Silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ mediated cyclization of 2′-amino and 2′-hydroxychalcones under solvent-free conditions

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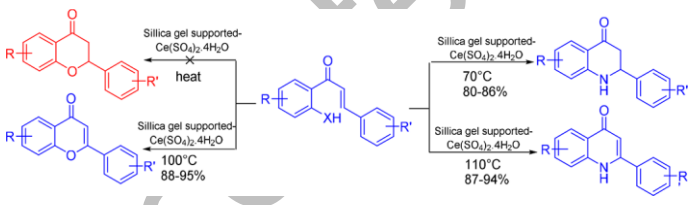
Abstract

A simple, efficient and environmentally friendly approach for the synthesis of flavones, *aza*-flavones, and *aza*-flavanones from corresponding 2′-hydroxy or 2′-aminochalcones has been developed. The reactions are successfully conducted in presence of silica gel supported- $Ce(SO_4)_2 \bullet 4H_2O$ under solvent free conditions.

GRAPHICAL ABSTRACT



KEYWORDS: 2′-hydroxychalcones; 2′-aminochalcones; Silica gel supported-$Ce(SO_4)_2 \bullet 4H_2O$; flavones; *aza*-flavonoids

INTRODUCTION

Substituted flavonoids and *aza*-flavonoids are important naturally occurring compounds isolated from various plants, and show a wide range of biological activities such as

antibacterial [1-4], anticancer [5,6], and anti-inflammatory [7,8], etc. [9-12]. Generally, their synthesis is of considerable interest. Most of the existing procedures were carried out via Michael reaction of 2′-hydroxy and 2′-aminochalcone in presence of various catalysts such as NH_4I [13], oxalic acid [14], Na_2SeO_3 [15], I_2 [16], SPB [17], $FeCl_3$ [18], $NaHSO_4$-SiO_2 [19], [bmin][BF_4] [20], etc. [21-31].

Generally, the cyclization of 2′-hydroxy and 2′-aminochalcone were carried out using different adducts. Although all of these procedures are effective, many of them involve toxic or expensive reagents [21-24], long reaction time [25], low yield [26], and use of excess of organic solvent [27]. Thus, there remains a need to develop a practical, mild and environmentally friendly protocol for the synthesis of flavones and *aza*-flavonoid.

Recently, organic reactions under solventless conditions have been increasingly attractive to synthetic organic chemists because of their simplicity and synthetic value. Moreover, solventless reactions have many advantages, including commercial viability, ecofriendliness, and operational simplicity. In the last decades, applications of lanthanide reagents cover almost every aspect of organic transformations, and they represent ideal promoters for being applied widely. And some lanthanide reagents have been developed as good catalysts for the synthesis of flavones or *aza*-flavonoids [23, 28-30]. Cerium, which is the most abundant element in the lanthanide series, is more inexpensive and abundant than other lanthanides. Cerium compounds have been widely used in variety of

transformations. Particularly, alumina supported $CeCl_3 \cdot 7H_2O$-NaI have emerged as an efficient catalyst for the isomerization of 2′-aminochalcones to the corresponding *aza*-flavonones [30], which failed to promote the cyclization of 2′-hydroxychalcones. Herein, we wish to report a mild and efficient method for the synthesis of flavones and *aza*-flavonoids via the oxidative cyclization of the corresponding chalcones mediated by silica supported-$Ce(SO_4)_2 \cdot 4H_2O$. This stable catalyst is easily prepared, safely handled, active under solvent-free conditions and employed under environmentally friendly conditions.

RESULTS AND DISCUSSION

Initial study was performed by absorbing 2′-hydroxychalcone (**1a**) on silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ (1 equiv $Ce(SO_4)_2 \cdot 4H_2O$), heating the reaction mixture at 100 °C. The crude product was obtained along with largely starting material. Inspired by this result, the cyclization of 2′-hydroxychalcone (**1a**) was chosen as a model reaction. In order to optimize the reaction conditions, various factors including amounts of oxidant, reaction time, and reaction temperature were investigated. The results are shown in Fig. 1.

In order to investigate the appropriate amount of silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$, the influence of the amount of silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ on oxidation of **1a** into **2a** was examined at 100 °C with a reaction time of 4h, and the results are given in Fig. 1(a).

It can be found that the yield of **2a** reached a maximum when the amount of silica gel supported-$Ce(SO_4)_2•4H_2O$ was 2.5 equiv. The yield of **2a** was almost unchanged as the loading of silica gel supported-$Ce(SO_4)_2•4H_2O$ increased from 2.5 equiv to 3.0 equiv. Thus, a dosage of 2.5 equiv was adopted to obtain acceptable reaction rate and yield. We also investigated the effect of reaction temperature on the cyclization of **1a**. In the low temperature range (<75 °C), the reaction processed slowly with a flavone yield less than 30% with 4h, and no flavanone was detected. Increasing the temperature could enhance the yield significantly. The yield of flavone reached 94% when the temperature increased from 70°C to 100 °C and then slowly decreased to 85% when the reaction temperature increased to 130°C. In the reaction system, the oxidative cyclization of chalcone was accelerated by increasing temperature, but chalcone or the desired product may be decomposed at higher temperature. Thus, 100°C is high enough to obtain satisfactory reaction rate and flavone yield. Based on the results above, we studied the influence of reaction time at 100 °C. From Fig. 1(c), we can see that when the reaction was conducted at 100 °C, the yield increased gradually with time at the beginning, and reached the maximum 94% at 4 h. With these preliminary results, in order to demonstrate the general applicability of silica gel supported-$Ce(SO_4)_2•4H_2O$ as an oxidizing agent for 2′-hydroxychalcone cyclization, a wide range of substrates were treated as described above and the results are summarized in Table 1. As shown in Table 1, the substrates with electron-withdrawing or electron-donating groups were well tolerated and the products were obtained in excellent yields; the assigned structures were confirmed by

their spectral properties (^{1}H NMR, ^{13}C NMR and HRMS) and by comparison with literature data.

The success encountered in the synthesis of flavones prompted us to study the action of silica gel supported-$Ce(SO_4)_2$•$4H_2O$ on 2′-aminochalcones. 2′-aminochalcone (**3a**) was subjected to the similar reaction conditions afforded to a complex mixture of *aza*-flavanone (**4a**) and *aza*-flavone (**5a**), together with unknown byproducts. In order to optimize the reaction temperature, the cyclization of 2′-aminochalcone (**3a**) was carried out at various temperatures (Fig. 1(d)). The reaction gave a mixture of *aza*-flavanone (**4a**) and *aza*-flavone (**5a**) when the reactions were carried out at 70-110°C. With increasing the temperature from 70 °C to 110°C, the yield of *aza*-flavanone (**4a**) was decreased and the yield of *aza*-flavone (**5a**) was increased. These results indicated that *aza*-flavanones maybe the intermediate for further be oxidized to the final product, *aza*-flavone. As shown in Fig. 1(d), it could be found that 70 °C is the optimum temperature to get satisfactory yield of *aza*-flavanone, as well as *aza*-flavone was obtained in 91% yield under 110 °C. Hence, we attempted to subject a wide range of substituted 2′-aminochalcones to the similar reaction conditions, with the exception of reaction temperature. To our delight, the reaction proceeded in a similar fashion, and substituted *aza*-flavanones and *aza*-flavones were yielded in moderate yields (Table 2).

Although the oxidative cyclization of chalcones with silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ required higher catalyst loading, a wider range of substrates (2′-hydroxychalcones and 2′-aminochalcones) was tolerated. Under above conditions, a number of substituted 2′-hydroxy and 2′-aminochalcone derivatives were found to give the corresponding flavones, *aza*-flavanones, and *aza*-flavones, respectively. Compared to previously reported methods (listed in Table 3), which still have some limitations, such as need of aqueous workup, high cost, or removal of metal ions as a water-soluble complex, the use of silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ as oxidizing agent in these reactions have advantages of high yields, simple work-up and low cost. According to literature, the plausible mechanism for the cyclization of 2′-hydroxychalcones and 2′-aminochalcones were performed in Scheme 1.

Finally, we also tried to cyclize chalcones (**1a** and **2a**) to their corresponding flavonoids under the same reaction conditions as described above, except using the recovered catalyst. The recovered catalyst was isolated from the reaction mixture at the end of the reaction, washed with methanol, and then dried at 50 °C under vacuum. Unfortunately, no appreciable conversion of chalcones was observed.

EXPERIMENTAL SECTIONS

Starting materials were purchased from commercial sources and all solvents were used without further purification. Melting points were recorded on a YRT-3 melting point

apparatus and are uncorrected. NMR spectra were recorded on Avance III 400 MHz and Avance III 500 MHz Bruker spectrometers [DMSO-d_6 as solvent and TMS as internal standard, chemical shifts (δ scale) are reported in parts per million (ppm). High resolution electrospray ionization mass spectroscopy (HRESIMS) was performed in an Agilent Technologies liquid chromatograph connected to Q-TOF mass spectra. Silica gel (200–300 mesh) was purchased from the Qingdao Marine Chemical Factory (Qingdao, China).

Typical Procedure for the Synthesis of 2-Aryl-4*H*-Chromen-4-Ones (2)

Silica gel (5.05 g, Qingdao Haiyang China, 200-300 mesh) was added to a stirred mixture of $Ce(SO_4)_2$•$4H_2O$ (5.05 g, 12.5 mmol) and H_2O, and further stirred overnight. After removing solvent in vacuo, the resulting powdered mixture was added to 2′-hydroxychalcones (**1**, 5.0 mmol, dissolved in a minimum amount of ethyl acetate). The solvent was removed by heating and the dry mixture is stirred at 100 ℃. After the completion of reaction (by TLC monitoring), the mixture was cooled to room temperature. The crude products were obtained by washing with ethyl acetate and solvent evaporation. The crude products were purified by recrystallization or column chromatography to give the desired product.

Typical Procedure for the Synthesis of 2-Aryl-2,3-Dihydroquinoline-4(1*H*)-Ones (4)

Silica gel (5.05 g, Qingdao Haiyang China, 200-300 mesh) was added to a stirred mixture of $Ce(SO_4)_2$•$4H_2O$ (5.05 g, 12.5 mmol) and H_2O, and further stirred overnight. After

removing solvent in vacuo, the resulting powdered mixture was added to 2′-aminochalcones (**3**, 5.0 mmol, dissolved in a minimum amount of ethyl acetate). The solvent was removed by heating and the dry mixture is stirred at 60 ℃. After the completion of reaction (by TLC monitoring), the mixture was cooled to room temperature. The crude products were obtained by washing with ethyl acetate and solvent evaporation. The crude products were purified by recrystallization or column chromatography to give the desired product.

Typical Procedure for the Synthesis of 2-Aryl-Quinolin-4(1*H*)-Ones (5)

Silica gel (5.05 g, Qingdao Haiyang China, 200-300 mesh) was added to a stirred mixture of $Ce(SO_4)_2•4H_2O$ (5.05 g, 12.5 mmol) and H_2O, and further stirred overnight. After removing solvent in vacuo, the resulting powdered mixture was added to 2′-hydroxychalcones (**3**, 5.0 mmol, dissolved in a minimum amount of ethyl acetate). The solvent was removed by heating and the dry mixture is stirred at 110 ℃. After the completion of reaction (by TLC monitoring), the mixture was cooled to room temperature. The crude products were obtained by washing with ethyl acetate and solvent evaporation. The crude products were purified by recrystallization or column chromatography to give the desired product.

Spectral Data for Selected Compounds

Compounds **2a-l**, **4a-g**, and **5b-f** are known compounds, compounds **5a** and **5g** are novel compounds.

2-Phenyl-4*H*-Chromen-4-One (2a) [32]

Purification by recrystallization frome 95% ethanol gave **2a** as pale white solid; yield: 1.04 g (94%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.13 (dd, *J* = 7.9, 1.4 Hz, 2 H), 8.07 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.58 (m, 3H), 7. 52 (td, *J* = 7.4, 1.0 Hz, 1H), 7.07 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.6, 163.1, 156.2, 134.8, 132.3, 131.6, 129.6, 126.8, 126.0, 125.3, 123.8, 119.1, 107.4. MS (ESI): m/z $[M+H]^+$ 223.08.

2-(2-Methylphenyl)-2,3-Dihydroquinoline-4(1*H*)-One (4a) [6]

Purification by recrystallized from ethyl acetate gave **4a** as yellow solid; yield: 0.95 g (80%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.62 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.60 (d, *J* = 6.5 Hz, 1H), 7.32 (td, *J* = 7.0, 1.7 Hz, 1H), 7.28 – 7.20 (m, 3H), 7.00 (s, 1H), 6.89 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.65 (td, *J* = 7.0, 1.0 Hz, 1H), 4.95 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.74 (dd, *J* = 16.1, 13.2 Hz, 1H), 2.61 (dd, *J* = 16.1, 4.0 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.0, 153.4, 134.0, 135.6, 135.4, 131.0, 127.9, 126.8, 126.7, 126.7, 118.0, 116.9, 116.8, 53.4, 44.6, 19.2. MS(ESI): m/z $[M+H]^+$ 238.13.

2-(2-Methylphenyl)Quinolin-4(1*H*)-One (5a)

Purification by recrystallized from ethyl acetate gave 5a as yellow solid; yield: 1.07 g (91%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.81 (s, 1H), 8.13 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.36 – 7.32 (m, 1H), 5.97 (d, *J* = 1.7 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.2, 151.1, 140.7, 136.1, 135.5, 132.2, 131.0, 130.1, 129.5, 126.5, 125.3, 125.1,123.7, 118.9, 109.8, 21.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{13}NO$ 236.1070, found 236.1076.

2-(3-Nitrophenyl)Quinolin-4(1*H*)-One (5g)

Purification by recrystallized from ethyl acetate gave **5a** as yellow solid; yield: 1.25 g (94%). m.p. >365°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.96 (s, 1H), 8.69 (t, *J* = 2.1 Hz, 1H), 8.43 – 8.38 (m, 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 8.12 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.72 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.41 – 7.35 (m, 1H), 6.54 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.5, 148.5, 146.5, 142.5, 136.6, 134.5, 132.4, 131.1, 127.7, 125.4, 125.0, 124.2, 123.7, 122.6, 119.0, 108.2. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{10}N_2O_3$ 267.0764, found 267.0762.

CONCLUSION

In summary, the present procedure mediated by $Ce(SO_4)_2$•$4H_2O$ supported by silica gel provides an operationally simple and environmentally friendly procedure for the preparation of flavones and *aza*-flavonoids by the cyclization of the corresponding

2′-hydroxychalcones and 2′-aminochalcones. In addition, low cost, easy availability, low toxicity, excellent yields of products, and the fairly mild reaction conditions make this protocol convenient for applications.

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SUPPLEMENTAL MATERIAL

Full experimental detail, ^{1}H NMR and ^{13}C NMR spectra for all the products. This material can be found via the "Supplementary Content" section of this article's webpage.

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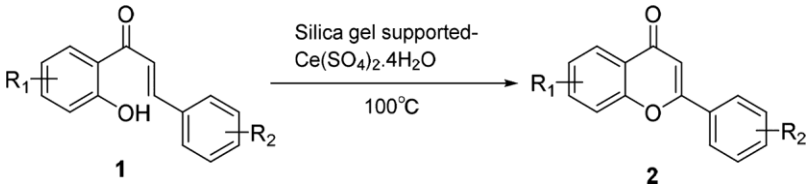
Table 1. Synthesis of flavones catalyzed by silica supported-$Ce(SO_4)_2$•$4H_2O$ [a]

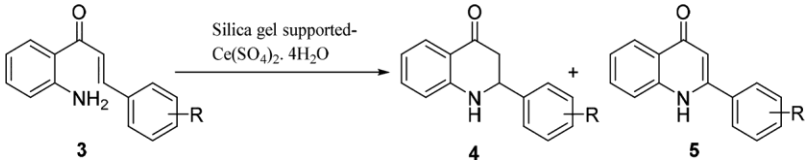


Entry	2′-hydroxychalcone	R_1	R_2	Time [h]	Product	Yield [b] [%]
1	**1a**	H	H	4	**2a** [32]	94
2	**1b**	H	2′-OCH_3	4	**2b** [32]	92
3	**1c**	H	3′-OCH_3	4	**2c** [32]	94
4	**1d**	H	4′-OCH_3	4	**2d** [32]	95
5	**1e**	H	2′-CH_3	4	**2e** [33]	89
6	**1f**	H	3′-CH_3	4	**2f** [33]	90
7	**1g**	H	4′-CH_3	4	**2g** [32]	92
8	**1h**	H	3′-Cl	3	**2h** [34]	88
9	**1i**	H	2′-F	3	**2i** [35]	93
10	**1j**	H	4′-OBn	4	**2j** [36]	94
11	**1k**	5,7-OCH_3	4′-NO_2	2	**2k** [37]	93
12	**1l**	5,7-OCH_3	4′-OBn	4	**2l** [38]	94

[a]Reaction conditions: Substrate (5.0 mmol) and silica supported-$Ce(SO_4)_2$•$4H_2O$ (10.1 g) were kept at 100 °C.

[b]Isolated yield.

Table 2. Synthesis of *aza*-flavonoids catalyzed by silica supported-$Ce(SO_4)_2 \cdot 4H_2O$ [a]



Entry	2′-aminochalcone	R	Temp [°C]	Time [h]	Product (**4**/**5**)	Yield [b] [%]
1	**3a**	2′-CH_3	70	1.5	**4a** [6]	80
2	**3a**	2′-CH_3	110	2.5	**5a**	91
3	**3b**	3′-CH_3	70	1.5	**4b** [6]	86
4	**3b**	3′-CH_3	110	2.5	**5b** [39]	87
5	**3c**	4′-CH_3	70	2.0	**4c** [19]	85
6	**3c**	4′-CH_3	110	2.5	**5c** [40]	90
7	**3d**	2′-OCH_3	70	2.0	**4d** [6]	83
8	**3d**	2′-OCH_3	110	2.5	**5d** [41]	88
9	**3e**	3′-OCH_3	70	1.5	**4e** [23]	85
10	**3e**	3′-OCH_3	110	2.5	**5e** [42]	91
11	**3f**	4′-Cl	70	2.5	**4f** [23]	81
12	**3f**	4′-Cl	110	3.0	**5f** [43]	91
13	**3g**	3-NO_2	70	2.0	**4g** [23]	83
14	**3g**	3-NO_2	110	1.5	**5g**	94

[a]Reaction conditions: Substrate (5.0 mmol) and silica supported-$Ce(SO_4)_2 \cdot 4H_2O$ (10.1 g) were heated for 1-3h.

[b]Isolated yield.

Table 3. Comparison silica gel supported-$Ce(SO_4)_2$•$4H_2O$ with other catalysts for the cyclization of 2′-hydroxy and 2′-aminochalcones

Entry	Substrate	Adducts	Temp [°C]	Time [h]	Product	Yield[%]
1	**3a**	Alumina supported-$CeCl_3$•$7H_2O$-NaI [a]	70	2	**4a**	98[30]
2	**1a**	Silica gel supported $InBr_3$ [a]	140	0.75	**2a**	96[44]
3	**3a**	silica gel supported $TaBr_5$ [a]	150	0.17	**4a**	92[22]
4	**1a**	$FeCl_3$•$6H_2O$ [a]	65	10	**2a**	55[18]
5	**1a**	CuI [a]	130	3	**2a**	71[25]
6	**1a**	silica gel supported-$Ce(SO_4)_2$•$4H_2O$ [b]	110	4	**2a**	94
7	**3a**	silica gel supported-$Ce(SO_4)_2$•$4H_2O$ [b]	70	1.5	**4a**	80
8	**3a**	silica gel supported-$Ce(SO_4)_2$•$4H_2O$ [b]	110	2.5	**5a**	91

[a]Reaction data were obtained from corresponding literatures.

[b]Reaction data were obtained from our experiments.

Scheme 1. Postulated catalytic pathway for silica gel supported-$Ce(SO_4)_2 \cdot 4H_2O$ mediated reaction.

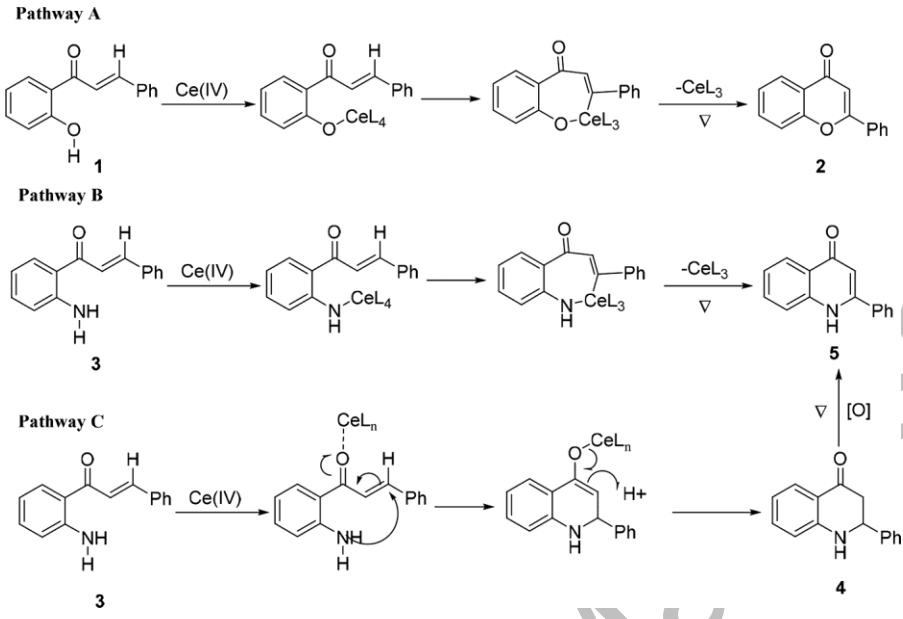


Figure 1. Optimized conditions of the cyclization of 2′-hydroxy and 2′-aminochalcones. **a)** Influence of the amount of $Ce(SO_4)_2•4H_2O$ on **2a** yield. Reaction conditions: **1a** (5mmol), silica gel-supported $Ce(SO_4)_2•4H_2O$, stirring at 100 ℃ for 4h; **b)** Influence of temperature on **2a** yield. Reaction conditions: **1a** (5mmol), silica gel-supported $Ce(SO_4)_2•4H_2O$ (250 mol%), heating for 4h; **c)** Influence of reaction time on **2a** yield. Reaction conditions: **1a** (5mmol), silica gel-supported $Ce(SO_4)_2•4H_2O$ (250 mol%), stirring at 110 ℃; **d)** Influence of temperature on **4a** and **5a** yields. Reaction conditions: **3a** (5mmol), silica gel-supported $Ce(SO_4)_2•4H_2O$ (250 mol%), heating for 4h.