Tetrahedron Letters 55 (2014) 5275–5279

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

CuI/glycerol mediated stereoselective synthesis of 1,2-bis-chalcogen alkenes from terminal alkynes: synthesis of new antioxidants

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ARTICLE INFO

Article history:
Received 1 July 2014
Revised 23 July 2014
Accepted 25 July 2014
Available online 2 August 2014

Keywords:
Catalysis
Bis-chalcogen alkenes
Glycerol
CuI/Zn
Antioxidant

ABSTRACT

(*E*)-1,2-Bis-chalcogen alkenes were stereoselectively prepared in good yields by the addition of diorganyl dichalcogenides to terminal alkynes using CuI/Zn/glycerol as a recyclable catalytic system. The antioxidant activity in vitro of four (*E*)-1,2-bis-chalcogen alkenes synthesized was evaluated and (*E*)-1,2-bis-(4-methoxyphenylselanyl)styrene **3b** presented excellent activity. The catalytic system used in the synthesis was recovered and used directly up to 5 cycles without loss of activity.

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New strategies for the preparation of bis-chalcogen alkenes have been the object of intense research, due to the continued interest in synthetic applications and, more recently, new pharmacological properties of vinyl chalcogenides, as can be observed in several articles.[1,2] Classical methods for the synthesis of 1,2-bis-chalcogen alkenes described over the years involve mainly three different approaches: reaction of vinyl dichlorides with thiolate anions,[3] reaction of alkynes with radical chalcogen species,[4] and reactions of alkynes with dichalcogenides mediated by transition metals,[5] amidst others.[6] However, most of these protocols described for the preparation of bis-chalcogen alkenes require the use of heavy metals, high temperature, and present other limitations, including toxicity and hazard associated with the use of volatile organic solvents. Besides, in a general way, these protocols afford selectively (*Z*)-1,2-bis-chalcogen alkenes or, in some cases, a mixture of *Z* and *E* isomers and other side products.[6]

On the other hand, pyrazoles are an important class of heterocyclic compounds, and molecules containing the pyrazole nucleus stand out due their application as catalysts,[7a] liquid crystal,[7b] and also their pharmacological activities, such as anti-inflammatory, antipyretic, and analgesic.[7c,d] Nevertheless, the synthesis of 1,2-bis-chalcogen alkenes containing the pyrazole unit has not been explored.

Volatile organic solvents (VOCs) are responsible for most of waste and pollution generated by chemical processes[8] and the search for green, reusable solvents is still a great challenge in organic synthesis.[9] Possessing a unique combination of physical and chemical properties and some advantages of water, such as highly polar, biodegradable, immiscible with hydrocarbons and ethers, and aptitude to dissolve inorganic compounds, glycerol is ideal for use as a sustainable solvent in organic synthesis.[10,11]

Recently, our group described environmental friendly procedures for the selective preparation of vinyl chalcogenides starting from terminal alkynes and diorganyl dichalcogenides.[12–14] We observed that $NaBH_4$/[bmim]BF_4 is a convenient recyclable system to prepare (*Z*)-vinyl chalcogenides starting from propargyl and derivative alcohols. When phenyl acetylene was used, (*E*)-1,2-bis-phenylchalcogen styrenes were obtained in good yields.[12] Additionally, (*E*)-bis-chalcogen styrenes were obtained in good yields and high selectivity using alumina/$NaBH_4$ under solvent-free conditions,[13] while the *Z* isomer was preferably obtained when PEG-400 was used as solvent.[14]

Herein, we report the direct copper-catalyzed addition of diaryl dichalcogenides to terminal alkynes, using CuI/Zn/glycerol[15] as the catalytic system (Scheme 1). This approach provides straightforward, efficient, and stereoselective access to a variety of (*E*)-1,2-bis-chalcogen alkenes, some of them are potent antioxidants, in a stereoselective fashion.

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http://dx.doi.org/10.1016/j.tetlet.2014.07.109
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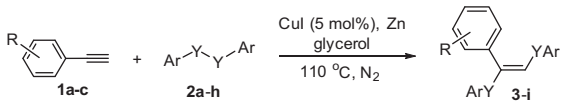


Scheme 1. General scheme of the reaction.

Phenyl acetylene **1a** and diphenyl diselenide **2a** were used as model substrates to determine the best reaction conditions (Table 1). Thus, a mixture of **1a** (0.6 mmol) and **2a** (0.6 mmol) was stirred at 110 °C (oil bath), in the presence of CuI as catalyst (5 mol %), Zn dust (0.6 mmol) and glycerol (1.0 mL) under N_2 atmosphere. After 5 h, (*E*)-1,2-bis-(phenylselanyl)styrene **3a** was obtained in 95% yield with a *E*:*Z* ratio of 90:10 (Table 1, entry 1). Aiming to improve the yield and selectivity of the reaction, the mixture was stirred for 24 h, giving **3a** in a similar yield and selectivity (Table 1, entry 2). When we used a lower amount of catalyst (3 mol %) the desired product **3a** was obtained in 72% yield, even after 24 h of reaction (Table 1, entry 3). Similarly, when the amount of zinc was diminished to 0.3 mmol, yield of **3a** was only 64% after 24 h (Table 1, entry 4). Remarkably, poor yields of **3a** were obtained in the absence of CuI or Zn (Table 1, entries 5 and 6) and only traces were formed when both of them were not present (Table 1, entry 7). We tested also the reaction at a milder temperature (60 °C) and a mixture of (*E*)- and (*Z*)-1,2-bis-(phenylselanyl)styrene **3a** in 39% yield was isolated after 24 h (Table 1, entry 8). It was observed also that nitrogen atmosphere is critical to the formation of **3a** in good yield, once decrease in yield and selectivity was observed in the reaction performed in an open flask (Table 1, entry 9).

With the best conditions in hand, we extended the protocol to other terminal alkynes and diaryl dichalcogenides (Table 2).[16] As it can be seen in Table 2, for most of studied cases, the desired products were obtained in excellent yields and stereoselectivity. It was observed that the best yields and higher stereoselectivities were obtained using diaryl diselenides **2a**–**d**, containing electron-donating and neutral groups at the aromatic ring (Table 2, entries 1–4). The presence of electron-donor groups in **2b**–**d** increases the electron density on the selenium atom, making it a more reactive nucleophile. Thus, while 5 h were necessary to prepare **3a** from diphenyl diselenide **2a** in 95% yield (entry 1), (*E*)-1,2-bis-(*p*-methylphenyl)seleno alkene **3b** was obtained exclusively in 92% yield after only 3 h (Table 2, entry 2). Similarly, **3c** and **3d** were prepared, respectively, from **2c** and **2d** in 82% and 80% yields after 3 h of stirring at 110 °C (entries 3 and 4). In contrast, diaryl diselenides **2e** (R = *p*-Cl) and **2f** (R = *m*-CF_3), containing electron-withdrawing groups, were less reactive, affording the respective products **3e** (56%, *E*:*Z* ratio = 100:0) and **3f** (60% yield, *E*:*Z* ratio = 75:25) only in moderated yields (Table 2, entries 5 and 6). A similar electronic effect was not observed in the alkyne component of the reaction, once lower yields were obtained both with 1-methyl-4-ethynilbenzene **1b** and 1-chloro-4-ethynylbenzene **1c**, which afforded the respective (*E*)-bis-chalcogen alkenes **3g** (73% yield, entry 7) and **3h** (55% yield, entry 8) in similar yields and selectivity. When diphenyl disulfide **2g** was used, a higher reaction time was needed to prepare (*E*)- and (*Z*)-1,2-bis-(phenylthio)styrene **3i** in 60% yield and a *E*:*Z* ratio of 68:32. In contrast, when diphenyl ditelluride **2h** was used, no product **3j** could be isolated and only traces were detected by GC/MS.

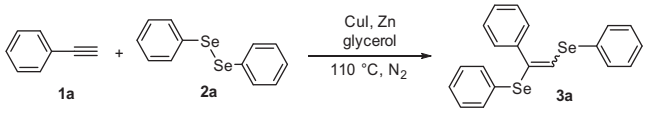
Due to the importance of the pyrazole unit in biologically active heterocyclic compounds, we decided to extend the methodology using *N*-propynyl pyrazoles **4a**–**c** as alkyne partners, aiming to prepare (*E*)-bis-chalcogen alkene pyrazoles. Differently to the observed for the aryl alkynes **1a**–**c**, propynyl pyrazoles **4a**–**c** afforded a mixture of bis- and mono-chalcogen alkenes (Table 3). Thus, when 1-(prop-2-yn-1-yl)-1*H*-pyrazole **4a** reacted with diphenyl diselenide **2a** under our conditions for 2 h, a mixture of (*E*)-**5a**, (*Z*)-**6a,** and *gem*-**7a** was obtained in a 50:13:37 ratio and in an overall yield of 90% (Table 2, entry 1). A higher selectivity for the bis-chalcogen alkene was observed for 3,5-dimethyl-1-(prop-2-yn-1-yl)-1*H*-pyrazole **4b**, which afforded exclusively a mixture of (*E*)-**5b** and (*Z*)-**5b** in 90% yield and a *E*:*Z* ratio of 90:10 (Table 2, entry 2). The reaction tolerates also the presence of a bromine atom in the pyrazole ring, as in 5-bromo-1-(prop-2-yn-1-yl)-1*H*-pyrazole **4c**; however, only mono-adducts (*Z*)-**6c**, (*E*)-**6c,** and **7c** were isolated in 85% yield after 3 h [(*Z*)-**6c**:(*E*)-**6c**:**7c** ratio = 66:6:28; Table 2, entry 3]. Similarly, a mixture of mono phenylthio alkenes was isolated after 6 h of reaction in 78% yield using diphenyl disulfide **2g** and 1-(prop-2-yn-1-yl)-1*H*-pyrazole **4a** (Table 3, entry 4). No reaction was observed when diphenyl ditelluride **2h** was used.

The use of this catalytic system showed good results in studies regarding their recyclability. Initially a reuse study of the CuI/Zn/glycerol system was carried out for the reaction of **1a** with **2a** to obtain **3a**. After stirring at 110 °C for 5 h, the reaction mixture was diluted and extracted with a mixture of hexane/ethyl acetate 95:5 (3 × 3.0 mL). The upper organic phase was removed, the solvent evaporated and the product **3a** was isolated. The remaining inferior phase containing a mixture of CuI/Zn/glycerol was dried under vacuum and directly reused for further reactions, simply by adding more reagents **1a** and **2a**. As shown in Table 4, the system CuI/Zn/glycerol presented a good level of efficiency even after reusing five times, being the product **3a** obtained in 95%, 94%, 91%, 88%, 84%, and 76% yields after successive cycles.

A plausible mechanism for the formation of (*E*)-1,2-bis-chalcogen alkenes **3a**–**i** is depicted in Scheme 2, involving the initial reduction of Cu(I) to Cu(0) by metal zinc; following which, Cu(0) undergoes oxidative addition with diaryl dichalcogenide **2** to form the intermediate $(ArY)_2Cu(II)$. Following which, zinc could reduce this intermediate to ArYCu, which reacts with the terminal alkyne **1a** to give the respective (*E*)-1,2-bis-chalcogen alkenes **3**. We believe the reuse of CuI/Zn/glycerol for additional reaction is possible in view of glycerol could be acting both, as a solvent and by reducing Zn(II) to Zn(0) (Scheme 2).[17]

Among organoselenium compounds, the class of bis-selanyl alkene has attracted some attention, due to their chemical

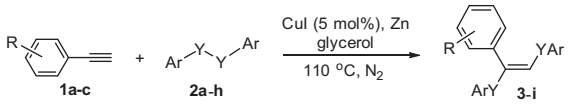
Table 1
Synthesis of (*E*)-1,2-bis-(phenylselanyl)styrene **3a** under different conditions[a]

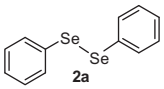
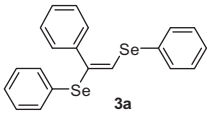
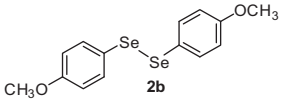
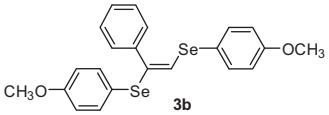
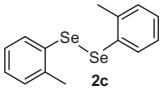
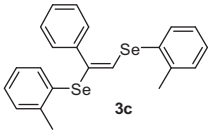
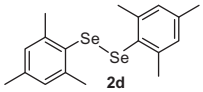
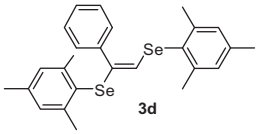
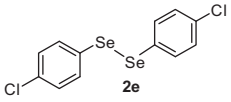
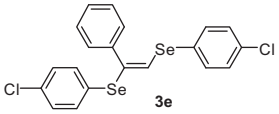
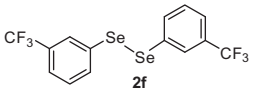
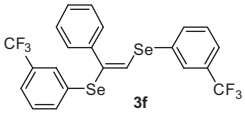
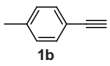
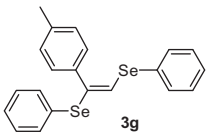
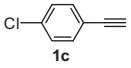
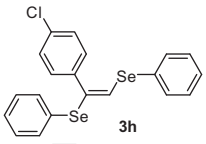
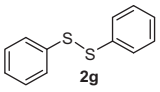
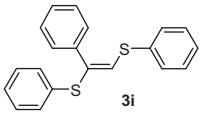
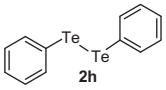
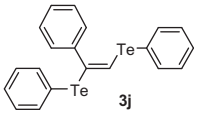


Entry	CuI (mol %)	Zinc (mmol)	Time (h)	Yield[b] (%)	Ratio[e] (*E*/*Z*)
1	5	0.6	5	95	90:10
2	5	0.6	24	93	88:12
3	3	0.6	24	72	85:15
4	5	0.3	24	64	82:18
5	—	0.6	24	26	80:20
6	5	—	24	45	80:20
7	—	—	24	Traces	nd
8	5	0.6	24	39[c]	82:18
9	5	0.6	24	57[d]	74:26

[a] Reactions performed using phenyl acetylene **1a** (0.6 mmol), diphenyl diselenide **2a** (0.6 mmol), and glycerol (1.0 mL) under N_2 atmosphere.
[b] Yields are given for isolated products.
[c] Reaction was performed at 60 °C.
[d] Reaction was performed in open atmosphere.
[e] Determined by GC/MS of the crude reaction mixture and confirmed after isolation of the individual isomers.

Table 2
Synthesis of 1,2-bis-chalcogen alkenes (**3a–i**)[a]



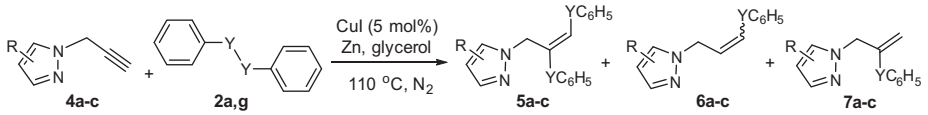
Entry	Alkyne **1**	ArYYAr **2**	Product **3**	Time (h)	Yield[b] (%)	Ratio[c] (*E*:*Z*)
1	 **1a**	 **2a**	 **3a**	5	95	90:10
2	**1a**	 **2b**	 **3b**	3	92	100:0
3	**1a**	 **2c**	 **3c**	3	82	90:10
4	**1a**	 **2d**	 **3d**	3	80	88:12
5	**1a**	 **2e**	 **3e**	2	56	100:0
6	**1a**	 **2f**	 **3f**	3	60	75:25
7	 **1b**	**2a**	 **3g**	5	73	86:14
8	 **1c**	**2a**	 **3h**	6	55	91:09
9	**1a**	 **2g**	 **3i**	8	60	68:32
10	**1a**	 **2h**	 **3j**	24	Traces	–

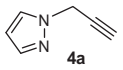
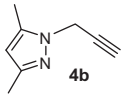
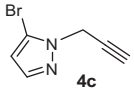
[a] All reactions were carried out with alkyne **1** (0.6 mmol) and diaryl chalcogenides **2** (0.6 mmol) in the presence of CuI (5 mol %), and Zn (1 equiv) in 1.0 mL of glycerol at 110 °C under N_2 atmosphere.[16]
[b] Yield after purification by column chromatography.
[c] Determined by GC/MS of the crude reaction mixture and confirmed after isolation of pure products.

properties and pharmaceutical potential.[2d] Moreover, bis-selanyl alkenes are known as potential antioxidant compounds.[2b] Based on these considerations, we evaluated the antioxidant potential of synthesized compounds (*E*)-**3a**, (*E*)-**3b**, (*E*)-**3e,** and (*E*)-**5a**. In order to evaluate their free radical scavenger ability, DPPH (diphenyl-2,4,6-trinitrophenyl-imino azanium)[18] and ABTS (2,2′-azinobis(3-ethyl benzothiazoline-6-sulfonic acid)[19,20] assays were used and results are presented in Figure 1.

In the DPPH test only compound (*E*)-**3b** presented radical scavenging activity at concentrations of 100 and 500 μM (see Fig. 1A), with a maximal inhibition (I_{max}) of 36.47 ± 5.22%. In the ABTS assay compound (*E*)-**3a** showed significant effect at concentrations ranging from 10 to 100 μM, with a maximal inhibition of 26.25 ± 2.33% (Fig. 1B), while compounds (*E*)-**3b** and (*E*)-**3e** did not present any effect in the ABTS scavenging assay (Data not shown). This observation is in agreement with the fact that ABTS and DPPH scavenging

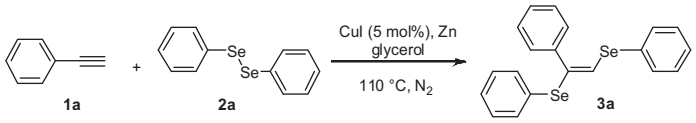
Table 3
Synthesis of bis- and mono-chalcogen alkenes derived from *N*-propynyl pyrazoles[a]



Entry	*N*-Propynyl pyrazole	Y	Product	Time (h)	Yield[b] (%)	Ratio[c]
1	 **4a**	Se	(*E*)-**5a** + (*Z*)-**6a** + **7a**	2	90	50:13:37
2	 **4b**	Se	(*E*)-**5b** + (*Z*)-**5b**	2	94	90:10
3	 **4c**	Se	(*E*)-**5c** + (*Z*)-**6c** + (*E*)-**6c** + **7c**	3	85	19:48:6:27
4	**4a**	S	(*Z*)-**6d** + (*E*)-**6d** + **7d**	6	78	19:38:43

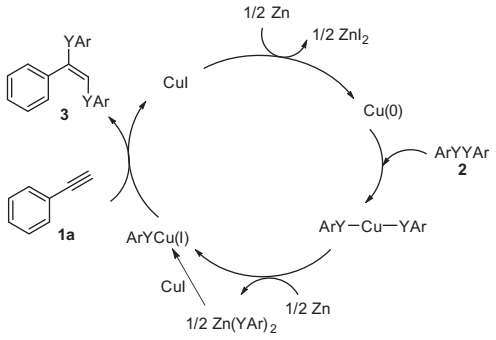
[a] Reaction conditions are the same as described in footnote of Table 2.
[b] Yield after purification by column chromatography.
[c] Determined by ^{1}H NMR of the pure products.

Table 4
Reuse of catalytic system CuI/Zn/glycerol



Cycle	Time (h)	Yield of **3a**[a] (%)
1	5	95
2	5	94
3	5	91
4	5	88
5	5	84
6	10	76

[a] Yields are given for isolated products.



Scheme 2. A plausible mechanism of the reaction.

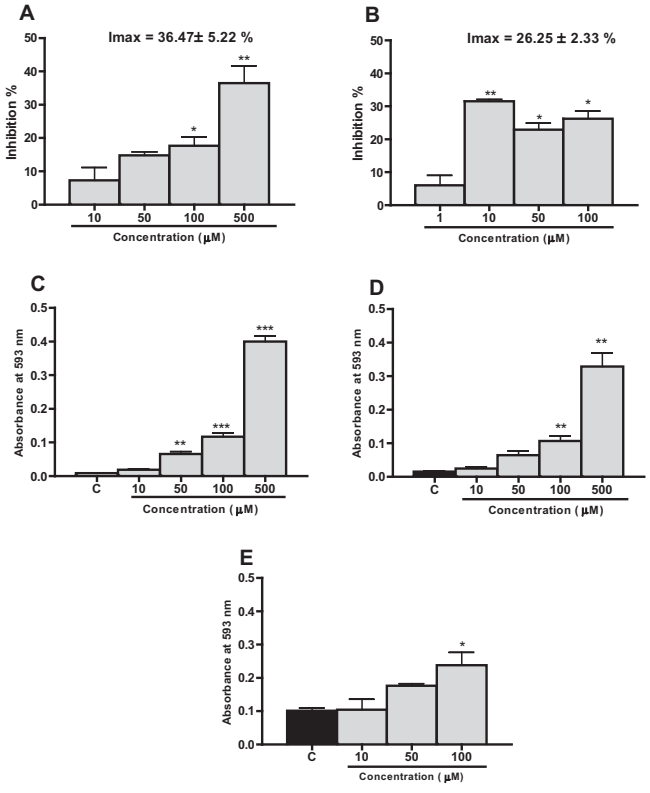


Figure 1. In vitro antioxidant effect of 1,2-bis-chalcogen alkenes (*E*)-**3a**, (*E*)-**3b**, (*E*)-**3e,** and (*E*)-**5a**. (A) Effect of (*E*)-**3b** on the DPPH assay; (B) Effect of (*E*)-**3a** on the ABTS assay; (C) Effect of compound (*E*)-**3a**, (D) (*E*)-**3b,** and (E) (*E*)-**5a** on the FRAP assay. Data were presented as mean ± standard error (SEM) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test one appropriate. The asterisks represent significant effect ($^*p$ <0.05; $^{**}p$ <0.01 and $^{***}p$ <0.001) of the respective controls (C).

activities involve different mechanisms: while DPPH neutralization involves the proton and electron transfer, the ABTS scavenging activity involves only electron transfer.

To extend the studies about the antioxidant capacity of (*E*)-**3a**, (*E*)-**3b**, (*E*)-**3d,** and (*E*)-**5a**, we evaluated their ferric ion reducing power (FRAP). This assay takes advantage of an electron transfer reaction in which a ferric salt is used as an oxidant.[21] In this test, compounds (*E*)-**3a**, (*E*)-**3b,** and (*E*)-**5a**, presented significant effect (Figs. 1C–E). Compound (*E*)-**3a** was more effective, presenting effect at concentrations equal to and higher than 50 μM, while (*E*)-**3b** showed effect at concentrations ranging from 100 to 500 μM and (*E*)-**5a** presented effect only at 100 μM.

Another important characteristic of an antioxidant compound is its effect in preventing or reducing the lipid peroxidation.[22] 1,2-Bis-chalcogen alkenes (*E*)-**3a**, (*E*)-**3b**, (*E*)-**3e,** and (*E*)-**5a** were evaluated for their potential on linoleic acid oxidation assay. All tested

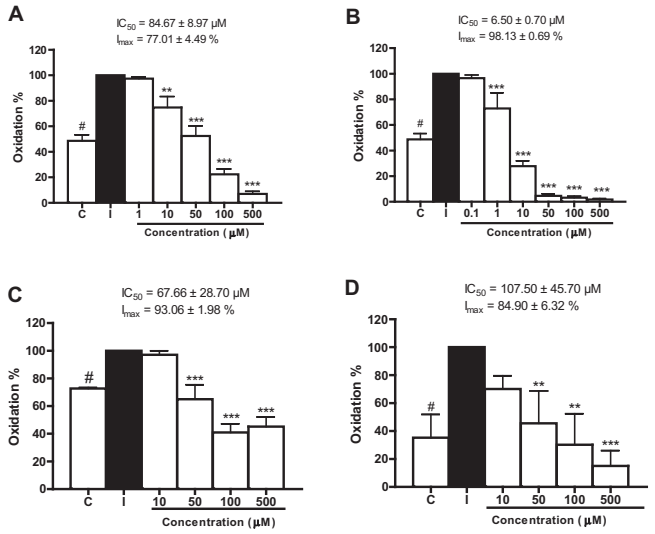


Figure 2. Effect of bis-chalcogen alkenes (*E*)-**3a** (A), (*E*)-**3b** (B), (*E*)-**3e** (C), and (*E*)-**5a** (D) on the linoleic acid oxidation assay. Data were presented as mean ± standard error (SEM) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test one appropriate. The asterisks represent significant difference from the induced group (I) (linoleic acid + SNP) (*p <0.05; **p <0.01 and ***p <0.001), # represent significant difference from the control group (C).

compounds showed significant effect in reducing the linoleic acid oxidation induced by SNP, as can be seen in Figure 2. Compound (*E*)-**3b** (containing OMe group) was more potent and efficient in reducing the linoleic acid oxidation, with an IC_{50} (concentration that inhibits 50% of the oxidation) of 6.50 ± 0.70 μM and I_{max} of 98.13 ± 0.69%, followed by compound (*E*)-**3e** (IC_{50} = 67.66 ± 28.70 μM and I_{max} = 93.06 ± 1.98%), (*E*)-**3a** (IC_{50} = 84.67 ± 8.97 μM and I_{max} = 77.01 ± 4.49%), and (*E*)-**5a** (IC_{50} = 107.50 ± 45.70 μM and I_{max} = 84.9 ± 6.32%).

Results indicated that modifications in the chemical structures of 1,2-bis-chalcogen alkenes changed the antioxidant potential of compounds. Data showed that (*E*)-1,2-bis[(4-methoxyphenyl) seleno]styrene **3b** was the more effective antioxidant among the tested compounds. This could be explained by the presence of an electron-donating substituent attached to the aromatic ring.

In summary, (*E*)-bis-chalcogen alkenes were synthesized using an efficient and recyclable catalytic system containing CuI/Zn and glycerol. The copper-catalyzed addition of diaryl dichalcogenides to terminal alkynes furnished stereoselectively (*E*)-bis-chalcogen alkenes in good to excellent yields. The catalytic system was re-used up to 5 times and the efficiency was maintained after each step of the reuse. This protocol is an efficient method to produce new bis-chalcogen alkenes with potent antioxidant activity.

Acknowledgments

Authors are grateful to FAPERGS (PRONEM 11/2026-4) CNPq, CAPES and FINEP for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.109.

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16. General procedure for the addition reaction: To a round-bottomed flask, under nitrogen atmosphere, containing CuI (0.03 mmol; 5 mol %) and Zn dust (0.6 mmol) was added glycerol (1.0 mL). The reaction mixture was stirred for 30 min at 110 °C and cooled to room temperature. After that, diaryl dichalcogenide (0.6 mmol) and appropriated terminal alkyne (0.6 mmol) were added and the reaction mixture was allowed to stir at 110 °C for the time indicated in Tables 2 and 3. After that time, the solution was cooled to room temperature, diluted with ethyl acetate (20.0 mL), and washed with saturated aqueous NH_4Cl (3 × 20.0 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent. Detailed experimental procedure and spectral data of products prepared are listed in the Supplementary data.
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