22% Co/CeO_2-ZrO_2-catalyzed Synthesis of 1, 2, 3, 4-tetrahydro-2-pyrimidinones and -thiones

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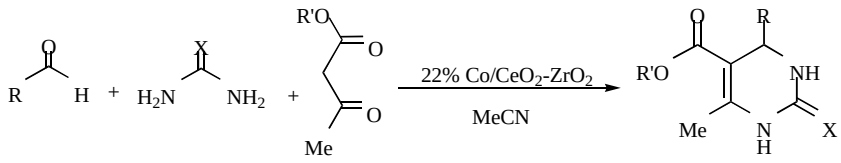
Abstract: Three-component condensation reaction of an aldehyde with β-ketoester and urea or thiourea in acetonitrile to afford the dihydropyrimidinones and thions (DHPMs) in the presence of 22% Co/CeO_2-ZrO_2 nano fine particle as a novel, reusable and green catalyst is reported. Utilizing of 22% Co/CeO_2-ZrO_2 nano fine particle catalyst also offers a cleaner process in that it can be reused and will not bring additional pollutants into the "environment" that is agreeable green chemistry point of view.

Keywords: 22% Co/CeO_2-ZrO_2, aldehydes, dihydropyrimidinones.

INTRODUCTION

Functionalized 3,4-dihydropyrimidin-2(1H) ones and their sulfur analogs represent a class of heterocyclic system that has attracted a considerable interest of organic and medicinal chemists due to interesting pharmacological and structural [1] profiles such as antiviral, antibacterial, antitumor, anti-inflammatory properties [2], as antihypertensive agents as well as calcium channel blockers, and α-1a-antagonists and neuropeptide antagonists [3]. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety [4]. The most important of them are Batzelladine alkaloids which have been found to be potent HIV gp-120-CD_4 inhibitors [5]. The most simple procedure for the synthesis of dihydropyrimidinones reported by Biginelli in 1893, involves the acid-catalyzed condensation of a, β-ketoester with aromatic aldehyde derivatives and urea/thiourea [6]. Several methods with catalysts, reagents and others techniques in organic synthesis [7] are also reported. However, some of them are associated with expensive and toxic reagent, stiochiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Thus, there is still a need for a simple and general procedure for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions.

Owed to importing of these pharmacological compounds, the synthesis of unprecedented DHPMs is also demanded. Therefore, in connection with our research using green and nano catalyst in organic reaction [8] and expansion of our study on multi component synthesis [9], herein, we are interested to report a simple and green method for the preparation of authentic and unknown 1,2,3,4-tetrahydro-2-pyrimidinones and -thiones in high yields from the reaction of various aldehydes, benzyl, ethyl and methyl acetoacetate, urea and thiourea in the presence of catalytic amount of 22% Co/CeO_2-ZrO_2 nano fine particles refluxing acetonitrile (Scheme **1**).



X= O, S R'= Me, Et, Bn

Scheme 1.

RESULTS AND DISCUSSION

The reaction conditions (solvent, temperature, and catalyst amount) were studied to optimize this procedure. At first, a model reaction was chosen for the synthesis of 5-ethoxy carbonyl-4-phenyl-6-methyl-3, 4-dihydropyrimidin-2(1H) one (**4a**). For this purpose, we carried out the model reaction under solvent-free conditions at room temperature and at 100 ^{0}C, but the product resulted on a trace. Then the effect of water, ethanol and acetonitrile was examined in the

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Table 1. Effect of Temperature and Varying the Solvent on the Yield of 4a.

Entry	Solvent	Temp. (°C)	Yield%
1	free	r.t./100	trace/15
2	H_2O	50/ reflux	30/45
3	EtOH	50/ reflux	55/60
5	CH_3CN	50/ reflux	78/93

Table 2. 22%Co/CeO_2-ZrO_2 Nano Fine Particles Catalyzed Synthesis of Dihydropyrimidinones and Thiones.

Entry	R_1	Product	R_2	X	Time(h)	Yield(%)	MP(°C) Found	MP(°C) Reported[Ref.]
1	Ph-	4a	Et	O	2.0	93	202–205	206-207 [11]
2	4-Cl-C_6H_4	4b	Et	O	2.0	92	209–211	210-212 [12]
3	4-NO_2-C_6H_4	4c	Et	O	2.5	85	206-208	207-208.5 [11]
4	3-NO_2-C_6H_4	4d	Et	O	7.0	90	224-226	226-227.5 [11]
5	4-OCH_3-C_6H_4	4e	Et	O	6.0	92	198-202	226-227 [13]
6	2-OCH_3-C_6H_4	4f	Et	O	5.0	88	253-260	258-259 [11]
7	4-CH_3-C_6H_4	4g	Et	O	2.5	86	199-204	212 [11]
8	4-Me_2N-C_6H_4	4h	Et	O	3.0	93	230–234	251-252 [14]
9	4-Br-C_6H_4	4i	Et	O	4.0	85	195-199	199 [15]
10	4-OH-C_6H_4	4j	Et	O	4.0	90	232-238	198–200 [14]
11	2-Cl-C_6H_4	4k	Et	O	4.0	91	215-217	220-223 [16]
12	2-Pyridyl	4l	Et	O	6.0	93	189–194	194-95 [17]
13	3-NO_2-C_6H_4	4m	Me	O	5.0	88	269–272	273-275 [18]
14	4-NO_2-C_6H_4	4n	Me	O	6.0	84	228-232	235-237 [11]
15	4-OCH_3-C_6H_4	4o	Me	O	5.0	95	185–189	190-192 [13]
16	4-Cl-C_6H_4	4p	Me	O	2.0	93	198-202	203-205 [19]
17	Ph-	4q	Et	S	2.0	90	185–190	190-192 [14]
18	4-OCH_3-C_6H_4	4r	Et	S	2.5	96	155-158	152-154 [13]
19	2-HO-C_6H_4	4s	Et	S	2.0	88	204-208	206-208 [20]
20	4-OH-C_6H_4	4t	Et	S	6.0	93	189-193	193-194 [14]
21	4-CH_3-C_6H_4	4u	Et	S	2.5	84	185-190	192-194 [21]
22	3,4-diOMe.C_6H_3	4v	Et	S	4.0	87	200-204	212-214 [20]
23	4-Me_2N-C_6H_4	4w	Et	S	5.0	88	198-201	209-210 [21]
24	4-Me_2N-C_6H_4	4x	Me	S	3.0	90	155-162	152-155 [12]
25	4-OCH_3-C_6H_4	4y	Bn	O	2.0	95	195-198	186-187 [18]
26	2-OCH_3-C_6H_4	4z	Bn	O	3.0	92	188-191	199-200 [22]
27	Ph-	4a'	Bn	O	3.0	95	172-174	169-171 [18]
[a]28	Ph-CH=CH	4b'	Bn	O	6.0	91	195	[New]
[a]29	2,4-diCl-C_6H_3	4c'	Bn	O	2.0	87	160	[New]
[a]30	4-NO_2-C_6H_4	4e'	Bn	S	3.0	85	215	[New]
[a]31	2,4-diCl-C_6H_3	4f'	Bn	S	5.0	92	203-206	[New]

model reaction under heating conditions. The best result was obtained in acetonitrile under reflux condition.

The 0.02 g of catalyst was optimized for 1mmol of aldehyde in the model reaction. Using excess of catalyst (0.1 g), did not show further increasing in yield. To study the effect of catalyst, the model reaction was carried out in the absence of catalyst in refluxing acetonitrile, but the reaction rate was very low. Clearly, the catalyst is an affecting component for this reaction. To establish the scope of these novel synthesis protocols, variety of aldehydes were subjected under the optimized reaction conditions. Both electron poor and rich aryl aldehydes gave excellent yields (Table **2**). The method is not applicable to aliphatic aldehydes.

Four compounds are also new dihydropyrimidinone and thione derivatives (entries 28-31, Table **2**). Their physical and spectroscopic data of the known product were in good

Table 3. The Various Catalysts that were Used in One-Pot Three Component Synthesis of 4a.

Ref.	Yield (%)	Time(h)	Mol% or g	Catalyst
14	90	4	10	$ZrCl_4$
18	90	3	40	NH_4Cl
21	91	3	10	$TiCl_4$-$MgCl_2$.$4CH_3OH$
20	92.31	0.06	25	HCOOH/MW
23	96	0.6	1.5	TBAB
13	75	22	20-100	$SbCl_3$
26	94	15	0.3g	PPE
15	96	0.33	0.35-0.50	N-butyl-N,N-dimethyl-α-phenylethylammonium bromide
24	96	3	0.25g	Nafion-NR-50
25	98	7	10	$InBr_3$
26	97	0.75	5-10	$TaBr_5$
27	77.8	6	5	$Sr(NO_3)_2$
29	92	3	10	LiBr
30	70	10	40	PPh_3
31	87	0.15	0.5-1.0	$Fe(ClO_4)_3$
This work	92	0.8	0.02g	22%Co/CeO_2-ZrO_2

adaptable conditions with those of authentic samples and new derivative compounds having been shown in experimental section. The reusability of the catalyst was also studied. At the end of the reaction, the product was filtered off, washed by diethyl ether, and dried at 40 °C. Then the catalyst was subjected for three runs. After three runs, the catalytic activity of the catalyst was almost the same as those of the freshly used catalysts (93, 91, 90% yields, entry 1, Table **5**). Small size of the catalyst also indicates a large external surface area which causes its improved catalytic performance. However, this interesting nano catalyst has previously shown high catalytic activity in (POM) or syngas reactions [10].

To show the merits of this catalytic method, the results of the formation of **4a** (Entry 1, Table **2**) were compared with previously reported catalytic methods. The advantages of our method are evident regarding the catalyst amount and high yield which are very important in chemical industry especially when it is combined with easy separation.

EXPERIMENTAL

The Synthesis of Nano Fine 22% Co/ ZrO_2CeO_2 Catalyst by Co-Precipitation Method

0.8 mole Ce $(NO_3)_3.6H_2O$, 0.2 mole $ZrOCl_2.8H_2O$ solution and $Co(NO_3)_2.6H_2O$ were dissolved in the mixture of distilled water, isopropyl alcohol and tylose (hydroxyl ethyl cellulose) as a dispersant, and the resulting solution was transferred to a round- bottom flask, to this solution, an aqueous solution of 20% KOH (w/w) was added drop-wise at 80°C with constant stirring to attain an alkaline pH of 9-10 at 80°C. The precipitate was digested at 80-90°C for suitable time. After that, they were thoroughly washed with distilled water several times to remove any potassium impurity and then initially air-dried for 48h, followed by drying at 100-120˚C for 6h. This material was finally calcined at 800-850˚C in an aerobic environment to get the final nanocatalyst product [10].

Spectra Data of the Catalyst

XRD pattern of 22% Co over the CeO_2-ZrO_2 as support

Powder X-ray diffraction (XRD) analysis of the catalysts was carried out by PW1840-philips with Cu K α radiation. Fig. (**1**) shows XRD patterns of nanospherical catalysts after calcination at 800-850°C. 22%Co indicates $Ce_{0.75}Zr_{0.25}O_2$ cubic structure with crystallite size of 32nm. This data is in accordance with the preparation of nanocatalyst.

SEM Image of Typical 22%Co Nanoparticale

SEM image for nanoparticle 22% Co over the ZrO_2-CeO_2 mixed oxide after calcination has shown morphology and homogeneous spherical nanoparticle in Fig. (**2**).

The Synthesis of Dihydropyrimidinones

In a two-neck flask, ethyl acetoacetate (5 mmol), aldehyde (5 mmol), urea (10 mmol) and acetonitrile (5 ml) were heated under reflux condition for indicated times in the Table **2**. The progress of the reaction was monitored by TLC. Upon completion of the reaction, acetonitrile was evaporated and boiling ethanol (40 ml) was added. At once, the catalyst was filtered off and the product was recovered at ambient temperature. For more purification, the solid residue recrystallized using ethanol and dihydropyrimidine derivatives was obtained in high yields.

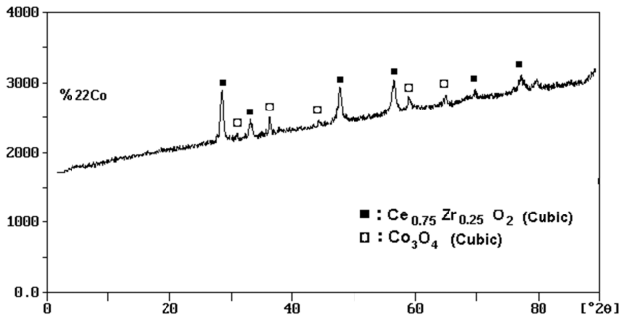

Fig. (1). XRD pattern 22% Co/ZrO_2CeO_2 nanoparticles catalysts.

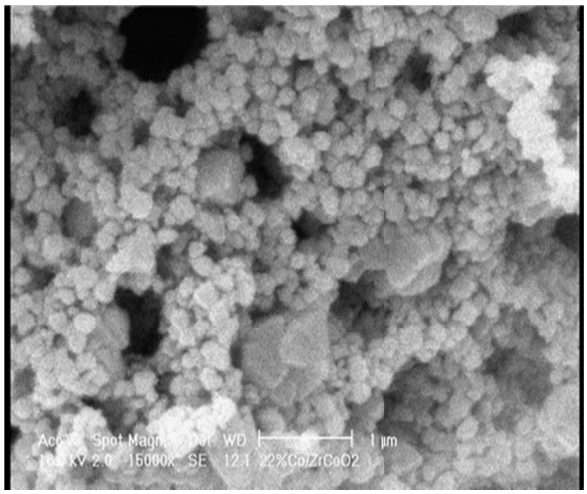

Fig. (2). SEM image and morphology of 22% Co nanoparticle catalyst.

Physical and Spectra Data for New Compounds

(E)-5-benzyloxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one (28): Mp 195°C; IR (KBr): υ [cm-1]3245, 3110, 3028, 2960, 1711, 1648, 1459, 1436, 1385, 1332, 1311.1H NMR (DMSO-d6, 300 MHz): δ(ppm) 9.21(s, 1H, NH), 7.55(s, 1H, NH), 7.21-7.38(m, 10H, arom), 6.32(dd, 1H, CH=CH), 6.13-.21(dd, 1H, CH=CH), 5.08 (d, 1H, CH_2) 5.19 (d, 1H, CH_2), 4.75(s, 1H, CH), 2.20 (s, 3H, CH_3). ^{13}C NMR: δ (ppm) 15.0, 48.9, 68.9, 108.2, 126.4, 128.7, 135.2, 141.2, 145.8, 150.3, 167.2. $C_{21}H_{20}N_2O_3$ GC/MS(M^+): 348.147. Eln. Anal. C, 72.10; H, 5.59; N, 7.94.

5-benzyloxycarbonyl-6-methyl-4-(2,4-dicholoro-phenyl)-3,4-dihydropyrimidin-2(1H)-one (29): Mp 160°C IR (KBr): υ [cm-1]3442,3301, 3067, 3034, 2974, 1718, 1656, 1590, 1547, 1498, 1470, 1456, 1377. ^{1}HNMR (DMSO-d6, 300 MHz) 9.23 (1H, s, NH), 7.25 (s, 1H, NH), 7.30–7.24 (m, 4H, arom.), 7.17–6.88 (m, 5H, arom.), 5.58 (s, 1H, CH), 5.02– 4.93 (m, 2H, CH_2Ph), 2.36 (s, 3H, CH_3). ^{13}C NMR: δ(ppm) 174.5, 167.2, 158.8, 140.9, 133.7, 130.2, 126.8, 141.2, 68.9, 45.5, 15.6 $C_{19}H_{16}Cl_2N_2O_3$ GC/MS(M^+): 390. Eln. Anal. C, 55.91; H, 3.66; Cl, 17.41; N, 6.83.

5-benzyloxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (30): Mp 215°C; IR (KBr): υ [cm-1]3280, 3182, 3087, 1733, 1607, 1567, 1518, 1451, 1439, 1384, 1349, 1320. ^{1}H NMR (DMSO-d6, 300 MHz): δH 2.25 (s, 3H, CH_3), 4.99 and 5.04 (d, 2H, OCH_2), 5.32 (s, 1H, CH), 6.83–7.27 (9H, m, arom.), 7.68 (1H, s, NH), 9.21 (1H, s, NH). ^{13}C NMR: δ (ppm) 174.5, 167.2, 158.8, 149.3, 141.2, 129.0, 127.2, 120.9, 106.0, 68.9, 54.6, 5.6; $C_{19}H_{17}N_3O_4S$ GC/MS: 383 (M^+); Eln. Anal C, 59.32; H, 4.26; N, 10.74.

5-benzyloxycarbonyl-6-methyl-4-(2,4-dicholoro-phenyl) -3,4dihydropyrimidin-2(1H)- thione (31): Mp 203-206°C; IR (KBr): υ [cm-1] 3285, 3030, 1692, 1638, 1584, 1567, 1463, 1372, 1312. ^{1}H NMR (300 MHz, DMSO) δ(ppm) 10.44 (s, 1H, NH), 9.62 (s, 1H, NH), 6.98-7.50(m, 8H, arom), 5.61 (s, 1H, CH), 5.05(d, 1H, CH_2), 4.92 (d, 1H, CH_2), 2.31 (s, 3H, CH_3). ^{13}C NMR: δ(ppm) 173.5, 167.2, 157.8, 140.9, 133.6, 130.2, 126.5, 141.2, 68.9, 45.5, 15.6 $C_{19}H_{16}Cl_2N_2O_2S$ GC/MS(M^+): 406. Eln. Anal. C, 55.66; H, 3.49; Cl, 16.93; N, 6.68.

Recyclability of the Catalyst

The reusability of the catalyst was also studied. At the end of the reaction, the catalyst was removed by filtration and washed with diethyl ether. The recycled catalyst could be subjected to a second or even another reaction. In the case of the model reaction, after three runs the catalytic activity of the catalyst was almost the same as that of the freshly used catalyst (Table **4**).

CONCLUSION

In conclusion, we have described a simple modification of the Biginelli dihydropyrimidinone and thion synthesis and developed four unprecedented DHPMs 22% Co/CeO_2-ZrO_2-catalyzed as a novel catalyst in refluxing acetonitrile. High yields of the products, mild reaction conditions and simple procedure make this protocol complementary to the existing methods. Further, the catalyst can be easily recovered and reused without a considerable loss in its activity that is adopted from green chemistry point of view. Another important aspect of this procedure is survival of a variety of functional groups such as NO_2, Cl, OH, OMe, N, N-dimethyl, 2-pridyl and cinnamyl under the reaction conditions.

Table 4. Reusability of the Catalyst was Examined by the Model Reaction at 2.0 h.

Entry	Run(s)	RCHO	Yield (%)
1	Fresh	Benzaldehyde	93
2	1st	"	90
3	2nd	"	90
4	3th	"	88

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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