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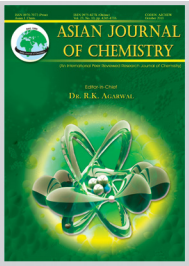

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones Using Molybdenum(V) Chloride as a Catalyst

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Molybdenum(V)chloride catalyzes efficiently the three component condensation reaction of aldehyde, β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones (DHPMs). Compared to the classical Biginelli reaction conditions, this new approach consistently has the advantage of excellent yields (80-91 %) and short reaction times 1.4-2.6 h.

Key Words: Aldehyde, β-Ketoester, Urea and thiourea, Molybdenum(V)chloride, Dihydropyrimidinones.

INTRODUCTION

The simplest and the most straightforward approach for dihydropyrimidinones involve one pot condensation of an aldehyde, β-ketoester and urea or thiourea in the presence of acid catalyst[1]. Many aryl substituted 3,4-dihydropyrimidin-2-ones (DHPMs) and their derivatives are an important class of compounds in the field of drugs and pharmaceuticals[2]. They are found to exhibit a wide range of biological activities[3] such as antibacterial, antiviral, antitumour, antiinflamatory properties. Most of the dihydropyrimidinones and their derivatives are medicinally important as calcium channel blockers, antihypertensive agents α_{1a}-antagonists and anti HIV agents[4]. The biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety[5]. However, this so-called Biginelli reaction often suffer from low yields practically in case of substituted aromatic and aliphatic aldehydes[6]. Even though high yields could be achieved by following complex multi-step procedures[7], these methods lack the simplicity of original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of milder and efficient procedures for the synthesis of dihydropyrimidinones.

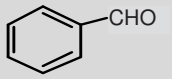
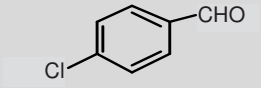
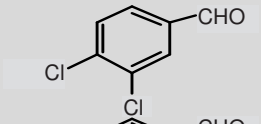
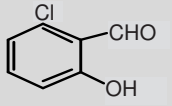
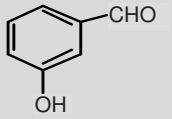
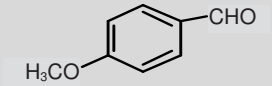
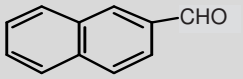
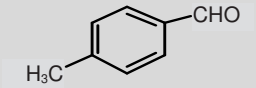
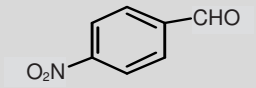
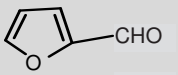
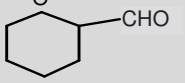
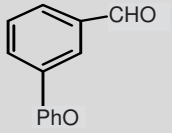
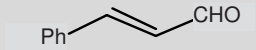
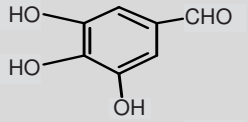
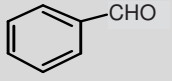
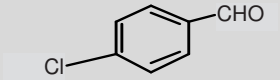
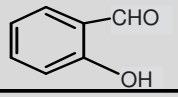
Due to this, several workers[8-18] reported the synthesis of dihydropyrimidinones including classical conditions with microwave irradiation[19] and by using Lewis acids as well as protic acids as promoters such as[20] Conc. HCl, BF_3·OEt_2, PPE, KSF clay, $InCl_3$, $LaCl_3$, lanthanide triflate, H_2SO_4, ceric ammonium nitrate (CAN), $Mn(OAc)_3$, ion-exchange resin, 1-*n*-butyl-3-methyl imidazolium tetra fluoroborate (BMImBF4), $BiCl_3$, $LiClO_4$, $InBr_3$, $FeCl_3$, $ZrCl_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, LiBr, ytterbium triflates, NH_4Cl, $MgBr_2$, SiO_2/$NaHSO_4$, AlKIT-5 and other reagents[21-25] have been found to be effective. Many of these methods involve expensive reagents, stochiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the Biginelli reaction. Molybdenum pentachloride is a widely available and inexpensive reagent, which is not fully explored as a Lewis acid catalyst. In view of this, we have used molybdenum(V) chloride[26] as an efficient catalyst for the Biginelli three-component one-pot synthesis.

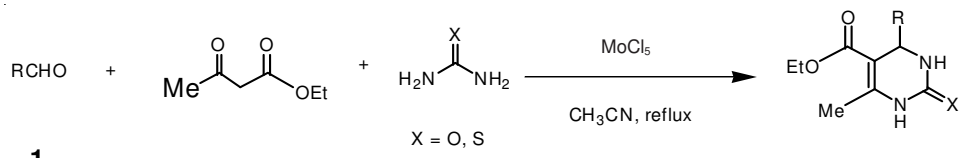
EXPERIMENTAL

Typical procedure: A solution of ethyl acetoacetate (156 mg, 1.2 mmol), aldehyde (1.0 mmol) and urea (72 mg, 1.2 mmol) in acetonitrile (8 mL) was heated under reflux conditions in the presence of catalyst (5 mol %) for 2.6 h. Completion of the reaction was monitored by TLC. The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallized from methanol. The spectral data of some of the compounds are given below.

Compound l: Solid, m.p. 193-194 ºC, ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 3H, J = 6.8 Hz), 2.36 (s, 3H), 4.10 (q, 2H, J = 6.8 Hz), 5.35 (s, 1H), 5.80 (brs, NH), 6.85 (m, 1H), 7.05-7.10 (m, 5H), 7.45 (m, 3H), 8.40 (brs, NH). EIMS: m/z 352 (M^+), 323, 279, 183, 155, 137, 91, 69. IR (KBr, ν_{max}, cm^{-1}): 3242,

TABLE-1
MOLYBDENUM(V) CHLORIDE CATALYZED SYNTHESIS OF DIHYDROPYRIMIDINONES AND THIO DERIVATIES

Entry(1)	R	X	Time (h)	Yield(%)
a		O	1.4	91
b		O	2.0	87
c		O	2.0	90
d		O	1.6	90
e		O	1.6	86
f		O	2.2	90
g		O	2.5	82
h		O	2.5	87
i		O	2.2	84
j		O	2.6	84
k		O	2.5	80
l		O	2.5	90
m		O	2.5	86
n		O	2.5	83
o		S	1.5	90
p		S	2.0	90
q		S	2.0	90



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Scheme-I: Synthesis of DHPMs using $MoCl_5$

3112, 2981, 1712, 1654, 1582, 1487, 1245, 1097, 786. Anal. calcd. for $C_{20}H_{20}N_2O_4$ (352.14): C, 68.15; H, 5.67; N, 7.95. Found: C, 68.10; H, 5.6; N, 7.94.

Compound m: Solid, m.p. 229-231 ºC (lit. 232-235 ºC), ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, *J* = 7.0 Hz), 2.50 (s, 3H), 3.95 (q, 2H, *J* = 7.0 Hz), 4.24 (d, 1H, *J* = 6.0 Hz), 6.05 (dd, 1H, *J* = 16.4 Hz), 6.2 (d, 1H, *J* = 16.4 Hz), 7.20-7.25 (m, 5H), 7.45 (d, NH, *J* = 1.7 Hz), 8.95 (brs, NH). EIMS: m/z 286 (M^+), 252, 224, 196, 149, 84. IR (KBr, ν_{max}, cm^{-1}): 3335, 3242, 3098, 2978, 1689, 1642, 1492, 1373, 1218, 1121, 785. Anal. calcd. for $C_{16}H_{18}N_2O_3$ (286.13): C, 67.05; H, 6.29; N, 9.78. Found: C, 67.04; H, 6.24; N, 9.73.

All other products were characterized by spectral (NMR and IR) data and by comparison with those of authentic samples and also by the melting points of the samples mixed with the authentic ones.

RESULTS AND DISCUSSION

Initially, we have studied the Bignelli's one-pot condensation reaction of benzaldehyde (1.0 mmol) with urea (1.2 mmol) and ethyl acetoacetate (1.2 mmol) using 5 -mol % of $MOCl_5$ under reflux and acetonitrile solvent conditions (**Scheme-I**).

Encouraged by these results, we examined several aromatic and aliphatic aldehydes under the optimized conditions. Furthermore, the use of just 5 mol % $MoCl_5$ is sufficient to promote the reaction. This three component condensation proceeded smoothly in refluxing acetonitrile and also complete with in 1.4-2.6 h of reaction time. There are no improvements in the reaction rates and yields by increasing the amount of the catalyst from 5 to 10 mol %. The best results were achieved when the reactions were carried out at reflux temperature in an oil bath for 1.4-2.6 h in the presence of catalytic amount of $MoCl_5$. Another important feature of this procedure is the stability of a variety of functional groups such as ether, hydroxy, halides, nitro, *etc.*, under these reaction conditions. This procedure not only preserves the simplicity of Biginelli reaction but also produces dihydropyrimidinones in excellent yields. Thus this procedure offers an easy access to substituted dihydropyrimidinones with a variety of substitution patterns. Among various solvents like acetonitrile, methanol, ether and THF used for this transformation, methanol and acetonitrile were the best choice. Thiourea has been used to obtain the corresponding thio-derivatives of dihydropyrimidi-nones, which possess good biological activities. Several examples illustrating this novel and general method for the synthesis of dihydropyrimidinones are summarized in Table-1.

Conclusion

We have developed a simple, convenient and effective method for the synthesis of 3,4-dihydropyrimidinones by using $MoCl_5$. This method is applicable to a wide range of substrates including aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes. To our knowledge, this is the first report of an efficient general method for the synthesis of dihydropyrimidinones by using $MoCl_5$.

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