Consecutive C1-Homologation / Displacement Strategy for Converting Thiosulfonates into O,S-Oxothioacetals

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Consecutive C1-Homologation / Displacement Strategy for Converting Thiosulfonates into *O,S*-Oxothioacetals

Laura Ielo,[a] Veronica Pillari,[a] Margherita Miele,[a] Wolfgang Holzer[a] and Vittorio Pace[a,b*]

[a] University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse 14 – 1090 Vienna (Austria). Tel. +43-1-4277-55035. http://drugsynthesis.univie.ac.at/ - e-mail: vittorio.pace@univie.ac.at

[b] University of Turin, Department of Chemistry, Via P. Giuria 7 – 10125 Turin (Italy) – e-mail; vittorio.pace@unito.it

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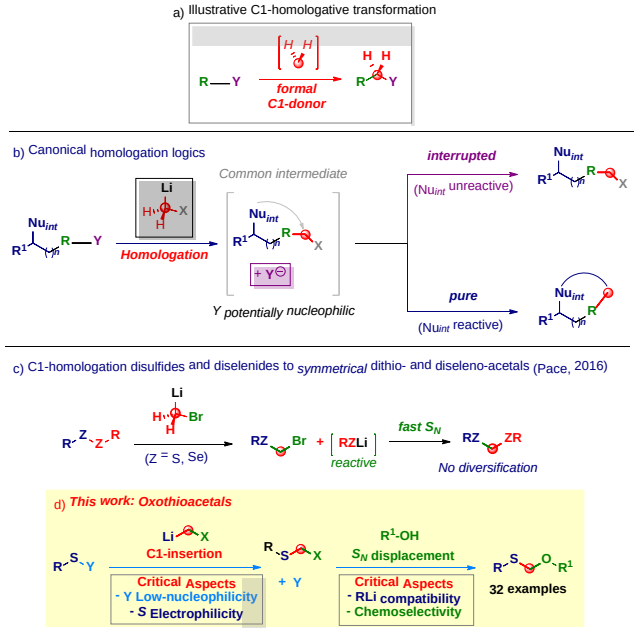
Abstract. A conceptually intuitive synthesis of oxothioacetals is reported starting from thiosulfonates as electrophilic sulfur donors. The installation of a reactive CH_2Cl motif with a homologating carbenoid reagent, followed by the immediate nucleophilic displacement with alcoholic groups [(hetero)-aromatic, aliphatic] offer a convenient access to the title compounds. Genuine chemoselectivity is uniformly observed in the case of multi-functionalized systems.

Keywords: Homologation; Carbenoids; Oxothioacetals; Sequential processes; Sulfur.

Introduction

Homologation chemistry represents a valid tactic for selectively introducing a methylene group (-CH_2) into a given array.[1] This operation underpins significant modifications of the organic skeleton, thus modulating important physical-chemical parameters such as the lipophilicity and the overall chemical reactivity, *inter alia*.[2] Ideally, the homologation event would precisely deliver the methylene fragment between a preformed R-Y linkage (Scheme 1a). Among the plethora of reagents developed to this end (*e.g.* diazomethane, ylides),[3] carbenoid reagents constitute important players for the release of the methylene under tuneable nucleophilic or electrophilic regime governed (mainly) by the nature of the metal.[4] Two main – intimately connected (Scheme 1b) - mechanistic pathways can be devised for the reaction of a metal carbenoid (*e.g.* $LiCH_2X$ – usually nucleophilic) with an electrophilic manifold (**R-Y**):[5] *i*) the *interrupted homologation* in which upon forming the new **R-CH$_2$**X bond, the X defining element remains constitutively in the final scaffold;[6] *ii*) the *pure* homologation leading through an *internal* displacement of the X element - carried out with an internal nucleophilic species (*e.g.* Nu_{int}) – to the homologue, as illustrated by the (aza)-carbonyl homologation to aziridines and epoxides[7] or by the elegant Matteson-type boronic esters homologation.[8] Motivated by the interest towards such chemistry, we designed selective processes characterized by the triggering of molecular rearrangements once the initial homologation was accomplished, *e.g.* fully α-substituted aldehydes from vinyl ketones[9] or, aziridines *via* telescoped homologations of TFAICs.[10] To the best of our knowledge, classical manifolds for conducting the C1-insertions have been restricted to X-Y systems (X, Y = carbon-carbon, carbon-heteroatom, heteroatom 1 – heteroatom 2)[11] whereas, analogous operations on homo-dimeric materials (X-X, X = heteroatom) are much less developed. In this context, in 2016 we reported a direct procedure for converting disulfides and diselenides into symmetrical dithioacetals and diselenoacetals, respectively (Scheme 1c).[12] This transformation, regarded as elusive for decades,[13] was successfully conducted with the highly nucleophilic $LiCH_2Br$, which by attacking the di-chalcogen link furnished an intermediate α-halo thio- or seleno-ether.[12] The subsequent internal nucleophilic displacement – with the anion released during the homologation (RS^- or RSe^-) – yielded the final homologated products. We wondered if an *externally* added (second) oxygen-centered nucleophile could be analogously employed and thus, diversifying the strategy for a modular synthesis of oxothioacetal (Scheme 1d). The following critical points had to be properly addressed during the protocol design: 1) to be productive, the expulsed leaving group (**Y**) on the

sulfur electrophile should manifest (almost) no nucleophilic behaviour to ensure no competitive phenomena with the external nucleophile; 2) the same **Y** group should impart a strong electrophilic behaviour to the RS- platform to ensure the attack of the nucleophilic carbenoid; 3) the oxygen-type reagent used for activating the displacement should be compatible with the adopted lithiating conditions, ideally ensuring wide flexibility of the substituents incorporated on the alcoholic partner.

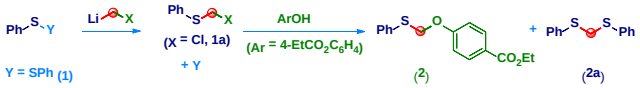


Scheme 1. General context of the presented work.

Results and Discussion

As the model substrates we selected diphenyl disulfide (Y = SPh) and the ester substituted phenol **1b** as the attacking nucleophile to gather initial information on the chemoselectivity. This was motivated by the innate reactivity of carbenoids towards carboxylic derivatives which may result in poor chemocontrol (Table 1).[7b, 14] Introducing the C1 unit in the form of $LiCH_2Br$ leaded to almost exclusive formation of the dithioacetal **2a**, probably because of the higher nucleophilicity of the released mercapto anion compared to the EWG-substituted phenol (entry 1). No improvement was noticed when $LiCH_2I$ – affording a more reactive methylene-iodide bond – was used (entry 2), while a detectable amount of the desired product **2** was formed in the presence of $LiCH_2Cl$ (entry 3). By solubilizing **1b** in a polar solvent such as DMF prior to the addition to the homologation mixture benefited the reaction, providing a detectable amount of the desired product **2** (entry 4). Raising the temperature from -78 °C to rt was pivotal for activating the phenoxide attack, since keeping the mixture at -78 °C or increasing up to 0 °C resulted in no reactivity (entries 5-6). In order to tame the nucleophilicity of the Y leaving group, as well as, to enhance the sulfur electrophilicity, we focused on different sulfenylating agents fulfilling these requirements. Accordingly, chloro-, cyano-phenylsulfide and *N*-phenylthiophtalimide (entries 7-9) were effective in suppressing the formation of the symmetrical dithioacetal **2a**, though chemical yields did not exceed 55% even in the presence of significant loadings of both carbenoid and second nucleophile (entry 10). Collectively, these initial experiements suggested that taming the nucleophilicity of the Y group had to be adequately complemented by a strong sulfur electrophilicity enhancing element. Thus, we turned our attention towards a *S*-thiosulfonate ester[15] which, pleasingly under the homologation /displacement conditions was transformed into the desired compound **2** in 78% isolated yield and excellent selectivity (entry 11). Moreover, the Finkelstein reaction with the phenol benefited from the addition of catalytic amount of NaI (0.1 equiv), thus delivering **2** in a 86% isolated yield (entry 12). From a practical and environmental perspective the use of the *S*-thiosulfonate is attractive because of the good manipulability and the avoiding of common drawbacks affecting sulfurating chemicals (odor, toxicity, instability).[16] It should be noted that the overall process was positively influenced by the basic conditions – due to the organolithium – of the mixture: by quenching the reaction with stoichiometric HCl (1N) after realizing the homologation and, then adding the phenol, the full recovery of the α-halothioether **1a** was obtained (entry 13).

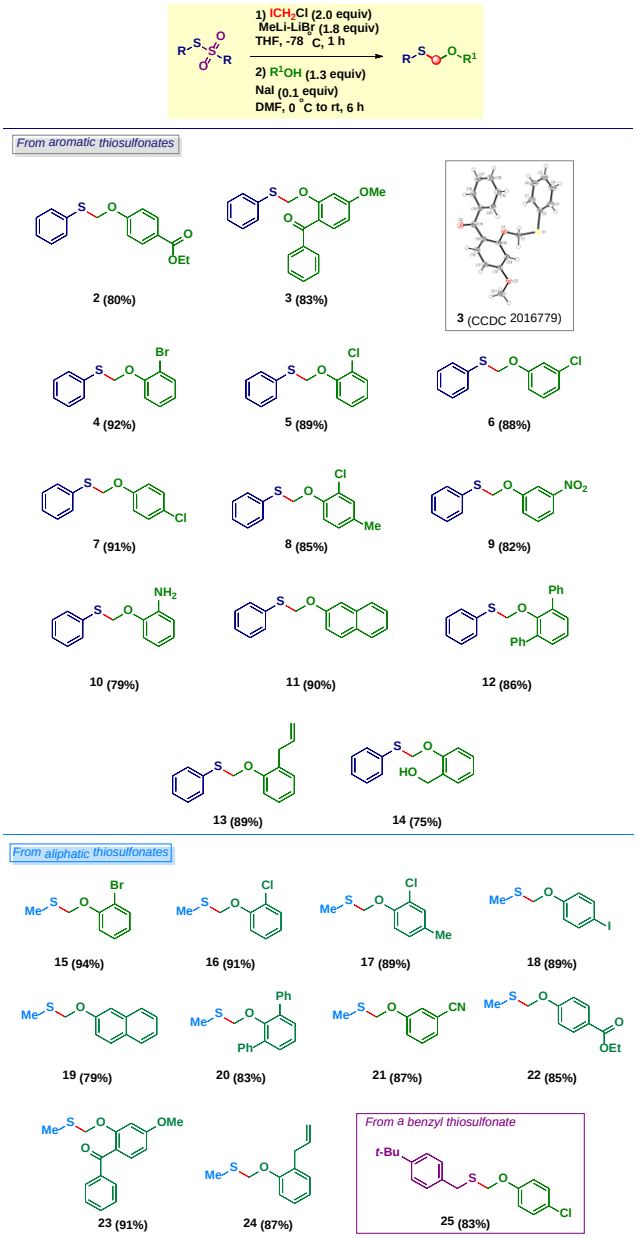
Table 1. Reaction optimization.[a)]



Entry	Y group ***Homologation***	$LiCH_2X$ (X, equiv)	Solv.[a] ***Nu Substitution***	Ratio **2**/**2a**[b]	Yield of **2** (%)[c]
1	PhS	(Br, 1.8)	THF	>1:99	-
2	PhS	(I, 1.8)	THF	>1:99	-
3	PhS	(Cl, 1.8)	THF	7:93	4
4	PhS	(Cl, 1.8)	DMF	11:88	7
5[d]	PhS	(Cl, 1.8)	DMF	1:99	-
6[e]	PhS	(Cl, 1.8)	DMF	2:98	-
7	Cl	(Cl, 1.8)	DMF	>99:1	25
8	CN	(Cl, 1.8)	DMF	>99:1	39
9	PhN-Phth	(Cl, 1.8)	DMF	>99:1	48
10[f]	PhN-Phth	(Cl, 2.8)	DMF	>99:1	55
11	SO_2Ph	(Cl, 1.8)	DMF	>99:1	78
12[g]	SO_2Ph	(Cl, 1.8)	DMF	>99:1	86
13[h]	SO_2Ph	(Cl, 1.8)	DMF	-	-

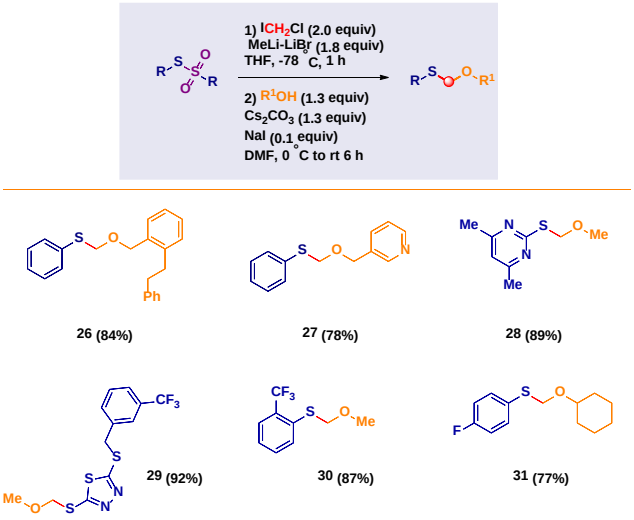
Carbenoids were formed in Barbier-type conditions using a dihalomethane (2.0 equiv) as precursors: *i.e.* ICH_2Br ($LiCH_2Br$), ICH_2I ($LiCH_2I$), ICH_2Cl ($LiCH_2Cl$) – respectively - and MeLi-LiBr (Et_2O solution 1.5 M, 1.8 equiv) in THF at -78 °C. [a] Otherwise stated after the addition of the phenol (1.3 equiv) at -78 °C, the cooling bath was removed and the mixture was allowed to reach rt. [b] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [c] Isolated yield. [d] Reaction kept at -78 °C for 12 h. [e] Reaction kept at 0 °C for 8 h after the addition of the nucleophile and removing of the cooling bath. [f] 4-$EtCO_2C_6H_4OH$ (3.0 equiv) were used. [g] NaI (0.1 equiv) was added. [h] **1a** was obtained in 89% isolated yield.

With the optimized condition in hand, we then studied the scope of the reaction (Scheme 2). The high chemocontrol of the sequential process was not only evident in the case of an ester-substituted phenol (**2**) but, also in the case of a more reactive (towards carbenoids) ketone-substituted system (**3**) presenting the benzoyl group in the phenol *ortho* position. The X-ray analysis of this derivative gave useful structural information on the oxothioacetal motif. The O1-C1 bond (1.421 Å) is significantly shorter than the S1-C1 bond (1.819 Å), whereas the distance between the heteroatoms (O1-S1) is 2.736 Å and the dihedral angle S1-C1 O1-C1 is 114.68 °. The presence of potentially exchangeable halogen on the core of the phenol did not minimally affect the transformation, as evidenced in the cases of bromo (**4**) or chloro (**5-8**) derivatives. The employment of nitrogen-substituted phenol at different oxidation state is fully compatible with the methodology, as indicated by the somehow reluctant (to organolithium carbenoids)[17] nitro compound **9**. With much of our delight, *o*-aminophenol was exclusively alkylated at the oxygen, thus leaving untouched the *per se* nucleophilic amino group (**10**). 2-Naphtol- (**12**) and the sterically demanding 2,6-diphenylphenol- (**13**) derivatives additionally illustrates the versatility of the method. Moreover, the installation of a sensitive element such as a terminal olefin – a cyclopropane manifold[18] – is tolerated (**14**). The different acidity between a phenol and a benzylic alcohol enabled to selectively functionalize the aromatic alcohol, thus preparing the hydroxymethyl-containing scaffold **15**. The protocol was flexible to prepare *S*-alkyl type oxothioacetals starting from the corresponding thiosulfonates. With comparable efficiency we could synthesize under full chemocontrol analogues embodying the aforementioned sensitive functionalities on the aromatic nucleus such as bromo (**16**), chloro (**17-18**) and even the highly reactive iodo compound (**19**). Polyaromatic (**20**) or encumbered systems (**21**) efficiently promoted the nucleophilic substitution upon completion of the homologation. In analogy to aromatic thiosulfonates, carboxylic (**22**), carbonyl (**23**) and alkenyl (**24**) oxothioacetals were assembled without compromising the chemical integrity of these reactive handles. The chemoselectively profile was further maintained when a nitrile-substituted phenol was used (**11**): this is particularly interesting because of the well-established chemistry dealing with the addition of carbanion-like reagents to the CN group *en route* to ketones.[19] Notably, also a benzylic thiosulfonate smoothly underwent the sequential homologation/displacement giving **25**.



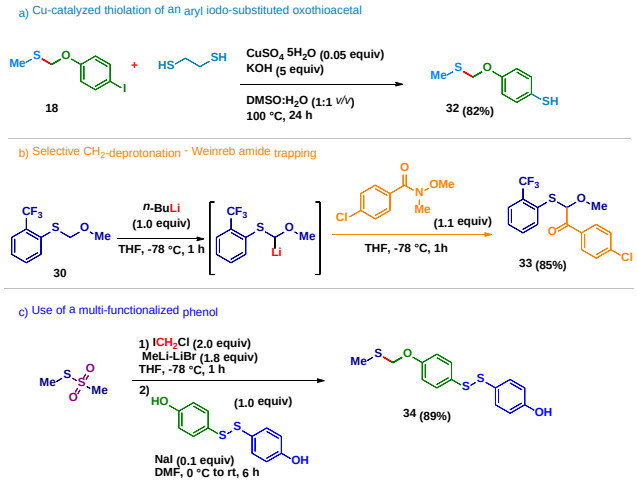
Scheme 2. Scope of the thiosulfonate homologation / nucleophilic displacement with aromatic alcohols.

To gain full advantage of the methodology the employment of aliphatic alcohols was also studied (Scheme 3). Based on the above seen evidence that a benzylic alcohol (**15**) was not alkylated under the reaction conditions, we found that by pre-treating the hydroxyl-derivative with stoichiometric Cs_2CO_3 in DMF at 0 °C – *i.e.* forming a caesium alkoxide – enabled to address the shortcoming. Thus, analogues **26** (from a *ortho*-substituted benzylic alcohol) and **27** (from 3-pyridinylmethanol) were easily prepared in high yield. Similarly, upon the formation of caesium methoxide, a series of *O*-methylated oxothioacetals (**28**-**30**) could be smoothly accessed. As showcased by the challenging poly-nitrogenated requested for synthesizing the pyrimidinyl- (**28**) and the 1,3,4-thiodiazolyl- (**29**) analogues, no alkylating effect was displayed by chloroiodomethane, thus allowing the correct genesis of the carbenoid.



Scheme 3. Thiosulfonate homologation / nucleophilic displacement with aliphatic alcohol derivatives.

Finally, selective manipulations on particular synthesized skeletons were realized for briefly screening their reactivity profile (Scheme 4). The iodo-substituted derivative **18** underwent a smooth I/SH interchange under Chae's Cu-catalyzed conditions[20] with 1,2-ethanedithiol as the mercapto source, yielding the oxothioacetal **32** presenting a free thiol group (*path a*). The selective deprotonation of the oxothioacetal methylene of **30** with *n*-BuLi furnished an intermediate oxo-thio geminal lithium anion which was intercepted with a Weinreb amide *en route* to a mixed oxo-thio ketone **33**, thus complementing our previous achievements on the synthesis of α-substituted ketones (*path b*).[6h, 21] Finally, we were pleased in using a bis-disulfide-containing diphenol as the displacing alcohol for the tandem protocol: upon completing the carbenoid homologation, the nucleophilic substitution could be executed on only one of the phenolic groups with full retention of the labile S-S bond (**34** – *path c*).



Scheme 4. Selective functionalizations of oxothioacetals.

Conclusion

In summa, we have developed a straightforward preparation of oxothioacetals starting from widely available thiosulfonates. The tactic relies on the selective installation of a halomethyl fragment with chloromethyllithium. Crucial for the success of the methodology is employing the thiosulfonate as a competent electrophilic sulfur manifold, which upon the homologation event releases a non-nucleophilic (reactive) sulfinate species. The subsequent treatment of the (isolable) α-halothioether with a hydroxy-containing nucleophile [(hetero)-aromatic, aliphatic alcohols] triggers the displacement, thus furnishing the desired oxothioacetals. Uniformly high yields and chemocontrol are observed: reaction partners may embody sensitive groups whose chemical integrity was not affected in the course of the sequential process.

Experimental Section

General procedure for the homologation of *S*-thiosulfonate ester to asymmetric dithioacetals

The *S*-thiosulfonate ester ($RSSO_2R$, 1.0 equiv) was dissolved in dry THF under Argon and cooled down to -78 °C. Chloroiodomethane (2.0 equiv) was added and, after 5 min, MeLi-LiBr (2.2 M solution in Et_2O, 1.8 equiv) was added *via* syringe pump (rate 0.2 mL/min) and then, the resulting mixture was stirred for 1 h. After increasing the temperature up to 0 °C, a solution of alcohol (R^1OH, 1.3 equiv) and NaI (0.1 equiv) in dry DMF was added dropwise. Upon reaching room temperature, the reaction mixture was further stirred for 6 h and, subsequently was quenched with aqueous saturated NH_4Cl solution. The resulting organic phase was extracted 3 times with Et_2O, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude compounds were purified as reported below through column chromatography.
The crystal structure of compound **3** is available at http://www.ccdc.cam.ac.uk/conts/retrieving.html with the CCDC code 2016779.

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