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Unusual nicotinoylation of 4-phenyl-5,7-dihydroxycoumarin

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Abstract

In the present work, we report a convenient synthesis of 5- and 7-substituted-4-phenyl coumarins. In contrast to previous results obtained with 4-alkylcoumarins, nicotinoylation of 5,7-dihydroxy-4-phenylcoumarin with nicotinoyl benzotriazole or nicotinoyl azide selectively provides 5-O protected ester. The combination of the nicotinoylation reaction followed by tosylation-denicotinoylation yields 5-hydroxy-7-tosyloxy-coumarin derivative, which may be useful in the synthesis of inophyllum, a tetracyclic HIV reverse transcriptase inhibitor, as well as its analogues.

Keywords

5,7-dihydroxy-4-phenylcoumarin
nicotinoylation
esterification
protecting group
inophyllum

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1. Introduction

Asymmetrically O-substituted 5,7-dihydroxycoumarins attract attention as important building blocks for the synthesis of biologically active compounds. Compounds of this class are widespread both in nature, especially in plants in the form of mono- and diterpenes, and in synthetic compounds with important biological activity [1–4]. They have anti-cancer, antibacterial [5, 6], anti-HIV, anti-inflammatory and others activities, For example, inophyllums (Fig. 1), a series of natural HIV reverse transcriptase inhibitors isolated from *Calophyllum inophyllum* tree [7], comprise asymmetrically O-substituted 5,7-dihydroxycoumarin scaffold. Asymmetrically O-substituted 5,7-dihydroxycoumarins also can be used to prevent and treat Parkinson's disease, brain lesions, and dementia [8].

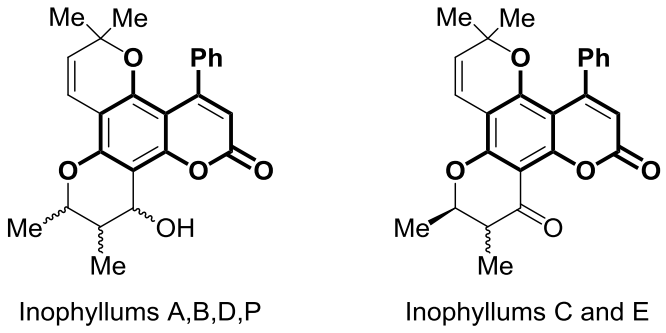


Fig. 1 Structure of naturally occurring inophyllums

We have previously demonstrated that nicotinoylation of 5,7-dihydroxy-4-alkylcoumarins is a convenient method for the synthesis of both 5- and 7-hydroxy-substituted coumarins [9,10]. In this case, the nicotinoylation reaction proceeds at the sterically less hindered hydroxy group at position C7 of coumarin system (Scheme 1). Subsequent modification of free 5-OH hydroxy group with a protective group orthogonal to nicotinoyl (tosyl or di(tert-butyl)phenylsilyl) and removal of the nicotinoyl moiety under acidic conditions allows the synthesis of complementary 5-OH protected coumarins [9].

In the presented work, we expand this methodology of selective nicotinoylation to 4-aryl-5,7-dihydroxycoumarins.

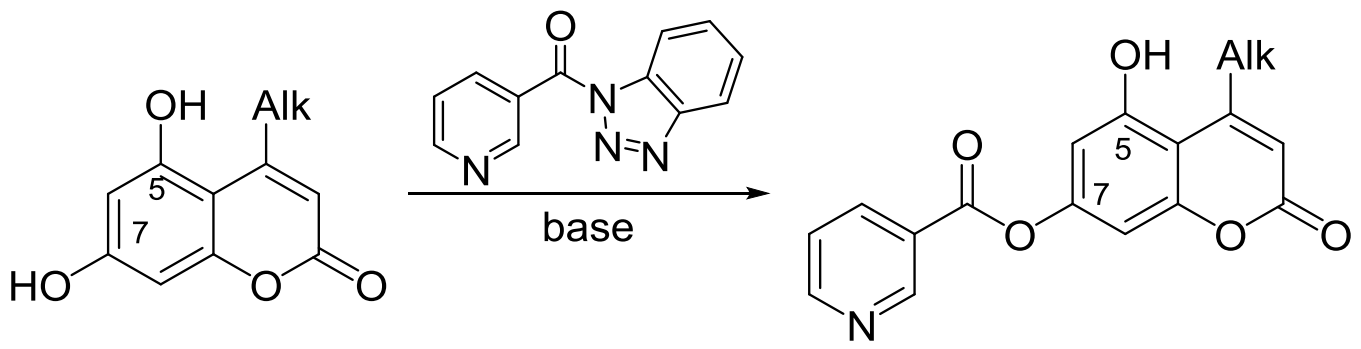
2. Experimental

Unless otherwise noted, all commercially available compounds were used without further purification.

1-Nicotinoyl benzotriazole [10], nicotinoyl azide [11], and 5,7-dihydroxy-4-phenylcoumarin [12] were prepared in accordance with published procedures.

^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 or DMSO-d_6:CCl_4 mixture as a solvent.

Chemical shifts (δ) are given in ppm relative to the DMSO residual peak (2.50 ppm) as an internal standard.



Scheme 1 Nicotinoylation of 5,7-dihydroxy-4-*alkyl*coumarin

The X-ray diffraction data for compound **2** were obtained from a 0.30×0.25×0.20 mm single crystal (colorless prism) at 295(2) K on an Xcalibur E diffractometer with a CCD detector (Cu Kα radiation, λ = 154.184 pm, graphite monochromator).

2.1. Procedure for synthesis of 2, 3, and 4 compounds

2.1.1. 7-Hydroxy-2-oxo-4-phenyl-2*H*-chromen-5-yl nicotinate 2

5,7-Dihydroxy-4-phenylcoumarin (2.540 g, 10.0 mmol), triethylamine (1.111 g, 11.0 mmol), and nicotinoyl azide or nicotinoylbenzotriazole (10.0 mmol) were dissolved in acetone (30 ml). The mixture was allowed to stand for 12 hours and the precipitate formed was filtered. Yield 1.860 g (52%).

^{1}H NMR (400 MHz, DMSO-d$_6$ + CCl_4) δ 10.83, 8.67 (*d*, *J* = 4.9 Hz, 1H), 8.57 (*s*, 1H), 7.78 (*d*, *J* = 8.0 Hz, 1H), 7.33 (*dd*, *J* = 8.0 Hz, *J* = 4.9 Hz, 1H), 7.22–7.22 (*m*, 2H), 7.04–7.08 (*m*, 2H), 6.77–6.80 (*m*, 2H), 6.54 (*s*, 1H), 5.88 (*s*, 1H). ^{13}C NMR (101 MHz, DMSO) δ 162.62, 161.26, 158.68, 156.03, 153.50, 153.13, 149.99, 147.91, 137.59, 136.73, 127.79, 127.45, 126.72, 123.53, 122.81, 113.28, 108.29, 104.88, 101.44. Anal. Calcd. for $C_{21}H_{13}NO_5$: C, 70.19; H, 3.65; N, 3.90. Found: C, 70.01; H, 3,75; N, 3.79.

An empirical correction for absorption (μ = 0.875 mm^{-1}) was applied. Triclinic crystal system, space group *P*-1; unit cell parameters: *a* = 9.240(7), *b* = 9.946(8), *c* = 10.604(10) Å; α = 83.33(7)°; β = 69.90(8)°; γ = 63.77(8)°; *V* = 820.2(12) Å^3; *Z* = 2. Total of 8848 reflection intensities were measured in the range 4.44<θ<65.28, including 2705 independent reflections (R_{int} = 0.0517), and 1795 reflections with $I>2\sigma(I)$; completeness 96.2% for θ = 65.28°. The structure was solved by the direct method and was refined by the least-squares method using SHELXTL package [13]. All hydrogen atoms were placed in directly calculated positions which were refined according to the riding model in isotropic approximation. Goodness of fit *S* = 1.005; final divergence factors: R_1 = 0.0569, wR_2 = 0.0942 for reflections with $I>2\sigma(I)$; R_1 = 0.0419, wR_2 = 0.0971 for all independent reflections. The X-ray diffraction data for compound **2** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 2129495) [14].

2.1.2. 2-Oxo-4-phenyl-7-(tosyloxy)-2*H*-chromen-5-yl nicotinate 3

To a suspension of 7-hydroxy-2-oxo-4-phenyl-2*H*-chromen-5-yl nicotinate **2** (1795 mg, 5.0 mmol) in DCM (35 ml) was added dimethylaminopyridine (2440 mg, 10.0 mmol) and tosyl chloride (1194 mg, 6.25 mmol). The mixture was stirred for 30 min., washed with water (3×50 ml), dried and evaporated to yield **3** (1.638 g, 65%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.74 (*dd*, *J* = 4.9 Hz, *J* = 1.7 Hz, 1H), 8.57 (*d*, *J* = 2.5 Hz, 1H), 7.87 (*d*, *J* = 8.2 Hz, 2H), 7.80 (*dd*, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.52 (*d*, *J* = 8.2 Hz, 2H), 7.41 (*dd*, *J* = 8.0 Hz, *J* = 4.8 Hz, 1H), 7.21–7.28 (*m*, 4H), 7.07–7.11 (*m*, 2H), 6.82 (*dd*, *J* = 7.51 Hz, 1H), 6.27 (*s*, 1H), 2.43 (*s*, 3H). ^{13}C NMR (101 MHz, DMSO) δ 162.64, 158.09, 154.58, 153.99, 152.01, 150.35, 150.03, 147.70, 146.40, 137.04, 136.77, 130.90, 130.46, 128.31, 128.01, 127.90, 126.98, 123.33, 123.20, 117.90, 114.45, 112.04, 108.98, 21.18. Anal. Calcd. for $C_{28}H_{19}NO_7S$: Elemental analysis: C, 65.49; H, 3.73; N, 2.73. Found: C, 65.35; H, 3,58; N, 2.93.

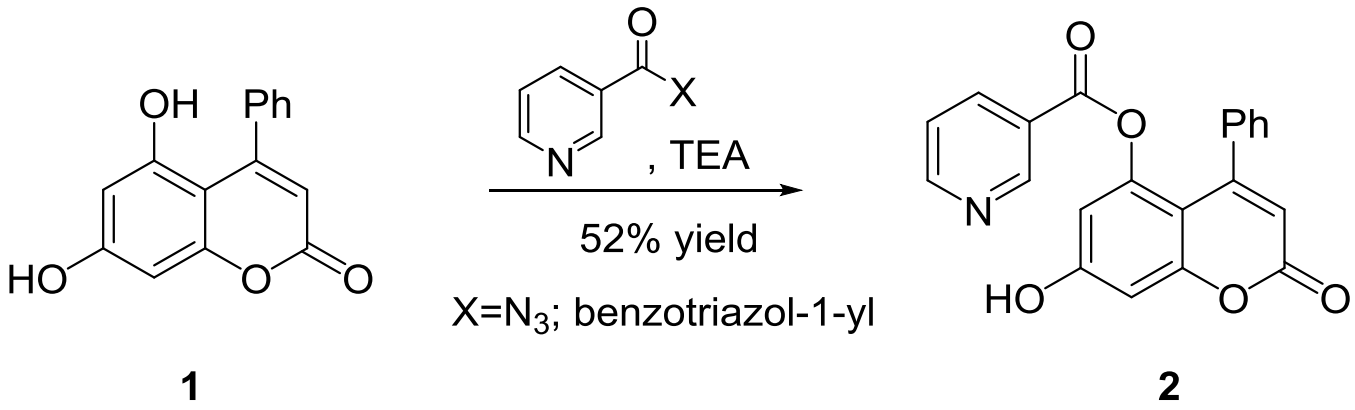
2.1.3. 5-Hydroxy-2-oxo-4-phenyl-2*H*-chromen-7-yl 4-methylbenzenesulfonate 4

A suspension of 2-oxo-4-phenyl-7-(tosyloxy)-2*H*-chromen-5-yl nicotinate **3** (1008 mg, 2.0 mmol) was stirred in a mixture of ethanol (20 ml) and 30% hydrochloric acid (12 ml) at 80 °C for 4 hours. The mixture was cooled and precipitate was filtered off. Yield 710 mg, 87%.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.77 (*s*, 1H), 7.82 (*d*, *J* = 8.0 Hz, 2H), 7.50 (*d*, *J* = 8.0 Hz, 2H), 7.32–7.38 (*m*, 5H), 6.57 (*d*, *J* = 2.4 Hz, 1H), 6.43 (*d*, *J* = 2.4 Hz, 1H), 6.04 (*s*, 1H), 2.43 (*s*, 3H). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 158.89, 156.90, 155.37, 154.71, 151.29, 146.15, 138.63, 131.20, 130.38, 128.22, 128.06, 127.40, 127.32, 114.70, 106.42, 104.82, 101.03, 21.19. Anal. Calcd. for $C_{22}H_{16}O_6S$: Elemental analysis: C, 64.70; H, 3.95. Found: C, 64.57; H, 4.02; N, 3.00.

3. Results and discussion

We found that nicotinoylation of 5,7-dihydroxy-4-phenylcoumarin **1** with nicotinoylbenzotriazole (X = benzotriazolyl) or nicotinic acid azide (X = N_3) leads to unexpected 5-nicotinoyloxy-4-phenylcoumarin **2** (Scheme 2).



1 2

Scheme 2 Nicotinoylation of 5,7-dihydroxy-4-*phenyl*coumarin

The reaction takes place at most sterically hindered 5-OH position as confirmed by X-ray structural analysis of compound (Fig. 2). One may assume that the selectivity of this reaction is associated with non-covalent interactions in the transition state, such as π-π stacking between the pyridyl ring of nicotinoyl derivatives and the phenyl ring of coumarin.

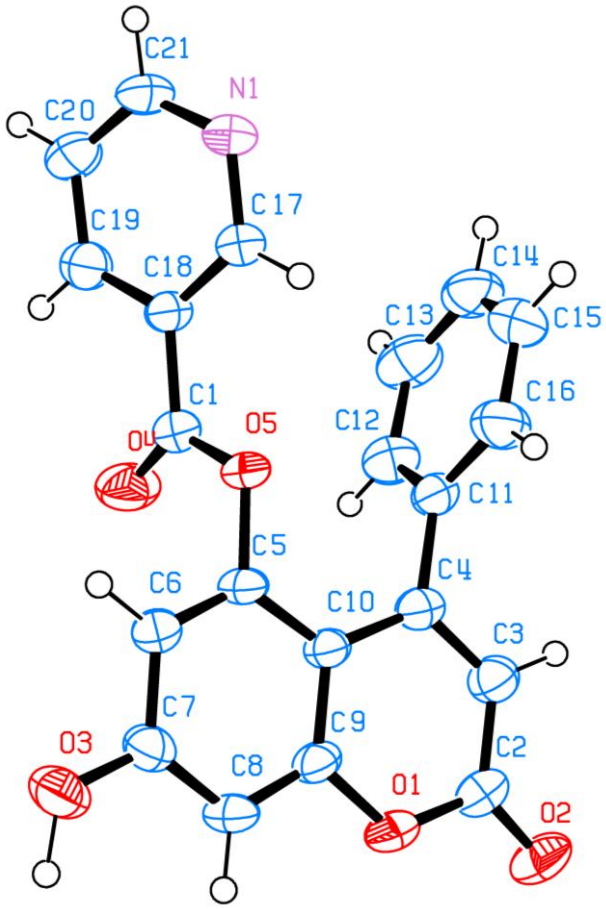


Fig. 2 The X-ray structure (CCDC 2129495) of compound **2**

To obtain 5-hydroxy-7-O-subsituted derivatives of coumarin 1, we carried out the exchange of hydroxy protective groups. Thus, tosylation of **2** with p-toluenesulfonyl chloride followed by denicotinoylation of **3** in an acidic media provides 7-protected tosyloxy derivative **4** (Scheme 3). Compound **4** may be further converted to inophyllum or inophillum analogues using adapted procedures [9].

4. Conclusions

Thus, we presented a convenient synthesis of 5- and 7-substituted 4-phenyl coumarins. It was demonstrated that 4-phenyl-5,7-dihydroxycoumarins, unlike 4-alkyl compounds, react with nicotinoylazide with the involvement of the 5-hydroxy group in the reaction. The structure of the nicotinoyl derivative was proved by X-ray diffraction analysis. Combination of the nicotinoylation with tosylation–denicotinoylation allows one to obtain 7-hydroxy protected 5,7-dihydroxycoumarins.

Acknowledgments

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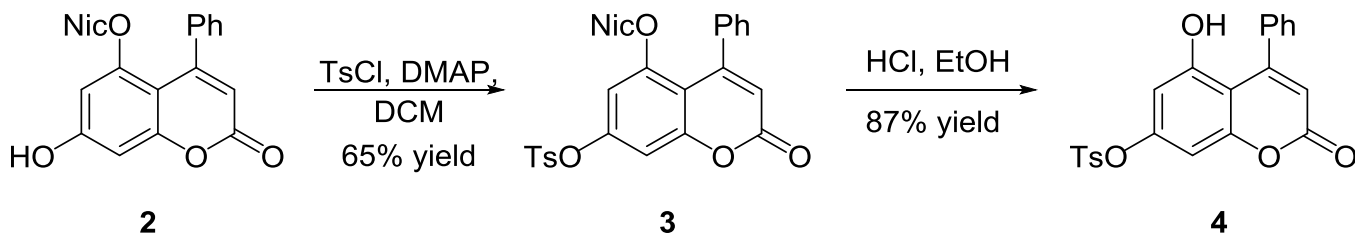
Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



2 3 4

Scheme 3 Protective groups exchange in compound **2**

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