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Synthesis of new furocoumarin analogues via cross-coupling reaction of triflate

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Dedicated to Professor Guy Queguiner for his contribution to heterocyclic chemistry

Abstract—Furocoumarins such as psoralen or angelicin showed important biological activities. We present here the synthesis of new furocoumarin analogues via Suzuki or Sonogashira cross-coupling reaction of triflate.

1. Introduction

Linear furocoumarins such as psoralen **1** have shown important biological activities in the PUVA therapy.[1] However, undesirable side effects (risks such as mutations or skin cancers) have been noticed[2] so that considerable efforts have been expended to develop new compounds which may prevent them. Indeed, due to their bifunctional nature (photoactive α-pyrone and furan sites), psoralens used to form interstrand crosslinks with DNA which is believed to be mainly responsible for their toxicity. Several ways have been developed to permit only monofunctional photobinding with DNA:

(a) use of angular furocoumarin such as angelicins **2** (their angular structure prevent crosslinking with DNA)[3]

(b) blocking the photoactive α-pyrone double bond by introduction of substituents[4] or by annelation of an additional aromatic ring such as in pyridopsoralen[5] **3**

(c) enlarging the space between the photoactive double bonds of the α-pyrone and furan like in furonaphtopyrone[6] **4**.

Moreover, various isosters (**5**) were prepared and studied[7,8] (Fig. 1).

We have previously described a rapid access to coumarin derivatives using Vilsmeier–Haack–Arnold and Suzuki cross-coupling reactions.[9] In order to complete this series of molecules, we wanted to replace the phenyl ring by a furan moiety (Scheme 1).

In a first attempt, we wanted to use the same methodology as before, including a Vilsmeier–Haack–Arnold reaction on the 4,5,6,7-tetrahydrobenzo[*b*]furan-4-one **6**. However, Jakobs et al.[7] have shown that this β-chloroacrolein can be obtained with only 34% yield and is unstable at room temperature, so that we envisaged another pathway. In order to keep the cyclization possibility, we synthesized triflates on β-ketoesters.

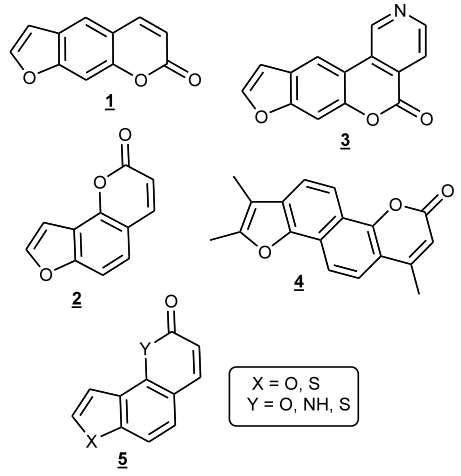

Figure 1.

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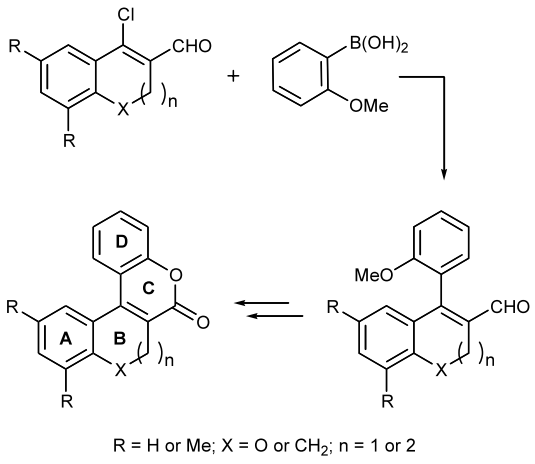
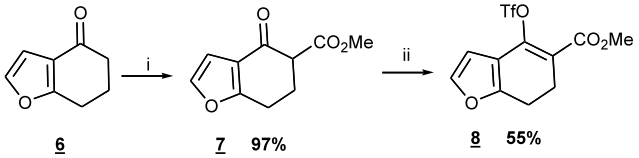


Scheme 1.

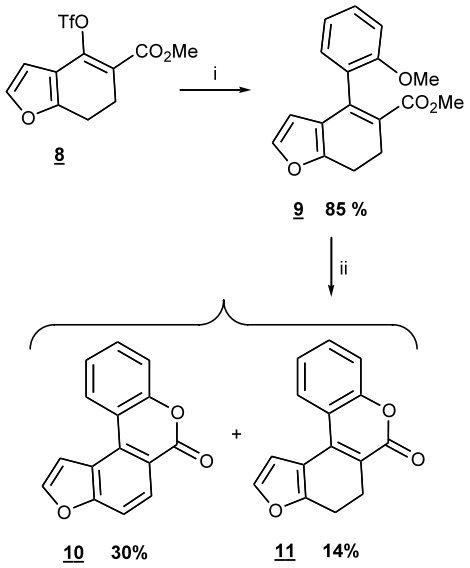
2. Results and discussion

4,5,6,7-Tetrahydrobenzo[*b*]furan-4-one **6** was synthesized by the condensation of 1,3-cyclohexanedione with chloroacetaldehyde[10] (Feist–Benary furan synthesis[11]). Ketone **6** was converted into β-ketoester **7** by a classical method[12] using sodium hydride and dimethyl carbonate. In a first attempt, β-ketoester **7** was treated with sodium hydride at 0°C followed by addition of triflic anhydride to generate the corresponding triflate. After treatment of the reaction mixture (which do not change anymore), a NMR spectrum of the crude product indicated that triflate was present in only 50%. The product was isolated by a column chromatography on silica gel in only 27% yield. We then tried other conditions (triflic anhydride in presence of 2,4,6-collidine) which allowed isolation of the triflate **8** in 55% yield (Scheme 2). We then performed Suzuki and Sonogashira coupling reactions with triflate **8**.

It is well known that an inorganic base (such as K_3PO_4) is recommended for the Suzuki reaction.[13] However in our case, those conditions failed and after many attempts, we found that only an organic base gave the coupling product **9**: triethylamine gave only a 25% yield, whereas diisopropylamine gave a 85% yield (Scheme 3). Cyclization of **9** (demethylation and concomitant lactonization) was made using boron tribromide in methylene chloride at room temperature; compounds **10** and **11** are obtained with 30 and 14% yield, respectively. Compound **11** was found to be quite unstable.



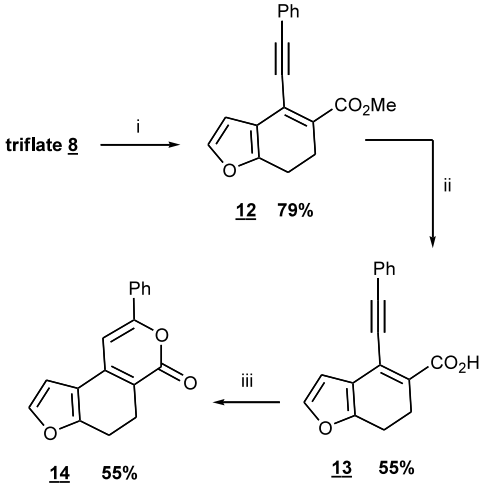
Scheme 2. *Reagents and conditions*: (i) NaH, $(MeO)_2CO$, DME, reflux; (ii) triflic anhydride, 2,4,6-collidine, CH_2Cl_2.



Scheme 3. *Reagents and conditions*: (i) *o*-anisylboronic acid, $PdCl_2$, PPh_3, iPr_2NH, toluene, 80°C, 24 h; (ii) BBr_3, CH_2Cl_2.

Sonogashira coupling of triflate **8** with phenylacetylene was performed in presence of 5 mol% $PdCl_2$ and PPh_3, 5 mol% of copper iodide and 1.5 equiv. of triethylamine in THF overnight at 55°C. Coupling product **12** was isolated after purification in 79% yield (Scheme 4). Hydrolysis of methyl ester **12** was done under mild conditions using LiOH 1.8 M in $MeOH/H_2O$ at 5°C. The corresponding 4-phenylethynyl-6,7-dihydrobenzo-[*b*]furan-5-carboxylic acid **13** was obtained with 55% yield.

It is well known that 2-(1-alkynyl)benzoic acids could easily be transformed either into phtalides or into isocoumarins. Bellina and co-workers[14] have shown that catalytic amount of silver nitrate in dry acetone at room temperature favored 6-endocyclization rather



Scheme 4. *Reagents and conditions*: (i) 1.1 equiv. phenylacetylene, 5 mol% $PdCl_2$, 10 mol% PPh_3, 5 mol% Cu(I), Et_3N, THF 18 h, 55°C; (ii) LiOH 1.8 M, $MeOH/H_2O$, 5°C, 20 h; (iii) 20 mol% $AgNO_3$, acetone, in dark, under argon, 18 h, rt.

than 5-exocyclization. So, cyclization of **13** was performed in the presence of 20 mol% of silver nitrate in dry acetone during 24 h at room temperature, in the dark and under an argon atmosphere; this process allowed the synthesis of **14** with 55% yield (cf. Scheme 3).

In conclusion, we described here new synthetic access to furocoumarin derivatives via cross-coupling reaction of triflate ester.

3. Data for compounds 10, 11 and 14

^{1}H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in $CDCl_3$.

3.1. 3,4-Dioxacyclopenta[*c*]phenanthren-6-one 10

Colorless solid; mp: 156°C; δ_H ($CDCl_3$) 7.44–7.45 (m, 2H), 7.53–7.54 (m, H_1+H), 7.72 (d, H_4, $J=8.6$ Hz), 7.92 (d, H_2, $J=2.3$ Hz), 8.36 (d, H, $J=8.0$ Hz), 8.42 (d, H_5, $J=8.7$ Hz); δ_C ($CDCl_3$) 107.22 (CH, C_1), 113.15 (CH, C_8), 117.14 (C), 117.77 (CH, C_4), 118.86 (C), 121.85 (C), 124.41 (CH), 125.12 (CH), 127.04 (CH), 130.01 (C), 130.22 (CH), 146.97 (CH, C_2), 151.41 (C_{7a}), 158.76 (C_{3a}), 161.34 (CO_2, C_6).

3.2. 4,5-Dihydro-3,4-dioxacyclopenta[*c*]phenanthren-6-one 11

Yellow oil; δ_H ($CDCl_3$) 2.97–2.10 (m, 2H), 3.05–3.08 (m, 2H), 7.00 (d, $1H_1$, $J=2.1$ Hz), 7.33–7.40 (m, 2H), 7.50–7.56 (m, 2H), 8.04 (d, $1H_{11}$, $J=7.9$ Hz).

3.3. 8-Phenyl-4,5-dihydrofuro[3,2-*f*]isochromen-6-one 14

Yellow oil; δ_H ($CDCl_3$) 2.84–2.91 (m, 2H), 2.97–3.09 (m, 2H), 6.21 (s, $1H_1$), 6.70 (s, $1H_9$), 7.30–7.44 (m, 3H), 7.48 (s, $1H_2$), 7.84 (d, 2H, $J=7.9$ Hz); δ_C ($CDCl_3$) 18.90 (CH_2), 21.32 (CH_2), 106.22 (CH, C_9), 110.87 (CH, C_1), 117.87 (C_{9b}), 128.79 (CH), 128.93 (CH), 130.62 (CH), 133.13 (C), 134.01 (C), 141.31 (C), 143.32 (CH, C_2), 145.22 (C), 157.51 (C), 167.76 (CO_2)

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