	-	Reaction Chemistry & Engineering, vol. 6, no. 10, Diab et al., "Flow synthesis kinetics for lomustine, an anti-cancer active pharmaceutical ingredient", pages 1819-1828 - See especially Figures 2, 3, 5
A	-	CN 111235593 A (NANJING UNVERSITY OF SCIENCE AND TECHNOLOGY) - See whole document, especially Figure 3

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

C07B; C07C; C07D; C25B

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC, INTERNET, CAS ONLINE, XPESP, XPSPRNG, SEARCH-PATENT, SEARCH-NPL

Intellectual Property Office

International Classification:

Subclass	Subgroup	Valid From
C07B	0043/02	01/01/2006
C07C	0241/00	01/01/2006
C07C	0243/06	01/01/2006
C07D	0209/44	01/01/2006
C07D	0211/98	01/01/2006
C07D	0213/74	01/01/2006
C07D	0217/08	01/01/2006
C07D	0295/30	01/01/2006
C25B	0003/09	01/01/2021
C25B	0003/20	01/01/2021
C25B	0003/23	01/01/2021

Intellectual Property Office

Application No: GB2317757.9 **Examiner:** Dr Alistair Longshaw

Claims searched: 11-13 and 15 **Date of search:** 17 May 2024

Patents Act 1977
Further Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	Chemical and Pharmaceutical Bulletin, vol. 34, no. 8, 1986, Ohmori et al., "Electrochemical Oxidation of N-nitrosopiperidines: Dual Pathways for N-Nitramine Formation", pages 3079-3086 Available from https://www.jstage.jst.go.jp/article/cpb1958/34/8/34_8_3079/_article/-char/en - See whole document, especially Abstract, Chart 1 and apparatus section
A	-	Chemical and Pharmaceutical Bulletin, vol. 33, no. 7, 1985, Masui et al., "Electrochemical Oxidation of N-Nitrosodialkylamines: Mechanism of N-Nitramine and beta-ketonitrosamine Formation", pages 2721-2730 Available from https://www.jstage.jst.go.jp/article/cpb1958/33/7/33_7_2721/_article/-char/en - See whole document, especially Abstract and Experimental
A	-	Journal of Electroanalytical Chemistry, vol. 389, no. 1/2, 1995, Gorski & Cox, "Oxidation of N-nitrosamines at a ruthenium-based modified electrode in aqueous solution", pages 123-128 - See especially the abstract and Section 2.2
A	-	WO 00/52011 A2 (CORDANT TECHNOLOGIES, INC.) - See whole document, especially page 3, line 25 - page 4, line 3; page 5, lines 7-9 and page 7, lines 13-30
A	-	US 2019/0284131 A1 (NIEDER et al.) - See whole document, especially paragraphs [0005]-[0010]
A	-	Advanced Synthesis & Catalysis, vol. 362, no. 22, 2020, Zhao et al., "Electrochemical Nonacidic N-Nitrosation/N-Nitration of Secondary Amines through a Biradical Coupling Reaction", pages 5036-5043 See whole document, especially Table 3

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of	P	Document published on or after the declared priority date but before the filing date of this invention.

Intellectual Property Office

	same category.		
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[X] :

Worldwide search of patent documents classified in the following areas of the IPC

C07B; C07C; C25B

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC, INTERNET, CAS ONLINE, SEARCH-PATENT, SEARCH-NPL

International Classification:

Subclass	Subgroup	Valid From
C07B	0043/02	01/01/2006
C07C	0241/00	01/01/2006
C07C	0243/06	01/01/2006
C07D	0209/44	01/01/2006
C07D	0211/98	01/01/2006
C07D	0213/74	01/01/2006
C07D	0217/08	01/01/2006
C07D	0295/30	01/01/2006
C25B	0003/09	01/01/2021
C25B	0003/20	01/01/2021
C25B	0003/23	01/01/2021