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Carbon–sulfur bond formation from 2-halochalcogenophenes via copper catalyzed thiol cross-coupling

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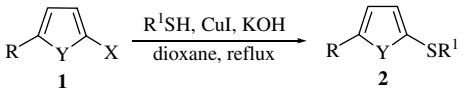
Abstract—We present herein our results of the thiol coupling reaction of 2-halochalcogenophenes with Cu(I) and establish the first route to prepare (2-sulfides)-chalcogenophenes in good yields. The reaction performed with both electron donating and electron withdrawing substituents on thiol in the absence of any supplementary additives. In addition, the reaction proceeded cleanly under mild reaction conditions and was sensitive to nature of catalyst, base, and solvent.

Chalcogenide compounds have found such wide utility because their effects on an extraordinary number of very different reactions, including many carbon–carbon bond formations,[1] under relatively mild reaction conditions. In addition, they have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions,[2] use in a wide variety of functional groups, thus avoiding protection group chemistry and useful biological activities.[3] Among chalcogenides, the chalcogenophenes (telurophene and selenophene) derivatives play an important role in organic synthesis because of their excellent electrical properties, processibility, and environmental stability. But studies of their chemistry are hampered by poor availability of material.

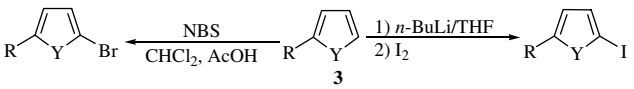
The palladium catalyzed carbon–carbon bond formation, a key stage in the synthesis of many currently interesting heterocycle-incorporated compounds,[4] has proved to proceed generally and effectively. By contrast, there are no reports on the use of halogenated selenophenes or tellurophenes as electrophilic substrate for the carbon–sulfur bond formation using palladium or copper cross-coupling reactions.[5] Considering the advantages of using copper catalysts, less expensive and toxic than palladium salts, we investigated a new methodology to build a carbon–sulfur bond,[6] without any ligand or co-catalyst. In this way, we present our first results of a copper catalyzed coupling reaction between 2-halochalcogenophenes **1** and thiols (Scheme 1).

The starting 2-iodochalcogenophene was readily available by using the metalation of chalcogenophene[7] **3** with *n*-butyllithium to give 2-(lithium)chalcogenophene derivatives. The treatment of 2-(lithium)chalcogenophene with iodine leads to the formation of the 2-iodochalcogenophene, isolated in 55–85% yield after purification (Scheme 2).[8] Conversely, the 2-bromochalcogenophene was prepared via bromination of chalcogenophene **3** with NBS in a mixture of CH_2Cl_2 and AcOH in 50–62% yield (Scheme 2).[9]



Y = Se, Te; X = I, Br; R = H, C_4H_9, C_6H_5; R^1 = alkyl, aryl, benzyl

Scheme 1.



1d - Y = Te; R = Ph - 50 %
1e - Y = Se; R = H - 55 %

1a - Y = Te; R = Ph - 72 %
1b - Y = Te; R = C_4H_9 - 85 %
1c - Y = Se; R = H - 55 %

Scheme 2.

Keywords: Tellurides; Selenides; Sulfides; Copper cross-coupling; Selenophene; Tellurophene.
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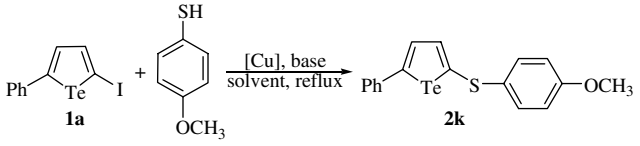
Since our initial studies have focused on the development of an optimum set of reaction conditions, the coupling reaction of 2-halochalcogenophenes with thiols was examined in order to optimize the reaction conditions. In this way, 2-iodo-5-phenyltellurophene **1a** (0.5 mmol), 4-methoxybenzenethiol (0.5 mmol), and KOH (1 mmol) as base, in dioxane were treated, at room temperature, with different copper catalysts and after 15 min at this temperature, the mixture was refluxed for different reaction times (Scheme 3).

As shown in Table 1, Cu(II) catalysts such as $Cu(acac)_2$, $Cu(CH_3CO_2)_2$, $CuCl_2$, $CuBr_2$, and $Cu(CF_3SO_3)_2$ did not exhibit catalytic activity in this reaction and only the staring materials were recovered, even so long reaction time was used (entries 1–5). The Cu(I) catalysts such as CuCN, CuBr, and CuCl gave unsatisfactory yields of the desired enynes (entries 6–8). The optimal catalyst was CuI and the reaction was greatly enhanced by using CuI from 1% to 5 % (entries 10–12). Furthermore, we observed that the addition of CuI (10 mol %) promoted a conversion of 88% (entry 9) instead 85% of the CuI (5 mol %) (entry 10) without any acceleration of the reaction. In addition, no coupling reactions were observed when the reaction was carried out in the absence of CuI (entry 13).

The nature of the base was critical for the success of the coupling. The reaction of 2-iodo-5-phenyltellurophene **1a** (0.5 mmol) with 4-methoxybenzenethiol (0.7 mmol) and CuI (5 mol %) in dioxane were refluxed with different bases such as triethylamine, pyrrolidine, piperidine or morpholine (1 mmol) and no reaction was observed. By using K_3PO_4, NaOH, K_2CO_3, Cs_2CO_3, Na_2CO_3, and EtONa (1 mmol), moderate yields were obtained (15–28%). However, by using KOH, the sulfide was formed in 85% isolated yield. We also investigated the influence of the solvent in the coupling reaction. THF, dichloromethane, toluene, and benzene did not give the expected sulfides. In acetonitrile and *N*,*N*-dimethylformamide only a small amount of coupling product was formed, while the use of dioxane afforded sulfides in higher yields.



Scheme 3.

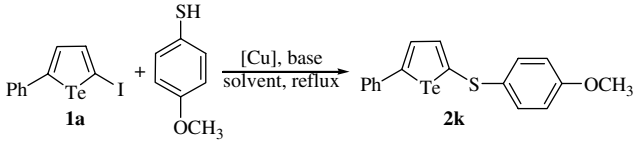
We found that the use of CuI (5 mol %), dioxane (5 mL), **1a** (0.5 mmol), the appropriate thiol (0.7 mol), and KOH (1 mmol) at reflux was optimal, and these conditions were subsequently applied to all other substrates in this study.[10] The results are summarized in Table 2.

Inspections of Table 2 show that the reaction worked well for a variety of iodides. It should be pointed out that functional groups such as methoxy, chloro, alkyl, and benzyl were unaffected. It is noteworthy that the reaction is not sensitive to the electronic nature of functional groups present in the thiols. In addition, no significant influence of the substituents at 5-position in the 2-iodotellurophene was observed (Table 2, entries 8–20).

Further, we observed that coupling of bromide **1d–e** with thiols, using our standard catalytic system for the coupling reaction described in Table 2, gave lower yields than that of corresponding iodides **1a–c** (Table 3). However, when the catalytic system was changed to CuI (10 mol %) and the base was changed to K_3PO_4, the yields were greatly improved (Table 3). To investigate the scope of the reaction, the 2-bromochalcogenophene **1d–e** (0.5 mmol)were reacted with thiols (0.7 mmol) in presence of CuI (10 mol %), dioxane (5 mL), and K_3PO_4 (1 mmol) at reflux. The reactions of 2-bromoselenophenes with thiols bearing a neutral, electron-rich and electron-poor group gave the desired product in good yields (Table 3, entries 1–3). At last, the use of more functionalized 2-bromotellurophenes afforded similar isolated yields with a higher reaction time (Table 3, entries 4–6).

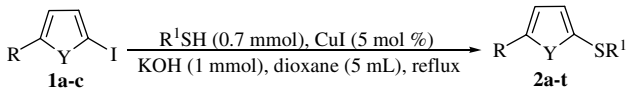
In summary, we have explored the thiol coupling reaction of 2-halochalcogenophenes with Cu(I) and established the first route to (2-sulfides)-chalcogenophenes in good yields. The reaction performed with both electron donating and electron withdrawing substituents on thiol in the absence of any supplementary additives. The advantages of the Cu(I) in a ligand-free system include its lower cost and it is important when considering the scale-up of a reaction. In addition, the reaction proceeded cleanly under mild reaction conditions and was sensitive to nature of catalyst, base and solvent. The pharmacological activities of these compounds are under study in our laboratory. Analysis of the ^1H and ^{13}C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.

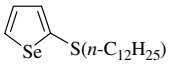
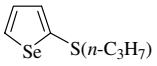
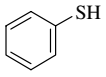
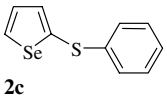
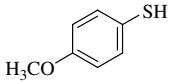
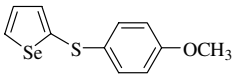
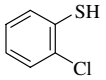
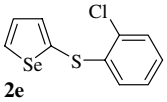
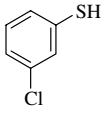
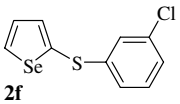
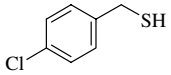
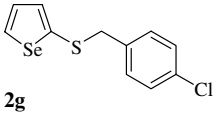
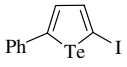
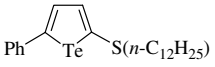
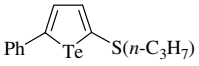
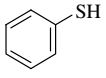
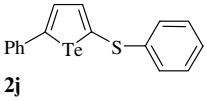
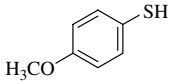
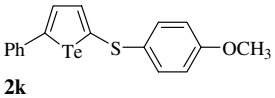
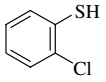
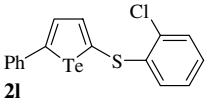
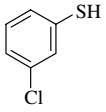
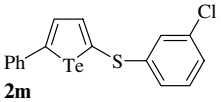
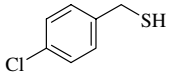
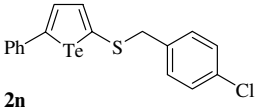
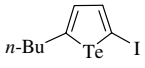
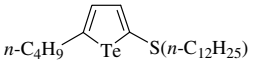
Table 1. Reaction conditions optimization



Entry	Copper catalyst (mol %)	Time (h)	Yield, **2k** (%)
1	$Cu(acac)_2$ (10)	36	NR
2	$Cu(CH_3CO_2)_2$ (10)	36	NR
3	$CuBr_2$ (10)	36	NR
4	$CuCl_2$ (10)	36	NR
5	$Cu(CF_3SO_3)_2$ (10)	36	NR
6	CuCN (10)	20	12
7	CuBr (10)	20	8
8	CuCl (10)	20	22
9	CuI (10)	8	88
10	CuI (5)	8	85
11	CuI (3)	20	63
12	CuI (1)	20	50
13		36	NR

Table 2. Sulfides prepared from 2-iodochalcogenophene **1a–c** and thiols



Entry	Chalcogenophene	Thiol	Product	Time (h)	Yield (%)
1	 **1c**	n-$C_{12}H_{25}SH$	 **2a**	8	82
2	**1c**	n-C_3H_7SH	 **2b**	8	80
3	**1c**		 **2c**	8	80
4	**1c**		 **2d**	8	85
5	**1c**		 **2e**	10	79
6	**1c**		 **2f**	9	77
7	**1c**		 **2g**	10	88
8	 **1a**	n-$C_{12}H_{25}SH$	 **2h**	12	85
9	**1a**	n-C_3H_7SH	 **2i**	12	80
10	**1a**		 **2j**	12	82
11	**1a**		 **2k**	8	90
12	**1a**		 **2l**	8	77
13	**1a**		 **2m**	8	80
14	**1a**		 **2n**	9	89
15	 **1b**	n-$C_{12}H_{25}SH$	 **2o**	12	85

(*continued on next page*)

Table 2 (*continued*)

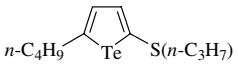
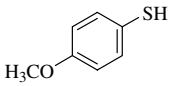
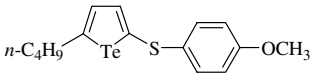
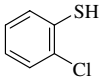
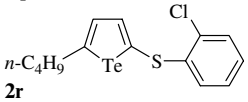
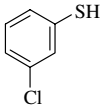
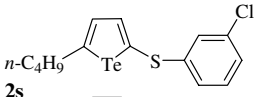
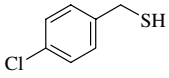
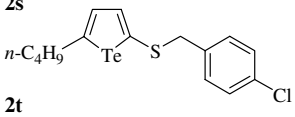
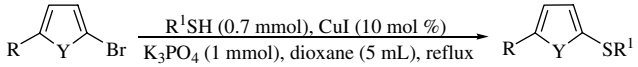
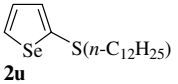
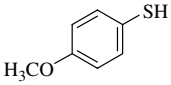
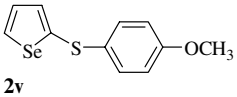
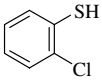
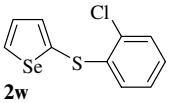
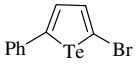
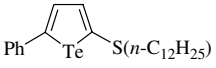
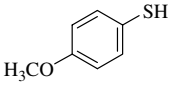
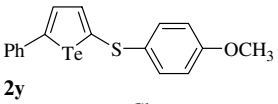
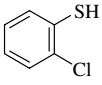
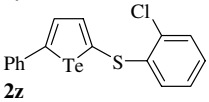
Entry	Chalcogenophene	Thiol	Product	Time (h)	Yield (%)
16	**1b**	n-C_3H_7SH	 **2p**	12	78
17	**1b**		 **2q**	8	91
18	**1b**		 **2r**	8	82
19	**1b**		 **2s**	10	80
20	**1b**		 **2t**	10	88

Table 3. Coupling products obtained using 2-bromochalcogenophene **1d-e** and thiols



1d-e **2u-z**

Entry	Bromine	Thiol	Product	Time (h)	Yield[a,b] (%)
1	 **1e**	n-$C_{12}H_{25}SH$	 **2u**	8	75(12)
2	**1e**		 **2v**	8	70(15)
3	**1e**		 **2w**	12	65(18)
4	 **1d**	n-$C_{12}H_{25}SH$	 **2x**	18	73(15)
5	**1d**		 **2y**	15	78(35)
6	**1d**		 **2z**	18	68(21)

[a] The reactions were carried out using CuI (10 mol %) and K_3PO_4 as base.
[b] Yield in parentheses correspond to reactions performed in CuI (10 mol %) and using KOH as base.

Acknowledgements

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10. *Typical procedure for thiol coupling reaction*: A 25 mL, two-necked, round-bottom flask equipped with a magnetic stir bar, and argon was charged sequentially with CuI (5 mol %), thiol (0.7 mmol), KOH (1 mmol), 2-iodochalcogenophene (0.5 mmol), and dioxane (5 mL). The mixture was stirred at room temperature for 10 min; then refluxed for the time indicated in Table 2. After this time, the mixture was filtered through a pad of alumina eluting with 50 mL of EtOAc. The organic phase was concentrated under vacuum and the residue was purified by flash chromatography. *Selected spectral and analytical data for: (2-dodecylsulfide)selenophene* **2a**: Yield: 0.272 g (82%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.98 (dd, 1 H, J = 5.9 and 1.7 Hz), 7.29–7.11 (m, 2 H), 2.83 (t, 2 H, J = 7.2 Hz), 1.62 (sex, 2 H, J = 7.2 Hz), 1.48–1.16 (m, 18 H), 0.88, (t, 3 H, J = 7.2 Hz). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 155.02, 139.60, 135.14, 133.45, 41.03, 37.00, 36.33, 31.89, 29.62, 29.48, 29.32, 29.13, 29.09, 28.63, 22.65, 14.07. MS *m/z* (%) 332 (100), 317 (50), 303 (29), 289 (73), 275 (33), 201 (55), 130 (83) HRMS Calcd $C_{16}H_{28}SSe$: 332,10769. Found: 332,10791.