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1,3-Dichloro-5,5-dimethylhydantoin as a Novel and Efficient Homogeneous Catalyst in Biginelli Reaction

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A new and efficient method for the preparation of substituted 3,4-dihydropyrimidin-2(1*H*)-ones *via* Biginelli synthesis using catalytic amounts of 1,3-dichloro-5,5-dimethylhydantoin is presented. Short reaction times, easy work-up, high yields of products and stability, easy-handling, non-toxicity and cheapness of the catalyst are noteworthy advantages of the present work.

Key Words: 3,4-Dihydropyrimidin-2(1*H*)-one, 1,3-Dichloro-5,5-dimethylhydantoin, Homogeneous, Aldehyde, *β*-Dicarbonyl

Introduction

Dihydropyrimidinones (DHPM) are an important class of organic compounds which have attracted special attention during the last decade due to their wide range biological and pharmaceutical activities. Dihydropyrimidinone derivatives have been found as calcium channel blocker,[1] alpha-1a-antagonist,[2] neuropeptide Y (NPY) antagonist[3] and antiviral, antitumor, antibacterial, antiinflammatory,[4-6] antihypertensive[7] and antimalarial[8] agents. The most important examples of pharmaceutically active dihydropyrimidinone derivatives are cambrine[3] and batzelladine[9] alkaloids, which have been isolated from marine sources and are potent HIV group-120-CD4 inhibitors.

The most common and extensively used method for the preparation of dihydropyrimidinone derivatives is Biginelli reaction which first has been described by the Italian chemist Pietro Biginelli more than a century ago.[10] This reaction involves a one-pot three-component condensation of *β*-dicarbonyl, aldehyde and urea. The original Biginelli reaction was performed under strong acidic conditions and led to poor yields of products. Up to now, numerous methods have been developed for the modification of Biginelli reaction.[11,12] Various catalysts and reaction conditions have been studied. Although some of the reported procedures have been successfully used for this purpose, most of them have several disadvantages such as long reaction times, low yields of products, anhydrous or strong acidic conditions and use of expensive and /or toxic catalysts. Therefore, we set out to find a simple method for the efficient preparation of dihydropyrimidinone derivatives.

1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) is a stable, inexpensive and commercially available heterocycle which has rarely used as a source of chlorine ion or radical in chlorination[13] or oxidation[14] reactions. It has been also exploited for decontamination of water.[15] But, as our knowledge, there are a few reports of catalytic application of DCDMH in organic synthesis. However, we were interested to examine the catalytic activity of DCDMH as a homogenous catalyst in the preparation of DHPs *via* Biginelli reaction.

Experimental

All materials are commercial reagent grades and were prepared from Merck or Fluka. ^{1}H NMR spectra were recorded on a Bruker AVANCE 500 MHz. Melting points were taken on a Bamstead Electrothermal apparatus.

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. A mixture of aldehyde (1 mmol), ethyl acetoacetate or acetylacetone (1 mmol), urea (1.5 mmol) and DCDMH (0.05 mmol) in CH_3CN was placed in a round-bottomed flask and stirred under reflux conditions. After completion of the reaction as indicated by TLC (n-hexane/EtOAc, 4:1), mixture let to cool to room temperature and crushed ice was added. The precipitate was filtered, washed with cold water, dried and recrystallized in EtOH to afford pure product in good to excellent yields.

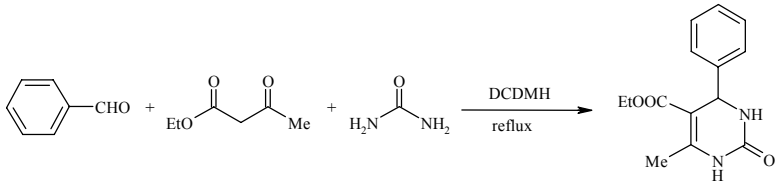
Physical and spectral data of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (Table 2, entry h). mp 197 - 198 °C; ^{1}H NMR (DMSO-d_6) δ 1.08 (t, J = 7.5 Hz, 3H), 2.24 (S, 3H), 3.71 (S, 3H), 3.97 (q, J = 7.5 Hz, 2H), 5.23 (d, J = 2.7 Hz, 1H), 6.88 (d, J = 8.58 Hz, 2H, ArH), 7.13 (d, J = 8.58 Hz, 2H, ArH), 7.67 (S, 1H, NH), 9.15 (S, 1H, NH).

Results and Discussion

In order to find the best reaction conditions, we started our study on the Biginelli reaction using DCDMH as catalyst by a model reaction (Scheme 1). Benzaldehyde reacted with ethyl acetoacetate and urea in the presence of various amounts of the catalyst. Different molar ratios of substrates were also examined. The optimum amounts were found to be 1:1:1.5:0.05 for benzaldehyde, ethyl acetoacetate, urea and DCDMH respectively.

Next, the model reaction was performed in different solvents such as ethanol, methanol, acetonitrile, methylene chloride, acetone and water (Table 1). As observed in Table 1, the best result was obtained in acetonitrile after 4 hours.

In order to show the catalytic effect of DCDMH, the reaction



Scheme 1

Table 1. The reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of DCDMH in different solvents after 4 h

Entry	Solvent	Yield (%)[a]
a	EtOH	65
b	MeOH	50
c	MeCN	89
d	CH_2Cl_2	30
e	acetone	25
f	H_2O	0

[a]Isolated yields.

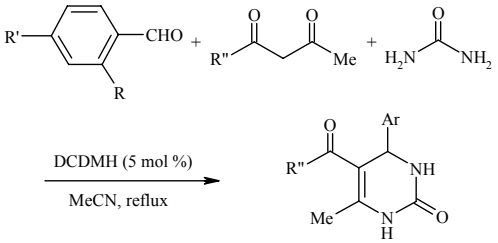
of benzaldehyde, ethyl acetoacetate and urea was carried out in the absence of the catalyst under optimized reaction conditions which result in only 5% of product after 4 hours. This result indicates that DCDMH is a highly efficient catalyst in the synthesis of DHPs. Furthermore, stability of DCDMH was examined by heating the catalyst at 110 °C for 3 hours. The heated DCDMH then used in model reaction under the same reaction conditions. Analysis of the reaction mixture showed that, this reaction was performed successfully without any loss of catalytic activity of DCDMH.

The scope and efficiency of the current procedure was investigated by the reaction of a series of aromatic aldehydes, ethyl acetoacetate or acetylacetone and urea in the presence of DCDMH (Scheme 2). Corresponding dihydropyrimidinones were obtained in good to excellent yields in appropriate times according to Table 2.

As shown in Table 2, the reaction of electron-withdrawing substituted benzaldehydes (entries b-e, k) lead to the products in very good yields. But, the yields decrease slightly with electron-donating substituted benzaldehydes (entries f-i, l) due to their stability rather than electron-withdrawing substituted ones.[16]

The applicability of the current method for the large scale synthesis was also examined by the reaction of 5 mol benzaldehyde with 5 mol ethyl acetoacetate and 7.5 mol urea in the presence of 0.25 mol DCDMH. The product was isolated in 91% yield after 4 hours.

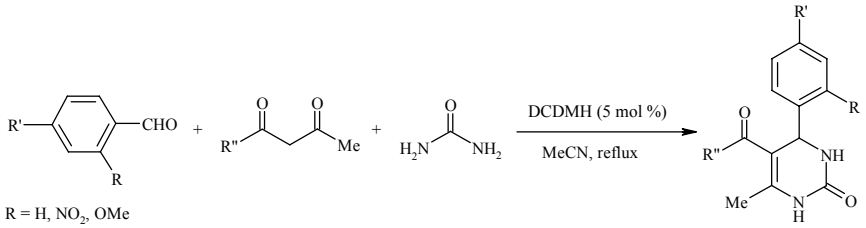
Table 2. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of DCDMH



Entry	R	R'	R"	Time (h)	Yield (%)[1,2,3]
a	H	H	OEt	4	89[11a]
b	NO_2	H	OEt	3	94[11b]
c	H	NO_2	OEt	3	97[11c]
d	H	Cl	OEt	3	92[11c]
e	H	Br	OEt	6	92[11d]
f	H	OH	OEt	5	51[11e]
g	OMe	H	OEt	3	74[11e]
h	H	OMe	OEt	3	67[11c]
i	H	Me	OEt	5	88[11f]
j	H	H	Me	5	63[11a]
k	H	NO_2	Me	3	85[11a]
l	H	Me	Me	4	81[11g]

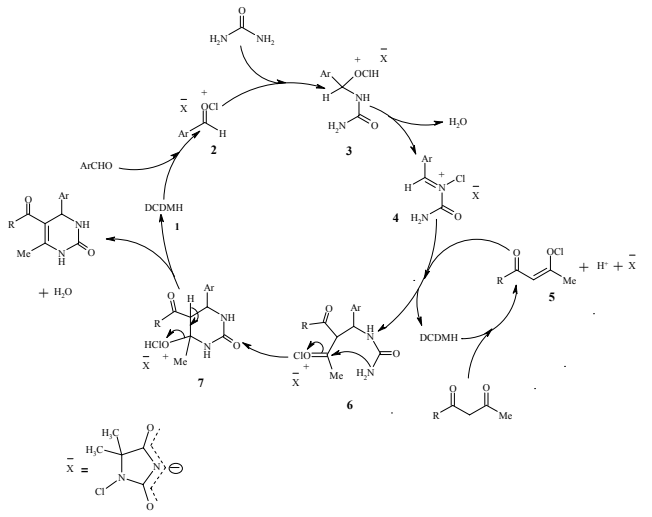
[a]Products were identified by comparison of their physical and spectral data with those reported in the literatures. [b]Isolated yields. [c]References for known compounds.

According to the mechanism presented by Kappe in 1997,[17] a reasonable reaction mechanism for the DCDMH catalyzed Biginelli condensation is shown in Scheme 3. 1,3-Dichloro-5,5-dimethylhydantoin **1** releases chlorine ion which activates the carbonyl group of aldehyde by formation of oxygrn cation. The reaction follows by nucleophilic attack of urea to activated aldehyde **2** which leads to **3** and **4**. Then nucleophilic attack of



R = H, NO_2, OMe
R' = H, NO_2, Cl, Br, OH, Me, OMe
R" = OEt, Me

Scheme 2



Scheme 3

Table 3. Comparison of some other procedures with the present method for the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Entry[ref]	Catalyst (mol %)	Solvent	Reaction conditions	Time (h)	Yield (%)
1	DCDMH (5)	MeCN	reflux	4	89
3[11e]	PPh_3 (10)	---	100 °C	10	70
6[12a]	KSF (50%, w/w)	---	130 °C	48	82
2[12h]	$SbCl_3$ (20)	MeCN	reflux	24	89
4[12i]	$Si(OEt)_4$·$FeCl_3$ (10)	MeCN	reflux	24	91
5[12j]	$ZnCl_2$ (25)	EtOH	reflux	7	73

enolate **5** to activated imine **4** is performed to afford **6** and **7**. And finally, dehydration of **6** produces 3,4-dihydropyrimidin-2(1*H*)-one and releases Cl^+ ion to return to catalytic cycle (Scheme 3).

In order to show the high catalytic activity of DCDMH, we have compared our result with obtained results by some other procedures for the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one *via* Biginelli reaction (Table 3). The data presented in this table show the promising feuture of this method in terms of molar ratio of the catalyst, reaction rate, the activity of the catalyst and, the yield of the product compared with those reported in the literature.

Conclusion

In conclusion, we have introduced a mild and efficient method for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones using DCDMH as a homogeneous catalyst. It is important to note that it is the first catalytic application of DCDMH in organic synthesis. The present procedure has some valuable advantages such as short reaction times, mild reaction conditions, simple work-up and high yields of products, in combination with stability, availability, cheapness and efficiency of the catalyst which make this method a valid contribution to the existing processes in the field of DHPs 's synthesis.

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