Tetrahedron Letters 49 (2008) 5618–5619

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 5-(2-aryl-2-haloethyl)salicylates by the first domino '[3+3] cyclization/ring-cleavage' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 3-acetyl-5-aryl-4,5-dihydrofurans

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ARTICLE INFO

Article history:
Received 3 June 2008
Revised 6 July 2008
Accepted 7 July 2008
Available online 11 July 2008

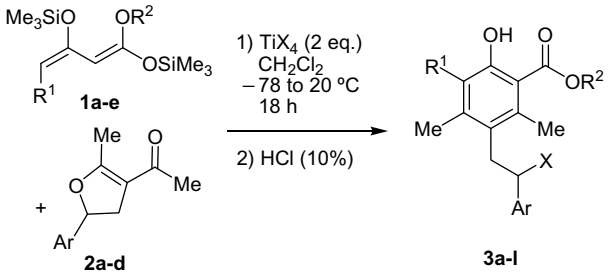
Keywords:
Arenes
Cyclizations
silyl enol ethers

ABSTRACT

5-(2-Aryl-2-haloethyl)salicylates are efficiently prepared by the first domino '[3+3] cyclization/ring-cleavage' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 3-acetyl-5-aryl-4,5-dihydrofurans.

Highly substituted salicylates are pharmacologically important molecules, which occur in a variety of natural products.[1] Recently, we have reported[2] the synthesis of functionalized salicylates by $TiCl_4$-mediated domino '[3+3] cyclization[3]/homo-Michael' reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[4] with 1,1-diacylcyclopropanes. We were intrigued by the possibility of extending this concept to new domino '[3+3] cyclization/ring-cleavage' reactions by application of other types of substrates. Herein, we report preliminary results of our studies directed to what are, to the best of our knowledge, the first domino '[3+3] cyclization/ring-cleavage' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 3-acetyl-5-aryl-4,5-dihydrofurans. These reactions provide a convenient and regioselective approach to 5-(2-aryl-2-haloethyl)salicylates which are not readily available by other methods.[5]

The CAN-mediated reaction of styrenes with acetylacetone afforded the 3-acetyl-5-aryl-4,5-dihydrofurans **2a**–**d** in 80–92% yields (Scheme 1).[6] 1,3-Bis(trimethylsilyloxy)-1,3-butadienes **1a**–**e** are readily available in two steps from the corresponding β-ketoesters.[7] The reaction of **2a** with **1a**, in the presence of $TiCl_4$, afforded the 5-(2-phenyl-2-chloroethyl)salicylate **3a**.[8] The best yields of **3a** were obtained when 1.0 equiv of **2a**, 1.7 equiv of **1a** and 2.0 equiv of $TiCl_4$ were employed. The low concentration (c(**2a**) = 0.017 M) and the use of hydrochloric acid (10%) for the aqueous work-up also played an important role.



Scheme 1. Synthesis of **3a**–**l**.

The formation of **3a** might be explained (Scheme 2) by chelation of $TiCl_4$ by the carbonyl group of **2a** (intermediate **A**). Attack of the terminal carbon atom of **1a** onto **2a** with extrusion of Me_3SiCl would afford intermediate **B**. The attack of a second molecule of $TiCl_4$ onto the furan oxygen atom would give intermediate **C**. The furan ring would then be cleaved by nucleophilic attack of a chloride ion, derived from $TiCl_4$, onto the carbon attached to the phenyl group to give intermediate **D**. The latter would undergo a cyclization via the central carbon atom of the 1,3-dicarbonyl unit to give intermediate **E**. The product would be subsequently formed by aromatization and hydrolysis upon aqueous work-up. Alternatively, the [3+3] cyclization might occur in the first and the cleavage of the furan moiety in the second step. The overall process can be regarded as a domino[9] '[3+3] cyclization/ring-cleavage' reaction.

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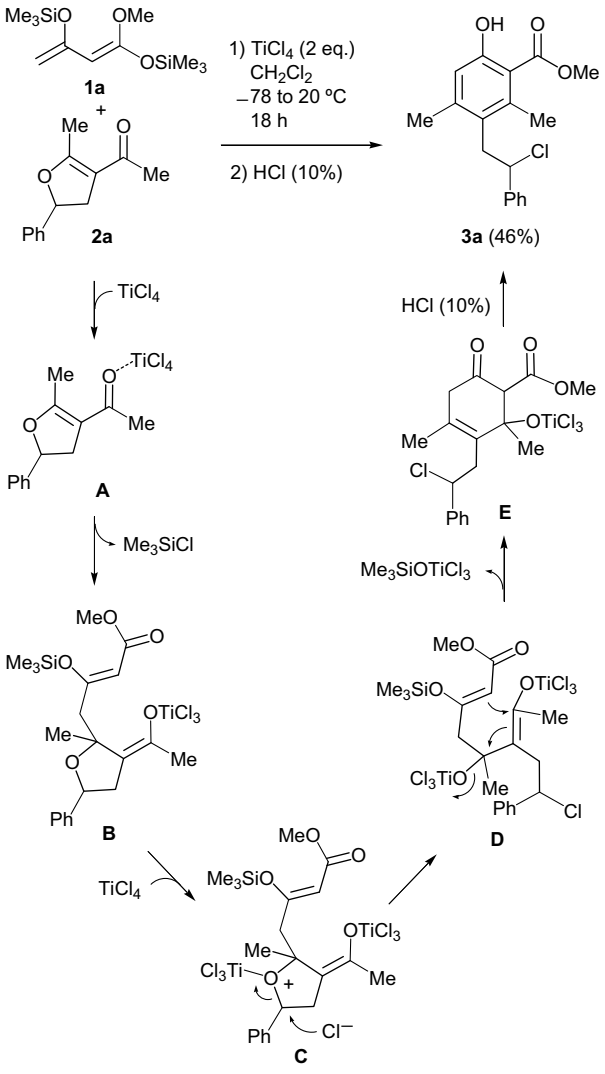
doi:10.1016/j.tetlet.2008.07.049



Scheme 2. Possible mechanism of the formation of **3a**.

The $TiCl_4$-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes **1a**–**e** with 3-acetyl-5-aryl-4,5-dihydrofurans **2a**–**d** afforded the 5-(2-aryl-2-chloroethyl)salicylates **3a**–**k** (Scheme 1, Table 1). The cyclization of **1a** with **2a** in the presence of $TiBr_4$ afforded the brominated product **3l**. The structure of the products was confirmed by spectroscopic methods (2D NMR). The yields of the products derived from halogenated 3-acetyl-5-aryl-4,5-dihydrofurans **2c** and **2d** tend to be slightly higher than those of the products derived from **2a** and **2b**. This can be explained by the electron-withdrawing effect of the halogen atoms which results in an activation of the dihydrofuran.

In conclusion, we have reported what are, to the best of our knowledge, the first domino '[3+3] cyclization/ring-cleavage' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 3-acetyl-5-aryl-4,5-dihydrofurans. These reactions provide a convenient approach to 5-(2-aryl-2-haloethyl)salicylates which are not readily available by other methods. The preparative scope and applications of the methodology are currently studied.

Table 1
Synthesis of **3a**–**l**

1	2	3	R^1	R^2	Ar	X	%[a]
a	**a**	**a**	H	Me	Ph	Cl	46
b	**a**	**b**	H	Et	Ph	Cl	44
c	**a**	**c**	Me	Me	Ph	Cl	36
d	**a**	**d**	Et	Me	Ph	Cl	51
a	**b**	**e**	H	Me	4-MeC_6H_4	Cl	35
a	**c**	**f**	H	Me	4-ClC_6H_4	Cl	58
b	**c**	**h**	H	Et	4-ClC_6H_4	Cl	74
d	**c**	**g**	Et	Me	4-ClC_6H_4	Cl	56
a	**d**	**h**	H	Me	4-BrC_6H_4	Cl	53
e	**d**	**i**	H	*i*Pr	4-BrC_6H_4	Cl	66
c	**d**	**j**	Me	Me	4-BrC_6H_4	Cl	62
d	**d**	**k**	Et	Me	4-BrC_6H_4	Cl	45
a	**a**	**l**	H	Me	Ph	Br	35

[a] Yields of isolated products. For all **3l**, a small amount of impurity could not be separated.

Acknowledgement

Financial support by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

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8. *General procedure for the synthesis of salicylates* **3a**–**l**: To a solution of CH_2Cl_2 and **1** (1.0 equiv), 1,3-bis(silyl enol ethers) **2** and (1.7 equiv) $TiCl_4$ (2.0 equiv) were added dropwise at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C during 18 h. To the reaction mixture was added an aqueous solution of HCl (10%). The organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, *n*-heptane/EtOAc) to give salicylates **3**. Starting with **1b** (0.167 g, 0.83 mmol), **2a** (0.340 g, 1.5 mmol) and $TiCl_4$ (0.18 mL, 1.65 mmol) in CH_2Cl_2 (50 mL), **3b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 50:1) as a colourless solid (0.120 g, 44%); mp = 66–68 °C; R_f = 0.67 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.42 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.12, 2.42 (s, 3H, CH_3), 3.26 (dd, $^2J_{Ha,Hb}$ = 14.8 Hz, $^3J_{Hab,Hx}$ = 7.3 Hz, 1H, CH_{ab}), 3.50 (dd, $^2J_{Ha,Hb}$ = 14.8 Hz, $^3J_{Hab,Hx}$ = 7.3 Hz, 1H, CH_{ab}), 4.41 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 4.96 (t, $^3J_{Hx,Hab}$ = 7.3 Hz, 1H, CHCl), 6.64 (s, 1H, CH_{Ar}), 7.30 (s, 5H, Ph), 10,78 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 19.1, 21.4 (CH_3), 40.3 (CH_2CHCl), 61.6 (OCH_2CH_3), 63.2 (CHCl), 112.0, 127.1, 139.4, 141.2, 144.8, 160.2 ($C_{Ar,Ph}$), 117.2 (C_{Ar}), 126.9, 128.3, 128.4 (C_{Ph}), 171.5 ($COOCH_2CH_3$). MS (EI, 70 eV): *m*/*z* (%) = 334 (M^+, ^{37}Cl, 0.8), 332 (M^+, ^{35}Cl, 2), 250 (7), 207 (65), 161 (100). Anal. Calcd for $C_{19}H_{21}ClO_3$ (332.82): C, 68.57; H, 6.36. Found: C, 68.67; H 6.36.
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