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A convenient synthesis of psoralens

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Abstract—An efficient synthesis (yields >70%) of linear 7*H*-furo[3,2-*g*]chromen-7-one derivatives (psoralens or furocoumarins) has been carried out starting from ring-substituted 2-(coumarin-7-yl)oxyaldehydes; moreover, the phototoxicity of these compounds has been tested on a cultured cell line of murine fibroblast.

1. Introduction

Psoralens, also known as furocoumarins, are naturally occurring or synthetic tricyclic aromatic compounds. They exhibit interesting photobiological activities such as skin photosensitization, characterized by the onset of erythema followed by dark pigmentation. The related angular isomers, namely angelicins, are also present in plants and have been chemically synthesized.[1] Psoralens are also of interest because they are used as a probe in molecular biology and nucleic acid chemistry.[2] The photochemistry of furocoumarins has been extensively studied.[3] In the dark, they are able to form a complex with base pairs of DNA in an intercalative manner and upon exposure to near UV light (300–380 nm) they give a covalent addition to the 5,6 double bond of pyrimidine bases of DNA. The photoreaction leads to the formation of monoadducts or cross-links between the two strands of the nucleic acid due to the presence of two reactive sites in the furocoumarin moiety.

Although photochemotherapy has important therapeutic effectiveness, it is also accompanied by undesired side effects, both short (erythema, hyperpigmentation, genotoxicity)[4] and long term (cataract, risk of skin cancer).[5] Cross-link formation is believed to be mainly responsible for the latter phenomena.

An important clinical application of psoralens and UVA light (PUVA therapy) was introduced into clinical practice by Parrish et al.[6] in 1974. A treatment consisting of oral administration of 8-methoxypsoralen (8-MOP), followed by artificial ultraviolet illumination (UVA) of patients' skin was applied for the first time to cure psoriasis, a disease characterized by hyperproliferation of skin cells. In 1987, an extracorporeal form of 8-MOP photochemotherapy (photopheresis) was developed for the treatment of cutaneous T-cell lymphoma, a CD4 positive T-cell malignancy.[7] Photopheresis was also found to be effective in a number of other T-cell mediated diseases: clinical trials have shown beneficial effects in *Pemphigo vulgaris*,[8] severe atopic dermatitis,[9] AIDS-related complex,[10] rheumatoid arthritis[11] and systemic lupus erythematosus.[12]

A recent application of photoexcited psoralens is the sterilization of blood products, mainly platelet concentrate. Different psoralen derivatives such as 8-MOP and 4′-aminomethyl-4,5′,8-trimethylpsoralen (AMT) combined with UVA were found to be useful in the sterilization of platelet concentrate, because of their capacity to target nucleic acids.[13] Lipid-enveloped viruses such as the model-virus vesicular stomatitis virus[14] as well as immunodeficiency virus[14,15] and duck hepatitis B virus[16] are sensitive to this photochemical treatment. On the other hand, platelets are well preserved especially in the presence of rutin that prevents damage to the platelet membrane by reactive oxygen species.[14]

Starting from 1934, many syntheses of furocoumarins have been reported; however, the yields were poor. The first approaches to psoralen synthesis started from the conversion of 6-hydroxycoumaran to 2,3-dihydro-7*H*-furo[3,2-*g*]chromen-7-one followed by dehydrogenation to the desired psoralen.[17–19] Subsequently, the synthetic methods were based on cyclocondensation reactions of 7-hydroxycoumarin derivatives to form the furan ring.[20–23] For example, Ray's method[22] accomplished the synthesis of 3-methyl- (**2**) and 3-phenyl-7*H*-furo[3,2-*g*]chromen-7-one

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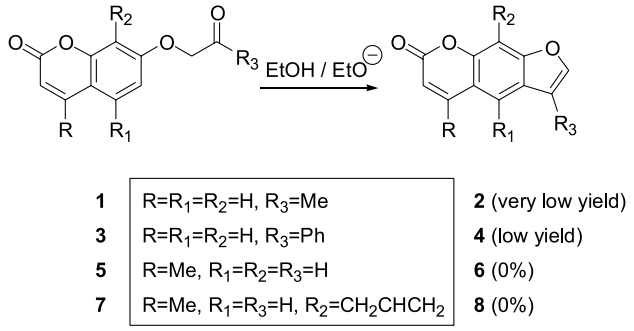
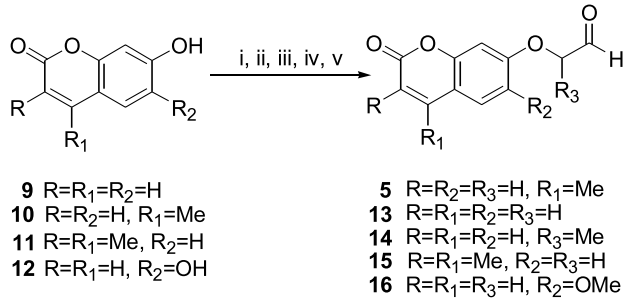


Scheme 1.



Scheme 2. (i) $BrCHR_3CO_2Et$, acetone, K_2CO_3. (ii) NaOH 1.25 M. (iii) HCl 6 M. (iv) $SOCl_2$, $CHCl_3$. (v) H_2, $Pd/BaSO_4$, toluene.

(**4**) by cyclisation of 7-(2-oxopropoxy)- (**1**) and 7-(2-oxo-2-phenylethoxy)-2*H*-chromen-2-one (**3**) in ethanolic medium using sodium ethoxide as the condensing agent (Scheme 1).

In addition to low overall yields, the method gives only 3-substituted furocoumarins.[24] Moreover, it is also claimed[24] that the corresponding 5-methyl-7*H*-furo[3,2-*g*]chromen-7-one (**6**) cannot be obtained by cyclisation of 4-methyl-7-(2-oxoethoxy)coumarin (**5**) using both acidic and basic catalysts. Various attempts led only to recovery of starting material, uncharacterizable tar, or ether cleavage with recovery of 4-methyl-7-hydroxycoumarin. More recently, Egyptian scientists investigated the possibility of obtaining psoralen derivatives by cyclisation of benzopyranyloxy ketones or aldehydes in a 2% ethanolic solution of NaOEt at reflux; once again, whereas the corresponding psoralens can be obtained when $R_3 \neq H$, several attempts starting from the aldehyde **7** failed.[25]

On this basis, alternative syntheses were undertaken with the aim to prepare psoralens and 3-unsubstituted psoralens in higher yields, for example, via intramolecular Diels–Alder reaction[26] (overall yield 1.5%, 12 steps) or anionic [4+2] cycloaddition[27] (overall yield 5%, 7 steps).

We wish to report here a more general, simple and efficient methodology (yields >70%) to obtain linear furocoumarins by alkaline treatment of ring-substituted 2-(coumarin-7-yl)oxyaldehydes.

2. Results and discussion

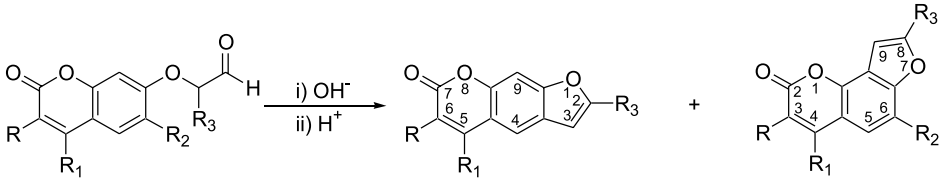
Recently,[28] we prepared the ring-substituted 2-(coumarin-7-yl)oxyaldehydes **5**, **13**–**16** (Scheme 2) in excellent overall yields (~97%) starting from the easily available 7-hydroxycoumarins **9**–**12**.

Whereas cyclisation of 2-(coumarin-7-yl)oxyaldehydes **5** and **7** was reported to be unsatisfactory,[24,25] in our hands, treatment of compounds **5**, **13**–**15** in alkaline aqueous solution gave, after acidification, with average overall yields of 80–90%, a mixture in which psoralens **6**, **18**, **20**, and **22** were largely predominant with respect to angelicins **17**, **19**, **21**, and **23**, respectively (see Scheme 3).

Thus, we observed that the 2-(coumarin-7-yl)oxyaldehydes **5**, **13**–**15** give rise to psoralens under basic but not acidic conditions (acidic conditions giving in this case only tarry materials). It is noteworthy that to improve the yield of this cyclisation it is strictly necessary to add the aldehyde to a NaOH solution at reflux.

Although the exact mechanism of the reaction is still not clear and no intermediates have been isolated, it is best described as shown in Scheme 4. The aldehyde first undergoes lactone ring opening[29] to generate the intermediate dianion which in turn gives rise to a nucleophilic addition–elimination reaction on the aldehyde carbon atom with furan ring formation. Subsequent acidification leads to lactone ring closure with formation of the target compounds.

We wish to point out that, for example, compound **20** was obtained for the first time in 1972 with a yield lower than 2%[30] and, more recently in 1997, by caesium-mediated Claisen rearrangement of phenyl propargyl ether (overall yield ~1%).[31]



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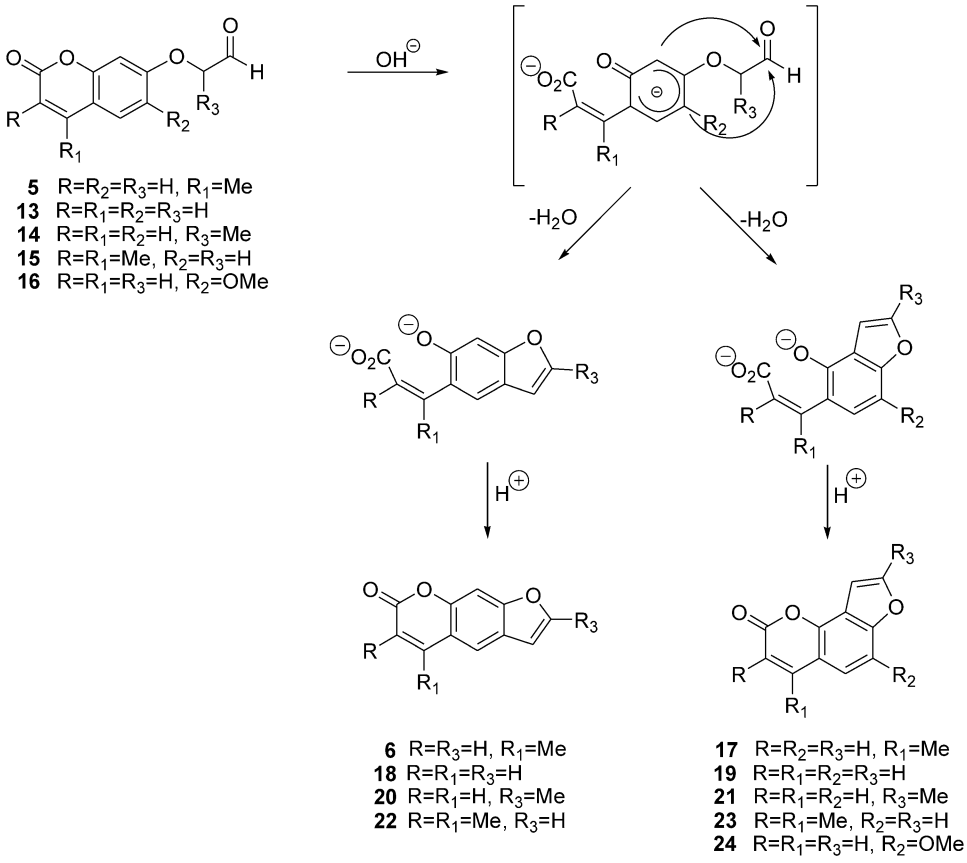

Scheme 4.

Finally, with the aim to obtain the angular furocoumarin sphondin (**24**), a natural product useful for its antifungal activity,[32] we carried out the same reaction starting from the newly synthesised aldehyde **16**.[28] Various attempts under the reported conditions gave only small amounts (4–5%) of **24**.

2.1. Cellular phototoxicity

The phototoxicity of test compounds **6**, **18**, **20**, and **22** was investigated on a cultured cell line of murine fibroblast (Balb/c 3T3). Table 1 shows the extent of cell survival expressed as IC_{50} that is the concentration expressed in μM inducing 50% inhibition of cell growth, after UVA irradiation, at different doses. Control experiments with UVA light or drugs alone were carried out without observing any cytotoxic effects (data not shown).

It can be noted that the four investigated compounds exhibit different values of IC_{50} depending on the substitution pattern, and a remarkable dose UVA-dependence. Moreover, the IC_{50} values show a significant correlation with the partition coefficients of the compounds indicating that the activity may be related to their active incorporation in the cellular membrane.[33]

3. Conclusion

In summary, a convenient route to psoralens is described; whereas it was reported that 2-(coumarin-7-yl)oxyaldehydes do not cyclise in alkaline alcoholic medium, psoralens can be efficiently obtained when the reaction is carried out in alkaline aqueous solution. Phototoxicity studies of the target compounds on a cultured cell line of murine fibroblast showed lower IC_{50} values with respect to psoralen itself.

Taking into account that research on the photobiological and pharmacological activities of psoralen is under

Table 1. Values of IC_{50} (μM) obtained for the test compounds **18**, **6**, **20**, and **22** at two different UVA doses

Compounds	log P[a]	1.41 ($J\,cm^{-2}$) UVA dose	4.22 ($J\,cm^{-2}$) UVA dose
18 (Psoralen)	1.97	25.5±3.0	19.42±2.42
6	2.27	21.12±0.56	8.2±1.61
20	2.48	18.89±1.61	4.12±0.07
22	2.77	13.71±0.69	4.63±0.03

Data expressed as mean±S.D. of two independent experiments performed in quadruplicate.
[a] Data taken from Ref. 34.

development,[35] the possibility to obtain psoralen derivatives in large amounts by a simple synthesis endowed with a high yield may be an important improvement.

4. Experimental

Melting points were measured using Büchi apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini 200 Instrument in the Fourier transform mode at 21±0.5°C in $CDCl_3$. ^1H (200 MHz) chemical shifts (δ) are in ppm relative to TMS as secondary reference standard; coupling constants are in Hz. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical tlc and for flash chromatography, respectively. Solvents were removed under reduced pressure. All experiments were carried out under nitrogen atmosphere.

4.1. General procedure for synthesis of the psoralens

A suspension of 2-(coumarin-7-yl)oxyaldehyde (1 mmol) in H_2O–Dioxane (9:1) (10 mL) was added very slowly (30 min) and under stirring to a refluxing solution of aqueous NaOH 1.25 M (20 mL) and the solution was refluxed for 4 h. After cooling to room temperature, the solution was acidified with 85% phosphoric acid and the precipitate was collected by vacuum filtration and separated by flash chromatography (petroleum ether–ethyl acetate=3:1, as eluent).

4.1.1. 5-Methyl-7*H*-furo[3,2-*g*]chromen-7-one 6. Cyclisation of 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetaldehyde[28] (**5**) afforded mainly compound **6** (142 mg, 71%) as colourless crystals: mp 177–178°C [lit.[21] 178–179°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (1H, s, H-4), 7.69 (1H, d, J=2.2 Hz, H-2), 7.48 (1H, d, J=0.9 Hz, H-9), 6.85 (1H, dd, J=2.2, 0.9 Hz, H-3), 6.28 (1H, q, J=1.5 Hz, H-6), 2.51 (3H, d, J=1.5 Hz, 5-Me).

The fastest running band was then identified as 4-methyl-2*H*-furo[2,3-*h*]chromen-2-one (**17**) (18 mg, 9%), colourless crystals: mp 191–192°C [lit.[36] 194°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (1H, d, J=2.2 Hz, H-8), 7.58–7.40 (2H, AB part of ABX system, H-5 and H-6), 7.15 (1H, dd, J=2.2, 0.7 Hz, H-9), 6.28 (1H, q, J=1.1 Hz, H-3), 2.51 (3H, d, J=1.1 Hz, 4-Me).

4.1.2. 7*H*-Furo[3,2-*g*]chromen-7-one 18. Cyclisation of 2-[(2-oxo-2*H*-chromen-7-yl)oxyacetaldehyde[28] (**13**) afforded mainly compound **18** (132 mg, 71%) as colourless crystals: mp 161–162°C [lit.[26] 160–161°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 (1H, d, J=9.5 Hz, H-5), 7.70 (1H, d, J=2.3 Hz, H-2), 7.69 (1H, s, H-4), 7.48 (1H, d, J=1.1 Hz, H-9), 6.83 (1H, dd, J=2.3, 1.1 Hz, H-3), 6.38 (1H, d, J=9.5 Hz, H-6).

The fastest running band was identified as 2*H*-furo[2,3-*h*]chromen-2-one (**19**) (17 mg, 9%), colourless crystals: mp 136–137°C [lit.[1] 137–137.5°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (1H, d, J=9.7 Hz, H-4), 7.70 (1H, d, J=2.2 Hz, H-8), 7.44–7.20 (2H, AB part of ABX system, H-5 and H-6), 7.15 (1H, dd, J=2.2, 0.7 Hz, H-9), 6.40 (1H, d, J=9.7 Hz, H-3).

4.1.3. 2-Methyl-7*H*-furo[3,2-*g*]chromen-7-one 20. Cyclisation of 2-[(2-oxo-2*H*-chromen-7-yl)oxy]propanal[28] (**14**) afforded compound **20** (174 mg, 87%) as colourless crystals: mp 149–150°C [lit.[31] 148–149°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (1H, d, J=9.7 Hz, H-5), 7.53 (1H, s, H-4), 7.38 (1H, d, J=1.0 Hz, H-9), 6.42 (1H, dq, J=1.0 Hz, H-3), 6.3 (1H, d, J=9.7 Hz, H-6), 2.48 (3H, d, J=1.0 Hz, 2-Me).

A very small sample of 8-methyl-2*H*-furo[2,3-*h*]chromen-2-one (**21**) (6 mg, 3%), colourless solid, was then recovered from the fastest running band: mp 153–154°C [lit.[31] 155–156°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (1H, d, J=9.7 Hz, H-4), 7.32–7.26 (2H, AB part of ABX system, H-5 and H-6), 6.71 (1H, qd appears as quintet, J=1.0 Hz, H-9), 6.35 (1H, d, J=9.7 Hz, H-3), 2.50 (3H, d, J=1.0 Hz, 8-Me).

4.1.4. 5,6-Dimethyl-7*H*-furo[3,2-*g*]chromen-7-one 22. Cyclisation of 2-[(3,4-dimethyl-2-oxo-2*H*-chromen-7-yl)oxy]acetaldehyde[28] (**15**) afforded mainly compound **22** (152 mg, 71%) as colourless crystals: mp 141–142°C [lit.[37] 140–141°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 (1H, s, H-4), 7.67 (1H, d, J=2.3 Hz, H-2), 7.44 (1H, d, J=1.0 Hz, H-9), 6.83 (1H, dd, J=2.3, 1.0 Hz, H-3), 2.47 (3H, q, J=0.6 Hz, 5-Me), 2.24 (3H, q, J=0.6 Hz, 6-Me).

The fastest running band was then identified as 3,4-dimethyl-2*H*-furo[2,3-*h*]chromen-2-one (**23**) (19 mg, 9%), colourless crystals: mp 178–179°C [lit.[38] 179–180°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, d, J=2.4 Hz, H-8), 7.60–7.40 (2H, AB part of ABX system, H-5 and H-6), 7.12 (1H, dd, J=2.4, 0.8 Hz, H-9), 2.48 (3H, q, J=0.7 Hz, 4-Me), 2.27 (3H, q, J=0.7 Hz, 3-Me).

4.1.5. 6-Methoxy-2*H*-furo[2,3-*h*]chromen-2-one 24. Cyclisation of 2-[(6-methoxy-2-oxo-2*H*-chromen-7-yl)-oxyacetaldehyde[28] (**16**) afforded compound **24** (9 mg, 4%) as colourless crystals: mp 187–189°C [lit.[1] 188.5°C]; ^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (1H, d, J=9.5 Hz, H-4), 7.71 (1H, d, J=2.0 Hz, H-8), 7.14 (1H, dd, J=2.0 Hz, H-9), 6.79 (1H, s, H-5), 6.41 (1H, d, J=9.5 Hz, H-3), 4.05 (3H, s, OMe).

4.2. Irradiation procedure

Two HPW 125 Philips lamps, mainly emitting at 365 nm, were used for irradiation experiments. The total energy was detected by a radiometer (Cole-Parmer Instrument Company, Niles, IL), equipped with a CX-365 sensor.

4.3. Cell cultures

Cultures of Balb/c mouse 3T3 fibroblast were grown in DMEM medium (Dulbecco's Modified Eagle Medium SIGMA Co.) supplemented with 115 units/mL of penicillin G (GIBCO Laboratories) 115 μg/mL streptomycin (GIBCO Laboratories) and 10% foetal calf serum (GIBCO Laboratories).

Individual wells of 96-well tissue culture microtiter plate (IWAKI Japan) were inoculated with 100 μL of DMEM containing 5×10^3 mouse 3T3 cells. The plate was incubated

at 37°C in a humidified 5% incubator for 72 h to form a monolayer of approximately 80% confluence.

After the medium was removed and 100 μL of the drug solution dissolved in ethanol and diluted with Hank's balanced salt solution (HBSS pH=7.2) was added to each well. The plate was then incubated for 30 min in an atmosphere of 5% CO_2 at 37°C, the control plate was placed in the dark and then irradiated. After irradiation, the solution was replaced by the growth medium and the plates were placed in the incubator for 24 h. After this period, cell viability was assayed by the MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, test as described.[39] Cell growth at each drug concentration was expressed as percentage of untreated controls and the concentration resulting in 50% (IC_{50}) growth inhibition was determined by linear regression analysis.

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