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# Facile one-pot synthesis of chromeno[4,3-*b*]quinoline derivatives catalyzed by Cu(II)-Schiff base/SBA-15

**Abstract:** A novel, one-pot, simple, environmentally benign and efficient protocol has been employed for the synthesis of chromeno[4,3-*b*]quinoline derivatives in the presence of catalytic amounts of Cu(II)-Schiff base/SBA-15 under solvent-free conditions in excellent yields and rates.

**Keywords:** chromeno[4,3-*b*]quinoline; heterogeneous catalyst; SBA-15.

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## Introduction

1,4-Dihydropyridines (1,4-DHPs), particularly 4-aryl-substituted 1,4-dihydropyridines, are well known as calcium channel modulators and have emerged as one of the most important class of drugs for the treatment of cardiovascular disease [1, 2]. They also possess a variety of other biological activities [3]. 1,4-DHPs can be obtained by classical Hantzsch method, which involves cyclocondensation of an aldehyde, a 1,3-diketone or  $\beta$ -ketoester and an amine either in acetic acid or in ethanol under reflux [4]. Recently, several modifications to this classical method have been reported, including the use of catalysts such as Bronsted acid [5], lithium iodide [6], scandium triflate [7], cerium ammonium nitrate [8], magnesium perchlorate [9], and copper(II) oxide [10]. We have recently synthesized a new class of coumarin-fused dihydropyridines **5a–k** (Table 1) in moderate yields under solvent-free conditions [11–14]. In this paper, we report a greatly improved synthesis of compounds **5a–k** in the presence of a catalyst Cu(II)-Schiff base/SBA-15 (structure in Figure 1). This work is part of our research

efforts to improve conditions for the Hantzsch reaction [15–19], in particular by using silica gel-supported catalysts [20–28].

There are a few literature reports regarding the application of silica supported Schiff base cobalt(II) (Co/SBA-15) and copper(II) (Cu/SBA-15) complexes as catalysts in organic synthesis [29–34].

Herein, we describe a one-pot, simple, new, and efficient protocol for the synthesis of chromeno[4,3-*b*]quinolines, using the catalytic Cu(II)-Schiff base/SBA-15. To the best of our knowledge, there is no report on the use of this type of catalyst in the synthesis of 1,4-DHPs. The catalyst is prepared by anchoring the copper complex to mesoporous silica SBA-15 [33, 34] (Figure 1).

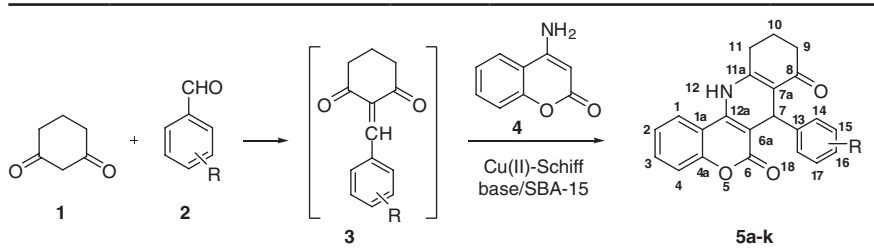
The synthetic pathway to the products **5a–k** by the reaction of 1,3-cyclohexanedione (**1**), a benzaldehyde **2**, and 4-aminocoumarin (**4**) is outlined in Table 1. The reaction with 4-nitrobenzaldehyde was chosen as a model for optimization. In the first step, substrates **1** and **2** were allowed to undergo Knoevenagel condensation under solvent-free conditions at 100°C for 10 min to yield the intermediate product **3**. This reaction was monitored by TLC analysis.

For the subsequent Michael addition, the intermediate product **3**, without isolation, was treated with 4-aminocoumarin (**4**) and the catalyst. This second step was conducted at 200°C for 5 min, at which time the intermediate Michael adduct underwent intramolecular cyclization to the desired product **5b**. It should be noted that this second step requires heating for 1 h to 200°C in the absence of the catalyst [11]. The yield of **5b** is low for the reaction conducted in the absence of the catalyst. To analyze the scope and limitations of this procedure, a number of products **5** were obtained by using the optimized conditions (Table 1). All products were obtained quickly and in high yields in the presence of the catalyst.

The reusability of the Cu(II)/SBA-15 catalyst was investigated. After the first catalytic cycle, the catalyst was removed from the mixture by filtration and successfully used in 10 subsequent runs, without any significant loss in catalytic activity. No pretreatment step was required,

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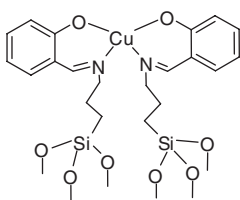
**Table 1** Synthesis of 7-aryl-8,9,10,12-tetrahydro-7*H*-chromeno[4,3-*b*]quinoline-6,8-diones **5a–k** catalyzed by Cu(II)-Schiff base/SBA-15.


Compound	R	mp <sup>a</sup>	Yield <sup>b,c</sup> (%)
<b>5a</b>	2-nitro	>300 (>300)	75 (35)
<b>5b</b>	4-nitro	260 (260–262)	70 (45)
<b>5c</b>	2-chloro	>310 (>310)	90 (50)
<b>5d</b>	3-chloro	207 (208–210)	93 (50)
<b>5e</b>	4-chloro	214 (214–216)	74 (55)
<b>5f</b>	3-bromo	265 (267–269)	71 (60)
<b>5g</b>	4-bromo	295 (294–296)	77 (65)
<b>5h</b>	2-methyl	190 (188–190)	86 (45)
<b>5i</b>	3-methyl	>310 (310)	78 (74)
<b>5j</b>	2-methoxy	>310 (>310)	89 (75)
<b>5k</b>	4-methoxy	275 (276–278)	80 (75)

<sup>a</sup>The numbers in parentheses refer to melting points in the literature [11].

<sup>b</sup>Isolated yields of pure compounds.

<sup>c</sup>The numbers in parentheses refer to yields in the literature [11].

**Figure 1** Structure of catalyst Cu(II)-Schiff base/SBA-15.

although the recovered catalyst was washed with 5 mL of MeOH to remove traces of the previous reaction mixture and dried before the next cycle.

The mechanism for the formation of **5a–k** in the absence of catalyst has been suggested [11]. Coordination of the carbonyl groups in the intermediate products by the Cu<sup>2+</sup> cation of the catalyst may increase electrophilicity of the carbonyl derivatives in both the Knoevenagel condensation and the Michael addition step.

In summary, a one-pot, convenient, environmentally benign, and safe synthetic method for chromeno[4,3-*b*]quinoline was developed. The simplicity of the method, including mild reaction conditions and the ease of product isolation, will make it attractive for use on an industrial scale. Most important, the purification procedure only involves filtration, washing, and drying.

## Experimental

### Preparation of the catalyst Cu(II)-Schiff base/SBA-15

The Cu(II)-Schiff base complex was prepared using the literature procedure [33] with the following modification. Activated silica gel SBA-15 (1.5 g) was suspended in a methanol solution of the Schiff base complex, and the mixture was stirred at room temperature for 24 h. The solvent was removed using a rotary evaporator, and the resulting green solid was dried at 80°C overnight. The final product was washed with MeOH and deionized water until the washings were colorless to ensure that the noncovalently grafted complex and physically adsorbed metal species were removed. Further drying was carried out in an oven at 80°C for 8 h. To measure the amount of copper loaded into SBA-15, the catalyst (0.1 g) was digested with HNO<sub>3</sub> by stirring at room temperature for a week. Then the mixture was filtered, and the total amount of copper in SBA-15 in the colorless sample was determined as 0.14 mmol/g by atomic absorption spectroscopy.

### General procedure for synthesis of chromeno[4,3-*b*]quinoline-6,8-diones **5a–k**

A mixture of an aromatic aldehyde (**1**, 1.0 mmol) and 1,3-cyclohexanedione (**2**, 1.0 mmol) were thoroughly mixed in a beaker using a spatula. Then the beaker was placed in an autoclave at 100°C for 10 min to complete the condensation reaction to **3**, as monitored by

TLC. After addition of 4-aminocoumarin (1.0 mmol) and the catalyst (0.01 g, 0.0014 mmol), the mixture was thoroughly mixed and placed in the autoclave at 200°C for 5 min. After cooling, the mixture was washed with acetone (50 mL) and the catalyst was removed by filtration, rinsed twice with MeOH, and then dried at 80°C for 60 min for subsequent reuse. Analytically pure product **5a–k** was obtained by evaporation of the solvent. The yields and melting points are shown in Table 1. The products were identified by comparison with the original samples [11].

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## References

- [1] Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–769.
- [2] Nakayama, H.; Kasoaka, Y. Chemical identification of binding sites of calcium channel antagonists. *Heterocycles* **1996**, *42*, 901–909.
- [3] Morshed, S. R.; Hashimoto, K.; Murotani, Y.; Kawase, M. Tumor-specific cytotoxicity of 3,5-dibenzoyl-1,4-dihydropyridines. *Anticancer Res.* **2005**, *25*, 2033–2038.
- [4] Hantzsch, J. L. Hantzsch pyridine synthesis. *Ann. Chem.* **1882**, *215*, 1–82.
- [5] Moreau, J.; Duboc, A.; Hubert, C.; Hurvois, J. P.; Renaud, J. L. Metal-free Brønsted acids catalyzed synthesis of functional 1,4-dihydropyridines. *Tetrahedron Lett.* **2007**, *48*, 8647–8650.
- [6] Geirsson, J. K. F.; Johannesdottir, J. F. Convenient synthesis of *N*-benzyl-1,4-dihydropyridines, cyclohexenones, and bicyclo[3.3.1]nonan-3-one derivatives from 1-aza-1,3-butadienes. *J. Org. Chem.* **1996**, *61*, 7320–7325.
- [7] Carranco, I.; Diaz, L. J.; Jimenez, O.; Lavilla, R. Dihydropyridine-based MCRs. New reaction pathways in the interaction with ethyl glyoxalate and non-aromatic amines. *Tetrahedron Lett.* **2003**, *44*, 8449–8452.
- [8] Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, C. A new three-component domino synthesis of 1,4-dihydropyridines. *Tetrahedron* **2007**, *63*, 4407–4413.
- [9] Bartoli, G.; Babiuch, K.; Bosco, M.; Carlone, A.; Galzerano, P.; Melchiorre, P.; Sambri, L. Magnesium perchlorate as efficient Lewis acid: a simple and convenient route to 1,4-dihydropyridines. *Synlett* **2007**, *18*, 2897–2901.
- [10] Kantam, M. L.; Ramani, T.; Chakrapani, L.; Choudary, B. M. Synthesis of 1,4-dihydropyridine derivatives using nanocrystalline copper(II) oxide catalyst. *Catal. Commun.* **2009**, *10*, 370–372.
- [11] Miri, R.; Motamedi, R.; Rezaei, M. R.; Firuzi, O.; Javidnia, A.; Shafiee, A. Design, synthesis and evaluation of cytotoxicity of novel chromeno[4,3-*b*]quinoline derivatives. *Arch. Pharm. Chem. Life Sci.* **2011**, *344*, 111–118.
- [12] Tanka, K.; Toda, F. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100*, 1025–1074.
- [13] Walsh, P. J.; Li, H.; De Parrodi, C. A. A green chemistry approach to asymmetric catalysis: solvent-free and highly concentrated reactions. *Chem. Rev.* **2007**, *107*, 2503–2545.
- [14] Garay, A. L.; Pichon, A.; James, S. L. Solvent-free synthesis of metal complexes. *Chem. Soc. Rev.* **2007**, *6*, 846–855.
- [15] Heravi, M. M.; Motamedi, R.; Seifi, N.; Bamoharram, F. Catalytic synthesis of 6-aryl-1H-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones by heteropolyacid:  $H_{14}[NaP_5W_{30}O_{110}]$  and  $H_3PW_{12}O_{40}$ . *J. Mol. Catal.* **2006**, *249*, 1–3.
- [16] Heravi, M. M.; Motamedi, R. S.; Bamoharram, N. F. A catalytic method for synthesis of 6-aryl-1H-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones by heteropolyacid:  $H_{14}[NaP_5W_{29}MoO_{110}]$  and  $H_3PMo_{12}O_{40}$ . *Catal. Commun.* **2007**, *8*, 1467–1471.
- [17] Motamedi, R.; Heravi, M. M.; Bamoharram, F. F.; Haeriyani, A. Facile routes to 1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazines and 1,2,4-triazino-[3,4-*b*][1,3,4]thiadiazine by heteropolyacids. *J. Heterocycl. Chem.* **2008**, *45*, 1211–1214.
- [18] Motamedi, R.; Monfared, A.; Ghahghai Nezamabadi, Z.; Bamoharram, F. F. Facile, one-pot synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and 3,7-dimethyl-4*H*-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazin-6-one using heteropolyacid catalysts. *J. Heterocycl. Chem.* **2010**, *48*, 604–607.
- [19] Motamedi, R.; Baghbani, S.; Bamoharram, F. F. A catalytic method for synthesis of benzopyrano[3,2-*c*]chromene-6,8-dione derivatives by heteropolyacids. *Synth. Commun.* **2012**, *42*, 1–9.
- [20] Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature* **1992**, *359*, 710–712.
- [21] Wight, A. P.; Davis, M. E. Design and preparation of organic-inorganic hybrid catalysts. *Chem. Rev.* **2002**, *102*, 3589–3614.
- [22] Corma, A.; Garcia, H. Lewis acids as catalysts in oxidation reactions: from homogeneous to heterogeneous systems. *Chem. Rev.* **2002**, *102*, 3837–3892.
- [23] Mallat, T.; Baiker, A. Oxidation of alcohols with molecular oxygen on solid catalysts. *Chem. Rev.* **2004**, *104*, 3037–3058.
- [24] Lu, Z. L.; Lindner, E.; Mayer, H. A. Applications of sol-gel-processed interphase catalysts. *Chem. Rev.* **2002**, *102*, 3543–3578.
- [25] Baleizao, C.; Garcia, H. Chiral Salen complexes: an overview to recoverable and reusable homogeneous and heterogeneous catalysts. *Chem. Rev.* **2006**, *106*, 3987–4043.
- [26] De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. Ordered mesoporous and microporous molecular sieves functionalized with transition metal complexes as catalysts for selective organic transformations. *Chem. Rev.* **2002**, *102*, 3615–3640.
- [27] Taguchi, A.; Schuth, F. Ordered mesoporous materials in catalysis. *Micropor. Mesopor. Mater.* **2005**, *77*, 1–45.
- [28] Meynen, V.; Cool, P.; Vansant, E. F. Verified syntheses of mesoporous materials. *Micropor. Mesopor. Mater.* **2009**, *125*, 170–223.
- [29] Rajabi, F. A heterogeneous cobalt (II) Salen complex as an efficient and reusable catalyst for acetylation of alcohols and phenols. *Tetrahedron Lett.* **2009**, *50*, 395–397.
- [30] Rajabi, F. A highly efficient and reusable mesoporous supported Co (II) catalyst for chemoselective deprotection of aryl acetates. *Tetrahedron Lett.* **2009**, *50*, 7256–7258.
- [31] Rezanejade Bardajee, G.; Malakooti, R.; Jami, F.; Parsaei, Z.; Atashin, H. Covalent anchoring of copper-Schiff base complex into SBA-15 as a heterogeneous catalyst for the synthesis of pyridopyrazine and quinoxaline derivatives. *Catal. Commun.* **2012**, *27*, 49–53.

- [32] Chisem, I. C.; Rafelt, J.; Shieh, M. T.; Chisem, J.; Clark, J. H.; Jachuck, R.; Macquarrie, D. J.; Ramshaw, C.; Scott, K. Catalytic oxidation of alkyl aromatics using a novel silica supported Schiff base complex. *Chem. Commun.* **1998**, 1949–1950.
- [33] Rajabi, F.; Karimi, B. Efficient aerobic oxidation of alcohols using a novel combination *N*-hydroxy phthalimide (NHPI) and a recyclable heterogeneous cobalt complex. *J. Mol. Catal. A* **2005**, 232, 95–99.
- [34] Masteri-Farahani, M.; Farzaneh, F.; Ghandi, M. Synthesis and characterization of a new epoxidation catalyst by grafting *cis*-MoO<sub>2</sub> (salpr) complex to functionalized MCM-41. *J. Mol. Catal. A Chem.* **2006**, 243, 170–175.