Microwave Promoted and Improved Thermal Synthesis of Pyranocoumarins and Furocoumarins†

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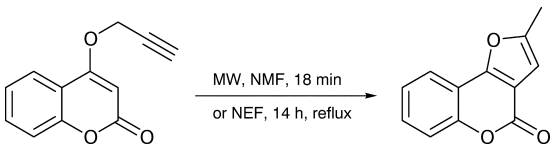
Propargyl ethers of 7-hydroxy-, 4-hydroxy-, and 4-methyl-7-hydroxycoumarins have been efficiently rearranged to pyranocoumarins and furocoumarins under microwave irradiation; improved thermal rearrangement of these ethers was also reported.

Many compounds containing coumarin moieties are reported to have hypnotic, insecticidal, antifungal, anthelminitic, and other physiological properties. Some of these heterocycles are often employed as important intermediates leading to bioactive substances.[1] In view of the natural occurrence and useful range of biological activity associated with many furano- and pyrano-coumarins, various methods have been developed for their syntheses Among them, synthesis of fused furano- and pyrano-coumarins *via* Claisen rearrangement of propargyl (prop-2-ynyl) ethers derived from hydroxycoumarins have been extensively studied.[2–6] In these reported methods, the rearrangement reactions take place at boiling temperature in various solvents such as *N*,*N*-diethylaniline (DEA), *N*,*N*-dimethylaniline (DMA), diphenyl ether, *etc*. (195–220 °C) for 4–14 h. These procedures required vigorous reaction conditions with tedious work-up.

The application of microwave irradiation for rapid organic synthesis has found widespread use, owing to the reduction in reaction time.[7] Strauss and co-workers reported a new batchwise and continuous microwave reactor for conducting organic reactions on a large scale.[8] Recently, a dramatic reduction in the reaction time of Claisen reactions, such as allyl phenyl ethers and ortho ester Claisen rearrangement, selective synthesis of naphthopyrans, naphthofurans and natural lapachenole, have been reported using a domestic microwave oven.[9]

In continuation of our work on microwave-assisted organic reactions, and rearrangement of propargyl ethers, here, a cleaner version of these transformations is described in which a microwave oven replaces the conventional reflux method. Also, an improved thermal rearrangement of 4-hydroxycoumarins to pyranocoumarins **2a**–**c** are reported in *N*-ethylformamide (NEF), with generally good yields (Scheme 1). Unlike DEA and DMA, which are very difficult to remove from the reaction mixture, NEF or *N*-methylformamide (NMF) are soluble in water and can be removed very easily from the product.

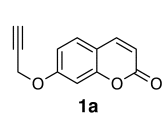
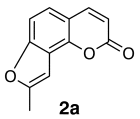
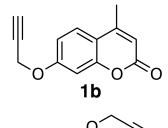
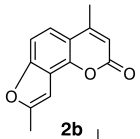
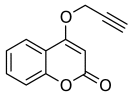
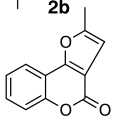
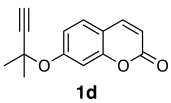
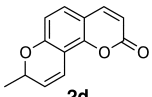
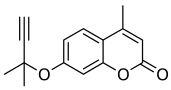
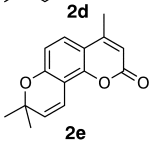
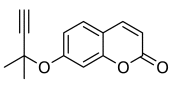
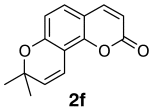
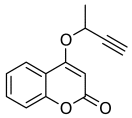
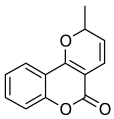
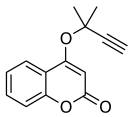
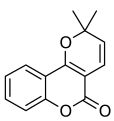


Scheme 1

The tandem Claisen rearrangement–cyclization reaction was examined with umbelliferone propargyl ether **1a** in the presence of various Lewis acids as catalyst, such as $AlCl_3$, $TiCl_4$ or BF_3, in different solvents and temperature. The product was either the starting ether or the cleavage products. No pyranocoumarins and furocoumarins could be isolated from the Lewis acid-catalyzed reactions.

Thermal Claisen rearrangement of 1,1-dimethylpropargyl ether **1f** was reported to give a mixture of angular pyranocoumarins, seselin (**2f**), linear pyranocoumarins, xanthyletin and furanocoumarines.[3] Here, only one product was isolated from the rearranged product. The speed and versatility of the microwave-assisted reactions (not purely thermal), and a comparison of the yields obtained with classical thermal conditions are shown in Table 1.

Table 1 Microwave promoted tandem Claisen rearrangement–cyclization of coumarin propargyl ethers

Entry	Starting ether	Product	MW, *t* /min (%Yield)[a]	NEF, *t* /h (%Yield)[a]	DEA, *t* /h (%Yield)[a]
1	 **1a**	 **2a**	18(70)	14(50)	
2	 **1b**	 **2b**	18(62)	14(50)	6(8)[b]
3	 **1c**	 **2c**	18(65)	14(52)	—
4	 **1d**	 **2d**	16(80)	—	14(68)
5	 **1e**	 **2e**	16(71)	—	14(60)
6	 **1f**	 **2f**	16(82)	—	14(70)
7	 **1g**	 **2g**	—	—	12(65)[c]
8	 **1h**	 **2h**	—	—	12(65)[c]

[a]Isolated yields. [b]From ref. 3. [c]These compounds were also formed directly when 4-hydroxycoumarin was reacted with methylpropargyl alcohol or dimethylpropargyl alcohol using the procedure outlined in ref. 10.

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Experimental

IR spectra were taken on Matt Son 1000 Unicam FTIR instrument, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 80 spectrometer and MS spectra were obtained on a Varian MAT 311A, and Varian CH 5 spectrometers. Chemicals were purchased from Fluka and used as received. All products were characterized by their IR, ^{1}H and ^{13}C NMR spectra. A domestic Westinghouse microwave oven (KM90VP-63/03, 1400 W) was used for irradiation of the samples. 7-Hydroxycoumarin, 4-hydroxycoumarin and 4-methyl-7-hydroxycoumarin were readily converted into the corresponding propargyl ether by known methods.[10]

General Procedure for the Preparation of Pyrano- or Furanocoumarins under Microwave Irradiation.—Propargyl ether (2.5 mmol) was dissolved in NMF (14 ml) in a sealed Teflon container (screw cap type, 50 ml). The mixture was subjected to microwave irradiation with high power for a given time (Table 1). The mixture was diluted with water (20 ml), and the product extracted with light petroleum (3×20 ml). Further purification of the crude reaction mixture on silica gel column, eluting with hexane–ethyl acetate (2:1), gave the pure product.

General Procedure for the Preparation of Furanocoumarins under Classical Thermal Conditions.—Propargyl coumarin ether (2.5 mmol) was dissolved in NEF (20 ml) in a 50 ml flask, and the mixture was refluxed for 14 h. The mixture was diluted with water (20 ml), and the product extracted with light petroleum (3×20 ml). Further purification of the crude reaction mixture on silica gel column, eluting with hexane–ethyl acetate (2:1), gave the pure product.

General Procedure for the Preparation of Pyranocoumarins under Classical Thermal Conditions.—1,1-Dimethylpropargyl or 1-methylpropargyl coumarin ether (2.5 mmol) was dissolved in DEA (10 ml) in a 25 ml flask, and the mixture was refluxed for 14 h. The mixture was diluted with aqueous HCl solution and the product extracted with CH_2Cl_2. (20 ml). Further purification of the crude reaction mixture on silica gel column, eluting with benzene, gave the pure product.

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