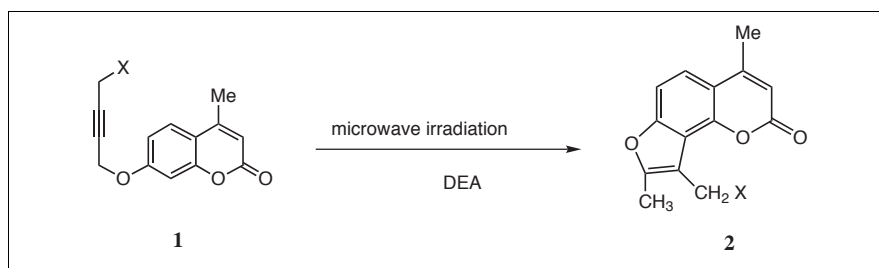


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4'-(Hydroxy, chloro, amino, acetoxy and methoxy)-methyl- 4,5'-dimethylangelicins were efficiently and rapidly synthesized *via* Claisen rearrangement of 4-methyl-7-[4-(hydroxy, chloro, amino, acetoxy and methoxy)-but-2-ynloxy]-coumarins respectively under microwave irradiation. Prominent among the advantages of this new method are operational simplicity, good yields in short reaction times and easy work-up procedures employed.

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Furocoumarins, such as the angular angelicin and the linear psoralen (Figure 1), are natural products derived from umbelliferone (7-hydroxycoumarin), which are present in members of the Apiaceae, Leguminosae, Rutaceae and Umbelliferae families [1]. Furocoumarins are active photosensitizing drugs widely used in photomedicine [2]. Furocoumarin/ultraviolet therapy, known as photophoresis, has recently been used for treatment of cutaneous T cell lymphoma, Sezary syndrome and related diseases [3,4]. Photochemotherapeutic effect of furocoumarins is based on intercalation of the furocoumarin molecule between pyrimidine bases of the microorganism DNA [5].

Given the interest in furocoumarins, it is no surprise that numerous synthetic ways to these compounds have been reported [6]. Most approaches can be seen as belonging to one of two types: 1) fusion of a furan ring to a coumarin derivative and 2) fusion of a pyrone ring to a benzofuran derivative.

Hydroxy and amino functional groups on the angelicins, lead to increasing of the lipophilic character of these compounds [7]. In many cases aminomethyl-angelicins were synthesized by a three-step technique involving initial chloromethylation, displacement of the halide by potassium phthalimide, and subsequent hydrazinolysis of phthalimidomethyl angelicin [8,9].

A survey of the literature revealed that the Claisen rearrangement under microwave irradiation has received little attention in the past [10]. There are several thermal methods for the preparation of five-membered heterocyclic ring in benzo[*b*]thiophenes and indoles *via* Claisen

rearrangement of the prop-2-ynloxy benzen derivatives [11]. Majumdar *et al.* have reported the regioselective synthesis of pyrano[2,3-*c*]coumarins from aryloxybut-2-ynloxy coumarins [12]. Otter *et al.* studied the Claisen rearrangement of 5-(prop-2-ynloxy)-uracil under a variety of conditions [13].

In this paper we wish to report the facile and inexpensive route to preparation of 4'-(hydroxy, chloro, amino, methoxy and acetoxy)methyl- 4,5'-dimethyl-angelicins *via* Claisen rearrangement under microwave irradiation.

The starting materials 4-methyl-7-[4-(hydroxy, chloro, amino, acetoxy and methoxy)-but-2-ynloxy]-coumarins **4(a-e)** were prepared as mentioned in Figure 1.

Compounds **4(a-e)** were placed in an house hold microwave oven for (20-30) minutes, products were purified by column chromatography and identified as related angelicins **5(a-e)** Figure 2. Negligible amounts of psoralens were detected in this methodology. The reaction was tested under thermal conditions also, but monitoring of the reaction by TLC in different solvent systems visualizing spots with UV lamp or iodine vapour show that in no case the progress of reaction was noticeable.

EXPERIMENTAL

All of melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 843. ¹H-NMR spectra were recorded on a Bruker Avance 500 MHz or JEOL FX90 MHz instruments. Mass spectrum was obtained on Shimadzu QP 1100EX instrument. Analytical calculation was obtained on LECO

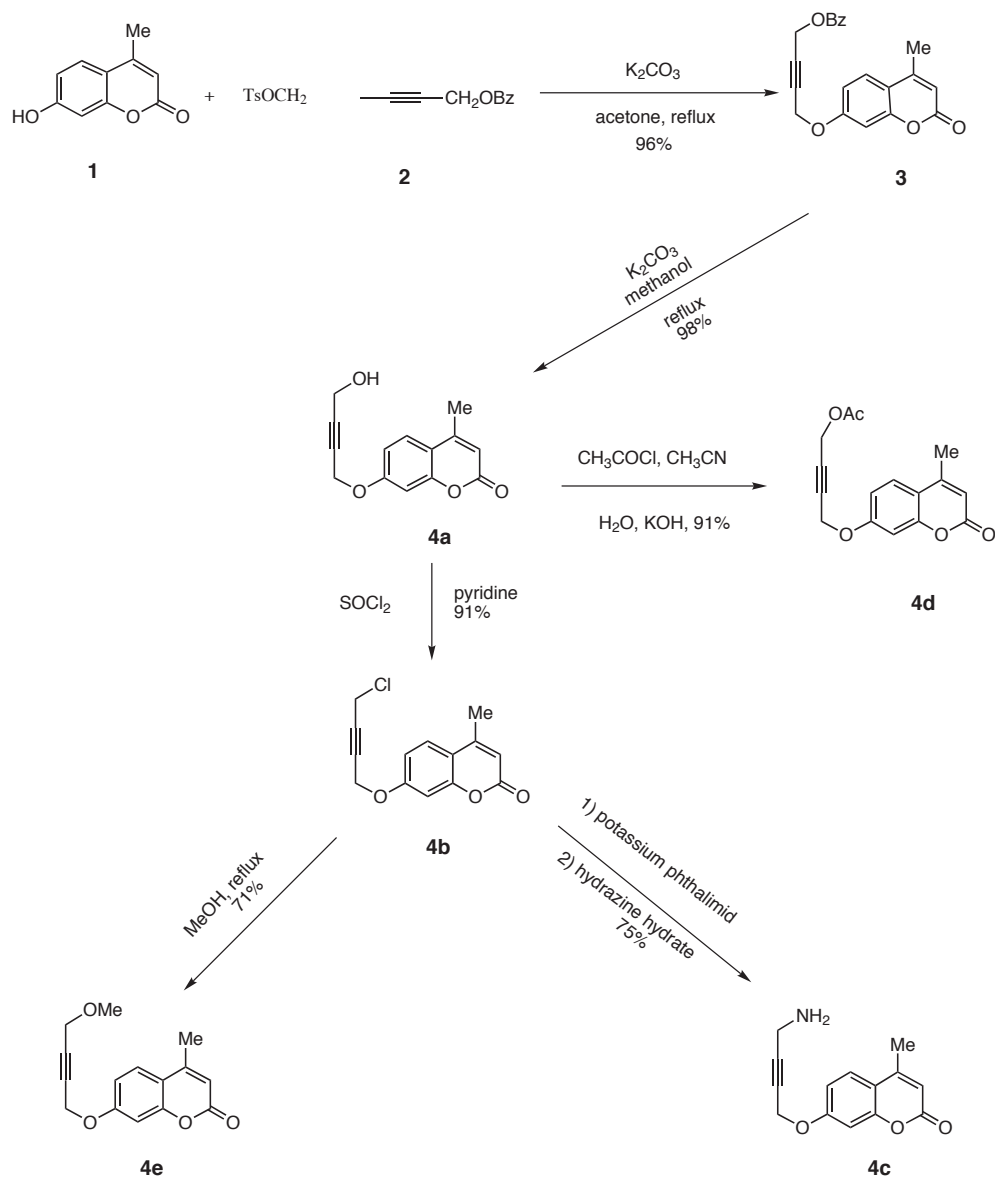


Figure 1

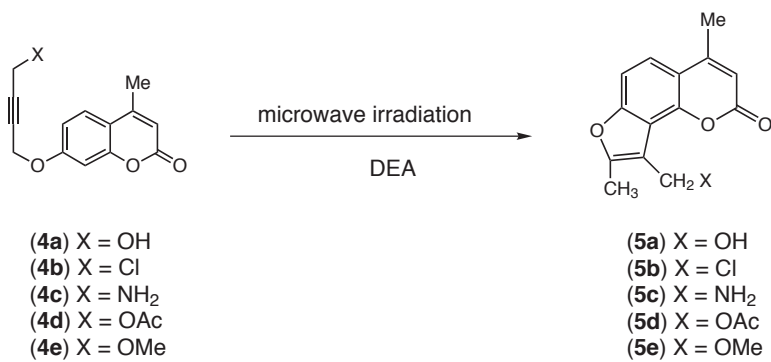


Figure 2

CHNO-932 Analyzer instrument. Miele Electronic M720 domestic oven was used for microwave irradiation.

Preparation of Angelicins.

General Procedure.

Compounds **4(a-e)** (0.008 mol) was dissolved in *N,N*-diethyl-aniline (DEA, 5ml) in a sealed Teflon container (screw cap type, 25 ml). The mixture was subjected to microwave irradiation with 540W for 20-30 minutes. The progress of the reaction was monitored by TLC. After the completion of the reaction, the intimate mixture was taken up to cold water and the precipitated solid was collected by filtration and washed with water. The crude was directly subjected to column chromatography using chloroform/ethylacetate (20/5) as eluent to obtain the related products.

Caution: Although we did not have any accident in this work, it is highly recommended that the reaction should be performed in an efficient hood.

Selected Data .

4'-Hydroxymethyl-4,5'-dimethylangelicin (**5a**).

Yield 56%, m.p: 201-202 °C; ¹H-NMR (CDCl₃, 500 MHz): δ 2.467(s, 3H, Me), 2.476 (s, 3H, Me), 4.87 (s, 2H, methylen), 6.25 (s, 1H, olefinic CH), 7.31(d, J =7.8, 1H, aromatic proton), 7.42 (d, J =7.8, 1H, aromatic proton); ¹³C-NMR (CDCl₃): δ 8.5, 21.2, 49.6, 108.3, 111.4, 112.5, 114.6, 118.2, 122.1, 148.6, 150.4, 152.7, 152.8, 160.9. IR (KBr disc), ν, cm⁻¹: 3220-3510 (O-H), 1700(C=O), 1610(C=C). EIMS (EI, 70ev) *m/z*: (M⁺ 244), 226, 198, 170.

Anal. Calcd. for C₁₄H₁₂O₄: C, 68.8; H, 4.9. Found %: C, 67.7; H, 5.2.

4'-Chloromethyl-4,5'-dimethylangelicin (**5b**).

Yield 60%, m.p: 213-14 °C; ¹H-NMR (CDCl₃, 90 MHz): δ 2.45 (s, 3H, Me), 2.42 (s, 3H, Me), 4.6 (s, 2H, methylen), 6.25 (s, 1H, olefinic CH), 7.30 (d, J =7.7, 1H, aromatic proton), 7.40 (d, J =7.7, 1H, aromatic proton); ¹³C-NMR (CDCl₃): δ 7.7, 21.2, 27.9, 108.3, 111.4, 112.5, 114.6, 118.2, 122.1, 148.6, 150.4, 152.7, 152.8, 160.9. IR (KBr disc), ν, cm⁻¹: 1710(C=O), 1620(C=C), EIMS (EI, 70ev) *m/z*: (M⁺ 262, M+2 264).

Anal. Calcd. for C₁₄H₁₁ClO₃: C, 64.12; H, 4.2. Found: C, 64.15; H, 4.21.

4'-Aminomethyl-4,5'-dimethyl angelicin (**5c**).

Yield 52%, m.p: 238-243 °C; ¹H-NMR (CDCl₃, 90 MHz): δ 2.43(s,3H, Me), 2.40(s,3H, Me), 2.81(s,2H, NH₂), 4.0(s,2H, methylen), 6.31(s,1H, olefinic CH), 7.3(d, J =7.8,1H, aromatic proton), 7.4(d, J =7.8, 1H, aromatic proton); ¹³C-NMR (CDCl₃): δ 8.2, 21.2, 34.0, 108.3, 111.4, 112.5, 114.6, 118.2, 122.1, 148.6, 150.4, 152.7, 152.8, 160.9. IR (KBr disc), ν, cm⁻¹: 3300-3500 (NH₂), 1715(C=O), 1615(C=C). EIMS (EI, 70ev) *m/z*: (M⁺ 243).

Anal. Calcd. for C₁₄H₁₃NO₃: C, 69.13; H, 5.34. Found: C, 69.16; H, 5.36; N, 5.71.

4'-Acetoxymethyl-4,5'-dimethylangelicin (**5d**).

Yield 48%, m.p: 108-10 °C ; ¹H-NMR (CDCl₃, 90 MHz): δ 2.40(s, 3H, Me), 2.43(s, 3H, Me), 2.48(s, 3H, OAc), 4.2(s, 2H,

methylen), 6.31(s, 1H, olefinic CH), 7.1(d, J =7.7,1H, aromatic proton), 7.3 (d, J =7.7, 1H, aromatic proton); ¹³C-NMR (CDCl₃): δ 8.5, 20.7, 21.2, 49.7, 108.3, 111.4, 112.5, 114.6, 118.2, 122.1, 148.6, 150.4, 152.7, 152.8, 160.9, 170.3. IR (KBr disc), ν, cm⁻¹: 1725(C=O), 1620(C=C). EIMS (EI, 70ev) *m/z*: (M⁺ 286).

Anal. Calcd. for C₁₆H₁₄O₅: C, 67.13; H, 4.89. Found: C 67.15. H 4.9.

4'-Methoxymethyl-4,5'-dimethylangelicin (**5e**).

Yield 62 %, m.p: 137-9 °C ; ¹H-NMR (CDCl₃, 90 MHz): δ 2.41 (s, 3H, Me), 2.43 (s, 3H, Me), 3.48 (s, 3H, OMe), 4.3 (s, 2H, methylen), 6.31 (s, 1H, olefinic CH), 7.2(d, J =7.8, 1H, aromatic proton), 7.3 (d, J =7.8, 1H, aromatic proton); ¹³C-NMR (CDCl₃): δ 8.5, 21.2, 58.7, 58.9, 108.3, 111.4, 112.5, 114.6, 118.2, 122.1, 148.6, 150.4, 152.7, 152.8, 160.9. IR (KBr disc), ν, cm⁻¹: 1725(C=O), 1610(C=C). EIMS (EI, 70ev) *m/z*: (M⁺ 258).

Anal. Calcd. for C₁₅H₁₄O₄: C, 69.76; H, 5.42. Found: C, 69.9; H, 5.44.

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