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Oligomerisation reactions of beta substituted thiols in water†

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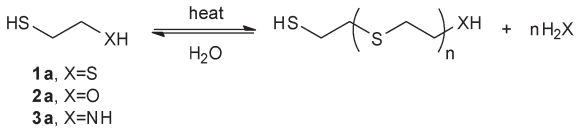
Beta substituted thiols and various derivatives containing the HX–C–C–SH motif oligomerise in water, preferably in the presence of a carbonate salt. The reaction yields oligomers consisting of one thiol end group, a thiaethylene backbone and an additional terminal group corresponding to the starting material used. Mechanistic studies, as well as the scope of substrates and products of these new promising condensation processes, are presented. In addition, strong nucleophiles were also reacted with mercaptoethanol under simple reaction conditions, leading to the selective formation of more complex molecules.

Synthetic methodologies for the construction of organic molecules by atom efficient procedures, devoid of environmentally harmful catalysts and using pure water as the solvent, are scarce.[1] The formation of heteroatom–carbon bonds elicits a high interest in modern organic synthesis, including the carbon–sulphur linkage whose importance is well appreciated in the biological realm and of course in many synthetic chemical systems, *i.e.* compounds formed by the ubiquitous thiol-ene "click" reactions,[2] macromolecular architectures,[3] macrocycles and supramolecular hosts,[4] *etc.* Thus, the development of a green, facile and direct synthetic route towards carbon–sulphur bond formation presents great appeal.

In a recent report we disclosed the unexpected polycondensation of 1,2-ethanedithiol (**1a**), both in water and organic solvents, selectively yielding short oligomers.[5] Now, we present new reactions based on other 1,2-heterothiol derivatives, namely mercaptoethanol (**2a**) and cysteamine (**3a**) (Scheme 1), and expand their scope for the generation of multiple carbon–sulphur bonds. Explicitly, heating these substrates in water under mildly basic conditions resulted in oligomerisation, without the need for metal catalysts, costly reagents, hazardous mustard by-products or environmentally undesirable solvents in a one-step procedure.[6] Thus, reaction of **2a** readily afforded a series of linear ω-mercaptopolythiaethylene-1-ol oligomers with one hydroxyl and one thiol end group (Fig. 1).



Scheme 1 Reaction of **1–3a** in water.

The reactions were mainly conducted in a microwave reactor; conventional heating gave similar results although longer reaction times were needed. Notably, the optimal solvent for the reaction was water. Reactions carried out neat or in ethylene glycol gave good yields of oligomers (similar to water), however, other organic solvents proved less efficient. The overall reaction observed was a substitution of the hydroxyl terminal by a thiolate nucleophile, with the only by-product generated being water. Remarkably, this simple reaction has not been reported in the chemical literature;[7] despite the fact that mercaptoethanol is a widely used molecule,

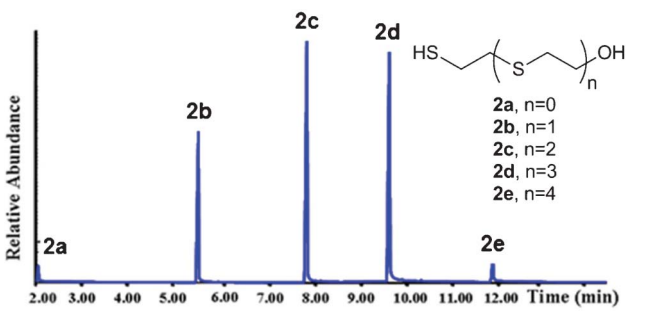


Fig. 1 GC-MS of the organic extract (CH_2Cl_2) after the reaction of 0.4 M **2a** and 1.2 M K_2CO_3 in water, 60 min, 120 °C in a microwave reactor.

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† Electronic Supplementary Information (ESI) available: NMR spectra of **2b–d**, **3b–c**, **2a–d$_2$** and isotope labeling experiments. Additional reaction results of: **2a** and **3a** in different solvents, **2a** with different additives, other dithiols and mercaptoalkanols and cross reactions with nucleophiles. See DOI: 10.1039/c2ra22131d

‡ These authors contributed equally to this work.

Table 1 Conversion of **2a** to oligomers with various additives[a]

Entry	Reagent	Conversion[b] 2a	2b	2c	2d	2e
1	No reagent	10%	53%	36%	1%	—
2	K_2CO_3	14%	40%	35%	10%	1%
3	Cs_2CO_3	15%	41%	34%	9%	1%
4	Na_2SO_3[c]	1%	38%	51%	10%	—
5	$NaHCO_3$	10%	42%	40%	8%	—
6	NaOH[d]	70%	30%	—	—	—
7	Triethylamine	63%	37%	—	—	—
8	Acetic acid[e]	64%	10%	—	—	—
9	KNO_3	11%	58%	31%	—	—
10	KI[f]+ K_2CO_3	16%	43%	30%	11%	—
11	BHT[g]+ K_2CO_3	7%	35%	37%	21%	—

[a] Reactions were carried out in water, in a microwave reactor at 120 °C for 60 min, 0.4 M **2a** and 3 eq. of chosen reagent. [b] Area % by GC-MS. [c] 20 min reaction. [d] pH = 13. [e] pH = 2; 26% esterification. [f] 1 eq. [g] 0.1 eq.

known for more than 150 years, and the only requirement for oligomerisation is heating in water.

To further analyse the reaction behaviour, the addition of different bases, salts and radical scavengers was probed. As shown in Table 1, the nature of the carbonate bases did not significantly modify the oligomeric product distribution and even the reaction in pure water (triply distilled) produced a fair amount of dimer **2b** and trimer **2c**. The addition of neutral salts, sodium or potassium, did not affect the outcome of the reactions. Moreover, sodium sulphite was just as efficient as carbonate. However, the use of strong bases, such as sodium hydroxide or weak organic bases, like triethylamine, significantly hindered oligomerisation. Acidification with acetic acid not only led to almost a complete arrest of oligomerisation, but also to the partial formation of the expected esters. The addition of butylhydroxytoluene (BHT), introduced to examine whether radical intermediates could be at play, also had no significant influence on the reaction.

One of the most attractive aspects of this part of the research is the quite straightforward methodology developed to obtain valuable oligomers possessing a thiol end group and an alcohol end group. For this reason we performed a larger scale reaction designed to provide useful quantities of the dimer and trimer compounds (**2b** and **2c**). This preparative run (see ESI for details†) easily afforded 1.8 g of pure compound **2b** and 1.0 g of pure compound **2c** by simple distillation under vacuum of the reaction products after work-up and evaporation of the starting material **2a**.

Having shown the reactivity of mercaptoethanol, it was compelling to probe cysteamine (**3a**), a universally used β-nitrogen sulphide. Oligomeric homologues of **3a** could be potentially useful in the preparation of lantibiotic homologues,[8] chelating agents and metal nanoparticle ligands.[9] A clean reaction, yielding the anticipated oligomers, was observed just by heating **3a** in water without the need to add a carbonate base (see ESI†). The leaving group in this case was ammonia, probably derived from the protonated form of **3a**.

In order to expand the reaction scope and obtain further insights into the mechanism in hand, other substrates were

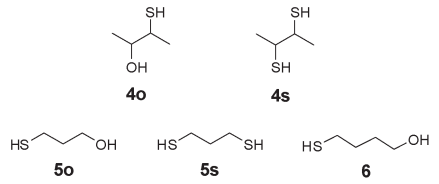


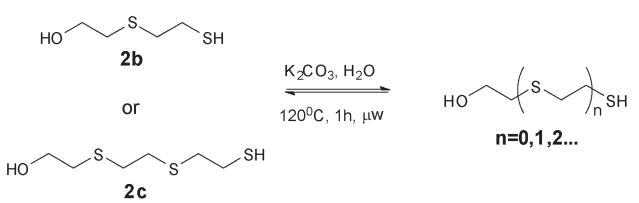
Fig. 2 Additional mercaptan substrates.

investigated (Fig. 2). Thus, diastereomeric mixtures of 2,3-mercaptobutanol and 2,3-butanedithiol (**4o** and **4s** respectively) were subjected to the same reaction conditions. These substituted homologues reacted to give oligomeric products similar to the basic parent molecules. Interestingly, the reaction with **4s** also afforded significant amounts of hydroxyl terminated products.

An additional parameter that was looked into was the number of methylene units between the sulphur atom and the additional heteroatom. Accordingly, 1,3-mercaptopropanol and 1,3-propanedithiol (**5o** and **5s**) were also heated in the presence of carbonate. These substrates reacted only sluggishly in comparison to the ethylene spaced counterparts, with very poor conversions to dimers. Nonetheless, even with this longer spacer, the condensation could be still observed and constitutes a novel reaction. To complete the series, 1,4-mercaptobutanol (**6**) did not react under all the conditions tried (see ESI†).

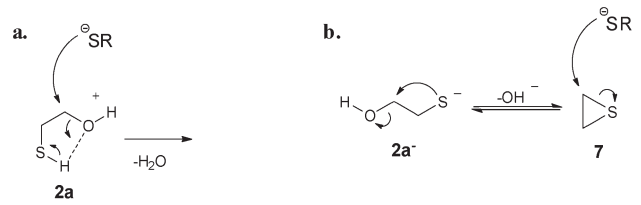
In an attempt to clarify the underlying mechanism of the oligomerisation reactions, several experiments were performed on the mercaptoethanol system. First, reactions starting from higher oligomers were carried out to analyse possible equilibrium processes. Thus, isolated oligomers **2b** and **2c** were each separately reacted in water with a carbonate base. As observed in Table 2, the oligomer product distributions starting from **2b**, **2c** or **2a** (Table 1, entry 2) are all similar. These results depict a system in a thermodynamic equilibrium, where thioether formation is reversible and the disproportionation of oligomers is apparent. This discovery may create a new entry into the realm of dynamic covalent combinatorial chemistry, and allow for selected templates to guide product selectivity.[10]

Table 2 Product distributions starting from **2b** and **2c**



Starting from	Product distribution[a] 2a	2b	2c	2d	2e
2b	<1%	27%	48%	25%	—
2c	1%	21%	43%	35%	<1%

[a] Reactions were heated at 120 °C in a microwave reactor, in water with 3 eq. K_2CO_3 for 60 min. Results in % area by GC-MS.



Scheme 2 Suggested condensation mechanisms. **a**. Hydrogen bond activated substitution. **b**. Intramolecular thiirane **7** formation.

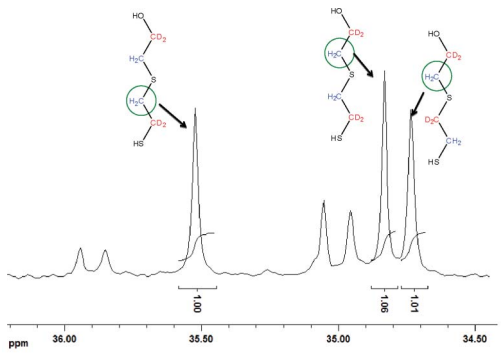


Fig. 3 ^{13}C NMR spectrum of the reaction of **2a–d$_2$** in water. Only **2b–d$_4$** signals are labeled (smaller peaks belong to **2c–d$_6$**).

At this point, we envisaged two plausible mechanisms that could govern the oligomerisation reaction. One may be a straightforward intermolecular substitution, with a thiolate anion as the nucleophile and a hydroxide as the leaving group (Scheme 2a). Hydrogen bonding in **2a** has been extensively explored in polar and non-polar solvents.[11] It was thus reasonable to assume an activated conformation of β-substituted alkylthiols, in which the thiol group plays the role of the hydrogen bond donor, enhancing the β-carbon electrophilicity. An alternative mechanistic pathway may result from an intramolecular reaction affording thiirane (7) (Scheme 2b), which could be then opened by a neighbouring thiolate to yield the thioether product. Thus, we set out to disprove one of the mechanisms by means of isotopic labeling.

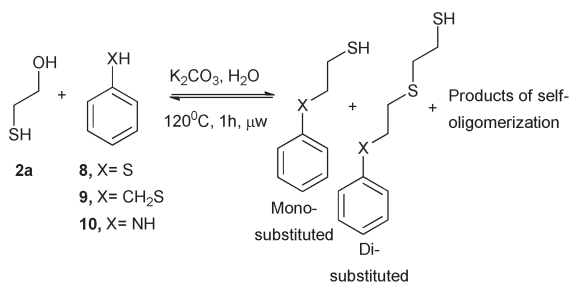
2-Mercaptoethan-1,1-D$_2$-ol (**2a–d$_2$**) was synthesised by $LiAlD_4$ reduction of ethyl-2-mercaptoacetate. 'Scrambling' of the deuterium signal in the oligomers should be expected for an intramolecular mechanism (due to the symmetry of 7), whereas if the alternative mechanism is at play the deuterated methylene should be confined to its original position. According to the ^{13}C NMR analysis shown in Fig. 3, statistical scrambling of the deuterated methylene signals along the thioether chain was obtained after **2a–d$_2$** was subjected to the typical reaction conditions, supporting a thiirane intermediate.

While the self-condensation products obtained by this reaction are important *per se*, the expansion of this method to form additional products would be of great interest. Given that the reactions presented proceed by the attack of a nucleophilic thiolate, reactions of **1a**, **2a–c** and **3a** with other nucleophiles were investigated (Table 3 and ESI†). Thus, while phenol or ethylene glycol (even as a solvent) did not react at all, the addition of strong sulphur nucleophiles such as thiophenol or benzyl mercaptan resulted in the formation of a new sulphur–carbon bond. By observing the products of the cross-reaction with the alternative nucleophile, a noticeable selectivity towards the incorporation of a single 2-mercaptoethyl unit was observed, consistent with the thiirane intermediate mechanism.

Finally, aniline addition to **2a** also afforded the predicted cross-product, resulting from the creation of a new nitrogen–carbon bond. The full results of all cross-reactions conducted are described in the ESI.†

Challenging the common knowledge that –SR and especially –OR are considered very poor leaving groups, we present substitutions of these functional groups promoted by the presence of a β-sulphide. Mercaptoethanol and cysteamine generate new carbon–heteroatom bonds either on their own or in the presence

Table 3 Cross reactions of various nucleophiles with **2a**[a]



Nucleophile	Thiol	Mono- substituted	Di- substituted	Self oligomerisation		
				2b	**2c**	**2d**
Thiophenol **8**	**2a**	28%	2%	40%	15%	15%
Benzylmercaptan **9**	**2a**	65%	—	35%	—	—
Aniline **10**	**2a**	69%	—	31%	—	—

[a] Reactions were heated at 120 °C in a microwave reactor, in water with 3 eq. K_2CO_3 for 60 min. Results in % area by GC-MS.

of an alternative strong nucleophile seemingly by means of a thiirane intermediate. Most significantly, no use is made of expensive or toxic metal catalysts, there is no need for hazardous vesicant reagents, and the reaction can be conducted in pure water. Taking into account the undemanding conditions employed, the extensive history and wide availability of the reagents involved, it is quite surprising that this explicit reaction has not been reported to date. Current efforts are focused on expanding the scope of the reaction by exploring other unusual leaving groups, the introduction of the mercaptoethyl unit to biologically relevant nucleophiles and the use of suitable templates to guide product selectivity.

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