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A Fast and Efficient Route to 5-Chloromethyl-1,4,7,10-Tetrathiacyclotridecane and its Behavior in a Chloroform Solution

HERVÉ THOMAS, JEAN-LUC MIELOSZYNSKI and NICOLAS OGET*
Laboratoire de Chimie et Applications, Université de Metz, 1 Bd Arago, Metz technopôle, F-57078, Metz Cedex 3, France

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Abstract

Chlorination of [14]aneS4-ol (1,4,8,11-tetrathiacyclotetradecan-6-ol) by a one pot reaction in 3 min produces quantitatively the ring-contracted product [13]aneS4-CH_2Cl (5-chloromethyl-1,4,7,10-tetrathiacyclotridecane). In a chloroform solution, [13]aneS4-CH_2Cl is slowly converted to an isomer [14]aneS4-Cl (6-chloro-1,4,8,11-tetrathiacyclotetradecane) until an equilibrium takes place. These results are discussed and a reaction mechanism involving an episulfonium ion intermediate is proposed.

Introduction

Polythiamacrocycles are well known for their complexing properties towards a large range of transition-metal or heavy-metal cations [1]. Due to their complete lack of protonation, these ligands complex equally well at any pH, including highly acidic media [2]. For their applications (liquid–liquid extraction [3], solid-phase extraction [4], ion transport [5], ion selective electrode [6], lipase-catalyzed reaction [7], photochromic systems [8] , biomedical agents [9]...), thiocrown ethers generally need to be functionalized. But, the introduction of a side chain function requires a new cyclisation of the macrocycle because the direct C-alkylation is impossible [10]. Consequently, few examples of functionalized polythiamacrocycles have been reported. Tetrathiamacrocycles **1**–**5** (Scheme 1) were obtained by the reaction of a dithiol with methallyl dichloride or 1,3-dichloroacetone (or its ketal) [11, 12]. The hydroboration of **1** and **3** gave **7** and **9** respectively [11, 12]. Compound **6** was obtained by the reaction of 1,4,8,11-tetrathiaundecane (TTU) and 1,3-dichloropropan-2-ol [13]. For the macrocycle **8**, firstly two equivalents of epichlorydrin have reacted with ethane-1,2-dithiol to lead a dichloro compound which reacted next with ethane-1,2-dithiol [13]. Some other hydroxylated polythiamacrocycles have been reported [9, 12, 14, 15]. The alcohol function(s) can be converted into many groups (halide, thiol, amine, ester...) for the further applications [15]. The Scheme 2 describes the synthesis of **10** from **6** *via* an Appel reaction (PPh_3, CCl_4, 18 h) [16]. The treatment of **10** under reflux in DMF for 26 h leads to **11** [17]. This is one of the rare examples of a 13-membered tetrathiamacrocycle with a chloro function which should be an appropriate point for further alkylations. In this paper, we report a fast and one-pot synthesis of **11** directly from **6** and the existence of an equilibrium state in a chloroform solution between **10** and **11**.

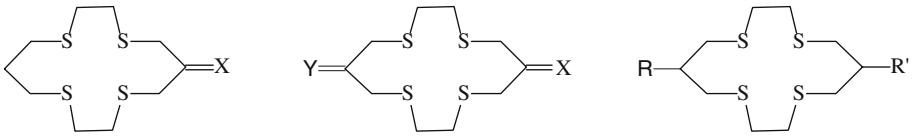
Experimental

General

^1H and ^{13}C NMR

Bruker AC250 spectrometer (250 MHz, $CDCl_3$), chemical shifts were reported in ppm referenced to the residual proton resonances of the solvents and constant coupling were reported in Hz. For the symmetric structures, the relative integration of ^{13}C signals is given as (1C) or (2C). The NMR study of equilibrium in solution ($CDCl_3$, DMSO-d_6) were performed in glass tube (5 mm) at 298 K: 10 mg of compound were dissolved in 0.5 mL of solvent and NMR spectra of this solution were recorded. FT-IR Perkin Elmer spectrophotometer (Spectrum one, ATR): υ is given in cm^{-1}. Mass spectra (MS) were recorded with a Hewlett-Packard HP GC/MS: HP 5890 gas chromatography (HP-1 column crosslinked Methyl Silicone Gum 50 m × 0.2 mm, 0.5 μm film thickness, carrier gas: He,

* Author for Correspondence. E-mail: oget@univ-metz.fr

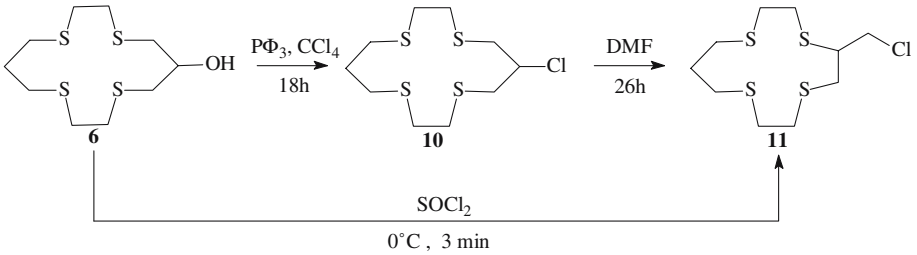


1 : X=CH_2 [11]
2 : X= O [12]

3 : X=Y=CH_2 [11]
4 : X=O, Y=CH_2 [12]
5 : X=Y=O [11]

6 : R=H, R'=OH [13]
7 : R=H, R'=CH_2OH [11]
8 : R=R'= OH [13]
9 : R=R'=CH_2OH [12]

Scheme 1. Examples of functionalized tetrathiamacrocycles.



Scheme 2. Synthesis of [13]aneS4-CH_2Cl **11** by Comba et al. [17].

temperature: Ti: 60 °C (3 min) and after 4 °C min^{-1}) with a HP mass selective detector 5971A. Materials and solvents were obtained from commercial suppliers. All the solvents were freshly distilled and all reactions were performed under nitrogen atmosphere. [14]aneS4-ol **6** (1,4,8,11-tetrathiacyclotetradecan-6-ol) was synthesized by the high-dilution condensation of 1,3-dichloro-2-propanol and 3,7-dithanonane-1,9-dithiol [13].

[14]aneS4-Cl, **10**
In a NMR tube, 10 mg of **11** was introduced in 0.5 mL of $CDCl_3$ and NMR spectra of this solution were recorded regularly. The NMR spectra show a second series of signals (the intensity of theses signals increases over time) which is characteristic of the symmetrical structure **10** [17]: ^{1}H NMR ($CDCl_3$): 1.87 (m, 2H), 2.52–2.95 (m, 16H), 4.13 (quintet, 1H, J = 7.3 Hz); ^{13}C NMR: 30.1 (1C), 30.4 (2C), 32.2 (2C), 33.0 (2C), 38.9 (2C), 60.4 (1C).

[13]aneS4-CH_2Cl, **11**
Under stirring, 1 mL (13.7 mmol) of thionyl chloride was added cautiously to 284 mg (1 mmol) of the alcohol **6** at 0 °C. After 3 min, the thionyl chloride excess was evaporated *in vacuo* and at 0 °C, 1 mL of methanol introduced. After 1 min stirring, the solution was evaporated at room temperature and 300 mg of pure **11** was obtained as a white solid (99%). The spectroscopic data are in agreement with those described by Comba *et al.* [17]: ^{1}H NMR ($CDCl_3$): 1.97 (m, 2H), 2.60–3.29 (m, 15H), 3.81 (dd, 1H, $^2J = -11.2$ Hz, $^3J = 4.8$ Hz), 3.92 (dd, 1H, $^2J = -11.2$ Hz, $^3J = 4.8$ Hz); ^{13}C NMR ($CDCl_3$): 29.4, 29.8, 30.3, 31.6, 31.7, 32.1, 32.4, 34.8, 46.8, 47.4.

*1,3-bis(ethylthio)propan-2-ol,***12:**
Under stirring, 4.6 g (0.2 mol) of sodium were added by small parts to ethanol (200 mL). After reaction, 12.42 g (0.2 mol) of ethanethiol were added at 0 °C. After 30 min at room temperature, 12.9 g (0.1 mol) of 1,3-dichloro-2-propanol (or 9.25 g (0.1 mol) of epichlorohydrin) were added dropwise, then the mixture was refluxed overnight. After cooling to room temperature, sodium chloride was eliminated by filtration and the solution evaporated *in vacuo*. Chloroform (50 mL) was added to the residue and the solution was washed with NaOH 1 M (20 mL) and water (2*20 mL). The organic layer was dried ($MgSO_4$) and evaporated to give 17.2 g of a pale yellow solution. Distillation under reduced pressure gave pure **12** as a colorless liquid (82%). ^{1}H NMR ($CDCl_3$): 1.26 (t, 6H, $J = 7.4$ Hz), 2.52–2.80 (m, 8H), 2.91 (s, 1H), 3.78 (m, 1H); ^{13}C NMR ($CDCl_3$): 14.6 (2C), 27.2 (2C), 37.8 (2C), 68.1 (1C); FT-IR: 3337 cm^{-1}; GC/MS (70eV), 41.5 min, *m/z*(%): 180 [$M^{\bullet+}$] (35), 162 (26), 151 (68), 123 (19), 105 (95), 101 (98), 77 (100), 75 (99), 61 (51), 59 (93), 47 (76).

4-chloromethyl-3,6-dithiaoctane, **13a**
The procedure used for the synthesis of **11** was applied to the alcohol **12**. This reaction gave 194 mg of **13a** as a colorless liquid 98%. ^{1}H NMR ($CDCl_3$): 1.21 (t, 6H, $J = 7.1$ Hz), 2.49–2.61 (m, 4H), 2.74–3.03 (m, 3H), 3.74 (dd, 1H, $^2J = -11$ Hz, $^3J = 7.5$ Hz), 3.88 (dd, 1H, $^2J = -11$ Hz, $^3J = 4.5$ Hz); ^{13}C NMR ($CDCl_3$): 14.4 (2C), 24.9 (1C), 25.2 (1C), 33.7 (1C), 46.0 (1C), 47.2 (1C); GC/MS (70 eV), 39.5 min, *m/z*(%) [1]: 198/200 [$M^{\bullet+}$] (30/12), 169/171 (26/10), 162 (21), 141/143 (18/6), 123 (12), 101 (100), 88 (33), 75 (74), 59 (30), 45 (32).

5-chloro-3,7-dithianonane, **14a**
In a NMR tube, 10 mg of **13a** was introduced in 0.5 mL of $CDCl_3$ and NMR spectra of this solution were recorded regularly. The spectra show a second series of signals (the intensity of theses signals increases over time) which is characteristic of the symmetrical structure **14a**: ^{1}H NMR ($CDCl_3$) 1.27 (t, 6H, $J = 7.1$ Hz), 2.63 (q, 4H, $J = 7.1$ Hz), 2.94 (dd, 2H, $^2J = -14.0$ Hz, $^3J = 6.0$ Hz), 3.05 (dd, 2H, $^2J = -14.0$ Hz, $^3J = 6.5$ Hz),

4.13 (quintet, 1H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$): 14.5 (2C), 26.2 (2C), 37.2 (2C), 59.3 (1C); GC/MS (70 eV), 39.5 min, m/z(%): 198/200 [$M^{\bullet+}$] (30/12), 169/171 (26/10), 162 (21), 141/143 (18/6), 123 (12), 101 (100), 88 (33), 75 (74), 59 (30), 45 (32).

Reaction of bromination of **12**

Under stirring, 0,5 mL (5.3 mmol) of phosphorus tribromide was added cautiously to 180 mg (1 mmol) of the alcohol **12** at 0 °C. After 3 min, 5 mL of cooled water was carefully added. The mixture was extracted with chloroform (3*20 mL) and the combined organic layers were washed with NaOH 1 M (10 mL), water (2*10 mL) and dried ($MgSO_4$). After evaporation, 209 mg of a mixture of **13b** and **14b** was obtained as colorless liquid (86%) [2]. **13b** (5-bromo-3,7-dithianonane): ^{1}H NMR ($CDCl_3$): 1.29 (t, 6H, $J = 7.4$ Hz), 2.63 (q, 4H, $J = 7.4$ Hz), δ 2.8–3.1 (m, 3H), 3.82 (dd, 1H, $^2J = -11.9$ Hz, $^3J = 4.7$ Hz), 3.92 (dd, 1H, $^2J = -11.9$ Hz, $^3J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): 14.3 (2C), 24.8 (1C), 26.2 (1C), 34.4 (1C), 35.4 (1C), 45.9 (1C). **14b**(5-bromomethyl-3,7-dithiaoctane): ^{1}H NMR ($CDCl_3$): 1.29 (t, 6H, $J = 7.4$ Hz), 2.63 (q, 4H, $J = 7.4$ Hz), 3.09 (dd, 2H, $^2J = -14.0$ Hz, $^3J = 5.9$ Hz), 3.21 (dd, 2H, $^2J = -14.0$ Hz, $^3J = 6.7$ Hz), 4.24 (quintet, 1H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$): 14.3 (2C), 26.1 (2C), 37.8 (2C), 52.5 (1C); GC/MS (70 eV), 42 min, m/z(%) [3]: 242/244 [$M^{\bullet+}$] (5/5), 213/215 (3/3), 167/169 (3/3), 163 (38), 101 (53), 75 (100), 45 (23).

Results

The reaction of **6** with $SOCl_2$ (1–3 equivalents) in $CHCl_3$ led to **10** and **11** in varying proportions [4], depending on temperature and reaction time. This experiment was not easily reproducible so that the **10**:**11** ratio seemed random but the unexpected compound **11** was always the main product. So, we firstly studied the simpler compound **12** which was synthesized [18] in good yields from ethanethiol and 1,3-dichloropropan-2-ol in sodium/ethanol solution (Scheme 3). Once more, the reaction of thionyl chloride and **12** in chloroform led to a mixture of **13a** (the main product) and **14a**. The proportion of **14a** increased both with the excess of thionyl chloride and the reaction time to reach a 50:50 ratio **13a:14a** after 72 h (Table 1). On the contrary, when the reaction in a large excess of $SOCl_2$ was carried out at 0 °C, during 3 min without solvent, **13a** was obtained nearly pure [5]. Nevertheless, at room temperature in a chloroform solution, we observed a rearrangement of **13a** into **14a** (Figure 1). When the chloroform solution was refluxed, a ratio 35:65 of **13a**:**14a** was reached after 24 h. In a DMSO solution at RT, **13a** isomerized to **14a** faster than in a chloroform solution: after 90 h, the ratio was 30:70 for **13a:14a** (Figure 1). So, the evolution was dependent on the polarity of the solvent. When **12** and PBr_3 were mixed together at 0 °C and without solvent, a similar behavior was observed. But in this case, the rearrangement in chloroform at room temperature was faster: after 180 min an equilibrium involving a ratio 30:70 for **13b:14b** was obtained (Figure 2).

We could now proceed to the system under study. So **6** was mixed with $SOCl_2$ at 0°C during 3 min. In these conditions pure **11** was obtained quantitatively. In a chloroform solution, **11** gave very slowly the isomer **10**. For example, after 48 h the ^{1}H NMR spectrum (Figure 3) shows a mixture of both isomers in a ratio 15:85 for **10:11**. The signals and the coupling constants at 3.81 ppm ($^2J_{AB} = -11.17$ Hz, $^3J_{AX} = 4.77$ Hz) and 3.92 ppm ($^2J_{AB} = -11.17$ Hz, $^3J_{AX} = 4.74$ Hz) are characteristic of the ABX system for the major compound **11** ($CHCH_2Cl$). The quintet at 4.13 ppm is coherent with the $ClCH(CH_2S)_2$ unit of **10**. After 50 days, an equilibrium 60:40 for **10:11** was obtained (Figure 4). This isomerization could be speed up by heating the chloroform solution of **11**, thus giving a 32:68 ratio of **10:11** after 24 h, against 15:85 at room temperature.

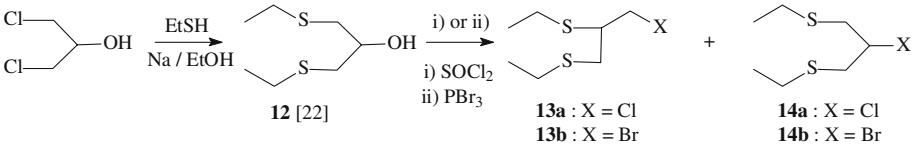
Discussions

The major compounds **11** and **13a** (or **13b**) obtained at the end of the reactions between **6** or **12** and $SOCl_2$ (or **12** and PBr_3) are consistent with a reaction mechanism involving the episulfonium ion intermediates (EPSI) **15**. This EPSI should be involved in order to explain the rearrangement of **11**, **13a** or **13b** into **10**, **14a** or **14b** respectively (Scheme 4).

When **6** is mixed with $SOCl_2$ at 0 °C during 3 min, **11** is obtained quantitatively. This result is quite unusual because the chlorination of an alcohol with $SOCl_2$ usually involves a SNi mechanism [19] which proceeds in a first step of a SN1 mechanism dissociation into an

Table 1. Chlorination of **12** with $SOCl_2$ in chloroform at RT

Ratio **12**:$SOCl_2$	Ratio of **13a:14a** after			
	1 h	3 h	48 h	72 h
1	98:2	98:2	76:24	59:41
1.2	95:5	88:12	58:42	52:48
1.4	91:9	90:10	55:45	50:50



12 [22] **13a** : X = Cl **13b** : X = Br **14a** : X = Cl **14b** : X = Br

Scheme 3. Synthesis and reactivity of **12.**

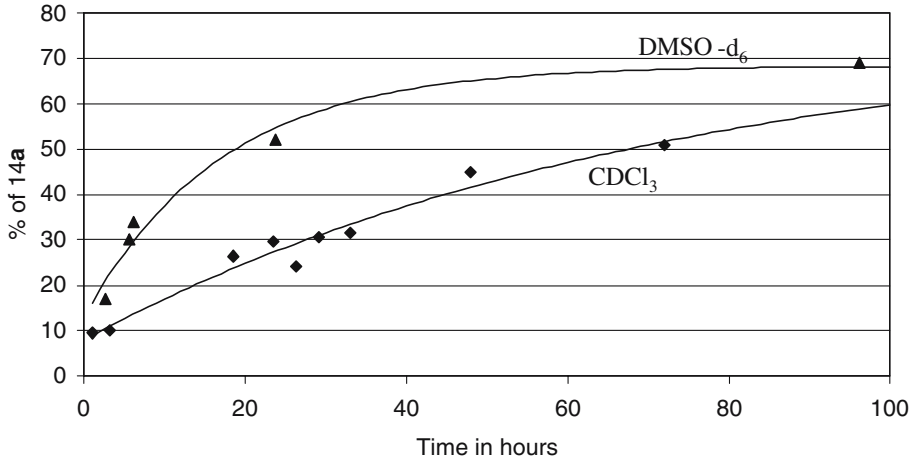


Figure 1. Evolution of **13a** and **14a** over time at RT.

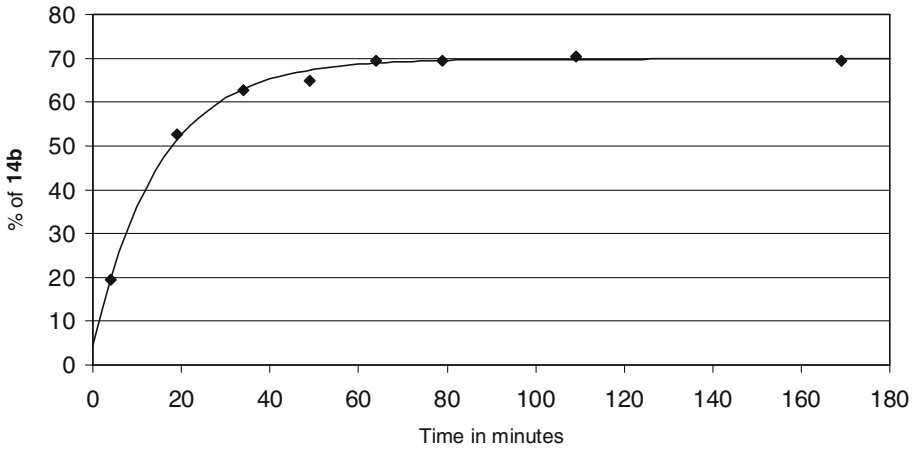


Figure 2. Evolution of the proportion of **13b** and **14b** over time at RT in $CDCl_3$.

intimate ion pair **16** when the second step is the chloride ion attack from the front with a configuration retention (Scheme 5). With this SNi mechanism, **10** should have been obtained quantitatively as in the Apple reaction used by Comba *et al.* [17]. But in the case of the tetrathiamacrocycle **6**, we suppose a SN2 mechanism with an anchimeric assistance by sulfur: the reaction mechanism involves the initial formation of chlorosulfite (Scheme 6). Then the sulfur atom in β position can bring about an SN2 displacement of the good leaving group $ClSO_2^-$ which, by decomposition, gives the gas SO_2 and the chloride ion. The result is not the formation of an intimate ion pair carbocation/chlorosulfinate **16** but a ion pair episulfonium/chloride **15**. The orientation of the ring opening of an unsymmetrically substituted EPSI depends on steric factors, polar effect of substituents and the polarity of the solvent [20, 21]. The chloride ion freed in this process attacks at the least substituted carbon atom regioselectively and gives **11** exclusively. No ^1H NMR signal, consistent with those of ethylenic products (loss of β proton to form allylic sulfide [22]) or CH-Cl of the compound **10**, has been observed. A similar mechanism can be proposed for **13a** and **13b** [6] (Scheme 6).

In a chloroform solution, the sulfur atom in β position acts as a nucleophile and displaces chloride ion to lead to the EPSI **15** which evolves in **10** and **11**. Unlike the compounds **13a** and **13b**, the kinetic of the partial rearrangement of **11** into **10** is clearly slower (>50 days) because the sulfur atom in β position is less available due to the structural rigidity of the macrocycle. Moreover, the stronger nucleophile and leaving group bromide ion (towards the chloride ion) explains the faster kinetic observed with **13b** (3 h) in comparison with **13a** (75 h). The equilibrium is shifted to **10** (or **14a**, **14b**) because on the one hand, the attack of a sulfur atom at the secondary halide (**10, 14a, 14b**) is less favorable than an attack at the primary halide (**11a, 13a, 13b**). On the other hand, the C1 and C2 positions of EPSI can be regarded as the primary carbocation **17** and the secondary carbocation **18** respectively (Scheme 7). Moreover, **18** is stabilized by the assistance of two sulfur atom in β position. So, **10** (or **14a**, **14b**) is the major product because the halide ion reacts preferentially with the more stable secondary carbocation **18**. These data suggest that the chlorination of alcohols **6** and **12** by $SOCl_2$ are consistent with a EPSI undergoing ring opening at the least substituted carbon atom to form the

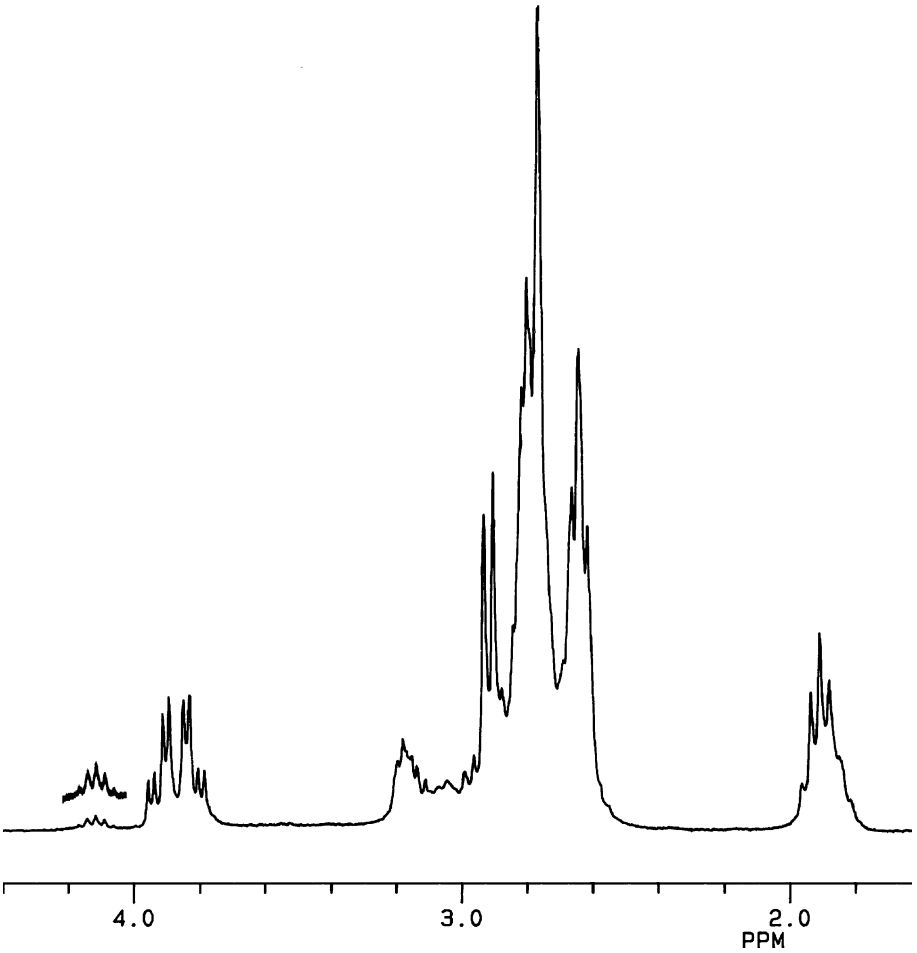


Figure 3. ^{1}H NMR spectra in $CDCl_3$ of mixture **10:11** after 48 h.

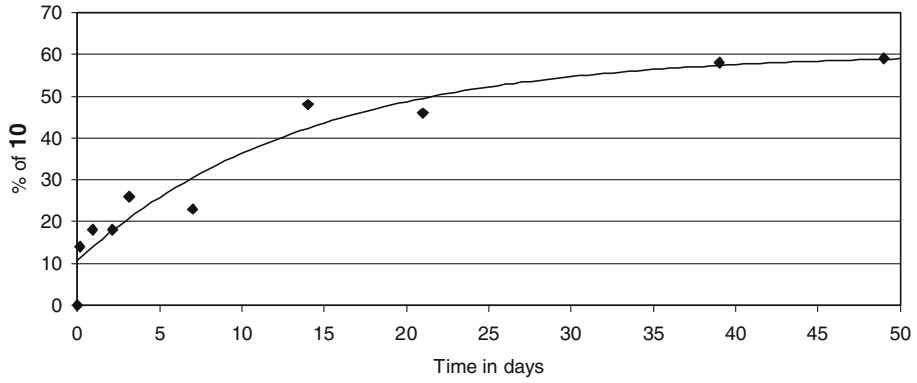
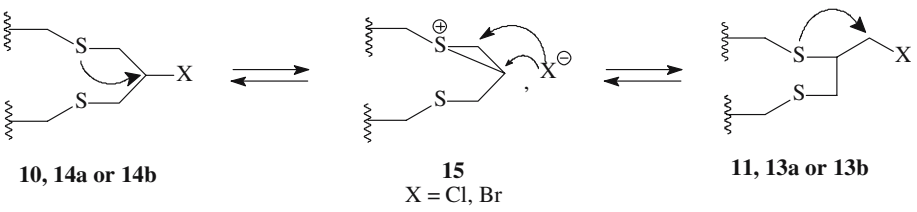
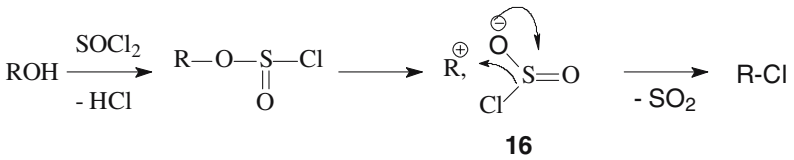


Figure 4. Evolution of the proportion of **10** and **11** over time at RT in $CDCl_3$.

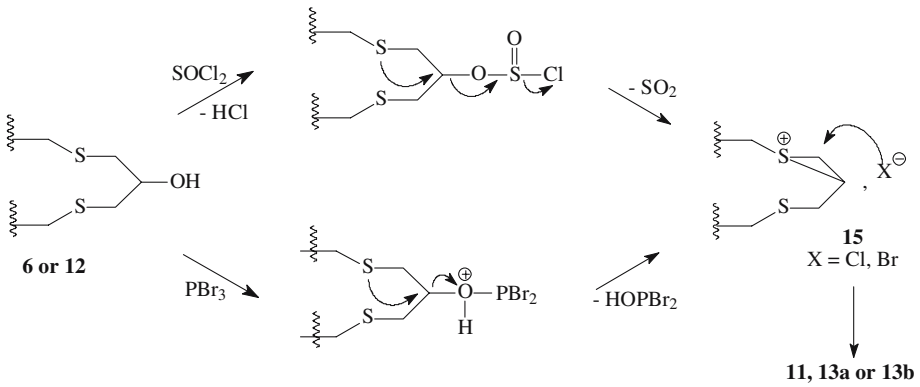


10, 14a or 14b **15** X = Cl, Br **11, 13a or 13b**

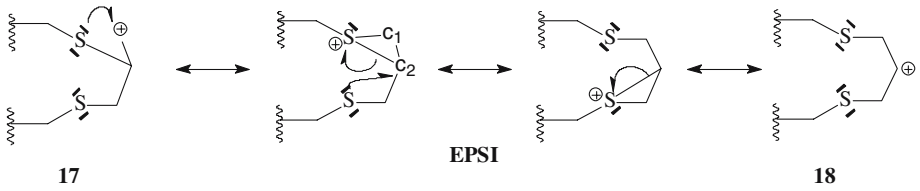
Scheme 4. Mechanism involving an EPSI.



Scheme 5. Chlorination of an alcohol with $SOCl_2$.



Scheme 6. Chlorination and bromination with an anchimeric assistance of sulfur.



Scheme 7. Canonical forms of EPSI.

kinetically controlled product **11** and **13a**. Then, in solution, these compounds may isomerize through EPSI to the thermodynamically favored products **10** and **14a**[7]. These assumption is supported by the chlorination reaction in a chloroform solution (Table 1): **13a** is firstly obtained regioselectively then the slow isomerization to **14a** takes place. Nevertheless, the total isomerization of **10** to **11** is possible when a solution of **10** in DMF was simply refluxed for 26 h and produced **11**. The high temperature and the strong polarity of DMF is in the favor of a separated ion pair episulfonium/chloride **15** and the attack of a free chloride ion at the least substituted carbon atom leads to the kinetically controlled product **11**.

These results show that it is not possible to obtain only one isomer when the halo-de-hydroxylation reaction is carried out with $SOCl_2$ or PBr_3 in chloroform solution. Furthermore, the experimental factors explaining the initial random ratio are: (i) the reaction time of the halogenation in a chloroform solution; (ii) the difference in time and temperature during the evaporation of thionyl chlorine excess with a rotary evaporator; (iii) the time spent before the NMR experiment when products are mixed with the chloroform-*d*, especially for the simple compounds **13a** and **14a**. So after the reaction, the mixture must be evaporated *in vacuo* at room temperature and the NMR experiment performed at once.

Conclusion

In this paper, we have described a one pot reaction giving a clean ring-contracted compound **11** in 3 min from the alcohol **6** and $SOCl_2$ at 0 °C. From a synthetic point of view, **11** is a 13-membered tetrathiamacrocycle and the chloro function can be substituted for further applications [2b, 17]. Finally, we have shown that in a chloroform solution, the isomers **10** and **11** are encountered in a state of equilibrium. At present, we are investigating whether the chlorination by $SOCl_2$ can be generalized for other hydroxylated polythiamacrocycles with $SCH_2CHOHCH_2S$ units to produce chloro-ring-contracted macrocycles.

Notes

1. The GC-MS experiment gives the same chromatogram for **13a** and **14a**. A mixture of **13a** and **14a** gives a chromatogram with a single signal. MS spectrum is consistent with the symmetrical compound **14a** (absence of peak at m/z: 149, lost fragment $ClCH_2^{\bullet}$).
2. To obtain the ratio of **13b:14b** in a chloroform solution, 10 mg of **12** and 0.5 mL of $CDCl_3$ were introduced in a NMR tube. 30 μL of PBr_3 was added and NMR spectra of this solution were recorded immediately and regularly over time.
3. The decomposition of compounds **13b** and **14b** is observed in the gas chromatograph. Nevertheless, the chromatogram shows the signal (7%) of **14b**

4. The ratio of isomers and their stereochemistry were determined using their NMR spectra and the analysis of coupling constants values, chemical shifts and signal intensity. The proportions of **10:11** varied from 1:99 to 10:90.
5. **14a** (< 3%) was the only byproduct.
6. For **13b**, the reaction involves the initial formation of a protonated alkyl dibromophosphite by nucleophilic displacement on phosphorus. The sulfur atom in β position acts as a nucleophile and displaces $HOPBr_2$ to lead the EPSI **15**. Then the bromide ion attacks at the least substituted carbon atom regioselectively to give **13b**
7. Similar results obtained for a variety of unsymmetrically substituted EPSI are reported in the reference [21].

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