

A Direct Preparation of Functionalized Aryl and Heteroaryl Disulfides from Functionalized Zinc Organometallics by Using Sulfur Monochloride (S₂Cl₂)

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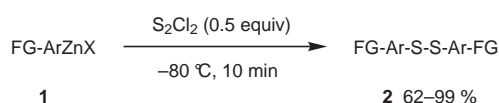
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Abstract: A range of functionalized aryl and heteroaryl disulfides has been prepared from zinc organometallics by using sulfur monochloride (S₂Cl₂). The zinc reagents were obtained by transmetalation from magnesium or lithium reagents with ZnBr₂.

Key words: zinc organometallic reagents, sulfur monochloride, aryl disulfides, heteroaryl disulfides, functionalized arylmagnesium halides

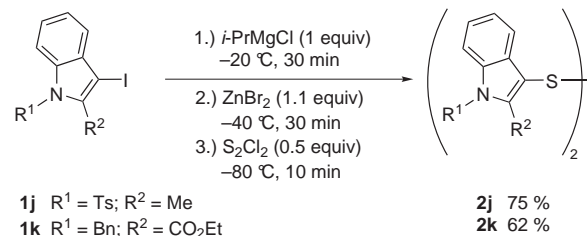
Aryl and heteroaryl disulfides (RSSR; R = Ar, Het) are usually prepared by the oxidation of the corresponding thiols (RSH).¹ In several cases, the thiols are not easily prepared and their oxidation can be complicated by side reactions.^{1,2} Alternative preparation methods are desirable since aryl or heteroaryl disulfides are found in many natural products and may have useful biological properties.³ Recently, several methods for preparing polyfunctional zinc organometallics have become available.⁴ Their moderate reactivity is compatible with sensitive functionalities especially with aryl disulfides at temperatures below –30 °C. We have therefore envisioned the reaction of polyfunctional zinc reagents FG-ArZnX (**1**) with sulfur monochloride (S₂Cl₂). This commercially available reagent has been used for the preparation of various sulfur containing molecules.⁵ Thus, the addition of sulfur monochloride (0.5 equiv) to a THF solution of an aryl or heteroaryl zinc reagent of type **1** (1.0 equiv) at –80 °C produces within ten minutes the expected disulfide (FG-Ar-S)₂ (**2**) in 62–99% yield (Scheme 1 and Table 1).



Scheme 1 Preparation of functionalized aryl disulfides of type **2** from functionalized zinc organometallics of type **1** by using S₂Cl₂

The arylzinc reagents can be prepared from the corresponding aryl bromides by the direct insertion of magnesium in THF (25 °C, 10 h) followed by a transmetalation with ZnBr₂ (–40 °C, 0.5 h). The resulting arylzinc reagents **1a** and **1b** react with S₂Cl₂ in excellent yield providing the aryl disulfides **2a,b** in 98–99% yield (entries 1 and 2 of Table 1). Alternatively, the zinc reagent **1** can be

prepared from the corresponding aryl or heteroaryl iodide by performing an I/Mg-exchange reaction with *i*-PrMgCl at –20 °C.⁶ Thus, 4-chloro-1-iodobenzene is converted to the arylzinc reagent **1a** leading to the expected disulfide **2a** in 91% yield. This preparation method, in contrast to the direct insertion reaction of magnesium,⁷ allows the preparation of functionalized arylmagnesium compounds. The ester-substituted arylzinc reagents (**1c–e**) were prepared via an I/Mg-exchange followed by the addition of ZnBr₂. Their reaction with S₂Cl₂ at –80 °C provides the corresponding disulfides in 65–89% (entries 3–5). The presence of an *ortho* substituent in the zinc reagent **1e** (entry 5) does not interfere with the preparation of the corresponding disulfide **2e** (89% yield). Interestingly, cheap and more easily available aryl bromides can also be used as substrates. The Br/Mg-exchange is, in this case, performed with *i*-PrMgCl·LiCl.⁸ The resulting Grignard reagents were as usually treated with ZnBr₂ leading to the functionalized zinc compounds **1f–h**, which are bearing a nitrile and an ester function, respectively. The reaction with S₂Cl₂ furnished the disulfides **2f–2h** in 62–77% yield (entries 6–8). The use of an aryllithium as precursor is possible. Thus, tributylstannylferrocene⁹ afforded by treatment with *n*-BuLi (–80 °C to 25 °C, 0.5 h) the monolithiated ferrocene, which was subsequently treated with ZnBr₂ and S₂Cl₂, affording the desired ferrocenyl disulfide **2i** in 65% yield (entry 9). Heterocyclic iodides like 3-iodo-2-methyl-*N*-tosylindole¹⁰ or 3-iodo-2-carbomethoxy-*N*-benzylindole¹¹ are readily converted to the corresponding zinc reagents **1j–k** by the reaction with *i*-PrMgCl at –20 °C (0.5 h) followed by the addition of zinc bromide. After the reaction with S₂Cl₂, the desired heterocyclic disulfides **2j–k**¹² are obtained in 75% and 62% yield, respectively (Scheme 2).



Scheme 2 Preparation of functionalized heteroaryl disulfides

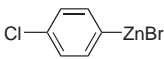
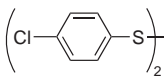
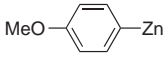
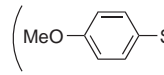
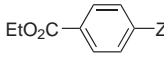
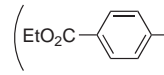
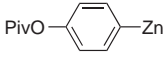
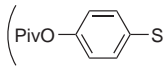
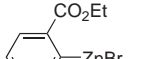
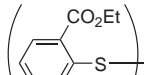
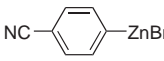
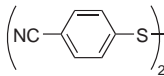
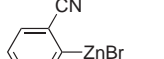
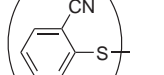
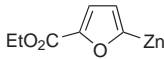
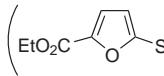

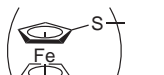
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Table 1 Reaction of Functionalized Aryl- and Heteroarylzinc Halides **1** with Sulfur Monochloride, Leading to Functionalized Organic Disulfides of Type **2**

Entry	Zinc reagent of type 1	Disulfide of type 2	Yield (%) ^a
1			98 ^b (91) ^c
	1a	2a	
2			99 ^b
	1b	2b	
3			87 ^c
	1c	2c	
4			65 ^c
	1d	2d	
5			89 ^c
	1e	2e	
6			62 ^d
	1f	2f	
7			63 ^{d,f}
	1g	2g	
8			77 ^{d,f}
	1h	2h	
9			65 ^e
	1i	2i	

^a Yield of analytically pure product.^b Preparation of the Grignard reagent via Mg-insertion.^c Preparation of the Grignard reagent via I/Mg-exchange with *i*-PrMgCl.^d Preparation of the Grignard reagent via Br/Mg-exchange with *i*-PrMgCl·LiCl.^e Preparation of the lithium reagent via Sn/Li-exchange with *n*-BuLi.^f The crude products contained some polysulfides, which were removed by recrystallization from Et₂O.

In summary, we have reported a new method for preparing functionalized disulfides using the reaction of various functionalized aryl- and heteroarylzinc reagents with S₂Cl₂. The scope and limitations of this method have been delineated and further applications are underway.

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(12) **Typical Procedure. Preparation of the Functionalized Indolyl Disulfide 2k.**

A dry and nitrogen flushed 25 mL Schlenk flask, equipped with a rubber septum and a magnetic stirring bar, was charged with dry THF (5.0 mL) and 3-iodo-1-(phenylmethyl)-1*H*-indole-2-carboxylic acid ethyl ester (403 mg, 0.99 mmol). The solution was cooled to $-20\text{ }^{\circ}\text{C}$ and *i*-PrMgCl (1.12 mL, 1.00 mmol, 0.9 M in THF) was added slowly. The reaction mixture was stirred at that temperature until the I/Mg-exchange was complete (0.5 h, checked by GC), cooled to $-40\text{ }^{\circ}\text{C}$, ZnBr₂ (0.64 mL, 1.09 mmol, 1.7 M

in THF) was added and the white suspension was stirred for 30 min at that temperature. The heterogeneous mixture was cooled to $-80\text{ }^{\circ}\text{C}$ and S₂Cl₂ (67 mg, 0.50 mmol) was added dropwise. After 10 min the reaction mixture was quenched with sat. NH₄Cl solution (50 mL), extracted with Et₂O (3 × 50 mL), the combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated in vacuo. Flash chromatographic purification on silica gel (pentane–Et₂O = 3:1) furnished **2k** as a light yellow solid (193 mg, 0.31 mmol, 62%, mp $>240\text{ }^{\circ}\text{C}$ decomposition).