COPPER (II) ACETYL ACETONATE: AN EFFICIENT CATALYST FOR ONE-POT SYNTHESIS OF 3, 4-DIHYDROPYRIMIDIN-2-(1*H*)-ONES

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ABSTRACT: Efficient and improved syntheses of 3,4-dihydropyrimidinones were reported using copper (II) acetylacetonate as catalyst. The reactants aldehydes, β-ketoester and urea/thiourea were reacted very smoothly at acetonitrile reflux to obtain the corresponding condensation products in excellent yields and the reactions were completed within 3-6 hours of reaction time.

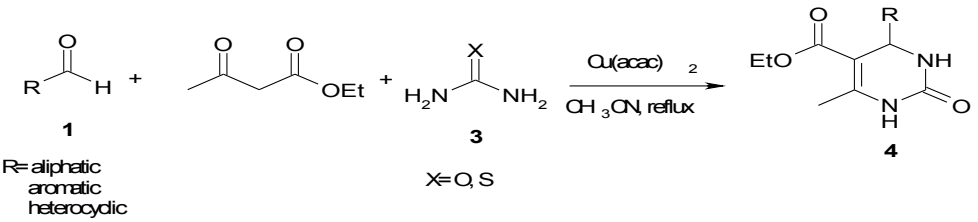
Keywords: Dihydropyrimidinones, copper acetylacetonate, urea, aldehydes, β-ketoester

INTRODUCTION

In recent years, the multicomponent condensation of Biginelli[1-3] reaction was attracted many researchers and academicians, because the obtained dihydropyrimidinones and their derivatives exhibiting a wide range of biological activity. Such as calcium channel blockes, antihypertensive agents, α-adrenergic antagonists and neuropeptide Y(NPY) anatagonists. Moreover, several marine alkaloids containing, the DHPMs as core unit, most notably among them are batnazelladine alkaloid, which have been found to be potent HIV gp-120-CD inhibitors.[4,5] Consequently synthesis of these compounds has gained popularity and a plethora of improved synthetic methodologies has recently been reported using various reaction conditions and different catalysts. The reported methods includes, metal halides,[6-11] metal triflates,[12-14] montmorillonite KSF, CAN, TPP,[15-18] microwave irradiation, ionic liquids, Bakers yeast and polyphosphate[19-21] esters also reported. Some of them are very fascinating from a synthetic point of view, but still some drawbacks are needed to overcome.

RESULTS AND DISCUSSIONS

In this regard, we have chosen the catalyst cupper (II) acetyl acetate for this multicomponent condensation reaction. This catalyst is commercially available at low cost, easy to handle without any special precautions. In a typical experiment, an aldehyde, ethyl acetoacetae and urea were reacted in presence of copper (II) acetyl acetonate at acetonitrile reflux as shown in the scheme 1. The reaction was completed with in 4 hours and the yield of corresponding derivative, 5-ethylcarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidint-2-(1*H*)-one (4a) was obtained in 90% yield. In this reaction, the catalyst copper (II) acetylacetonate was used in equivalent amounts.



1 **3** **4**

Scheme 1

The same reaction was carried out at similar reaction conditions using the catalyst in 10% mol, but the reaction was not completed even after 10 hours also. This reaction was repeated again while using the catalyst in 50% mole, the reaction was completed within 4 hours. This observation clearly shows that the quantity of catalyst must be in 50% mole ratio. Encouraged by this result, we have applied this methodology for various aldehydes at the similar reactions.

Using the optimized reaction conditions, applied this protocol to various aldehydes, with 1,3-dicarbonyl compound and urea/thiure. In the case of heterocyclic aldehydes (entry d, h) the rate of reaction is fast and the yields were in excellent. Similar manner, in the case of aromatic aldehydes, the condensation takes place very rapidly and the yields were also excellent. But in the case of aliphatic aldehydes (entry k, m) the reaction rate was slightly slower than aromatic aldehydes. The scope of this methodology was found to be applicable to a variety of aromatic aldehydes bearing electron with drawings or electron donating substituents in *ortho*, *para* & *meta* positions afforded high yields of the products. In all cases, the reactions proceeded smoothly in refluxing acetonitrile and were completed within 3-6hours and the generality of this protocol was clearly mentioned in the table 1. This methodology was successfully applied to various aldehydes such as aromatic, aliphatic and hetero aromatic aldehydes. The important feature of this methodology is the survival for the variety of functional groups, such as hydroxy, nitro, halides and ethers, under these reaction conditions.

Conclusion:

In conclusion, we have developed an efficient methodology for the synthesis of 3, 4-di hydropyrimidines by one-pot three-component condensation using copper (II) acetyl acetonate in catalytic amount. Mild reaction conditions, high yields (80-95%) and wide applicability are the important features of this protocol.

Experimental section:

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}HNMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure: A mixture of β-ketoester (10 mmol), aldehyde (5 mmol), urea (8 mmol) and the catalyst copper (II) acetylacetonate (2.5 mmol) in acetonitrile (20 ml) was refluxed for specified period (table 1) and the reaction progress was monitored by TLC. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. To the obtained crude product was added crushed ice and stirred for some time. The obtained solid compound was filtered, dried and purified by recrysta lization from methanol.

Table 1: Copper (II) acetylacetonate catalyzed synthesis for DHPMs:

Entry	R	Product (4a-4r)	Reaction Time(h)	Yield(%)	MP ^{0}C Found
a	C_6H_5-	4a	4.0	90	208-209
b	4-NO_2-C_6H_4-	4b	5.0	84	210-212
c	4-Cl-C_6H_4-	4c	3.5	88	208-210
d	2- Furyl-	4d	3.0	95	211-213
e	4-OH-C_6H_4-	4e	4.0	89	190-192
f	3,4,5-$C_6H_2(OMe)_3$-	4f	3.0	95	195-196
g	1- Napthyl-	4g	4.0	89	240-242
h	2-Thienyl-	4h	3.5	85	212-214
i	4-Me-C_6H_4-	4i	4.0	90	225-226
j	C_6H_5-CH=CH-	4j	4.0	80	229-230
k	C_4H_9-	4k	6.0	79	0
l	C_6H_5-CH_2-	4l	3.5	91	201-202
m	C_9H_{19}-	4m	6.0	83	160-162
n	2, 4-$(Cl)_2$-C_6H_3-	4n	4.0	89	245-247
o	4-F-C_6H_4-	4o	4.5	86	190-192
p	C_6H_5-CH_2-CH_2-	4p	5.0	87	0
q	Cyclohexyl-	4q	5.5	83	0
r	n-Hexyl-	4r	6.0	78	0

Spectral data for selected Compounds:

5-Ethylcarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidint-2-(1*H*)-one (**4b**). IR (KBr): υ 3241, 2983, 1726, 1705, 1647, 1581, 1362, 1209, 1156, 1037, 952, 843, 756 cm.$^{-1}$; ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3 H, *J* = 6.8 Hz), 2.30 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 5.22 (s, 1H), 7.50 (d, 2H, *J* = 8.0 Hz), 7.90 (s, 1H, NH), 8.30 (d, 2H, *J* = 8.0 Hz) 9.40 (brs, 1H, NH). ^{13}CNMR (DMSO-d_6, 75 MHz): δ 14.3, 17.9, 53.5, 58.9, 97.4, 124.6, 127.5, 146.8, 149.3, 152.7, 153.1, 164.8. EIMS *m/z* (%): 306 (m^+, 21), 276 (29), 232 (18), 183 (100), 155 (47), 137 (31), 76 (41), 51 (29).

5-Ethoxycarbonyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**). IR (KBr): υ 3349, 3228, 3123, 2978, 2841,1659, 1506, 1461, 1278, 1059,927, 871, 761 cm.$^{-1}$; ^{1}H NMR (DMSO-d_6): δ 1.30 (t, 3H, *J* = 6.6 Hz), 2.34 (s, 3H), 4.20 (q, 2H, *J* = 6.8 Hz), 5.20 (d, 1H, *J* = 3.0 Hz), 7.60 (s,1H), 7.83 (brs, 1H, NH), 9.20 (s, 1H, NH).; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 14.1, 18.2, 47.6, 60.3, 97.1, 105.8, 110.9, 142.7, 149.6, 153.1, 157.2, 165.3. EIMS *m/z* (%): 250 (m^+, 42), 221 (100), 177 (92), 110 (26), 95 (12), 57 (19).

5-Ethoxycarbonyl-4-(styryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4J**). IR (KBr): υ 3297, 3241, 3091, 2976, 2842, 698, 1508, 1493, 1371, 1223, 1137, 1051, 963, 769 cm.$^{-1}$; ^{1}H NMR (DMSO-d_6): δ 1.22 (t, 3H, *J* = 7.0 Hz), 2.23 (s, 3H), 4.12 (q, 2H, *J* = 7.0 Hz), 4.85 (d, 1H, *J* = 3.0 Hz) 6.26 (d, 1H, *J* = 14.0 & 5.0 Hz), 7.38 (d, 2H, *J* = 7.0 Hz), 7.43(d, 2H, *J* = 7.0 Hz), 7.68 (brs, 1H, NH), 9.24 (brs, 1H, NH).; ^{13}C NMR.(DMSO-d_6, 75 MHz) δ14.6, 18.0, 52.3, 59.9, 98.1, 126.7, 127.8, 128.2, 128.9, 130.3, 136.5, 148.7, 153.1, 165.3. EIMS *m/z* (%): 286 (m^+, 27), 259 (100), 224 (66), 196 (31), 149 (22), 103 (16), 91(10), 84 (19), 51 (39).

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