Diversity-Oriented Synthesis of Kröhnke Pyridines

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An efficient reagent-controlled approach for the regiospecific synthesis of new 2,2′-bipyridine derivatives in high-temperature water via microwave-assisted multicomponent reactions of aldehydes, 3-aryl-3-oxopropanenitrile, 2-acetylpyridine, and ammonium acetate is reported. Furthermore, aromatic aldehydes reacted with 1,2-diphenylethanone, resulting in structurally complex penta-arylpyridines. This chemistry provides an efficient and promising synthetic strategy to diversity-oriented construct poly arylpyridine skeleton.

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Introduction

The use of combinatorial chemistry has tremendously changed the theory and practice of design and synthesis of new substances for pharmaceutical research. Great efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents.[1] However, the range of suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[2] In this context diversity-oriented synthesis (DOS) of compound collections have proven to be very effective approaches.[3] In addition to the multiple formations of carbon−carbon or -heteroatom bonds, DOS has the following advantages: consecutive reaction pattern, high reaction rate and efficiency, target product specificity, and minimal environmental impact. Consequently, the design and development of new DOS for the collections of small bioactive molecules receives growing interest.

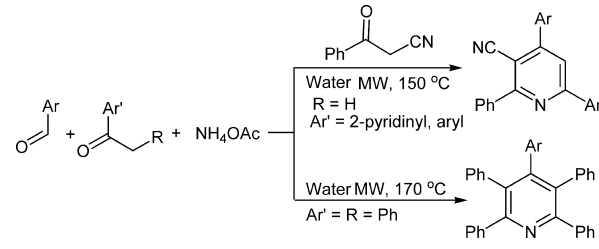
Pyridines are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B_6), and pyridine alkaloids.[4] The fused pyridines (Kröhnke pyridines) including the related bipyridines[5] are prominent building blocks in supramolecular chemistry with their π-stacking and H-bonding forming ability. In particular, substituted-2,2′-bipyridine (bpys) ligands have attracted widespread attention[6] due to their ability to form complexes with transition metals. The bpys have found applications in various fields such as supramolecular chemistry,[7] asymmetric catalysis[8] and polymer and dendrimer science.[9] With all these fascinating potential applications, much research has devoted to develop directed synthetic routes to suitable bipyridine units, as well as effective functionalization strategies.[10]

Pyridines with a multiaryl substitution pattern (Kröhnke pyridines) have been synthesized using various methods and procedures. Traditionally, these compounds have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate.[11] More recently, several new improved methods and procedures have been developed for the synthesis of these pyridines,[12] including solvent-free condition[13] and microwave heating.[14] Although the diverse synthetic routes to Kröhnke pyridines have been developed, utilization of diversity-oriented strategy to build 2,2′-bipyridine framework and penta-aryl pyridine skeleton in one-pot has not stimulated much interest so far. In this paper, we have successfully developed microwave-assisted multicomponent reaction for the diversity-oriented synthesis of pyridine collections, including 2,2′-bipyridines, unsymmetrical 2,4,6-triarylpyridines and penta-aryl pyridines, by varying the substrates using water as reaction media (Scheme 1).

Results and Discussion

It is well-known that carbonyl compounds involving in the different pK_a value in the active hydrogen show different reactivity. Therefore, various carbonyl compounds were selected in a one-pot reaction and used their different reactivity for control of their reaction sequence to realize the reaction control. In continuation of our recent interest in the construction of pyridine scaffolds,[15] we became interested

Scheme 1. Synthesis of Multisubstituted Pyridines



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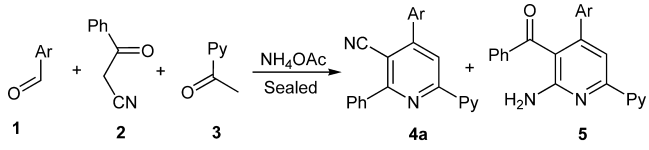
Scheme 2. Optimization of Reaction Conditions for 2,2′-Bipyridines



Ar = 4-bromophenyl Py = 2-pyridinyl

Table 1. Optimization of Reaction Solvents and Temperature

entry	solvent	*T*/°C	time/min	yield/%
1	EtOH	100	30	47
2	HOAc	100	30	69
3	glycol	100	30	61
4	CH_3CN	100	30	46
5	DMF	100	30	75
6	water	100	30	72
7	water	110	28	75
8	water	130	28	78
9	water	140	24	81
10	water	150	22	84
11	water	160	22	82

in devising an efficient regiospecific synthesis of new 2,2′-bipyridines in high-temperature water via a reagent-controlled multicomponent reaction. Thus, the aromatic aldehydes were employed to react with 3-oxo-3-phenylpropanenitrile and 2-acetylpyridine in the present of ammonium acetate. As a result, a series of new 2,2′-bipyridines were synthesized by screening the pK_a value in the active hydrogen of carbonyl compounds in one pot. We first chose *p*-bromobenzaldehyde and investigated the optimized conditions for its reaction with 3-oxo-3-phenylpropanenitrile, 2-acetylpyridine, and ammonium acetate under microwave irradiation (the pK_a value of 3-oxo-3-phenylpropanenitrile is far lower than that of 2-acetylpyridine), and the new 2,2′-bipyridine (**4a**) was obtained. The 3-oxo-3-phenylpropanenitrile has two electrophilic centers, which may lead to two different products **4** or **5**. In this reaction, only product **4a** was isolated; it is dedicated that the reaction has high regioselectivity. An overview of the synthetic details is summarized in Scheme 2. As shown in Table 1, the reactions using water or *N*,*N*-dimethylformamide (DMF) as the solvent resulted in higher yields and shorter reaction times than those using acetic acid, glycol, and ethanol as solvents. Water is a good absorber for microwave energy[16] and has been successfully employed as a solvent for various organic syntheses;[16h] it turned out to be one of the best choices in view of its relatively environmental-friendly characteristics, as a "cleaner" reaction medium.[16g] To optimize the reaction temperature, the synthesis of **4a** was performed using water as the solvent at temperatures ranging from 100 to 160 °C, with an increment of 10 °C each time. The yield of product **4a** was increased and the reaction time was shortened when the temperature was increased from 100 to 150 °C. The yield leveled off when the temperature was further increased to 160 °C. Therefore, the most suitable temperature should be 150 °C.

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aryl aldehydes were investigated, and a series of new unsymmetrical poly arylpyridines were afforded in good yields, with a 2-pyridinyl group presenting in position 2 of the pyridine nucleus. As shown in Table 2, at the beginning, we made a search for the aldehyde substrate scope, 2-acetylpyridine **3a** and 3-aryl-3-oxopropanenitrile were used as model substrates (Table 2, entries 1−11), and the results indicated that aromatic aldehydes bearing either electron donating or electron withdrawing functional groups such as nitro, bromo, chloro, or methoxy were able to affect the synthesis of compounds **4**. Moreover, the heterocyclic aldehyde such as thiophene-2-carbaldehyde (Table 2, entry 11) still displayed high reactivity under this standard condition. It is worth noting that this result is significant since there is no literature precedent for the synthesis of highly functionalized 2,2′-bipyridines.

To further expand the scope of aromatic ketone substrates, different aldehydes and 3-aryl-3-oxopropanenitrile as model substrates and examined various aromatic ketone including **3b**−**3i**. In all these cases, the reactions proceeded smoothly to give the corresponding unsymmetrical 2,4,6-triaryl-pyridines in good yields of 69−86%. Indeed, the protocol provides a straightforward pathway to construct highly functionalized 2,2′-bipyridines and unsymmetrical 2,4,6-triarylpyridines. Moreover, The symmetrical 2,4,6-triarylpyridines were generally synthesized through classical Kröhnke procedure. This methodology describes a direct route to unsymmetrical 2,4,6-triarylpyridines, which are generally prepared via multistep reactions.[17]

In a further test, 1,2-diphenylethanone **3j** was employed instead of aromatic ketone **3a** to react with **1a** and **2**. Surprisingly, we could not get the expected polysubstituted pyridines **6** in any cases. Instead, the pure 1,4-dihydropyridine **7a** and a small amount penta-arylpyridines **8a** were obtained by column chromatography on silica gel, respectively (Scheme 3). With the aim to improve the yields of 1,4-dihydropyridine **7** and penta-arylpyridines **8**, aromatic aldehydes **1** reacted with **2** or **3j** in 1:2 (or 1:3) mole ratio in the presence of ammonium acetate in high-temperature water under microwave irradiation, respectively. The corresponding 1,4-dihydropyridine **7** and penta-arylpyridines **8** were afforded. It is worth noting that the reaction of aromatic aldehydes **1** with **2** was finished in shorter reaction time and higher yield whereas the synthesis of penta-arylpyridines **8** demanded longer reaction time (46−60 min) and higher reaction temperature (170 °C) in moderate yield because of steric hindrance of 1,2-diphenylethanone. However, the results is significant since this protocol is superior to the existing methods.[18] In general, the chemistry could be controlled to exclusively yield **4**, **7**, or **8** by varying the substrates.

To the best of our knowledge, the *p*K$_a$ value in the active hydrogen of 3-aryl-3-oxopropanenitrile is lower than that of aromatic ketones, indicating that the aldehyde was preferably condensed with 3-aryl-3-oxopropanenitrile. Therefore, the formation of **4** is expected to proceed via initial condensation of aldehydes with 3-aryl-3-oxopropanenitrile to afford 2-benzoyl-3-aryl-acrylonitrile **9**, which further undergoes in situ Michael addition with 1-(pyridin-2-yl)ethenamine **10** from reaction of 2-acetylpyridine with ammonia to yield the intermediate **11**. The intermediate **11** is then cyclized and

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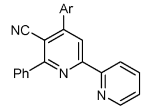
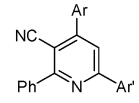
Table 2. Microwave Synthesis of Polysubstituted Pyridines **4** in Water at 150 °C

Entry	4	Product (Ar)	3	Py or Ar'	Time/ min	Yield[a]/ %
1		**4a** 4-Bromophenyl (**1a**)	**3a**	2-Pyridyl	22	84
2		**4b** 4-Fluorophenyl (**1b**)	**3a**	2-Pyridyl	20	86
3		**4c** 3-Nitrophenyl (**1c**)	**3a**	2-Pyridyl	18	89
4		**4d** 2,4-Dichlorophenyl (**1d**)	**3a**	2-Pyridyl	18	86
5		**4e** Phenyl (**1e**)	**3a**	2-Pyridyl	30	80
6		**4f** 4-Tolyl (**1f**)	**3a**	2-Pyridyl	28	83
7	**4a–4k**	**4g** 4-Methoxyphenyl (**1g**)	**3a**	2-Pyridyl	26	82
8		**4h** 3,4,5-Trimethoxyphenyl (**1h**)	**3a**	2-Pyridyl	32	84
9		**4i** 4-Dimethylaminophenyl (**1i**)	**3a**	2-Pyridyl	30	79
10		**4j** Benzo[*d*][1,3]dioxol-5-yl (**1j**)	**3a**	2-Pyridyl	32	82
11		**4k** Thien-2-yl (**1k**)	**3a**	2-Pyridyl	34	70
12		**4l** 4-Bromophenyl (**1a**)	**3b**	4-Methoxyphenyl	24	86
13		**4m** 4-Methoxyphenyl (**1g**)	**3b**	4-Methoxyphenyl	28	79
14		**4n** Benzo[*d*][1,3]dioxol-5-yl (**1j**)	**3b**	4-Methoxyphenyl	26	82
15		**4o** Thien-2-yl (**1k**)	**3b**	4-Methoxyphenyl	22	69
16		**4p** 4-Methoxyphenyl (**1g**)	**3c**	Phenyl	24	82
17		**4q** Benzo[*d*][1,3]dioxol-5-yl (**1j**)	**3c**	Phenyl	22	80
18		**4r** 4-Chlorophenyl (**1l**)	**3d**	4-Chlorophenyl	20	84
19	**4l–4x**	**4s** Thien-2-yl (**1k**)	**3d**	4-Chlorophenyl	18	82
20		**4t** 4-Bromophenyl (**1a**)	**3e**	4-Bromophenyl	20	81
21		**4u** 4-Bromophenyl (**1a**)	**3f**	2,4-Dichlorophenyl	18	80
22		**4v** 4-Bromophenyl (**1a**)	**3g**	4-Tolyl	26	84
23		**4w** 4-Bromophenyl (**1a**)	**3h**	3-Tolyl	26	78
24		**4x** 4-Bromophenyl (**1a**)	**3i**	3-Methoxyphenyl	28	75

[a] Isolated yield.

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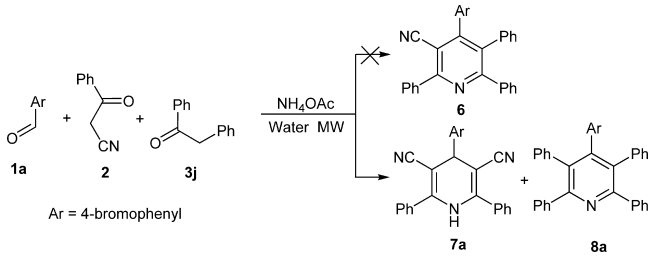
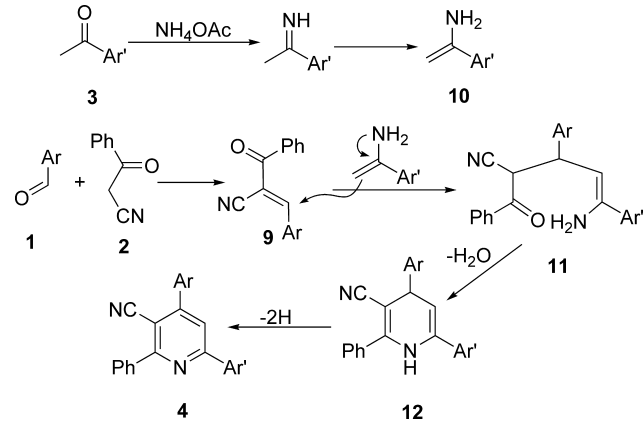
Scheme 3. Microwave Synthesis of Polysubstituted Pyridines **7** and **8**



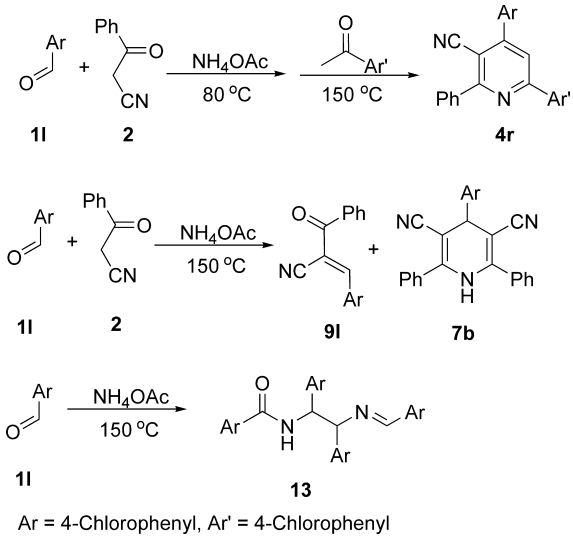
Scheme 4. Proposed Mechanism for Products **4**



subsequently dehydrogenated to afford the aromatized products **4** (Scheme 4). This type of hydrogen loss was well precedented.[19]

To support the proposed mechanism, *p*-chlorobenzaldehyde **1l** was first condensed with 3-aryl-3-oxopropanenitrile in the present of ammonium acetate (excess) under microwave heating at 80 °C for 8 min, followed by reaction with 4-chlorophenylethanone **3d** at 150 °C for 20 min, to give the target compound **4r** in 82% yield. During this reaction process, *p*-chlorobenzaldehyde **1 L** was condensed with 3-aryl-3-oxopropanenitrile in the present of ammonium acetate (excess) under microwave heating at 80 °C for 8 min to generate 2-benzoyl-3-(4-chlorophenyl)-acrylonitrile **9l** in high yield. When the reaction temperature was improved to 150 °C, the above reaction gave 2-benzoyl-3-(4-chlorophenyl)-acrylonitrile **9l** in 40% yield and 1,4-dihydropyridine **7b** in 27% yield. In the further study, the reaction between

Scheme 5. Test Proposed Mechanism for Products **4**



p-chlorobenzaldehyde and ammonium acetate (excess) was performed under microwave heating at 150 °C for 10 min to generate benzylbenzoyl derivative **13**, which was reported by Proskurnina et al.[21] (Scheme 5).

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The IR spectrum of compound **4g** showed a strong absorption at 2218 cm^{-1} because of the CN group. The ^1H NMR spectrum of **4g** showed a singlet at δ 8.48 from the CH proton in the formed pyridine ring, and a singlet at δ 3.88 from the $-OCH_3$ group. Furthermore, the structures of **7h** was further confirmed by single crystal X-ray (Figure 1).[22]

Conclusion

In summary, we have developed a new regiospecific reaction that offered a simple and efficient route for diversity-oriented synthesis of highly functionalized 2,2′-bipyridine derivatives and unsymmetrical 2,4,6-triarylpyridines in high-temperature water. Furthermore, under controlled microwave heating, aromatic aldehydes reacted with 1,2-diphenylethanone, resulting in crowded penta-arylpyridines. This methodology alleviates the need for isolation of β-benzoylacrylonitrile and provides rapid access to pyridines with predictable control of substituent introduction. The versatility of this chemistry offers a valuable addendum to methodology for the synthesis of Kröhnke pyridines.

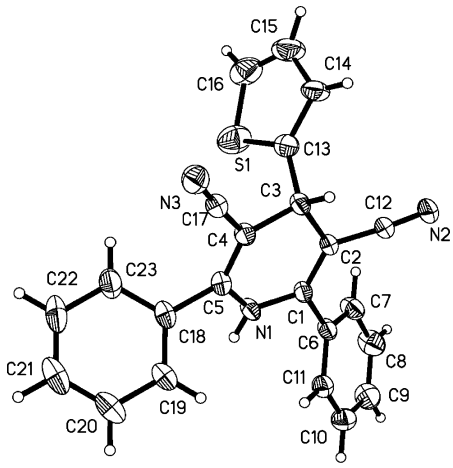


Figure 1. ORTEP drawing of **7h**.

Table 3. Diversity-Oriented Synthesis of Polysubstituted Pyridines **7** and **8**[20]

Entry	7	Product (Ar)		Time / min	Yield[a] / %
1		**7a**	4-Bromophenyl (**1a**)	10	87
2		**7b**	4-Chlorophenyl (**1l**)	12	84
3		**7c**	3-Nitrophenyl (**1c**)	8	91
4		**7d**	4-Tolyl (**1f**)	14	87
5		**7e**	4-Methoxyphenyl (**1g**)	12	84
6	**7a–7h**	**7f**	4-Dimethylaminophenyl (**1i**)	16	76
7		**7g**	Benzo[*d*][1,3]dioxol-5-yl (**1j**)	12	80
8		**7h**	Thien-2-yl (**1k**)	16	73
9		**8a**	4-Bromophenyl (**1a**)	50	54
10		**8b**	4-Fluorophenyl (**1b**)	50	51
11		**8c**	4-Nitrophenyl (**1m**)	46	60
12		**8d**	Phenyl (**1e**)	56	49
13		**8e**	4-Methoxyphenyl (**1g**)	50	47
14	**8a–8i**	**8f**	3,4,5-Trimethoxyphenyl (**1h**)	60	45
15		**8g**	4-Dimethylaminophenyl (**1i**)	60	42
16		**8h**	Benzo[*d*][1,3]dioxol-5-yl (**1j**)	54	53
17		**8i**	3,4-Dimethoxyphenyl (**1n**)	56	51

[a] Isolated.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**4x**, **7a**−**7h**, **8a**−**8i**, and crystallographic information files (CIF) of **7h**. This material is available free charge via the Internet at http://pubs.acs.org.

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