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Condensation of 2-Substituted 2-Oxazolin-5-ones with *o*-Hydroxyaromatic Carbonyl Compounds and Their Imines Under Microwave Activation

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Condensation of 2-substituted 2-oxazolin-5-ones (**2**) with salicylaldehyde or *o*-hydroxyacetophenone and/or their N-substituted imines (**3**) under microwave activation affords 3-N-acylaminocoumarins (**5**) exclusively, whereas 2-acetoxy-aromatic aldehydes (**4**) produce (Z)-2-substituted-4-(*o*-acetoxybenzylidene)-2-oxazolin-5-ones (**6**). The reaction seems to be initiated by the formation of an adduct through Aldol type condensation at 4-position of the oxazolone ring, followed by intramolecular 1,5-bond cleavage of the ring by the *vicinal* free -OH group and subsequent ring expansion in the resultant 3-N-acylaminocoumarins (**5**). It is mentioned here that acetic anhydride mediated cyclocondensation of hippuric acid and salicylaldehyde afforded a mixture of 3-N-benzoylaminocoumarin (**5**) and 4-(*o*-acetoxybenzylidene)-2-phenyl-2-oxazolin-5-one (**6**) from which coumarin was isolated with low yield as reported in the literature. The present method overcomes all the disadvantages and the solo targeted product can be achieved in a disciplined route. The reaction time is decreased from hours to minute along with a higher yield under microwave irradiation with better purity. All the steps can be carried out in one flask starting from α-N-acylamino-acids (1) under mild and non-hazardous condi-tions using green chemistry methodology.

Key Words: α-N-acylaminoacids, 3-N-Acylaminocoumarins, Microwave activation, Green chemistry.

INTRODUCTION

The objective of the present investigation was to develop a method for a fast and facile synthesis of 3-N-acylaminocoumarins (**5**) by using a non-conventional green chemistry methodology which led to higher yield and a remarkable reaction rate enhancement with the optimum utilization of energy. Interest in the chemistry of coumarins (**5**) continues unabated because of their usefulness as synthons[1-3] for the construction of several heterocycles and their diverse bio-potentiality as insecticidal[4-7], antimicrobial[8] property including as plant growth regulator[9].

EXPERIMENTAL

Melting points were recorded by Toshniwal melting point apparatus and are uncorrected. The UV, IR and ^{1}H NMR were on a Cary-14, Perkin-Elmer 720 and/or 257 and Jeol FX 90 Q spectrometers, respectively. Microwave irradiation was carried out by using domestic LG-microwave oven, model No. MS 194A with a 230V- 50 Hz power source, 900 W output and 2450 MHz operating frequency.

Preparation of 3-N-acylaminocoumarins (5): To a suspension of α-N-acylaminoacids (**1**; 1.0 mol) in dry benzene (25mL/g of the acid) containing triethylamine (2.5 mol), ethylchloroformate/benzenesulphonyl chloride (1.1 mol) was added and the mixture was shaken at room temperature until the crystals of the acid disappeared and triethylamine hydrochloride salt separated out which was filtered under suction and washed with benzene (5 mL). The solvent was removed to dryness under reduced pressure and to the viscous residue was added *o*-hydroxyaromatic aldehydes/ketones or their imines (**3**), taken in molar ratio with respect to α-N-acylaminoacids and the mixture was intimately mixed and heated in microwave oven for 5 min only. Trituration with ethanol gave a solid which was recrystallized from ethanol.

5a: Yield, 70 %; m.p. 205-206 ºC (Lit.[10] 201.5 ºC), IR (Nujol, ν_{max}, cm^{-1}): 3320 (NH), 1710 (CO, coumarin), 1670 (CO, amide), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ: 2.22 (s, 3H, -$COCH_3$), 7.31 (m, 4H, Ar-H), 8.06 (s, 1H, exchangeable, -NH-CO-), 8.53 (s, 1H, 4-CH).

5b: Yield, 80 %; m.p. 175 ºC (Lit.[11], IR (Nujol, ν_{max}, cm^{-1}): 3350 (NH), 1710 (CO, coumarin), 1660 (CO, amide), 1620 (C=C); ^{1}H NMR ($CDCl_3$) δ: 7.06- 7.93 (m, 9H, Ar-H), 8.71 (s, 2H, one proton exchangeable, -NH-CO- and 4-CH).

5c: Yield, 80 %; m.p. 215 ºC (Lit.[12], IR (Nujol, ν_{max}, cm^{-1}): 3300 (NH), 1710 (CO, coumarin), 1670 (CO, amide), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ: 2.41 (s, 3H, -CH_3), 7.18-8.93 (m, 9H, Ar-H), 8.16 (s, 1H, exchangeable, -NH-CO-). M^+ (m/z): 279 (molecular mass).

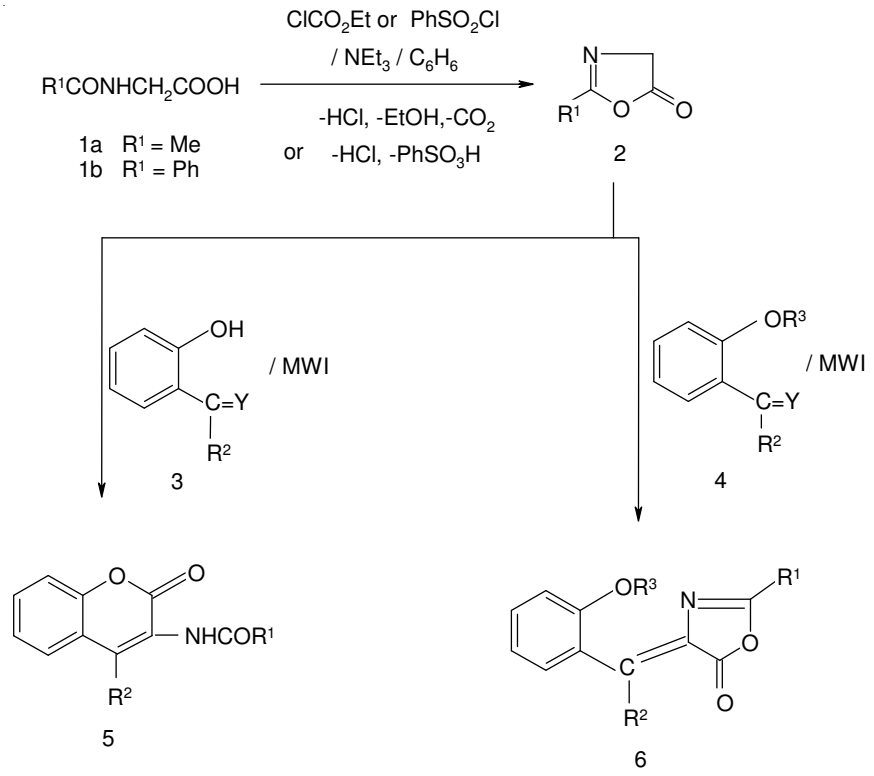
6f: Yield, 90 %; m.p. 198-200 ºC (Lit.[13] 198-200 ºC).

Yields are based on the α-N-acylaminoacids (hippuric/aceturic) acid taken.

RESULTS AND DISCUSSION

Acetic anhydride mediated condensation of hippuric acid (**1b**) with salicylaldehyde (**3**, R^2 = H, Y=O) is known[11] to give a mixture of 4-(*o*-acetoxybenzylidene)-2-phenyl-2-oxazolin-5-one (**6**, R^1 = Ph, R^2 = H, R^3 = Ac) and 3-N-benzoylaminocoumarin (**5**, R^2 = Ph, R^2 = H). However, this reaction failed with aceturic acid (**1a**). The condensation of 2-substituted 2-oxazolin-5-ones (**2**) with *o*-hydroxyaromatic carbonyl compounds and

their imines (**3**) under modified route afford coumarins (**5**) exclusively. It has been found when the condensation is extended to 2-acetoxybenzaldehyde (**4**, R^2 = H, R^3 = Ac, Y=O), the product is (Z)-4-(*o*-acetoxybenzylidene)-2-phenyl-2-oxazolin-5-one (**6**, R^1 = Ph, R^2 = H, R^3 = Ac) exclusively.



3 - 6	R^1	R^2	R^3	Y
a	Me	H	H	O
b	Ph	H	H	O
c	Ph	Me	H	O
d	Ph	Me	H	$C_6H_{11}N$
e	Ph	Me	H	n-BuN
f	Ph	H	Ac	O

The conversion of α-N-acylaminoacids (**1**) to 2-substituted 2-oxazolin-5-ones (**2**) was carried out at room temperature by ethylchloroformate/benzene sulphonyl chloride mediated cyclization in benzene in the presence of triethylamine base. The triethylamine hydrochloride salts were filtered under suction and the solvent was removed to dryness under reduced pressure, followed

by the addition of suitable *o*-hydroxyaromatic aldehydes/ketones or their imines (**3**) to the reaction mixture. The contents were mixed thoroughly and then heated under microwave irradiation only for 5 min. On work-up, coumarins (**5**) obtained in pure form with appreciable yields. The generation of **2** at room temperature declined the risk of high pressure development associated with solution phase reaction at higher temperature as well. The reaction seems to be initiated by the formation of an adduct (**6**, R^3 = H), followed by intramolecular 1,5-bond cleavage of the ring **6** by the vicinal phenolic group and subsequent β-elimination in the resultant dihydrocoumarins. The formation of (Z)-4-(*o*-hydroxybenzylidene)-2-phenyl-2-oxazolin-5-one (**6**, R^3 = H) was not discernible in this reaction. It is worthwhile to mention that an improved yield of coumarins (**5**) was obtained in the case of the imines of the respective aldehydes/ketones used. The coumarins obtained have been characterized on the basis of their relevant spectral data and by the comparison with authentic samples.

The present procedure overcomes some of the disadvantages of the earlier methods regarding reaction time and purity of the products. In view of the ready availability of the starting materials, mild experimental conditions and excellent overall yields, the present proposed route appears to be potentially important.

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