Tetrahedron Letters 49 (2008) 4467–4469

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of functionalized 6(5*H*)-phenanthridinones based on a [3+3]-cyclocondensation/lactamization strategy

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ARTICLE INFO

Article history:
Received 9 April 2008
Revised 8 May 2008
Accepted 13 May 2008
Available online 16 May 2008

ABSTRACT

Functionalized 6(5*H*)-phenanthridinones (dibenzo[*b*,*d*]pyrid-6-ones) were prepared by [3+3]-cyclocondensation of 1-trimethylsilyloxy-1,3-butadienes with nitro-substituted 1-aryl-1-silyloxy-1-en-3-ones and subsequent reductive lactamization.

6(5*H*)-Phenanthridinones (dibenzo[*b*,*d*]pyrid-6-ones) are pharmacologically important molecules which occur in a variety of natural products. This includes, for example, sanguinarinone which shows antiparasitic activity against the dog roundworm, anticoagulant activity, and antiproliferative activity against leukemia HL-60 cells.[1] Oxotoddaline has been reported to possess anti-proliferative activity against P-388 and human colon carcinoma HT-29 cells.[2] A number of other pharmacologically active natural products, for example, cytotoxic oxynitidine,[3] have been reported.[4,5] 6(5*H*)-Phenanthridinones have been prepared by reductive cyclization of 2-nitro-2′-alkoxycarbonyl-biphenyls under various conditions (including Fe/AcOH, Fe/THF, Zn/HOAc, Raney-Ni, and H_2-Pd/C).[6] The corresponding biaryls have been prepared by Ullmann-type reactions and by nucleophilic aromatic substitutions.[7] An alternative approach relies on the nitration of appropriate biphenyls.[8] The scope of these reactions is limited by the harsh reaction conditions and by steric effects. In fact, sterically encumbered and highly functionalized derivatives are not readily available by this approach. In addition, the synthesis of the starting materials, highly functionalized arenes, is often not an easy task. These problems can be circumvented by application of a 'building block approach'. To the best of our knowledge, only a single application of this strategy has been reported to date. Ashburn and coworkers reported the synthesis of 2-nitro-2′-alkoxycarbonyl-biphenyls based on [4+2]-cycloadditions.[9]

Chan and coworkers were the first to report a convenient synthesis of functionalized phenols by $TiCl_4$-mediated [3+3]-cyclization[10] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[11] with 3-silyloxy-2-en-1-ones. 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.[12] Herein, we report what is, to the best of our knowledge, the first synthesis of 6(5*H*)-phenanthridinones by application of a [3+3]-cyclocondensation/lactamization strategy. Notably, the products are formed with very good regioselectivity and are not readily available by other methods.

The LDA-mediated condensation of acetone (**1a**) and pentan-2-one (**1b**) with benzoyl chlorides **2a–c** afforded the nitro-substituted benzoylacetones **3a–d** which were transformed into the 1-aryl-1-silyloxy-1-en-3-ones **4a–d** (Scheme 1, Table 1). The $TiCl_4$-mediated cyclization of **4a–d** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5a–f**, readily available in two steps from the corresponding β-ketoesters,[13] afforded the novel nitro-substituted biaryls **6a–n** (Scheme 1, Table 2).[14] All cyclizations proceeded with very good regioselectivity. During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution. The structures of all products were established by spectroscopic methods. The structure of **6m** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[15]

The regioselective formation of products **6a–n** can be explained, following a mechanism first suggested by Chan,[13a] by $TiCl_4$-mediated isomerization of **4** into intermediate type **A**, $TiCl_4$-mediated attack of the terminal carbon atom of 1,3-bis(silyl enol ether) **5** onto the carbon located next to substituent R^1 to give intermediate type **B** (conjugate addition), cyclization (intermediate type **C**), and subsequent aromatization (Scheme 1).

The Pd/C-catalyzed hydrogenation of **6a–h** directly afforded the 6(5*H*)-phenanthridinones **7a–h** (Scheme 2, Table 3). The products are formed by transformation of the nitro into an amino group and subsequent spontaneous lactamization.[16]

The hydrogenation of 3-nitro-3′-hydroxy-biphenyls **6j** and **6k** afforded the 3-amino-3′-hydroxy-biphenyls **8a** and **8b** (Scheme 3). Notably, 3-amino- and 3-nitro-3′-hydroxy-biphenyls are of considerable current interest, due to their wide range of pharmacological properties. This includes, for example, antimalarial activity, binding affinity to C5a receptor (human monocyte cell line

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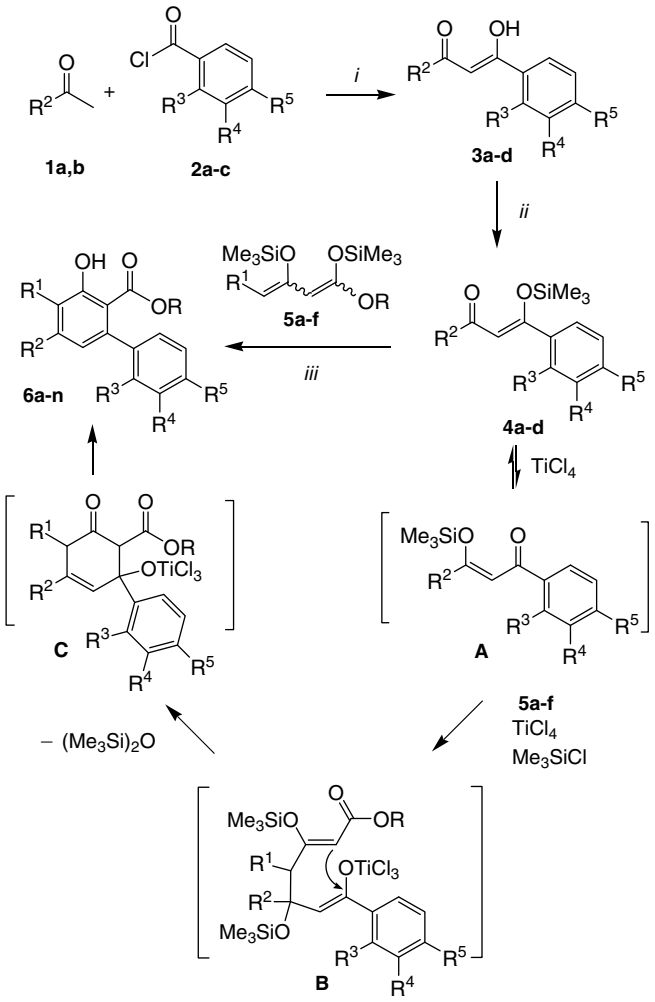
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.067



Scheme 1. Synthesis of **6a–n**. Reagents and conditions: (i) LDA (1.5 equiv), THF; (ii) (1) NEt_3 (1.6 equiv), Me_3SiCl (1.8 equiv), C_6H_6, 20 °C, 3 d; (iii) $TiCl_4$, CH_2Cl_2, −78→20 °C, 18 h.

Table 1
Synthesis of **3a–d**

1	2	3	R^2	R^3	R^4	R^5	% (**3**)[a]	% (**4**)[a]
a	**a**	**a**	Me	NO_2	H	H	54	91
b	**a**	**b**	*n*Pr	NO_2	H	H	45	88
a	**b**	**c**	Me	H	NO_2	H	34	90
a	**c**	**d**	Me	H	H	NO_2	43	92

[a] Yields of isolated products.

Table 2
Synthesis of **6a–n**

4	5	6	R	R^1	R^2	R^3	R^4	R^5	% (**6**)[a]
a	**a**	**a**	Me	H	Me	NO_2	H	H	36
a	**b**	**b**	Me	Me	Me	NO_2	H	H	41
a	**c**	**c**	Et	Et	Me	NO_2	H	H	35
a	**d**	**d**	Me	*n*Oct	Me	NO_2	H	H	40
b	**a**	**e**	Me	H	*n*Pr	NO_2	H	H	48
b	**b**	**f**	Me	Me	*n*Pr	NO_2	H	H	38
b	**c**	**g**	Et	Et	*n*Pr	NO_2	H	H	37
b	**e**	**h**	Me	*n*Hex	*n*Pr	NO_2	H	H	25
c	**a**	**i**	Me	H	Me	H	NO_2	H	32
c	**b**	**j**	Me	Me	Me	H	NO_2	H	50
c	**c**	**k**	Et	Et	Me	H	NO_2	H	37
d	**a**	**l**	Me	H	Me	H	H	NO_2	36
d	**b**	**m**	Me	Me	Me	H	*H*	NO_2	46
d	**f**	**n**	Me	Et	Me	H	H	NO_2	33

[a] Yields of isolated products.

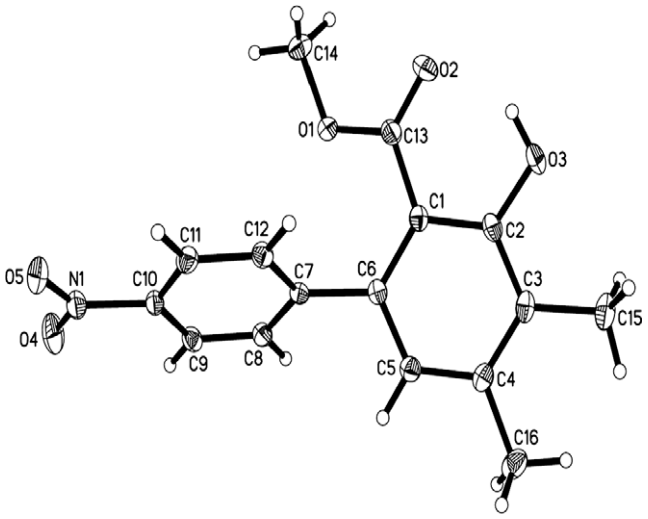
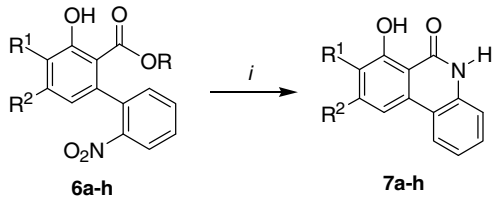


Figure 1. Ortep plot of **6m**.

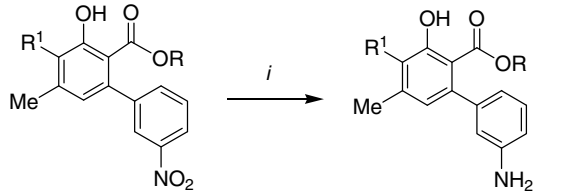


Scheme 2. Synthesis of **7a–h**. Reagents and condition: (i) H_2, Pd/C (10 mol %), 20 °C, 48 h.

Table 3
Synthesis of **7a–h**

6, 7	R	R^1	R^2	% (**7**)[a]
a	Me	Me	H	64
b	Me	Me	Me	52
c	Et	Me	Et	70
d	Me	Me	*n*Oct	69
e	Me	*n*Pr	H	56
f	Me	*n*Pr	Me	50
g	Et	*n*Pr	Et	63
h	Me	*n*Pr	*n*Hex	74

[a] Yields of isolated products.



Scheme 3. Synthesis of **8a,b**. Reagents and condition: (i) H_2, Pd/C (10 mol %), MeOH, 20 °C, 48 h.

U937), inhibition of cyclic nucleotide phosphorodiesterases (PDEs), activity for topoisomerases I and II-mediated DNA cleavage, and anti-hepatitis activity.[17]

In conclusion, we have reported a regioselective approach to functionalized 6(5*H*)-phenanthridinones by application of a

[3+3]-cyclization/lactamization strategy. The products are not readily available by other methods.

Acknowledgment

Financial support by the State of Pakistan (HEC scholarships for I.H., M.A.Y, and I.I.) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

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14. *General procedure for the synthesis of salicylates* **6a**–bf n: To a CH_2Cl_2 solution of silyl enol ether **4** (1.0 equiv) and 1,3-bis(silyl enol ether) **5** (1.1 equiv) was dropwise added $TiCl_4$ (1.1 equiv) at −78 °C under argon atmosphere. The solution was stirred at −78 °C for 30 min and then allowed to warm to 20 °C during 18 h. To the solution was added hydrochloric acid (10%). The organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, *n*-hexane/EtOAc) to give salicylates **6**. *Synthesis of methyl 3-hydroxy-5-methyl-2′-nitro[1,1′-biphenyl]-2-carboxylate* (**6a**). Starting with **5a** (1.145 g, 4.4 mmol), $TiCl_4$ (0.835 g, 4.4 mmol), CH_2Cl_2 (6 mL), and **4a** (1.117 g, 4.0 mmol), **6a** was isolated (0.420 g, 36%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.21 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 6.35 (d, ^4J = 1.9 Hz, 1H, CH_{Ar}), 6.74 (d, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.10–7.13 (m, 1H, CH_{Ar}), 7.36 (ddd, ^3J = 7.4 Hz, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.47 (ddd, ^3J = 7.5 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.92 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ar), 11.10 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 21.6 (CH_3), 51.9 (OCH_3), 108.4 (C_{Ar}), 118.0, 122.5, 123.6, 127.8, 131.1. 132.4 (CH_{Ar}), 138.2, 140.2, 145.6, 147.8, 162.4 (C_{Ar}), 170.4 (C=O). GC–MS (EI, 70 eV): *m/z* (%) = 287 ([M]$^+$, 26), 255 (100), 227 (27), 197 (5), 181 (11), 152 (30), 115 (5), 76 (7). HRMS (EI): calcd for $C_{15}H_{13}NO_5$: 287.07882; found: 287.07873.
15. CCDC-684633 (**6m**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. *General procedure for the synthesis of 6(5H)-phenanthridinones* **7a–h**: To a stirred methanol suspension (25 mL) of Pd/C (10 mol %) was added **6a–h** (1.0 equiv). The mixture was set under a hydrogen atmosphere. After stirring for 48 h at 20 °C, the reaction mixture was filtered (celite) and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexanes→hexanes/EtOAc = 2:1). *Synthesis of 7-hydroxy-9-methyl-6(5H)-phenanthridinone* (**7a**). Starting with **6a** (0.429 g, 1.65 mmol), **7a** was isolated (0.237 g, 64%) by column chromatography (silica gel, heptanes/EtOAc = 30:1→20:1) as a colorless solid. ^{1}H NMR (DMSO-d_6, 250 MHz): δ = 2.45 (s, 3H, CH_3), 6.82 (s, 1H, CH_{Ar}), 7.27–7.30 (m, 1H, CH_{Ar}), 7.33–7.41 (m, 1H, CH_{Ar}), 7.49–7.55 (m, 1H, CH_{Ar}), 7.76 (m, 1H, CH_{Ar}), 8.34 (d, ^3J = 7.9 Hz, 1H, CH_{Ar}), 12.02 (br, 1H, NH), 13.25 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 62 MHz): δ_C = 21.8 (CH_3), 107.9 (C_{Ar}), 113.1 115.0, 116.6 (CH_{Ar}), 118.0 (C_{Ar}), 123.2, 123.6, 128.4 (CH_{Ar}), 129.8, 135.6, 146.0, 159.4 (CAr), 165.7 (C=O). MS (EI 70 eV): *m/z* (%) = 225 ([M]$^+$, 100), 206 (10), 196 (16), 99 (14), 73 (16), 57 (27), 43 (52). HRMS (EI): calcd for $C_{14}H_{11}NO_2$: 225.07853; found: 225.07843.
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