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Reactions of Resin-Bound Triazenes with Dithianylium Tetrafluoroborates: Efficient Synthesis of α-Azo Ketene Dithioacetals and Related Hydrazones

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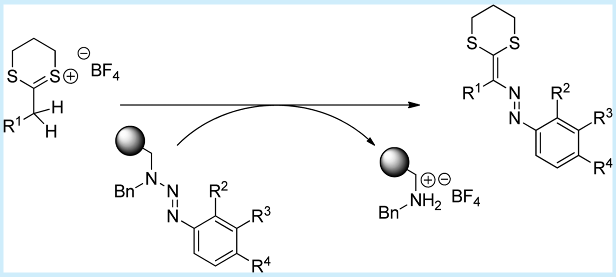
S Supporting Information

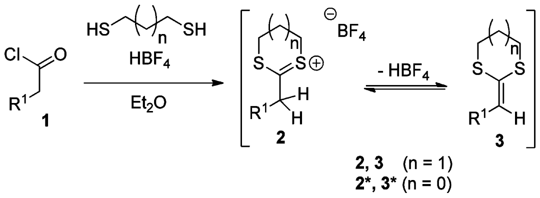
ABSTRACT: The conversion of dithianylium cations into α-azo ketene dithioacetals via addition of polymer-bound diazonium precursors is shown. This new procedure allows the synthesis of α-azo ketene dithioacetals in one step within 2−90 min at rt and yields highly pure compounds that do not have to be purified in most cases. The α-azo ketene dithioacetals obtained have been shown to be valuable intermediates for the synthesis of hydrazones, α-halogenated α-azo ketene dithioacetals, and azo-functionalized dienes.



As 1,3-dithianes and their derivatives are excellent precursors for the introduction of diverse functional groups, electro- and nucleophilic dithiane derivatives and methods for their modification are of high interest in organic chemistry. Out of the group of 1,3-dithian-containing compounds, the ketene dithioacetals are very attractive intermediates[1] that have been investigated for their ability to add electrophiles as halonium ions,[2] α,β-unsaturated carbonyls[3] (via Pd catalysis[4]) or acyl chlorides[5] for a long time. In addition, these ylidene-dithioketals offer a wide range of chemical diversity. They can be e.g. oxidized enantioselectively to their bissulfoxides,[6] fluorinated *via* oxidative difluorodesulfuration,[7] can be derived by C−S bond cleavage, or converted into diverse heterocycles.[8] In addition to various well-known transformations of the α-position, the reaction of the versatile dithiane moiety with azo-building blocks has been shown to yield α-azo ketene dithioacetals recently.[9] These α-azo ketene dithioacetals are interesting intermediates for organic syntheses. They are formal precursors for α-arylazo-carbonyls[10] or hydrazones[11] which are very famous building blocks in organic chemistry, as they can be used for the formation of heterocycles (e.g., via the Fischer indole synthesis). As far as we know, only two procedures for the synthesis of α-azo ketene dithioacetals from diazonium precursors have been described,[9,12] both suffering from the mandatory presence of an α-carboxy functionality and additional electron-withdrawing groups. In addition, a related procedure from dithiafulvene has been described.[13]

The benefits of dithianylium tetrafluoroborates **2** (Scheme 1) for transformations in organic syntheses are of current concern in our group.[14] As the latter ones are highly reactive compounds and precursors for the formation of ketene dithioacetals **3**,[15] we were interested in their use for the formation of α-arylazo ketene dithioacetals. The necessary diazonium ion for the α-arylazo ketene formation has been added in the form of solid-supported triazenes **4** (see Table 1) that act as a protecting group for diazonium ions.[16]

Scheme 1. Formation of Dithianylium Tetrafluoroborates 2 and Ketene Dithioacetals 3[15]



While the reactions of triazene linkers with ketene dithioacetals **3** were not successful, the reaction of the dithianylium tetrafluoroborate salts **2** (as activated form of the ketene dithioacetals) with several immobilized triazenes in dichloromethane gave excellent results without any additives within short reaction times. These results encouraged us to develop an efficient protocol for the diazo-transfer to dithiane building blocks yielding α-azo ketene dithioacetals in a very simple manner (Table 1). The synthesis of the starting materials has been performed according to well-established protocols for the synthesis of dithianylium salts **2** by reaction of propanedithiol with acyl chlorides **1** in tetrafluoroboric acid or boron trifluoride (Scheme 1).[15] Depending on the aromatic or aliphatic residue R^1, the corresponding dithianylium tetra-

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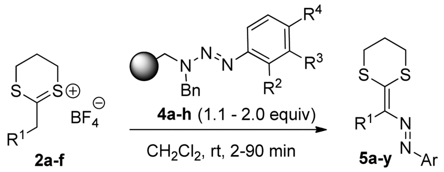
Table 1. Synthesis of α-Azo Ketene Dithioacetals 5 from Dithianylium Tetrafluoroborates 2 and Resin-Bound Triazenes 4

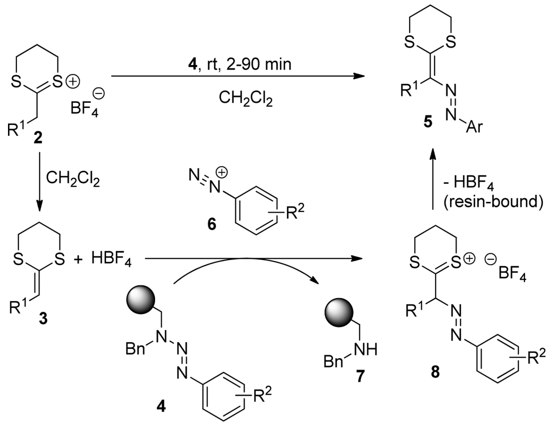


	2	4	5	R^1	R^2	R^3	R^4	yield [%]
1	**2a**	**4a**	**5a**	Ph	H	H	I	99
2	**2a**	**4b**	**5b**	Ph	H	CH_2OH	H	74
3	**2a**	**4c**	**5c**	Ph	H	OMe	H	quant[a,b]
4	**2a**	**4d**	**5d**	Ph	benzo	benzo	Br	93
5	**2a**	**4e**	**5e**	Ph	H	H	F	99
6	**2a**	**4f**	**5f**	Ph	H	H	OPh	97
7	**2a**	**4g**	**5g**	Ph	Me	Cl	H	98[a]
8	**2a**	**4h**	**5h**	Ph	H	H	CO_2Et	96[a]
9	**2b**	**4e**	**5i**	H	H	H	F	quant
10	**2b**	**4f**	**5j**	H	H	H	OPh	88[a]
11	**2b**	**4a**	**5k**	H	H	H	I	93[a]
12	**2c**	**4f**	**5l**	CO_2Me	H	H	OPh	99
13	**2c**	**4e**	**5m**	CO_2Me	H	H	F	87[b]
14	**2d**	**4g**	**5n**	CH_2CO_2Me	Me	Cl	H	86[a]
15	**2d**	**4e**	**5o**	CH_2CO_2Me	H	H	F	90[a]
16	**2d**	**4c**	**5p**	CH_2CO_2Me	H	OMe	H	83[a]
17	**2d**	**4a**	**5q**	CH_2CO_2Me	H	H	I	78[a]
18	**2d**	**4f**	**5r**	CH_2CO_2Me	H	H	OPh	97[a]
19	**2e**	**4c**	**5s**	CH_2CH_3	H	OMe	H	75
20	**2e**	**4e**	**5t**	CH_2CH_3	H	H	F	quant[b]
21	**2e**	**4g**	**5u**	CH_2CH_3	Me	Cl	H	90[a]
22	**2e**	**4f**	**5v**	CH_2CH_3	H	H	OPh	90
23	**2f**	**4e**	**5w**	CH_3	H	H	F	81[a]
24	**2f**	**4g**	**5x**	CH_3	Me	Cl	H	94[b]
25	**2f**	**4f**	**5y**	CH_3	H	H	OPh	96

[a] Purification *via* column chromatography has been performed. [b] Up to 3.8 equiv of the resin have been added (see details in Supporting Information).

fluoroborates **2** were obtained as crystals or as highly viscous oils that could be isolated *via* separation of the organic layers in a separation funnel. In both cases, no further purification of the starting material was necessary. The formation of the protected diazonium-electrophile **4** has been achieved via diazotization of diverse amines and following immobilization on amino benzyl-modified Merrifield resin according to published procedures.[16] The combination of these stable, less toxic immobilized triazenes **4** (Scheme 2) with highly reactive dithianylium cations **2** resulted in an α-azo ketene dithioacetal synthesis with several beneficial aspects. The synthesis of the target compounds **5** (Table 1) is independent of additional electron-withdrawing groups or the presence of carboxylic acid functionalities in α-position to the starting dithiane moiety. The reaction can be conducted at rt without the addition of acids, and the product can be easily obtained by filtration of the crude material. For less reactive substrates **2** (bearing electron-withdrawing substituents in α-position), an excess of solid-supported triazene can be added without loss of purity as unreacted resin-bound material is removed by filtration. All of the substances were obtained in good to excellent yields very often without the need for further purification (Table 1). All reactions have been performed in small scale according to a combinatorial application (using ~0.1 mmol of starting material **2a**−**f**), and the applicability for synthesis in mmol scale has been proven as well. The reaction has been performed with 2.6 mmol of the starting material **2a** furnishing the target compound **5e** with a slightly diminished yield of 96% (in comparison to 99% in 0.1 mmol scale) (Table 1, entry 5).

Scheme 2. Proposed Mechanism of the α-Azo Ketene Dithioacetal Formation



As similar α-azo ketene dithioacetals have been isolated as not only six- but also five-membered derivatives and in the form of the noncyclic acetals before,[9] we decided to show the scope of the reaction by using dithiolanylium tetrafluoroborates (**2***) instead of dithanylium tetrafluoroborates (**2**) as starting material (Scheme 1). The corresponding five-membered ketene dithioacetals have been isolated in 64–72% yield after chromatographic purification proving the utility of the herein presented concept for the formation of five-membered *α*-azo ketene dithioacetals as well.[17]

The addition of the diazonium moiety to the *α*-position of dithianylium tetrafluoroborates as shown in Table 1 gave exclusively the *E*-isomer which has been proven via the crystal structures of compounds **5a** and **5h**. The molecular structure of (*E*)-1-((1,3-dithian-2-ylidene)(phenyl)methyl)-2-(4-iodophenyl) diazene **5a** (Scheme 2) shows exemplarily the almost flat core of the *α*-azo ketene dithioacetal which the phenyl residue (R^1) is stacked to orthogonally (Figure 1).

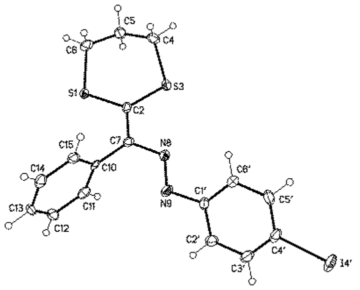
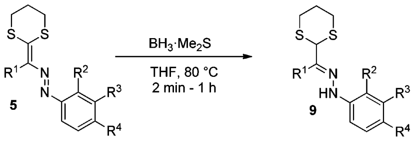


Figure 1. Molecular structure of (*E*)-1-((1,3-dithian-2-ylidene)-(phenyl)methyl)-2-(4-iodophenyl)diazene **5a** (one of the two crystallographic independent molecules is shown; displacement parameters are drawn at the 50% probability level). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-972508 (**5a**) and CCDC-972509 (**5h**)[21] and are available as data of the Chemotion repository via DOI: 10.14272/QPYBP-CGVZSEXOY-FMQUCBEESA-N/Xray (**5a**) and DOI: 10.14272/OHDRPYNAGNRNNM-QURGRASLSA-N/Xray (**5h**).

In accordance with previous investigations[18] we proposed the following mechanism for the formation of *α*-azo ketene dithioacetals **5** (Scheme 2). The dissolved dithianylium salts **2** form, to some extent, free tetrafluoroboric acid that is known to cleave the acid labile triazene linkage of the T1-linker.[19] At rt, the released diazonium ions **6** react with the *in situ* generated ylidene-dithianes **3** to give dithianylium tetrafluoroborates **8**. The latter ones decompose immediately to *α*-azo ketene dithioacetals **5** with elimination of HBF_4. Due to the presence of solid supported benzylamine as a side product of the reaction, the resulting HBF_4 reacts to form an immobilized salt and is removed via filtration of the crude reaction mixture.

To prove the potential of the furnished *α*-azo ketene dithioacetals **5** for the formation of precursors for e.g. heterocycle synthesis or the construction of complex conjugated systems, some key transformations into common building blocks for cyclization and cross-coupling reactions have been disclosed for the first time. As one of the most popular name reactions for the formation of heterocycles, the Fischer indole reaction uses hydrazones as starting material; we developed a very fast protocol for the reduction of *α*-azo ketene dithioacetals **5** to highly functionalized hydrazones **9**. Upon reaction with several reducing agents, the freshly prepared target substances **5** have been shown to be stable against sodium borohydride, lithium aluminum hydride, and many other reducing agents. The desired hydrazones **9** have been obtained only *via* treatment with $BH_3{\cdot}Me_2S$. In a typical procedure, the starting material **5** was dissolved in THF and an excess of $BH_3{\cdot}Me_2S$ was added. All reactions have been completed after heating of the reaction mixture for 2–60 min at 80 °C, giving (*E*)-1-(1-(1,3-dithian-2-yl)ylidene)-2-phenylhydrazines **9** in moderate to good yields over one or two steps (Table 2).

Table 2. Reduction of *α*-Azo Ketene Dithioacetals 5 to Their Corresponding Hydrazones 9

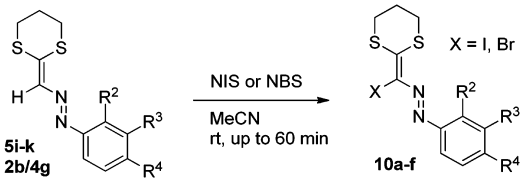


	sm	9	R^1	R^2	R^3	R^4	yield [%]
1	**5i**	**9a**	Ph	H	H	F	49
2	**5f**	**9b**	Ph	H	H	OPh	58[a]
3	**5u**	**9c**	CH_2CH_3	Me	Cl	H	68[a]
4	**5t**	**9d**	CH_2CH_3	H	H	F	51
5	**5m**	**9e**	COOMe	H	H	F	50
6	**2e**	**9f**	CH_2CH_3	H	I	Me	67[b]
7	**2c**	**9g**	COOMe	Me	Cl	H	46[b]

[a] Yield calculated over 2 steps. [b] Yield of a one-pot procedure: reaction of dithianylium tetrafluoroborates **2c** and **2e** with triazenes **4i** (R^2 = H; R^3 = I; R^4 = Me) and **4g** and following reduction with $BH_3{\cdot}Me_2S$; sm = starting material.

To provide an access to the novel compound class of (*E*)-1-((1,3-dithian-2-ylidene)halomethyl)-2-phenyldiazenes (**10**), the reaction of the cleaved azo-derivatives **5** with *N*-iodo- and *N*-bromosuccinimide has been successfully shown (Table 3).

Table 3. Synthesis of (*E*)-1-((1,3-Dithian-2-ylidene)halomethyl)-2-phenyl Diazenes (10)



	sm	10	X	R^2	R^3	R^4	yield [%]
1	**5i**	**10a**	Br	H	H	F	99
2	**5i**	**10b**	I	H	H	F	99
3	**5j**	**10c**	Br	H	H	OPh	60
4	**5j**	**10d**	I	H	H	OPh	50
5	**5k**	**10e**	I	H	H	I	72
6	**2b/4g**	**10f**	I	Me	Cl	H	57[a]

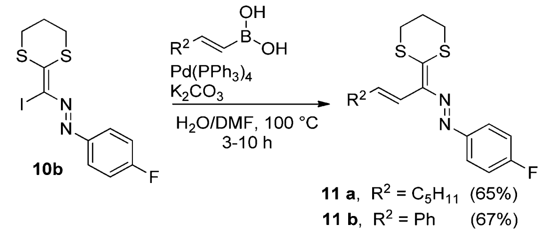
[a] Yield of a one-pot procedure from reaction of 2-2-methyl-5,6-dihydro-4*H*-1,3-dithianyliumtetrafluoroborate (**2b**) with triazene **4g** and following iodination with NIS; sm = starting material.

According to similar procedures that are known for the halogenation of ketene dithioacetals, the functionalized target compounds **10** have been isolated in good to excellent yields by addition of 1.0–1.5 equiv of NBS or NIS and stirring in acetonitrile at rt for 60 min (Table 3).

While electron-withdrawing groups on the aromatic residue of the *α*-azo ketene dithioacetal core seem to stabilize the halogenated products and high yields could be reached, the reaction of derivatives bearing electron-donating substituents (entries 3, 4, and 6) gave lower yields. The reaction proceeded cleanly with only small amounts of side products, but the chromatographic purification was accompanied with partly decomposition of the target substances **10**. The reaction to chloro-substituted derivatives **10** was successful as well (GC-MS analysis of the crude product), but the chlorinated products decomposed immediately during the chromatographic purification.

The new halogenated α-azo ketene dithioacetals **10** offer a wide range of possible transformations of which we chose the Suzuki cross-coupling reaction to demonstrate exemplarily the utility to synthesize functionalized dienes **11a** and **11b** in good yields (Scheme 3). As the precursors **2**, **5**, and **10** could be obtained in high purity without the need for chromatographic purification, the reaction from the starting dithianylium tetrafluoroborates **2** to the dienes **11a** and **11b** has been shown to be very fast and efficient. Only the crude product of the last step of this four-step synthetic route had to be purified via chromatography.

Scheme 3. Synthesis of 2-Azo-dienes 11 *via* Suzuki Cross-coupling of α-Halo-α-azo Ketene Dithioacetals 10a with Boronic Acids



Herein, a fast, efficient, and straightforward protocol for the synthesis of α-azo ketene dithioacetals **5** has been presented. The procedure benefits from the use of dithianylium tetrafluoroborates and immobilized triazenes as precursors, which react immediately after their dissolution in a convenient organic solvent giving fast reactions with high purity of the target compounds, often without the need for chromatographic purification. The resulting α-azo ketene dithioacetals **5** have been shown to be valuable intermediates for the synthesis of hydrazones **9**, α-halo-azo ketene dithioacetals **10**, and dithioacetal functionalized 2-azo-dienes **11**. All of the very efficient reactions proceed very fast, and the isolation of e.g. the target substances **11** is possible within 1 day (starting from acyl chlorides and following a four-step synthetic protocol).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Syntheses of dithianylium tetrafluoroborates **2a−f**; general procedures for resins **4a−i**, α-azo ketene dithioacetals **5a−y**, hydrazones **9a−g**, α-halo-azo ketene dithioacetals **10a−f**, and dienes **11a,b**; analytical data for all synthesized compounds and crystallographic data for **5a** and **5h** (including cif files).[20] 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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(17) The results of the reactions with dithiolanylium tetrafluoroborates are given in the Supporting Information.

(18) Copies of the data can be obtained free of charge on application to: The Director, CCDC, 12 Union Road, GB-Cambridge CB2 1EZ (Fax int. +1223/336033; E-mail: deposit@ccdc.cam-ak.uk).

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(20) The T1 linker has been used to immobilze anilines (via formation of diazonium salts and addition to benzylamino-modified Merrifield resin).

(21) http://www.chemotion.net/.