Tetrahedron Letters 50 (2009) 115–117

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First synthesis of 4-(arylsulfonyl)phenols by regioselective [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones

Abdolmajid Riahi [a,b], Mohanad Shkoor [a], Olumide Fatunsin [a], Mathias Lubbe [a], Helmut Reinke [a], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

ARTICLE INFO

Article history:
Received 20 August 2008
Revised 18 October 2008
Accepted 21 October 2008
Available online 1 November 2008

Keywords:
Arenes
Cyclizations
Sulfones
Regioselectivity
Silyl enol ethers

ABSTRACT

The formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with readily available 2-arylsulfonyl-3-ethoxy-2-en-1-ones resulted in regioselective formation of 4-(arylsulfonyl)phenols.

4-(Arylsulfonyl)phenols are of considerable pharmacological relevance. This includes antibacterial activity,[1] inhibition of phospholipidase A_2,[2] inhibition of catechol O-methyltransferase,[3] inhibition of dihydropteroate synthase of *Escherichia coli*,[4] hypolipidemic activity,[5] cytotoxicity against HeLa cells and the antipicornavirus,[6] neuropeptide Y_1 receptor binding activity,[7] anti-HIV activity,[8] anticholesteremic activity,[9] binding to human muscarinic M_1 and M_2 receptors,[10] histamine H_3-receptor antagonistic activity,[11] antiprotozoal activity,[12] binding to neuroblastoma cells,[13] binding to the human cannabinoid CB_1 receptor,[14] and inhibition of the main protease of the recombinant SARS coronavirus.[15]

Diaryl sulfones are available by oxidation of diaryl sulfides. For example, 4-(phenylsulfonyl)anisole has been prepared by oxidation of 4-(phenylthio)anisole with hydrogen peroxide.[16] An alternative approach to this compound relies on the aluminum(III)chloride-mediated reaction of anisole with phenylsulfonic acid chloride.[17] However, this approach suffers from the formation of a regioisomeric mixture, which is difficult to be separated. The reaction of phenol with benzenesulfonic acid has been reported to give 4-(phenylsulfonyl)phenol.[18] However, no yield was given, and the reaction required harsh conditions (240 °C). Recently, an efficient approach to 4-(phenylsulfonyl)phenol, based on the CuI/proline-mediated reaction of aryl iodides with sodium benzenesulfinate, has been reported.[19] 4-(Phenylsulfonyl)anisole has been prepared by Suzuki reaction of 4-methoxybenzeneboronic acid with phenylsulfonic acid chloride.[20] Recently, its synthesis by $Cu(OAc)_2$-catalyzed reaction of 4-methoxybenzeneboronic acid with sodium benzenesulfinate in the presence of 1,10-phenanthroline and oxygen has been reported.[21] All of these reactions rely on the coupling of two arene moieties. The application of these reactions to the synthesis of sterically encumbered or functionalized products can be difficult in some cases. In addition, the synthesis of the required starting materials, functionalized arenes, can be a tedious task.

Chan and coworkers were the first to report[22] the $TiCl_4$-mediated [3+3] cyclization[23] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[24] with 3-silyloxy-2-en-1-ones, which allows a convenient synthesis of salicylates. In recent years, the application of this methodology to the synthesis of various functionalized arenes has been reported.[23] Herein, we report, for the first time, the synthesis of 4-(arylsulfonyl)phenols by [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones. These reactions allow a convenient and regioselective access to functionalized 4-(arylsulfonyl)phenols, which are not readily available by other methods. In contrast to the C–S coupling reactions that are outlined above, the method reported herein

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

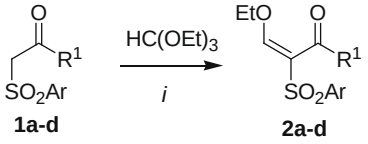
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.097

involves the formation of one of the two arene moieties by formation of two C–C bonds.

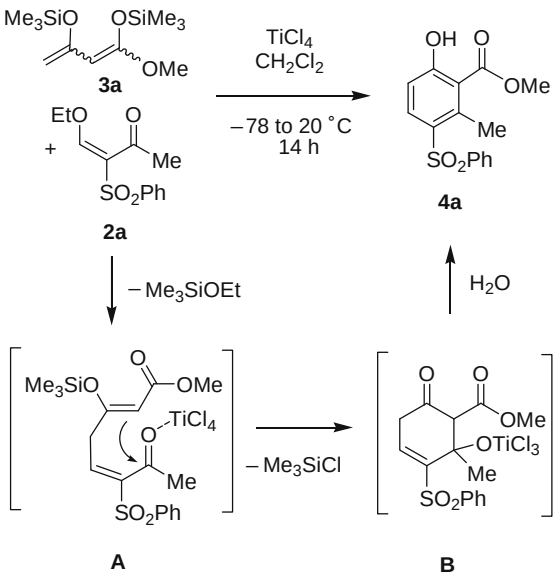
1,3-Bis(silyloxy)-1,3-butadienes **3a–g** were prepared from the corresponding β-ketoesters in two steps.[22] 2-Arylsulfonyl-3-ethoxy-2-en-1-ones **2a–d** were prepared, following a known procedure,[25] by reaction of β-ketosulfones **1a–d** with triethyl orthoformate and acetic anhydride (Scheme 1).

The $TiCl_4$-mediated cyclization of **2a** with **3a** afforded the novel 4-(arylsulfonyl)phenol **4a** in up to 80% yield (Scheme 2). The best yield was obtained when the reaction was carried out, in a highly concentrated solution.[26] It is worth to be noted that the cyclization proceeded with excellent regioselectivity. The formation of product **4a** might be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **3a** onto **2a** to give intermediate **A**, cyclization via the central carbon (intermediate **B**) and subsequent aromatization.

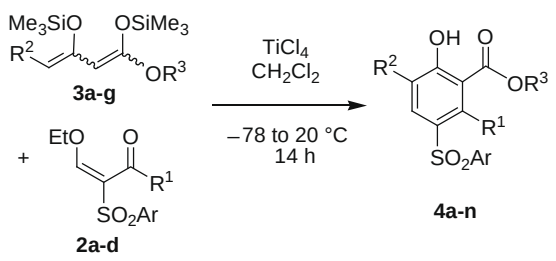
The formal [3+3] cyclization of 2-arylsulfonyl-3-ethoxy-2-en-1-ones **2a–d** with 1,3-bis(silyloxy)-1,3-butadienes **3a-g** afforded the 4-(arylsulfonyl)phenols **4a–n** in 45–80% yield (Scheme 3, Table 1). The aryl groups located at the sulfonyl group of enones **2** have



Scheme 1. Synthesis of **2a–d**. Reagents and conditions: (i) **1a–d** (1.0 equiv), $HC(OEt)_3$ (1.2 equiv), Ac_2O, reflux, 2 h.



Scheme 2. Possible mechanism of the formation of **4a**.



Scheme 3. Synthesis of **4a–n**.

Table 1
Synthesis of **4a–n**

2	3	4	Ar	R^1	R^2	R^3	%[a]
a	**a**	**a**	Ph	Me	H	Me	80
a	**b**	**b**	Ph	Me	*n*Bu	Me	76
a	**c**	**c**	Ph	Me	*n*Hept	Me	75
b	**a**	**d**	4-MeC_6H_4	Me	H	Me	57
b	**d**	**e**	4-MeC_6H_4	Me	Me	Me	65
b	**b**	**g**	4-MeC_6H_4	Me	*n*Bu	Me	65
b	**c**	**h**	4-MeC_6H_4	Me	*n*Hept	Me	60
b	**e**	**f**	4-MeC_6H_4	Me	*n*Oct	Me	59
c	**a**	**i**	4-ClC_6H_4	Me	H	Me	47
c	**d**	**j**	4-ClC_6H_4	Me	Me	Me	48
c	**f**	**k**	4-ClC_6H_4	Me	Et	Et	47
c	**g**	**l**	4-ClC_6H_4	Me	*n*Hex	Me	50
c	**e**	**m**	4-ClC_6H_4	Me	*n*Oct	Me	52
d	**a**	**n**	4-MeC_6H_4	4-$(O_2N)C_6H_4$	H	Me	45

[a] Yields of isolated products.

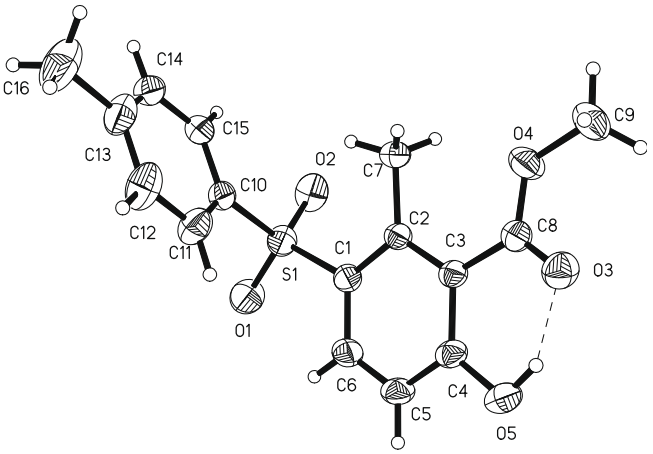


Figure 1. Ortep plot of **4d** (30% probability level).

some influence on the yields. The best yields were obtained for products **4a–c** derived from phenyl-substituted enone **2a**. In contrast, the presence of a substituent located at carbon atom C-4 of the 1,3-bis(silyloxy)-1,3-butadiene has no significant effect on the yield. Products **4a–m**, derived from enones **2a–c**, contain a methyl group located at carbon C-3 of the phenol moiety. Product **4n**, containing an aryl group located at C-3, was prepared from enone **2d**. The yield was slightly lower than the yield of **4d** (which also contains, like **4n**, a tosyl group located at C-4). All products were formed with excellent regioselectivity.

The structures of all products were confirmed by spectroscopic methods. The structure of **4d** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[27]

In conclusion, we have reported a convenient and regioselective synthesis of 4-(arylsulfonyl)phenols by what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 2-arylsulfonyl-3-ethoxy-2-en-1-ones. The reactions are easy to be carried out and the starting materials are readily available. We currently study the preparative scope of the methodology and applications to the synthesis of pharmacologically active products.

Acknowledgment

Financial support by the State of Mecklenburg-Vorpommern (Landesgraduierten-scholarship for M.S.) is gratefully acknowledged.

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26. *General procedure for the synthesis of 4-(arylsulfonyl)phenols* **4a–n**: To a CH_2Cl_2 solution (2 mL/1 mmol of **2a–d**) of **2a–d** were added **3a–g** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at 78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purifed by chromatography (silica gel, heptanes/EtOAc) to give **4a–n**.
Methyl 6-hydroxy-2-methyl-3-tosylbenzoate (**4d**): Starting with **2a** (0.402 g, 1.5 mmol) and **3a** (0.429 g, 1.65 mmol), **4d** was isolated (0.274 g, 57%) as a yellowish solid (0.274 g, 57%), mp 109–110 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_{3Ar}), 2.47 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.87 (d, ^3J = 8.4 Hz, 1H, Ar), 7.14–7.17 (m, 2H, Ar), 7.35–7.58 (m, 2H, Ar), 8.22 (d, ^3J = 8.7 Hz, 1H, Ar), 11.03 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.0, 21.5 ($2 \times CH_3$), 52.7 (OCH_3), 115.1 (CCO_2CH_3), 115.6 (CH_{Ar}), 127.3 ($2 \times CH_{Tol}$), 129.6 ($2 \times CH_{Tol}$), 131.8 ($C_{Ar}SO_2$), 135.2 (CH_{Ar}), 138.9 ($C_{Ar}CH_3$), 142.6 ($C_{Tol}SO_2$), 143.8 ($C_{Tol}CH_3$), 165.2 (COH), 171.0 (CO). IR (KBr, cm^{-1}): ν = 3072 (w), 3029 (w), 2953 (w), 2922 (w), 2852 (w), 1715 (w), 1673 (m), 1592 (m), 1574 (m), 1495 (w), 1435 (m), 1348 (m), 1300 (m), 1286 (m), 1218 (m), 1188 (m), 1155 (m), 1142 (s), 1109 (m), 1081 (m), 1040 (w), 1018 (w), 997 (m), 939 (m), 848 (w), 815 (m), 759 (w), 709 (m), 692 (m), 649 (m), 597 (w), 587 (m), 565 (m), 549 (m), 533 (s). GC–MS (EI, 70 eV): *m/z* (%) = 320 ($[M]^+$, 34), 289 (27), 288 (100), 271 (23), 269 (18), 256 (9), 255 (48), 224 (16), 223 (20), 222 (17), 181 (10), 152 (11), 149 (12), 121 (12), 105 (10), 91 (19), 77 (22), 65 (20), 51 (14). HRMS (EI): Calcd for $C_{16}H_{16}O_5S$ ($[M]^+$): 320.07130; found: 320.071076. All products gave correct elemental analyses and/or HRMS data.
27. CCDC-699679 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, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.