One-pot synthesis of 2-amino-3-cyanopyridine derivatives under microwave irradiation without solvent

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Abstract

A series of 2-amino-3-cyanopyridine derivatives have been prepared by one-pot condensation from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave irradiation without solvent. This method has the advantage of short routine, high yields and being environmentally-friendly.

Keywords: Pyridine derivatives, one-pot synthesis, microwave irradiation, solvent-free

Introduction

Many natural occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties.[1] Among them, 2-amino-3-cyanopyridines have been identified as IKK-βinhibitors.[2] Besides, they are important and useful intermediates in preparing variety of heterocyclic compounds.[3] Therefore, the synthesis of 2-amino-3-cyanopyridine derivatives continues to attract much interest in organic chemistry.

It has been reported that the 2-amino-6-aryl-3-cyano-4-piperidinylpyridine core structure can be constructed using a one-pot coupling reaction of acetophenone, piperidine, malononitrile and ammonium acetate in conventional heating mode.[4] Nevertheless, the protocol gives comparatively lower yields and longer reaction time.

Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions within short time and with high yields, especially in the absence of solvents.[5-8] Not long ago, Satya et al has prepared 2-amino-3-cyanopyridines from arylidenemalanonitrile, ketone and ammonium acetate under microwave irradiation.[9] However, arylidenemalanonitriles as one of the starting materials must be synthesized from malononitrile and aromatic aldehyde, which results in longer routine.

It goes without saying that the most efficient synthesis of functionalized organic compounds would be one-pot reaction from commercially available and inexpensive starting materials [10].In

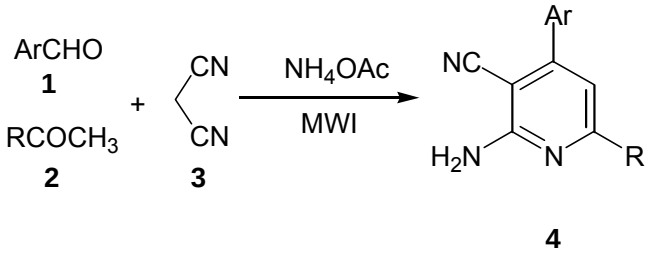
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our previous study,[11-16] we have synthesized large amounts of heterocyclic compounds by one-pot under microwave irradiation. Through further investigation, we found that one-pot synthesis of the target compounds from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave irradiation without solvent can be successfully achieved in excellent yields and short reaction time.

Herein, we wish to report this convenient and efficient method, which is, to the best of our knowledge, the 1st one-pot synthesis of 2-amino-3-cyanopyridines from cheap reagents under microwave irradiation and solvent-free.

Results and Discussion

When a mixture of aromatic aldehyde **1**, methyl ketone **2**, malononitrile **3** and ammonium acetate was irradiated in a microwave oven (Scheme 1), the reactions were almost completed in 7-9 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 (72-86%). The main results for the synthesis of these compounds are given in Table 1. It is seen that this procedure has the advantage of short routine, good yields, convenient workup and being environmentally friendly.



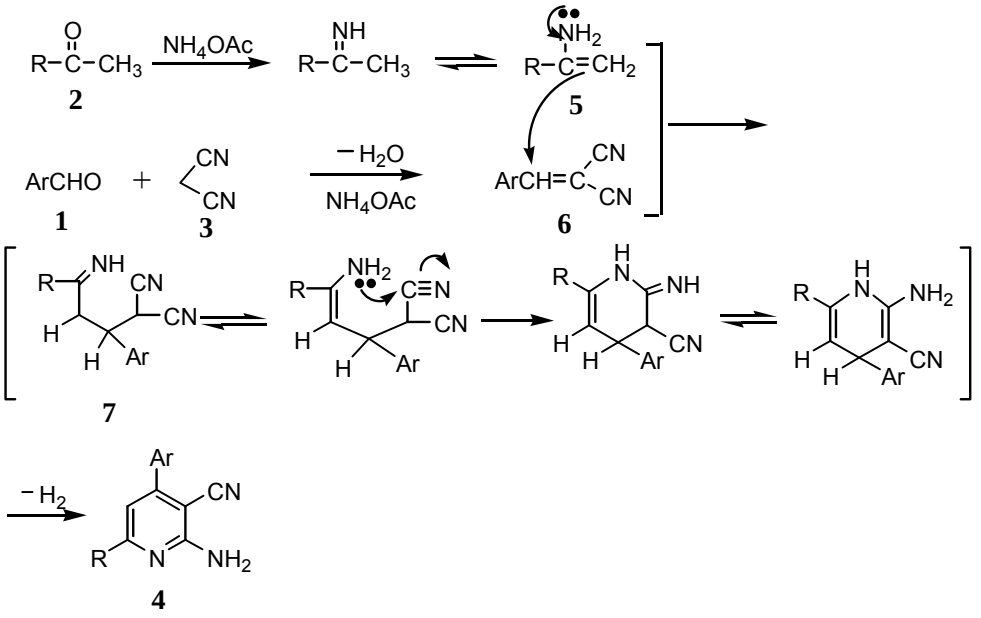
Scheme 1. One-pot synthesis of 2-amino-3-cyanopyridines.

Table 1. Synthesis of 2-amino-3-cyanopyridines under microwave irradiation

Entry	Ar	R	Time(min)	Yield(%)	Mp(°C)
4a	4-ClC_6H_4	4-$OCH_3C_6H_4$	8	83	195-196
4b	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	7	80	159-160
4c	4-$OCH_3C_6H_4$	2,4-$Cl_2C_6H_3$	7	75	184-185
4d	4-$OCH_3C_6H_4$	C_6H_5	9	85	180-182
4e	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	9	72	198-199
4f	4-ClC_6H_4	4-FC_6H_4	8	78	219-220
4g	3-Indolyl	4-$OCH_3C_6H_4$	7	86	244-245
4h	4-ClC_6H_4	CH_3	8	84	172-173

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The reaction may proceed via imine **5** formed from aldehyde and ammonium acetate, imine **5** reacts with alkylidenemalononitrile **6**(from condensation of aromatic aldehyde with malononitrile) to give **7,** followed by cycloaddition, isomerization, aromatization to afford the 2-amino-3-cyanopyridine **4**(Scheme 2).



Scheme 2. Mechanisms of the reaction.

All the products were characterized by IR and ^{1}H NMR analysis. Furthermore, the structure of **4a** was established by the X-ray crystallographic analysis (Figure 1).

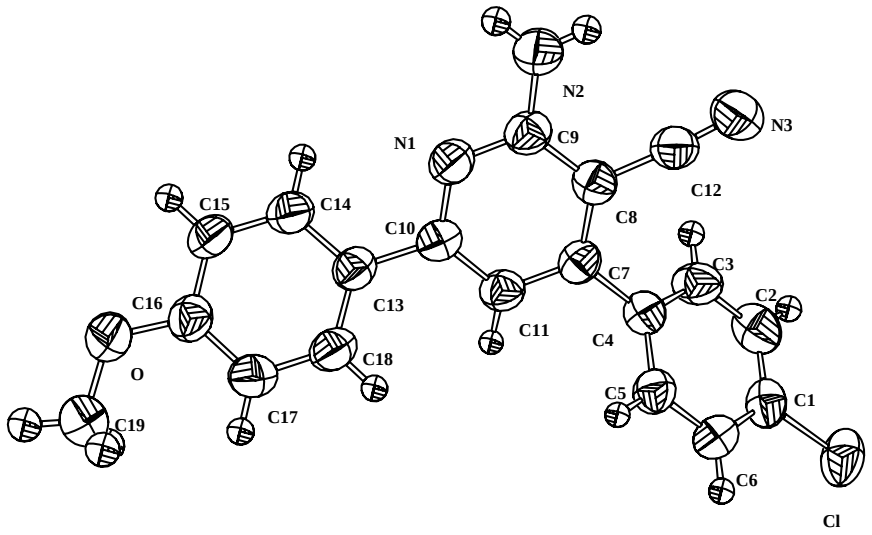


Figure 1. Molecular structure of **4a**.

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Conclusions

We have synthesized a series of 2-amino-3-cyanopyridine derivatives by one-pot method under microwave irradiation and solvent-free conditions, thus providing a facile, rapid, efficient and environmentally friendly method.

Experimental Section

General Procedures. Melting points were determined in a capillary tube and were uncorrected. The ^{1}H NMR spectra were recorded on a DPX 400 MHz spectrometer with TMS as internal standard. The IR spectra were obtained with SE-1730 instrument as potassium bromide pellets. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

Typical procedure for the preparation of 2-amino-3-cyanopyridines

The preparation of **4**: A dry flask (25 mL) charged with aldehyde (2 mmol), methyl ketone (2 mmol), malononitrile (2 mmol) and ammonium acetate (3 mmol) was placed in a microwave oven. The flask was then connected with refluxing equipment. After being irradiated for 7-9 min, the reaction mixture was washed with ethanol (2 mL). The crude products were purified by recrystallization from 95% ethanol to afford pure products.

4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-2-amino-3-cyanopyridine (4a). Colour- less crystals (0.557g, 83%); mp 195–196 °C. IR (KBr): *v* 3454 and 3361 (NH_2), 3232 (ArH), 2201 (CN) cm^{-1}.^{1}H NMR (400MHz, DMSO-d_6): δ 8.12 (2H, d, *J*=8.4 Hz, ArH), 7.70 (2H, d, *J*=8.4 Hz, ArH), 7.63 (2H, d, *J*=8.4 Hz, ArH), 7.23 (1H,s, PyrH), 7.04 (2H, d, *J*=8.4 Hz, ArH), 6.99 (2H, s, NH_2), 3.83 (3H, s, OCH_3). Anal. Calcd for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51. Found: C, 67.58; H, 4.58; N, 12.20.

4-(4-Methoxyphenyl)-6-(4-methoxyphenyl)-2-amino-3-cyanopyridine (4b). Colourless crystals (0.530g, 80%); mp 159–160 °C. IR (KBr): *v* 3458 and 3361 (NH_2), 3232 (ArH), 2201 (CN) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.10 (2H, d, *J*=8.4 Hz, ArH), 7.64 (2H, d, *J*=8.4 Hz, ArH), 7.19 (1H, s, CH), 7.11 (2H, d, *J*=8.4 Hz, ArH), 7.03 (2H, d, *J*=8.4 Hz, ArH), 6.88 (2H, s, NH_2), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.73; H, 4.85; N, 12.94.

4-(4-Methoxyphenyl)-6-(2,4-dichlorophenyl)-2-amino-3-cyanopyridine (4c). Colourless crystals (0.555g, 75%); mp 184–185 °C. IR (KBr): *v* 3467 and 3364 (NH_2), 3309 (ArH), 2201 (CN) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.08-7.75 (9H, m, ArH and NH_2), 6.19 (1H, s, CH). Anal. Calcd for $C_{19}H_{13}Cl_2N_3O$: C, 61.64; H, 3.54; N, 11.35. Found: C, 671.25; H, 3.90; N, 11.03.

4-(4-Methoxyphenyl)-6-phenyl-2-amino-3-cyanopyridine (4d). Colourless crystals (0.512g, 85%); mp 180–182 °C. IR (KBr): *v* 3462 and 3307 (NH_2), 3184 (ArH), 2201 (CN) cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.11-8.12 (2H, m, ArH), 7.66 (2H, d, *J*=8.4 Hz, ArH), 7.48-7.49 (3H, m, ArH), 7.25 (1H, s, CH), 7.11 (2H, d, *J*=8.4 Hz, ArH), 6.96 (2H, s, NH_2), 3.85 (3H, s, OCH_3). Anal.

Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.40; H, 5.38; N, 13.68.

4-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)-2-amino-3-cyanopyridine (4e). Colourless crystals (0.539g, 72%); mp 198–199 °C. IR (KBr): *v* 3462 and 3307 (NH_2), 3185 (ArH), 2202 cm^{-1}.^{1}H NMR (400MHz, DMSO-d_6): δ 7.55-7.76 (7H, m, ArH), 7.19 (2H, s, NH_2), 6.95 (1H, s, CH). Anal. Calcd for $C_{18}H_{10}Cl_3N_3$: C, 57.71; H, 2.69; N, 11.22. Found: C, 57.48; H, 2.83; N, 11.56.

4-(4-Chlorophenyl)-6-(4-flurophenyl)-2-amino-3-cyanopyridine (4f). Colourless crystals (0.505g, 78%); mp 219–220 °C. IR (KBr): *v* 3483 and 3350 (NH_2), 3217 (ArH), 2214 (CN)cm^{-1}.^{1}H NMR (400MHz, DMSO-d_6): δ 8.20 (2H, d, *J*=8.4 Hz, ArH), 7.72 (2H, d, *J*=8.4 Hz, ArH), 7.64 (2H, d, *J*=8.4 Hz, ArH), 7.35 (2H, d, *J*=8.4 Hz, ArH), 7.30 (1H, s, CH), 7.06 (2H, s, NH_2). Anal. Calcd for $C_{18}H_{11}ClN_3F$: C, 66.78; H, 3.42; N, 12.98. Found: C, 66.32; H, 3.08; N, 12.59.

4-(3-Indolyl)-6-(4-methoxyphenyl)-2-amino-3-cyanopyridine (4g). Colourless crystals (0.585g, 86%); mp 244–245 °C. IR (KBr): *v* 3489 and 3396 (NH_2), 3363 (NH), 3307 (ArH), 2207 (CN)cm^{-1}.^{1}H NMR (400MHz, DMSO-d_6): δ 12.18 (1H, s, Indole NH), 8.07 (2H, dd, *J*=8.8, 1.6 Hz, ArH), 7.94 (1H, d, *J*=2.4 Hz, Indole H), 7.76 (1H, d, *J*=8.0 Hz, Indole H), 7.53 (1H, d, *J*=8.0 Hz, Indole H), 7.34 (1H, s, PyrH), 7.25-7.15 (2H, m, Indole H), 7.06 (2H, dd, *J*=8.8, 1.6 Hz, ArH), 6.78 (2H, s, NH_2), 3.83 (3H, s, OCH_3). Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 73.83; H, 4.65; N, 16.24.

4-(4-Chlorophenyl)-6-methyl-2-amino-3-cyanopyridine (4h). Colourless crystals (0.409g, 84%); mp 172–173 °C. IR (KBr): *v* 3402 and 3313 (NH_2), 3170 (ArH), 2213 (CN)cm^{-1}.^{1}H NMR (400MHz, DMSO-d_6): δ 7.60 (2H, d, *J*=8.4 Hz, ArH), 7.58 (2H, d, *J*=8.4 Hz, ArH), 6.89 (2H, s, NH_2), 6.62 (1H, s, PryH), 2.36 (3H, s, CH_3). Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 63.88; H, 3.98; N, 17.10.

X-ray structure determination of 4a. Colourless prisms, $C_{40}H_{46}O_6$, *Mr*=620.77, Monoclinic, space group *P*2(1)/*c*, *a*= 0.74282(11), *b*=1.27959(18) nm, *c*= 1.7681(3) nm, β= 97.449(3)°, *V*= 1.6664(4) nm^3, *Z*=4, D_{calc}= 1.338 g·cm^{-3}, *F*(000)= 696, μ (MoK_α)= 0.239 mm^{-1}, crystal dimensions 0.62 × 0.48 × 0.18 mm^3. Intensity data were collected using a Siemens SMART diffractometer at 293(2) K, graphite monochromator Mo Kα radiation (λ=0.071073 nm), using the ω-2θ scan technique to a maximum 2θ of 50.26º. A total of 4800 reflections were collected with 2907 unique ones (R_{int} = 0.0884), of which 1881 reflections were observed with $I > 2\sigma(I)$. The final *R* and *wR* values were 0.0884 and 0.2096, *s*= 1.135, $(\Delta/\sigma)_{max}$= 0.000. The maximum peak and minimum peak in the final difference map is 343 and -310 *e*·nm^{-3}.

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