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A novel photorearrangement of (coumarin-4-yl)methyl phenyl ethers

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ABSTRACT

In the present study, we describe synthesis and photochemical behaviour of the coumarinylmethyl phenyl ethers **1** and **6**–**10**. Irradiation of the compounds in polar solvents leads to *o*-, *p*- and *m*-hydroxybenzyl substituted coumarins as main products. A side reaction is the photosolvolysis of the ethers that gives the (coumarin-4-yl)methyl alcohol and the corresponding phenol. Detailed studies of the quantum yields and product distributions upon irradiation of **6** as a function of the solvents are indicative of a dominant role of an ionic pathway in photochemical conversions. The found photochemical rearrangement is a useful tool for the preparation of hydroxylated 4-benzylcoumarins. A series of such compounds have been synthesised.

1. Introduction

In the course of our studies on photoactivatable derivatives of vanilloid receptor ligands [1] we synthesised and photolysed the coumarinylmethyl capsaicin ether **1**. Compound **1** should be developed as so-called caged compound which upon illumination with UV/vis light releases temporally and spatially controlled the vanilloid capsaicin **2** [(*E*)-*N*-(4-hydroxy-3-methoxybenzyl)-8-methyl-non-6-enamide]. The biomolecule **2** is the pungent ingredient of chili peppers and is used in pain research as an activating ligand of heat-sensitive transduction channels in nociceptive neurons. However, contrary to our expectations light-induced reaction of **1** in aqueous buffer and quantification of the products by calibrated HPLC yielded the solvent-assisted photoheterolysis product **2** [2] only in small amounts (about 8%), but gave the novel rearrangement compound **4** as main product in a yield of 34% (Scheme 1).

To our knowledge, photochemical rearrangements of (coumarin-4-yl)methyl aryl ethers have not been described. However, well-known is the Photo-Claisen rearrangement [3] which was reported for the first time for allyl phenyl ethers and for benzyl phenyl ethers [4], and later also for naphthylmethyl phenyl ethers [5]. The reaction is usually carried out in nonpolar solvents and involves commonly an intramolecular radical process within a solvent cage to give a mixture of *ortho*- and *para*-rearranged products [3,5]. In the case of naphthylmethyl phenyl ethers (*o*-hydroxybenzyl)- and (*p*-hydroxybenzyl)naphthalenes are formed. The excitation energy is mainly localised in the phenyloxy and not in the arylmethyl chromophore.

Furthermore, thermal sigmatropic rearrangements of 3-(aryloxymethyl)coumarins at high temperatures (240 °C) resulting in 3-(*o*-hydroxybenzyl)- or 3-(*p*-hydroxybenzyl)-coumarins have been reported [6], but the corresponding 4-(aryloxymethyl)coumarins failed to undergo any such rearrangement [7].

The novel photorearrangement of the (coumarin-4-yl)-methyl phenyl ethers is of considerable interest both as a preparative method and for its theoretical implications. With the aim to get more information about this reaction we investigated the photochemical behaviour of **1** and of a series of various simply substituted (coumarin-4-yl)methyl phenyl ethers. Here, we present the results of the studies.

2. Experimental

2.1. Materials

Capsaicin (**2**) was obtained from Sigma (Germany). 4-(Bromomethyl)-7-methoxycoumarin (**5**), 7-methoxy-4-methylcoumarin

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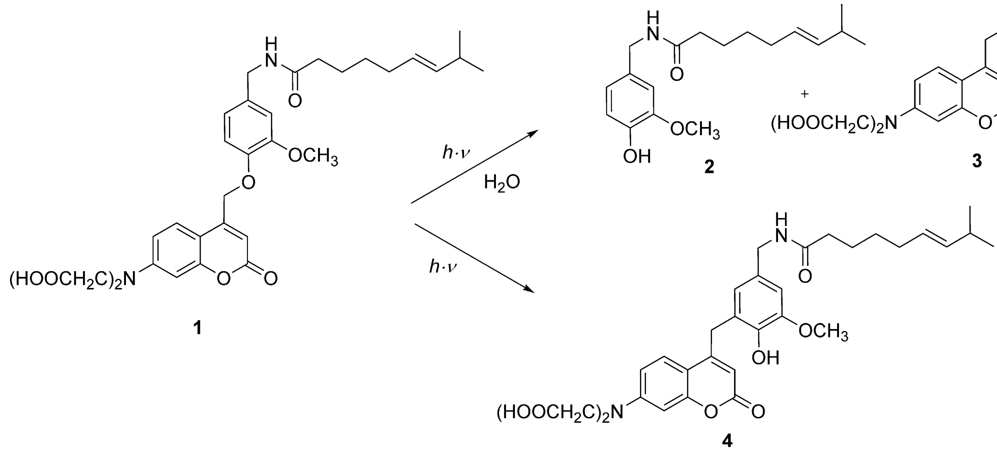

Scheme 1. Photochemical rearrangement of **1**.

(**20**), 7-methoxycoumarin (**22**), phenol, 2-methylphenol, 2,6-dimethylphenol, 2,4,6-trimethylphenol, 2-methoxyphenol, thiophenol, aniline, and trifluoroacetic acid (TFA) were purchased from Aldrich (Germany). The remaining chemicals were of the highest grade commercially available and were used without further purification. 7-[Bis(*tert*-butoxycarbonylmethyl)amino]-4-(bromomethyl)coumarin was prepared as described previously [8]. TLC plates (silica gel 60 F_{254}) were purchased from E. Merck (Germany). Silica gel for flash chromatography was from J.T. Baker (The Netherlands). CH_3CN from Riedel-deHaen (Germany) was HPLC grade. Water was purified with a Milli-Q-Plus system (Millipore, Germany). The synthetic and analytical procedures with the coumarinylmethyl phenyl ethers were performed under yellow light provided by sodium vapor lamps.

2.2. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV 300 spectrometer. Chemical shifts are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. *J* values are given in Hz. Mass spectra were measured by electrospray ionization (ESI-TOF) mass spectrometry on an Acquity UPLC system coupled to LCT Premier (Waters) or on an Agilent 6220 ESI-TOF spectrometer (Agilent Technologies, U.S.A.). UV/vis spectra were recorded on a UV/vis spectrophotometer Lambda 9 (PerkinElmer). Fluorescence spectra were taken on a Jasco FP-6500 spectrometer. Phosphorescence was measured on a Fluoromax-4P spectrofluorometer (HORIBA Jobin Yvon). Analytical reversed-phase HPLC (RP-HPLC) was carried out on a Shimadzu LC-20 system (flow rate: 1 mL min^{-1}) equipped with a DAD-UV detector and a fluorescence detector (λ_{exc} = 320 nm, λ_{em} = 420 nm) by using a Nucleodur 100-5 C18 ec column, 100 Å, 5 μm, 250 mm × 4 mm, Macherey-Nagel (Germany). The given retention times (t_R) with exception of those of compounds **1** and **4** are related to a linear gradient of 20–95% B in A in 30 min (eluent A, H_2O/0.1% TFA; eluent B, CH_3CN). Preparative RP-HPLC was run on a Shimadzu LC-8A system (flow rate: 10 mL min^{-1}) with a UV/vis detector (SPD-6AV, λ_{det} = 320 nm) over a Nucleodur 100-5 C18 ec column (100 Å, 5 μm, 250 mm × 21 mm) from Macherey-Nagel (Germany). Photolysis of all synthesised photoprotected compounds in solution was performed by using a high-pressure mercury lamp (HBO 500, Oriel, U.S.A.) with controlled light intensity and metal interference filter (334 nm, Oriel, U.S.A.). For all experiments, UV and fluorescence quartz cuvettes with a path length of 1 cm and a cross-sectional area of 1 cm^2 were used. During irradiation, the solutions in the cuvettes were mixed by a magnetic stirrer. The melting points are uncorrected.

2.3. Synthesis

2.3.1. (E)-{7-[Bis(tert-butoxycarbonylmethyl)amino] coumarin-4-yl}methyl 2-methoxy-4-[(8-methylnon-6-enamido) methyl]-phenyl ether

A mixture of 7-[bis(*tert*-butoxycarbonylmethyl)amino]-4-(bromomethyl)coumarin (48.2 mg, 0.1 mmol) and capsaicin (30.4 mg, 0.1 mmol) was stirred in DMF (1 mL) for 24 h at room temperature in the presence of K_2CO_3 (72.6 mg, 0.2 mmol). The reaction mixture was filtered and evaporated. The residue was dissolved in CH_2Cl_2, washed with water (3×), dried with $MgSO_4$, evaporated and purified by preparative RP-HPLC. The desired product was eluted using a linear gradient 45–95% B in A in 60 min; eluent A, H_2O; eluent B, CH_3CN. The main fraction with a retention time of 58.1 min was collected, evaporated *in vacuo*, redissolved in CH_3CN/H_2O, and lyophilised to give 39.5 mg (56%) of a yellow solid, mp 130–132 °C; TLC, R_f 0.45 (*n*-hexane/THF = 1:1); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.92 (6H, d, *J* = 6.7, 2 × CH_3), 1.29 (2H, quintet, *J* = 7.4, CH_2CH$_2$CH=CH), 1.42 (18H, s, 2 × 3 × CH_3), 1.51 (2H, quintet, *J* = 7.4, CH$_2$CH_2CH$_2$CH$_2$), 1.94 (2H, q, *J* = 7.0, CH_2CH=CH), 2.11 (2H, t, *J* = 7.3, CH_2CONH), 2.20 [1H, sextet, *J* = 6.6, C*H*(CH$_3$)$_2$], 3.78 (3H, s, OCH$_3$), 4.20 (6H, m, CH_2NH and 2 × CH$_2$N), 5.29 (2H, s, Coum-CH_2), 5.31–5.38 (2H, m, C*H*=C*H*), 6.21 (1H, s, CoumH-3), 6.47 (1H, d, *J* = 2.2, CoumH-8), 6.59 (1H, dd, *J* = 9.0 and 2.2, CoumH-6), 6.76 (1H, d, *J* = 8.5, PhH-5), 6.91 (1H, s, PhH-3), 7.06 (1H, d, *J* = 8.3, PhH-6), 7.64 (1H, d, *J* = 8.9, CoumH-5), 8.22 (1H, t, *J* = 5.8, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 22.5 (2 × CH$_3$), 24.9 (CH$_2$CH$_2$CH$_2$CH$_2$), 27.7 (6 × CH$_3$), 28.6 (*C*H$_2$CH$_2$CH=CH), 30.3 [*C*H(CH$_3$)$_2$], 31.6 (*C*H$_2$CH=CH), 35.2 (*C*H$_2$CONH), 41.7 (CH$_2$NH), 53.5 (2 × CH$_2$N), 55.6 (OCH$_3$), 66.0 (Coum-*C*H$_2$), 81.1 [2 × *C*(CH$_3$)$_3$], 98.1 (CoumC-8), 106.6 (CoumC-3), 107.2 (CoumC-4a), 109.0 (CoumC-6), 111.6 (PhC-3), 113.8 (PhC-6), 119.2 (PhC-5), 125.5 (CoumC-5), 126.6 (CH$_2$*C*H=CH), 133.4 (PhC-4), 137.3 (CH$_2$CH=*C*H), 145.8 (PhC-1), 149.0 (PhC-2), 151.3 (CoumC-7), 151.7 (CoumC-4), 155.0 (CoumC-8a), 160.5 (CoumC-2), 168.8 (2 × *C*OO*t*-Bu), 171.9 (CONH); HRMS (ESI): $C_{40}H_{54}N_2O_9$, *m*/*z* [*M*+Na]$^+$ calcd 729.3727; found: 729.3695; elemental analysis calcd (%) for $C_{40}H_{54}N_2O_9$ (706.9): C, 67.97; H, 7.70, N, 3.96; found: C, 67.87; H, 7.68; N, 3.82.

*2.3.2. (E)-7-{[Bis(carboxymethyl)amino]coumarin-4-yl}methyl 2-methoxy-4-[(8-methylnon-6-enamido)methyl]-phenyl ether (**1**)*

(*E*)-7-{[Bis(*tert*-butoxycarbonylmethyl)amino]coumarin-4-yl} methyl 2-methoxy-4-[(8-methylnon-6-enamido)-methyl]-phenyl ether (30 mg, 0.042 mmol) was stirred in a mixture (10 mL) of TFA/CH_2Cl_2/H_2O (74:25:1) at room temperature for 30 min. The