Research article
International Journal of Heterocyclic Chemistry,
Vol. 6, No. 1, pp. 56-68 (2016)
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http://ijhc.iauahvaz.ac.ir

$CuCl_2$ Catalyzed Solvent-free One Pot Synthesis of Dihydropyrimidinones

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Abstract

An effective one-pot synthesis of dihydropyrimidinonoes in solvent free conditions using $CuCl_2$ as an inexpensive and readily available reagent through Biginelli condensation reaction of aldehyde derivatives, 1,3-dicarbonyl compounds and urea is described. Excellent yields, short reaction times for formation of the products and simple work-up are attractive features of this green protocol.

***Keywords**:* Biginelli reaction; Dihydropyrimidinones; One-pot ; Solvent-free.

Introduction :

Due to the increasing sensitivity for environmental protection, the improved procedure doesn’t only research by industrial groups but also by academic laboratories.

The Biginelli reaction was first reported more than a century ago and recently reviewed [1], and involves the synthesis of 3,4- dihydropyrimidin-2(1H)-ones (DHPMs) by a very simple one-pot condensation reaction of ethylacetoacetate, benzaldehyde and urea in ethanol. However, this one-step protocol often provides only low to moderate yields of the desired target molecules, in particular when substituted aromatic or aliphatic aldehydes are employed.

In recent years, 3, 4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives have attracted considerable interest because of their therapeutic and pharmacological properties. [2]They have emerged as integral backbones of several channel blockers, antihypertensive agents, α-1a antagonists and neuropeptide Y (NPY) antagonists. [3] Moreover several alkaloids containing the DHPM unit have been isolated from marine sources, which also exhibit interesting biological properties. [4]The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative called monastrol, [5]as a novel cell-permeable lead compound for the development of new anticancer drugs bearing the dihydropyrimidinone core Thus the development of facile and environmentally friendly synthetic methods towards dihydropyrimidinones constitutes an active area of investigation in organic synthesis.

There is considerable current interest in the Biginelli reaction, because 3,4-dihydropyrimidin-2-(1H)-ones and their derivatives have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic properties such as antibacterial and antihypertensive activity as well as behaving as calcium channel blockers, a-1a-antagonists and neuropeptides Y (NPY) antagonists. [6]The Biginelli reaction is one of the multicomponent reactions (MCRs) and the most important procedures for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones.

As Biginelli reaction for the synthesis of DHPMs has received renewed attention, several improved procedures have been reported based on metal-catalyzed Biginelli reaction during the last decade. Among the simple metal/ammonium salts with nucleophilic anions, LiBr [7], NH4Cl [8], $MgBr_2$[9], $FeCl_3$ Æ $6H_2O$ [10], $Mn(OAc)_3$. $2H_2O$ [11], $InBr_3$ [12], ZnI_2 [13], $CdCl_2$ [14] and CuI [15] are active catalysts. The catalytic effect of metal cations is even more pronounced with methods based on metal salts with non-nucleophilic anions such as $LiClO_4$ [14], $CuSO_4$ Æ $5H_2O$ [16], $Cu(OTf)_2$ [17], $Al(HSO_4)_3$ [18], trimethylsilyl triflate [19,20] which allow the preparation of DHPMs in good to high yields.

However, a number of the reported protocols to synthesize DHPs and DHPMs requiring solvents and catalysts are not acceptable in the context of green synthesis, utilize reagents and catalysts which are either toxic or expensive and stoichiometric use of reagents with respect to reactant. In connection with our ongoing work on multi-component condensations (MCCs) [21,22] And an our interest to metal catalyzed reactions, we now wish to report a facile and rapid one-pot solvent free three component procedure preparation of DHPMs derivatives with $CuCl_2$ as a non-toxic, reusable, inexpensive and easily available reagent, under solvent-free conditions at the range of temperatures.

Experimental

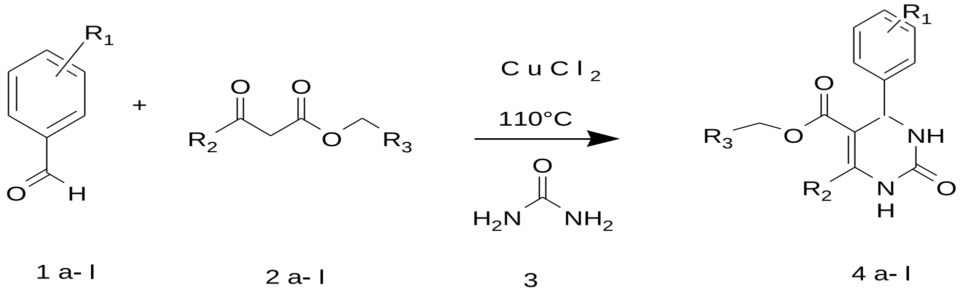
Materials and instruments :

All material compounds were purchased from chemical companies and used without further purification. Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomen FT-IR-MB 100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as internal standard.

General procedure

General procedure for preparation of 3, 4- dihdropyrimidin-2(1H)-ones

A mixture containing an appropriate β-ketoesters (3 mmol), corresponding aldehydes (3 mmol), urea (6 mmol) and $CuCl_2$ (0.4 g) was heated in oil bath at 110 C for the time period as indicated in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, chloroform (10 ml) was added and filtered through a sinter funnel, then was washed with cold water and recrystallized from ethanol to afford pure products that characterized with comparison of their m.p with other reported references . [12-20] (scheme 1)



Scheme 1. Biginelli type reaction for synthesis of dihydropyrimidone derivatives

Results and discussions

The results of optimization experiments for the three component Biginelli condensation involving acetoacetate 1a-l, benzaldehyde and carbonyl compounds 2a-l and urea 3 with $CuCl_2$ without any solvents that are presented in Table 1. It is remarkable to note that the condensation proceeded with a low catalyst concentration $CuCl_2$ (0.4 gr) at heating in oil bath conditions and gave 3,4-dihydropyrimidin-2(1H)-ones 4a-l in high yields. Promoted by this success, we extended this reaction of urea with a range of other 1,3-dicarbonyl compounds and aldehydes (Scheme 2), under similar conditions, furnishing the respective 3,4-dihdropyrimidin-2(1H)-ones 4b–q and 5a in good to excellent yields. The optimized results are summarized in Table 2. We examined the proceed of the reaction in four temperature (80 , 90 , 110 , 130) and cleared that the optimized temperature is 110 and the reaction wasn't significantly proceed in lower temperatures . The reaction was extended to aromatic, heteroaromatic, alicyclic, unsaturated and aliphatic aldehydes and also to b-diketone to furnish the expected 1,4-DHPs 4a–m in high to excellent yields (Table 1).

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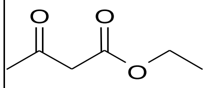
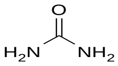
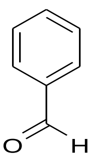
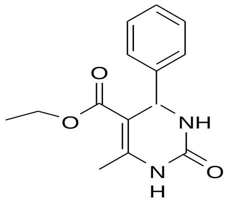
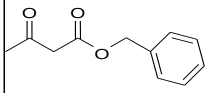
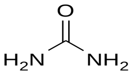
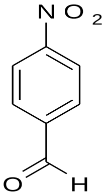
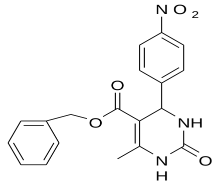
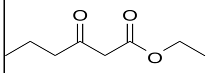
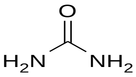
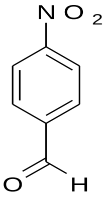
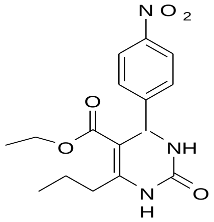
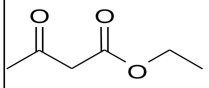
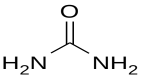
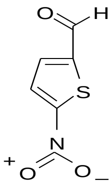
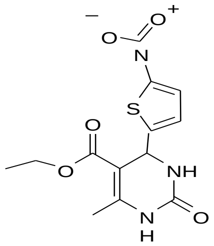
١					٤٠	%٩٤	151
٢					٥٠	%٧٩	١٥۶
٣					٧٥	%٨٣	١٨٧
٤					٥٢	%٦٠	

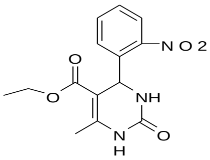
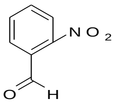
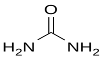
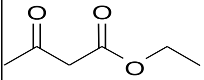
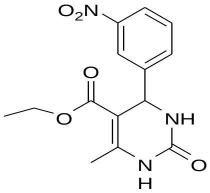
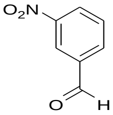
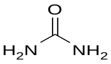
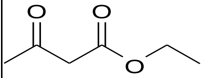
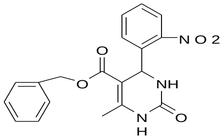
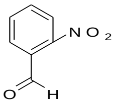
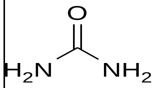
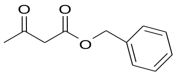
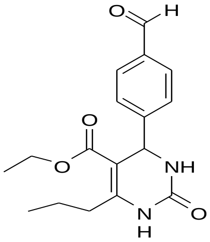
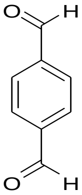
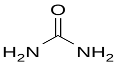
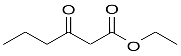
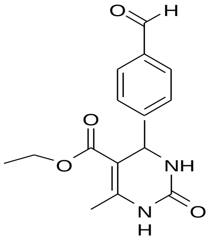
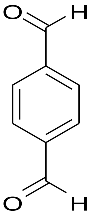
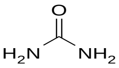
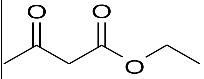
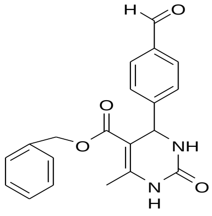
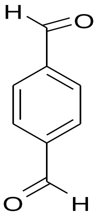
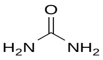
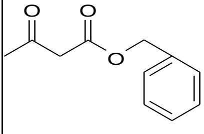
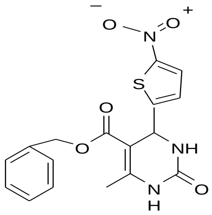
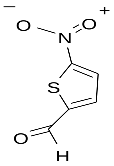
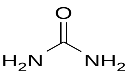
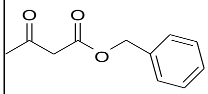
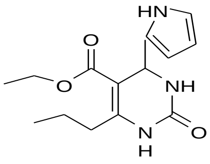
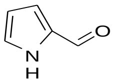
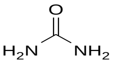
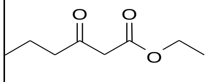
	٨٤%	٨٢					٥
	٨٠%	٨٥					٦
	٨١%	٥٥					٧
	٩٢%	٣٥					٨
	٩١%	٥٠					٩
	٧٨%	٥٩					١٠
	٨٨%	٦٠					١١
	٧٨%	٦٦					١٢

Table 1 . one pot synthesis of Dihydropyrimidinone derivatives (4 a –l) with $CuCl_2$ in Solvent-free condition

Another advantage of this approach is that catalysts are recyclable and reusable. In view of environmentally friendly methodologies, recovery and reuse of the catalyst is highly preferable.

Conclusion

In summary, we have described a successful strategy, efficient and convenient green synthesis for the preparation of 3,4-dihdro pyrimidin-2(1H)-ones in valuing cyclocondensation reaction of1,3-dicarbonyl compounds, aldehydes and urea using the inexpensive, non-toxic and easily available $CuCl_2$ catalyst. The method offers several advantages including high yield of products, recyclable of the catalyst and easy experimental work-up procedure, which makes it a useful process for the synthesis of 3,4-dihdropyrimidin-2(1H)-ones.

Acknowledgment:

The authors wish to thank shiraz medicinal and natural product research center for their valuable helps .

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