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-propyl-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 \( \alpha,\beta \)-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 thioethers 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\(_2\)O\(_3\) (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\(_2\)O\(_3\) (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\(_2\)O\(_3\) 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 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 \( \times \) 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 thioethers 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 \( p \)-chlorobenzenethiol 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

![Scheme 1. General scheme of reaction.](image-url)
Markovnikov adduct, could be less favorable due to steric interactions between the two bulky groups.

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: Fe²⁺-ascorbic acid and sodium nitroprusside (SNP) (see supplemental Material for experimental details).
As can be seen in Table 2, all tested compounds showed high antioxidant activity in lipid peroxidation inhibition induced by Fe$^{3+}$-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) dia-mmonium (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$^+$ scavenging activity similar to the precursor eugenol 1e and BHA, as presented in Table 4. Because the neutralization of ABTS$^+$

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

| 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.
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 scavenger 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

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

| 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.

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### 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 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.
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% H2SO4 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 CDCl3 as a solvent, and the machine was calibrated using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm relative to (CH3)4Si for 1H and CDCl3 for 13C 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/C29 3.0 mL) and the upper organic phase was separated from glycerol, dried with MgSO4, 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)

\[ \text{IC50} \] 6.8 \text{mM} 22.1 ± 2.3 μM 22.1 ± 4.5 μM 26 ± 3.8 μM 36 ± 6.3 μM 9 ± 2.5 μM

Table 5. Scavenging DPPH radical activity (%) and concentration required for 50% scavenging (IC50) of eugenol (1e), thioeugenols (3g-i) and BHA.

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

Notes: Data are presented as the mean of three 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.
1.65 (m, 1H), 1.26–1.46 (m, 8H), 0.88 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, CDCl3): 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)
1H NMR (300 MHz, CDCl3): 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). 1H NMR (57 MHz, CDCl3): 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
1H NMR (300 MHz, CDCl3): 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). 1H NMR (75 MHz, CDCl3): 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 C16H18O2S [M + H]^+: 275.1106; found: 275.1102.

4.2.8. 4-[3-(4-Chlorophenylthio)propyl]-2-methoxyphenol 3h
1H NMR (300 MHz, CDCl3): 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). 1H NMR (75 MHz, CDCl3): 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 C16H17ClO2S [M + H]^+: 309.0717; found: 309.0544.

4.2.9. 2-Methoxy-4-[3-(m-tolylthio)propyl]phenol 3i
1H NMR (300 MHz, CDCl3): 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). 1H NMR (75 MHz, CDCl3): 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 C17H19O2S [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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