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# Synthesis of dibenzo[*b*,*d*]pyran-6-ones based on a '[3+3] cyclization–Suzuki cross-coupling' strategy

Van Thi Hong Nguyen and Peter Langer*

*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, D-18051 Rostock, Germany*

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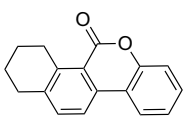
**Abstract**—Functionalized dibenzo[*b*,*d*]pyran-6-ones were prepared by sequential '[3+3] cyclization–Suzuki cross-coupling' reactions.

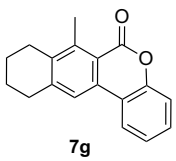

Functionalized dibenzo[*b*,*d*]pyran-6-ones are of pharmacological relevance and occur in a number of natural products, such as alternariol, autumnariol, autumnariniol and altenuisol;[1] dibenzo[*b*,*d*]pyran-6-ones containing an additional lactone bridge are present in ellagic and coruleoellagic acid.[2] Benzo[*d*]naphthopyran-6-ones occur in antibiotics and antitumor compounds isolated from *Streptomyces*; this includes, for example, defucogilvocarcin V, gilvocarcins, chrysomycins and ravidomycins.[3] A classic method for the synthesis of dibenzo[*b*,*d*]pyran-6-ones relies on the cyclization of *o*-bromobenzoic acid with phenols. However, the scope of this method is limited to highly activated substrates and the yields are often rather low.[4] Harris and Hay prepared 9-*O*-methylalternariol by condensation of dilithiated 2,4-pentanedione with a protected salicylate and subsequent domino cyclization.[5] Bringmann and Reuscher developed an approach to dibenzo[*b*,*d*]pyran-6-ones by intramolecular Pd(II) catalyzed coupling reactions of ester-linked aryl bromides and phenols.[6] Snieckus and co-workers reported a versatile and efficient synthesis of dibenzo[*b*,*d*]pyran-6-ones by sequential 'directed *ortho* metallation (DOM)-Suzuki cross-coupling' reactions.[3] This approach relies on the preparation of amide-substituted boronic acids by DOM of benzoic amides. Suzuki cross-coupling reactions of the products with aryl bromides afforded biaryls which were transformed into the target molecules by lactonization.

Herein, we wish to report an alternative approach to dibenzo[*b*,*d*]pyran-6-ones based on sequential '[3+3] cyclization–Suzuki cross-coupling' reactions. Our approach relies on the [3+3] cyclization of 1,3-bis-silyl enol ethers[7,8] with 3-silyloxyalk-2-en-1-ones, a methodology developed by Chan and co-workers.[9] The functionalized salicylates prepared were transformed into their corresponding aryl triflates, which were coupled with boronic acids by Suzuki reactions.[10] The biaryls thus formed were transformed into dibenzo[*b*,*d*]pyran-6-ones by $BBr_3$ mediated lactonization.[11]

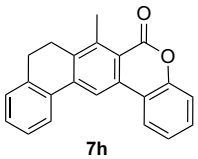
The [3+3] cyclization of ethyl acetoacetate derived 1,3-bis-silyl enol ether **1a** with 4-silyloxypent-3-en-2-one (**2a**), following the procedure reported by Chan and co-workers,[9] afforded the salicylate **3a**, which was transformed into the triflate **4a** (Scheme 1). The Suzuki reaction of **4a** with boronic acid **5a** afforded the biaryl **6a**, which was transformed into the dibenzo[*b*,*d*]pyran-6-one **7a** by $BBr_3$ mediated lactonization.[12,13]



**7f**



**7g**



**7h**

The preparative scope of our methodology was studied (Scheme 1, Table 1). The [3+3] cyclization[9] of 1,3-bis-silyl enol ethers **1a** (R = Et) and **1b** (R = Me) with 3-silyloxyalk-2-en-1-ones **2a–c** afforded the salicylates **3a–c**,

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* Corresponding author: Tel.: +49 3834 864461; fax: +49 3834 864373; e-mail: peter.langer@uni-greifswald.de

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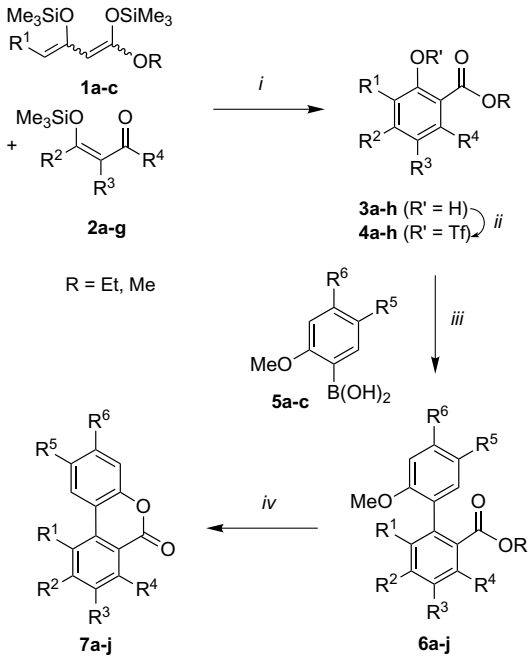
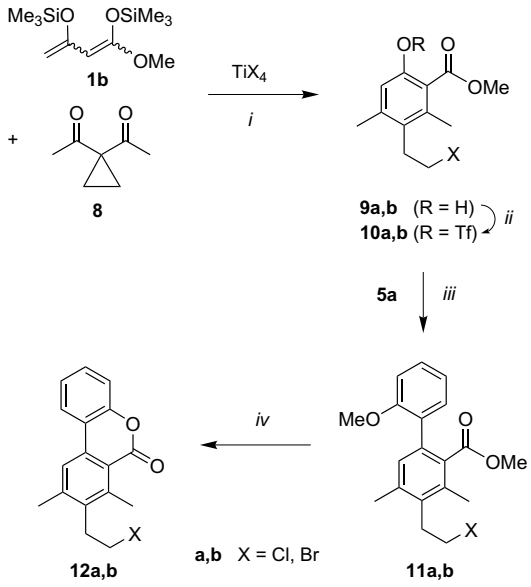



**Scheme 1.** Synthesis of **7a**–**j**. Reagents and conditions: (i) $TiCl_4$, $CH_2Cl_2$, 78 → 20 °C; (ii) $Tf_2O$, pyridine, 78 → 10 °C; (iii) $Pd(PPh_3)_4$ (3 mol %), $K_3PO_4$ (1.5 equiv), dioxane, reflux, 4 h; (iv) (1) $BBr_3$ (4 equiv), $CH_2Cl_2$, 0 → 20 °C, 18 h; (2) KO-*t*-Bu, $H_2O$, 15 min, 20 °C.




**Scheme 2.** Synthesis of **12a**,**b**. Reagents and conditions: (i) $TiX_4$ (X = Cl, Br, 2 equiv), $CH_2Cl_2$, 78 → 20 °C; (ii) $Tf_2O$, pyridine, 78 → 10 °C; (iii) $Pd(PPh_3)_4$ (3 mol %), $K_3PO_4$ (1.5 equiv), dioxane, reflux, 4 h; (iv) (1) $BBr_3$ (4 equiv), $CH_2Cl_2$, 0 → 20 °C, 18 h; (2) KO-*t*-Bu, $H_2O$, 15 min, 20 °C.

which were transformed into the dibenzo[*b*,*d*]pyran-6-ones **7a**–**c** in good overall yields. The reaction of **1a** with silyl enol ether **2d**, prepared from benzoylacetone, regioselectively afforded **3d**, which was transformed into **7d**. The [3+3] cyclization of 1,3-bis-silyl enol ether **1c** with **2a** afforded the salicylate **3e** containing an additional methoxy group. This product was transformed into the hydroxy-substituted dibenzo[*b*,*d*]pyran-6-one **7e**. The tetra- and pentacyclic dibenzo[*b*,*d*]pyran-6-ones **7f**–**h** were prepared based on [3+3] cyclizations[9] of silylated (2-hydroxymethylidene)cyclohexan-1-one, 2-acetylcyclohexan-1-one and 2-acetyltetralone. The reaction of triflate **4c** with the dimethoxyphenylboronic acids **5b**,**c** afforded the biaryls **6i**,**j**, which were transformed into the hydroxy-substituted dibenzo[*b*,*d*]-pyran-6-ones **7i**,**j** .

The $TiCl_4$ and $TiBr_4$ mediated cyclizations of 1,3-bis-silyl enol ether **1b** with 1,1-diacetylcyclopropane (**8**), following our recently reported procedure,[14] afforded the chloro and bromo substituted salicylates **9a** and **9b**, respectively (Scheme 2, Table 2). The Suzuki reaction of triflates **10a** and **10b** with boronic acid **5a** afforded the biaryls **11a** and **11b**. The latter were transformed into the chloro and bromo substituted dibenzo-[*b*,*d*]pyran-6-ones **12a** and **12b** with very good chemoselectivity.

**Table 2.** Products and yields

| 9–12 | X | % (9)[a] | % (10)[a] | % (11)[a] | % (12)[a] |
|---|---|---|---|---|---|
| **a** | Cl | 61 | 92 | 78 | 98 |
| **b** | Br | 51 | 90 | 90 | 76 |

[a] Yields of isolated products; for **9a**,**b**, see Ref. 14.

**Table 1.** Products and yields

| 3–7 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | % (3)[a] | % (4)[a] | % (6)[a] | % (7)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| **a** | H | Me | H | Me | H | H | 38 | 73 | 75 | 92 |
| **b** | H | Me | Me | Me | H | H | 51 | 74 | 73 | 71 |
| **c** | H | Me | Et | Me | H | H | 45 | 85 | 95 | 81 |
| **d** | H | Ph | H | Me | H | H | 31 | 90 | 95 | 73 |
| **e** | OMe | Me | H | Me | H | H | 50 | 65 | 83 | — |
| **e** | OH | Me | H | Me | H | H | — | — | — | 76 |
| **f** | H | H | $-(CH_2)_4-$ | | H | H | 30 | 92 | 79 | 91 |
| **g** | H | $-(CH_2)_4-$ | | Me | H | H | 32 | 75 | 61 | 67 |
| **h** | H | $C_6H_4(CH_2)_2$ | | Me | H | H | 48 | 61 | 55 | 62 |
| **i** | H | Me | Et | Me | OMe | H | 45 | 85 | 65 | — |
| **i** | H | Me | Et | Me | OH | H | — | — | — | 79 |
| **j** | H | Me | Et | Me | H | OMe | 45 | 85 | 47 | — |
| **j** | H | Me | Et | Me | H | OH | — | — | — | 96 |

[a] Yields of isolated products.

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12. *General procedure for the synthesis of* **6**: A dioxane solution of the boronic acid, potassium phosphate, $Pd(PPh_3)_4$ and of the triflate **4** was stirred at 110 °C for 4 h. After cooling, a saturated aqueous solution of $NH_4Cl$ was added. The organic and the aqueous layer were separated and the latter was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography. Synthesis of **6b**: Starting with (2-methoxy)phenylboronic acid (296 mg, 1.95 mmol), potassium phosphate (509 mg, 2.40 mmol), $Pd(PPh_3)_4$ (52 mg, 0.045 mmol), **5b** (510 mg, 1.5 mmol) and dioxane (5 mL), **6b** was isolated by chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colourless solid (320 mg, 73%), mp = 92 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.24 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$), 3.51 (s, 3H, $CH_3O$), 3.74 (s, 3H, $CH_3O$), 6.89 (d, 1H, Ar), 6.92–6.98 (m, 1H, Ar), 7.00 (s, 1H, Ar), 7.14–7.18 (dd, 1H, Ar), 7.28–7.31 (dd, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 15.6 ($CH_3$), 17.6 ($CH_3$), 20.9 ($CH_3$), 51.4 ($CH_3$), 55.5 ($CH_3$), 110.5 (CH), 120.3 (CH), 128.6 (CH), 129.8 (CH), 130.0 (C), 130.6 (CH), 131.9 (C), 133.5 (C), 133.9 (C), 134.8 (C), 137.7 (C), 156.4 (C), 170.4 (C). IR (KBr, $cm^{-1}$): $\tilde{\nu}$ = 2997 (m), 2949 (m), 1719 (s), 1600 (m), 1497 (s), 1464 (s), 1436 (s), 1269 (s), 1239 (s), 1634 (s, 1108 (s), 1048 (s), 1269 (s), 1239 (s), 1164 (s), 1108 (s), 1048 (s), 772 (s). UV–vis (nm): $\lambda_{max}$ (lg $\varepsilon$) = 210.3 (4.59), 281.0 (3.63). MS (EI, 70 eV): *m*/*z* (%) = 285 ($[M+1]^+$, 2), 284 ($M^+$, 17), 253 (21), 210 (43), 182 (15), 152 (4), 28 (100). HRMS (ESI): calcd for $C_{18}H_{21}O_3$ ($[M+1]^+$): 285.14907. Found: 285.14871.
13. *General procedure for the synthesis of* **7**: To a $CH_2Cl_2$ solution of **6** was added $BBr_3$ at 0 °C. The solution was allowed to warm to 20 °C during 18 h. To the solution was added an aqueous solution of KO-*t*-Bu (0.1 M) and the solution was stirred for 15 min. The organic and the aqueous layer were separated and the latter was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and the filtrate was concentrated in vacuo. The product was purified by chromatography (silica gel, *n*-hexane/EtOAc = 25:1) as a colourless solid. Synthesis of **7b**: Starting with **6b** (284 mg, 0.95 mmol) in $CH_2Cl_2$ (3 mL), $BBr_3$ (477 mg, 1.9 mmol) and an aqueous solution of KO-*t*-Bu (0.1 M, 10 mL), **7b** was isolated by chromatography as a colourless solid (160 mg, 71%), mp = 184 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.35 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 2.84 (s, 3H, $CH_3$), 7.25–7.32 (m, 2H, Ar), 7.39–7.45 (m, 1H, Ar), 7.81 (s, 1H, Ar), 8.01–8.05 (dd, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 16.2 ($CH_3$), 18.4 ($CH_3$), 22.2 ($CH_3$), 116.9 (CH), 117.8 (C), 118.4 (C), 120.5 (CH), 122.6 (CH), 123.9 (CH), 129.6 (CH), 133.2 (C), 137.7 (C), 142.2 (C), 143.7 (C), 151.2 (C), 160.8 (C). IR (KBr, $cm^{-1}$): $\tilde{\nu}$ = 3428 (m), 2927 (m), 1726 (s), 1606 (s), 1473 (s), 1272 (s), 1210 (s), 1119 (s), 1010 (s), 753 (s). UV–vis (nm): $\lambda_{max}$ (lg $\varepsilon$) = 239.5 (4.59), 265.4 (4.06), 275.1 (4.08), 289.7 (3.83), 299.5 (3.92), 322.2 (3.87). MS (EI, 70 eV): *m*/*z* (%) = 239 ($[M+1]^+$, 16), 238 ($M^+$, 100), 223 (28), 195 (17), 165 (11), 151 (5), 28 (21). HRMS (ESI): calcd for $C_{16}H_{15}O_2$ ($[M+1]^+$): 239.10721. Found: 239.10736. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.61; H, 5.92. Found: C, 80.19; H, 6.18.
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