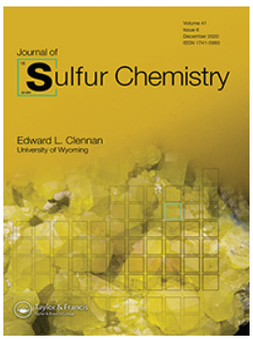

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1,3,5-Trithianes and sulfur monochloride/sodium sulfide: an alternative route to 3,5-disubstituted 1,2,4-trithiolanes

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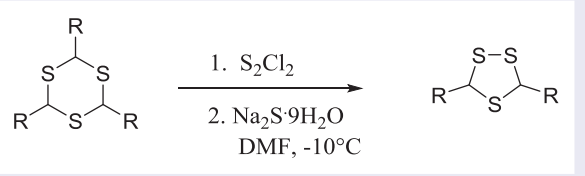
ABSTRACT

Treatment of substituted 1,3,5-trithianes with S_2Cl_2 and Na_2S under mild conditions provides 3,5-disubstituted 1,2,4-trithiolanes, as mixture of diastereoisomers.



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1,3,5-trithianes; sulfur monochloride; α,α′-dichloro sulfides; sodium sulfide; 3,5-disubstituted 1,2,4-trithiolanes

1. Introduction

A large number of sulfurated moieties are present in many organic compounds, which possess a variety of different properties. Together with their wide use in organic synthesis, sulfurated molecules find application in different fields, as pharmaceutical [1–5], agrochemical [6,7], food [8–10], materials and polymer chemistry [11,12]. Despite the high variety of linear and cyclic sulfurated structures, the methods for their synthesis are often limited by the availability of sulfur reagents and by the harsh conditions. Additionally, various reaction steps and the use of expensive, or hardly to access, reagents are often required.

During our investigation on the synthesis of chalcogen-containing derivatives [13–19] we became interested in the study of new convenient methods to prepare polysulfurated heterocycles. Five membered systems, such as 1,2,4-trithiolanes, as well as six and seven membered derivatives, namely tetrathianes and trithiepanes, represent interesting compounds both for their organoleptic properties and for their use as precursors of other polysulfurated compounds. In particular, as has been very recently reported by Mloston and coworkers [20], trithiolanes and their oxides take part in a variety of organic and organometallic transformations. Furthermore, several trithiolanes are present in nature, and are responsible of the typical flavorings and fragrances of various foods and plants, such

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as garlic, onion, mushrooms, meat [21]. Some of them, as 1- and 4-oxo-1,2,4-trithiolanes, isolated together with other cyclic polysulfides from the marine alga *Chondria californica*, also exhibited antibiotic activity [22].

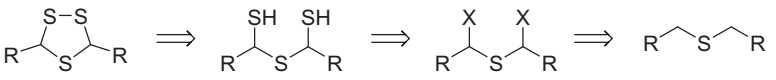
Trithiolanes, therefore, represent an interesting class of compounds and the development of alternative and convenient methods for their preparation is highly desirable. To the best of our knowledge, a rather limited number of synthetic protocols are reported, through a multistep reaction by chlorination of disulfides, followed by treatment with sodium sulfide, where the final cyclization to 1,2,4-trithiolanes has low yields, also because of the formation of polysulfides [23]. Treatment of ketones or aldehydes with hydrogen sulfide led to bis(1-mercaptoalkyl)sulfides, which can be oxidized to 3,5-disubstituted-1,2,4-trithiolanes [24,25]. Reaction of aldehydes with $(NH_4)_2S$ [26,27] or treatment with H_2S in the presence of ammonia [28], or α,ω-diamines [29] allowed the isolation of substituted 1,3,5-dithiazines as precursors of trithiolanes after suitable elaboration. Thioketones as well behaved as convenient reagents to prepare substituted trithiolanes in the presence of oxidizing agents [30,31]. In particular, [3 + 2] cycloadditions of aryl, heteraryl and cycloalkyl thioketones with organic azides represent an efficient way to provide sterically crowded unsymmetrical and symmetrical disubstituted-spiro- or dispiro-1,2,4-trithiolanes, likely *via* a thiocarbonyl-*S*-sulfide intermediate [32–34]. However, these methods frequently lead to the target heterocycles in complex mixtures, with a variety of sulfurated compounds and often in rather low yields. In fact, some synthetic procedures provide 1,2,4-trithiolanes as minor products together with other thiaheterocycles, as tetrathianes [26,27], penthathiepanes [26–29], thiadiazepines [29], or in some cases trithiolanes are formed as side products in the preparation of pentathianes [31]. On the other hand, slightly better yields were observed when 3,3,5,5-tetrasubstituted trithiolanes were prepared through thionation of carbonyl derivatives [24,25,30,32].

In this context, we became interested in developing an alternative synthetic approach to 1,2,4-trithiolanes. During the course of our studies on the thionation of carbonyl compounds [35–37] we found that a direct conversion of aldehydes, ketones and acylsilanes to the corresponding thiocarbonyl derivatives was accomplished with bis(trimethylsilyl)sulfide (HMDST) under Lewis acid catalytic conditions. However, for their well-known tendency to oligomerize, thioaldehydes were *in situ* trapped with 1,3-dienes to afford the Diels–Alder cycloadducts. On the other hand, when the reaction was carried out without any trapping agent, the corresponding trimers, namely 2,4,6-trisubstituted 1,3,5-trithianes, were isolated in high yields. We then envisaged that these six-membered thia-heterocycles could be regarded as potential starting compounds to prepare trithiolanes. We report in this communication an alternative synthetic approach to this class of pentatomic sulfurated molecules under mild conditions.

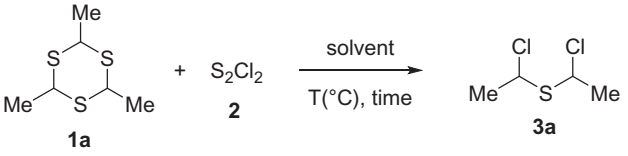
2. Results and discussion

Following the retrosynthetic approach, trithiolanes might be prepared from the parent 1,1'-bis(mercapto)-dialkyl sulfides, which could be accessible from α,α'-(dichloro)dialkyl sulfides after chlorination of the appropriate dialkyl sulfides (Scheme 1).

Several drawbacks are nevertheless linked to the use of the most common chlorinated reagents. In fact, the reaction of dialkylsulfides with *N*-chlorosuccinimide (NCS) leads primarily to mono-chloro sulfides ($RCH(Cl)SCH_2R$), instead of the desired α,α'-dichloro



Scheme 1. Retrosynthetic approach to 1,2,4-trithiolanes.



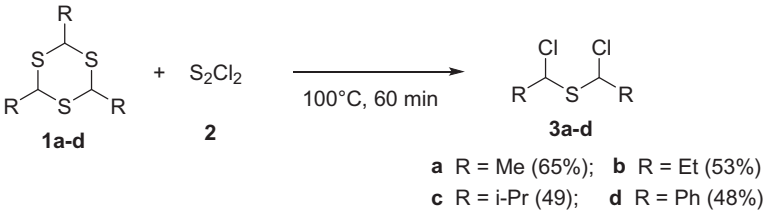
Entry	Solvent	T (°C)	Time (min)	Yield (%)[a]
1	THF	rt	120	--
2	THF	60	90	--
3	CH_2Cl_2	rt	120	< 5[b]
4	CH_2Cl_2	35	90	< 5[b]
5	H_2O	100	30	15[c]
6	H_2O	50	60	< 5[b]
7	--	rt	90	34[d]
8	--	100	60	65[e]

[a] Isolated yield
[b] Determined by H-NMR
[c] ca. 50% of sulfurated side products[b]
[d] ca. 30% of sulfurated side products[b]
[e] ca. 10% of sulfurated side products

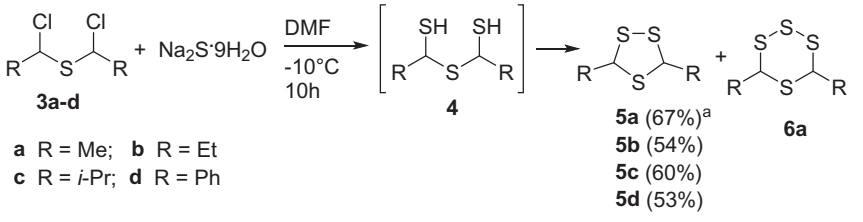
Scheme 2. Optimization of the chlorination reaction to synthesize dichlorosulfide **3a**.

sulfides [38,39]. Indeed, dichloro sulfides were prepared through multistep reactions from α-chloro vinylsulfides/HCl [40], or by reaction of ethanal with H_2S/HCl [41]. Time ago was likewise reported the synthesis of α-dihalogeno sulfides upon treatment of 1,3,5-trithianes with bromine [42]. In this connection, searching for a convenient synthetic route to trithiolanes, our attention was focused to the behavior of 1,3,5-trithianes, prepared following our reported procedure [35–37] from aldehydes and HMDST under catalytic conditions ($CoCl_2{\cdot}6H_2O$ or TfOTMS), in the presence of S_2Cl_2, which is commonly used as powerful sulfurating agent in the synthesis of heterocycles, and only rarely as chlorinating reagent [43,44]. In order to search for chlorination conditions, a first screening was performed investigating the reaction of trithiane **1a** (R = Me) with S_2Cl_2 **2** under different conditions (Scheme 2).

We found that when the reaction was carried out in THF or CH_2Cl_2, at room temperature or by heating, the desired α,α'-dichloro sulfide **3a** was not formed, or it was observed in traces amount (Scheme 2, entries 1–4). When trithiane **1a** was heated in water with S_2Cl_2, polysulfurated compounds were obtained as predominant products, however **3a** was obtained, albeit in low yield (Scheme 2, entry 5). Prompted by this result, **1a** was



Scheme 3. Synthesis of 1,1′-dichlorosulfides **3**.



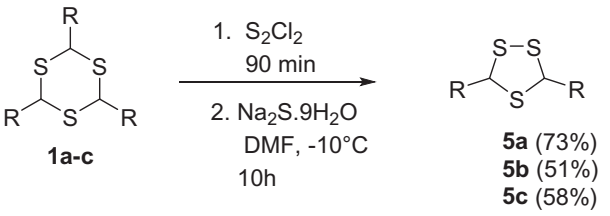
Scheme 4. Synthesis of 3,5-disubstituted 1,2,4-trithiolanes **5a–d**. [a]**5a** was isolated in 22% yield performing the reaction at r.t. or in the presence of TBAB.

reacted with **2** at lower temperature, leading to traces of the desired α,α'-dichlorosulfide **3a**, whereas trithiane and polysulfides were still present as main products (Scheme 2, entry 6). An interesting result was indeed achieved performing the reaction at room temperature in neat S_2Cl_2: a better yield of **3a** was achieved, even if polysulfurated products were observed together with unreacted trithiane (Scheme 2, entry 7). Finally, when **1a** was heated in neat sulfur monochloride, we were pleased to observe the formation of the dichloro derivative **3a** as major compound, along with a reduced amount of polysulfides (Scheme 2, entry 8).

Other substituted trithianes **1b–d** were reacted under these conditions, providing α,α'-dichlorosulfides **3b–d** bearing aliphatic and aromatic groups (Scheme 3).

Subsequently, **3a** was reacted in DMF at ambient temperature with hydrate sodium sulfide (Scheme 4), which is used in the reaction with halides to form symmetrical disulfides [45], and indeed the trithiolane **5a** was isolated, even if in moderate yield (22%), together with other sulfurated products, amongst which the 1,2,3,5-tetrathiane **6a** was the major compound. Under these conditions the parent 1,1'-bis(mercapto)-dialkyl sulfide intermediate **4** was not isolated, being quickly oxidized to provide a direct access to **5a** from **3a**. In order to increase the yield of **5a** the reaction was carried out in the presence of TBAB (tetrabutylammonium bromide) as phase transfer catalyst, but no considerable increase in yield was observed. On the contrary, when the reaction was performed at lower temperature (−10°C) the trithiolane **5a** was achieved in higher yield (67%) as equimolar mixture of stereoisomers, and tetrathiane **6a** was observed as minor compound (< 5%) (Scheme 4). The reaction was also efficient with differently substituted trithianes, leading to variously 3,5-disubstituted 1,2,4-trithiolanes **5b–d** under mild conditions (Scheme 4).

A better result was achieved when performing a one-pot reaction, to avoid any manipulation of the dichlorosulfide intermediate **3a**. After the formation of **3a** as previously



Scheme 5. Direct synthesis of 3,5-dialkyl 1,2,4-trithiolane **5a–c** from **1a–c**.

described, the mixture was cooled and diluted with DMF. After that, sodium sulfide was *in situ* added. Under these conditions the desired trithiolane **5a** was isolated as almost pure compound in 73% yield (*cis*:*trans* 55:45) (Scheme 5).

Likewise, the reaction can be extended to synthesize trithiolanes **5b**,**c** under similar conditions, as a 1:1 mixture of stereoisomers (Scheme 5).

Further studies on the application of this synthetic approach to differently substituted 1,3,5-trithianes, and to the selenated analogues (1,3,5-triselenanes), are currently under investigation in our laboratories, in order to study their characteristics and properties as well as a possible reaction mechanism.

3. Conclusion

We have found an alternative and simple method to prepare 3,5-disubstituted 1,2,4-trithiolanes under mild conditions by reaction of 1,3,5-trithianes with sulfur monochloride and sodium sulfide. Trithiolanes can also be prepared in one-pot reaction, by adding sodium sulfide to the reaction medium, without the isolation of the dichloro sulfide intermediate.

4. Experimental

4.1. General

All reagents and solvents were purchased from various commercial sources and used without further purification. Preparative TLC was performed by using silica gel plates (60 F-254). NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 spectrometer operating at 200 MHz for ^1H and 50 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million (ppm) measured relative to the solvent peak (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration and coupling constants. Mass spectra were recorded using ionization potential (EI, 70 eV) and electrospray ionization (ESI).

4.2. General procedure A

4.2.1. Synthesis of 2,4,6-trisubstituted 1,3,5-trithianes 1 [32,33]

A solution of aldehyde (1 mmol) and bis(trimethylsilyl)sulfide (2 mmol) in CH_3CN (1 mL) was treated under inert atmosphere with a solution of $CoCl_2{\cdot}6H_2O$ (0.2 mmol) in 1.5 mL

of CH_3CN (or with TfOTMS, 0.2 mmol), and stirred at room temperature for 4 h. The reaction mixture was quenched with water (1 mL) and extracted with diethyl ether (2 mL). The organic layer is separated, washed with water and brine, dried over Na_2SO_4 and filtered. Evaporation of the solvent afforded the crude product, which was purified on silica gel (petroleum ether/diethyl ether), leading to a mixture of two stereoisomers.

2,4,6-Trimethyl-1,3,5-trithiane 1a: Yield 73% (petroleum ether/diethyl ether 9:1). Major isomer (> 95:5): ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.11 (q, 3H, $J = 7.4$ Hz), 1.59 (d, 9H, $J = 7.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 40.1, 20.4. MS (m/z %): 180 (M^+, 41), 120 (27), 116 (31), 60 (100), 59 (44), 55 (48).

2,4,6-Triethyl-1,3,5-trithiane 1b: Yield 75% (petroleum ether/diethyl ether 9:1). Major isomer (> 95:5): ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.07 (t, 3H, $J = 6.9$ Hz), 1.96–1.85 (m, 6H), 1.06 (t, 9H, $J = 7.2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 43.1, 27.4, 10.6. MS (m/z %): 222 (M^+, 15), 106 (21), 74 (100).

2,4,6-Triisopropyl-1,3,5-trithiane 1c: Yield 65%. Major isomer (> 95:5): ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.38 (d, 3H, $J = 6.8$ Hz), 2.31–2.19 (m, 3H), 1.17 (bd, 18H, $J = 7.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 51.2, 29.8, 18.6. MS (m/z %): 264 (M^+, 15), 144 (21), 88 (100), 87 (92).

2,4,6-Triphenyl-1,3,5-trithiane 1d: Yield 77%. Major isomer (> 95:5): ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.69–7.15 (m, 15H), 5.46 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 137.9, 128.0, 127.5, 126.2, 46.1. MS (m/z %): 366 (M^+, 34), 212 (22), 180 (44), 122 (78), 121 (100).

4.3. General procedure B

4.3.1. Synthesis of α,α′-dichloro sulfides 3

Trithiane **1** (1 mmol) was slowly added under nitrogen with sulfur monochloride (1.1 mmol) and heated at 100°C for 60 min. After cooling, the solution was filtered and evaporated under reduced pressure to afford sulfides **3**, which were used without further purification.

Bis(1-chloroethyl)sulfane 3a: Yield 65%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.46 (q, 2H, $J = 6.6$ Hz), 1.86 (d, 6H, $J = 6.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 56.4, 22.3. MS (m/z %): 162 (M^++4, 1.4), 160 (M^++2, 8.9), 158 (M^+,14), 125 (23), 123 (65), 95 (10), 65 (14), 63 (49), 61 (100), 60 (48), 59 (40).

Bis(1-chloropropyl)sulfane 3b: Yield 53%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.18 (t, 2H, $J = 6.9$ Hz), 2.25–2.01 (m, 4H), 1.04 (t, 6H, $J = 7.0$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 59.6, 30.3, 9.8. MS (m/z %): 190 (M^++4, 1.6), 188 (M^++2, 9.2), 186 (M^+,18), 171 (20), 153 (25), 151 (65), 109 (16), 77 (52), 75 (96), 74 (100).

Bis(1-chloro-2-methylpropyl)sulfane 3c: Yield 49%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.98 (d, 2H, $J = 7.1$ Hz), 2.53–2.24 (m, 2H), 1.11 (bd, 12H, $J = 7.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 60.4, 33.9, 16.3, 16.2. MS (m/z %): 218 (M^++4, 0.9), 216 (M^++2, 10), 214 (M^+, 14), 199 (26), 181 (23), 179 (59), 123 (13), 91 (58), 89 (83), 88 (100).

Bis(chloro(phenyl)methyl)sulfane 3d: Yield 48%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.29–7.10 (m, 10H), 5.83 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 141.0, 132.5, 131.9, 128.0, 61.6. MS (m/z %): 286 (M^++4, 4.6), 284 (M^++2, 10), 282 (M^+, 45), 249 (26), 247 (72), 205 (48), 157 (26), 125 (60), 122 (100).

4.4. General procedure C

4.4.1. Synthesis of 3,5-disubstituted 1,2,4-trithiolanes 5

(a) A solution of dichloro sulfide (1 mmol) in DMF (1.5 mL) was cooled at −10°C and then slowly treated with hydrate sodium sulfide (2 mmol). The reaction was stirred overnight. After extraction with hexane, the mixture was washed with water (3 × 1 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the trithiolane (mixture of *cis/trans* stereoisomers ∼1:1), which was purified on TLC (petroleum ether). The stereochemistry of trithiolanes (*cis/trans*) was assigned by comparison with literature reported data [23].

(b) *One-pot synthesis*: Sulfur monochloride (1.1 mmol) was slowly added to trithiane **1** (1 mmol) and stirred for 60 min at 100°C. The dark yellow oil was cooled to room temperature and diluted with DMF (2 mL). Sodium sulfide (2 mmol) was then added portionwise at −10°C with stirring (10 h). After addition of dichlorometane, the mixture was washed with water (3 × 1 mL) and dried over Na_2SO_4. Filtration, evaporation of the solvent and purification on silica gel afforded the product **5** as *cis/trans* isomers (ca. 1:1).

3,5-Dimethyl-1,2,4-trithiolane 5a [23]**:** Yield 67%. Diastereoisomer *cis*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 5.04 (q, 2H, J = 6.6 Hz), 1.65 (d, 6H, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 55.7, 21.4. Diastereoisomer *trans*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.86 (q, 2H, J = 6.6 Hz), 1.77 (d, 6H, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 56.9, 22.3. MS (m/z %): 154 (9), 152 (M^+, 76), 92 (58), 88 (48), 64 (61), 60 (55), 59 (100).

3,5-Diethyl-1,2,4-trithiolane 5b [23]**:** Yield 54%. Diastereoisomer *cis*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.71 (t, 2H, J = 6.9 Hz), 1.98–2.17 (m, 4H), 1.19 (t, 6H, J = 7.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 63.5, 30.3, 11.2. Diastereoisomer *trans*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.65 (t, 2H, J = 6.9 Hz), 1.98–2.17 (m, 4H), 1.27 (d, 6H, J = 7.1 Hz). MS (m/z %): 182 (11), 180 (M^+, 65), 116 (29), 74 (100), 73 (57).

3,5-Diisopropyl-1,2,4-trithiolane 5c [23]**:** Yield 60%. Diastereoisomer *cis*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.66 (d, 2H, J = 7.3 Hz), 2.12–2.34 (m, 2H), 1.21 (bd, 6H, J = 6.6 Hz), 1.18 (bd, 6H, J = 6.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 65.7, 29.6, 18.5, 18.2. Diastereoisomer *trans*: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.57 (d, 2H, J = 7.5 Hz), 2.12–2.34 (m, 2H), 1.09–1.17 (m, 6H). MS (m/z %): 208 (M^+, 42), 193 (10), 88 (97), 87 (22), 55 (100).

3,5-Diphenyl-1,2,4-trithiolane 5d [46]**:** Yield 53%. Diastereoisomer A: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 6.19 (s, 2H), 7.35–7.56 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 139.2, 129.1, 128.8, 126.9, 67.3. Diastereoisomer B: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 6.15 (s, 2H), 7.35–7.56 (m, 10H). MS (m/z %): 276 (M^+, 100), 212 (55), 152 (52), 91 (22), 122 (78), 121 (84).

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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