Regioselective Synthesis of Functionalized 3-(Methylthio)phenols by the First Formal [3+3] Cyclocondensations of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with 1,1-Bis(methylthio)-1-en-3-ones

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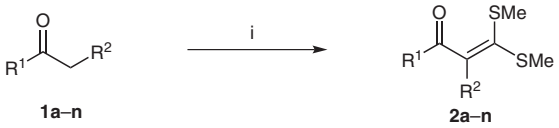
Abstract: The [3+3] cyclocondensation of 1,3-bis(silyl enol ethers) with 1,1-bis(methylthio)-1-en-3-ones results in the regioselective formation of 3-(methylthio)phenols. The products represent useful synthetic building blocks, which are not readily available by other methods.

Key words: arenes, cyclizations, regioselectivity, silyl enol ethers



1a–n 2a–n

Scheme 1 Synthesis of 1,1-bis(methylthio)-1-en-3-ones **2a**–**n**. *Reagents and conditions*: (i) 1. THF, KO*t*-Bu, 15 min, 20 °C; 2. THF, CS_2, MeI, 20 °C, 10 h.

Functionalized methylthio-substituted arenes, such as 2-acyl-3-(methylthio)phenols, are of considerable importance as building blocks for the synthesis of pharmaceuticals and fine chemicals. The methylthio group of these compounds has been oxidized to sulfoxides[1] and sulfones.[2] Other synthetic transformations include Grignard reactions[3] and reductions with $LiAlH_4$.[4] 2-(Methylthio)benzoates have been transformed into thioindoxyls, 2-alkylidenebenzo[*b*]thiophen-3-ones (thioaurones), and benzo[*b*]thiophenes. These transformations rely on the deprotonation of the methylthio group and subsequent cyclization by attack of the carbanion onto a neighboring ester or amide group.[5,6] 2-(Methylthio)benzoates have been employed also as starting materials for the synthesis of benzo[*d*]isothiazoles,[7] 3*H*-benzothiazol-2-ones,[8] and 2-(*tert*-butyl)-1,2-benzothiazol-3(2*H*)-ones.[9] A 4-oxo-1,4-dihydro-quinoline-3-carboxylate has been prepared by intramolecular nucleophilic replacement of the thiomethyl group, located at a benzene moiety, by an amino group.[10] Thiochromen-4-ones have been prepared by cleavage of the thiomethyl group and subsequent attack of the sulfur atom onto an ynone.[11] 2-Acyl-3-(methylthio)phenols have been prepared by Reformatzky reaction of ethyl bromoacetate with 1,1-bis(methylthio)-1-en-3-ones,[12] based on the directed *ortho* metalation (D*o*M) using *n*-BuLi,[13] by *n*-BuLi-mediated reaction of carbon dioxide with 1-methoxy-3-(methylthio)benzene,[14] and by [5+1] annulations of nitro compounds.[15]

Chan and coworkers developed[16] a convenient synthesis of salicylates by cyclocondensation of 1,3-bis(silyl enol ethers)[17] with 3-silyloxy-2-en-1-ones. In recent years, we have extended the scope of this chemistry and studied its application to the synthesis of a variety of functionalized arenes.[18] For example, we have reported formal [3+3] cyclocondensations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetraalkoxypropanes.[19] 3-Alkoxy-1-aryl-2-en-1-ones and 3-alkoxy-1-trifluoromethyl-2-en-1-ones have also been successfully applied in [3+3] cyclocondensations with 1,3-bis(silyl enol ethers).[20] In most reactions developed so far, the products – functionalized phenols – contain no functional group located at carbon atoms C-3 and C-5. This is a severe limitation to this methodology, since most naturally occurring phenols do contain such a functional group, since they are often derived from polyketides. Recently, we reported a regioselective synthesis of functionalized resorcins by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride.[21] Herein, we report a new and convenient synthesis of 3-(methylthio)phenols by what are, to the best of our knowledge, the first cyclocondensations of 1,3-bis(silyl enol ethers) with 1,1-bis(methylthio)-1-en-3-ones. Noteworthy, the functionalized 3-(methylthio)phenols prepared are not readily available by other methods.

The required starting materials, 1,1-bis(methylthio)-1-en-3-ones **2a**–**n**, were prepared, following a known procedure,[22] by base-mediated reaction of ketones **1a**–**n** with carbon disulfide and methyl iodide (Scheme 1, Table 1).

The $TiCl_4$-mediated cyclocondensation of 1,1-bis(methylthio)-1-en-3-ones **2a**–**n** with 1,3-bis(silyl enol ethers) **3a**–**g** afforded the 3-(methylthiophenols) **4a**–**z** in 37–90% yield (Scheme 2, Table 2).[23] The best yields were obtained for reactions of open-chain, alkyl-substituted 1,1-bis(methylthio)-1-en-3-ones **2a**–**e** with 1,3-bis(silyl enol ethers) **3b**–**d** derived from unsubstituted alkyl acetoacetates. The yields slightly dropped for the (less-reactive) acetylacetone-derived diene **3e**. The yields also dropped for dienes **3a**,**f**,**g** containing a terminal substituent. The yields of cyclic and aryl-substituted 1,1-bis(methylthio)-

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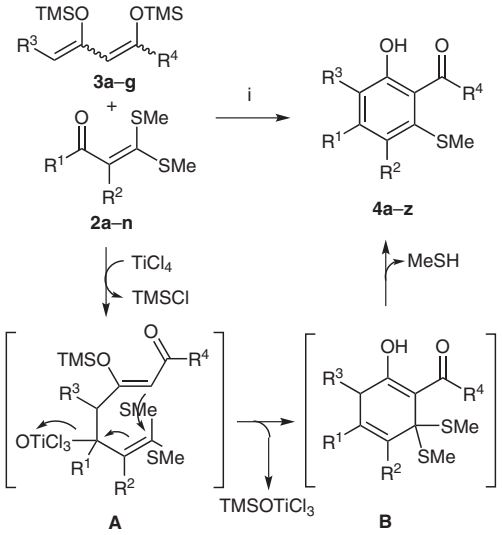
Table 1 Synthesis of **2a–n**

2	R^1	R^2	Yield of **2** (%)[a]
2a	Me	H	70
2b	Et	Me	46
2c	*n*-Pr	Me	50
2d	Me	Et	50
2e	Me	Me	70
2f	*t*-Bu	H	61
2g	-$(CH_2)_4$-		62
2h	-$(CH_2)_5$-		76
2i	-$(CH_2)_6$-		87
2k	Ph	H	61
2l	4-ClC_6H_4	H	83
2m	4-FC_6H_4	H	85
2n	4-FC_6H_4	Cl	70

[a] Yields of isolated products.



Scheme 2 Synthesis of 3-(methylthio)phenols **4a–z**. *Reagents and conditions*: (i) 1. $TiCl_4$, –78 °C to 20 °C, 14 h; 2. HCl (10%).

1-en-3-ones (**2g–i** and **2k–n**) were lower than those of open-chain, alkyl-substituted derivatives (except for **4y** which was isolated in 88% yield). The structures of the products were elucidated by spectroscopic methods (NOESY, HMQC, HMBC). The structure of **4m** was independently confirmed by X-ray crystal structure analysis (Figure 1).[24]

The formation of the products can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **3** onto the carbonyl group of **2** (intermediate **A**), cyclization by S_N' reaction (intermediate **B**), and subsequent aromatization by extrusion of methylthiol (Scheme 2). Noteworthy, the regioselectivity (initial 1,2-addition) is opposite to the one observed for cyclocondensations of 1,3-bis(silyl enol ethers) with 3-alkoxy- and 3-silyloxy-2en-1-ones (initial 1,4-addition).[18]

Table 2 Synthesis of 3-(Methylthio)phenols **4a–z**

2	3	4	R^1	R^2	R^3	R^4	Yield of **4** (%)[a]
2a	**3a**	**4a**	Me	H	Me	OMe	65
2b	**3b**	**4b**	Et	Me	H	OEt	89
2b	**3c**	**4c**	Et	Me	H	OMe	90
2c	**3c**	**4d**	*n*-Pr	Me	H	OMe	80
2c	**3d**	**4e**	*n*-Pr	Me	H	$O(CH_2)_2OMe$	80
2d	**3b**	**4f**	Me	Et	H	OEt	81
2d	**3d**	**4g**	Me	Et	H	$O(CH_2)_2OMe$	76
2e	**3e**	**4h**	Me	Me	H	Me	70
2e	**3c**	**4i**	Me	Me	H	OMe	82
2f	**3e**	**4k**	*t*-Bu	H	H	Me	50
2g	**3d**	**4l**	-$(CH_2)_4$-		H	$O(CH_2)_2OMe$	40
2g	**3b**	**4m**	-$(CH_2)_4$-		H	OEt	55
2h	**3b**	**4n**	-$(CH_2)_5$-		H	OEt	70
2h	**3c**	**4o**	-$(CH_2)_5$-		H	OMe	62
2i	**3b**	**4p**	-$(CH_2)_6$-		H	OEt	61
2i	**3e**	**4q**	-$(CH_2)_6$-		H	Me	50
2k	**3c**	**4r**	Ph	H	H	OMe	60
2l	**3c**	**4s**	4-ClC_6H_4	H	H	OMe	45
2l	**3f**	**4t**	4-ClC_6H_4	H	OMe	OMe	37
2l	**3b**	**4u**	4-ClC_6H_4	H	H	OEt	50
2m	**3c**	**4v**	4-FC_6H_4	H	H	OMe	76
2m	**3b**	**4w**	4-FC_6H_4	H	H	OEt	62
2n	**3a**	**4x**	4-FC_6H_4	Cl	Me	OMe	62
2n	**3c**	**4y**	4-FC_6H_4	Cl	H	OMe	88
2n	**3g**	**4z**	4-FC_6H_4	Cl	Et	OEt	63

[a] Yields of isolated products.

In conclusion, we reported a convenient synthesis of functionalized 3-(methylthio)phenols by the first [3+3] cyclocondensations of 1,3-bis(silyl enol ethers) with 1,1-bis(methylthio)-1-en-3-ones. The products represent useful synthetic building blocks, which are not readily available by other methods.

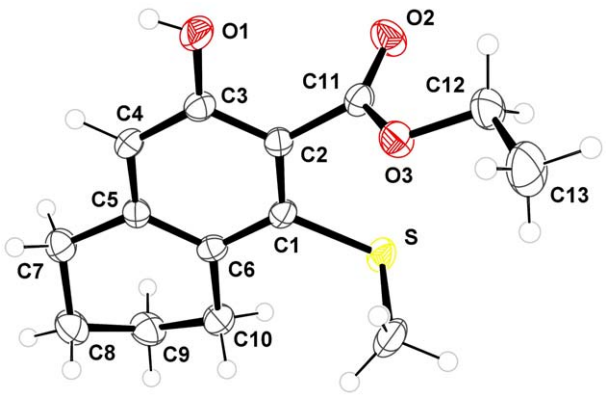


Figure 1 Crystal structure of **4m**

Acknowledgment

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References and Notes

(1) Campiani, G.; Nacci, V.; Bechelli, S.; Ciani, S. M.; Garofalo, A.; Fiorini, I.; Wikström, H.; de Boer, P.; Liao, Y.; Tepper, P. G.; Cagnotto, A.; Mennini, T. *J. Med. Chem.* **1998**, *41*, 3763.

(2) Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Demontis, S.; Fattuoni, C.; Melis, S. *Tetrahedron* **2002**, *58*, 4529.

(3) Ritchie, C. D.; Hofelich, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7039.

(4) Ohkata, K.; Takee, K.; Akiba, K.-y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1946.

(5) Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Demontis, S.; Fattuoni, C.; Melis, S.; Usai, M. *Synthesis* **2002**, 875.

(6) (a) Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767. (b) Mukherjee, C.; De, A. *Synlett* **2002**, 325. (c) Kamila, S.; Mukherjee, C.; De, A. *Synlett* **2003**, 1479. (d) Pradhan, T. K.; De, A. *Tetrahedron Lett.* **2005**, *46*, 1493.

(7) Weber, R. *J. Heterocycl. Chem.* **1978**, *15*, 865.

(8) Dhareshwar, G. P.; Chhaya, P. N.; Hosangadi, B. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1980**, *19*, 831.

(9) Uchida, Y.; Kozuka, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1183.

(10) Grohe, K.; Heitzer, H. *Liebigs Ann. Chem.* **1987**, 29.

(11) (a) Luxen, A. J.; Christiaens, L. E. E.; Renson, M. J. *J. Organomet. Chem.* **1985**, *287*, 81. (b) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626.

(12) Ila, H.; Junjappa, H. *J. Org. Chem.* **1990**, *55*, 5589.

(13) Cipollina, J. A.; Ruediger, E. H.; New, J. S.; Wire, M. E.; Shepherd, T. A.; Smith, D. W.; Yevich, J. P. *J. Med. Chem.* **1991**, *34*, 3316.

(14) Cabiddu, S.; Maccioni, A.; Piras, P. P.; Plumitallo, A. *Gazz. Chim. Ital.* **1981**, *111*, 123.

(15) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578.

(16) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.

(17) For a review of 1,3-bis(silyl enol ethers) in general, see: Langer, P. *Synthesis* **2002**, 441.

(18) For a review of [3+3] cyclocondensations of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.

(19) (a) Sher, M.; Ahmed, Z.; Rashid, M. A.; Fischer, C.; Langer, P. *J. Org. Chem.* **2007**, *72*, 6284. (b) Mamat, C.; Büttner, S.; Trabhardt, T.; Fischer, C.; Langer, P. *J. Org. Chem.* **2007**, *72*, 6273.

(20) Mamat, C.; Pundt, T.; Dang, T. H. T.; Klassen, R.; Reinke, H.; Köckerling, M.; Langer, P. *Eur. J. Org. Chem.* **2008**, 492.

(21) Sher, M.; Langer, P. *Synlett* **2008**, 1050.

(22) Potts, K. T.; Winslow, P. A. *Synthesis* **1987**, 839.

(23) **Typical Procedure: Synthesis of Ethyl 4-Ethyl-6-hydroxy-3-methyl-2-(methylthio)benzoate (4b)**
To a solution of **2b** (0.190 g, 1.0 mmol) and **3b** (0.549 g, 2.0 mmol) in CH_2Cl_2 (2 mL) was added $TiCl_4$ (0.11 mL, 1.0 mmol) at –78 °C under argon. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and an aq HCl solution (10%, 10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. After column chromatography (SiO_2, heptane–EtOAc = 10:1), **4b** was obtained as a colorless solid (227 mg, 89%); mp 120–121 °C; R_f = 0.39 (heptane–EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.06 (s, 1 H, OH), 6.78 (s, 1 H, ArH), 4.43 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 2.60 (q, ^3J = 7.5 Hz, 2 H, $ArCH_2$), 2.45 (s, 3 H, $ArCH_3$), 2.28 (s, 3 H, SCH_3), 1.41 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.18 (t, ^3J = 7.5 Hz, 3 H, $ArCH_2CH_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 170.2 (C=O), 156.9 (CO), 148.8, 136.2, 132.7, 117.3 (C_{Ar}), 116.9 (CH_{Ar}), 61.8 (OCH_2), 27.6 ($ArCH_2$), 20.0, 16.2, 14.0, 13.8 (CH_3). IR (ATR): ν = 3298 (OH), 1699 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 254 (39) [M$^+$], 209 (21), 208 (100), 193 (8), 180 (27), 165 (32). Anal. Calcd for $C_{13}H_{18}O_3S$ (254.10): C, 61.39; H, 7.13. Found: C, 61.35; H, 7.27.

(24) CCDC-685823 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk.