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Convenient synthesis of thiols and disulfides in the polyfluorinated series incorporating a butylic spacer

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Abstract

New fluorinated thiols $R_F(CH_2)_pSH$ and disulfides $[R_F(CH_2)_pS]_2$ containing a butylic spacer ($p=4$) between the perfluorinated part and the thiol (or disulfide) function were easily obtained in good yields with a purity higher than 98%. This allows us to obtain homologues ($p>4$) for their use as synthetic intermediates or as constituents for molecular organized systems.   2000 Elsevier Science Ltd. All rights reserved.

The association of a perfluorinated tail with a thiol or disulfide functional group within the same molecular shape leads to the conjugation of the intrinsic properties of these two parts (the specific reactivity of the mercaptan function and its affinity for metallic substrates on one hand, and the chemical and thermal inertness with hydrophobic and oleophobic properties of the perfluorinated tail on the other hand), in order to use these thiol or disulfide compounds as part of a highly fluorinated series in the field of materials and to investigate their physical properties. The use of perfluorinated thiols or disulfides results from the fact that they form self-assembled organic monolayers.¹ These materials are used in electronic devices (as low voltage connector coatings), in electronics (for hard disk lubrication) or else in biology, including the development and understanding of membrane models. The resulting materials show improved performance: better chemical and thermal stability,² a decrease of the surface tension of the coating surface and low wetting,³ and an increase of the resistance against frictional forces.⁴ Moreover, mercaptans also have the advantage of showing excellent properties as intermediates for the synthesis of a large range of elaborated molecules, such as surfactants^{5,6} or polymers for fire retardants,^{7,8} liquid crystals,⁹ biocides^{10–12} or blood substitutes,¹³ etc.

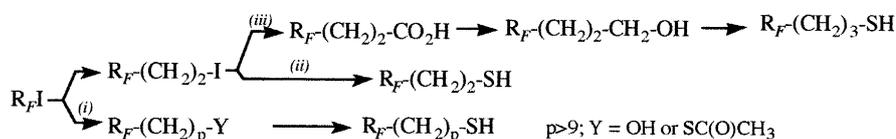
However, even if the presence of the thiol function gives remarkable and unique properties for obtaining molecular or supramolecular organized systems, it is worth noting that these properties are exacerbated by the nature and the lengthening of the hydrocarbon spacer $(CH_2)_p$ bonding the thiol function to the perfluorinated tail (R_F).¹⁴ In fact, the interaction between perfluorinated tails is relatively weak compared to their homologous hydrocarbon tails, and the order obtained in the layer within

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organized systems is, in this case, governed, amongst others, by the lengthening of this methylenic spacer which induces a favourable phase microsegregation. Therefore, it is necessary to control and to develop new strategies for obtaining thiols or disulfides within a perfluorinated series showing a variable number of methylene moieties. The aim of this work is to describe a reliable method for obtaining fluorinated thiols or disulfides with the general formula $R_F(\text{CH}_2)_p\text{SH}$ and $[\text{R}_F(\text{CH}_2)_p\text{S}]_2$ where $R_F = F$ -butyl, F -hexyl or F -octyl and with $p=4$ but also to give the possibility of reaching higher homologues ($p>4$).

In spite of the increasing interest in highly fluorinated thiols and disulfides, their preparation has received, until now, little attention. Numerous difficulties have arisen against the lengthening of the hydrocarbon segment to be introduced between the sulfur atom and the perfluorinated chain (p value). Furthermore, these difficulties are increased by the small number of available raw materials within the F -alkyl series. The available structures described up to now are developed principally from two raw materials (cf. Scheme 1):

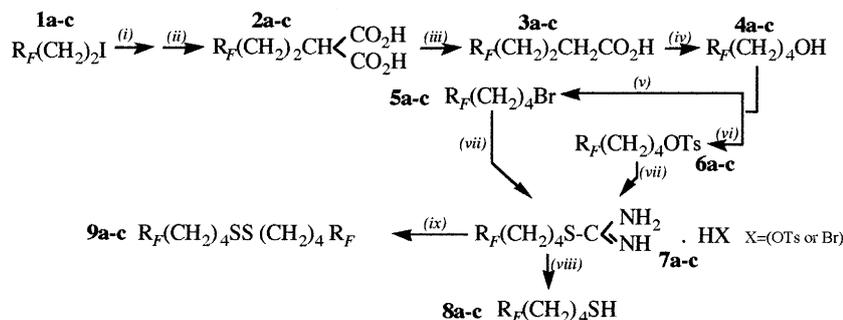
- either perfluorinated iodides ($R_F\text{-I}$) into which the introduction of the methylenic spacer is achieved from a radical reaction,¹⁵ and which are then converted into the thiol. This leads to the possibility of reaching a methylenic moiety number (p) superior to 9^{16,17} (cf. pathway *i*);



Scheme 1.

- or the 2- F -alkylethyl iodides which lead directly to the thiols, either with $p=2$,¹⁸ cf. pathway *ii*, under phase transfer catalysis¹⁹ conditions, or with $p=3$ via the acids obtained by the Grignard reaction (cf. pathway *iii*).²⁰

Hence, the increase in length of the methylenic spacer in the fluorinated series is a relatively delicate procedure. The strategy of the synthesis involved is based upon the malonic ester condensation. In order to carry out this first step we have improved, and rendered specific, the malonic ester condensation within the fluorinated series; this requires some particular specifications.^{21–25} The overall steps are described in Scheme 2.



Scheme 2. a,b,c= R_F value, i.e. C_4F_9 , C_6F_{13} , C_8F_{17} ; (i) $\text{CH}_2(\text{CO}_2\text{Et})_2/\text{THF}/\text{K}_2\text{CO}_3$, 70°C, 24 h; (ii) $\text{KOH}/\text{EtOHabs}$, 10–15 h, 80°C; (iii) 195°C, 3 h; (iv) $\text{Et}_2\text{O}/\text{AlLiH}_4$, 40°C, 12 h; (v) 0°C, $\text{PBr}_3/\text{Et}_2\text{O}$, 40°C, 12 h; (vi) TsCl/EtOH , 70°C, 1 h; (vii) thiourea/ EtOHabs ., 80°C, 20 h; (viii) NaOH (2 equiv.), N_2 , 70°C, 2 h; (ix) NaOH (10 equiv.), 70°C, 12 h

The monosubstituted malonic diesters (65–70%) are obtained by nucleophilic substitution between 2- F -alkylethyl iodides, **1a–c** and the dialkyl malonate, according to the reaction plan. In opposition to previous work described in the literature,^{21,22} it appears a necessary condition to use a weak alkaline medium in order to minimize the formation of byproducts. The presence of a strong base promotes

the elimination reaction and the possibility of a second alkylation of the malonate. Hence, anhydrous potassium carbonate was used in order to avoid the elimination of hydrogen iodide from the starting materials, which would lead to the build-up in formation of 2-*F*-alkylethene. It is important to work with highly anhydrous solvents and reagents under an inert atmosphere to avoid the build-up in the reaction medium of hydroxyl ions liable to lead to the byproducts previously cited. The formation of disubstituted compounds (8–10%) is not, however, to be completely avoided. It is worth noting with regard to this nucleophilic substitution reaction that it is also possible to use 18-crown as a crown ether catalyst,^{26,27} to significantly reduce the reaction time (6 h compared to 24 h for the non-catalyzed reaction). The diacid salts (89–93%) are easily obtained by saponification of the corresponding monosubstituted malonic diesters, in an alkaline medium under controlled heating conditions.²⁷ Acidic hydrolysis of the salts allows us to obtain the corresponding carboxylic diacids (**2a–c**). The 4-*F*-alkylbutanoic acids (**3a–c**) are obtained in high yield (97–98%) by decarboxylation of the corresponding geminated diacid at high temperature. The alcohols (**4a–c**) are obtained by the reduction of the previous acids (96–97%) using lithium aluminium hydride. These alcohols allow us to obtain the corresponding bromides (64–72%, **5a–c**) or tosylates (**6a–c**).

The production of thiols (**8a–c**) can be carried out according to several routes. Most of the methods used for the synthesis of thiols, and without spacers different from the methylenic unit,²⁸ either within the hydrocarbon or fluorinated series, involve the high nucleophilicity of the sulfide ion. The action of sodium thiosulfate on the halogenated compounds,²⁹ or of thioacetic acid on the alkene in a two-step process,³⁰ or on 2-*F*-alkylethyl iodide,¹⁸ gives thiols within controlled pressure and temperature conditions. The disulfides can also be reduced to thiols with mild reducing reagents such as zinc in a diluted acid media,³¹ by heating in alkaline media,³² or by hydrogenolysis.³³ The yields of thiol conversion are mainly dependent on the method employed but it is possible in some cases to record the competitive formation of sulfide or disulfide byproducts. We have, therefore, chosen a reliable method from an industrial point of view which allows us to obtain high yields. Moreover, this method allows the use of phase transfer catalysis, previously described by our team, to improve the access to functionalized 2-*F*-alkylethyl compounds.¹⁹ The action of thiourea on the brominated or tosylated derivatives within an anhydrous ethanolic medium leads to the obtention of the isothiuronium salts (95–96%, **7a–c**).

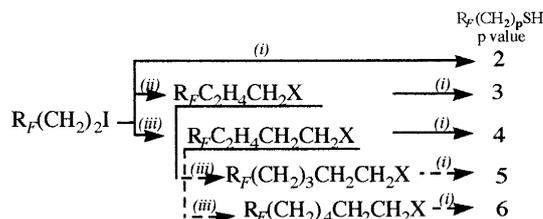
Hydrolysis of isothiuronium salts in alkaline medium (2 equiv.) under a controlled atmosphere gives thiols (88–90%) which can be considered as new raw materials within the *F*-alkylated series. In spite of precautions taken, however, this method does not allow the formation of disulfide in low proportions (<5%) easily separable by distillation. Hydrolysis of these isothiuronium salts in an excess of base (10 equiv.) over atmospheric oxygen and with an increased heating time (overnight), compared to the thiol procedures (2 h), leads to disulfides (**9a–c**) in higher yields (93–96%). The physicochemical characteristics of thiols and disulfides are reported in Table 1.

Table 1
Preparation of thiols and disulfides with a butylic spacer

Cpd N°	R _F value	mp / (bp /3.10 ⁻² mb)	Yield ^(a)	Yield ^(b)
7a	C ₄ F ₉	(40 °C)	89	32
7b	C ₆ F ₁₃	(58 °C)	88	35
7c	C ₈ F ₁₇	(76 °C)	90	31
8a	C ₄ F ₉	33-34 °C	93	33
8b	C ₆ F ₁₃	61-62 °C	94	37
8c	C ₈ F ₁₇	93-94 °C	96	33

(a) from the final step; (b) from 2-*F*-alkylethyl iodides (7 steps)

Lastly, the achievement of higher homologues with $p > 4$ is effective when using a similar pathway of a recurrent³⁴ synthetic nature, as summarized in Scheme 3.



Scheme 3. X=I, Br or OTs, (i) see Refs. 18 and 19 and this work; (ii) see Ref. 20; (iii) this work

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