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Convenient synthesis of fused pyrano[3,2-*h*]- and furo[3,2-*h*]benzo[*f*]coumarins from naphthalene-2,3-diol☆

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ABSTRACT

The treatment of 8-propargyloxy-benzo[*f*]coumarin with boron trifluoride diethyl etherate in *N*,*N*-dimethylformamide under reflux or MW irradiation resulted in pyrano[3,2-*h*]benzo[*f*]coumarin, while the furo[3,2-*h*]benzo[*f*]coumarin is received from the treatment with *N*-methylformamide under MW irradiation.

1. Introduction

Coumarin derivatives are an interesting class of heterocyclic system, since the coumarin ring is an essential core moiety for a variety of natural and synthetic biologically active compounds.[1–3] In particular, fused coumarins and among them furocoumarins are important as photochemotherapeutic[4–9] agents and exhibit antitumorial,[10] antioxidant[3] and *anti*-inflammatory[3] activities. Pyranocoumarins are used also as photoactive drugs for skin disorders[11] and possess antifungal,[12] insecticidal,[12] anticancer,[12] *anti*-HIV,[6,13] *anti*-inflammatory,[3,14] antioxidant,[3,14] and antibacterial[15] activities.

The synthesis of furocoumarins[5,7,8,16–25] or pyranocoumarins[5,16,17,24–28] has been achieved mainly by formation of furan or pyran ring starting from hydroxycoumarins and using the Claisen[16,29] rearrangement of the intermediate propargyloxy- or allyloxycoumarins. The tandem Claisen rearrangement-cyclization reaction of 3- or 7-propargyloxycoumarins resulted in the formation of fused furo[2,3-*c*]- or [2,3-*h*]coumarins under pyrolysis at 150 °C without solvent[18] or by heating of *N*,*N*-dimethylformamide (DMF) solution[19] at 80–90 °C (when bulky substituents are present in the propargyloxy moiety). Furocoumarins were received also by the heating of the mixture of propargyloxycoumarin with NaOAc[21] at 190 °C or of *N*,*N*-dimethylaniline (*N*,*N*-DMA)[22] solution at 130 °C or by refluxing of pyridine solution[22] or by microwave irradiation[25] of *N*-methylformamide (NMF) solution (no substituents in the propargyloxy moiety). When the same reactions were performed under reflux in *N*,*N*-DMA[24] or *N*,*N*-diethylaniline (*N*,*N*-DEA)[19,24,25,26] or by heating in chlorobenzene[27] solution at 100 °C or in xylene or toluene solution[28] at 110 °C or by microwave irradiation[25] in NMF solution (with bulky substituents in propargyloxy moiety), the fused pyrano[2,3-*c*]- or [2,3-*h*]- or [3,2-*g*]-coumarins were received. Dihydrofurocoumarins were obtained also by tandem Claisen rearrangement-cyclization reaction of allyloxycoumarins with $BF_3 \cdot Et_2O$ and NMF[23] under microwave irradiation or by a step by step procedure[24] including Claisen rearrangement and subsequent cyclization by H_2SO_4. The dihydrofurocoumarins were oxidized with DDQ to furocoumarins.[24]

As we can see in the above procedures, $BF_3 \cdot Et_2O$ is not yet in use in the Claisen rearrangement of the propargyloxycoumarins. In the course of our interest on the synthesis[3,14,30–34] of fused coumarin derivatives and the study of their biological activity[3,14,33,34] we wish to report here the application of $BF_3 \cdot Et_2O$ on the synthesis of title compounds from 8-propargyloxy-benzo[*f*]coumarins. The reactions studied and the products received are depicted in Schemes 1 and 2.

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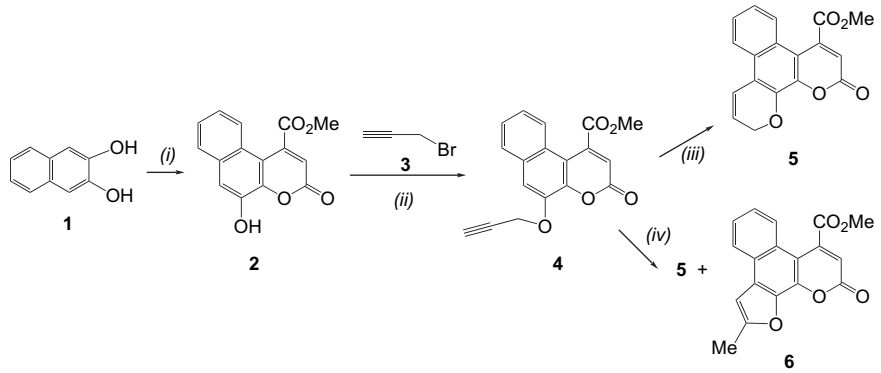
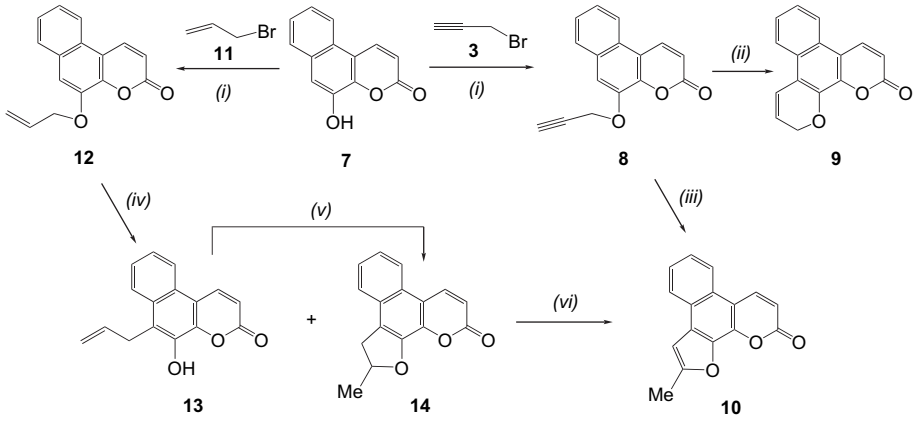


Scheme 1. Reagents and conditions: (i) Ph_3P, DMAD, DCM, 0 °C (15 min) then reflux (2 h). (ii) K_2CO_3, acetone (dry), reflux, 4 h. (iii) BF_3/Et_2O, DMF, reflux, 24 h or BF_3/Et_2O, DMF, MW (180 °C, 10 min) or *N*,*N*-DEA, reflux, 20 h. (iv) BF_3/Et_2O, NMF, MW (180 °C, 10 min).



Scheme 2. Reagents and conditions: (i) K_2CO_3, acetone (dry), reflux, 24 h. (ii) BF_3/Et_2O, DMF, reflux, 48 h or BF_3/Et_2O, DMF, MW (180 °C, 10 min). (iii) NMF, MW (180 °C, 10 min). (iv) BF_3/Et_2O, NMF, MW (200 °C, 20 min). (v) conc. H_2SO_4, 90 °C, 20 min. (vi) DDQ, toluene (dry), reflux, 24 h.

2. Results and discussion

By the treatment of a dichloromethane (DCM) solution of naphthalene-2,3-diol (**1**) in the presence of Ph_3P with a solution of dimethylacetylenedicarboxylate (DMAD)[31] in DCM at 0 °C for 15 min and reflux for 2 h we received after the separation of the reaction mixture by column chromatography the methyl 5-hydroxy-3-oxo-3*H*-benzo[*f*]chromen-1-carboxylate (**2**) in 52% yield (Scheme 1). We prepared the propargyloxycoumarin[26] derivative **4** (73%) by refluxing of a mixture of compound **2**, propargylbromide (**3**) and K_2CO_3 in dry acetone. Table 1 contains the efforts for the tandem Claisen rearrangement-cyclization of propargyloxy derivative **4**. The use of $BF_3\cdot Et_2O$ in DMF under MW irradiation gave the best results for the formation of pyran derivative **5** (90% yield), in comparison to the heating under reflux with the same solvent or with *N*,*N*-DEA. When we irradiated in $BF_3\cdot Et_2O$ in NMF the furan derivative **6** increased from 8%–22%, while the pyranocoumarin **5** received in 66% yield. The irradiation in NMF without the $BF_3\cdot Et_2O$ resulted to a complicated mixture without any –COOMe group in ^{1}H NMR, while in DMF the starting material remained unchanged.

Treatment of the recently[34] prepared by us 5-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**) with the bromide **3** and K_2CO_3 in boiling dry acetone resulted in propargyloxycoumarin[26] derivative **8** in 82% yield (Scheme 2). MW irradiation (Table 1) of the solution of compound **8** in $BF_3\cdot Et_2O$ and DMF resulted in the pyranocoumarin **9** (92% yield) and to the furan derivative **10** (4%). We succeeded to isolate the furan derivative **10** in 80% yield, when we followed an analogous procedure,[25] by heating compound **8** in NMF solution under MW irradiation. The starting compound **8** remained unchanged under MW irradiation (180 °C, 10 min) in *N*,*N*-DEA.

Table 1
Tandem Claisen rearrangement-cyclization of propargyloxycoumarin derivatives **4** or **8** to **5**, **6** or **9**, **10**

Solvent	Reflux, h	MW, 180 °C, min	From **4**		From **8**	
			5 (yield %)	**6** (yield %)	**9** (yield %)	**10** (yield %)
$BF_3\cdot Et_2O$/DMF	24	—	78	—	57[a]	—
$BF_3\cdot Et_2O$/DMF	—	10	90	8	92	4
$BF_3\cdot Et_2O$/NMF	—	10	66	22	—	—
NMF	—	10	[b]	[b]	—	80
N,*N*-DEA	20	—	35	—	—	—
N,*N*-DEA	—	10	—	—	[c]	[c]
DMF	—	5	[c]	[c]	—	—

[a] Reflux for 48 h.
[b] Complicated mixture at 100 °C.
[c] Unreacted starting material.

We prepared also the furan derivative **10** by another way. The mixture of compound **7**, allylbromide (**11**) and K_2CO_3 was heated under reflux in dry acetone and led to the allyloxycoumarin[26] derivative **12** in 84% yield. Treatment of the latter with $BF_3\cdot Et_2O$ in NMF under MW irradiation (200 °C, 20 min) gave the *o*-hydroxyallyl derivative **13** (82% yield) and the dihydrofuran derivative **14** (16% yield). When the compound **12** was irradiated at 180 °C for 10 min only the Claisen rearrangement product **13** was isolated (98%). Treatment of compound **13** with drops of concentrated H_2SO_4 resulted in the derivative **14** (72%). We received the furan derivative **10** (80% yield) by the oxidation of compound **14** with DDQ.[24]