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Synthesis of 2-(arylthio)benzoates by [3+3] cyclocondensations of 3-arylthio-1-silyloxy-1,3-butadienes with 3-oxo-orthoesters, 1,1,3,3-tetramethoxypropane and 1,1-bis(methylthio)-1-en-3-ones

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ABSTRACT

A variety of 2-arylthio-4-methoxybenzoates are regioselectively prepared by $TiCl_4$-mediated [3+3] cyclocondensations of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 3-oxo-orthoesters. Unsubstituted 2-(arylthio)benzoates were prepared by Me_3SiOTf-catalyzed cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1,3,3-tetramethoxypropane. The $TiCl_4$-mediated cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1-bis(methylthio)-1-en-3-ones results in regioselective formation of 2-arylthio-6-(methylthio)benzoates.

1. Introduction

Diaryl sulfides occur in several pharmacologically relevant natural products (e.g., the lissoclibadins, dibenzothiophenes, cyclic sulfides, varacins).[1] Diaryl sulfides have been prepared by reaction of sulfur[2] or sulfur dichloride[3] with arenes, by reaction of organometallic reagents with chlorophenyl-sulfides[4] or by base-mediated reactions of thiophenols with chloroarenes.[5] The scope of these methods is limited by polysulfide formation and low regioselectivities. These problems can be successfully addressed by the application of novel transition metal-catalyzed[6] and metal-free[7] C–S coupling reactions. However, the synthesis of the starting materials, substituted aryl halides or triflates, can be a difficult and tedious task.

An alternative strategy relies on a building block approach. For example, diaryl sulfides have been prepared by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[8] 3- and 5-(Arylthio)salicylates have been prepared by $TiCl_4$-mediated formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 3-silyloxy-2-en-1-ones.[9] Chan et al. reported the reaction of 1-methoxy-3-phenylthio-1-trimethylsilyloxy-1,3-butadiene with 3-silyloxy-2-en-1-ones and with enones.[10] We have reported the cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1-diacylcyclopropanes,[11] 3-alkoxy-2-en-1-ones,[12] 1,1,3,3-tetramethoxypropane[13] and dimethyl acetylenedicarboxylate.[14] Recently, we have reported preliminary results related to the synthesis of 2-arylthio-4-methoxybenzoates by cyclocondensation of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 3-oxo-orthoesters.[15] Herein, we report full details of these studies. In addition, a full account of the cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1,3,3,-tetramethoxypropane is included. We also report, for the first time, the synthesis of 2-arylthio-6-(methylthio)benzoates by cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1-bis(methylthio)-1-en-3-ones.

The chemistry reported herein provides a regioselective approach to a wide range of novel diaryl sulfides, which are not readily available by other methods. In contrast to the C–S coupling reactions outlined above, our method relies on the assembly of one of the two arene moieties.

2. Results and discussion

The known 3-oxo-orthoesters **1a**,**b** were prepared, according to literature procedures,[16] by condensation of 1,1-dichloroethene with

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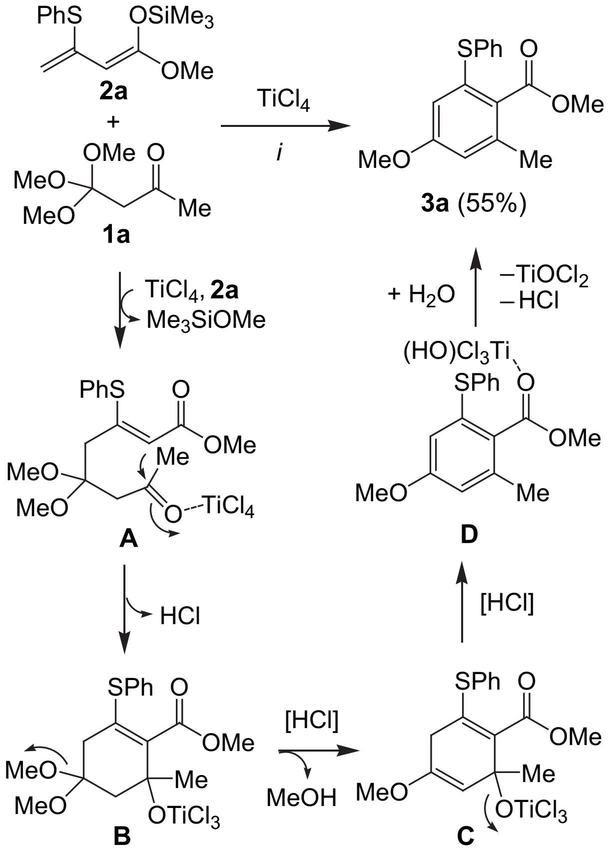
acetyl and propionyl chloride, respectively, to give 3,3,3-trichloroketones, which were subsequently transformed into the products by reaction with methanol. The known 3-arylthio-1-trimethylsilyloxy-1,3-butadienes **2a**–**m** were prepared from methyl acetoacetate, methyl 3-oxopentanoate and various thiophenols in two steps.[12]

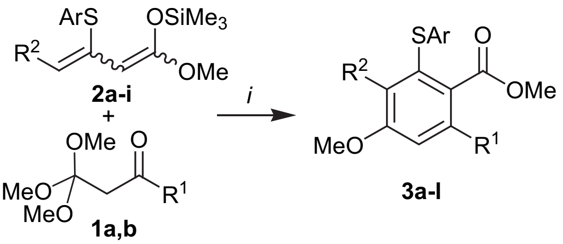
The $TiCl_4$-mediated cyclization of **1a** with 3-phenylthio-1-trimethylsilyloxy-1,3-butadiene **2a** afforded 2-phenylthio-4-methoxybenzoate **3a** (Scheme 1). The cyclization proceeded with very good regioselectivity. The formation of 2-phenylthio-6-methoxybenzoate, a regioisomer of **3a**, was not observed. The best yields were obtained when a stoichiometric ratio of **2a**/**1a**/$TiCl_4$=1.0:1.5:1.5 was used and when the reaction was carried out in a fairly concentrated solution (c(**1a**)=0.33 M). The relatively low yield (55%) can be explained by practical problems during the chromatographic purification and by partial hydrolysis of the starting materials.



Scheme 1. Possible mechanism of the formation of arene **3a**; i: (1) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78→20 °C, 20 h; (2) HCl (10%).

The formation of **3a** can be explained by the mechanism depicted in Scheme 1. The $TiCl_4$-mediated attack of diene **2a** to the orthoester gives intermediate **A**. The attack of carbon atom C-2 of **A** onto the carbonyl group results in cyclization (intermediate **B**). Aromatization (intermediates **C** and **D**) and hydrolysis (during the aqueous work-up) provide the final product. The cyclization might proceed also by $TiCl_4$-mediated extrusion of methanol from **1a** to give 4,4-dimethoxy-3-buten-2-one, conjugate addition of the terminal carbon atom of **2a** onto the latter and subsequent cyclization. This process would follow a mechanism earlier suggested for the cyclization of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 3-alkoxy-2-en-1-ones.[12]

The $TiCl_4$-mediated cyclization of 3-oxo-orthoesters **1a**,**b** with 3-arylthio-1-trimethylsilyloxy-1,3-butadienes **2a**–**i** gave the novel 2-arylthio-4-methoxybenzoates **3a**–**l** (Scheme 2, Table 1). Various substituents can be introduced at carbon atoms C3 and C6 of the benzoate moiety (substituents R^1 and R^2) and at the arylthio group. The yields of the products **3h**,**i**, derived from dienes **2h**,**i**, containing a substituent located at the terminal carbon atom, are lower than the yields of the other products. The yields of the products derived from **1a** are slightly higher than the yields of the products derived from **1b**. The substituents located at the aryl group of the diene seem to have no major influence on the yield. The moderate yields can be explained by problems during the chromatographic purification and by partial hydrolysis of the starting materials. In some reactions a small amount of hydrolyzed starting material was recovered.



Scheme 2. Synthesis of arenes **3a**–**l**; conditions: i: (1) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78→20 °C, 20 h; (2) HCl (10%).

Table 1
Synthesis of **3a**–**l**

1	2	3	R^1	R^2	Ar	Yield[a] % (**3**)
a	**a**	**a**	Me	H	Ph	55
a	**b**	**b**	Me	H	3-MeC_6H_4	50
a	**c**	**c**	Me	H	3-ClC_6H_4	46
a	**d**	**d**	Me	H	4-MeC_6H_4	51
a	**e**	**e**	Me	H	4-EtC_6H_4	45
a	**f**	**f**	Me	H	4-FC_6H_4	40
a	**g**	**g**	Me	H	4-ClC_6H_4	46
a	**h**	**h**	Me	Me	Ph	37
a	**i**	**i**	Me	Me	4-EtC_6H_4	35
b	**c**	**j**	Et	H	3-ClC_6H_4	37
b	**d**	**k**	Et	H	4-MeC_6H_4	38
b	**g**	**l**	Et	H	4-ClC_6H_4	40

[a] Isolated yields.

The reaction of 3-phenylthio-1-silyloxy-1,3-butadiene **2a** with 1,1,3,3-tetramethoxypropane (**4**), in the presence of catalytic amounts of Me_3SiOTf, afforded the 2-(phenylthio)benzoate **5a** (Scheme 3). The best yields were obtained when 0.1 equiv of Lewis acid was used. The use of 0.2 or 1.0 equiv of Me_3SiOTf did not result in an increase of the yield. The yields decreased when less than 0.1 equiv of Lewis acid was employed. The use of 1.0 equiv of $TiCl_4$ proved to be possible, but again did not increase the yield. The work-up procedure (diluted hydrochloric acid), the temperature (−78→20 °C, 20 h), and the concentration (ca. 2 mL of CH_2Cl_2 per **1** mmol of **4**) proved to be important parameters during the optimization. The high concentration is a significant difference to the procedure reported[17] for the Me_3SiOTf-catalyzed cyclization of 1,3-bis(silyloxy)-1,3-butadienes with **4**. The use of tetraethoxypropane rather than **4** proved to be unsuccessful. The use of trifluoroacetic acid or triflic acid (rather than Me_3SiOTf) failed to give the desired product.

The formation of **5a** can be explained by Me_3SiOTf-catalyzed formation of oxonium cation **E**, attack of the terminal carbon atom of **2a** onto **E** to give intermediate **F**, Me_3SiOTf-catalyzed formation of oxonium cation G, cyclization to give intermediate **H** and subsequent aromatization by extrusion of methanol. The suggested mechanism has not been experimentally proved.

The cyclization of dienes **2a**–**j**,**n**–**p** with **4** afforded the 2-(arylthio)benzoates **5a**–**m** in moderate yields (Scheme 4, Table 2). Comparable yields were obtained for products **5b**,**d**, which are derived from dienes containing an electron-withdrawing halogen atom located at the arylthio group, and for products **5a**,**c**,**e**.