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Direct Synthesis of Unsymmetrical Dithioacetals

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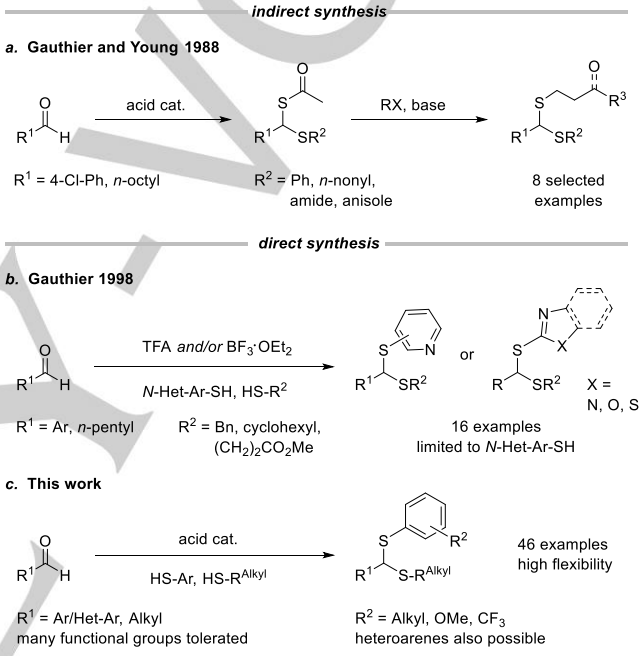
Abstract: Dithioacetals are a frequently used motif in synthetic organic chemistry and have recently seen increasing attention as structural motif in promising antiviral agents against plant pathogens. Most existing reports, however, only discuss symmetrical dithioacetals. Examples of mixed dithioacetals are scarce and no general method for the selective synthesis of these compounds exists. Herein, we present a synthetically simple general one-step protocol for the synthesis of a broad range of unsymmetrical dithioacetals consisting of one aromatic and one aliphatic thiol moiety from the corresponding aldehyde/thiol mixture. The mixed *S*,*S*-acetals are obtained is high yields and a great variety of functional groups is tolerated. Kinetic control enables an excellent selectivity in regard to the unsymmetrical dithioacetal.

Dithioacetals are most commonly found as protecting groups in carbonyl chemistry due to their relatively higher stability towards acidic and basic conditions compared to *O*,*O*-acetals.[1] Furthermore, *S*,*S*-acetals are also prominent Umpolung reagents and serve as acyl anion equivalents or thionium ion precursors (for example for Pummerer-type reactions),[2] as well as precursors in transition metal-catalyzed olefin and allene syntheses.[3] Very recently, proline derived dithioacetals have been reported as promising class of organocatalysts[4] and vanillin- and naphthalene-derived dithioacetals were found to be key motifs in promising drug candidates against tobacco mosaic virus and related plant pathogens.[5] Other applications of *S*,*S*-acetals include products for the removal of mercury from water[6] and the synthesis of dynamic combinatorial compound libraries.[7] Despite the broad range of applications, the majority of protocols employ only symmetrical dithioacetal structures. Examples using mixed dithioacetals remain scarce and, to the best of our knowledge, have only been reported as promising compounds in the treatment of asthma.[8] We wondered, if applications of unsymmetrical dithioacetals are underexplored due to the lack of a general synthetic protocol giving direct access to this class of compounds from the corresponding aldehydes and thiols. Symmetrical *S*,*S*-acetals are readily formed from the acid catalyzed reaction of an aldehyde with a (di)thiol. For the synthesis of mixed dithioacetals however, simply mixing an aldehyde with two different thiols is expected to result in a statistical 1:2:1 mixture of the mixed and the two symmetrical dithioacetals. Indeed, there is less than a handful of reports on the selective synthesis of unsymmetrical dithioacetals from an aldehyde and two different thiols. The existing protocols can be categorized into methods forming the unsymmetrical *S*,*S*-acetal directly from an aldehyde/thiol mixture and those introducing the second thiol into a previously formed *X*,*S*-acetal (Scheme 1).



Scheme 1. Types of reported strategies for the synthesis of unsymmetrical dithioacetals and this work.

The two-step approach has been reported for nucleophilic substitution on a thioacetic acid derived *S*,*S*-acetal analogue (Scheme 1a).[9] However, the protocol has only been shown for a limited number of examples with varying reaction conditions and the formation of trace amounts of both symmetrical acetal by-products was observed despite the stepwise nature of these syntheses. Aditionally, two isolated examples based on acetal exchange in an *O*TMS,*S*-[10a] or an *O*Me,*S*-acetal[10b] facing the same challenge have been reported. Finally, a stepwise synthesis of unsymmetrical dithioacetals based on the homologization and subsequent nucleophilic functionalization of thiosulfonates has recently been described by Pace and coworkers.[11] Reacting an aldehyde with two different thiols in one step would be the synthetically shorter process but faces the challenge that in general mixtures of unsymmetrical and symmetrical *S*,*S*-acetals are expected to form. Early studies suggested that stepwise addition of thiols with different reactivity could shift the composition of the obtained mixtures away from the expected statistical distribution of 1:2:1 to give more of the mixed product.[12] This effect was exploited in the first step of the abovementioned

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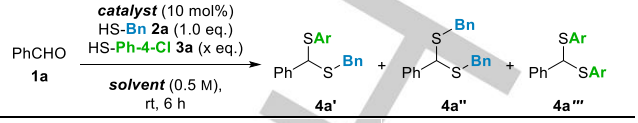
stepwise protocol, where a competition of an alkyl thiol with a thioacid enables a highly selective reaction (Scheme 1a).[8] Later the idea of using reactants with strongly differing reactivities served as the starting point towards the development of a protocol for the direct synthesis of unsymmetrical dithioacetals (Scheme 1b).[13] However, this protocol remained limited to dithioacetals composed of an aliphatic thiol and an electron-poor nitrogen-containing heteroaromatic thiol. Furthermore, the formation of 5-10% of the bis-aliphatic dithioacetals was usually observed. Overall, no general protocol for the direct synthesis of unsymmetrical *S*,*S*-acetals has been reported so far.[14] Thus, when the need to synthesize a variety of mixed dithioacetals arose in our laboratories, we quickly realized the need to develop a more general direct synthesis of unsymmetrical dithioacetals from aldehydes and the two respective thiols.

Building upon the previously reported[13] observation that thermodynamic stability of the product can favor the formation of the mixed dithioacetal from thiol mixtures in the case of two electronically very distinct thiol reagents, we hypothesized that a kinetically controlled product formation might give access to a broader range of products. In principle such a kinetically controlled reaction should be possible for combinations of one aliphatic and one aromatic thiol, considering that the aliphatic thiol would be more prone to engage in thionium ion formation, while the aromatic thiol would preferentially act as the nucleophilic reaction partner (especially if an excess of this component were to be employed).

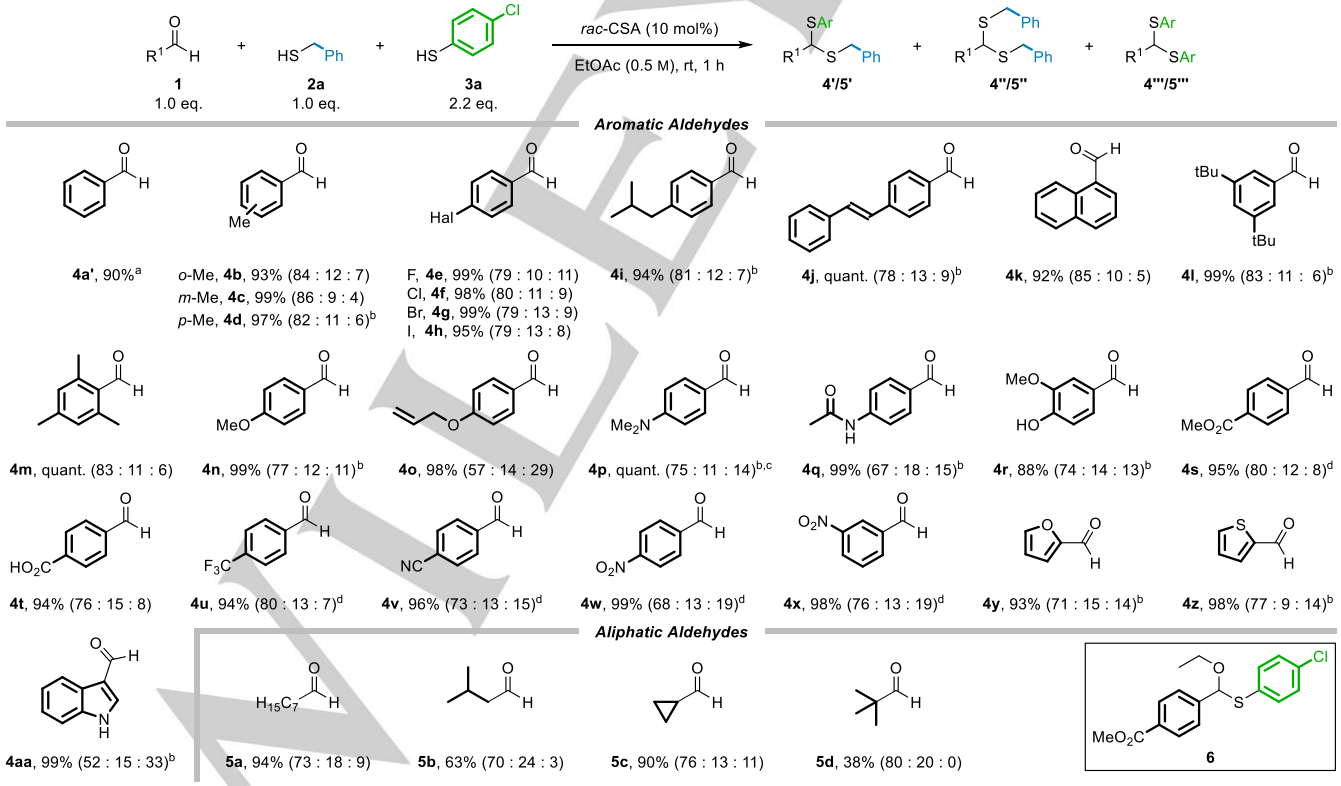
We began our studies starting from commonly used acid catalyst/solvent combinations for acetalization choosing benzaldehyde, benzyl mercaptan and 4-chlorothiophenol as model substrates (Table 1).

Table 1. Optimization of the reaction conditions.



entry	catalyst	x	solvent	4a'[a]	4a''[a]	4a'''[a]
1	*p*TsOH	1.0	$CHCl_3$	48%	33%	11%
2	$BF_3 \cdot OEt_2$	1.0	$CHCl_3$	10%	17%	3%
3	CSA	1.0	$CHCl_3$	70%	14%	1%
4	CSA	2.2	$CHCl_3$	79%	7%	5%
5	CSA	2.2	toluene	67%	7%	3%
6	CSA	2.2	THF	76%	8%	5%
7	CSA	2.2	1,4-dioxane	81%	7%	6%
8	CSA	2.2	EtOAc	83%	10%	5%
9	-	2.2	EtOAc	0%	3%	7%

[a] Yields determined via HPLC analysis with 1,3,5-Trimethoxybenzene (TMB) as internal standard.



Scheme 2. Scope of aldehydes. All reactions were conducted on a 1 mmol scale. For simplicity, only the respective starting materials being varied are shown. The reported yields correspond either to the isolated product (only yield is given) or the yield of the isolated mixture. The ratio of the three products x':x'':x''' given in parentheses was determined by ^{1}H-NMR analysis). [a] Reaction conducted on a 0.25 mmol scale; isolated by preparative HPLC. [b] 6 h reaction time, basic workup. [c] 1.1 eq. of *rac*-CSA were used. [d] 1,4-dioxane as solvent. *rac*-CSA = racemic 10-camphorsulfonic acid

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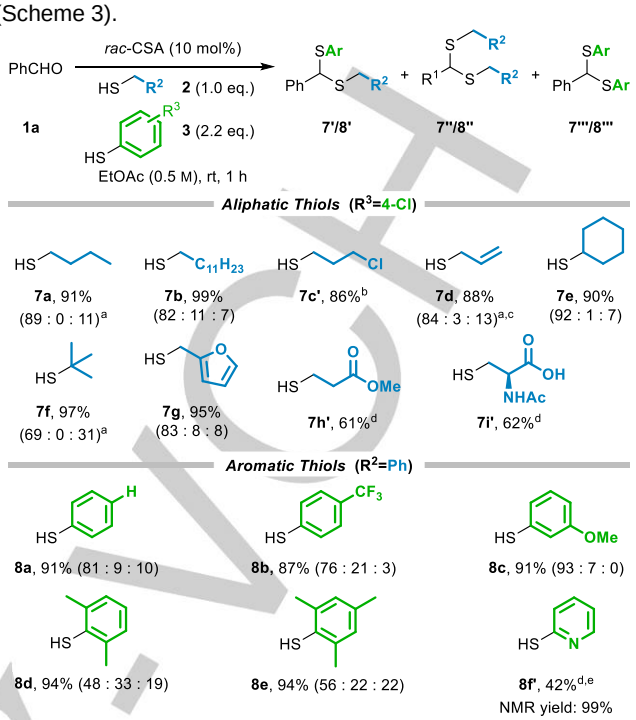
Sulfonic acids, especially 10-camphorsulfonic acid (CSA)[15], were quickly identified as promising catalysts (other Brønsted and Lewis acids delivered inferior results, see Supporting Information). Employing CSA as catalyst, excellent ratios in favor of the unsymmetrical product were obtained (Table 1, entries 1-3). During further optimization, it was found that using an excess (2.2 eq.) of 4-chlorothiophenol instead of equimolar amounts of all three starting materials reduced the amount of symmetrical bisaliphatic *S,S*-acetal **4a''** formed from around 19% to 7% without leading to an increase in symmetrical bisaromatic by-product **4a'''** (entry 4). CSA was found to favor the formation of the unsymmetrical dithioacetal product in several solvents (entries 5-8). We chose to continue our studies with EtOAc, also due to its comparably lower toxicity, cost, and good solubilizing properties. Furthermore, the reaction did not proceed without catalyst (entry 9) and became slightly faster with an increase in concentration (see Supporting Information). However, at higher concentrations some starting materials were not completely soluble, such that an increase of the concentration was not included in the optimal reaction conditions. With the optimized conditions in hand, we began to explore the scope of the reaction. The standard substrate **4a'** was isolated in 90% yield after separation from the structurally very similar symmetrical acetal by-products by preparative HPLC (Scheme 2). Our protocol proved to be very general delivering high yields of the unsymmetrical *S,S*-acetals for *ortho*-, *meta* and *para*-substituted benzaldehydes (**4b-4d**, **4l**, **4m**). A broad range of functional groups was tolerated including halides (**4e-4h**), amides (**4q**), an ester (**4s**), and a free carboxylic acid (**4t**). Double bonds were not affected by the Brønsted acid catalyst (**4j**, **4o**), and the preferred formation of unsymmetrical dithioacetals was observed both with electron-donating and electron-withdrawing substituents (**4n**, **4u-4x**). However, when submitting different electron-poor benzaldehydes to our reaction conditions, e.g. in the synthesis of **4s**, we observed the formation of a fourth compound that was identified to be the *O,S*-acetal **6** by synthesizing this compound individually. The formation of this *S,O*-acetal requires the participation of ethanol. Initially, we speculated that ethanol could be liberated from the solvent through an attack of the thiol nucleophile during the course of the reaction. Importantly, our original protocol involved a basic workup of the reaction mixture to remove remaining thiol. Through control experiments we found that this workup is responsible for the formation of most side product **6**. Thus, modifying the protocol to avoid the basic workup, as well as changing the solvent for particularly challenging cases, prevented the formation of the undesired *O,S*-acetal. For electron-rich (basic) nitrogen containing substituents stoichiometric amounts of *rac*-CSA were used in order to achieve faster conversion (**4p**). The reaction also proceeded with catalytic amounts of *rac*-CSA but an impractically long reaction time was needed in order to achieve full conversion. Besides benzaldehydes, furan (**4y**), thiophene (**4z**), and indole (**4aa**) derived aldehydes also resulted in high yields of the mixed acetal. It is noteworthy, that the entries **4k**, **4r** and **4aa** contain the core structures of recently discovered promising dithioacetal compounds against the tobacco mosaic virus[5]. Finally, high selectivities towards the unsymmetrical *S,S*-acetal and generally good yields were also obtained with primary, secondary and tertiary aliphatic aldehydes under our conditions (**5a-5d**).

Next, we explored the scope in terms of different thiol partners (Scheme 3).



Scheme 3. Scope of thiols. All reactions were conducted on a 1 mmol scale. For simplicity, only the respective starting materials being varied are shown. The reported yields correspond either to the isolated product (only yield is given) or the yield of the isolated mixture. The ratio of the three products x':x'':x''' given in parentheses was determined by ^{1}H-NMR analysis). [a] 6 h reaction time. [b] Separated from the symmetrical products by preparative HPLC. [c] The sample additionally contained 12% of a thiol-ene reaction side-product, see Supporting Information for details. [d] Separated from the symmetrical products by column chromatography. [e] 1.1 eq. of *rac*-CSA were used.

Different primary (**7a-7d**) aliphatic thiols worked well in the reaction. Secondary and tertiary aliphatic thiols, such as cyclohexylthiol (**7e**) and *tert*-butylthiol (**7f**) showed no or almost no bisaliphatic *S,S*-acetal presumably as a consequence of reduced reactivity between the bulky thiol with the sterically hindered thionium ion derived of the said thiol.

Furan- (**7g**) and ester-containing (**7h'**) thiols and *N*-protected cysteine (**7i'**) all delivered the mixed *S,S*-acetal in good yield. In the latter two cases, the unsymmetrical products were easily separated from the symmetrical minor components by column chromatography due to the significantly different polarities of the three thioacetal products. On the side of the aromatic thiol partner both electron-poor and electron- rich thiols were tolerated (**8b**, **8c**). However, for sterically hindered thiophenols (**8d**, **8e**) the preferred formation of the unsymmetrical product was substantially reduced to give a nearly statistical product distribution. As expected based on the literature report on analogous compounds,[13] we observed the exclusive formation of the unsymmetrical thioacetal when using pyridine-2-thiol as aromatic thiol component (**8f'**). The compound was formed in near quantitative yield as confirmed by NMR analysis, but proved unstable during chromatographic purification.

In order to better understand the preferred formation of the unsymmetrical acetal under our reaction conditions we followed the reaction of benzaldehyde with 1.0 eq. of benzyl thiol **2a** and

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2.2 eq. of 4-chlorothiophenol **3a** over time (Figure 1A). Under standard conditions, the reaction proceeded very fast with around 50% conversion after only 5 min. Interestingly, the strong preference towards formation of the mixed *S,S*-acetal was immediately visible. The amount of symmetrical by-products remained low and constant over the course of the reaction. In a second experiment, we monitored a reaction between the same components, however using a 1:1:1 ratio of benzaldehyde and the two thiols (Figure 1B). As expected based on our optimization studies, the reaction proceeded slower. While the unsymmetrical *S,S*-acetal remained the main product, the selectivity was reduced compared to the optimized protocol. Most importantly, the amount of bisaliphatic acetal **4a''** was substantially increased. The reaction was monitored until no substantial change could be observed in the composition of the reaction mixture. Then, we added another 1.2 eq. of 4-chlorothiophenol, thereby creating the same overall stoichiometry as in the first experiment. This led to the consumption of the remaining benzaldehyde. Notably, the resulting mixture contained substantially higher amounts of the two symmetric products **4a''** and **4a'''** alongside lower amounts of **4a'**. Even after allowing for a possible equilibration overnight, no convergence towards the composition obtained in Figure 1a was observed.

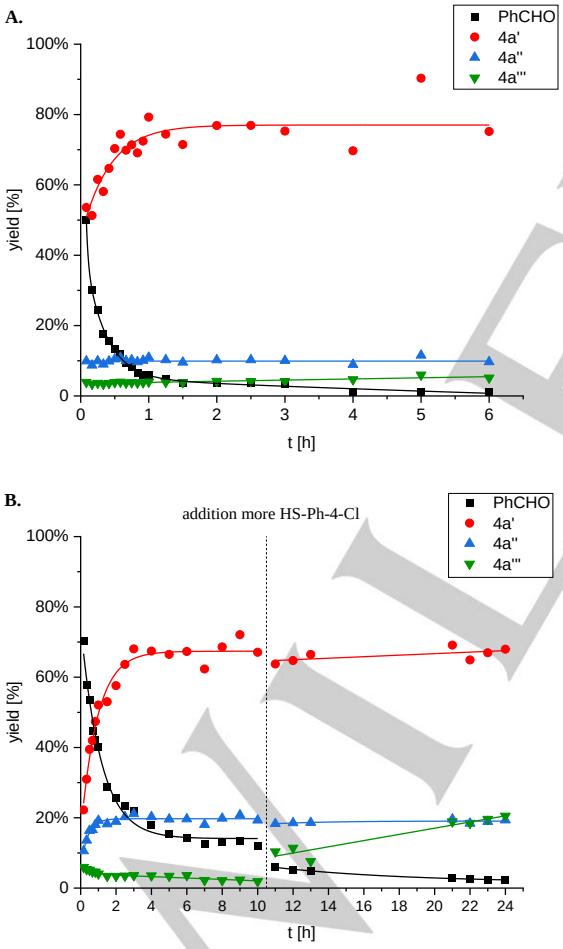

Figure 1. Product formation over time, monitored by HPLC with TMB as internal standard. **A.** Standard reaction conditions, PhCHO:HSBn:HS-Ph-4-Cl = 1:1:2.2. **B.** PhCHO:HSBn:HS-Ph-4-Cl = 1:1:1, 1.2 eq. of HS-Ph-4-Cl added after 10.5 h when the system had reached a constant composition.

Considering that in Figure 1a we observed a fast reaction towards the observed ratios, a thermodynamically controlled reaction would have converged to the same ratio within this timeframe.[16] This allowed us to rule out thermodynamic control as the source of the observed selectivities, leading us to conclude that the process is kinetically controlled.

The preferential formation of the mixed dithioacetal thus seems to be a consequence of differences in the reactivity of aromatic and aliphatic thiols,[17] as well as properties of the catalyst/protocol which support a kinetically controlled reactivity.

In summary, we have developed a simple and general protocol for the synthesis of unsymmetrical dithioacetals bearing an aromatic and an aliphatic thiol. The protocol shows a high selectivity for the mixed dithioacetals and the isolation of these major products through common chromatography methods was shown. In contrast to previous reports, our protocol is suitable for the construction of large compound libraries tolerating a broad range of functional groups and heterocycles. The observed selectivity was shown to result from a kinetically controlled product formation and renders this protocol attractive for the generation of a broad spectrum of unsymmetrical dithioacetals.

Acknowledgements

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Keywords: (unsymmetrical) dithioacetals • thioacetalization • Brønsted acid catalysis• aldehydes • thiols

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[17] As expected, when we submitted benzaldehyde and two electronically very similar aromatic or aliphatic thiols to our reaction conditions the statistically expected 2:1:1 ratio of unsymmetrical to symmetrical *S*,*S*-acetals was obtained.

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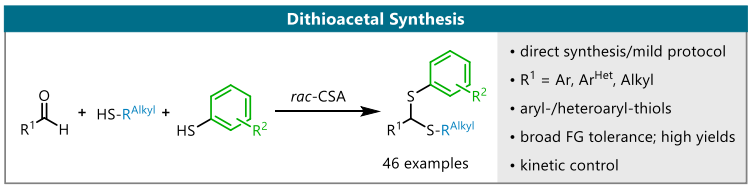

A general protocol for the direct synthesis of unsymmetrical dithioacetals is reported. A variety of unsymmetrical *S*,*S*-acetals consisting of one (hetero)aromatic and one aliphatic thiol bearing diverse functional groups was synthesized in excellent yields. A high selectivity towards the mixed product was achieved through a kinetically controlled reaction and renders this protocol attractive for the generation of compound libraries.

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