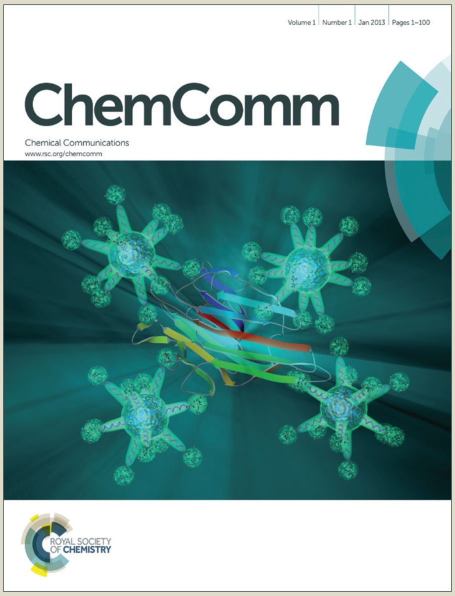
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COMMUNICATION

Palladium-catalyzed thiolation of alkanes and ethers with arylsulfonyl hydrazides

Sheng-rong Guo [a, b] Wei-ming He [a] Jian-nan Xiang* [a] and Yan-qin Yuan * [b]

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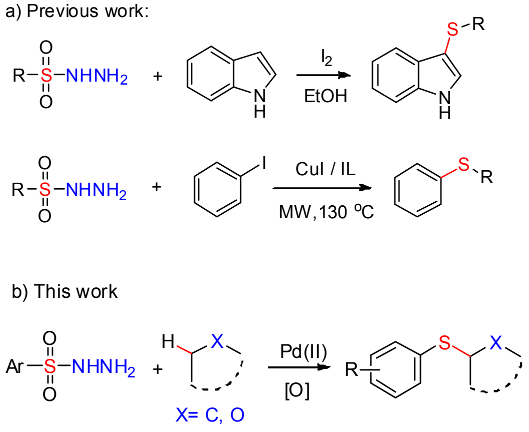
A new method for the preparation of alkyl and aryl sulfides through direct oxidative thiolation of alkanes or ethers with arylsulfonyl hydrazide using *di*-tert-butyl peroxide (DTBP) as oxidant catalyzed by $Pd(OAc)_2$ has been reported. The C-H bond in various alkanes or ethers were successfully converted into C-S bond to yield the e corresponding sulfides in moderate to good yields.

The formation of the carbon-sulfur bond has received much attention as organosulfur compounds widely exist in many natural products, functional materials, and synthetic drugs.[1] With the devolepment of the direct functionalization of C-H bonds, remarkable progress has been made in the direct C-S bond formations.[2] The first example of direct C(sp^2)-H bond thiolation catalyzed by copper salt was reported by Yu in 2006, [2a] Subsequently, many sulfuration agents like disulfides,[2c-2f,] *S*-arylthiophthalimides,[3] sulfonyl hydrazide,[2i,4] sulfonyl chlorides,[5] mesitylphenyl sulfide [6] have been used for direct arylthiolation of the benzoxazole, benzothiazole, indole in presence of different metal catalysts. However, these reactions also suffer from the high loading of metal catalyst or addition of superstoichiometric amounts of metal additives and harsh reaction conditions.

Free-radical-initiated sp^3-hybridized C−H bond activation received much importance now adays. The α-position of C-H bond in many stable compounds such as alcohols,[7] ethers,[8] amines,[9] and 1,3-dicarbonyl compounds [10] were activated by the radical ion and formed a more usable C-X (X = C, O, N, S) bond. However, the selective activation of the inactive sp^3-hybridized C−H bonds in simple alkanes or ethers to generate C−S bonds has remained a challenging task.

Sulfonyl hydrazides have been widely used as reductants and as well as a source of sulfonylation and arylation[11]. Very recently, Tian [2i] reported sulfenylation of indoles using sulfonyl hydrazides as an effective sulfur electrophiles and aryl thiol surrogate. Singh [4b] also observed a similar C-S bond formation reaction of sulfonyl hydrazides with aryl halides or aryl acetylenes under microwave irradiation (Scheme 1, ***a***). Our group is interested in the arylthiolation of C-H bond, [3e] To the best of our knowledge, no reports of oxidative C (sp^3)-H bond thiolation of alkanes or ethers with sulfonyl hydrazide as a thiol equivalent are known till now, Herein, we have reported a novel protocol to construct unsymmetrical sulfides using arylsulfonyl hydrazides as sulfur sources (Scheme 1, ***b***).

Scheme 1. Approaches of C-S Bond Formation using arylsulfonyl hydrazides as sulfur sources



Inspired by the work of Tian, [2i] our initial attempt started with the reaction of *p*-toluenesulfonyl hydrazide **1a** (1.0 mmol) and cyclohexane **2a** (4 ml) catalyzed with 20 mol% iodine at 120 °C (Table 1, entry 1), but the reaction did not occur. We were delighted from the results of GC-MS, that the reaction could take place with a low yields using DTBP (2.0eq) as an oxidant in absence of iodine (Table 1, entry 2). Attracted by this reductive elimination reaction promoted by the DTBP, efforts were then made to improve the yield of this novel direct arylthiolation reaction.

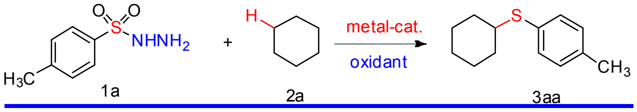
We initiated optimization of the arylthiolation using transition-metal catalysts. The reaction was carried out using **1a** (1.0 mmol) in cyclohexane (4ml) with 2 mol % $PdCl_2$ as catalyst and 2.0 eq DTBP as an oxidant at 120 °C. The yield was found to be increased up to 38% (Table 1, entry 3), so we envisioned that metal-catalyst might be utilized to the cleavage of sulfur–nitrogen bonds and hence the important variable to be optimized in the arylthiolation process. So, different transition metal catalysts viz. $Pd(OAc)_2$, $PdBr_2$, $(CH_3CN)_2PdCl_2$ $(Ph_3P)_2PdCl_2$, CuI, $Cu(OTf)_2$ and $FeCl_3{\cdot}6H_2O$ were tested to determine their catalytic efficacy. Exceedingly high product yield (83%) was obtained in the presence of $Pd(OAc)_2$ (Table 1, entry 4). As a result, other palladium salts such as $PdBr_2$, $(CH_3CN)_2PdCl_2$ and $(Ph_3P)_2PdCl_2$ were also screened (table 1, entries 5-7), but none of them was found to be superior. The formation of the desired product halted with other metal catalysts, such as CuI, $Cu(OTf)_2$, and $FeCl_3{\cdot}6H_2O$. (table 1, entries 8-10). Obviously, the palladium, play a pivotal role in the catalytic cycle, although the exact reason is unclear.

However, the oxidant also plays an important role in the activation of the inactive C−H bond. In the absence of oxidant, diaryl disulfide was observed as the major product. To investigate the importance of oxidants for the thiolation reaction, we replaced DTBP with other oxidants, such as *tert*-butyl hydroperoxide (TBHP), ceric ammonium nitrate (CAN), $(NH_4)_2S_2O_8$, $PhI(OAc)_2$ or benzoquinone (BQ) under identical conditions, but no conversion was observed (entries 11-16). While a moderate yield was obtained with dicumyl peroxide (DCP) and *tert*-butyl perbenzoate (TBPB) (entries 17-18), DTBP was proved to be the best oxidant. The appropriate amount of DTBP was 2.0 equiv and no significant increased yield of **3aa** was observed with less or more than 2.0 equiv of DTBP (entries 19-20). It is worth noting that a moderate yield could be achieved when the amount of the catalyst loading was decreased to 1 mol % (entry 21). A lower yield was obtained when we further decreased the catalyst loading to 0.5 mol % (entry 22).

Under the optimized reaction conditions, the reactivities of different arylsulfonyl hydrazides as arylthiolation reagents were investigated. The results are revealed in Table 2. Arylsulfonyl hydrazides bearing both electron-donating groups (R = Me, OMe, *t*-Bu) and electron-withdrawing groups (R = Br, Cl, F, CF_3) at the *para* and *ortho* positions reacted with cyclohexane and afforded the desired sulfides in moderate to good yields (entries 3aa-3ah), but the yield was decreased for the effect of sterically hindered functional groups (entries 3aj-3ao). It is worth noting that this protocol is also applicable to heterocyclic aromatics such as thiophene (entry 3ai). However, when arylsulfonyl hydrazides containing-nitro or hydroxyl was used as substrate, no desired crosscoupling product was observed.

Subsequently, the scope of alkanes in the present reaction was also examined (Table 3). It was gratifying to find that a variety of alkanes could couple with hydrazides and the results did not show evident difference compared with the reaction of cyclohexane. The cyclopentane and cyclooctane were all found to be effective with a series of arylsulfonyl hydrazides, and the corresponding products were obtained in moderate to good yields (entries 1-12). The sterics hindrance of arylsulfonyl hydrazides have some influence to the yield of the reaction (entries 5-6, 10-12). It is interesting that the reaction showed intramolecular regioselectivity, in which secondary C−H had a less reactivity than tertiary C−H (Table 3, entries 13-14), a more active than primary C−H (Table 3, entry 15). In the case of adamantine, the reaction achieved with moderate yields, but the main thiolation reaction take place on the tertiary carbon atom and the two regioisomers ratio was 92 % : 8 % detected by the NMR analysis (entry 13). While the reaction of *n*-pentane with **1a** led to at least three regioisomers with 82 % combined yield and the ratio is about 54% : 20 %: 26 % (entry 15).

Table 1. Optimization of the Reaction Conditions [a]

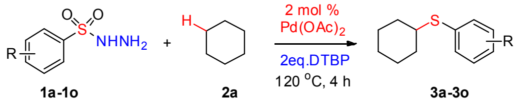


entry	Oxidant (equiv)	Catalyst (mol%)	yield (%) [b]
1	I_2 (0.2)	—	N.D.
2	DTBP (2.0)	—	18
3	**DTBP (2.0)**	$PdCl_2$(2.0)	38
4	DTBP (2.0)	$Pd(OAc)_2$(2.0)	**83**
5	DTBP (2.0)	$PdBr_2$(2.0)	31
6	DTBP (2.0)	$(CH_3CN)_2PdCl_2$(2.0)	76
7	DTBP (2.0)	$(Ph_3P)_2PdCl_2$(2.0)	70
8	DTBP (2.0)	CuI(2.0)	N.D. [c]
9	DTBP (2.0)	$Cu(OTf)_2$(2.0)	N.D. [c]
10	DTBP (2.0)	$FeCl_3{\cdot}6H_2O$(2.0)	N.D. [c]
11	TBHP (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
12	CAN (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
13	$(NH_4)_2S_2O_8$ (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
14	$K_2S_2O_8$ (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
15	$PhI(OAc)_2$ (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
16	BQ (2.0)	$Pd(OAc)_2$(2.0)	N.D. [c]
17	DCP (2.0)	$Pd(OAc)_2$(2.0)	78
18	TBPB (2.0)	$Pd(OAc)_2$(2.0)	65
19	DTPB (1.0)	$Pd(OAc)_2$(2.0)	67[d]
20	DTPB (3.0)	$Pd(OAc)_2$(2.0)	82[e]
21	TBPB (2.0)	$Pd(OAc)_2$(1.0)	78
22	TBPB (2.0)	$Pd(OAc)_2$(0.5)	51

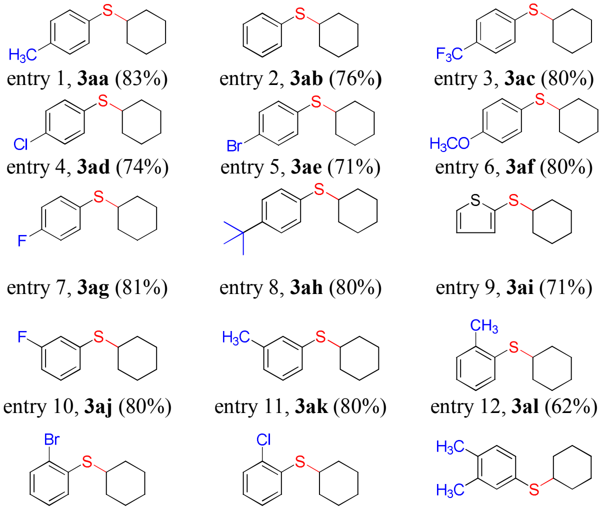
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (4 mL), heated at 120 °C for 4 h with 2.0 mmol % catalyst. [b] Isolated yield. [c] Not detected by GC-MS. [d] DTBP (1.0 equiv). [e] DTBP (3.0 equiv).

Encouraged by above successful synthesis and our previous work, we lastly tried the direct thiolation reaction with ethers such as THF, 1,4-dioxane and methyl *tert*-butyl ether (Table 3, entries 16-24). Under the same reaction conditions, the reactions of THF and 1,4-dioxane with arylsulfonyl hydrazides proceeded smoothly to generate the corresponding sulfides in moderate to good yields (Table 3, entries 16-21). as evident from the yields of products 3cg-3ci (Table 3, entries 22-24), the steric effect of methyl *tert*-butyl ether plays an important role in the reaction.

Table 2. Thiolation of Cyclohexane with arylsulfonyl hydrazides [a,b]



1a-1o **2a** **3a-3o**



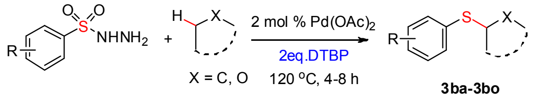
entry 1, **3aa** (83%)
entry 2, **3ab** (76%)
entry 3, **3ac** (80%)
entry 4, **3ad** (74%)
entry 5, **3ae** (71%)
entry 6, **3af** (80%)
entry 7, **3ag** (81%)
entry 8, **3ah** (80%)
entry 9, **3ai** (71%)
entry 10, **3aj** (80%)
entry 11, **3ak** (80%)
entry 12, **3al** (62%)
entry 13, **3am** (61%)
entry 14, **3an** (51%)
entry 15, **3ao** (74%)

[a] Reaction were acrried out using **1** (1.0 mmol), **2a** (4mL), DTBP (4 mmol) at 120 °C for 4 h. [b] Isolated yield based on **1**.

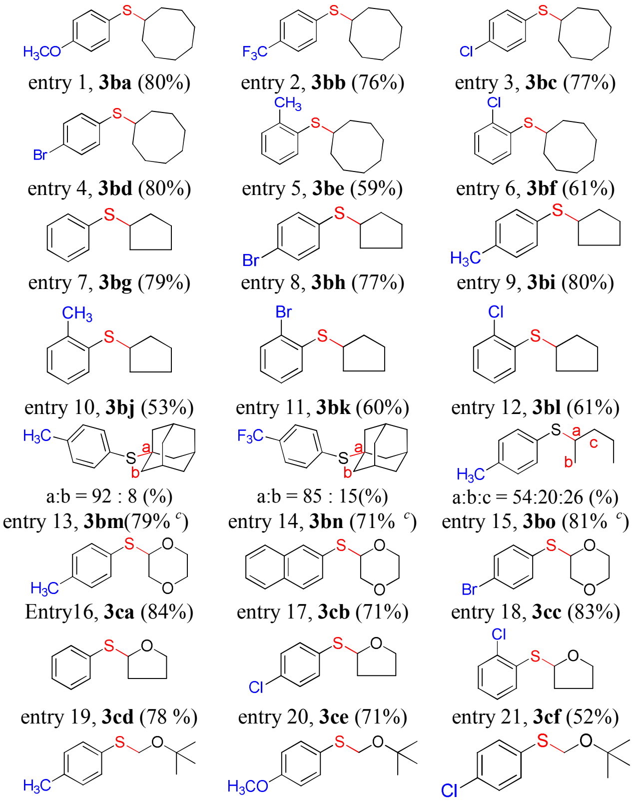
To investigate the possible mechanism for this arylthiolation, a series of experiments were carried out. The disulfide was the major product when the model reaction was carried out only using 2 mol % Pd(OAc)$_2$ as catalyst without DTBP. We also found the diaryl disulfide could react with cyclohexane smoothly with 92% yield (Scheme 2). While the formation of desired product **3aa** was suppressed by addition of TEMPO as a radial inhibitor, thus revealing that the initial step of the transformation probably caused by a radical process.[8, 10]

According to above experimental results and the literature precedent,[2e, 2i, 2j, 4b] we propose a plausible mechanism. Arylsulfonyl hydrazide converted into the intermediate of disulfide catalyzed by Pd(OAc)$_2$. On the other side, the *tert*-butoxyl radical, which formed by the decomposition of DTBP under heating condition, can abstract hydrogen from the cylclohexane to generate the corresponding alkyl radical intermediate, and then the radical intermediate reacted with disulfide affording the product and ArS· free radical which was be trapped by another alkyl radical (Scheme 3).

Table 3. Thiolation of Alkanes and Ethers [a,b]



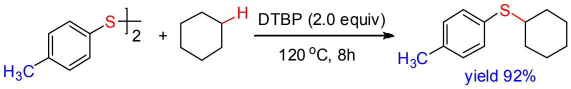
1 **2b-2c** **3ba-3bo** **3ca-3ci**



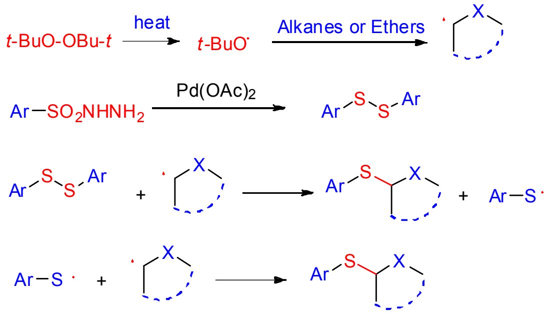
entry 1, **3ba** (80%)
entry 2, **3bb** (76%)
entry 3, **3bc** (77%)
entry 4, **3bd** (80%)
entry 5, **3be** (59%)
entry 6, **3bf** (61%)
entry 7, **3bg** (79%)
entry 8, **3bh** (77%)
entry 9, **3bi** (80%)
entry 10, **3bj** (53%)
entry 11, **3bk** (60%)
entry 12, **3bl** (61%)
a:b = 92 : 8 (%)
entry 13, **3bm**(79% [c])
a:b = 85 : 15(%)
entry 14, **3bn** (71% [c])
a:b:c = 54:20:26 (%)
entry 15, **3bo** (81% [c])
Entry16, **3ca** (84%)
entry 17, **3cb** (71%)
entry 18, **3cc** (83%)
entry 19, **3cd** (78 %)
entry 20, **3ce** (71%)
entry 21, **3cf** (52%)
entry 22, **3cg** (68%)
entry 23, **3ch** (65%)
entry 24, **3ci** (58%)

[a] Reaction were carried out using **1** (1.0 mmol), **2** (2 mL), DTBP (4 mmol) at 120 ºC for 12 h. [b] Isolated yield based on **1**. [c] **1** (1.0 mmol), **2** (2.0 mmol), DTBP (4 mmol), CH_3CN (3 ml) at 120 ºC for 4-8 h.

Scheme 2. the reaction of diphenyldisulfide with cyclohexane using DTBP as oxidant



Scheme 3. A Plausible Reaction Mechanism



In summary, we have developed an novel and efficient oxidative arylthiolation reaction using arylsulfonyl hydrazides as sulfur sources for the synthesis of aryl alkyl sulfides. In the presence of 2 mol% of Pd(OAc)$_2$ and DTBP as an oxidant, a broad range of arylsulfonyl hydrazides react with alkanes and ethers smoothly giving arylthioyl substituted alkenes in moderate to good yields and with excellent regioselectivity. Importantly, this system provides a free-radical pathway for the sp^3 C–H activation/ C–S bond formation of hydrocarbons and ethers.

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Notes and references

[a] *College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China*
[b] *Department of Chemistry, Lishui University, 323000, Lishui, P.R. China,*
[*] *E-mail: guosr9609@lsu.edu.cn , jnxiang@hnu.edu.cn*

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