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CdS nanoparticles: An efficient, clean and reusable heterogeneous catalyst for one-pot procedure for synthesis of 3,4-Dihydropyrimidin-2(1H)-ones in solvent-free conditions

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ABSTRACT: 3,4-Dihydropyrimidinones and their derivatives are synthesized via Biginelli routes involving an aromatic aldehydes, ethylacetoacetates and urea in one-pot procedure by using CdS nanoparticles as efficient heterogeneous catalyst in solvent-free conditions. Compared with classical Biginelli reaction reported in 1893, this new method provides much improved modification in terms of simplicity. The present methodology offers several advantages such as a simple procedure with an easy work-up, short reaction times and excellent yields. Excellent yields and mild reaction conditions as well as the environmentally friendly character of CdS make it an important alternative to the classic acid catalyzed Biginelli's reactions. The catalysts could be recycled and reused for five times, without substantial reduction in their catalytic activities. The results are shown that electron-releasing group on aromatic ring causes reduced rate of reaction and electron with drawing group's causes increased the rate of reactions. The structure of products has been characterized by IR and ^{1}HNMR spectra.

Keywords: *CdS nanoparticles; 3,4-Dihydropyrimidinones; Heterogeneous catalyst; One-pot reactions; Solvent-free conditions*

INTRODUCTION

In recent years, notable attention has been focused on solid acid reagent in organic synthesis. Many of them are reusable easy to separation from liquid products, high stability, grater selectivity and less harm to environment (Keneva, *et al.*, 2010). The efficiency of heterogeneous catalysis has been improved by employing nano-sized catalyst, because of their extremely small size, high surface area and non-toxicity (Xia, *et al.*, 2003). Currently the study of multicomponent reactions by heterogeneous nano-sized catalysts has become an active part of ongoing research due to several advantages associated with the heterogeneous catalysts over homogeneous counterpart such as high atom efficiency, simplified isolation, easy of recovery, recyclability, non-toxicity of catalysts and minimization of metal trace in products after isolation etc. (Martinez-Castanon, *et al.*, 2005).

In the past decade, dihydropyrimidinones ($DHPM_S$) have exhibited important pharmacolo -gical and biological properties (Aly, 2008, Pinna, *et al.*, 2005, Reznik, *et al.*, 2004, Sondhi, *et al.*, 2005, Bruno, *et al.*, 2001, Gangjcc, *et al.*, 2001, Banjanac, *et al.*, 2009, Mangalagiu, *et al.*, 2001, Wamhoff, *et al.*, 1992, Kappe, 1993,

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Kappe, 2000). So the synthesis of $DHPM_S$ has been revalued. The classical synthesis of dihydropyrimidinone was the Biginelli reaction of aldehyde, ethylacetoacetate, and urea or thiourea under acidic conditions (Biginelli, 1893).

The method, however, requires harsh conditions leading often to low yields despite long reaction times. In order to circumvent these drawbacks many improvements and modifications have been developed, including microwave promotion (Li and Bao, 2003, Jain, *et al.*, 2011, Pasunooti, 2011), ultrasound irradiation (Yadav and Reddy, 2001, Li, *et al.*, 2003), ionic liquids (Peng and Deng, 2001; Abbaspour-Oliaded, *et al.*, 2014, Niralwad, *et al.*, 2010, Azimi and Hariri, 2016, Zhang, *et al.*, 2015), tetrabutylammonium bromide (TBAB) (Slimi, *et al.*, 2013), $Bi(NO_3)_3$ (Slimi, *et al.*, 2011) , Al-MCM-41 (Oskooei, *et al.*, 2011), NH_4Cl (Shaabani, *et al.*, 2003), nafion-H (Lin, *et al.*, 2007), $Cu(ClO_4)_2.6H_2O$ (Lei, *et al.*, 2011), trichloro acetic acid (Yu, *et al.*, 2011), $Fe(OTs)_3$ (Starcevich, *et al.*, 2013), $Zn((L)\text{-proline})_2$ (Siddiqui, 2013), MnO_2-MWCNT (Safari and Gandomi-Ravandi, 2013), nanomagnetic-supported sulfonic acid (Kolvari, *et al.*, 2014), SiO_2-$CuCl_2$ (Kour, *et al.*, 2014), Fe_3O_3 NP (Zamani and Izadi, 2014), boehmite nanoparticle (Keivanloo, *et al.*, 2014), L-proline nitrate (Bahekar, *et al.*, 2015), L-ascorbic acid (Kodape, *et al.*, 2015), MoO_2Cl_2 (Guggilapu, *et al.*, 2015). Chiral DHPMS via Biginelli condensation reaction have been realized (wang, *et al.*, 2011, Isambert, *et al.*, 2011, Alshammari, *et al.*, 2013). A variety of substituents including N-substituted urea (Ryabukhin, *et al.*, 2010) and *N*-acylpyruvates (Ryabukhin, *et al.*, 2010) in the components have been investigated to produce differently substituted DHPMS for however most of these procedures have significant drawbacks such as high temperature, long reaction times, and low yields of products, harsh reaction conditions and difficult workup.

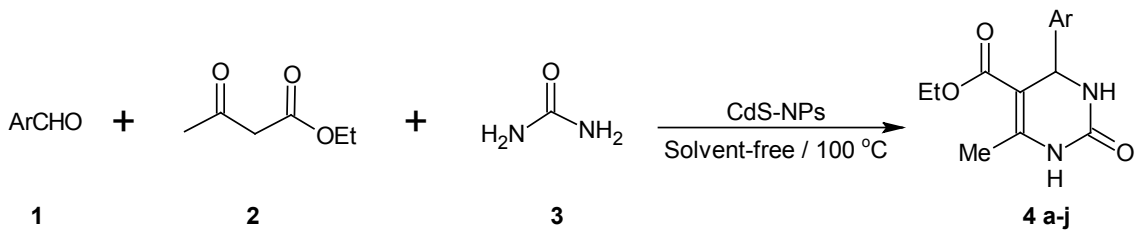
EXPERIMENTAL

All known compounds were identified by comparison of their melting points and ^{1}HNMR data with those reported in the literature. All reagents were prepared from analytical grade chemicals and purchased from Merck Company. Melting points were determined by using an Electrothermal 9100s apparatus in an open capillary tube and are uncorrected. FT-IR spectra were recorded in FT-IR Shimadzu IR-470 spectrophotometer in KBr matrix in the range of 4000-400 cm^{-1}. The ^{1}HNMR was run on a Bruker Avance DRX-400 MHz spectrometer, using TMS as the internal standard and $CDCl_3$ as solvent.

RESULTS AND DISCUSSION

In this research we report CdS-nanoparticles as efficient and reusable catalyst for synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivatives in mild, one-pot and three component procedure in solvent-free conditions. In order to determine the most appropriate reaction conditions and evaluate the catalytic activity of CdS-nanoparticles, initially, a model reaction was carried out with the aim of 3,4-dihydropyrimidin-2-(1H)-ones derivatives by the condensation of urea (1.5 mmol), ethyl acetoacetate (1 mmol) and benzaldehyde (1 mmol) using different amounts of CdS-NP's in solvent-free conditions (Scheme 1).

In the absence of catalyst, the yield of reaction was trace (Table 1, entry 1), after addition of a catalytic amount of CdS-NP's the yield of reaction increased. In order to optimize the amount of catalyst, the model



1 2 3 4 a-j

Scheme1: Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivatives in mild, one-pot and three component procedure in solvent-free conditions

reaction was repeated under different amount of catalyst. The experimental results were shown 20 mol% catalyst in 100°C after 30 min, are ideal conditions for this reaction (Table 1, entry 6). The increase in the amount of catalyst did not improve the yield of reaction (Table 1, entry 7, 8). The model reaction carried out in different solvents. The results indicate that different solvents affected the efficiency of the reaction. The results summarized in Table 3. Thus, using 20 mol% of CdS-NP's in solvent-free conditions at 100 °C was selected as the optimized condition for the synthesis of 4a. To show the ability of catalyst, different aromatic aldehydes were reacted with urea and ethyl acetoacetates under optimized conditions. In all cases the 4a-j compounds were obtained in excellent yields. The results summarized in Table 2. The recyclability of catalyst was investigated. To investigate these properties, the reaction of urea, benzaldehyde and ethyl acetoacetate was selected as the model. After completion the reaction, the catalyst was collected, washed with acetone and after drying, we reused in the next similar procedure. The results showed that the catalyst can be reused up to six runs without any significant loss in its activity.

General procedure for synthesis of 3,4-dihydropyrimidin-2(1H)-ones (4a-j)

A mixture of different aromatic aldehydes (1 mmol), ethyl acetoacetate (1 mmol), urea (1.4 mmol) and CdS-NP's (0.2 mmol) as catalyst were poured into a test tube in solvent-free conditions were stirred for an appropriate time. The progress of reaction was monitored by TLC. After completion of the reaction, the hot EtOH was added to the mixture and the heterogeneous insoluble CdS-NP's catalyst was separated by filtration. The residue solution was evaporated in vacuum condition, the collected impure solids were recrystallized with ethanol: water (1:1) and the pure products were obtained. Selected spectral data for some products:

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a).

White powder; Yield: 88%; mp: 205-207°C; IR (ν_{max}/ cm^{-1}) (KBr): 3244, 3116 (NH Str.); 3010 (arom. CH Str.); 1704 (ester, C=O Str.); 1647 (amid, C=O Str.); 1596 (arom. C=C Str.); ^{1}HNMR (400 MHz $CDCl_3$) δ (ppm): 1.06 (3H, t, J = 7.1 Hz, CH_3); 2.24 (3H, s, CH_3); 3.95 (2H, dq, CH_2); 5.27 (H, d, J = 1.93 Hz, CH); 6.55 (H, s, NH); 7.13-7.25 (5H, m, Ar-H); 8.67 (H, s, NH).

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4d).

White powder; Yield: 92%; mp: 209-211°C; IR (ν_{max}/ cm^{-1}) (KBr): 3228, 3120 (NH Str.); 3010 (arom. CH Str.); 1731 (ester, C=O Str.); 1704 (amid, C=O Str.); 1643 (arom. C=C Str.); 1519, 1350 (NO_2 Str.); ^{1}HNMR (400 MHz $CDCl_3$) δ (ppm): 0.97 (3H, t, J = 6.7 Hz, CH_3); 2.14 (3H, s, CH_3); 3.86 (2H, dq, CH_2); 5.24 (H, d, J = 1.9 Hz, CH); 7.11 (H, s, NH); 7.32 (2H, d, J = 8.0 Hz, Ar-H); 7.94 (2H, d, J = 7.9 Hz, Ar-H); 8.80 (H, s, NH).

5-(Ethoxycarbonyl)-4-(2-Chloro phenyl)-6-methyl-3, 4-dihydro pyrimidin-2(1H)-one (4f).

White powder; Yield: 89%; mp: 219-220°C; IR (ν_{max}/ cm^{-1}) (KBr): 3352, 3228 (NH Str.); 3112 (arom. CH Str.); 1702 (ester, C=O Str.); 1650 (amid, C=O Str.); 1586 (arom. C=C Str.); ^{1}HNMR (400 MHz $CDCl_3$) δ (ppm): 0.94 (3H, t, J = 7.1 Hz, CH_3); 2.29 (3H, s, CH_3); 3.86 (2H, dq, CH_2); 5.71 (H, d, J = 2.6 Hz, CH); 6.23 (H, s, NH); 7.06-7.23 (4H, m, Ar-H); 8.97 (H, s, NH).

5-(Ethoxycarbonyl)-4-(4-dimethylamino-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4h).

Yellow powder; Yield: 80%; mp: 253-254°C; IR (ν_{max}/ cm^{-1}) (KBr): 3249, 3115 (NH Str.); 3012 (arom. CH Str.); 1700 (ester, C=O Str.); 1647 (amid, C=O Str.); 1614 (arom. C=C Str.); ^{1}HNMR (400 MHz $CDCl_3$) δ (ppm): 1.08 (3H, t, J = 4.3 Hz, CH_3); 2.22 (3H, s, CH_3); 2.85 (6H, s, $N(CH_3)_2$); 3.95 (2H, dq, CH_2); 5.18 (H, d, J = 1.9 Hz, CH); 6.21 (H, s, NH); 7.04 (2H, d, J = 7.0 Hz, Ar-H); 7.12 (2H, d, J = 6.8 Hz, Ar-H); 8.43 (H, s, NH).

5-(Ethoxycarbonyl)-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4i).

White powder; Yield: 89%; mp: 212-214°C; IR (ν_{max}/ cm^{-1}) (KBr): 3244, 3116 (NH Str.); 3010 (arom. CH Str.); 1704 (ester, C=O Str.); 1650 (amid, C=O Str.);

Table 1: Effect of CdS-NP's catalyst amount on the model reaction [a]

Entry	Catalyst (mol%)	T (°C)	Time (min)	Yield (%)[b]
1	None	80	150	trace
2	10	80	100	30
3	15	90	80	55
4	20	90	60	68
5	20	90	35	72
6	20	100	30	88
7	20	110	40	87
8	25	100	50	86
9	30	100	50	85

[(a)] Reaction condition: Benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), urea (1.4 mmol) and CdS-NP's (different amount) under solvent-free conditions at different temperature; [(b)] Isolated yields

Table 2: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones-2(1H)-ones 4a-j [a]

Entry	Aromatic aldehyde	Product	Yield (%)[b]	Mp°C	
				Found [c]	Reported [Ref]
1	C_6H_5CHO	4a	88	205-207	207 (Wamhoff, *et al.*, 1992)
2	4-ClC_6H_4CHO	4b	92	210-211	212 (Mangalagiu, *et al.*, 2001)
3	4-$MeOC_6H_4CHO$	4c	84	205-206	202 (Mangalagiu, *et al.*, 2001)
4	4-$NO_2C_6H_4CHO$	4d	92	209-211	207 (Pinna, *et al.*, 2005)
5	3- $NO_2C_6H_4CHO$	4e	90	222-224	226-228 (Pinna, *et al.*, 2005)
6	2- ClC_6H_4CHO	4f	89	219-220	222-223 (Reznik, *et al.*, 2004)
7	3-$MeOC_6H_4CHO$	4g	84	200-201	203-204 (Reznik, *et al.*, 2004)
8	4-$(CH_3)_2NC_6H_4CHO$	4h	80	253-254	256-258 (Reznik, *et al.*, 2004)
9	4-MeC_6H_4CHO	4i	89	212-214	215-216 (Reznik, *et al.*, 2004)
10	Salicylaldehyde	4j	85	205-207	201-203 (Reznik, *et al.*, 2004)

[(a)] Reaction condition: Aromatic aldehyde (1mmol), ethylacetoacetate (1 mmol), urea (1.4 mmol) and CdS-NP's (0.2 mmol) under solvent-free conditions at 100°C; [(b)] Isolated yields; [(c)] Uncorrected

Table 3: The effect of solvent on model reaction at refluxing conditions [a]

Entry	Solvent	T (min)	Yield [b]
1	CH_2Cl_2	180	trace
2	$CHCl_3$	150	trace
3	CH_3OH	100	76
4	CH_3CH_2OH	100	70
5	CH_3CN	80	68
6	THF	100	70
7	Toluene	80	72
8	H_2O	120	35
8	Solvent-free	50	88

[(a)] Reaction condition: Benzaldehyde (1mmol), ethylacetoacetate (1 mmol), urea (1.4 mmol) and CdS-NP's (0.2 mmol); [(b)] Isolated yields

1461 (arom. C=C Str.); ^{1}HNMR (400 MHz $CDCl_3$) δ (ppm): 1.19 (3H, t, J = 7.1 Hz, CH_3); 2.33 (3H, s, CH_3); 2.36 (3H, s, CH_3); 4.04 (2H, dq, CH_2); 5.39 (H, d, J = 1.7 Hz, CH); 6.17 (H, s, NH); 7.13 (2H, J = 7.6 Hz, Ar-H); 7.22 (2H, d, J = 7.8 Hz, Ar-H); 8.11 (H, s, NH).

CONCLUSIONS

In summary we have introduced CdS-NP's as a new highly efficient, reusable and green catalyst for the one-pot, three component synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions.

The promising points for the presented methodology are the high efficiencies, generality, short reaction times, clean method, environmentally compatibility, easiness of isolation of product and excellent reusability of the catalyst. The present method gave the products good yields at reduced reaction time, which might be due to the increased reactivity of the reactions on high surface area of CdS-NP's.

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