



Convenient method to obtain homoallylic thioethers from aromatic dithioacetal derivatives

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Received: 8 February 2019 / Accepted: 28 May 2019 / Published online: 3 June 2019
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Abstract

A new, convenient, and efficient method for the synthesis of homoallylic aromatic thioethers was developed. The present method consists of the formation of arylthionium intermediates from aromatic dithioacetals, which are trapped by a π -nucleophile. Screening of diverse aromatic substrates, selected Lewis acids, and allylstannane and allylsilane were evaluated. The method was found suitable for the preparation of homoallylic aryl thioethers bearing electron donating *o*- and *p*-groups only, as substrates with electron withdrawing groups were found unreactive to this system.

Keywords Aromatic dithioacetals · Allylation · Lewis acid · Homoallyl sulfides

Addition of π -nucleophiles to Lewis acids (LA)-activated carbonyl compounds or oxonium cations is one of the fundamental methods of construction of a new carbon–carbon bond (Yamamoto and Asao 1993; Masse and Panek 1995; Marshall 1996). As such, in a highly regioselective manner, in case of chiral substrates or catalysts with strong asymmetric induction, it is possible to obtain relevant alcohols or homoallylic ethers which are applicative building blocks in the synthesis of natural and biologically active products (Yus et al. 2013). Allyl metal reagents used in such process are allylborons, allylstannanes, allylsilanes, allyl halides, allyl acetates, allylindium (Yus et al. 2013; Shen et al. 2013; Kaib et al. 2016), or allyl transition metal complexes (e.g., Pd and Pt) that feature η^1 -allyl or η^3 -allyl bonding mode, respectively (Sone et al. 1995). Introduction of allyl function to the organic compounds gives opportunity for further double-bond transformations such as ozonolysis, epoxidation, dihydroxylation, cycloaddition hydroformylation, and olefin metathesis.

Limited literature data are available for the appropriate reactions of sulfur analogs of carbonyl compounds such as dithioacetal derivatives. Trost group (Trost and Sato 1985; Trost et al. 2012) used a thiocarbocation, generated in a cleavage of dithioacetal by dimethyl(methylthio)sulfonium fluoroborate (DMTSF), as electrophiles in the intramolecular reaction with allylic tin compound or silyl enol ether. Also Padwa and Waterson (2000) used the same LA for functionalization of electron-rich arenes with thionium cations. Mori et al. (1990) described method for the conversion of aldehydes into arylthionium ions using (mesitylthio)trimethylsilane or DMTSF. These short-lived and reactive intermediates were in situ picked up by π -nucleophiles to produce expected homoallylic thioethers.

The main goal of our work was the development of a LA catalyzed nucleophilic displacement of a sulfanyl group on arene dithioacetals, using π -nucleophiles such as allyl metals reagents. We screened diverse substrates bearing both electron withdrawing and electron donating groups, with different substitution patterns.

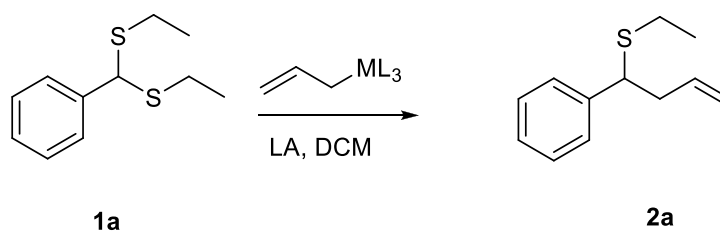
We noticed that a direct precedent of our work was developed by Saigo et al. (1990), where homoallylic sulfides were prepared from dithioacetals with gallium chloride, which served as a catalyst. For the (phenylmethylene)bis(ethylsulfane), **1a**, using allyltributylstannane as an allyl reagent, homoallyl sulfide **2a** was obtained with 87% yield. The molar ratio of the reagents dithioacetal:allylstannane:LA was 1:2:2 and the process was conducted at $-45\text{ }^\circ\text{C}$ (Scheme 1a). We found that such a process can be carried

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11696-019-00837-3>) contains supplementary material, which is available to authorized users.

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Scheme 1 Allylation of (phenylmethylene)bis(ethylsulfane), **1a**



(a) According to Saigo [Saigo et al. 1990]: M=Sn; L=Bu; LA=GaCl₃; -45 °C, 2h; Ar,
(b) M=Sn or Si; L=Bu or Me; LA=TiCl₄ or Sc/Yt(OTf)₃ or BF₃·Et₂O; rt;
from 0.3 to 24 h.

Table 1 Tested Lewis acids in allylation reaction of dithioacetal **1a**

Entry	LA	ML ₃	Time (h)	Yield (%)
1	Sc(OTf) ₃	SnBu ₃	3.5	57 ^a
2	Yt(OTf) ₃	SnBu ₃	24	52 ^a
3	Sc(OTf) ₃	SiMe ₃	24	20 ^a
4	TiCl ₄	SiMe ₃	0.3	56
5	BF ₃ ·Et ₂ O	SiMe ₃	24	21 ^a

^aSubstrate was recovered

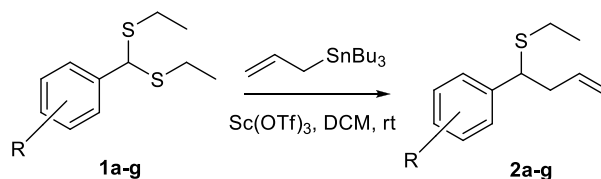
out in mild conditions using smaller amount of substrates: dithioacetal:allyl reagent:LA in molar ratio 1:1.1:1.1 at room temperature (Scheme 1b).

At first, we examined selected LA using [phenylmethylene)bis(ethylsulfane), **1a**, as a probe and allyltributylstannane and allyltrimethylsilane as allyl reagents (Scheme 1b) and Table 1].

From tested LA (Table 1), scandium triflate (entry 1) and titanium tetrachloride (entry 4) gave satisfactory results at a short time. Usage of ytterbium triflate (entry 2) can be suitable for conducting our process (Kobayashi et al. 2002), but required longer reaction time. For further study, we selected scandium triflate, because the use of TiCl₄ is less friendly and required greater attention when conducting the experiment (degradation by-products may increase). As an allyl reagent allyltributylstannane was selected, since allyltrimethylsilane performed poorly, as the yield decreased drastically to 20%, and this can be understood by its inferior nucleophilicity (Mayr and Patz 1994).

For study of the feasibility of generating and trapping thionium cation by π -nucleophile, we selected range of aromatic dithioacetal derivatives with various activating nature of substituents on the aromatic ring (Scheme 2). Moreover, we decided to evaluate the effect of thionium cation stabilization as a function of the substituent position in the aromatic ring (Scheme 2 and Table 2).

Considering the effect of substituents on the stabilization of thionium cation, according to the Crum Brown–Gibson rule (1892) and later contribution of Hammett (1937) and Taft group (Hansch et al. 1991), we obtained good results



R: a = H; b = OCH₃; c = OH; d = Cl or Br; e = NO₂; f = CN; g = CF₃

Scheme 2 Allylation reaction of dithioacetal **1a–g** substituted on *ortho*, *meta*, and *para* positions

Table 2 Reaction of substituted aromatic dithioacetals **1a–g** with allyltributylstannane and scandium triflate in DCM at rt

Entry	Substrate	Product	Yield (%)
1	1a	2a ^a	57 ^b
2	<i>o</i> - 1b	<i>o</i> - 2b	65 ^b
3	<i>o</i> - 1c	<i>o</i> - 2c	80 ^b
4	<i>o</i> - 1d (Cl)	<i>o</i> - 2d (Cl)	25 ^b
5	<i>p</i> - 1b	<i>p</i> - 2b	59 ^b
6	<i>p</i> - 1c	<i>p</i> - 2c	15 ^b
7	<i>p</i> - 1d (Br)	<i>p</i> - 2d (Br)	32 ^b
8	<i>p</i> - 1e	<i>p</i> - 2e	– ^{b,c}
9	<i>p</i> - 1f	<i>p</i> - 2f	– ^{b,c}
10	<i>p</i> - 1g	<i>p</i> - 2g	– ^{b,c}

^aObtained and described by Ando et al. (1972)

^bSubstrate recovered

^cNo reaction

for (phenylmethylene)bis(ethylsulfane), **1a** (Table 2, entry 1). Phenyl group shows very good effect for π -nucleophile addition to thionium cation and yield of product **2a** was 57%.

On the other hand, strongly electron donating groups (+M effect) should give better yield of addition reaction, and so it is for the OCH₃ and OH substituents. We obtained the regioisomer *o*-**2b** with 65% yield (entry 2). The best results observed for the regioisomer *o*-**1c**, where yield was up to 80% (entry 3).

For a series of substituents in the *para* position, we obtained homoallyl thioether *p*-**2b** with yield of 59% (entry

5). We expected to get a similar result for the substrate with OH substituent, but **p-2c** was obtained with only 15% yield (entry 6). Moreover *p*-hydroxybenzaldehyde was isolated from postreaction mixture. Presumably, complexation of the hydroxyl substituent by LA took place. Therefore, we decided to carry out the π -nucleophile addition process in the presence of superstoichiometric amount of LA (3 eq.) at higher temperatures. We improved the efficiency of the process up to 39%. This fact could also explain the high yield for OH substituent in *ortho* position (**o-1c**), since, due to steric hindrance, complexation of the OH substituent by LA is restrained.

Weakly deactivating substituent such as Cl gave modest yield of only 25% for product **o-2d** (entry 4). The reason is a poor stabilization of the thionium cation due to inductive effect of chlorine substituent. We obtained moderate 32% yield of product **p-2d** (entry 7) what is consistent with the result for Cl substituent in *ortho* position (**o-2d**).

For strongly electron withdrawing groups, where inductive effect ($-I$) dominates, π -nucleophile addition to thionium cation did not take place (entry 8–10) due to lack of stability.

For better understanding of the process, we carried out the described procedure with *meta* regioisomers of **1b–e**. The reaction did not take place and substrates were recovered.

In conclusion, we described a new, convenient, and efficient method for the synthesis of homoallylic aromatic thioethers. It appears that the allylation of aromatic dithioacetal derivatives, substituted in *para* or *ortho* position, is limited only for electron donating groups in terms of resonance such as OCH₃ or OH and for Cl/Br. The yield of the process depends strongly on the nature and position of substituents and on the applied conditions, what is going to be foundation for the next experiments in this subject in the future.

Substrates, dithioacetal derivatives **1a–g**, were prepared according to the Ali procedure (Ali and Gomes 2005) from commercially available aldehyde derivatives. All described above products were obtained using general procedure: dithioacetal derivative (1.0 mmol) was dissolved in DCM (5 mL) in a round bottom flask, equipped with a magnetic stirring bar. Then, Sc(OTf)₃ (1.1 mmol) was added and the mixture was stirred for 10 min at room temperature. Next, the allyl-SnBu₃ (1.1 mmol) was added and reaction mixture was stirred overnight at room temperature. After 24 h, the reaction mixture was poured into water (30 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After solvent evaporation, product was purified or isolated by flash chromatography on silica gel (hexane:ethyl acetate). Structures of new obtained products were confirmed by spectral analysis (see Electronic Supplementary Material).

Acknowledgements The project was supported by Polish Ministry of Science and Higher Education, Grant DS.CM.19.001.

Compliance with ethical standards

Conflict of interest There authors declare no competing financial interest.

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