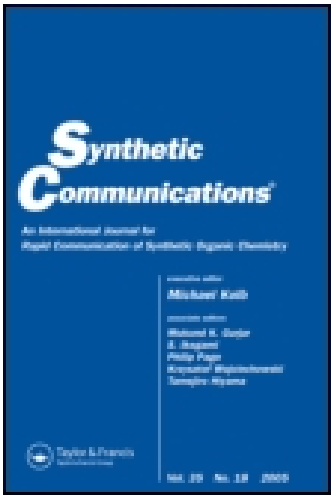

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TBHP-Mediated Oxidative Cross-Coupling of Disulfides with Ethers through a C(sp^3)-H Thiolation Process

Ya-Ping Hu [a] & Ri-Yuan Tang [b]

[a] Food Science and Technology College , Hunan Agricultural University , Changsha , China

[b] College of Chemistry and Materials Engineering , Wenzhou University , Wenzhou , China

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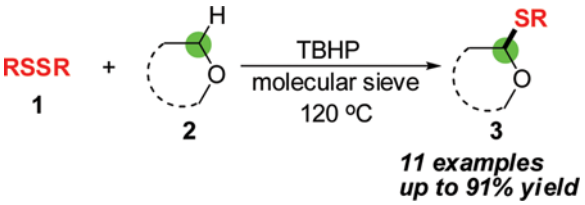
TBHP-MEDIATED OXIDATIVE CROSS-COUPLING OF DISULFIDES WITH ETHERS THROUGH A C(sp^3)-H THIOLATION PROCESS

Ya-Ping Hu[1] and Ri-Yuan Tang[2]

[1]*Food Science and Technology College, Hunan Agricultural University, Changsha, China*

[2]*College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, China*

GRAPHICAL ABSTRACT



Abstract *A new* tert*-butyl hydroperoxide (TBHP)–mediated oxidative cross-coupling of disulfides with ethers is presented for the synthesis of etherified sulfides. This method is achieved by a C(sp^3)-H thiolation strategy under metal-free conditions and provides a simple route to constructing the C-S bonds.*

Keywords Cross-coupling reaction; 1,2-disulfides; ethers; oxidation; TBHP

INTRODUCTION

The oxidative cross-coupling reaction comprising a C-H functionalization process has emerged as one of the most important methodologies for various chemical bond constructions in organic synthesis; moreover, this reaction remains an active area of research because it is environmental benign, sustainable, and highly atom-economical because it avoids the use of halides, pseudohalides, and/or organometallic reagents.[1] Despite impressive progress in the field, examples on the construction of the C-S bond using the oxidative cross-coupling strategy are quite rare.[2,3] Recently, the group of Tang et al. established the *tert*-butyl hydroperoxide (TBHP)–mediated oxidative thiolation of a sp^3 C-H bond adjacent to a nitrogen

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Address correspondence to Ya-Ping Hu, Food Science and Technology College, Hunan Agricultural University, Changsha, China. E-mail: huyaping@hunau.net

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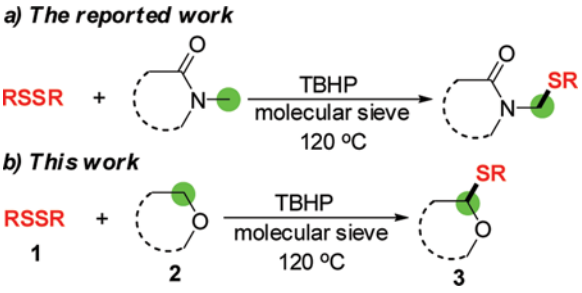


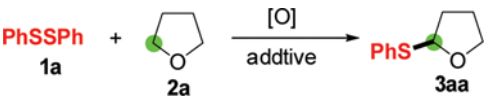
Scheme 1. Oxidative cross-coupling with disulfides.

atom to construct the C-S bond without the aid of metals (Scheme 1a).[2a] Herein, we report that this oxidative cross-coupling strategy could be expanded to a sp^3 C-H bond adjacent to an oxygen atom (ethers).[4] In the presence of TBHP and molecular sieve, a variety of disulfides reacted with ethers and resulted in the new C-S bond formation in moderate to good yield (Scheme 1b). Notably, etherified sulfides are important units found in organic materials, bioactive molecules, and pharmaceuticals and widely serve as valuable intermediates in synthetic chemistry.[5–7]

RESULTS AND DISCUSSION

As shown in Table 1, the reaction between 1,2-diphenyldisulfane (**1a**) and tetrahydrofuran (THF, **2a**) was chosen as the model to optimize the reaction conditions. Disulfide **1a** was initially treated with THF **2a** and TBHP, and the target product **3aa** was isolated in 21% yield (entry 1). To our delight, the presence of molecular sieve

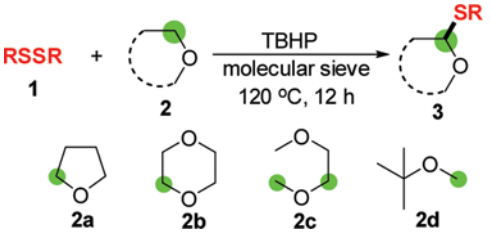
Table 1. Screening optimal conditions[a]

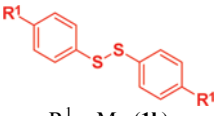
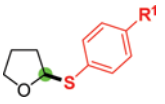
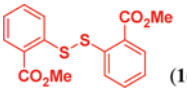
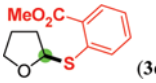
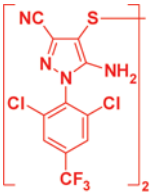
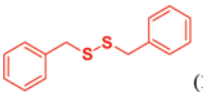
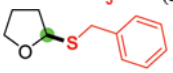
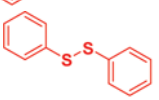
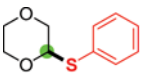
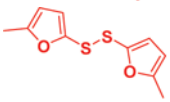
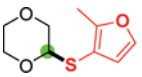
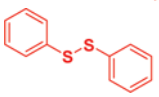
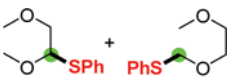
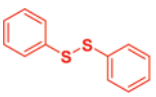
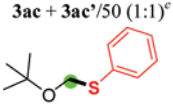


Entry	[O] (equiv)	Additive (mg)	T (°C)	Isolated yield (%)
1[b]	TBHP (2)	—	120	21
2	TBHP (2)	4 Å MS (100)	120	91
3	TBHP (4)	4 Å MS (100)	120	90
4	TBHP (2)	4 Å MS (100)	80	35
5	TBHP (2)	4 Å MS (100)	130	89
6	DTBP (2)	4 Å MS (100)	120	78
7[c]	DDQ	4 Å MS (100)	120	Trace
8[d]	TBHP (2)	4 Å MS (100)	120	85
9[e]	TBHP (2)	4 Å MS (100)	120	90

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (2 mL), [O], and additive for 12 h. TBHP is hydrous (70% in water solution).
[b]68% of **1a** was recovered.
[c]>90% of **1a** was recovered.
[d]**2a** (20 equiv) in ^{n}BuOAc (2 mL).
[e]**1a** (3 mmol, 0.654 g) for 48 h.

Table 2. Thiolation of disulfides (**1**) with ethers (**2**)[a]



Entry	Disulfide **1**	Ether **2**	Product/isolated yield (%)
1		**2a**	
	R^1 = Me (**1b**)	**2a**	R^1 = Me (**3ba**)/65
2	R^1 = Cl (**1c**)	**2a**	R^1 = Me (**3ca**)/87
3	R^1 = Br (**1d**)	**2a**	R^1 = Me (**3da**)/75
4	 (**1e**)	**2a**	 (**3ea**)/85
5	 (**1f**)	**2a**	 (**3fa**)/83
6	 (**1g**)	**2a**	 (**3ga**)/53
7[b]	 (**1a**)	**2b**	 (**3ab**)/63
8	 (**1h**)	**2b**	 (**3hb**)/56
9	 (**1a**)	**2c**	 **3ac** + **3ac'**/50 (1:1)[c]
10	 (**1a**)	**2d**	 (**3ad**)/61

[a]Reaction conditions: **1** (0.3 mmol), **2** (2 mL), TBHP (2.0 equiv; 70% in water solution), and 4 Å MS (100) at 120 °C for 12 h.

[b]For 48 h.

[c]The ratio given in parentheses was determined by ^{1}H NMR analysis.

could favor the oxidative cross-coupling reaction.[2a] The yield of product **3aa** was sharply enhanced to 91% when 100 mg molecular sieve was added (entry 2). Identical results were observed at 4 equiv TBHP and 100 mg molecular sieve (entry 3). Subsequently, the effect of the reaction temperatures was examined, and the results demonstrated that the reaction at 120 °C gave the best yield (entries 2, 4, and 5). Two other oxidants, di-*tert*-butyl peroxide (DTBP) and 2,3-dichloro-5,6-dicyano-1, 4-benzoquinone (DDQ), were also tested (entries 6 and 7). Screening revealed that DTBP was viable to mediate the reaction, albeit reducing the yield (entry 6). However, DDQ was ineffective for the reaction (entry 7). We were pleased to find that good yield was still achieved when the reaction was carried out in ^{n}BuOAc (entry 8). It is noteworthy that 3-mmol scale of substrate **1a** is successfully performed, providing the desired product **3aa** in 90% yield (entry 9).

With the optimal conditions in hand, we next decided to explore the scope of the oxidative cross-coupling reaction (Table 2). In the presence of TBHP and molecular sieve, THF **1a** was successfully reacted with various disulfides **1b–1g** in moderate to excellent yields (entries 1–6). Gratifyingly, a number of functional groups, including Me, Cl, Br, and CO_2Me groups, on the aryl ring of disulfides were tolerated well (entries 1–4). 1,2-Di(*p*-tolyl)disulfane (**1b**), for instance, was reacted with THF **2a**, TBHP, and molecular sieve smoothly, providing the target product **3ba** in 65% yield (entry 2). Importantly, halo groups, including Cl and Br groups, were also consistent with the optimal conditions, thereby facilitating possible additional modifications at the halogenated positions (entries 2 and 3). It was noted that this oxidative cross-coupling reaction method could be applied to synthesize new fipronil analog **3fa** in good yields (entry 5).[14] This successful S-S bond cleavage of pyrazole disulfide followed by the sp^3 C-S bond formation would be significant for pesticide and drug design.[15] To test indoor pesticidal activities, compound **3fa** was subsequently dissolved in dimethylformamide (DMF), followed by dilution with 0.1% (v/v) tween-80 distilled water. We were happy to find that this solution displayed highly pesticidal activities (Scheme 2). Notably, aliphatic disulfide, dibenzyldisulfide **1 g**, was also a suitable substrate, furnishing product **3ga** in moderate yield after prolonging the reaction time (entry 6).

To our delight, the optimal conditions were compatible with other ethers, such as 1,4-dioxane (**2b**), 1,2-dimethoxyethane (**2c**), and 2-methoxy-2-methylpropane (**2d**) (entries 7–10). The reactions of 1,4-dioxane **2b** with diphenyldisulfide (**1a**) or 1,2-bis(2-methylfuran-3-yl)disulfane (**1h**) were efficiently conducted, giving the corresponding products **3ba** and **3hb** in 63% and 56% yields, respectively (entries 7 and 8). Using 1,2-dimethoxyethane (**2c**), a mixture of products **3ac** and **3ac′** in 50% total

3ha

Indoor Pesticidal Activities Test

Compound	Concentration (mg/L)	Death rate (%) Mythimna sepatara
3ha	500	100
CK	-	0

Scheme 2. Indoor pesticidal activity test of product **3ha**.

yield with 1:1 ratio (entry 9). Interestingly, bulky 2-methoxy-2-methylpropane (**2d**) was also viable for the reaction with THF (**1a**) and TBHP, leading to the desired product **3ad** isolated in moderate yield (entry 10).

CONCLUSION

In summary, we have illustrated a new oxidative cross-coupling of disulfides with ethers to form the C(sp^3)-S bond through a C(sp^3)-H thiolation strategy. In the presence of TBHP and a molecular sieve, a variety of disulfides, including aromatic and aliphatic disulfides, were treated with ethers to afford the corresponding etherified sulfides in moderate to good yields. Notably, this method is simple and general with a wide range of disulfide compatibility, which provides a new route to the construction of the C-S bonds.

EXPERIMENTAL

NMR spectroscopy was performed on a Bruker advanced spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). Mass spectrometric analysis was performed on GC-MS (Shimadzu GCMS-QP2010) and ESI-Q-TOF (Bruker MicroQTOF-II) instruments.

Typical Experimental Procedure for TBHP-Mediated Oxidative Cross-Coupling of Disulfides with Ethers

To a Schlenk tube were added disulfide **1** (0.2 mmol), TBHP (2 equiv), 4-A molecular sieve (100 mg), and ether **2** (2 mL). Then the tube was charged with argon and stirred at 120 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by thin-layer chromatography (TLC) and GC-MS analysis. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in ethyl acetate (5 mL), and washed with brine (3×1 mL). The aqueous phase was extracted with ethyl acetate (3×2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 20:1) to afford product **3**.

2-(Phenylthio)tetrahydrofuran (3aa)[8]

Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, $J = 8.0$ Hz, 2H), 7.15–7.24 (m, 3H), 5.57 (m, 1H), 3.93–3.98 (m, 1H), 3.87–3.91 (m, 1H), 2.28–2.32 (m, 1H), 1.87–1.97 (m, 2H), 1.79–1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.7, 131.1, 128.8, 126.8, 87.1, 67.3, 32.6, 24.8; IR (KBr, cm^{-1}): 2971, 2923, 2869, 1476, 1434, 1040, 1018, 902, 736, 688; LRMS (EI, 70 eV) m/z (%): 180 (M^+, 5), 71 (100).

FUNDING

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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