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Application of tris (trihexyltetradecylphosphonium) gadolinium hexachloride as magnetically recoverable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in solvent-free conditions

Maryam Gorjizadeh

Department of Chemistry, Shoushtar Branch, Islamic Azad University, Shoushtar Iran
E-mail address: m.gorjizadeh@iau-shoushtar.ac.ir

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Abstract

A Simple and environmentally friendly procedure for the one-pot multi-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives has been developed by one pot three component reaction of various aldehydes, β-dicarbonyl, and urea in the presence of catalytic amount of tris (trihexyltetradecylphosphonium) gadolinium hexachloride $[P_{6,6,6,14}]_3$ $[GdCl_6]$ as a solid acid catalyst without any additional organic solvent. The reactions were carried out at 100 °C under solvent-free conditions. The solid magnetic catalyst was prepared by a simple method and readily separated from the reaction media by external magnet and has excellent reusability several cycles without considerable loss of activity. The advantages of this method are low scale catalyst, waste-free, inexpensive catalyst, solvent-free conditions and easy work up, green and efficient synthetic entry to high yield of products (80-92 %) in a high reusability and a short

reaction time (20-45 min). This is the first report on for direct use of $[P_{6,6,6,14}]_3$ $[GdCl_6]$ as catalyst in organic transformation.

Keywords: 3,4-Dihydropyrimidin-2(1*H*)-ones, Tris (trihexyltetradecylphosphonium) gadolinium hexachloride, Magnetic ionic liquid, Aldehyde**s**.

Introduction

Room temperature ionic liquids (RTILs) are defined as salts that are liquid below room temperature. They exhibit very interesting physicochemical properties including thermal stability, non-volatility, non-flammability, high thermal, high conductivity and controlled miscibility properties by the appropriate selection of the cation or anion in their structure [1-6]. Recently, considerable attention has been focused on magnetic ionic liquids (MILs), Magnetic ILs are one group of room temperature ionic liquids (RTILs) which exhibit an unexpectedly strong response to magnetic fields. These properties make magnetic ILs have more advantages than conventional ILs in the fields of catalytic reactions, photophysical properties, solvent effects and separation processes [7-15]. Del Sesto and co-workers have described a large variety of MILs with iron, Fe(III), cobalt, Co(II), and manganese, Mn(II)-containing anions. Furthermore, the incorporation of lanthanide ions (i.e. Gd, Nd or Dy) into MILs offers the advantage of a metal ion that has a considerably higher effective magnetic moment than transition metals [16].

3,4-dihydropyrimidin-2(1*H*)-ones are an important class of heterocyclic compounds with broad spectrum of biological activities. 4-Substituted 3,4-dihydropyrimidin-2(1*H*)-ones have revealed antibacterial [17], antiviral [18], antioxidative [19], anti-inflammatory [20], and antihypertensive properties [19]. 3,4-dihydropyrimidin-2(1*H*)-ones find use as calcium channel blockers and also act as neuropeptide Y (NPY) antagonists [21]. The common synthetic route to these compounds

involves the three component cyclocondensation reaction of β-dicarbonyl compounds, aromatic aldehyde and urea with a variety of reagents such as $SbCl_3$ [22], $Cu(NH_2SO_3)_2$ [23], CsF–Celite [24], $H_3PMo_{12}O_{40}$ [25], Al-MCM-41 [26], I_2 [27], $V(HSO_4)_3$ [28], triethylammonium hydrogen sulfate [29], Nafion-H [30] and Nano-Silica phosphoric acid [31]. However, some of these methods suffer from disadvantages such as long reaction times, low yields, safety problems, cost of the reagents and tedious work-up. Therefore, it seems that a major task of current research is to replace less efficient procedures with more acceptable methods based on improved, stable, and recoverable catalysts. Herein, tris (trihexyltetradecylphosphonium) gadolinium hexachloride $[P_{6,6,6,14}]_3$ $[GdCl_6]$ has been successfully applied to provide a series of 3,4-dihydropyrimidin-2(1*H*)-one . The method provides rapid and easy access to dihydropyrimidinone compounds in high to excellent yields. To the best of our knowledge, there is no reports for direct use of $[P_{6,6,6,14}]_3$ $[GdCl_6]$ as catalyst in organic transformation.

2. Experimental

2.1. General

All products were characterized by comparison of their physical data, IR, ^{1}H NMR, and ^{13}C NMR spectra with authentic samples. ^{1}H NMR and ^{13}C NMR spectra were taken on a 400 MHz Brucker Spectrometer. IR spectra were recorded on Bomem MB-Series 1998 FT-IR spectrometer. Melting points were measured by KSPIN apparatus. All chemical materials were purchased from the Merck Chemical Company, Darmstadt, Germany. The purity determination of the products and reaction monitoring were accomplished by TLC on polygram SILG/UV 254 plates.

General procedure for the synthesis of tris (trihexyltetradecylphosphonium) gadolinium hexachloride

For our investigations, $[P_{6,6,6,14}]_3$ $[GdCl_6]$ was prepared according to the literature procedure [32]. To a solution of trihexyl (tetradecyl) phosphonium chloride (50 gr) in dichloromethane was added gadolinium(III)chloride hexahydrate (11.92 g) and the mixture was stirred at room temperature for 24 h. Upon completion of the reaction, Water (15 mL) was added and extracted with dichloromethane (3×15 mL). The combined organic layers solution was dried over $MgSO_4$. The solvent was concentrated in vacuo; the resulting product was stirred at 60 ^oC overnight.

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

Aldehyde (1 mmol), ethylacetoacetate (1 mmol), urea (1.5 mmol) and the magnetic ionic liquid $[P_{6,6,6,14}]_3$ $[GdCl_6]$) (100 mg) were added to a round bottom flask. This mixture was heated at 100 °C for the appropriate time indicated in Table 2. At the end of the reaction, the mixture was cooled to room temperature, $CHCl_3$ (20 mL) was added to the reaction mixture. The magnetic ionic liquid was magnetically separated from the product solution. 4-substituted 3,4-dihydropyrimidin-2(1*H*)-ones were obtained by evaporation of the solvent, followed by recrystallization from methanol.

Results and Discussion

To show the catalytic activity, synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones through coupling of aldehyde, ethylacetoacetate and urea is selected to represent activity of the prepared catalysts. In order to optimize the reaction conditions, initially, the reaction of benzaldehyde, ethylacetoacetate and urea was selected as model reaction. The reaction was optimized for the various parameters such as temperature, solvent and catalyst .To investigate the effect of reaction

temperature, the reaction was performed initially in solvent free condition at various temperature (Table 1 entries 1–5). The best result was obtained at 100 °C. Increasing in the reaction temperature up to 120 °C led to a decrease in the yield of desired product due to the increasing in by-products and emission of the volatile precursors from the reaction media. To optimize the catalyst amount, the reaction was performed in the presence of various amount of the catalyst and according to the obtained results (Table 1, entries 6–9) 100 mg of the catalyst was chosen as the best catalyst amount. The effect of solvent was also investigated by performing the model reaction in the presence of 100 mg catalyst in various solvents (Table 1, entries 10–12). The model reaction in the presence of dichloromethane as solvent showed convenient yield but it suffered from high loading of catalyst and long reaction time (Table 1, entry 10).

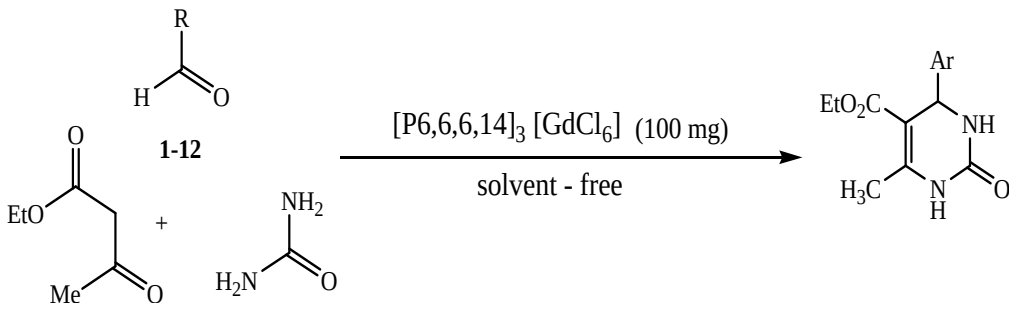
Table 1 Optimization of reaction conditions for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of catalytic amount of $[P_{6,6,6,14}]_3$ $[GdCl_6]$

No	Temp. (°C)	Catalyst amount(mg)	Solvent	Time (min)	Yield [a] (%)
1	80	100	-	45	70
2	90	100	-	45	85
3	100	100	-	45	90
4	110	100	-	40	85
5	120	100	-	40	80
6	100	60	-	45	60
7	100	80	-	45	75
8	100	90	-	45	80
9	100	110	-	45	90
10	Reflux	110	CH_2Cl_2	55	90
11	Reflux	100	THF	55	75

12	Reflux	100	$PhCH_3$	60	70

Thereafter, the above optimized reaction conditions were explored for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives (Scheme 1) and the results are summarized in Table 2. As shown in Table 2, this procedure is rather general for a wide variety of electron donating as well as electron withdrawing aromatic

aldehydes.



Scheme 1

This procedure is also convenient for aliphatic aldehydes (Table 2, entry 13-14). Due to the paramagnetic nature of the $[P_{6,6,6,14}]_3$ $[GdCl_6]$, separation of the catalyst is very easy and workup of the reaction is simple. After completion of the reaction, simple filtration of the reaction mixture and recrystallization give the product in high purity. Another important feature of this procedure is the survival of a variety of functional groups under the reaction conditions.

Table2. One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

No	R	Time (min)	Yield [a] (%)	Mp (°C)
1	Ph	45	89	131-133
2	4-Cl–C_6H_4	25	82	183-186
3	4-Me–C_6H_4	30	81	139-141

4	4-MeO–C_6H_4	40	85	151-153
5	4-O_2N–C_6H_4	20	80	155-156
6	3-O_2N–C_6H_4	25	89	167-170
7	3-Br–C_6H_4	30	92	106-108
8	2,4-Cl_2–C_6H_3	20	85	197-199
9	4-CN–C_6H_4	20	87	180-182
10	2-OH-5-Br	35	86	230-231
11	3-Pyridyl	30	84	128-130
12	2-Furyl	25	91	99-100
13	n-C_3H_7	45	81	107-109
14	C_6H_{11}	45	86	100-102

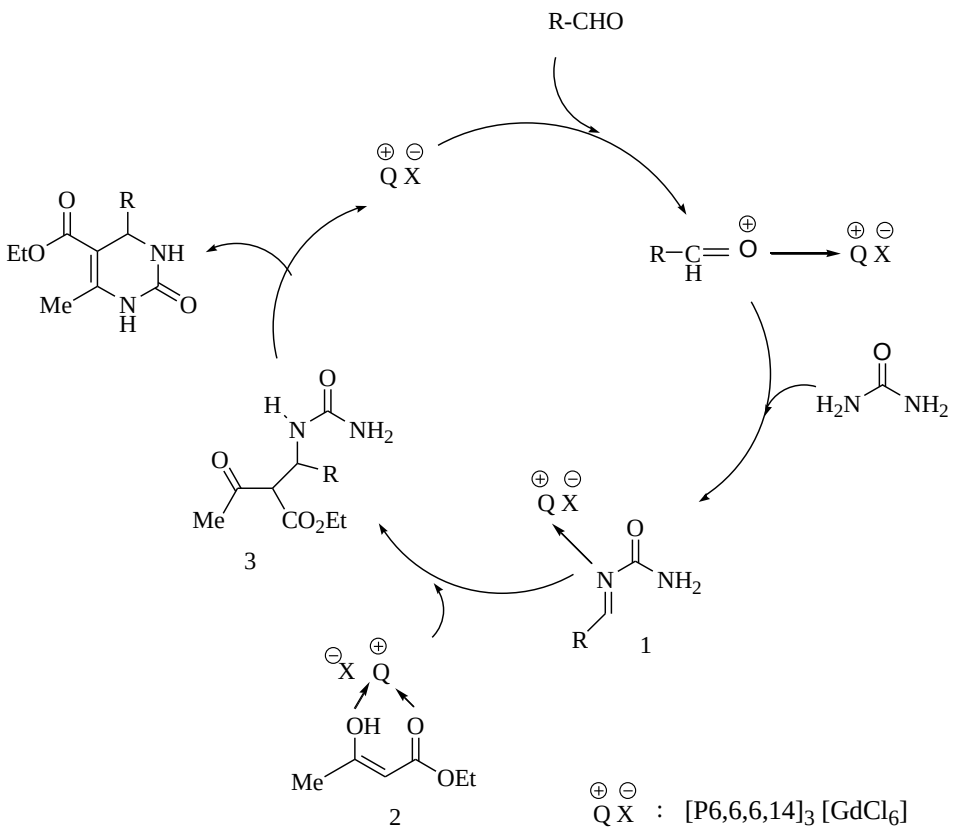
[a]Isolated yield based on the aldehyde.

The recovery and reusability of the catalyst is very important from practical and economical point of views. Therefore, the reusability of $[P_{6,6,6,14}]_3$ $[GdCl_6]$**,** was investigated using multiple sequential synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one from reaction of benzaldehyde, ethylacetoacetate and urea under magnetic ionic liquids catalysis. For each of the repeated reactions, the catalyst was recovered, washed exhaustively with ethyl acetate and ethanol, successively, and dried before being used with fresh benzaldehyde. The catalyst was consecutively reused four times without significant loss of its activity (Table 3). Blank experiment in the absence of catalyst was also investigated in the reaction of benzaldehyde, ethylacetoacetate and urea. The obtained results showed that only small amounts of product was detected in the absence of catalyst in the reaction mixture.

Table 3 Reusability of the catalyst in the model reaction

Entry	Fresh	Cycle 1	Cycle 2	Cycle 3
Yield (%)	89	85	82	78
Time (min)	45	45	45	45

A Plausible mechanism is shown in Scheme 2. Aldehyde and imine intermediate formed by the reaction of the aldehyde and urea are activated by the $[P_{6,6,6,14}]_3$ $[GdCl_6]$. The ionic liquid also acts as a Lewis acid, catalyzing the addition of acyl imine 1 to the β-ketoesterenolate 2, to furnish intermediate 3. Cyclization of 3 gives the final product and releases of the catalyst for the next catalytic cycle.



Scheme 2

4. Conclusions

In summary, we have presented the tris (trihexyltetradecylphosphonium) gadolinium hexachloride is an efficient, eco-friendly and reusable catalyst for synthesis of Biginelli type

compounds under solvent-free condition. Short reaction times, high yields of the desired products, low cost, simple experimental and work-up procedures are some advantages of this method.

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