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Metallophthalocyanines (MPcs) as efficient heterogeneous catalysts for Biginelli condensation: Application and comparison in catalytic activity of different MPcs for one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

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Abstract

The catalytic efficiency of various metallophthalocyanines was investigated for three-component condensation reaction of aldehyde, β-dicarbonyl compound and urea to afford corresponding 3,4-dihydropyrimidinones. These phthalocyanine complexes were found to be efficient, recyclable heterogeneous catalyst and showed rate enhancements, high yields and short reaction times in this transformation. Among the various metallophthalocyanines studied, cobalt(II)- phthalocyanine was found to be most active for this transformation.

Keywords: Biginelli reaction; Metallophthalocyanines; Heterogeneous catalysis; Dihydropyrimidinones

1. Introduction

Evolution of clean and environmentally benign chemical processes using less hazardous catalysts has become a primary goal in synthetic organic chemistry. In particular, running a reaction under heterogeneous condition is more promising since it involves the facile recovery and reuse of the expensive catalyst [1,2]. Metallophthalocyanine complexes (MPcs) structurally similar to metal porphyrins, are easily accessible, more stable to degradation than porphyrins, have been extensively used to catalyze a variety of organic reactions [3–6]. Being insoluble in common organic solvents they can be easily separated from the reaction mixture by filtration and reuse without further treatment.

Thus, metallophthalocyanines behave like heterogeneous catalysts without having the inherent limitation of leaching commonly associated with heterogeneous and heterogenized homogeneous catalysts.

3,4-Dihydropyrimidin-2-(1*H*)-ones and their synthetic analogues are widely known to possess diverse therapeutic and pharmaceutical properties including antiviral, antitumor and antibacterial activities [7–9]. In addition to this, these compounds can act as calcium channel modulator, antihypertensive and α-1a-antagonist. Thus, due to their great importance the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal chemistry. Biginelli condensation first reported in 1983 [10], which involves the acid catalyzed one pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones. However, this method suffers from the drawbacks such as the lower yields of the desired products (20–40%) particularly in case of substituted aldehydes and loss of sensitive functional groups during the reaction. Therefore, in the recent years several improved methodologies mainly using Lewis acids [11–15], triflates [16–19], silica–sulfuric acid [20], silver salts of heteropoly acids [21], silica supported sodium hydrogen sulfate [22], iodine–alumina system [23], poly(4-vinylpyridine-co-divinylbenzene)–Cu(II) complex [24], iodotrimethylsilane [25], solid super acid [26], ion-exchange resins [27] L-proline [28], microwave assisted methodologies [29–30], ultrasonic mediated [31], ionic liquid mediated [32–33] ceria/vinyl pyridine polymer [34], $KAl(SO_4)_2 \cdot 12H_2O$ supported on silica [35]and polyoxometallates [36] have been reported in the literature. However, in spite of their potential utility many of the existing methods involve the use of expensive reagents, strong acidic conditions, longer reaction times, tedious work-up,

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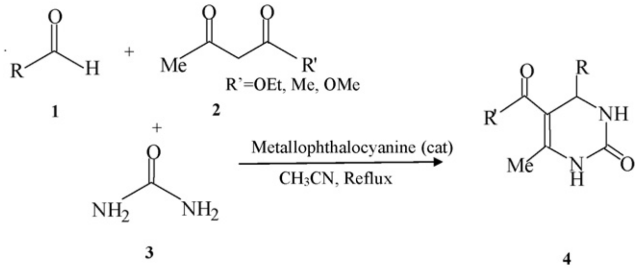

Scheme 1.

multi step preparation of catalyst, environmental disposal problems and moreover use of homogeneous catalysts which are difficult in separation from reaction mixture for reuse. Therefore, in spite of a large number of methods reported for this transformation, there is still need to develop a more efficient, simple, milder and high yielding protocol using reusable and environmentally friendly catalyst. In continuation to our studies on development of new synthetic methodologies herein [37–40], we report for the first time the application of metallophthalocyanines as reusable heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidinones through one-pot cyclocondensation of aldehyde, urea and dicarbonyl compound under mild reaction conditions (Scheme 1).

2. Results and discussion

To evaluate the catalytic efficiency of various metallophthalocyanines, the condensation of 4-nitrobenzaldehyde, ethylacetoacetate and urea was studied by using different metallophthalocyanines as catalysts and acetonitrile as solvent for 1.5 h under refluxing condition. These results are summarized in Table 1 and show that Co(II)Pc is the most active catalyst followed by tetraphenoxyvanadyl (II)- and Fe(II)-phthalocyanines, Cu(II)- and Ru(II)-phthalocyanines were found to be least active for this reaction. In a controlled blank experiment reaction was found to be very slow in the absence of catalyst and afforded very poor yield of the corresponding 3,4-dihydropyrimidinone (Table 1, entry 13). Furthermore, the use of 2 mol% catalyst is sufficient to promote the reaction, further increase in catalyst concentration from 2 to 10 mol% showed only marginal enhancement in reaction rates (Table 1, entries 2, 10–12). The effect of various solvents was also studied for the formation of dihydropyrimidinone using benzaldehyde, ethyl acetoacetate and urea as substrates. Acetonitrile was found to be most promising solvent in terms of reaction time and yield than all other solvents tested such as THF, ethanol, acetone and benzene (Table 1, entries 6–10).

In order to examine the versatility of cobalt(II)-phthalocyanine [Co(II)Pc], a variety of aliphatic, heterocyclic and aromatic aldehydes both having electron withdrawing and donating groups were reacted with ethylacetoacetate and urea in presence of catalytic amount of Co(II)-phthalocyanine under similar reaction condition. Results of these experiments are presented in Table 2. All the aldehydes studied were smoothly converted to their corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields, which were identified by comparing their physical (mps) and spectral data (1H NMR and IR) with those of authentic samples. Other functional groups such as double bond, OMe, OH were remained intact under these reaction conditions. The use of methyl acetoacetate and acetyl acetone as 1,3-dicarbonyl moieties in place of ethyl acetoacetate also gave similar results as shown in Table 2 (entry 16–21). To examine the reusability of the catalyst, the condensation of benzaldehyde, urea and ethylacetoacetate in presence of catalytic amounts of Co(II)-phthalocyanine was chosen as a model reaction. After completing the reaction, the catalyst could be separated from the reaction mixture by filtration and reused as such for subsequent experiments (up to 3 cycles), afforded the comparable yields of the product as shown in Table 3, indicating that the catalyst does not lose its activity and can be reused as such with out further treatment. Furthermore the reaction was found to be slow at room temperature and could be conducted more efficiently in refluxing acetonitrile. This developed protocol not only affords the 3,4-dihydropyrimidinones in high yields with enhanced reaction rate but also solve the environmental disposal problems, associated with the use of homogeneous or liquid acid catalysts. The MPcs are easily

Table 1
Biginelli condensation using different metallophthalocyanines as catalysts under different reaction conditions

Entry	Substrate	MPc	Reaction time (h)	Solvent	Catalyst concentration (mol%)	Yields (%)[a]
1	4-Nitrobenzaldehyde	Co(II)Pc	1.5	CH_3CN	2	97
2	4-Nitrobenzaldehyde	VO(II)Pc	2.5	CH_3CN	2	85
3	4-Nitrobenzaldehyde	Fe(II)Pc	2.0	CH_3CN	2	90
4	4-Nitrobenzaldehyde	Ru(II)Pc	6.0	CH_3CN	2	40
5	4-Nitrobenzaldehyde	Cu(II)Pc	4.5	CH_3CN	2	45
6	Benzaldehyde	Co(II)Pc	2.5	EtOH	2	92
7	Benzaldehyde	Co(II)Pc	5.5	C_6H_6	2	75
8	Benzaldehyde	Co(II)Pc	6.0	CH_3COCH_3	2	55
9	Benzaldehyde	Co(II)Pc	3.0	THF	2	82
10	Benzaldehyde	Co(II)Pc	1.0	CH_3CN	2	98
11	Benzaldehyde	Co(II)Pc	0.75	CH_3CN	5	98
12	Benzaldehyde	Co(II)Pc	0.50	CH_3CN	10	98
13	Benzaldehyde	Co(II)Pc	5.0	CH_3CN	–	Trace

Reaction conditions: aldehyde (5 mmol), urea (5 mmol), ethyl acetoacetate (5 mmol), solvent (5 ml) and catalyst (2–10 mol%) at refluxing temperature.

[a] Isolated yields.