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Regioselective synthesis of functionalized 2-(phenylthio)benzoates by '[3+3] cyclization/homo-Michael' reactions of 1-methoxy-1-trimethylsilyloxy-3-phenylthio-1,3-butadienes with 1,1-diacylcyclopropanes

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Abstract

2-(Phenylthio)benzoates containing a remote halide function are regioselectively prepared by '[3+3] cyclization/homo-Michael' reactions of 1-methoxy-1-trimethylsilyloxy-3-phenylthio-1,3-butadienes with 1,1-diacylcyclopropanes.

Keywords: Cyclizations; Cyclopropanes; Diaryl sulfides; Regioselectivity; Silyl enol ethers

Functionalized diaryl sulfides (diaryl thioethers) are present in a number of pharmacologically relevant natural and non-natural products.[1] For example, it has been reported that fluorinated diaryl sulfides act as serotonin transporter ligands.[2] The scope of classic methods[3] for the synthesis of diaryl sulfides is often limited by their low regioselectivity and by the formation of polysulfides, due to the harsh reaction conditions. Relatively mild transition metal-catalyzed[4] and metal-free[5] syntheses of diaryl sulfides have been reported. These reactions are limited by the fact that the synthesis of highly substituted and sterically encumbered products is often difficult or not possible at all. In addition, the synthesis of substituted arenes, which are required as starting materials, can be a difficult task. All reactions outlined above rely on the formation of a carbon–sulfur bond. An alternative approach is based on a building block strategy which relies on the assembly of the arene moiety by the formation of two carbon–carbon bonds. Only a few examples of this type of reaction have been reported to date. For example, diaryl sulfides were prepared by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[6] Chan and co-workers reported a convenient synthesis of diaryl sulfides by [3+3] cyclizations of 1-methoxy-3-phenylthio-1-trimethylsilyloxy-1,3-butadiene.[7a] In addition, Michael reactions of this reagent have been reported.[7b] Diaryl sulfides were prepared also by [4+2] cycloadditions of 1-methoxy-3-phenylthio-1-trimethylsilyloxy-1,3-butadiene.[8] Recently, we reported the synthesis of salicylates by the cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes.[9] Herein, we report our preliminary results related to what are, to the best of our knowledge, the first 'cyclization/homo-Michael' reactions of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1-diacylcyclopropanes. These reactions provide a new and convenient approach to functionalized 2-(arylthio)benzoates, which are not readily available by other methods.

The P_2O_5-mediated reaction[7a] of methyl acetoacetate (**1**) with various thiophenols afforded 3-(phenylthio)crotonates **2a**–**d** which were transformed, by deprotonation (LDA)

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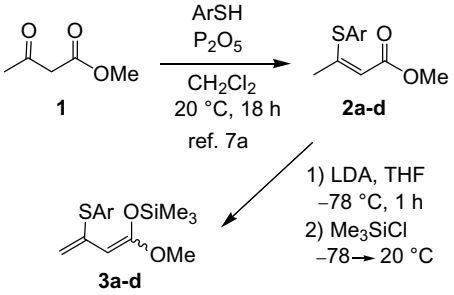


Scheme 1. Synthesis of **3a–d**.

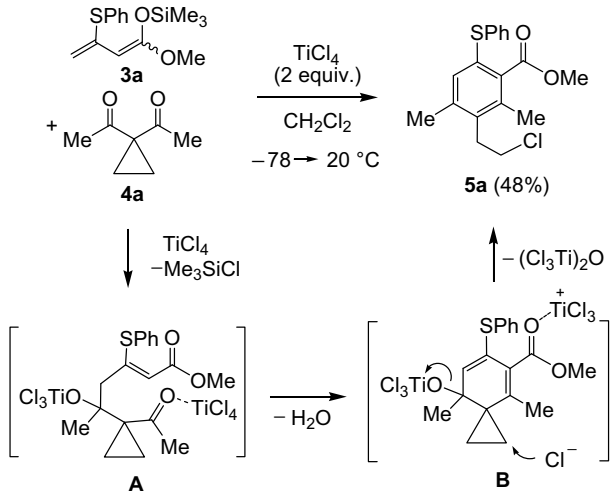
and subsequent silylation, into 1-methoxy-1-trimethylsilyloxy-3-arylthio-1,3-butadienes **3a–d** (Scheme 1, Table 1). The synthesis of **3a** has been previously reported.[7a]

The $TiCl_4$-mediated cyclization of **3a** with 1,1-diacetylcyclopropane (**4a**) afforded 2-(phenylthio)benzoate **5a** (Scheme 2). During optimization, the stoichiometry (1.5 equiv of $TiCl_4$ and of **4a**) and the concentration (30 mL/mmol of **3a**) played an important role.[10] The yields dropped when only 1.0 equiv of $TiCl_4$ and of **4a** were employed. The yield also decreased when an excess of **3a** was used. A complex mixture was obtained when the reaction was carried out in a highly concentrated solution (as reported[7a] for the reaction of **3a** with 4-(trimethylsilyloxy)pent-3-en-2-one). The formation of **5a** can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **3a** onto **4a** to give intermediate **A**, cyclization via the central carbon atom (intermediate **B**), $TiCl_4$-assisted

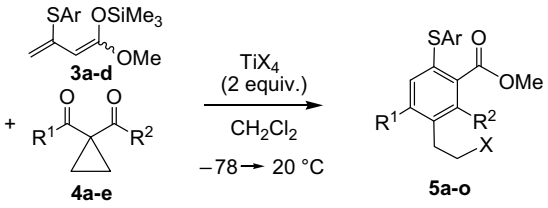
Table 1
Products and yields

2,3	Ar	% (**2**)[a]	% (**3**)[a]
a[7a]	Ph	85	90
b	4-MeC_6H_4	84	91
c	4-ClC_6H_4	86	88
d	3-$(MeO)C_6H_4$	71	88

[a] Yields of isolated products.



Scheme 2. Possible mechanism of the formation of **5a**.



Scheme 3. Synthesis of **5a–o**.

Table 2
Products and yields

3	4	5	Ar	R^1	R^2	X	% (**5**)[a]
a	**a**	**a**	Ph	Me	Me	Cl	48
a	**b**	**b**	Ph	Me	Ph	Cl	47
a	**c**	**c**	Ph	Me	4-ClC_6H_4	Cl	43
a	**d**	**d**	Ph	Me	4-FC_6H_4	Cl	40
a	**a**	**e**	Ph	Me	Me	Br	58
a	**e**	**f**	Ph	Et	Et	Br	30
a	**b**	**g**	Ph	Me	Ph	Br	40
b	**a**	**h**	4-MeC_6H_4	Me	Me	Cl	40
b	**b**	**i**	4-MeC_6H_4	Me	Ph	Cl	41
b	**b**	**j**	4-MeC_6H_4	Me	Ph	Br	45
c	**a**	**k**	4-ClC_6H_4	Me	Me	Cl	43
c	**b**	**l**	4-ClC_6H_4	Me	Ph	Cl	47
c	**a**	**m**	4-ClC_6H_4	Me	Me	Br	41
d	**a**	**n**	3-$(MeO)C_6H_4$	Me	Me	Cl	35
d	**b**	**o**	3-$(MeO)C_6H_4$	Me	Ph	Cl	33

[a] Yields of isolated products.

cleavage of the spirocyclopropane moiety and aromatization. The process can be regarded as a domino '[3+3] cyclization/homo-Michael' reaction. Reactions of acceptor-substituted cyclopropanes have been classified by Danishefsky in terms of 'strictly nucleophilic ring openings', 'electrophilically assisted ring openings', and 'spiro-activations'.[11] In the domino '[3+3]-cyclization/homo-Michael' reaction reported herein a 'spiro-activation' and an activation by an electrophile are operating.[12]

The cyclization of 1-trimethylsilyloxy-3-arylthio-1,3-butadienes **3a–d** with 1,1-diacylcyclopropanes **4a–e**, in the presence of $TiCl_4$ or $TiBr_4$, afforded 5-haloethyl-2-(arylthio)benzoates **5a–o** (Scheme 3, Table 2). Products **5b–d,g,i,j,l,o**, derived from the unsymmetrical cyclopropanes **4b–d**, were formed with very good regioselectivity. This can be explained by the regioselective attack of the terminal carbon atom of **3a–d** onto the acetyl rather than the less reactive aroyl group of **4b–d**.

In conclusion, we reported the first '[3+3] cyclization/homo-Michael' reaction of 1-trimethylsilyloxy-3-arylthio-1,3-butadienes with 1,1-diacylcyclopropanes. This reaction provides a convenient approach to 2-(phenylthio)benzoates containing a remote halide function. The products are not readily available by other methods.

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10. *General procedure for the synthesis of diaryl sulfides* **5a–o**: To a dichloromethane solution (30 mL/mmol) of 1-trimethylsilyloxy-3-arylthio-1,3-butadienes **3** (1.0 mmol) and 1,1-diacylcyclopropane **4** (1.5 mmol) was added TiX_4 (1.5 mmol, X = Cl, Br) at −78 °C. The solution was allowed to warm to ambient temperature within 14 h. To the solution was added an aqueous solution of HCl (25 mL, 1 M). The organic and the aqueous layers were separated and the latter was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/*n*-heptane).
    Methyl 5-(2-chloroethyl)-4,6-dimethyl-2-(phenylthio)-benzoate (**5a**): Starting with **4a** (378 mg, 3.0 mmol), **3a** (562 mg, 2.0 mmol), $TiCl_4$ (0.33 mL, 3.0 mmol) and CH_2Cl_2 (60 mL), **5a** was isolated as highly viscous oil (322 mg, 48%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.19$ (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.09 (t, 2H, $J = 7.5$ Hz, CH_2), 3.43 (t, 2H, $J = 7.1$ Hz, CH_2), 3.76 (s, 3H, OCH_3), 6.96 (s, 1H, ArH), 7.11–7.21 (m, 5H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 16.8$, 20.1 (CH_3), 33.0, 41.6 (CH_2), 52.2 (CH_3), 126.9.0 (CH), 129.04 (2C, CH), 130.3 (C), 130.5 (2C, CH),133.1 (CH), 134.1, 135.1, 136.0, 136.6, 138.9 (C), 169.3 (C=O); IR (ATR): $\tilde{\nu} = 2948$ (w), 2871 (w), 1727 (s), 1579 (m), 1437 (m), 1268 (s), 1148 (s), 1039 (m), 1023 (m), 933 (w), 777 (w), 738 (s), 689 (s), 557 (w) cm^{-1}; GC–MS (EI, 70 eV): *m*/*z* (%): 336 (M^+, ^{37}Cl, 37), 334 (M^+, ^{35}Cl, 100), 301 (61), 285 (56), 267 (36) 253 (66), 210 (13), 115 (8), 77 (9); elemental Anal. Calcd for $C_{18}H_{19}ClO_2S$ (334.86): C, 64.56; H, 5.72. Found: C, 64.59; H, 5.84.
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