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Chemoselective nitration of aromatic sulfonamides with *tert*-butyl nitrite†

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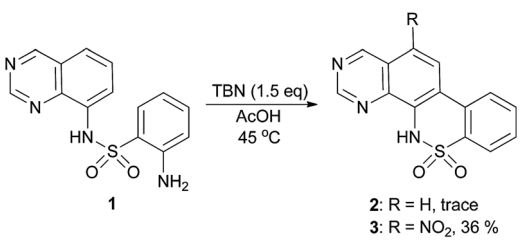
A methodology for the efficient conversion of aromatic sulfonamides into their mono-nitro derivatives using *tert*-butyl nitrite is reported. The reaction exhibits a high degree of chemoselectivity for sulfonamide functionalized aryl systems, even in the presence of other sensitive or potentially reactive functionalities.

The nitration of aromatic compounds has been of interest for over 150 years due to the importance of nitro compounds and their derivatives as synthetic intermediates, pharmaceuticals, dyes, explosives, plastics, and countless other industrial or commercial products.[1] Nitrated aryl compounds can be made with relative ease from unfunctionalized aryl precursors and inexpensive, widely available reagents. The most ubiquitous and readily identified nitrating reagent is nitric acid, often used in the presence of another strong acid catalyst.[2]

These classical nitration methods suffer from a number of drawbacks, key among them being the high acidity and oxidizing power of the reagents. Consequently, such reaction conditions are limited in scope due to a lack of compatibility with easily oxidized and/or acid sensitive functionalities. In addition, there are also concerns surrounding the spent acid waste generated by such procedures. To overcome these difficulties, a number of techniques have been developed to perform nitrations under milder conditions. Some recent advances in this field include the use of nitrate salts,[3] the palladium catalyzed nitration of aryl chlorides and triflates,[4] and the nitration of arylboronic acids without the use of a catalyst.[5] These methods are successful in limiting the use of harsh reagents; however the reagents are often expensive, difficult to prepare and work with, and/or they are difficult to store. They also do not offer high degrees of chemoselectivity towards specific aromatic systems within a substrate. In recent years there have been reports of chemoselective nitrations; however to date these have been limited to highly activated electron rich systems such as phenols[6] and anilines.[7]

Aryl sulfonamides are an important class of compounds that are a fundamental structural unit of a diverse group of pharmaceuticals, pesticides and other materials.[8] Methods by which they can be functionalized, particularly in the presence of other reactive groups, represents an ongoing challenge for synthetic chemists. Herein we report a method by which aromatic sulfonamides can be converted to their nitrated derivatives in near quantitative yield using *tert*-butyl nitrite (TBN) as a mild, easily handled and commercially available nitrating reagent. This method exhibits a high degree of chemoselectivity towards aryl sulfonamides in the presence of other activating functional groups. To the best of our knowledge this is the first report of *tert*-butyl nitrite being used in the nitration of aromatic sulfonamides. In fact, reports of TBN being used in any case as a nitrating reagent are limited; it has been shown TBN is an effective, chemoselective nitrating reagent for phenols,[6] and nitrated byproducts have been periodically observed in the diazotization reaction of anilines with TBN.[9]

Our initial observation of a nitration using TBN occurred during the attempted cyclization of **1** to **2**. (Scheme 1) When compound **1** was treated with TBN in AcOH at 45 °C, an unexpected nitrated by-product **3** was recovered along with a trace amount of the target compound **2**. Presumably the diazo cyclization precedes formation of the nitrated product, which could arise *via* the direct nitration of the cyclized product, or the interception of an intermediate in the cyclization process. Regardless of the process that arrives at the nitrated product, we recognized the novelty of this reaction and we decided to further examine the use TBN as a nitrating agent.



Scheme 1 Initial observation of nitration using TBN.

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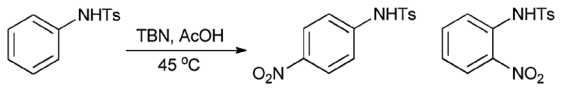
† Electronic supplementary information (ESI) available: For experimental procedures and spectral data (^{1}H, ^{13}C NMR, MS) of all new compounds, including select regiochemical assignments (2D NMR). See DOI: 10.1039/c2cc37481a

Table 1 Optimization of nitration conditions[a]



4 5a 5b

Entry	Solvent	Temp. (°C)	Time (h)	AcOH (eq.)	Yield (%) 4	5a	5b
1	AcOH	45	0.75	—	0	51	44
2	MeOH	45	6	3	No reaction		
3	MeOH	Reflux	24	3	No reaction		
4	DMSO	45	6	3	84	7	5
5	Acetone	45	6	3	56	21	18
6	$CHCl_3$	45	6	3	58	24	14
7	DMF	45	6	3	41	27	26
8	DCM	45	6	3	33	31	25
9	THF	45	6	3	26	39	32
10	EtOAc	45	6	3	11	45	39
11	ACN	45	6	3	0	52	47
12	ACN	45	6	1.5	3	45	39
13	ACN	45	6	0.5	0	47	36
14	ACN	45	6	0	8	46	39
15	ACN	Reflux	6	0	1	49	43

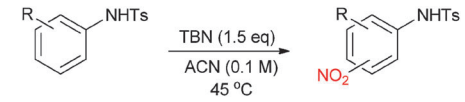
[a] All reactions were run using 1.5 equivalents of TBN and with a starting material concentration of 0.1 M.

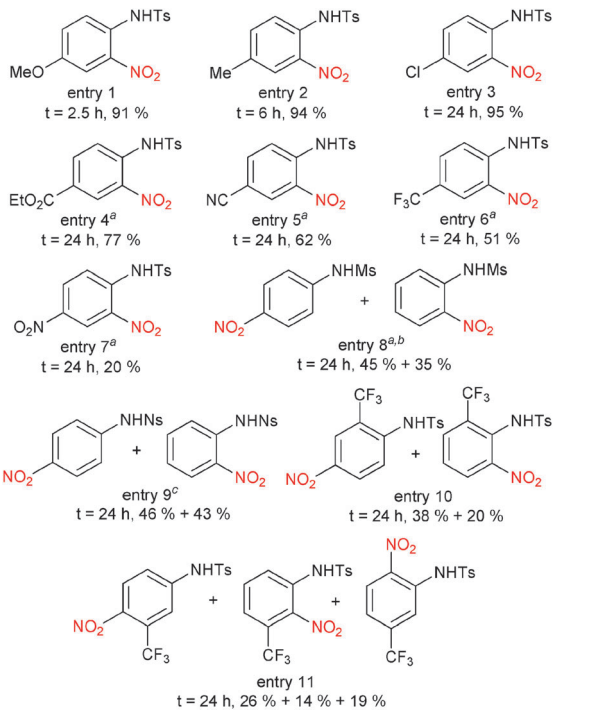
To investigate this mode of reactivity, *N*-Ts aniline **4** was treated with TBN under the same conditions in which the original nitration was observed. After only 45 minutes, compound **4** was completely converted into a regioisomeric mixture of nitrated derivatives **5a** and **5b** in 51% and 44% yields respectively (Table 1, entry 1). Over-nitrated products were only observed if the substrate was left under the reaction conditions until well after the starting material was fully consumed, and then only in small quantities. The presence of a nitro group in the products was determined by mass spectroscopy and corroborated by reduction of the nitro group to an aniline.

With a preliminary set of conditions in hand we were confident we could modify this protocol to establish a new procedure that would be of greater synthetic value by eliminating the use of acetic acid as the solvent. To this end a solvent screen was performed, as described in Table 1, using acetic acid as an additive. Methanol (Table 1, entries 2 and 3) completely inhibited the reaction. To varying extents, the reaction was seen to proceed in all aprotic solvents screened. The use of dimethyl sulfoxide, acetone, chloroform, dimethylformamide, or dichloromethane (Table 1, entries 4–8) resulted in incomplete reactions. Though yields of **5a** and **5b** were low in these examples, pure unreacted starting material could be recovered. Conversions were improved significantly by the use of tetrahydrofuran, ethyl acetate or acetonitrile (Table 1, entries 9–11) with combined yields of **5a** and **5b** exceeding 80% in all cases. Ultimately acetonitrile was found to produce the most favourable results, with reactions easily running to completion after 6 hours. Finally, we were pleased to find that reducing or even eliminating acetic acid had little effect on reaction outcome (Table 1, entries 12–15). Running the nitration at reflux had no negative effect on the outcome of the reaction while decreasing reaction time. (Table 1, entry 15).

A summary of the reaction scope are presented in Table 2. A variety of substituted *N*-Ts anilines were seen to undergo

Table 2 Substrate scope of TBN nitration



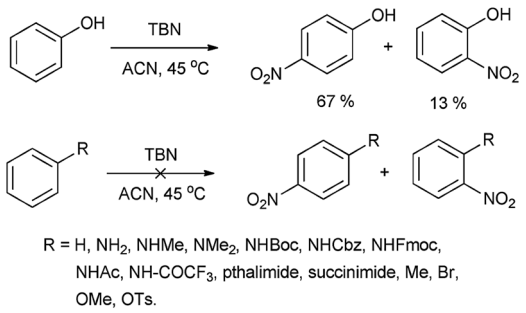


[a] Reaction did not run to completion over the indicated time. [b] The starting material was *N*-Ms aniline. [c] The starting material was *N*-Ns aniline.

nitration as expected, with reaction rates depending on the overall electron density of the substrate. Generally, more electron rich substrates were found to be more reactive, and a variety of common functional groups were well tolerated under the reaction conditions. In all cases the regioselectivity was seemingly directed by the sulfonamide, even in the presence of other powerful directing groups such as methoxy (Table 2, entry 1). The regiochemical designation of the products was unequivocally proven by 2D NMR analysis. Other sulfonamides (Ns and Ms, entries 9 and 10) were also successfully nitrated in high yields and in reasonable reaction times. Attempts at nitrating tertiary sulfonamides, those without a proton on the nitrogen, were unsuccessful.

Efforts to extend this nitration methodology beyond substrates containing a sulfonamide were largely unsuccessful. Attempting the reaction on unfunctionalized anilines resulted in the generation of complex mixtures. Functionalized or protected anilines were generally unreactive, with attempted nitrations yielding unreacted starting material. A range of other functionalized aryl compounds were also found to be resistant to nitration using TBN. One exception was observed in the case of phenol, which was easily nitrated in excellent yield, as has been previously observed (Scheme 2).[6]

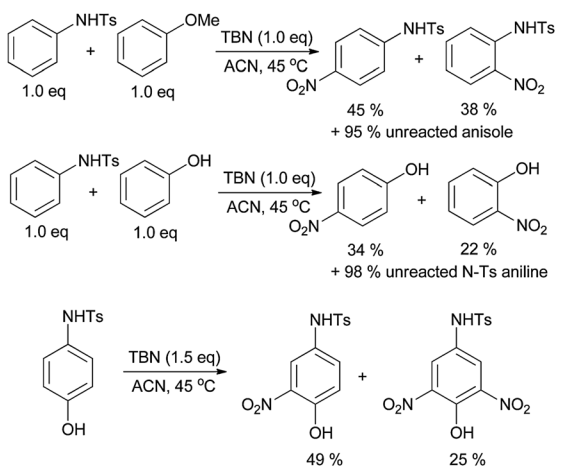
Perhaps the most remarkable aspect of nitration using TBN is the high level of selectivity that is displayed for sulfonamides over other functional groups. This initially came to light upon the nitration of a sulfonamide that also contained a functional



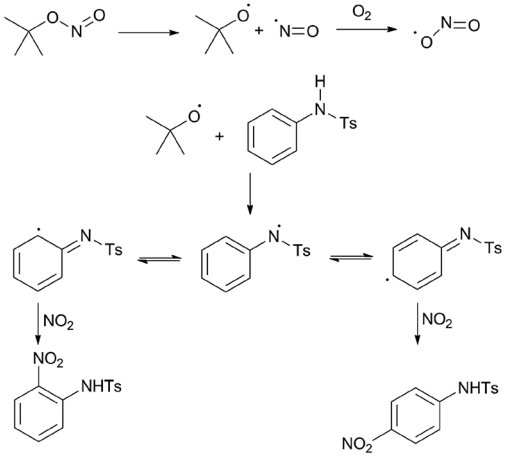
Scheme 2 Nitration of other aryl compounds.

group typically associated as being a strong director of nitration (Table 2, entry 1), where the nitro group was installed only in an *ortho*/*para* sense relative to the sulfonamide functionality. In fact, regardless of the other functionalities decorating an aryl system containing a sulfonamide, the nitro group is always installed in an *ortho*/*para* sense relative to the sulfonamide. Competition studies show complete selectivity for the nitration of sulfonamide-containing systems, except in the case of being compared against phenol (inter- and intramolecular examples) where the phenol is selectively nitrated (Scheme 3).

In an effort to unravel the mechanism by which this reaction operates, we doped the typical nitration reaction of *N*-Ts aniline with TEMPO, a well known radical scavenger.[10] Much to our surprise, the combined yield of nitrated products dropped from 95% to just 24% on the addition of 2.0 equivalents of TEMPO, strongly implying a radical based mechanism. TBN is known to undergo thermal homolysis to liberate an alkoxyl radical and nitric oxide (NO).[11] Abstraction of the sulfonamide *N*-H proton would afford a nitrogen-based radical that can be delocalized onto the aromatic ring. NO_2, which is produced by oxidation of NO with molecular oxygen,[12] can intercept the aryl radical to give the observed nitrated products *ortho* and *para* to the sulfonamide functionality (see Scheme 4 for proposed mechanism). The observation that running the reaction under an inert atmosphere significantly impedes the reaction rate while an oxygen atmosphere offers a slight rate enhancement suggests an oxidation promoted by oxygen is a crucial feature of the reaction mechanism.[13]



Scheme 3 Competition experiments.



Scheme 4 Proposed mechanism of nitration.

Alternatively, the sulfonamide radical and NO could be generated by initial nitrosation of the sulfonamide followed by thermally induced homolysis of the resulting N–N bond.[14] In either case, this reactivity is analogous to that proposed in the nitration of phenols using TBN,[6] and it effectively explains why nitration is observed *ortho*/*para* with the sulfonamide functionality, even in the presence of opposing strong *ortho*/*para* directors that would override the directing ability of the sulfonamide were the reaction to proceed *via* a cationic manifold.

In conclusion, we have developed a novel method by which sulfonamides can be nitrated selectively in high yield using TBN as the nitrating agent. This method uses very mild conditions and generates little waste compared with alternative nitration protocols. This method tolerates a wide variety of functional groups with no negative effects on reaction outcome, and it exhibits a high degree of chemoselectivity for sulfonamide functionalized aryl systems, even in the presence of other potentially reactive substrates. Preliminary results suggest that the reaction proceeds through a radical based mechanism. Efforts in further expanding the scope of the reaction and elucidating the mechanism are ongoing and will be reported in due course.

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