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A Direct Synthesis of Selenophenes by Cu-Catalyzed One-Pot Addition of a Selenium Moiety to (*E,E*)-1,3-Dienyl Bromides and Subsequent Nucleophilic Cyclization

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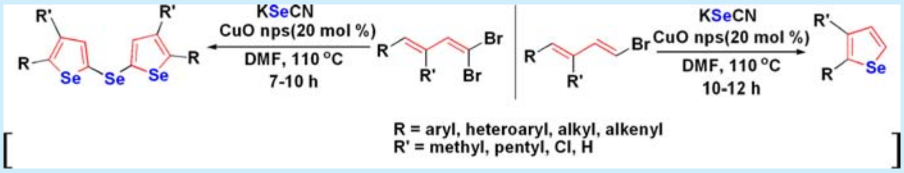
Supporting Information

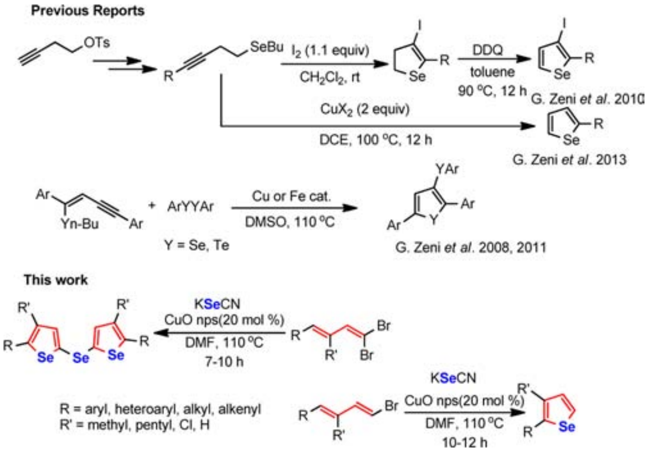


ABSTRACT: An efficient protocol for the synthesis of selenophenes and selanyl selenophenes has been achieved by a simple one-pot reaction of 1,3-dienyl bromides and 1,3-dienyl-*gem*-dibromides respectively with KSeCN catalyzed by CuO nanoparticles. Several aryl, alkenyl, heteroaryl, and alkyl substituted selenophenes were obtained with a broad array of functional group tolerance. This is found to be a general methodology for chalcogenophenes being effective for the synthesis of thiophenes too.

Chalcogenophene derivatives are of considerable interest in organic synthesis because of their useful applications as pharmaceuticals and materials.[1] In this family, selenophenes have received tremendous attention recently, as they have shown promising photobiological[2] and diverse biological activities including antioxidant,[3] antitumoral,[4] anti-inflammatory,[5] antihypertensive,[6] and anticonvulsant.[7] In addition, these compounds are versatile building blocks being used in the synthesis of many biologically active compounds and natural products.[8] Thus, synthesis of selenophenes is of much importance. Surprisingly the methods for their synthesis are very limited. The classical methods for the synthesis of selenophenes involved heating of hexane-2,5-dione and phosphorus pentaselenide in a sealed tube[9] or acetylene and selenium powder.[10] Obviously they required harsh conditions and a high temperature, and thus their large scale application in industry is limited.[11] Recently, electrophilic cyclization of homopropargyl selenides by I_2 or ICl or CuX_2 (4 equiv) and subsequent oxidation by DDQ to produce halosubstituted selenophenes has been reported.[12] Another similar approach involves one-pot electrophilic cyclization of selenoenynes catalyzed by CuI/PhSeSePh.[13] However, both of these procedures are multistep as they require preparation of homopropargyl selenide/selenoenynes in the initial step. A recent report for the synthesis of benzothiophenes and benzoselenophenes involves reaction of arylzinc reagents, alkynes, and elemental chalcogens.[14] However, it is limited to benzochalcogenophenes only and did not address any selenophenes and thiophenes as a unit. Thus, development of an efficient and convenient method for the preparation of selenophenes still remains a challenging task.

We report here a conceptually different and novel protocol involving coupling of 1,3-dienyl bromides with KSeCN leading to the formation of selenophenes where addition of a selenium moiety to the dienyl system and subsequent nucleophilic cyclization take place in one pot catalyzed by CuO nanoparticles (Scheme 1).

Scheme 1. Copper Catalyzed Coupling of 1,3-Dienyl Bromides with KSeCN



To standardize the reaction conditions a series of experiments for a representative reaction of (*E,E*)-4-phenyl-1,3-dienyl bromide and KSeCN with variation of reaction parameters such as solvent, catalyst loading, Cu-source, temperature, and reaction time were performed. 20 mol % CuO was found to

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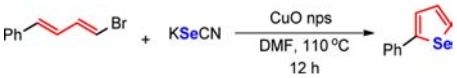
be most effective in catalyzing the reaction in DMF at 110 °C (Table 1, entry 1). DMSO and NMP were also found to be effective (Table 1, entries 2–3). Toluene, CH_3CN, and dioxane failed to initiate the reaction (Table 1, entries 4–6). The reaction did not proceed at all in H_2O (Table 1, entry 7). Only marginal formation of the product was observed when 20 mol % of $Cu(OAc)_2$ and $Cu(acac)_2$ were used as the catalyst (Table 1, entries 8 and 9). The reaction did not progress at lower temperature (90 °C) (Table 1, entry 10). Use of 15 mol % of the catalyst lowered the yield of the reaction (Table 1, entry 11). Use of Se(0) powder in place of KSeCN did not produce any encouraging result (Table 1, entry 12). Virtually no product was formed in the absence of any catalyst (Table 1, entry 13). The reaction using ordinary CuO powder (non NP) provided only a 30% yield of product (Table 1, entry 14).

Table 1. Standardization of Reaction Conditions



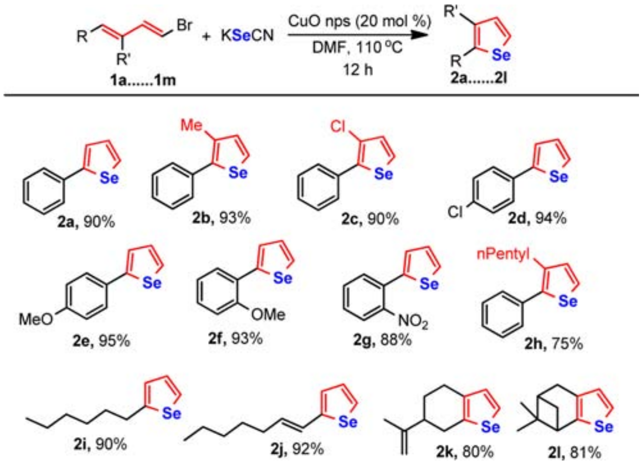
entry	catalyst	catalyst (mol %)	solvent	yield (%)[a]
1	CuO	20	DMF	90
2	CuO	20	DMSO	84
3	CuO	20	NMP	86
4	CuO	20	toluene	–
5	CuO	20	CH_3CN	–
6	CuO	20	1,4-dioxane	–
7	CuO	20	H_2O	–
8	$Cu(OAc)_2$	20	DMF	trace
9	$Cu(acac)_2$	20	DMF	trace
10[b]	CuO	20	DMF	–
11	CuO	15	DMF	48
12[c]	CuO	20	DMF	trace
13	–	–	DMF	trace
14[d]	CuO	20	DMF	30

[a] Reaction conditions: (*E*,*E*)-4-phenyl-1,3-dienyl bromide (0.5 mmol), KSeCN (0.6 mmol), CuO NP (20 mol %), DMF, 110 °C, 12 h. [b] Reaction was carried out at 90 °C. [c] Se powder was used in place of KSeCN. [d] CuO powder (non NP) was used.

Thus, in a typical procedure, a mixture of 1,3-dienyl bromide and KSeCN was heated in DMF at 110 °C in the presence of 20 mol % of CuO nanoparticles for a certain period of time (TLC). The results are summarized in Scheme 2. A variety of aryl or alkyl substituted 1,3-dienyl bromides underwent selenylation followed by cyclization to produce the corresponding selenophenes. Both electron-donating and -withdrawing group substituted dienyl bromides are compatible in this reaction (Me, **2b**, OMe, **2f**, Cl, **2d**, NO_2, **2g**). Reactions with aryl-1,3-dienyl bromides having alkyl substituents (-Me, -pentyl, and Cl) on the vinyl carbon were successful, producing 2-phenyl-3-alkyl selenophenes (**2b**, **2h**, **2c**). Long alkyl chain substituted 1,3-dienyl bromides also produced the corresponding selenophenes (**2i**) although 4-Me- and unsubstituted counterparts did not produce any product. Interestingly 1,3,5-trienyl bromide furnished 2-vinyl selenophene only (**2j**) and formation of no selenepine was observed. This procedure is also effective for the synthesis of tetrahydro benzo[*b*] selenophenes from the corresponding 1,3- dienyl bromides (**2k**, **2l**).

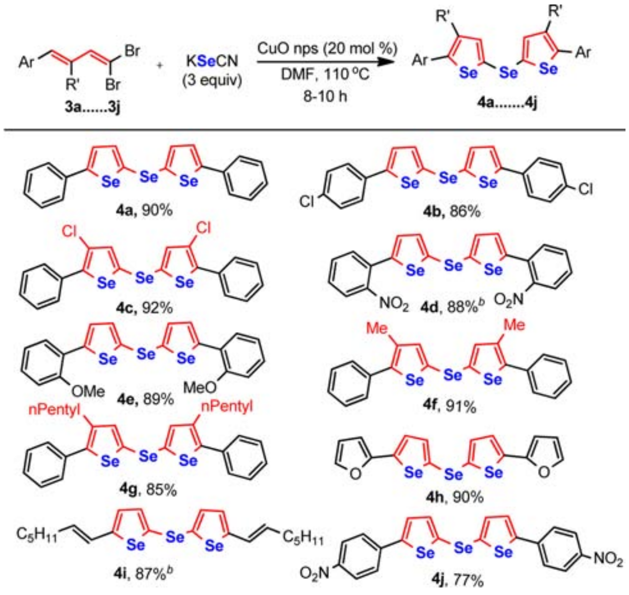
When 1,3-dienyl-*gem*-dibromides were subjected to reaction under these conditions in the presence of 3 equiv of KSeCN, selanyl selenophenes were obtained (Scheme 3). Several diverse aryl substituted 1,3-dienyl-*gem*-dibromides underwent reactions using this procedure to produce the corresponding products. The heteroaryl furan substituted 1,3-dienyl-*gem*-dibromide also participated in this reaction successfully to provide **4h**. The identity of **4h** was established by spectroscopic and crystallographic data[15] (Figure 1).

Scheme 2. Synthesis of Substituted Selenophenes by Copper Catalyzed Coupling of KSeCN and 1,3-Di-enyl Bromides[a]



[a] Reaction conditions: 1,3-dienyl bromide (1 mmol), KSeCN (1.2 mmol), CuO (20 mol %), DMF (2 mL), 110 °C, 12 h.

Scheme 3. Synthesis of Selanyl Selenophenes by Coupling of 1,3-Di-enyl-*gem*-dibromides and KSeCN[a]



[a] Reaction conditions: 1,3-dienyl-*gem*-dibromide (1 mmol), KSeCN (3.0 mmol), CuO (20 mol %), DMF (2 mL), 110 °C, 8 h. [b] 10 h.

The 1,3,5-trienyl-*gem*-dibromide furnished selanyl vinyl substituted selenophenes (**4i**) without any difficulty. Significantly, formation of no diselenepinyl selenide was observed.

Interestingly, the reactions of alkyl substituted 1,3-dienyl-*gem*-dibromides under similar conditions using 3 equiv of KSeCN produced a mixture of selanyl selenophenes and diselanyl selenophenes in varying ratios (NMR) (Scheme 4).

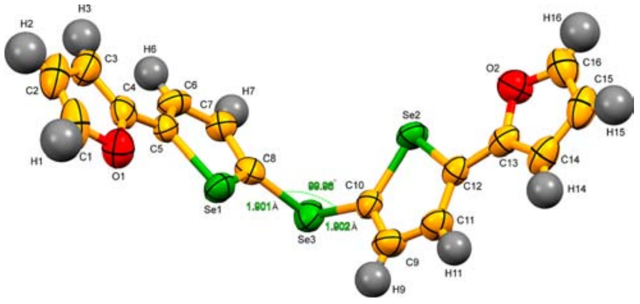
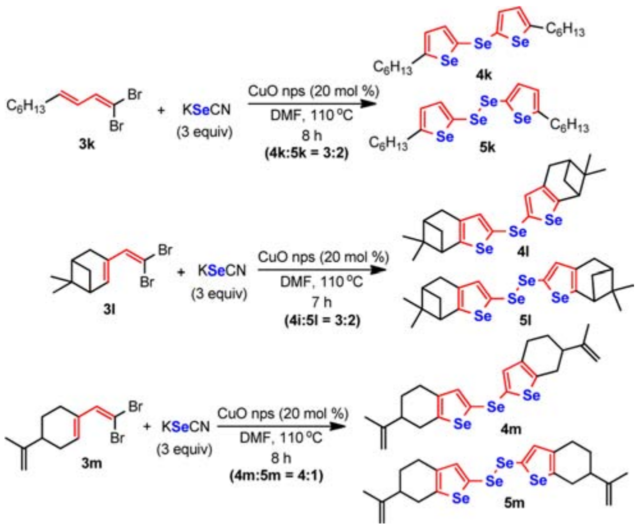


Figure 1. ORTEP diagram of compound **4h**.

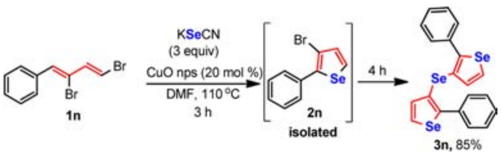
Use of 4 equiv of KSeCN also produced the same result. These diselanyl selenophenes are reported for the first time and may be of potential for biological screening.

Scheme 4. Synthesis of Alkyl-Substituted Selanyl Selenophenes



When 1,3-dienyl-1,3-dibromide (**1n**) underwent copper catalyzed selenylation in the presence of excess KSeCN the initially formed **2n** underwent further reaction with KSeCN to furnish a new selanyl selenophene, **3n** (Scheme 5). The formation of a similar intermediate was observed in the reaction of 1,3-dienyl-*gem*-dibromide also (Scheme 6).

Scheme 5. Selenylation of 3-Bromo-1,3-dienyl Bromide

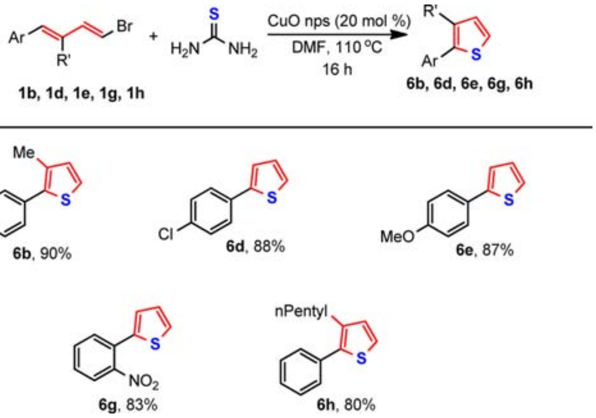


Scheme 6. Isolation of Intermediate during Formation of Selanyl Selenophenes

In general, all the reactions are very clean and high yielding. The pure products were obtained just by simple column chromatography. A wide variety of sensitive functionalities are compatible with the reaction conditions. Many of these selenophenes are reported for the first time, and these molecules, particularly the diheteroaryl selenophene **4h**, may be of interest for biological screening. The compound **2i** was found as a precursor of ClOS-Dye which is a high molar extinction coefficient sensitizer in dye-sensitized solar cells.[16]

To extend the scope of this strategy for the synthesis of thiophenes when the reaction was performed with KSCN under identical reaction conditions, no thiophene was formed. However, the use of thiourea in place of KSCN as a source of a sulfide anion triggered the reaction toward thiophene formation. A few 2-aryl substituted thiophenes were obtained efficiently by the coupling of 1,3-dienyl bromides and thiourea (Scheme 7).

Scheme 7. Synthesis of Substituted Thiophenes by Coupling of 1,3-Dienyl Bromides and Thiourea[a]



[a] Reaction conditions: 1,3-dienyl bromide (1 mmol), thiourea (1.2 mmol), CuO (20 mol %), DMF (2 mL), 110 °C, 16 h.

In summary, we have developed an efficient and general protocol for the synthesis of chalcogenophenes, specifically selenophenes and thiophenes in high yields by a simple one-pot CuO nanoparticle-catalyzed coupling of 1,3-dienyl bromides and potassium selenocyanide and thiourea, respectively. The reaction of 1,3-dienyl *gem*-dibromides produced selanyl selenophenes, a new class of organoselenocycles. This procedure gives an easy access to a series of alkyl, aryl, and heteroaryl substituted selenophenes and selanyl selenophenes, and many of these molecules are reported for the first time. The significant distinctive features of this reaction are use of inexpensive CuO nanoparticles in place of expensive CuI[14] as the catalyst, KSeCN as the selenium source, and an intramolecular nucleophilic cyclization of a selenium moiety to an alkene unit. To the best of our knowledge we are not aware of any such nucleophilic cyclization to selenophene.

We are currently investigating the mechanism of the reaction and scope of this protocol for the synthesis of other molecules. These results will be communicated in a full paper in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical experimental procedure and characterization data of all products and copies of their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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