

# Ceria/vinylpyridine polymer nanocomposite: an ecofriendly catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones<sup>☆</sup>

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**Abstract**—The three-component condensation of aldehydes,  $\beta$ -ketoesters and urea has been carried out in water using ceria (cerium oxide, CeO<sub>2</sub>) nanoparticles supported on poly(4vp-co-dvb) as a catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones in good yields. The catalyst was recovered easily and reused without loss of its activity.

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The development of efficient and environmentally acceptable synthetic methods is an important task of modern chemistry. Conventional organic syntheses are generally based on homogeneous catalysts. However, homogeneous reactions suffer disadvantages in separation, regeneration, etc. From the viewpoint of green chemistry, the use of heterogeneous catalysts is desirable. The consequent advantages of heterogeneous catalysts from the environmental and economic points of view are clearly understandable, since these procedures allow money to be saved and the production of waste at source to be minimized. In addition to this, the use of water as a reaction medium represents a remarkable benefit. In recent years, metal nanoparticles supported on polymers<sup>1</sup> have attracted much attention in organic transformations.

The Biginelli reaction<sup>2</sup> was first reported more than a century ago and involves the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea in ethanol. The synthesis of dihydropyrimidinones has gained much attention due to their wide range of pharmacological and biological properties.<sup>3</sup> They have

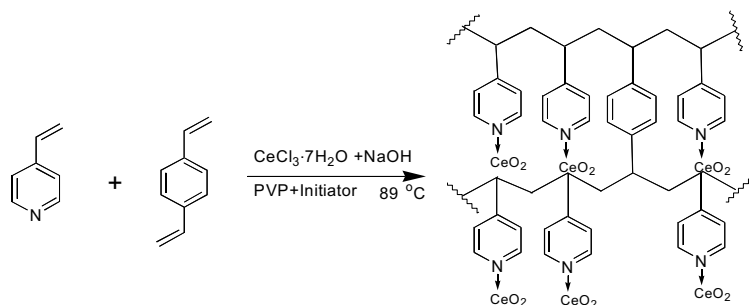
emerged as potent calcium channel blockers,<sup>4</sup> antihypertensive agents,<sup>5</sup> adrenergic<sup>6</sup> and neuropeptide Y antagonists.<sup>7</sup> Apart from this they are also of interest as agents for treating anxiety,<sup>8</sup> and optic nerve dysfunction.<sup>9</sup> Therefore, many research groups have focused their attention on the synthesis of these compounds. However, this one-pot, one-step protocol often provides low yields of the products, when substituted aromatic or aliphatic aldehydes are employed. Therefore, the use of catalysts has become essential to obtain higher yields.

3,4-Dihydropyrimidines have previously been synthesized by Biginelli reaction in the presence of strong acids and Lewis acids. These have included BF<sub>3</sub>·Et<sub>2</sub>O/CuCl,<sup>10</sup> InCl<sub>3</sub>,<sup>11</sup> LaCl<sub>3</sub>·H<sub>2</sub>O,<sup>12</sup> ZrCl<sub>4</sub>,<sup>13</sup> Yb(OTf)<sub>4</sub>,<sup>14</sup> boric acid<sup>15</sup> and silica-sulfuric acid.<sup>16</sup> However, many of these reagents are expensive, harmful and difficult to handle especially on a large scale and moreover are homogeneous in nature. Recently, we have reported a room temperature protocol using and a library generation using TMSI<sup>17</sup> and VCl<sub>3</sub>,<sup>18</sup> respectively, for the synthesis of Biginelli compounds. We now report the three-component synthesis of dihydropyrimidines in water in the presence of a heterogeneous catalyst [ceria (cerium oxide, CeO<sub>2</sub>) nanoparticles supported on poly(4vp-co-dvb) via *in situ* polymerization],<sup>19</sup> under mild conditions (Scheme 1). The catalyst can be prepared easily and has added advantages of recovery, reusability and high activity.

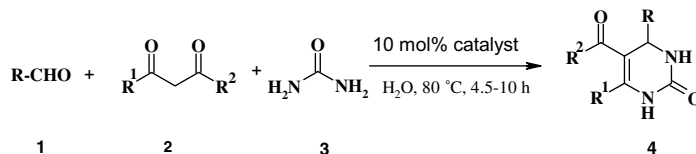
**Keywords:** Biginelli reaction; Water; Heterogeneous catalysis; Ceria nanoparticles; Reusability.

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**Catalyst** : Ceria nanoparticles supported on poly(4vp-co-dvb) via *in situ* polymerization



Scheme 1.

**Table 1.** Polymer supported ceria nanoparticles-catalyzed synthesis of dihydropyrimidinones **4**<sup>a</sup>

Entry	Esters <b>2</b>	Aldehydes <b>1</b>	Time (h)	Yield (%) <sup>b</sup> <b>4</b>
a			4.5	92
b			5.0	84
c			5.0	88
d			5.0	86
e			10	55
f			10	51
g			6.0	82
h			6.0	78
i			5.5	76
j			4.5	89
k			5.0	87
l			5.0	78

<sup>a</sup> All products are characterized by IR, <sup>1</sup>H NMR and mass spectroscopy.

<sup>b</sup> Isolated yields after purification.

Thus, the reaction of benzaldehyde **1a**, ethyl acetoacetate **2a** and urea **3** was performed in water at 80 °C for 4.5 h in the presence of 10 mol % catalyst to give 3,4-dihydropyrimidine **4a** in 92% yield. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate. The catalyst was recovered from the water by simple filtration and reused. The product was isolated from ethyl acetate and purified by recrystallization. To investigate the generality of the catalyst, various aldehydes were used to prepare the corresponding Biginelli products in good yields under similar conditions (Table 1). A variety of substituted aromatic, aliphatic and heteroaromatic aldehydes carrying either electron-donating or -withdrawing groups afforded high yields of products. Acid-sensitive aldehydes such as furfural worked well without the formation of any side products. It is noteworthy that this catalyst was also successfully used for the synthesis of methyl 6-cyclopropyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (Table 1, entry e) in moderate yield.<sup>20</sup> The products **4e** and **4f** have not been previously reported.

We also examined the reusability of the catalyst. As a model reaction, the condensation reaction of ethyl acetoacetate, benzaldehyde and urea was repeated three times with the regenerated catalyst and the yields were 92%, 89% and 85%, respectively, indicating that it is indeed a recyclable catalyst.

In conclusion, the three-component condensation has been efficiently performed in water as a 'green' solvent and by using ceria nanoparticles supported on poly(4vp-co-dvb) via in situ polymerization. The easy purification of products, easy catalyst handling, reusability of the catalyst, the use of water as solvent combined with the exploitation of a multi-component strategy open good prospects to this process for industrial applicability.

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### References and notes

- (a) Kralik, M.; Biffis, A. *J. Mol. Catal. A: Chem.* **2001**, *177*, 113–138; (b) Kralik, M.; Corain, B.; Zecca, M. *Chem. Papers* **2000**, *54*, 254–264.
- Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
- For a review on DHPMS, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
- (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Mallay, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635; (b) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119–129.
- Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811.
- (a) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT Int. WO 99 07,695, 1999; (b) Nagarathnam, D.; Wong, W. C.; Miao, S. W.; Patance, M. A.; Gluchowski, C. PCT Int. Appl. WO 97 17,969, 1997.
- Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int. Appl. WO 98 33,791, 1998.
- Horovitz, Z. P. (Squibb, E. R. and Sons). Eur. Pat. Appl. EP 1990,400,665; *Chem. Abstr.* **1991**, *115*, 64793.
- Crosson, C. E.; Potter, D. E.; Ondetti, M. A.; Floyd, D.; Aberg, G. (Houston Biotechnology Inc.; Squibb, E. R. and Sons). PCT Int. Appl. WO 1990,06,118; *Chem. Abstr.* **1991**, *114*, 157224w.
- Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454–3457.
- Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272.
- Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075–9078.
- Reddy, Ch. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657–2659.
- Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868.
- Tu, S.; Fang, F.; Miao, C.; Jiang, H.; Feng, Y.; Shi, D.; Wang, X. *Tetrahedron Lett.* **2003**, *44*, 6153–6155.
- Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889–2891.
- Sabitha, G.; Reddy, G. S. K. K.; Reddy, Ch. S.; Yadav, J. S. *Synlett* **2003**, *6*, 858–860.
- Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 6497–6499.
- Materials: 4-Vinyl pyridine (4VP), divinyl benzene (DVB), *t*-amylperoxy 2-ethylhexane carbonate (Luperox 101) and 2,5-bis(*tert*-butylperoxy) 2,5-dimethylhexane (Lupersol TAEC) were purchased from Aldrich Chemicals, USA. Polyvinylpyrrolidone (K-30) (PVP), cerium trichloride heptahydrate (CeCl<sub>3</sub>·7H<sub>2</sub>O), sodium hydroxide (NaOH) and reagent grade methanol were procured from SD Fine Chemicals, India. 4VP was purified by distillation under vacuum prior to use while the others were used as obtained without further purification.
- Preparation of poly(4vp-co-dvb)/CeO<sub>2</sub>nanocomposite:<sup>21</sup> The nanocomposite was prepared by the suspension copolymerization method using 4vp and dvb (2 mol % with respect to 4vp). To a four-neck resin kettle, fitted with a half moon Teflon blade agitator, a nitrogen purge adaptor and a reflux condenser containing 2.5% (by weight) PVP distilled aqueous solution, a mixture of 4vp, dvb, CeCl<sub>3</sub>·7H<sub>2</sub>O (5 mol % on monomers) and 2% Lupersol TAEC initiator (w/w on monomers) was added dropwise while operating the blade agitator at 650 rpm at room temperature. The nitrogen purge was continued throughout the reaction. A pH of 10 was maintained using 0.1 N NaOH for 30 min in order to obtain nanosized ceria particles. The bath temperature was raised to 89 °C and maintained for 1 h before increasing further to 100 °C. The second initiator, 1% Luperox 101 (w/w based on monomers) was then added to the reaction mixture. The reaction was allowed to proceed for 5 h with continuous agitation. The ceria nanoparticles supported on the copolymer thus formed were filtered and washed thoroughly with hot water to remove the water soluble PVP followed by methanol to remove the linear polymer and traces of unreacted monomers. The yellow coloured composite was dried overnight under vacuum at 65 °C.
- Typical procedure: To a mixture of benzaldehyde **1** (4.7 mol, 500 mg), methyl 3-cyclopropyl-3-oxo-propionate **2e** (4.7 mmol, 670 mg), urea **3** (7.1 mmol, 425 mg) and ceria nanoparticles (0.47 mmol, 650 mg) was added 5 mL

of distilled water and the reaction mixture was stirred for 10 h at 80 °C. After cooling to room temperature, ethyl acetate was added to the reaction mixture which was then filtered through a Buchner funnel. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated under reduced pressure. The crude product was recrystallized from a hexane:ethyl acetate mixture to afford pure **4e**.

Spectral data for compound **4e**: White solid, mp 113–115 °C; IR (KBr)  $\nu_{\text{max}}$  3245, 1735, 1647  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.80–1.04 (m, 4H), 3.04 (m, 1H), 3.60 (s, 3H), 5.34 (s, 1H), 6.55 (br s, NH), 7.15–7.31 (m, 5H); LS-MS:  $m/z$  273.2 (M+1).

21. Sivudu, K. S.; Reddy, K. B.; Sabitha, G.; Yadav, J. S.; Shailaja, D. *Macromol. Rapid Commun.* submitted for publication.