Tetrahedron Letters 53 (2012) 3907–3910

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A concise synthetic strategy to alkynyl sulfides via transition-metal-free catalyzed C–S coupling of 1,1-dibromo-1-alkenes with thiophenols

Zhangqin Ni, Sichang Wang, Hui Mao, Yuanjiang Pan *

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

ARTICLE INFO

Article history:
Received 13 March 2012
Revised 7 May 2012
Accepted 15 May 2012
Available online 19 May 2012

Keywords:
Transition-metal-free
C–S cross-coupling
Alkynyl sulfides

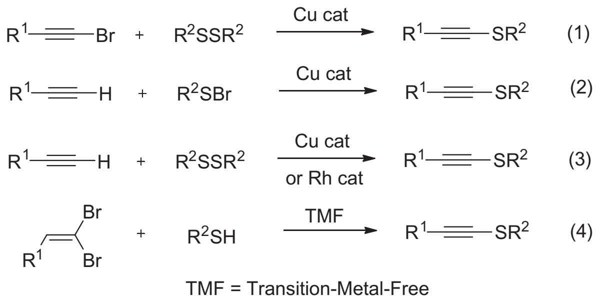
ABSTRACT

A novel synthetic strategy to alkynyl sulfides via transition-metal-free catalyzed C–S coupling of 1,1-dibromo-1-alkenes with thiophenols has been developed. The new strategy which avoided the transition-metal toxicities is environmental friendly and very important for alkynyl sulfides synthesis.

The development of transition-metal-catalyzed cross-coupling reactions is one of the most significant advances in modern organic synthesis and has received much attention due to their efficient construction of C–C bond and C–X bond.[1] Alkynyl sulfides are very important intermediates in organic synthesis and can be used as versatile building blocks for a variety of chemical purposes, such as cycloaddition[2] and cross-coupling reactions.[3] Generally, the most precedent methodologies are based on the use of transition-metal catalysts (Scheme 1). A report by Braga et al. in 1993 described the synthesis of alkynyl sulfides by reacting alkynyl bromides with disulfides in the presence of CuI (Eq. 1).[4] Later, they also developed an alternative preparation by employing terminal alkynes with thiophenols (Eq. 2).[5] Recently, copper and rhodium reagents were, respectively, used by the groups of Bieber[6] and Yamaguchi[7] to catalyze the C–S coupling of 1-alkynes with disulfides (Eq. 3).

To our knowledge, few studies[8] are focused on the formation of alkynyl sulfides without transition metal reagents. These methods suffer from strict conditions and limited scopes. On the basis of the promising potentialities of alkynyl sulfides, it would be desired to develop a general method for the synthesis without any transition-metals. Drawing from recent experiences in the field of construction of C–X bond, vinyl dibromides were used to construct alkynes by the groups of Evano,[9] Rao,[10] and Hayes.[11] Herein, we report the first example for the synthesis of alkynyl sulfides from vinyl dibromides without any transition-metals (Eq. 4).

We initiated our studies by examining the reaction of thiophenol (**2a**) with 1.2 equiv of (2,2-dibromovinyl)benzene[12] (**1a**) in DMSO in the presence of CuI (10 mol %), DMEDA (10 mol %), and K_2CO_3 (4 equiv) (Table 1, entry 1). The reaction was completely ineffective in this condition. The desired product still could not be obtained adopting other similar ligands (Table 1, entries 2–4). It was interesting to find that the reaction could occur in the absence of CuI and ligand, and gave the product (phenylethynyl)(phenyl)sulfide (**3a**) with 39% yield (Table 1, entry 5). Inspired by this result, we further investigated this transformation under different conditions. Various bases were evaluated in this reaction and Cs_2CO_3 was proved to be most effective (Table 1, entries 5–10). Further optimization was focused on reaction temperature and solvent effect. The reaction got lower yield in 90 °C or 110 °C compared with that in 100 °C (Table 1, entries 6, 11, 12). It was turned out that the solvent is an important factor of the reaction. The non-polar solvents such as dioxane and toluene could not afford the desired product. The reaction could happen in polar solvents, but the yield in DMF was lower than that in DMSO (Table 1, entries 6, 13–15). Finally, it was realized that the optimum condition to



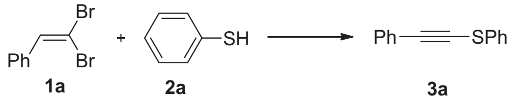
Scheme 1. The synthetic methodologies of alkynyl sulfides.

---

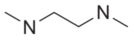
* Corresponding author.
E-mail address: cheyjpan@zju.edu.cn (Y. Pan).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.072

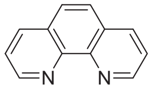
Table 1
Screening of reaction conditions for synthesis of alkynyl sulfides[a]



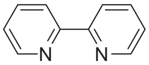
Entry	Additive	Base	Temp (°C)	Solvent	Yield[b] (%)
1	CuI/L$_1$	K_2CO_3	100	DMSO	N.R[c]
2	CuI/L$_2$	K_2CO_3	100	DMSO	N.R
3	CuI/L$_3$	K_2CO_3	100	DMSO	N.R
4	CuI/L$_4$	K_2CO_3	100	DMSO	N.R
5	No	K_2CO_3	100	DMSO	39
6	No	Cs_2CO_3	100	DMSO	55
7	No	K_3PO_4	100	DMSO	50
8	No	Na_2CO_3	100	DMSO	30
9	No	Et_3N	100	DMSO	N.R
10	No	*t*-BuONa	100	DMSO	N.R
11	No	Cs_2CO_3	90	DMSO	45
12	No	Cs_2CO_3	110	DMSO	34
13	No	Cs_2CO_3	100	DMF	48
14	No	Cs_2CO_3	100	1,4-Dioxane	N.R
15	No	Cs_2CO_3	100	Toluene	N.R



L1



L2



L3

PPh_3

L4

---

[a] All the reactions were conducted with (2,2-dibromovinyl)benzene (1.2 equiv, 0.75 mmol), thiophenol (1 equiv, 0.5 mmol), and base (4 equiv, 2 mmol) in 3 mL of solvent under nitrogen atmosphere, 10 h.

[b] Isolated yield.

[c] Pure product was not obtained.

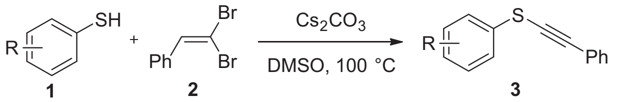
obtain high coupling yield was Cs_2CO_3 (4 equiv) in DMSO at 100 °C (Table 1, entry 6). The product of the reaction was fully characterized by ^1H and ^{13}C NMR and mass spectroscopic data.

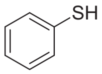
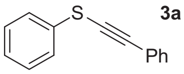
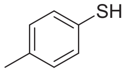
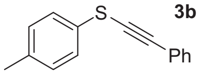
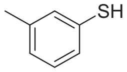
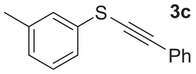
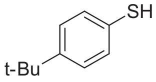
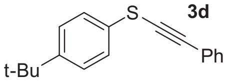
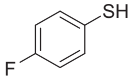
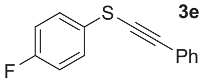
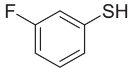
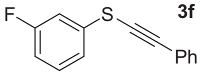
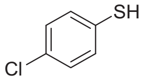
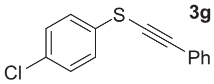
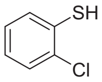
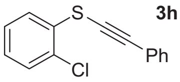
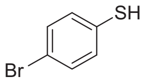
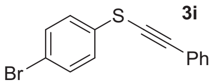
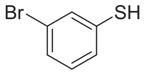
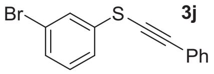
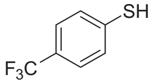
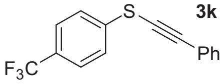
With the optimized condition in hand, we investigated the scope and limitation of this coupling with various thiophenols. As shown in Table 2, thiophenols bearing electron-donating or -withdrawing groups on the aromatic ring could react with (2,2-dibromovinyl)benzene smoothly to afford the corresponding products in moderate yields (Table 2, entries 2–11). The presence of electron-withdrawing groups on the aromatic ring decreased the nucleophilicity of thiophenols and the products were obtained in lower yields (Table 2, entries 5–11). Moreover, the homo-coupling product was not isolated in these reactions.

To further explore the utility of the reaction, different 1,1-dibromo-1-alkenes were subjected to the reaction. The substrates prepared for examining the scope of this synthesis were readily synthesized. It was pleased to find that 1,1-dibromo-1-alkenes with electron-donating or -withdrawing groups on the aromatic ring could react with thiophenol to get the desired product with acceptable yields (Table 3, entries 1–7). The presence of electron-donating groups decreased the efficiency of the reaction and the products were obtained in lower yields (Table 3, entry 2). In turn, the derivates having electron-withdrawing groups got higher yields (Table 3, entries 3–5). Furthermore, 1,1-dibromo-1-alkenes with heteroaromatic ring were found to be good partners in this reaction (Table 3, entries 6 and 7).

Based on these results, the mechanism of the reaction can be proposed as shown in Scheme 2. There may be two possible pathways for the thiol to form the corresponding alkynyl sulfides. Path A: 1,1-dibromo-1-alkene was dehydrobrominated firstly and the resulted alkynyl bromide could convert to the corresponding product by treating with thiol anion. Path B: thiol anion attacked 1,1-dibromo-1-alkene. Then the resulted (1-bromo-2-phenylvinyl)(phenyl)sulfane could be dehydrobrominated to form alkynyl sulfide.

Table 2
Transition-metal-free coupling of (2,2-dibromovinyl)benzene with various thiophenols [a]



Entry	Thiophenol	Product	Yield[b] (%)
1		 3a	55
2		 3b	58
3		 3c	43
4		 3d	40
5		 3e	48
6		 3f	37
7		 3g	40
8		 3h	38
9		 3i	43
10		 3j	34
11		 3k	38

---

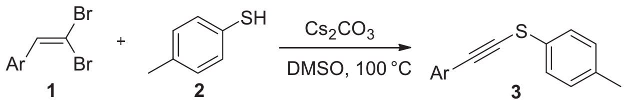
[a] All the reactions were conducted with 1,1-dibromo-1-alkenes (1.2 equiv, 0.75 mmol), thiophenols (1 equiv, 0.5 mmol), and Cs_2CO_3 (4 equiv, 2.0 mmol) in 3 mL of DMSO at 100 °C in nitrogen atmosphere.

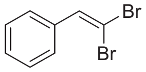
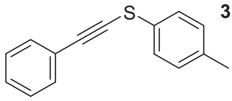
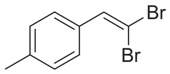
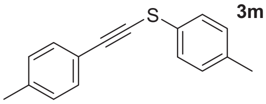
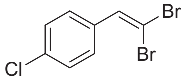
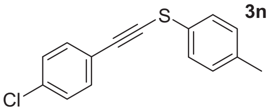
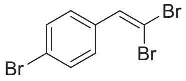
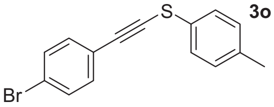
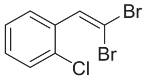
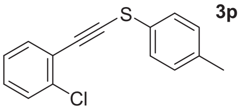
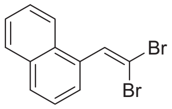
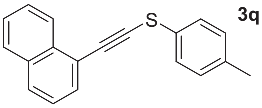
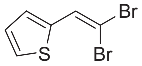
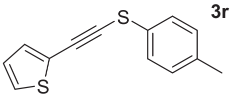
[b] Isolated yield.

In order to confirm which could be the proposed mechanism, we designed such experiment. (2,2-Dibromovinyl)benzene and benzenethiol were stirred in standard condition for 4 h. Then the extract was analyzed by GC–MS (see Supplementary data). There were three main peaks. The peak retention time at 4.2 min corresponded to alkynyl sulfide and the molecular weight was 210. The peak retention time at 4.4 min might correspond to (1-bromo-2-phenylvinyl)(phenyl)sulfane. The molecular weight was 290 and the peak ratio was 1:1. From the peak ratio, we could confirm there was one bromine atom in the compound. Thus, we felt that the path B (Scheme 2) is more favorable for the present conversion.

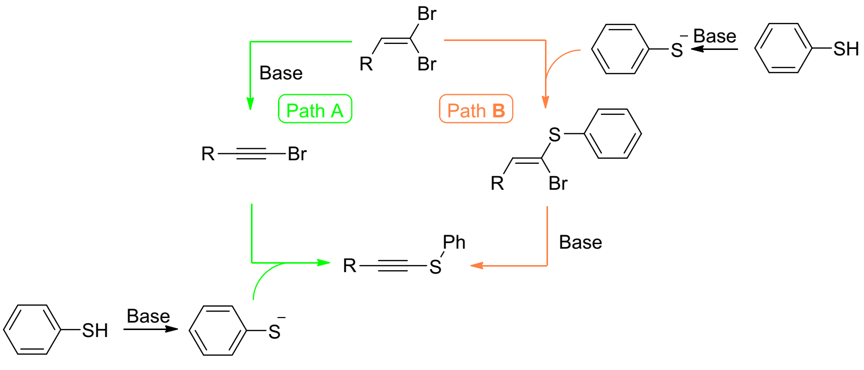
In conclusion, a novel synthetic strategy to alkynyl sulfides via transition-metal-free catalyzed C–S coupling of 1,1-dibromo-1-alkenes with thiophenols has been developed. Through this efficient and general protocol, a series of alkynyl sulfides have been prepared from readily available starting material. This method provided a facile and useful supplement for those already established routes. Further studies on the C–S coupling are underway in our laboratory.

Table 3
Transition-metal-free coupling of thiophenol with various 1,1-dibromo-1-alkenes[a]



Entry	Ar	Sulfide		Yield[b] (%)
1			**3l**	58
2			**3m**	42
3			**3n**	70
4			**3o**	65
5			**3p**	76
6			**3q**	80
7			**3r**	40

[a] All the reactions were conducted with 1,1-dibromo-1-alkenes (1.2 equiv, 0.75 mmol), thiophenols (1 equiv, 0.5 mmol), and Cs_2CO_3 (4 equiv, 2.0 mmol) in 3 mL of DMSO at 100 °C in nitrogen atmosphere.
[b] Isolated yield.



Scheme 2. Proposed mechanism.

Acknowledgments

Financial support from the Natural Science Foundation of China (Nos. 21025207 and 20975092) is greatly acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.072.

References and notes

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365; (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655; (d) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.
2. (a) Bouillon, J. P.; Musyanovich, R.; Portella, C.; Shermolovich, Y. *Eur. J. Org. Chem.* **2001**, 3625–3629; (b) Manarin, F.; Roehrs, J. A.; Gay, R. M.; Brandão, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153–2162; (c) Riddell, N.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1934–1937; (d) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624–630.

3. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91–93.
4. Braga, A. L.; Reckziegel, A.; Menezes, P. H.; Stefani, H. A. *Tetrahedron Lett.* **1993**, *34*, 393–394.
5. Braga, A. L.; Silveira, C. C.; Reckziegel, A.; Menezes, P. H. *Tetrahedron Lett.* **1993**, *34*, 8041–8042.
6. Bieber, L. W.; da Silva, M. F.; Menezes, P. H. *Tetrahedron Lett.* **2004**, *45*, 2735–2737.
7. Arisawa, M.; Fujimoto, K.; Morinaka, S.; Yamaguchi, M. *J. Am. Chem. Soc.* **2005**, *127*, 12226–12227.
8. (a) Truce, W. E.; Hill, H. E.; Boudaklan, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 2760–2762; (b) Ziegler, G. R.; Welch, C. A.; Orzech, C. E.; Kikkawa, S.; Miller, S. I. *J. Am. Chem. Soc.* **1963**, *85*, 1648–1651; (c) Votes, M.; Smet, M.; Dehaen, W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1473–1475; (d) Zheng, Wx.; Zheng, Ff.; Hong, Y.; Hu, Lf. *Heteroat. Chem.* **2012**, *23*, 105–110.
9. Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381–4385.
10. Rao, M. L. N.; Jadhav, D. N.; Dasgupta, P. *Org. Lett.* **2010**, *12*, 2048–2051.
11. Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873–3875.
12. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.