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A facile one-pot, three-component synthesis of 3, 3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives under microwave irradiation

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Abstract A series of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives have been synthesized by the one-pot, three-component reaction of 3-acetylcoumarin, an aromatic aldehyde, and ammonium acetate in acetic acid under microwave irradiation. This procedure has the major advantages of short reaction time, good yields, low energy consumption, easy operation, and environmental friendliness. All of the products were characterized by IR and NMR spectroscopy, MS, and elemental analysis.

Keywords 3,3′-(4-Arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) · 3-Acetylcoumarin · Multicomponent reaction · Microwave irradiation

Introduction

Substituted pyridines and condensed pyridines are highly reactive reagents that have been extensively used in heterocyclic synthesis and have biological and pharmacological activity [1]. Pyridine ring systems, especially 2,4,6-triarylpyridines, are of immense interest because of their unique position in medicinal chemistry [2–6]. Therefore, recent studies have highlighted the biological activity of triarylpyridines, providing impetus for further studies in utilizing this structure in new therapeutic drug classes [7–10].

Coumarin is also a biologically active substance, with numerous metabolites, and is widespread in nature [11]. Coumarin derivatives constitute an important class of

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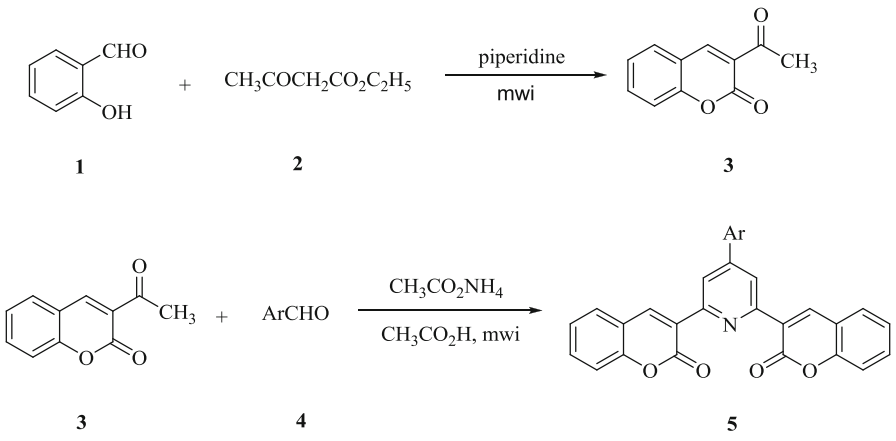
heterocyclic compounds that have attracted significant attention in recent years [12–14]. Hence, it would be interesting to combine the coumarin and pyridine ring systems.

One method developed for synthesis of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives involves reaction of 3-coumarin methyl pyridinium salts with appropriate 1-(2*H*-1-benzopyran-2-on-3-yl)-3-arylprop-2-en-1-ones in the presence of ammonium acetate and acetic acid under Kröhnke reaction conditions [15].

Verma et al. [16] synthesized a variety of 4-aryl-2,6-dicoumarinyl pyridines by condensation of 1-(2*H*-1-benzopyran-2-on-3-yl)-3-aryl-prop-2-en-1-ones with urea or amide derivatives using bismuth(III) nitrate–Al_2O_3 as catalyst. However, these methods suffer from disadvantages such as long reaction time, critical product isolation procedures, and harsh reaction conditions, which limit their use as environmentally benign processes. For example the reaction mixture was further stirred for 1 h and then heated for 8 h at 140 °C [15]), substrates were absorbed on Bi(III) nitrate–Al_2O_3–$ZnCl_2$ [16].

For the past few years, in our laboratory, because of continuing interest in the synthesis of organic compounds by multi-component reactions under microwave irradiation conditions, we have synthesized quinoxaline derivatives containing the coumarin moiety [17], 2-amino-6-(2-oxo-2*H*-chromen-3-yl)-4-pyridine-3-carbonitriles [18], and double coumarin derivatives [19] from coumarin compounds as substrates. Herein, we report the synthesis of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) by one-pot, multi-component reaction of 3-acetylcoumarin, aromatic aldehydes, and ammonium acetate in acetic acid under microwave



Ar: a: C_6H_5 b: 4-ClC_6H_4 c: 2-ClC_6H_4 d: 4-$CH_3OC_6H_4$ e: 4-$CH_3C_6H_4$ f: 4-$(CH_3)_2NC_6H_4$ g: 4- $O_2NC_6H_5$ h: 3,4-$OCH_2OC_6H_3$ i: Furyl

Scheme 1 Synthesis of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives

irradiation conditions (Scheme 1). The reactions were completed in 5–8 min, with 60–86 % yields, low energy consumption, and easy work-up.

Experimental

Mps were determined by use of an XT-5 digital melting point instrument and uncorrected. IR spectra were recorded on a Nicolet Avatar360FT-IR instrument. ^{1}H NMR were measured on a Burke 400-MHz spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on an LCQ Advantage instrument. Elemental analysis was performed with a Perkin−Elmer 240C elemental analyzer. Reactions under microwave conditions were performed in a CEM Discover monomode microwave reactor. All the reagents are commercially available.

General procedure for preparation of 3,3′-(4-arylpyridine-2,6-diyl)bis (2*H*-chromen-2-one) derivatives (5a–5i)

A mixture of the aromatic aldehyde (1 mmol), 3-acetylcoumarin (2 mmol) [20], and ammonium acetate (4 mmol), in acetic acid (5 mL) was sealed in a vial with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 150 W and 150 °C for 5–8 min (monitored by TLC). The reaction mixture was left to stand at room temperature to solidify. The crude product was collected, washed with ethanol, and recrystallized from 95 % ethanol.

3,3′-(4-Phenylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5a)

M.p 252–253 °C (253–254 °C) [15]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39–7.78 (13H, m, Ar–H), 8.27, 8.29 (2H, s, 3-H and 5-H of pyridine ring), 9.19, 9.23 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3017, 1721, 1610, 1577, 1532, 761 cm^{-1}; LC–MS (ESI): m/z = 444.7 (M + H); Anal. Calcd. for $C_{29}H_{17}NO_4$: C, 78.55; H, 3.86; N, 3.16 %. Found: C, 78.46; H, 3.94; N, 3.25 %.

3,3′-(4-(4-Chlorophenyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5b)

M.p 268–269 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39–7.84 (8H, m, Ar–H), 8.13 (2H, d, J = 7.60, Ar–H), 8.29 (2H, d, J = 7.60, Ar–H), 8.84 (2H, s, 3-H and 5-H of pyridine ring), 9.20 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3111, 1726, 1608, 1577, 1534, 756 cm^{-1}; LC–MS (ESI): m/z = 478.7 (M + H); Anal. Calcd. for $C_{29}H_{16}ClNO_4$: C, 72.88; H, 3.37; N, 2.93 %. Found: C, 72.79; H, 3.44; N, 3.01 %.

3,3′-(4-(2-Chlorophenyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5c)

M.p 233–234 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37–7.84 (12H, m, Ar–H), 8.82 (2H, s, 3-H and 5-H of pyridine ring), 9.21 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3111, 1732, 1609, 1576, 1534, 754 cm^{-1}; LC–MS (ESI): m/z = 478.7

(M + H); Anal. Calcd. for $C_{29}H_{16}ClNO_4$: C, 72.88; H, 3.37; N, 2.93 %. Found: C, 72.79; H, 3.44; N, 3.01 %.

3,3′-(4-(4-Methoxyphenyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5d)

M.p 275–276 °C (277–278 °C) [15]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.91 (3H, s, OCH_3), 7.32–7.80 (8H, m, Ar–H), 8.13 (2H, d, $J = 7.60$, Ar–H), 8.32 (2H, d, $J = 7.60$, Ar–H), 8.62 (2H, s, 3-H and 5-H of pyridine ring), 8.88 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3108, 1725, 1607, 1569, 1510, 756 cm^{-1}; LC–MS (ESI): $m/z = 474.7$ (M + H); Anal. Calcd. for $C_{30}H_{19}NO_5$: C, 76.10; H, 4.04; N, 2.96 %. Found: C, 76.01; H, 4.12; N, 3.04 %.

3,3′-(4-(*p*-Tolyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5e)

M.p 267–268 °C (269–270 °C) [15]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (3H, s, CH_3), 7.41–7.70 (12H, m, Ar–H), 8.11 (2H, d, $J = 7.60$, Ar–H), 8.27 (2H, d, $J = 7.60$, Ar–H), 8.81 (2H, s, 3-H and 5-H of pyridine ring), 9.20 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3110, 1727, 1608, 1574, 1532, 756 cm^{-1}; LC–MS (ESI): $m/z = 458.7$ (M + H); Anal. Calcd. for $C_{30}H_{19}NO_4$: C, 78.76; H, 4.19; N, 3.06 %. Found: C, 78.67; H, 4.28; N, 3.15 %.

3,3′-(4-(4-(Dimethylamino)phenyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5f)

M.p 261–262 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.08 (6H, s, CH_3), 7.40–7.65 (12H, m, Ar–H), 8.28 (2H, s, 3-H and 5-H of pyridine ring), 9.22 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3120, 1725, 1609, 1578, 1525, 755 cm^{-1}; LC–MS (ESI): $m/z = 487.8$ (M + H); Anal. Calcd. for $C_{31}H_{22}N_2O_4$: C, 76.53; H, 4.56; N, 5.76 %. Found: C, 76.44; H, 4.65; N, 5.92 %.

3,3′-(4-(4-Nitrophenyl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5g)

M.p 248–250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40–7.86 (8H, m, Ar–H), 8.16 (2H, d, $J = 7.60$, Ar–H), 8.35 (2H, d, $J = 7.60$, Ar–H), 8.86 (2H, s, 3-H and 5-H of pyridine ring), 9.24 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3124, 1726, 1608, 1575, 1512, 757 cm^{-1}; LC–MS (ESI): $m/z = 489.55$ (M + H); Anal. Calcd. for $C_{29}H_{16}N_2O_6$: C, 71.31; H, 3.30; N, 5.74 %. Found: C, 71.23; H, 3.37; N, 5.90 %.

3,3′-(4-(Benzo[*d*][1,3]dioxol-5-yl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5h)

M.p 249–250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.06 (2H, s, CH_2), 7.74–7.64 (12H, m, Ar–H), 8.67 (2H, s, 3-H and 5-H of pyridine ring), 9.20 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) ν: 3104, 1725, 1608, 1578, 1532, 756 cm^{-1}; LC–MS (ESI): $m/z = 488.6$ (M + H); Anal. Calcd. for $C_{30}H_{17}NO_6$: C, 73.92; H, 3.52; N, 2.87 %. Found: C, 73.84; H, 3.59; N, 2.95 %.

3,3′-(4-(furan-2-yl)pyridine-2,6-diyl)bis(2*H*-chromen-2-one) (5i)

M.p 208–209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39–7.82 (11H, m, Ar–H), 8.78 (2H, s, 3-H and 5-H of pyridine ring), 8.89 (2H, s, 4′-H and 4″-H of coumarin rings); IR (KBr) v: 3110, 1726, 1609, 1576, 1533, 754 cm^{-1}; LC–MS (ESI): $m/z = 434.6$ (M + H); Anal. Calcd. for $C_{27}H_{15}NO_5$: C, 74.82; H, 3.49; N, 3.23 %. Found: C, 74.73; H, 3.56; N, 3.32 %.

Table 1 Effect of microwave power on the yield of product **5b**

Entry	Microwave power (W)[a]	Yield (%)[b]
1	80	56
2	100	65
3	120	80
4	150	86
5	180	79
6	200	60

[a] Reaction conditions: irradiation temperature, 150 °C; irradiation time, 8 min

[b] Yields of the isolated products

Table 2 Effect of microwave irradiation temperature on the yield of product **5b**

Entry	Reaction temperature (°C)[a]	Yield (%)[b]
1	100	65
2	120	76
3	150	86
4	180	60

[a] Reaction conditions: microwave power, 150 W; irradiation time, 8 min

[b] Yields of the isolated products

Table 3 Results of synthesis of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives

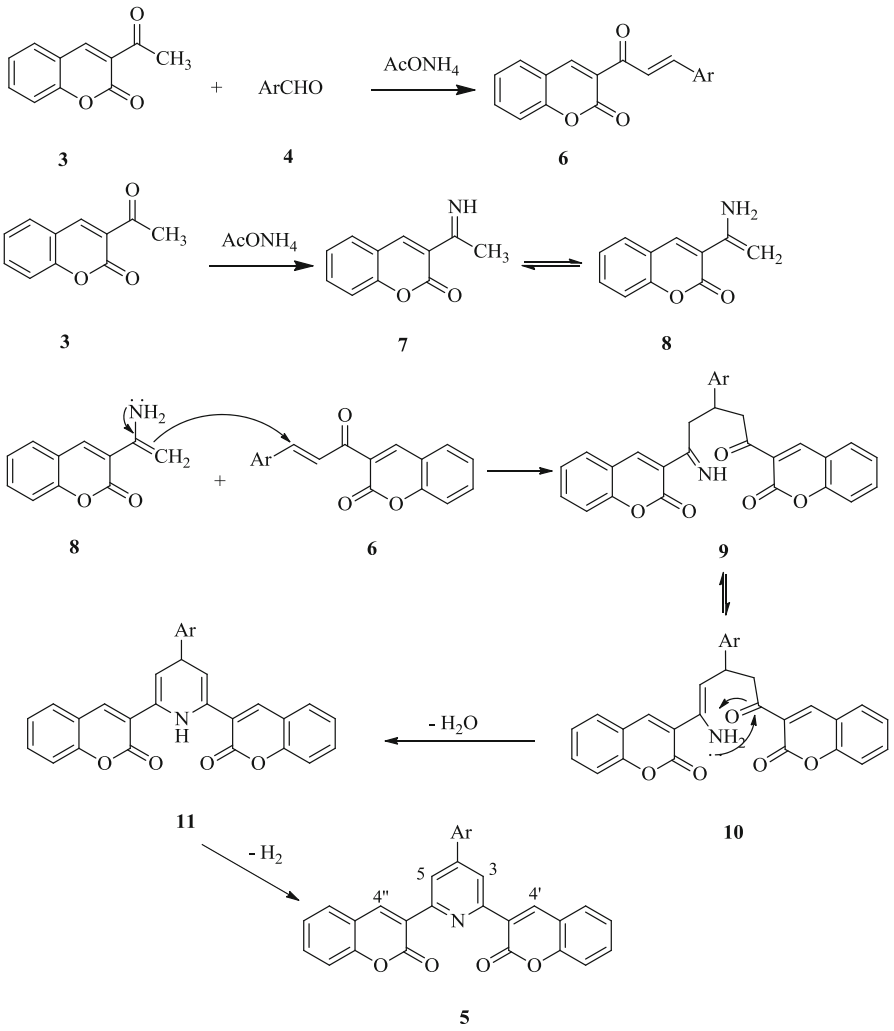
Product	Ar	Irradiation time (min)[a]	Yield (%)[b]
5a	C_6H_5	8	75
5b	4-ClC_6H_4	8	86
5c	2-ClC_6H_4	8	80
5d	4-$CH_3OC_6H_4$	5	61
5e	4-$CH_3C_6H_4$	7	62
5f	4-$(CH_3)_2NC_6H_4$	6	68
5g	4-$O_2NC_6H_5$	8	82
5h	3,4-$OCH_2OC_6H_3$	8	65
5i	Furyl	5	60

[a] Reaction conditions: microwave power, 150 W; irradiation temperature 150 °C

[b] Yields of the isolated products

Results and discussion

In this work, we initially investigated the effect of different microwave power settings on the yield of product **5b** when the microwave temperature and irradiation time were fixed. It was observed that irradiation at 150 W gives better results (Table 1, entry 4). Moreover, we also found that the yield of this reaction was affected by the irradiation temperature. Synthesis of **5b** was tested at different irradiation temperatures in the range 80–150 °C. The results showed 150 °C was the optimum irradiation temperature because it generated the highest yield of **5b** (Table 2, entry 4).



Scheme 2 Probable mechanism of formation of 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) derivatives

Under these optimized reaction conditions, a series of 3,3′-(4-arylpyridine-2, 6-diyl)bis(2*H*-chromen-2-one) derivatives **5** were synthesized under microwave irradiation; the results are summarized in Table 3. As is shown in Table 3, when a mixture of 3-acetylcoumarin **3**, aromatic aldehyde **4**, and ammonium acetate in acetic acid were irradiated at 150 W and 150 °C, the reactions were almost complete in 5–8 min. The reaction mixtures were then washed with a small amount of ethanol. The crude products were purified by recrystallization from 95 % ethanol to afford products in 60–86 %yields. The structures of all the synthesized compounds were established on the basis of their spectroscopic data and results from elemental analysis.

The IR spectra of compounds **3a**–**3i** contained a very strong band between 1,721 and 1,732 cm^{-1} from the δ-lactone carbonyl (C=O) stretching vibration. Strong bands from aromatic C=C and C=N stretching vibrations were observed between 1,608 and 1,575 cm^{-1}. The aromatic C–H stretching vibrations were observed as a medium band between 3,017 and 3,124 cm^{-1}. In the ^{1}H NMR spectra of compounds **3a**–**3i**, the aromatic protons appeared in the form of multiplets between δ 7.32 and 7.86. The signals of the pyridine 3-H and 5-H protons were downfield of the coumarin ring protons, with the 4′-H and 4″-H signals the most downfield. For compounds with identical coumarin substitution at the 2 and 6-positions of the pyridine, the 3-H and 5-H appeared as a singlets. Similarly in these compounds, the coumarin ring 4′-H and 4″-H also gave singlets.

The reaction may proceed via imine **7** formed from 3-acetylcoumarin and ammonium acetate; imine **7** reacts with coumarin chalcone **6** (from condensation of the aromatic aldehyde with 3-acetylcoumarin) to give **9**, followed by cycloaddition, dehydration, and aromatization to afford the 3,3′-(4-arylpyridine-2,6-diyl)bis(2*H*-chromen-2-one) **5** (Scheme 2).

Conclusions

In conclusion, under microwave irradiation, an efficient one-pot, multi-component reaction has been developed for synthesis of 3,3′-(4-arylpyridine-2,6-diyl)bis (2*H*-chromen-2-one) derivatives from 3-acetylcoumarin, the corresponding aromatic aldehydes, and ammonium acetate. This facile procedure is not only an economical and efficient synthetic strategy for synthesis of this class of significant compounds but also enriches investigations on microwave-assisted multi-component reactions. Moreover, this procedure has the major advantages of short reaction time, good yields, low energy consumption, easy operation, and environmental friendliness.

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