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MICROWAVE AND BF_3 PROMOTED REARRANGEMENT OF ALLYLOXYCOUMARINS TO ALLYLCOUMARINS AND DIHYDROFUROCOUMARINS

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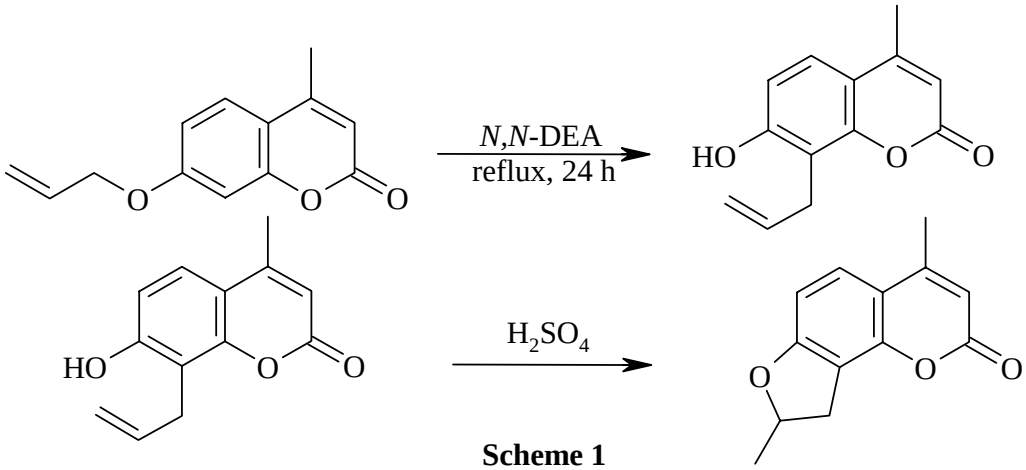
Abstract-Allyl, crotyl, methallyl and cinamyl ethers of 4-hydroxy-, 7-hydroxy-, and 4-methyl-7-hydroxycoumarins have been efficiently synthesized and rearranged to substituted allylcoumarins under microwave irradiation. Irradiation of allylcoumarins in the presence of BF_3/ether directly produced substituted dihydrofurocoumarins in good yields.

Coumarins and furocoumarins are a class of natural compounds that in recent years have attracted growing synthetic interest, while some of them have been found to be useful in photochemotherapy, antitumoral, fragrances, agrochemicals and anti-HIV therapy or as CNS-active compounds.[1] In the view of the natural occurrence and useful range of biological activity associated with many dihydrofurocoumarins, various methods have been developed for the synthesis of fused dihydrofurocoumarins *via* Claisen rearrangement of allyl ethers and then acid-catalyzed cyclization of allylcoumarins to dihydrofurocoumarins.[2] In these reported methods, the Claisen rearrangement reactions take place at boiling temperature in various solvents such as *N*,*N*-diethylaniline, *N*,*N*-dimethylaniline, diphenyl ether, *etc*. for about 24 h. These procedures required vigorous reaction conditions with tedious work-up procedure. Cyclization of allylcoumarins under acidic conditions,

usually sulfuric acid, resulted the expected dihydrofurocoumarins, but in low yields (Scheme 1). Cerric ammonium nitrate, CAN, mediated formation of dihydrofurocoumarin from 4-hydroxycoumarin and α-methylstyrene was recently reported by Kobayashi.[3]

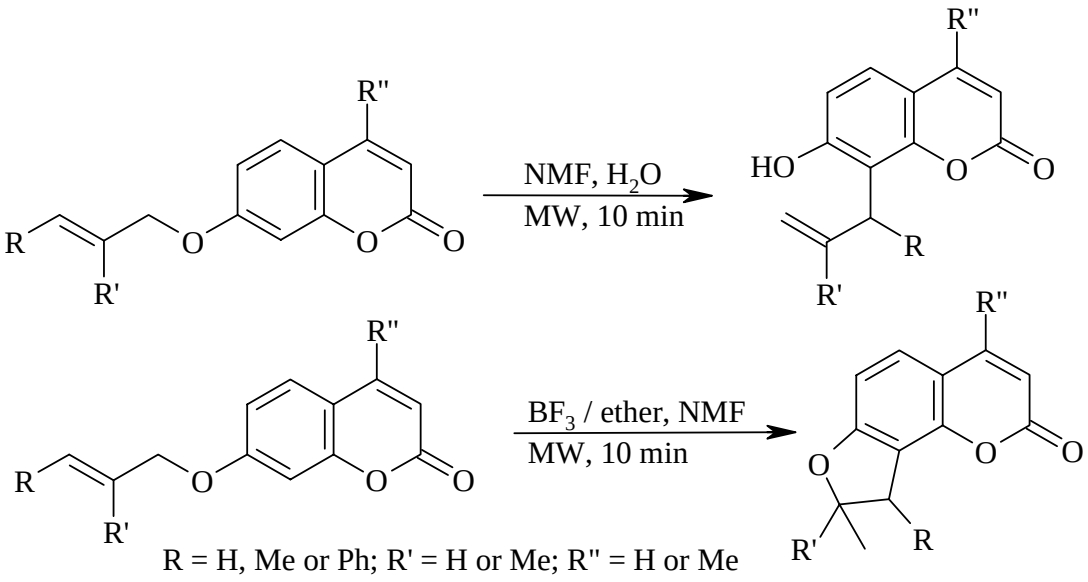


Scheme 1

Microwave-assisted organic synthesis has become an increasing used technique for the generation of organic molecules and has attracted much attention due to enhanced reaction rates, increased yield, selectivity and ease of manipulation of the product.[4] One of the serious constraint in the use of microwave ovens in organic synthesis is the selection of solvent for the reaction.[5]

In continuation of our work on microwave promoted selective rearrangement of propargyl naphthyl ethers to naphthopyrans, naphthofurans, and application to the synthesis of natural lapachenole, pyranocoumarins and furocoumarins,[6] here we report a fast and cleaner method for rearrangement of allyl, crotyl, methallyl and cinnamyl ethers of 4-hydroxycoumarin, 7-hydroxycoumarin, and 4-methyl-7-hydroxycoumarin to substituted allylcoumarins. The allyloxycoumarins were rearranged to allylcoumarines under microwave irradiation in *N*-methylformamide, NMF (Scheme 2, Table1). The irradiation time was between 18 to 22 min, and longer irradiation time did not increase the yield. By addition of about 10 drops of water to the NMF (5 mL), the irradiation time decrease to 10 min with almost the same yield. In the case of 7-allyloxycoumarin and 4-methyl-7-allyloxycoumarin small amount of 6-allyl derivatives were also formed. The microwave promoted tandem Claisen rearrangement-cyclization reaction of allyloxycoumarins in the presence of BF_3 / ether directly produce

the dihydrofurocoumarins in good yields, Scheme 2. The results are summarized in Table 2. The products obtained by microwave irradiation in NMF can be purified with more ease, since NMF is soluble in water. The results clearly show that the rearrangement of allyloxycoumarins to allylcoumarins and preparation of dihydrofurocoumarins *via* tandem Claisen rearrangement-cyclization reaction of allyloxycoumarins in the presence of BF_3 / ether using microwave irradiation are the best alternative for preparation of these compounds.



R = H, Me or Ph; R' = H or Me; R" = H or Me

Scheme 2

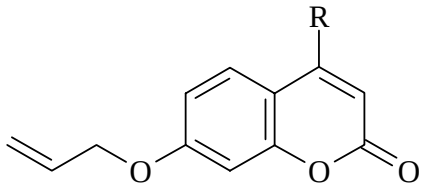
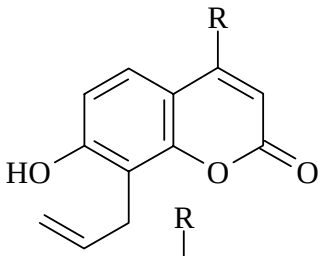
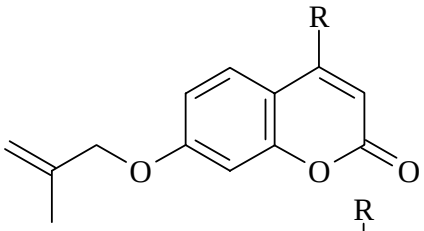
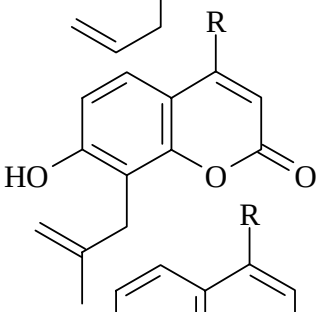
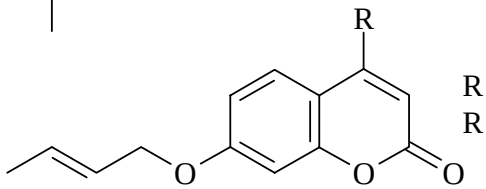
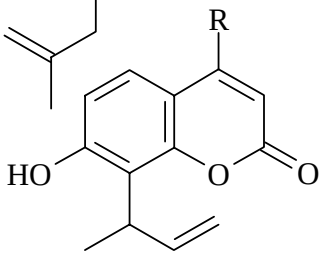
The allyl, crotyl, methallyl and cinnamyl ethers of 4-hydroxy-, 7-hydroxy-, and 4-methyl-7-hydroxycoumarins were prepared from the corresponding coumarins and allyl, crotyl, methallyl and cinnamyl chloride or bromide in refluxing dry acetone in the presence of potassium carbonate.[7] All the products have been characterized through IR, MS and NMR spectra and by comparison with those reported in the literature.

EXPERIMENTAL

IR spectra were taken on Matt Son 1000 Unicam FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 80 spectrometer in $CDCl_3$. MS spectra were obtained on Fisson 800 Trio, and GC-Mass HP 5973 MSD.

*General Procedure for the Preparation of Allyloxycoumarins (***1-3***).* - To a solution of hydroxycoumarin (1.62 g, 10 mmol) in acetone (100 mL), K_2CO_3 (2.8 g, 20 mmol), and allyl bromide (1.8 g, 15 mmol) were added. The resulting mixture was refluxed for 6 h (TLC monitoring). After cooling, the solvent was evaporated, the residue poured into water (100 mL) and extracted with CH_2Cl_2 (3 x 20 mL), the combined extract washed with brine, dried over $MgSO_4$, and evaporated to get a white solid. The white solid crystallized from ether if needed. Allyloxycoumarins (**1-3**) are known compounds, and their spectroscopic data were similar to those reported in the literature.[7]

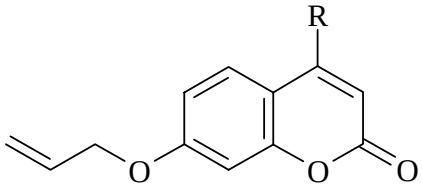
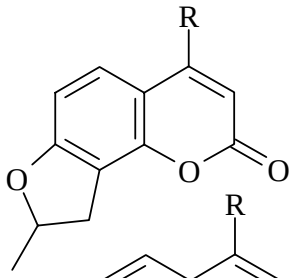
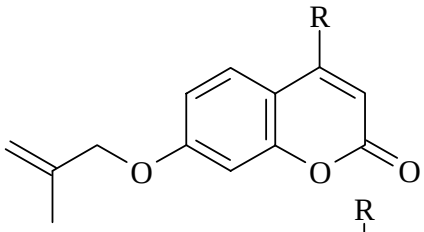
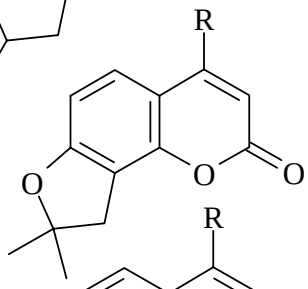
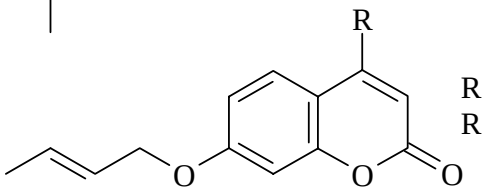
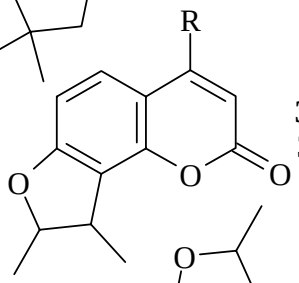
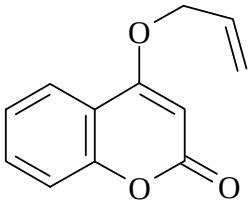
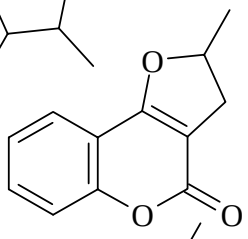
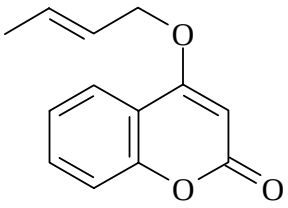
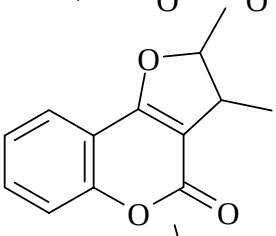
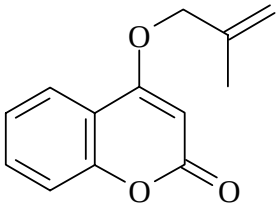
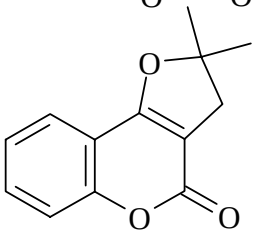
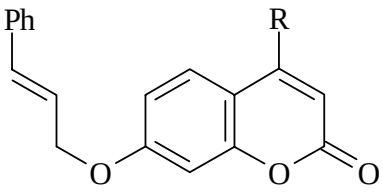
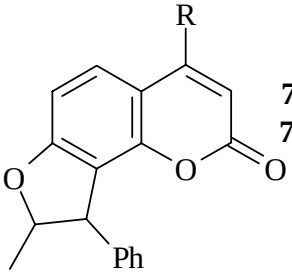
Table 1: Rearrangement of allyloxycoumarins to allylcocoumarins in NMF under microwave irradiation

Substrate	R	Product	Yield (time) % (min)
	R = H R = Me		**1a** 75(22) **1b** 74(18)
	R = H R = Me		**2a** 65(20) **2b** 68(22)
	R = H R = Me		**3a** 70(18) **3b** 74(18)

General Procedure for the Rearrangement of Allyloxycoumarins to Allylcoumarins in a Microwave oven[6].- Allyloxycoumarin (1.5 mmol) was dissolved in NMF (5 mL) and about 10 drops of water was added. The mixture was placed in a sealed Teflon container (screw cap type, 50 mL), and subjected to microwave irradiation with high power for 20 min. The mixture was diluted with water (20 mL), and the product extracted with ether (3 x 20 mL). Further purification of the crude reaction mixture on silica gel

column, eluting with hexane-ethyl acetate (2:1) gave the pure product.

Table 2: Rearrangement of allyloxycoumarin to dihydrofurocoumarin in the presence of NMF, BF_3/ether in microwave oven

Substrate	R	Product	Yield (time) % (min)
	R = H R = Me		**1a** 70(18) **1b** 74(18)
	R = H R = Me		**2a** 68(20) **2b** 65(20)
	R = H R = Me		**3a** 74(18) **3b** 70(18)
			**4a** 65(20)
			**5a** 50(20)
			**6a** 45(22)
	R = H R = Me		**7a** 52(25) **7b** 50(22)

General Procedure for the Rearrangement of Allyloxycoumarins to dihydrofuranocoumarins with BF_3/Ether under Microwave Irradiation.- Allyloxycoumarin (1.5 mmol) was dissolved in NMF (5 mL) and 1.0 mL of BF_3/ether was added. The mixture was placed in a sealed Teflon container (screw cap type, 50 mL), and subjected to microwave irradiation with high power for 20 min. The mixture was diluted with water (20 mL), and the product extracted with ether (3 x 20 mL). Further purification of the crude reaction mixture on silica gel column, eluting with hexane-ethyl acetate (2:1) gave the pure product.

Dihydrofurocoumarin (**4a**); mp 112-113 ^{0}C, lit.,[2] 114 ^{0}C. Dihydrofurocoumarin (**4b**); mp 129-130 ^{0}C. Dihydrofurocoumarin (**5a**); mp 108 ^{0}C, lit.,[2] 105-106 ^{0}C. Dihydrofurocoumarin (**5b**); mp 110-112 ^{0}C. Dihydrofuranocoumarin (**6a**); oil; ^{1}H NMR ($CDCl_3$): δ 1.20 (d, *J* = 6.5 Hz, 3H), 1.35 (d, *J* = 6.5 Hz, 3H), 3.00-3.75 (m, 1H), 4.28-5.98 (m, 1H), 6.09 (d, *J*= 9.5 Hz, 1H), 6.21-7.30 (m, 2H), 7.50 (d, *J* = 9.5 Hz, 1H). IR (KBr): ν, 1735, 1515, 1461, 1261 cm^{-1}. MS: 216 (M^+), 201 (base peak). Dihydrofurocoumarin (**6b**); oil; ^{1}H NMR ($CDCl_3$): δ 1.28 (d, *J* = 6.5 Hz, 3H), 1.41 (d, *J* = 6.5 Hz, 3H), 2.33 (s, 3H), 3.04-3.70 (m, 1H), 4.25-5.94 (m, 1H), 6.04 (s, 1H), 6.50-7.50 (m, 2H). IR (KBr): ν, 1707, 1569, 1361, 1300 cm^{-1}. MS: 230 (M^+), 215 (base peak). Dihydrofurocoumarin (**7a**); oil; ^{1}H NMR ($CDCl_3$): δ 1.50 (d, *J* = 6.4 Hz, 3H), 2.25-3.70 (m, 2H), 4.75-5.50 (m, 1H), 6.50-7.71 (m, 4H). IR (KBr): ν, 1723, 1646, 1500, 1415, 1276 cm^{-1}. MS: 202 (M^+), 187 (base peak). Dihydrofurocoumarin (**9a**); oil; ^{1}H NMR ($CDCl_3$): δ 1.51 (s, 6H), 2.98 (s, 2H), 7.00-7.70 (m, 4H). IR (KBr): ν, 1715, 1638, 1500, 1376, 1259, 1092 cm^{-1}. MS: 216 (M^+), 201 (base peak), Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.01; H, 5.65. Dihydrofurocoumarin (**10a**); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, *J* = 6.9 Hz, 3H), 3.95 (d, *J* = 7.2 Hz, 1H), 4.91 (m, 1H), 6.22 (d, *J* = 9.4 Hz, 1H), 6.40-7.60(m, 7H), 7.59 (d, *J* = 9.4 Hz, 1H),. IR (KBr): ν, 1730, 1615, 1453, 1253, 1123 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.63; H, 5.16. Dihydrofurocoumarin (**10b**), mp 230-232 ^{0}C, lit.,[2] 230 ^{0}C.

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