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A Divergent Synthesis of 1,8-Naphthyridines and Hydropyridopyrimidinones by the Reactions of *o*-Aminonitriles with Ketones

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An efficient divergent synthesis of substituted 1,8-naphthyridine and hydropyridopyrimidinone derivatives was developed by the reactions of *o*-aminocyanopyridines and ketones based on different catalytic conditions.

Keywords Friedländer annulations, divergent synthesis, 1,8-naphthyridine, hydropyridopyrimidinone

Introduction

Among the various synthetic strategies, divergent reactions are particularly attractive because they can synthesize a variety of heterocyclic motifs from a single class of precursor. In order for this strategy to be of synthetic utility, many efforts have dealt with the control of divergent reactions to provide one of several products selectively,[1] for examples, Fan *et al.*[1b] reported a solvent-controlled oxidative cyclization for a divergent synthesis of highly functionalized oxetanes and cyclopropanes, Liang *et al.*[2] developed a palladium-catalyzed divergent reaction of α-diazocarbonyl compounds with allylic esters. However, metal catalysts are always used in the control of divergent reactions, thus the control of divergent reactions based solely on catalyst selection especially metal-free and ligand-free is still one of the challenges in modern synthetic community.[3]

1,8-Naphthyridine derivatives have been extensively investigated and remain an ongoing interest because of their wide biological activities including antibacterials,[4] anticonvulsants,[5] and antihypertensives[6] and have appeared as a key core in numerous compounds and drugs over the past few decades. The fused pyrido[2,3-*d*]pyrimidiones ring system has also received considerable interest because of its wide range of biological and pharmacological properties such as antihistaminic,[7] antibacterial,[8] antifolate,[9] and PED4 inhibiting activities[10] as well as diuretic activity.[11] During studying Friedländer cyclocondasation of aryl *o*-aminonitrile and ketone possessing an active α-methylene group, the formations of new skeleton products have been reported by us and other groups.[12] Although synthesis of some hydropyridopyrimidinones was mentioned in our previous research,[12d,12j] further investigating the scope as well as controlling of divergent reactions are still desirable. Herein we wish to report the divergent synthesis of 1,8-naphthyridine and hydropyridopyrimidinone derivatives through controlled cyclization pathways of *o*-aminocyanopyridines with ketones.

Results and Discussion

To standardize the reaction conditions for the different way of this divergent conversion,[12e] we selected compound **1a** and cyclohexanone as the model substrates for the optimization of the reaction conditions. Based on the possible mechanism of Friedländer condensation, the direction of the designed divergent conversion depends on dehydration of the key intermediate **I**. Various catalysts such as Brønsted and Lewis acids, and base were evaluated for the reaction. The data indicated that PPA was the most effective catalyst for the formation of Friedländer product **3b** (Scheme 1, Route A) and only a single product **4b** was obtained in high yield in the presence of strong bases such as NaOH, $NaOCH_3$ (Scheme 1, Route B). Screening of other catalyst gave 1,8-naphthyridine **3b** along with varying amounts of hydropyridopyrimidinone **4b**. The effect of solvents was also investigated, and cyclohexanone itself was the best choice for the formation of **4b**. The function of PPA and $NaOCH_3$ can be explained as follows: PPA, as a common dehydrant strongly favors Friedländer conversion resulting in the formation of 1,8-naphthyridine whereas $NaOCH_3$ leads the intramolecular Pinner reaction to give pyrido[2,3-*d*]-oxazine **II** (Pinner reaction[13]), which subsequently rearranges to afford the final product (Dimroth rearrangement[14]). And this conversion is called PDF

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Scheme 1 Proposed mechanism for the divergent conversion

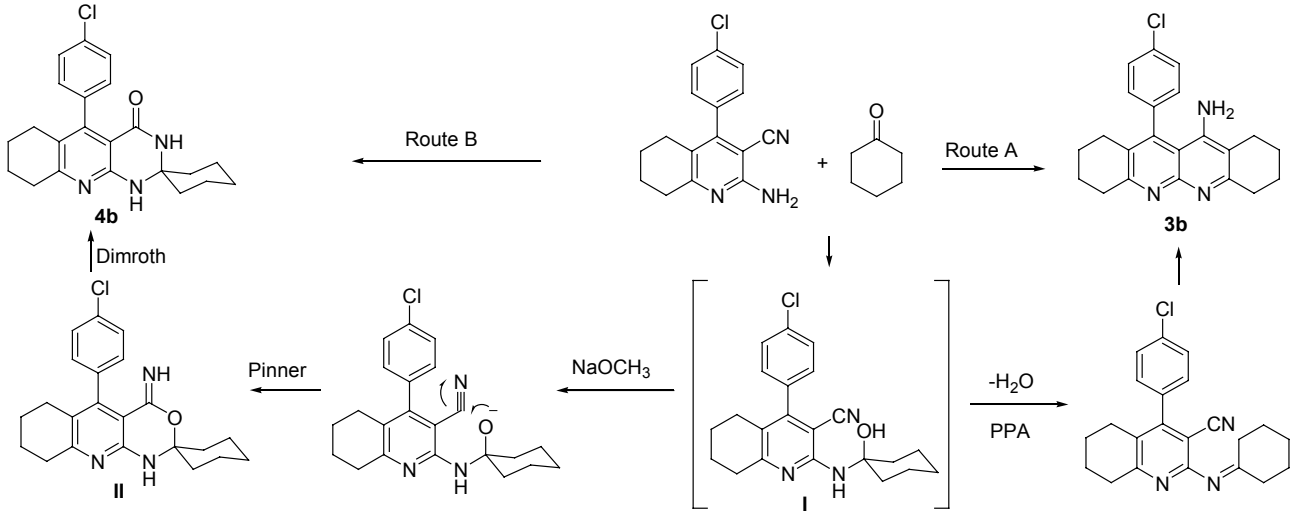
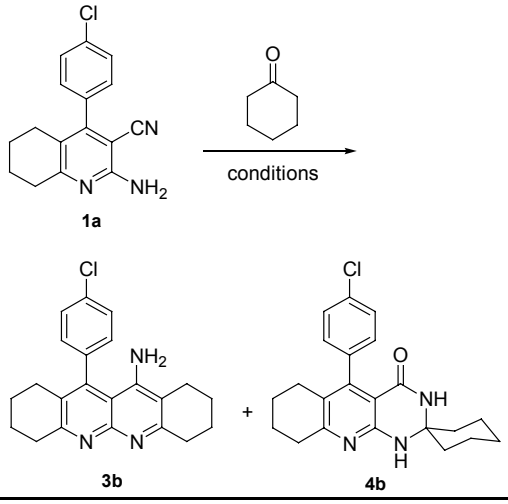


Table 1 Evaluation of reaction conditions[a]



Entry	Catalyst[b]	Solvent	Temp./℃	Yield[c]/%	
				3b	**4b**
1	$AlCl_3$	DCE	80	55	0
2	$CuCl_2$	none	140	7	32
3	$ZnCl_2$	none	140	10	75
4	*p*-PSA	none	140	47	13
5	HCl	none	140	24	10
6	PPA	toluene	120	80	0
7	Na_2CO_3	none	140	0	0
8	Pyridine	none	140	0	0
9	NaOH	none	140	0	77
10	$NaOCH_3$	none	140	0	83
11	$NaOCH_3$	DMF	140	0	73
12	$NaOCH_3$	DMSO	160	0	65
13	$NaOCH_3$	toluene	120	0	0
14	$NaOCH_3$	xylne	130	0	12

[a] Reaction conditions: **1a** (2 mmol), solvent (3 mL). [b] For Entry 1—6, 1.5 equiv. based on **1a**; Entry 7—12, 0.5 equiv. based on **1a**. [c] Isolated yield.

conversion which means a transformation from Pinner to Dimroth rearrangement in the Friedländer reaction.[12c]

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction (Table 2). Under the catalysis of PPA, most ketones were reacted with *o*-aminocyanopyridines to give the corresponding 1,8-naphthyridines via Friedländer conversion. In the case of acetone and 3-methylbutan-2-one without an active α-methylene group only PDF conversion occurred, and the products **4f** and **4l** were isolated in 85% and 87% yields, respectively. It was noted that the electronic influence of *o*-aminocyanopyridines has a profound impact on the reaction pathway. Hence, substrates with electron withdrawing groups adjacent to phenyl ring strongly favor PDF pathway resulting in the formation of hydropyridopyrimidinone, the method underwent well for most cyclic and branched ketone tested except cycloheptanone (Table 2, Entries 1—14), whereas those substituted with electron-donating groups only favor formation of 1,8-naphthyridine (Table 2, Entries 15 and 16).

The structures of all products were established on the basis of spectroscopic data such as IR, NMR, and ESI spectra and elemental analyses. A couple structures of the divergent products **3b** and **4b** were determined unambiguously by X-ray crystallography (Figure 1).[15]

Conclusions

In summary, we have developed the first example of a PPA and $NaOCH_3$ promoted cyclization of *o*-aminocyanopyridines and readily available ketones to selectively achieve 1,8-naphthyridines and fused pyrido[2,3-*d*]pyrimidines. Compared with the traditional used catalysts of Friedländer cyclization for the synthesis of tacrine analogues, the PPA-catalyzed process can be performed at fast reaction rates, no special precautions were required such as N_2 or argon to carry out the reac-

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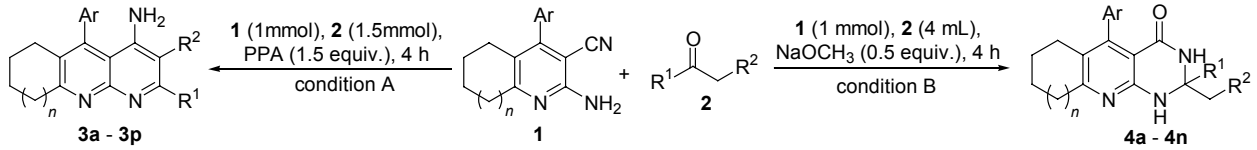
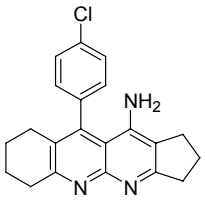
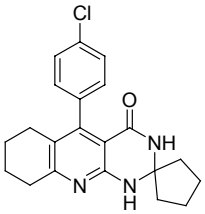
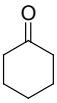
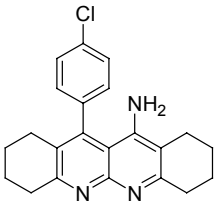
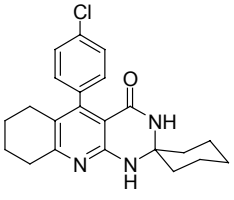
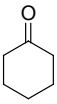
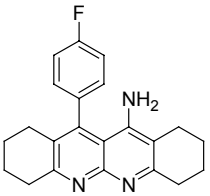
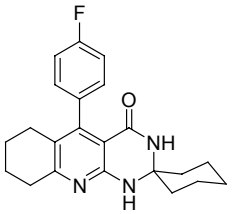
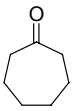
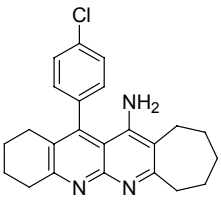
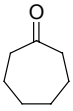
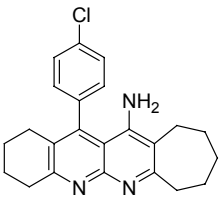
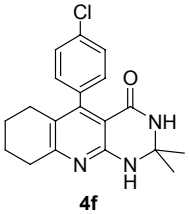
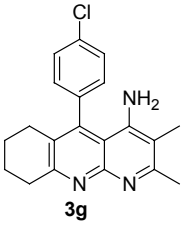
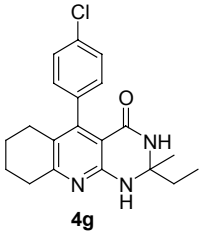
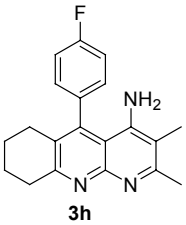
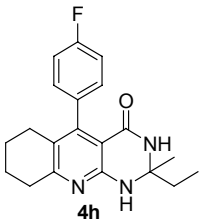
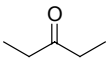
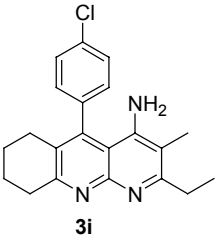
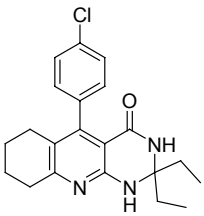
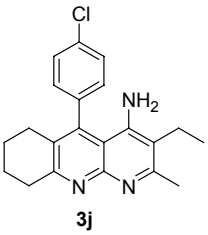
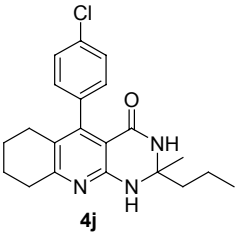
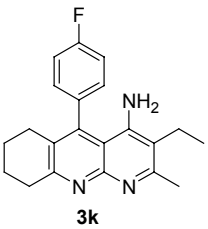
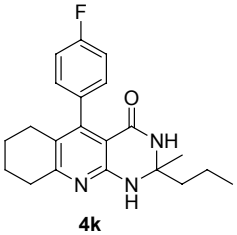
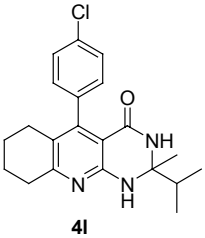
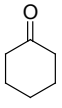
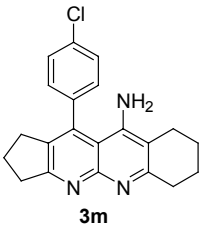
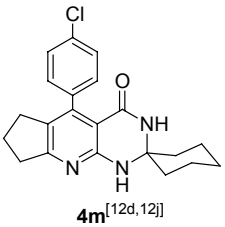
Table 2 Catalyst-controlled cyclization of *o*-aminocyanopyridines with ketones

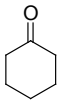
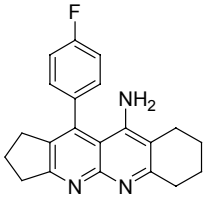
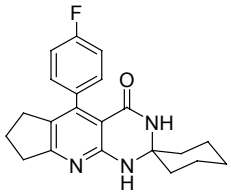
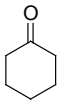
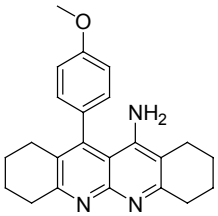
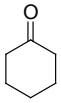
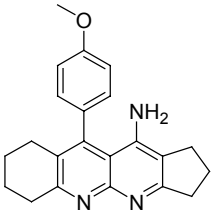


Entry	*n*, Ar	**2**	Condition A		Condition B	
			Product	Yield[a]/%	Product	Yield[a]/%
1	1, *p*-Cl-Ph		 **3a**	76	 **4a**	78
2	1, *p*-Cl-Ph		 **3b**	80	 **4b**[12d,12 j]	83
3	1, *p*-F-Ph		 **3c**	81	 **4c**[12d,12 j]	84
4	1, *p*-Cl-Ph		 **3d**	72	—	trace
5	1, *p*-F-Ph		 **3e**	72	—	trace
6	1, *p*-Cl-Ph		trace		 **4f**	85

Continued

Entry	*n*, Ar	**2**	Condition A		Condition B	
			Product	Yield[a]/%	Product	Yield[a]/%
7	1, *p*-Cl-Ph		 **3g**	88	 **4g**	87
8	1, *p*-F-Ph		 **3h**	88	 **4h**	86
9	1, *p*-Cl-Ph		 **3i**	82	 **4i**	86
10	1, *p*-Cl-Ph		 **3j**	85	 **4j**	84
11	1, *p*-F-Ph		 **3k**	88	 **4k**	82
12	1, *p*-Cl-Ph		—	trace	 **4l**	87
13	0, *p*-Cl-Ph		 **3m**	80	 **4m**[12d,12j]	80

Continued

Entry	*n*, Ar	**2**	Condition A		Condition B	
			Product	Yield[a]/%	Product	Yield[a]/%
14	0, *p*-F-Ph		 **3n**	74	 **4n**[12d, 12j]	85
15	1, *p*-OMe-Ph		 **3o**	88	—	trace
16	1, *p*-OMe-Ph		 **3p**	81	—	trace

[a] Isolated yield.

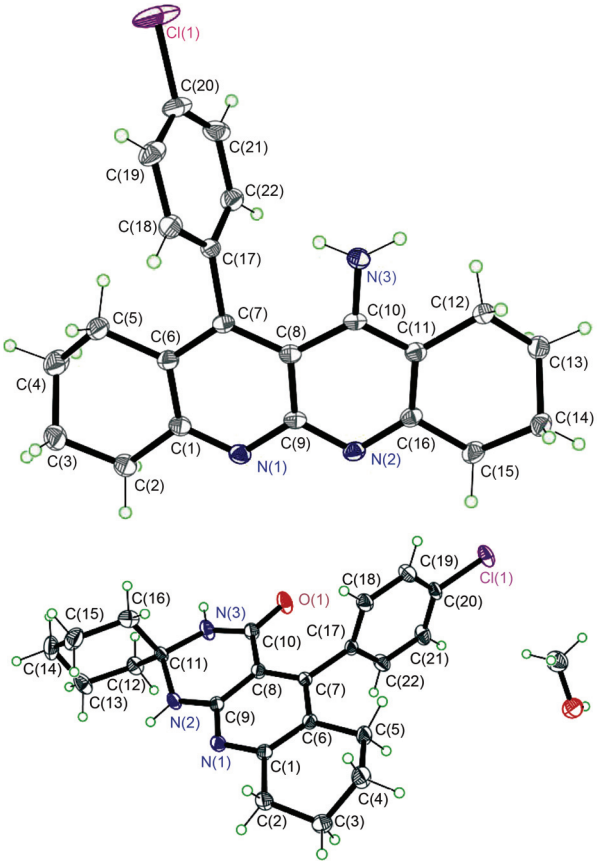


Figure 1 X-ray structure of **3b** (top) and **4b** (bottom).

tion and avoid the use of silica gel column chromatography for purify. The PDF pathway is an atom economical process, pyrido[2,3-*d*]pyrimidines can be obtained *via* simple filtration since the products directly precipitate out of solution after cooled to room temperature with good yields.

Experimental

The starting materials *o*-aminocyanopyridines were synthesized from using a standard methodology reported by El-Salam.[16] Toluene was distilled from P_2O_5 and dried over MS 4 Å. Other reagents were used as purchased from commercial suppliers without further purification. Melting points were determined using XT4 micro-scope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at a Varian mercury-plus 400 spectrometer with TMS as the internal standard. Mass spectra were recorded on a Varian 500-MS using ESI ionization. Elemental analyses were performed on an Elementar Vario EL.

General procedure for the synthesis of 1,8-naphthyridine derivatives

PPA (1.5 mmol), *o*-aminocyanopyridines (1 mmol) and the corresponding ketones (1.5 mmol) were added to 5 mL anhydrous toluene, the reaction mixture was

stirred for 4 h under reflux, the reaction mixture was poured into 20 mL H_2O and stirred for 30 min, the mixture was extracted with ethyl ether (5 mL×3), concentrated ammonia liquor was added dropwise to the aqueous phase until the aqueous solution was basic and the precipitate was isolated by filtration. The crude product was recrystallized from 95% enthol to afford pure compounds.

General procedure for the synthesis of hydropyridopyrimidinone derivatives

To a stirred suspension of o-aminocyanopyridines (1 mmol) in corresponding ketone (4 mL), MeONa (0.5 mmol) was added. The resulting mixture was stirred for 5 h at proper temperature. The reaction mixture was cooled to room temperature and the precipitate was isolated by filtration. The solid was purified by crystallization from proper solvent to provide the corresponding pure product.

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[15] Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-900015 (**3b**) and no. CCDC-854866 (**4b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (Fax:＋44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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