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Glycerol as a promoting and recyclable medium for catalyst-free synthesis of linear thioethers: new antioxidants from eugenol

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We describe herein the use of glycerol as an efficient and recyclable solvent for the addition of thiols to nonactivated alkenes. The catalyst-free reactions take place easily using glycerol at room temperature or heating and the corresponding linear thioethers were obtained in good to excellent yields. The method was used to synthesize new sulfur-containing eugenols, which were tested for their antioxidant activities. The semisynthetic thio-derivatives were more effective in inhibition of induced lipid peroxidation compared to the precursor eugenol and the synthetic antioxidant butylated hydroxyanisole.

Keywords: glycerol; sulfur compounds; green chemistry; antioxidant; eugenol

1. Introduction

Glycerol has emerged as a safe and environmentally friendly solvent for organic synthesis in recent years (*1–3*) because of its peculiar physical and chemical properties, such as low toxicity, high boiling point, polarity, biodegradability, and ready availability from renewable feedstock (*4*). Besides, with the increase in biodiesel production worldwide, the market spreading of glycerol, a coproduct of biodiesel production, is predictable (*1*, *2*). Glycerol was successfully used as a solvent in Pd-catalyzed Heck and Suzuki cross-coupling reactions, base- and acid-promoted condensations, catalytic hydrogenation, asymmetrical reduction, and oxidation of thiols (*5–9*). More recently, the electrophilic activation of carbonyl compounds in glycerol-promoted reactions, allowing the elimination of the use of acidic catalysts was demonstrated (*10*, *11*).

Thioethers are important building blocks in organic synthesis and play crucial roles in biological processes (*12*, *13*). Benzylic sulfides moieties are present in several anticancer inhibitors (*14*, *15*) while bis(arylthio)ethers are used as building blocks for coordination polymers (*16*). In this sense, the protic-acid (*17*) as well as the Lewis-acid (*18*, *19*) catalyzed reaction of thiols with nonactivated alkenes is a powerful synthetic tool for the preparation of thioethers. Although a plethora of protocols allowing to access thioethers were described in literature (*17–22*), some of them have disadvantages, such as high temperature, long reaction times, and use of harmful reagents, catalysts, or solvents. Greener approaches using water were recently described (*23*, *24*). In a detailed study performed by Ranu and Mandal dozens of linear thioethers were synthesized in good yields starting from aromatic and nonaromatic thiols at room temperature (*24*). However, the number of green methods to access thioethers which allows the solvent reuse is limited.

On the other hand, lipid oxidation is the primary cause of quality deterioration in many foodstuffs and can lead to a significant loss of nutritional quality as well as the formation of toxic compounds. The use of appropriate agents with antioxidant activities may maintain the safety of foodstuffs, extend shelf-lives, and prevent economic losses (*25*, *26*).

The most common synthetic antioxidants used in foods are butylated hydroxytoluene, butylated hydroxyanisole (BHA), propyl gallate (PG), and tertiary butyl hydroquinone. Although they are highly efficient preservatives, their use has been limited because they are suspected to promote negative effects on health (*27–29*).

In this sense, the search for naturally occurring nontoxic antioxidants as food preservatives as well as useful drug candidates are continuously going on. Among natural antioxidants, eugenol (1-allyl-3-methoxy-4-hydroxybenzene), a major phenolic

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component from clove oil (*Eugenia caryophyllata*), has several biological activities, such as anti-inflammatory (*30*), analgesic (*31*), and antimicrobial properties (*32*).

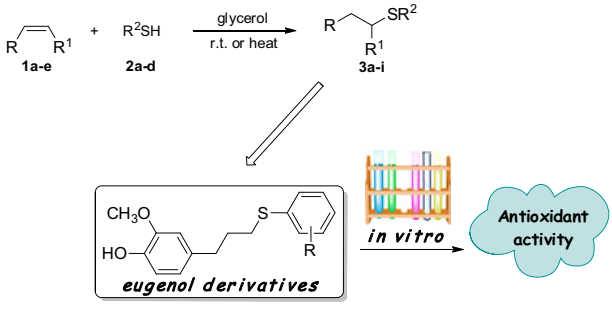
Searching for new, bioactive thioethers and due to our interest in green protocols correlated to the organochalcogen chemistry (*33–37*), we described recently the synthesis of several 3-organylthio citronellal by means of the Michael-addition of thiol to citral, a natural occurring α,β-unsaturated terpenoid aldehyde (*38*). The thio-functionalized aldehydes were tested for their antimicrobial activity, and they showed activity against *Staphylococcus* sp. higher than that observed for the parent citral or even for nonfunctionalized citronellal (*39*).

In view of the promising results in the preparation of functionalized thioethers, we decided to explore the use of glycerol as a solvent in the reaction of thiols with nonactivated alkenes and to evaluate the antioxidant potential of new eugenol derivatives (Scheme 1).

2. Results and discussion

2.1. Synthesis of thioethers

Based on our previous results starting from activated alkenes in the first assay, we reacted styrene **1a** and benzenethiol **2a** in glycerol (3 mL) in presence of KF/Al_2O_3 (50%). It was found that when **1a** (1.2 mmol) and **2a** (1.0 mmol) were stirred at room temperature in the presence of 0.08 g of KF/Al_2O_3 (50%), 1-[(2-phenylethyl)thio]benzene **3a** was obtained in 93% yield after 4 h. To our satisfaction, when the same reaction was performed just using glycerol, without base, it proceeds smoothly, furnishing **3a** in 94% yield after 4 h. On the other hand, when the reaction was performed under solvent-free conditions, using KF/Al_2O_3 alone, the desired product **3a** was obtained only in 11% yield after 4 h. Thus, in an optimized reaction, styrene **1a** (1.2 mmol) was dissolved in glycerol (3 mL) and reacted with benzenethiol **2a** (1.0 mmol) at room temperature during 4 h, yielding **3a** in 94% yield (Table 1, entry 1). A study regarding



Scheme 1. General scheme of reaction.

the recovering and reusing of glycerol was also performed. After the total consumption of benzenethiol **2a**, the crude reaction was diluted and extracted with hexane (3 × 3 mL). The upper hexanic phase was dried and the solvent evaporated. The inferior, glycerol phase was dried under vacuum and directly reused, furnishing the **3a** in 91% yield. It was observed that the solvent could be reused four times, giving **3a** in 94, 91, 92, 89, and 81% yields after successive cycles (Figure 1).

Using the optimized conditions, the protocol was extended to other thiols and alkenes to produce linear thioethers **3b-i** in moderated to good yields (Table 1). When the alkenes **1b-e** were used, however, a gentle heating was necessary to obtain the thioethers in satisfactory yields (Table 1, entries 3–9). Regarding the selectivity of the addition, it was observed that the anti-Markovnikov adduct was formed exclusively when alkenes **1a,c,d** were used as starting materials (Table 1, entries 1, 2, 5, and 6). However, a little amount of the Markovnikov adduct was formed from eugenol **1e**, with prevalence of the anti-Markovnikov one (Table 1, entries 7–9).

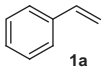
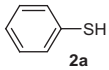
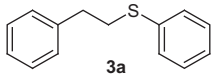
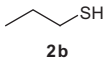
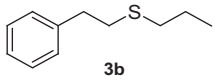
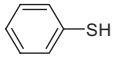
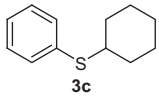
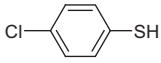
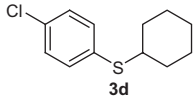
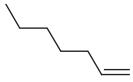
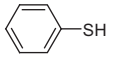
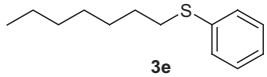
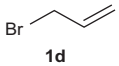
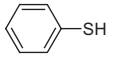
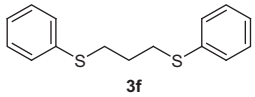
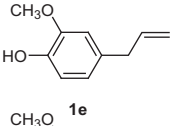
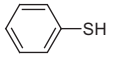
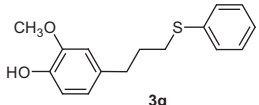
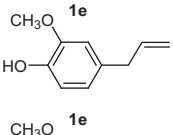
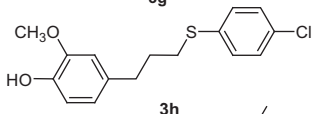
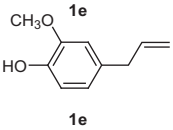
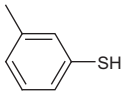
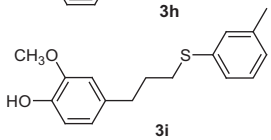
For example, the 1-[(2-phenylethyl)thio]benzene **3a** was obtained exclusively in 94% yield, starting from styrene and benzenethiol, while eugenol **1e** reacted with **2a** to afford **3g** in 67% yield as a mixture of anti-Markovnikov:Markovnikov adducts in a 78:22 ratio (Table 1, entry 7). Higher selectivities were observed for the reaction of eugenol with *p*-chlorobenzenthiol **2c** and with *o*-methylbenzenethiol **2d** (Table 1, entries 8–9). When allyl bromide **1d** reacted with two equiv. of benzenethiol **2a**, 1,3-bis(phenylthio)propane **3f** was obtained exclusively in 70% after 10 h at 60°C (Table 1, entry 6).

By analyzing these results, it was gratifying to note that the thioether synthesis in glycerol was achieved with good yields and selectivity compared to the methods using catalysts and volatile organic solvents, making this new protocol a cleaner alternative for preparation of new semisynthetic thioethers.

To investigate the possible involvement of a radical mechanism, the reaction of styrene **1a** with benzenethiol **2a** was also performed in the presence of hydroquinone, a radical inhibitor. It was observed that the desired thioether **3a** was obtained in 93% yield after 4 h at 25°C, i.e., a radical mechanism is not working here.

A plausible mechanism to explain the preference for the anti-Markovnikov adduct in the reaction in the presence of glycerol is depicted on Scheme 2. As exemplified in the preparation of **3a**, the formation of the pseudo six-membered ring in **4** could be involved, with the glycerol acting both as a proton-donor to the C-2 and a proton-acceptor of the thiol. A transition state like **5**, which would lead to the

Table 1. Catalyst-free synthesis of linear thioethers **3** using glycerol.

Entry	Alkene **1**	Thiol **2**	Product **3**	Time (h)[a]	Yield (%)[b]	Temperature (°C)
1	 **1a**	 **2a**	 **3a**	4	94	25
2	**1a**	 **2b**	 **3b**	9	41	25
3	 **1b**	 **2a**	 **3c**	6	71	60
4	1b	 **2c**	 **3d**	8	65	60
5	 **1c**	 **2a**	 **3e**	10	66	60
6	 **1d**	 **2a**	 **3f**	10	70[c]	60
7	 **1e**	 **2a**	 **3g**	6	67[d]	80
8	 **1e**	 **2c**	 **3h**	6	57[d]	80
9	 **1e**	 **2d**	 **3i**	6	63[d]	80

[a]The reaction progress was followed by TLC.
[b]Yields after purification by column chromatography.
[c]Used 2.0 equivalent of **2a**.
[d]Anti-Markovnikov: Markovnikov adducts ratio: **3g** = 78:22; **3h** = 97:3 and **3i** = 96:4.

Markovnikov adduct, could be less favorable due to steric interactions between the two bulky groups.

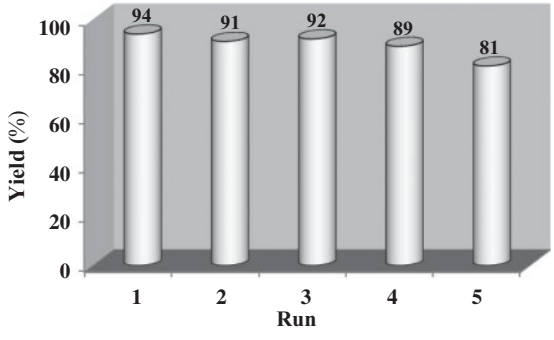


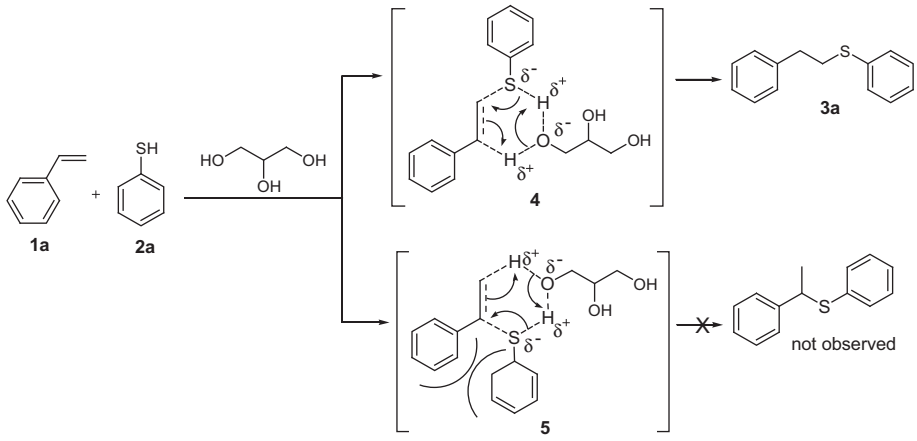
Figure 1. Reuse of glycerol in the synthesis of thioether **3a**.

2.2. *Antioxidant activity assays*

After outlining a general, green protocol to synthesize the thioethers, we decided to study the antioxidant activity of the new thioeugenols **3g-i** by evaluating their ability to inhibit lipid peroxidation and comparing it to that of the parent, unmodified eugenol **1e**.

2.2.1. Lipid peroxidation

In this study, the antioxidant activity was evaluated using linoleic acid emulsion system as a substrate for mediating the lipid peroxidation, which is a non-enzymatic method induced by two pro-oxidants: Fe^{2+}-ascorbic acid and sodium nitroprusside (SNP) (see supplemental Material for experimental details).



Scheme 2. Mechanism to anti-Markovnikov adduct **3a**.

As can be seen in Table 2, all tested compounds showed high antioxidant activity in lipid peroxidation inhibition induced by Fe^{2+}-AA. The IC_{50} values for the semisynthetic thioeugenols **3g-i** indicate that they are more effective than the parent eugenol **1e**. For example, **3i** was fivefold more active than **1e** on the inhibition of lipid peroxidation, with IC_{50} of 84.0 ± 11.1 μM and 418.0 ± 11.3 μM, respectively. Thioeugenol **3i** was even more effective than BHA in lipid peroxidation model induced by Fe^{2+}-ascorbic acid.

The ability of thioeugenols **3g-i** and eugenol **1e** in the inhibition of lipid peroxidation induced by SNP, a NO donor, was also evaluated (Table 3). The results indicated that all new antioxidants synthesized protected linoleic acid emulsion from oxidative degradation induced by SNP.

Compared to eugenol, compounds **3g-i** were significantly more potent antioxidants in this system. BHA and the novel antioxidant **3g** protected the system with the same efficiency and showed equal antioxidant potential, with maximal inhibition ranging from 61.8 to 64.1% and IC_{50} values of 86.0 ± 5.3 μM and 90.0 ± 10.2 μM, respectively. Gratifyingly, thioeugenol **3i** (IC_{50} = 10.0 ± 8.5 μM) offered much better protection of system than BHA, with maximal oxidation inhibition of 97%.

2.2.2. *Radical scavenging activity*

The total antioxidant capacity was determined by the assay based on the preformed radical cation 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium (ABTS) (Table 4) and the hydrogen atom or electron-donation ability of thioeugenols **3g-i** was measured by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and compared to that of unmodified eugenol **1e** (Table 5). It can be seen that all the tested compounds presented a considerable radical scavenging activity.

Based on IC_{50} values, the thioeugenol **3g-i** had an $ABTS^{\cdot+}$ scavenging activity similar to the precursor eugenol **1e** and BHA, as presented in Table 4. Because the neutralization of $ABTS^{\cdot+}$

Table 2. The individual antioxidant activity of eugenol (**1e**), thioeugenols (**3g-i**) and BHA against Fe^{2+}-AA induced lipid oxidation of linoleic acid.

	Lipid peroxidation (%)				
Concentration (μM)	**1e**	**3g**	**3h**	**3i**	BHA
5	nt	nt	nt	94.0 ± 5.2	77.0 ± 11.0 b
10	91.9 ± 8.7	97.6 ± 2.5	95.5 ± 4.7	78.0 ± 17.9 a	73.9 ± 1.0 b
50	78.6 ± 13.9	84.5 ± 17.5	70.8 ± 12.2 b	58.5 ± 16.5 c	60.9 ± 1.1 c
100	67.5 ± 12.6 b	62.9 ± 14.3 b	70.1 ± 11.1 b	42.8 ± 12.3 c	48.8 ± 9.7 c
250	54.8 ± 9.3 c	50.2 ± 24.3 c	51.8 ± 12.6 c	26.5 ± 8.3 c	47.4 ± 10.9 c
500	50.4 ± 12.4 c	36.9 ± 8.6 c	40.8 ± 6.8 c	21.1 ± 6.9 c	47.8 ± 10.7 c
IC_{50}	418 ± 11.3 μM	264 ± 13.4 μM	262 ± 9.4 μM	84 ± 11.1 μM	96 ± 7.4 μM

Notes: nt: not tested; a: $p < 0.05$; b: $p < 0.01$; c: $p < 0.001$ when compared with control sample (induced by Fe^{2+}-AA and absence **1e** or **3g-i** = 100% oxidation) by Student–Newman–Keuls test for post-hoc comparison.

Table 3. The individual antioxidant activity of eugenol (**1e**), thioeugenols (**3g-i**) and BHA against SNP induced lipid oxidation of linoleic acid.

	Lipid peroxidation (%)				
Concentration (μM)	**1e**	**3g**	**3h**	**3i**	BHA
5	nt	nt	nt	85.6 ± 17.8	87.0 ± 7.0
10	77.4 ± 9.4 b	87.2 ± 19.2	99.4 ± 1.0	40.9 ± 15.9 b	73.2 ± 3.5 a
50	64.1 ± 3.1 b	60.2 ± 12.9 a	96.6 ± 5.8	27.7 ± 7.7 b	62.1 ± 4.1 b
100	64.2 ± 3.2 b	58.8 ± 16.3 a	70.3 ± 6.1 a	11.5 ± 4.2 b	45.6 ± 8.0 b
250	52.1 ± 4.4 b	36.9 ± 0.9 b	50.8 ± 7.0 b	5.8 ± 4.2 b	42.5 ± 1.9 b
500	51.0 ± 3.7 b	35.9 ± 2.2 b	59.1 ± 15.6 b	3.0 ± 1.3 b	38.2 ± 7.4 b
IC_{50}	460 ± 4.7 μM	90 ± 10.2 μM	268 ± 7.1 μM	10 ± 8.5 μM	86 ± 5.3 μM

Notes: nt: not tested; a: $p < 0.05$; b: $p < 0.01$ when compared with control sample (induced by SNP and absence of **1e** or **3g-i** = 100% oxidation) by Student–Newman–Keuls test for post-hoc comparison.

radical is an electron transfer process, it is possible that the presence of electron-rich groups S-aryl in the thio-eugenols could contribute to their scavenger activities (*40*).

The novel antioxidants **3g** (IC_{50} = 22.1 ± 4.5 μM), **3h** (IC_{50} = 26.0 ± 3.8 μM), and **3i** (IC_{50} = 36.0 ± 6.3 μM) exhibited high reactivity against DPPH, with maximal scavenge activity ranging from 86.2 to 93.4%. Considering that low IC_{50} values correspond to high radical scavenging capacity, eugenol **1e** and BHA (positive control) showed the highest activity, with IC_{50} of 6.8 ± 2.3 and 9.0 ± 2.5 μM, respectively.

2.2.3. Ferric reducing antioxidant power

Reducing power of the thioeugenol compounds **3g-i** was investigated by ferric reducing antioxidant power (FRAP) assay, a method based on the reduction of the ferric tripyridyltriazine [$Fe(TPTZ)_2$(III)] complex to the ferrous tripyridyltriazine [$Fe(TPTZ)_2$(II)] one, indicating an antioxidant capacity of tested compound (*41*). FRAP values (absorbance at 593 nm) of thioeugenols **3g-i**, eugenol **1e,** and BHA are shown in Table 6. Compound **3h**, containing a *p*-Cl-benzenethiol group, eugenol **1e,** and BHA showed significant FRAP activity at a concentration of 1.0 μM, while **3g** and **3i** were actives at 5.0 μM. The reducing power of all the tested compounds increased with the increasing in their concentrations, with a maximal activity at 500.0 μM.

3. Conclusion

In summary, it was shown that glycerol can be used as an efficient solvent for the addition of thiols to alkenes to afford linear thioethers in the absence of any catalyst. The reaction proceeds easily, and the products were selectively obtained in good to excellent yields. The use of glycerol as a renewable and nontoxic solvent opens new possibilities for future applications of glycerol in green and sustainable chemistry. This greener method was efficiently used in the synthesis of new thioeugenols, which were tested for their antioxidant activities. The semisynthetic

Table 4. Scavenging ABTS radical cation activity (%) and concentration required for 50% scavenging (IC_{50}) of eugenol (**1e**), thioeugenols (**3g-i**) and BHA.

	Compounds				
Concentration (μM)	**1e**	**3g**	**3h**	**3i**	BHA
1	10.7 ± 4.1 a	11.8 ± 0.6 a	1.6 ± 2.7	4.5 ± 3.6	6.0 ± 3.0
5	51.1 ± 3.4 a	32.9 ± 24.2 b	30.2 ± 0.6 c	26.2 ± 15.1 a	21.8 ± 13.7 c
10	87.4 ± 9.3 c	48.6 ± 12.2 c	51.9 ± 8.0 c	57.6 ± 22.9 c	51.7 ± 8.4 c
50	97.6 ± 0.9 c	96.3 ± 2.6 c	93.9 ± 8.0 c	98.5 ± 0.6 c	99.3 ± 0.7 c
100	98.6 ± 1.2 c	98.1 ± 1.6 c	99.6 ± 0.7 c	99.1 ± 0.5 c	100.0 c
250	100.0 c	92.7 ± 6.4 c	100.0 c	100.0 c	100.0 c
500	100.0 c	100.0 c	100.0 c	100.0 c	100.0 c
IC_{50}	4.0 ± 2.4 μM	10.5 ± 4.0 μM	9.0 ± 3.0 μM	8.5 ± 3.1 μM	10.0 ± 3.6 μM

Notes: a: $p < 0.05$; b: $p < 0.01$; c: $p < 0.001$ when compared with control sample ($ABTS^{\cdot+}$ radical solution) by Student–Newman–Keuls test for post-hoc comparison.

Table 5. Scavenging DPPH radical activity (%) and concentration required for 50% scavenging (IC_{50}) of eugenol (**1e**), thioeugenols (**3g-i**) and BHA.

	Compounds				
Concentration (μM)	**1e**	**3g**	**3h**	**3i**	BHA
1	nt	14.9 ± 10.9	16.8 ± 12.5 a	–	nt
5	48.5 ± 1.9 c	27.4 ± 10.9	22.5 ± 3.8 b	12.8 ± 2.0	19.4 ± 2.4
10	52.6 ± 2.7 c	35.0 ± 3.2 b	33.2 ± 5.0 c	22.2 ± 4.3	56.9 ± 2.4 b
50	83.4 ± 5.7 c	79.6 ± 1.7 c	76.5 ± 2.2 c	64.1 ± 2.6 c	87.3 ± 2.2 c
100	88.7 ± 1.3 c	89.1 ± 1.5 c	86.7 ± 0.5 c	77.9 ± 12.3 c	87.1 ± 6.2 c
250	91.3 ± 1.0 c	93.8 ± 0.9 c	91.9 ± 2.5 c	77.1 ± 2.6 c	90.6 ± 0.8 c
500	90.8 ± 1.1 c	93.4 ± 2.8 c	90.3 ± 0.4 c	86.2 ± 14.0 c	92.2 ± 1.1 c
IC_{50}	6.8 ± 2.3 μM	22.1 ± 4.5 μM	26 ± 3.8 μM	36 ± 6.3 μM	9 ± 2.5 μM

Notes: nt: not tested; a: $p < 0.05$; b: $p < 0.01$; c: $p < 0.001$ when compared with control sample (DPPH radical solution) by Student–Newman–Keuls test for post-hoc comparison.

thioeugenols are more active than the parent, unmodified eugenol and even than the synthetic preservative BHA in the lipid peroxidation model.

4. Experimental

4.1. Materials and methods

The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Absorbance values were collected in a Biospectro Model SP-22 Spectrophotometer. NMR spectra were recorded with a Bruker DPX 200 and a Varian Inova 300 (200 and 300 MHz) instruments using $CDCl_3$ as a solvent, and the machine was calibrated using tetramethylsilane as an internal standard. Chemical shifts are reported in δ ppm relative to $(CH_3)_4Si$ for ^1H and $CDCl_3$ for ^{13}C NMR. Coupling constants (J) are reported in Hertz. Mass spectra (MS) were measured on a Shimadzu GCMS-QP2010 mass spectrometer. The high-resolution MS, HR-ESI-MS, were obtained on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific).

4.2. General procedure for the synthesis of linear thioethers 3

A mixture of the appropriate alkene **1** (1.2 mmol) and thiol **2** (1.0 mmol) in glycerol (3.0 mL) was stirred at room temperature or heating in an oil bath for the time indicated in Table 1. After that, the reaction mixture was washed with hexanes (3 × 3.0 mL) and the upper organic phase was separated from glycerol, dried with $MgSO_4$, and evaporated under reduced pressure. The product was isolated by column chromatography using hexane or hexane/ethyl acetate as eluents.

4.2.1. 1-[(2-Phenylethyl)thio]benzene 3a (19)

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.15–7.36 (m, 10H), 3.13 (t, $J = 7.5$ Hz, 2H), 2.91 (t, $J = 7.5$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 140.1, 136.3, 129.0, 128.8, 128.4, 126.3, 125.9, 35.5,

Table 6. Ferric ion reducing antioxidant power (FRAP) of eugenol (**1e**), thioeugenols (**3g-i**) and BHA.

	Compounds				
Concentration (μM)	**1e**	**3g**	**3h**	**3i**	BHA
Control	0.158	0.159	0.178	0.161	0.182
0.5	0.197	0.164	0.176	0.242	0.186
1	0.404 b	0.292	0.560 b	0.309	0.250 b
5	0.798 b	0.808 b	0.694 b	0.627 a	0.450 b
10	1.082 b	0.975 b	1.160 b	0.918 b	0.820 b
50	2.000 b	2.000 b	2.000 b	2.000 b	2.000 b

Notes: Data are presented as the mean of tree repetitions in duplicate of absorbance at 593 nm. a: $p < 0.05$; b: $p < 0.01$ when compared to control sample (absence of **1e** or **3g-i**) by Student–Newman–Keuls test for post-hoc comparison.

35.0. MS *m/z* (rel. int.,%) 214 (M^+, 37.3), 123 (100.0), 105 (40.0), 77 (29.9).

*4.2.2. (Propylthio)benzene **3b** (42)*
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27–7.31 (m, 2H), 7.19–7.22 (m, 3H), 2.86–2.90 (m, 2H), 2.74–2.78 (m, 2H), 2.51 (t, $J = 7.5$ Hz, 2H), 1.62 (sex, $J = 7.5$ Hz, 2H), 0.99 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 140.7, 128.5, 128.4, 126.3, 36.4, 34.3, 33.6, 22.9, 13.5. MS *m/z* (rel. int.,%) 180 (M^+, 21.7), 104 (85.1), 91 (35.6), 89 (100.0), 77 (20.0), 43 (42.0).

*4.2.3. (Cyclohexylthio)benzene **3c** (24, 43, 44)*
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.37–7.41 (m, 2H), 7.24–7.32 (m, 3H), 3.05–3.15 (m, 1H), 1.97–2.02 (m, 2H), 1.75–1.80 (m, 2H), 1.57–1.64 (m, 1H), 1.20–1.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 135.1, 131.8, 128.7, 126.5, 46.5, 33.3, 26.0, 25.7. MS *m/z* (rel. int.,%) 192 (M^+, 14.5), 110 (100.0), 83 (8.5), 55 (28.7).

*4.2.4. 1-Chloro-4-[(cyclohexylthio)benzene **3d** (44)*
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.21–7.34 (m, 4H), 3.01–3.10 (m, 1H), 1.94–1.99 (m, 2H), 1.73–1.79 (m, 2H), 1.58–1.64 (m, 1H), 1.21–1.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 135.1, 133.2, 129.3, 128.8, 46.8, 33.2, 26.0, 25.7. MS *m/z* (rel. int.,%) 226 (M^+, 9.2), 144 (63.1), 108 (15.8), 83 (22.0), 55 (100.0).

*4.2.5. (Hepthylthio)benzene **3e** (45)*
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.18–7.34 (m, 4H), 7.08–7.16 (m, 1H), 2.91 (t, $J = 7.4$ Hz, 2H); 1.65 (qui, $J = 7.5$ Hz, 2H), 1.26–1.46 (m, 8H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 130.2, 128.8, 128.7, 125.6, 33.6, 31.7, 29.1, 28.8 (2C), 22.6, 14.1. MS *m/z* (rel. int.,%) 208 (M^+, 33.8), 110 (100.0), 57 (17.3).

*4.2.6. 1,3-Bis(phenylthio)propane **3f** (46)*
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.22–7.32 (m, 8H), 7.13–7.19 (m, 2H), 3.03 (t, $J = 7.0$ Hz, 4H), 1.94 (qui, $J = 7.0$ Hz, 2H). ^{1}H NMR (75 MHz, $CDCl_3$): δ (ppm) 136.0, 129.3, 128.9, 126.0, 32.3 (2C), 28.2. MS *m/z* (rel. int.,%) 260 (M^+, 100.0), 151 (92.2), 135 (55.7), 123 (72.5), 109 (53.0), 77 (27.6).

*4.2.7. 2-Methoxy-4-[3-(phenylthio)propyl]phenol **3g***
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.22–7.32 (m, 5H), 6.82 (t, $J = 8.7$ Hz, 1H), 6.63–6.66 (m, 2H), 5.49 (s, 1H), 3.82 (s, 3H), 2.90 (t, $J = 7.5$ Hz, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 1.92 (qui, $J = 7.5$ Hz, 2H). ^{1}H NMR (75 MHz, $CDCl_3$): δ (ppm) 146.5, 143.9, 136.7, 132.1, 129.2, 128.9, 125.8, 121.1, 114.3, 111.1, 55.9, 34.3, 32.9, 30.9. MS *m/z* (rel. int.,%) 274 (M^+, 4.3), 164 (100.0), 137 (72.7). HRMS (ESI): *m/z* calcd. for $C_{16}H_{18}O_2S$ $[M + H]^+$: 275.1106; found: 275.1102.

*4.2.8. 4-[3-(4-Chlorophenylthio)propyl]-2-methoxyphenol **3h***
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.21–7.24 (m, 4H), 6.82 (t, $J = 8.4$ Hz, 1H), 6.63–6.66 (m, 2H), 5.47 (s, 1H), 3.84 (s, 3H), 2.87 (t, $J = 7.2$ Hz, 2H), 2.67 (t, $J = 7.2$ Hz, 2H), 1.91 (qui, $J = 7.2$ Hz, 2H). ^{1}H NMR (75 MHz, $CDCl_3$): δ (ppm) 146.5, 143.9, 135.2, 133.0, 131.8, 130.5, 129.0, 121.1, 114.3, 111.0, 55.9, 34.2, 33.1, 30.8. MS *m/z* (rel. int.,%) 308 (M^+, 24.3), 164 (100.0), 137 (71.0). HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}ClO_2S$ $[M + H]^+$: 309.0717; found: 309.0544.

*4.2.9. 2-Methoxy-4-[3-(m-tolylthio)propyl]phenol **3i***
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.10–7.23 (m, 3H), 6.94–6.98 (m, 1H), 6.82 (t, $J = 8.7$ Hz, 1H), 6.64–6.67 (m, 2H), 5.47 (s, 1H), 3.83 (s, 3H), 2.89 (t, $J = 7.2$ Hz, 2H), 2.68 (t, $J = 7.2$ Hz, 2H), 2.30 (s, 3H), 1.92 (qui, $J = 7.2$ Hz, 2H). ^{1}H NMR (75 MHz, $CDCl_3$): δ (ppm) 146.4, 143.9, 138.6, 136.4, 133.2, 129.8, 128.7, 126.7, 126.1, 121.1, 114.3, 111.1, 55.9, 34.3, 32.8, 30.9, 21.3. MS *m/z* (rel. int.,%) 288 (M^+, 17.9), 164 (59.9), 91 (100.0). HRMS (ESI): *m/z* calcd. for $C_{17}H_{20}O_2S$ $[M + H]^+$: 289.1262; found: 289.1258.

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Supplemental Material

All Supplemental Material is available alongside this article on www.tandfonline.com – go to http://dx.doi.org/10.1080/17518253.2013.811298.

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