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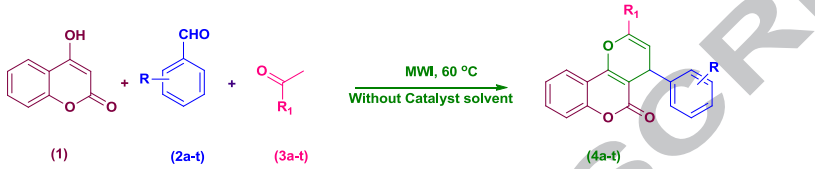

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[a] *Department of Image Science and Engineering, Pukyong National University, Busan, Korea, 608-737*

[b] *Department of Chemistry, SRM University, Kattankulathur, Kanchipuram (Dt), TamilNadu, India-603203*

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ABSTRACT

An efficient and rapid synthesis of a new class of diversely functionalized pyrano[3,2-c]chromen-5(4*H*)-ones has been achieved via one-pot three-component reaction of 4-hydroxy-2*H*-chromen-2-one, aldehydes, and acetophenones under microwave irradiation in catalyst and solvent-free conditions. The present methodology offers several advantages such as short reaction time, simple operational procedure, avoid toxic solvent and catalyst, high yield of product and endures the substrate diversity.

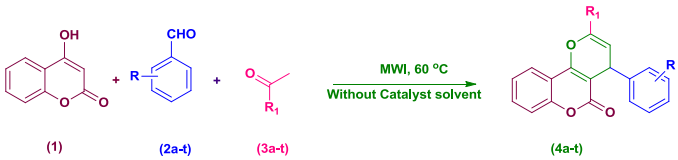
Multi-component reactions (MCRs) have been recognized as an important device for the expedient creation of various chemical libraries of 'drug like' heterocyclic compounds with high levels of molecular diversity and complexity.[1] Microwave irradiation (MWI), which has proved to be clean, increased selectivity, easier experimental procedures, fast and convenient energy source, improved yields and high purity of compounds, has taken an undeniable role in chemical laboratory practice.[2] Moreover microwave promoted solvent-free reactions are particularly welcome due to their essential advantages such as minimize reaction time, energy consumption, manipulative simplicity, and to maximize synthetic efficiency and environmental benefits. Currently, multi-component procedures employing MWI under solvent-free conditions are particularly welcome due to their vital advantages, mainly under the present paradigm shift to green methodologies.[3]

Chemistry of heterocyclic compounds has been ubiquitous in natural products, biologically active agrochemicals, pharmaceutical agents, organic materials, and several well-designed molecules.[4] Hence, the attention for developing new, versatile, and efficient synthesis of heterocyclic compounds has always been a thread in the synthetic organic and bio-organic chemistry. Pyrano[3,2-c]chromen-5(4*H*)-ones are the promising class of oxygen containing heterocyclic compounds which are ubiquitous to a diversity of biologically active products and have been shown to a broad series of biological activities.[5] Therefore, the synthesis of the pyrano[3,2-c]chromen-5(4*H*)-ones has fascinated much noticed in organic synthesis. So far, only few methods have been reported for the synthesis of pyrano[3,2-c]chromen-5(4*H*)-ones.[6]

* Corresponding author. * Tel.: +82-51-629-6411; fax: +82-51-629- 6408; e-mail: ytjeong@pknu.ac.kr

However, these methods suffered with one or more drawbacks such as relatively long reaction time, harsh reaction conditions, high reaction temperature, require stoichiometric amounts of toxic catalysts and the use of an organic solvent. Consequently, there is a need to develop a new and efficient, environmentally benign practical procedure and operational simplicity method for the synthesis of heterocycles containing pyrano[3,2-c]chromen-5(4*H*)-ones.

As part of our continuing research to be develop a green reaction methodology by MWI under solvent-free conditions.[7] Herein, we report a facile catalyst and solvent-free one-pot synthesis of pyrano[3,2-c]chromen-5(4*H*)-ones via three-component reaction of 4-hydroxy-2*H*-chromen-2-one, aldehydes, and acetophenones under microwave irradiation at 60 ºC (**Scheme 1**).[8]



Scheme 1: Synthesis of pyrano[3,2-c]chromen-5(4*H*)-ones under MWI.

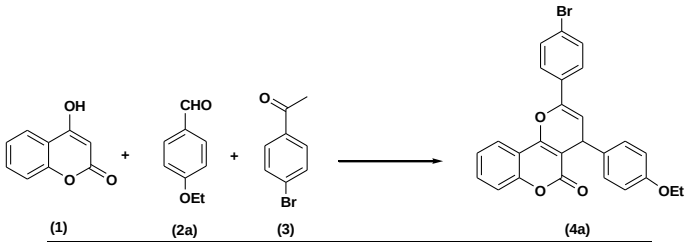
To develop optimal reaction conditions, we carried out the reaction between 4-hydroxy-2*H*-chromen-2-one (**1,** 1.0 mmol), 4-ethoxybenzaldehyde (**2a**, 1.0 mmol) and 4-bromoacetophenone (**3a**, 1.0 mmol) as a model. It was investigated under conventional and microwave conditions under without catalyst in ethanol solvent at room temperature. Desired product, **4a**, could not obtain even after 18 h stirring under conventional method (**Table 1, entry 1**). Only a trace amount of

this product was formed even after 5 h under MWI (**Table 1, entry 2**). We next examined the model reaction using different temperature ranging from 50 to 80 ºC under both conditions. It was found that at 50 ºC and 120 min of time, the yield of the product was low (**Table 1, entry 3**). Only at 60 ºC and with 60 min of reaction time, the highest product yield of 75% was observed (**Table 1, entry 4**). Further increase in the temperature did not affect the product yield. Thus it was proved that 60 ºC is the optimized temperature required for effecting this reaction by MWI (**Table 1, entry 5**). Obtained the desired product, **4a**, in low yield at long reaction time and the majority of un-reacted starting materials were recovered under conventional method at 50 to 80 ºC (**Table 1, entries 6-8**).

With this observation, we have subsequently studied the effect of various solvents and temperatures under MWI. Methanol was used as a solvent for this reaction at room temperature and desired product obtained low yield (**Table 1, entry 9**). The yield of product **4a** could be improved to 52% when the reaction was performed in acetonitrile at 60 ºC temperature (**Table 1, entry 10**). The yield of the products was improved to 60% (**Table 1, entry 11**), when the temperature of the reaction was increased to 60 ºC in methanol. We became interested to study the progress of the reaction under the influence of different organic solvents. In our observation at most of the solvent conditions the reaction did not proceed effectively and even though ethanol and DMF more polar solvent medium shown moderate product yields even at higher temperature and reaction times (**Table1 entries 4 & 13**). When the reaction was carried out under solvent-free conditions at 60 ºC, the expected product was obtained in high yield and short reaction time (**Table 1, entry 15**). After finding the solvent-free condition as best one at 60 ºC, we are also performed the reaction at various temperatures between 60-80 ºC and find that no more enhancement in the product yields appreciably (**Table 1, entries 15- 17**).The better yield in solvent-free conditions could be explained by a uniform distribution of the eutectic mixture of reactants, being in closer proximity to react than in conditions using ethanol as the solvent.

We also investigated effect of solvents under CTH at different temperature. But, to our surprise, we observed that the reaction did not proceed efficiently (**Table 1, entries 18-22**) in any solvent. In absence of the solvent, the model reaction could be carried out but the product was obtained in very low yield after prolonged reaction time (**Table1, entry 23**).

Table 1. Optimization of reaction conditions for the synthesis of **4a**[a]



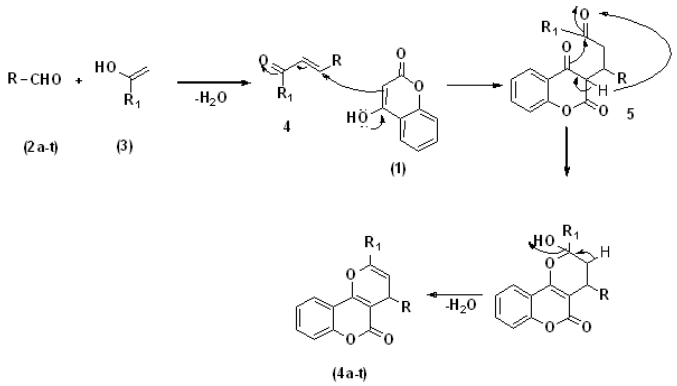
(1) (2a) (3) (4a)

Entry	Solvent (3mL)	Methods	Tem(°C)	Time (h)	Yield[b]
1	Ethanol	[c]CTH	RT	18	0
2	Ethanol	[d]MWI	RT	5	20
3	Ethanol	MWI	50	2	40
4	Ethanol	MWI	60	1	75
5	Ethanol	MWI	80	1	75
6	Ethanol	CTH	50	15	0
7	Ethanol	CTH	60	15	10
8	Ethanol	CTH	80	15	15
9	Methanol	MWI	RT	6	15
10	Acetonitrile	MWI	60	3	52
11	Methanol	MWI	60	3	60
12	Toluene	MWI	100	6	45
13	DMF	MWI	120	4	70
14	Acetone	MWI	60	4	46
15	Neat	MWI	60	15 min	95
16	Neat	MWI	70	15 min	95
17	Neat	MWI	80	15min	96
18	Acetonitrile	CTH	80	20	25
19	Methanol	CTH	60	22	15
20	Toluene	CTH	100	25	10
21	DMF	CTH	120	15	35
22	Acetone	CTH	55	20	18
23	Neat	CTH	80	10	40

[a]Reaction of 4-hydroxy-2*H*-chromen-2-one (**1**, 1 mmol), 4-bromoacetophenone (**2a**, 1 mmol), 1-(4-bromophenyl)ethanone (**3a**, 1 mmol); [b]Isolated yield; [c]Conventional thermal heating (CTH); [d]Microwave irradiation (MWI).

Encouraged by this initial success, we next designed to perform the generalized the applicability of this method for the synthesis of pyrano[3,2-c]chromen-5(4*H*)-ones from various aromatic aldehydes and acetophenones (**Table 2**). In all the cases the reaction worked efficiently and we found that phenyl groups bearing electron-withdrawing, as well as electron-donating, groups gave the corresponding products were obtained in excellent yield as well as in high purity. It is noteworthy that the reaction worked also with heterocyclic acetophenone provided good yield.

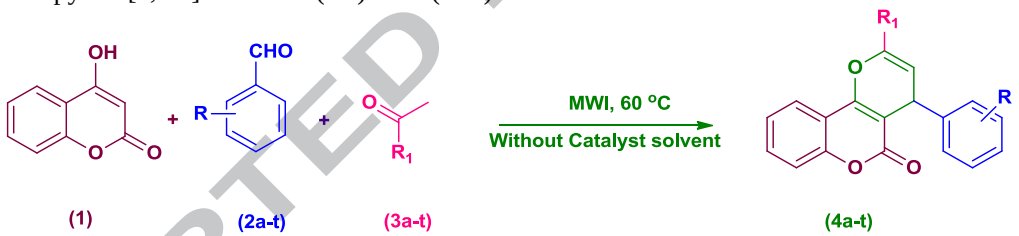
Upon these the results a reasonable reaction mechanism has been proposed in **Scheme 2**. Initially aldehyde (**2a-t**) reacts with the enolic form of the ketone (**3a-t**) to give achalcone (**4**) by removal of H_2O. Michael addition of 4-hydroxycoumarin (**1**) to the chalcone gave the intermediate **5** which on intramolecular cyclisation gave the desired pyrano[3,2-c]chromen-5(4*H*)-ones (**4a-t**) by removal of H_2O.



Scheme 2. The possible pathway of mechanism of formation of titled compounds (4a-t)

In summary, A highly sustainable and efficient multi-component reaction of readily available 4-hydroxy-2*H*-chromen-2-one, aldehydes, and acetophenones was developed for the synthesis of pyrano[3,2-c]chromen-5(4H)-ones under solvent-catalyst free condition in microwave irradiation. The notable features of this methodology are eco-friendly reaction conditions, no side product, avoidance of toxic catalysts and solvents, column chromatography purification is not required to obtain the pure products and products are obtained in excellent yields.

Table 2. Synthesis of pyrano[3,2-c]chromen-5(4*H*)-ones (**4a-t**)[a]



(1) (2a-t) (3a-t) (4a-t)

Entry	R	R_1	Product	Time (min)	Yield[b] (%)
1	4-OEt	4-Br-C_6H_4	4a	15	95
2	3-4-5-OMe	4-Br-C_6H_4	4b	16	90
3	3-NO_2	4-Br-C_6H_4	4c	22	91
4	3-OMe	4-Br-C_6H_4	4d	18	90
5	2-Cl-6-F	4-Br-C_6H_4	4e	14	89
6	2-NO_2	4-Cl-C_6H_4	4f	19	91
7	3-OMe	4-Cl-C_6H_4	4g	20	92
8	3-NO_2	4-Cl-C_6H_4	4h	21	91
9	4-OEt	4-Cl-C_6H_4	4i	20	93
10	3-4-5-OMe	4-Cl-C_6H_4	4j	21	92
11	4-OMe	C_6H_5	4k	24	93
12	4-Br	4-Cl-C_6H_4	4l	18	89
13	H	2-OMe-C_6H_4	4m	23	90
14	H	C_5H_4OS	4n	19	90
15	4-NO_2	4-Me-C_6H_4	4o	17	91
16	4-Cl	4-OMe-C_6H_4	4p	15	90
17	H	2-Br-C_6H_4	4q	19	90
18	4-Cl	4-Me-C_6H_4	4r	21	91
19	H	C_6H_5	4s	15	92
20	4-OMe	4-Br-C_6H_4	4t	17	91

[a]Reaction of 4-hydroxy-2*H*-chromen-2-one (**1**, 1 mmol), aldehydes (**2a-t**, 1 mmol), acetophenones (**3a-t**, 1 mmol) under catalyst and solvent-free conditions in MWI at 60 °C; [b]Isolated yield.

Supporting Information

All new compounds data and NMR spectra were provided as Supplementary data.

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8. 2-(4-bromophenyl)-4-(4-ethoxyphenyl)pyrano[3,2-c]chromen-5(4H)-one (4a).

A mixture of 4-hydroxy-2*H*-chromen-2-one (**1**, 1 mmol),), 4-bromoacetophenone (**2a**, 1 mmol), 1-(4-bromophenyl)ethanone (**3a**, 1 mmol) was taken in an open vessel in CATA-4R Scientific Microwave oven and irradiated at 60 ℃ in catalyst and solvent-free condition for 15 min. The progress of the reaction was monitored by TLC. After completion of the reaction (TLC), the resulting solid obtained was recrystallized from ethanol to obtain a pure white product. Yield 95%; white solid; mp 153-155 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, J = 1.4, 8.0 Hz, 1H), 7.59-7.54 (m, 5H), 7.38-7.28 (m, 4H), 6.83 (d, J = 8.4 Hz, 2H), 5.82 (d, J = 4.7 Hz, 1H), 4.62 (d, J = 4.7 Hz, 1H), 3.98-3.95 (q, 2H), 1.37 (t, J = 6.9 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 161.5, 158.3, 155.4, 152.8, 145.9, 135.4, 132.1, 131.9, 131.7, 129.6, 126.2, 124.3, 123.4, 122.6, 116.9, 114.7, 144.5, 104.5, 104.0, 63.5, 35.8, 14.9 ppm. HRMS (ESI, m/z): calcd for $C_{26}H_{19}BrO_4$ ($M+H^+$) 475.331; found: 475.325.