Article

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Pseudo Five-component Domino Strategy for the Combinatorial Library Synthesis of [1,6] Naphthyridines - An *On Water* Approach

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Keywords: on water, 1,6-naphthyridines, hydrophobic aggregation, selectivity

Abstract: This work features the base-promoted *on water* synthesis of [1,6]-naphthyridines from methyl ketones, malononitrile and phenols or thiols. The reaction conditions were carefully tuned to drive the product selectivity from 3*H*-pyrroles to [1,6]-naphthyridines. The advantages of this method lie in its simplicity, cost effectiveness, and environmental friendliness, representing a new effort towards the *on water* synthesis of [1,6]-naphthyridines without starting from a nitrogen-containing heterocycle and highlighting the versatility of the nitrile functional group.

INTRODUCTION

Multicomponent reactions (MCRs)[1a,b] provide effective tools for combinatorial synthetic chemistry because highly diverse compound libraries can be prepared via convenient one-pot procedures. Attention is often focused on natural product scaffolds and drug-like molecules,[1c]

with particular emphasis on heterocyclic compounds.[1d,e] As a consequence, multicomponent reactions and related domino reactions have received much recent attention.[1f]

Water is known to enhance the rates and to affect the selectivity of a wide variety of organic reactions.[2] Even when rate accelerations are modest, water provides advantages of large heat capacity, making exothermic processes safer and more selective, and easily isolation of organic compounds.

Functionalized [1,6]-naphthyridines and their benzo/hetero-fused analogues have attracted much attention from synthetic and medicinal view points.[3] Naphthyridine derivatives are widely used for various pharmacological purposes (Figure 1) such as antiproliferative activity,[4] HIV-1 integrase inhibition,[5] allosteric inhibition of Akt_1 and Akt_2,[6] and selective antagonism of 5-HT_4 receptors.[7]

The majority of the synthetic strategies toward these units[8] have relied on condensation of 2-amino pyridine derivatives with carbonyl compounds containing an active methylene group or with β-keto esters.[9] Transition metal mediated cyclotrimerisation of dialkynyl nitriles has also been recognized as a general method toward [1,6]-naphthyridines[10] in addition to the common approach of Lewis acid catalysis of intramolecular hetero Diels-Alder reactions of aldimines.[11] Many of these methods suffer from the use of multistep sequences, expensive catalysts,[12] hazardous organic solvents, inert atmosphere, lengthy reaction time, and laborious workup.[13] Moreover, there are only a few reports of the simple and convenient synthesis of this moiety from readily available and inexpensive starting materials.[14,15]

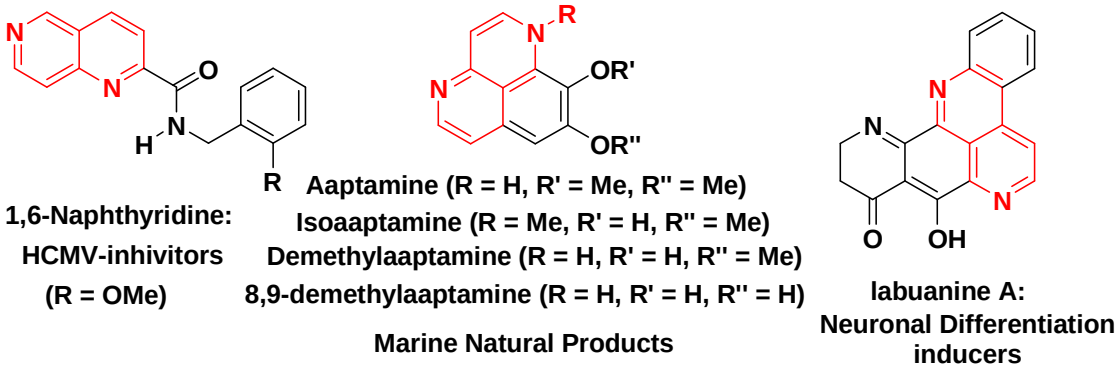
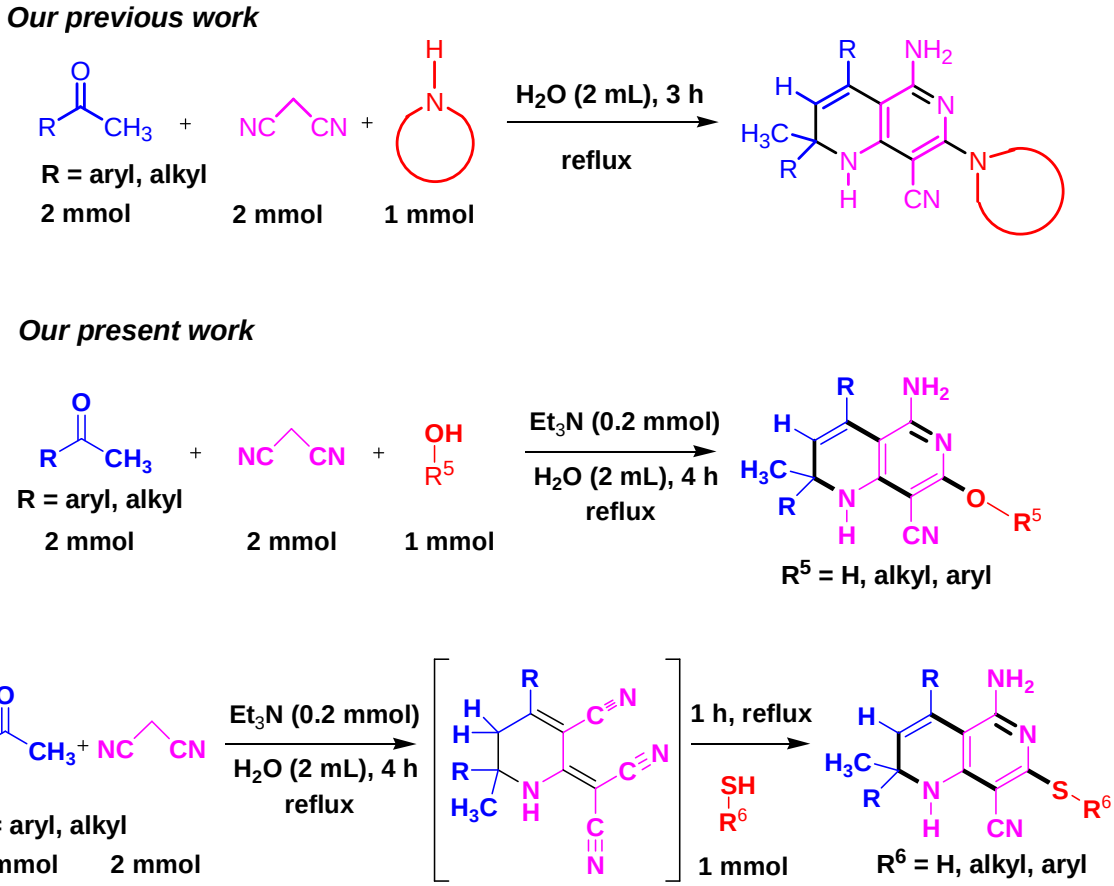


Figure 1. Examples of biologically active 1,6-naphthyridines.

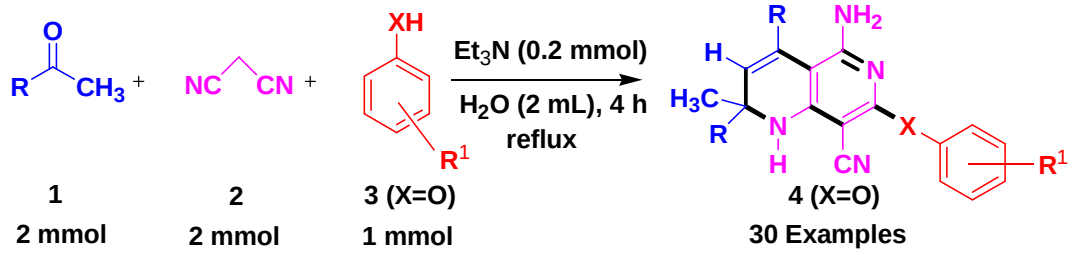
RESULTS AND DISCUSSION

We explored the use of phenols and thiols as synthon for an unprecedented coupling with methyl ketones and malononitrile to create highly substituted [1,6]-naphthyridines (Scheme 1). In previous work,[15] we have used ketones, malononitrile and aliphatic amines for the synthesis of [1,6]-naphthyridines. While no base other than the reactant amine was required, the method reported here needs an additional base catalyst. Scheme 2 shows the use of triethylamine as catalysis for a one-pot, pseudo-five-component synthesis of 1,2-dihydro[1,6]-naphthyridines from ketones, malononitrile and phenols in the ecofriendly solvent water. The products were well characterized by ^{1}H NMR, ^{13}C NMR, 2D NMR, FTIR, elemental analysis, melting point determination, and X-ray crystallographic analysis.

Scheme 1. Previous[15] and present approaches to substituted [1,6]-napthylpyridines.



Scheme 2. Pseudo-five component synthesis of [1,6]-naphthyridines

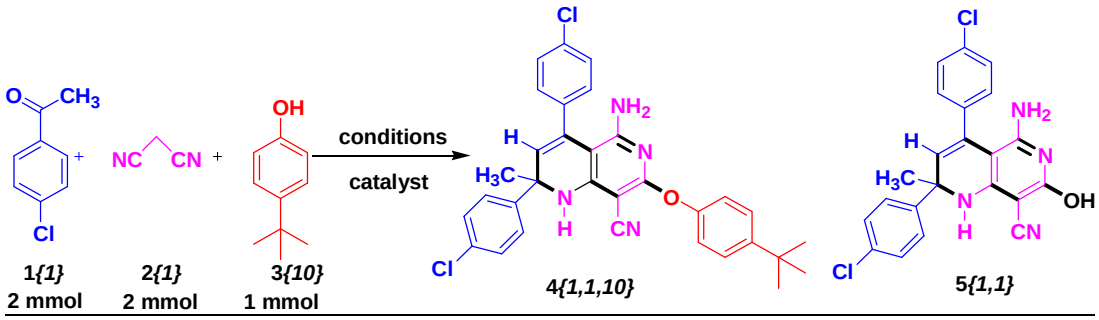


Optimization of Reaction Conditions

To optimize the reaction conditions, a series of experiments were conducted with a representative reaction of 4-chloro acetophenone (**1***{1}*) (2 mmol), malononitrile (**2***{1}*) (2 mmol) and 4-tert-butyl-phenol (**3***{10}*) (1 mmol) with variation of reaction parameters. The results,

summarized in Table 1, showed that the nature of the catalyst and the reaction temperature had a significant effect on the yield of the desired [1,6]-naphthyridines (**4***{1,1,10}*) and 7-hydroxy-[1,6]-naphthyridines (**5***{1,1}*). Sodium hydroxide was ineffective, at both low and high temperatures (Table 1, entries 1 and 2). In the latter case (100 °C), an unexpected compound **5***{1,1}* was isolated in 10% yield, presumably by nucleophilic attack of hydroxide in competition with phenoxide. Therefore, the use of a higher concentration of NaOH as base catalyst gave significant improvements in the yield of the 7-hydroxy compound **5***{1,1}*, isolated in greater proportions relative to naphthyridine (**4***{1,1,10}*) as the temperature was lowered (Table 1, entries 3-5). No product was observed when a background reaction was carried out with no catalyst (entry 6).

Table 1. Optimization of Reaction Conditions for the Multicomponent Coupling Reactions[a]



entry	catalyst	amount (mmol)	solvent	temp (°C)	time (h)	yield (%)[b] 4{1,1,10}	5{1,1}
1	NaOH	0.2	H_2O	35	12	0	0
2	NaOH	0.2	H_2O	100	3	15	10
3	NaOH	1.0	H_2O	100	3	20	40
4	NaOH	1.0	H_2O	80	3.5	25	55
5	NaOH	1.0	H_2O	70	4	15	65
6	-	-	H_2O	100	24	-	-
7	K_2CO_3	1.0	H_2O	100	4	30	40
8	guanidine	0.2	H_2O	100	4	84	0
9	DBU	0.2	H_2O	100	4	86	0
10	Et_3N	0.2	H_2O	100	4	94	0
11	Et_3N	0.2	H_2O	60	8	49	0
12	pyridine	0.2	H_2O	100	4	91	0
13	Et_3N	0.2	DMSO	120-130	8	74	0
14	Et_3N	0.2	DMF	120-130	8	79	0
15	Et_3N	0.2	Toluene	100-110	8	81	0
16	Et_3N	0.2	ACN	70-80	10	52	0
17	Et_3N	0.2	EtOH	70-80	10	51	0
18	Et_3N	0.2	MeOH	50-60	12	41	0

19	Et_3N	0.2	DCM	30-35	12	10	0

[a]Reaction conditions: 4-chloro acetophenone (2 mmol), malononitrile (2 mmol), 4-tert-butyl-phenol (1 mmol), different solvents (2 mL), different catalysts, different temperatures, different times. [b]Isolated yields.

To prevent the intrusion of the 7-hydroxycompound (**5***{1,1}*) and to acquire the desired [1,6]-naphthyridine (**4***{1,1,10}*) under environmentally benevolent conditions, we tested a panel of organic bases. Guanidine and DBU provided only the desired [1,6]-naphthyridine (***4****{1,1,10}*), but yields were found to be slightly better with pyridine and Et_3N at 100 °C (Table 1, entries 8-12). Here, the weaker bases may induce less polymerization of the ketone as a competitive side reaction, leading to higher yields. Triethylamine was chosen as the catalyst for further tests of solvent effects. Interestingly, isolated yields were found to be comparatively low in common high boiling organic solvents such as DMSO, DMF, and toluene (entries 13-15), due mainly to difficulties in isolation. Also prolonged times were required for reaction completion in these mixtures. Lower-boiling solvents (acetonitrile, EtOH, MeOH, DCM) did not allow the required high temperatures with standard glassware, and afforded poor yields of **4***{1,1,10}* (Table 1, entries 16-19). Thus, the best yield, cleanest reaction, and most facile workup were achieved in water as a solvent employing 0.2 mmol Et_3N (Table 1, entries 10).

Substrate scope

Various methyl ketones, phenols, and malononitrile were tested with the optimized reaction conditions, giving 30 variants using this protocol (Figure 2, Table 2). Both aliphatic alcohols and phenols afforded excellent yields, the latter tolerating both electron-withdrawing and electron-donating substituents on the aromatic ring. Acid-sensitive (containing hydroxy groups) and sterically bulky alcohol phenols (β-naphthol, α-naphthol) also reacted very efficiently with no

side products. Therefore, the present protocol has general applicability, accommodating a variety of substitution patterns.

Good diversity in the ketone component was also tolerated. Especially noteworthy was the successful use of electron-rich ketones [4'-methoxyacetophenone and 3',4'-dimethoxyacetophenone], considering the difficulty usually associated with Knoevenagel condensation reactions of these substrates (Table 2, **4***{4,1,2}*-**4***{5,1,10}*). Sterically bulky 2-acetylfluorene was readily converted into the desired product (**4***{6,1,10}*), and aliphatic ketones were also examined (**4***{7,1,1}*). To further expand the scope of the reaction the use of heteroaryl methyl ketones was investigated (**4{***2,1,1}*-**4***{2,1,10}*). Steric considerations seem to have limited the process in one case (**4***{7,1,1}*), in which the methyl ketone, but no other ketone, gave good yield, perhaps because of crowding in intermediate **10** (Scheme 3). A representative structure was confirmed by X-ray crystallographic analysis of compound (**4***{1,1,11}*) (CCDC **926217**) (Table 2).

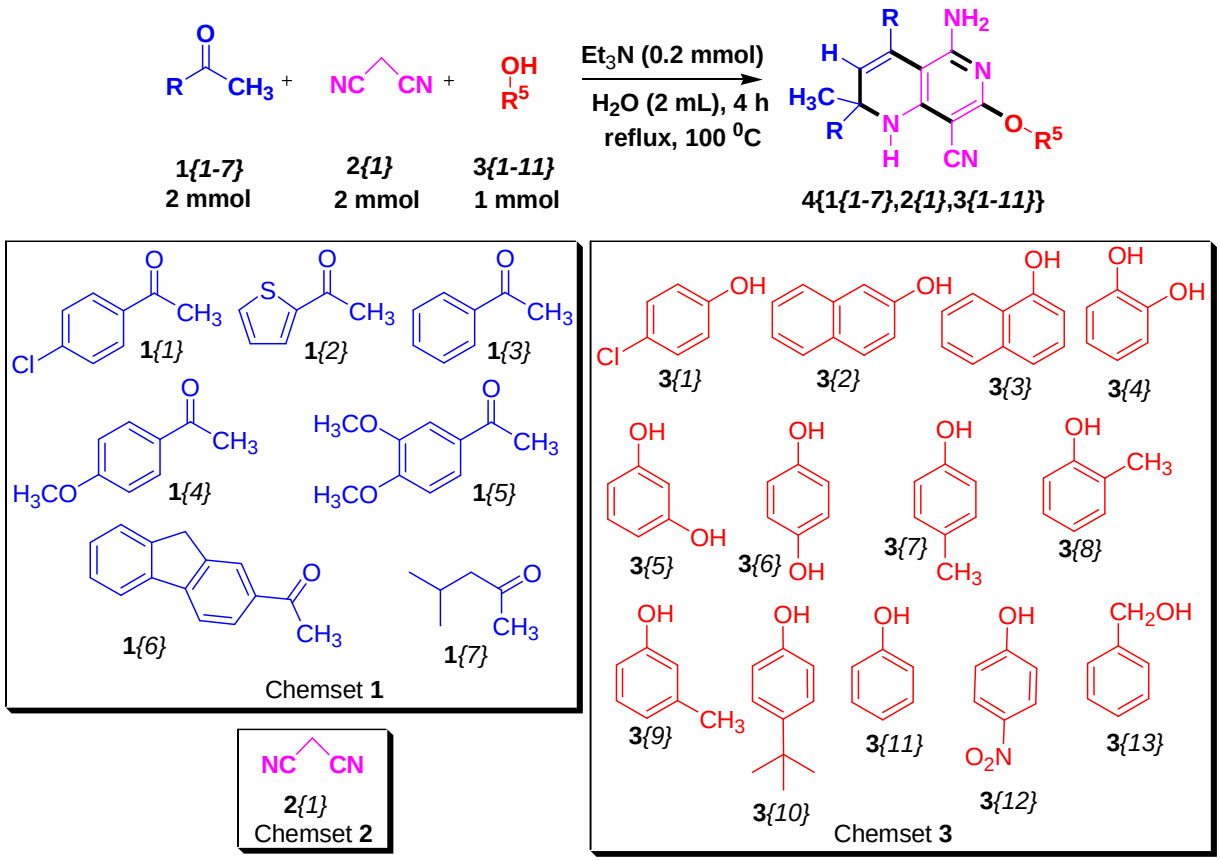
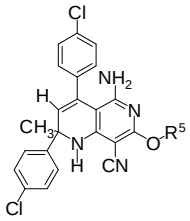
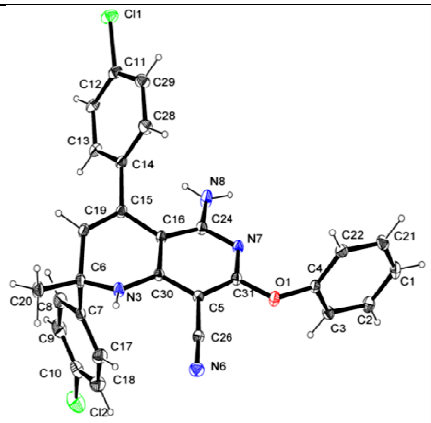


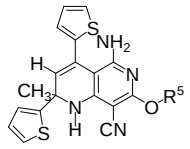
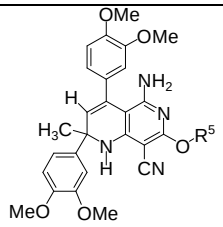
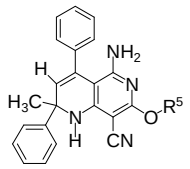
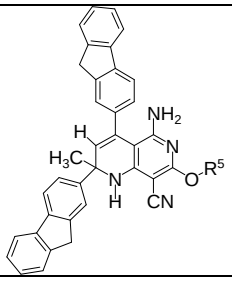
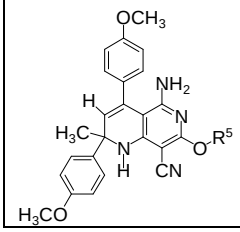
Figure 2. Components used for the synthesis of [1,6]-naphthyridines.

Table 2. Synthesized [1,6]-naphthyridines and ORTEP representation of **4***{1,1,11}* **(**CCDC 926217).

Structure	R^5OH	Product	Yield (%)
	**3***{1}*	**4***{1,1,1}*	94
	3*{2}*	**4***{1,1,2}*	89
	3*{3}*	**4***{1,1,3}*	91
	3*{4}*	**4***{1,1,4}*	91
	3*{5}*	**4***{1,1,5}*	89
	3*{6}*	**4***{1,1,6}*	90
	3*{7}*	**4***{1,1,7}*	93
	3*{8}*	**4***{1,1,8}*	92
	3*{9}*	**4***{1,1,9}*	92
	3*{10}*	**4***{1,1,10}*	94
	3*{11}*	**4***{1,1,11}*	93
	3*{12}*	**4***{1,1,12}*	92
	3*{13}*	**4***{1,1,13}*	88

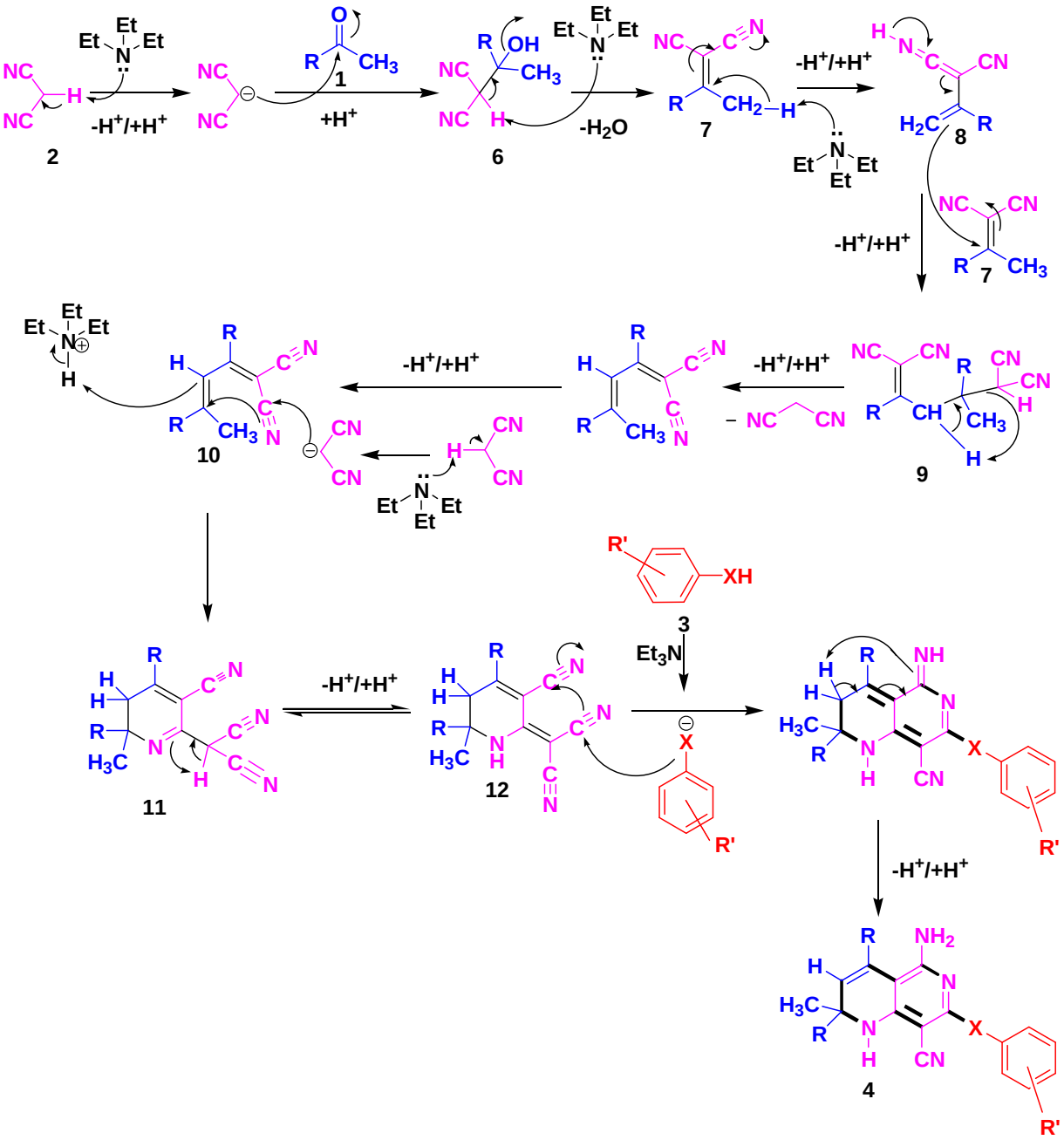


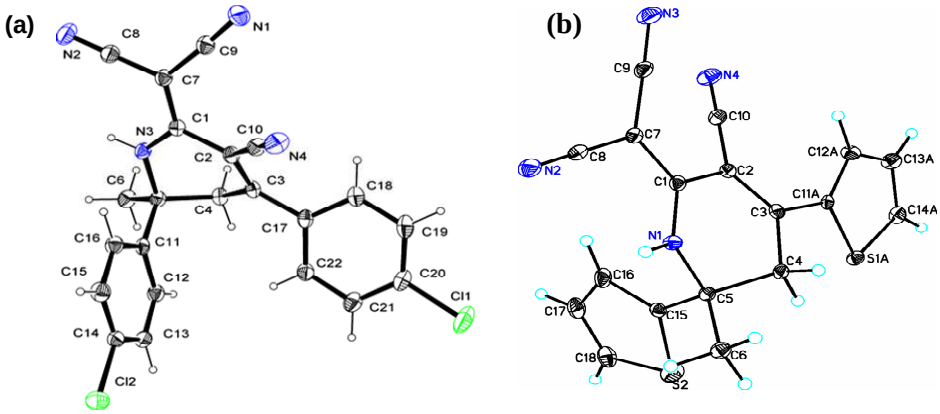
4*{1,1,11}* **(**CCDC **926217)**

Structure	R^5OH	Product	Yield (%)
	**3***{1}*	**4***{2,1,1}*	92
	3*{2}*	**4***{2,1,2}*	91
	3*{3}*	**4***{2,1,3}*	91
	3*{4}*	**4***{2,1,4}*	92
	3*{7}*	**4***{2,1,7}*	93
	3*{8}*	**4***{2,1,8}*	93
	3*{9}*	**4***{2,1,9}*	90
	3*{10}*	**4***{2,1,10}*	93
	**3***{1}*	**4***{5,1,1}*	92
	3*{10}*	**4***{5,1,10}*	93
	**3***{1}*	**4***{3,1,1}*	93
	3*{10}*	**4***{3,1,10}*	94
	**3***{10}*	**4***{6,1,10}*	93
	**3***{2}*	**4***{4,1,2}*	91
	3*{10}*	**4***{4,1,10}*	94
	3*{11}*	**4***{4,1,11}*	93

A plausible mechanism for the multicomponent condensation process is shown in Scheme 3. Initial Knoevenagel condensation of the carbonyl compound with malononitrile in the presence of a base[15,16] was supported by NMR observation of the resulting product [(**7**), (R = 4'-Cl-C_6H_4-)] isolated after 30 min. This intermediate (**7**) is proposed to undergo Michael-type reaction with another molecule of **7**, with subsequent malonitrile elimination to form intermediate **10**. Another attack of malononitrile triggers ring closure to yield intermediate **11**, which tautomerises to give **12**. Though we could not isolate the intermediate **10**, structures **12***{1,1}* and **12***{2,1}* were characterized by X-ray analysis (Figure 3a,b). Finally the second ring is produced by attack of phenols on the electrophilic nitrile group in intermediate **12**, driven by aromatization in the target compound.

Scheme 3. A plausible mechanism for the formation of [1,6]-naphthyridines.





12*{1,1}* **12***{2,1}*

Figure 3. (a) ORTEP representation of intermediate **12***{1,1}* **(**CCDC **926218). (b) 12***{2,1}* **(**CCDC **926219)**.

Thus the present reaction comprises a relay processes of the following domino sequences: (1) two-component Knoevenagel reaction, (2) two-component Michael-type reaction followed by elimination, (3) two-component ring closure, and (4) two-component cyclization aromatization process (Scheme 3). This pathway was examined by DFT calculations,[17] in which the proposed transition structures were identified (see Supporting Information, Fig S1-S6). All the optimized geometries of reactants, products and corresponding TS are shown in energy profile diagrams in Supporting Information (Fig S7), which identify reasonable "downhill" energetics for the intermediates.

Rationale of rate acceleration in water

Even though Knoevenagel condensations accomplish a net dehydration event, the reaction described here is favored in an aqueous medium. Both a standard hydrophobic effect (i.e., the propensity of hydrophobic molecules to associate in order to minimize their contact surface with water, leading to effective concentration of the reactants[18]) and an "on-water" effect (in which

OH groups at oil-water phase boundary can then play an important role in catalyzing reactions *via* the formation of hydrogen bonds) can be proposed.

Table 1 shows much faster and higher yielding reactions using the same catalyst and reactants in water (entry 10) than in organic other solvents (entries 13-19). Since the aqueous reaction mixture remains heterogeneous throughout the course of reaction, this qualifies as an *on water* synthesis.

The replacement of phenols with thiols gave the anticipated thiol-substituted [1,6] naphthyridines (Figure 4, Table 3). Both aromatic and aliphatic thiols afforded excellent yields, including those with electron-withdrawing as well as electron-donating groups. Sterically bulky naphthalene-2-thiol also reacted very efficiently (**19***{1,1,6}*, **19***{2,1,6}*and **19***{3,1,6}*). We have confirmed the structure of compound (**19***{4,1,1}*) unambiguously by X-ray crystallographic analysis (CCDC **956062**) (Table 3).

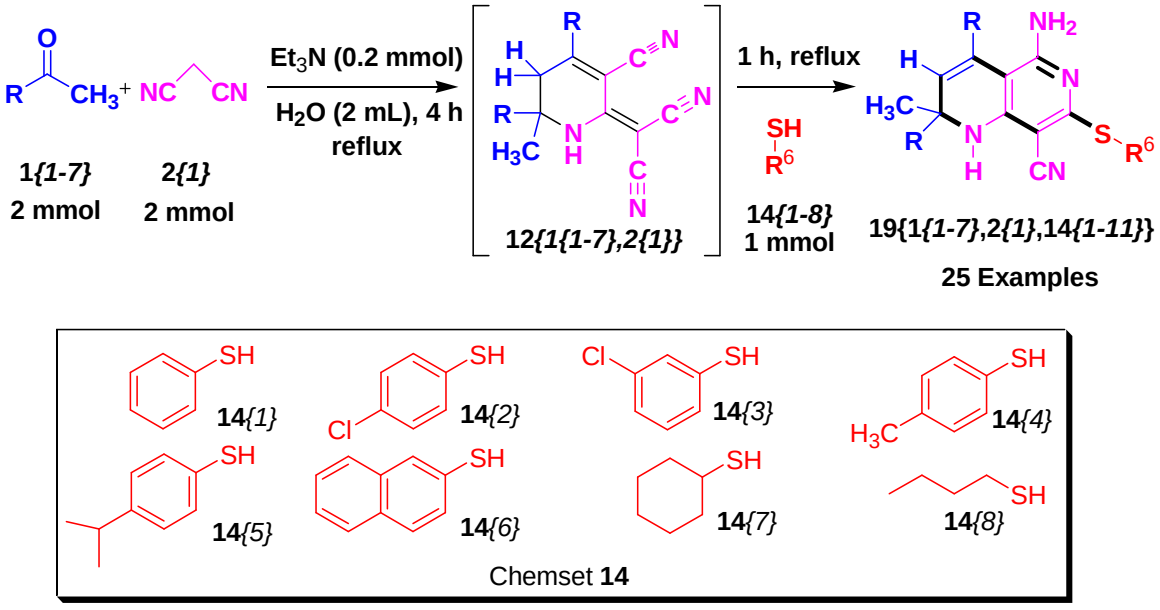
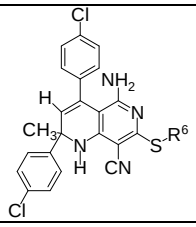
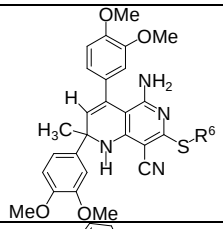
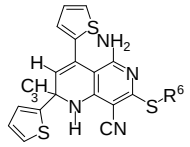
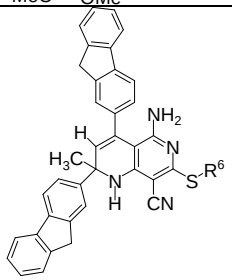
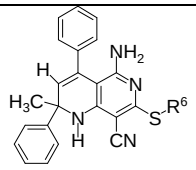
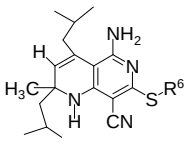
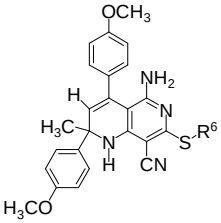
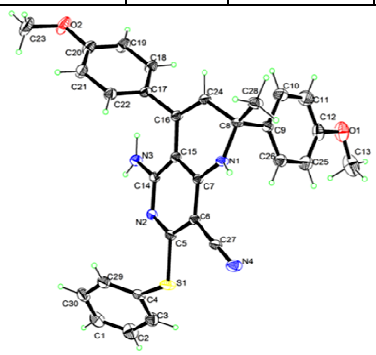


Figure 4. Components used for the synthesis of thiol-substituted naphthyridines.

Table 3. Naphthyridines synthesized with thiol nucleophiles; ORTEP representation of **19***{4,1,1}* **(**CCDC 956062**)**.

Structure	R^6SH	Product	Yield (%)	Structure	R^6SH	Product	Yield (%)
	**14***{2}* **14***{3}* **14***{5}* **14***{6}* **14***{7}*	**19***{1,1,2}* **19***{1,1,3}* **19***{1,1,5}* **19***{1,1,6}* **19***{1,1,7}*	93 93 95 90 91		**14***{1}* **14***{2}* **14***{3}*	**19***{5,1,1}* **19***{5,1,2}* **19***{5,1,3}*	90 91 89
	**14***{1}* **14***{2}* **14***{3}* **14***{4}* **14***{5}* **14***{6}* **14***{7}*	**19***{2,1,1}* **19***{2,1,2}* **19***{2,1,3}* **19***{2,1,4}* **19***{2,1,5}* **19***{2,1,6}* **19***{2,1,7}*	93 93 92 93 91 91 90		**14***{1}*	**19***{6,1,1}*	91
	**14***{3}* **14***{5}* **14***{6}* **14***{7}* **14***{8}*	**19***{3,1,3}* **19***{3,1,5}* **19***{3,1,6}* **19***{3,1,7}* **19***{3,1,8}*	93 92 90 92 90		**14***{1}*	**19***{7,1,1}*	87
	**14***{1}* **14***{2}* **14***{4}*	**19***{4,1,1}* **19***{4,1,2}* **19***{4,1,4}*	91 90 91	 **19***{4,1,1}* **(**CCDC **956062)**			

Hydroxide was similarly used as a nucleophile to prepare four 7-hydroxy-[1,6]-naphthyridines (**5**). The optimized reaction condition and structures, obtained in moderate yields, are shown in Figure 5.

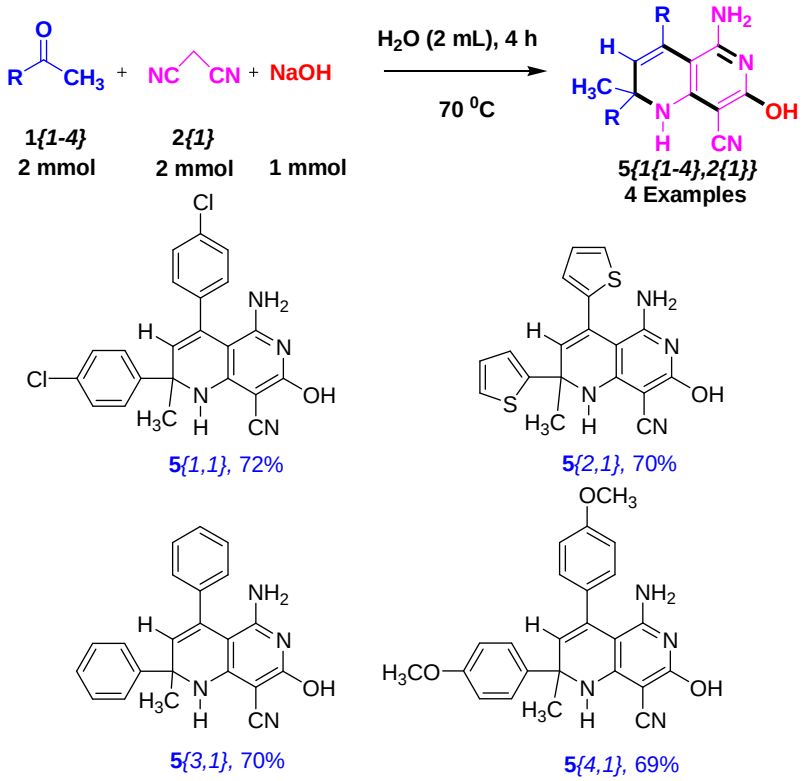


Figure 5. Synthesis of hydroxy-inserted [1,6]-naphthyridines.

CONCLUSION

We highlight here the synergistic effects of the combined use of multi-component reactions between methyl ketones, malononitrile, and phenols or thiols in water as an environmentally benevolent solvent for the preparation of functionally rich heterocycles. This is an excellent example of a true on water synthesis since the rate enhancement in water in comparison to organic solvents is vividly discernible and thus it adds a new entry to the list of *on water* transformations. By controlling the addition time of thiol nucleophiles, we were able selective prepare either 3*H*-pyrroles or[1,6]-naphthyridines. This protocol not only represents a promising green route to an interesting new class of compounds, involving the creation of three C-C, two C-N, and one C-S or C-O bond in a single operation. Two nitrogen-containing rings are

made without starting from any nitrogen-containing heterocyclic moiety, and the presence of a cyano group in the naphthyridines makes them useful synthetic intermediates for the preparation of other nitrogen-containing heterocycles.[19]

ASSOCIATED CONTENT

Supporting Information.

Supporting Information Detailed computational studies, Molecular coordinate of optimized geometries, IRC plots of the Transition states, experimental procedure, spectral data, copies of ^{1}H and ^{13}C NMR spectra of all the new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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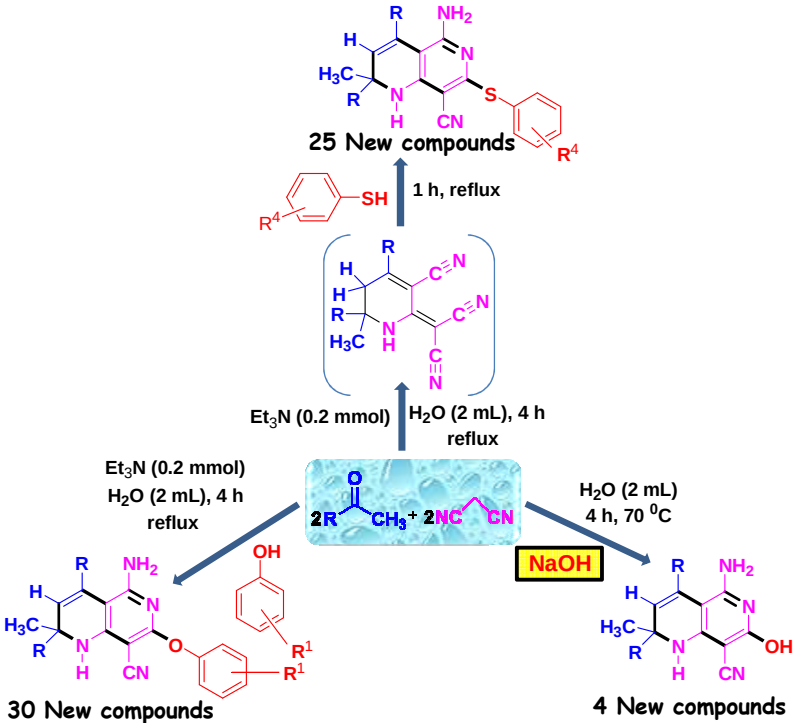
Pseudo Five-component Domino Strategy for the Combinatorial Library Synthesis of [1,6] Naphthyridines - An *On Water* Approach

GRAPHICAL ABSTRACT



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