# Silica Gel-Catalyzed One-Pot Syntheses in Water and Fluorescence Properties Studies of 5-Amino-2-aryl-3*H*-chromeno[4,3,2-*de*]-[1,6]naphthyridine-4-carbonitriles and 5-Amino-2-aryl-3*H*-quinolino-[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles

Hui Wu,*,† Wei Lin,† Yu Wan,† Hai-qiang Xin,† Da-qing Shi,‡ Yan-hui Shi,† Rui Yuan,† Rong-cheng Bo,† and Wei Yin†

*School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, China, and College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China*

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The silica gel-catalyzed synthesis of 5-amino-2-aryl-3*H*-chromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles and 5-amino-2-aryl-3*H*-quinolino[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles were simply achieved upon the one-pot cascade reaction of malononitrile with substituted 2-hydroxyacetophenone (or 2-aminoacetophenone) and aromatic aldehyde in aqueous media. The mechanistic investigation results based on electrospray ionization mass spectrometry (ESI-MS) indicated that malononitrile displayed a dual role during this transformation. Thirteen bonds were cleaved and 12 new bonds were constructed in the formation of 5-amino-2-aryl-3*H*-chromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles, while only 2 $H_2O$ molecules were removed. The fluorescence properties screening showed five new compounds have high fluorescence quantum yields.

## Introduction

As an important aspect of combinatorial chemistry, multicomponent reactions (MCRs) are among the most proliferative reaction classes.[1] Malononitrile (**1**) is one of the most versatile reagents to be used in MCRs because of the high reactivity of both the methylene and the cyano groups.[2] Traditionally, it is a very useful method to extend carbon chains and to prepare heterocyclic and luminescent active compounds that have medical and industrial utility.[3]

Silica gel has been used as catalyst in organic synthesis because it is easily available, inexpensive, and nontoxic. Use of such a heterogeneous catalyst benefits several potential catalyst reuses and waste production minimizations.[4]

Naphthyridine derivatives were not only used as luminescence materials in molecular recognition because of their rigid planar structure,[5,6] but also as new drug leaders[7,8] and anticancer active screening agents in new drug discovery.[9,10] However, there is no report for the synthesis of chromeno-[4,3,2-*de*][1,6]naphthyridine thus far, and only three papers have ever reported the synthesis of some analogous frameworks.[11–13] Only one ring of the product was constructed in these processes. Furthermore, these methods usually required high reaction temperature (180−200 °C), long reaction time, and toxic solvents, and the yields were low (∼50%). These shortcomings limited the scope of appropriate substrates. Moreover, multistep, corrosive catalysts such as KOH and unavailable starting materials were necessary, for example, poly amino and cyano substituted 1*H*-benzo[*f*]chromen, 2-(2-phenyl-4*H*-chromen-4-ylidene)-malononitrile[14] and (*E*)-3-(2,3-dihydro-2-phenylchromen-4-ylidene) but-1-ene-1,1,4-tricarbonitrile.[15]

As a continuation of our efforts on synthesizing bioactive heterocyclic compounds with efficient and green approaches,[16] herein, we would like to report an unexpected and efficient synthesis of 5-amino-2-aryl-3*H*-chromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles and 5-amino-2-aryl-3*H*-quinolino[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles via one-pot cascade reaction of malononitrile with aromatic aldehyde and substituted 2-hydroxyacetophenone (or 2-aminoacetophenone) in aqueous media catalyzed by silica gel in good yields.

## Results and Discussion

Using the conversion of malononitrile (**1**), 3,4-dimethoxybenzaldehyde (**2h**) and 2-hydroxyacetophenone (**3**) as a model reaction, we tested different reaction conditions to optimize the conditions first. A summary of the optimization experiment is provided in Table 1. It was found that this transformation could not run smoothly except in the presence of silica gel (Entries **1**−**5**, Table 1), and other acids or bases such as HCl, $NaHSO_3$, silica sulfonic acid (SSA), or NaOH could not be employed as promoters in this reaction. The important role of silica gel in this interesting reaction may be attributed to its fitting acidity and ability to form H-bonds. The H-bond formation between silica gel and the OH group in 2-hydroxyacetophenone made it act as a phase transformation catalysis and enhance the solubility of reactant in water.

* To whom correspondence should be addressed. E-mail: wuhui72@yahoo.com.cn. Phone: +86051683403163. Fax: +86051683403164.
† Xuzhou Normal University.
‡ Soochow University.

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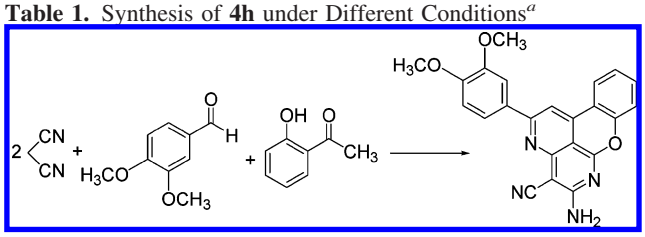
**Table 1.** Synthesis of **4h** under Different Conditions[a]



| entry | solvent | catalyst (g) | time (h) | *T* (°C) | yield of **4h** (%)[b] |
|---|---|---|---|---|---|
| **1** | $H_2O$ | HCl (0.07) | 2 | 80 | 0 |
| **2** | $H_2O$ | NaOH (0.08) | 2 | 80 | 0 |
| **3** | $H_2O$ | $NaHSO_3$ (0.20) | 2 | 80 | 0 |
| **4** | $H_2O$ | SSA (0.50) | 2 | 80 | 0 |
| **5** | $H_2O$ | silica gel (0.03) | 2 | 80 | 78 |
| **6** | THF | silica gel (0.03) | 2 | 80 | 0 |
| **7** | DMF | silica gel (0.03) | 2 | 80 | 0 |
| **8** | [bmim]$BF_4$ | silica gel (0.03) | 2 | 80 | 56 |
| **9** | [bpy]$BF_4$ | silica gel (0.03) | 2 | 80 | 50 |
| **10** | $H_2O$ | silica gel (0.03) | 0.5 | 80 | 0 |
| **11** | $H_2O$ | silica gel (0.03) | 1 | 80 | 14 |
| **12** | $H_2O$ | silica gel (0.03) | 1.5 | 80 | 63 |
| **13** | $H_2O$ | silica gel (0.03) | 2.5 | 80 | 76 |
| **14** | $H_2O$ | silica gel (0.03) | 2 | 60 | 0 |
| **15** | $H_2O$ | silica gel (0.03) | 2 | 65 | 0 |
| **16** | $H_2O$ | silica gel (0.03) | 2 | 70 | 21 |
| **17** | $H_2O$ | silica gel (0.03) | 2 | 75 | 69 |
| **18** | $H_2O$ | silica gel (0.03) | 2 | 85 | 78 |
| **19** | $H_2O$ | silica gel (0.03) | 2 | 90 | 78 |
| **20** | $H_2O$ | silica gel (0.01) | 2 | 80 | 49 |
| **21** | $H_2O$ | silica gel (0.02) | 2 | 80 | 63 |
| **22** | $H_2O$ | silica gel (0.04) | 2 | 80 | 77 |
| **23** | $H_2O$ | silica gel (0.05) | 2 | 80 | 79 |
| **24** | $H_2O$ | silica gel (0.06) | 2 | 80 | 79 |

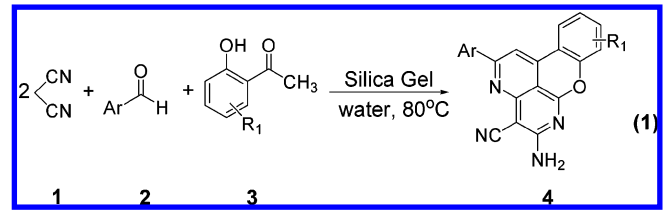
[a] All reactions were carried out in the scale of 2.0 mmol of 3,4-dimethoxybenzaldehyde **2h**, 4.0 mmol of malononitrile **1**, and 2.0 mmol of 2-hydroxyacetophenone **3** in 10 mL of given solvent. [b] Isolated yield.

Classic organic solvents such as tetrahydrofuran (THF) and *N*, *N*-dimethylformamide (DMF) can not be used as efficient solvents in this transformation (Entries **6** and **7**, Table 1). Two classic ionic liquids can also promote this process (Entries **8**, **9**, Table 1) but with lower efficiency than water. When 0.03 g of silica gel was used, the reaction proceeded in good yield (Entries **5**, **20**−**21** Table 1) of **4h**. Increasing the amount of silica gel did not affect the efficiency of this transformation (Entries **22**−**24**, Table 1). Finally, when the temperature was increased to 80 °C with $H_2O$ as the solvent, the reaction proceeded smoothly (Entries **14**−**19**, Table 1). However, prolonging the reaction time did not enhance the yield of the product (Entries **10**−**13**, Table 1).

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes (Table 2). It appeared that the electronic nature of the substituted groups in the aromatic ring had slightly influence on the yield. It is noteworthy that no remarkable steric hindrance on the reaction was observed, for example, the desired products were obtained in moderate to good yields when the *ortho* substitutes on the benzaldehyde were used (Entries **5**, **7**, **12**, **15**, **19** and **28**, Table 2).

To the best of our knowledge, fused poly cycle especially the fused heterocycle has efficient luminescence. All of our products exhibit strong fluorescence which can be distinguished by our eyes readily in EtOH or under UV light (360 nm) (Supporting Information, Figure 1), so their fluorescence properties were screened (Table 2). Following three points are clearly: (i) the emission wavelength of all products

**Table 2.** Synthesis of 5-Amino-2-aryl-3*H*-chromeno[4,3,2-*de*]-[1,6]naphthyridine-4-carbonitrile[a]




| Entry | Product | Ar | $R_1$ | Yield | $\lambda_{em}$ (nm) | $\Phi^c$ |
|---|---|---|---|---|---|---|
| **1** | **4a** | $C_6H_5$ | H | 69 | 482 | 0.707 |
| **2** | **4b** | 4-$CNC_6H_4$ | H | 72 | 501 | 0.268 |
| **3** | **4c** | 4-$CH_3C_6H_4$ | H | 71 | 477 | 0.513 |
| **4** | **4d** | 4-$OHC_6H_4$ | H | 73 | 471 | 0.550 |
| **5** | **4e** | 2-$MeOC_6H_4$ | H | 74 | 481 | 0.558 |
| **6** | **4f** | 4-$MeOC_6H_4$ | H | 78 | 474 | 0.514 |
| **7** | **4g** | 2,3-$(MeO)_2$ $C_6H_3$ | H | 66 | 485 | 0.404 |
| **8** | **4h** | 3,4-$(MeO)_2C_6H_3$ | H | 68 | 473 | 0.460 |
| **9** | **4i** | 3,4,5-$(MeO)_3C_6H_2$ | H | 69 | 480 | 0.384 |
| **10** | **4j** | 3-$FC_6H_4$ | H | 67 | 486 | 0.699 |
| **11** | **4k** | 4-$FC_6H_4$ | H | 78 | 481 | 0.457 |
| **12** | **4l** | 2-$ClC_6H_4$ | H | 64 | 490 | 0.259 |
| **13** | **4m** | 3-$ClC_6H_4$ | H | 66 | 453 | 0.493 |
| **14** | **4n** | 4-$ClC_6H_4$ | H | 75 | 486 | 0.485 |
| **15** | **4o** | 2-$BrC_6H_4$ | H | 65 | 487 | 0.144 |
| **16** | **4p** | 3-$BrC_6H_4$ | H | 68 | 489 | 0.338 |
| **17** | **4q** | 4-$BrC_6H_4$ | H | 76 | 487 | 0.540 |
| **18** | **4r** | 4-$IC_6H_4$ | H | 80 | 488 | 0.305 |
| **19** | **4s** | 2,4-$Cl_2C_6H_3$ | H | 62 | 495 | 0.399 |
| **20** | **4t** | 4-$OMeC_6H_4$ | 4-F | 73 | 472 | 0.426 |
| **21** | **4u** | 4-$OMeC_6H_4$ | 4-Cl | 74 | 485 | 0.424 |
| **22** | **4v** | 4-$OMeC_6H_4$ | 4-OH | 81 | 465 | 0.536 |
| **23** | **4w** | 4-$OMeC_6H_4$ | 4-$OCH_3$ | 77 | 465 | 0.583 |
| **24** | **4x** | 4-$OMeC_6H_4$ | 5-$CH_3$ | 76 | 488 | 0.716 |
| **25** | **4y** | 4-$OMeC_6H_4$ | 5-$OCH_3$ | 80 | 477 | 0.618 |
| **26** | **4z** | 4-$OMeC_6H_4$ |  | 72 | 460 | 0.813 |
| **27** | **4aa** | Pyridine-4-yl | H | 69 | 440 | 0.337 |
| **28** | **4bb** | Thiophene-2-yl | H | 67 | 440 | 0.380 |

[a] All reactions were carried out in the scale of 0.03 g of silica gel in 10 mL water at 80 °C for 2 h, and starting materials (1:2:3 = 4.0:2.0:2.0 mmol) were completely consumed. [b] Isolated yield. [c] Quantum yields, were calculated based on 9,10-diphenylanthrance.

appeared in the range of visible light, showing the potential applications of these compounds (e.g., as fluorescent probe, luminescence material or organic light-emitting diodes) in the future. Because of the lower electron density of the heteroaromatic ring, the emission wavelength of two products derived from heteroaromatic aldehydes (entries **27**, **28**, Table 2) have little blue shift; (ii) the electro and steric effect of substituted group on aromatic aldehydes have little influence on the fluorescence properties, which clearly showed that the fluorescence of products came from their framework directly; (iii) from the library, four members **4a**, **4j**, **4x**, and **4z** with intensive fluorescence were selected, while the corresponding fluorescent quantum yields[17] were calculated based on 9,10-diphenylanthrance (Table 2). The advantage

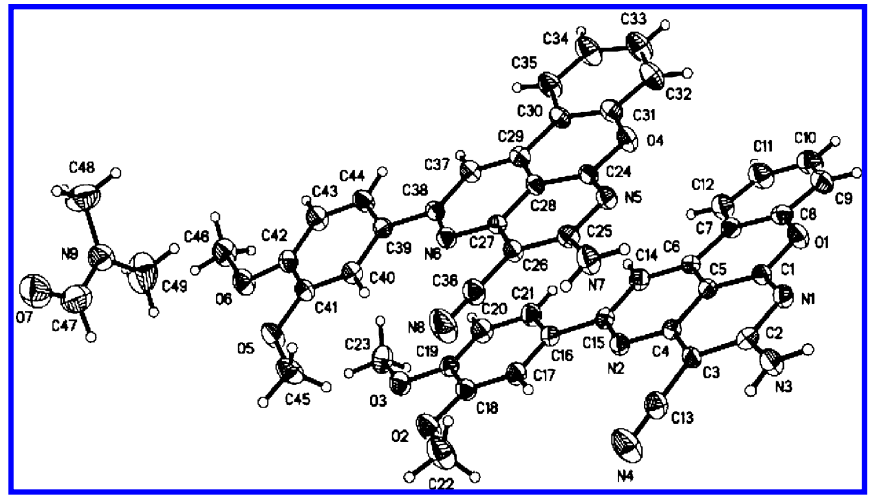



**Figure 1.** ORTEP diagram of **4h**.

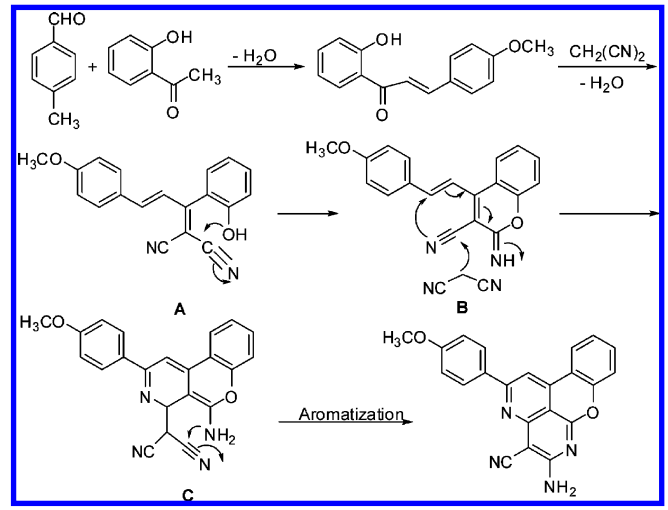
of this kind of novel framework is that it can be transformed into more thermostable derivatives through their amino groups.

The products **4** were fully characterized by IR, $^1$H NMR, and HRMS. The data were in agreement with their structures. To further confirm the structure, the X-ray diffraction analysis of the product **4h** was carried out. As expected, the structure is 5-amino-2-(3,4-dimethoxy-phenyl)-3*H*-chromeno[4,3,2-*de*][1,6]naphthyridine-4-carbonitrile, and the crystal structure of **4h** is shown in Figure 1.

A reasonable mechanism for the formation of the products was speculated based on the results of online ESI-MS monitoring of the product under the optimal reaction condition. At room temperature, a clear reaction solution was directly injected to the ESI source. The ESI-MS was operated in the position of ion mode. Approximately 5 min after mixing malononitrile (**1**), 3,4-dimethoxybenzaldehyde (**2h**), and 2-hydroxyacetophenone (**3**), ESI-MS detected a major ion attributed to the chalcone derived from **2h** and **3**. Thirty minutes later, **A** (Scheme 2) which came from the condensation of chalcone and malononitrile was detected as the major ion. Fifty minutes later, the ion of **4f**+**H** was detected as the base peak. When the reaction time was increased to 2 h, the abundance of **4f**+**H** increased and some residual ions were detected because of the occurrence of side-reaction. So we supposed that the reaction was via a cascade procedure (Scheme 1): the aldol condensation of aldehyde and 2-hydroxyacetophenone give chalcone, then malononitrile attacks the carbonyl of chalcone to form **A**. Interestingly, malononitrile does not react with chalcone via Michael addition in this step as usual. The intramolecular cyclization of **A** affords **B**, and **B** condensates with another malononitrile give **C**. The tandem intramolecular cyclization and aromatization of **C** afford the final product.

From the above mechanism, it seems that the *ortho* substituted $NH_2$ of the acetyl group can also act as an efficient nucleophilic agent which attacks the cyano group of malononitrile. So we were going to research the one-pot reaction of malononitrile with 2-aminoacetophenone and aromatic aldehyde catalyzed by silica gel at 95 °C (eq 2, Table 3). As expected, 5-amino-2-aryl-3*H*-quinolino[4,3,2-*de*][1,6]-naphthyridine-4-carbonitriles were successfully obtained.

**Scheme 1.** Possible Mechanism for the Formation of the Product



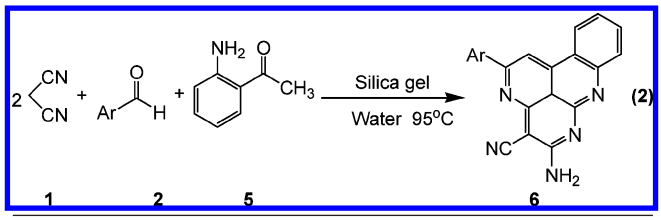

However, with higher temperature (>80 °C) and longer reaction times than 2 h, only low to moderate yields were obtained. It may be due to the activity of 2-aminoacetophenone lower than that of 2-hydroxyacetophenone. From the library, one compound **6a** with the most intensive fluorescence was discovered (Table 3).

Interestingly, in the $^1$H NMR of **6**, one proton signal disappeared. The possible reason is the strong shielding effect of H17 which sits in the center of the quinolino[4,3,2-*de*][1,6]naphthyridine core. The surrounding situation of H17 made the disappearance of its signal in $^1$H NMR spectra (Figure 2).

## Conclusions

In summary, we have discovered a novel and simple silica gel-catalyzed construction of 5-amino-2-aryl-3*H*-chromeno (or quinolino)[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles from commercially available starting materials in water. Silica gel showed its important role in this interesting reaction. The screening for fluorescence properties identified five new compounds with high fluorescence quantum yields which may have a good application as fluorescence material in the future. Thirteen bonds were cleaved, and twelve new bonds (two C−N single bonds, two C−N double bonds, three C−C

**Table 3.** Synthesis and Fluorescence of 5-Amino-2-aryl-3*H*-quinolino[4,3,2-*de*][1,6]naphthyridine-4-carbonitriles[a]




| entry | product | Ar | yield (%)[b] | $\lambda_{em}$ (nm) | $\Phi^c$ |
|---|---|---|---|---|---|
| **1** | **6a** | $C_6H_5$ | 39 | 482 | 0.780 |
| **2** | **6b** | 4-$CNC_6H_4$ | 35 | 506 | 0.110 |
| **3** | **6c** | 4-$CH_3C_6H_4$ | 37 | 482 | 0.523 |
| **4** | **6d** | 4-$OHC_6H_4$ | 39 | 476 | 0.488 |
| **5** | **6e** | 2-$MeOC_6H_4$ | 38 | 488 | 0.514 |
| **6** | **6f** | 4-$MeOC_6H_4$ | 40 | 478 | 0.612 |
| **7** | **6g** | 2,3-$(MeO)_2C_6H_3$ | 37 | 487 | 0.572 |
| **8** | **6h** | 3,4-$(MeO)_2C_6H_3$ | 38 | 478 | 0.370 |
| **9** | **6i** | 3,4,5-$(MeO)_3C_6H_2$ | 34 | 491 | 0.131 |
| **10** | **6j** | 3-$FC_6H_4$ | 40 | 488 | 0.452 |
| **11** | **6k** | 4-$FC_6H_4$ | 42 | 485 | 0.610 |
| **12** | **6l** | 2-$ClC_6H_4$ | 41 | 490 | 0.106 |
| **13** | **6m** | 3-$ClC_6H_4$ | 32 | 455 | 0.168 |
| **14** | **6n** | 4-$ClC_6H_4$ | 42 | 486 | 0.485 |
| **15** | **6o** | 2-$BrC_6H_4$ | 38 | 491 | 0.167 |
| **16** | **6p** | 3-$BrC_6H_4$ | 34 | 492 | 0.485 |
| **17** | **6q** | 4-$BrC_6H_4$ | 36 | 490 | 0.364 |
| **18** | **6r** | 4-$IC_6H_4$ | 27 | 490 | 0.351 |
| **19** | **6s** | 2,4-$Cl_2C_6H_3$ | 35 | 497 | 0.320 |
| **20** | **6t** | pyridine-4-yl | 22 | 434 | 0.389 |
| **21** | **6u** | thiophene-2-yl | 33 | 397 | 0.289 |

[a] All reactions were carried out in the scale of 0.03 g of silica gel in 10 mL of water at 95 °C for 6 h, and starting materials (1:2:3 = 4.0:2.0:2.0 mmol) were completely consumed. [b] Isolated yield. [c] Quantum yields, were calculated based on 9,10-diphenylanthrance.

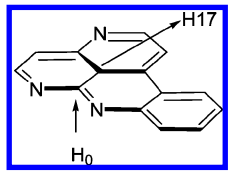



**Figure 2**

double bonds, two C−C single bonds, two N−H single bonds, and one C−O single bond) were constructed in the formation of **4**, while only two $H_2O$ molecules were removed. Three rings of the fused-ring framework were constructed in one-pot. In addition, there are several modifiable and coordinate sites in these two new interesting types of framework, so the subsequent step of the combinatorial development process, namely, structural optimization, should be possible. Future efforts to explore the coordination effect of products and the synthetic utility of the reaction are underway.

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**Supporting Information Available.** Details of experimental procedures and analytical data were given. It includes $^1H$ NMR, $^{13}C$ NMR spectra, IR and partial MS spectra of all compounds, and the X-ray structure determination of compound **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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