

MgCl₂ AS EFFICIENT AND INEXPENSIVE CATALYST FOR THE SYNTHESIS OF 1,4-DIHYDROPYRIDINE DERIVATIVES

(MgCl₂ Sebagai Pemangkin Cepak dan Murah untuk Sintesis Terbitan 1,4-Dihidropiridina)

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Abstract

The synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives in the presence of alkaline earth metal chlorides was reported. Specifically, the MgCl₂ catalyzed the synthesis of 1,4-DHP derivatives in good yields, ranging from 69 – 87%. The Mg²⁺ serves as the Lewis acid catalyst in the formation of 1,4-DHP and the proposed mechanism of the formation of 1,4-DHP was elaborated in this manuscript. There are many advantages employing MgCl₂ as a catalyst in this study, including inexpensive, ubiquitous availability of this metal, simple filtration protocol, which has spark considerable interest in the use of this catalyst in promoting organic reactions.

Keywords: alkaline earth metal, magnesium chloride; 1,4-dihydropyridine

Abstrak

Sintesis terbitan 1,4-dihidropiridina (1,4-DHP) dalam kehadiran logam alkali bumi dibincangkan dalam artikel ini. Secara khususnya, sintesis terbitan 1,4-DHP melalui pemangkin MgCl₂ memberi peratusan hasil yang baik, dalam lingkungan 69 – 87%. Ion Mg²⁺ bertindak sebagai pemangkin asid Lewis dalam pembentukan 1,4-DHP dan cadangan mekanisma terhadap pembentukan 1,4-DHP telah diuraikan dalam manuskrip ini. Terdapat banyak kelebihan menggunakan MgCl₂ sebagai pemangkin dalam kajian ini, termasuk kos yang murah, ketersediaan logam ini, protokol pengekstrakan yang mudah, yang mana ini telah mencetuskan minat yang besar dalam penggunaan pemangkin ini dalam pelbagai tindak balas organik.

Kata kunci: logam alkali bumi, magnesium klorida, 1,4-dihidropiridin

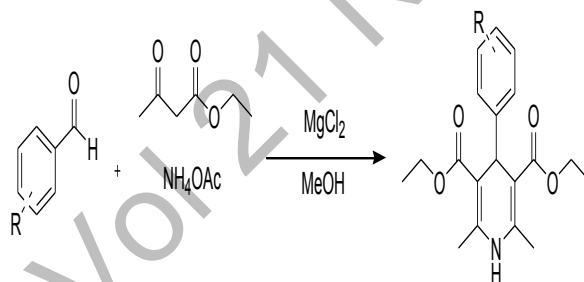
Introduction

1,4-dihydropyridines (1,4-DHPs) are important classes of pharmaceutical compounds that are usually prescribed clinically for the treatment of cardiovascular diseases, such as heart failure, angina pectoris and hypertension [1]. In the pharmaceutical pipeline today, there are more than twelve 1,4-DHPs drug candidates commercially available in the global market, such as the nifedipine [2], felodipine [3], nifedipine [4] and etc., which were used to treat cardiovascular diseases.

Due to the attractiveness of the 1,4-DHPs in pharmaceutical application, various synthetic approaches to produce 1,4-DHP derivatives have been reported, such as the use microwave irradiation [5], solar thermal energy [6], ultrasound irradiation [7], ionic liquids [8], and AlCl_3 as Lewis catalyst [9]. In spite of the above efforts to improve further on the 1,4-DHPs reactions, a number of drawbacks have been identified such as unsatisfactory yields, high reaction temperatures and long reaction hours [10].

Recently, there are a number of literatures reported on the use of alkaline earth metals for organic transformations. For instance, MgCl_2 has been successfully employed for the aldol synthesis of α -dimethylsilylestere [11]. An improved method on the Biginelli reaction by using alkaline earth metal chlorides such as MgCl_2 , CaCl_2 , BaCl_2 and SrCl_2 as homogenous catalysts in the presence of acetic acid as solvent had been reported [12]. The synthesis of dihydropyridine, acridine and xanthene derivatives with $\text{Ca}(\text{OTf})_2$ in the presence of Bu_4NPF_6 as additive and water as solvent has also been disclosed recently [13]. The alkaline earth metals are the most abundant elements encountered in our daily lives in which most of it can be found buried in the earth crust and in the ocean [14]. On green chemistry perspective, the use of alkaline earth metals in organic reactions are favorable due to the fact that, metals such as calcium and magnesium are ubiquitously available in nature compared to other transition and lanthanide elements [15]. However, only limited organic reactions which employ alkaline earth metals as catalysts were reported as their applications are not being fully explored [16].

In the course of our research to synthesize bioactive heterocyclic compounds, herein we report the synthesis of 1,4-DHP derivatives catalyzed by MgCl_2 from the starting materials benzaldehydes, ethyl acetoacetate and ammonium acetate (as shown in Scheme 1). The advantages of this protocol include the exclusion of additional additive, for example Bu_4NPF_6 and the reaction could be accomplished within four hours. The synthesized products were obtained in good yield as described in this paper.



Scheme 1. The MgCl_2 catalyzed the synthesis of 1,4-DHP derivatives

Materials and Methods

All the chemicals and solvents used without further purification in this study are supplied by Merck, Acros organic and HmbG® chemicals. These include benzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-bromobenzaldehyde, ethylacetoacetate, ammonium acetate, methanol, ethyl acetate, n-hexane and silica gel 60 (0.063-0.200mm). The FT-IR spectra were recorded on Perkin Elmer 100 FT-IR spectrometer, in spectral range of 4000 – 400 cm^{-1} . ^1H and ^{13}C -NMR spectra were recorded using Bruker Avance III 400 spectrometer, with deuterated chloroform as solvent at room temperature at 400 MHz. GC-MS analyses were performed using Shimadzu QP2010SE.

Synthesis of the 1,4-DHP derivatives

To a mixture of benzaldehyde derivatives (1.47 mmol), ammonium acetate (1.47 mmol), and ethyl acetoacetate (1.47 mmol) in methanol (3 ml), MgCl_2 was added (0.15 mmol) and the mixture were heated under reflux for four hours. After the completion of the reaction, the solvent was evaporated under reduced pressure to obtain the crude product. The crude product was then purified over silica gel column chromatography (hexane: ethyl acetate = 7:3, v/v) to give the title compounds **1a-1k**.

Results and Discussion

The optimized condition was determined using a model reaction that consisted of benzaldehyde, ethyl acetoacetate and ammonium acetate. The model reaction was first conducted without adding any catalysts, recorded only 30% yield after the reaction was heated under reflux for four hours in methanol. The use of catalytic amount of MgCl_2 greatly enhanced the yield of the desired product and the best yield was recorded with the use of 5 mmol of MgCl_2 which afforded 87% yield of the desired product. Next, the study of using various alkaline earth metals in different solvents was evaluated. Based on the optimization study (Table 1), the maximum yield of **1a** was recorded when the reaction was heated under reflux for four hours in the presence of 5 mmol of MgCl_2 as catalyst in MeOH.

Table 1. Synthesis of **1a** under different solvents and alkaline earth metals.

Entry	Solvent	MgCl_2 Time/ Yield (%)	CaCl_2 Time/ Yield (%)	SrCl_2 Time/ Yield (%)	BaCl_2 Time/ Yield (%)
1	MeOH	4h/ 87	4h/ 75	4h/ 79	4h/ 82
2	AcOH	4h/ 37	4h/ 33	4h/ 32	4h/ 35
3	THF	4h/ 70	4h/ 65	3h/ 72	4h/ 67
4	DMSO	5h/ 82	4h/ 80	4h/ 76	5h/ 78

The improved protocol was employed to synthesize different substituted 1,4-DHP derivatives by using a variety of benzaldehydes. As shown in Table 2, all the reactions proceeded smoothly in the presence of MgCl_2 and the desired products were isolated in moderate to good yields, ranging from 69 – 87%. The electronic effect of different substituted groups on benzaldehydes was also evaluated. Specifically, the benzaldehydes bearing the electron-withdrawing group gave a higher yield compared to benzaldehydes bearing electron-donating group (Table 2, **1b** -**1j** vs **1k**). This result was in agreement with a previous study on the synthesis of the 1,4-DHP derivatives using ultrasound method [17]. Among the investigated electron-withdrawing substituents, the *para*- position gave a higher yield compared to *ortho*- and *meta*- position (Table 2, **1b** -**1e** vs **1f**-**1j**). In the previous study, the side products (Figure 1) were usually yielded along with the desired products [17]. Gratifyingly, under this improved protocol which utilized MgCl_2 as catalyst, only one 1,4-DHP derivative was isolated for each reaction, with no side products isolated during the purification process in the column chromatography.

Table 2. The isolated yields and melting point obtained for compounds **1a** – **1k**

Product	R	Time (h)	Isolated Yield (%)	M. P (°C)	
				Observed	Reported
1a	Ph-	4	87	155.7	158 – 160 [18]
1b	4- NO_2	4	83	130.3	-
1c	4-Br	4	80	168.1	165 – 167 [19]
1d	4-F	4	81	157.9	155 – 157 [20]
1e	4-Cl	4	80	147.9	147 – 148 [21]
1f	2-Cl	4	73	121.3	122 – 123 [22]
1g	2-F	4	72	150.5	148 – 152 [23]
1h	2-Br	4	70	142.7	140 – 141 [19]
1i	3-F	4	72	103.7	102 – 104 [24]
1j	3-Br	4	71	125.7	115 – 117 [24] 126 – 127 [19]
1k	4- $\text{CH}(\text{CH}_3)_2$	4	69	95.7	97 [25]

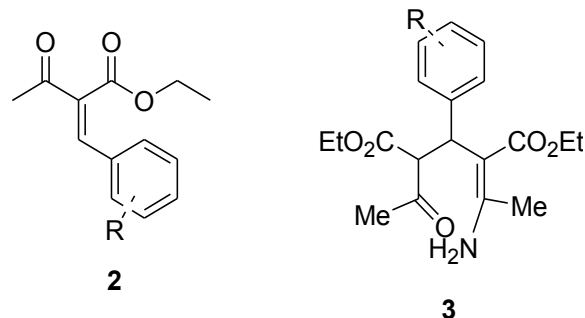
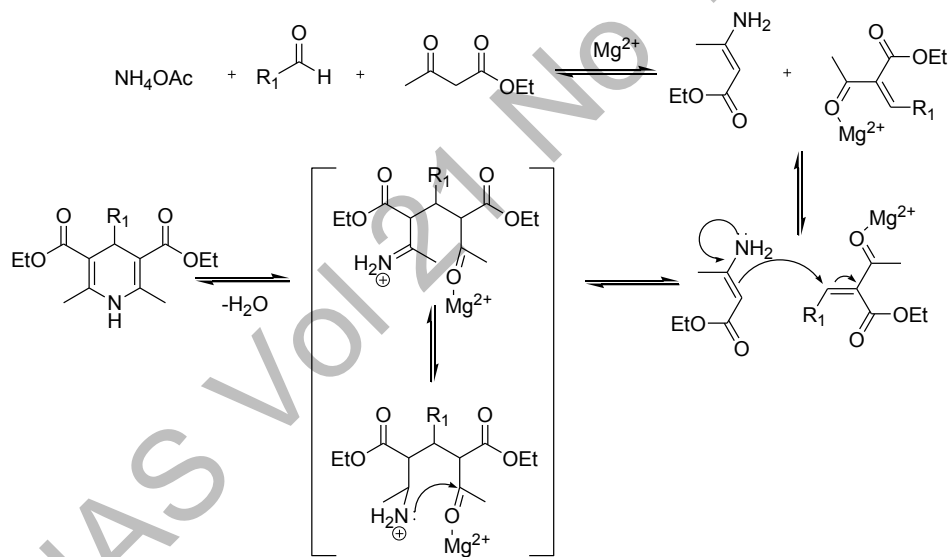


Figure 1. The side products, 2 and 3 were reported to be produced from the Hantzsch 1,4-dihydropyridine synthesis [17]

The proposed mechanism for the formation of 1,4-DHP catalyzed by MgCl_2 was elaborated in Scheme 2. Firstly, one equivalent of ethyl acetoacetate reacted with benzaldehyde to form the Knoevenagel adduct and one equivalent of ammonium acetate reacted with ethyl acetoacetate to form ester enamine. Subsequently, the Michael-type addition and condensation occurred to yield 1,4-DHP derivative as the final product. The Mg^{2+} serves as the Lewis acid catalyst in the formation of 1,4-DHP derivatives.



Scheme 2. The proposed mechanism for the formation of 1,4-DHP derivatives catalyzed by MgCl_2

Physical and spectral data

The spectroscopic data of the synthesized compounds **1a** – **1k** is as follows:

2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (**1a**)

M.p: 98.4 °C; IR (cm⁻¹): $\nu(\text{N-H})$ 3343.60, $\nu(\text{C-H})_{\text{sp}^2}$ 3088.64, $\nu(\text{CH})_{\text{sp}^3}$ 2982.34, $\nu(\text{C=O})$ 1687.24, $\nu(\text{C=C})$ 1651.62, $\nu(\text{C-N})$ 1373.70; ¹H- NMR (ppm): (t, 6H, CH₃) 1.149, (s, 6H, CH₃) 2.266, (m, 4H, CH₂) 4.018, (s, 1H, CH) 4.917, (s, 1H, NH) 5.463, (t, 2H, CH) 7.150, (m, 1H, CH) 7.047, (d, 2H, CH) 7.21; ¹³C- NMR (ppm): 19.2, 14.8, 30.2, 130.8, 60.8, 128.2, 128.6, 126.2, 100.4, 165.4, 143.6. GC-MS: m/z 329 [M+H]⁺.

2,6-dimethyl-4-(4-nitro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1c)

M.p: 130.3 °C; IR (cm⁻¹): ν (N-H) 3345.61, ν (C-H)sp² 3091.14, ν (C-H)sp³ 2987.30, ν (C=O) 1689.11, ν (C=C) 1648.32, ν (C-N) 1373.61; ¹H- NMR (ppm): (t, 6H, CH₃) 1.215, (s, 6H, CH₃) 2.294, (m, 4H, CH₂) 4.086, (s, 1H, CH) 4.951, (s, 1H, NH) 6.125, (d, 2H, CH) 7.324, (d, 2H, CH) 7.165; ¹³C- NMR (ppm): 18.9, 13.6, 30.8, 130.5, 60.6, 148.2, 123.7, 145.7, 100.8, 165.8, 142.7. GC-MS: m/z 375 [M+H]⁺.

2,6-dimethyl-4-(4-bromo-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1c)

M.p: 168.1 °C; IR (cm⁻¹): ν (N-H) 3343.10, ν (C-H)sp² 3078.12, ν (C-H)sp³ 2983.14, ν (C=O) 1689.20, ν (C=C) 1654.22, ν (C-N) 1371.21; ¹H- NMR (ppm): (t, 6H, CH₃) 1.215, (s, 6H, CH₃) 2.331, (m, 4H, CH₂) 4.087, (s, 1H, CH) 4.962, (s, 1H, NH) 5.576, (d, 2H, CH) 6.876, (d, 2H, CH) 7.247; ¹³C- NMR (ppm): 18.4, 13.8, 59.9, 30.2, 130.6, 131.8, 120.2, 136.2, 100.6, 165.4, 142.2. GC-MS: m/z 407 [M+H]⁺.

2,6-dimethyl-4-(4-fluoro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1d)

M.p: 157.9 °C; IR (cm⁻¹): ν (N-H) 3346.12, ν (C-H)sp² 3087.22, ν (C-H)sp³ 2984.32, ν (C=O) 1688.34, ν (C=C) 1653.12, ν (C-N) 1374.20; ¹H- NMR (ppm): (t, 6H, CH₃) 1.231, (s, 6H, CH₃) 2.325, (m, 4H, CH₂) 4.070, (s, 1H, CH) 4.962, (s, 1H, NH) 5.648, (d, 2H, CH) 6.879, (d, 2H, CH) 7.277; ¹³C- NMR (ppm): 18.9, 13.8, 30.8, 130.8, 60.3, 133.6, 159.4, 115.4, 100.7, 165.2, 142.8. GC-MS: m/z 347 [M+H]⁺.

2,6-dimethyl-4-(4-chloro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1e)

M.p: 177.7 °C; IR (cm⁻¹): ν (N-H) 3338.60, ν (C-H)sp² 3087.23, ν (C-H) sp³ 2982.10, ν (C=O) 1689.10, ν (C=C) 1652.24, ν (C-N) 1373.12; ¹H- NMR (ppm): (t, 6H, CH₃) 1.244, (s, 6H, CH₃) 2.336, (m, 4H, CH₂) 4.100, (s, 1H, CH) 4.962, (s, 1H, NH) 5.671, (d, 2H, CH) 7.104, (d, 2H, CH) 7.238; ¹³C- NMR (ppm): 18.7, 14.2, 30.6, 130.6, 59.6, 130.5, 128.2, 135.4, 100.8, 165.5, 143.2. GC-MS: m/z 363 [M+H]⁺.

2,6-dimethyl-4-(2-chloro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1f)

M.p: 145.6 °C; IR (cm⁻¹): ν (N-H) 3338.54, ν (C-H)sp² 3089.10, ν (C-H) sp³ 2982.27, ν (C=O) 1689.37, ν (C=C) 1653.24, ν (C-N) 1373.23; ¹H- NMR (ppm): (t, 6H, CH₃) 1.224, (s, 6H, CH₃) 2.340, (m, 4H, CH₂) 4.118, (s, 1H, CH) 4.996, (s, 1H, NH) 5.579, (d, 1H, CH) 7.075, (t, 1H, CH) 7.164, (t, 1H, CH) 6.940, (d, 1H, CH) 6.983; ¹³C- NMR (ppm): 18.1, 13.4, 20.5, 130.6, 59.8, 134.5, 100.3, 136.2, 126.4, 126.8, 128.3, 165.8, 142.2. GC-MS: m/z 363 [M+H]⁺.

2,6-dimethyl-4-(2-fluoro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1g)

M.p: 150.4 °C; IR (cm⁻¹): ν (N-H) 3337.18, ν (C-H)sp² 3089.22, ν (C-H) sp³ 2985.16, ν (C=O) 1687.46, ν (C=C) 1653.17, ν (C-N) 1372.54; ¹H- NMR (ppm): (t, 6H, CH₃) 1.224, (s, 6H, CH₃) 2.337, (m, 4H, CH₂) 4.100, (s, 1H, CH) 4.996, (s, 1H, NH) 5.630, (d, 1H, CH) 6.951, (t, 1H, CH) 6.816, (t, 1H, CH) 7.164, (d, 1H, CH) 7.074; ¹³C- NMR (ppm): 18.5, 13.6, 19.7, 130.6, 59.9, 124.5, 100.5, 115.2, 127.4, 123.9, 162.8, 165.2, 142.4. GC-MS: m/z 347 [M+H]⁺.

2,6-dimethyl-4-(2-bromo-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1h)

M.p: 145.7 °C; IR (cm⁻¹): ν (N-H) 3337.37, ν (C-H)sp² 3086.93, ν (C-H) sp³ 2983.33, ν (C=O) 1688.76, ν (C=C) 1653.70, ν (C-N) 1372.14; ¹H- NMR (ppm): (t, 6H, CH₃) 1.150, (s, 6H, CH₃) 2.267, (m, 4H, CH₂) 4.031, (s, 1H, CH) 5.663, (s, 1H, NH) 5.774, (d, 1H, CH) 7.179, (t, 1H, CH) 6.864, (t, 1H, CH) 6.893, (d, 1H, CH) 7.205; ¹³C- NMR (ppm): 18.7, 13.7, 23.1, 131.6, 59.8, 134.5, 100.8, 131.2, 127.7, 123.7, 126.8, 165.3, 142.8. GC-MS: m/z 407 [M+H]⁺.

2,6-dimethyl-4-(3-fluoro-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1i)

M.p: 151.8 °C; IR (cm⁻¹): ν (N-H) 3337.97, ν (C-H)sp² 3089.24, ν (C-H) sp³ 2983.45, ν (C=O) 1689.35, ν (C=C) 1653.66, ν (C-N) 1372.72; ¹H- NMR (ppm): (t, 6H, CH₃) 1.200, (s, 6H, CH₃) 2.291, (m, 4H, CH₂) 4.107, (s, 1H, CH) 5.360, (s, 1H, NH) 5.672, (s, 1H, CH) 6.788, (d, 1H, CH) 6.779, (t, 1H, CH) 7.124, (d, 1H, CH) 6.833; ¹³C- NMR (ppm): 18.4, 13.2, 30.2, 130.5, 59.3, 139.4, 124.8, 113.0, 118.0, 162.0, 100.8, 165.4, 142.8. GC-MS: m/z 347 [M+H]⁺.

2,6-dimethyl-4-(3-bromo-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic diethyl ester (1j)

M.p: 140.1 °C; IR (cm⁻¹): $\nu(\text{N-H})$ 3339.61, $\nu(\text{C-H})\text{sp}^2$ 3088.24, $\nu(\text{C-H})\text{sp}^3$ 2982.14, $\nu(\text{C=O})$ 1689.15, $\nu(\text{C=C})$ 1652.26, $\nu(\text{C-N})$ 1373.10; ¹H- NMR (ppm): (t, 6H, CH₃) 1.303, (s, 6H, CH₃) 2.328, (m, 4H, CH₂) 4.190, (s, 1H, CH) 4.438, (s, 1H, NH) 5.762, (s, 1H, CH) 7.233, (d, 1H, CH) 7.249, (t, 1H, CH) 7.037, (d, 1H, CH) 7.012; ¹³C- NMR (ppm): 18.7, 13.3, 29.5, 132.6, 59.8, 139.7, 130.7, 123.5, 128.6, 129.0, 100.4, 165.6, 142.8. GC-MS: m/z 407 [M+H]⁺.

4-(4-isopropyl-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (1k)

M.p: 95.7 °C; IR (cm⁻¹): $\nu(\text{N-H})$ 3337.33, $\nu(\text{C-H})\text{sp}^2$ 3090.62, $\nu(\text{C-H})\text{sp}^3$ 2869.61, $\nu(\text{C=O})$ 1692.76, $\nu(\text{C=C})$ 1655.24, $\nu(\text{C-N})$ 1370.93, $\nu(\text{C-O})$ 1211.51; ¹H- NMR (ppm): (t, 6H, CH₃) 1.207, (d, 6H, CH₃) 1.248, (s, 6H, CH₃) 2.316, (m, 1H, CH) 2.824, (m, 4H, CH₂) 4.090, (s, 1H, CH) 4.961, (s, 1H, NH) 5.732, (d, 2H, Ar-H) 7.046, (d, 2H, Ar-H) 7.178; ¹³C- NMR (ppm): 19.6, 14.3, 33.6, 127.8, 59.7, 143.8, 125.9, 146.3, 39.1, 23.9, 104.3, 167.8, 145.1. GC-MS: m/z 371 [M+H]⁺.

There are many advantages of using of MgCl_2 in the Hantzsch dihydropyridine synthesis, including the simple separation process, mildness of this technique, no side products and good yields. The alkaline earth metals are inexpensive, especially MgCl_2 which can be found ubiquitously buried in the earth's crust. Although various literatures have been generated with respect to the synthesis of 1,4-DHP derivatives, most of these methods relied on the use of an expensive, toxic chemicals or harsh condition.

Conclusion

A simple, mild and high yielding protocol for the synthesis of 1,4-DHP derivatives catalyzed by MgCl_2 , an alkaline earth metal has successfully developed. The mildness of this technique, experimental simplicity and the inexpensive of this catalyst have rendered this protocol an attractive way for the synthesis of 1,4-DHP derivatives. Furthermore, this heterogeneous catalyst can be easily removed with simple filtration technique. Further application using alkaline earth metals in other organic reactions are continuously been explored in our laboratory.

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