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Chapter 3: Synthesis of pyranocoumarin and furocoumarin derivatives

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Abstract: In this chapter, we present the synthesis of new coumarine derivatives starting from the 8-acetyl-7-hydroxy-4-methylcoumarin and subsequently by the cyclisation of 7-hydroxy-4-methyl-8-(3-aryl acrolyl)-2*H*-chromen-2-ones. Another series of novel coumarin-chromene compounds have been synthesized using 8-aryl-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-diones and the Vilsmeier Haack reagent. Further, a novel series of 8-acetyl-4-methyl-9-styryl-2*H*-furo [2,3-*h*] chromen-2-ones have been synthesized by the cyclisation of 7-hydroxy-4-methyl-8-(3-aryl acrolyl)-2*H*-chromen-2-ones and chloroacetone. Other new series of 4-methyl-8-phenyl-pyrano[2,3-*f*] chromen-2,10-diones have been synthesized from 7-hydroxy-4-methyl-8-(3-aryl acrolyl)-2*H*-chromen-2-ones by using DMSO/I_2 as oxidation media. And one more new series of hybrid compounds, substituted 4-chloro-8-methyl-2-phenyl-1,5-dioxa-2*H*-phenanthren-6-one, have been synthesized from substituted (*E*)-1-(7-hydroxy-4-methyl-8-coumarinyl)-3-phenyl-2-propen-1-ones by employing the Vilsmeier-Haack reaction, by conventional and microwave-assisted method.

Keywords: Chromene, Coumarin, Cyclisation, Microwave irradiation, Vilsmeier-Haack reagent.

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1 Introduction

Coumarins are important oxygen containing fused heterocyclic compounds embedded in several natural products and drugs (Gregory J. F., Emma K et al., 2002). They are present at high levels in few essential oils. In particular, they are present in cassia leaf oil (up to 87,300 ppm), cinnamon bark oil (7,000 ppm) and lavender oil. Coumarin is also found in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory (B G Lake., 1999). Majority of coumarins exist in higher plants, the richest sources are Rutaceae, Umbelliferae and tonkabeans. They occur in all parts of the plant, but exist at high levels in fruits, roots, stems and leaves.

Coumarins occupy a prominent place in the area of natural products and synthetic chemistry because of their biological properties. Coumarins encompass an important group among natural products and present in a various plant sources as benzopyrene derivatives. They have significant effects in plant biochemistry and physiology, since they act as enzyme inhibitors, antioxidants and precursors of toxic compounds. Besides, they are involved in many actions of plant such as growth hormones, growth regulators, respiration control, photosynthesis and defence against infections. Further, physiological, bacteriostatic and anti-tumour activities of these compounds make them attractive for further derivatisation and evaluation as new therapeutic agents. Weber and co-workers (Weber, U.S., Steffen, B et al., 1998) have shown that coumarin and its metabolite 7-hydroxycoumarin have antitumour activity against several human tumour cell lines. Both coumarin and coumarin derivatives have shown promise as potential inhibitors of cellular proliferation in various carcinoma cell lines (Egan, D., James, P. et al., 1997). Besides, reports show that 4- and 7-hydroxycoumarin inhibited cell explosion in gastric carcinoma cell line. Coumarins have long been recognized to possess anti-inflammatory, anti-oxidant, anti-allergic, anti-thrombotic, anti-viral, antimicrobial (Ashok, D., Vijaya, B.L., et al., 2016) and anti-carcinogenic activities. In addition to biological activities, they are used as additives to food and cosmetics and optical brightening agents (Budzisz**,** E., Elzbieta, B. et al., 2003).

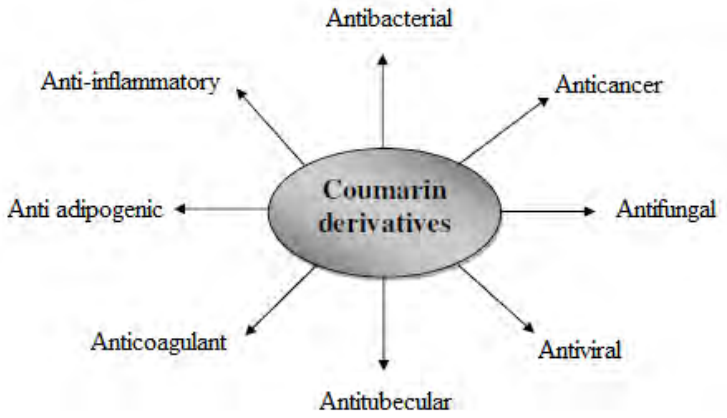


Fig. 1.1: Biological activities of coumarins

Synthetic and natural heterocycles play crucial role among chemical biology and drug discovery. The heterocyclic compounds are mainly of the classes of alkaloids, pyrazoles, pyrazolines, substituted imidazoles, substituted triazoles, 1,2,4,5 tetra substituted imidazoles, pyrazolo[1,5-*a*]pyrimidines, flavonoids, chromones etc. The natural heterocycles are plant metabolites, which protect plant from attack by insects, pathogens, bacteria and fungi. Biodynamic heterocycles demonstrates a wide variety of biological properties (Fig 1.1), many of which can be exploited for medicinal purposes and are essential for the well-being of human life. Synthetic heterocyclic compounds have empowered as a very essential class of compounds in different disciplines of science such as agriculture, agro-chemical industry, medicine and pharmacy. They have been the subject of chemical and biological studies due to variety of biological and pharmacological activities such as antibacterial, anticoagulant, antioxidant, anticancer, antifungal, antihypertension, anti HIV, anti-AIDS, antiviral, anti-inflammatory, anti-allergic, antifertility, antiproliferic and antiarthritic activities. Mono-substituted-triazole and imidazole compounds are important both as pharmaceutical and agrochemical fungicides. Diclobutrazol, paclobutrazol, fluconazole, triconazole and Ketoconazole are used as antifungal and antimicrobial agents. 1,3,5-Trisubstituted pyrazoline derivatives act as antimycobacterial and anticancer agents (Ashok, D., Padmavathi, K. et al., 2016).

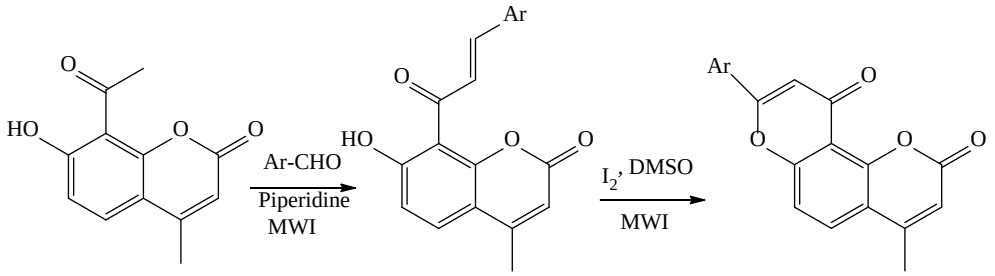
This chapter presents the synthesis of diverse heterocyclic substituted and heterocyclic fused coumarin derivatives such as furocoumarins and pyranocoumarins.

2 Synthesis of pyrano[2,3-*f*]chromen-2-ones

The condensation of 8-acetyl-7-hydroxy-4-methylcoumarin (**1**) with (het)aryl aldehydes in the presence of catalytic amont of piperdine under microwave irradiation furnished 7-hydroxy-4-methyl-8-(3-aryl/acrolyl)-2*H*-chromen-2-ones (**2a-h**) in

excellent yields (90-95%). In the next step, oxidative cyclization of these chalcones (**2a-h**) in the presence of I_2 in DMSO under microwave irradiation and also under conventional heating produced 4-methyl-8-phenyl-pyrano[2,3-*f*]chromen-2,10-diones (**3a-h**) in good yields (Ashok, D., Vijaya B. L. et al., 2012).

Table 1. Substrate scope for the synthesis of pyrano[2,3-*f*]chromen-2-ones (3a-h) with corresponding physical data

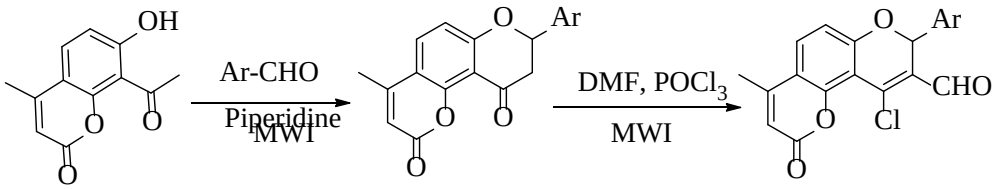


Compound	Ar	Conventional heating		Microwave irradiation	
		Time (min)	Yield (%)	Time (min)	Yield (%)
3a	Phenyl	30	68	2	85
3b	4-Methoxyphenyl	30	70	2	83
3c	3,4-Dimethoxyphenyl	40	70	3	83
3d	4-Methylphenyl	30	69	2	83
3e	2-Chlorophenyl	40	65	3	82
3f	1-Naphthyl	40	70	3	85
3g	4-Fluorophenyl	30	70	2	84
3h	2-Thienyl	30	68	2	84

3 Synthesis of dihydropyrano[2,3-*f*]chromene-9-carbaldehydes

The reaction of 8-acetyl-7-hydroxy-4-methyl coumarin (**1**) with (het)aryl aldehydes in the presence of piperdine at room temperature gave flavanones, 8-aryl-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-diones (**4a-j**). These flavanones **4a-j** on reaction with Vilsmeier-Haack reagent (DMF/ $POCl_3$) at room temperature afforded 10-chloro-8-aryl-4-methyl-2-oxo-2,8-dihydropyrano[2,3-*f*] chromene-9-carbaldehydes (**5a-j**) (Ashok, D., Vijaya B. et al., 2014).

Table 2. Substrate scope for the synthesis of dihydropyrano[2,3-*f*] chromene-9-carbaldehydes with corresponding physical data



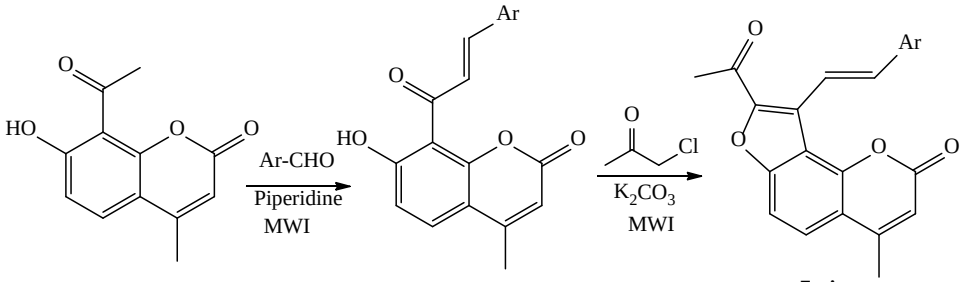
1 **4a-j** **5a-j**

5	Ar	Conventional heating		Microwave irradiation	
		Time (min)	Yield (%)	Time (min)	Yield (%)
5a	Phenyl	6	68	5	80
5b	4-Methoxyphenyl	6	65	6	82
5c	3,4-Dimethoxyphenyl	7	62	6	80
5d	3,4,5-Trimethoxyphenyl	6	65	6	85
5e	2-Chlorophenyl	7	60	5	82
5f	4-Methylphenyl	6	65	6	85
5g	4-Bromophenyl	6	68	5	82
5h	4-Isopropylphenyl	8	65	6	83
5i	4-Fluorophenyl	6	64	6	86
5j	1-Napthyl	8	62	6	80

4 Synthesis of furo[2,3-*h*]chromen-2-ones

Furocoumarin derivatives are well known for exhibiting phototherapic activity in the treatment of diverse of skin diseases. They also show bactericide and fungicide properties. The condensation of 8-acetyl-7-hydroxy-4-methyl Coumarin (**1**) with (het)aryl aldehydes in the presence of piperdine catalyst under microwave irradiation gave 7-hydroxy-4-methyl-8-(3-aryl/acrolyl)-2*H*-chromen-2-ones (**6a-j**) in excellent yields (90-95%). Subsequently, cyclisation of these chalcones (**6a-j**) with chloroacetone using K_2CO_3 under microwave irradiation and also under conventional heating afforded 9-styryl-8-acetyl-4-methyl-2*H*-furo[2,3-*h*] chromen-2-ones (**7a-j**) in good yields (Ashok, D., Vijaya B. Lakshmi, et al., 2012).

Table 3. Substrate scope for the synthesis of furo[2,3-*h*]chromen-2-ones (7a-j) with corresponding physical data



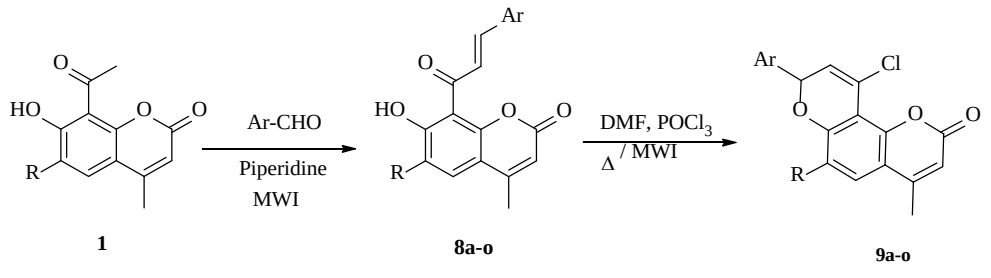
1 **6a-j** **7a-j**

7	Ar	Conventional heating		Microwave irradiation	
		Time (min)	Yield (%)	Time (min)	Yield (%)
7a	Phenyl	5	68	4	90
7b	4-Methoxyphenyl	6	70	5	93
7c	3,4-Dimethoxyphenyl	6	70	4	93
7d	4-Methylphenyl	5	69	5	93
7e	4-Chlorophenyl	6	65	5	90
7f	4-NMe_2Phenyl	5	70	4	95
7g	4-Isopropylphenyl	6	70	5	94
7h	4-Fluorophenyl	6	68	5	90
7i	1-Naphthyl	6	65	5	90
7j	2-Thienyl	6	70	5	94

5 Synthesis of phenyl-1,5-dioxa-2*H*-phenanthren-6-ones

The condensation of 8-acetyl-7-hydroxy-4-methyl coumarin (**1**) with aromatic or hetero aromatic aldehydes in the presence of piperdine under microwave irradiation gave substituted (*E*)-1-(7-hydroxy-4-methyl-8-coumarinyl)-3-phenyl-2-propen-1-ones (**8a-o**) in excellent yields. Subsequently, these chalcones **8a-o** on reaction with Vilsmeier–Haack reagent (DMF/$POCl_3$) yield substituted 4-chloro-8-methyl-2-phenyl-1,5-dioxa-2*H*-phenanthren-6-ones (**9a-o**) (Ashok, D., et al., 2017).

Table 4. Substrate scope for the synthesis of phenyl-1,5-dioxa-2*H*-phenanthren-6-ones (9a-j) with corresponding physical data



9	R	Ar	Conventional heating		Microwave irradiation	
			Time (min)	Yield (%)	Time (min)	Yield (%)
9a	H	Ph	5	68	4	80
9b	Cl	Ph	5	70	4	83
9c	H	4-$MeOC_6H_4$	6	70	5	83
9d	Cl	4-$MeOC_6H_4$	6	69	5	83
9e	H	3,4-$(MeO)_2C_6H_3$	5.5	65	5	80
9f	Cl	3,4-$(MeO)_2C_6H_3$	5.5	70	5	85
9g	H	4-FC_6H_4	6	70	5	84
9h	Cl	4-FC_6H_4	6	68	5	80
9i	H	4-MeC_6H_4	5	65	4	80
9j	Cl	4-$MeOC_6H_4$	5	70	4	84
9k	H	2-ClC_6H_4	5	65	4	82
9l	Cl	2-ClC_6H_4	5	60	4	80
9m	H	1-Naphthyl	5.5	62	5	80
9n	Cl	1-Naphthyl	5.5	65	5	80
9o	H	2-Thienyl	5	70	4	85

Conclusions

In summary, we herein report the synthesis of new coumarine derivatives starting from the 8-acetyl-7-hydroxy-4-methylcoumarin and subsequently by the cyclisation of 7-hydroxy-4-methyl-8-(3-aryl/acrolyl)-2*H*-chromen-2-ones. A novel series of coumarin-chromene compounds have been synthesized from 8-aryl-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-diones, by employing the Vilsmeier Haack reagent. Another novel series of 8-acetyl-4-methyl-9-styryl-2*H*-furo[2,3-*h*]chromen-2-ones have been prepared by the cyclisation reaction between 7-hydroxy-4-methyl-

8-(3-aryl/acrolyl)-2*H*-chromen-2-ones and chloroacetone. Other new series of 4-methyl-8-phenyl-pyrano[2,3-*f*]chromen-2,10-diones have been obtained by oxidative annulation of 7-hydroxy-4-methyl-8-(3-aryl/acrolyl)-2*H*-chromen-2-ones by utilizing DMSO/I_2. And one more new series of hybrid compounds: substituted 4-chloro-8-methyl-2-phenyl-1,5-dioxa-2*H*-phenanthren-6-one, have been produced from substituted (*E*)-1-(7-hydroxy-4-methyl-8-coumarinyl)-3-phenyl-2-propen-1-ones employing the Vilsmeier-Haack reagent, under conventional and microwave-assisted methods.

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