An efficient and facile synthesis of substituted 3-aminocoumarins under mw irradiation in dry media

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Abstract: A variety of 3-aminocoumarins were prepared by reaction of salicylaldehyde derivatives with benzoylglycine catalyzed by piperidine under microwave irradiation (MWI) and subsequent acid hydrolysis. The structure of products was proven by elemental analysis, IR, NMR and Mass spectra. These investigations will contribute to development of environmentally friendly and inexpensive processes in organic synthesis.

KEYWORDS: solvent-free system, Knoevenagel condensation, benzoylglycine

Introduction:

The chemistry of coumarins and their derivatives has been studied for over a century due to the association of these systems with a variety of biological properties. Coumarins are common in nature and used as intermediates in the synthesis of pharmaceuticals, insecticides, fluorescent brightners and anticoagulant agents.[1,2,3,4]

Nowadays, the microwave dielectric heating effect uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions. This in situ mode of energy conversion has many attractions to the chemists[5,6], because its magnitude depends on the properties of the molecules. There is a variety of methods for carrying out microwave assisted organic reactions using domestic or commercial ovens, this is basically known as MORE (Microwave Induced Organic Reaction Enhancement) Chemistry.[7]

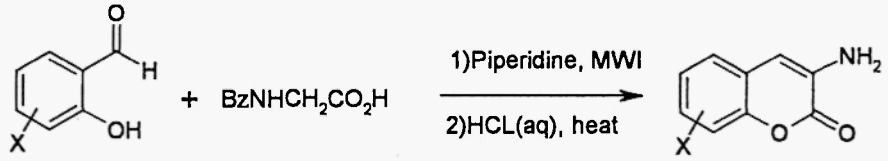
The starting of microwave activated synthesis using dry media on solid inorganic support seems to be the most efficient and eco-friendly technology.[8,9] The main advantage being that solid supports do not absorb microwaves at 2450 MHz, so are not an obstacle for the transition of microwaves to the reactants. In addition, the limitations of the MWI assisted reaction in solvents, namely, the development of high pressure and the need for specialized sealed vessels are circumvented via this solid state technique which enables organic reactions to occur rapidly at atmospheric pressure.[10] Moreover, the obtaining of clean products in a short duration of time is also advantageous.[11]

Reactions between neat reactants, avoiding organic solvent during the reactions in organic synthesis leads to a clean, efficient and economical technology (green chemistry); safety is largely increased, work up is considerably simplified, cost is reduced, increased amounts of reactants can be used in the some equipment. Due to all these advantages there is an increasing interest in the use of environmentally benign reagents and procedures. Or in other words, the absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for synthesis.

Though many synthetic strategies have been applied for preparation of coumarins, most of these methods suffer from some drawbacks, which include drastic reaction conditions and longer time with difficult workup. Recently we have reported

simple synthesis of coumarins and furocoumarins in solvent-free conditions.[12,13,14] We have also reported a simple methodology for the regioselective bromination of furocoumarins in dry media.[15] In continuation of our work in this area we became interested in studying the solvent-free preparation of 3-aminocoumarins under MWI. The aim of this work was the focile and economical preparation of 3-aminocoumarins as potentially useful intermediates for synthesis of aminoangelicines which are active photosensitizing drugs widly used in photomedicune[16].

A claim[17] that 3-aminocoumarin can be prepared directly from salicylaldehyde and glycine has not been confirmed.[18] In this communication we wish to report the facile synthesis of 3-aminocoumarins via the reaction of benzoylglycine and salicylaldehyde derivatives catalyzed by pipridine under MWI and subsequent acid hydrolysis of the N-benzoylaminocoumarin derivatives in solventless system (scheme 1).



Scheme 1

Table 1.

Product (X)	Reaction time (min)	mp(°C) / [lit.mp][ref.]	Yield(%)
2a (H)	2.5	135-138/[136][19]	87
2b (6-Br)	3	195-197	72
2c (6-OH)	4	214-217	58
2d (6-NO_2)	4	205-207/[209][20]	58
2e (8-OMe)	3.5	123-126	71
2f (7-OMe)	3.2	139-142	75
2g (5,6-benzo)	3.4	155-157	72

The reaction is conducted by exposure of a mixture of salicylaldehyde, benzoylglycine and piperidine to microwave irradiation. Most of salicylaldehyde disappeared within first 2 min as determined by TLC. Phthalimidoaceticacid and its ethylester derivative were examined in place of benzoylglycine in this procedure and in no case any product was detected which is probably related to steric hindrance of large phthalimide group. Solid supports such as molecular sieve, silica gel and MgO were also used in this procedure but reaction between neat reactants found to give the best yields.

In conclusion this method describes a noticeable improvment in reaction condition for the synthesis of substituted 3-aminocoumarins and takes advantages of the reaction under solvent-free conditions. As shown in Table1 the time of reaction is reduced to few minutes. We believe this strategy will find utility in organic synthesis.

Experimental

All of the melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 843. ^{1}H-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 CHNO-932 Analyzer instrument.

General procedure

Salicylaldehyde (20 mmol), freshly prepared benzoyglycine (22 mmol) and a few drops of piperidine were mixed thoroughly using a spatula in a beaker. The beaker was placed in an house hold microwave oven. The progress of reaction was monitored by TLC. After the completion of the reaction, The intimate mixture was then taken up to HCl(aq) solution and refluxed for about 1h. The reaction mixture was then allowed to cool to room temperature was then extracted with ethylacetate and dried over anhydrous magnesium sulfate, the excess acid was removed by washing with 1M $NaHCO_3$ solution and water. The solvent was removed by distillation under reduced prassure and the resulting crude product was subjected to column chromatography using (hexane/AcOEt , 7/1) as solvent to obtain related 3-aminocoumarins (**2a-g**).

Selected spectroscopic data

2a: ^{1}HNMR δ: 4.4(s*(br)*,2H,NH_2), 6.8(s,1H,4-H), 7.1-7.3(m,4H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3300,3410(NH2), 1700(CO); EIMS (70ev) m/z: (M^+ 161), Anal.Calcd. for $C_9H_7NO_2$: C, 67.07%; H, 4.38 %; N, 8.69%; found C, 66.95 %; H, 4.31%; N, 8.75%. **2b**: ^{1}HNMR δ: 4.4(s*(br)*,2H,NH_2), 6.6(s,1H,4-H), 7.1-7.4(m,3H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3340,3420(NH2), 1700(CO); EIMS (70ev) m/z: (M^+ 240), Anal.Calcd. for $C_9H_6BrNO_2$: C, 45.02%; H, 2.52%; N, 5.84%; found C, 45.20%; H, 2.50%; N, 6.05%. **2c**: ^{1}HNMR δ: 5.5(s*(br)*,2H,NH_2), 6.8(s,1H,4-H), 6.8-7.3(m,3H,Ar), 9.4(δOH); IR, ν (Cm^{-1}), (KBr disc): 3360,3480(NH2), 1685(CO); EIMS (70ev) m/z: (M^+ 177), Anal.Calcd. for $C_9H_7NO_3$: C, 61.02%; H, 3.98%; N, 7.91%; found C, 60.50%; H, 3.80%; N, 7.71%. **2d**: ^{1}HNMR δ: 4.6(s*(br)*,2H,NH_2), 6.7(s,1H,4-H), 7.2-8.2(m,3H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3400,3480(NH2), 1715(CO); EIMS (70ev) m/z: (M^+ 206), Anal.Calcd. for $C_9H_6N_2O_4$: C, 52.43%; H, 2.93%; N, 13.59%; found C, 52.05%; H, 2.90%; N, 13.35%. **2e**: ^{1}HNMR δ: 3.9(s,3H,OMe), 4.4(s*(br)*,2H,NH_2), 6.8(s,1H,4-H), 6.8-7.3(m,3H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3380,3460(NH2), 1705(CO); EIMS (70ev) m/z: (M^+ 191), Anal.Calcd. for $C_{10}H_9NO_3$: C, 62.82%; H, 4.75%; N, 7.33%; found C, 63.12%; H, 4.90%; N, 7.20%. **2f**: ^{1}HNMR δ: 3.8(s,3H,OMe), 3.9(s*(br)*,2H,NH_2), 7.1(s,1H,4-H), 6.8-7.3(m,3H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3419,3324(NH2), 1707(CO); EIMS (70ev) m/z: (M^+ 191), Anal.Calcd. for $C_{10}H_9NO_3$: C, 62.82%; H, 4.75%; N, 7.33%; found C, 63.20%; H, 4.65%; N, 7.34%. **2g**: ^{1}HNMR δ: 4.4(s*(br)*,2H,NH_2), 7.6(s,1H,4-H), 7.4-

8.3(m,6H,Ar); IR, ν (Cm^{-1}), (KBr disc): 3330,3440(NH2), 1690(CO); EIMS (70ev) m/z: (M^+ 211), Anal.Calcd. for $C_{13}H_9NO_2$: C, 73.90%; H, 4.26%; N, 6.62%; found C, 73.51%; H, 4.18%; N, 6.60%.

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