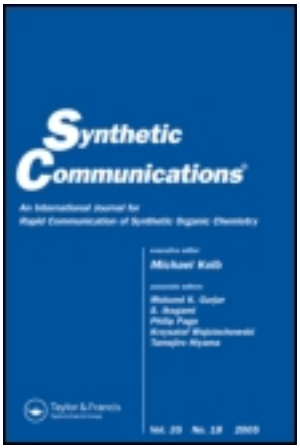

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Facile One-Pot, Multicomponent Synthesis of Pyridines Under Microwave Irradiation

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Abstract: A series of 2-amino-6-(2-oxo-2H-chromen-3-yl)-4-pyridine-3-carbonitriles were synthesized by the one-pot, multicomponent reaction of 3-acetylcoumarin, aromatic aldehydes, malononitrile, and ammonium acetate in acetic acid under microwave irradiation. The reactions were completed in 10–13 min with 61–86% yields, were environmental benign, and had easy workup. Their structures were confirmed by ^{1}H NMR, IR, and MS spectra and elemental analysis.

Keywords: 3-Acetylcoumarin, 2-amino-6-(2-oxo-2H-chromen-3-yl)-4-pyridine-3-carbonitrile, microwave irradiation, multicomponent reaction

Heteroaromatic rings containing nitrogen atoms often play important roles as the scaffolds of bioactive substances.[1] Pyridine is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals. Among them, 2-amino-3-cyano-4-(3-(5-oxo-2-tetrahydrofuran)carboxyanilido)-6-(2-hydroxyphenyl)pyridine has been identified as a IKK-β inhibitor.[2] Besides, pyridine derivatives are also important and useful intermediates in preparing a variety of heterocyclic compounds.[3] It has been reported that the 2-amino-6-aryl-3-cyano-4-piperidinylpyridine core structure can be constructed using a one-pot

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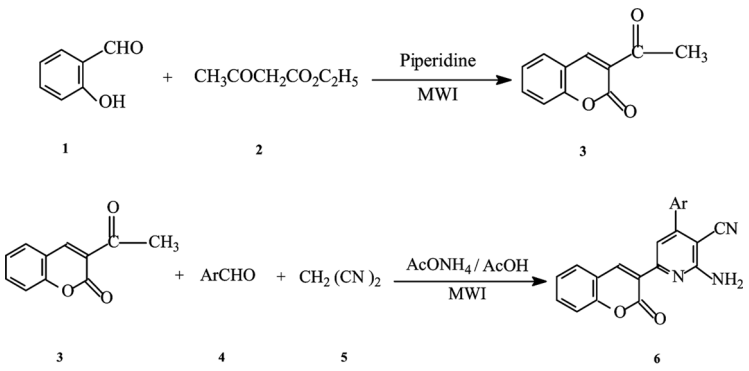
coupling reaction of acetophenone, piperidine, malononitrile, and ammonium acetate in conventional heating mode.[4]

It is well known that coumarin is a biologically active substance, with numerous metabolites, and is widespread in nature.[5] Coumarin derivatives constitute an important class of heterocyclic compounds that has attracted significant attention in recent years.[6] Abdel-latif,[7] Birada and Anekal,[8] and Mulwad and Pawal[9] reported synthesis of 2-oxo-2H-chromen-3-yl pyridine derivatives by conventional heating. Nevertheless, the protocols give comparatively lower yields and longer reaction times. Therefore, the synthesis of 2-amino-4-aryl-3-cyano-pyridine derivatives continues to attract much interest in organic chemistry.[10]

Multicomponent reactions (MCRs) are powerful tools in modern medicinal chemistry, enabling straightforward access to large libraries of structurally related, drug-like compounds and thereby facilitating lead generation. Hence, combined with the use of combinatorial chemistry and high-throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug discovery efforts in recent years.[11–16] Continuing our interest in the synthesis of organic compounds by MCRs under microwave irradiation,[17–19] we report the synthesis of 2-amino-6-(2-oxo-2H-chromen-3-yl)-4-pyridine-3-carbonitriles by the one-pot MCR of 3-acetyl coumarin, aromatic aldehydes, malono-nitrile, and ammonium acetate in acetic acid under microwave irradiation. The reactions were completed in 10–13 min with 61–86 °C yields, were environmental benign, and had easy workup.

The synthetic route is shown in Scheme 1.



Scheme 1. Ar: (a) C_6H_5, (b) 4-ClC_6H_4, (c) 4-$NO_2C_6H_4$, (d) 3-$NO_2C_6H_4$, (e) 4-HOC_6H_4, (f) 4-$CH_3C_6H_4$, (g) 3,4-$(OCH_2O)C_6H_3$, and (h) 4-$CH_3OC_6H_4$.

RESULTS AND DISCUSSION

When a mixture of 3-acetylcoumarin **3**, aromatic aldehyde **4**, malononitrile **5**, and ammonium acetate was irradiated in a microwave oven (Scheme 1), the reactions were almost completed in 10–13 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 with good yields (61–86%). However, the yields are only 55–72% after refluxing 2–4.5 h. The main results for the synthesis of these compounds are given in Table 1. This procedure has the advantage of a short routine, good yields, convenient workup, and environmental friendliness. Their structures were confirmed by ^{1}H NMR, IR, and MS spectra and elemental analysis.

The reaction may proceed via imine **8**, formed from aldehyde and ammonium acetate. Imine **8** reacts with alkylidenemalononitrile **7** (from condensation of aromatic aldehyde with malononitrile) to give **10**, followed by cycloaddition, isomerization, and aromatization to afford the 2-amino-3-cyanopyridine **6** (Scheme 2).

In conclusion, an efficient, one-pot MCR for the synthesis of 2-amino-6-(2-oxo-2H-chromen-3-yl)-4-pyridine-3-carbonitrile from the corresponding 3-acetyl coumarin, aromatic aldehydes, and malononitrile has been developed.

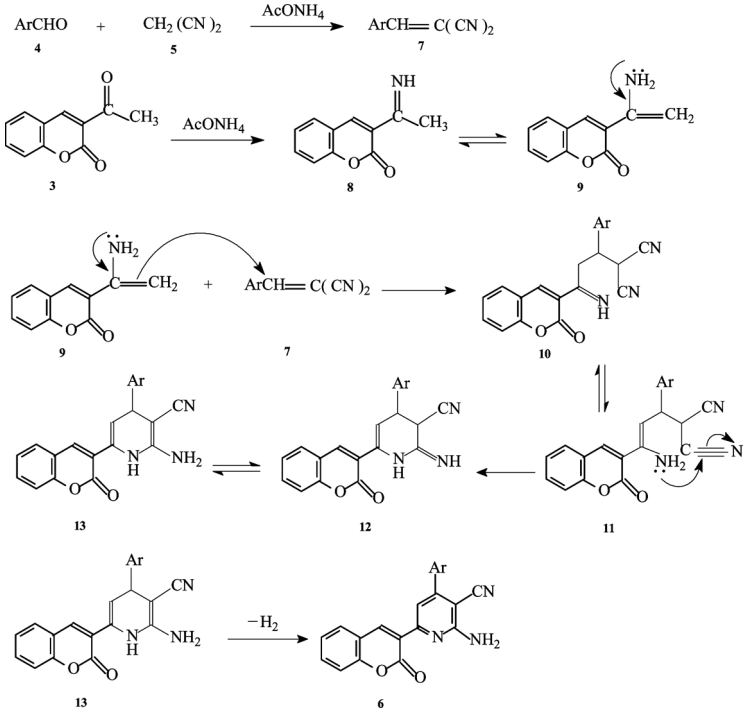
EXPERIMENTAL

Melting points were determined on a XT-5 digital melting-point instrument and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument. ^{1}H NMR were measured on a Burke 400-MHz

Table 1. Microwave irradiation synthesis of compounds **6a–6h**

		Heating		Microwave		
Compound	Ar	Time (h)	Yield[a] (%)	Time (min)	Yield[a] (%)	Mp (°C)
6a	C_6H_5	4.5	65	11	75	234–236 (202–204)[7]
6b	4-ClC_6H_4	4.5	65	10	79	245–247
6c	4-$NO_2C_6H_4$	2	72	10	86	252–254 (227–229)[7]
6d	3-$NO_2C_6H_4$	2	71	10	79	286–288
6e	4-HOC_6H_4	4	55	13	61	263–264 (263–265)[7]
6f	4-$CH_3C_6H_4$	4	60	13	65	271–273
6g	3,4-$(OCH_2O)C_6H_3$	4	60	13	70	223–225
6h	4-$CH_3OC_6H_4$	4	61	13	70	268–270

[a]Yields of the isolated products.



Scheme 2.

spectrometer in dimethyl sulfoxide (DMSO)-d_6 with terramethyl silane (TMS) as internal standard. Mass spectra were recorded on an LCQ Advantage instrument. Elemental analyses were determined using a Perkin-Elmer 240C elemental analyses. The reactions were carried out with a modified commercial microwave oven (Sanle WP650D 650 W) under atmospheric pressure. All the reagents are commercially available.

General Procedure for the 2-Amino-6-(2-oxo-2 H-chromen-3-yl)-4-3-carbonitriles (6a–6h)

A mixture of the aromatic aldehyde (1 mmol), 3-acetylcoumarin (1 mmol), malononitrile (1 mmol), ammonium acetate (2 mmol), and acetic acid (5 mL) in an Erlenmeyer flask (25 ml) equipped with reflux condenser was irradiated in a microwave oven for 10–13 min (as indicated by thin-layer chromatography TLC). The reaction mixture was allowed to stand at room temperature to solidify. The crude product was collected, washed with ethanol, and recystallized from 95% ethanol.

Data

Compound **6a**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H, coumarin 4-H), 7.86 (s, 1H, PyrH), 7.64–7.40 (m, 9H, ArH), 7.09 (s, 2H, NH_2); IR (KBr): 3450, 3359, 3132, 2215, 1725, 1612 cm^{-1}; LC-MS (ESI): $m/e = 340.6$ $(M + H)^+$. Anal. calcd. for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 73.95; H, 3.84; N 12.29.

Compound **6b**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H, coumarin 4-H), 7.88 (s, 1H, PyrH), 7.65–7.41 (m, 8H, ArH), 7.13 (s, 2H, NH_2); IR (KBr): 3458, 3347, 3126, 2217, 1728, 1625 cm^{-1}; LC-MS (ESI): $m/e = 374.6$ $(M + H)^+$. Anal. calcd. for $C_{21}H_{12}ClN_3O_2$: C, 67.48; H, 3.24; N, 11.24. Found: C, 67.13; H, 3.22; N, 11.16.

Compound **6c**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H, coumarin 4-H), 8.40 (s, 1H, PyrH), 7.91–7.43 (m, 8H, ArH), 7.24 (s, 2H, NH_2); IR (KBr): 3455, 3365, 3127, 2211, 1725, 1647 cm^{-1}; LC-MS (ESI): $m/e = 385.7$ $(M + H)^+$. Anal. calcd. for $C_{21}H_{12}N_4O_4$: C, 65.63; H, 3.15; N, 14.58. Found: C, 65.20; H, 3.13; N, 14.48.

Compound **6d**

^{1}H NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H, coumarin 4-H), 8.43 (s, 1H, PyrH), 7.89–7.43 (m, 8H, ArH), 7.22 (s, 2H, NH_2); IR (KBr): 3452, 3395, 3130, 2203, 1723, 1606 cm^{-1}; LC/MS (ESI): $m/e = 385.7$ $(M + H)^+$. Anal. calcd. for $C_{21}H_{12}N_4O_4$: C, 65.63; H, 3.15; N, 14.58. Found: C, 65.18; H, 3.13; N, 14.49.

Compound **6e**

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H, OH), 8.80 (s, 1H, coumarin 4-H), 7.86 (s, 1H, PyrH), 7.69–7.43 (m, 9H, ArH), 6.98 (s, 2H, NH_2); IR (KBr): 3362, 3130, 2208, 1723, 1606 cm^{-1}; LC-MS (ESI):$m/e = 356.6$ $(M + H)^+$. Anal. calcd. for $C_{21}H_{13}N_3O_3$: C, 70.98; H, 3.69; N, 11.82. Found: C, 70.62; H, 3.67; N, 11.74.

Compound **6f**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H, coumarin 4-H), 7.85 (s, 1H, PyrH), 7.74–7.45 (m, 8H, ArH), 7.10 (s, 2H, NH_2), 2.42 (s, 3H, CH_3); IR (KBr): 3440, 3376, 3130, 2207, 1726, 1608 cm^{-1}; LC-MS (ESI): $m/e = 354.0$ $(M + H)^+$. Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.40; H, 4.26; N, 11.81.

Compound **6g**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H, coumarin 4-H), 7.85 (s, 1H, PyrH), 7.69–7.43 (m, 7H, ArH), 7.13 (s, 2H, NH_2), 6.14 (s, 2H, OCH_2O); IR (KBr): 3450, 3376, 3129, 2208, 1727, 1606 cm^{-1}; LC-MS (ESI): $m/e = 385.0$ $(M + H)^{+\cdot}$ Anal. calcd. for $C_{22}H_{14}N_3O_4$: C, 68.88; H, 3.42; N, 10.96. Found: C, 68.53; H, 3.40; N, 10.88.

Compound **6h**

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H, coumarin 4-H), 7.87 (s, 1H, PyrH), 7.75–7.45 (m, 8H, ArH), 7.07 (s, 2H, NH_2), 3.84 (s, 3H, OCH_3); IR (KBr): 3420, 3360, 3126, 2213, 1724, 1605 cm^{-1}; LC-MS (ESI): $m/e = 370.0$ $(M + H)^+$. Anal. calcd. for $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.18; H, 4.07; N, 11.30.

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