

Article

Diversity Synthesis of N-Substituted 2-Amino-1,6-naphthyridine Derivatives under Microwave Irradiation

Zheng-Guo Han,[†] Chun-Bao Miao,[‡] Feng Shi,[†] Ning Ma,[†] Ge Zhang,[†] and Shu-Jiang Tu^{*,†}

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, Jiangsu, 221116, P.R. China, and School of Chemistry and Chemical Engineering, Jiangsu Polytechnic University, Changzhou, Jiangsu, 213164, P.R. China

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A sequential three-component reaction of 3,5-diarylidene-piperidin-4-one, malononitrile, and amine (such as aromatic amine, cyclopropanamine, and NH₄OAc) in acetic acid under microwave irradiation has been developed. In this one-pot reaction, a series of new N-substituted 2-amino-1,6-naphthyridine derivatives were synthesized with excellent yields. This method has the advantages of operational simplicity and increased safety for small-scale fast synthesis of N-aryl 2-amino-1,6-naphthyridines for biomedical screening.

Introduction

Various naphthyridine derivatives have received considerable attention over the past years because of their wide range of biological activities, such as antitumor, anti-inflammatory, and antifungal properties.^{1–4} Compounds incorporating this motif are useful in the treatment of hypertension, myocardial infarction, hyperlipidemia, cardiac arrhythmia, and rheumatoid arthritis.^{5–8} Therefore, the synthesis of these compounds is of great significance. A number of reports on this topic have appeared in the literature.^{2–4,6} El-Subbagh et al. have reported the synthesis of 1,6-naphthyridine derivatives through two-component reactions between α,β -unsaturated ketones and cyanoacetamide in BuOH catalyzed by piperidine.² Although the above method offered a synthetic approach to this class of important compounds, quite surprisingly, the investigation of N-aryl 2-amino-1,6-naphthyridines has not stimulated much interest so far. Thus, development of an efficient and simple method for the synthesis of N-aryl substituted 1,6-naphthyridines is still desired.

The diversity generating potential of multicomponent reactions (MCRs) has been recognized, and their utility in preparing libraries to screen for functional molecules is well appreciated.^{9,10} Microwave-assisted organic synthesis has rapidly gained popularity since it accelerates a variety of synthetic transformations,¹¹ and have the prominent advantages of short reaction time and high yield.¹²

With the aim to develop more efficient synthetic processes and minimized byproducts, and in continuation of our recent interest in the construction of heterocyclic scaffolds,¹³ we herein describe a practical, inexpensive and rapid microwave (MW)-promoted method for diversity synthesis of 2-amino-1,6-naphthyridine derivatives via MCRs of 3,5-diarylidene-

piperidin-4-one **1**, malononitrile **2**, and amine **3** in acetic acid (HOAc) (Scheme 1). It is an efficient and promising method to construct the 2-amino-1,6-naphthyridine skeleton.

Results and Discussion

Initially, the three-component reaction of 3,5-dibenzylidene-1-methylpiperidin-4-one **1a** (1 mmol) with equimolar amounts of malononitrile **2** and aniline **3** was employed to optimize the reaction conditions. As illustrated in Table 1, acetic acid (HOAc) was preferred as the optimal solvent and 110 °C was chosen as the most suitable reaction temperature (Scheme 2).

On the basis of the optimized conditions [HOAc, 110 °C, 200W (maximum power)], reactions of different substrates **1**, malononitrile **2**, and aniline **3a** were performed, and a series of N-substituted 2-amino-1,6-naphthyridine derivatives

Scheme 1

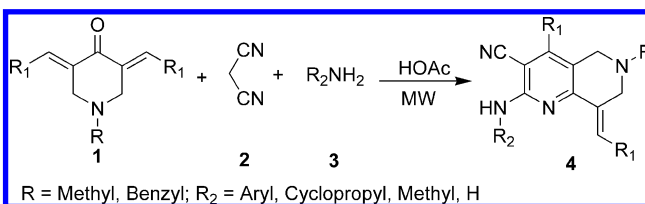


Table 1. Optimization for the Synthesis of **4a**

entry	solvent ^a	temp (°C)	time (min)	yield (%)
1	HOAc	100	7	92
2	Glycol	100	7	35
3	DMF	100	7	22
4	EtOH	100	7	32
5	HOAc	90	8	89
6	HOAc	110	5	94
7	HOAc	120	5	92
8	HOAc	130	4	91
9	HOAc	140	4	88

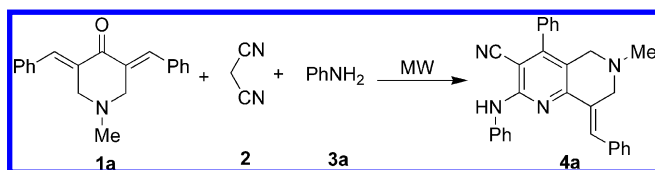
^a The volume of solvent is 2.0 mL.

* To whom correspondence should be addressed. E-mail: laotu2001@263.net. Phone: 0086-516-83500065. Fax: 0086-516-83500065.

[†] Xuzhou Normal University.

[‡] Jiangsu Polytechnic University.

Scheme 2



were synthesized with good yields. The results (Table 2, entries 1–15) indicated that substrates **1** bearing both electron-donating groups (such as alkoxy and methyl) and electron-withdrawing groups (such as nitro or halide) can be involved in these MCRs to afford desired products **4** with high yields. So it is concluded that the electronic nature of the substituents has no significant effect on this reaction.

Table 2. Synthesis of N-Aryl Substituted 1,6-Naphthyridines **4** under Microwave Irradiation

entry	4	R	R ₁	R ₂	time/min	yield/%	Mp/°C
1	4a	Methyl	C ₆ H ₅ (1a)	Phenyl (3a)	5	94	229–231
2	4b	Methyl	4-FC ₆ H ₄ (1b)	Phenyl (3a)	5	94	244–246
3	4c	Methyl	4-ClC ₆ H ₄ (1c)	Phenyl (3a)	5	96	253–255
4	4d	Methyl	4-BrC ₆ H ₄ (1d)	Phenyl (3a)	6	89	268–270
5	4e	Methyl	3-NO ₂ C ₆ H ₄ (1e)	Phenyl (3a)	6	92	244–247
6	4f	Methyl	4-NO ₂ C ₆ H ₄ (1f)	Phenyl (3a)	6	93	243–245
7	4g	Methyl	4-CH ₃ C ₆ H ₄ (1g)	Phenyl (3a)	8	92	233–235
8	4h	Benzyl	C ₆ H ₅ (1h)	Phenyl (3a)	6	93	232–233
9	4i	Benzyl	4-FC ₆ H ₄ (1i)	Phenyl (3a)	6	94	243–245
10	4j	Benzyl	4-ClC ₆ H ₄ (1j)	Phenyl (3a)	7	93	249–252
11	4k	Benzyl	4-BrC ₆ H ₄ (1k)	Phenyl (3a)	7	89	259–261
12	4l	Benzyl	4-CH ₃ C ₆ H ₄ (1l)	Phenyl (3a)	8	91	251–253
13	4m	Benzyl	3-NO ₂ C ₆ H ₄ (1m)	Phenyl (3a)	7	90	197–199
14	4n	Benzyl	4-NO ₂ C ₆ H ₄ (1n)	Phenyl (3a)	7	91	229–231
15	4o	Benzyl	4-CH ₃ OC ₆ H ₄ (1o)	Phenyl (3a)	9	92	240–242
16	4p	Benzyl	C ₆ H ₅ (1h)	4-ClC ₆ H ₄ (3b)	6	92	220–222
17	4q	Benzyl	4-ClC ₆ H ₄ (1j)	4-ClC ₆ H ₄ (3b)	6	91	247–249
18	4r	Methyl	3-NO ₂ C ₆ H ₄ (1e)	4-ClC ₆ H ₄ (3b)	6	90	230–233
19	4s	Methyl	2-Thienyl (1p)	4-ClC ₆ H ₄ (3b)	6	90	238–241
20	4t	Benzyl	2-Thienyl (1q)	4-CH ₃ OC ₆ H ₄ (3c)	6	91	217–219
21	4u	Benzyl	4-CH ₃ C ₆ H ₄ (1l)	4-CH ₃ OC ₆ H ₄ (3c)	8	91	225–227
22	4v	Benzyl	4-ClC ₆ H ₄ (1j)	4-CH ₃ OC ₆ H ₄ (3c)	7	90	227–230
23	4w	Benzyl	4-FC ₆ H ₄ (1i)	4-CH ₃ OC ₆ H ₄ (3c)	6	91	176–178
24	4x	Methyl	4-ClC ₆ H ₄ (1c)	4-CH ₃ OC ₆ H ₄ (3c)	6	92	238–241
25	4y	Methyl	4-CH ₃ OC ₆ H ₄ (1r)	4-CH ₃ OC ₆ H ₄ (3c)	9	90	232–233
26	4z	Methyl	2-Thienyl (1p)	4-CH ₃ OC ₆ H ₄ (3c)	6	91	229–231
27	4aa	Benzyl	4-ClC ₆ H ₄ (1j)	2-CH ₃ OC ₆ H ₄ (3d)	6	92	218–220
28	4ab	Methyl	3-NO ₂ C ₆ H ₄ (1e)	4-CH ₃ C ₆ H ₄ (3e)	6	91	230–232
29	4ac	Methyl	2-Thienyl (1p)	4-CH ₃ C ₆ H ₄ (3e)	6	92	228–230
30	4ad	Methyl	3-NO ₂ C ₆ H ₄ (1e)	3-CH ₃ C ₆ H ₄ (3f)	5	90	215–218
31	4ae	Benzyl	4-CH ₃ C ₆ H ₄ (1l)	Naphthalen (3g)	8	90	209–211
32	4af	Methyl	4-CH ₃ C ₆ H ₄ (1g)	Naphthalen (3g)	8	91	204–206

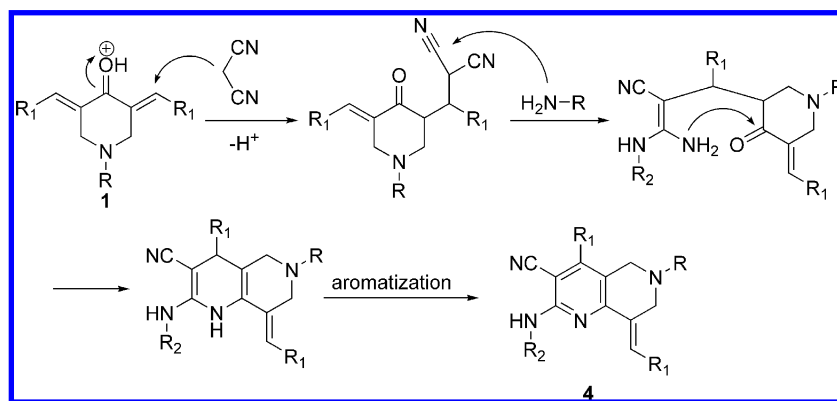
Table 3. Synthesis of N-Substituted 1,6-Naphthyridines **4** under Microwave Irradiation

entry	4	R	R ₁	R ₂	time/min	yield/%	Mp/°C
1	4ag	Benzyl	4-FC ₆ H ₄ (1i)	Cyclopropyl (3h)	7	92	202–204
2	4ah	Benzyl	4-BrC ₆ H ₄ (1k)	Cyclopropyl (3h)	8	89	214–216
3	4ai	Benzyl	4-CH ₃ C ₆ H ₄ (1l)	Cyclopropyl (3h)	8	90	177–179
4	4aj	Benzyl	4-CH ₃ OC ₆ H ₄ (1o)	Cyclopropyl (3h)	10	89	219–221
5	4ak	Methyl	4-CH ₃ OC ₆ H ₄ (1r)	Cyclopropyl (3h)	10	91	195–197
6	4al	Methyl	4-CH ₃ C ₆ H ₄ (1g)	Cyclopropyl (3h)	7	92	220–222
7	4am	Methyl	4-BrC ₆ H ₄ (1d)	Cyclopropyl (3h)	8	90	226–228
8	4an	Methyl	4-FC ₆ H ₄ (1b)	Cyclopropyl (3h)	6	92	194–196
9	4ao	Methyl	3-NO ₂ C ₆ H ₄ (1e)	Cyclopropyl (3h)	7	89	240–242
10	4ap	Benzyl	2-Thienyl (1q)	Cyclopropyl (3h)	8	92	195–197
11	4aq	Benzyl	4-ClC ₆ H ₄ (1j)	Cyclopropyl (3h)	8	91	202–204
12	4ar	Benzyl	2-Thienyl (1q)	H (3i)	5	89	219–222
13	4as	Benzyl	4-NO ₂ C ₆ H ₄ (1n)	H (3i)	5	90	200–202
14	4at	Methyl	4-CH ₃ C ₆ H ₅ (1g)	H (3i)	7	92	254–256
15	4au	Methyl	4-CH ₃ OC ₆ H ₄ (1r)	H (3i)	8	90	239–240
16	4av	Methyl	4-ClC ₆ H ₄ (1c)	H (3i)	5	91	229–231
17	4aw	Methyl	4-FC ₆ H ₄ (1b)	H (3i)	4	93	256–258
18	4ax	Methyl	4-NO ₂ C ₆ H ₄ (1f)	H (3i)	4	91	>300
19	4ay	Methyl	3-NO ₂ C ₆ H ₄ (1e)	H (3i)	4	90	220–221
20	4az	Methyl	4-CH ₃ C ₆ H ₄ (1g)	Me (3j)	8	85	230–231

To expand the scope of aromatic amines substrates, we used various 3,5-dibenzylidenepiperidine-4-ones and malononitrile as model substrates to examine various aromatic amines **3** including 4-chlorobenzeneamine **3b**, 4-methoxybenzeneamine **3c**, 2-methoxybenzeneamine **3d**, *p*-toluidine **3e**, 3-toluidine **3f**, and naphthalen-1-amine **3g**. In all these cases, the reactions proceeded steadily to produce corresponding N-aryl substituted 2-amino-1,6-naphthyridines in good to excellent yields of 89–92% (Table 2, entries 1–32).

To further expand the scope of the present method, the replacement of aromatic amines with cyclopropanamine **3h**, NH₄OAc **3i**, and methylamine **3j** were employed in the chemistry. To our delight, under the optimized conditions

Scheme 3



described above, the reactions proceeded smoothly to afford a sets of *N*-substituted 2-amino-1,6-naphthyridines in good to excellent yields (Table 3, entries 1–20). The results showed that the reaction is suitable not only for aromatic amines, but also for aliphatic amines.

Encouraged by the above interesting results, we also attempted to synthesize non-symmetric substrates **1** to further broaden the scope of this three-component reaction. However, we have not achieved good results yet since very complex mixtures were generated.

The mechanism for the formation of *N*-substituted 2-amino-1,6-naphthyridines **4** includes Michael addition, nucleophilic addition, cyclization, and subsequently aromatization (Scheme 3), which is similar to that we reported.¹⁴

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The IR spectrum of compound **4b** showed strong absorptions at 3317 cm^{-1} due to the NH group, and at 2217 cm^{-1} due to the CN group. The ^1H NMR spectrum of **4b** showed a singlet at $\delta = 9.06$ due to the NH proton and a singlet at $\delta 7.81$ due to the =CH proton. Moreover, the structure of **4ar** was established by X-ray crystallography (Figure 1).

Conclusion

In conclusion, we have demonstrated a simple, efficient and practical method for the synthesis of a wide range of

2-amino-1,6-naphthyridine derivatives with a new substitution pattern under microwave irradiation. In addition, the procedure offers several advantages including operational simplicity, and increased safety for small-scale high-speed synthesis, which make it a useful and attractive process for the synthesis of structure-diversity *N*-substituted 2-amino-1,6-naphthyridines. Moreover, this series of *N*-substituted 2-amino-1,6-naphthyridine derivatives may provide a new substitution pattern of biological active compounds for biomedical screening.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a-4az**, and crystallographic information file (CIF) of **4ar**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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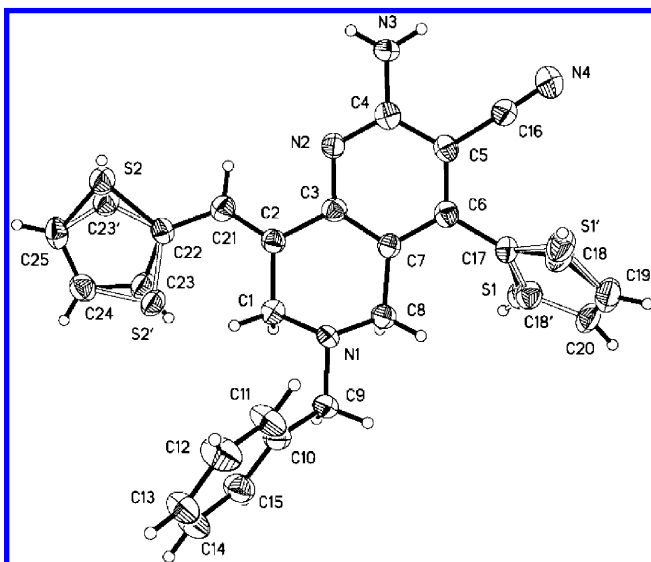


Figure 1. ORTEP drawing of **4ar**

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