Article

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

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A sequential three-component reaction of 3,5-diarylidenepiperidin-4-one, malononitrile, and amine (such as aromatic amine, cyclopropanamine, and NH_4OAc) 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]

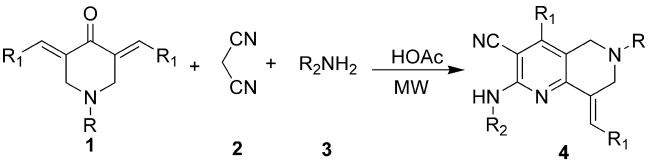
With the aim to develop more efficient synthetic processes and minimized byproducts, and in continuation of our recent interest in the construction of heterocyclic scaffolds,[13] we herein describe a practical, inexpensive and rapid microwave (MW)-promoted method for diversity synthesis of 2-amino-1,6-naphthyridine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



1 2 3 4

R = Methyl, Benzyl; R_2 = Aryl, Cyclopropyl, Methyl, H

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.

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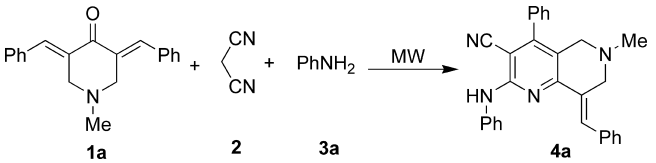
Scheme 2



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.

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-chlorobenzenamine **3b**, 4-methoxybenzenamine **3c**, 2-methoxybenzenamine **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**, NH_4OAc **3i**, and methylamine **3j** were employed in the chemistry. To our delight, under the optimized conditions

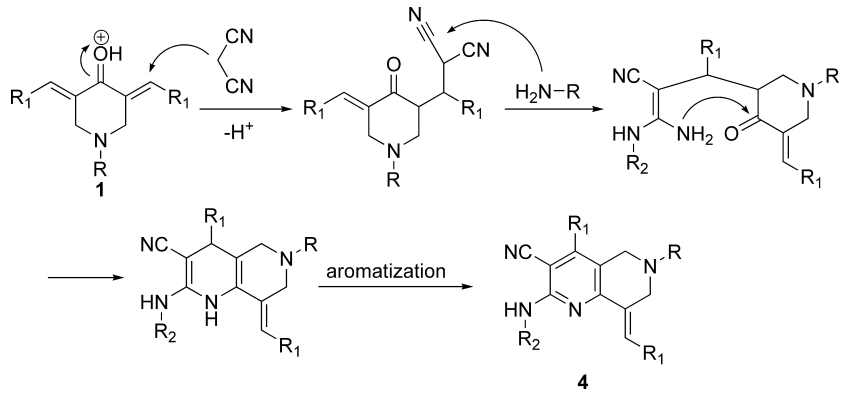
Table 2. Synthesis of N-Aryl Substituted 1,6-Naphthyridines **4** under Microwave Irradiation

entry	4	R	R_1	R_2	time/min	yield/%	Mp/°C
1	**4a**	Methyl	C_6H_5 (**1a**)	Phenyl (**3a**)	5	94	229−231
2	**4b**	Methyl	4-FC_6H_4 (**1b**)	Phenyl (**3a**)	5	94	244−246
3	**4c**	Methyl	4-ClC_6H_4 (**1c**)	Phenyl (**3a**)	5	96	253−255
4	**4d**	Methyl	4-BrC_6H_4 (**1d**)	Phenyl (**3a**)	6	89	268−270
5	**4e**	Methyl	3-$NO_2C_6H_4$ (**1e**)	Phenyl (**3a**)	6	92	244−247
6	**4f**	Methyl	4-$NO_2C_6H_4$ (**1f**)	Phenyl (**3a**)	6	93	243−245
7	**4g**	Methyl	4-$CH_3C_6H_4$ (**1g**)	Phenyl (**3a**)	8	92	233−235
8	**4h**	Benzyl	C_6H_5 (**1h**)	Phenyl (**3a**)	6	93	232−233
9	**4i**	Benzyl	4-FC_6H_4 (**1i**)	Phenyl (**3a**)	6	94	243−245
10	**4j**	Benzyl	4-ClC_6H_4 (**1j**)	Phenyl (**3a**)	7	93	249−252
11	**4k**	Benzyl	4-BrC_6H_4 (**1k**)	Phenyl (**3a**)	7	89	259−261
12	**4l**	Benzyl	4-$CH_3C_6H_4$ (**1l**)	Phenyl (**3a**)	8	91	251−253
13	**4m**	Benzyl	3-$NO_2C_6H_4$ (**1m**)	Phenyl (**3a**)	7	90	197−199
14	**4n**	Benzyl	4-$NO_2C_6H_4$ (**1n**)	Phenyl (**3a**)	7	91	229−231
15	**4o**	Benzyl	4-$CH_3OC_6H_4$ (**1o**)	Phenyl (**3a**)	9	92	240−242
16	**4p**	Benzyl	C_6H_5 (**1h**)	4-ClC_6H_4 (**3b**)	6	92	220−222
17	**4q**	Benzyl	4-ClC_6H_4 (**1j**)	4-ClC_6H_4 (**3b**)	6	91	247−249
18	**4r**	Methyl	3-$NO_2C_6H_4$ (**1e**)	4-ClC_6H_4 (**3b**)	6	90	230−233
19	**4s**	Methyl	2-Thienyl (**1p**)	4-ClC_6H_4 (**3b**)	6	90	238−241
20	**4t**	Benzyl	2-Thienyl (**1q**)	4-$CH_3OC_6H_4$ (**3c**)	6	91	217−219
21	**4u**	Benzyl	4-$CH_3C_6H_4$ (**1l**)	4-$CH_3OC_6H_4$ (**3c**)	8	91	225−227
22	**4v**	Benzyl	4-ClC_6H_4 (**1j**)	4-$CH_3OC_6H_4$ (**3c**)	7	90	227−230
23	**4w**	Benzyl	4-FC_6H_4 (**1i**)	4-$CH_3OC_6H_4$ (**3c**)	6	91	176−178
24	**4x**	Methyl	4-ClC_6H_4 (**1c**)	4-$CH_3OC_6H_4$ (**3c**)	6	92	238−241
25	**4y**	Methyl	4-$CH_3OC_6H_4$ (**1r**)	4-$CH_3OC_6H_4$ (**3c**)	9	90	232−233
26	**4z**	Methyl	2-Thienyl (**1p**)	4-$CH_3OC_6H_4$ (**3c**)	6	91	229−231
27	**4aa**	Benzyl	4-ClC_6H_4 (**1j**)	2-$CH_3OC_6H_4$ (**3d**)	6	92	218−220
28	**4ab**	Methyl	3-$NO_2C_6H_4$ (**1e**)	4-$CH_3C_6H_4$ (**3e**)	6	91	230−232
29	**4ac**	Methyl	2-Thienyl (**1p**)	4-$CH_3C_6H_4$ (**3e**)	6	92	228−230
30	**4ad**	Methyl	3-$NO_2C_6H_4$ (**1e**)	3-$CH_3C_6H_4$ (**3f**)	5	90	215−218
31	**4ae**	Benzyl	4-$CH_3C_6H_4$ (**1l**)	Naphthalen (**3g**)	8	90	209−211
32	**4af**	Methyl	4-$CH_3C_6H_4$ (**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_6H_4 (**1i**)	Cyclopropyl (**3h**)	7	92	202−204
2	**4ah**	Benzyl	4-BrC_6H_4 (**1k**)	Cyclopropyl (**3h**)	8	89	214−216
3	**4ai**	Benzyl	4-$CH_3C_6H_4$ (**1l**)	Cyclopropyl (**3h**)	8	90	177−179
4	**4aj**	Benzyl	4-$CH_3OC_6H_4$ (**1o**)	Cyclopropyl (**3h**)	10	89	219−221
5	**4ak**	Methyl	4-$CH_3OC_6H_4$ (**1r**)	Cyclopropyl (**3h**)	10	91	195−197
6	**4al**	Methyl	4-$CH_3C_6H_4$ (**1g**)	Cyclopropyl (**3h**)	7	92	220−222
7	**4am**	Methyl	4-BrC_6H_4 (**1d**)	Cyclopropyl (**3h**)	8	90	226−228
8	**4an**	Methyl	4-FC_6H_4 (**1b**)	Cyclopropyl (**3h**)	6	92	194−196
9	**4ao**	Methyl	3-$NO_2C_6H_4$ (**1e**)	Cyclopropyl (**3h**)	7	89	240−242
10	**4ap**	Benzyl	2-Thienyl (**1q**)	Cyclopropyl (**3h**)	8	92	195−197
11	**4aq**	Benzyl	4-ClC_6H_4 (**1j**)	Cyclopropyl (**3h**)	8	91	202−204
12	**4ar**	Benzyl	2-Thienyl (**1q**)	H (**3i**)	5	89	219−222
13	**4as**	Benzyl	4-$NO_2C_6H_4$ (**1n**)	H (**3i**)	5	90	200−202
14	**4at**	Methyl	4-$CH_3C_6H_5$ (**1g**)	H (**3i**)	7	92	254−256
15	**4au**	Methyl	4-$CH_3OC_6H_4$ (**1r**)	H (**3i**)	8	90	239−240
16	**4av**	Methyl	4-ClC_6H_4 (**1c**)	H (**3i**)	5	91	229−231
17	**4aw**	Methyl	4-FC_6H_4 (**1b**)	H (**3i**)	4	93	256−258
18	**4ax**	Methyl	4-$NO_2C_6H_4$ (**1f**)	H (**3i**)	4	91	>300
19	**4ay**	Methyl	3-$NO_2C_6H_4$ (**1e**)	H (**3i**)	4	90	220−221
20	**4az**	Methyl	4-$CH_3C_6H_4$ (**1g**)	Me (**3j**)	8	85	230−231

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 δ 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.

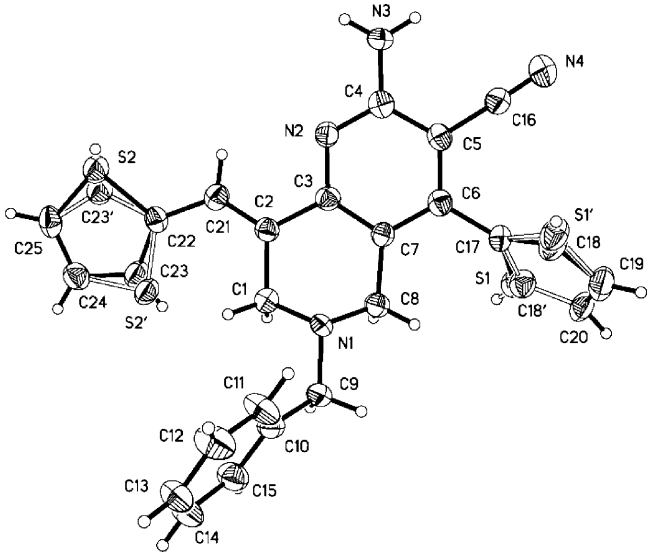


Figure 1. ORTEP drawing of **4ar**

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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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