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Heterogeneous Catalytic Method for the One-pot Three-component Synthesis of Isoquinolonic Acid Derivatives Catalyzed by a 4Å Molecular Sieves Supported Lanthanum Catalyst

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Abstract

Lanthanum supported on 4Å molecular sieves proved to be an efficient heterogeneous catalyst for the one-pot three-component synthesis of 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acid derivatives from homophthalic anhydride, aromatic aldehydes and an amine component, ammonium acetate or aralkyl amines, with good to excellent yields. The catalyst could be recovered easily and reused without significant loss of its initial activity.

Keywords

3-aryl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids, homophthalic anhydride, lanthanum, 4Å molecular sieves, multicomponent reactions, heterogeneous catalysis, green chemistry

1 Introduction

Tetrahydroisoquinolonic acids form an important class of heterocyclic compounds since they possess exhibit several pharmaceutical and biological activities. These compounds have been demonstrated to act as anticancer [1, 2], anticonvulsant [3, 4] and antidiabetic agents [5]. Furthermore, they are known have served as starting material for the total synthesis of natural products, such as the benzophenanthridine alkaloids nitidine chloride [6] and (±)-corynoline [7], as well as the 3-arylisoquinoline alkaloid decumbenine B [8].

Tetrahydroisoquinolonic acids can be synthetized via the Castagnoli-Cushman reaction [9, 10] of homophthalic anhydride with imines [11–16] or the one-pot three component version of the reaction [17, 18]. In recent years, multicomponent reactions (MCRs) have gained much interest among synthetic organic chemists, since they allow the formation of multiple bonds in a single reaction composition within shorter reaction times providing the desired products with higher yields.

In view of the importance of tetrahydroisoquinolonic acid derivatives, it is not surprising that several synthetic procedures have been reported for the synthesis of these valuable compounds via multicomponent reaction in the presence of different catalysts, such as BF_3-Et_2O [19], $ZnCl_2$, $AlCl_3$-SiO_2 [20], $Yb(OTf)_3$ [21], $KAl(SO_4)_2 \cdot 12\ H_2O$ [22, 23], silica sulfuric acid [24], sulfonic acid functionalized silica [25], aspartic acid [26] and even an ionic liquid [27].

Our research group focuses on the elaboration of new heterogeneous catalytic methods using supported metal catalysts for the synthesis of various organic compounds. We've previously demonstrated the efficacy of numerous supported metal catalysts in a wide range of organic reactions providing the desired products with high yields, for instance 4Å molecular sieves (4A) supported lanthanum [28, 29], titanium [30, 31], zinc [32], iron [33] and copper catalysts [34, 35]. Herein we report a method for the one-pot three-component synthesis of 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acids in the presence of a heterogeneous, 4Å molecular sieves supported lanthanum catalyst.

The methods described in the literature mainly apply acidic type catalysts for the one-pot three-component preparation of 1,2,3,4-tetrahydroisoquinolinone-4-carboxylic acid derivatives. Only very few examples can be found for the base catalysed synthesis of these compounds [36, 37],

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although such a method could be useful in case of acid sensitive starting materials. Thus, the development of novel methods for the synthesis of tetrahydroisoquinolonic acid derivatives still has great importance. Our La^{3+}/4A catalyst has slightly basic properties, its pH value is 8.40. As this catalyst successfully promoted the synthesis of 2,3-dihydroquinazolin-4(1H)-ones [28] and polyhydro-quinolines [29], for the synthesis of which compounds acidic catalysts were also mainly used, we examined the reaction of homophthalic anhydride, various aromatic aldehydes, and ammonium acetate or an aralkyl amine as nitrogen source in the presence of this La^{3+}/4A catalyst.

2 Results and discussion

The structure and physicochemical properties of the La^{3+}/4A catalyst has been described earlier [28]. The characteristic cuboctahedron shape of the molecular sieve did not change after the impregnation with the lanthanum salt (see Fig. 1). The lanthanum is evenly distributed on the surface of the support. EDS showed 3.65 w/w% lanthanum on the surface, while the lanthanum content determined by ICP-OES was 3.88 w/w%. This verifies that lanthanum is distributed mostly on the surface. From the nitrogen adsorption/desorption measurements the specific surface of the catalyst is 35 m^2/g.

To optimize the reaction conditions, we investigated the model reaction of homophthalic anhydride, 4-chlorobenzaldehyde and ammonium acetate in the presence of different 4A supported metal catalysts under different reaction conditions. The results are summarized in Table 1.

Beside La^{3+}/4A, In^{3+}/4A and Zn^{2+}/4A catalysts were tested in the model reaction in refluxing acetonitrile (entries 1–3). In these reactions large amount of starting material remained in the system even after 14 hours. Heating the components without solvent at 150 °C (entries 4–6), within about 1 h the reaction mixture partly solidified that impeded the proper stirring leading to lower yields. The best result was obtained using La^{3+}/4A; thus, we chose this catalyst for our further investigations. Considerable amount of starting material could be detected by TLC and ^{1}H NMR, when the reaction was carried out in ethanol or toluene (entries 7 and 8). Based on our previous experience in the synthesis of 2,4,5-triaryl-imidazoles [31], where the reaction was started neat, then after 1 h a small amount of toluene was added to aid the stirring of the reaction mixture as the product precipitated, we applied this approach in this reaction as well. When xylene (mixture of isomers) was added after 1 h, the reaction mixture darkened, and decomposition products were found (entry 9). Then we conducted the reaction neat, 150 °C for an hour, then the temperature was reduced to 110 °C followed by the addition of 1 mL toluene, and the mixture was stirred for further 5 hours (entry 10). This way the desired product was formed with 99% yield. The optimal amount of ammonium acetate was also investigated (1 mmol, 1.1 mmol, 1.3 mmol and 1.5 mmol); the best result was obtained when 1.3 mmol was applied.

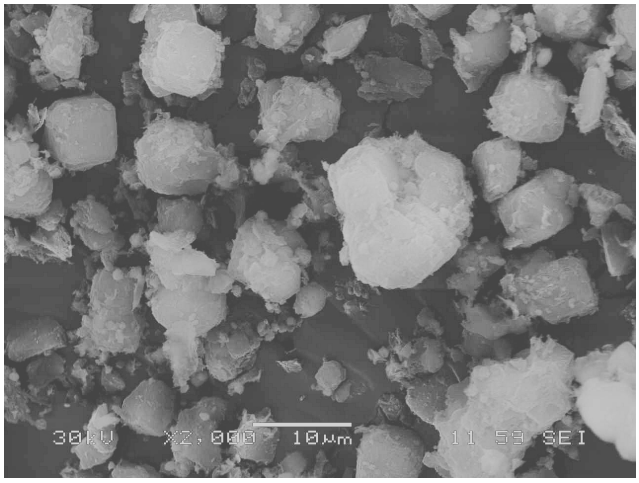
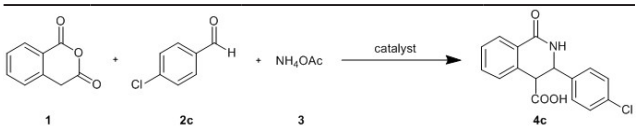


Fig. 1 SEM image of the catalyst

Table 1 Optimization of the reaction conditions[a]



1 2c 3 4c

Entry	Catalyst	Reaction conditions	Yield [%][b]
1	La^{3+}/4A	CH_3CN, reflux, 14 h	–[c]
2	In^{3+}/4A	CH_3CN, reflux, 14 h	–[c]
3	Zn^{2+}/4A	CH_3CN, reflux, 14 h	–[c]
4	La^{3+}/4A	neat, 150 °C, 6 h	78
5	In^{3+}/4A	neat, 150 °C, 6 h	67
6	Zn^{2+}/4A	neat, 150 °C, 6 h	63
7	La^{3+}/4A	EtOH, reflux, 10 h	42
8	La^{3+}/4A	toluene, reflux, 10 h	38
9	La^{3+}/4A	neat, 150 °C, then xylenes, 140 °C, 9 h	–[d]
10	La^{3+}/4A	neat, 150 °C, then toluene, 110 °C, 6 h	99[e]

[a] Reaction conditions: 1 mmol homophthalic anhydride, 1 mmol 4- chlorobenzaldehyde, 1.5 mmol ammonium acetate, 0.1 g catalyst, 3 mL solvent. In entries 9 and 10, 1 mL solvent was used.
[b] Isolated yield.
[c] The reaction was incomplete, large amount of starting material remained in the reaction mixture.
[d] Complex reaction mixture was formed.
[e] 1.3 mmol ammonium acetate was used.

We examined the reaction using a wide range of aromatic aldehydes under the optimized reaction conditions. The results are summarized in Table 2. Substituted aromatic aldehydes were reacted with homophthalic anhydride and ammonium acetate in the presence of the La^{3+}/4A catalyst to provide the corresponding 1,2,3,4-tetrahydroisoquinolone-4-carboxylic acids with good to excellent yields. The *ortho*- and *meta*-substituted aldehydes gave generally lower yields (entries 2, 4, 9) that can be explained by steric effects. Using 3-tolylaldehyde, the desired product was formed with good yield (entry 5) probably because of the smaller size of the methyl group. When benzaldehydes substituted in the para-position were used, the products were formed generally with good yields, except for 4-methoxybenzaldehyde (entry 8). No significant substituent effect could be observed in the reactions; aromatic aldehydes containing both electron-donating and electron-withdrawing groups gave similar results. Applying heteroaryl aldehydes, no product formation could be detected probably due to a polymerization-type side reaction of the aldehydes.

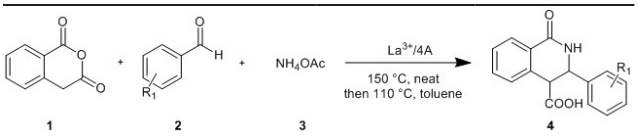
To further investigate the scope of the reaction, we applied different aralkyl amines instead of ammonium acetate in the reaction. The results are shown in Table 3. In all cases, the desired products were formed with good yields, which prove the effectiveness of our method.

According to the reported mechanisms by Yu et al. [19] and Wang et al. [21], we propose a plausible mechanism for the formation of the 1,2,3,4-tetrahydroisoquinolonic acid derivatives (Scheme 1). Though the bulk phase of the catalyst is slightly basic, lanthanum located at the surface of the 4A support forms acidic sites that may facilitate the reaction through coordination with the heteroatoms in the transition states. In the first step, the reaction of the aldehyde 2 with the amine component 3 affords an imine intermediate A, which is stabilized by the La^{3+}/4A catalyst. Subsequently, the homophthalic anhydride 1 is activated by the catalyst, leading to intermediate B. The nucleophilic attack of the nitrogen of the imine intermediate A on the carbonyl group of intermediate B provides intermediate C and finally the desired product 4.

In our previous experiments [28] it was shown that the La^{3+}/4A catalyst was stable, no leaching of lanthanum during the reaction was observed. This was confirmed also in these experiments when the catalyst was filtered out from the reaction mixture and the filtrate was subjected to an XRF examination.

The reusability of the catalyst was also examined in the reaction of homophthalic anhydride, 4-chloro-benzaldehyde, and ammonium acetate. After 6 h reaction time, the reaction mixture was worked up as described in

Table 2 Synthesis of 1-oxo-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids catalyzed by La^{3+}/4A[a]

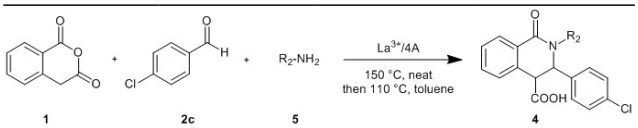


1 2 3 4

Entry	R_1	Product	Yield [%][b]
1	H	**4a**	65
2	3-Br	**4b**	40
3	4-Cl	**4c**	99
4	2-Me	**4d**	35
5	3-Me	**4e**	72
6	4-Me	**4f**	80
7	3-MeO	**4g**	78
8	4-MeO	**4h**	38
9	3-NO_2	**4i**	30
10	4-NO_2	**4j**	74

[a] Reaction conditions: 1 mmol homophthalic anhydride, 1 mmol aldehyde, 1.3 mmol ammonium acetate, 0.1 g catalyst, 150 °C, neat for 1 h, then 1 mL toluene, 110 °C, further 5 h.
[b] Isolated yield.

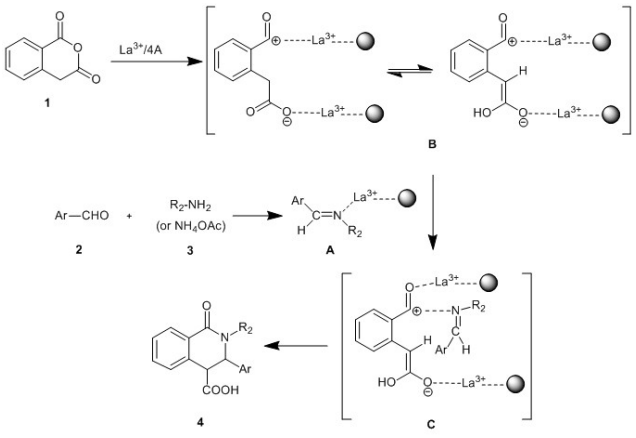
Table 3 Synthesis of 3-aryl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids from amines[a]



1 2c 5 4

Entry	Amine	Product	Yield [%][b]
1	Bn-NH_2	**4k**	80
2	4-Cl-Bn-NH_2	**4l**	75
3	$Ph(CH_2)_2$-NH_2	**4m**	65
4	$Ph(CH_2)_3$-NH_2	**4n**	62

[a] Reaction conditions: 1 mmol homophthalic anhydride, 1 mmol aldehyde, 1 mmol amine, 0.1 g catalyst, 150 °C, neat for 1 h, then 1 mL toluene, 110 °C, further 5 h.
[b] Isolated yield.



Scheme 1 Proposed mechanism of the reaction

Experimental, then the catalyst was heated at ca. 150 °C for 1 h. It was reused in two more runs without significant loss of its activity. The isolated yields in the two successive runs were 97% and 94%, respectively, this clearly demonstrates the recyclability of the catalyst. ICP-OES examination of the used catalyst showed no significant loss in the lanthanum content (3.81%).

3 Experimental

3.1 General methods

Melting points were determined on a Gallenkamp apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were made on a BRUKER Avance-500 instrument in DMSO-d6 using TMS as an internal standard.

All compounds and solvents were purchased from Merck Hungary Ltd.

3.2 Catalyst preparation

The catalyst was prepared according to the method described in [28]; 1 mmol of $La(NO_3)_3 \cdot 6H_2O$ was dissolved in 100 mL of deionised water and stirred with 1 g powdered 4A at room temperature for 24 h. The solid was filtered, washed with deionised water and with acetone, then dried in an oven at 150 °C for 1 h. Samples of the catalyst were heated at 120 °C for 1 h before the reactions.

3.3 General procedure for the synthesis of 3-substituted-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid derivatives

A typical reaction was carried out in a 10 mL flask. Homophthalic anhydride (0.16 g, 1 mmol), aldehyde (1 mmol), amine component (ammonium acetate (0.1 g, 1.3 mmol) or aralkyl amine (1 mmol)) and La^{3+}/4A (0.1 g) were stirred at 150 °C. After 1 h, the reaction mixture was cooled down to 110 °C and 1 mL toluene was added, then the mixture was stirred for further 5 h. The progression of the reaction was monitored by TLC. After completion (6 h), the mixture was cooled to room temperature and the catalyst was filtered out and washed with acetone, then the filtrate was evaporated. The residue was dissolved in 5 mL dichloromethane and was extracted with 4 × 5 mL saturated sodium bicarbonate solution. The aqueous phases were combined, and the pH was adjusted to acidic (pH 2–3) with 25% HCl solution under vigorous stirring because of the gas evolution. The precipitated solid product was filtrated off, washed with water, and dried in air overnight. The obtained product was pure and did not require further purification. The product was analyzed by ^{1}H and ^{13}C NMR spectroscopy and by comparison of its melting point to literature value:

- 1-Oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4a**):
  White solid, m.p. 177–178 °C (lit.: 181–182 °C [26]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.16 (s, 1H); 5.11 (s, 1H); 7.11–7.21 (m, 6H); 7.31 (t, J = 7.0 Hz, 1H); 7.37 (t, J = 6.5 Hz, 1H); 7.84 (d, J = 7.5 Hz, 1H); 8.46 (d, J = 3.0 Hz, 1H); 12.98 (brs, 1H).
- 3-(3-Bromophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4b**):
  White solid, m.p. 178–180 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.29 (s, 1H); 5.19 (s, 1H); 7.23–7.47 (m, 8H); 7.90 (d, J = 7.8 Hz, 1H); 8.55 (d, J = 4.2 Hz, 1H); 13.01 (brs, 1H).
- 3-(4-Chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4c**):
  White solid, m.p. 223–224 °C (lit.: 227–228 °C [26]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.23 (s, 1H); 5.17 (s, 1H); 7.26 (t, J = 8.0 Hz, 3H); 7.33 (d, J = 8.0 Hz, 2H); 7.39 (t, J = 7.0 Hz, 1H); 7.46 (t, J = 7.0 Hz, 1H); 7.89 (d, J = 7.0 Hz, 1H); 8.53 (d, J = 4.0 Hz, 1H); 13.04 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.5; 55.0; 127.2; 128.3; 128.6; 128.8; 129.3; 129.7; 132.4; 132.6; 135.0; 140.8; 164.3; 172.6. Anal. Calcd. for $C_{16}H_{12}ClNO_3$: C 63.68, H 3.98, N 4.64%, found: C 63.57, H 4.08, N 4.56%.
- 1-Oxo-1,2,3,4-tetrahydro-3-o-tolylisoquinoline-4-carboxylic acid (**4d**):
  White solid, m.p. 166–168 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.44 (s, 3H); 4.05 (s, 1H); 5.37 (s, 1H); 6.82 (d, J = 7.5 Hz, 1H); 6.99 (t, J = 7.0 Hz, 1H); 7.10 (t, J = 7.0 Hz, 1H); 7.17–7.24 (m, 2H); 7.41–7.45 (m, 2H); 7.95 (d, J = 6.5 Hz; 1H); 8.29 (s, 1H); 13.08 (brs, 1H).
- 1-Oxo-1,2,3,4-tetrahydro-3-m-tolylisoquinoline-4-carboxylic acid (**4e**):
  White solid, m.p. 198–200 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.21 (s, 3H); 4.19 (s, 1H); 5.11 (s, 1H); 6.96–7.00 (m, 2H); 7.05 (s, 1H); 7.13 (t, J = 7.5 Hz, 1H); 7.25 (d, J = 7.0 Hz, 1H); 7.37 (t, J = 7.0 Hz, 1H); 7.44 (t, J = 7.0 Hz, 1H); 7.88 (d, J = 7.0 Hz, 1H); 8.45 (d, J = 3.5 Hz, 1H); 12.95 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.8; 50.0; 54.9; 122.9; 126.4; 126.5; 127.5; 127.7; 128.0; 128.8; 129.0; 131.7; 134.4; 137.3; 141.1; 163.7; 172.1.

- 1-Oxo-1,2,3,4-tetrahydro-3-p-tolylisoquinoline-4-carboxylic acid (**4f**):
  White solid, m.p. 200–201 °C (lit.: 203–204 °C [26]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.19 (s, 3H); 4.16 (s, 1H); 5.12 (s, 1H); 7.05 (d, J = 7.5 Hz, 2H); 7.09 (d, J = 7.5 Hz, 2H); 7.24 (d, J = 7.0 Hz, 1H); 7.37 (t, J = 7.0 Hz, 1H); 7.43 (t, J = 7.0 Hz, 1H); 7.88 (d, J = 7.5 Hz, 1H); 13.00 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.5; 50.5; 55.0; 126.0; 126.6; 127.7; 128.9; 129.0; 129.3; 131.9; 134.8; 136.4; 138.4; 164.0; 172.5.
- 3-(3-Methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4g**):
  White solid, m.p. 197–198 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.66 (s, 3H); 4.23 (s, 1H); 5.12 (s, 1H); 6.74–6.77 (m, 3H); 7.17 (t, J = 7.5 Hz, 1H); 7.26 (d, J = 7.2 Hz, 1H); 7.37–7.47 (m, 2H); 7.88 (d, J = 7.2 Hz, 1H); 8.48 (d, J = 4.2 Hz, 1H); 12.99 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.8; 54.7; 111.9; 112.1; 118.0; 126.3; 127.5; 128.7; 129.1; 129.2; 131.7; 134.5; 142.8; 158.9; 163.6; 172.0. Anal. Calcd. for $C_{17}H_{15}ClNO_4$: C 68.67, H 5.05, N 4.71%, found: C 68.53, H 5.13, N 4.63%.
- 3-(4-Methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4h**):
  White solid, m.p. 233–234 °C (lit.: 235–236 °C [26]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.67 (s, 3H); 4.16 (s, 1H); 5.09 (s, 1H); 6.81 (d, J = 8.5 Hz, 2H); 7.12 (d, J = 8.5 Hz, 2H); 7.25 (d, J = 7.0 Hz, 1H); 7.38 (t, J = 7.0 Hz, 1H); 7.45 (t, J = 7.0 Hz, 1H); 7.89 (d, J = 7.5 Hz, 1H); 8.44 (d, J = 3.5 Hz, 1H); 12.93 (brs, 1H).
- 3-(3-Nitrophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4i**):
  White solid, m.p. 194–195 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.38 (s, 1H); 5.33 (s, 1H); 7.29 (d, J = 7.2 Hz, 1H); 7.38–7.50 (m, 2H); 7.59 (t, J = 7.8 Hz; 1H); 7.72 (d, J = 7.5 Hz, 1H); 7.91 (d, J = 6.9 Hz, 1H); 8.07 (d, J = 8.1 Hz, 1H); 8.12 (s, 1H); 8.67 (d, J = 4.2 Hz, 1H); 13.07 (brs, 1H).
- 3-(4-Nitrophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4j**):
  Yellow solid, m.p. 220–221 °C (decomp.) (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.32 (s, 1H); 5.32 (s, 1H); 7.27 (d, J = 6.9 Hz, 1H); 7.40–7.47 (m, 2H); 7.52 (d, J = 8.7 Hz, 2H); 7.90 (d, J = 7.2 Hz, 1H); 8.13 (d, J = 8.7 Hz, 2H); 8.64 (d, J = 4.5 Hz, 1H); 13.09 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.2; 50.2; 55.2; 124.1; 127.3; 128.1; 128.5; 129.2; 129.9; 132.7; 134.7; 147.2; 149.5; 164.3; 172.3. Anal. Calcd. for $C_{16}H_{12}N_2O_5$: C 62.54, H 3.85, N 8.97%, found: C 62.56, H 3.76, N 8.86%.
- 2-Benzyl-3-(4-chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4k**):
  White solid, m.p. 178–179 °C (lit.: 180–181 °C [22]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.01 (d, J = 15.0 Hz, 1H); 4.09 (s, 1H); 5.17 (d, J = 15.0 Hz, 1H); 5.33 (s, 1H); 7.04 (d, J = 8.0 Hz, 2H); 7.20–7.28 (m, 9H); 7.43 (t, J = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.6; 51.3; 61.0; 127.0; 127.7; 127.9; 127.9; 127.9; 128.1; 128.5; 128.8; 129.5; 131.9; 132.0; 134.0; 137.1; 138.5; 163.5; 172.1.
- 2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4l**):
  White solid, m.p. 255–256 °C (lit.: 258–260 °C [4]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.96 (d, J = 15.0 Hz, 1H); 4.12 (s, 1H); 5.18 (d, J = 15.0 Hz, 1H); 5.31 (s, 1H); 7.06 (d, J = 8.4 Hz, 2H); 7.21–7.23 (m, 1 H); 7.29–7.32 (m, 6H); 7.44 (t, J = 3.3 Hz, 2H); 7.98–8.01 (m, 1H); 12.99 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.2; 49.3; 51.0; 61.1; 127.5; 128.5; 128.6, 129.1; 129.2; 130.1; 13.6; 132.3; 132.6, 132.7, 133.9; 136.8; 138.6; 163.8; 172.3.
- 3-(4-Chlorophenyl)-1-oxo-2-phenylethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4m**):
  White solid, m.p. 196–198 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.76–2.78 (m, 1H); 3.03–3.09 (m, 1H); 4.11–4.15 (m, 1H); 4.2 (s, 1H); 5.5.7 (s, 1H); 7.13 (d, J = 8.0 Hz, 2H); 7.19–7.21 (m, 1H); 7.21–7.32 (m, 7H); 7.39–7.45 (m, 2H); 7.95 (d, J = 6.5 HZ, 1H); 13.10 (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.6; 48.0; 50.4; 60.2; 126.2; 126.8; 127.9; 128.1; 128.4; 128.5; 128.6; 128.9; 129.6; 131.9; 132.1; 133.5; 138.6; 138.9; 162.7; 171.9. Anal. Calcd. for $C_{24}H_{20}ClNO_3$: C 74.02, H 4.93, N 3.45%, found: C 73.88, H 4.81, N 3.31%.
- 3-(4-Chlorophenyl)-1-oxo-3-phenylpropyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4n**):
  White solid, m.p. 160–162 °C (lit.: –). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.83–1.86 (m, 2H); 2.51–2.56 (m, 2H); 2.84–2.87 (m, 1H); 3.45 (s, 1H); 3.87–3.89 (m, 1H); 5.52 (s, 1H); 7.02–7.29 (m, 12H); 7.86 (d, J = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.7; 33.3; 46.6; 55.4; 62,6; 126.1; 126.3; 126.6; 128.2; 128.7; 128.9; 130.5; 131.2; 131.9; 138.7; 141.9; 142.5; 163.8; 172.6. Anal. Calcd. for $C_{25}H_{22}ClNO_3$: C 71.34, H 5.23, N 3.33%, found: C 71.16, H 5.27, N 3.21%.

4 Conclusion

To sum up, lanthanum supported on 4Å molecular sieves effectively catalysed the one-pot three-component synthesis of 3-aryl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid derivatives under slightly basic conditions, which is exceedingly rare in the literature. The method provided the desired products with good yields. The preparation of the catalyst is simple, and it can be reused without considerable loss of activity.

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