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ARTICLE

Straightforward Chemoselective Access to Unsymmetrical Dithioacetals through a Thiosulfonates Homologation-Nucleophilic Substitution Sequence

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A sequential C1-homologation – nucleophilic substitution tactic is presented for preparing rare unsymmetrical dithioacetals. The judicious selection of thiosulfonates as convenient sulfur electrophilic sources – upon the homologation event conducting to an intermediate α-halothioether - guarantees the release of the non reactive sulfonate group, thus enabling the subsequent nucleophilic displacement with an external added thiol [(hetero)aromatic and/or aliphatic]. Uniformly high yields and excellent chemocontrol were deducted during an extensive scope study, thus documenting the versatility of the direct technique for preparing these unique and manipulable materials.

Dithioacetals (RS-CH_2-SR) represent entities featuring a plethora of versatile characteristics which make them important motifs across the chemical sciences.[1] By transforming a carbonyl group into a dithioacetal, Corey and Seebach introduced the concept of *umpolung*, enabling the switching of the reactivity of the prototypal electrophilic carbon (CO) to a nucleophilic one.[2] Besides this synthetic significance of dithioacetals, in recent years they emerged as privileged structures enabling to properly address elusive drawbacks of disulfides. In fact, their well-known lability to reducing and/or nucleophilic agents - posing severe difficulties for their application in biological systems – has been elegantly circumvented by homologating the sensitive disulfide bridge to a more robust dithioacetal.[3] As illustrated by Cramer in the case of challenging native peptides, this operation – enlarging the S-S distance by 0.90 Å – not only imparts an enhanced stability but, also preserves the pharmacodynamic profile of the resulting adducts (*e.g.* oxytocin, octreotide, bactenecin).[3a] The tactic of assembling dithioacetal *via* an homologative transformation of disulfides appeared particularly suited because of the simplicity of inserting the C1 unit between the two sulfur atoms.[4] Though the methylene donor source can act in both nucleophilic (*e.g.* diazomethane,[5] sulfur ylides[6]) and electrophilic regime (*e.g.* zinc carbenoids),[7] this logic remained eclipsed for decades because of the inherent difficulties in achieving good chemical yields (Scheme 1 – *path i*).[8] In this context, our group individuated the nucleophilicity of the C1 carbenoid source as a critical parameter for ensuring the success: we demonstrated that the highly nucleophilic bromomethyllithium ($LiCH_2Br$) acts as a competent homologating agent furnishing the (symmetrical) dithioacetals through a single operation under full chemocontrol [Scheme 1 – *path (i)* - Pace].[9] Notably, the transformation is also flexible for preparing diselenoacetals from diselenides. On a conceptually analogous homologative logic is levered the prior reduction of the disulfide linkage to thiol which, treated with a convenient dihalomethane (as C1 donor) in the presence of a base, furnishes the dithioacetal scaffold [Scheme 1 – *path (ii)* - Cramer].[3a,10] The search for alternative C1 sources motivated the development of alternative strategies became available in recent years: a) the use of CO_2 which through a selective four-electron reduction delivers the formal methylene group (CH_2) to connect the two (identical) thiol moieties [Scheme 1 – *path (ii)* - Xi];[11] b) the employment of *acetone* under basic conditions for a sequential enolization- sulfenylation-decarboxylation process [Scheme 1 – *path (iii)* - Chen];[12] c) the use of orthoesters amenable of In-catalyzed reductive insertion into disulfides [Scheme 1 – *path (iii)* - Sakai].[13] As a common feature, *all* these approaches conduct uniformly to *symmetrical* dithioacetals, leaving practically undisclosed the synthesis of *unsymmetrical analogues* (RS-CH_2-SR^1). Inspired by our previous findings that a lithium carbenoid ($LiCH_2X$)[14] attacks a disulfide forming an (isolable) α-chlorothioether and a mercapto anion,[9] we reasoned that taming or eliminating the nucleophilicity of the released sulfur-nucleophile (leaving group) could strategically impede its attack *en route* to the symmetrical dithioacetal. Ideally, upon realizing the initial C1-homologation on a proper disulfide surrogate releasing a *non-nucleophilic* leaving group, the subsequent substitution carried out with an externally added thiol would establish a modular access to *unsymmetrical* dithioacetals.

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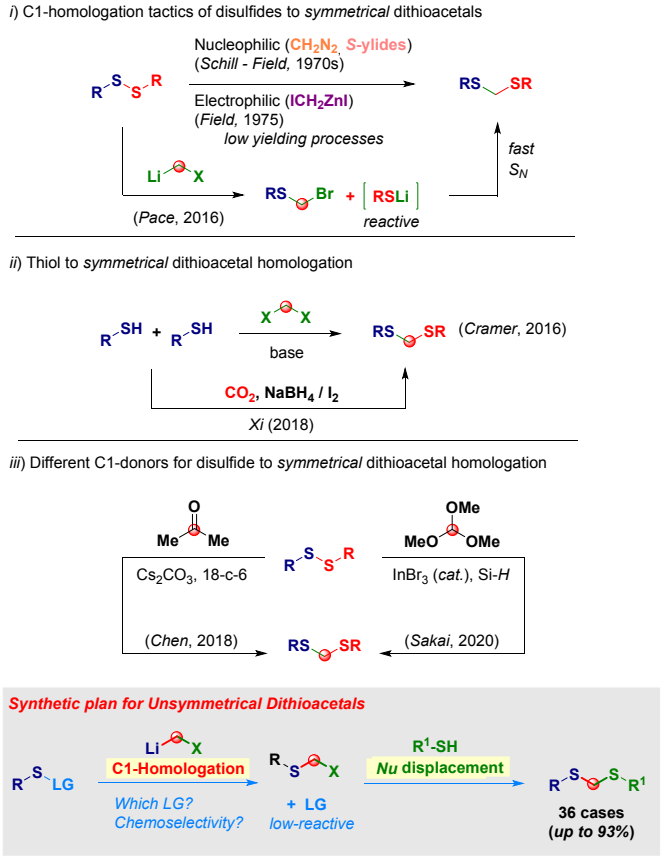
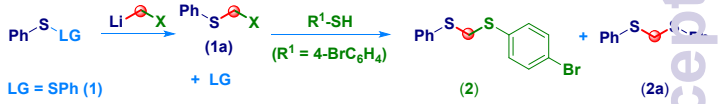


Scheme 1. General context of the presented work.

We targeted the formation of the unsymmetrical dithioacetal **2** presenting an aromatic bromine potentially sensitive to the lithiating environment and, thus constituting a diagnostic element for the chemoselective profile of the reaction (Table 1). Conducting the homologation with $LiCH_2Br$ on diphenyl disulfide **1**, followed by the addition of *p*-bromothiophenol, resulted in the formation of the symmetrical adduct **2a** with only traces of the desired motif **2** (entry 1). Realizing the homologation with $LiCH_2I$ (entry 2) substantially confirmed the previous outcome, while homologating with $LiCH_2Cl$ resulted in noticeable formation of **2** (13%, entry 3). Further improvement was achieved by dissolving the external thiol in DMF (entry 4) – a medium known to facilitate nucleophilic displacements on alkyl halide systems[15] (as the intermediate α-chlorothioether, **1a**) - prior to the addition to the homologating reaction crude. Increasing the loading of *p*-bromothiophenol (2.6 equiv., entry 5) or, the temperature for the displacement (entry 6) did not result in a significant improvement, furnishing in both instances variable mixtures of symmetrical and unsymmetrical adducts. Collectively, these experiments confirmed the feasibility of the two distinct part of the process and, in particular, the effectiveness of the nucleophilic substitution constituting the *conditio sine qua non* for preparing the unsymmetrical dithioacetal. In agreement with the initial hypothesis of rendering innocent the leaving group expulsed from the electrophilic sulfur during the homologation step, a series of alternative sulfenylating agents were screened. The reactions run on chlorophenylsulfide (PhS-Cl, entry 7) and *N*-phenylthiophthalimide (entry 8) – two common electrophilic sulfur agents - produced the desired dithioacetal in promising 37% and 44% yield respectively, with no detectable formation of the compounds resulting from the attack of the expulsed leaving groups (Cl^- and $PhthN^-$). Finally, we were pleased to identify the thiosulfonate ester[16] (PhS-SO_2Ph, entry 9) as the optimal electrophilic sulfur source delivering – upon the coupled nucleophilic substitution – the unsymmetrical dithioacetal in an excellent 86% isolated yield. The process benefited from the addition of catalytic (0.1 equiv) NaI, whose use maximized the yield up to 93% (entry 10). Some additional points merit mention: a) a weaker nucleophile as a Mg carbenoid did not trigger the homologation event, thus resulting in full recovery of the thiosulfonate (entry 11);[17] 2) removing the cooling bath and executing the displacement from 0 °C to rt was pivotal for activating the benzenethiolate attack, since keeping the mixture at 0 °C resulted in no reactivity (entry 12); 3) the acidic quenching just after the homologation allows to obtain the α-chlorothioether as the sole product in comparable yield (entry 13); 4) the use of the reactive and easily accessible[18] thiosulfonate does not entail practical shortcomings normally affecting sulfenylating agents (odor, toxicity, low stability), thus guaranteeing a good manipulability.

Table 1. Reaction optimization.



Entry	LG Substrate *Homologation*	$LiCH_2X$ (X, equiv)	Solv.,Temp [° C] *Nu Substitution*	Ratio **2**/**2a**[a]	Yield of **2** (%)[b]
1	PhS	(Br, 1.8)	THF, -78 to rt	>1:99	-
2	PhS	(I, 1.8)	THF, -78 to rt	>1:99	-
3	PhS	(Cl, 1.8)	THF, -78 to rt	18:82	13
4	PhS	(Cl, 1.8)	DMF, -78 to rt	25:75	21
5[c]	PhS	(Cl, 1.8)	DMF, -78 to rt	33:67	27
6	PhS	(Cl, 1.8)	DMF, -78 to 60	28:72	23
7	Cl	(Cl, 1.8)	DMF, -78 to rt	>99:1	37
8	PhN-Phth	(Cl, 1.8)	DMF, -78 to rt	>99:1	44
9	SO_2Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	86
10[d]	SO_2Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	93
11[e]	SO_2Ph	(Cl, 1.8)	DMF, -78 to rt	-	-
12[d]	SO_2Ph	(Cl, 1.8)	DMF, 0	-	-
13[f]	SO_2Ph	(Cl, 1.8)	DMF, -78 to rt	-	-

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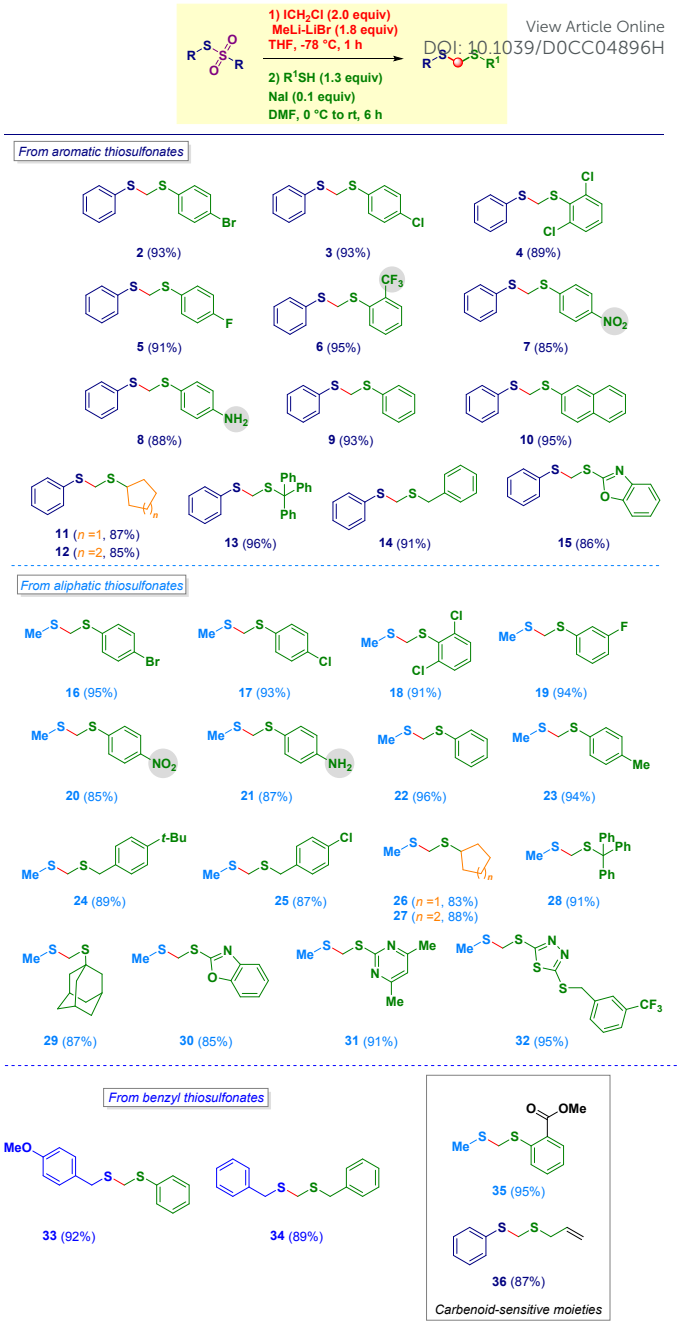
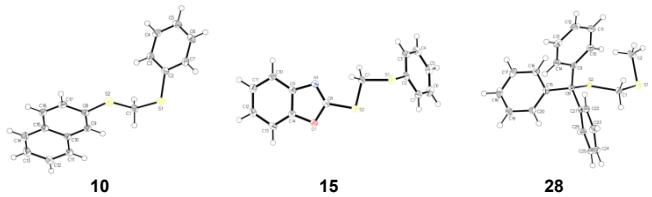
Otherless stated the corresponding carbenoid was generated under Barbier-type conditions starting from the corresponding dihalomethane (2.0 equiv): ICH_2Br ($LiCH_2Br$), ICH_2I ($LiCH_2I$), ICH_2Cl ($LiCH_2Cl$) – respectively - and MeLi-LiBr (Et_2O solution 1.5 M, 1.8 equiv) in THF at -78 °C. 4-BrC_6H_4SH (1.3 equiv) were used. For entries 7-12 the ratio **2**/**2a** is referred to the possible adduct generated through S_N conducted with the leaving group expulsed during the homologation (Cl^-, $PhthN^-$, $PhSO_2^-$).
[a] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [b] Isolated yield. [c] 4-BrC_6H_4SH (2.6 equiv) were used. [d] NaI (0.1 equiv) was added. [e] $ClCH_2MgCl$-LiCl [generated – *coeteris paribus* - from ICH_2Cl (2.0 equiv) and *i*-PrMgCl-LiCl (1.8 equiv) under non-Barbier conditions at -78 °C in THF]. [f] **1a** was obtained in 89% isolated yield.

With the optimized condition in hand, we then studied the scope of the method documenting a wide tolerance of functional groups potentially sensitive to the lithiating conditions (Scheme 2). Differently substituted halogenated thiophenols [4-bromo (**2**), 4-chloro (**3**), the sterically hindered 2,6-dichloro analogue (**4**), 4-fluoro (**5**), 2-trifluoromethyl (**6**)] act as competent partners in the nucleophilic substitution. Taming the nucleophilicity of the thiophenol by installing a strong electron-withdraming group as a nitro, only marginally affects the chemical yield (**7**). With much of our delight, a genuine selectivity for the *S*-alkylation (**8**) was deducted when employing the bis-nucleophilic species 4-aminothiophenol, thus leaving not affected the *per se* nucleophilic amino group. Unsubstituted thiophenols smoothly reacted as noticed in the case of the canonical one (**9**) or the naphthyl-analogue (**10**). Switching to aliphatic thiols do not alter the efficiency of the method [cyclopentyl (**11**), cyclohexyl (**12**)]; of particular relevance is the outcome of the reaction with a sterically encumbered tertiary mercaptane (**13**). Additional evidence of the generality of the technique was deducted when using benzyl- (**14**) and the heteroaromatic benzoxazolyl- (**15**) thiols. The flexibility of the method to alkyl-type thiosulfonates enabled to prepare different unsymmetrical alkyl-aryl and alkyl-alkyl dithioacetals. Comparable yields with the above discussed aryl thiosulfonates were ensured when using halogenated-type thiophenols (**16**-**19**), or nitrogen-containing motifs [4-nitro (**20**)] and 4-aminothiophenol whose precise *S*-alkylation confirmed the excellent chemoselectivity profile mentioned with the aromatic analogue. Again, simple thiophenols (**22**-**23**) were amenable materials for the reaction, as well as, benzyl- (**24**-**25**) and cycloalkyl (**26**-**27**) ones. Steric factors do not affect the success of the transformation, as indicated by the trityl- (**28**) and 1-adamantyl- (**29**) derivatives. A series of heteroaromatic dithioacetals of potential biological interest [benzoxazolyl- (**30**), pyridinyl- (**31**) and the elaborated 1,3,4-thiadiazolyl- (**32**)] complement the plethora of structures accessible with the method. Benzyl-type thiosulfonates analogously undergo the homologation – nucleophilic displacement strategy yielding a benzyl-aryl mixed dithioacetal (**33**) or, a simple bis-benzylic (symmetrical) one (**34**). As showcased by this latter example, the homologation realized on the thiosulfonate, provides compound **34** in sensitively higher yield (*ca.* 10%) respect to the transformation carried out on the less reactive disulfide.[9] Further insights into the chemoselectivity is gathered in the case of the ester-containing thiol (**35**) which did not suffer any concomitant nucleophilic attack despite the organolithium environment and, the allyl-system (**36**) in principle constituting a cyclopropanation manifold.[19]



Scheme 2. Scope of the homologation – nucleophilic substitution strategy for converting thiosulfonates into unsymmetrical dithioacetals.

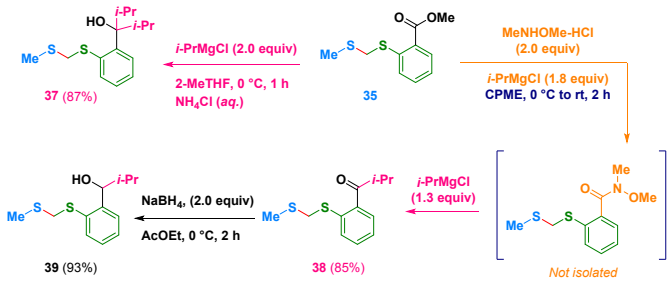
The X-ray analysis of selected representatives (compounds **10**, **15** and **28**) revealed interesting structural features of the constitutive S-CH_2-S moiety of unsymmetrical dithioacetals (Figure 1). In all cases, a small - but evident - bond length difference between C1-S1 and C1-S2 was noticed, presumably due to the stereoelectronic alteration imparted by the two different sulfur atoms.



Compound	CCDC	C1-S1 (Å)	C1-S2 (Å)	S1-S2 (Å)
10	2016505	1.795	1.814	2.943
15	2016506	1.801	1.819	2.932
28	2016507	1.804	1.816	2.945

Figure 1. X-ray structural analysis of selected unsymmetrical dithioacetals (for additional details see the ESI).

In order to take full advantage of the procedure and setting a modular synthesis of dithioacetals manifesting tyrosinase inhibition,[20] selected modifications on the ester-decorated analogue **35** were realized (Scheme 3). The treatment with a Grignard reagent resulted in the double addition product (**37**), whereas forming a transient (non isolated) Weinreb amide[21] enabled the selective mono-addition giving the ketone-containing structure **38**, direct precursor – through trivial carbonyl reduction - of carbinol **39**.



Scheme 3. Synthetic manipulation of an unsymmetrical dithioacetal.

In summary, we have developed a straightforward preparation of rare unsymmetrical dithioacetals *via* a synthetic sequence constituted by chloromethyllithium-mediated homologation – nucleophilic substitution with a proper thiol. The opportune selection of thiosulfonate as the sulfenylating agent is pivotal for ensuring the chemical inertness – as nucleophile - of the released sulfonate leaving group. Accordingly, upon completing the homologation event, the (eventually isolable) α-chlorothioether undergoes the nucleophilic displacement, furnishing the requested dithioacetals. The uniformly high-yield and the high chemocontrol – deducted by selectively preparing variously decorated motifs – further document the potential of this operationally simple and intuitive methodology.

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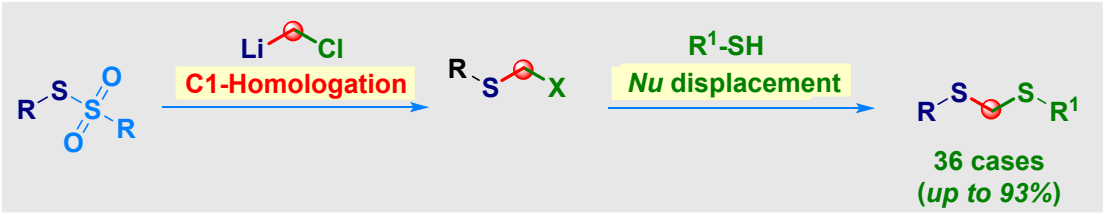

A two-steps electrophilic sulfur homologation strategy for building up unsymmetrical dithioacetals