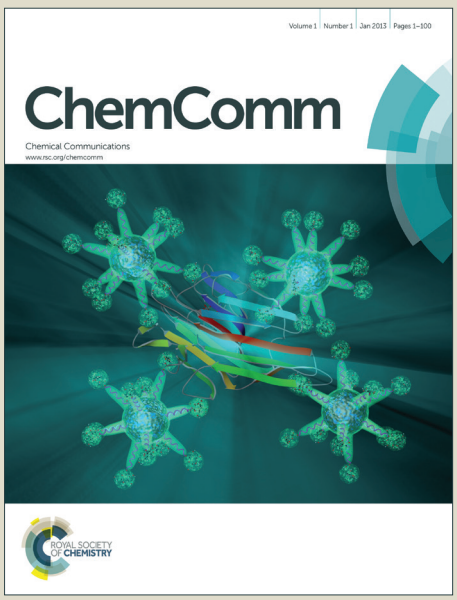
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Direct Oxidative Nitration of Aromatic Sulfonamides under Mild Conditions

Cite this: DOI: 10.1039/x0xx00000x

Ying-Xiu Li[a], Lian-Hua Li[a], Yan-Fang Yang[a], Hui-Liang Hua[a], Xiao-Biao Yan[a], Lian-Biao Zhao[b], Jin-Bang Zhang[a], Fa-Jin Ji[c] and Yong-Min Liang[a,*]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

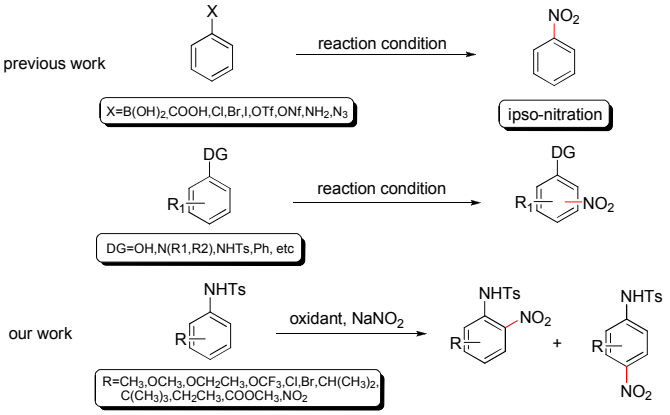
www.rsc.org/

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

In the past 150 years, there has been a growing interest in nitration of aromatic compounds due to the importance of nitro compounds and their derivatives as synthetic blocks, agrochemicals, pharmaceuticals, explosives, dyes, polymers.[1] The aromatic nirtro 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 wastes can be generated by these pocedures. To overcome these difficulties, many useful methods had 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 catalyst.[8] Although nitration methods of 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.

Aryl sulfonamides are one 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, ^{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 chemoselctivity and can be applied into gram-scale preparation.

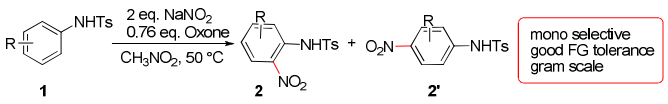


Scheme 1. Nitration of aromatic compounds.

We started our study by examining whether the aryl sulfonamide **1a** could be converted into aryl sulfonamide derivative **2a**. 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 Supporting Information, Table SI, entry 1). Notably, only mono-substituted product was obtained under this condition. 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

[a]*State Key Laboratory of Applied Organic Chemistry, LanzhouUniversity, Lanzhou 730000, China. E-mail:liangym@lzu.edu.cn; Fax: +86-931-8912582; Tel: +86-931-8912582*
[b]*College of Chemical Engineering, Northwest University for Nationalities, Lanzhou 730030, China*
[c]*The eighth middle school, Yong jing 731605, China*
Electronic supplementary information (ESI) available. CCDC987527(**2a**). For ESI and crystallographic datainCIF or electronic format see DOI: 10.1039/c000000x/

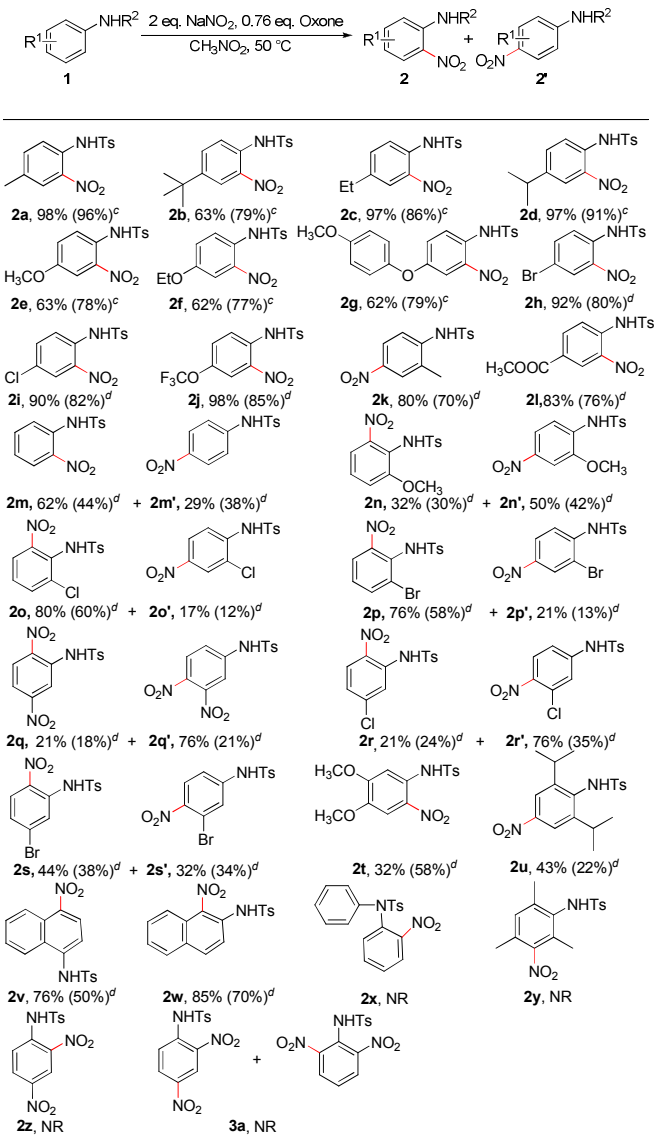
improve the efficiency of the reaction, optimization studies were then performed by screening solvents, oxidants and *N*-protecting groups. The results indicated that the oxidants such as DDQ, PPTS,



Scheme 2. The optimised condition

$(NH_4)_2S_2O_8$, Oxone, KHS_2O_8, except BQ were effective for this reaction (Table SI, entries 1-6). Further examination of solvent effects revealed that DCM and CH_3NO_2 were superior to others (Table SI, entries 7-15). The influence of protecting groups on nitrogen was also investigated (Table SI, entries 16-23) and finally

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



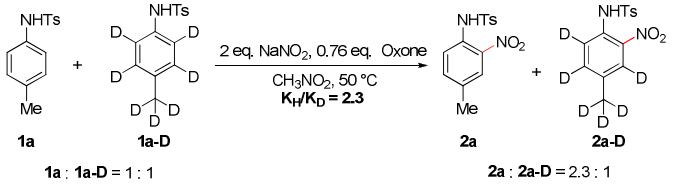
[a] Conditions: 0.3 mmol **1**, 0.6 mmol $NaNO_2$ and 0.23 mmol Oxone in nitromethane (3 mL) at 50 °C, 5 h. [b] Isolated yield. [c] in DCM at room temprature, 30 h . [d] in CH_3CN at 50 °C, 5 h.

N-tosyl aniline was found to be the best one (Table SI, entry 23, 98%). Thus, the use of 2.0 equiv $NaNO_2$ and 0.76 equivalent Oxone in nitromethane at 50 ºC were 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 arylamine as illustrated in Table 1. When *para*-position of *N*-tosyl aniline was occupied by electron-withdrawing group such as OCF_3, the yields were better than electron-donating groups (Table 1, **2a-2l**). With one substituent in *ortho*- or *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 would be significantly reduced (Table 1, **2t**, **2u**). It was noteworthy that naphthyl sulfonamides gave the nitration products under the standard condition in satisfactory yields (Table 1, **2v**, **2w**). In addition, when the nitrogen of aryl sulfonamides had no hydrogen or the *ortho*- and *para*-position of the benzene ring had substituent groups, nitration reaction would not occur (Table 1, **2x**, **2y**) The reason might be that this type of aromatic ring is not easily oxidized. Also, no reaction occured when the *ortho*- or *para*-position of the aromatic ring had a nitro group because the nitro group severely passivated the benzene ring and made it difficult to be oxidized (Table 1, **2z**, **3a**). For decreasing the cost of this reaction in industry production, we also chosed DCM as solvent to examine the capacity of the substrates, the result showed in table 1. The reaction occurred smoothly with the electron-donating groups on the aromatic ring after 30 hours at room temprature. But for the substracts 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 starting material and enlarged the reaction to 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.

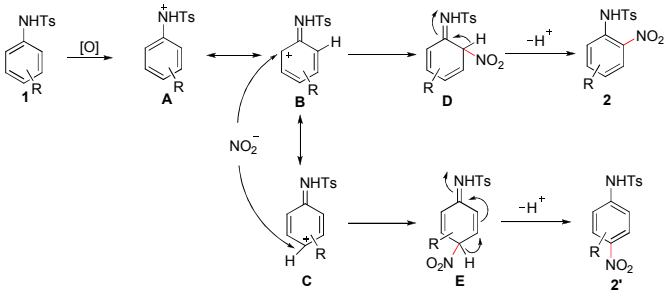
To further investigate the mechanism, relative experiments were carried out. When 2.0 equivalent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction mixture as a radical scavenger, it was found that the yields of **2** and **2′** were not affected. We also used the EPR monitoring experiment to detect radicals, but no radical was detected (see Supporting Information). 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]



Scheme 3. Control experiment.

Based on the above results and previous reports, a possible cation mechanism is proposed as shown in Scheme 4. In the presence of oxidant, aryl sulfonamides **1** is oxidized into the cation **A**, which has another two resonance structure **B** and **C**. The nitro anion attacks carbocation **B** or **C** to afford the intermediate **D** and **E**, which undergoes a re-aromatization step by deprotonation to give

the products **2** or **2′**.



Scheme 4. Proposed mechanism for nitration of aryl sulfonamides.

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 reagents. 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 detail mechanistic studies to understand the nitration process are underway.

We thank the National Science Foundation (NSF21072081，21302076) and the National Basic Research Program of China (973 Program) 2010CB8-33203 for financial support. We also acknowledge support from the "111" Project and Program for Changjiang Scholars, Innovative Research Team in University (IRT1138), the Fundamental Research Funds for the Central Universities (lzujbky-2013-190, lzujbky-2014-194).

Notes and references

1 (a) K. Hunger, Industry Dyes: Chemistry, Properties and Applications, Wiley-VCH, Weinheim, 2003; (b) S. A. Lawrence, Amines: Synthesis, Properties and Application; Cambridge University Press, Cambridge, 2004; (c) P. F. Vogt and J. J. Gerulis, Amines, Aromatic. In Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH, Weinheim, 2005; (d) Z. Rappoport, Chemistry of Anilines, Part 1, in Patai Series: The Chemistry of Functional Groups; Rappoport, Z., Ed.; John Wiley & Sons Ltd, Chichester, West Sussex, 2007.

2 Nitration: (a) G. A. Olah, R. Malhotra and S. C. Narang, Nitration: Methods and Mechanisms; VCH: New York, 1989; (b) L. F. Albright, R. V. C. Carr and R. J. Schmitt, Eds. ACS Symposium Series 623; American Chemical Society: Washington, DC, 1996.

3 (a) S. M. Dirk, E. T. Mickelson, J. C. Henderson and J. M. Tour, *Org. Lett*., 2000, **2**, 3405–3406; (b) N. Ono, The Nitro Group in Organic Synthesis. Wiley-VCH: New York, 2001; (c) J. P. Das, P. Sinha and S. Roy, *Org. Lett.*, 2002, **4**, 3055–3058; (d) S. Rozen and M. Carmeli, *J. Am. Chem. Soc*., 2003, **125**, 8118–8119; (e) S. Saito and Y. Koizumi, *Tetrahedron Lett*., 2005, **46**, 4715–4717; (f) X. Yang, C. Xi, Y. Jiang, *Tetrahedron Lett*., 2005, **46**, 8781–8783; (g) B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc*., 2009, **131**, 12898–12899; (h) D. Koley, O. C. Colón, S. N. Savinov, *Org. Lett*., 2009, **11**, 4172–4175; (i) K. R. Reddy, C. U. Maheswari, M. Venkateshwar and M. L. Kantam, *Adv. Synth. Catal*., 2009, **351**, 93–96; (j) P. LaBeaume, M. Placzek, M. Daniels, I. Kendrick, P. Ng, M. McNeel, R. Afroze, A. Alexander, R. Thomas, A. E. Kallmerten and G. B. Jones, *Tetrahedron Lett*., 2010, **51**, 1906–1909; (k) H. J. Yang, Y. Li, M. Jiang, J. M. Wang and H. Fu, *Chem. Eur. J*., 2011, **17**, 5652–5660; (l) L. Zhang, Z. Liu, H. Li, G. Fang, B.-D. Barry, T. A. Belay, X. Bi and Q. Liu, *Org. Lett*., 2011, **13**, 6536–6539; (m) S. Manna, S. Maity, S. Rana, S. Agasti, D. Maiti, *Org. Lett*., 2012, **14**, 1736–1739; (n) M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, A. Zare, H. G. Kruger, Z. Asgari, V. Khakyzadeh and M. Kazem-Rostami, *J. Org. Chem*., 2012, **77**, 3640–3645; (o) P. J. A. Joseph, S. Priyadarshini, M. L. Kantam and H. Maheswaran, *Tetrahedron Lett*., 2012, **53**, 1511–1513; (p) S. Wang, C. C. Shu, T. Wang, J. Yu and G. B. Yan, *Chin. Chem. Lett*., 2012, **23**, 643–646; (q) B. Kilpatrick, M. Heller and S. Arns, *Chem. Commun*., 2013, **49**, 514–516; (r) M. Kol and S. Rozen *J. Chem. Soc., Chem. Commun.,* 1991,567-568.

4 H. B. Sun, R. Hua and Y. Yin, *J. Org. Chem*., 2005, **70**, 9071–9073.

5 Recent examples: (a) J. Lindley, *Tetrahedron.,* 1984, **40**, 1433–1456; (b) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc*., 2001, **123**, 7727–7729; (c) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315–4317; (d) R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, **42**, 4791–4793; (e) J.-B. Clement, J. F. Hayes, H. M. Sheldrake, P. W. Sheldrake, A. S. Wells, *Synlett.,* 2001, 1423–1427; (f) A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc*., 2002, **124**, 7421–7428; (g) F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett*., 2002, **4**, 581–584; (h) G. E. Job and S. L. Buchwald, *Org. Lett*., 2002, **4**, 3703–3706; (i) A. A. Kelkar, N. M. Patil and R. V. Chaudhari, *Tetrahedron Lett*., 2002, **43**, 7143–7146; (j) K. Yamada, T. Kubo, H. Tokuyama and T. Fukuyama, *Synlett.,* 2002, 231–234; (k) S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400–5449; (l) G. Evindar, R. A. Batey, *Org. Lett.*, 2003, **5**, 133–136; (m) F. Y. Kwong and S. L. Buchwald, *Org. Lett*., 2003, **5**, 793–796; (n) B. Mallesham, B. M. Rajesh, P. R. Reddy, D. Srinivas and S. Trehan, *Org. Lett*., 2003, **5**, 963–965; (o) L. Jiang, G. E. Job, A. Klapars and S. L. Buchwald, *Org. Lett.,* 2003, **5**, 3667–3669; (p) D. Ma, C. Xia, J. Jiang, J. Zhang and W. Tang, *J. Org. Chem*., 2003, **68**, 442–451; (q) Z. Lu, R. J. Twieg and S. D. Huang, *Tetrahedron Lett*., 2003, **44**, 6289–6292; (r) A. Klapars, S. Parris, K. W. Anderson and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529–3533; (s) S. Saito and Y. Koizumi, *Tetrahedron Lett.*, 2005, **46**, 4715–4717.

6 Recent examples: (a) S. R. Stauffer, S. Lee, J. P. Stambuil, S. I. Hauck amd J. F. Hartwig, *Org. Lett.*, 2000, **2**, 1423–1426; (b) L. M. Alcazar-Roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-Sands, I. A. Guzei, *J. Am. Chem. Soc.*, 2000, **122**, 4618–4630. (c) L. M. Alcazar-Roman and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 12905–12906; (d) R. Kuwano, M. Utsunomiya and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 6479–6486; (e) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653–6655; (f) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 13978–13980; (g) D. Zim and S. L. Buchwald, *Org. Lett*., 2003, **5**, 2413–2415; (h) M. W. Hooper, M. Utsunomiya and J. F. Hartwig, *J. Org. Chem*., 2003, **68**, 2861–2873; (i) Y. K. Liu, S. J. Lou, D. Q. Xu and Z. Y. Xu, *Chem. Eur. J*., 2010, **16**, 13590–13593.

7 Reviews: (a) J. F. Hartwig, *Synlett.,* 1997, 329–340; (b) J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852–860; (c) J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805–818; (d) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046–2067; (e) J. F. Hartwig, *Pure Appl. Chem.*, 1999, **71**, 1417–1423.

8 G. K. S. Prakash, C. Panja, T. Mathew, V. Surampudi, N. A. Petasis and G. A. Olah, *Org. Lett.*, 2004, **6**, 2205–2207.

9 S. Salzbrunn, J. Simon, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett.*, 2000, 1485−1487.

10 (a) D. M. Roundhill, *Chem. Rev.*, 1992, **92**, 1−27; (b) K. Weissermel and H. J. Arpe, Industry Organic Chemistry, Wiley-VCH, Weinheim, 1997.

11 D. I. Weisblatr, J. Magerlein and D. R. Myers, *J. Am. Chem. Soc*., 1953,**75**, 3630–3632.

12 (a) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791; (b) Y. Li, B.-J. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2011, **50**, 2115−2119.