Tetrahedron Letters 49 (2008) 5400–5402

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 3-aryl-3,4-dihydroisocoumarins by regioselective domino '[3+3] cyclization/lactonization' reactions of 1,3-bis-(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones

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ARTICLE INFO

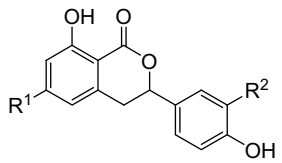
Article history:
Received 22 May 2008
Revised 25 June 2008
Accepted 1 July 2008
Available online 4 July 2008

Keywords:
Arenes
Cyclizations
Regioselectivity
Silyl enol ethers

ABSTRACT

The [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones afforded 6-(2-aryl-2-chloroethyl)salicylates, which were transformed into 3-aryl-3,4-dihydroisocoumarins by silica gel-mediated lactonization.

3-Aryl-3,4-dihydroisocoumarins (3-aryl-isochroman-1-ones) are of considerable pharmacological relevance and occur in many natural products. For example, the natural products thunberginol C, D, and E (Chart 1) and related natural products have been reported to promote the adipogenesis of murine 3T3-L1 cells[1a] and show antiproliferative activity against mouse splenocytes.[1b] Hydrangenol exhibits cytotoxic activity against human gastric cancer cell lines and human nasopharyngeal carcinoma cell lines.[2] Related natural products[3] have been reported to show antifungal activity,[4] inhibition of rat basophilic leukemia RBL-2H3 cells,[5] antiproliferative activity against C57/BL6 mouse splenocytes,[6] antiallergic activity,[7] induction of steroidogenesis,[8] phagocytic activity,[9] immunomodulatory activity on spleen lymphocyte proliferation (activated by lipopolysaccharide, concanavalin A, and phytohemagglutinin in mice),[10] and antimicrobial activity.[11] In a number of natural products, one of the hydroxyl groups of the 3-aryl-3,4-dihydroisocoumarin core structure is glycosylated;[12] this includes, for example, (−)-hydrangenol 4′-O-glucoside[9] and phyllodulcin 8-O-glucoside.[1a,11a]



Hydrangenol (R^1 = H, R^2 = H)
Thunberginol C (R^1 = OH, R^2 = H)
Thunberginol D (R^1 = OH, R^2 = OH)

Chart 1. 3-Aryl-3,4-dihydroisocoumarins in nature.

Chan and coworkers were the first to report[13] the $TiCl_4$-mediated [3+3] cyclization[14] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[15] with 3-silyloxy-2-en-1-ones, which allows a convenient synthesis of salicylates. In recent years, we studied the application of this reaction to the synthesis of various functionalized arenes.

Recently, we reported the synthesis of dibenzo[*b*,*d*]pyran-6-ones based on a [3+3] cyclization/lactonization strategy.[16] Herein, we report what are, to the best of our knowledge, the first domino[17] '[3+3] cyclization/lactonization' reactions of 1,3-bis-(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones. These reactions proceed with very good regioselectivity and provide a convenient approach to 3-aryl-3,4-dihydroisocoumarins, which are not readily available by other methods.

The reaction of the dianion of acetylacetone (**1**) with aldehydes **2a**–**c** afforded, following a known procedure,[18] condensation products **3a**–**c** (Scheme 1, Table 1). The NEt_3-mediated reaction of **3a**–**c** with Me_3SiCl resulted in chemoselective formation of 1-aryl-1-hydroxy-5-silyloxy-4-en-3-ones **4a**–**c**. Notably, a silylation of the hydroxy group was not observed.

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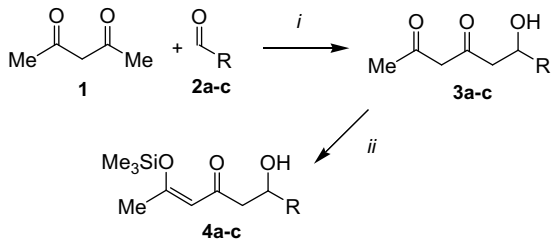
doi:10.1016/j.tetlet.2008.07.014



Scheme 1. Synthesis of 1-aryl-1-hydroxy-5-silyloxy-4-en-3-ones **4a**–**c**: Reagents and conditions: (i) (1) **1**, 2.5 LDA, THF, 1 h, 0 °C; (2) **2a**–**c**, −78→20 °C, 14 h; (3) $NaHCO_3$, H_2O; (ii) NEt_3, Me_3SiCl, CH_2Cl_2, 20 °C, 14 h.

Table 1
Synthesis of 1-hydroxy-5-silyloxy-4-en-3-ones **4a**–**c**

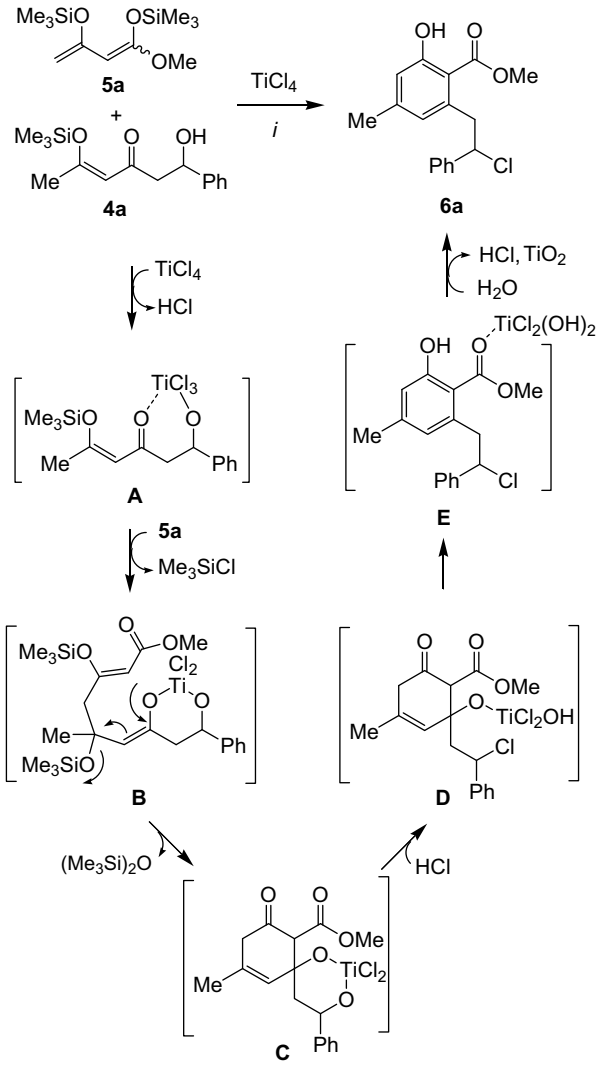
3,4	R	%[a]	%[a]
a	Ph	70	86
b	4-MeC_6H_4	66	92
c	4-ClC_6H_4	60	88

[a] Yields of isolated products.

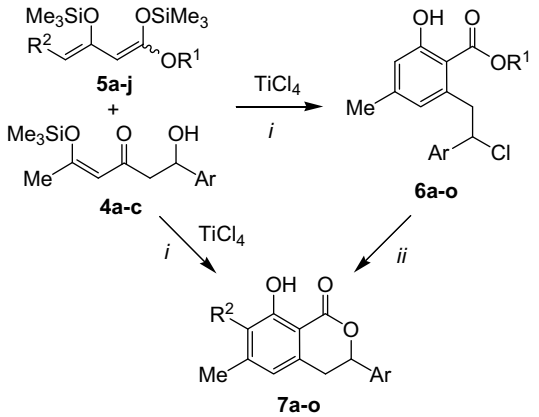
The $TiCl_4$-mediated [3+3] cyclization of **4a** with 1,3-bis(silyl enol ether) **5a**, readily available from methyl acetoacetate,[13] afforded the novel 6-(2-phenyl-2-chloroethyl)salicylate **6a** (Scheme 2). The best yield was obtained when the reaction was carried out in a highly concentrated solution.[19] Notably, the cyclization proceeded with excellent regioselectivity. In fact, the formation of the regioisomeric 4-(2-phenyl-2-chloroethyl)salicylate was *not* observed. The formation of product **6a** might be explained by reaction of $TiCl_4$ with **4a** to give intermediate **A** and hydrogen chloride. The conjugate addition of the (most reactive) terminal carbon atom of **5a** to **A** afforded intermediate **B**, which underwent a cyclization to give intermediate **C**. The reaction of HCl with the carbon atom attached to the phenyl group resulted in nucleophilic substitution and formation of intermediate **D**. The latter underwent aromatization to give intermediate **E**. Product **6a** is formed upon aqueous work-up. Interestingly, the presence of the *free* hydroxy group of **4a** seems to be important to achieve a high degree of regioselectivity. The presence of a methoxy rather than a hydroxyl group resulted in the formation of a mixture of regioisomers.

Stirring of a solution of **6a** in wet THF in the presence of silica gel afforded the 3-phenyl-3,4-dihydroisocoumarin **7a** in 69% yield (Scheme 3, Table 2).[20] The formation of **7a** can be explained by acid-mediated hydrolysis of the chloride and subsequent lactonization.

The [3+3] cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadienes **5b**–**d**, containing an alkyl group attached to carbon atom C4, directly afforded the 3-phenyl-3,4-dihydroisocoumarins **7b**–**d**. The formation of **7b**–**d** can be explained by [3+3] cyclization to give 6-(2-phenyl-2-chloroethyl)salicylates, which subsequently hydrolyzed and underwent a lactonization during the aqueous work-up or silica gel chromatography. This process can be regarded as a domino '[3+3] cyclization/lactonization' reaction. The cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadienes **5e**,**f** resulted in the formation of 6-(2-phenyl-2-chloroethyl)salicylates **6e**,**f**, which were transformed, by treatment with silica gel, into the 3-phenyl-3,4-dihydroisocoumarins **7e**,**f**. The cyclization of **4a** with 1,3-bis(silyloxy)-1,3-butadienes **5g**,**h** afforded the ethyl and isopropyl salicylates **6g**,**h**. Notably, the SiO_2-mediated lactonization proved to be unsuccessful for these substrates. The cyclization of **4b** with **5a**,**b**,**e**,**i** directly afforded the 3-(4-tolyl)-3,4-dihydroisocoumarins **7i**–**l**. The reaction of **4b** with **5j** gave the benzyl salicylate **6m**, which could not be transformed into **7m**.



Scheme 2. Possible mechanism of the formation of **6a**: Reagents and conditions: (i) (1) $TiCl_4$, CH_2Cl_2, −78→20 °C, 14 h; (2) $NaHCO_3$, H_2O.



Scheme 3. Synthesis of **6a**–**o** and **7a**–**o**: Reagents and conditions: (i) (1) $TiCl_4$, CH_2Cl_2, −78→20 °C, 14 h; (2) $NaHCO_3$, H_2O; (ii) SiO_2, wet THF, 14 h.

The cyclization of **5a** with **4c** directly afforded the 3-(4-chlorophenyl)-3,4-dihydroisocoumarin **7n**. The reaction of **4c** with **5j** gave the benzyl salicylate **6o**; its transformation into **7o** proved to be unsuccessful.

Table 2
Synthesis of 6-(2-aryl-2-chloroethyl)salicylates **6a–o** and 3-aryl-3,4-dihydroisocoumarins **7a–o**

4	5	6,7	R^1	R^2	Ar	% (**6**)[a]	% (**7**)[a]
a	**a**	**a**	Me	H	Ph	52	69
a	**b**	**b**	Me	Me	Ph	0	48
a	**c**	**c**	Me	Et	Ph	0	33
a	**d**	**d**	Me	*n*Dec	Ph	0	54
a	**e**	**e**	Me	Allyl	Ph	33	55
a	**f**	**f**	Me	OMe	Ph	44	66
a	**g**	**g**	Et	H	Ph	37	0
a	**h**	**h**	*i*Pr	H	Ph	40	0
b	**a**	**i**	Me	H	4-MeC_6H_4	0	41
b	**b**	**j**	Me	Me	4-MeC_6H_4	0	43
b	**i**	**k**	Me	*n*Bu	4-MeC_6H_4	0	62
b	**e**	**l**	Me	Allyl	4-MeC_6H_4	0	35
b	**j**	**m**	Bn	H	4-MeC_6H_4	32	0
c	**a**	**n**	Me	H	4-ClC_6H_4	0	55
c	**j**	**o**	Bn	H	4-ClC_6H_4	34	0

[a] Yields of isolated products.

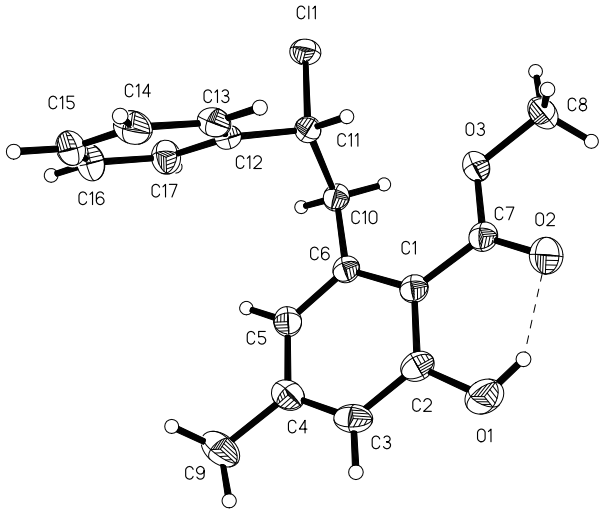


Figure 1. Ortep plot of **6a** (50% probability level); the position of the OH-proton was calculated from the difference map and refined freely.

The structures of all products were confirmed by spectroscopic methods. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[21]

In conclusion, we have reported a convenient synthesis of 3-aryl-3,4-dihydroisocoumarins by domino '[3+3] cyclization/lactonization' reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones. These reactions proceed by regioselective [3+3] cyclization to give 6-(2-aryl-2-chloroethyl)-salicylates and subsequent silica gel-mediated lactonization. Under the reaction conditions, a smooth lactonization is observed for methyl, but not for ethyl, isopropyl, and benzyl salicylates. We are currently studying the preparative scope of our methodology and applications to the synthesis of pharmacologically active natural products and their analogues.

Acknowledgement

Financial support by the Friedrich-Irmgard-Harms-Stiftung (scholarship for A.A.) is gratefully acknowledged.

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19. *Typical procedure: synthesis of methyl 4-methyl-6-(2-phenyl-2-chloroethyl)-salicylate* (**6a**): To a CH_2Cl_2 solution (5 mL) of **5a** (500 mg, 1.91 mmol) and **4a** (490 mg, 2.07 mmol) was dropwise added $TiCl_4$ (0.22 mL, 2.07 mmol) at −78 °C. The reaction mixture was allowed to warm to 20 °C during 6–12 h. After stirring for additional 2–6 h at 20 °C, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried ($NaSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/ethyl acetate) to give **6a** as a colorless solid (302 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3H, CH_3), 3.61 (dd, 2H, J = 7.4, 2.9 Hz, CH_2), 3.93 (s, 3H, OCH_3), 5.02 (dd, 1H, J = 7.4, 6.2 Hz), 6.41 (s, 1H, ArH), 6.72 (s, 1H, ArH), 7.29–7.35 (m, 5H, Ph), 11.23 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 46.7 (CH_2), 52.3 (OCH_3), 64.1 (CH), 109.5 (C), 117.3, 125.9, 126.9, 128.3, 128.5 (CH_{Ar}), 139.4, 141.6, 145.3, 163.0, 171.3 (C). IR (KBr): $\tilde{\nu}$ = 2955 (w), 1653 (s), 1568 (m), 1452 (s), 1317 (s), 1261 (s), 1207 (s), 1092 (s), 955 (m), 855 (m) 728 (s), 691 (s) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 304 (M^+, ^{35}Cl, 35), 306 (M^+, ^{37}Cl, 13), 268 (32), 237 (86), 208 (24), 179 (100), 165 (31), 125 (45), 119 (21), 89 (15), 77 (13). HRMS (EI): calcd for $C_{17}H_{17}O_3Cl$ $[M]^+$: 304.087148; found: 304.08607.
20. *Typical procedure: synthesis of 8-hydroxy-6-methyl-3-phenylisochroman-1-one* (**7a**): To a THF solution of **6a** (190 mg, 0.62 mmol), silica gel (Merck Silica Gel 60, 0.063–0.200 mm, 70–230 mesh, 1.5 g) was added and the mixture was stirred at room temperature for 6–14 h. After completion of the reaction (tlc control), THF was removed in vacuo. The residue was purified by chromatography (silica gel, heptane/ethyl acetate) to give **7a** as a colorless solid (110 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.07 (dd, 1H, J = 16.5, 3.3 Hz, CH_2), 3.27 (dd, 1H, J = 16.3, 3.3 Hz, CH_2), 5.56 (dd, 1H, J = 12.0, 3.3 Hz), 6.56 (s, 1H, ArH), 6.74 (s, 1H, ArH), 7.39–7.45 (m, 5H, Ph), 10.92 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (CH_3), 35.2 (CH_2), 80.7 (CH), 105.9 (C), 116.5, 119.1, 126.1, 128.7, 128.8 (CH_{Ar}), 138.0, 139.0, 148.1, 1662.2, 169.7 (C). IR (KBr): $\tilde{\nu}$ = 3089 (w), 1652 (s), 1455 (m), 1277 (m), 1097 (s), 1060 (s), 912 (w), 845 (s), 798 (s), 699 (s) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 254 (M^+, 100), 236 (69), 208 (61), 179 (40), 165 (51), 148 (31), 91 (28), 77 (22). Elemental Anal. Calcd for $C_{16}H_{14}O_3$ (254.28): C, 75.57; H, 5.55. Found: C, 75.11; H, 5.56.
21. CCDC 689390 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.