Diversity Synthesis of Pyrimido[4,5-*b*][1,6]naphthyridine and Its Derivatives under Microwave Irradiation

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A series of new heterocyclic compounds, involving pyrimido[4,5-*b*][1,6]-, benzo[*b*][1,6]-, pyrazolo[3,4-*b*]-[1,6]naphthyridine, and aza-benzo[*b*]fluorene skeletons were successfully synthesized via the reaction of structurally diverse 3,5-dibenzylidenepiperidin-4-one with various enamine-likes (2,6-diaminopyrimidin-4(3*H*)-one, 3-amino-5,5-dimethylcyclohex-2-enone, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 1*H*-benzo-[*d*]imidazol-2-amine) in glycol under microwave irradiation. This method has the advantages of short synthetic route, operational simplicity, and increased safety for small-scale fast synthesis for biomedical screening.

Introduction

Microwave-assisted (MW) organic synthesis has attracted considerable attention in the past decade.[1] Microwave irradiation often leads to remarkably decreased reaction time, increased yield, and easier workup. In conjunction with our continued interest in developing new protocols in combinatorial synthesis,[2,3] we explore the use of microwave irradiation at the heat source in the synthesis of conformationally rigid heterocycles.

Since the cytotoxic activity of (*E*)-3,5-bis(benzylidene)-4-piperidones **1** and their specificity toward leukemia cell lines have been reported in 1992,[4] the design and synthesis of their derivatives have been an object of interest because of their potential application in drug discovery. Structure−activity relationship studies have shown that structural modification to the molecular center leads to significant changes in bioactivities and is important in the search for possible lead compounds with more potent pharmaceutical activity and less toxicity. The practice of incorporating chalcones into oxygen-containing and nitrogen-containing heterocyclic rings have been noticed recently, represented by the synthesis of the potentially antiviral compounds pyrano[3,2-*c*]pyridines **2a**[5] and pyrazolo[4,3-*c*]pyridine **2b**[5] (Figure 1). In addition, Naphthyridine have received considerable attention over the past years because of their wide range of biological activities including antitumor,[5−7] anti-inflammatory,[8−10] and antifungal[8−10] activities. Pyridopyrimidine is one of the most important "privileged medicinal scaffolds," which are molecular frameworks used for the development of pharmaceutical agents for diverse applications. A large variety of pyridopyrimidine derivatives have been used as antitumor,[11] antibaceterial,[12] anti-inflammatory,[13] antifungal,[14] and antileishmaniasis[15] agents. Therefore, the synthesis of these molecules has attracted considerable attention. Gangjee and co-workers have described the construction of pyrimidonaphthyridine skeleton via multistep reaction.[7] However, the continued development of diversity synthesis of compounds library, including pyrimidonaphthyridine, benzonaphthyridine, pyrazolonaphthyridine, and aza-benzo[*b*]fluorene frameworks, is still strongly desired, because of their profound chemical and biological significance. In this paper, we would like to report highly efficient synthesis of compounds library containing pyrimido[4,5-*b*][1,6]naphthyridine, benzo[*b*][1,6]naphthyridine, pyrazolo[3,4-*b*][1,6]naphthyridine, and aza-benzo[*b*]fluorine moieties via microwave-assisted, one-pot reaction between (*E*)-3,5-bis(benzylidene)-4-piperidones **1** and various enamine-likes **4** (Scheme 1).

Results and Discussion

Enamines and enamine-like compounds are versatile synthetic intermediates in organic chemistry,[16] which are frequently applied in the preparation of heterocycles.[17] Although a large variety of enamine-like compounds, such as 2,6-diaminopyrimidin-4(3*H*)-one, 3-amino-5,5-dimethylcyclohex-2-enone, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 1*H*-benzo[*d*]imidazol-2-amine, have been involved in the construction of pyridopyrimidinone, pyrazoloquinolin, pyrimidoquinoline, and pyrazolopyridine frameworks,[18] quite surprisingly, utilization of 3,5-dibenzylidenepiperidin-4-one with important biological activity as starting materials to react with enamine-likes has not stimulated much interest so far. Our strategy constructed polysubstitueted pyrimido[4,5-*b*]-[1,6]naphthyridine, benzo[*b*][1,6]naphthyridine, pyrazolo[3,4-*b*]-[1,6]naphthyridine and aza-benzo[*b*]fluorene derivatives through a single-step reaction of enamine-likes (**4a**, **4b, 4c** and **4d**) with preformed 3,5-dibenzylidenepiperidin-4-ones (Scheme 1).

Initially, the reaction of 3,5-dibenzylidenepiperidin-4-one (**3a**) with 2,6-diaminopyrimidin-4(3*H*)-one (**4a**) (Scheme 2) was employed for the formation of pyrimido[4,5-*b*]-

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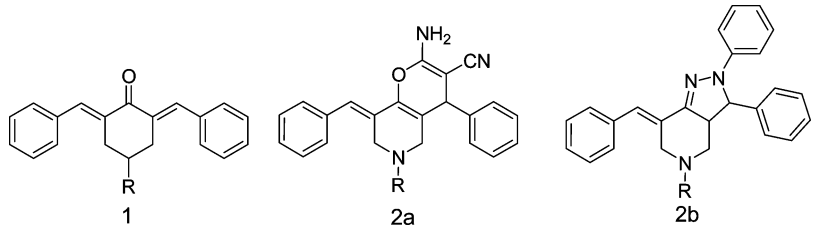
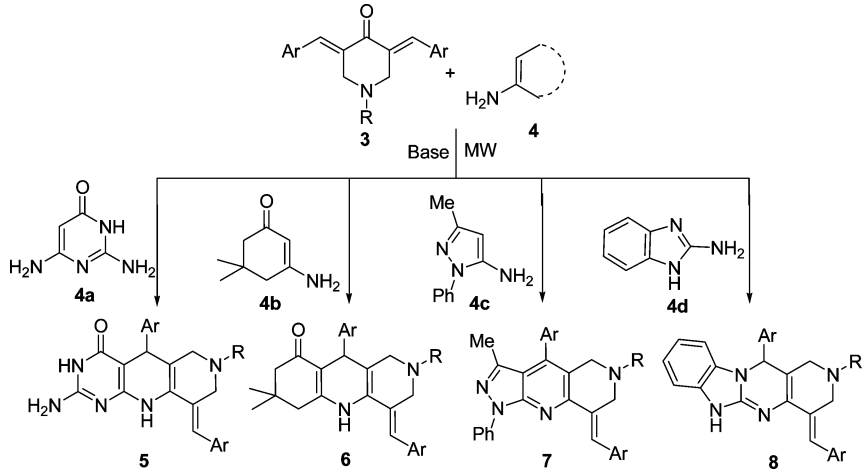
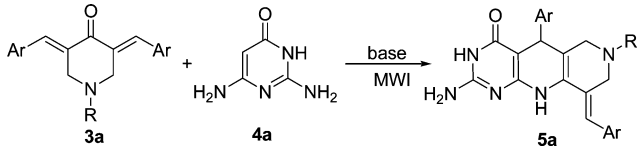


Figure 1

Scheme 1



Scheme 2



[1,6]naphthyridines under microwave irradiation. Various reaction conditions were investigated, including base catalyst, solvent and temperature. First, we employed various base catalysts to determine one which has the most effective catalytic activity. The substrate **3a** reacted with **4a** at 100 °C in glycol using various bases as catalysts. The results of these comparative experiments are summarized in table 1. From the results it is obvious that in this reaction 1.0 M NaOH demonstrates superior catalytic activity and is the best catalyst among those examined. Subsequently, the reaction was examined in different solvents such as glycol, DMF, and ethanol at 100 °C using 1.0 M NaOH as a base catalyst (Table 2, entries 1−3). As shown in Table 2, the reaction in glycol (Table 2, entry 1) resulted in higher yields and requires shorter reaction time than in other solvents. Therefore, glycol was chosen as the reaction media for the further investigation. To further optimize the reaction conditions, the same reaction was carried out in glycol at temperatures ranging from 90 to 140 °C (Table 2, entries 4−8) in increment of 10 °C. As shown in Table 3, the yield of product was increased and the reaction time was shortened when the temperature was increased from 90 to 120 °C(Table 2, entries 4−6). However, further increase of the temperature to 130−140 °C failed to improve the yield of product (Table 2, entries 7−8). Therefore, 120 °C was chosen as the most suitable temperature for all the further microwave-assisted reactions.

Table 1. Optimization of the Catalyst in the Synthesis of **5a** under MW

entry	base[a]	*T* (°C)	time (min)	yield[b] (%)
1	1.0 M NaOH	100	10	92
2	1.0 M KOH	100	10	89
3	K_2CO_3	100	10	49
4	$(CH_3CH_2)_3N$	100	10	33
5	C_5H_5N	100	10	24
6		100	10	trace

[a] The solvent of the reaction is glycol. [b] Isolated yields.

Table 2. Optimization for the Synthesis of **5a**

entry	solvent[a]	*T* (°C)	time (min)	yield [b] (%)
1	glycol	100	8	92
2	DMF	100	8	89
3	EtOH	100	8	87
4	glycol	90	10	88
5	glycol	110	8	93
6	glycol	120	7	95
7	glycol	130	6	92
8	glycol	140	6	90

[a] The volume of solvent is 2.0 mL. [b] Isolated yields.

Table 3. Synthesis of Compounds **5** under Microwave Irradiation

entry	product	R	Ar	time (min)	yield[a](%)	mp (°C)
1	**5a**	methyl	C_6H_5	7	95	>300
2	**5b**	methyl	4-$CH_3C_6H_4$	8	94	>300
3	**5c**	methyl	4-$CH_3OC_6H_4$	8	93	>300
4	**5d**	methyl	4-ClC_6H_4	7	94	>300
5	**5e**	methyl	4-FC_6H_4	7	93	>300
6	**5f**	methyl	4-BrC_6H_4	8	95	>300
7	**5g**	methyl	3-$NO_2C_6H_4$	8	91	>300
8	**5h**	methyl	2-thienyl	8	92	>300
9	**5i**	benzyl	C_6H_5	7	93	223−225
10	**5j**	benzyl	4-$CH_3C_6H_4$	8	94	265−267
11	**5k**	benzyl	4-$CH_3OC_6H_4$	8	92	253−255
12	**5 L**	benzyl	4-ClC_6H_4	8	94	276−278
13	**5m**	benzyl	4-FC_6H_4	7	95	270−272
14	**5n**	benzyl	4-BrC_6H_4	8	91	259−262
15	**5o**	benzyl	3-$NO_2C_6H_4$	8	93	209−211
16	**5p**	benzyl	2-thienyl	8	93	269−271

[a] Isolated yields.

Table 4. Synthesis of **5b**, **5c**, and **5d** under Microwave Irradiation at 120 °C

entry	product	R	Ar	time (min)	yield[a] (%)	mp (°C)
1	**6a**	methyl	4-$CH_3C_6H_4$	7	90	208−210
2	**6b**	methyl	4-FC_6H_4	5	92	254−256
3	**6c**	methyl	4-BrC_6H_4	6	91	245−247
4	**6d**	benzyl	C_6H_5	6	93	217−219
5	**6e**	benzyl	4-$CH_3C_6H_4$	7	92	225−227
6	**6f**	benzyl	4-$CH_3OC_6H_4$	7	91	203−204
7	**6g**	benzyl	4-ClC_6H_4	6	93	244−246
8	**6h**	benzyl	4-FC_6H_4	6	93	194−196
9	**6i**	benzyl	4-BrC_6H_4	6	94	260−262
10	**7a**	methyl	C_6H_5	7	95	199−201
11	**7b**	methyl	4-$CH_3C_6H_4$	8	94	182−184
12	**7c**	methyl	4-ClC_6H_4	7	94	174−176
13	**7d**	methyl	4-FC_6H_4	7	93	214−216
14	**7e**	methyl	2-thienyl	8	92	179−180
15	**7f**	benzyl	4-$CH_3C_6H_4$	8	94	145−146
16	**7g**	benzyl	4-ClC_6H_4	7	93	160−162
17	**8a**	methyl	C_6H_5	7	90	176−177
18	**8b**	benzyl	C_6H_5	7	93	234−236
19	**8c**	benzyl	4-$CH_3C_6H_4$	9	92	244−246
20	**8d**	benzyl	4-$CH_3OC_6H_4$	10	90	244−246
21	**8e**	benzyl	4-ClC_6H_4	8	94	251−253
22	**8f**	benzyl	4-BrC_6H_4	8	94	253−256
23	**8g**	benzyl	4-FC_6H_4	7	93	259−261

[a] Isolated yields.

On the basis of these optimized conditions [glycol, 120 °C, 1.0 M NaOH], reactions of different substrates **3** with 2,6-diaminopyrimidin-4(3*H*)-one **4a** were performed, and a series of pyrimido[4,5-*b*][1,6]naphthyridines **5** were synthesized with good yields. The results (Table 3, entries 1−16) indicated that substrates **1** bearing either electron-donating (such as alkoxy and methyl) and electron-withdrawing (such as nitro or halide) groups afforded high yields of pyrimido[4,5-*b*][1,6]naphthyridine derivatives **5**. We therefore conclude that the electronic nature of the substituents has no significant effect on this reaction.

To expand the application scope of this reaction, the enaminone **4b** and enamine-likes including **4c** and **4d** were employed instead of 2,6-diaminopyrimidin-4(3*H*)-one **4a** to react with 3,5-dibenzylidenepi- peridin-4-ones. To our delight, under the above optimized conditions, all the reactions proceeded smoothly to generated corresponding benzo[*b*][1,6]naphthyridines **6,** pyrazolo[3,4-*b*][1,6]naphthyridines **7** and aza-benzo[*b*]fluorenes **8** in good to excellent yields (Table 4, entries 1−23). It is worth noting that this result is significant since there is no literature precedent for the synthesis of benzo[*b*][1,6]naphthyridine, pyrazolo[3,4-*b*]-[1,6]naphthyridine and aza-benzo[*b*]fluorene derivatives.

Additionally, to compare with microwave heating conditions, the same temperature was applied to the synthesis of some examples of **5**, **6**, **7**, and **8** under classical heating conditions. A comparison of the results for these compounds is listed in Table 5, which indicated that the reaction was efficiently promoted by microwave irradiation, and the reaction time was strikingly shortened to minutes from hours required in traditional heating condition, the yields were increased too.

Table 5. Synthesis of Various **5**, **6**, **7**, and **8** Using Conventional Heating

entry	product	time (h)	yield[a] (%)
1	**5b**	11	80
2	**5d**	9	83
3	**5g**	10	74
4	**5j**	11	82
5	**5p**	10	81
6	**6a**	12	81
7	**6b**	10	83
8	**6g**	11	82
9	**7b**	12	83
10	**7c**	10	84
11	**7g**	10	83
12	**8c**	11	81
13	**8g**	9	82

[a] Isolated yields.

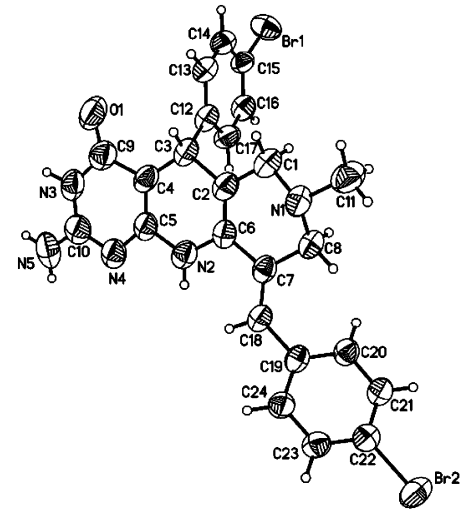


Figure 2. Molecular structure of **5f**.

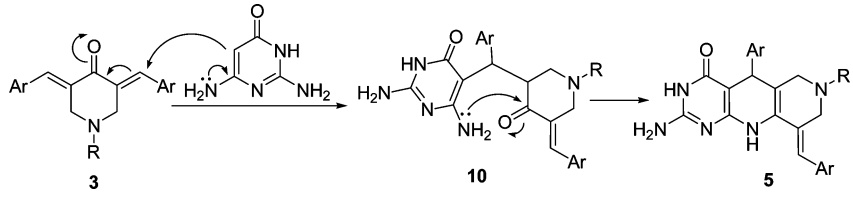
The above reactions are proposed to proceed by a similar mechanism as we have previously reported[19] via sequential addition, cyclization, and elimination. As shown in Scheme 3, the Michael addition between **3** and **4** furnished **10**, which upon intermolecular cyclization and dehydration gave rise to **5**.

The structures of all the synthesized compounds were based on their spectroscopic data. Furthermore, the structures of the compounds (**5f**, **7e**, **8a**) were established by X-ray crystallographic analyses (Figures 2−4).

Conclusion

In summary, we have provided a simple and highly effective method for the diversity synthesis of functionalized molecules. The general approach to synthesize different compound collections from a common intermediate by control with different reagents should provide efficient access to collections of small molecules for chemical biology and medicinal chemistry research. Furthermore, this series of pyrimido[4,5-*b*][1,6]naphthy-

Scheme 3



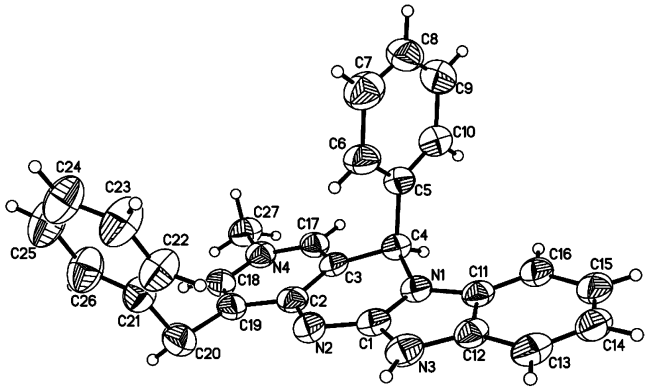


Figure 3. Molecular structure of **7e**.

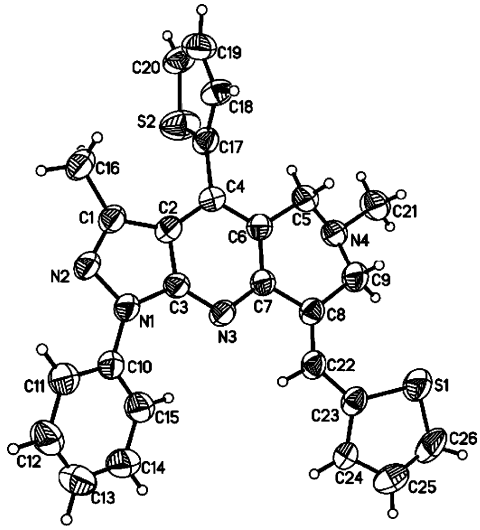


Figure 4. Molecular structure of **8a**.

ridine, benzo[*b*][1,6]naphthyridine, pyrazolo[3,4-*b*][1,6]naphthyridine and aza-benzo[*b*]fluorene derivatives may provide new class of biologically active compounds for biomedical screening.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **5**, **6**, **7**, and **8**, and crystallographic information files (CIF) of **5f**, **7e**, and **8a**. This material is available free charge via the Internet at http://pubs.acs.org.

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