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A rapid access to coumarin derivatives (using Vilsmeier–Haack and Suzuki cross-coupling reactions)

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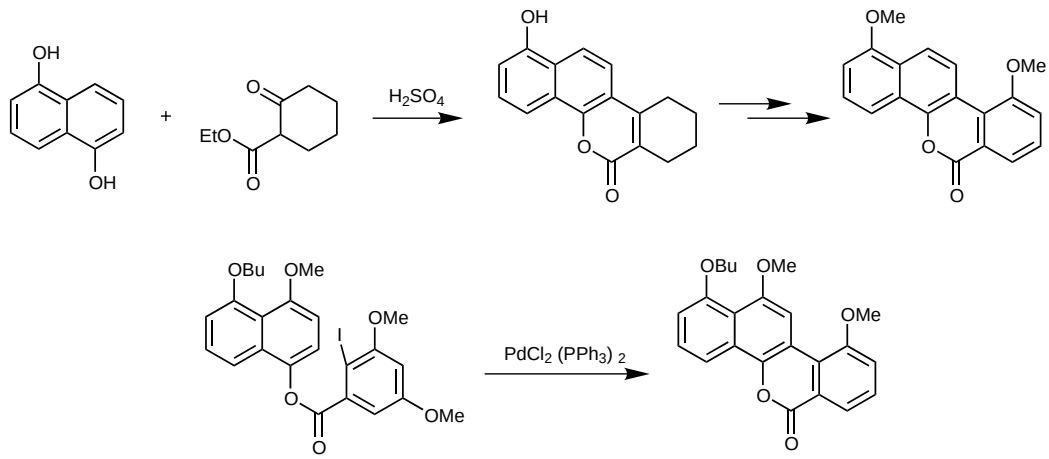
Abstract—A four-step preparation of compounds containing a coumarinic moiety is presented. This synthesis involves notably a Suzuki cross-coupling reaction (performed in aqueous media) and a ring closure by formation of δ-lactone. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Several polycyclic natural products with a coumarinic moiety display a large number of biological properties (anti-bacterial,[1] anti-tumoral,[2] anti-HIV[3]…). Due to those varied biological activities, a considerable amount of synthetic work in the field of coumarins with [3,4]-carbocyclic or [3,4]-heterocyclic fused ring systems has been done[4]. Classical reactions (such as Pechmann condensation, Michaël addition…) are still used but the development of palladium-catalyzed cross-coupling reactions offers new synthetic possibilities. For example, the synthesis of defucogilvocarcins was reported the same year by two different approaches[5] (Scheme 1). The cross-coupling methodology can be used in the ring-closure step or in the formation of the biaryl system.[6] We present here a rapid access to polycyclic compounds containing a coumarinic moiety. (Scheme 2). A key connection to the target molecules is the closure of ring C by formation of the δ-lactone. Another important step of this retrosynthetic pathway is the cross-coupling reaction between β-chloroacroleins and boronic acids.



Scheme 1.

Keywords: coumarin; palladium catalysis; β-chloroacroleins; Vilsmeier–Haack reaction.
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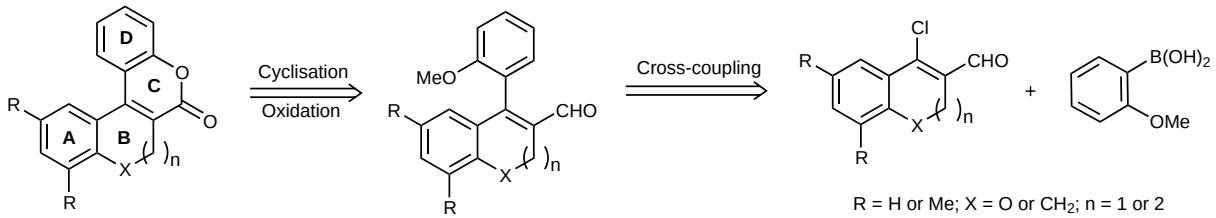


Scheme 2.

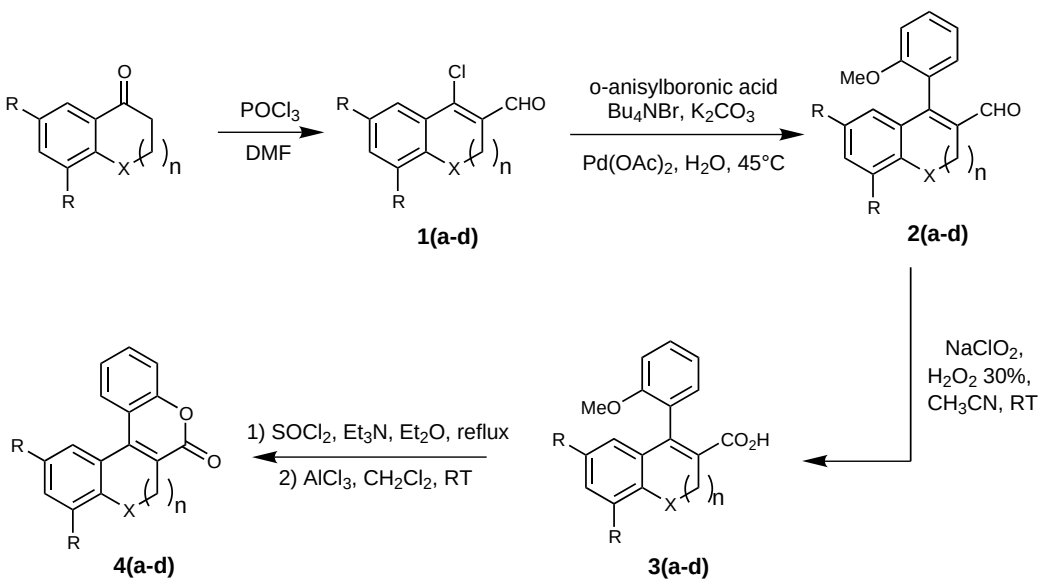
2. Results and discussion

β-Chloroacroleins **1** (**a**–**d**) are easily synthesized from the corresponding ketones by a Vilsmeier–Haack–Arnold reaction.[7] Those vinyl chlorides activated by the presence of an electron-withdrawing group allow good yields in coupling with boronic acids under mild conditions:[8] reactions were performed in aqueous media in presence of 2 mol% of palladium(II) acetate, tetrabutylammonium bromide and potassium carbonate; they were almost complete after three hours at 45°C (Scheme 3).

Oxidation of aldehydes **2** (**a**–**d**) with sodium chlorite[9] in the presence of 30% H_2O_2 in acetonitrile at room temperature allowed the formation of acids **3** (**a**–**d**). Treatment of the corresponding acyl chlorides with aluminum chloride in dichloromethane at room temperature led to the desired tetracyclic systems **4** (**a**–**d**)[10] (Scheme 3 and Table 1).

3. Conclusion

An easy access to β-chloroacroleins and boronic acids associated to mild procedures in this four-step synthesis allowed us the preparation of new coumarin derivatives with moderate to good yields: compounds **4a** and **4b** are obtained, respectively from α-tetralone and 5,7-dimethyl-1-tetralone with only 25 and 29% yield whereas products **4c** and **4d** are, respectively synthesized from 4*H*-chromanone and 3,4-dihydro-2*H*-benzo[*b*]oxepin-5-one with 62 and 53% of global yield.



Scheme 3.

Table 1.

R	X	*n*	**1** (Yield)	**2** (Yield)	**3** (Yield)	**4** (Yield)
H	CH_2	1	**1a** (95)	**2a** (75)	**3a** (86)	**4a** (40)
Me	CH_2	1	**1b** (96)	**2b** (89)	**3b** (96)	**4b** (35)
H	O	1	**1c** (96)	**2c** (98)	**3c** (69)	**4c** (96)
H	O	2	**1d** (85)	**2d** (86)	**3d** (90)	**4d** (80)

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10. Data for tetracyclic systems **4** (**a**–**d**):
    ^{1}H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in $CDCl_3$. Mass spectra were obtained on a Hewlett–Packard 5971 A GCMS instrument with an ionization voltage of 70 eV.

7,8-Dihydro-naphtalen[1,2-*c*]chromen-6-one 4a: yellow oil; δ_H ($CDCl_3$): 2.74–2.85 (m, 4H), 7.29 (ddd, 1H, $J=7.6$ 7.5 and 1.2 Hz), 7.34–7.42 (m, 4H), 7.51 (ddd, 1H, $J=7.8$ 7.5 and 1.1 Hz), 7.82 (dd, 1H, $J=8.0$ and 1.9 Hz), 8.03 (dd, 1H, $J=8.0$ and 0.8 Hz); δ_C ($CDCl_3$): 22.54 (CH_2), 28.45 (CH_2), 117.89 (CH), 118.03 (C), 124.19 (CH), 124.60 (C), 126.71 (CH), 126.74 (CH), 128.32 (CH), 128.87 (CH), 130.42 (CH), 130.72 (C), 130.81 (CH), 140.49 (C), 144.74 (C), 153.76 (C), 162.00 (CO_2); m/z (%): 248 (100), 203 (27)

9,10-Dimethyl-7,8-dihydro-naphtalen[1,2-*c*] chromen-6-one 4b: yellow oil; δ_H ($CDCl_3$): 2.38 (s, 6H, 2Me), 2.72 (sl, 4H, $2CH_2$), 7.12 (s, 1H), 7.29 (dd, 1H, $J=7.7$ and 7.4 Hz), 7.39 (d, 1H, $J=8.1$ Hz), 7.47–7.52 (m, 2H), 7.99 (d, 1H, $J=8.1$ Hz); δ_C ($CDCl_3$): 20.22 (CH_3), 21.63 (CH_3), 22.42 (CH_2), 23.71 (CH_2), 117.87 (CH), 118.36 (C), 124.17 (CH), 124.26 (C), 126.96 (CH), 127.04 (CH), 130.61 (C), 130.69 (CH), 133.36 (CH), 135.40 (C), 135.92 (C), 136.03 (C), 145.42 (C), 153.81 (C), 162.75 (CO_2); m/z (%): 276 (100), 275 (79), 233 (17)

Benzopyrano[3,4-c]chromen-6-one 4c: yellow solid; mp: 125°C; δ_H ($CDCl_3$): 5.03 (s, CH_2O), 7.15–7.21 (m, 2H), 7.35 (ddd, 1H, $J=7.9$ 7.4 and 1.3 Hz), 7.42–7.48 (m, 2H), 7.58 (ddd, 1H, $J=7.8$ 7.7 and 1.2 Hz), 7.91 (dd, 1H, $J=7.2$ and 1.5 Hz), 8.12 (d, 1H, $J=8.2$ Hz); δ_C ($CDCl_3$): 63.42 (CH_2O), 116.51 (C), 117.85 (CH), 118.33 (CH), 118.67 (C), 120.09 (C), 122.11 (CH), 124.31 (CH), 126.19 (CH), 127.73 (CH), 131.34 (CH), 132.40 (CH), 140.94 (C), 153.92 (C), 157.73 (C), 158.94 (CO_2)

2,3-Dihydro-benzo[*b*]oxepine[4,5-*c*]chromen-6-one 4d: colorless solid; mp: 167°C; δ_H ($CDCl_3$): 2.39–2.53 (m, 1H), 3.18–3.26 (m, 1H), 4.49–4.67 (m, 2H), 7.18–7.28 (m, 2H), 7.31–7.40 (m, 2H), 7.44–7.53 (m, 3H), 7.61 (dd, 1H, $J=8.0$ and 1.2 Hz); δ_C ($CDCl_3$): 26.29 (CH_2), 79.92 (CH_2O), 117.67 (CH), 119.04 (C), 123.50 (C), 124.01 (CH), 124.54 (CH), 124.55 (CH), 126.82 (CH), 129.40 (C), 130.55 (CH), 131.50 (CH), 131.80 (CH), 148.73 (C), 154.09 (C), 156.51 (C), 161.71 (CO_2); m/z (%): 264 (52), 249 (100)