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One-Pot Synthesis of Biaryl Lactones by Sonogashira Cross-Coupling Reactions of 4-Chloro-3-formylcoumarin and Subsequent Domino [5+1] Cyclization/Deacetylation Reactions with 1,3-Dicarbonyl Compounds

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Abstract: Biaryl lactones were prepared by a new palladium(0) and base-catalyzed one-pot reaction of 4-chloro-3-formylcoumarin with alkynes and 1,3-dicarbonyl compounds.

Keywords: biaryl lactones; 4-chloro-3-formylcoumarin; cyclization; domino reactions; heterocycles

Biaryl lactones (benzo[*c*]chromen-6-ones) are pharmacologically important core structures that occur in several natural products. Examples include autumnariol, autumnariniol, alternariol, and altenuisol (Figure 1),[1] as well as molecules containing two lactone moieties, e.g., ellagic and coruleoellagic acid,[2] and benzo[*d*]naphthopyran-6-ones, such as the gilvocarcins, chrysomycins and ravidomycins and defucogilvocarcin V. Benzo[*d*]naphthopyran-6-ones show a wide range of pharmacological properties, such as antibiotic and antitumor activities.[3]

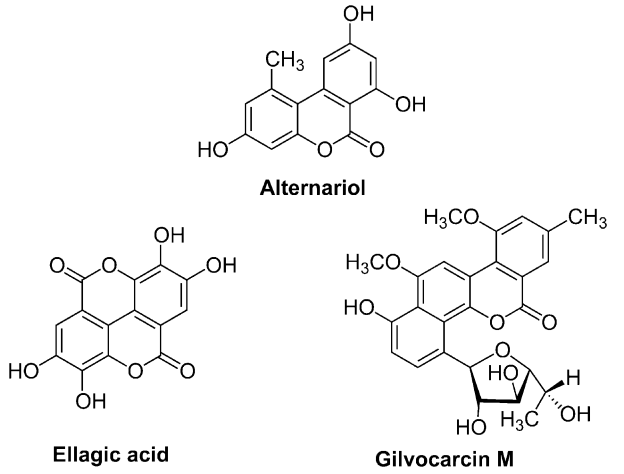
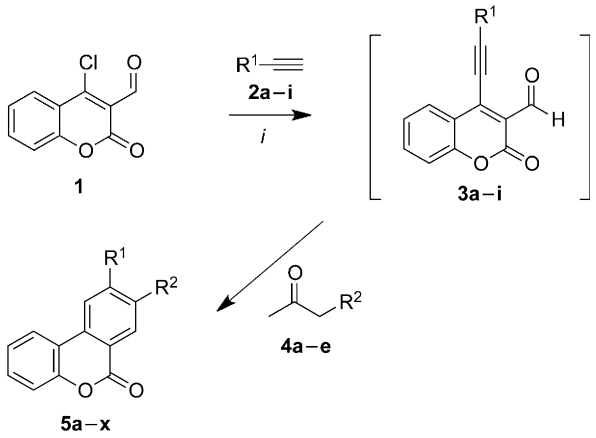


Figure 1. Natural products with benzo[*c*]chromen-6-one subunit.

Biaryl lactones have been prepared by several methods which are based on Pd-catalyzed coupling reactions[4] and are also available by building block syntheses. Examples include the $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 3-(2-methoxyphenyl)-3-silyloxy-2-en-1-ones and subsequent BBr_3-mediated lactonization,[5] the reaction of 1,3-bis(silyloxy)-1,3-butadienes with chromones,[6] and the cyclization[7] of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde[8] with 1,3-bis(silyloxy)-1,3-butadienes.[9] Müller and co-workers reported the synthesis of various heterocycles by consecutive multicomponent reactions initiated by Sonogashira reactions.[10] Herein, we report a new one-pot synthesis of biaryl lactones by Sonogashira reactions of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde and subsequent cyclocondensation with 1,3-dicarbonyl compounds. The cyclization step proceeds by a domino [5+1] cyclization/deacetylation process which has, to the best of our knowledge, not been reported so far.[11] The substitution pattern of the products reported herein is not readily accessible by other methods.

4-Chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**1**) was prepared, according to a literature procedure, by formylation of commercially available 4-hydroxycoumarin with $POCl_3$ and DMF.[12] The Sonogashira reaction of **1** with arylacetylenes **2a–i**, using $PdCl_2(PPh_3)_2$



Scheme 1. *Reagents and conditions: i*, 1) **2a–i**, $PdCl_2(PPh_3)_2$ (4 mol%), CuI (7 mol%), THF, K_2CO_3, 20 °C, 8–10 h; 2) **4a–e**, 50 °C, 5–6 h

as the catalyst (CuI, K_2CO_3, THF, 20 °C, 8–10 h), and subsequent addition of 1,3-dicarbonyl compounds **4a–e** (50 °C, 5–6 h) afforded the biaryl lactones **5a–x** in a one-pot process (Scheme 1, Table 1). In the first step, the (unstable) 4-alkynyl-2-oxo-2*H*-chromene-3-carbaldehydes **3a–i** were formed which were, without isolation, directly transformed to products **5a–x**. The formation of intermediate **3a** was proven by its isolation and characterization and subsequent transformation into the corresponding product **5a**.

Table 1. Yields of pyrrolo[2,3-*b*]pyridines **5a–x**.

2	4	5	R^1	R^2	Time [h]	Yield [%][a]
a	**a**	**a**	4-MeC_6H_4	CO_2Me	8+5	48
a	**b**	**b**	4-MeC_6H_4	CO_2Et	8+5	47
a	**c**	**c**	4-MeC_6H_4	COMe	8+5	43
b	**c**	**d**	Ph	COMe	8+5	42
b	**b**	**e**	Ph	CO_2Et	8+5	46
b	**a**	**f**	Ph	CO_2Me	8+5	47
b	**d**	**g**	Ph	CO_2-*i*-Pr	8+5	44
c	**d**	**h**	*n*-Pr	CO_2-*i*-Pr	10+6	41
c	**a**	**i**	*n*-Pr	CO_2Me	10+6	38
c	**b**	**j**	*n*-Pr	CO_2Et	10+6	43
c	**c**	**k**	*n*-Pr	COMe	10+6	41
d	**c**	**l**	*n*-Pent	COMe	10+6	43
d	**a**	**m**	*n*-Pent	CO_2Me	10+6	45
d	**b**	**n**	*n*-Pent	CO_2Et	10+6	44
e	**a**	**o**	*t*-BuC_6H_4	CO_2Me	8+5	50
e	**b**	**p**	*t*-BuC_6H_4	CO_2Et	8+5	47
e	**d**	**q**	*t*-BuC_6H_4	CO_2-*t*-Bu	8+5	45
e	**e**	**r**	*t*-BuC_6H_4	CO_2Allyl	8+5	44
f	**a**	**s**	2-MeC_6H_4	CO_2Me	8+5	44
g	**a**	**t**	4-*n*-PrC_6H_4	CO_2Me	8+5	46
h	**a**	**u**	4-FC_6H_4	CO_2Me	8+5	54
h	**b**	**v**	4-FC_6H_4	CO_2Et	8+5	52
i	**a**	**w**	4-(MeO)C_6H_4	CO_2Me	8+5	55
i	**b**	**x**	4-(MeO)C_6H_4	CO_2Et	8+5	54

[a] Yields of isolated products.

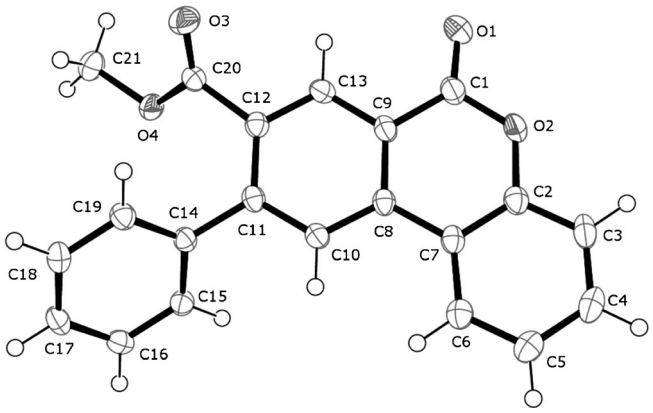
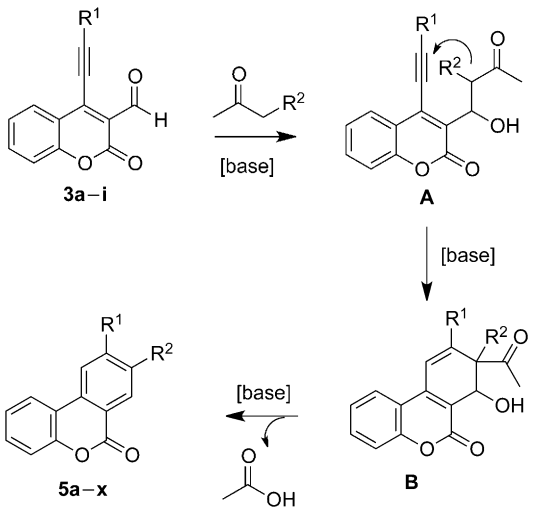


Figure 2. Molecular structure of **5f**.

The best yields were obtained when $PdCl_2(PPh_3)_2$ was used as the catalyst. The use of $Pd(PPh_3)_4$ or $Pd(OAc)_2$ in the presence of XPhos or SPhos resulted in lower yields. In addition, we have found that longer reaction times were required when less than 4 mol% of the catalyst and less than 7 mol% of CuI were employed. Equally successful results were obtained when (dry) potassium carbonate or triethylamine was used as the base. The structure of **5f** was independently confirmed by X-ray crystal structure analysis (Figure 2).[13]

The formation of the products can be explained by base-mediated attack of the 1,3-dicarbonyl compound onto the aldehyde (Knoevenagel reaction) to give intermediate **A**, base-mediated cyclization to give intermediate **B**, and subsequent base-mediated deacetylation (Scheme 2). The overall process can be regarded as a formal [5+1]cyclization. Both β-ketoesters and acetylacetone and both aryl- and alkyl-substituted alkynes could be successfully employed as the starting materials.



Scheme 2. Possible mechanism for the formation of **5a–x**.

In conclusion, we have reported the one-pot synthesis of biaryl lactones by Sonogashira reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde and subsequent cyclocondensation with 1,3-dicarbonyl compounds. The cyclization proceeds by a novel domino [5+1] cyclization/deacetylation reaction. From a preparative viewpoint, the substitution pattern of the products is not readily available by other methods. From a methodology viewpoint, the domino process reported has, to the best of our knowledge, not been reported so far and might be of general interest. At present, we are exploring the scope of the reaction reported herein and its application to other halogenated enals.

Experimental Section

General Procedure for the Synthesis of 5a–n

To a solution of **1** (0.20 g, 1.0 mmol) in THF (7–8 mL) was added K_2CO_3 (0.20 g, 1.5 equiv.). Under a continuous supply of argon were added $PdCl_2(PPh_3)_2$ (4 mol%) and CuI (7 mol%), followed by dropwise addition (an interval of 2 min) of **2** (1.5 equiv.). The reaction mixture was allowed to stir at room temperature for 8 to 10 h and monitored by TLC. To the same reaction vessel was dropwise added the 1,3-dicarbonyl compound (1.5 equiv.). The reaction mixture was then stirred at 50 °C for 5 to 6 h. After completion of the reaction, the reaction mixture was acidified by addition of a few drops of hydrochloric acid (1 M). The mixture was then extracted with ethyl acetate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptanes/EtOAc).

***Methyl 6-oxo-9-phenyl-6H-benzo[c]chromene-8-carboxylate* (5f):** Starting with **1** (0.20 g, 1.0 mmol), K_2CO_3 (0.20 g, 1.5 equiv.), $PdCl_2(PPh_3)_2$ (4 mol%), CuI (7 mol%), **2d** (0.15 g, 1.5 equiv.), and **4d** (0.174 g, 1.5 equiv.), **5d** was isolated by chromatography as a white crystalline solid; yield: 0.155 g (47%); mp 185–187 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.66 (s, 3H, OCH_3), 7.24–7.36 (m, 4H, Ar-H), 7.37–7.50 (m, 4H, Ar-H), 7.98–8.01 (m, 2H, Ar-H), 8.81 (s, 1H, Ar-H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 117.2 (C), 118.0 (CH), 119.9 (C), 123.3, 124.3, 124.8 (CH), 128.2 (2CH), 128.4 (3CH), 131.3 (C), 131.6, 132.9 (CH), 136.8, 140.0, 148.85 (C), 152.0, 160.3, 167.0 (CO); IR (ATR): ν = 2947 (w), 1716 (s), 1608(m), 1228 (s), 1184 (m) 1083(m), 977(m), 751 (s), 703 cm^{-1} (m); GC-MS (EI, 70 eV): *m/z* (%) = 330 ([M]$^+$, 97), 330 (100), 271 (8), 255 (20), 226 (25); HR-MS (EI): *m/z* = 330.0884, calcd. for $C_{21}H_{14}O_3$ ([M]$^+$): 330.0886.

***2-Oxo-4-(p-tolylethynyl)-2H-chromene-3-carbaldehyde* (3a):** yellow crystalline solid; mp 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 7.19–7.37 (m, 4H, Ar-H), 7.58–7.63 (m, 3H, Ar-H), 8.12 (dd, *J* = 8.07 Hz, *J* = 1.38 Hz, 1H, Ar-H), 10.47(s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.91 (CH_3), 83.30, 113.41, 117.21, 117.90, 118.66, 120.59 (C), 125.07, 128.77 (CH), 129.69, (2CH), 133.22 (2CH), 134.65 (CH), 140.10, 142.34 (C), 154.23, 159.68 (CO) 187.67 (CHO); IR (ATR): ν = 2858 (w), 2182 (s), 1698 (m), 1268 (m), 819 (s), 747 cm^{-1} (s); GC-MS (EI, 70 eV): *m/z* (%) = 288 ([M]$^+$, 100), 260 (41), 231 (51), 203 (42), 189 (43), 101 (14); HR-MS (EI): *m/z* = 288.0789, calcd. for $C_{19}H_{12}O_3$ ([M]$^+$): 288.0781.

Acknowledgements

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[13] CCDC 864456 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; Fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk.

