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An efficient synthesis of formyl coumarins by microwave irradiation method-duff formylation

Omprakash S. Chavan[1], S. B. Chavan[2] and M. A. Baseer*[2]

[1]Department of Chemistry, Badrinarayan Barwale College, Jalna
[2]Department of Chemistry, Yashwant College, Nanded, M.S., India

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ABSTRACT

A series of formyl derivatives of Coumarins have been synthesized by Duff formylation method, in this method hydroxyl Coumarins was reacted with hexamethylene tetramine (HMTA) in presence of tri-fluoroacetic acid (TFAA) under microwave irradiation techniques. The structures of all synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis. This is a newly developed efficient synthesis of formyl Coumarins under microwave irradiation technique by Duff formylation method.

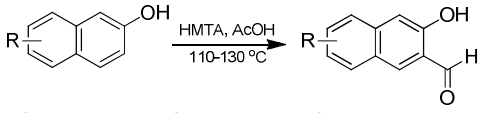
Keywords: Coumarins, MWI, Duff Formylation

INTRODUCTION

Coumarin is an important class of synthetic and naturally occurring compounds. Many of which exhibits several pharmacological properties, such as anti-oxidant[1], anti-bacterial[2], anti-tumor[3], anti-coagulant[4], anti-carcinogenic[5], anti-microbial[6], anti-HIV[7], anti-inflammatory[8], anti-Histamic[9], anti-protocol and analgesic [10] etc. In addition of this compounds used as good additives for food and cosmetics [11]. Various analogues of substituted Coumarins such as derivatives of formyl Coumarin [12][13][14] exhibits luminescent properties [15] .

In 1932 J. Duff described a synthesis of aromatic aldehydes involved hexamethylene tetramine was treated with phenolic compounds usually in the presence of Glycero Boric acid to convert to its formyl derivatives [16]. In 1934 J. Duff also reported that synthesis of sixteen phenolic aldehydes from phenols that is β-napthols with hexamethylene tetramine in anhydrous acetic acid at 110 °C and the product on hydrolysis with dilute HCl yield phenolic aldehydes [17] (Scheme 1)

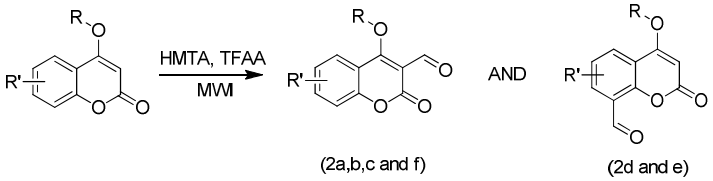
Scheme 1



In 1907 Breslauer and Pictet successfully reported formylation of phenolic compounds by using formaldehyde. [18] In 1972 HTML by Rhodium published research work of formylation of aromatic compounds with HMTA and trifluoroacetic acid for preparation of regioselective product specially para position [19]

Recently many scientist follow duff reaction and published research work with respective hydroxyl Coumarins to convert ortho formyl hydroxyl Coumarins with the help of HMTA and acetic acid. Each of above process has certain limitations. In addition to this, required conditions used are quite vigorous and yields are generally very low in the range of 15-20% only. Expectedly we have discovered hydroxyl Coumarins easily formylated by using HMTA along with excess TFAA. Excess trifluoroacetic acid works as solvent and markly enhance yield of reaction.

Scheme 2



MATERIALS AND METHODS

All the compounds used in synthesis were of analytical grade, the melting points of the compounds were determined in open head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm^{-1} by using KBr pallet on FT-IR Perkin spectrophotometer. H^1 NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in $CDCl_3$. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC). The Microwave oven was used of Domestic types.

General Procedure for synthesis of Formyl Coumarins by Microwave Irradiation techniques

A mixture of Coumarin compound (*1mmol*) and HMTA (*3 mmol*) was dissolved in 10 ml of TFAA and irradiated under microwave irradiation at 800 W for 3 min. with proper stirring, course of reaction was monitored by TLC. After complication of reaction, reaction mixture was treated with 1:1 hot solution of Conc. H_2SO_4 and water then boil for 30 min., followed by extracted with ethyl acetate, solid was collected on evaporation of Ethyl acetate. Yield of the products was listed in table 2.

Table: 1 Structure of synthetic compounds. (2a-2f)

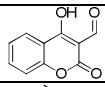
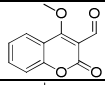
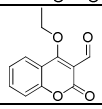
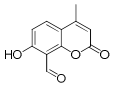
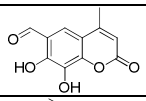
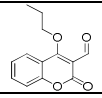
Compound	Molecular Structure	IUPAC Name	Mol. formula	Mol. Weight
2-a		4-hydroxy-2-oxo-2H-chromene-3-carbaldehyde	$C_{10}H_6O_4$	190
2-b		4-methoxy-2-oxo-2H-chromene-3-carbaldehyde	$C_{11}H_8O_4$	204
2-c		4-ethoxy-2-oxo-2H-chromene-3-carbaldehyde	$C_{12}H_{10}O_4$	218
2-d		7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde	$C_{11}H_8O_4$	204
2-e		7,8-dihydroxy-4-methyl-2-oxo-2H-chromene-6-carbaldehyde	$C_{11}H_8O_5$	220
2-f		2-oxo-4-propoxy-2H-chromene-3-carbaldehyde	$C_{13}H_{12}O_4$	232

Table: 2. Physicochemical data of Coumarin derivatives (2a-2f).

Comp. Code	Solubility	% yield	Melting Range C	R_f Value
2a	Methanol	70	163-165	0.58
2b	Methanol	79	122-125	0.74
2c	Methanol	76	147-149	0.76
2d*	Methanol	64	139-141	0.61
2e	Methanol	59	179-182	0.50
2f	Methanol	66	158-161	0.81

(Combined yield of both isomers)*

In the present work, we have developed an efficient, rapid, and simple procedure involving microwave irradiation technique for converting Coumarin compounds to formyl Coumarin compounds. (Scheme 2) This process gives the desire formylated products in excellent yield and purity under mild conditions.

RESULTS AND DISCUSSION

At first, selection of Watt for formylation of Coumarin derivatives was investigated, therefore initially acetic acid was used as a model solvent for formylation of Coumarins [5] by increasing watt (heat) microwave irradiation from 100, 150, 300, 400, 600 and 800 W. There is increase in yield of the product with increase in watt power. Best result obtained from used of 800 W for 3 min. compare to other. (Fig.1, Table 2)

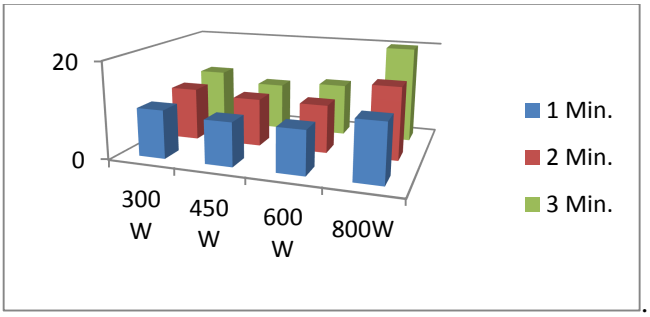


Figure 1. Reaction Condition: 1 *mol.* of Hydroxyl Coumarin, 6 *mol.* HMTA and AcOH as solvent, MWI, isolated yield[a]

Table: 2. Optimization of MWI time

Entry	Solvent	Time	Yield[a]	Watt
1	AcOH	1 Min.	10%	300 W
	AcOH	2 Min.	11%	300 W
	AcOH	3 Min.	12%	300 W
2	AcOH	1 Min.	9%	450 W
	AcOH	2 Min.	10%	450 W
	AcOH	3 Min.	10%	450 W
3	AcOH	1 Min.	9%	600 W
	AcOH	2 Min.	10%	600 W
	AcOH	3 Min.	11%	600 W
4	AcOH	1 Min.	12%	800 W
	AcOH	2 Min.	15%	800 W
	AcOH	3 Min.	20%	800 W

Table: 3. Optimization of Solvent effect

Entry	Solvent	MWI Time	Yield[a]
1	AcOH	3 Min.	20%
2	PEG-400	3 Min.	00%
3	AcOH with PEG-400	3 Min.	00%
4	TFAA	3 Min.	**70%**
5	TFAA with PEG-400	3 Min.	30%

Along with optimization of MWI time, investigation studies were done on the solvent effect on reaction yield. Formylation of Coumarin derivatives with HMTA and MWI at 800 W for 3 Min. was chosen as the model reaction condition for optimization of solvent effect. (Table 3)

From result PEG-400 and AcOH with PEG-400 gives zero yield (Table 3, Entry 2 and 3), TFAA with PEG-400 gives moderated amount of yield that is 30% (Table 3, Entry 5), finally better result obtained when TFAA was used as solvent as well as catalyst. (Table 3, Entry 4) With the help of optimization of time and solvent effect the scope and efficiently of reaction condition was explored for synthesis of wide variety of substituted formyl Coumarins and obtained result are summarized in table 1.

Table: 4. Spectral analysis data of Synthesized Coumarin derivatives

Compound Code	I.R. (KBr, cm^{-1})	Mass (M^++1)	^{1}HNMR($CDCl_3$) (δ in ppm)
2a	3320, 1724	190.0264	>13(s, 1H), 10.36 (s, 1H), 7.42-7.86 (m, 4H)
2b	1718, 1310	204.0422	3.55(s, 3H), 10.33 (s, 1H), 7.44-7.87 (m, 4H)
2c	2860,1725, 1620	218.0574	1.21(t, 3H), 4.0(q,2H),10.38 (s, 1H), 7.43-7.89 (m, 4H)
2d	3050, 1720, 1610.	204.0421	12.24 (s, 1H), 10.64 (s, 1H), 7.76-7.73 (d, 1H), 6.94-6.91 (d, 1H), 6.23 (s, 1H), 2.45 (s, 3H).
2e	3350, 1725	220.0371	2.44 (s,3H), 10.38 (s,1H), 5.38(s,2H), 6.25 (s,1H)
2f	2858, 1724	232.0735	0.92(t,3H), 1.85(m,2H), 4.04(t,2H), 10.37(s,1H),7.44-7.85 (m,4H)

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