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Mild hypervalent iodine mediated oxidative nitration of *N*-aryl sulfonamides†

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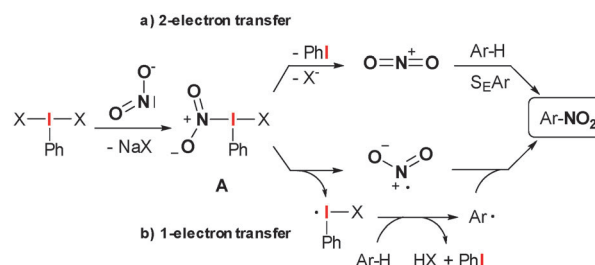
An oxidative and acid-free method for the nitration of *N*-aryl sulfonamides has been developed using a combination of sodium nitrite as cheap and easy to handle NO₂-source and the hypervalent iodine reagent PIFA as stoichiometric oxidant. Under very mild reaction conditions, the desired mononitrated aryl sulfonamides were isolated in up to 87% yield. This is the first example of an iodane-mediated oxidative nitration.

Nitroarenes are versatile structural motifs since they have been widely utilized as important precursors for the synthesis of pharmaceuticals and biological active compounds. Furthermore, nitrated arenes and heteroarenes can be found in a variety of drugs, pesticides and explosives.¹ The most common approach to synthesize nitroarenes is the direct electrophilic nitration of arenes. Traditionally, this transformation requires harsh reaction conditions such as concentrated nitric acid or mixtures of nitric acid and sulphuric acid in order to generate the reactive nitronium cation (NO₂⁺) through dehydration of nitric acid.² As an alternative, stoichiometric amounts of metal nitrates such as Bi(NO₃)₃ or expensive nitronium salts can be applied.³ Even though these methods turned out to be mild alternatives to classical nitration conditions, they are usually restricted to reactive, electron rich arenes and unfortunately, stoichiometric amounts of metal oxides are generated as undesired side products. Recently, *tert*-butyl nitrite (TBN) was found by Savinov and co-workers to be a mild nitration reagent for phenols.^{4–6} Subsequently, this reagent was used extensively for oxidative radical nitrations of alkenes and nitration cascade reactions.^{7–13} In 2013 Arns reported an elegant chemoselective nitration of *N*-aryl sulfonamides using *tert*-butyl nitrite.¹⁴ Despite its great versatility, TBN is potential hazardous due to

its known highly exothermic decomposition (1200 J g^{−1}) at elevated temperatures (above 110 °C).¹⁵

A so far neglected way to generate nitronium cations under non-acidic conditions would be a direct 1- or 2-electron oxidation of sodium nitrite.¹⁶ In this communication we want to describe such a reaction mediated by aryl-λ³-iodanes as mild and safe oxidants and atom transfer reagents.^{17–25} Aryl-λ³-iodanes of type ArIX₂ readily undergo ligand exchange reactions to substitute one or both ligands X against external anions or neutral nucleophiles (Scheme 1). We proposed that ligand exchange with sodium nitrite should give the highly reactive key intermediate **A** which should subsequently decompose in a 2-electron transfer process to generate phenyl iodide and a nitronium cation (Scheme 1a). As an alternative, a radical mechanism can be proposed through generation of NO₂ (Scheme 1b). However, herein we want to report the development of such an oxidative transformation, which is not only a remarkable mild alternative to classical nitration reactions, but is also, to the best of our knowledge, the first example of a hypervalent iodine mediated oxidative nitration.

To start our investigations, we chose to use *N*-phenyl sulfonamide **1a** as a comparatively unreactive arene. We were pleased to find that our first attempt using a combination of the aryl-λ³-iodane PIFA (phenyl iodine bis(trifluoroacetate)) and NaNO₂ in DMSO at room temperature already resulted in formation of the desired nitrated *N*-phenyl sulfonamide **2a** in 55% yield with a 1 : 1.4 mixture of the *ortho* and *para* isomers (Table 1, entry 1).

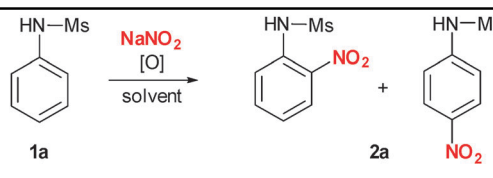


Scheme 1 Proposed oxidative generation of nitronium ions (a) or NO₂ (b) using aryl-λ³-iodanes.

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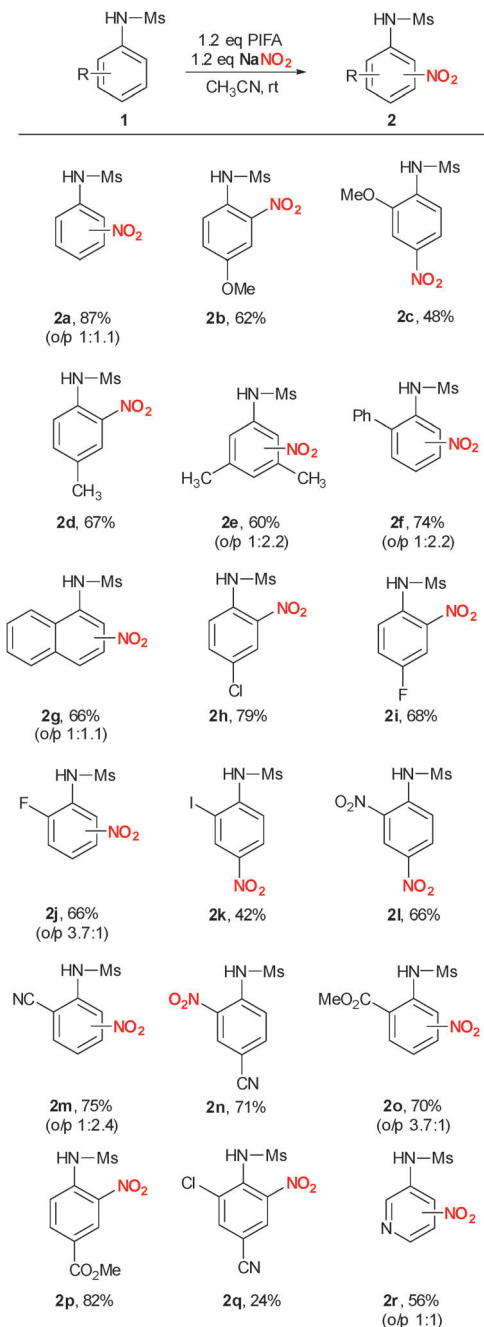
Table 1 Optimization of the reaction conditions^a

|  | | | | | | |
|---|---------|------|----------|------------|-------------|-----------|
| Entry | Solvent | [O] | Time (h) | Temp. (°C) | Ratio (o:p) | Yield (%) |
| 1 | DMSO | PIFA | 2 | rt | 1:1.4 | 55 |
| 2 | EtOAc | PIFA | 5 | rt | 1:1.1 | 72 |
| 3 | DMF | PIFA | 5 | rt | 1:1.4 | 85 |
| 4 | MeCN | PIFA | 4 | rt | 1:1.1 | 87 |
| 5 | MeCN | PIDA | 3.5 | rt | 1:1.1 | 47 |
| 6 | MeCN | PIFA | 32 | 0 | 1:1.6 | 59 |
| 7 | MeCN | PIFA | 4 | 50 | 1:1.6 | 52 |

^a Reaction conditions: 0.2 mmol **1a**, 0.24 mmol NaNO₂, 0.24 mmol PIFA or PIDA in acetonitrile at rt.

Addition of more than 1.2 equivalents of either PIFA or NaNO₂ did not result in improved yields or regioselectivities (data not shown). Therefore, we concentrated our further optimization on solvent and temperature. In ethyl acetate and DMF the yields could be further improved to 85% (Table 1, entries 2 and 3). Finally, acetonitrile turned out to be the solvent of choice giving **2a** in 87% yield. However, it has to be mentioned that *o/p* selectivity dropped slightly (Table 1, entry 4).

Changing the aryl-λ³-iodane from PIFA to PIDA (phenyl iodine diacetate) resulted in a significant lower yield of 47% (Table 1, entry 5). This observation is in good agreement with our proposal including a ligand-exchange as the initiating step since ligand exchange to generate **A** should be much faster with a less coordinating anion. Finally, lowering or increasing the temperature to 0 °C or 50 °C did also not result in improved product yields (Table 1, entries 6 and 7). Therefore, we decided to use the almost optimal reaction conditions described in entry 4 for our further systematic investigation of the substrate scope (Scheme 2). Electron-rich *N*-aryl sulfonamides bearing additional methoxy or alkyl substituents reacted well and in perfect regioselectivity. *p*-Methoxy and *p*-methyl derivatives **1b** and **1d** gave the corresponding *o*-nitro derivatives **2b** and **2d** in 62% and 67% yield whereas the *o*-methoxy substituted derivative **1c** gave *para* selective nitration to yield **2c** in 48%. Nitration of the 3,5-dimethyl substituted sulfonamide **1e** resulted in formation of **2e** in 60% yield. Interestingly, when phenyl substituted sulfonamide **1f** was used, exclusive nitration of the *N*-aryl group of the sulfonamide was observed in 74% yield (**2f**). *N*-(1-Naphthyl) sulfonamide gave **2g** in 66% yield in an almost 1:1 mixture of *o/p* regioisomers. Next, we investigated halogenated *N*-aryl sulfonamides. Chlorinated- and fluorinated derivatives reacted smoothly to give the desired products **2h–j** in 66–79% yield. However, an additional iodine-substituent had a negative influence on reactivity resulting in formation of **2k** in only 42% yield. Very electron-poor nitro-, cyano-, and ester-containing sulfonamides could be nitrated as well to give the desired products **2l–2p** in 66–82% yield. Cyano- and chloro substituted sulfonamide **1q** gave **2q** in poor isolated yield of 24%. *N*-(3-Pyridyl) sulfonamide yielded the

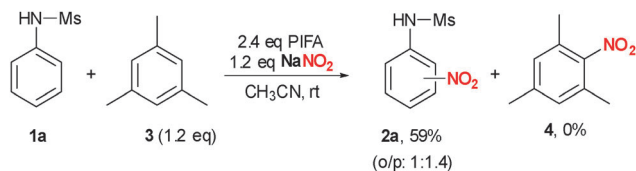


Scheme 2 Substrate scope. Reaction conditions: 0.2 mmol **1a**, 0.24 mmol NaNO₂, 0.24 mmol PIFA in acetonitrile at rt. Reaction time: 1–48 h.

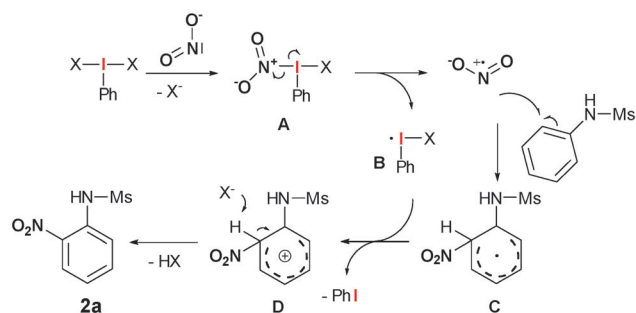
desired nitro-substituted pyridine derivative **2r** in 56% yield. Finally, it is worth mentioning that *N*-unprotected aniline, *N*-methyl aniline and *N,N*-dimethylaniline gave messy reaction mixtures under similar reaction conditions.

To prove our initial proposal presented in Scheme 1, in particular the generation of a nitronium ion (Scheme 1a), a replacement experiment was performed (Scheme 3). When a mixture of **1a** was treated with PIFA and NaNO₂ in the presence of a slight excess of mesitylene **3**, formation of **2a** was observed exclusively in 59%. If a nitronium ion would be the active species in this transformation, the more electron-rich arene **3**





Scheme 3 Replacement experiment.



Scheme 4 Proposed reaction mechanism.

should react significantly faster leading to significant amounts of **4**. However, formation of **4** was not observed. In addition, we could not detect formation of the nitronium ion by Raman spectroscopy at a characteristic band at 1394 cm^{-1} when PIFA and NaNO_2 were combined in acetonitrile.²⁶

These experiments together with the observation that a brown gas with a characteristic pungent odour is formed at the beginning of the reaction, is a strong evidence for the oxidative formation of nitrogen dioxide *via* an 1-electron transfer-mediated decomposition of the aryl- λ^3 -iodane (Scheme 4).

Initially, ligand exchange of the nitrite anion at the hypervalent iodine atom should give intermediate **A**. The labile N–I bond subsequently decomposes to give nitrogen dioxide and the iodine-centred radical **B**. A radical reaction between NO_2 and the arene gives a stabilized cyclohexadienyl radical **C**. Formation of this radical should be strongly stabilized by heteroatom containing functional groups which might be the reason for the high chemoselectivity of this transformation towards *N*-aryl sulphonamides. However, **C** can subsequently be oxidized by **B** to the corresponding cyclohexadienyl cation **D**. Final proton elimination yields the desired nitro arene **2a**.

In conclusion we described the first hypervalent iodine-mediated nitration of electron deficient *N*-aryl sulphonamides. By using a combination of sodium nitrite as a remarkable

cheap and easy to handle nitro source and the aryl- λ^3 -iodane PIFA as a mild oxidant the desired nitro (hetero)arenes could be isolated in up to 87% yield. This novel nitration method is acid free and subsequently tolerates a variety of additional functional groups on the (hetero)arene moiety. Based on these initial results we want to use the combination of a hypervalent iodine reagent and nitrite salts in the near future to introduce nitro functionalities into other, less reactive substrates in an oxidative manner.

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