Synthesis of Hexahydrobenzo[*b*]pyrimido[4,5-*h*][1,6]naphthyridines via an Intramolecular Hetero-Diels−Alder Reaction

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Method development was completed for a strategy to access a novel pyrimidine-fused heterocyclic scaffold. The key step for this synthetic route entails an intramolecular inverse electron demand hetero-Diels−Alder reaction of imines or iminiums formed in situ from allylaminopyrimidinealdehydes **3** and anilines. The reactions provided exclusively *cis*-configuration products **6**. Products **6** were readily precipitated in the reaction solution in good to excellent yields. Further transformations of the phenylthio group were demonstrated by an oxidation and subsequent nucleophilic substitution sequence. The synthetic strategy provides an efficient way to access libraries of the tetracyclic pyrimidine-fused heterocycles that can be explored for potential pharmaceutical or biological activities.

Introduction

Access to libraries of novel heterocyclic scaffolds is an important component of medicinal chemistry and chemical biology.[1] Pyrido[2,3-*d*]pyrimidine **1** derivatives are reported to exhibit a variety of biological activities, such as CRF-1 receptor binding and protein tyrosine kinases inhibition (Figure 1).[2] Tetrahydroquinoline derivatives are an important class of natural products displaying a wide range of interesting biological activities, such as antitumor and antibiotic activity.[3] Octahydrobenzonaphthyridines **2** are pharmacologically active as central nervous system depressants (Figure 1).[4] The tetracyclic ring systems are also found among compounds with important biological activities, such as antitumor,[5a,b] angiogenesis,[5c] antibiotic,[5d] and aromatase inhibition.[5e] Several methods were reported for the synthesis of compounds **1** and **2**. For example, treatment of lactams with Viehe's salt followed by the reaction of the resultant iminium dichlorides with amidines gives compounds **1**.[6] A Dieckmann cyclization of diesters has been used to build the bicyclic pyridopyrimidine ring.[2b] The Diels−Alder reaction of amidines and 1,3,5-triazines has been applied to prepare analogs of compound **1**.[7] Compounds **2** were prepared through condensation of *o*-carbonyl aniline and 4-piperidone, followed by hydrogenation.[4] Our laboratory has been interested in developing efficient methodologies for the syntheses of novel pyrimidine-fused heterocycles.[8] We envisioned that a novel hybrid scaffold **6** of structures **1** and **2** with multiple diversification points could be readily prepared via a cascade reaction: condensation of *N*-allylaminopyrimidinealdehydes **3** and anilines **4** followed by an acid catalyzed intramolecular inverse electron demand hetero-Diels−Alder reaction[9] should give the desired *cis*-configured[10] tetracycle **6**, and **6** could be further transformed[8b,h] as described in Scheme 1. Herein, the investigation of the cascade reactions and preparation of a representative library are reported.

Results and Discussion

To investigate the proposed cascade reaction shown in Scheme 1, we initially screened reactions of aniline with pyrimidines **3**, prepared from 4,6-dichloro-5-formylpyrimidine **9a**[11] (Scheme 2), and results are summarized in Table 1. Trifluoroacetic acid (TFA) was selected as a Brønsted acid catalyst based on the previous examples of similar reactions.[12] No desired product was obtained, and the starting material **3a** was recovered in the absence of TFA in acetonitrile (CH_3CN) (Table 1, entry 1). The reaction of compound **3a** (X = Cl) and aniline with 0.1 equiv of TFA in CH_3CN after 13 h at 25 °C yielded the desired product **6a** (78%) and Cl-hydrolyzed aniline adduct **6′** (8%, Table 1, entry 2). Although increase of TFA to 2.0 equiv resulted higher yield (82%) and shorter reaction time (2 h), Cl-hydrolyzed aniline adduct **6′** was still present in the reaction (Table 1, entry 3). To avoid the Cl-hydrolysis, pyrimidine **3b** (X = pyrrolidinyl) was used instead, but unfortunately, no desired product was detected by both TLC and HPLC (Table 1, entry 4). To circumvent these problems and place a strategic functional group for further transformation, pyrimidine **3c** (X = PhS) was investigated. The treatment of **3c** with aniline in the similar condition generated the desired compound **6c** in 87% yield without hydrolysis of the 6-SPh group (Table 1, entry 5). The formation of **6c** was

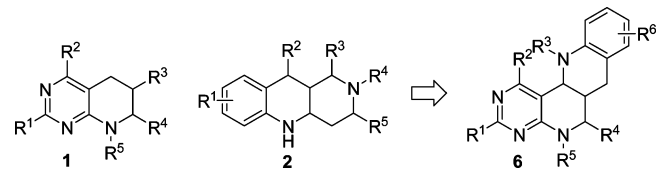

Figure 1. Hybridization of **1** and **2** into **6**.

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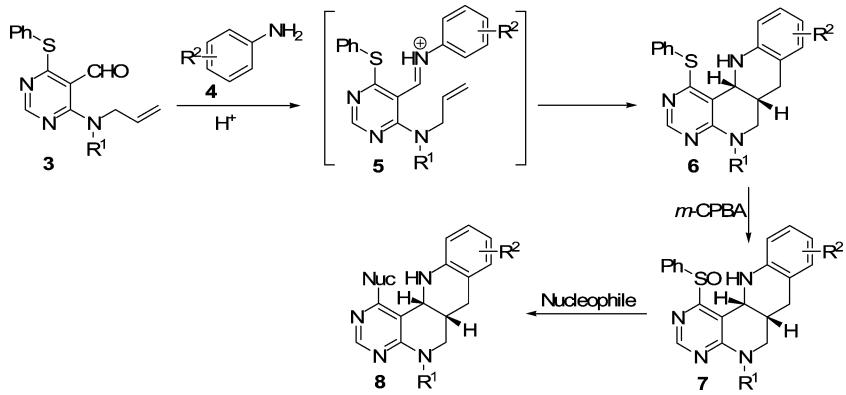
Scheme 1. Strategy for Preparation of Hexahydrobenzo[*b*]pyrimido[4,5-*h*][1,6]naphthyridines



Scheme 2. Synthesis of Substrate 3

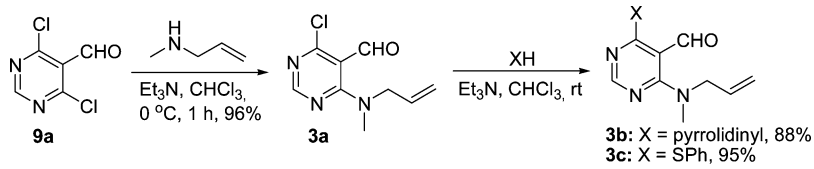
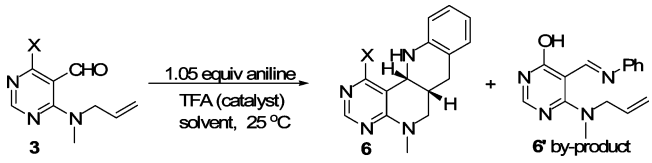


Table 1. Screening of the Substrates and Optimization of the Reaction



entry	3	X	TFA (equiv)	solvent	time (h)	6	yield (%)
1	**3a**	Cl		CH_3CN	10	**6a**	
2	**3a**	Cl	0.1	CH_3CN	13	**6a**	78 (8)[a]
3	**3a**	Cl	2.0	CH_3CN	2	**6a**	82 (4)[a]
4	**3b**	pyrrolidinyl	0.1	CH_3CN	13	**6b**	
5	**3c**	SPh	0.1	CH_3CN	24	**6c**	87
6	**3c**	SPh	1.0	CH_3CN	4	**6c**	90
7	**3c**	SPh	2.0	CH_3CN	1	**6c**	91
8	**3c**	SPh	2.0	CH_3CN/H_2O (1:1)	11	**6c**	94

[a] Yield of **6′** isolated.

found to be exclusively *cis*-selective based on a X-ray analysis and the ^{1}H NMR spectrum ($J_{12a,6a} = 2.4$ Hz) (Figure 2).[13] This result supported the proposed concerted intramolecular hetero-Diels−Alder mechanism.[14] Therefore, compound **3c** was selected for further investigation. The increase of TFA to 1.0 equiv shortened the reaction time to 4 h with slight increase of product yield (91%, Table 1, entry 6). Further increase of TFA to 2.0 equiv reduced the reaction time to 1 h (Table 1, entry 7), and the employment of a 1:1 mixture of CH_3CN and H_2O as the solvent[15] resulted the precipitation of product **6c**, which simplified the reaction workup (Table 1, entry 8). Therefore, this condition was chosen as the optimized condition for further studies.

To explore the scope of this reaction, a series of aromatic amines were reacted with pyrimidines **3** under the optimized conditions, and the results are reported in Table 2.

As shown in Table 2, various substituted aromatic amines could react with **3c** to give the desired products **6** in good to excellent yields (entries 1, and 3−16). All the products were determined to be *cis*-configured by comparison of ^{1}H NMR spectra with **6c** (determined by X-ray analysis) and no *trans* isomers were observed in the crude reaction product by LC-MS. The reactions with aromatic amines containing electron-withdrawing groups (entries 3−8) were faster than those with electron-donating groups (entries 9−15), which suggests that the cycloaddition reactions fall into the category of inverse electron demand Diels−Alder reactions. When the anilines had an *ortho* substituent, the reactions were either sluggish (entries 7, 9, and 12) or resulted no desired product (entry 2). The reaction of compound **3c** with *o*-nitroaniline under the current condition did not yield the desired product. This could be attributed to the combination of steric and strong electron-withdrawing effects which impeded the formation of imine or iminium intermediate. It is worth noting that various functional groups such as carboxyl, hydroxyl, nitro (except in *ortho* position), chloro, and fluoro are tolerated. Regio isomers were observed by ^{1}H NMR when *meta*-Cl (entry 8) and *meta*-Me (entry 10) substituted anilines were used. However, when *meta*-nitroaniline (entry 3) was used, only C2-cyclized product was obtained and the employment of 3,4-(methylenedioxy)aniline (entry 15) resulted the C6-cyclized product as the sole isomer. When R^1 was H, the reaction stopped at the stage of imine intermediate (entry 17). When R^1 was phenyl, no desired product was isolated (Table 2, entry 18). When R^1 was Bn and CH_2CO_2Et (entries 19 and 20), the reactions were accelerated in comparison to

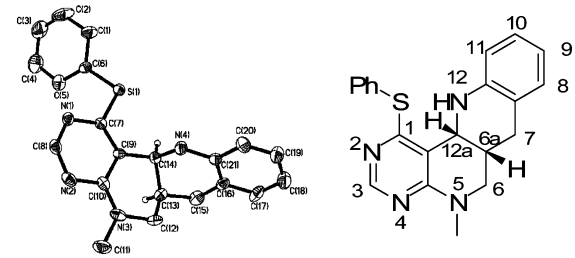
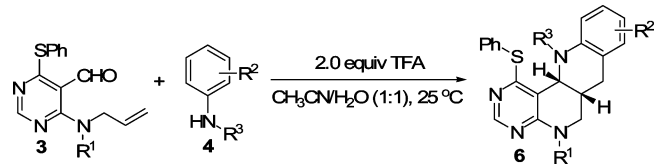


Figure 2. X-ray structure of product **6c**.

Table 2. Reaction of Substrates **3** with Substituted Anilines and Analogs



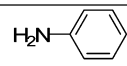
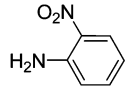
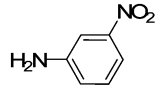
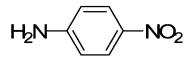
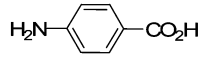
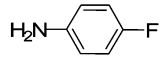
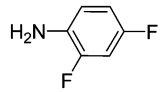
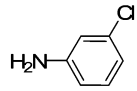
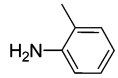
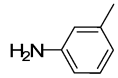
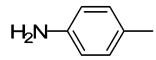
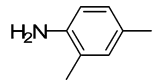
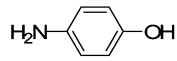
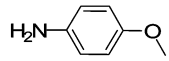
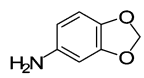
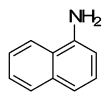
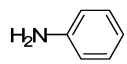
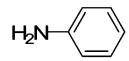
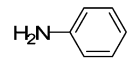
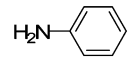
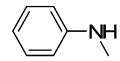
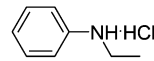
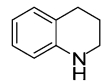
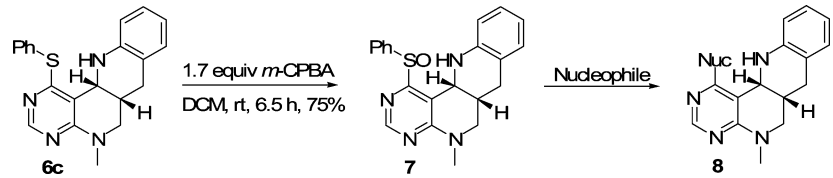
entry	**3**	R^1	$ArNH_2$	products	time (h)	yield (%)
1	**3c**	CH_3		**6c**	11	94
2	**3c**	CH_3		**6d**	3	0
3	**3c**	CH_3		**6e**	4	92[a]
4	**3c**	CH_3		**6f**	7	87
5	**3c**	CH_3		**6g**	6	86
6	**3c**	CH_3		**6h**	11	91
7	**3c**	CH_3		**6i**	23	83
8	**3c**	CH_3		**6j**	8	80 (1:1)[b]
9	**3c**	CH_3		**6k**	24	91
10	**3c**	CH_3		**6l**	10	88 (3:1)[b]
11	**3c**	CH_3		**6m**	18	87
12	**3c**	CH_3		**6n**	27	78
13	**3c**	CH_3		**6o**	20	98
14	**3c**	CH_3		**6p**	23	85
15	**3c**	CH_3		**6q**	27	85[c]
16	**3c**	CH_3		**6r**	15	83
17	**3d**	H		**6s**	3	0[d]

Table 2. Continued

entry	3	R^1	$ArNH_2$	products	time (h)	yield (%)
18	**3e**	Ph		**6t**	2	0
19	**3f**	Bn		**6u**	3	98
20	**3g**	CH_2CO_2Et		**6v**	7	95
21	**3c**	CH_3		**6w**	33[e]	78
22	**3c**	CH_3		**6x**	85[e]	49
23	**3c**	CH_3		**6y**	27[e]	82

[a] Single regio-isomer (cyclized to C2 of aniline). [b] A mixture of regio-isomers. [c] Single regio-isomer [cyclized to C6 of 3,4-(methylenedioxy)aniline]. [d] 92% yield of imine intermediate was isolated. [e] Anilines (1.05 equiv), TsOH (0.05 equiv), in refluxing toluene with a Dean−Stark trap.

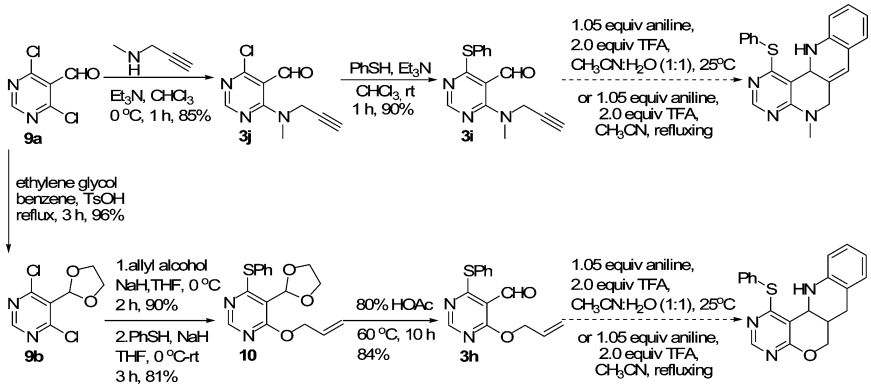
Table 3. Oxidation and Substitution



entry	products	nucleophile	base	solvent	temp (°C)	time (h)	yield (%)
1	**8a**	pyrrolidine		toluene	100[a]	7	98
2	**8b**	aniline	NaH	THF	50	1	60
3	**8c**	EtSH	pyridine	toluene	100[a]	18	55[b]
4	**8d**	BnSH	pyridine	toluene	100	14	87
5	**8e**	*n*-BuONa[c]		THF	r.t.	10	80
6	**8f**	PhONa[c]		THF	r.t.	12	60

[a] Sealed tube. [b] 37% yield of **6c** was isolated. [c] Formed in situ by adding sodium to butan-1-ol (or phenol).

Scheme 3. Attempted Reactions of Substrate **3h-i** with Aniline



when R^1 was Me (entry 1). Despite limited report on the applications of secondary aryl amines as substrates used to assemble the iminium diene,[16] the reaction of secondary aryl amines and pyrimidine **3c** yielded the desired products under a modified reaction condition of 0.05 equiv of *p*-tolunesufonic acid in refluxing toluene with a Dean−Stark trap (entries 21−23). These results indicated that formation of the iminium ion could be the key to the cycloaddition reaction.

To increase the diversity, transformation of the phenylthio group on the pyrimidine ring to a variety of substituents, such as alkylamino, alkoxy, and alkylthio groups, was explored using our previously developed methods.The representative **6c** was readily oxidized by *m*-CPBA to sulfoxide **7**. When intermediate **7** was treated with nucleophiles, the desired products **8** were obtained (Table 3). The reaction proceeded with nearly quantitative yield when pyrrolidine was used (Table 3, entry 1). On the other hand, aniline led

to lower yield of the final product **8b** (Table 3, entry 2). The reaction of compound **7** and ethanethiol with pyridine as base yielded the desired product **8c** (55%) and reduction product **6c** (37%) (Table 3, entry 3). The reaction of **7** with benzyl mercaptan generated compound **8d** in 87% yield without reduction product **6c** (Table 3, entry 4). Butan-1-ol as the nucleophile yielded product **8e** in good yield (Table 3, entry 7). The weak nucleophile phenol also gave the desired product **8f** (Table 3, entry 6). These reactions demonstrated the feasibility of the proposed transformations of phenylthio group to increase the structural diversity.

In an attempt to expand the scope of this reaction to other olefins and alkynes, pyrimidines **3h** and **3i** were synthesized as depicted in Scheme 3.[17] However, neither **3h** nor **3i** produced the desired products under the above reaction conditions. In the reaction with aniline in refluxing CH_3CN, substrate **3h** decomposed. Substrate **3i** was recovered after refluxing for 2 h with aniline in CH_3CN. These results are likely due to the lack of reactivity of the dienophiles and consistent with those of the similar molecular systems reported in the literature.[18]

Conclusion

In conclusion, a novel pyrimidine-fused tetracyclic scaffold was designed and synthesized by a methodology involving the intramolecular inverse electron demand hetero-Diels−Alder reaction of an imine or iminium ion formed in situ from *N*-allylaminopyrimidinealdehyde with suitable primary or secondary aryl amines. The reactions yielded exclusively *cis*-configured products in good to excellent yields and are simple in operation. Further transformations of the phenylthio group in this tetracyclic scaffold were demonstrated by an oxidation and subsequent nucleophilic substitution sequence. This method provides convenient access to a library of structurally diversified compounds for drug discovery.

Experimental Section

General Procedure for the Synthesis of Hexahydrobenzo[b]pyrimido[4,5-h][1,6]naphthyridines 6. To a solution of **3c** (143 mg, 0.5 mmol) and aniline (0.048 mL, 0.525 mmol) in CH_3CN (2 mL) and water (2 mL) was added a solution of TFA (0.075 mL, 1.0 mmol). The reaction mixture was stirred for 11 h at 25 °C. The precipitate was filtered and washed with ethanol to give the desired product **6c**. The filtrate was diluted with 20 mL of water and extracted with EtOAc (4 × 8 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by flash chromatography to give the product **6c**. The combined product weighed 169 mg (94% yield). ^{1}H NMR ($CDCl_3$, δ): 8.28 (s, 1H), 7.56−7.52 (m, 2H), 7.43−7.39 (m, 3H), 7.06−7.00 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 4.75 (d, J = 2.4 Hz, 1H), 3.92 (s, 1H), 3.56 (t, J = 12.3 Hz, 1H), 3.30 (dd, J_1 = 6.3 Hz, J_2 = 17.1 Hz, 1H), 3.16 (s, 3H), 3.12 (dd, J_1 = 4.8 Hz, J_2 = 12.6 Hz, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.47 (m, 1H); ^{13}C NMR ($CDCl_3$, δ): 162.88, 157.66, 157.27, 141.53, 134.84, 129.73, 129.35, 128.99, 127.62, 118.24, 118.12, 114.76, 111.32, 90.60, 49.65, 47.52, 36.30, 29.24, 28.77; MS (ESI): m/z 361.1 [M + H$^+$].

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Supporting Information Available. Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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