MAGNESIUM PERCHLORATE [Mg $(ClO_4)_2$] CATALYST ONE-POT SYNTHESIS OF 3,4-DI HYDROPYRIMIDIN-2(*1H*)-ONES: AN IMPROVED PROCEDURE FOR BIGINELLI CONDENSATION

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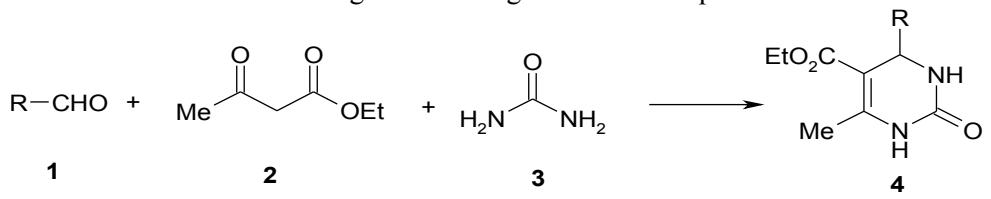
ABSTRACT: 3, 4-Dihydropyrimidinones were synthesized very efficiently in excellent yields, while using the magnesium perchlorate as catalyst. This protocol can be applicable to a wide range of aldehydes, ethylacetoacetate and urea. The reaction conditions were very mild and the isolation of products also very easy.
Keywords: Aldehydes,ethylacetoacetate, urea, magnesium perchlorate, dihydropyrimidinone.

Introduction:

Great interest has been accumulated in recent years, in the chemistry of multicomponent condensation reactions. Among them, Biginelli reaction[1] is one which attracted many researchers and academicians because the obtained dihydropyrimidinones and their derivatives occupy an important place due to their therapeutic and pharmacological properties. The dihydropyrimidinoines (DHPMs) have emerged as the integral back-bones of several calcium channel blockes,[2] antihypertensive agents,[3] α-adrenergic antagonists[4] and neuropeptide Y(NPY) anatagonists.[5] Moreover, several marine alkaloids containing, the DHPMs as core unit, most notably among them are batazelladine alkaloid, which have been found to be potent HIV gp-120-CD^4 inhibitor.[6,7] Consequently synthesis of these compounds have gained popularity and a plethora of improved synthetic methodologies have recently been reported. The original Biginelli protocol for the preparation of the DHPMS consisted, the heating of a mixture containing β-ketoester, aldehyde and urea in ethanol catalyzed by hydrochloric acid. The main drawback of this procedure is low yields. Therefore the discovery of mild protocols for the synthesis of DHPMs attracts the attention of researchers. Recently, several improved procedures have been developed using various catalysts, such as the metal chlorides,[7-15] metal triflates,[16-19] acidic clay montmorillonite KSF,[20] CAN,[21] Microwave irradiation,[22] ionic liquids [23] and polyphosphate[24] esters. Some of them are very fascinating from a synthetic point of view but many of the existing procedures have some drawbacks such as the catalysts are expensive, not easily available and moisture sensitive, high tempe rature and highly acidic conditions.

RESULTS AND DISCUSSION:

In this communication we wish describe, an improved method for the Biginelli condensation using magnesium perchlorate as the catalyst. This catalyst is cheaply available at low cost, easy to handle and water-soluble which is a great advantage to isolate the products.



1 2 3 4

Scheme 1

In a typical general experimental procedure, a mixture of aldehyde (**1**), ethylacetoacetate (**2**) and urea (**3**) were reacted in acetonitrile reflux in presence of a catalytic (10 mol%) amount of magnesium perchlorate as shown in the scheme 1. The reaction progress was monitored by thin layer chromatography (TLC). When the complete conversion of the aldehyde was confirmed by TLC, the solvent was removed under reduced pressure. To the obtained crude product, cold water was added and stirred for some time. The precipitated solid was filtered and purified by recrystalization from methanol.

Using the optimized reaction conditions, we have applied this method to various aldehydes with ethylacetoacetate and urea and results were clearly mentioned in the table 1. In general the reaction of aliphatic aldehydes required slightly longer reaction time and the obtained yields also comparatively less. In the case of heterocyclic aldehydes, the rate of reaction is fast and the yields were in excellent. Whereas, in the case of aromatic aldehydes, the condensation takes place very rapidly and the yields were also excellent. The scope of this methodology was found to be applicable to a variety of aromatic aldehydes bearing electron withdrawing or electron donating substituents present on aromatic system. In all cases, the reactions proceeded smoothly at acetonitrile reflux, while using the catalyst in 10 mole % and the reactions were completed within 3-5 hours of reaction time. The important feature of this procedure is the survival of the variety of functional groups, such as hydroxy, nitro, halides and ethers, under these reaction conditions.

Table1: Magnesium perchlorate catalyzed synthesis of 3,4-dihydropyrimidinones

Entry	Aldehydes (R)	Methyl	Ethyl	Product[a] (4a-4p)	Reaction Time(h)	Yield[b] (%)	MP. ^{0}C Found
a	C_6H_5	CH_3	C_2H_5	4a	3.0	91	208-209
b	4-NO_2-C_6H_4	CH_3	C_2H_5	4b	4.0	86	210-212
c	4-Cl, C_6H_4	CH_3	C_2H_5	4c	3.5	90	208-210
d	2-Furyl	CH_3	C_2H_5	4d	3.0	95	211-213
e	3-C_6HO-C_6H_2	CH_3	C_2H_5	4e	4.5	88	190-192
f	3,4,5-(OCH_3(3 C_6H_2	CH_3	C_2H_5	4f	3.0	95	195-196
g	1-Napthyl	CH_3	C_2H_5	4g	5.0	89	240-242
h	2-Thienyl	CH_3	C_2H_5	4h	4.5	85	212-214
i	4-OH-C_6H_4	CH_3	C_2H_5	4i	4.0	82	225-226
j	C_6H_5-CH = CH	CH_3	C_2H_5	4j	4.0	80	229-230
k	C_5H_{11}	CH_3	C_2H_5	4k	5.0	81	150-152
l	4-OCH_3-C_6H_4	CH_3	C_2H_5	4l	3.5	93	201-202
m	C_9H_{19}	CH_3	C_2H_5	4m	5.0	84	160-162
n	2, 4-$(Cl)_2$-C_6H_3	CH_3	C_2H_5	4n	4.0	88	245-247
o	4-F-C_6H_4	CH_3	C_2H_5	4o	3.5	87	190-192
p	3, 4-(OCH_3)-C_6H_3	CH_3	C_2H_5	4p	4.5	91	178-180

[a]All the products were characterized by ^{1}HNMR, ^{13}CNMR, IR and mass spectroscopy data.

[b]Isolated and optimized yields.

Conclusion:

In conclusion, we have developed an efficient and improved procedure for the synthesis of 3, 4-dihydropyrimidines by one-pot three component condensation using magnesium perchlorate as catalyst. The mild reaction conditions, easy isolation of products, high yields, economically viability of the catalyst and wide applicability are the important features of this protocol.

General Procedure: A mixture of β-ketoester (15mmol), the aldehyde (10mmol), urea (15mmol) and magnesium perchlorate (2mmol) in acetonitrile (20ml) was heated at reflux for 3-5 hr. The complete conversion of the starting material was confirmed by TLC. Then the solvent from the reaction mixture was removed under reduced pressure. To the obtained crude product was added cooled water and stirred for some time. The precipitated solid compound was filtered, dried and purified by recrystalization from ethanol.

Spectral data for selected Compounds:

5-Ethylcarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidint–2(*1H*)-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, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 5.22 (s, 1H), 7.50 (d, 2H, *J* = 7.0 Hz), 7.90 (s, 1H), 8.30 (d, 2H, *J* = 7.0 Hz) 9.40 (brs, 1H).; ^{13}C N MR (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(*1H*)-one (4d):

IR (KBr): υ 3349, 3228, 3123, 2978, 2841, 1659, 1506, 1461, 1278, 1059, 927, 871, 761 cm^{-1}.; ^{1}HN MR (DMSO-d_6): δ 1.30 (t, 3H, *J* = 6.5 Hz), 2.34 (s, 3H), 4.20 (q, 2H, *J* = 6.5 Hz), 5.20 (d, 1H, *J* = 3.0 Hz), 7.60 (s, 1H), 7.83 (s, 1H), 9.20 (brs, 1H).; ^{13}C NMR (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(*1H*)-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 (s, 1H), 9.24 (brs, 1H).; ^{13}C NMR (75 MHz): δ 14.6, 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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