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N_2S_2 tetradentate ligands for soft cationic species: preparation of new ligands of potential interest in nuclear medicine†

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Summary – The synthesis of N_2S_2 tetradentate ligands of the bis-(enaminothioester) type was carried out starting from 3-(methylthio)-3*H*-1,2-dithiolylium iodides and diamines. The title compounds, which are potential ligands for soft cationic species, can be obtained from 1,3 diaminopropan-2-ol and subsequently modified into the dissymmetrical succinic acid ester of the ligand and *N*-hydroxysuccinimide. The appendage of such a linking group on the chelating structure should allow further grafting to monoclonal antibodies in view of potential applications in nuclear medicine.

3*H*-1,2-dithiole-3-thione / 1,3-diaminopropan-2-ol / bis-(enaminothioester) / N_2S_2 tetradentate ligand / *N*-hydroxysuccinimidyl ester

Introduction

The availability of monoclonal antibodies via cellular hybridization techniques [1] has promoted new applications in medicine, the idea being to use these recognizing agents for vectorization of drugs.

In the field of the use of nuclear medicine for cancer patients, this strategy has been proposed for both diagnosis (radioimmunoscintigraphy) and therapy (radioimmunotherapy) [2-6]. The first approach requires the use of γ-emitting radionucleides with a short half-life (a few hours) and an energy level in the range 100-200 keV, in order to obtain good detection with a γ-camera. Furthermore, the newly obtained species must be stable isotopes or radionucleides with a very short half-life (less than 1 d). The isotopes ^{123}I [7], ^{111}In [8] and ^{99m}Tc [2, 6, 9] offer the best compromise.

The second approach (radioimmunotherapy) requires β- or α emitting radionucleides with an emission of appropriate energy and a half-life in the range of 1 to 10 d. For such a purpose, ^{67}Cu, ^{90}Y, ^{109}Pd, ^{153}Sm or ^{186}Re are potential β^- candidates [2-6] while ^{212}Bi and ^{211}At could be of interest if α particles are required [10, 11]. However, two other points are crucial : the availability of the radionucleide and the *in vivo* stability of the radiolabeled compounds obtained.

In the case of radiohalogenated compounds (mainly ^{123}I and ^{131}I), the preparation of the organic precursors appears to be fairly easy using exchange methods or halodestannylation [7, 12], and their linkage to monoclonal antibodies has been achieved using *N*-succinimidyl esters [11, 13-15]. However, the *in vivo* deiodation on the target cells constitutes a problem because it induces a significant thyroid uptake [16, 17].

In the case of metallic radionucleides, the availability of the radionucleides remains a key parameter as well as their stability as chelates [18]. For radioimmunoscintigraphy, ^{99m}Tc ($T_{1/2}$ = 6.02 h, γ-emission at 140 keV) is readily produced from ^{99}Mo [19-20] as $^{99m}TcO_4^-$ and thus appears to be one of the more convenient isotopes. However, to obtain a chelate, the pertechnetate anion must be reduced before complexation. This implies that the reduction must be performed in the presence of the appropriate ligand and that the oxidation state of technetium decreases from seven to five (or less) with an oxotechnetium core [21-29] or a mononitrurotechnetium core [28-32]. Considering the lower oxidation state of the metal center, the cation appears to be softer according to Pearson theory [33] and is expected to give fairly stable chelates when the ligand contains soft bases (for instance, sulfur atoms).

According to this approach, sulfur-containing ligands have been proposed as substitutes of polyaminocar-

† Dedicated to Professor Raymond Calas, doctor in chemistry and medicine, in recognition of his efficient and enthusiastic contribution to the development of organic and organosilicon chemistry.

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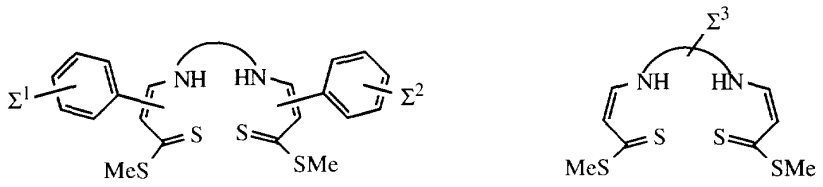
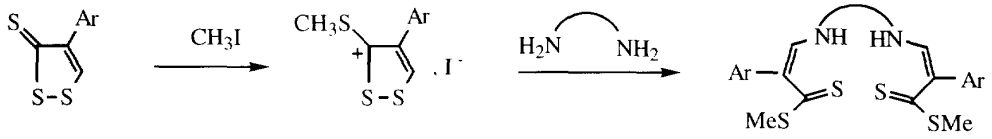


$\Sigma^1 = \Sigma^2$ or $\Sigma^1 \neq \Sigma^2$

- type A - **- type B -**

Scheme 1



Scheme 2

boxylates [6, 34] or tetraazamacrocycles [26, 35, 36], and examples of FDA-approved radiopharmaceuticals with sulfur ligands are already known [6]. Sulfur-containing ligands for soft cations include S_4 tetradentate ligands [37] as well as N_2OS or N_3S tetradentate ligands [29, 38]. However, the more usual chelating structures are N_2S_2 tetradentate ligands derived from bis-(thiosemicarbazones) [39, 40], diamidodithiols [23, 41], diaminodithiols [42-44] or bis-(enaminothioketones) and bis-(enaminodithioesters) [29, 45].

In order to obtain a link to monoclonal antibodies, a functionalized side chain ("linker") is required on the ligand and several approaches have been developed for this purpose [2, 6, 39, 41, 46-48]. The *N*-succinimidyl or *N*-phthalimidyl esters are potentially useful for obtaining coupling with the amine functions of the antibody [2, 6, 11, 14, 49-53], but the presence of several functional groups of this type must be avoided because it leads to polymers [54].

In this context, we decided to build two types of N_2S_2 tetradentate ligands using bis-(enaminodithioesters) as shown in scheme 1.

Previous work in our laboratory has shown that structures of type A can be obtained via reaction of diamines with 4-aryl-3-methylthio-1,2-dithiolylium iodides, which can be obtained from 4-aryldithiolethiones [55] according to scheme 2.

With such ligands, we can reasonably expect an efficient chelation of cations like ^{99m}Tc or ^{186}Re (in a low oxidation state), but also soft cations like Zn^{2+}, $^{57}Co^{2+}$ or $^{67}Cu^{2+}$, the last of which is potentially useful for radioimmunotherapy. Furthermore, compared with diaminodithiols, these conjugated molecules are expected to give a less easy chelation (higher activation energy) and a higher stability for the chelates.

As regards the construction of the linker, the appropriate functional chain must be grafted on the aromatic rings for type A ligands or on the diamine for type B ligands. These two possible routes have been examined successively.

Results

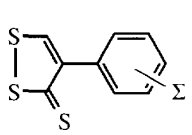
N_2S_2 tetradentate ligands from functionalized 4- or 5-aryl-3H-1,2-dithiole-3-thiones (type A ligands)

- *Synthesis of 1,2-dithiole-3-thiones*

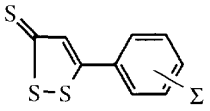
Our approach to type A ligands required the synthesis of the appropriate 4- or 5-(aryl functionalized) 3*H*-1,2-dithiole-3-thiones, which could be used to graft a linker that could react with monoclonal antibodies. However the synthesis of such starting materials implies the use of experimental conditions that are too drastic to be compatible with highly functionalized substrates [56-58]. As a consequence, we decided to test aryldithiolethiones with a side chain including an ester function and to attempt substitution of (haloaryl) dithiolethiones and related compounds under mild experimental conditions. For this purpose, 4- and 5-(aryl)-3*H*-1,2-dithiole-3-thiones (**1a-14a**) and unsubstituted dithiolethione **15a** (which should be useful for the synthesis of unsymmetrical ligands) were prepared according to previously described procedures (*cf* scheme 3 and *Experimental section*).

Cross-coupling of functional vinyltins with the aryl halides **6a**, **13a** and **14a** was expected to give the desired products [59], and 1-tributylstannyl-3,3-diethoxyprop-1-ene was expected to allow the grafting of a 3-formylvinyl unit on the aromatic ring [60]. Unfortunately, when these reactions were attempted in standard experimental conditions ($Pd(PPh_3)_4$ catalyst) no cross-coupling product was obtained, just a small amount of 1,1,6,6-tetraethoxyhexa-2,6-diene [61, 62].

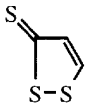
The cross-coupling was also unsuccessful when the reaction was attempted in DMF and in the presence of silver oxide to provide thiophilic cations [63]; similarly it failed from **14a** using other types of palladium catalysts [64-66]. Other attempts to cross-couple from **8a** using $PdCl_2(PPh_3)_2$/LiCl or $Pd(PPh_3)_4$/LiCl as catalysts [67] or from **9a** in the presence of $Pd(PPh_3)_4$ [68] were also unsuccessful.



1a Σ = H
2a Σ = 4-COOMe
3a Σ = 4-COOH
4a Σ = 4-$COOSiMe_3$
5a Σ = 4-$COOCH_2CCl_3$
6a Σ = 4-Br
7a Σ = 4-OH
8a Σ = 4-OSO_2CF_3
9a Σ = 3-SO_2Cl

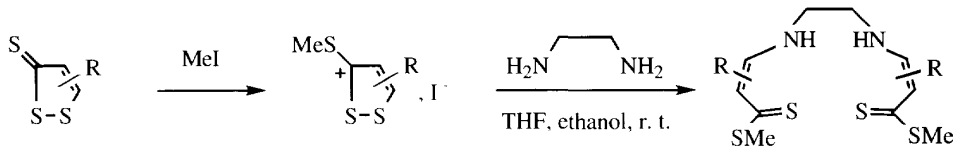


10a Σ = H
11a Σ = 4-(E)-CH=CHCOOMe
12a Σ = 4-(E)-CH=CHCOOt-Bu
13a Σ = 4-Br
14a Σ = 4-I



15a

Scheme 3

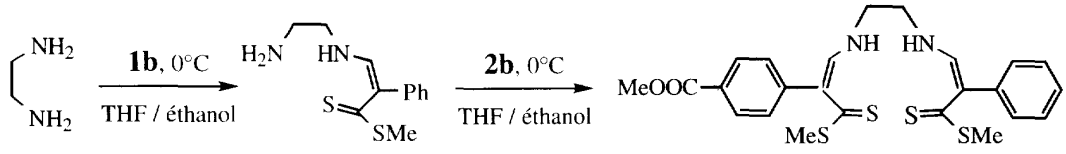


1a [R = 4-C_6H_5]
2a [R = 4-$C_6H_4COOCH_3$]
10a [R = 5-C_6H_5]
13a [R = 5-C_6H_4Br]
15a [R = H]

1b (81%)
2b (85%)
10b (61%)
13b (77%)
15b (92%)

16 (40%, ZZ/ZE = 80/20)
17 (44%, ZZ/ZE = 85/15)
18 (31%, ZZ isomer only)
19 (33%, ZZ isomer only)
20 (40%, ZZ/ZE = 95/5)

Scheme 4



21 35%; $ZZ/(ZE/EZ)$ = 82/18)

Scheme 5

Considering that this failure might be due to the presence of the highly labile disulfide bridge in the 3*H*-1,2-dithiole-3-thiones, we decided to examine the ability of these compounds to give the corresponding dithiolylium salts and subsequently "type A" ligands after reaction on diamines, expecting easier modifications of the obtained structures in order to introduce convenient linkers on the ligands.

• *Synthesis of "type A" N_2S_2 tetradentate ligands*
The synthesis involved conversion of 3*H*-1,2-dithiole-3-thiones into the corresponding 3-(methylthio)-1,2-dithiolylium iodides upon treatment with methyl iodide [69] and subsequent addition of an ethanolic solution of ethylenediamine to these salts in order to obtain the symmetrical ligands (*cf* scheme 4).

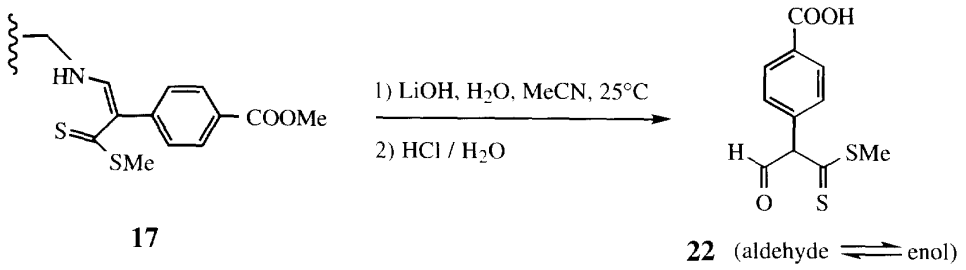
Compounds **16-20** were obtained with a high preference for the *ZZ* isomers in agreement with previous reports in related series [70]. The lower yields obtained in the case of 5-aryl-3*H*-1,2-dithiole-3-thione derivatives might be due to a higher contribution of side reactions compared with 4-aryl or unsubstituted substrates as already mentioned in the case of reactions of dithiolylium salts with aliphatic monoamines [71].

Another point of interest is the possible synthesis of dissymmetrical ligands using a reversed two step addition (*cf* scheme 5).

At this point it is of interest to examine the possibilities for conversion of the ester function contained in ligands **17** or **21** into a more appropriate function for further linkage on the monoclonal antibodies (for instance, *N*-succinimidyl ester). For this purpose, a saponification of the ester function of ligand **17** was attempted using lithium hydroxide and subsequent acidification, but in such experimental conditions the N_2S_2 structure was destroyed according to scheme 6.

Such behavior (sensitivity to basic or acidic media) is prohibitive for numerous precursors and, for these reasons, the construction of ligands from **11b** and **12b** has not been attempted.

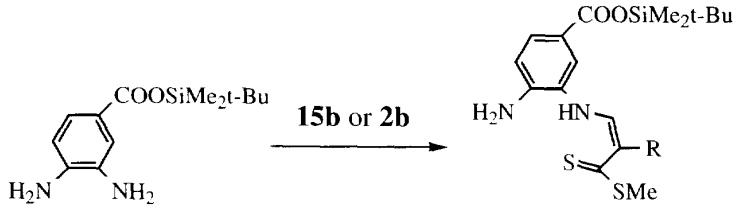
Starting from dithiolethione **3a** (Σ = COOH), dithiolethiones **4a** (Σ = $COOSiMe_3$) and **5a** (Σ = $COOCH_2CCl_3$) were easily obtained, but **4a** appeared to be useless because its desilylation occurred in the presence of methyl iodide to return to **3a** instead of dithiolylium iodide **4b**. In the case of **5a**, the dithiolylium iodide **5b** was obtained and reacted with ethylenediamine to afford the expected ligand **23** (R =



17

22 (aldehyde ⇌ enol)

Scheme 6



24

25 (R = H, 38%)
26 (R = C_6H_4COOMe, 30%)

Scheme 7

4-$C_6H_4COOCH_2CCl_3$, 20% yield), but the regeneration of the acidic function failed. In neutral experimental conditions (Zn, pH = 7) [72], **23** remained unmodified and in acidic media (Zn/AcOH) the N_2S_2 ligand was destroyed once more affording compound **22**.

Finally, the failure of the cross-coupling between the vinyltins and ligand **19** in the presence of tetrakis-(triphenylphosphine)palladium, even after protection of the labile enamino hydrogens using tris-(dimethylamino)borane [73] in order to prevent complexation of palladium, led us to stop our attempts involving "type A" ligands.

N_2S_2 tetradentate ligands from functionalized diamines (type B ligands)

In spite of the failure to reach "type A" ligands with an appropriate side chain for further grafting on monoclonal antibodies, the above study demonstrates the possible access to N_2S_2 tetradentate ligands in mild experimental conditions and the possibility of obtaining symmetrical or dissymmetrical ligands as a function of the experimental conditions. Futhermore, the construction of the N_2S_2 ligands appears to be compatible with the presence of functional groups.

In this second approach we chose to react the unsubstituted dithiolylium salt **15b** (in order to decrease the liposolubility of the obtained compounds) with easily available diamines.

Our first attempt starting from **15b** and *t*-butyldimethylsilyl-3,4-diaminobenzoate **24** led to the monosubstitution product **25** only; the dithiolylium salt **2b** behaves similarly because of the poor reactivity of the 4-amino group (*cf* scheme 7).

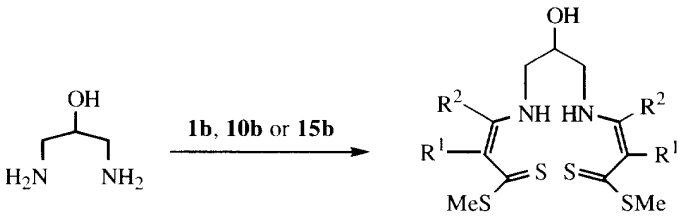
This lack of reactivity of the *para*-amino function led us to use 1,2- or 1,3-aliphatic diamines and commercially available 1,3-diaminopropan-2-ol appeared to be a suitable reagent. Indeed, upon reaction with dithiolylium salts **1b**, **10b** or **15b**, 1,3-diaminopropan-2-ol afforded the expected compounds **27-29** (*cf* scheme 8).

At this stage, the hydroxyl function was used for the grafting of a side chain with a highly reactive *N*-succinimidyl ester function (-COO"NHS") according to scheme 9.

The obtained structure **31** is consistent with the above-mentioned prerequisites for potential use in nuclear medicine. Futhermore, coupling of **29** with *N*-Boc-protected *β*-alanine in similar experimental conditions afforded a compound **32** (40% yield) with an -NH-Boc function instead of the -COO"NHS" function. This opens the way to another type of possible linkage on monoclonal antibodies.

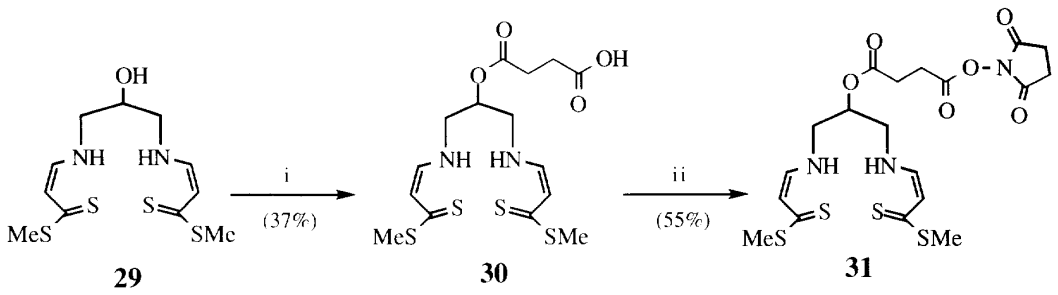
Considering the reactivity of the *N*-succinimidyl ester, a ligand like **31** implies very mild experimental conditions for the complexation of metallic species. To give more extended possibilities, it is imperative to carry out the complexation on compound **29** followed by further grafting of the linker in an expedious fashion. For this purpose, bifunctional reagents containing an acyl chloride and an *N*-succinimidyl ester function have been prepared from anhydrides and *N*-hydroxysuccinimide according to scheme 10.

Compound **34** constitutes a potential reagent for the rapid conversion of chelates obtained from **29** into chelates with a linker (formally identical to chelates which might be obtained from **31**). This strategy will be compatible with further adaptation of the linker (if necessary) starting from the same ligand.



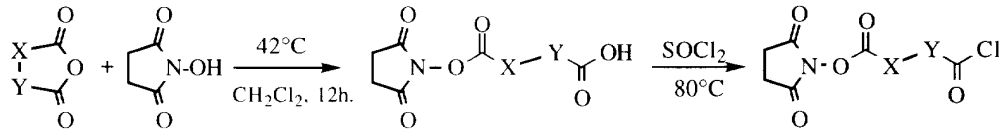
27 ($R^1 = C_6H_5$, R^2 = H, 53%)
28 (R^1 = H, $R^2 = C_6H_5$, 35%)
29 ($R^1 = R^2$ = H, 60%)

Scheme 8



i = succinic anhydride/DMAP, methylene chloride 42°C, 15 h (⇒ **30**, 37% isolated)
ii = *N*-hydroxysuccinimide/DMAP/DCC, methylene chloride 0°C, 15 h (⇒ **31**, 55% isolated)

Scheme 9



X-Y = CH_2-CH_2 **33** (84%) **34** (91%)

X-Y = C(Me)=C(Me) **35** (98%) **36** (92%)

Scheme 10

Conclusion

This work demonstrates that N_2S_2 tetradentate ligands can be obtained with a linker bearing an *N*-succinimidyl function, which can lead to grafting on monoclonal antibodies for further applications in nuclear medicine. The ligands obtained can give chelates with Cu^{II}, Ni^{II}, Co^{II} or $(TcN)^{2+}$ [74], which must be studied in terms of synthesis, structure and stability before examining a possible use as radiopharmaceuticals for both radioimmunoscintigraphy (^{99m}Tc) and radioimmunotherapy (^{67}Cu). As regards these chelates, a point which must be examined will be the size of the N_2S_2 tetradentate system (reaction of dithiolylium salt on 1,3- or 1,2-diamines) and its solubility. The present procedure used functionalized diamines and appears to be versatile enough to be optimizable on both points, since functionalized 1,2-diamines are also available [74]. Another important point in terms of biodegradability will be the nature of the linker and, for this purpose, the possible access to structures like **34** and **36** seems promising in view of further optimization.

Experimental section

General

The obtained compounds were characterized on the basis of their physicochemical data. The NMR spectra were recorded on a Jeol FX 90 Q apparatus (89.55 MHz for ^1H and 22.49 MHz for ^{13}C) or on a Bruker AC200 apparatus (200.132 MHz for ^1H and 50.323 MHz for ^{13}C). Chemical shifts are given in ppm referring to tetramethylsilane used

as an internal standard and coupling constants in hertz. Unless mentioned otherwise, the samples were in deuterochloroform solution. The IR spectra were recorded in KBr plates on a Bruker IFS 85 WHR apparatus and the mass spectra (EI, 70 eV) on a Hewlett Packard (Engine 5989 A) apparatus in direct introduction mode. The melting points were obtained on a Köfler heating plate fitted with a RCH (Reichert) microscope. Elemental analysis were performed by the CNRS microanalysis center (Vernaison). After preparative chromatography on silica gel, the purities of the samples were checked in thin-layer chromatography (kiesel gel 60 plates F_{254}, Merck).

Preparation of 4-aryl-3H-1,2-dithiole-3-thiones **1a-9a** *and precursors*

4-Aryl-3*H*-1,2-dithiole-3-thiones were obtained from the appropriate cumyl derivatives, which were prepared according to previously described procedures.

- *4-Isopropylbenzoic acid and methyl 4-isopropylbenzoate*

4-Isopropyl benzoic acid was obtained in a Friedel-Crafts reaction between oxalyl chloride and cumene followed by hydrolysis (98% yield, white crystals, mp = 117-118°C) [76]. When the crude intermediate acyl chloride was trapped with sodium methanolate, methyl 4-isopropylbenzoate was obtained in 90% yield (bp_{14} = 126°C).

^{1}H NMR : 1.23 (6H, d, $^3J_{1H}$ = 6.8), 2.92 (1H, spt, $^3J_{6H}$ = 6.8), 3.86 (3H, s), 7.24 (2H, d, $^3J_{1H}$ = 8.1), 7.95 (2H, d, $^3J_{1H}$ = 8.1).

^{13}C NMR : 23.4 (2C), 34.0, 51.4, 126.2 (2C), 129.5 (2C), 128.1, 153.9, 166.7.

MS : m/z = 178 (M^+, 43), 163 (100), 147 (34), 131 (26), 119 (57), 104 (11), 103 (18), 91 (43), 77 (18), 59 (21), 51 (12), 41 (12).

IR : 3 100-2 800, 1 723, 1 610, 1 465, 1 437, 1 311, 1 278, 1 181, 1 113, 1 019, 775, 708 cm^{-1}.

- *4-Bromo-1-isopropylbenzene*

This compound was obtained as a pure regioisomer from 4-isopropyl aniline using a Sandmeyer reaction [77] (65% yield, bp = 183-185°C)

^{1}H NMR : 1.23 (6H, d, $^3J_{1H}$ = 6.8), 2.88 (1H, spt, $^3J_{6H}$ = 6.8), 7.09 (2H, d, $^3J_{1H}$ = 8.3), 7.41 (2H, d, $^3J_{1H}$ = 8.3).

^{13}C NMR : 24.1 (2C), 33.8, 119.6, 128.4 (2C), 131.6 (2C), 147.8.

MS : m/z = 198/200 (M^+, 32/33), 183/185 (87/82), 169/171 (2/2) 119 (14), 104 (100).

IR : 3 100-2 800, 1 600, 1 490, 1 462, 1 406, 1 361, 1 089, 1 011, 882, 755, 716, 530 cm^{-1}.

- *4-Aryl-3H-1,2-dithiole-3-thiones* **1a-9a**

4-Phenyl derivative **1a** was obtained as red crystals (mp = 117-120°C, 57% yield) by reaction of sulfur on cumene in the presence of di-*o*-tolylguanidine [78] while 4-(4-functionalized-phenyl) derivatives **2a**, **6a** and **7a** were obtained by direct heating (200-240°C) of the appropriate cumyl derivative in the presence of sulfur [57]. According to this route, **2a** (orange crystals, mp = 139-142°C) was obtained in 80% yield, **6a** (orange crystals, mp = 95-97°C) in 4% yield and **7a** (orange crystals, mp = 187-189°C) in 28% yield.

Other 4-aryl-3*H*-1,2-dithiole 3-thiones were obtained by modification of **1a**, **2a** or **7a**. For instance, hydrolysis of compound **2a** with an acetic acid/sulfuric acid mixture according to Russel-Melby [79] afforded **3a** (orange crystals, mp = 220-223°C) in 97% yield. The dithiolethione **3a** (Σ = COOH) was subsequently modified into dithiolethione **4a** (Σ = $COOSiMe_3$, orange crystals, 44% yield) using chlorotrimethylsilane and DBU in methylene chloride [80] or in dithiolethione **5a** (Σ = $COOCH_2CCl_3$, orange crystals, 92% yield) upon treatment with 2,2,2-trichloroethanol in the presence of *p*-toluenesulfonic acid (toluene solution, Dean-Stark apparatus). Similarly **7a** was modified into dithiolethione **8a** (Σ = *p*-OTf, orange crystals, 48% yield) upon treatment with imidazolyl triflate in the presence of sodium phenolate (solvent : benzene) [81]. Finally dithiolethione **9a** (Σ = *m*-SO_2Cl, orange crystals, 60% yield) was obtained from **1a** upon treatment with chlorosulfonic acid according to a previously described procedure [82].

- *Physicochemical data*

A remarkable feature of the mass spectra of 4-aryl-3*H*-1,2-dithiole-3-thiones is the presence of an intense peak corresponding to the loss of one hydrogen [83]. Some compounds have been considered simply as intermediates and some physicochemical data are missing when these compounds proved to be inefficient in the desired syntheses.

1a : ^{1}H NMR : 7.45 (5H ar, m), 8.38 (1H, s).

^{13}C NMR : 129.0 and 129.6 (2 × 2 CH ar), 129.8 (CH ar), 133.7 (C_{IV}), 149.9 (=C_{IV}), 154.5 (=CH), 214.7 (C=S).

MS : m/z = 210 (M^+, 61), 209 (100), 177 (11), 145 (5), 133 (10), 121 (4).

IR : 3 080-2 800 (CH), 1 510, 1 484, 1 317, 1 299, 1 278, 1 125, 1 116, 999, 833, 750, 695 cm^{-1}.

2a : ^{1}H NMR : 3.93 (3H, s), 7.61 (2H, d, $^3J_{1H}$ = 8.2), 8.1 (2H, d, $^3J_{1H}$ = 8.2), 8.46 (1H, s).

^{13}C NMR : 51.8 (OCH_3), 129 and 129.7 (2 × 2 CH ar), 130.5 (C_{IV}), 137.7 (C_{IV}), 148.3 (=C_{IV}), 154.5 (=CH), 166.5 (C=O), 213.4 (C=S).

MS : m/z = 268 (M^+, 95), 267 (100), 253 (15), 237 (11), 235 (9), 209 (99), 177 (7), 145 (6), 121 (8).

IR : 3 080-2 800 (CH), 1 721, 1 608, 1 567, 1 521, 1 479, 1 434, 1 313, 1 286, 1 127, 1 024, 995, 833, 766, 612 cm^{-1}.

3a : ^{1}H NMR (DMSO d_6) : 7.70 (2H, d, $^3J_{1H}$ = 8.3), 7.98 (2H, d, $^3J_{1H}$ = 8.3), 9.21 (1H, s).

MS : m/z = 254 (M^+, 80), 253 (100), 209 (53), 165 (8), 133 (20).

IR : 3 490, 3 040-2 840, 1 675 (C=O), 1 610, 1 430, 1 320, 1 290, 840, 790, 770 cm^{-1}.

4a : ^{1}H NMR : 0.32 (9H, s), 7.58 (2H, d, $^3J_{1H}$ = 8.8), 8.00 (2H, d, $^3J_{1H}$ = 8.8), 8.4 (1H, s).

^{13}C NMR : −1.5 ($SiMe_3$), 127.4 and 131.1 (2 × 2 CH ar), 131.9 (C_{IV}), 137.7 (C_{IV}), 148.3 (=C_{IV}), 154.7 (=CH), 166.3 (C=O), 213.4 (C=S).

5a : ^{1}H NMR : 4.99 (2H, s), 7.67 (2H, d, $^3J_{1H}$ = 8.4), 8.2 (2H, d, $^3J_{1H}$ = 8.4), 8.47 (1H, s).

6a : ^{1}H NMR : 7.41 (2H, d, $^3J_{1H}$ = 8.7), 7.58 (2H, d, $^3J_{1H}$ = 8.7), 8.41 (1H, s).

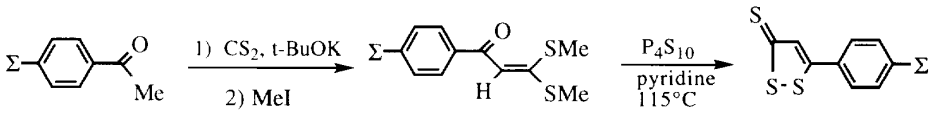
7a : ^{1}H NMR : 6.88 (2H, d, $^3J_{1H}$ = 8.7), 7.05 (1H, m), 7.46 (2H, d, $^3J_{1H}$ = 8.7), 8.83 (1H, s).

^{13}C NMR : 115.4 and 130.7 (2 × 2 CH ar), 125.2 (C_{IV}), 148.9 (=C_{IV}), 156.2 (=CH), 158.2 (O-C_{IV}), 214.7 (C=S).

MS : m/z = 226 (M^+, 84), 225 (100), 209 (18), 133 (14), 121 (27), 69 (19).

IR : 3 550-3 100, 3 050-2 800, 1 610, 1 594, 1 526, 1 512, 1 479, 1 437, 1 364, 1 316, 1 285, 1 174, 1 023, 1 018, 1 001, 832, 615 cm^{-1}.

8a : ^{1}H NMR : 7.34 (2H, d, $^3J_{1H}$ = 9.00), 7.66 (2H, d, $^3J_{1H}$ = 9.00), 8.46 (1H, s).



37a Σ = Br
38a Σ = I
39a Σ = -CH=CH-COOMe
40a Σ = -CH=CH-COOt-Bu

37b Σ = Br
38b Σ = I
39b Σ = -CH=CH-COOMe
40b Σ = -CH=CH-COOt-Bu

13a Σ = Br
14a Σ = I
11a Σ = -CH=CH-COOMe
12a Σ = -CH=CH-COOt-Bu

Scheme 11

^{13}C NMR : 118.7 (q, J_{C-F} = 412), 121.5 and 131.1 (2×2 CH ar), 128.9 and 133.6 (C_{IV}), 149.7 (=C_{IV}), 154.7 (=CH), 213.3 (C=S).

MS : m/z = 358 ($M^{+\cdot}$, 95), 357 (44), 225 (75), 197 (41), 69 (100), 45 (46).

9a : ^{1}H NMR : 7.40 (1H, s), 7.91 (3H, m), 8.54 (1H, s).

^{13}C NMR : 127.5, 128.6 and 130.6 (CH ar), 127.6 and 130.1 (C_{IV}), 135.0 (=CH), 155.0 (=C_{IV}), 155.8 (CH ar), 210.1 (C=S).

*Preparation of 5-aryl-3*H*-1,2-dithiole-3-thiones* **10a-14a** *and precursors*

• *5-phenyl-3*H*-1,2-dithiole-3-thione* **10a**

Compound **10a** was obtained in two steps from methyl cinnamate [84]. Upon heating with sulfur at 250°C, 5-phenyl-3*H*-1,2-dithiol-3-one was obtained in 50% yield and subsequently converted into 5-phenyl-3*H*-1,2-dithiole-3-thione (**10a**; orange crystals, mp = 120-125°C, 58% yield) upon heating with phosphorus pentasulfide in pyridine (4 h, 110°C).

^{1}H NMR : 6.84 (1H, s), 7.53 (CH ar, m).

^{13}C NMR :126.9 (2C, CH ar), 129.6 (2C, CH ar), 132.1 (CH ar), 131.9 (C_{IV}), 135.9 (=CH), 172.7 (=C_{IV}), 215.6 (C=S).

MS : m/z = 210 ($M^{+\cdot}$, 82), 145 (100), 102 (50).

IR : 3 080-3 000, 1 627, 1 521, 1 482, 1 446, 1 323, 1 183, 1 032, 1 020, 846, 760, 704 cm^{-1}.

It is worth noting a different fragmentation mode in the MS spectra with a main fragment resulting from the loss of $HS_2^{\bullet}$ instead of hydrogen as observed in **1a** [83].

• *5-(4-functionalized-phenyl)-3*H*-1,2-dithiole-3-thiones* **11a-14a**

In this series the desired dithiole thiones were obtained according to Thuillier and Vialle [85] from the suitable acetophenones via 1-aryl-3,3-bis(methylthio)prop-2-en-1-ones (*cf* scheme 11).

• *Synthesis of precursors* **37-40**

Obviously, from this reaction scheme, commercially available 4-bromoacetophenone **37a** appears to be a key reagent in order to obtain **37b** and subsequently **13a**, and also for the preparation of the precursors **38a**, **39a** and **40a**.

To obtain 4-iodoacetophenone **38a**, **37a** was first protected as 2-(4-bromophenyl)-2-methyl-1,3-dioxolane which was converted into 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (BuLi, THF, −78°C then I_2, −78°C) before deprotection (0.5 M aqueous H_2SO_4, THF, 0°C). **38a** was obtained as white crystals (mp = 81-83°C, overall yield = 74%). Further conversion into 1-(4-iodophenyl)-3,3-bis(methylthio)prop-2-en-1-one **38b** achieved according to scheme 11 [85] led to **38b** in 87% yield (mp = 109-112°C).

4-Acetylcinnamates **39a** and **40a** were obtained by Heck coupling of 4′-bromoacetophenone **37a** with methyl or *t*-butyl acrylates. Yields were improved using palladium acetate as a catalyst in the presence of sodium hydrogenocarbonate and tetrabutylammonium bromide in dimethylformamide [86]. According to this route **39a** (mp = 113-115°C) and **40a** (mp = 98-101°C) were obtained in 80% and 91% yield, respectively, and converted into **39b** (mp = 121-132°C, 85% yield) and **40b** (mp = 114-117°C, 87% yield) under the usual experimental conditions (*cf* scheme 11 and typical experimental procedure for the preparation of **37b**).

• *Typical experimental procedure for* **37b**

In a three-necked reactor, a benzene solution containing 25 mmol of **37a** and 25 mmol of carbon disulfide was added dropwise at 0°C under stirring to 5.6 g (50 mmol) potassium *tert*-butanolate in benzene (25 mL). After addition, the reaction mixture was kept 2 h at room temperature before addition of methyl iodide (3.1 mL, 50 mmol) at 0°C over a period of 1 h. After further stirring during 3 h and addition of water (as solvent for potassium iodide), the organic layer was washed with 2 × 100 mL aqueous 1 M NaOH solution and underwent the usual treatment before recrystallization of **37b** from ethyl acetate (5.6 g, 74% yield, orange crystals, mp = 100-103°C).

• *Physicochemical data for compounds* **37b-40b**

37b : ^{1}H NMR : 2.50 (3H, s), 2.52 (3H, s), 6.66 (1H, s), 7.52 (2H, ~ d, $^3J_{1H}$ ~ 9), 7.76 (2H, ~ d, $^3J_{1H}$ ~ 9).

^{13}C NMR : 15.1 (SCH_3), 17.4 (SCH_3), 108.8 (=CH), 126.6 (C_{IV}-Br), 129.3 and 131.7 (2 × 2 CH ar), 138.1 (C_{IV}), 167.6 (=C_{IV}), 184.2 (C=O).

MS : m/z = 302/304 ($M^{+\cdot}$, 12/14), 285/287/289 (30/80/85), 255/257 (2/2), 241/243 (8/7), 208 (4), 183/185 (58/58), 155/157 (31/31), 76 (70), 75 (100), 50 (82), 45 (63).

IR : 3 044, 2 989, 2 917, 1 614, 1 583, 1 487, 1 475, 1 229, 1 177, 1 067, 1 008, 952, 815, 629 cm^{-1}.

38a : ^{1}H NMR : 2.57 (3H), 7.57 to 7.89 (4H, system AA′BB′ with 4 lines to 7.58, 7.69, 7.78 and 7.87, $^3J_{1H}$ ~ 8.5).

^{13}C NMR : 26.4 (CH_3), 101.0 (C_{IV}), 136.3 (C_{IV}), 129.6 and 137.8 (2 × 2 CH ar), 197.1 (C=O).

MS : m/z = 246 ($M^{+\cdot}$, 42), 231 (100), 203(28).

IR : 3 075-3 020, 2 995-2 890, 1 673 (C=O), 1 583, 1 556, 1 392, 1 262, 819 (*para*), 586 cm^{-1}.

38b : ^{1}H NMR : 2.51 (2H, s), 2.53 (3H, s), 6.66 (1H, s), 7.59 (2H, ~ d, $^3J_{1H}$ ~ 8.6), 7.77 (2H, ~ d, $^3J_{1H}$ ~ 8.6).

^{13}C NMR : 15.2 (SCH_3), 17.5 (SCH_3), 99.1 (C-I), 109.1 (=CH), 129.3 and 137.8 (2×2 CH ar), 138.8 (C_{IV}), 167.4 (=C_{IV}), 184.5 (C=O).

MS : m/z = 350 (M^{+}, 35), 335 (89), 333 (82), 303 (3), 289 (13), 231 (100), 208 (17), 203 (35), 132 (23), 104 (22), 76 (51), 47 (39), 45 (73).

IR : 3 080-2 900, 1 611, 1 579, 1 489, 1 472, 1 233, 1 181, 1 055, 995, 830, 763, 624 cm^{-1}.

39a : ^{1}H NMR : 2.61 (3H, s), 3.82 (3H, s), 6.51 (1H, d, $^{3}J_{1H}$ = 15.8), 7.58 (2H, d, $^{3}J_{1H}$ = 8.2), 7.7 (1H, d, $^{3}J_{1H}$ = 15.8), 7.96 (2H, d, $^{3}J_{1H}$ = 8.2).

^{13}C NMR : 26.4 (CH_3), 51.7 (OCH_3), 120.3 (=CH), 128.0 and 128.7 (2 × 2 CH ar), 138.1 (C_{IV}), 138.7 (C_{IV}), 143.1 (=CH), 166.7 (C=O), 196.9 (C=O).

MS : m/z = 204 (M^{+}, 32), 189 (100), 173 (7), 161 (14), 131 (8), 102 (12), 76 (7), 43 (20).

39b : ^{1}H NMR : 2.53 (3H, s), 2.57 (3H, s), 3.81 (3H, s), 6.49 (1H, d, $^{3}J_{1H}$ = 16), 6.75 (1H, s), 7.57 (2H, d, $^{3}J_{1H}$ = 8.3), 7.71 (1H, d, $^{3}J_{1H}$ = 16), 7.93 (2H, d, $^{3}J_{1H}$ = 8.3).

^{13}C NMR : 15.1 (SCH_3), 17.3 (SCH_3), 51.7 (OCH_3), 109.3 (=CH), 119.6 (=CH), 128.0 and 128.1 (2 × 2 CH ar), 137.4 (C_{IV}), 140.6 (C_{IV}), 143.4 (=CH), 166.7 (C=O or =C_{IV}), 167.3 (=C_{IV} or C=O), 184.1 (C=O).

MS : m/z = 308 (M^{+}, 24), 293 (84), 291 (58), 261 (20), 247 (12), 244 (9), 215 (8), 189 (100), 161 (19), 147 (15), 118 (15), 102 (30), 75 (30).

40a : ^{1}H NMR : 1.54 (9H, s), 2.59 (3H, s), 6.44 (1H, d, $^{3}J_{1H}$ = 15.5), 7.57 (2H, d, $^{3}J_{1H}$ = 8.2), 7.59 (1H, d, $^{3}J_{1H}$ = 15.5), 7.94 (2H, d, $^{3}J_{1H}$ = 8.2).

^{13}C NMR : 26.3 (CH_3), 28.0 ($3CH_3$), 80.6 (C_{IV}), 122.7 (=CH), 127.8 and 128.6 (2 × 2 CH ar), 137.8 (C_{IV}), 139.0 (C_{IV}), 141.8 (=CH), 165.5 (C=O), 196.9 (C=O).

MS : m/z = 246 (M^{+}, 5), 231 (2), 191 (17), 190 (28), 175 (100), 173 (19), 147 (5), 131 (8), 102 (13), 91 (8), 57 (33), 43 (34).

IR : 3 050-2 800, 1 699, 1 682, 1 632, 1 392, 1 328, 1 257, 1 213, 1 152, 1 003, 839 cm^{-1}.

40b : ^{1}H NMR : 1.53 (9H, s), 2.53 (3H, s), 2.57 (3H), 6.42 (1H, d, $^{3}J_{1H}$ = 15.9), 6.74 (1H, s), 7.55 (2H, d, $^{3}J_{1H}$ = 8.2), 7.59 (1H, d, $^{3}J_{1H}$ = 15.9), 7.91 (2H, d, $^{3}J_{1H}$ = 8.2).

^{13}C NMR : 15.0 (SCH_3), 17.3 (SCH_3), 28.1 ($3CH_3$), 80.7 (C_{IV}), 109.4 (=CH), 122.1 (=CH), 127.9 and 128.2 (2 × 2 CH ar), 137.3 (C_{IV}), 139.0 (C_{IV}), 142.2 (=CH), 165.5 (C=O), 167.0 (=C_{IV}), 184.6 (C=O).

MS : m/z = 350 (M^{+}, 25), 335 (67), 333 (71), 293 (2), 279 (100), 277 (55), 261 (17), 175 (31), 157 (21), 147 (30), 102 (21), 91 (14), 75 (18), 41 (7).

IR : 3 010-2 800 (CH), 1 704, 1 684, 1 621, 1 511, 1 490, 1 479, 1 441, 1 375, 1 330, 1 240, 1 145, 1 065, 995, 853, 780, 704 cm^{-1}.

• *Synthesis of 5-(4-bromophenyl)-3H-1,2-dithiole-3-thione* **13a** *[85]*

In a four-necked reactor, a solution of **37b** (9.06 g, 30 mmol) in dry pyridine (100 mL) was allowed to warm to 120°C with simultaneous stepwise addition of sulfur (4.7 g). When the solution became brown-yellow, 6.66 g of phosphorus pentasulfide was added in small portions (as fast as possible) and the reflux of pyridine maintained for 30 min. After cooling to 60°C and addition of benzene (100 mL), diluted hydrochloric acid was added in order to eliminate pyridinium salts. The organic layer was subsequently washed with sodium hydrogenocarbonate until obtention of a colorless solution. After the usual treatment and removal of the solvent, the solid residue was dissolved in boiling acetone in order to eliminate residual sulfur and the dithiolethione **13a** was purified by crystallization from ethyl acetate or by liquid chromatography on silica gel (eluent : petroleum ether/methylene chloride 50:50). **13a** was obtained as red crystals (mp = 127-130°C, 4.6 g, 53% yield).

A similar experimental procedure was also used for the preparation of dithiolethiones **11a**, **12a** and **14a**.

• *Physicochemical data for compounds* **11a-14a**

11a : ^{1}H NMR (CD_2Cl_2) : 3.80 (3H, s), 6.55 (1H, d, $^{3}J_{1H}$ = 15.8), 7.47 (1H, s), 7.65 (2H, ~ d, $^{3}J_{1H}$ ~ 8.5), 7.69 (1H, d, $^{3}J_{1H}$ = 15.8), 7.73 (2H, ~ d, $^{3}J_{1H}$ ~ 8.5).

MS : m/z = 294 (M^{+}, 100), 279 (5), 263 (9), 229 (93), 186 (5).

IR : 3 100-2 800, 1 734, 1 634, 1 517, 1 492, 1 422, 1 325, 1 281, 1 212, 1 191, 1 168, 1 121, 1 027, 979, 820, 668 cm^{-1}.

12a : ^{1}H NMR : 1.52 (9H, s), 6.59 (1H, d, $^{3}J_{1H}$ = 16), 7.63 (1H, d, $^{3}J_{1H}$ = 16), 7.64 (1H, s), 7.81 (2H, ~ d, $^{3}J_{1H}$ ~ 9), 7.95 (2H, ~ d, $^{3}J_{1H}$ ~ 9).

^{13}C NMR : 28.1 (CH_3), 80.9 (C_{IV}), 122.9 (=CH), 127.2 and 128.7 (2 × 2 CH ar), 132.6 (C_{IV}), 135.9 (=CH), 138.4 (C_{IV}), 141.4 (=CH), 165.5 (C=O), 171.4 (=C_{IV}), 215.2 (C=S).

MS : m/z = 336 (M^{+}, 84), 280 (100), 263 (20), 245 (7), 235 (13), 215 (86), 171 (8), 170 (13), 169 (15), 127 (13), 57 (32), 44 (28), 41 (32).

IR : 3 100-2 800, 1 700, 1 696, 1 624, 1 521, 1 491, 1 415, 1 360, 1 320, 1 284, 1 213, 1 021, 1 008, 980, 825 cm^{-1}.

13a : ^{1}H NMR : 7.39 (1H, s), 7.5 (2H, ~ d, $^{3}J_{1H}$ ~ 8.5), 7.64 (2H, ~ d, $^{3}J_{1H}$ ~ 8.5).

^{13}C NMR : 126.9 (C-Br), 130.5 (C_{IV}), 128.2 and 132.9 (2 × 2 CH ar), 136.0 (=CH), 171.2 (=C_{IV}), 215.4 (C=S),

MS : m/z = 288/290 (M^{+}, 88/90), 257/255 (1/1), 223/225 (98/100), 212/214 (5/5), 209 (7), 199/201 (5/5), 180/182 (20/19), 155/157 (1/1), 145 (14), 144 (22), 133 (8), 120 (18), 104 (25), 101 (43), 75 (33), 72 (26), 69 (28), 50 (26).

IR : 3 100-3 000, 1 583, 1 517, 1 481, 1 397, 1 317, 1 192, 1 072, 1 029, 995, 889, 819, 717, 668 cm^{-1}.

14a : ^{1}H NMR : 7.37 (2H, ~ d, $^{3}J_{1H}$ ~ 8.8), 7.40 (1H, s), 7.84 (2H, ~ d, $^{3}J_{1H}$ ~ 8.8).

MS : m/z = 336 (M^{+}, 100), 271 (51), 260 (3), 247 (2), 228 (8), 209 (4), 145 (5), 144 (10), 120 (46), 101 (8), 69 (5), 50 (3).

IR : 3 100-3 000, 1 474, 1 317, 1 201, 1 185, 1 020, 1 006, 820, 485 cm^{-1}.

• *3H-1,2-dithiole 3-thione* **15a** *[87]*

A mixture of 1,1,3,3-tetramethoxypropane (14.2 g) and sulfur (13.8 g) in dry pyridine (170 mL) was warmed up to 130°C before addition of phosphorus pentasulfide (19.2 g) in small amounts (0.5 g) over 30 min. After cooling to 60°C, benzene (200 mL) and 2 M hydrochloric acid solution (200 mL) were added and the organic layer washed with a 2 M hydrogenocarbonate solution. After drying and removal of solvents, the residue was dissolved in boiling acetone and the dithiolethione **15a** recrystallized from carbon tetrachloride (red crystals, mp = 79-81°C, 5.76 g, 50% yield).

^{1}H NMR : 7.22 (1H, d, $^{3}J_{1H}$ = 5.6), 8.85 (1H, d, $^{3}J_{1H}$ = 5.6).

^{13}C NMR : 140.8 (=CH), 158.8 (=CH), 218.4 (C=S).

MS : m/z = 134 (M^{+}, 100), 108 (2), 102 (3), 101 (4), 90 (4), 76 (6), 70 (10), 69 (59), 58 (19), 57 (9), 45 (15), 26 (1).

IR : 3 062, 3 047, 1 469, 1 329, 1 172, 1 126, 989, 960, 786, 767, 668 cm^{-1}.

Preparation and characterization of dithiolylium iodides

3-Methylthio-3*H*-1,2-dithiolylium iodides were obtained in benzene (10 mL) from dithiole thione (10 mmol) and methyl iodide (100 mmol) after 5 h reflux [69]. Crystals were obtained directly from the reaction mixture and washed with ether before physicochemical characterizations.

1b : Yellow crystals, mp = 155-160°C, 81% yield.

^{1}H NMR (DMSO d_6) : 3.1 (3H, s), 7.57 (5H, m), 9.87 (1H, s).

MS : m/z = 225 (22), 210 (25), 209 (100), 177 (43), 142 (48), 127 (32), 89 (24).

IR : 3 100-3 000, 3 000-2 800, 1 460, 1 442, 1 349, 1 307, 1 201, 1 046, 850, 757, 694 cm^{-1}.

2b : Orange crystals, mp = 173-174°C, 61% yield.

^{1}H NMR (DMSO d_6) : 3.11 (3H, s), 3.89 (3H, s), 7.63 (2H, d, $^3J_{1H}$ = 8.1), 8.14 (2H, d, $^3J_{1H}$ = 8.1), 9.94 (1H, s).

MS : m/z = 283 (13), 268 (93), 267 (100), 237 (14), 209 (85), 142 (78), 127 (52).

IR : 3 100-3 000, 3 000-2 800, 1 722, 1 716, 1 610, 1 459, 1 423, 1 344, 1 299, 1 291, 1 116, 1 042, 955, 852, 767, 706 cm^{-1}.

10b : Orange crystals, mp = 155°C, 61% yield.

^{1}H NMR (DMSO d_6) : 3.16 (3H, s), 7.7 (3H ar, m), 8.1 (2H ar, m), 8.93 (1H, s).

MS : m/z = 225 (29), 210 (51), 177 (5), 145 (100), 142 (50), 134 (8), 127 (26), 121 (19).

13b : Orange crystals, mp = 159-162°C, 77% yield.

^{1}H NMR (DMSO d_6) : 3.13 (3H, s), 7.86 (2H, d, $^3J_{1H}$ = 8.8), 8.06 (2H, d, $^3J_{1H}$ = 8.8), 8.95 (1H, s).

MS : m/z = 303/305 (3/3), 288/290 (61/68), 223/225 (64/68), 212/214 (3/3), 209 (5), 180/182 (12/12), 142 (100), 127 (32).

IR : 3 050-3 000, 3 000-2 750, 1 581, 1 501, 1 467, 1 396, 1 339, 1 212, 1 070, 1 033, 833, 728, 524 cm^{-1}.

15b : Yellow crystals, mp = 154-155°C, 92% yield.

^{1}H NMR (DMSO d_6) : 3.07 (3H, s), 8.44 (1H, d, $^3J_{1H}$ = 5.7), 9.98 (1H, d, $^3J_{1H}$ = 5.7).

^{13}C NMR (DMSO d_6) : 20.1, 135.0, 170.8, 198.0.

MS : m/z = 149 (86), 142 (35), 134 (100), 127 (44), 101 (44), 69 (84), 58 (28).

IR : 3 059, 3 023, 2 960, 2 883, 1 453, 1 421, 1 349, 1 311, 1 212, 1 018, 979, 772, 553 cm^{-1}.

Synthesis of N_2S_2 tetradentate ligands from ethylenediamine

In a three-necked reactor containing a suspension of dithiolylium iodide (20 mmol) in THF was added dropwise an ethanolic solution of ethylenediamine (11 mmol in 70 mL EtOH). After 2 h stirring, the reaction mixture was extracted with methylene chloride (100 mL) and washed with water (3 × 100 mL). After drying the organic phase and removal of the solvents, the crude product was chromatographed on silica gel. For dissymmetrical ligand **21**, a reversed addition was performed at 0°C : dithiolylium salt **1b** (5 mmol) was first added by small portions into a THF/ethanol (1:1) solution of ethylenediamine (5.5 mmol) and, after isolation of the crude product, dithiolylium salt **2b** (5 mmol) was added similarly, the end of the work-up being identical to those of symmetrical ligands.

- *Physicochemical data for compounds* **16-21**, **23**

16 : Eluent : CH_2Cl_2/petroleum ether (75:25), 40% yield, yellow crystals, mp = 168-171°C, *ZZ*/*ZE* = 80:20.

^{1}H NMR : *ZZ* isomer : 2.51 (6H, s), 3.52 (4H, m), 6.87 (2H, d, $^3J_{1H}$ = 12.8), 7.30 (10H, m),12.67 (2H, m); *ZE* isomer : 2.51 (3H, s), 2.61 (3H, s), 3.52 (4H, m), 6.81 (1H, d, $^3J_{1H}$ = 12.8), 7.30 (5H, ~ s), 7.40 (5H, ~ s), 8.52 (1H, d, $^3J_{1H}$ = 12.5), 12.67 (2H, m).

^{13}C NMR : *ZZ* isomer : 18.3 (2C, SCH_3), 50.7 (2C, CH_2), 121.9 (2C, =C_{IV}), 127.9 (2 CH ar), 128.7 and 129.9 (2×4 CH ar), 140.5 (2C, C_{IV}), 153.3 (2C, =CH), 210.1 (2C, C=S); *ZE* isomer : 18.3 (SCH_3, *Z*), 19.5 (SCH_3, *E*), 49.5 and 50.5 (2C, $2CH_2$), 121.9 (=C_{IV}, *Z*), 125.6 (=C_{IV}, *E*), 127 to 132 (CH ar, signals superimposed with those of *ZZ* isomer excepted 129.9), 135.4 (C_{IV}, *E*), 140.5 (C_{IV}, *Z*), 148.2 (=CH, *E*), 152.6 (=CH, *Z*), 210 (C=S).

MS : m/z = 444 (M^+, 12), 429 (6), 397 (100), 263 (6), 236 (18), 222 (15), 209 (20), 198 (25), 190 (30), 188 (33), 175 (40), 171 (38), 162 (50), 147 (35).

Anal calc for $C_{22}H_{24}N_2S_4$: C : 59.42, H : 5.44, N : 6.30, S : 28.84; found : C : 59.31, H : 5.44, N : 6.23, S : 28. 97.

17 : Eluent CH_2Cl_2/AcOEt (95:5), 44% yield, orange crystals, mp = 194°C, *ZZ*/*ZE* = 85:15.

^{1}H NMR : *ZZ* isomer : 2.51 (6H, s), 3.40 to 3.65 (4H, m), 3.90 (6H, s), 6.83 (2H, d, $^3J_{1H}$ = 13.2), 7.33 (2×2H, ~ d, $^3J_{1H}$ = 8.2), 7.96 (2×2H, ~ d, $^3J_{1H}$ = 8.2), 12.35 to 12.75 (2H, m); *ZE* isomer (meaningful signals) : 2.51 (3H, s), 2.60 (3H, s), 3.40 to 3.65 (4H, m), 3.90 (3H, s), 3.92 (3H, s), 6.78 (1H, d, $^3J_{1H}$ = 13.4), 8.34 (1H, d, $^3J_{1H}$ = 13.7), 12.35 to 12.75 (2H, m).

^{13}C NMR : *ZZ* isomer : 17.9 (2C, SCH_3), 50.2 (2C, CH_2), 52.0 (2C, OCH_3), 120.4 (2C, =C_{IV}), 129.4 and 131.3 (2×4 CH ar), 129.1 and 144.7 (2 × 2 C_{IV}), 152.7 (2C, =CH), 166.7 (2C, C=O), 209.4 (2C, C=S); *ZE* isomer : 17.9 (SCH_3), 19.0 (SCH_3), 48.9 and 49.7 (2C, CH_2-N), 52.0 and 52.1 (2C, OCH_3), 120.3 (=C_{IV}, *Z*), 123.9 (=C_{IV}, *E*), 129.1 to 131.3 (CH ar + 2C_{IV}), 140.4 (C_{IV}, *E*), 144.7 (C_{IV}, *Z*), 147.2 (=CH, *E*), 151.8 (=CH, *Z*), 166.4 (C=O, *E*), 166.7 (C=O, *Z*), 209.4 and 209.6 (C=S).

MS : m/z = 560 (M^+, 1), 545 (2), 529 (3), 513 (62), 419 (13), 321 (17), 319 (16), 294 (11), 283 (25), 280 (17), 273 (21), 265 (19), 248 (32), 246 (56), 240 (33), 234 (24), 229 (48), 220 (57), 161 (39), 91 (57), 59 (42), 47 (22), 44 (100).

IR : 3 500-3 350, 3 070-2 800, 1 712, 1 604, 1 307, 1 273, 1 250, 1 098, 940, 830, 774, 709 cm^{-1}.

Anal calc for $C_{26}H_{28}N_2O_4S_4$: C : 55.68, H : 5.03, N : 5.00, S : 22.87; found : C : 55.80, H : 4.99, N : 5.04, S : 22.82.

18 : Eluent : CH_2Cl_2/petroleum ether (50:50), 31% yield, orange crystals, mp = 155-157°C, *ZZ* isomer only.

^{1}H NMR : 2.58 (6H, s), 3.25 to 3.50 (4H, m), 6.10 (2H, s), 7.1 to 7.9 (10H, m), 12.5 to 12.9 (2H, m).

^{13}C NMR : 17.0 (2C, SCH_3), 45.2 (2C, CH_2), 110.3 (2C, =CH), 127.9 and 129.0 (2 × 4 CH ar), 129.7 (2CH ar), 128.5 (2C, C_{IV}), 162.7 (2C, =C_{IV}), 207.1 (2C, C=S).

MS : m/z = 444 (M^+, 19), 429 (14), 397 (64), 234 (74), 222 (67), 188 (100), 175 (62), 171 (86), 162 (57), 144 (67), 104 (45), 77 (40), 61 (40).

19 : Eluent : CH_2Cl_2/petroleum ether (50:50), 33% yield, yellow crystals, mp = 165-168°C, *ZZ* isomer only.

^{1}H NMR : 2.58 (6H, s), 3.25 to 3.50 (4H, m), 6.05 (2H, s), 7.09 (2H, d, $^3J_{1H}$ = 8.5), 7.55 (2H, d, $^3J_{1H}$ = 8.5), 12.35 to 12.65 (2H, m).

^{13}C NMR : 17.0 (2C, SCH_3), 45.2 (2C, CH_2), 110.1 (2C, =CH), 124.3 (2C, C-Br), 129.4 and 132.1 (2 × 4 CH ar), 134.0 (2C, C_{IV}), 161.2 (2C, =C_{IV}), 208.5 (2C, C=S).

MS : m/z = 600/602/604 (M^+, 2/5/3), 585/587/589 (2/5/3), 567/569/571 (2/4/3), 553/555/557 (48/98/60), 474/476/478 (6/10/5), 473/475/477 (6/10/6), 312/314 (37/52), 300/302 (100/98), 266/268 (55/72), 252/254 (33/47), 240/242 (47/50), 222/224 (38/46), 182/184 (29/32), 146 (27), 102 (24), 61 (68).

IR : 3 550-3 300, 3 050-2 800, 1 584, 1 575, 1 553, 1 435, 1 305, 1 255, 1 138, 1 072, 1 009, 921, 831, 715 cm^{-1}.

20 : Eluent = CH_2Cl_2/petroleum ether (60:40), 40% yield, red crystals, mp = 121-124°C, ZZ/ZE = 95:5.

^1H NMR : ZZ isomer : 2.55 (6H, s), 3.35-3.60 (4H, m), 6.02 (2H, d, $^3J_{1H}$ = 7.9), 6.78 (2H, dd, $^3J_{1H}$ = 13.2, $^3J_{1H}$ = 7.9), 11.6 to 12.1 (2H, m); ZE isomer : 2.53 (3H, s), 2.65 (3H, s), 3.35-3.60 (4H, m), 6.04 (1H Z, d, $^3J_{1H}$ = 7.5), 6.28 (1H E, d, $^3J_{1H}$ = 13.1), 6.77 (1H, dd, $^3J_{1H} \sim 13$, $^3J_{1H}$ = 7.5), 7.52 (1H, dd, $^3J_{1H}$ = 13.1, $^3J_{1H}$ = 4.3), 11.6 to 12.1 (2H, m).

^{13}C NMR : ZZ isomer : 17.1 (2C, SCH_3), 50.0 (2C, CH_2), 106.6 (2C, =CH), 150.5 (2C, =CH), 210.6 (2C, C=S); ZE isomer : 17.1 (SCH_3), 18.9 (SCH_3), 50.0 (2C, CH_2), 106.4 and 106.6 (=CH), 148.6 and 150.5 (=CH), ~ 211 (C=S).

MS : m/z = 292 (M^+, 10), 277 (6), 245 (67), 201 (100), 175 (8), 165 (14), 146 (29), 133 (10), 112 (35), 99 (65), 95 (80).

IR : 3 600-3 300, 3 150-2 850, 1 610, 1 472, 1 247, 1 220, 1 120, 914, 777 cm^{-1}.

21 : Eluent : CH_2Cl_2/AcOEt (95:5), 35% yield, orange crystals, mp = 129-132°C, $ZZ/(Z_1E_2+Z_2E_1)$ = 82:18 (1 and 2 refer to dithiolylium salts precursors **1b** and **2b**).

^1H NMR : *superimposed signals for the three isomers* : 3.30 to 3.80 (CH_2-N, m), 3.86 (OCH_3, ~ s), 7.23 (C_6H_5), 7.32 (C_6H_4, ~ d, $^3J_{1H} \sim 7.9$), 7.92 (C_6H_4, ~ d, $^3J_{1H} \sim 7.9$), 12.30 to 12.70 (NH) : *specific signals* : Z_1Z_2 (82%) : 2.47 (6H, s), 6.82 (2H, d, $^3J_{1H}$ = 13); mixture Z_1E_2 + Z_2E_1 with Z_1E_2 as major isomer (18%) : 2.47, 2.56 and 2.64 (SCH_3), 6.77 (1H, d, $^3J_{1H}$ = 13), 7.41 (C_6H_5, s, Z_2E_1), 8.10 (2H, ~ d, $^3J_{1H} \sim 8.1$, Z_1E_2), 8.34 (1H, d, $^3J_{1H}$ = 13).

MS : m/z = 502 (M^+, 60), 500 (100), 453 (4), 441 (4), 406 (43), 350 (4), 251 (3), 245 (10), 232 (15), 186 (8), 171 (9), 147 (13).

IR : 3 060-3 830, 1 720, 1 618, 1 567, 1 481, 1 439, 1 312, 1 275, 1 115, 1 023, 995, 832, 767, 704 cm^{-1}.

23 : Eluent : CH_2Cl_2/hexane (50:50 to 100:0), 20% yield, ZZ/ZE = 85:15.

^1H NMR : ZZ isomer : 2.53 (6H, s), 3.35 to 3.60 (4H, m), 4.95 (4H, s), 6.86 (2H, d, $^3J_{1H}$ = 12.8), 7.40 (2 × 2H, d, $^3J_{1H}$ = 8), 8.04 (2 × 2H, d, $^3J_{1H}$ = 8), 12.35 to 12.75 (2H, m); ZE isomer, meaningful signals : 2.51 (3H, s), 2.61 (3H, s), 4.95 and 4.97 (2 × 2H, 2s), 6.81 (1H, d, $^3J_{1H}$ = 13), 8.35 (1H, d, $^3J_{1H}$ = 13).

Hydrolysis of compound **17**

A solution of lithium hydroxide (3 mmol) in water (10 mL) was added dropwise to a solution of **17** (1 mmol) in acetonitrile (8 mL). After further stirring for 24 h at room temperature and addition of aqueous HCl 1 M (10 mL), the reaction mixture was extracted with ethyl acetate. After drying the organic phase and evaporation of the solvent, **22** was obtained as yellow crystals (84% yield).

^1H NMR : 2.56 (3H, s), 7.36 (1H, d, $^3J_{1H}$ = 13.3), 7.46 (2H, d, $^3J_{1H}$ = 8.3), 8.15 (2H, d, $^3J_{1H}$ = 8.3), 9.57 (COOH), 14.85 (1H, d, $^3J_{1H}$ = 13.3).

MS : m/z = 254 (M^+, 32), 225 (13), 207 (33), 206 (28), 189 (12), 178 (46), 173 (40), 161 (36), 157 (95), 149 (26), 145 (25), 143 (26), 142 (30), 128 (25), 115 (22), 91 (100), 85 (35), 79 (29), 51 (27), 47 (25), 45 (56), 43 (50), 41 (35), 39 (43), 29 (41).

IR : 3 440, 3 150-2 800, 2 670, 2 550, 1 690, 1 603, 1 565, 1 505, 1 433, 1 295, 1 250, 1 075, 965, 895, 860, 800, 705 cm^{-1}.

Attempts for the synthesis of N_2S_2 ligands from 3,4-diaminobenzoic acid

A solution of (*t*-butyldimethyl)silyl-3,4-diaminobenzoate **24** (4.4 mmol) in ethanol (30 mL) was added to dithiolylium salt **15b** (4 mmol) in THF (50 mL) under sonication (maintained 1 h after the end of the addition). After drying and removal of the solvents, the residue was flash-chromatographed on florisil using methylene chloride as eluent to give **25** (orange crystals, 38% yield). Increasing the amount of **15b** to 10 mmol did not modify the obtained product (reaction at the *meta* amino function only). The same lack of reactivity of the 4-amino-group was observed in the reaction of **24** with **2b** under similar experimental conditions (obtention of **26**).

25 : ^1H NMR = 0.28 (6H, s), 0.90 (9H, s), 2.57 (3H, s), 4.25 (2H, NH_2), 6.27 (1H, d, $^3J_{1H}$ = 8.5), 6.7 (1H ar, d, $^3J_{1H}$ = 8.4), 7.33 (1H, dd, $^3J_{1H}$ = 12.7, $^3J_{1H}$ = 8.5), 7.64 (1H ar, d, $^3J_{1H}$ = 8.4, $^4J \sim 1$), 7.76 (1H ar, ~ s), 13.3 (1H, d, $^3J_{1H}$ = 12.7).

26 : ^1H NMR : 0.38 (6H, s), 0.99 (9H, s), 2.55 (3H, s), 3.94 (3H, s), 4.36 (2H, NH_2), 6.79 (1H ar, d, $^3J_{1H}$ = 8.5), 7.45 (1H, d, $^3J_{1H}$ = 12.7), 7.47 (2H ar, ~ d, $^3J_{1H}$ = 8.5), 7.69 (1H ar, d, $^3J_{1H} \sim 8.4$), 7.83 (1H ar, ~ s), 8.08 (2H ar, ~ d, $^3J_{1H} \sim 8.5$), 14.06 (1H, d, $^3J_{1H}$ = 12.7).

^{13}C NMR : Z *isomer* (93%) : −4.7 (2C), 17.8 (C_{IV}), 18.2 (SCH_3), 25.7 (3C), 52.2 (O-CH_3), 115.5, 120.8 and 128.7 (3CH ar), 122.4, 122.6, 126.3, 129.5, 142.0 and 144.6 (C_{IV}), 129.7 and 131.4 (2 × 2 CH ar), 145.0 (CH=), 166.1 (C=O), 166.8 (C=O), 211.2 (C=S); E *isomer* (7%) : additional signals at 116.2, 118.9, 130.4 (3 CH ar), 123.0, 136.3, 142.6 (C_{IV}), 212.2 (C=S).

Synthesis of N_2S_2 ligands from 1,3-diaminopropan-2-ol

• *Typical experimental procedure for preparation of ligand* **29** *(dimethyl 2-hydroxypropane-1,3-diyl-diamino-3′,3′-bis-prop-2-enedithioate)*

A solution of 1,3-diamino-propan-2-ol (11 mmol) in ethanol (70 mL) was added dropwise at room temperature to a suspension of **15b** (10 mmol) in THF. After 2 h, the reaction mixture was dissolved in methylene chloride (100 mL) and washed with water (3 × 100 mL) before decantation and drying of the organic layer. After removal of the solvent, the residue was chromatographed on silica gel (eluent : CH_2Cl_2/AcOEt : 100:0 to 80:20). Compound **29** was obtained as a red oil (60% yield). Compounds **27** and **28** were obtained similarly from **1b** and **10b**.

27 : Orange crystals, mp = 86-88°C, 53% yield, $ZZ/ZE/EE$ = 87:12:1.

^1H NMR : ZZ isomer : 2.44 (6H, s), 3.11 (1H, hydroxyl), 3.37 (4H, m), 3.89 (1H, m), 6.93 (2H, d, $^3J_{1H}$ = 13.2), 7.20 to 7.40 (10H, m), 12.5 (2H, $^3J_{1H}$ = 13.2, $^3J_{1H}$ = 6.6); ZE isomer : additional signals at : 2.44 (3H, s), 2.55 (3H, s), 6.87 (1H, d, $^3J_{1H}$ = 13.7), 8.41 (1H, d, $^3J_{1H}$ = 13.7); EE isomer : signal at 8.36 (d, $^3J_{1H}$ = 14.3).

^{13}C NMR : ZZ isomer : 17.9 (2C, SCH_3), 52.3 (2C, CH_2), 70.3 (C-O), 121.5 (2C, $=C_{IV}$), 127.6 (2CH ar), 128.3 and 131.4 (2 × 4 CH ar), 140.2 (2C, C_{IV}), 153.2 (2C, =CH), 209.4 (2C, C=S); ZE isomer : 17.9 (SCH_3), 19.2 (SCH_3), 51.5 and 52.3 (2C, CH_2), 70.5 (C-O), 121.5 and 124.8 ($2C_{IV}$), 127.6, 128.3, 128.9, 129.1, 129.4 and 131.4 (10CH ar), 130.1 and 132.2 ($2C_{IV}$), 148.4 and 153.0 (2, =CH), ~ 209.4 (C=S).

IR : 3 550-3 200, 3 080-2 850, 1 617, 1 600, 1 443, 1 404, 1 312, 1 242, 1 108, 950, 911, 760, 733, 595 cm^{-1}.

28 : Orange crystals, mp = 94-96°C, 35% yield, ZZ/ZE = 90:10.

^{1}H NMR : ZZ isomer : 2.55 (6H, s), 3.05 (1H, hydroxyl), 3.35 (4H, m), 3.79 (1H, m), 6.10 (1H, ~ s), 7.15 to 7.70 (10H, m), 12.58 (2H, ~ t, $^3J_{2H}$ = 5.9) ; ZE isomer : meaningful signal at 6.83 (1H, s).

^{13}C NMR : ZZ isomer : 17.1 (2C, SCH_3), 48.5 (2C, CH_2), 70.3 (C-O), 110.2 (2C, =CH), 128.8 and 129 (2 × 4 CH ar), 129.5 (2CH ar), 135.3 (2C, C_{IV}), 163.2 (2C, =C_{IV}), 205.8 (2C, C=S).

MS : m/z = 474 (M^+, 3), 459 (3), 427 (48), 321 (18), 252 (11), 222 (12), 220 (15), 201 (24), 190 (21), 176 (69), 174 (61), 162 (35), 147 (37), 105 (100), 91 (62), 77 (52), 59 (69).

IR : 3 500-3 100, 3 100-2 800, 1 600, 1 585, 1 560, 1 516, 1 481, 1 442, 1 307, 1 258, 1 133, 1 024, 916, 769, 704 cm^{-1}.

29 : Red oil, 60% yield, ZZ/ZE = 95:5.

^{1}H NMR : ZZ isomer : 2.53 (6H, s), 2.95 to 4.10 (5H + hydroxyl, bm), 6.04 (2H, d, $^3J_{1H}$ = 7.8), 6.86 (2H, dd, $^3J_{1H}$ = 13.3, $^3J_{1H}$ = 7.8), 11.82 (2H, m) ; ZE isomer : meaningful signal at 6.29 ppm ($^3J_{1H}$ = 12.6).

^{13}C NMR : ZZ isomer : 17.7 (2C, SCH_3), 52.1 (2C, CH_2), 70.2 (C-O), 106.5 (2C, =CH), 151.5 (2C, =CH), 209.7 (2C, C=S) ; ZE isomer : 17.1, 17.9, 52.1 (2C), 69.3, 106.5, 109.9, 149.1, 151.5, 207.2, 209.7.

MS : m/z = 322 (M^+, 22), 307 (6), 289 (12), 275 (100), 216 (26), 189 (10), 169 (46), 142 (31), 128 (33), 125 (71), 114 (65), 106 (35), 101 (42), 100 (76), 98 (77), 91 (22), 86 (31), 71 (42), 61 (29), 59 (53), 45 (22).

IR : 3 550-3 200, 3 044, 2 989, 2 918, 1 614, 1 583, 1 475, 1 229, 1 067, 1 008, 1 000, 940, 846, 806, 629 cm^{-1}.

Anal calc for $C_{11}H_{18}N_2OS_4$: C : 41.09, H : 5.61 ; found, C : 40.88, H : 5.33.

Synthesis of N_2S_2 ligands having a functionalized linker

• *Preparation of ligand* **30** *(1,3-bis{[3-(methylthio)-3-thioxoprop-1-enyl]amino}propan-2-yl butanedioic acid monoester*

Succinic anhydride (157 mg, 1.57 mmol) and 19.5 mg of DMAP (10% mol) were added to 480 mg of **29** (1.5 mmol) in methylene chloride (15 mL). After reflux during 15 h and removal of the solvent, the residue was purified on silica gel (eluent : CH_2Cl_2/AcOEt = 90:40 to 50:50) affording compound **30** (red crystals, mp = 162-164°C, 0.23 g, 37% yield, ZZ/ZE = 95:5).

30 : ^{1}H NMR : ZZ isomer : 2.55 (6H, s), 2.69 (4H, ~ s), 3.50 (4H, m), 5.02 (1H, m), 6.04 (2H, d, $^3J_{1H}$ = 8.1), 6.81 (2H, dd, $^3J_{1H}$ = 13, $^3J_{1H}$ = 8.1), 8.57 (1H, hydroxyl), 11.78 (2H, $^3J_{1H}$ = 13, $^3J_{2H}$ = 6.5) ; ZE isomer : meaningful signal at 6.28 (1H, d, $^3J_{1H}$ = 12.7).

^{13}C NMR : ZZ isomer : 17.1 (2C, SCH_3), 28.8 (CH_2), 29.0 (CH_2), 48.7 (2C, CH_2), 71.5 (CH-O), 106.7 (2C,=CH), 150.7 (2C,=CH), 171.4 (C=O), 176.8 (C=O), 210.7 (2C, C=S) ; ZE isomer : 17.1 (SCH_3), 17.9 (SCH_3), 29.0 (2C), 48.9 (2C), 71.3 (CH-O), 106.7 and 109.8 (=CH), 149.2 and 152.3 (=CH), 172.4 (C=O), 176.8 (C=O), 210.7 and 217.7 (C=S).

MS : m/z = 348 (47), 301 (100), 254 (19), 210 (8), 195 (8), 164 (8), 149 (17), 106 (43), 69 (17), 59 (55).

IR : 3 600-2 500, 1 728, 1 615, 1 416, 1 252, 1 206, 1 155, 958, 922, 832, 620 cm^{-1}.

• *Preparation of ligand* **31** *(1,3-bis{[3-(methylthio)-3-thioxoprop-1-enyl]amino}propan-2-yl* N*-succinimidyl butanedioate)*

N-Hydroxysuccinimide (138 mg, 1.2 mmol) and 13 mg DMAP (10% mol) were added to a stirred solution of **30** (422 mg, 1 mmol) in methylene chloride (20 mL) before addition of dicyclohexylcarbodiimide (206 mg, 1.1 mmol) in small portions. After stirring during 15 h, the reaction mixture was concentrated and chromatographied on silica gel (eluent : CH_2Cl_2/AcOEt = 90:10). The desired ligand **31** with an "NHS" ester function on the linker was obtained as red crystals (mp = 194-196°C, 0.23 g, 45% yield, ZZ/ZE = 96:4).

31 : ^{1}H NMR : ZZ isomer : 2.55 (6H, s), 2.83 (8H, bs), 3.52 (4H, ~ t, $^3J_{1H}$ ~ 6), 5.04 (1H, $^3J_{4H}$ = 5.5), 6.05 (2H, d, $^3J_{1H}$ = 8.1), 6.82 (2H, dd, $^3J_{1H}$ = 13, $^3J_{1H}$ = 8.1), 11.8 (2H, $^3J_{2H}$ = 6.3, $^3J_{1H}$ = 13) ; ZE isomer : additional signal : 6.27 (1H, d, $^3J_{1H}$ = 10.5).

^{13}C NMR : ZZ isomer : 16.9 (2C, SCH_3), 25.6 (2C, CH_2), 26.3 (CH_2), 28.8 (CH_2), 48.7 (2C, N-CH_2), 72.0 (C-O), 106.7 (2C, =CH), 150.7 (2C, =CH), 167.5 (C=O), 168.9 (2C, C=O), 170.0 (C=O), 210.7 (C=S) ; ZE isomer : additional signals : 17.2 (SCH_3), 49.0 (N-CH_2), 71.6 (C-O), 110.1 (=CH), 148.7 (=CH), 167.5 (C=O).

MS : m/z = 403 (1), 338 (2), 321 (2), 288 (9), 241 (24), 233 (5), 148 (12), 142 (22), 115 (17), 94 (23), 47 (70), 45 (100).

IR : 3 550-3 200, 3 100-2 850, 1 742 and 1 719, 1 618, 1 620, 1 477, 1 259, 1 211, 1 154 to 1 071, 920, 805, 650 cm^{-1}.

• *Preparation of ligand* **32**

Compound **29** (322 mg, 1 mmol) 13 mg of DMAP (10% mol) and 256 mg of DCC were added at 0°C to 189 mg (1.1 mmol) of 3-[(N-*tert*-butoxycarbonyl)amino)]propanoic acid in methylene chloride (30 mL). After warming to room temperature and stirring over 3 h, dicyclohexylurea was removed by filtration and the organic phase concentrated before purification on silica gel (eluent : CH_2Cl_2/AcOEt = 95:5). Compound **32** (190 mg) was obtained as red crystals (mp = 125-127°C, 40% yield, ZZ/ZE = 93:7).

32 : ^{1}H NMR : ZZ isomer : 1.46 (9H, s), 2.59 (6H, s), 2.50-2.61 (2H, m), 3.38 (2H, ~ t, $^3J_{2H}$ = 5.2), 3.53 (4H, m), 5.02 (2H, m), 6.06 (2H, d, $^3J_{1H}$ = 7.1), 6.72 (2H, dd, $^3J_{1H}$ = 11.7, $^3J_{1H}$ = 7.1), 11.7 (2H, dt, $^3J_{1H}$ = 11.7, $^3J_{2H}$ = 6.8) ; ZE isomer : additional signal : 2.68 (3H, s), 6.33 (1H, d, $^3J_{1H}$ = 10.9).

^{13}C NMR : ZZ isomer : 17.0 (2C, SCH_3), 28.3 (3C, CH_3), 34.8 (CH_2), 36.3 (CH_2), 48.9 (2C, CH_2), 71.4 (CH-O), 79.4 (C_{IV}-O), 106.6 (2C, =CH), 150.6 (2C, =CH), 155.7 (C=O), 171.2 (C=O), 210.8 (2C, C=S) ; ZE isomer : 17.00 (SCH_3), 17.8 (SCH_3), 28.3 (3C, CH_3), 34.6 (CH_2), 36.3 (CH_2), 48.9 and 49.5 (2C, CH_2), 71.4 (CH-O), 79.6 (C_{IV}-O), 106.6 and 110.0 (2C, =CH), 148.9 and 150.6 (2C, =CH), 156.1 (C=O), 171.3 (C=O), 210.8 and 218.4 (C=S).

MS : m/z = 493 (M^+, 1), 446 (3), 390 (2), 284 (2), 148 (5), 106 (34), 59 (100), 57 (49), 47 (43).

IR : 3 550-3 200, 3 080-2 890, 1 738, 1 732, 1 700, 1 618, 1 575, 1 475, 1 251, 1 160, 1 124, 920, 767 cm^{-1}.

Synthesis of bifunctional linkers

• *Synthesis of* N*-succinimidyl monosuccinate* **33**

A mixture of succinic anhydride (5 g) and *N*-hydroxysuccinimide (40 g) in methylene chloride (100 mL) was refluxed during 12 h. After cooling and filtration of *N*-hydroxysuccinimide, the filtrate was concentrated under vacuum affording **33** (white solid, 9.03 g, 84% yield).

33 : ^{1}H NMR (acetone-d_6) : 2.78 (4H, s), 2.97 (2H, s), 3.15 (2H, s), 8.9 (1H, COOH).

^{13}C NMR (acetone-d_6) : 26.0 (2C, CH_2), 28.7 (CH_2), 29.2 (CH_2), 169.1 (C=O), 170.5 (C=O), 172.9 (2C, C=O).

MS : m/z = 115 (34), 101 (3), 99 (7), 87 (22), 70 (6), 59 (8), 56 (33), 55 (37), 43 (10), 42 (16), 28 (100).

IR : 3 600-2 500, 1 819, 1 781, 1 723, 1 715 (C=O very strong), 1 215, 1 095-1 060 (C-O), 930, 645 cm^{-1}.

• *Synthesis of* N-*succinimidyl 3-(chlorocarbonyl) propanoate* **34**

A mixture of **33** (8.62 g, 40 mmol) and thionyl chloride (95.4 g, 0.8 mol) was refluxed during 3 h before elimination of excess thionyl chloride. After several washings with ether, compound **34** was obtained as a white solid (7.83 g, 91% yield).

34 : ^{1}H NMR : 2.85 (4H, s), 3.05 (2H, ~ t, $^3J_{2H}$ ~ 6), 3.31 (2H, ~ t, $^3J_{2H}$ ~ 6).

^{13}C NMR : (DMSO-d_6) : 25.15 (CH_2), 25.3 (CH_2), 28.7 (2C, CH_2), 167.7 (C=O), 169.9 (C=O), 173.5 (2C, C=O).

• *Synthesis of compounds* **35** *and* **36**

The experimental procedures used to obtain these compounds were similar to those used for **33** and **34** (succinic anhydride was replaced by 2,3-dimethylmaleic anhydride).

35 : ^{1}H NMR : 2.0 (6H, s), 2.63 (4H, s), 8.50 (COOH).

^{13}C NMR : 9.4 (2C, CH_3), 26.0 (2C, CH_2), 141.5 (2C, $=C_{IV}$), 167.3 (2C, C=O), 172.9 (2C, C=O).

MS : m/z = 116 (36), 115 (54), 100 (6), 99 (14), 88 (19), 87 (31), 70 (13), 59 (13), 55 (77), 44 (13), 43 (18), 42 (30), 28 (100).

36 : ^{1}H NMR (acetone-d_6) : 2.04 (6H, s), 2.66 (4H, s).

^{13}C NMR (acetone-d_6) : 9.27 (2C, CH_3), 25.8 (2C, CH_2), 141.4 (2C, $=C_{IV}$), 167.2 (2C, C=O), 172.8 (2C, C=O).

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