Letter

Dechalcogenization of Aryl Dichalcogenides To Synthesize Aryl Chalcogenides via Copper Catalysis

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Dechalcogenization of Aryl Dichalcogenides to Synthesize Aryl Chalcogenides via Copper Catalysis

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ABSTRACT: An application of dechalcogenization of aryl dichalcogenides via copper catalysis to synthesize aryl chalcogenides is disclosed. This approach is highlighted by the practical conditions, broad substrates scope and good functional group tolerance with several sensitive groups such as aldehyde, ketone, ester, amide, cyanide, alkene, nitro and methylsulfonyl. Furthermore, the robustness of this methodology is depicted by the late-stage modification of estrone and synthesis of vortioxetine. Remarkably, synthesis of more challenging organic materials with large ring tension under milder conditions and synthesis of some halogen contained diaryl sulfides which could not be synthesized using metal-catalyzed coupling reactions of aryl halogen are successfully accomplished with this protocol.

KEYWORDS: Aryl chalcogenides, aryl dichalcogenides, copper catalysis, dechalcogenization, organic materials

Aryl chalcogen-containing compounds have captured widespread attention due to their essential and manifold applications in biologically active molecules,[1] pharmaceuticals[2] and organic materials.[3] For instance (Figure 1), aryl chalcogenides could be found in 5-lipoxygenase inhibitor AZD4407,[1a] antitumor drug Axitinib, and organic electronic material triselenasumanene.[3c] In view of their significance

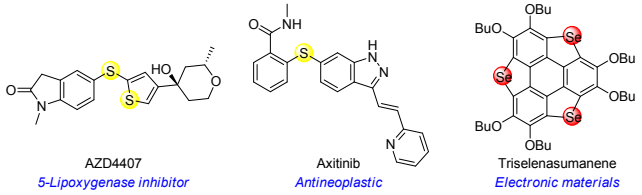
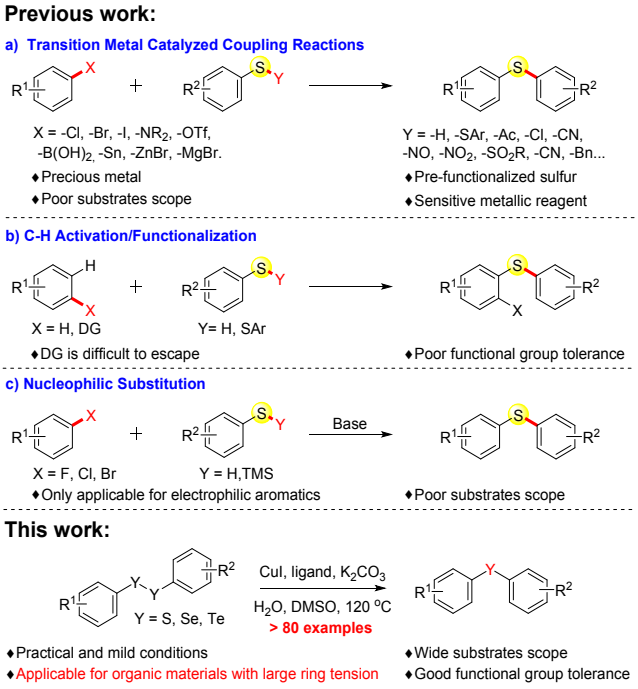


Figure 1. Examples of aryl chalcogen-containing bioactive compounds, pharmaceutical molecules and organic materials.

in such broad fields, various methods for synthesizing aryl sulfides have been developed,[4] mainly including the following three strategies: a) transition-metal-catalyzed coupling[5] of aryl halides, arylboronic acids or other metal reagents with thiols, disulfides or functionalized sulfurs[6] (Scheme 1a), several of these protocols use precious metal, pre-functionalized sulfur and sensitive metallic reagent; b) metal-catalyzed functionalization of C-H bonds,[7] application and substrates scope of some of which have been restricted for the difficulty of directing group escaping (Scheme 1b); c) nucleophilic substitution (S_NAr) reactions,[8] which are exclusively applicable for electrophilic aromatics (Scheme 1c). Despite significant progress has been made in aryl sulfides synthesis, the longstanding issues existed in the above-mentioned strategies should not be overlooked, thus alternatives are in great need.



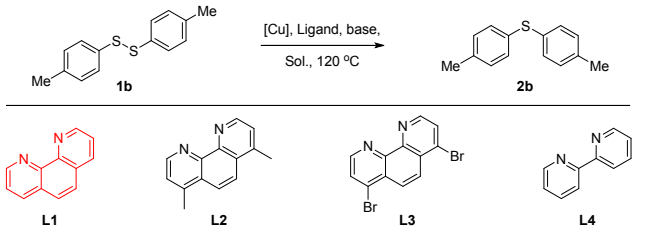
Scheme 1. Methods for Synthesis of Aryl Sulfides

According to the previous literature, desulfurization of aryl disulfides to hydrocarbons has been uncovered,[9] whereas, selective remove of one sulfur in aryl disulfides is challenging. At present, selective dechalcogenization of aryl dichalcogenides en route to aryl chalcogenides is mainly applied to synthesize organic materials with large

ring tension, moreover, high temperature (200 - 300 °C) and excessive copper powder are required but the yield is unsatisfying.[3c, 10] Remarkably, there is no precedent on dechalcogenization of ordinary aryl dichalcogenides to ordinary aryl chalcogenides, which are important moieties of many biological molecules. In this context, we herein reveal the unprecedented application of dechalcogenization of aryl dichalcogenides in synthesizing aryl chalcogen-ides and bowl-shaped organic materials under milder conditions.

Giving the fact that copper species could insert into C–C bond through extrusion of CO_2 to form a stable aryl-copper intermediate in decarboxylative coupling reactions,[11] we wonder if copper salts are also amenable to show similar effects in the extrusion of SO_2. To verify our hypothesis, we commenced our study by performing desulfurization of 1,2-di-*p*-tolyldisulfane (**1b**) in the presence of 20 mol % $Cu(OAc)_2$, 40 mol % 1,10-phenanthroline, and 3 equivalents of K_2CO_3 under air atmosphere at 120 °C for 24 h, and the desired product **2b** was obtained in 40% yield (Table 1, entry 1). Subsequently, optimization of the reaction conditions was carried out by evaluating a variety of reaction parameters. At first, copper salts were screened and CuI was the best to generate product **2b** in 48% yield (Table 1, entries 2 – 3; Table S1). Solvents (Table 1, entries 4 – 5; Table S2) and base (Table 1, entries 6 – 7; Table S3) were

Table 1. Optimization of The Reaction Conditions[a]

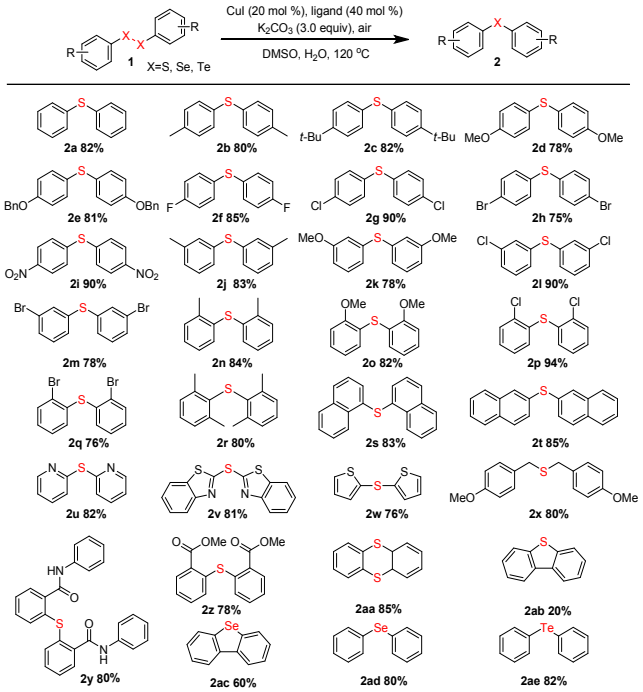


entry	[Cu]	sol.	base	l.	time/h	yield/%[b]
1	$Cu(OAc)_2$	DMSO	K_2CO_3	L1	24	40
2	CuBr	DMSO	K_2CO_3	L1	24	30
3	CuI	DMSO	K_2CO_3	L1	24	48
4	CuI	DMF	K_2CO_3	L1	24	4
5	CuI	Mes.	K_2CO_3	L1	24	0
6	CuI	DMSO	Cs_2CO_3	L1	24	35
7	CuI	DMSO	KOH	L1	24	Trace
8[c]	CuI	DMSO	K_2CO_3	L1	7	80
9[c]	CuI	DMSO	K_2CO_3	L2	7	55
10[c]	CuI	DMSO	K_2CO_3	L3	7	20
11[c]	CuI	DMSO	K_2CO_3	L4	7	Trace
12[c]	-	DMSO	K_2CO_3	L1	7	0
13[c]	CuI	DMSO	-	L1	7	0
14[c]	CuI	DMSO	K_2CO_3	-	7	0
15[c, d]	CuI	DMSO	K_2CO_3	L1	7	Trace

[a]Reaction conditions: **1b** (0.10 mmol, 1.0 equiv), [Cu] (0.02 mmol, 20 mol %), Ligand (0.04 mmol, 40 mol %), Base (0.30 mmol, 3.0 equiv), solvent (1.0 mL), air, 120 °C. [b]Isolated yields. [c]50 μL H_2O (DMSO : H_2O = 20 : 1) was added. [d]Air was replaced by Ar. Mes. = Mesitylene; L = Ligand

ensuing tested, but no enhancement on the yield was observed. Considering the low solubility of base in DMSO, we attempted to increase the solubility of the base by adding water. As we predicted, the yield dramatically jumped to 80% and the reaction time was shortened to 7h (Table 1, entry 8; Table S3). Next, we managed to arise the yield by screening a variety of ligands, but no satisfactory result was presented (Table 1, entries 9 – 11; Table S4). In the absence of CuI or base or ligand or air, no product was detected (Table 1, entries 12 - 15), indicating the necessity of copper salt, base, ligand and air.

With the optimized conditions in hand, we assessed the reaction scope with various symmetrical aryl dichalcogenides (Scheme 2). In terms of electronical effect, both electron-donating and electron-withdrawing substituents at *para*-, *meta*- and *ortho*-positions of benzene ring provided the desired products in good to excellent yields (**2a - 2q,** 75% - 94%). In general, electron-withdrawing groups on the phenyl ring were apt to generate products in high yields than electron-donating ones. As for steric hindrance effect, 2, 6-dimethylated **1r**, fused aromatic rings **1s** and **1t** showed good compatibility in this reaction to give rise to the corresponding products in good yields (**2r – 2t**, 80% - 85%), which suggested steric hindrance of substrates had marginal influence on yields. Several heterocycle disulfides were also feasible to afford the products in good yields (**2u - 2w**, 76% - 82%). Of particular note was that 4-methoxybenzyl disulfide **2x** proceeded well under standard conditions to offer the desulfurated product in 80% yield. Some sensitive functional groups including amide and ester were well tolerant, providing **2y** and **2z** in 80% and 78% yields respectively. Moreover, the organic syn-

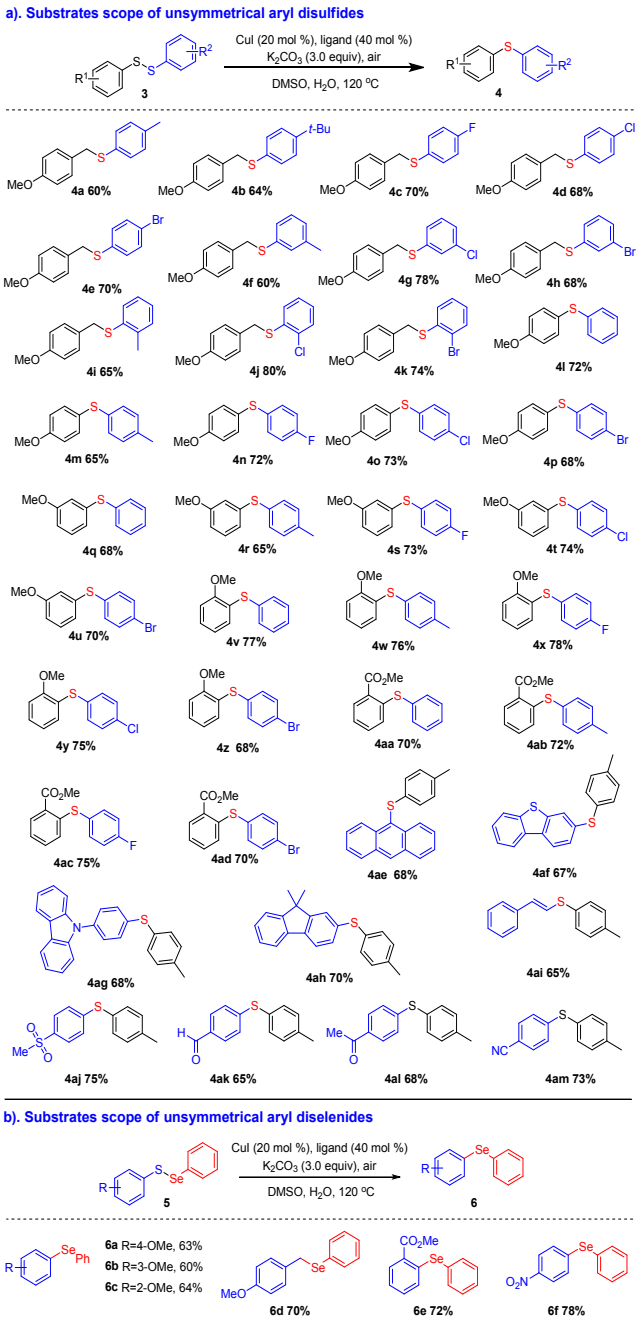


Scheme 2. Substrates Scope of Symmetrical Aryl Dichalcogenides.[a, b] [a]Reaction conditions: **1** (0.10 mmol, 1.0

equiv), CuI (0.02 mmol, 20 mol %), 1,10-phenanthroline (0.04 mmol, 40 mol %), K_2CO_3 (0.30 mmol, 3.0 equiv), DMSO : H_2O = 20 : 1, air, 120 °C. [b]Isolated yields.

thesis intermediates **2aa** and **2ab** could be obtained in 85% and 20% yields respectively. Interestingly, even deselenization and detellurization were also successfully achieved to produce the desirable products in moderate to good yields (**2ac**: 60%; **2ad**: 80%; **2ae**: 82%).

Next, we further assessed the scope of unsymmetrical aryl disulfides (Scheme 3a). Desulfuration of **3a - 3k** bearing an electron-withdrawing group (-F, -Cl -Br) or an electron-donating group (Me) on *ortho, mate* or *para*-position of benzene ring provided **4a - 4k** in moderate to good yields (60% - 80%), and similar results (**4l - 4p**, 65% -73%) were disclosed when using unsymmetrical aryl disulfides



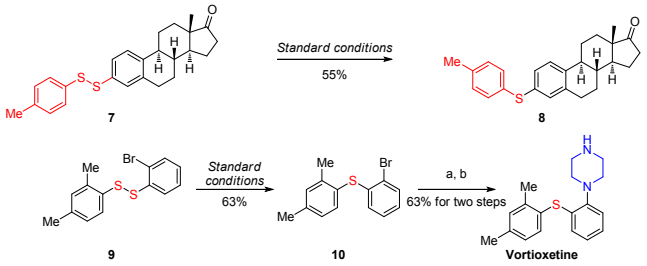
Scheme 3. Substrates Scope of Unsymmetrical Aryl Dichalcogenides.[a, b] [a]Reaction conditions: **3**/**5** (0.10 mmol, 1.0 equiv), CuI (0.02 mmol, 20 mol %), 1,10-phenanthroline (0.04 mmol, 40 mol %), K_2CO_3 (0.30 mmol, 3.0 equiv), DMSO: H_2O = 20 : 1, air, 120 °C. [b]Isolated yields.

derived from 4-methoxyphenyl and several 4-substituted phenyls (**3l - 3p**). Additionally, unsymmetrical aryl disulfides created from the combination of 3-methoxyphenyls (**3q - 3u**) or 2-methoxyphenyls (**3v - 3z**) with several 4-substituted phenyls were compatible in this transformation to provide **4q - 4z** in good yields (65% - 78%); unsymmetrical aryl disulfides originated from 2-methyl benzoate and several 4-substituted phenyls (**3aa - 3ad**) proceeded well to allow access to the expected products in good yields as well (**4aa - 4ad**, 70% - 75%). Significantly, several more complicated molecules (**4ae - 4ah**) were obtained in moderate yields, and various functional groups such as alkenyl (**4ai**), methylsulfonyl (**4aj**), aldehyde (**4ak**), ketone (**4al**) and nitrile (**4am**) were all tolerant in this reaction. Overall, this protocol provides a convenient way to synthesize various unsymmetrical aryl sulfides.

Having obtained many symmetrical and unsymmetrical chalcogenides by dechalcogenization, we wondered if there was any preference between desulfuration and deselenization, thus dechalcogenization of a series of selanylsulfanes were examined (Scheme 3b). To our surprise, when we exploited (4-methoxyphenyl) (phenylselanyl)sulfane **5a** as the starting material, the desulfurization product **6a** was obtained in 63% yield. However, the deselenization product was too little to obtain but only permitted to be observed in GC-MS. Subsequently, several selanylsulfanes were tested and all examples provided desulfuration products **6b - 6f** in moderate to good yields (60 - 78%). This transformation affords a feasible alternative to remove sulfur, where both sulfur and selenium existed in one compound.

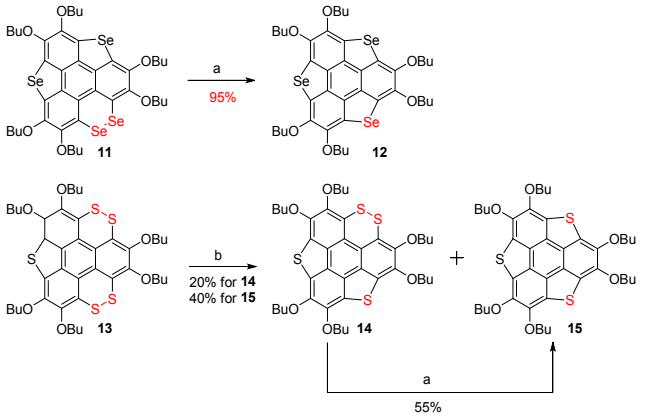
The robustness of this method was shown by the late-stage modification of biological molecule and synthesis of pharmaceutical (Scheme 4). Estrone as an estrogen secreted by human and animals, was modified by desulfuration of **7** under our optimal conditions and rendered aryl sulfide **8** in 55% yield. Subsequently, vortioxetine as a new medicine for treating depression was also synthesized. Starting from disulfide **9**, the key precursor **10** was synthesized using our protocol, which then could be trans-formed into vortioxetine via palladium-catalyzed Buchwald-Hartwig cross coupling[12] and deprotection of amine[13] in 63% yield for two steps.

Encouraged by the above outcomes, our method was further extended for synthesis of more challenging bowl-shaped organic materials with great ring tension (Scheme 5).[3c] Deselenization of **11** was achieved with **12** obtained



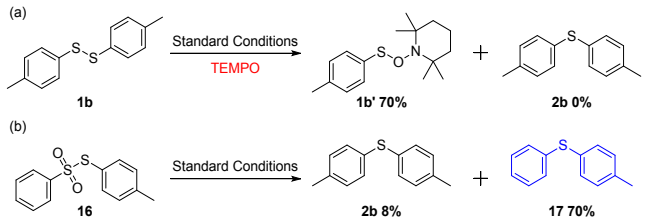
Scheme 4. Modification of Estrone and Synthesis of Vortioxetine. a. $Pd_2(dba)_3$ (2.5 mol %), BINAP (10 mol %), *t*-BuONa (1.4 equiv), toluene, 100 °C, tert-butyl piperazine-1-carboxylate (1.2 equiv). b. TFA, DCM, R.T., 63% over two steps.

in 95% yield. Then desulfurization of **13** was explored and afforded **15** in 40% yield, along with 20% of **14**, which could be further transformed into **15** by desulfurization. In lieu of a large amount of copper powder and high temperature needed in previous reports, catalytic amount of CuI and a lower reaction temperature were used in our protocol, this milder condition provides a new way for synthesis of these chalcogenides-containing organic materials.



Scheme 5. Synthesis of Triselenasumanene 12 and Trithiasumanene 15. a. CuI (20 mol %), 1,10-phenanthroline (40 mol %), K_2CO_3 (3.0 equiv), DMSO : H_2O = 20 : 1, air, 160 °C. b. CuI (40 mol %), 1,10-phenanthroline (80 mol %), K_2CO_3 (6.0 equiv), DMSO : H_2O = 20 : 1, air, 160 °C.

To dig in on the mechanism details, two control experiments were designed and conducted. When TEMPO was added to the reaction system, the 2,2,6,6-tetramethyl-1-((*p*-tolylthio)oxy)piperidine **1b'** was obtained (Scheme 6a) and the desired product **2b** was not observed at all, depicting this protocol might involve a radical process. Subsequently, S-*p*-tolyl benzenesulfonothioate (**16**) was prepared and employed in this reaction, to our delight, the resulting product **17** was obtained in 70% yield, along with **2b** in 8% yield, which demonstrated that compound **16** may be the intermediate of this reaction (Scheme 6b). The plausible mechanism is shown in Supporting Information (Scheme S1) and further detailed studies are still required to verify.



Scheme 6. Control Experiments

In conclusion, we revealed an unprecedented dechalcogenization of aryl dichalcogenides via copper catalysis for the synthesis of aryl chalcogenides in moderate to excellent yields, using simple and accessible aryl dichalcogenides as starting materials rather than odorous thiophenols. This approach featured the practical conditions, broad substrates scope and excellent functional group tolerance, even compatible with several sensitive groups such as aldehyde, ketone, ester, amide, cyanide, alkene, nitro and methylsulfonyl. Moreover, the robustness of this strategy was confirmed by successful modification of estrone and synthesis of vortioxetine. There are two innovations of this work which are over the previously reported synthetic methods of diaryl sulfides using metal-catalyzed C-S coupling reactions: 1) one is this protocol could be served as an important and new supplementary method for synthesis of diaryl sulfides, especially for the synthesis of challenging bowl-shaped organic materials with great ring tension and for the synthesis of some halogen contained diaryl sulfides which could not be synthesized by using metal-catalyzed coupling reactions of aryl halogen with sulfur sources; 2) the other one is this transformation affords a feasible alternative to remove sulfur, where both sulfur and selenium atoms existed in one compound. The powerful strategy holds a promise to apply in biological sulfur-containing lead compound discovery, sulfur-containing medicine and functional organic materials synthesis. Related works are under way in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures, characterization data and spectra of compounds, and other additional data (PDF)

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Y. W. and J. D. contributed equally.

Notes

The authors declare no competing financial interest.

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