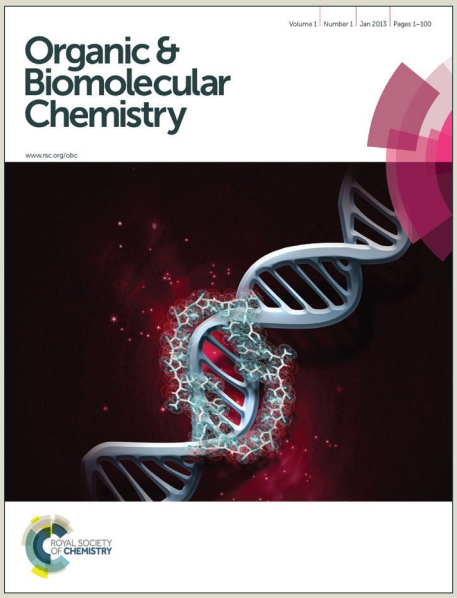
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. feng and X. Wu, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01301E.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB01301E

Journal Name

COMMUNICATION

A General Iodine-mediated Synthesis of Primary Sulfonamides from Thiols and Aqueous Ammonia

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

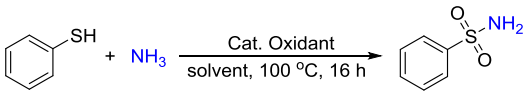
Jian-Bo Feng,[a,b] Xiao-Feng Wu[a,b*]

A general and efficient methodology for preparing primary sulfonamide has been developed. In the presence of iodine as the catalyst and TBHP (70% in water) as the oxidant, a wide range of primary sulfonamides were prepared from the corresponding thiols and aqueous ammonia in moderate to good yields.

Sulfonamide and its derivatives are very important structural moiety in biological compounds for their pharmaceutical activities including anticonvulsant,[1] anticancer,[2] antitumor,[3] anti-inflammatory[4] antibacterial[5] and HIV protease inhibitory activities.[6] Additionally, due to their easy removability, sulfonamides have also been utilized as protecting groups for both oxygen and nitrogen functionalizations.[7] As a consequence, numerous endeavours have been devoted to the construction of sulfonamides. The traditional procedures are based on the reaction of sulfonyl chlorides with amines.[8] Catalytic procedures with transition metals Pd,[9] Cu,[10] Ru,[11] Fe,[12] and Ir[13] as the catalysts have been developed as well. However, drawbacks still exist such as harsh reaction conditions, limited substrates scope, expensive transition metals catalysts demanding and so on. On the other hand, among all the sulfonamides, primary sulfonamides are known as zinc-binding groups (ZBGs) and presenting in natural products such as (−)-altemicidin and psammaplin C. But new synthetic procedure for primary sulfonamides synthesis is still limited. Notably, Song and co-workers developed an interesting iodine-mediated procedure in 2015.[14] The reaction proceeds at room temperature in water under metal- and base-free conditions, good yields of sulfonamides can be prepared from the corresponding sodium sulfinates and amines or ammonia. As our continuing interest in developing green synthetic methodologies,[15] here we would like to report our newly developed procedure on the direct synthesise of primary sulfonamide from thiols and aqueous ammonia under metal-free conditions.

Initially, a variety of iodide salts and iodine in the combination with TBHP were tested. As shown in table 1, all of them could afford the desired sulfonamide in moderate to good yields while no desired product could be detected under the catalyst-free condition (Table 1, entries 1-5). Among them, 89% of isolated yield can be achieved with iodine as the catalyst (Table 1, entry 2). Interestingly, decreasing the reaction temperature or the loading of catalyst or oxidant all lead to lower yields (Table 1, entries 2, 6, 7). Then different solvents were examined, although the desired primary sulfonamide can be obtained but acetonitrile still shown to be the most suitable solvent (Table 1, entries 8-12). TBHP is proven to be the best oxidant for this reaction system, after the testing of other organic oxidants (Table 1, entries 13-16).

Table 1. Optimization of reaction conditions.[a]



Entry	Catal.	Oxidant	Solvent	Yield (%)[b]
1	-	TBHP	CH_3CN	0
2	I_2	TBHP	CH_3CN	89 64[c]
3	KI	TBHP	CH_3CN	60
4	NaI	TBHP	CH_3CN	58
5	TBAI	TBHP	CH_3CN	56
6	I_2	TBHP	CH_3CN	58[d]
7	I_2	TBHP	CH_3CN	57[e]
8	I_2	TBHP	DMSO	24
9	I_2	TBHP	DCE	63
10	I_2	TBHP	1,4-Dioxane	85
11	I_2	TBHP	H_2O	9

a: Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou, Zhejiang Province 310018, People's Republic of China. E-mail: xiao-feng.wu@catalysis.de
b: Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany
Electronic Supplementary Information (ESI) available: [general procedure, analytic data and NMR spectrum]. See DOI: 10.1039/x0xx00000x

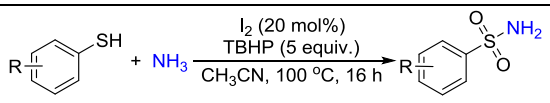
View Article Online
DOI: 10.1039/C6OB01301E

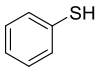
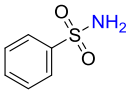
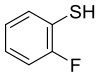
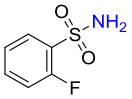
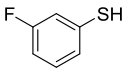
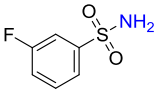
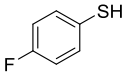
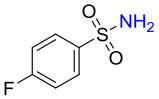
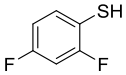
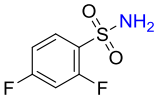
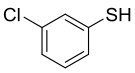
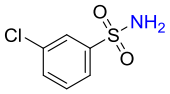
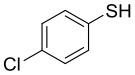
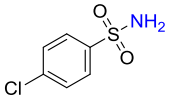
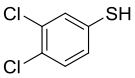
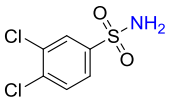
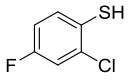
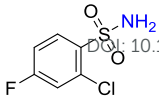
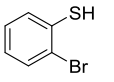
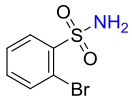
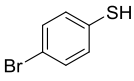
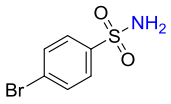
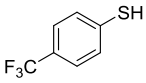
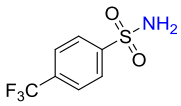
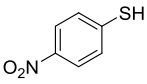
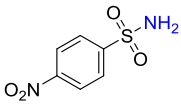
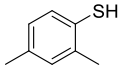
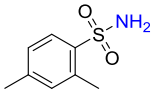
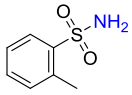
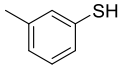
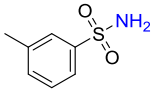
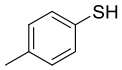
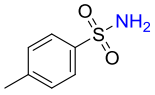
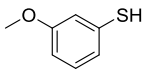
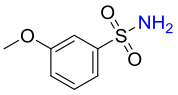
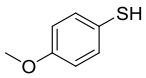
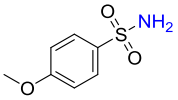
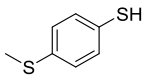
12	I_2	TBHP	EtOAc	78
13	I_2	H_2O_2	CH_3CN	0
14	I_2	DTBP	CH_3CN	0
15	I_2	TBP	CH_3CN	37
16	I_2	CHP	CH_3CN	32

a: reaction condition: thiol (1 mmol), NH_3 (5 equiv.; 25% in H_2O), TBHP (5 equiv.; 70% in water), CH_3CN (1 mL), 100 ℃, 16 h; b: isolated yields; c: 80℃; d: I_2 (5 mol%); e: TBHP (4 equiv.; 70% in water). H_2O_2 (30 wt. % in H_2O). DTBP: di-*tert*-butyl peroxide. TBP: *tert*-butyl perbenzoate. CHP: cumene hydroperoxide. TBAI: tetrabutylammonium iodide.

With the best reaction conditions in hand, a variety of functional group substituted substrates were tested subsequently. The obtained results shows, the yields of the desired products were found not influenced by the strict effects or electronic effects. In general, good yields can be achieved in all the tested cases. Interestingly, the 1*H*-benzo[*d*]imidazole-2-thiol can be tolerated well under this reaction condition and give 1*H*-benzo[*d*]imidazole-2-sulfonamide in 70 % yield (Table 2, entry 22).

Table 2. Synthesis of Primary Aromatic Sulfonamides.[a]



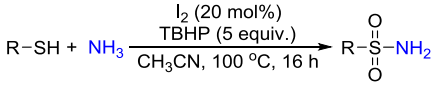
Entry	Substrate	Product	Isolated yield
1			89%
2			94%
3			65%
4			80%
5			42%
6			55%
7			64%
8			62%
9			60%
10			75%
11			70%
12			60%
13			75%
14			88%
15			87%
16			80%
17			86%
18			72%
19			56%
20			86%
21			87%
22			70%

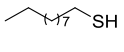
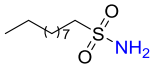
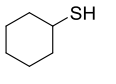
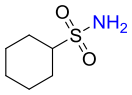
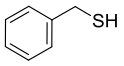
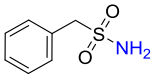
a: reaction condition: I_2 (20 mol%), thiol (1 mmol), NH_3 (5 equiv.; 25% in H_2O), TBHP (5 equiv.; 70% in water), CH_3CN (1 mL), 100 ℃, 16 h.

Then aliphatic and benzylic thiols were tested under our condisitons as well (Table 3). Moderate to good yields of the target products can be produced from decane-1-thiol, cyclohexanethiol and phenylmethanethiol successfully. In addition to ammonia, 2-methylpropan-2-amine was applied as well and give the desired product *N*-(*tert*-*butyl*)benzenesulfonamide in 97% yield (Scheme 1). Notably, *N*-(*tert*-

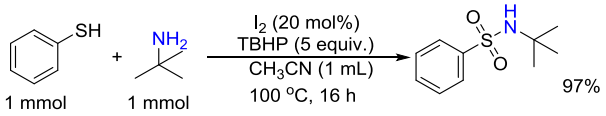
butyl)benzenesulfinamide can be isolated by decreasing the TBHP added.

Table 3. Synthesis of Primary Aliphatic Sulfonamides.[a]



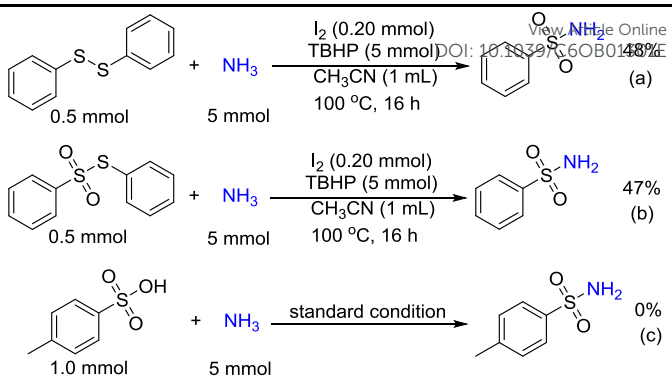
Entry	Substrate	Product	Isolated yield
1			57%
2			46%
3			71%

a: reaction condition: I_2 (20 mol%), thiol (1 mmol), NH_3 (5 equiv.; 25% in H_2O), TBHP (5 equiv.; 70% in water), CH_3CN (1 mL), 100 ℃, 16 h.



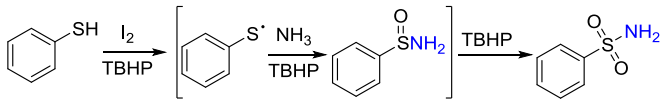
Scheme 1. The synthesis of *N*-(*tert-butyl*)benzenesulfonamide.

In order to get some understanding of the reaction pathway, several control experiments were performed. Disulfide as the possible intermediate was applied as starting material and treated under the optimal conditions. Unfortunately, only 48 % of the corresponding sulfonamide was obtained (Scheme 2, eq. a). S-phenyl benzenesulfonothioate which is considered as an oxidative intermediate of disulfide was tested under standard conditions as well, 47 % of the primary sulfonamide was afforded (Scheme 2, eq. b). We suspect that sulfonic acid which produced in situ from thiol might be the intermediate, but no corresponding product could be found with 4-methylbenzenesulfonic acid under our best conditions (Scheme 2, eq. c). These experiments exclude the possibility of them as intermediates. Additionally, no sulfonamide could be detected when TEMPO (2 equiv.) was added to the reaction mixture under our standard conditions.



Scheme 2. Control experiments.

Based on these results and literature,[16] a possible reaction pathway is been proposed (Scheme 3). Initially, thiol is been transformed into the corresponding radical which reacted with ammonia to give sulfinamide as the intermediate. Then sulfinamide can be further oxidized into the desired amide as the terminal product.



Scheme 3. Proposed reaction pathway for the synthesis of sulfonamide.

In conclusion, we have developed an efficient, practical and green methodology for the synthesis of primary sulfonamides. Various types of thiols can be applied as the substrates and give the desired sulfonamides in good to excellent yields.

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF), and the Deutsche Forschungsgemeinschaft for financial support. In addition, the research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (CHEM21) under grant agreement no. 115360, resources of which are composed of a financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. We also thank Dr C. Fischer, S. Schareina, and Dr W. Baumann for their excellent technical and analytical support. We also appreciate the general support from Prof. Matthias Beller.

Notes and references

[1] N. Siddiqui, S. N. Pandeya, S. A. Khan, J. Stables, A. Rana, M. Alam, M. F. Arshad and M. A. Bhat, *Bio.Med. Chem. Lett.,***2007**, *17*, 255-259.

[2] a) S. Andrea, O. Takashi, M. Antonio and T. S. Claudiu, *Curr. Med. Chem.,* **2003**, *10*, 925-953; b) A. Natarajan, Y. Guo, F. Harbinski, Y.-H. Fan, H. Chen, L. Luus, J. Diercks, H. Aktas, M. Chorev and J. A. Halperin, *J. Med. Chem.,* **2004**, *47*, 4979-4982; c)

N. S. Reddy, M. R. Mallireddigari, S. Cosenza, K. Gumireddy, S. C. Bell, E. P. Reddy and M. V. R. Reddy, *Bio. Med. Chem. Lett.,* **2004**, *14*, 4093-4097; d) S. Oh, H. I. Moon, I. H. Son and J. C. Jung, *Molecules,* **2007**, *12*, 1125.

[3] M. Banerjee, A. Poddar, G. Mitra, A. Surolia, T. Owa and B. Bhattacharyya, *J. Med. Chem.,* **2005**, *48*, 547-555.

[4] C. T. Supuran, A. Casini and A. Scozzafava, *Med. Res. Rev.,* **2003**, *23*, 535-558.

[5] M. Basanagouda, K. Shivashankar, M. V. Kulkarni, V. P. Rasal, H. Patel, S. S. Mutha and A. A. Mohite, *Eur. J. Med. Chem.,* **2010**, *45*, 1151-1157.

[6] a) S. Thaisrivongs, M. N. Janakiraman, K.-T. Chong, P. K. Tomich, L. A. Dolak, S. R. Turner, J. W. Strohbach, J. C. Lynn, M.-M. Horng, R. R. Hinshaw and K. D. Watenpaugh, *J. Med. Chem.,* **1996**, *39*, 2400-2410; b) M. N. Janakiraman, K. D. Watenpaugh, P. K. Tomich, K.-T. Chong, S. R. Turner, R. A. Tommasi, S. Thaisrivongs and J. W. Strohbach, *Bio. Med. Chem. Lett.,* **1998**, *8*, 1237-1242.

[7] a) W. Yuan, K. Fearon and M. H. Gelb, *J. Org. Chem.,* **1989**, *54*, 906-910; b) J. F. O'Connell and H. Rapoport, *J. Org. Chem.,* **1992**, *57*, 4775-4777; c) S. Chandrasekhar and S. Mohapatra, *Tetrahedron Lett.,* **1998**, *39*, 695-698.

[8] a) F. E. Scully and K. Bowdring, *J. Org. Chem.,* **1981**, *46*, 5077-5081; b) S. L. Graham and T. H. Scholz, *Synthesis,* **1986**, 1031-1032; c) Y. Huang, Y. Zhang and Y. Wang, *Tetrahedron Lett.,* **1997**, *38*, 1065-1066; d) A. Kamal, P. S. M. M. Reddy and D. R. Reddy, *Tetrahedron Lett.,* **2002**, *43*, 6629-6631; e) C. G. Frost, J. P. Hartley and D. Griffin, *Synlett,* **2002**, 1928-1930; f) S. Caddick, J. D. Wilden and D. B. Judd, *J. Am. Chem. Soc.,* **2004**, *126*, 1024-1025; g) Z. Liu and R. C. Larock, *J. Org. Chem.,* **2006**, *71*, 3198-3209; h) J. L. García Ruano, A. Parra, F. Yuste and V. M. Mastranzo, *Synthesis,* **2008**, 311-319; i) K. Bahrami, M. M. Khodaei and M. Soheilizad, *J. Org. Chem.,* **2009**, *74*, 9287-9291; j) R. J. Wakeham, J. E. Taylor, S. D. Bull, J. A. Morris and J. M. J. Williams, *Org. Lett.,* **2013**, *15*, 702-705; k) S. Yotphan, L. Sumunnee, D. Beukeaw, C. Buathongjan and V. Reutrakul, *Org. Biomol. Chem.,* **2016**, *14*, 590-597; l) A. S. Tsai, J. M. Curto, B. N. Rocke, A.-M. R. Dechert-Schmitt, G. K. Ingle and V. Mascitti, *Org. Lett.,* **2016**, *18*, 508-511.

[9] a) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.,* **2002**, *124*, 6043-6048; b) G. Burton, P. Cao, G. Li and R. Rivero, *Org. Lett.,* **2003**, *5*, 4373-4376; c) B. R. Rosen, J. C. Ruble, T. J. Beauchamp and A. Navarro, *Org. Lett.,* **2011**, *13*, 2564-2567; d) J. R. DeBergh, N. Niljianskul and S. L. Buchwald, *J. Am. Chem. Soc.,* **2013**, *135*, 10638-10641; e) B. Nguyen, E. J. Emmet and M. C. Willis, *J. Am. Chem. Soc.*, **2010**, *132*, 16372-16373; f) E. J. Emmet, C. S. Garcia-Rubia, B. Nguyen, A. B. Garcia-Rubia, R. Hayter and M. C. Willis, *Org. Biomol. Chem.*, **2012**, *10*, 4007-4014; g) H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson and M. C. Willis, *Org. Lett.,* **2011**, *13*, 4876-4878; h) W. Li, H. Li, P. Langer,M. Beller and X.-F.Wu, *Eur. J. Org. Chem.*, **2014**, 3101-3103; i) W. Li, M. Beller and X.-F. Wu, *Chem. Commun.*, **2014**, *50*, 9513-9516; j) A. S. Deeming, C. J. Russell and M. C. Willis, *Angew. Chem., Int. Ed.*, **2015**, *54*, 1168-1171; k) S. Ye and J. Wu, *Chem. Commun.*, **2012**, *48*, 7753-7755; l) S. Ye and J. Wu, *Chem. Commun.*, **2012**, *48*, 10037-10039; m) D. Zheng, Y. An, Z. Li and J. Wu, *Angew. Chem., Int. Ed.,* **2014**, *53*, 2451-2454; n) S. Ye, H. Wang, Q. Xiao, Q. Ding and J. Wu, *Adv. Synth. Catal.*, **2014**, *356*, 3225-3230; o) Y. An, D. Zheng and J. Wu, *Chem. Commun.*, **2014**, *50*, 11746-11748; p) Y. Luo, X. Pan, C. Chen, L. Yao and J. Wu, *Chem. Commun.*, **2015**, *51*, 180-182; q) D. Zheng, Y. Li, Y. An and J. Wu, *Chem. Commun.*, **2014**, *50*, 8886-8888.

[10] a) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon and P. K. Jadhav, *Tetrahedron. Lett.,* **2001**, *42*, 3415-3418; b)W. Deng, L. Liu, C. Zhang, M. Liu and Q.-X. Guo, *Tetrahedron. Lett.,* **2005**, *46*, 7295-7298; c) J. Baffoe, M. Y. Hoe and B. B. Touré, *Org. Lett.,* **2010**, *12*, 1532-1535; d) D. Audisio, S. Messaoudi, J. -F. Peyrat, J. -D. Brion and M. Alami, *J. Org. Chem.,* **2011**, *76*, 4995-5005; e) X. Tang, L. Huang, C. Qi, X. Wu, W. Wu and H. Jiang, *Chem. Commun.,* **2013**, *49*, 6102-6104; f) S. -Y. Moon, J. Nam, K. Rathwell and W.-S. Kim, *Org. Lett.,* **2014**, *16*, 338-341; g) N. Taniguchi, *Eur. J. Org. Chem.* **2010**, 2670-2673.

[11] F. Shi, M. K. Tse, S. Zhou, M.-M. Pohl, J. Radnik, S. Hübner, K. Jähnisch, A. Brückner and M. Beller, *J. Am. Chem. Soc.,* **2009**, *131*, 1775-1779.

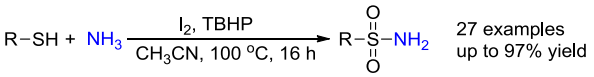
[12] W. Zhang and M. Luo, *Chem. Commun.,* **2016**, *52*, 2980-2983.

[13] D. Lee, Y. Kim and S. Chang, *J. Org. Chem.,* **2013**, *78*, 11102-11109.

[14] K. Yang, M. Ke, Y. Lin and Q. Song, *Green. Chem.,* **2015**, *17*, 1395-1399.

[15] a) J. -B. Feng, D. Wei, J. -L. Gong, X. Qi and X. -F. Wu, *Tetrahedron. Lett.,* **2014**, *55*, 5082-5084; b) J. -L. Gong, X. Qi, D. Wei, J. -B. Feng and X.-F. Wu, *Org. Biomol. Chem.,* **2014**, *12*, 7486-7488; c)J. -B. Feng and X. -F. Wu, *ChemistryOpen,* **2016**, DOI: 10.1002/open.201600023.

[16] a) D. Liu, A. Lei, *Chem. Asian J.* **2015**, *10*, 806-823; b) X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.*, **2014**, *12*, 5807-5817.



An efficient, practical and green methodology for the synthesis of primary sulfonamides has been developed. Various types of thiols can be applied as the substrates and give the desired sulfonamides in good to excellent yields.