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Metals as Renewable Catalysts in MCR Synthesis of Dihydropyrimidinones

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Various metals (Cu, Fe, Al and Zn) have been successfully employed in the MCR of aryl carbaldehydes, ethyl acetoacetate and urea to give respective dihydropyrimidinones in good to excellent yields. The catalysts in these reactions are easily recovered and used many times without losing its catalytic activity. The products were duly characterized through their spectral analysis.

Keywords: Biginelli synthesis, Zn, Cu, Al, Fe, Pyrimidines.

INTRODUCTION

The Biginelli reaction[1] is a well known, simple and straightforward procedure for the synthesis of dihydropyrimidinones (DHPMs) by the three component condensation of an aliphatic or aromatic aldehyde, active methylene compounds such as β-ketoesters or 1,3-diketones and urea, thiourea or guanidines. The original reaction was first reported[2] by Pietro Biginelli in 1893 and was catalyzed by mineral acids. These dihydropyrimidinones are very interesting due to their wide spectra of biological activities[3] and are used as a starting point to prepare complex heterocyclic scaffolds with pharmacological properties[4] such as calcium channel modulation[4], mitotic kinesin Eg 5 inhibition[5], antiviral[6], antibacterial and antifungal activity[7], anticancer[8], *etc.*[9]. In order to improve the reaction yields or the scope of reaction numerous catalysts have been employed. Some of which could be mentioned here such as: ethyl polyphosphate[10], TMSCl[11], TMSCl/NaI[12], $FeCl_3$/$Si(OEt)_4$[13], H_2SO_4[14], $BF_3{\cdot}Et_2O/CuCl$[15], $LaCl_3{\cdot}7H_2O$ conc. HCl[16], $CeCl_3.7H_2O$[17], $InCl_3$[18], $BiCl_3$[19], $Cu(OTf)_2$[20], LiBr[21], $InBr_3$[22]. More recently a solvent free procedure involving water-based biphasic reaction media has been applied using PTSA as catalyst[23]. Other green conditions include $ZrCl_4$ or $ZrOCl_2$ under neat conditions[24], heteropolyacids[25] and Baker's yeast[26]. In many of the Biginelli reactions carried out in the presence of catalysts, metal salts[15-19,21,22] have often been used.

In our continuous studies about synthetic utility of MCRs and more specifically Biginelli synthesis, we have been experimenting with novel catalysts for these reactions[27]. In the present communication we would like to submit a preliminary report of our successful application using metals as environment friendly, low-cost, easily available and recyclable catalysts for Biginelli reaction. To our best of knowledge metals in their free states have not been reported as catalysts in these reactions. It is an ongoing project where the scope of these catalysts and using other active methylene compounds and thiourea is under investigations. The yields reported have not been optimized.

EXPERIMENTAL

All the chemicals and reagents used in the present study were commercially available. These were purified by usual methods of distillation (for liquids) and crystallization from appropriate solvents (for solids). Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer spectrum BX 1 and NMR on a Brucker 400MHz spectrometer using tetramethylsilane as an internal reference. The instrument used for low-resolution electron impact mass spectra was Finningan MAT 311 with MASPEC data system. All the products of the reactions were compared with the authentic samples prepared by the literature methods and were found to be identical in all respects (*e.g.*, m.p., mixed m.p., FTIR or other spectra).

Ethyl 6-methyl-2-oxo-4-phenyl-l,2,3,4-tetrahydropyrimidine-5-carboxylate (1): A mixture of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (10 mmol), 15 mL of ethanol and weighed amount of catalyst were refluxed until the reaction was completed. The reaction was monitored by TLC. The catalyst was insoluble in hot ethanol and was therefore separated by simple filtration. After cooling the reaction mixture was diluted with 100 mL of water and the precipitates were filtered off, washed with water and dried. The product was recrystallized with ethanol to afford the pure compound **1** (Table-1). IR λ_{max} (KBr, ν_{max}, cm^{-1}): 3234 (N-H), 1699 (C=O, amide), 1721 (C=O, ester). ^{1}H NMR (DMSO): δ 1.1 (3H, t), 2.3 (3H, s), 4.0 (2H, q), 5.2 (1H, s), 7.2-7.3 (5H, m), 7.8 (1H, s), 9.2 (1H, s). EIMS (*m/z*): 260 [M^+, 28 %].

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-l,2,3,4-tetrahydropyrimidine-5-carboxylate (2): A mixture of 4-chlorobenzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (10 mmol), 15 mL of ethanol and weighed amount of catalyst were refluxed until the reaction was completed. The reaction was monitored by TLC. The catalyst was insoluble in hot ethanol and was therefore separated by simple filtration. After cooling the reaction mixture was diluted with 100 mL of water and the precipitates were filtered off, washed with water and dried. The product was recrystallized with ethanol to afford the pure compound **2** (Table-1). IR λ_{max} (KBr, ν_{max}, cm^{-1}): 3238 (N-H), 1696 (C=O, amide), 1703 (C=O, ester), 685 (C-Cl). ^{1}H NMR (DMSO): δ 1.1 (3H, t), 2.2 (3H, s), 4.0 (2H, q), 5.1 (1H, s), 7.3-7.4 (5H, m), 7.8 (1H, s), 9.2 (1H, s). EIMS (*m/z*): 294.5 [M^+, 20 %, ^{35}Cl], 296.5 [M^+2, 8 %, ^{37}Cl].

Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-l,2,3,4-tetrahydropyrimidine-5-carboxylate (3): A mixture of 3-nitrobenzaldehyde (10 mmol), ethylacetoacetate (10 mmol), urea (10 mmol), 15 mL of ethanol and weighed amount of catalyst were refluxed until the reaction was completed. The reaction was monitored by TLC. The catalyst was insoluble in hot ethanol and was therefore separated by simple filtration. After cooling the reaction mixture was diluted with 100 mL of water and the precipitates were filtered off, washed with water and dried. The product was recrystallized with ethanol to afford the pure compound **3** (Table-1). IR λ_{max} (KBr, ν_{max}, cm^{-1}): 3226 (N-H), 1698 (C=O, amide), 1715 (C=0, ester), 1522 and 1454 (NO2), 867 (C-N). ^{1}H NMR (DMSO): δ 1.1 (3H, t), 2.2 (3H, s), 4.0 (2H, q), 5.2 (1H, s), 7.3-7.4 (5H, m), 7.8 (1H, s), 9.2 (1H, s). EIM S (*m/z*): 305[M^+, 4 %].

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4): Using Cu powder by following the same procedure as for compounds **1** to **3** and using 10 mg of Cu powder gave 4 in 51 % yield; m.p. 200 °C (lit.[30], m.p. 208 °C).

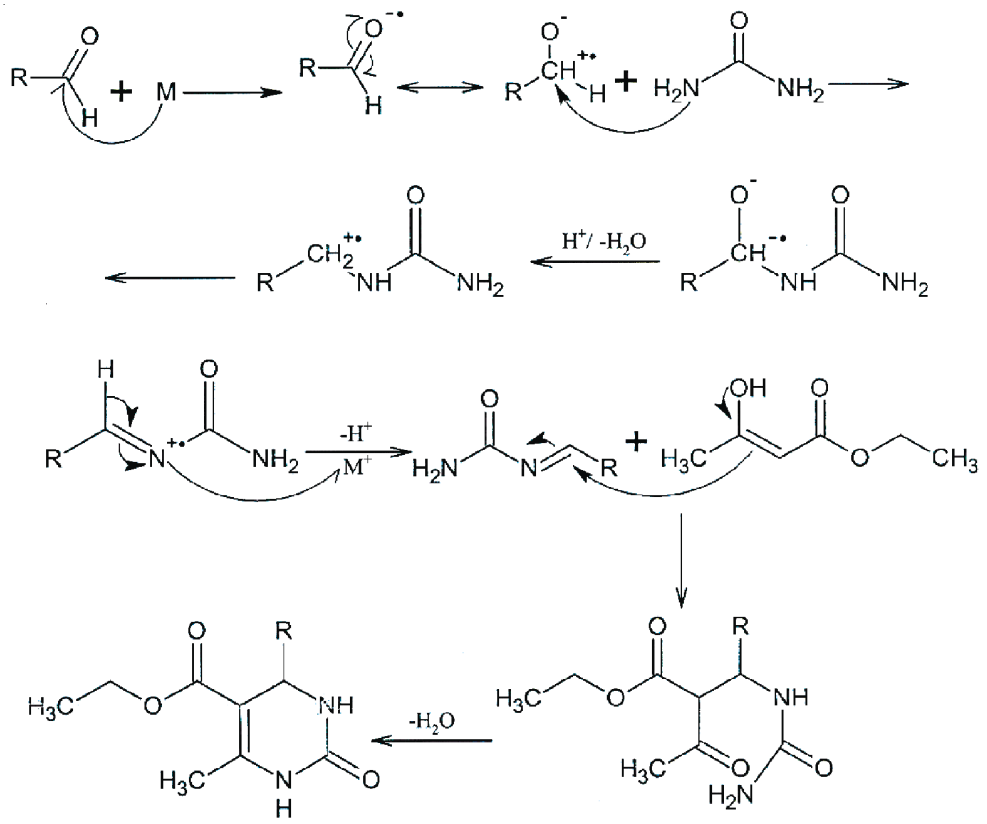
Ethyl 4-(fur-2-yl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (5): Using Al foil by following the general procedure and employing 10 mg of Al foil compound **5** was obtained in 42% yield; m.p. 196 °C (lit.[30], m.p. 209 °C).

RESULTS AND DISCUSSION

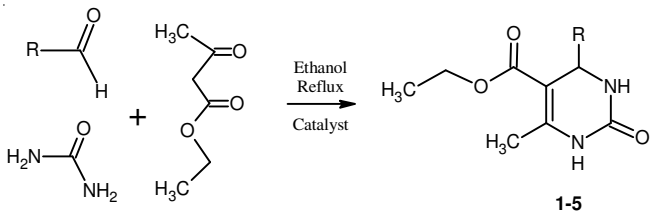
Originally Biginelli performed this reaction using HCl as an acid catalyst[1]. Later on other catalyst were tried with varying success. In the present work we have tried metals in free states such as Fe (metal, powder), Cu, Zn (powder) and Al (foil) as catalysts. Reactants were aromatic aldehydes, ethyl acetoacetate and urea, ethanol was used as a solvent. After the dissolution of reactants in the solvent, metal in catalytic amount was added and the reaction mixture was refluxed on a hot plate till the completion of reaction (TLC). This led to formation of the expected dihydropyrimidinones in satisfactory yields which were, at present, however not optimized. The metal catalyst remained undissolved during the course of the reaction, and was separated, dried under vacuum and reused without affecting the products both physically and chemically. The metal catalyzed the reaction by lowering the activation energy barrier of the reactants, which is high especially in case of substituted aromatic aldehydes, as they were somewhat sterically crowded. 3-Nitrobenzaldehyde gave lower yield of product, whereas for benzaldehyde and 4-chlorobenzaldehyde the results were comparable. Since free metals are good electron donors so the pathway might proceed by a single electron transfer mechanism (**Scheme-II**).

TABLE-1
DIHYDROPYRIMIDINONE FORMATION WITH DIFFERENT ALDEHYDES

Comp. No.	Catalyst	Weight of catalyst (mg)	Reflux time (h)	Yield (%)	m.p. °C	
					Found	Reported
1	Fe metal	40	4.5	70	195	202-204[28]
	Fe powder	20	4.0	41	197	
	Cu powder	25	3.5	72	200	
	Zn powder	10	7.0	64	202	
	Al foil	25	6.0	85	201	
2	Fe powder	5	11	26	201	211-213[29]
	Cu powder	5	9.5	56	212	
	Cu wire	5	15	34	162	
	Zn powder	5	22	20	170	
	Al foil	5	12	56	208	
	Al foil	5	16 (stirring) Room temp.	51	198	
3	Fe powder	5	12	38	192	224-228[30]
	Cu powder	5	9.0	30	198	
	Zn powder	5	8.0	42	208	
	Al foil	5	13	70	200	



Scheme-II



1-5

R = Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-furyl **1 R** = Ph, **2 R** = 4-ClC_6H_4, **3 R** = 3-$NO_2C_6H_4$, **4 R** = 3-$NO_2C_6H_4$, **5 R** = 2-furyl

Catalyst = Fe metal, Fe powder, Cu powder, Zn powder, Cu wire, Al foil

Scheme-I

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