RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Disulfides as Efficent Thiolating Reagents Enabling Selective Bis-sulfenylation of Aryl Dihalides Under Mild Copper-Catalyzed Conditions

Yunyun Liu,*[a] Hang Wang,[a] Jida Zhang,[b] Jie-Ping Wan[a] and Chengping Wen*[b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

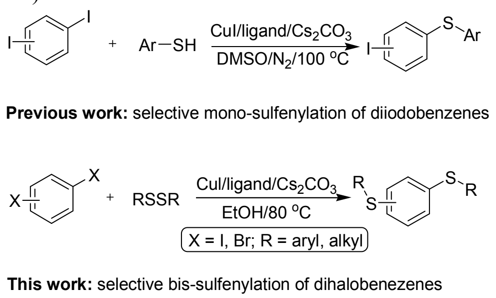
The selective bis-sulfenylation reactions of aryl dihalides have been achieved by copper-catalyzed C-S coupling reactions under mild conditions of refluxing EtOH (80 ^oC). Employment of disulfides as thiolating reagents enables the production of various bis(phenylthio)benzenes with excellent selectivity, and no products from mono C-S coupling are isolated.

Introduction

The formation of C-S bonds is one of the fundamental transformations of organic synthesis. Owing to the prevalent presence of C-S bond in biologically relevant compounds, natural products, argrochemicals and organic materials, the researches on the construction of C-S bonds, especially sp^2C-S bonds that involving the transformation of inactive sp^2C-X (X = halide, H etc) bonds have become an issue of widespread interests.[1-7] Presently, transition metal-catalyzed C-S coupling reactions between thiol nucleophiles and aryl/vinyl halides are amongst the most practical approach for the generation of sp^2C-S bonds.[8-9] Originally, this kind of reaction has been dominantly performed in the presence of a transition metal catalyst and high temperature in polar solvents such as DMSO, DMF or NMP.[10-12] Among the different transition metal species which have been used in the C-S cross-coupling reactions, copper catalysts have attracted tremendous attention because of their low cost as well as low toxicity.[13-30]

While spectacular progress has been witnessed in filed of C-S coupling chemistry during the past decade, interestingly, few attentions have been paid on the chemo-selective C-S coupling reactions of dihalide substrates. These kind of selective reactions providing mono- and bis-sulfenylated aryls, however, are crucial in expanding the application scope of C-S coupling chemistry by affording structurally diverse S-containing products. In 2011, Mao and coworkers reported the ligand-free bis-sulfenylation of diiodoaryls using thiols as S-nucleophiles in the presence of iron/copper mixed catalysts at 140 ^oC.[31] In addition, Bagley and coworkers reported the microwave irradiated, copper-catalyzed protocol which has also been found selectively promote the bis-sulfenylation of dihalobenzenes.[26] While these methods rely on the tough reaction conditions to achieve bis-sulfenylation, developing new methodologies enabling selective bis-sulfenylation reactions under milder conditions is highly demanding.

Following our previous work on copper-catalyzed selective mono-sulfenylation (Scheme 1)[32] as well as other related copper-catalyzed coupling chemistry,[33-37] we report herein the copper-catalyzed selective bis-sulfenylation of dihaloaryls under mild and clean conditions by using disulfides as bis-thiolating agents[38] (Scheme 1).



Scheme 1 Tunable mono- and bis-sulfenylation of dihaloaryls

Results and discussion

Since we previously discovered that using thiols in the coupling reactions with diiodobenzenes led to selective mono-sulfenylation,[32] in order to achieve the tunable selective bis-sulfenylation, we tentatively chosen disulfides as thiolating reagents in the reactions. Firstly, a class of aryl and alkyl disulfides were synthesized following a simple and clean method developed in our lab.[39] The reaction of 1,2-diiodobenzene **1a** and phenyl disulfide **2a** was then employed as model reaction for optimizing investigation. In the presence of CuI, Cs_2CO_3 at 120 ^oC in DMSO, a series of different ligands were firstly screened. It was found that the bis-sulfenylation could be achieved in the presence of CuI and different types of ligands. Among the examined ligands, including 1,10-phenanthroline (**L1**), 8-hydroxylquinoline (**L2**), L-proline (**L3**), D-glucose (**L4**) and two enaminone-based ligands (**L5** and **L6**), 2-hydroxylphenyl functionalized enaminone ligand **L5**[40] displayed the best effect in assisting the bis-sulfenylation reaction with 93 % yield of product **3a** (Fig. 1).

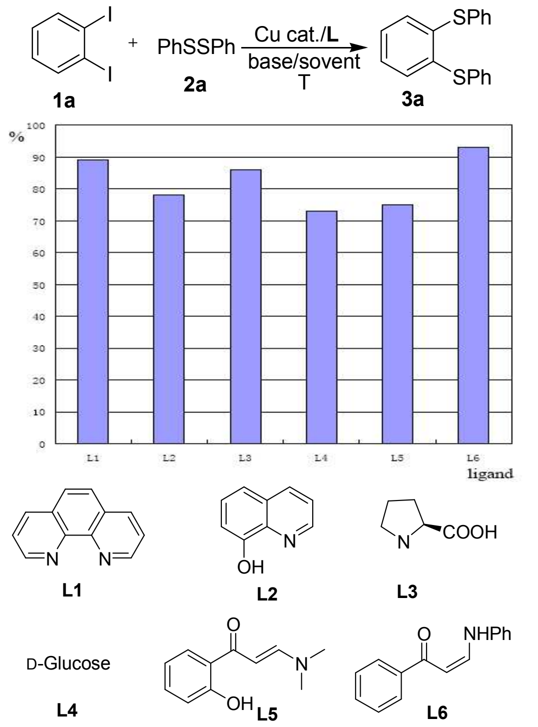


Figure 1 Different ligands for bis-sulfenylation of 1,2-diiodobenze; conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), Cs_2CO_3 (0.30 mmol), CuI (0.03 mmol) and ligand (0.03 mmol) in DMSO (1 mL), 120 °C, 15 h (TLC).

Subsequently, other parameters of the model reaction were investigated. The experiments employing different copper catalysts, including cupric, cuprous salts and copper dust, suggested that CuI was the most efficient catalyst (entries 1-6, Table 1). Examination on the effect of different organic and inorganic bases found no better alternative to Cs_2CO_3 (entries 7-10, Table 1). Experiments in different solvents implied that DMF, toluene or dioxane were not able to provide improved yield over DMSO, however, it has been found that ethanol as the solvent allowed smooth bis-sulfenylation reaction with excellent yield of **3a** at reflux and open air conditions (entries 11-14, Table 1). Other low boiling point solvent such as acetonitrile was not able to mediate the reaction effectively (entry 15, Table 1), demonstrating the unique advantage of ethanol in this selective bis-sulfenylation process. Finally, reducing the amount of CuI to 10 mol % loading gave **3a** with equally excellent yield (entry 16, Table 1). Further decreasing the catalyst loading, however, was not favored (entry 17, Table 1).

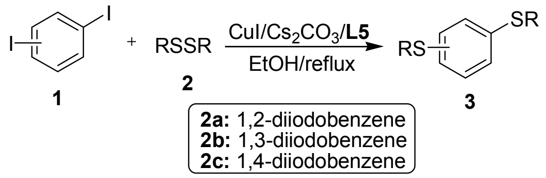
Table 1 Experiments on optimizing reaction conditionsa

Entry	Cat.	base	solvent	T(°C)	Yield (%)[b]
1	$CuCl_2\cdot 2H_2O$	Cs_2CO_3	DMSO	120	64
2	CuBr	Cs_2CO_3	DMSO	120	79
3	$CuBr_2$	Cs_2CO_3	DMSO	120	67
4	CuO	Cs_2CO_3	DMSO	120	59
5	Cu (dust)	Cs_2CO_3	DMSO	120	76
6	$Cu(OAC)_2\cdot H_2O$	Cs_2CO_3	DMSO	120	62
7	CuI	NaOH	DMSO	120	36
8	CuI	Et_3N	DMSO	120	67
9	CuI	t-BuOK	DMSO	120	trace
10	CuI	K_2CO_3	DMSO	120	87
11	CuI	Cs_2CO_3	DMF	120	89
12	CuI	Cs_2CO_3	toluene	reflux	69
13	CuI	Cs_2CO_3	dioxane	reflux	59
14	CuI	Cs_2CO_3	ethanol	reflux	95
15	CuI	Cs_2CO_3	MeCN	reflux	46
16[c]	CuI	Cs_2CO_3	ethanol	90	95
17[d]	CuI	Cs_2CO_3	ethanol	90	59

[a]General conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), Cu cat. (20 mol %), **L5** (20 mol %) and base (0.3 mmol) in solvent (1 mL), stirred for 15 h (TLC). [b]Yield of isolated product. [c]CuI in 10 mol %. [d]CuI in 5 mol %.

Under the optimal conditions, the application scope of this catalytic method has been investigated by subjecting different diiodoaryls and disulfides. As outlined in Table 2, this method has been found with excellent applicability for the synthesis of various bis(phenylthio)benzenes. 4-Substituted phenyl disulfides such as alkyl, halide substituted phenyl disulfides reacted with different diiodobenzenes **2a-2c** with generally excellent yields (**3a-3f**, **3n-3r** and **3u-3y**, Table 2). Similarly, 2- and 3-substituted phenyl disulfides also displayed excellent tolerance to this synthetic method by providing corresponding products with satisfactory yields (**3g-3i**, **3s-3t** and **3z**, Table 2). More importantly, other aryl disulfides such as naphthyl disulfide and heteroaryl disulfides also acted as double thiolating reagents to yield structurally divergent bis-thiolated benzenes **3j-3l** (Table 2).

Table 2 Application scope of the copper-catalyzed, EtOH mediated bis-sulfenylation of diiodoaryls.[a]

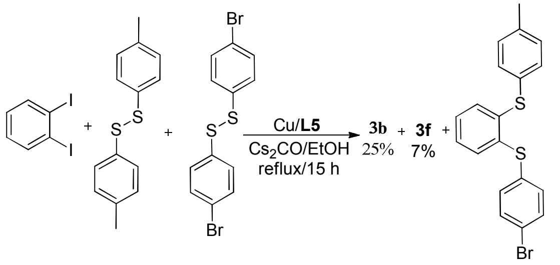


R	Diiodobenzene	Product	Yield (%)[b]
Ph	**2a**	**3a**	94
4-$CH_3C_6H_4$	**2a**	**3b**	91
4-*i*-PrC_6H_4	**2a**	**3c**	86
4-FC_6H_4	**2a**	**3d**	86
4-ClC6H4	**2a**	**3e**	85
4-BrC_6H_4	**2a**	**3f**	79
2-ClC_6H_4	**2a**	**3g**	82
2-$CH_3C_6H_4$	**2a**	**3h**	83
3-$CH_3C_6H_4$	**2a**	**3i**	94
naphth-2-yl	**2a**	**3j**	92
pyridine-2-yl	**2a**	**3k**	84
benzothiazol-2-yl	**2a**	**3l**	81
sec-butyl	**2a**	**3m**	72
Ph	**2b**	**3n**	91
4-$CH_3C_6H_4$	**2b**	**3o**	85
4-*i*-PrC_6H_4	**2b**	**3p**	82
4-FC_6H_4	**2b**	**3q**	82
4-ClC_6H_4	**2b**	**3r**	86
2-$CH_3C_6H_4$	**2b**	**3s**	81
2-ClC_6H_4	**2b**	**3t**	83
Ph	**2c**	**3u**	92
4-$CH_3C_6H_4$	**2c**	**3v**	94
4-*i*-PrC_6H_4	**2c**	**3w**	86
4-FC_6H_4	**2c**	**3x**	87
4-ClC_6H_4	**2c**	**3y**	87
3-$CH_3C_6H_4$	**2c**	**3z**	91
2-$NH_2C_6H_4$	-	-	-
2-$NO_2C_6H_4$	-	-	-

[a]General conditions: **1** (0.5 mmol), **2** (0.5mmol), CuI (0.05 mmol), **L5** (0.1 mmol) and Cs_2CO_3 (1.0 mmol) in alcohol (2 mL) , reflux for 15h. [b]Yield of isolated product.

Finally, it is noteworthy that alkyl disulfide was also able to incorporate diiodobenzene to give corresponding bis(alkylthio)benzene **3m**, albeit with lower yield than equivalent entries using aryl disulfides. Further attempts on running the bis-sulfenylation with amino and nitro functionalized phenyl disulfides revealded the intolerance of these groups to the present protocol (Table 2).

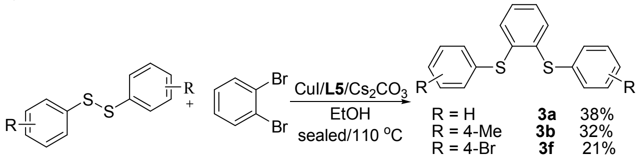
Based on the known conditions for bis-sulfenylation, the cross bis-sulfenylation using two different disulfides to incorporate 1,2-diiodobenzene was attempted. As outlined in Scheme 2, the reaction employin simultaneously tolyldisulfide and *p*-bromophenyl disulfide led to the production of three mixted products, including the products **3b**, **3f** from homo-bis-sulfenylation as well as product **3bf** from cross bis-sulfenylation.



3bf, 36%

Scheme 2 Bis-sulfenylation with 2 different disulfides

Following the good results provided the reactions of diiodobenzenes, the entries using 1,2-dibromobenzene have also been investigated. However, the expect products could only be obtained with low to fair yields from these experiments, although harsher conditions (sealed tube, 110 °C) were employed (Scheme 3).



Scheme 3 Bis-sulfenylation reactions of 1,2-dibromobenzene

Conclusions

The selective bis-sulfenylation reactions of aryl dihalides have been achieved with excellent efficiency by employing the disulfides as double thiolating reagent. The present method provided a highly useful methodology for the synthesis of bis(phenylthio)benzenes of type **3**. This method also possessed notable advantages such as green reaction medium, mild conditions and full utility of thiolating reagents.

Acknowledgments

This work is financially supported by NSFC of China (No. 21202064), a research project of the Jiangxi Provincial Department of Education (No. GJJ12211), a Sponsored Program for Cultivating Youths of Outstanding Ability in Jiangxi Normal University (Y. Liu) and a program Sponsored by Zhejiang Provincial Program for the Cultivation of High-level Innovative Health talents (C. Wen).

Notes and references

[a] *Key Laboratory of Functional Small Organic Molecules, Ministry of Education, College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. of China. Fax: +86 791 8812 0380; Tel: +86 791 8812 0380; E-mail: chemliuyunyun@gmail.com*
[b] *College of Basic Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, P R China. E-mail: cpwen.zcmu@yahoo.com; Fax: +86 571 86633131; Tel: +86 571 86633131*

† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data of all products, ^1H and ^{13}C NMR spectra of all products]. See DOI: 10.1039/b000000x/

1 F. M. Menger and V. A. Azov, *J. Am. Chem. Soc.*, 2002, **124,** 11159-11166.
2 J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.
3 W. Ge and Y. Wei, *Synthesis,* 2012, **44**, 934.
4 D. N. Jones, *Comprehensive Organic Chemistry,* Vol. 3, Eds.: D. H. Barton and D. W. Ollis, Pergamon, New York, 1979.
5 J. H. Hutchinson, D. Riendeau, C. Brideau, C. Chan, J.-P. Falgueyret, J. Guay, T. R. Jones, C. Lepine, D. Macdonald, C. S. MeFarlane, H. Piechuta, J. Scheigetz, P. Tagari, M. Therien and Y. Girard, *J. Med. Chem.*, 1994, **37**, 1153.
6 S. S. Khandekar, D. R. Gentry, G. S. Van Aller, M. L. Doyle, P. A. Chambers, A. K. Konstantinidis, M. Brandt, R. A. Daines and J. T. Lonsdale, *J. Biol. Chem.*, 2001, **276**, 30024.
7 J. Sun, X. Lu, J. Shao, Z. Cui, Y. Shao, G. Jiang, W. Yu and X. Shao, *RSC Adv.*, 2013, **3**, 10193.
8 I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596.
9 K. Kunz, U. Scholz and D. Ganzer, *Synlett,* 2003, 2428.
10 Pd-catalyzed C-S coupling: T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato and M. Kosugi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1385.
11 Ni-catalyzed C-S coupling : C. Millois and P. Diaz. *Org. Lett.*, 2000, **2**, 1705.
12 Co-catalyzed C-S coupling: Y.-C. Wong, T. T. Jayanth and C.-H. Cheng, *Org. Lett.*, 2006, **8**, 5613.
13 C. Palomo, M. Oiarbide, R. Lopez and E. Gomez-Bengoa, *Tetrahedron Lett.*, 2000, **41**, 1283.
14 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517.
15 C. G. Bate, R. K. Gujadhur and D. Venkataraman, *Org. Lett.*, 2002, **4**, 2803.
16 W. Deng, Y. Zou, Y.-F. Wang, L. Liu and Q.-X. Guo, *Synlett,* 2004, 1254.
17 Y.-J. Wu and H. He, *Synlett,* 2003, 1789.
18 C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.* 2002, **4**, 4309.
19 Y.-J. Chen and H.-H. Chen, *Org. Lett.*, 2006, **8**, 5609.
20 L. Rout, T. K. Sen and T. Punniyamurthy, *Angew. Chem. Int. Ed.*, 2007, **46**, 5583.
21 P. S. Herradura, K. A. Pendola and R. K. Guy, *Org. Lett.*, 2000, **2**, 2019.
22 S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400.
23 D. Ma, X. Lu, L. Shi, H. Zhang, Y. Zhang and X. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 1118.
24 D. Zhu, L. Xu, F. Wu and B. S. Wan, *Tetrahedron Lett.*, 2006, **47**, 5781.
25 C. Gonzalez-Arellano, R. Luque and D. J. Macquarrie, *Chem. Commun.*, 2009, 1410.
26 M. C. Bagley, M. C. Dix and V. Fusillo, *Tetrahedron Lett.*, 2009, **50**, 3661.
27 Li, X. Li, H. Wang, T. Chen and Y. Xie, *Synthesis,* 2010, 3602.
28 M.-T. Lan, W.-Y. Wu, S.-H. Huang, K.-L. Luo and F.-Y. Tsai, *RSC Adv.*, 2011, **1**, 1751.
29 H.-J. Xu, Y.-F. Liang, X.-F. Zhou and Y.-S. Feng, *Org. Biomol. Chem.*, 2012, **10**, 2562.
30 S. G. Babu and R. Karvembu, *Tetrahedron Lett.*, 2013, **54**, 1677.
31. X. Qu, T. Li, Y. Zhu, P. Sun, H. Yang and J. Mao, *Org. Biomol. Chem.*, 2011, **9**, 5043.
32. Y. Liu, H. Wang, X. Cao, Z. Fang and J.-P. Wan, *Synthesis,* 2013, **45**, 2977.

33. Y. Liu and J.-P. Wan, *Chem. Asian J.,* 2012, **7**, 1488.
34. Y. Liu and J.-P. Wan, *Org. Biomol. Chem.,* 2011, **9**, 6873.
35. J.-P. Wan, C. Wang and Y. Liu, *Org. Biomol. Chem.,* 2011, **9**, 6481.
36. Y. Liu, C. Wang, X. Wang and J.-P. Wan, *Tetrahedron Lett.,* 2013, **54**, 3953.
37 J.-P. Wan, C. Wang and Y. Liu, *Appl. Orgnometal. Chem.,* 2012, **26**, 445.
38 For example on the Cu-catalyzed S-S cleavage of disulfides, J. Srogl, J. Hývl, Á. Révész and D. Schröder, *Chem. Commun.,* 2009, 3463.
39 Y. Liu, H. Wang, C. Wang, J.-P. Wan and C. Wen, *RSC Adv.,* 2013, **3**, 21369.
40 For the application of enaminone-based ligand in copper-catalyzed C-heteroatom coupling reactions, see also: (a) R. Xu, J.-P. Wan, H. Mao and Y. Pan, *J. Am. Chem. Soc.,* 2010, **132**, 15531. (b) R.-S. Xu, L. Yue and Y.-J. Pan, *Tetrahedron,* 2012, **68**, 5046. (c) C. Cheng, G. Sun, J. Wan and C. Sun, *Synlett,* 2009, 2663.