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PII: S0040-4039(15)30369-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.11.062
Reference: TETL 47002

To appear in: *Tetrahedron Letters*

Received Date: 11 October 2015
Revised Date: 20 November 2015
Accepted Date: 21 November 2015

Please cite this article as: Zhang, S., Koe, A., Heintz, C., Senior, A., Jin, J., Copper-catalyzed one-pot tandem synthesis of unsymmetrical diaryl chalcogenides from two different aryl iodides, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.11.062

Graphical Abstract

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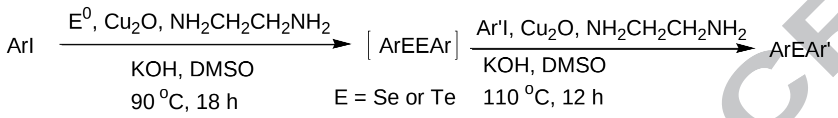

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
unsymmetrical
Diaryl chalcogenides
One-pot tandem synthesis
Aryl iodides
Copper (I) oxide

ABSTRACT

Unsymmetrical diaryl chalcogenides were synthesized by a novel one-pot tandem process from two different aryl iodides. A symmetrical diaryl dichalcogenide (ArEEAr, E = Se or Te) was initially obtained by a Cu_2O-cataylzed coupling reaction of ArI with elemental selenium or tellurium in the presence of KOH. Without purification, it was subsequently coupled with a different aryl iodide (Ar'I) to give the unsymmetrical diaryl chalcogenides (ArEAr') in good yield.

Introduction

There has been a growing interest in organochalcogen compounds in the past few decades. A major breakthrough for the development of organoselenium chemistry was the recognition of selenoxide *syn*-elimination as a powerful olefin forming method in 1970s.[1] It prompted a renewed interest to discover other chalcogen-based reagents and reactions. A number of organochalcogenides are known to be biologically active.[2] In particular, diaryl chalcogenides are known to have anticancer, antitumor, antiviral, antimicrobial and antioxidant properties.[3] Today chalcogen chemistry find application in many areas such as organic synthesis,[2c, 4] synthesis of conducting materials and semiconductors,[5] and ligand chemistry.[6] Additionally, organochalcogen compounds have been used extensively in carbon-carbon bond forming reactions.[7] For example, diaryl tellurides have been used as electrophilic partners in some palladium-catalyzed cross-coupling reactions including Heck[8] and Negishi reactions.[9]

The preparation of unsymmetrical diaryl chalcogenides was mainly achieved by two pathways: (a) traditional methods in which aryllithiums/aryl Grignard reagents were coupled with aryl dichalcogenide (ArEEAr, E = Se, Te) precursors[10] and (b) transition metal-catalyzed coupling of aryl halides/boronic acids with aryl dichalcogenide precursors.[11] Transition metal-catalyzed aryl carbon-chalcogen bond formation is an important method for the preparation of unsymmetrical organo-chalcogenides and have been explored by many researchers.[11] Various metals including palladium, nickel, iron, indium and copper have been utilized to catalyze the coupling reactions of aryl halides or boronic acids with aryl dichalcogenide precursors.[11] Many of the syntheses, however, are limited to phenyl selenides (PhSeAr) or phenyl tellurides (PhTeAr), since only limited numbers of diaryl dichalcogenides are commercially available such as PhSeSePh and PhTeTePh. Otherwise the dichalcogenide precursors need to be prepared in advance.

In order to avoid the foul-smelling, expensive and less available arene chalcogens, the use of easily available chalcogen sources as coupling partners is of great interest. Li and coworkers developed a Cu-catalyzed approach for the synthesis of symmetrical diaryl sulfides or selenides with Na_2S or Se as chalcogen sources.[12] We recently reported a microwave-assisted one-pot protocol to prepare symmetrical diaryl selenides using Se as the chalcogen source in the catalyst of Cu_2O.[13] A one-pot synthesis is much desired by chemists since avoiding a lengthy separation process and purification of the intermediate compounds would save time and resources while increase chemical yields.

Here we report a one-pot tandem process to synthesize unsymmetrical diaryl selenides and tellurides involving two coupling reactions. The first coupling reaction was accomplished by aryl iodide (ArI) and elemental selenium or tellurium catalyzed by Cu_2O to give a symmetrical diaryl dichalcogenide (ArEEAr), which was subsequently coupled with a second aryl iodide (Ar'I) in a one-pot reaction without any purification. With this protocol, a various combination of unsymmetrical diaryl selenides (ArSeAr') and tellurides (ArTeAr') were obtained in good yields.

Results and discussion

In the one-pot synthesis, intermediate purification isn't necessary, so the risk of unwanted products and side reactions are more probable. In order to get better yields and selectivity, selection of the catalyst is critical to the catalytic system. Tandem catalysis is categorized into three subclasses: orthogonal-, auto-, and assisted-tandem catalysis. Auto-tandem catalysis is defined as a process in which one catalyst promotes more than two

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fundamentally different reactions in a single reactor. Since diaryl dichalcogenide (ArEEAr) is an important intermediate to prepare unsymmetrical diaryl chalcogenide (ArEAr') through the coupling reaction, our main goal in this work is to seek a catalyst which will work effectively for both symmetrical diaryl dichalcogenides (ArEEAr) and unsymmetrical diaryl chalcogenides (ArEAr') syntheses. Therefore if the common catalyst is found, the tandem synthesis of unsymmetrical diaryl chalcogenide could be accomplished.

There are a variety of methods to prepare organic diselenides or ditellurides,[14] such as the reaction between Grignard or organolithium reagents and elemental selenium or tellurium followed by oxidation. However these methods are not suitable for our tandem synthesis in consideration of the second coupling leading to the final product ArEAr'. Since we successfully prepared symmetrical diaryl selenides (ArSeAr) through the coupling reaction between aryl iodide and elemental selenium in the presence of a catalytic amount of Cu_2O,[4] we attempted to use the same catalytic system to first give diaryl diselenide (ArSeSeAr) intermediate, which expectantly would further couple with a second aryl iodide (Ar'I) to form the final unsymmetrical diaryl selenide (ArSeAr') under the same catalyst.

In order to find proper reaction conditions and to explore the influence of different variables in the one-pot synthesis, several components were studied. To this end, our initial investigation aimed at the preparation of 4-methylphenyl 4'-methoxyphenyl selenide as a model target molecule. We undertook a detailed study on the two consecutive coupling reactions and the results are summarized in Table 1.

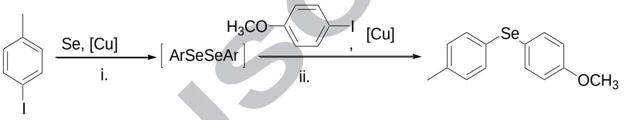
The first coupling reaction to generate the intermediate 1,2-di(*p*-tolyl)diselenide employed 4-iodotoluene and elemental Se as substrates. Without purification, the diselenide intermediate would subsequently couple with 4-iodoanisole to give the final unsymmetrical product 4-methylphenyl 4'-methoxyphenyl selenide, **1**. Herein several variables for the reactions were studied: copper catalyst, amount of Se powder, and reaction temperatures for the two coupling reactions. It should be noted that the two possible by-products in the one-pot synthesis are the symmetrical diaryl selenides (ArSeAr and Ar'SeAr') formed from the first and second aryl iodide respectively.

Using Cu_2O as the catalyst, different equivalents of Se powder were attempted. We found the best yield was obtained when 2 equiv. of Se powder was used (Table 1, entry 2). With 3 equiv. of Se (Table 1, entry 1), an increased ratio of the symmetrical selenide from the second aryl iodide $(p\text{-OMePh})_2Se$ was detected due to the residue of excess selenium source. However, when the amount of Se was reduced to 1.5 equiv. or 1 equiv. (Table 1, entry 3 and 4), an increased ratio of the symmetrical selenide from the first aryl iodide $(p\text{-MePh})_2Se$ suggested that the diselenide intermediate was not efficiently prepared. With 2 equiv. of Se powder, we also tried other copper catalysts such as CuO (Table 1, entry 5), CuI (Table 1, entry 6), $Cu(OAc)_2$ (Table 1, entry 7) or the combination of two catalysts (CuI and Cu_2S, Table 1, entry 8) for the two coupling reactions respectively, but none obtained better yields compared to Cu_2O. The reaction temperature was also studied and we found the first coupling reaction to give the diselenide intermediate required a relatively lower temperature 90 °C to prevent the decomposition, while the second coupling reaction between diselenide and a second aryl iodide would benefit from a higher temperature 110 °C.

Under the optimized conditions, various combinations of aryl iodides were investigated for the one-pot tandem synthesis of unsymmetrical diaryl selenides as well as unsymmetrical diaryl tellurides.[15] The outcome is listed in Table 2. It was observed that the electronic properties of different substituents on the aryl rings did not affect the two coupling reactions much since both electron-donating groups (e.g., Me, NH_2, and OMe) and electron-withdrawing groups (e.g., Cl, NO_2, and CN) worked well. It was also noticed that sterically hindered ortho and meta substrates also provided good yields of unsymmetrical diaryl selenides. A larger scale (5 mmol) reaction was performed on the one-pot synthesis of 4-chlorophenyl 4'-methylphenyl selenide, **2**. The yield was found to be 64%, which suggests this methodology also applies to larger scale reactions.

Table 1

Optimum of reaction conditions



Entry	[Cu]	Se (equiv.)	Yield (%)[a]
1	Cu_2O	3	50
2	**Cu_2O**	**2**	**72**
3	Cu_2O	1.5	64
4	Cu_2O	1	50
5	CuO	2	60
6	CuI	2	54
7	$Cu(OAc)_2$	2	39
8	CuI/Cu_2S[b]	2	trace

a. Isolated yield

b. CuI in step i; Cu_2S in step ii.

Reaction conditions: i. 4-iodotoluene (1 mmol), Se, [Cu] (0.2 equiv.), $H_2NCH_2CH_2NH_2$ (0.2 equiv.), KOH (2 equiv.), and DMSO (2 mL) stirred at 90 °C for 18 h under N_2. ii. 4-iodoanisole (1 mmol), [Cu] (0.2 equiv.), $H_2NCH_2CH_2NH_2$ (0.2 equiv.), KOH (2 equiv.), and DMSO (2 mL) stirred at 110 °C for 12 h under N_2.

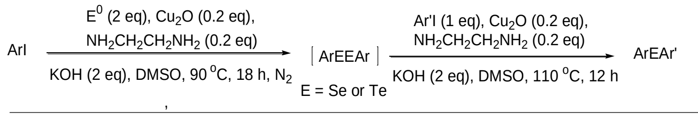
Finally a plausible reaction pathway based on the Cu_2O-catalyzed one-pot tandem synthesis of unsymmetrical diaryl selenides was proposed as shown in Figure 1.

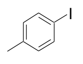
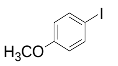
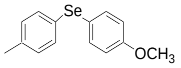
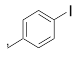
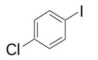
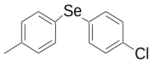
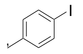
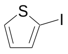
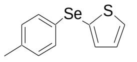
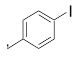
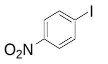
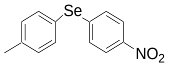
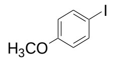
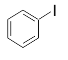
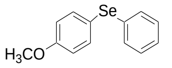
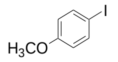
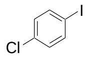
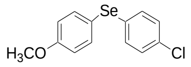
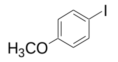
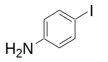
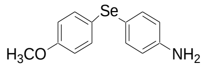
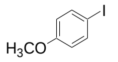
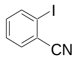
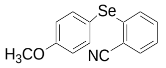
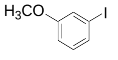
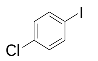
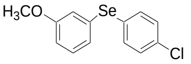
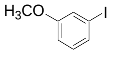
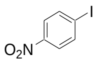
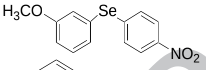
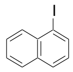
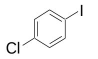
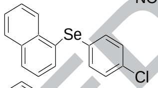
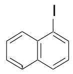
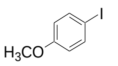
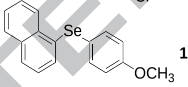
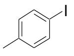
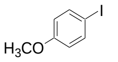
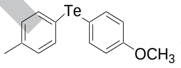
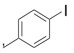
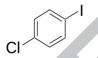
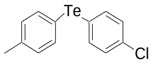
Under a superbasic DMSO-KOH system, elemental selenium undergoes a disproportionation reaction to give selenolate anion **a**, which may further react with Se^0 to give diselenolate anion **b**. The oxidative addition of ArI to Cu_2O catalyst forms complex **c**, which is converted to complex **d** by the ligand exchange with the diselenolate anion **b**. Complex **d** could undergo reductive elimination to give the initial coupling product $ArSeSe^-$ **e** and regenerate the Cu_2O catalytst. The intermediate **e** $ArSeSe^-$ would react with another complex **c** furnishing the complex **f**. A reductive elimination could afford the diselenide intermediate **g** and release Cu_2O for use in the next catalytic cycle.

Similarly, the second coupling reaction started once complex **h** was formed after addition of the second aryl iodide Ar'I. Ligand exchange might give complex **i**, which would undergo reductive elimination to give the final unsymmetrical diaryl selenide.

Table 2.

Synthesis of unsymmetrical diaryl selenides via the one-pot procedure



Entry	Ar	Ar'	E	Product		Yield (%)
1			Se		**1**	72
2			Se		**2**	69
3			Se		**3**	58
4			Se		**4**	68
5			Se		**5**	70
6			Se		**6**	65
7			Se		**7**	81
8			Se		**8**	62
9			Se		**9**	76
10			Se		**10**	57
11			Se		**11**	88
12			Se		**12**	82
13			Te		13	56
14			Te		**14**	64

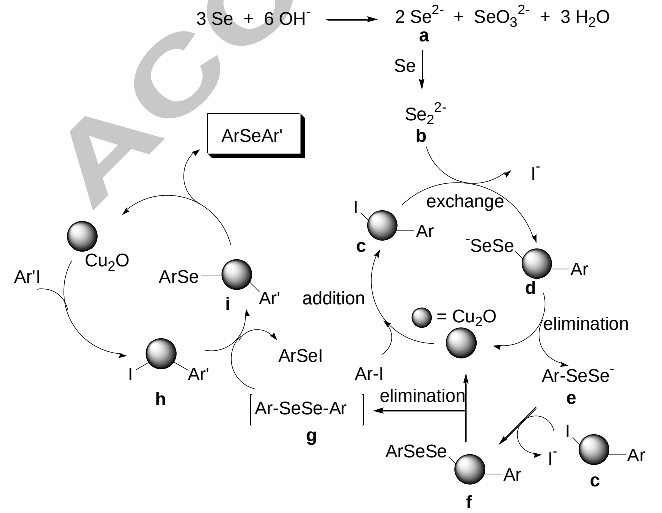


Figure 1. Proposed mechanism for the Cu_2O-catalyzed synthesis of ArSeAr'

Conclusion

In conclusion, we have developed a one-pot tandem process to prepare unsymmetrical diaryl chalcogenides from two different aryl iodides. The synthesis involves two consecutive coupling reactions catalyzed by Cu_2O. The first coupling reaction between the first aryl iodide and elemental chalcogen (Se/Te) afforded the intermediate diaryl dichalcogenide. Without purification, it was subsequently coupled with a second aryl iodide (Ar'I) to give the final product unsymmetrical diaryl selenide (ArEAr') in good yield.

Acknowledgments

We are grateful to NSF MRI award (Acquisition of a 400-MHz NMR Spectrometer to Support Faculty-Student Research and Training at WIU and Partner Institutions), college of arts and science at WIU for financial support.

Supplementary data

Full experimental details and spectroscopic data of all compounds, ^{1}H and ^{13}C NMR, HRMS data can be found. Supplementary data associated with this article can be found.

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15 General procedure for the synthesis of diaryl selenides:

A sealed tube containing a magnetic stirring bar was charged with the first aryl iodide I (ArI) (1.0 mmol), Se^0 (or Te^0, 2.0 mmol), Cu_2O (0.2 mmol), ethylene diamine (0.2 mmol), KOH (2.0 mmol) and DMSO (2 mL) under nitrogen. The reaction mixture was heated in oil bath at 90 ^oC for 18 h. The reaction mixture was allowed to cool, and then the second aryl iodide II (Ar'I) was added, followed by adding Cu_2O (0.2 mmol), ethylene diamine (0.2 mmol). The tube was resealed and the mixture was heated at 110 ^oC for 12 h. The reaction mixture was treated with CH_2Cl_2 and H_2O. The organic layer was washed with brine solution, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with an eluent consisting of hexanes and ethyl acetate affording the corresponding unsymmetrical diaryl chalcogenides.