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Direct oxidative nitration of aromatic sulfonamides under mild conditions†

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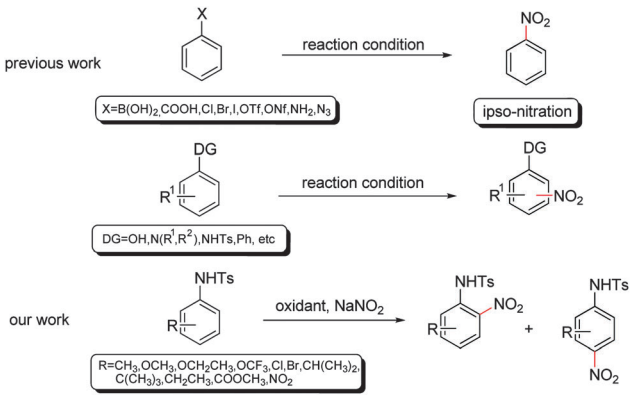
A direct nitration of aromatic sulfonamides using sodium nitrite as the nitrating agent has been developed. The reaction shows typically mono-substitution selectivity and can be enlarged to the gram scale with good yield.

In the past 150 years, there has been growing interest in nitration of aromatic compounds due to the importance of nitro compounds and their derivatives as synthetic blocks, agrochemicals, pharmaceuticals, explosives, dyes, and polymers.[1] The aromatic nitro compounds are traditionally synthesized by electrophilic aromatic substitution reaction using nitric acid as the nitrating reagent, which is usually catalyzed by another strong Brønsted acid, in the industry and laboratory.[2]

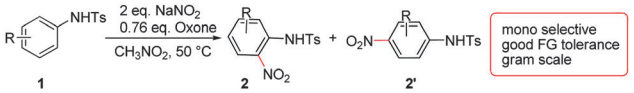
The traditional nitration methods suffer from some drawbacks, such as the high acidity and oxidizability of the reagents, and thus many by-products and acid waste can be generated by these procedures. To overcome these difficulties, many useful methods have been reported (Scheme 1).[3] There are some recent advances in this field, including the use of nitrate salts,[4] the copper[5] or palladium[6,7] catalyzed C(aryl)–nitrogen bond formation reactions and the nitration of arylboronic acids without a catalyst.[8] Although nitration methods for aromatic compounds have gained significant development, the synthesis of aromatic nitro compounds is elusive due to severe limitations. For example, the reagents are often difficult to prepare and work up. In addition, the reaction also exhibits poor chemoselectivity towards specific aromatic systems.[9] Thus, exploration of a new, convenient and efficient method to synthesize aromatic nitro compounds is still highly desired.



Scheme 1 Nitration of aromatic compounds.

Aryl sulfonamides are some of the most attractive nitrogen sources because of their great abundance and extremely low cost.[10] They can be functionalized by various reactive reagents. Recently, Arns's group has developed a method to convert aromatic sulfonamides into the corresponding mono-nitro derivatives by using *tert*-butyl nitrite as the nitrating agent.[3q] Herein, we report a novel and convenient method for the direct oxidative nitration of aromatic sulfonamides with sodium nitrite as the nitrating reagent under mild conditions (Scheme 2). The product can be easily detosylated to form *ortho*-nitroaniline, which was unambiguously confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy analysis.[11] This efficient reaction proceeds under very mild conditions with low cost nitration reagents and easily prepared, available reagents. The method allows good functional group tolerance, high chemoselectivity and can be applied in gram-scale preparation.

We started our study by examining whether the aryl sulfonamide **1a** could be converted into aryl sulfonamide derivative **2a**.



Scheme 2 The optimised conditions.

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To our delight, when $PhI(OAc)_2$ was used as an oxidant in DCM, the desired product 4-methyl-*N*-(4-methyl-2-nitrophenyl)benzenesulfonamide **2a** could be isolated in 82% yield after 3.0 h (see ESI,† Table SI, entry 1). Notably, only the mono-substituted product was obtained under these conditions. The desired product **2a** was unambiguously confirmed by X-ray crystallographic analysis. Although the yield was good, a by-product was obtained. In order to improve the efficiency of the reaction, optimization studies were then performed by screening solvents, oxidants and *N*-protecting groups. The results indicated that the oxidants such as DDQ, PPTS, $(NH_4)_2S_2O_8$, oxone, and KHS_2O_8, except BQ, were effective for this reaction (Table SI, ESI,† entries 1–6). Further examination of solvent effects revealed that DCM and CH_3NO_2 were superior to others (Table SI, ESI,† entries 7–15). The influence of protecting groups on nitrogen was also investigated (Table SI, ESI,† entries 16–23) and finally *N*-tosyl aniline was found to be the best one (Table SI, ESI,† entry 23, 98%). Thus, the use of 2.0 equiv. of $NaNO_2$ and 0.76 equivalent of oxone in nitromethane at 50 °C was considered as the optimal reaction conditions.

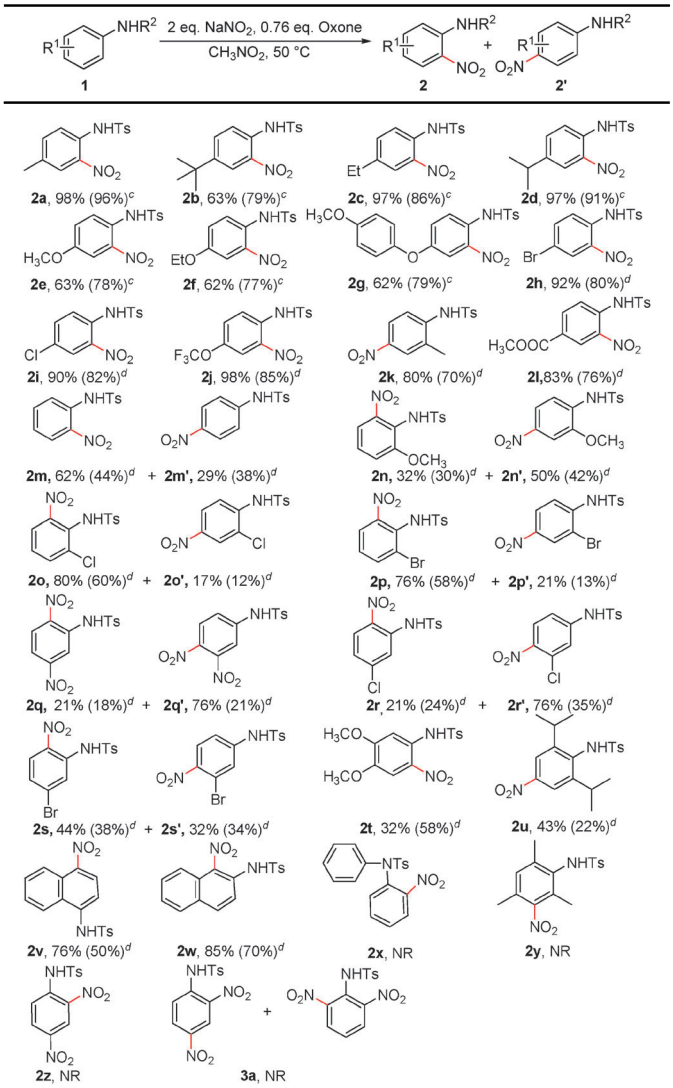
With the optimized conditions in hand, we next examined the scope of the nitration reaction. These conditions were found to be compatible with a wide range of substituted *N*-tosyl arylamines as illustrated in Table 1. When the *para*-position of *N*-tosyl aniline was occupied by an electron-withdrawing group such as OCF_3, the yields were better than when occupied by electron-donating groups (Table 1, **2a–2l**). With one substituent in the *ortho*- or the *meta*-position of the aromatic ring, it would generate *ortho*- and *para*-nitrated products at the same time (Table 1, **2m–2s**). When there were two electron-donating groups in the aromatic ring, the yield was significantly reduced (Table 1, **2t** and **2u**). It is noteworthy that naphthyl sulfonamides gave the nitration products under the standard conditions in satisfactory yields (Table 1, **2v** and **2w**). In addition, when the nitrogen of aryl sulfonamides does not have hydrogen or the *ortho*- and the *para*-position of the benzene ring has substituent groups, nitration reaction would not occur (Table 1, **2x** and **2y**). The reason might be that this type of aromatic ring is not easily oxidized. Also, no reaction occurred when the *ortho*- or the *para*-position of the aromatic ring has a nitro group because the nitro group severely passivated the benzene ring and made it difficult to be oxidized (Table 1, **2z** and **3a**). For decreasing the cost of this reaction in industry production, we also chose DCM as solvent to examine the capacity of the substrates, the result is shown in Table 1. The reaction occurred smoothly with the electron-donating groups on the aromatic ring after 30 hours at room temperature. But for the substrates with electron-withdrawing groups, the yield reduced significantly, which could be improved by using CN_3CN as the solvent.

To fully demonstrate the applicability of this method, we employed **1a** as the starting material and enlarged the reaction to the gram scale (5 mmol). The yield of the reaction was still up to 85%. It indicates that this method could be synthetically useful and suitable for the industrial preparation.

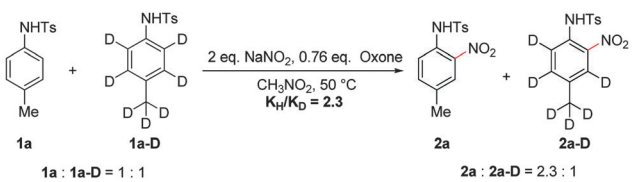
To further investigate the mechanism, relative experiments were carried out. When 2.0 equivalent of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction mixture as a radical scavenger, it was found that the yields of **2** and **2′** were not affected. We also used the EPR monitoring experiment to detect radicals, but no radical was detected (see ESI†). A notable primary kinetic isotope effect (KIE, k_H/k_D = 2.3) was observed for two competition reactions with **1a** and **1a-D** (Scheme 3), suggesting that the C–H bond cleavage is likely involved in the rate-limiting step.[12]

Based on the above results and previous reports, a possible cation mechanism is proposed as shown in Scheme 4. In the

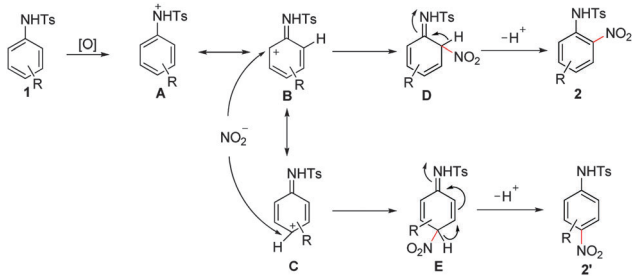
Table 1 Scope of nitration with aryl sulfonamides[a,b]



[a] Conditions: 0.3 mmol **1**, 0.6 mmol $NaNO_2$ and 0.23 mmol oxone in nitromethane (3 mL) at 50 °C, 5 h. [b] Isolated yield. [c] In DCM at room temperature, 30 h. [d] In CH_3CN at 50 °C, 5 h.



Scheme 3 Control experiment.



Scheme 4 Proposed mechanism for nitration of aryl sulfonamides.

presence of an oxidant, aryl sulfonamide **1** is oxidized to cation **A**, which has another two resonance structures **B** and **C**. The nitro anion attacks carbocation **B** or **C** to afford intermediate **D** and **E**, which undergoes a re-aromatization step by deprotonation to give product **2** or **2′**.

In conclusion, we have developed an efficient, convenient and highly chemoselective method for the direct oxidative nitration of aromatic sulfonamides with sodium nitrite as the nitrating reagent. The mild conditions, good functional group compatibility, operational simplicity and high yield are expected to make this reaction attractive to chemists. The reaction can also be scalable when operated on a gram scale. Efforts toward detailed mechanistic studies to understand the nitration process are underway.

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