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An Expeditious and Efficient Synthesis of Highly Functionalized [1,6]-Naphthyridines under Catalyst-Free Conditions in Aqueous Medium

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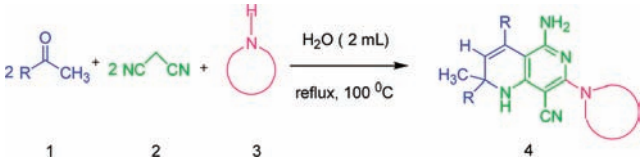
ABSTRACT



This is the first report of an innovative, one-pot, catalyst-free, pseudo-five-component synthesis of 1,2-dihydro[1,6]naphthyridines from methyl ketones, amines, and malononitrile in ecofriendly solvent water. The protocol avoids the use of expensive catalysts, toxic organic solvents and anhydrous condition. The approach to naphthyridines presented herein offers for the first time an unprecedented coupling which leads to the construction of both the nitrogen containing rings during the synthesis without starting from any nitrogen-containing heterocycle moiety.

Functionalized [1,6]-naphthyridines and their benzo/heterofused analogues are present in numerous products of marine origins[1] and possess a wide range of biological activities such as antiproliferative activity[2] and act as HIV-1 integrase inhibitors,[3] allosteric inhibitors of Akt1 and Akt2,[4] and selective antagonists of 5-HT_4 receptors.[5] The remarkable applications of these compounds prompted us to synthesize them. A survey of the literature shows that the majority of the strategies involve either multistep sequences,[6] or expensive catalysts,[6c−f,7] inert atmosphere,[6b,c,e,7a] anhydrous conditions, lengthy reaction times,[6c,d] and laborious workup.[6b−d]

Therefore, we wish to disclose the one-pot, catalyst-free, pseudo-five-component synthesis of 1,2-dihydro[1,6] naphthyridines from methyl ketones, amines, and malononitrile in ecofriendly solvent water. The synthetic route is convergent and allows easy placement of a variety of

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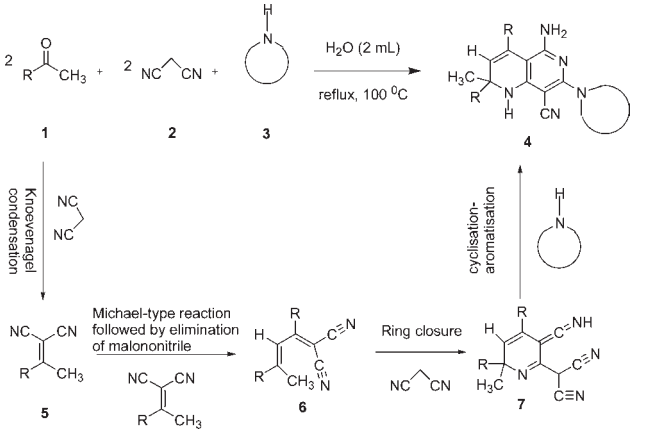
substituents around the periphery of the heterocyclic ring system. Our approach could comprise the relay processes of the following domino sequences (Scheme 1): (1) two-component Knoevenagel reaction, (2) two-component Michael-type reaction followed by elimination, (3) two-component ring closure, and (4) two-component cyclization–aromatization process.

Scheme 1

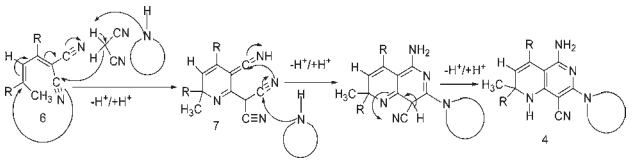


It is proposed that the aromatic ketones undergo a Knoevenagel condensation reaction first with malononitrile which is a very characteristic reaction of carbonyl compounds in the presence of a base.[8] This is evident from NMR spectrum of the major product [(**5**), (R = 4′−Cl-C_6H_4-)] isolated after 30 min. This intermediate (**5**) undergoes Michael-type reaction with another molecule of **5**, and subsequent elimination of the malononitrile leads to intermediate **6**. Again the attack of malononitrile on intermediate **6** triggers the ring closure to yield intermediate (**7**). The structure of **7** is confirmed from NMR spectrum of the major product (R = 4′−Cl-C_6H_4-) isolated by quenching the reaction after 2 h. Finally the second ring is produced by attack of amino group on −CN functionality in intermediate **7**. The driving force may be the aromatization in the target compound.

The detailed mechanism of the formation of **4** (final compound) from **6** is shown in Scheme 2.

Here, despite Knoevenagel condensation being a net dehydration of the water molecule, the reaction is favored in aqueous medium. A plausible explanation is that water

Scheme 2



brings the active methylene compound to the lone pair of electrons of amine nitrogen of the catalyst through hydrogen-bonding.[9] Thus, realizing environmental concerns,[10] as well as vast utility and scope of reactions[10a,11] carried out in water, we established water to be the preferred solvent.

To find the optimized reaction conditions, we initiated a catalyst screen employing 4′-chloro acetophenone (**1b**) (2 mmol), malononitrile (**2**) (2 mmol), and morpholine (**3c**) (1 mmol) in the presence of various base catalysts under refluxing conditions, and the results are summarized in Table 1. Screening of the reaction conditions established that the nature of the catalyst had significant effect on the yield of naphthyridine (**4bc**). The yield decreased substantially with stronger base catalysts, since the carbonyl compounds undergo extensive polymerization reaction (entries 1 and 2, Table 1) in the presence of a strong base and at high temperature conditions. Interestingly, in absence of any base catalyst, this pseudo-five-component coupling cyclization reaction proceeded smoothly to afford the desired 5-amino-2,4-bis(4-chlorophenyl)-2-methyl-7-morpholin-4-yl-1,2-dihydro[1,6]naphthyridine-8-carbonitrile (**4bc**) in excellent yield after 3 h of heating at 100 °C in water as solvent (entry 5, Table 1). Therefore, the amines itself are acting as a bronsted base catalyst in the formation of intermediate **5**–**7** and also as a nucleophile in the last step. This is why the weaker bases than morpholine have no effect on reaction yield (entries 10 and 11, Table 1). Hence, we vary the amount of morpholine to monitor any effect on the yield of the reaction. With a higher amount of morpholine no increase in the yield of **4bc** is observed (entries 5–8, Table 1). However, diminishing the amount of morpholine resulted in incomplete conversion (entry 9, Table 1).

With these optimized conditions in hand, this multicomponent reaction can be readily diversified through a combination of a range of methyl ketones, amines, and malononitrile. Among the amines, cyclic secondary amines afforded excellent yields (Scheme 3). Remarkably, low nucleophilic diallylamine and low boiling dimethylamine also gave products **4bf**, **4ff**, and **4ae**, **4be**, **4fe** in excellent yields (88% for **4bf**, 90% for **4ff**, and 90% for all **4ae**, **4be**, and **4fe**). Similarly, aliphatic primary amines were also successfully employed to give naphthyridines in excellent yields (Scheme 3, **4bg**). However, the yield was low with benzylamine (Scheme 3, entry **4fh**). It should be noted that

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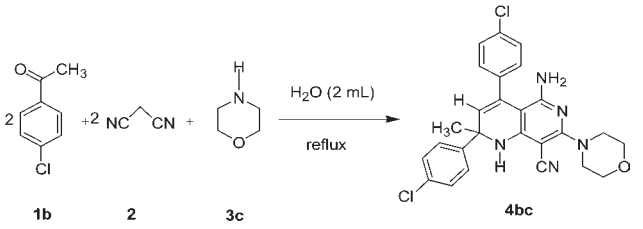
Table 1. Optimization of Reaction Conditions for the Multicomponent Coupling Reactions[a]



entry	amt of morpholine (mmol)	base catalyst (0.2 mmol)	temp/time (°C) (h)	yield of **4bc**[b] (%)
1	1.0	NaOH	100, 2	41
2	1.0	K_2CO_3	100, 2.5	50
3	1.0	guanidine	100, 3	72
4	1.0	DBU	100, 3	85
5	1.0		100, 3	93
6	1.1		100, 3	93
7	1.2		100, 3	93
8	1.4		100, 3	93
9	0.7		100, 3	66
10	1.0	*N*,*N*-dimethylaniline	100, 12	91
11	1.0	urea	100, 12	90

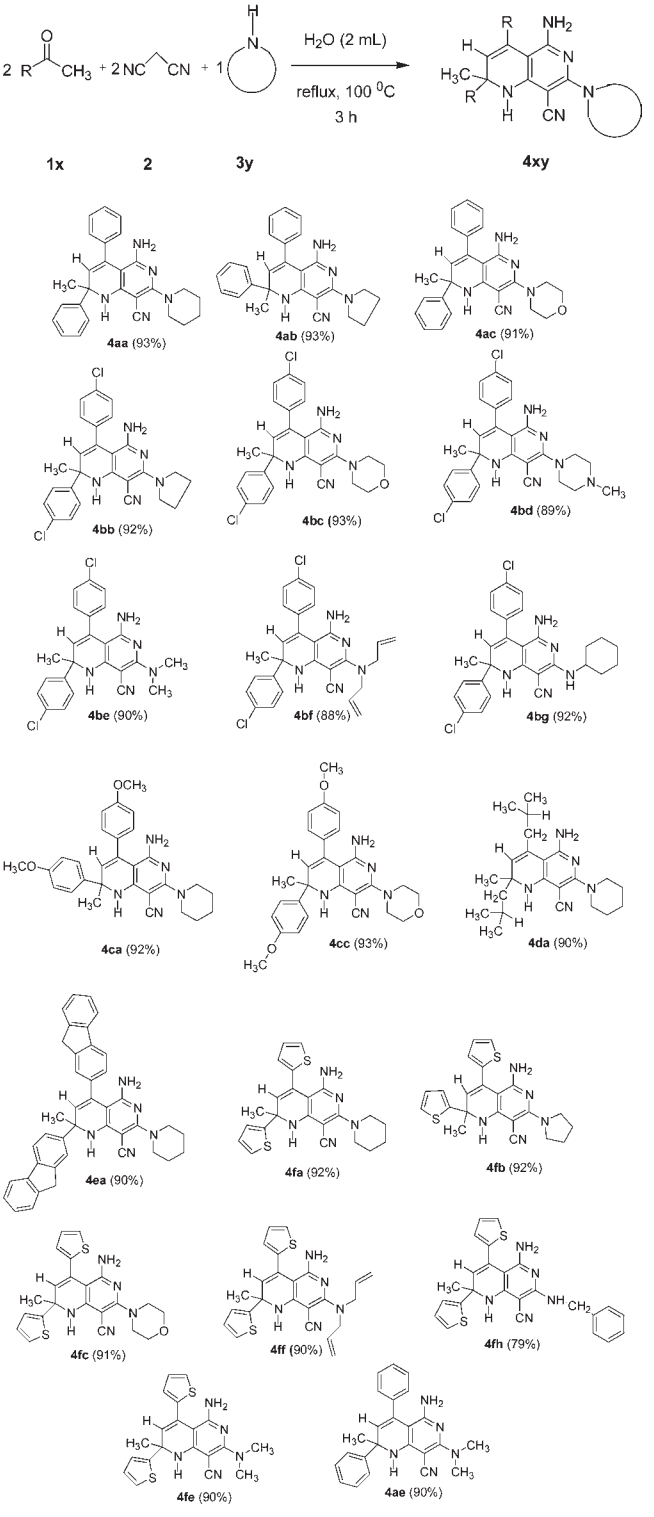
[a] All reactions were carried out in H_2O (2 mL) at 100 °C using the substrates according to the indicated ratio in mmol scale. [b] Isolated yields.

while the current primary amines are quite effective for naphthyridine synthesis, the substrates of primary aromatic amines such as $PhNH_2$ could not be used for this reaction.

Despite the difficulty of a Knoevenagel condensation reaction with electron-rich ketones, the reaction occcured successfully with 4′-methoxy acetophenone (Scheme 3, **4ca** and **4cc**). To check the generality of the reaction, ketones with electron-withdrawing substituents on aromatic ring were also employed (Scheme 3, entries **4bb**−**bg**). Noteworthy is that, sterically bulky 2-acetylfluorene was readily converted into the desired product (**4ea**) (Scheme 3). In addition, the use of aliphatic ketones was also examined (Scheme 3, **4da**). It is important to mention that the selectivity of this reaction toward CH_3CO- rather than RCH_2CO- [R = $CH(CH_3)_2$] observed in the case of product **4da** (Scheme 3), probably resulted from the instability of the carbanion **5d** because of the electron-donating inductive effect of the alkyl group (Figure 1a). When $RCOCH_2R'$ (R′ = Ph, CH_3) is utilized instead of $RCOCH_3$ instability of the intermediate (**8**) arising out of steric crowing among the substituents (Figure 1b) may be the plausible reason of the non formation of this intermediate.

To further expand the scope of the reaction the use of heteroaryl methyl ketones was investigated (Scheme 3). 2-Acetylthiophene was easily transformed into the desired products in excellent yields (Scheme 3, **4fa**−**fh**).

Scheme 3. Catalyst-Free Pseudo-Five-Component Coupling Reactions to [1,6]-Naphthyridines



The final structure was confirmed by X-ray crystallographic analysis of compound 5-amino-7-dimethylamino-2-methyl-2,4-diphenyl-1,2-dihydro[1,6]naphthyridine-8-carbonitrile (**4ae**) (**CCDC 823011**) (Figure 2) (Supporting Information).

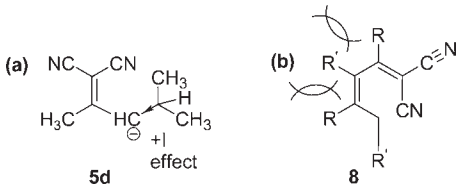


Figure 1. (a) Instability of the carbanion in **5d**. (b) Steric repulsion among the substituents in **8**.

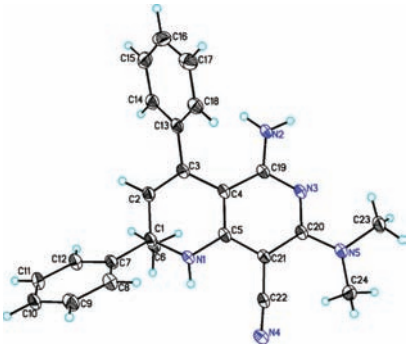


Figure 2. ORTEP representation of **4ae**.

Previous synthesis of these heterocycles mostly relied upon annulation of a pyridine ring[6a,b,d,e] onto a 4-piperidone or equivalent[12] or reductions or reductive additions to the fully aromatized 1,6-naphthyridine system.[13,14] The approach to naphthyridines presented herein offers for the first time an unprecedented coupling of methyl ketones, amines, and malononitrile which leads to the construction of the nitrogen-containing ring during the synthesis without starting from any nitrogen-containing heterocycle moiety. Thus, from a practical point of view, the newly developed protocol is significant proof of the fact that nitrile is one of the most versatile functional groups as it can be readily transformed into various other functional groups or reactive intermediates. Significantly, the reaction occurred in a catalyst-free fashion with high selectivity and atom economy. To our knowledge, the use of four different catalyst-free reactions, namely Knoevenagel reaction, Michael-type reaction, ring closure, and subsequent cyclization–aromatization, has not been previously reported.

In conclusion, we have recently disclosed a novel and convenient one-pot synthesis of multisubstituted [1,6]naphthyridine analogues via multicomponent reactions. This catalyst-free domino reaction proceeded smoothly in good to excellent yields and offered several other advantages including short reaction time, simple experimental workup procedures, and no toxic byproducts. This approach to naphthyridine systems presented herein avoids the use of catalyst, toxic organic solvents, and anhydrous conditions. This protocol represents a promising green route to the class of compounds. In addition, the route takes advantage of the abundance of amines available commercially to make substituted naphthyridines. All of the cycloadducts were quite stable and easy to handle under standard conditions.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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