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To be cited as: *Chem. Eur. J.* 10.1002/chem.201605359

Link to VoR: http://dx.doi.org/10.1002/chem.201605359

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10.1002/chem.201605359
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Sustainable synthesis of balsalazide and sulfasalazine based on diazotization with low concentrated nitrogen dioxide in air

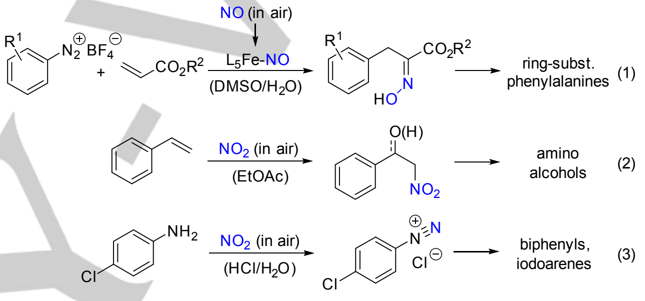
Dagmar Hofmann, Eva Gans, Jasmin Krüll and Markus R. Heinrich*[a]

Dedication ((optional))

Abstract: Low concentrated nitrogen dioxide, which arises as side product from a range of industrial processes, can effectively be recycled through the diazotization of anilines. The studies reported herein now demonstrate that the removal of nitrogen dioxide from gas streams is even more effective when hydrophilic anilines are used as starting materials. The diazonium salts, which are obtained in this way in up to quantitative yields, can directly be employed in azo coupling reactions, thus opening an attractive access to the industrially important group of azo compounds.

With a yearly global production in the range of 80 million tons, nitric acid represents one of the industrially most important bulk chemicals.[1] Besides its main application, which is the preparation of the fertilizer ammonium nitrate,[2] considerable amounts of nitric acid are used for the nitration of aromatics (ca. 8 million tons/year)[3] and for inorganic reactions such as the production of diverse metal nitrate salts[4] or the etching of silicon.[5] Despite many improvements introduced over the last decades, a significant number of those organic and inorganic transformations based on nitric acid are linked to the formation of gaseous nitric oxides.[6] Denitrification of the resulting gas streams is nowadays commonly achieved by selective catalytic reduction (SCR),[7] selective non-catalytic reduction (SNCR)[8] or by wet scrubber techniques.[9] In such processes, nitrogen monoxide and nitrogen dioxide (NO_x) are either reduced to simple dinitrogen with the aid of a reductant (e.g. ammonia, urea), or, in the case of the wet scrubber, are converted back to nitric acid.

With the aim to devise new sustainable synthetic methods[10] that are able to make use of such nitrogen oxides, thus following the concept from “waste to value”,[11] a new access to oximes and aromatic amino acids could recently be developed using dilute nitrogen monoxide in air (Scheme 1, (1)).[12] Although the obtained products are comparably valuable, this first strategy was limited to gas streams containing nitric monoxide in concentrations of at least 10 vol.-%. Much lower concentrations of nitric dioxide could be utilized in the oxidative nitration of styrenes (down to 0.1 vol.-%), at which dilution of the gas stream even led to a favorable increase in product selectivity (Scheme 1, (2)).[13] Aromatic nitro alcohols and nitro ketones accessible in this way are direct precursors for widely applied amino alcohols. Regarding possible fields of application, the third strategy combining denitrification with the diazotization of anilines, and thus with the preparation of aromatic diazonium salts, is certainly the most versatile.[14] Starting from nitrogen dioxide[15,16] at concentrations in the range of 0.25 to 6 vol.-% and a scrubber solution containing 4-chloro-anilinium hydrochloride, denitrification coupled to diazotization enabled the synthesis of biphenyls and iodoarenes via radical Gomberg-Bachmann and Sandmeyer-type reactions (Scheme 1, (3)).[17]



Scheme 1. Organic synthesis combined with denitrification: utilization of low-concentrated nitrogen monoxide and nitrogen dioxide.[12],[13],[17]

In this communication, we now demonstrate that the combination of denitrification and diazotization is even more effective for structurally more demanding and more hydrophilic diazonium salts, which serve as precursors in the syntheses of the pharmaceuticals balsalazide, olsalazine and sulfasalazine.

The pharmaceuticals balsalazide (**1**), olsalazine (**2**) and sulfasalazine (**3**) were chosen as target compounds due to their particular substitution pattern on the azobenzene substructure, which enables synthetic access via diazotization (see arylamine substructures, Figure 1) and azo coupling.[18-20] In this way, the effectiveness of the denitrification-diazotization step can be evaluated in combination with a subsequent azo coupling reaction at which this two-step sequence is also of fundamental importance for the multi-ton scale production of a broad range of azo compounds used as dyes for textiles and many other purposes.[21],[22]

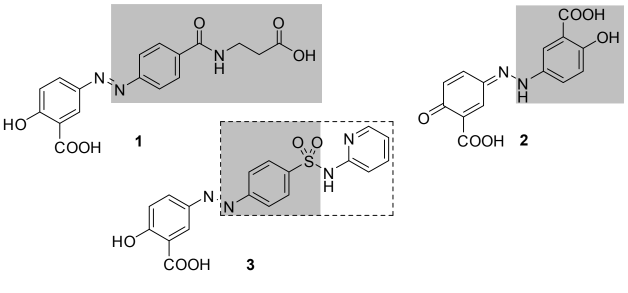


Figure 1. Balsalazide (**1**), olsalazine (**2**) and sulfasalazine (**3**).

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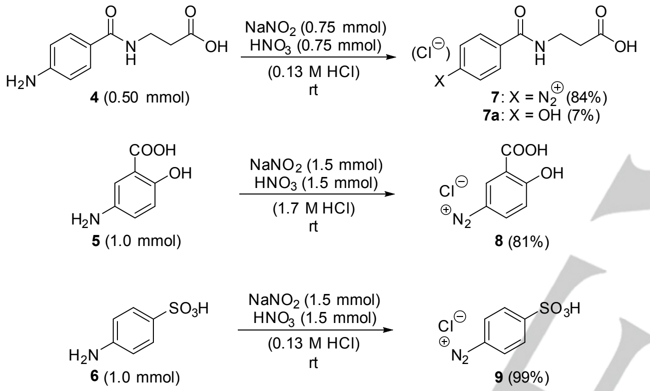
10.1002/chem.201605359

From a pharmaceutical point of view, treatments with balsalazide (**1**), olsalazine (**2**) and sulfasalazine (**3**) require significant amounts of these compounds reaching maximum doses in the range of 2-6 grams/day for acute illnesses.[23] Through cleavage in the intestine, all three compounds can act as pro-drugs for 5-aminosalicylic acid (5-ASA, mesalazine), which is active against inflammatory bowel disease including ulcerative colitis and Crohn's disease.[24]

The first series of diazotization experiments with arylamines **4**-**6**[25] were carried out on small scale (0.50 - 1.0 mmol) to get insights into the feasibility of each diazotization under wet scrubber conditions, and to evaluate the formation of possible side products. In a more general sense, it was of interest in how far results from small scale reactions would be useful to predict the later process in a wet scrubber. To simulate the conditions after uptake and disproportionation of nitrogen dioxide in the acidic scrubber solution, leading to nitrous and nitric acid, a 1:1 mixture of sodium nitrite and nitric acid was used. The results obtained after several optimization experiments are summarized in Scheme 2 (see Supporting Information for details).

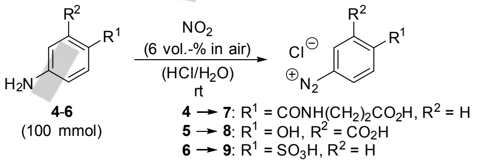


Scheme 2. Reaction conditions for diazotization optimized on small scale. Yields determined by ^{1}H-NMR using maleic acid as internal standard.

The desired diazonium salts **7**-**9** were obtained in high yields from all diazotizations, and only the reaction starting from the balsalazide precursor **4** led to a detectable by-product **7a**.[26] As the intended transfer of the reaction into the wet scrubber requires full solubility of reactant and product, the diazotization of 5-aminosalicylic acid (**5**) had to be conducted under more strongly acidic conditions. For the synthesis of sulfasalazine, sulfanilic acid (**6**) was used as starting material, as diazotization of the larger pyridinylsulfonamide (see dotted substructure of sulfasalazine (**3**), Figure 1) gave low yields and several side-reactions including the loss of SO_2. In the next step, the diazotization reactions were transferred into a 10-Liter wet scrubber miniplant (see Supporting Information for pictures of setup). The required stream of nitrogen dioxide in air was generated through addition of copper powder to concentrated nitric acid, which leads to nitrogen dioxide in high purity.[27] This reaction is also of high industrial importance for the production of copper(II) nitrate, which is used as a precursor for a broad variety of copper oxide and Claycop catalysts, in materials science and as a mild nitration reagent.[28],[29]

The data summarized in Table 1 show that comparable or even better yields can be obtained in the 10-Liter wet scrubber than in the small scale diazotization reactions (Scheme 2). No by-products were formed except for the small amount of phenol **7a** (entry 1), at which the ratio of **7**:**7a** demonstrates the good predictability of the reaction by the small scale experiment (Scheme 2). For the diazotization of sulfanilic acid (**6**), a larger excess of four equivalents of nitrogen dioxide had to be used to achieve full conversion to diazonium salt **9**, whereas the usual three equivalents led to only 70% yield and 30% of remaining starting material **6**. The fact that samples from each reaction mixture were concentrated under reduced pressure at 50 °C to enable analysis by NMR points to a remarkable stability of diazonium salts **7**-**9** in acidic aqueous solution. Referring to this, we can currently not exclude that the formation of phenol **7a** from **4** did not occur during diazotization, but may have been caused by the slightly evelated temperature prior to analysis.

Table 1. Diazotization with nitrogen dioxide in air performed in a 10-Liter wet scrubber.



Entry	Reaction conditions[a]	Diazotization Yield[b]	By-product
1	NO_2 (3 equiv.), 0.13 M HCl	**7** (77%)	**7a** (7%)
2	NO_2 (3 equiv.), 1.5 M HCl	**8** (100%)	--
3	NO_2 (4 equiv.), 0.13 M HCl	**9** (100%)	--

[a] Scrubber solution: Arylamine **4**-**6** (100 mmol) in 4 L HCl/H_2O (see Table). Stream of nitrogen dioxide in air (6 vol%, 5 L/min) generated from Cu powder and conc. HNO_3 was passed through the scrubber solution over 22.4 min (or 30.0 min, entry 3). [b] Yield determined by ^{1}H-NMR analysis using maleic acid as internal standard.

The NO_2 concentrations measured in the outgoing gas streams are depicted in Figure 2.

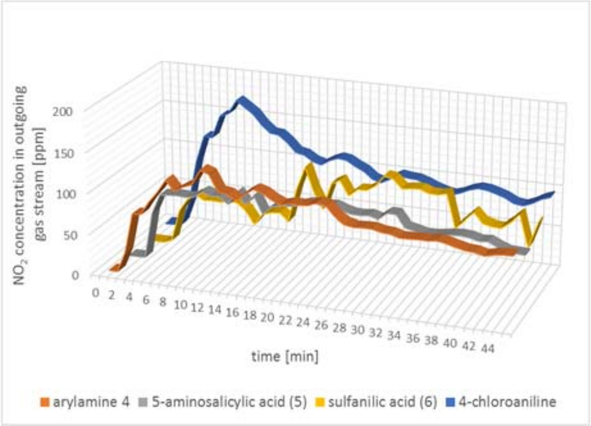
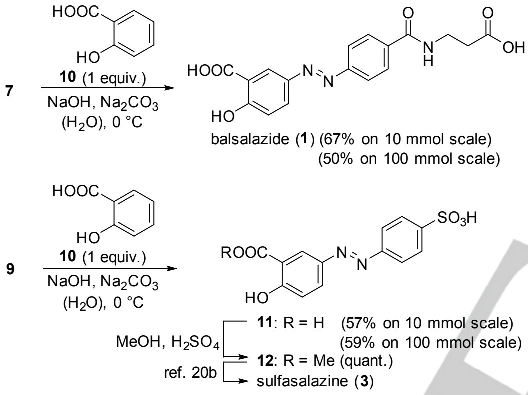


Figure 2. Concentrations of nitrogen dioxide in outgoing gas stream after diazotization of arylamines **4**-**6** and 4-chloroaniline.[13]

10.1002/chem.201605359

Proportional to the ingoing concentration of ca. 60000 ppm (6 vol.-% NO_2 in air), all diazotization reactions led to a highly effective removal of nitrogen dioxide from the gas stream. A comparison to the previously studied diazotization of 4-chloroaniline (max. 172 ppm after wet scrubber)[14] shows that more polar arylamines such as **4**-**6** are even better suited for the combination of denitrification and diazotization. In detail, the best performance was achieved with 5-aminosalicylic acid (**5**) (max. 97 ppm) followed by sulfanilic acid (**6**) (max. 119 ppm) and balsalazide precursor **4** (max. 139 ppm). Under the chosen conditions, 5-aminosalicylic acid (**5**) does meet the requirements of the European Union for environmental protection (max. NO_2 concentration of 100 ppm).[6] Finally, the diazonium salt solutions obtained from denitrification in the wet scrubber were evaluated with regard to their suitability for azo coupling reactions. In contrast to known protocols for azo coupling, the use of the scrubber solution inevitably results in a much higher dilution.[18-20] The final outcome of a series of optimization experiments, which mainly included variations of the pH value and changes of the reaction temperature, are depicted in Scheme 3 (see Supporting Information for details).



Scheme 3. Azo coupling of diazonium salts **7** and **9** – as obtained from wet scrubber - to salicylic acid (**10**) and synthesis of balsalazide (**1**) and sulfasalazine (**3**).

The two azo coupling reactions of diazonium salts **7** and **9** to salicylic acid (**10**) were found to proceed best at a pH value of 10. Despite the unfavorable dilution of the reaction mixture, which does probably not only affect the coupling itself - but does also complicate the isolation of the azo compounds through precipitation, useful yields were obtained for reactions on 10 and 100 mmol scales. Whereas balsalazide (**1**) was directly formed from the reaction of diazonium salt **7** and salicylic acid (**10**), a formal synthesis of sulfasalazine could be accomplished through the quantitative esterification of azo compound **11** to give **12**.[20b],[30] From a more general point of view, the successful use diazonium salt **9** is also an important indicator for a future application in the field of azo dye production, as many currently used azo dyes comprise a sulfanilic acid substructure.[31]

In summary, it has been shown that the coupling of denitrification and diazotization can be successfully applied to the synthesis of pharmaceutically important azo compounds. In the denitrification-diazotization step, polar arylamines were found to be significantly more effective than the previously studied 4-chloroaniline. Besides the significance of this work with a regard to a future combination of denitrification and azo dye production, the denitrification-diazotization principle could be used to design a sustainable process in which nitric oxides arising from an arene nitration reaction would be employed in a later stage of the same synthetic sequence to enable diazotization and azo coupling.

Experimental Section

General procedure for denitrification-diazotization in a 10-Liter wet scrubber. A stream of nitrogen dioxide (generated by slow addition of copper powder (9.53 g, 150 mmol) to concentrated nitric acid (180 mL, 15.5 M) over 22.4 minutes) in air (6 vol.-% NO_2, total flow: ca. 5 L/min) was passed through a 10-Liter wet scrubber containing the arylamine (100 mmol) in a mixture of water (3.5 L) and 1 N HCl (0.5 L) at room temperature After the NO_2 generation was finished, the air flow through the scrubber was maintained for another 38 min. The content of NO_2 in the outgoing gas stream was measured over the time of NO_2 generation and for further 23 minutes. A sample of 20 mL (max. 0.50 mmol) of the reaction mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR spectroscopy using maleic acid as internal standard. The remaining main part of the scrubber solution was used in the azo coupling step.

Acknowledgements

The authors are grateful for the financial support of this project by the Deutsche Bundesstiftung Umwelt (DBU) (PhD grant No. 80014/189 and Research Grant No. 30388-31). We are further grateful for support by the Graduate School of Molecular Science (GSMS), for experimental assistance by Clara Schäfer and for helpful discussions with Dr. Bernd Schricker (Luft- und Thermotechnik Bayreuth).

Keywords: Nitrogen dioxide • Aniline • Diazonium • Balsalazide • Sulfasalazine

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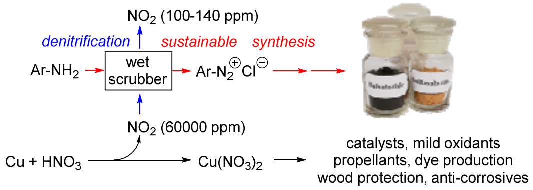
[31] Important azo dyes possessing a sulfanilic acid substructure are α-naphthol orange, chryosin S (tropaeolin 0, resorcine yellow), methyl orange and orange IV (tropaeolin 00, acid orange 5).

COMMUNICATION



The removal of nitrogen dioxide from gas streams was found to be highly effective when combined with the diazotization of polar anilines. In this way, the preparation of copper(II) nitrate can be coupled to a sustainable synthesis of industrially important azo compounds such as the pharmaceuticals balsalazide and sulfasalazine.

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Sustainable synthesis of balsalazide and sulfasalazine based on diazotization with low-concentrated nitrogen dioxide in air