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Solid-Supported Odorless Reagents for the Dithioacetalization of Aldehydes and Ketones

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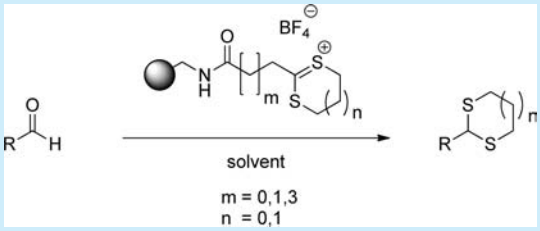
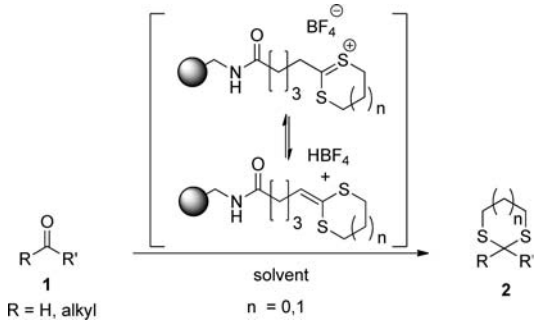
Supporting Information

ABSTRACT: A solid supported, odorless reagent for the dithioacetalization of aldehydes and ketones has been developed. The new reagent provides the dimercaptoalkane equivalent in combination with stoichiometric amounts of immobilized acid and enables the formation of dithianes and dithiolanes from aldehydes without any additives in good to very good yields with high purities. The reaction is chemoselective for aldehydes, but ketones can be reacted to the corresponding dithioketals if an additional Lewis acid such as BF_3 is added.



Methods for the introduction of dithioacetal groups are very important, as dithiolanes as well as dithianes are well-known intermediates for some fundamental reactions in organic chemistry and in natural product synthesis.[1] Dithioacetals are important protecting groups that offer various possibilities for the functionalization of carbonyls.[2] Thus they can be converted into *gem*-difluorinated compounds[3] or they can be used in the famous Corey–Seebach Umpolung reaction to allow the reaction of carbonyls with electrophiles. The latter reaction allows e.g. the synthesis of unsymmetrically substituted ketones.[4] The standard procedure for the formation of dithianes or dithiolanes from ketones or aldehydes is the reaction of a carbonyl compound with propane-1,3-dithiol or ethane-1,2-dithiol in the presence of Lewis acids.[5] The reaction proceeds in good to excellent yields for a large number of compounds that are stable under the required acidic conditions but suffers from several disadvantages such as the toxicity of the reagents, very strong odor of the dithioalkane starting material, and laborious workup and purification of the target substances. Within the past decade, alternative strategies have been developed to overcome some of the above-mentioned drawbacks. Hitherto, the published procedures provide new catalysts for the dithioacetalization, e.g. heterogeneous or solid supported catalysts.[6] In addition, solid supported insoluable dithiane linkers[7] and some sulfur-containing compounds that act as transdithioacetalization reagents have been reported. In 2003, Qun Liu et al. introduced a nonvolatile, odorless dithiolan-ylidene derivative as a 1,3-propanedithiol equivalent that could be used to convert carbonyls into the corresponding dithianes effectively.[8] Upon addition of acid, e.g. HCl, the reagent has been shown to be chemoselective for aldehydes in both organic solvents and water. As it has known for a long time that dithiane-ylidene derivatives (such as the ones used by Liu et al. and others) can be produced by dissolving dithiane salts, e.g. dithianylium triflates, in appropriate organic solvents to yield dithiane-ylidenes and the corresponding acid, we developed a strategy to immobilize these dithiane ylidene precursors. We have been successful in forming dithianylium salts **3**–**8** on solid phases that fulfill all requirements to act as immobilized reagents for the effective dithioacetalization of diverse aldehydes and ketones **1** (Scheme 1).

Scheme 1. Resin-Bound Reagents 3–8 for the Dithioacetalization of Aldehydes and Ketones (1)



The herein described developments combine the benefits of resin-bound reagents with the advantages of using nonvolatile dithiols allowing for transformations in very good to excellent yields with high purity of the target substances. The dithianes and dithiolanes could be obtained mostly by simple filtration of the reaction mixtures and evaporation of the solvent or *via* filtration over a short pad of silica gel without the need of chromatographic purification. Searching for the most active acetalization reagent, we synthesized several dithiolanylium and dithianylium derivatives on solid supports. All resins have been shown to be completely odorless and have been, even without storage under inert atmosphere, stable over several weeks at

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room temperature. In Figure 1, six of our resin-bound equivalents of ethanedithiol **3**, **5**, and **7** and propanedithiol **4**,

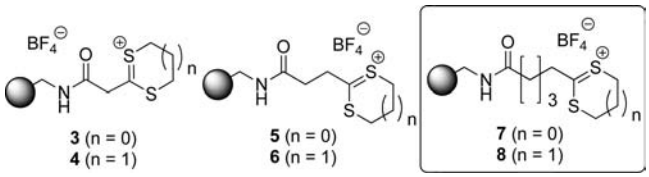
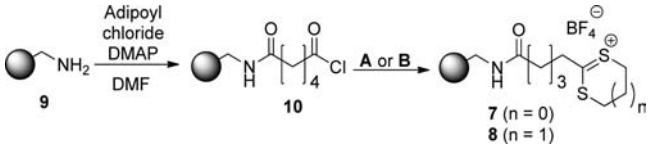


Figure 1. Resin-bound reagents **3**–**8** for the dithioacetalization of aldehydes and ketones (**1a**–**t**).

6, and **8** with varying linker lengths are shown. All resins can be used to convert aldehydes into the corresponding dithioacetals in organic solvents such as chloroform or acetonitrile without the need for further additives and can be used for the formation of dithioketals in the presence of a Lewis acid such as BF_3. It has been shown that the length of the linker entity unit has only a slight influence on the result of the dithioacetalization reaction, as complete conversion of the starting material can be achieved for all resins. Differences can only be detected with regards to the purity of the obtained products. While resins **3** and **4** give crude products that are contaminated with impurities of dithiols, resins **5**–**8** could be used in many cases to synthesize the target substances as crude products that are of high purity even without chromatography. The synthesis of the two preferably used resins **7**–**8** is shown in Scheme 2.[9]

Scheme 2. Syntheses of Solid-Supported Dithiolanylium and Dithianylium Tetrafluoroborate Salts 7 and 8[a]

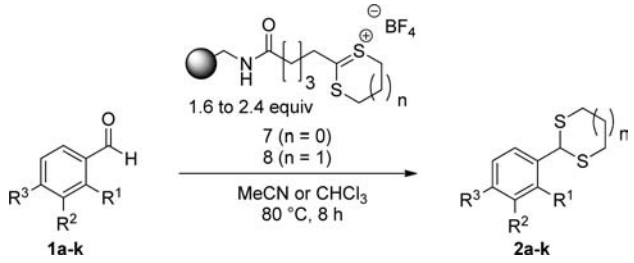


[a]**A**: 1,3-propanedithiol, HBF_4·Et_2O, Et_2O. **B**: 1,2-ethanedithiol, HBF_4·Et_2O, Et_2O.

As the formation of dithianylium or dithiolanylium tetrafluoroborate salts on solid phases requires acidic reaction conditions, the linker unit has been attached onto the solid support *via* an amide bond. The immobilization of the linker types **7** and **8** onto the solid support was achieved by reacting aminomethyl resin **9** with with adipoyl dichloride to give resin **10**. The acyl chloride **10** has then been converted into the corresponding dithiolanylium (resin **7**) and dithianylium tetrafluoroborates (resin **8**) *via* refluxing with ethanedithiol or propanedithiol and HBF_4·Et_2O in diethyl ether. For the following thioacetalization protocols, we used resin **7** for dithiolane and resin **8** for the dithiane formation, as they are accessible *via* the shortest synthetic protocol (Scheme 2).

Table 1 summarizes the results of the dithioacetalization reactions of aldehydes in acetonitrile or chloroform at 80 °C in crimp cap vials. The reaction tolerates traces of water, and there is no need to perform the reactions under an inert atmosphere. The products **2a**–**k** have been isolated in good to excellent yields, and complete conversion of all substances was achieved within a few hours (full conversion of compounds **1a** and **1b** within 3 h). To reach high yields and purities for all derivatives, reaction overnight is recommended. The reaction can be performed successfully at lower temperatures (dependent on

Table 1. Syntheses of Diverse Substituted Aromatic Dithioacetals via Addition of Resin Bound Reagent 7 or 8



		starting material					
entry		R^1	R^2	R^3	*n*	solvent[a]	yield[b] [%]
1	**1a**	H	H	H	1	A	quant.[c]
2	**1b**	OH	H	H	1	A	98
3	**1c**	H	H	CN	1	A	98
4	**1d**	H	H	OBn	1	A	98
5	**1e**	H	H	OBn	0	B	74
6	**1f**	H	OMe	OH	1	A	86
7	**1g**	H	OMe	OH	0	B	81
8	**1h**	H	H	Ph	1	A	99
9	**1i**	H	OMe	H	1	A	98
10	**1j**	H	OMe	H	0	B	70
11	**1k**	H	C(O)Me	H	1	A	92

[a]A = MeCN, B = $CHCl_3$. [b]Isolated yield after chromatography. [c]The reaction was performed in mmol scale giving an 87% yield.

the starting material at 50–60 °C), but for full conversion within less than 10 h the temperature of 80 °C is chosen in a standardized protocol. All compounds have been purified *via* chromatography to determine the correlation of full conversion (TLC control) and isolated yield and to verify the absence of salt impurities of the filtered reaction mixture (Table 1).

In a standard procedure, 1.6 to 2.4 equiv of the resin are used for the formation of dithiolanes or dithianes, but it has been shown that 1.2 equiv of resin **7** or **8** are sufficient for a complete conversion of aldehydes to the corresponding dithianes. But in the latter case, prolonged reaction times up to 48 h can be necessary. Besides the conversion of aromatic aldehydes, aliphatic and vinylic carbonyls have been dithioacetalizated *via* addition of the resins **7** and **8** as well. Whereas the results of the aromatic aldehydes have been mostly independent of the substituents on the aromatic ring, the success of the reaction in giving aliphatic or vinylic dithioacetals depends strongly on the nature of the given starting carbonyl **1l**–**q**. While the conversion of phenylacetic aldehyde **1l** to its dithiane derivative **2l** proceeds very fast and in very good yields, the synthesis of the compounds **2q** and **2r** proceeds only in moderate yields. Interestingly, the yields of the reactions given in Table 2 are not related to the purity of the crude product. Even compounds **2q** and **2r** with an isolated yield of 22% and 26% have been obtained as crude material with high purity (≥95%, GCMS results of the crude products). We assume that some aldehydes, especially α,β-unsubstituted carbonyls, are able to react with the linker unit giving resin bound side products that may reduce the yields without affecting the purity of the desired dithioacetalizated compound.[10] Under the given reaction conditions of Tables 1 and 2 (without any additives), the herein presented dithioacetalization reagents are chemoselective for aldehydes and allow e.g. the conversion of 3-acetyl benzaldehyde (**1k**) and the chromenone derivative **1m** in high yields. The dithioactals **2k**, **2m**, and **2n** have been obtained

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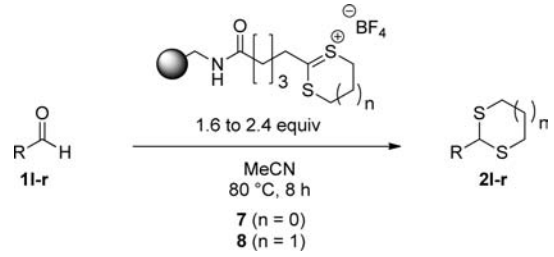
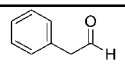
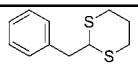
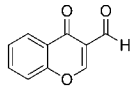
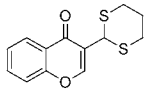
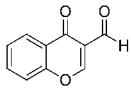
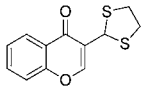
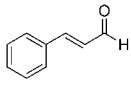
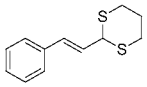
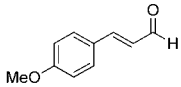
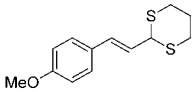
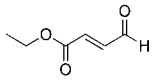
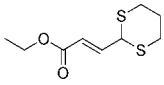
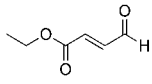
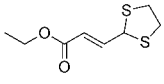
Table 2. Syntheses of Aliphatic and Vinylic Dithioacetals via Addition of Resin Bound Reagent 7 or 8



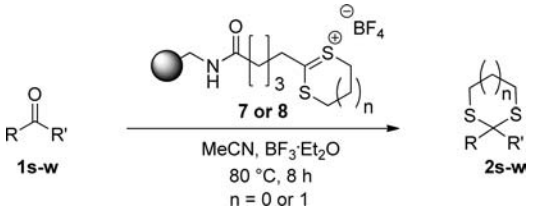
	starting material	product	yield [%]
1	 1l	 2l	97
2	 1m	 2m	79
3	 1m	 2n	83
4	 1o	 2o	55
5	 1p	 2p	46
6	 1q	 2q	22
7	 1q	 2r	26

in high purity without the formation of dithioketal side products by simply removing the resin bound reagent and the solvent.[11]

The herein presented resins are not restricted to the conversion of aldehydes. They also allow the synthesis of dithioketals under similar reaction conditions in the presence of an additional Lewis acid such as $BF_3{\cdot}Et_2O$ (Table 3, **2s–2w**).

In summary, a solid supported, odorless, easy to handle reagent for the efficient thioacetalization of aldehydes and ketones has been developed. The combination of dimercaptoalkane equivalents and acid immobilized as dithianylium or dithiolanylium tetrafluoroborate salt on solid supports allows the conversion of aldehydes into dithianes or dithiolanes with high yields and purities often without the need for purification. The reaction of ketones to the corresponding dithioketals has been shown under similar reaction conditions by using Lewis acids as additives. The conversion of the carbonyls has been proven to be complete with only 1.2 equiv of the resin, but for combinatorial approaches the reaction can be performed with a 2- to 3-fold excess of the reagent to speed up the reaction.

Table 3. Syntheses of Dithioketals via Addition of the Resin Bound Reagent 8 and $BF{\cdot}Et_2O$



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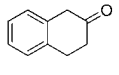
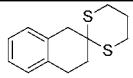
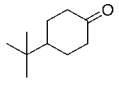
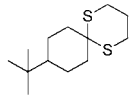
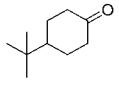
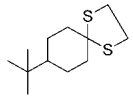
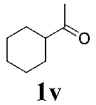
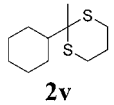
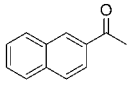
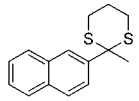
1	 1s	 2s	84
2	 1t	 2t	quant
2	 1t	 2u	49
3	 1v	 2v	54
4	 1w	 2w	74

■ ASSOCIATED CONTENT

Supporting Information

Supporting Information covering the experimental procedures for resins **3–8**, the syntheses of the dithioacetals **2a–r** and dithioketals **2s–w**, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) For a description of the synthesis of resins **3** and **4**, see Supporting Information.

(10) For similar reactions of ketene dithioacetals with Michael acceptors, see e.g.: Yin, Y.; Zhang, Q.; Li, J.; Sun, S.; Liu, Q. *Tetrahedron Lett.* **2006**, *47*, 6071−6074.

(11) For NMR spectra of the crude and the purified compounds **2m** and **2n**, see Supporting Information.