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Reductive Addition of the Benzenethiyl Radical to Alkynes by Amine-Mediated Single Electron Transfer Reaction to Diphenyl Disulfide

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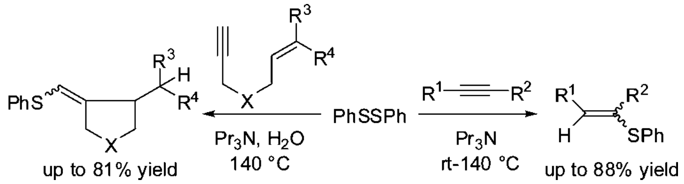
ABSTRACT



Hydrothiolation of alkynes proceeds with diphenyl disulfide and tripropylamine. Amine-mediated single electron transfer to diphenyl disulfide can be proposed for the reaction mechanism. Applications of the method to radical cyclizations of eneyne compounds are also presented.

A radical reaction is an efficient tool in synthetic organic chemistry.[1] Bu_3SnH has frequently been used for a hydrogen donor in the presence of a radical initiator such as AIBN (2,2′-azobisisobutyronitrile). There are, however, some disadvantages in using Bu_3SnH, due to its toxicity and difficulty in removing tin residue. Therefore, several substitutes for Bu_3SnH have been studied in recent years.[2,3] We have recently reported the synthesis of γ-lactams by a cyclization of trichloroacetamides in heated 1,4-dimethylpiperazine used as a solvent.[4] We considered that this reaction was a tin-free radical cyclization that proceeded by a single electron transfer (SET) reaction[5,6] of amine to trichloroacetamides.

In 1964, Wang reported that the sulfur−sulfur bond in diphenyl disulfide (**1**) was cleaved by an amine such as *N*,*N*-dimethylaniline to give solidified materials (polymers) by reaction with acrylonitrile.[7] The author proposed that this reaction proceeded by a single electron transfer mechanism. However, unfortunately, no synthetic usefulness of this reaction has so far been demonstrated.

Herein, we report an efficient synthesis of vinyl sulfides **3** by treatment of a mixture of diphenyl disulfide (**1**) and alkynes **2** with tripropylamine (Scheme 1, eq 1). Applications

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(1) For reviews, see: (a) Renaud, P.; Sibi, M. P. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Gansäuer, A., Ed. *Topics Current Chemistry; Radicals in Synthesis I and II*; Springer: Berlin, 2006; Vols. 263 and 264.

(2) For reviews, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835.

(3) For recent examples, see: (a) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847. (b) Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2007**, *9*, 4427. (c) Smith, D. M.; Pulling, M. E.; Norton, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 770. (d) Gansäuer, A.; Fan, C.-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916. (e) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, E.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082. (f) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279. (h) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345.

(4) (a) Ishibashi, H.; Haruki, S.; Uchiyama, M.; Tamura, O.; Matsuo, J. *Tetrahedron Lett.* **2006**, *47*, 6263. (b) Taniguchi, T.; Kawajiri, R.; Ishibashi, H. *Arkivoc* **2008**, *xiv*, 7. (c) Ishibashi, H.; Sasaki, M.; Taniguchi, T. *Tetrahedron* **2008**, *64*, 7771.

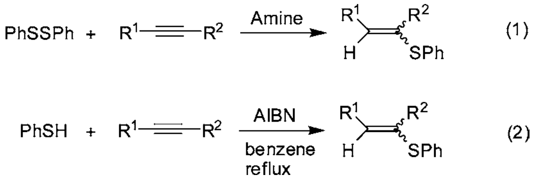
(5) For a review, see: Rossi, R. A.; Pierini, A. B.; Peory, A. B. *Chem. Rev.* **2003**, *103*, 71.

(6) For recent examples of a single electron reaction, see: (a) Murphy, J. A.; Khan, T. A.; Zhou, S.-Z.; Thomason, W. D.; Mahesh, M. *Angew. Chem., Int. Ed.* **2005**, *45*, 1356. (b) McGlacken, G. P.; Khan, T. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1819.

(7) (a) Wang, C.-H. *Nature* **1964**, *203*, 75. (b) Wang, C.-H.; Linnell, S. M.; Rosenblum, R.; Wang, N. *Experientia* **1971**, *27*, 243. (c) Wang, C.-H.; Linnell, S. M.; Wang, N. *J. Org. Chem.* **1971**, *36*, 525.

10.1021/ol901084k CCC: $40.75

Scheme 1. Thiol-Mediated Radical Hydrothiolation of Alkynes



of the method to radical cyclizations of eneyne compounds **12** are also presented.[8]

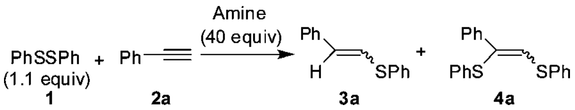
It is well-known that the benzenethiyl radical formed from thiophenol in the presence of AIBN undergoes an addition reaction with alkynes to give vinyl sulfides (Scheme 1, eq 2).[9] In this reaction, the use of ill-smelling thiophenol and a hazardous radical initiator such as AIBN was required.

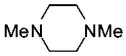
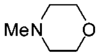
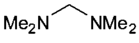
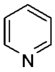
Although many reactions of alkynes with disulfides have developed, disulfidation products are generally obtained.[10] To the best of our knowledge, reductive radical reaction of alkynes with disulfide to give 1-alkenyl sulfides has not been explored.[11]

We initiated our investigation by examining the reaction of diphenyl disulfide (**1**) with phenylacetylene (**2a**) with 40 equiv of boiling 1,4-dimethylpiperazine to give vinyl sulfide **3a** in 63% yield as a 4:1 mixture of *E*- and *Z*-isomers along with a small amount (7% yield) of disulfidated compound **4a** (Table 1, entry 1). A similar reaction using triethylamine was found to improve the yield of desired compound **3a** in a short reaction time (Table 1, entry 3). Pyridine, however, gave no compounds **3a** and **4a** (Table 1, entry 7). Of the several amines examined, tripropylamine gave the best results, affording **3a** in 83% yield (E:Z = 85:15) together with **4a** (4%) (Table 1, entry 4).[12]

Reactions of a mixture of **1** and **2a** with tripropylamine were examined in more detail. The use of a reduced amount of tripropylamine gave products in lower yield.[13] When the reactions were carried out in a temperature range of 80−140 °C, no dramatic change in the yield of **3a** was observed.[13]

Table 1. Screening of Amines

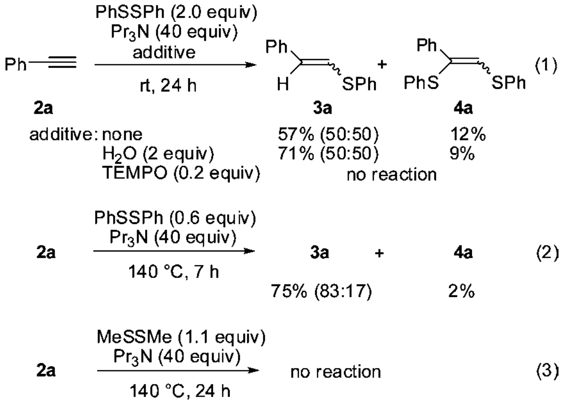


entry	amine	t (h)	temp (°C)	yield (%)[a] 3a (E:Z)[b]	yield (%)[a] 4a
1		20.5	130	63 (80:20)	7
2		24	110	43 (70:30)	15
3	Et_3N	8	90	74 (58:42)	11
4	Pr_3N	3	140	83 (85:15)	4
5	$i$$Pr_2NEt$	4.5	125	69 (80:20)	5
6		24	80	18 (50:50)	13
7		24	115	no reaction	

[a] Yield of isolated products. [b] Ratio of E:Z determined by ^{1}H NMR analysis.

At room temperature, however, a long reaction time was required, and the yield of **3a** also decreased (Scheme 2, eq 1). We soon found that the addition of water at room temperature improved the yield of **3a** (Scheme 2, eq 1). This was presumed to be because water accelerated the hydrogen atom donation to the vinyl radical intermediate **10** (vide infra) to give **3a**.[14] On the other hands, no reaction occurred with the addition of a substoichiometric amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyl 1-oxyl) as a radical scav-

Scheme 2. Amine-Mediated Radical Hydrothiolation of Phenylacetylene under Various Reaction Conditions



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(8) For a review on thiol-mediated radical cyclizations, see: Majumdar, K. C.; Debnath, P. *Tetrahedron* **2008**, *64*, 9799.

(9) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103.

(10) For recent examples of disulfination of alkynes, see: (a) Usugi, S.-i.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 601. (b) Ananikov, V. P.; Kabeshov, M. A.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Organometallics* **2005**, *24*, 1275. Thioselenation of alkynes using disulfide and photoirradiation has also been reported by Ogawa and co-workers, see: (c) Ogawa, A.; Obayashi, R.; Ine, H.; Tsuboi, Y.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 881.

(11) For recent examples of hydrothiolation of alkynes, see: (a) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, *70*, 6468. (b) Wang, Z.-L.; Tang, R.-Y.; Luo, P.-S.; Deng, C.-L.; Zhong, P.; Li, J.-H. *Tetrahedron* **2008**, *64*, 10670. (c) Sato, A.; Yorimitsu, H.; OshimaK. *Synlett* **2009**, 28. (d) Weiss, C. J.; Wobser, S. D.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 2062. (e) Yang, J.; Sabarre, A.; Fraser, L. R.; Patrick, B. O.; Love, J. A. *J. Org. Chem.* **2009**, *74*, 182.

(12) It is well known that the thiyl radical isomerizes the *Z*-isomer of the olefinic compound to the corresponding *E*-isomer. However, (*Z*)-1-phenyl-2-(phenylsulfanyl)ethene was not entirely isomerized to the *E*-isomer by treatment of diphenyl disulfide (**3**) with tripropylamine. For a example of thiol-mediated olefin isomerization, see: Chatgilialoglu, C.; Ferreri, C. *Acc. Chem. Res.* **2005**, *38*, 441.

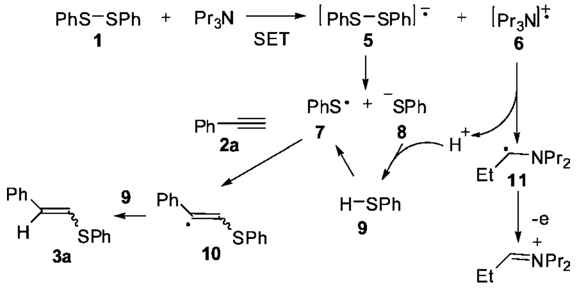
(13) See Supporting Information.

(14) It was reported that the rate of radical trapping by thiol was increased in the presence of water. See: Tranche, C.; Martinez, F. N.; Horner, J. H.; Newcomb, M. *Tetrahedron Lett.* **1996**, *37*, 5845.

enger, suggesting that this reaction proceeds by a radical mechanism (Scheme 2, eq 1). The use of 0.6 equiv of **1** at 140 °C did not result in a significant decrease in yield of **3a** (Scheme 2, eq 2), suggesting that two sulfur atoms of disulfide might be incorporated into phenylacetylene (**2a**). Interestingly, the use of dimethyl disulfide in place of diphenyl disulfide gave no product (Scheme 2, eq 3).

A plausible mechanism for the reaction is shown in Scheme 3. The reaction may be initiated by single electron transfer (SET) reaction of tripropylamine to disulfide **1** to generate an anion radical **5** and a cation radical **6**. The S−S bond fission of anion radical **5** generates benzenethiyl radical (**7**) and thiolate anion **8**. An attack of thiyl radical **7** on the alkyne **2a** gives the vinyl radical **10**, which then abstracts a hydrogen atom from benzenethiol (**9**) to give vinyl sulfide **3a** together with the benezenthiyl radical (**7**). It should be noted that the formation of benzenethiol (**9**) might be a result of the removal of a proton of cation radical **6** (proton removal of **6** gives radical **11**). Therefore, a single electron transfer reaction between tripropylamine and diphenyl disulfide (**3**) to form cation radical **6** is important to give vinyl sulfides **3a**. Partial formation of compound **4a** might be a result of an attack of vinyl radical **10** on diphenyl disulfide (**1**).

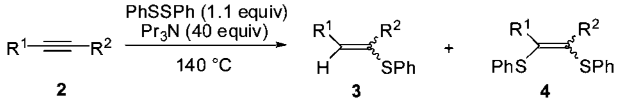
Scheme 3. Plausible Mechanism



The results of the reactions of **1** with other alkynes **2** (1.0 equiv) with tripropylamine are summarized in Table 2. Arylacetylenes **2b** and **2c** bearing a halogen and an electron-donating group on the aromatic ring provided the corresponding vinyl sulfides **3b** and **3c** in good yields (Table 2, entries 1 and 2), whereas *p*-nitrophenylacetylene (**2d**) gave only a trace amount of the desired product **3d** (Table 2, entry 3). Several aliphatic alkynes **2e**−**g** gave the corresponding vinyl sulfides **3e**−**g** in good yields (Table 2, entries 4−6). Furthermore, the internal alkynes **2h**,**i** underwent the desired reaction to give the corresponding vinyl sulfides **3h**,**i** in good yields (Table 2, entries 7 and 8).[15]

The advantages of the present reaction are as follows: (1) all reagents employed herein are inexpensive and have low toxicity, and the reaction does not require the use of ill-smelling thiophenol, and (2) products can be obtained after simple removal of tripropylamine by a conventional evaporator followed by usual chromatography.

Table 2. Amine-Mediated Addition of Benzenethiyl Radical to Various Alkynes

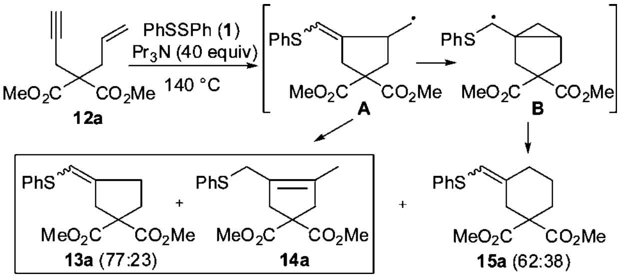


					yield (%)[a]	
entry	**2**	R^1	R^2	*t* (h)	**3** (*E*:*Z*)[b]	**4**
1	**b**	4-ClC_6H_4	H	3	64 (71:29)	2
2	**c**	4-$MeOC_6H_4$	H	2	79 (71:29)	trace
3	**d**	4-$NO_2C_6H_4$	H	24	trace	trace
4	**e**	C_6H_{13}	H	2.5	74 (50:50)	trace
5	**f**	$TBDPSOCH_2$	H	18.5	63 (67:33)	5
6	**g**	$TsNHCH_2$	H	6	68 (63:37)	-
7	**h**	Ph	Me	2	66 (57:43)	-
				2	88 (57:43)[c]	-
8	**i**	Ph	Ph	10	52 (n.d.)	-
				10	60 (n.d.)[c]	-

[a] Yield of isolated products. [b] Ratio of *E*:*Z* determined by ^{1}H NMR analysis. [c] 2 equiv of water was added.

Applications of this method to radical cyclization of eneyne derivatives **12** were examined next. When the cyclization precursor **12a** was treated with 1.1 equiv of phenyl disulfide in 40 equiv of tripropylamine at 140 °C, a mixture of 5-*exo* products **13a** and **14a** and 6-*endo* products **15a** was obtained in 76% total yield (Table 3, entry 1).

Table 3. Amine-Mediated Radical Cyclization of Eneyne **14a**



entry	**1** (equiv)	*t* (h)	yield (%)[a]	ratio[b] (**13a**:**14a**:**15a**)
1	1.1	8	76	46:11:43
2[c]	1.1	10	84	28:4:68
3[d]	1.1	8	79	50:11:39
4[d]	2.0	7	79	56:17:27

[a] Yield of isolated products. [b] Ratio determined by ^{1}H NMR analysis. [c] 400 equiv of Pr_3N was employed. [d] 2 equiv of water was added.

Formation of **15a** can be explained by a rearrangement of intermediate **A** via a ring expansion process of the cyclo-

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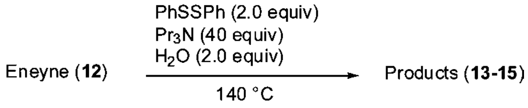
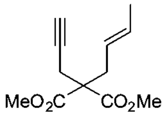
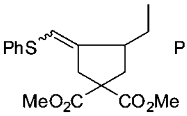
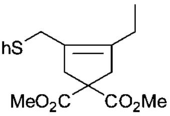
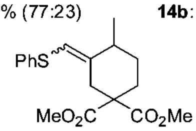
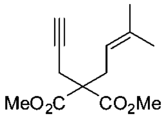
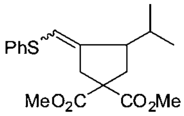
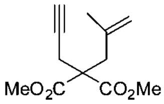
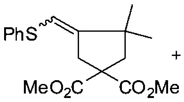
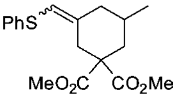
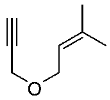
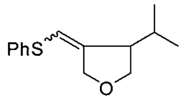
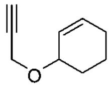
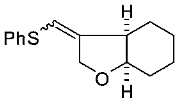
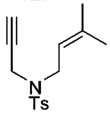
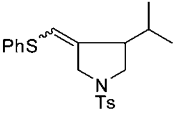
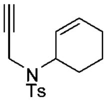
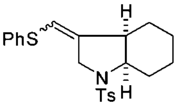
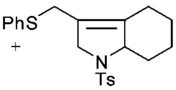
[15] For examples of addition of thiyl radical to internal alkynes, see: (a) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, *16*, 1647. (b) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219. (c) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Tetrahedron* **1998**, *54*, 8207. (d) Fernández-González, M.; Alonso, R. *J. Org. Chem.* **2006**, *71*, 6767.

Table 4. Amine-Mediated Radical Cyclization of Various Eneynes



entry	alkyne	*t* (h)	products[a,b]
1	 **12b**	5	 **13b**: 65% (77:23)  **14b**: 12%  **15b**: trace
2	 **12c**	8	 **13c**: 81% (81:19)
3	 **12d**	10	 **13d** (not determined) +  **15d** (55:45) **13d**+**15d**: 80% (**13d**:**15d** = 5:95)
4	 **12e**	7	 **13e**: 45% (single isomer)
5	 **12f**	8	 **13f**: 57% (70:30)
6	 **12g**	2.5	 **13g**: 61% (84:16)
7	 **12h**	4	 **13h**: (79:21) +  **14h** **13h**+**14h**: 61% (**13h**:**14h** = 89:11)

[a] Yield of isolated products. [b] Ratios determined by ^{1}H NMR analysis.

propane intermediate **B**.[16] This assumption is supported by the fact that a similar reaction in 400 equiv of tripropylamine gave predominantly 6-*endo* product **15a** (Table 3, entry 2). It is well-known that the yield of the rearrangement product increases when the concentration of the substrate is low.[17] Addition of 2.0 equiv of water caused an increase in the ratio of 5-*exo* products **13a** and **14a** (Table 3, entries 3 and 4).

Table 4 shows the results of radical cyclization of several eneyne compounds **12** by heating with 2.0 equiv of phenyl disulfide (**1**) and 40 equiv of tripropylamine at 140 °C in the presence of 2.0 equiv of water. The radical precursors **12b** and **12c** bearing mono- or dimethylated alkene provided cyclization products **13b** and **13c** in good yields (Table 4, entries 1 and 2). Compound **12d** underwent radical cyclization in a 6-*endo-trig* manner to give cyclohexane derivative **15d** along with a small amount of 5-*exo* products **13d** (Table 4, entry 3). The radical precursors **12e**, **12f**, and **12g** gave the corresponding heterocyclic five-membered products **13e**, **13f**, and **13g**, respectively, in good yields (Table 4, entries 4−6). Compound **12h** gave a mixture of **13h** and **14h** in 61% yield (Table 4, entry 7).

In conclusion, we have developed a method for the formation of benzenethiyl radical **7** from diphenyl disulfide (**1**) with tripropylamine via a single electron transfer (SET) reaction. Inexpensive and environmentally friendly reagents were employed, and the experimental procedure is very simple and safe. Further studies directed toward the elucidation of the reaction mechanism and the application of amine-mediated radical formation to the various disulfides, heteroatoms, and radical precursors are currently underway in our laboratory.

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Supporting Information Available: Expermental detail and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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