



A Journal of



## Accepted Article

**Title:** A common, facile and eco-friendly method for the reduction of nitroarenes, selective reduction of poly-nitroarenes and deoxygenation of N-oxide containing heteroarenes

**Authors:** Angel Romero and Hugo Cerecetto

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.202000064

**Link to VoR:** <http://dx.doi.org/10.1002/ejoc.202000064>

Supported by



WILEY-VCH

# A common, facile and eco-friendly method for the reduction of nitroarenes, selective reduction of poly-nitroarenes and deoxygenation of *N*-oxide containing heteroarenes using elemental sulfur

Angel H. Romero,<sup>a\*</sup> Hugo Cerecetto<sup>a\*</sup>

<sup>a</sup>Laboratorio de Química Orgánica Medicinal, Instituto de Química Biológica, Facultad de Ciencias, Universidad de la Republica, Igual 4225, 11400 Montevideo, Uruguay.

**Corresponding Authors:** Prof. Dr. Angel H. Romero (E-mail: [angel.ucv.usb@gmail.com](mailto:angel.ucv.usb@gmail.com); <http://orcid.org/0000-0001-8747-5153>); Prof. Dr. Hugo Cerecetto (E-mail: [hcerecetto@gmail.com](mailto:hcerecetto@gmail.com); <https://orcid.org/0000-0003-1256-3786>)

**Abstract:** A transition metal-free, environment-friendly and practical protocol was developed either for the reduction of nitroarenes or for the deoxygenation of *N*-oxide containing heteroarenes. The reaction proceeded with the use of a non-toxic and cheap feedstock as elemental sulfur in aqueous methanol under relatively mild conditions. Green chemistry credentials were widely favorable compared to traditional and industrial protocols with good *E*-factors and a low production of waste. The strategy allowed the efficient reduction of a large variety of substituted-nitroarenes including various *o*-nitroanilines as well as selective reduction of various poly-nitroarenes in excellent yields with a broad substrate scope. The protocol was successfully extended to the deoxygenation of some *N*-oxide containing heteroarenes, like benzofuroxans, phenazine *N,N'*-dioxides, pyridine *N*-oxides, 2*H*-indazole *N*<sup>1</sup>-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides and benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides. A gram-scale example for the synthesis of luminol, in green conditions, was reported. A solid mechanism of reaction was proposed from experimental evidences.

**Keywords:** reduction, nitroarenes, *N*-oxide containing heteroarenes, deoxygenation, elemental sulfur, Green Chemistry.

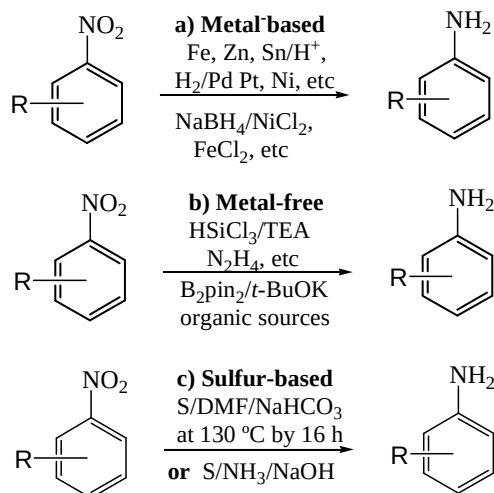
## Introduction

Nitroarenes and *N*-oxide containing heteroarenes are frequently encountered in the preparation of final product in organic chemistry, bioactive compounds and intermediates in the production of fertilizing, dyes, pigments, additives and polymers

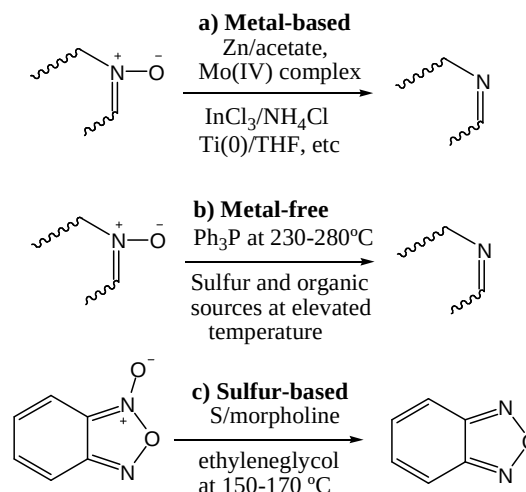
[1]. Traditionally, the most common methods for the synthesis of anilines, from the nitroarenes as starting materials, involves the use of large amounts of tin or zinc in presence of a Brønsted acid at high temperature (*e.g.* the Bechamp's reduction) [2]. This type of reduction is mediated by a direct electron transfer process from metal to nitro group. Alternatively, the reduction of nitroarene to aromatic amines can be achieved through two chemical processes: (i) catalytic hydrogenation or (ii) hydrogenation transfer. The first process requires the use of molecular hydrogen ( $H_2$ ) and catalytic amount of specific transition-metal (iron, nickel, palladium or platinum) under special pressure conditions [3], whereas the strategy based on hydrogenation transfer needs a hydrogen source such as hydrides (*e.g.*  $NaBH_4$  or hydrosilanes) [4,5], hydrazine hydrate [4,6], organic reagents (*e.g.* alcohol or formic acid) [4,7a-b] and more recently, boron reagents [7c-d]. Despite the strategies based on these two processes have found in the last two decades significant improvements from Green Chemistry point of view [4], the requirements of special high pressure equipment as well as the use of flammable hydrogen gas, hazardous reagents and sophistic organometallic complexes/nanometallic catalyst compromise the practicality and economy of these synthetic strategies. Other disadvantage of these traditional reductive processes (Beckman's reduction, catalytic hydrogenation and hydrogenation transfer) is its limited efficacy for the selective reduction of nitro group in polynitroarenes. In general, the selective reduction of polyarenes represents a challenge for chemist in organic synthesis field and a limited number of examples are found in literature. Some examples of reduction of 1,3-dinitrobenzene to 3-nitroaniline under catalytic hydrogenation conditions using specific metal nano-catalyst systems (PVP-Ru/ $Al_2O_3$ , Ru/C, Ru-SnOx/ $Al_2O_3$  or supported gold nanocatalyst) have recently reported [8a-c]. However, these modified catalytic hydrogenation strategies require a rigorous control of reaction condition to obtain the monoreduced product from polynitroarenes as well as sophistic and specific uncommon supported metal nanosystems are needed for a good selectivity. A more accessible procedure sulfur-based (sulfide, polysulfide or hydrosulfide) have been successfully employed to industrial level for the preparation of some monoreduced products from the corresponding polynitroarenes, requiring prolonged time and high temperature ( $>100$  °C) [8d-e]. Then, economic, efficient and eco-friendly synthetic methods using feedstock material are required for the selective reduction of polynitroarenes.

## I. Reduction of nitroarenes

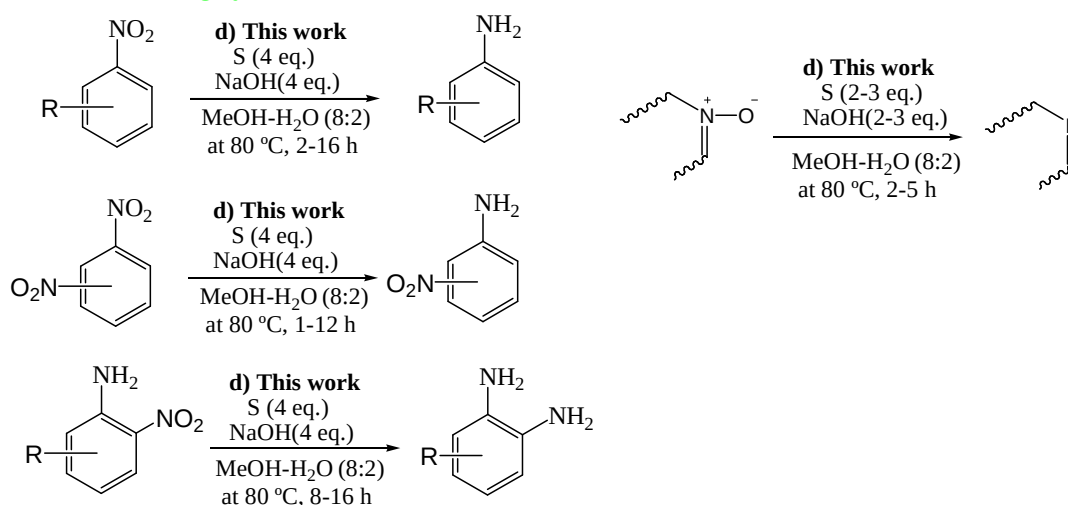
Previous works:

II. Deoxygenation of *N*-oxide containing heteroarenes

Previous works:



**Present work:** metal-free & eco-friendly sulfur as reductant & aqueous methanol & mild conditions & highly selective



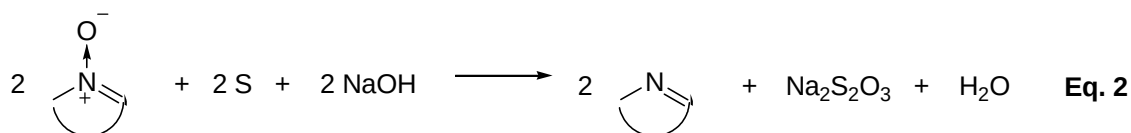
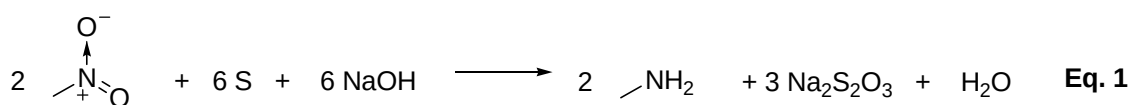
**Scheme 1.** Different methods for the reduction of aromatic nitro compounds and *N*-oxide containing heteroarenes and the methods described herein.

Regarding to the deoxygenation of *N*-oxide containing heteroarenes, a variety of non eco-friendly methods involving metals have been described [9]. Other non-metal methods involving the use of sulfur-derived reagents (*e.g.* sulfurous acid [10a], SO<sub>2</sub> [10b], sulfur monoxide [11], trimethyl(or triethyl)amine-SO<sub>2</sub> complex [12], di-*n*-propyl sulfoxylate [13] and CS<sub>2</sub> [14]), phosphorus-derived reagents (*e.g.* PCl<sub>3</sub> [15] and PPh<sub>3</sub> at high temperatures [16]) and other organic compounds [17,18] have been also reported for the deoxygenation of *N*-oxide containing heteroarenes. Many of these deoxygenation protocols are far on the Green Chemistry principles involving some drawbacks such as the generation of complex metallic waste, large quantities of the

reducing reagent, high temperatures, long reaction time, tedious purification procedure and the use of hazardous and expensive reagents. Curiously, there are a few methods applicable either for the reduction of nitroarenes or for the deoxygenation of *N*-oxide containing heteroarenes. Zinc dust-ammonium salt system has been utilized separately either for the reduction of nitroarenes or for the deoxygenation of *N*-oxide containing heteroarenes [19,20]. Tervalent phosphorus such as (EtO)<sub>3</sub>P [21,22] reduced efficiently *N*-oxide heteroarenes and, in some cases, it has been reported for reduction of nitroarenes. Recently, diboron reagents such as bis-(pinacolato)- and bis(catecholato)diboron also allowed efficiently the synthesis of anilines [23] and azaheterocycles [24] from nitroarenes and deoxygenation of *N*-oxide containing heteroarenes, respectively. Therefore, the design of a common, efficient and selective protocol involving the use of feedstock material as reductant and eco-friendly-safer solvent (water or aqueous solvent) under mild conditions is expected either for the reduction of nitroarenes to aminoarenes or for deoxygenation of *N*-oxide heteroarenes.

Elemental sulfur, a by-product of oil and gas industries, is an ideal raw material as reductant due to its abundance, low industrial cost (~120 USD per ton), high sulfur-atom content and lack of toxic by-products. Moreover, elemental sulfur is a user-friendliness reagent by its non-toxic, non-volatile, inodorous, non-hygroscopic, free-flowing and bench-stable properties. Elemental sulfur in combination with base has previously been used for the reduction of some nitroarenes; however, the reaction has proceeded under extreme conditions (high temperatures from 130 °C to 150 °C and prolonged time of reactions) with the use of hazardous reagents such as ammonia or environment unfriendly solvent such as DMF, that have a negative impact on the different ecosystems (Scheme 1) [25]. With regards to deoxygenation of *N*-oxide containing heteroarenes directed by elemental sulfur, a unique example has been reported for a limited number of deactivated benzofuroxans using morpholine as base and in ethylene glycol at extreme temperature from 145 °C to 160 °C [25e]. In order to enhance the efficacy of the elemental sulfur as reductant in these reductions, we believe that is crucial the optimization of redox process in solution. For this purpose, it is important to consider two features: (i) the use of a strong base (*e.g.* NaOH) to facilitate the oxidation of elemental sulfur to sulfur species with higher oxidation state (equations 1 and 2), (ii) the use of a polar solvent more similar to water (*e.g.* methanol or methanol-H<sub>2</sub>O mixtures) that allow to an efficient dissolution of the three components of the reaction, *i.e.* the inorganic base, the elemental sulfur and the starting organic

material. Then, taken into account: (i) these two mentioned issues and, (ii) the twelve Green-Chemistry principles, herein we reported a common and eco-friendly protocol either for the efficient and selective reduction of aromatic nitro compounds to the corresponding amines or for the deoxygenation of a variety of *N*-oxide containing heteroarenes, including benzofuroxans, phenazine *N,N'*-dioxides, pyridine *N*<sup>1</sup>-oxides, 2*H*-indazole *N*<sup>1</sup>-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides and 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides, to the corresponding reduced azaheteroarenes using a feedstock material as elemental sulfur in aqueous methanol milieu under relatively mild conditions. The present strategy represents an economical, practical and eco-friendly alternative to reported protocols either for the reduction of nitroarenes with a high selectivity to the monoreduction of polynitroarenes or for the deoxygenation of some *N*-oxide heteroarenes, in particular, benzofuroxans and phenazine *N,N'*-dioxides.



## Results and discussion

Our initial study was focused on the optimization of reduction of nitroarenes to anilines using as model 1,3-dinitrobenzene (1 equiv.), elemental sulfur (from 2 to 5 equiv.), in presence of NaOH (from 0 to 5 equiv.), in different solvents and mixtures (MeOH, H<sub>2</sub>O, DMF and different proportions of MeOH:H<sub>2</sub>O) at different temperatures and by 1 hour (Table 1). Optimization experiments were focused on the determination of minimal amounts of sulfur and base as well as on the selection of the best solvent for an accuracy reaction. Initially, working with an excess of sulfur and sodium hydroxide (4.0 equiv. respect to nitroarene and according to stoichiometry from Eq. 1), the optimization solvent results showed that methanol:water mixture in proportion 8:2 was the most convenient milieu of reaction producing the best yield of final product **2k** (82 %, entry 5). It was better than sole water, methanol or DMF (entries 1-3) and other aqueous methanol mixtures (entries 4, 6 and 7). For the best mixture of solvents, i.e. methanol:water (8:2), it was observed a homogeneous reaction milieu after the first 10

minutes initiated the heating with the complete dissolution of all inorganic and organic reagents, which probably facilitates the redox process shown in equation 1 and thus, the efficacy of the reaction. An incomplete dissolution of inorganic base was appreciated for the sole methanol or methanol:water 9:1 mixture, while a partial precipitation of organic substrate was detected for aqueous methanol with more than 20 % of water. Thus, the partial dissolution of any of the starting reagents may have an effect in the reaction efficacy for the mentioned methanol:water mixture as well as for sole methanol and water solvent (entries 1-2, 4, 6 and 7). Regarding to the minimal quantities of sulfur and base, the best reaction yields were obtained using four equivalent or more of both reagents (entries 5 and 8). The reactions were incomplete when less than 3 equivalents of both sulfur and base were used (entries 9-11). The particular requirement of excess in sulfur and NaOH (1 equivalent of excess according to Eq. 1) is associated to the disproportionation further reactions between sulfur and NaOH under heating to form thiosulfate and sulfur anions (see below in Eq. 7) as well as other collateral reactions (Eq. 8-10). On the other hands, the reaction temperature was crucially important, and temperatures between 80 °C and 90 °C are essentials (compare entry 5 to entries 12 and 13). Lowering the reaction temperature (*e.g.* 50 °C) led to the incomplete conversion of nitroarene to corresponding aniline (entry 12). Sodium hydroxide demonstrated to be the most optimal base over NaHCO<sub>3</sub> (compare entries 5 and 14), which confirm that the efficient sulfur transformation to oxidized sulfur species requires the use of a strong base. Under optimized conditions, the complete conversion of 1,3-dinitrobenzene was achieved in 1 hour. Then, the optimized reaction conditions for the reduction of other nitroarenes (1.0 equiv.) to the corresponding aniline were determined as the combination of elemental sulfur (4 equiv.) with NaOH (4 equiv) in a MeOH:water, 8:2, solvent mixture at 80 °C by 1-16 hours depending on nature of starting material (Table 2).

**Table 1.** Conditions optimization for the reduction of nitroarenes.<sup>a</sup>

Reaction scheme: 1,3-dinitrobenzene (1k)  $\xrightarrow[\text{solvent, T, 1 h}]{\text{S, NaOH}}$  3-nitroaniline (2k)

Entries	Solvent	NaOH eq.	Sulfur eq.	T (°C)	Yield (%) <sup>b</sup>
1	H <sub>2</sub> O	4	4	80	42
2	MeOH	4	4	80	45
3	DMF	4	4	80	62

4	MeOH-H <sub>2</sub> O (9:1)	4	4	80	70
5	<b>MeOH-H<sub>2</sub>O (8:2)</b>	<b>4</b>	<b>4</b>	<b>80</b>	<b>82</b>
6	MeOH-H <sub>2</sub> O (7:3)	4	4	80	79
7	MeOH-H <sub>2</sub> O (6:4)	4	4	80	61
8	MeOH-H <sub>2</sub> O (8:2)	5	5	80	80
9	MeOH-H <sub>2</sub> O (8:2)	3	3	80	70
10	MeOH-H <sub>2</sub> O (8:2)	2	2	80	51
11	MeOH-H <sub>2</sub> O (8:2)	0	4	80	0
12	MeOH-H <sub>2</sub> O (8:2)	4	4	50	30
13	MeOH-H <sub>2</sub> O (8:2)	4	4	90	83
14	MeOH-H <sub>2</sub> O (8:2)	4 <sup>c</sup>	4	80	52

<sup>a</sup>Reaction conditions: 1.0 mmol substrate **1a**, elemental sulfur (2-5 equiv.), and base (0-5 equiv.) in 6 mL of solvent.

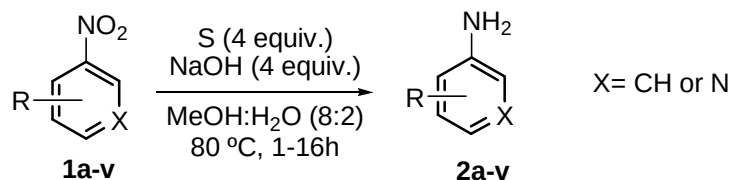
<sup>b</sup>Yield of isolated yields of pure product **2a**. <sup>c</sup>NaHCO<sub>3</sub> as base instead of NaOH.

With the optimal reaction conditions in hand, the scope of the reduction of aromatic nitro compounds was explored. The nitro group was chemoselectively reduced in the presence of a variety of electron-withdrawing and electron-donor groups on aromatic and heteroaromatic rings, affording the desired anilines, in general, in good to excellent yields (50 to 90 %) (entries 1-22, Table 2). Nitroarenes bearing electron-withdrawing groups, such as carboxylic acid, ketone, nitrile and nitro groups gave the desired anilines **2b-2d**, **2j** and **2k** in excellent yields and, in general, at lowest reaction time (1-3 hours) (entries 2-4 and 10 and 11, Table 2). The efficient and selective reduction of *p*-nitrobenzotrile to product **2d** represents a valuable result due to that nitrile group is not compatible with typical protocols including catalytic hydrogenation, hydride addition and Bechamp's reduction. The low reaction yield (38 %) obtained for the substrate **1c** (entry 3, Table 2), a ketone-nitroarene, may be associated to the generation of water-soluble by-products of auto-condensation and other compounds derived from oxidation of acetyl group by action of elemental sulfur, which has recently been reported for acetophenone derivatives [26]. On the other hands, nitroarenes bearing mesomeric electron-donor groups (*p*-mercapto, *p*-dimethylamino, *p*-methoxy) and 2-amino-substituted nitroarenes were efficiently reduced to their corresponding anilines in good to excellent reaction yields (70-88 %) at longer reaction time by about 8-16 hours (entries 5-7 and 17-19, Table 2). *p*-Nitrotoluene and *p*-nitrobenzylamine were incompatible for our protocol due to that a simultaneous oxidation of benzyl carbon was detected, giving a complex reaction mixture containing the corresponding benzaldehydes, benzylimines, anilines and the starting materials. These last findings were expected because it is well documented that the benzyl carbon in toluenes or benzyl derivatives bearing withdrawing groups (*e.g.* *o*-NO<sub>2</sub> or *p*-NO<sub>2</sub>) are susceptible to

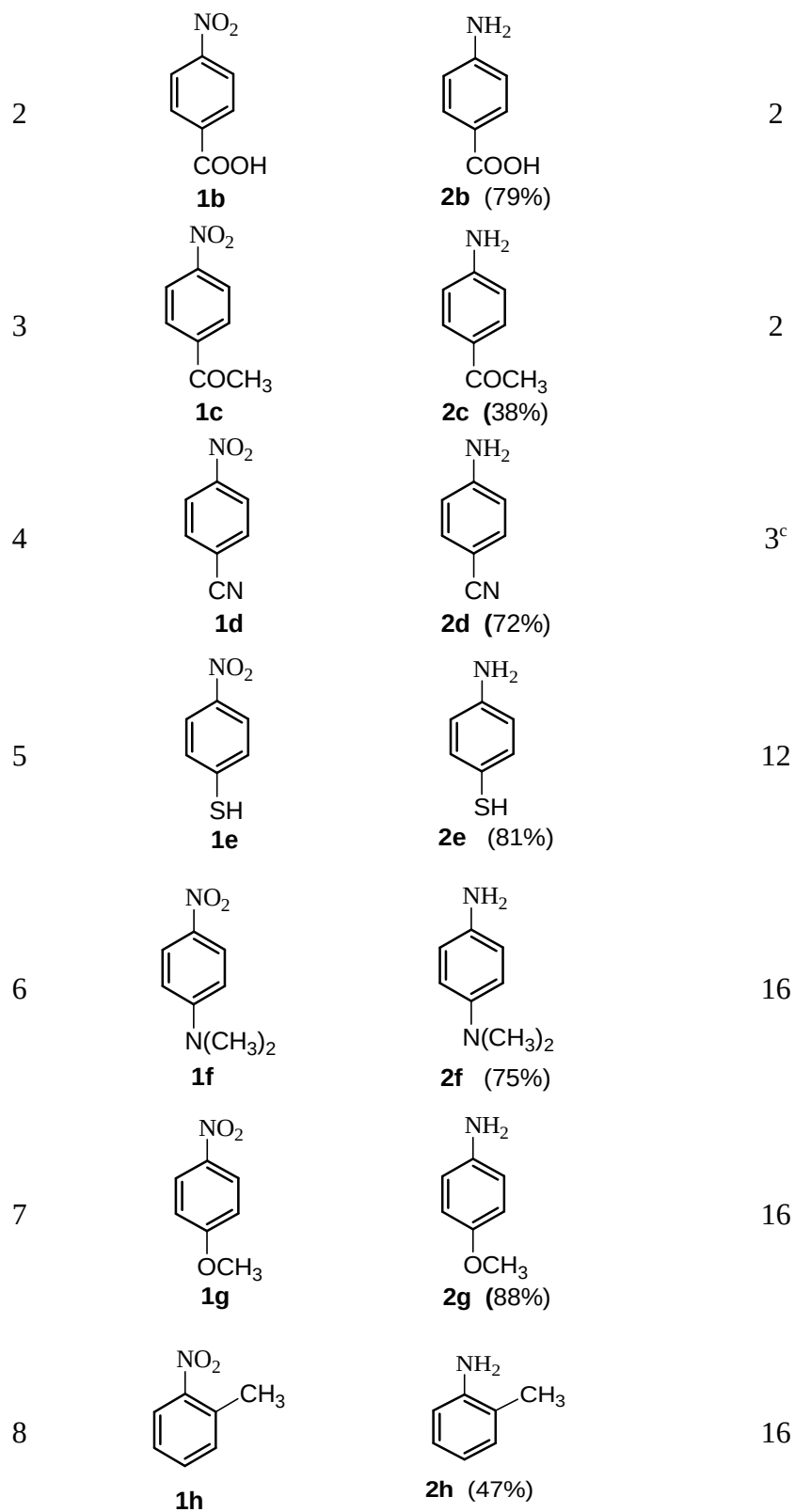


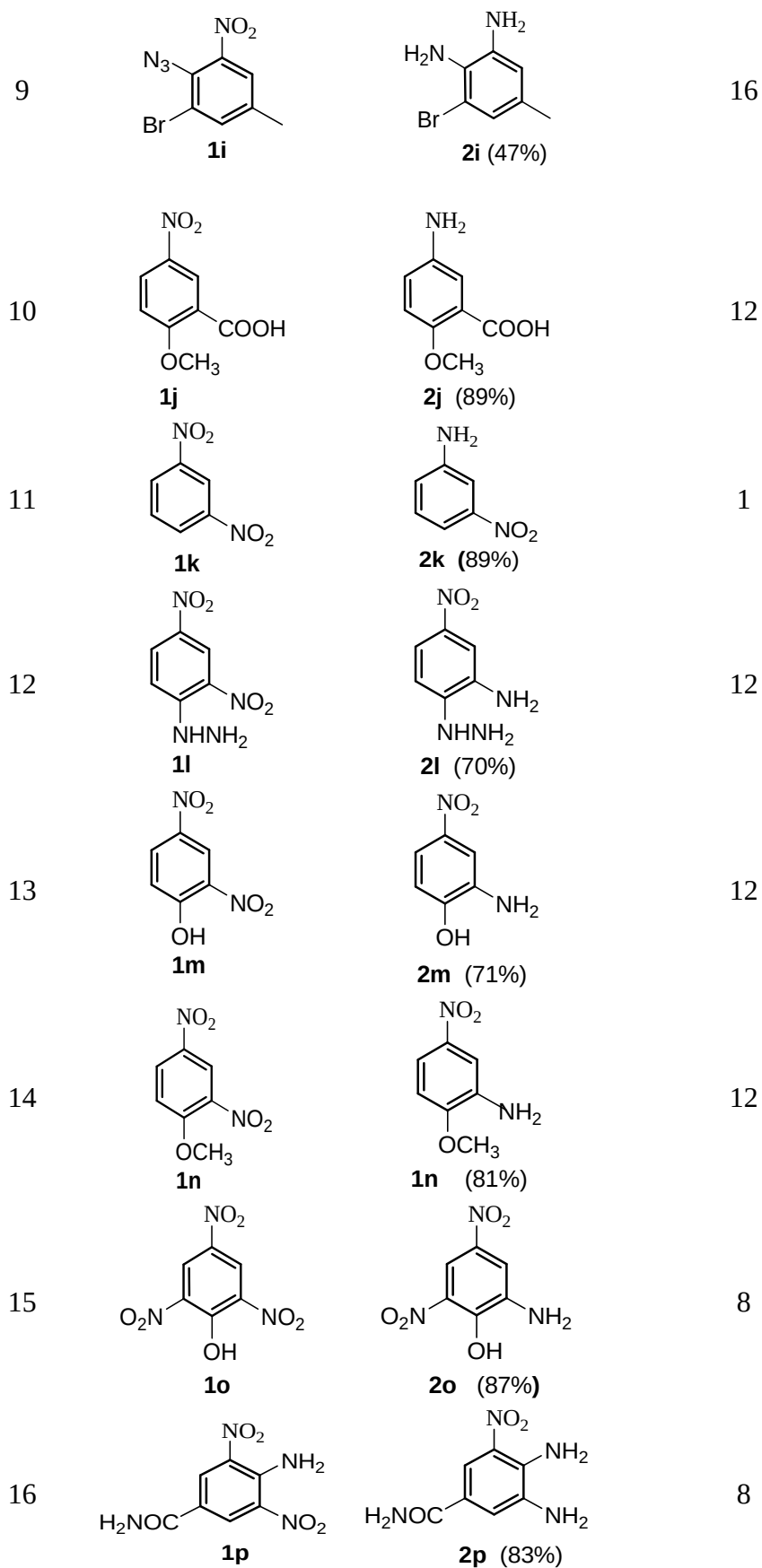
the oxidation by elemental sulfur action under basic conditions [26a, 27, 28]. Thus, a moderate reaction yield (47 %) of the desired product was obtained for the *o*-nitrotoluene (entry 8, Table 2) with the partial oxidation of methyl moiety, whereas a good conversion was found for the 3-methyl-nitroarene **1i** (entry 9, Table 2) without apparent oxidation of the corresponding methyl group. Nitro group into nitroarene bearing azide moiety is well reduced, but the strong basic conditions also reduced the azide group in an amino group (see entry 9, Table 2). Halogens at 3-position respect to nitro-moiety were well tolerated under reaction conditions (entries 9, 18, 19 and 21), proceeding with longer reaction times. Exotic moieties such as hydrazine and amide were suitable for the protocol (see entries 12 and 16, Table 2). The reductions of 4-nitrophenol and 2-nitrophenol to the corresponding anilines were not effective, even when increasing the equivalents of base and sulfur and extending the reaction time, which could be attributed to the acidity of the phenolic group and to the concomitant increase of the electron-donor ability of the phenol as phenoxide. Only polynitrophenols **1m** and **1o** afforded the reduced products (see entries 13 and 15, Table 2). Substituted heteroarenes such as 3-nitropyridines and nitro-1,4-phthalazindione also were compatible for our reduction protocol, obtaining excellent yields of desired product (85-88 %) (entries 20-22, Table 2). Finally, nitro-aliphatic and nitro-alkenyl derivatives (*e.g.* *trans*-nitrostyrene) were not suitable substrates for this nitro-reduction, which open the possibility to extend the current technique to the selective reduction of nitroarenes containing a nitro-alkyl or nitro-alkenyl chain.

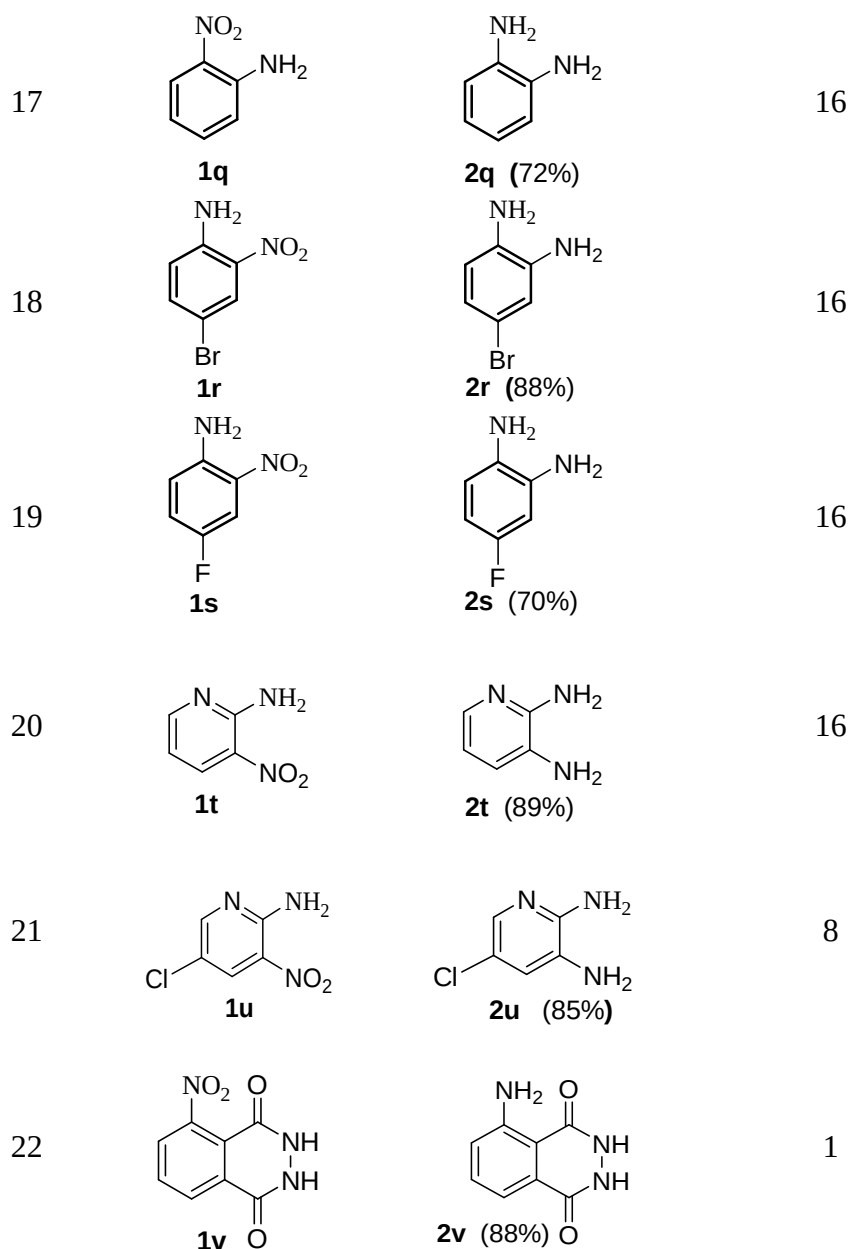
**Table 2.** Substrate scope for the reduction of nitro group in nitroarenes.<sup>a</sup>



Entry s	Nitroarenes <b>1a-v</b>	Aniline <b>2a-v</b> <sup>b</sup>	Time (h)
1		 <b>2a (82%)</b>	12



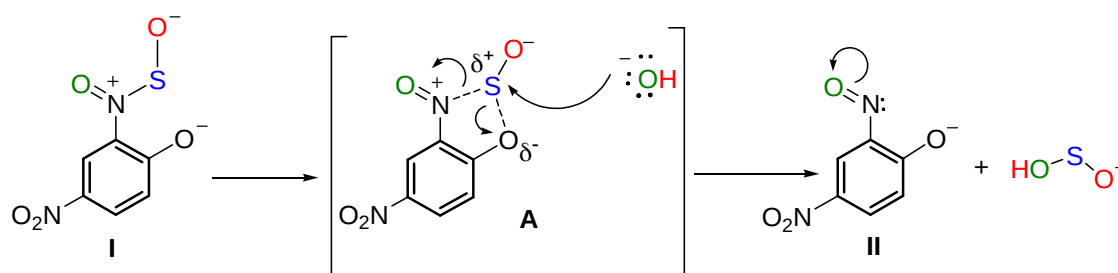




<sup>a</sup>**Reaction conditions:** To a solution of substrate **1a-v** (1.0-2.0 mmol) dissolved in methanol (5 mL), followed by a minimal amount of water (1 mL) was added elemental sulfur (4.0-8.0 mmol, 4 equiv.) and sodium hydroxide (4.0-8.0 mmol, 4 equiv.) and heated at 80 °C. <sup>b</sup>Isolated yields of pure product **2a-v** after purification. <sup>c</sup>Yield (%) determined from <sup>1</sup>H-NMR analysis of isolated product.

In order to extend the applicability of our protocol to typical challenge in reduction of nitro group, we worked on: (i) the selective reduction of a series of symmetric and asymmetric dinitrobenzenes (six examples, entries 11-16, Table 2) to the corresponding nitroanilines, and (ii) the reduction of *o*-nitroamines (six examples, entries 16-21, Table 2), a common toxic pollutant and harmful waste from industrial waste-water, to *o*-diamines. The protocol showed to be highly selective for a variety of asymmetrical 1-substituted-dinitrobenzenes, obtaining exclusively a mono-reduced product in excellent

yields at acceptable reaction time and with a good group tolerance (entries 11-16, Table 2). In particular, the nitro group *ortho* to the substituent (OH, OCH<sub>3</sub>, NHNH<sub>2</sub>, etc) was preferentially reduced in the asymmetrical 1-substituted-2,4-dinitrobenzenes, which is in concordance with the Zinnin's finding for asymmetrical polynitroarenes [29a-b]. A trinitroarene such as 2,4,6-trinitrophenol also was selectively reduced to the 2-amino-4,6-dinitrophenol in excellent yield (87 %) without evidences of any poly-reduced product. We think that the preferential reduction of *ortho*-nitro in these 1-substituted polyarenes may be associated to the extra reactivity that may bring substitutions possessing electron pair (OH, OCH<sub>3</sub>, NHNH<sub>2</sub>, etc) to the sulfur atom in intermediate **A** (Figure 1), a chelating structure generated under basic environment, which is a more stable intermediate than that formed from 4-nitrosubstitution. Recently, T.B. Nguyen and co-workers demonstrated that nitro-arenes have the ability to form the Ar-N(O)S(O) functionalization, which is stabilized by a nucleophilic vicinal *ortho*-carbanion to form sultams as a reaction stable product [29b]. This fact supports our proposal that *ortho*-electron donor possessing free electron pair may stabilize the intermediate X generated during reduction process mediated by elemental sulfur. In summary, the current technique emerges as an alternative for the selective reduction of polynitro-arenes: (i) to traditional methods (*e.g.* Bechamp's reduction, hydrazine-Pd/C reaction or catalytic hydrogenation), that are poorly selective giving mixture of reduced product or exclusively the di-reduced product (phenylendiamines) from 1,3-dinitrobenzenes [29c] and, (ii) to catalytic hydrogenation based on metal nano-catalyst [8a-c], which are in general tedious, costly, with further separation and waste disposal. In addition, for the selective reduction of polynitro-arenes, our protocol is significantly valuable from economical and environment point of view compared with industrial selective procedures sulfur-based (sulfide, polysulfide or hydrosulfide) by its low cost, low potential toxic effects, low corrosion impact and facile manipulation of elemental sulfur feedstock sources [8e-f] (see details in Supplementary material).



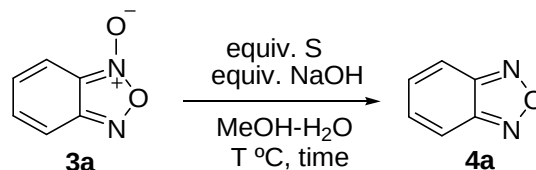
**Figure 1.** Proposed chelating intermediate X from an intramolecular *ortho* interaction (compound **1m** is used as model).

With regards to the reduction of *o*-nitroanilines, they were successfully reduced to give the corresponding *o*-phenyldiamines in excellent yields (> 70 %) with a good group tolerance (entries 16-21, Table 2), representing an attractive technique with a low environment impact to remove *o*-nitroanilines from industrial waste-water and other sources. Furthermore, it is important to mention that the isolating procedure to obtain the corresponding anilines was extremely simple and practical, requiring to evaporate the methanol, under vacuum, filter off the product from resulting aqueous solution and purified by flash chromatography whether is not sufficient pure from direct filtration (see details in Supporting material).

Next, we proceeded with the deoxygenation of a series of *N*-oxide containing azaheteroarenes including benzofuroxans, phenazine *N,N'*-dioxides, pyridine *N*-oxides, 2*H*-indazole *N*<sup>1</sup>-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides, and 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides. Optimization experiments were performed taken into account the optimal condition found for reduction of nitroarenes (see Table 1). Then, we initiated with the deoxygenation of benzofuroxans using benzofuroxan as model, elemental sulfur (2 equiv.) and sodium hydroxide (2 equiv.) in methanol:water (8:2) as solvent at 80-90 °C by 4-5 hours (entry 4, Table 3). Further optimization conditions including variable amount of sulfur (1-3 equiv.) and base (0-3 equiv.), temperature (50-90 °C) and time were investigated (entries 1-3 and 5-10, Table 3). Two equivalents of elemental sulfur and base were sufficient to afford a good conversion to the corresponding benzofurazan according to stoichiometry from Eq. 2 (entry 4, Table 3). An incomplete conversion of benzofuroxan substrate was appreciated when 1 equiv. of elemental sulfur and 1 equiv. of NaOH were employed (entry 7, Table 3). No reaction occurred in absence of base (entry 8, Table 3). Similarly to reduction of nitroarenes, aqueous methanol offered the best results being the methanol:water in proportion 8:2 the most convenient mixture, while a decrease in yield was appreciated for pure methanol (41 %), methanol:water (9:1) (72 %), methanol:water (7:3) (68 %) and pure water (0 %) as solvent (compare entries 1-5, Table 3). No detrimental impact on yield was observed when more than two equivalents (three or four equiv.) of both sulfur and base were used (i.e. entry 6, Table 3). Reaction time of three to six hours and temperature of 80 °C were found as the most convenient conditions for the total conversion of benzofuroxan (entries 9 and 10, Table 3). Next, having the optimized conditions in hand (2.0 equiv. of sulfur, 2.0 equiv. of NaOH in methanol:water (8:2) solvent at 80 °C by 5 hours), we investigated the

substrate scope of the transformation using a variety of substituted benzofuroxans (Table 4).

**Table 3.** Condition optimization for the deoxygenation of benzofuroxan.<sup>a</sup>



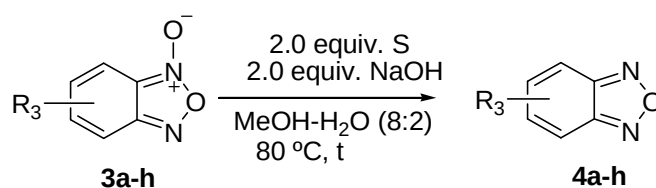
Entries	Solvent	NaOH eq.	Sulfur eq.	T (°C)	Yield (%) <sup>b</sup>
1	H <sub>2</sub> O	2	2	80	0
2	MeOH	2	2	80	41
3	MeOH-H <sub>2</sub> O (9:1)	2	2	80	72
<b>4</b>	<b>MeOH-H<sub>2</sub>O (8:2)</b>	<b>2</b>	<b>2</b>	<b>80</b>	<b>79</b>
5	MeOH-H <sub>2</sub> O (7:3)	2	2	80	68
6	MeOH-H <sub>2</sub> O (8:2)	3	3	80	74
7	MeOH-H <sub>2</sub> O (8:2)	1	1	80	59
8	MeOH-H <sub>2</sub> O (8:2)	0	2	80	0
9	MeOH-H <sub>2</sub> O (8:2)	2	2	50	22
10	MeOH-H <sub>2</sub> O (8:2)	2	2	90	78

<sup>a</sup>Reaction conditions: 1.0 mmol substrate **3a**, elemental sulfur (1-3 equiv.), and NaOH (0-3 equiv.) in solvent (6 mL).<sup>b</sup>Isolated yields of pure product **4a** from column chromatography.

In general, a good group tolerance was found for the deoxygenation of benzofuroxans with good to excellent reaction yields (from 54 % to 92 %). Some notable points can be noted from Table 4: (i) the protocol showed to be compatible for benzofuroxan bearing methyl and protected formyl groups (see entries 2, 7 and 8, Table 4), which is very interesting because it is well documented that they are sensitive to oxidize by the action of elemental sulfur under basic conditions [26,27,30,31]; (ii) lower reaction time for benzofuroxans bearing electron-withdrawing moieties were required, which put in evidence that electron-deficient benzofuroxan (3-4 h) are more reactive than electron-rich benzofuroxan (4-5 h); (iii) higher reaction yields were detected for benzofuroxans bearing electron-donor moieties (from 72 to 92 %) such as methyl, protected formyl or ethoxy moieties compared to benzofuroxans bearing electron-withdrawing groups (from 54 to 63 %), which may be associated to the partial decomposition of more reactive electron-deficient benzofurazans under basic conditions; (iv) small amount (by about 10%) of benzothiofuroxane (or benzo[*c*][1,2,5]thiadiazole) was identified from <sup>1</sup>H-NMR as by-product into all final mixture reactions. These results put in evidence that the appropriate selection of the solvent and base led a significant improvement in the reductive efficacy of elemental sulfur

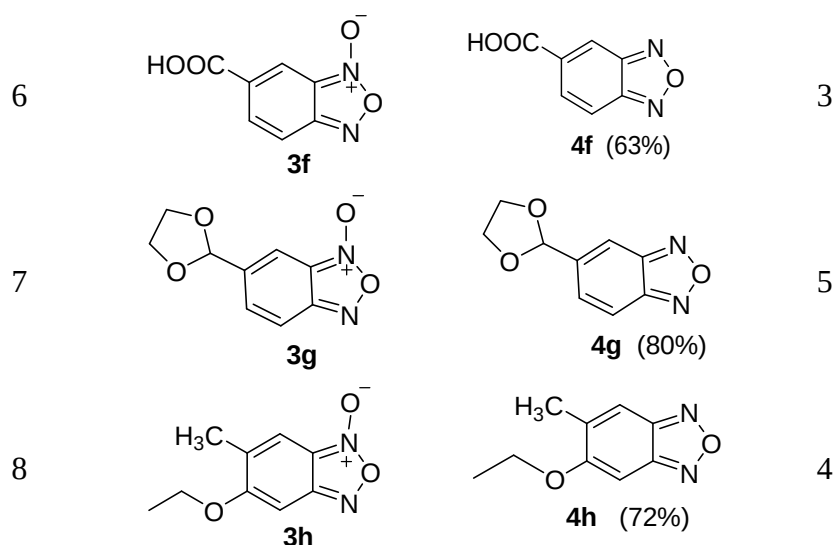
compared to other related sulfur-procedures. Moreover, comparison with traditional methods [32], our protocol represents a competitive and eco-friendly alternative for the deoxygenation of benzofuroxans to benzofurazans due to that many of them required the use of highly toxic reagents (*e.g.* trisubstituted phosphines and phosphites, and sodium azide), high cost of reagents, extreme conditions of temperature (between 140 and 250 °C), complex isolating procedure, the use of unfriendly solvent such as xylene, benzene or ethyleneglycol and the generation of toxic hazardous waste (*e.g.* explosive hydrazoic acid when azide reagent is used or phosphorus species when is used phosphines or phosphites).

**Table 4.** Substrate scope for the deoxygenation of benzofuroxans<sup>a</sup>



Entrie s	Substrate	Product <sup>b</sup>	Time (h)
1		 4a (79%)	4
2		 4b (92%)	5
3		 4c (54%)	4
4		 4d (61%)	3
5		 4e (78%)	4





**\*Reaction conditions:** To a solution of substrate **3a-h** (0.5-1.0 mmol) dissolved in methanol (5 mL), followed by a minimal amount of water (1 mL) was added elemental sulfur (1.0-2.0 mmol, 2 equiv.) and sodium hydroxide (1.0-2.0 mmol, 2 equiv.) at 80 °C. <sup>b</sup>Isolated yields of pure product **4a-h** after column chromatography or recrystallization.

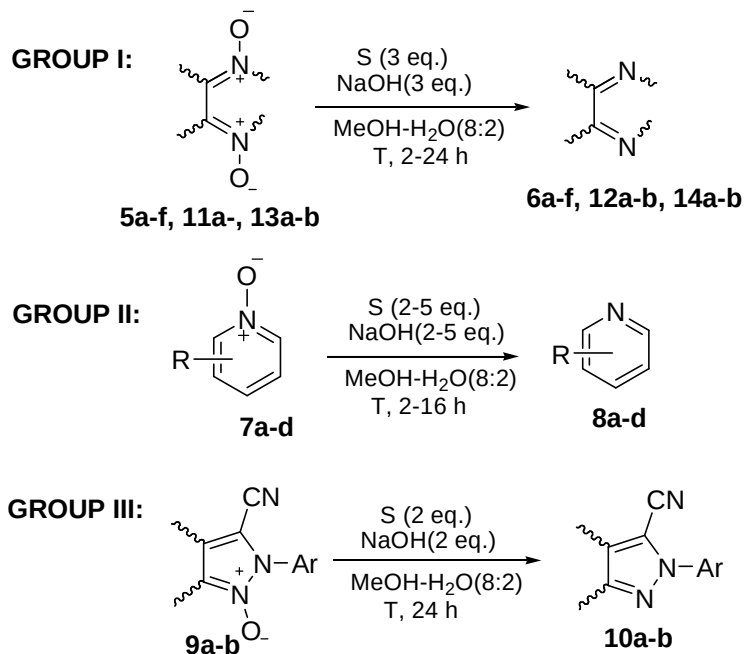
Regarding to the deoxygenation of phenazine *N,N'*-dioxides, pyridine *N*-oxides, 2*H*-indazole *N*<sup>1</sup>-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides and 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides, we performed the reaction using the optimized condition of the reduction of nitroarenes (see Table 1) and deoxygenation of benzofuroxans (Table 4), which in general employs NaOH as base, a methanol:water (8:2) mixture as solvent, a reaction temperature from 80 to 90 °C and elemental sulfur as reductant. Then, optimization experiments were focused on the determination of the minimal amounts of sulfur and NaOH for the reactions. Experiments revealed that three equivalent of elemental sulfur in combination with three equivalent of sodium hydroxide in methanol:water (8:2) at 80 °C were the optimal conditions for the deoxygenation of *N,N'*-dioxide containing heteroarenes (phenazine *N,N'*-dioxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides and 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides), while two equivalent of elemental sulfur and two equivalent of base are sufficient for the deoxygenation of pyridine *N*-oxides and 2*H*-indazole *N*<sup>1</sup>-oxides (Table 5). Similarly to previous reaction, herein the use of water resulted to be essentially important for a good efficacy of the deoxygenation of these five heterocyclic systems. A substrate scope was performed and general results are listed in Table 5. Results reflected the difference in reactivity among the five studied heterocyclic systems. In general, the phenazine *N,N'*-dioxides reacted notably faster than pyridine *N*-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides, 2*H*-indazole *N*<sup>1</sup>-oxides and 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides (compared entries 1-6 to entries 7-16). From scope phenazine, a series of 2-amino-substituted and 2-hydroxy-substituted phenazines were

prepared in good yield (73-95 %) under relatively mild conditions (entries 1-6, Table 5). It should be noted that substitution on both benzenic ring has an important effect on the reactivity of the phenazine dioxides. In particular, the substitution of an amine moiety by a hydroxyl moiety on phenazine ring reduced partially the reactivity to the deoxygenation (compared entry 1 with entry 5, Table 5). It is associated to the phenolic acid nature of hydroxyl group, which increase its electron-donor ability, reducing the reactivity of nitrogen atoms. The 2-hydroxyl-substituted phenazine required, in general, more reaction time than 2-amino-substituted phenazine dioxides. On the other hand, the incorporation of a methyl group at the 8-position of phenazine ring decreased the reactivity of the system, displaying a complex mixture of product constituting mainly by the starting material and by a product partially reduced of phenazine *N*-oxide (entry 4, Table 5) (see spectra in Supporting material). A high conversion was found for the 2-aminophenazine dioxides bearing bromine, fluorine and hydrogen at 8-position, giving the deoxygenated product in excellent yields (76-95 %) and relatively shorter reaction time (entries 1-3, Table 5). In particular, the fluorine atom attached at 8-position of phenazine dioxide **5b** reacted simultaneously with methoxy anion from reaction milieu to form the deoxygenated 2-amino-8-methoxyphenazine, which is expected due to the susceptibility of fluorine atom to aromatic nucleophilic substitution under basic conditions. As last example, a partially activated phenazine dioxides such as phenazine **5f** was less reactive toward the total deoxygenation than 2-aminophenazine *N,N'*-dioxides **5a-c**, requiring longer reaction time and generating a complex mixture between mono-reduced and deoxygenated derivatives (entry 6, Table 5).

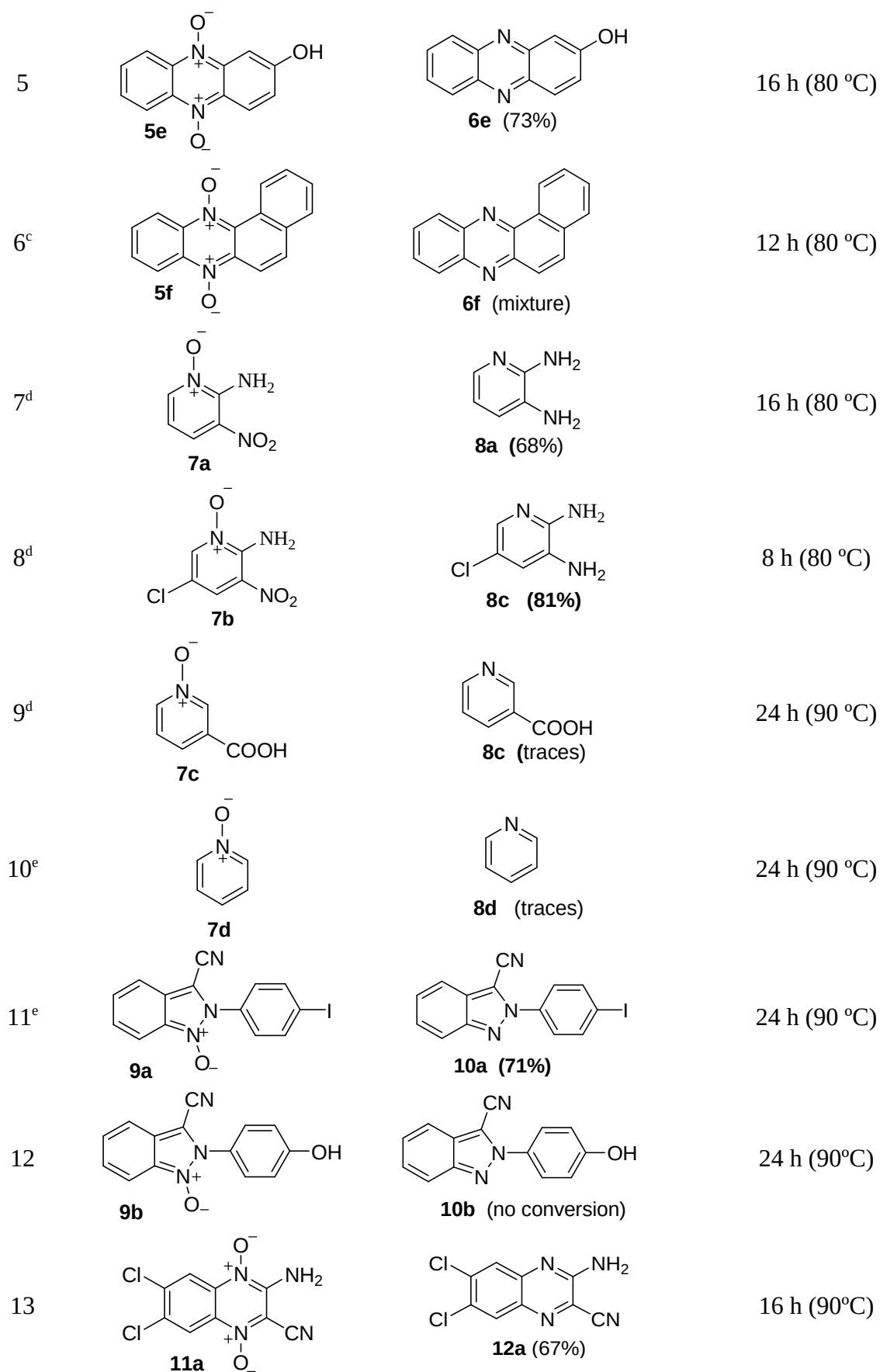
On other hands, some other azaheteroarenes *N*-oxides such as pyridine *N*-oxides, 2*H*-indazole *N*<sup>1</sup>-oxides, quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides and benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides showed a limited substrate scope. For examples, only pyridine *N*-oxides containing withdrawing NO<sub>2</sub>-moiety were compatible with the protocol (entries 7 and 8, Table 5), yielding the products with complete moiety-reductions (nitro and *N*-oxide groups), while other pyridine *N*-oxides were practically inert (entries 9 and 10, Table 5). Similar phenomenon was found for 2*H*-indazole *N*<sup>1</sup>-oxides and quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxides where the heterocyclic system bearing withdrawing moiety were significant more reactive (entries 11 and 13, Table 5), while electron-donor-substituted 2*H*-indazole *N*<sup>1</sup>-oxide **9b** and quinoxaline *N*<sup>1</sup>,*N*<sup>4</sup>-dioxide **11b** did not react under reaction conditions or more extreme ones. Finally, 2*H*-benzo[*d*]imidazole *N*<sup>1</sup>,*N*<sup>3</sup>-dioxides displayed an

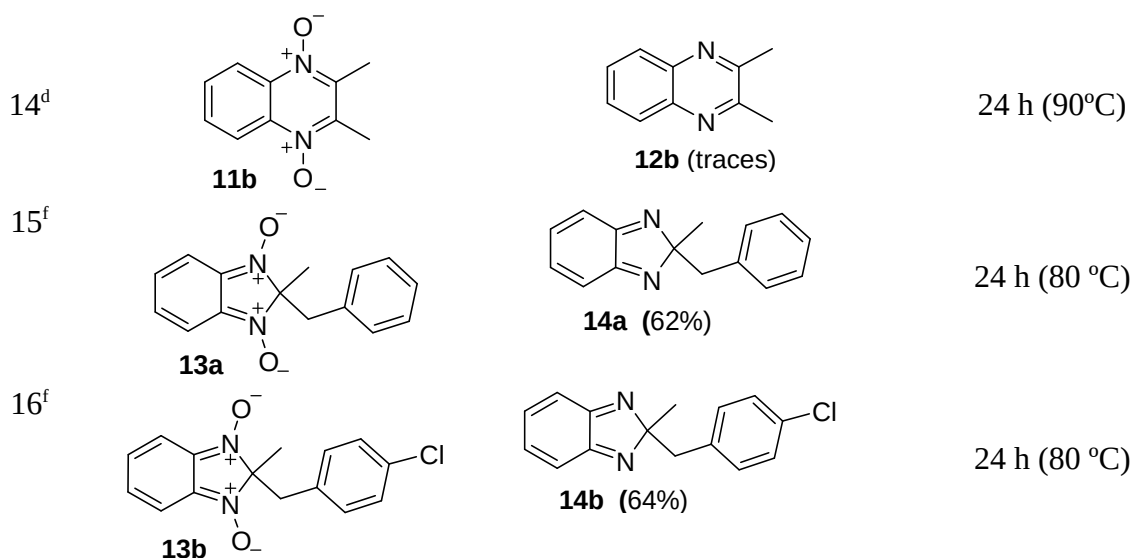
incomplete reaction after 24 h under over-reflux, giving near to 60 % of desired products according to  $^1\text{H-NMR}$  analysis (entries 15 and 16, Table 5).

**Table 5.** Substrate scope for the deoxygenation of *N*-oxide containing heteroarenes.<sup>a</sup>



Entries	Substrate	Product <sup>b</sup>	Time (temperature)
1			4 h (80 °C)
2			3 h (80 °C)
3			3 h (80 °C)
4			24 h (80 °C)



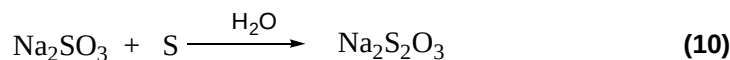
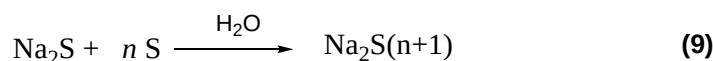
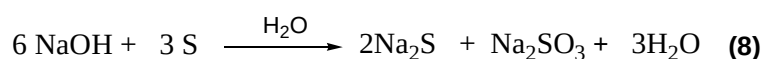
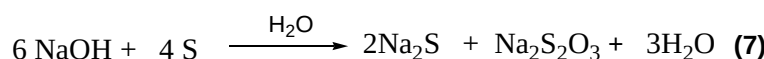
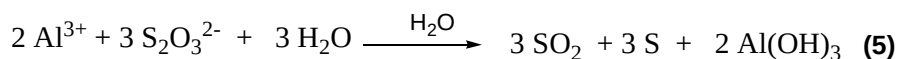
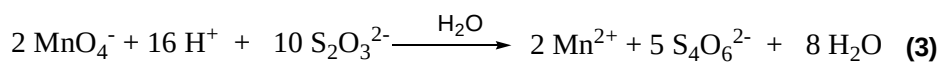


<sup>a</sup>**Reaction conditions:** To a solution of substrate (0.5-1.0 mmol) dissolved in methanol (5 mL), followed by a minimal amount of water (1 mL) was added corresponding elemental sulfur and sodium hydroxide at 80-90 °C.

<sup>b</sup>Isolated yields of pure product after column chromatography or recrystallization. <sup>c</sup>Yield from <sup>1</sup>H-NMR analysis. <sup>d</sup>5 equiv. of elemental sulfur and 5 equiv. of NaOH were used. <sup>e</sup>2 equiv. of elemental sulfur and 2 equiv. of NaOH were used. <sup>f</sup>Yield determined from <sup>1</sup>H-NMR analysis of isolated product.

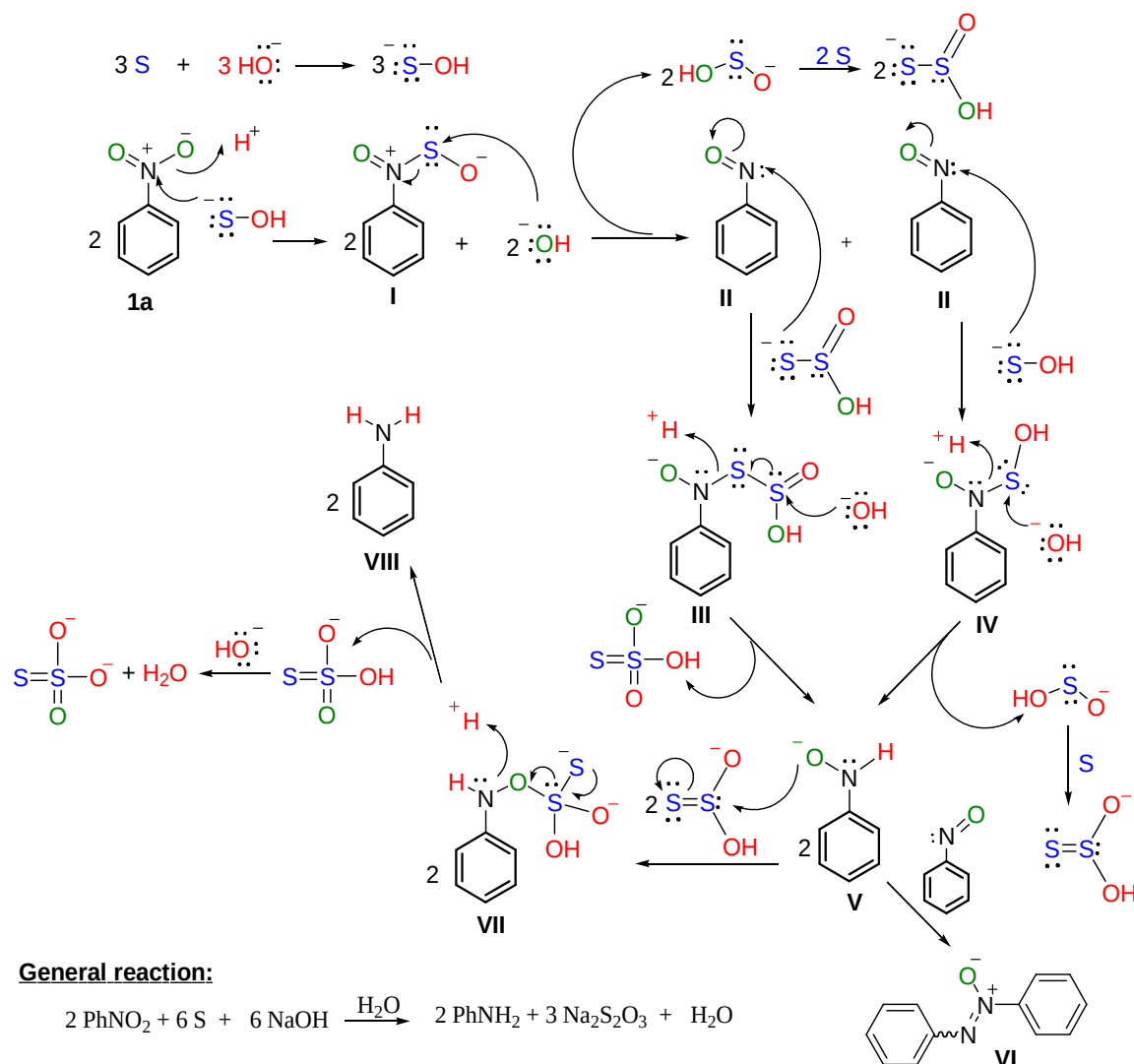
The mechanism of reaction proposed herein was inspired into previous findings derived from Zinnin's protocol for the reduction of nitroarenes [33]. In general, kinetic and analytical studies have identified to the nitroso-arene and hydroxylamine-arene as potential organic intermediates as well as to the thiosulfate as oxidized sulfur specie, both formed during the reaction [33]. With these principles in mind, we performed two groups of experiments: (i) focusing on the identification of sulfur anionic species formed post-reaction and, (ii) other focusing on the identification of organic intermediate species by *in situ* <sup>1</sup>H-NMR experiments. Firstly, the expected presence of thiosulfate anion (S<sub>2</sub>O<sub>3</sub><sup>2-</sup>) was confirmed by four analytical tests including: (i) permanganate discoloration test, (ii) iodine/iodide discoloration test, (iii) precipitation with aluminum (III) solution and, (iv) complexation with silver chloride [34a-d], which all these resulted positive according equations 3-6 for crude aqueous layers either from the reduction of 1,3-dinitrobenzene reduction or from the deoxygenation of benzofuroxan. Also, the presence of sulfur anion (S<sup>2-</sup>) was detected through the cadmium test. This sulfur anion can be derived from the disproportionation of elemental sulfur under strong basic and heating conditions according to Eq. 7 and 8 [34e]. The elemental sulfur may react with sulfide and sulfite anions generated from equations 7 and 8 accordingly to equations 9 and 10. These all reactions contribute to decrease the effective amount of elemental sulfur needed for the reduction processes, which obligates

to use a small excess of elemental sulfur for an optimal reduction of nitro-arenes or deoxygenation of *N*-oxide azaheteroarenes as was described in optimization experiments (see Tables 1 and 3).



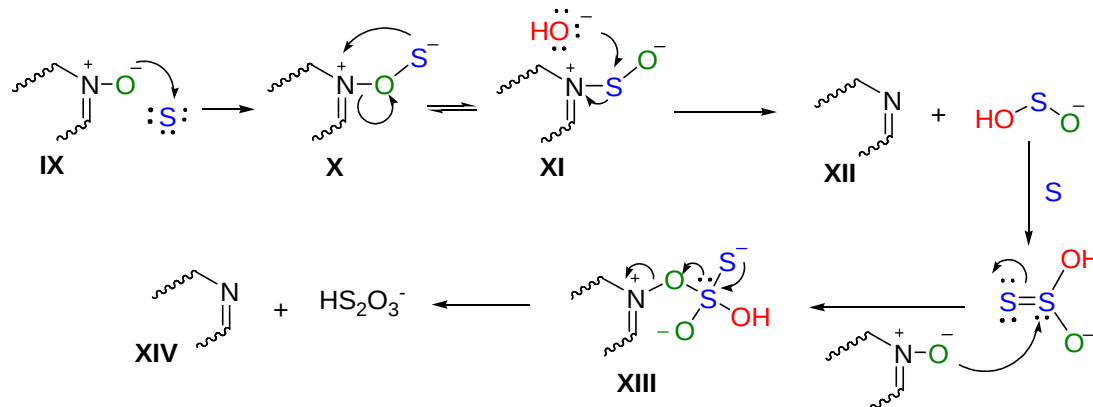
Regarding to the identification of organic intermediates, an experiment on resulting reaction mixture was performed for the incomplete reduction of *N,N'*-dimethyl-4-nitroaniline. This substrate was selected because it was the unique nitroarene in which it was possible to evidence the formation of several intermediates during reaction using TLC analysis. The reaction was stopped at 2 hour, solvent was evaporated and resulting crude was analyzed by a <sup>1</sup>H-NMR experiment. From <sup>1</sup>H-NMR spectra, the starting material, the aniline product, *N,N'*-dimethyl-4-hydroxylaminoaniline, a small amount of *N,N*-dimethyl-4-nitrosoaniline, and a good proportion of the diazene intermediate (see details and spectrum in Supporting information material) were identified. The chemical shifts of hydroxylamine, nitroso- and diazene intermediates are in concordance with typical data reported for analogues of them [35]. The detected diaryl diazene *N*-oxide intermediate is derived from coupling between the *N,N'*-dimethyl-4-hydroxylaminoaniline and *N,N*-dimethyl-4-nitrosoaniline, and its formation demonstrated that both reduced intermediates are formed during the studied reduction of nitroarenes (see Figure 2). The condensation between *N,N'*-dimethyl-4-hydroxylaminoaniline and *N,N'*-dimethyl-4-nitroso intermediates under a variety of reaction conditions has been widely reported [36]. It is important to mention that the diaryl diazene *N*-oxide intermediate was only detected for the reduction of *N,N'*-dimethyl-4-nitroaniline, which may be associated to the presence of the electron-donating group of dialkylamine, facilitating the nucleophilic attack from hydroxylamine nitrogen to nitroso nitrogen to

form the diaryl diazene *N*-oxide after dehydration process. Multiple small peak nearby to chemical shifts of all mentioned intermediates suggested that other short life-time intermediates containing sulfur may be involved into the formation of nitroso- and hydroxylamino-intermediates. The formation of intermediates containing N-S(O) bond has been previously reported for reduction of nitro group using sulfur reductant agents [29b, 37]. Then, with these all information in hand, we proposed a tentative mechanism of reaction for the reduction of nitroarenes (Figure 2). Firstly, elemental sulfur reacts with sodium hydroxide under heating in solution to form oxy-sulfur specie ( $\text{HO-S}^-$ ). The nucleophilic oxy-sulfur ( $\text{HO-S}^-$ ) anion attacks to positive nitrogen atom of nitro group in substrate **1a** to form an unstable sulfinyl-nitroso intermediate **I**, which releases nitrosoaryl intermediate **II** and hydro-sulfoxylate anion through a new nucleophilic attack of hydroxide anion to sulfur atom in intermediate **I**. Intermediate **II** may react: (i) with a nucleophilic thio-hydrosulfoxylate species [ $\text{HOS(O)S}^-$ ] (a thiosulfite anion) derived from reaction between the hydro-sulfoxylate ( $\text{HO-SO}^-$ ) anion and elemental sulfur to form an intermediate **III** or, (ii) with a nucleophilic oxy-sulfur to form intermediate **IV**. Then, intermediate **III** and **IV** are attacked by hydroxide anion on sulfur atom to form the hydroxylamino intermediate **V**, releasing thiosulfate and hydro-sulfoxylate anions, respectively. The hydro-sulfoxylate anion reacts with elemental to generate other molecule of thiosulfite anion. Finally, nucleophilic oxygen of hydroxylamine attack to sulfur atom of thiosulfite anion to form intermediate **VII**, which disproportionates to release the desired aniline **VIII** and two molecules of thiosulfate anion. During the reaction, three molecules of thiosulfate are formed by each two molecules of nitroarenes, requiring six equivalents of sulfur and six of hydroxide. The hydroxylamine intermediate **V** may react with the nitroso-arene intermediate **II** to display the diaryl diazene *N*-oxide intermediate **VI**. This last intermediate **VI** only was detected in the reduction of *N,N'*-dimethyl-4-nitroaniline. From proposal mechanism, it is clear that a strong base is essential to induce the first oxygenation of the elemental sulfur to form the oxy-sulfur anion, which is highly rich-electron specie to initiate the electron transfer to nitro group. Furthermore, the high nucleophilic power of hydroxide as well as the relative stability of S-O bond facilitates the formation of oxygenated sulfur species (*e.g.* thiosulfate) leading the reduction of oxidized nitrogen moieties. The reaction between oxygenated sulfur anions and elemental sulfur suggests that polar mixture solvent such as methanol-water that has the ability to dissolve partially both the elemental sulfur and hydroxide sodium is essential for an optimal redox process.

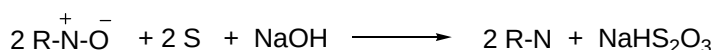


**Figure 2.** Plausible proposed mechanism of reaction for nitro-arenes (compound **1a** is used as model).

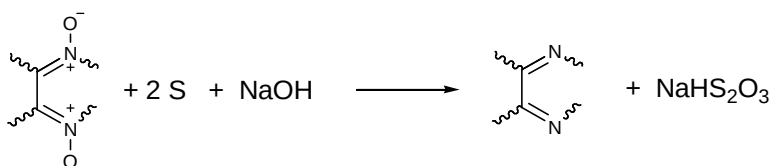




**General reaction for *N*-oxide azaheteroarenes:**



**General reaction for *N,N*-dioxide azaheteroarenes:**



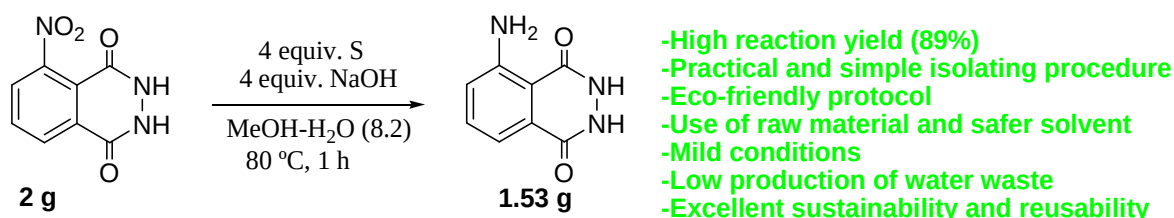
**Figure 3.** Plausible proposed mechanism for *N*-oxide azaheteroarenes.

Regarding to *N*-oxide containing azaheteroarenes, no intermediates were detected from the  $^1\text{H-NMR}$  experiments; however, we think that short-life sulfur intermediates may be involved in the deoxygenation of *N*-oxide heteroarenes. Initially, oxygen of *N*-oxide moiety of substrate **IX** (Figure 3) ensemble with empty orbital in elemental sulfur to form intermediate **X**, which may easily to release the sulfinyl intermediate **XI**. The formation of intermediate **XI** is well supported by the generation of thiobenzofurazan, which were detected for the deoxygenation of benzofuroxans. Subsequently, the desulfinylation of **XI** mediated by nucleophilic action of hydroxide anion lead to the desired heteroarene **XII** and hydrosulfoxylate anion according to Figure 3. A thio-hydrosulfoxylate derived from coupling between hydro-sulfoxylate ( $\text{HO-SO}^-$ ) and elemental sulfur may deoxygenate other *N*-oxide unit from other molecule of benzofuroxan or a second *N*-oxide unit in a dioxide derivative to form the reduced product **XIV**, passing by intermediate **XIII**. In particular, *N*-oxide containing heteroarene such as benzofuroxan, pyridine or indazole needed one equivalent of elemental sulfur by substrate, while the *N,N*-dioxides required two equivalents of elemental sulfur by substrate.

Next, we evaluated the green chemistry credentials for our protocol using *E*-factor (see details in Supporting information for calculations) [38]. In general, the protocol

presented good *E*-factor values from 3.26-7.85 for reduction of nitroarenes, from 1.98-3.01 for the deoxygenation of benzofuroxans and from 1.60-2.38 for the phenazine *N,N*-dioxides. A moderate *AE* value was obtained for the reduction of nitroarenes and deoxygenation of *N*-oxide containing heteroarenes. To evaluate the purity of the wastewater used as a solvent in our protocol, we analyzed through a simple <sup>1</sup>H-NMR experiment the resulting water mixture after reaction and the extraction with ethyl acetate. It should be noted that water solution was free of organic compounds, which demonstrated together to the good *E*-factor value the sustainability of the reaction (all these details can be seen in supporting information material). Furthermore, we demonstrated that resulting water solution can be re-used for further reduction of 1,3-dinitrobenzene using only two equivalents more of elemental sulfur and sodium hydroxide, putting in evidence the sustainability and reusability of the protocol.

To verify the scalability of the protocol, a gram-scale (2 g) synthesis of the luminol was performed (Figure 4). Luminol is a chemiluminescence agent that presents a variety of applications including the detection of ion concentrations in aqueous solutions [39], monitoring H<sub>2</sub>O<sub>2</sub>-dependent reactions [40] and the detection of blood at crime scenes [41]. In our conditions, the reaction proceeded during 1 hour under optimized conditions of reduction with an excellent yield by about 89 % and a facile and practical isolating procedure. Previous reports permitted the synthesis of luminol with moderate yield using sophisticated reagent such as dithionite or hazardous reagents such as ammonia and hydrogen sulfur [42]. Therefore, our protocol represents an efficient, competitive and eco-friendly procedure for the preparation of luminol to gram-scale.



**Figure 4.** A gram-scale example for the synthesis of Luminol.

## Conclusion

We developed a transition metal-free, practical and eco-friendly procedure for the reduction of nitroarenes and for the deoxygenation of *N*-oxide containing heteroarenes using a non-toxic and economical raw reducing agent such as elemental sulfur in aqueous methanol solvent under relatively mild conditions. Our protocol provide a

variety of important compounds in organic chemistry such as substituted anilines, benzofurazans, phenazines, pyridines, indazoles, quinoxalines and benzimidazoles, emerging as a powerful route to the synthesis of bioactive molecules and intermediates in organic chemistry. Compared to other reported method of reduction of nitroarenes and deoxygenation of *N*-oxide containing heteroarenes, the current protocol highlights by its simplicity, efficiency and eco-friendly characteristic with reduced compound manipulations in work-up and purification procedures. Finally, this strategy represents a valuable strategy for industrial applications in: (i) the preparation of valuable chemical agent such as luminol to a gram-scale in excellent yield (89 %), (ii) selective reduction of symmetric and asymmetric substituted dinitrobenzene to nitroanilines, and (iii) effective conversion of pollutant *o*-nitroaniline to *o*-diamines with good Green chemistry metrics.

### Acknowledgments

The authors thank to Facultad de Ciencias (Universidad de la República, Montevideo, Uruguay) and PEDECIBA-Química (Uruguay) for financial support. AH Romero thanks Agencia Nacional de Investigación e Innovación (ANII) by financial supports under code PD\_NAC\_2018\_1\_150515. Authors are also grateful with Horacio Pesaroglo and Gonzalo Hernández (NMR Laboratory, Facultad de Química, Universidad de la República) for the NMR spectra.

### Conflicts of interest

Authors declared not conflict of interest.

### Supplementary material

Full experimental details, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra associated with the all compounds obtained herein can be found in the online version of the Supplementary material.

### References

1. (a) S.A. Lawrence, *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004. (b) N. Ono, *The Nitro Group in Organic Synthesis*; Wiley: New York, 2001. (c) A.S. Travis, in *The Chemistry of Anilines*, ed. Z. Rappoport, Wiley, 2007, ch. 13, pp. 715–782; (d) A. Albin, *Synthesis* 1993, 263.
2. A. Béchamp, *Annales de chimie et de physique* 1854, **42**, 186.
3. (a) P.N. Rylander, *Hydrogenation Methods*; Academic: New York, 1985. (b) M. Hudlicky, *Reductions in Organic Chemistry*; Ellis Horwood Ltd: Chichester, 1984, 1. (c) G.V. Smith, F. Nothessiz, *Heterogeneous Catalysis in Organic Chemistry*; Academic: New York, 1999, 71. (d) [J. Song, Z.F. Huang, L. Pan, K. Li, X. Zhang, L. Wang, J.J. Zou](#), *Applied Catalysis B: Environmental*, 2018, **227**, 386. (e) H.U. Blaser, H. Steiner, M. Studer, *ChemCatChem*. 2009, **1**, 210. (f) C. Campos, T. Cecilia, M. Oportus, M.A. Pena, J.L.G. Fierro, P. Reyes, P. *Catal. Today*, 2013, **213**, 93. (g) [Y. Sun, A.J. Darling, Y. Li, K. Fujisawa, C.F. Holder, H. Liu, M.J. Janik, M. Terrones, R.E. Schaak](#), *Chem. Sci.*, 2019, **10**, 10310.
4. D. Formenti, F. Ferretti, F. Korbinian Scharnagl, M. Beller, *Chem. Rev.* 2019, **119**, 2611.
5. (a) K. Junge, B. Wendt, N. Shaikh, M. Beller, *Chem. Commun.* 2010, **46**, 1769. (b) P.K. Mandal, J.S. McMurray, *J. Org. Chem.* 2007, **72**, 6599. (c) M. Paul, N. Pal, A. Bhaumik, *Eur. J. Inorg. Chem.* 2010, 5129. (d) T. V. Nykaza, J. C. Cooper, G. Li, N. Mahieu, A. Ramirez, M. R. Luzung, A. T. Radosevich, *J. Am. Chem. Soc.*, 2018, **140**, 15200. (e) M. Orlandi, F. Tosi, M. Bonsignore, M. Benaglia, *Org. Lett.* 2015, **17**, 3941. (f) M. Orlandi, M. Benaglia, F. Tosi, R. Annunziata, F. Cozzi, *J. Org. Chem.* 2016, **81**, 3037. (g) M. Orlandi, F. Tosi, M. Bonsignore, M. Benaglia, *Org. Lett.* 2015, **17**, 16, 3941-3943. (h) D. Porwal, M. Oestreich, *Eur. J. Org. Chem.* 2016, 2016, 3307.
6. (a) Q. Shi, R. Lu, L. Lu, X. Fu, D. Zhao, *Adv. Synth. Catal.* 2007, **349**, 1877. (b) J.K. Niemeier, D.P. Kjell, *Org. Process Res. Dev.* 2013, **17**, 1580. (c) [F. Li, B. Frett, H. Li](#), *Synlett*, 2014, 1403. (d) R.V. Jagadeesh, G. Wienhofer, F.A. Westerhaus, A. Surkus, M. Pohl, H. Junge, K. Junge, M. Beller, *Chem. Commun.* 2011, **47**, 10972. (e) [B. Lakshminarayana, G. Satyanarayana](#), C. Subrahmanyam, *ACS Omega*, 2018, **3**, 13065.
7. (a) D. Giomi, R. Alfini, A. Brandi, *Tetrahedron* 2011, **67**, 167. (b) M. Miyagawa, R. Yamamoto, N. Kobayashi, T. Akiyama, *Synlett*, 2019, **30**, 499. (c) D. Chen, Y. Zhou, H. Zhou, S. Liu, Q. Liu, K. Zhang, Y. Uozumi, *Synlett*, 2018, 29, 1765. (d) H. Hosoya, L.C.M. Castro, I. Sultan, Y. Nakajima, T. Ohmura, K. Sato, H. Tsurugi, M. Sugimoto, K. Mashima, *Org. Lett.* 2019, 21, 9812.
8. (a) S.K. Maity; N.C. Pradhan; A.V. Patwardhan, *Chemical Eng. J.* 2008, **141**, 187. (b) S.L. Zhao; H.D. Liang; Y.F. Zhou, *Catal. Commun.* 2007, **8**, 1305. (c) J. Hou; Y.H. Ma; Y.H. Li; F. Guo; L.H. Lu, *Chem. Lett.* 2008, **37**, 974. (d) US Patent N° 2669584, Selective reduction of polynitro aromatics, 1954. (e) J.P. Idoux, *J. Chem. Soc. (C)*, 1970, 435.
9. Some a few examples: (a) S. Kumar; A. Saini; J.S. Sandhu. *Tetrahedron Lett.* 2005, **46**, 8737. (b) A. Saini; S. Kumar; J.S. Sandhu. *Synlett* 2006, 395. (c) Y. Wang; J.H. Espenson. *Org. Lett.* 2000, **2**, 3525.
10. (a) E. Hayashi, E. Ijima, *Ch. Yakugaku Zasshi* 1962, **82**, 1093. (b) F.A. Daniher, B.E. Hackley Jr., *J. Org. Chem.* 1966, **31**, 4267.
11. B.F. Bonini, G. Maccagnani, G. Mazzanti, P. Pedrini, *Tetrahedron Lett.* 1979, **20**, 1799.
12. G.A. Olah, M. Arvanaghi, Y.D. Vankar, *Synthesis*, 1980, 660.

13. H. Kagami, S. Motoki, *J. Org. Chem.* 1978, **43**, 1267.
14. T. Yoshimura, K. Asada, S. Oae, *Bull. Chem. Soc. Jpn.* 1982, **55**, 3000.
15. W.B. Lutz, S. Lazarus, S. Klutchko, R.I. Meltzer, *J. Org. Chem.* 1964, **29**, 1645.
16. E. Howard Jr., W.F. Olszewski, *J. Am. Chem. Soc.* 1959, **81**, 1483.
17. M. Takeshita, S. Yoshida, *Heterocycles* 1990, **30**, 871.
18. H.R. Bjørsvik, C. Gambarotti, V.R. Jensen, R.R. Gonzalez, *J. Org. Chem.* 2005, **70**, 3218.
19. S. M. Kelly, B. H. Lipshutz, *Org. Lett.*, 2014, **16**, 98.
20. R. Balicki, M. Cybulski, G. Maciejewski, *Synth. Commun.* 2003, **33**, 4137.
21. J.I.G. Cadogan, M. J. Todd, *J. Chem.Soc. C :Organic*, 1969, 2808. (b) R.J. Sundberg, W.G. Adams, R.H. Smith, D.E. Blackburn *Tetrahedron Lett.* 1968, 777.
22. P.H. Scott, C.P. Smith, E. Rober, J.W. Churchill, *Tetrahedron Lett.* 1970, 1153.
23. H. Lu, Z. Geng, J. Li, D. Zou, Y. Wu, Y. Wu, *Org. Lett.* 2016, **18**, 2774.
24. H.P. Kokatla, P.F. Thomson, S. Bae, V.R. Doddi, M.K. Lakshman, *J. Org. Chem.* 2011, **76**, 7842.
25. (a) N.J. Hirao, *Osaka Inst. Sci. Technol.* 1950, **1**, 57.(b) K. Niknam, A.R. Kiasat, F. Kazemi, A. Hossieni, *Phosphorus, Sulfur Silicon Relat. Elem.* 2003, **178**, 1385. (c) A. McLaughlin, D.M. Barnes, *Tetrahedron Lett.* 2006, **47**, 9095. (d) Q. Shuai, J. Li, F. Zhao, W. Su, G. Deng, *Chemical Papers*, 2019, **73**, 965-975. (e) I.Z. Kondyukov, Y.V. Karpichev, P.G. Belyaev, G.K. Khisamutdinov, S.I. Valeshnii, S.P. Smirnov, V.P. Il'in, *Russian J. Org. Chem.* 2007, **43**, 635.
26. (a) K. Wang, D. Kim, A. Dçmling, *J. Comb. Chem.* 2010, **12**, 111. (b) A. Rais, H. Ankati, E. Biehl, *J. Heterocycl. Chem.* 2009, **46**, 599. (c) A.Y. Solovyev, D.A. Androsov, D.C. Neckers, *J. Org. Chem.* 2007, **72**, 3122; (d) D.A. Androsov, A.Y. Solovyev, M.L. Petrov, R.J. Butcher, J.P. Jasinski, *Tetrahedron* 2010, **66**, 2474.
27. (a) T.B. Nguyen, *Adv. Synth. Catal.* 2017, **359**, 1066. (b) F.H. McMillan, *J. Am. Chem. Soc.* 1948, **70**, 868. (b) T.B. Nguyen, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* 2012, **14**, 4274. (c) M.K. Denk, S. Gupta, J. Brownie, S. Tajammul, A.J. Lough, *Chem. Eur. J.* 2001, **7**, 4477.
28. (a) D. Kadzimirsz, D. Kramer, L. Sripanom, I. M. Oppel, P. Rodziejewicz, N. L. Doltsinis, G. Dyker, *J. Org. Chem.* 2008, **73**, 4644. (b) A. Poser, R. Lohmayer, C. Vogt, K. Knoeller, B. Planer-Friedrich, D. Sorokin, H. H. Richnow, K. Finster, *Extremophiles* 2013, **17**, 1003. (c) T.B. Nguyen, L. Ermolenko, W. A. Dean, A. Al- Mourabit, *Org. Lett.* 2012, **14**, 5948.
29. (a) H. K. Porter, "The Zinin Reduction of Nitroarenes," *Organic Reactions* 1973, **20**, 455. (b) T. B. Nguyen, P. Retailleau, *Org. Lett.* 2017, **19**, 3879. (c) E. F. Lejarazo Gómez, E. Santos Santos, S. Suarez Torres, *J. Chem. and Chemical Eng.* 2018, **12**, 74.
30. (a) R. Mayer, K. Gewald, *Angew. Chem. Int. Ed. Engl.* 1967, **6**, 294. (b) O.I. Zubruyev, N. Stiasni, C. O. Kappe, *J. Comb. Chem.* 2003, **5**, 145. (c) B. Bottcher, F. Bauer, *Justus Liebigs Ann. Chem.* 1950, **568**, 218. (d) H. Xu, H. Deng, Z. Li, H. Xiang, X. Zhou, *Eur. J. Org. Chem.* 2013, 7054. (e) S. Tandel, I. Bliznets, K. Ebinger, Y.A. Ma, D. Bhumralkar, M. Thiruvazhi, *Tetrahedron Lett.* 2004, **45**, 2321. (f) F. Shibahara, R. Sugiura, E. Yamaguchi, S. Kitagawa, T. Murai, *J. Org. Chem.* 2009, **74**, 3566.
31. (a) T. B. Nguyen, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* 2013, **15**, 4218. (b) A. Samzadeh-Kermani, *Synlett*, 2015, **26**, 643. (c) H. Xie, J. Cai, Z. Wang, H. Huang, G. Deng, *Org. Lett.* 2016, **18**, 2196.(d) B. Eftekhari-Sis, S.V. Khajeh, O. Buyukgungor, *Synlett*, 2013, **24**, 977. (e) A.O. Lifshits, P.N.

- Ostapchuk, V.K. Brel, *Russ. J. Org. Chem.* 2015, **51**, 744; (f) R. Wegler, E. Kghle, W. Schfer, *Angew. Chem.* 1958, **70**, 351
32. (a) J.H. Boyer, S.E. Ellzey, *J. Org. Chem.*, 1961, **26**, 4684. (b) S. Merritt, S. Di Pierto, S.W. Hand, *J. Chromatogr.*, 1975, **112**, 301. (c) F.B. Mellory, S.P. Varimbi, *J. Org. Chem.*, 1963, **28**, 1656. (d) F.S. Levinson, M.I. Evgenev et al. *Chemical & pharmaceutical journal*, 2003, **37**, 12. (e) A.S. Baily, J.M. Evans, *J. Chem. Soc. S.*, 1967, №21, r.2105-2109. (f) L. Di Nunno, S. Florio, *Chem. E ind (Ital)*, 1957, **57**, 243. (g) L. Di Nunno, S. Florio, *J. Chem. Soc. Perkin Trans.*, 1973, **1**, 1954.
33. (a) H.U. Blaser, *Science*, 2006, **313**, 312. (b) P.L. Breuer, M.I. Jeffrey, *Hydrometallurgy*, 2003, **70**, 163. (c) S.K. Maity, N.C. Pradhan, A.V. Patwardhan, *Applied Catalysis A: General*, 2006, **301**, 251. (d) G.D. Yadav, Y.B. Jadhav, S. Sengupta, *Chemical Engineering Science*, 2003, **58**, 2681.
34. (a) T.R. Dulki (1996) "Ch.8: Separation by precipitation", A manual for the chemical Analysis of Metals, West Conshohocken, p 99. (b) A.F. Holleman, E. Wiberg, N. Wiberg (2001), *Inorganic Chemistry*, San Diego, Academic Press. (c) H.M. Gordin (1913), "Elementary Chemistry, Vol. 1. (d) T. Lister, (1945), "Classic chemistry demonstration", (London; The Royal Society of Chemistry). (e) D.G. Oei, *Inorg. Chem.*, 1973, **12**, 438.
35. (a) For aryl-nitroso derivatives: comparison with 4-ethyl nitrobenzene analogue, B. Priewisch, K. Rück-Braun, *J. Org. Chem.* 2005, **70**, 6, 2350. (b) For aryl-hydroxylamine derivatives: comparison with 4-methoxy nitrobenzene analogue, [Y. Takenaka](#), [T. Kiyosu](#), [J.C. Choi](#), [T. Sakakura](#), [H. Yasuda](#), *Green Chem.* 2009, **11**, 1385. (c) For diaryl diazene N-oxide and aryl-nitroso derivatives: comparison with diphenyl diazene N-oxide, F. Tripoteau, L. Eberlin, M.A. Fox, B. Carboni, A. Whiting, *Chem. Commun.*, 2013, 49, 5414.
36. (a) W.W. Wood, J.A. Wilkin, *Synth. Comm.* 1992, **22**, 1683. (b) S. Liu, Y. Hao, J. Jiang, *Ind. Eng. Chem. Res.* 2014, **53**, 8372. (c) H. Tao, X.C. Liu, J.H. Su, Y.X. Wang, X.M. Gu, D.J. Yang, E.R. Waclawik, H.Y. Zhu, Z.F. Zheng, *Sci. Rep.* 2019, **9**, 1280. (d) H.U. Blaser, H. Steiner, M. Studer, *ChemCatChem*, 2009, **1**, 210. (e) W. Anderson, *J. Chem. Soc.*, 1952, 1722.
37. A.H. Romero, J. Salazar, S.E. López, *Synthesis*. **2013**, 45, 2043-2050.
38. R.A. Sheldon, *ACS Sustain. Chem. Eng.* 2018, **6**, 32.
39. T. Nieman, In *Chemiluminescence and Photochemical Reaction Detection in Chromatography*; Birks, J. W., Ed.; VCH: New York, 1989, pp 99-123.
40. J. Yuan, A.M. Shiller, *Anal. Chem.* 1999, **71**, 1975.
41. E.J.M. Kent, D.A. Elliot, G.M. Miskelly, *J. Foren. Sci.* 2003, **48**, 64.
42. (a) E. Huntress, L. Stanley, A. Parker, *J. Am. Chem. Soc.* 1934, **56**, 241. (b) K.L. Williamson, In *Macroscopic and Microscale Organic Experiments*; 2nd ed.; D.C. Heath: Lexington, MA, 1994, pp 153-162. (c) E.H. White, K. Matsuo, *J. Am. Chem. Soc.*, 1967, **32**, 1921.