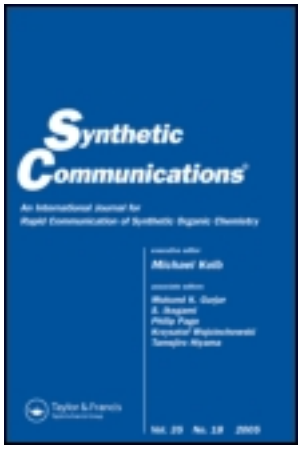


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# Simple, Catalyst-Free, One-Pot Procedure for the Synthesis of 2-Amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one Derivatives

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# SIMPLE, CATALYST-FREE, ONE-POT PROCEDURE FOR THE SYNTHESIS OF 2-AMINO-3-CYANO-1,4,5,6-TETRAHYDROPYRANO[3,2-c]QUINOLIN-5-ONE DERIVATIVES

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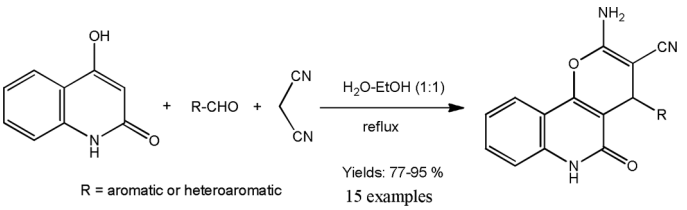
## GRAPHICAL ABSTRACT




**Abstract** *A one-pot, three-component reaction of 4-hydroxyquinolin-2(1*H*)-one, malononitrile, and various aldehydes for the synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives is reported. The reaction is performed without any catalysts in a mixed solvent of water and ethanol to give products in good yields. The present method provided a clean, simple, and economical alternative for the synthesis of potential biologically active pyranoquinoline derivatives.*

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**Keywords** Catalyst-free; multicomponent reaction; pyranoquinoline derivative; synthesis

## INTRODUCTION

As safety, health, and environmental issues are key drivers for process improvements in the chemical industry,[1] the development of environmentally benign reactions or pathways is a major focus. In recent years, the multicomponent reaction (MCR) has attracted remarkable attention from chemists for the preparation of chemicals following environmentally friendly and less expensive strategies.[2] MCRs are convergent reactions, in which three or more starting materials react to form a product in one pot without isolation of any intermediate, where basically all or most of the atoms contribute to the newly formed product. MCRs have merits over conventional

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linear-type syntheses in several aspects including high atom economy, simple procedures, possible structural variations, resource efficiencies (time and cost), and rapid access to complex molecules.[3]

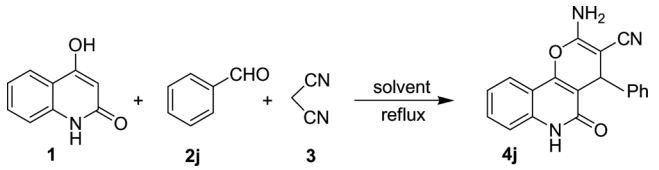
Pyranoquinoline derivatives are of significant importance because of their presence in many natural products possessing significant biological activities.[4–6] Pyranoquinoline derivatives possess antiplatelet aggregation, antiallergic activity, insecticidal, antifungal, antibacterial, analgesic, antimicrobial, antipyretic, cytotoxic, and antihistaminic properties and are used for the treatment of proliferate diseases such as cancer.[4–8] Moreover, pyranoquinolines are starting materials for the synthesis of quinolylhydantions.[9] There have been several methods of synthesizing pyranoquinoline derivatives, including the three-component reaction of 4-hydroxyquinolin-2(1*H*)-one, malononitrile, and various aldehydes for the synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives catalyzed by $Et_3N$,[10] KF-$Al_2O_3$,[11] TEBA (benzyltriethylammonium chloride),[12] piperidine,[13] and ammonium acetate.[14] However, these methods have limitations such as the use of toxic reagents, large amounts of catalysts, and tedious workup procedures. From the viewpoint of green chemistry, there is still an urgent need to develop new and environmentally benign strategies for the preparation of potential biologically active pyranoquinoline derivatives. In the course of development of new catalyst systems for the synthesis of these compounds, we unexpectedly found that 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives could be prepared without catalyst in a mixed solvent of ethanol and water. This catalyst-free approach offers a less expensive, much simpler, and more environmentally friendly way to pyranoquinoline derivatives. Herein, we report this catalyst-free, one-pot, three-component condensation reaction.



## RESULTS AND DISCUSSION

In our initial study, the one-pot, three-component condensation reaction of 4-hydroxyquinolin-2(1*H*)-one (**1**), benzaldehyde (**2j**), and malononitrile (**3**) was used as a model reaction. Different solvents were tested for the reaction, and the results are listed in Table 1. The model reaction in water at reflux temperature for 5 h gave the product in the yield of 78% (Table 1, entry 1). However, reactant dispersion was very bad and easy caked in water. Furthermore, the intermediate arylmethylidenemalononitrile was easy to sublimate. It was observed that a large amount of colorless needle-shaped crystals appeared in the condenser when refluxing in water. To overcome these disadvantages, we used ethanol as a solvent. Although the problems of dispersion and sublimation did not exist in ethanol, the reaction took a long reaction time (21 h) to get the product in a yield of 83% (Table 1, entry 2). We then tested the mixed solvents of $H_2O$–EtOH (Table 1, entries 3–5). The reactant dispersion was not much better in $H_2O$–EtOH (3:1), and a yield of 84% was obtained after 4 h (Table 1, entry 3). However, almost any obstacle could be overcome in $H_2O$–EtOH (1:1), and the reaction was rapid and yield was slightly better (Table 1, entry 4). Further increasing the ratio of ethanol in the mixed solvent to $H_2O$–EtOH (1:3) led to a decrease of yield (Table 1, entry 5). Therefore, $H_2O$–EtOH (1:1) was used as the optimal solvent system for the catalyst-free, one-pot synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives.

**Table 1.** Effect of solvents on the catalyst-free, three-component reaction[a]




| Entry | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | $H_2O$ | 5 | 78 |
| 2 | EtOH | 21 | 83 |
| 3 | $H_2O$-EtOH (3:1) | 4 | 84 |
| 4 | $H_2O$-EtOH (1:1) | 2.5 | 85 |
| 5 | $H_2O$-EtOH (1:3) | 2.5 | 78 |

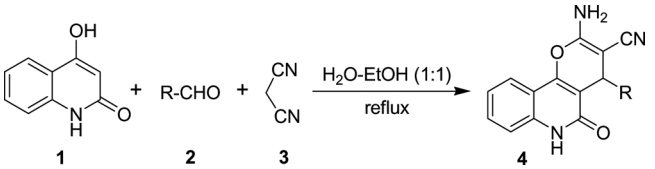
[a]Reaction conditions: 4-hydroxyquinolin-2(1*H*)-one **1** (1.0 mmol), benzaldehyde **2j** (1.2 mmol), and malononitrile **3** (1.2 mmol) in solvent (2 ml) at the reflux temperature.
[b]Isolated yields.



Encouraged by these results, we tried to extend the scope of the present protocol for condensation of different aldehydes, 4-hydroxyquinolin-2(1*H*)-one, and malononitrile to afford 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives in $H_2O$–EtOH (1:1) at reflux temperature. The results are summarized in Table 2. It was very clear that aromatic aldehydes containing electron-withdrawing groups (such as nitro group, cyano group, and halide) or electron-donating groups (such as hydroxyl group, methyl group and alkoxyl group) could react smoothly to give the corresponding products **4** in good to excellent yields (77–95%). No clear electronic effect of the aromatic aldehydes on the reaction was observed. Moreover, 2-substitution on the aromatic aldehydes did not appear to deter the condensation process. The best yield of 95% was obtained with 2,4-dichlorobenzaldehyde (Table 2, entry 6), and 2-chlorobenzaldehyde gave an excellent yield of 93% (Table 2, entry 2), but 3- and 4-chlorobenzaldehyde gave lower yields after longer reaction times (Table 2, entries 3 and 4). This condensation reaction was applicable to the hydroxyl group substituted aromatic aldehydes and good yields were obtained (Table 2, entries 11 and 14). In addition, furfural could react smoothly with 4-hydroxyquinolin-2(1*H*)-one and malononitrile under the optimized reaction conditions to give a good yield (Table 2, entry 15). We also attempted the reaction with aliphatic aldehydes but failed. Finally, the procedure was simple, and products **4** could be obtained merely by filtration from the reaction medium.

Considering the structure of products **4** and based on the previous reports about the catalytic synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano [3,2-c]quinolin-5-one derivatives,[11,14] we think the condensation of 4-hydroxyquinolin-2(1*H*)-one **1**, aldehyde **2**, and malononitrile **3** may occur by a sequential reaction of the Knoevenagel condensation, Michael addition, intramolecular cyclization, and isomerization, as shown in Scheme 1. First, the Knoevenagel condensation of

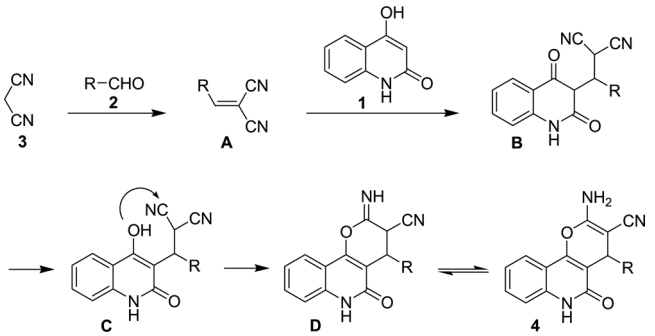
**Table 2.** Catalyst-free, one-pot condensation of 4-hydroxyquinolin-2(1*H*)-one, aldehyde, and malononitrile[a]




| Entry | R | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 4-$FC_6H_4$ **2a** | 6.5 | **4a** | 81 |
| 2 | 2-$ClC_6H_4$ **2b** | 4 | **4b** | 93 |
| 3 | 3-$ClC_6H_4$ **2c** | 5 | **4c** | 77 |
| 4 | 4-$ClC_6H_4$ **2d** | 13 | **4d** | 82 |
| 5 | 4-$BrC_6H_4$ **2e** | 13 | **4e** | 81 |
| 6 | 2,4-$Cl_2C_6H_3$ **2f** | 9 | **4f** | 95 |
| 7 | 3-$NO_2C_6H_4$ **2g** | 4 | **4g** | 84 |
| 8 | 4-$NO_2C_6H_4$ **2h** | 5 | **4h** | 90 |
| 9 | 4-$CNC_6H_4$ **2i** | 4 | **4i** | 80 |
| 10 | $C_6H_5$ **2j** | 2.5 | **4j** | 85 |
| 11 | 4-$OHC_6H_4$ **2k** | 9 | **4k** | 84 |
| 12 | 4-$CH_3C_6H_4$ **2l** | 10 | **4l** | 85 |
| 13 | 4-$OCH_3C_6H_4$ **2m** | 13 | **4m** | 84 |
| 14 | 3-$OCH_3$-4-$OHC_6H_3$ **2n** | 8 | **4n** | 83 |
| 15 | 2-Furyl **2o** | 9 | **4o** | 88 |

[a]Reaction conditions: 4-hydroxyquinolin-2(1*H*)-one **1** (1.0 mmol), aldehyde **2** (1.2 mmol), and malononitrile **3** (1.2 mmol) in $H_2O$–EtOH (1:1) (2 mL) under reflux.
[b]Isolated yields.

aldehyde **2** and malononitrile **3** gives intermediate **A**. Second, the Michael addition of intermediate **A** and 4-hydroxyquinolin-2(1*H*)-one **1** results in the formation of **B**. Subsequently, the tandem intramolecular cyclization of **C** and isomerization of **D** afford the final product **4**.




**Scheme 1.** Possible sequential reaction for the catalyst-free, one-pot synthesis of **4**.

## CONCLUSION

In summary, we describe here a new and facile catalyst-free method for the synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives. The one-pot, three-component condensation of various aldehydes, 4-hydroxyquinolin-2(1*H*)-one, and malononitrile could be performed without any catalysts in a mixed solvent of water–ethanol (1:1) at reflux temperature. The salient advantages of the methodology are clean reaction conditions, no workup procedure, easy isolation, and good yields of the products. Undoubtedly, by removing the catalyst from the reaction system, the present method provided a more environmentally benign, much simpler, and more economical alternative for the synthesis of potential biologically active compounds 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives.



### Typical Procedure for the Synthesis of 2-Amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one Derivatives 4 (4j as an Example)

A 10-mL, round-bottom flask was charged with 4-hydroxyquinolin-2-one **1** (1.0 mmol), phenyl aldehyde **2j** (1.2 mmol), malononitrile **3** (1.2 mmol), and a mixed solvent of $H_2O$–EtOH (1:1) (2 mL). The mixture was stirred at reflux temperature for 2.5 h (Table 2, entry 10). After completion (by thin-layer chromatography, TLC), $H_2O$–EtOH (1:1) (1.5 mL) was added, and the mixture was stirred for 5 min. Then the reaction mixture was cooled to rt, and the solid was collected by filtration. The crude product was purified by recrystallization from methanol to give the pure product **4j** (269 mg, 85% yield).

### 2-Amino-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4j)[14]

$^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.75 (s, 1H), 7.90 (d, 1H, $J = 7.9$ Hz), 7.56 (t, 1H, $J = 7.5$ Hz), 7.18–7.34 (m, 9H), 4.48 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 161.03, 159.37, 151.74, 144.63, 137.95, 131.72, 128.83, 127.71, 127.24, 122.63, 122.28, 120.29, 115.75, 112.35, 109.83, 58.27, 36.99; IR ($cm^{-1}$): 3464, 3336, 3182, 2191, 1676, 1379, 1117, 1022, 847, 760, 586; MS (ESI): $m/z = 315.0$ ($M^+$), 311.8, 297.7, 286.8, 273.7, 247.7.

Please see the Supplemental Material, available online, for complete experimental details.

## ACKNOWLEDGMENT

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