Dichloro Dicyano Quinone (DDQ) as Coupling Reagent for High Yield Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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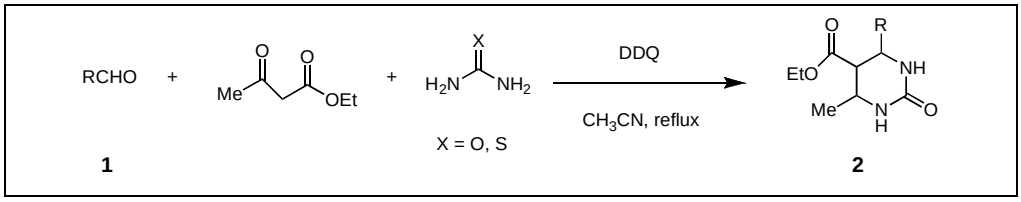

DDQ catalyzes efficiently the three-component condensation reaction of aldehyde, β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones. Compared to the classical Biginelli reaction conditions, this new approach consistently has the advantage of excellent yields (80-92%) and short reaction times 1.5-2.5 h.

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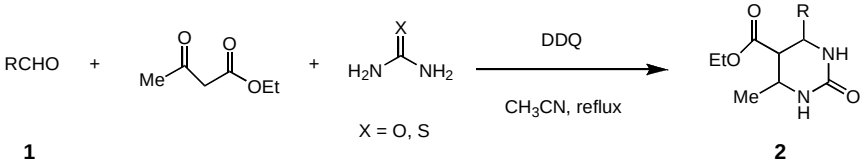
INTRODUCTION

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 [1]. They are found to exhibit a wide range of biological activities [2] such as antibacterial, antiviral, antitumour, antiinflamatory properties. Most of the DHPMs and their derivatives are medicinally important as calcium channel blockers, antihypertensive agents α_{1a}-antagonists and anti HIV agents [3]. The biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety [4]. The simplest and the most straightforward approach for DHPMs involve one pot condensation of an aldehyde, β-ketoester and urea or thiourea in the presence of acid catalyst [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] have been reported the synthesis of DHPMs 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-methylimidazolium tetrafluoroborate (BMImBF4), $BiCl_3$, $LiClO_4$, $InBr_3$, $FeCl_3$, $ZrCl_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, LiBr, ytterbium triflates, NH_4Cl, $MgBr_2$, $SiO_2/NaHSO_4$ 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. In view of this, we have utilized DDQ as an efficient reagent for the Biginelli three-component one-pot synthesis in our laboratory.

The use of the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [26] is well known for oxidation, in dehydrogenation reactions as a coupling reagent and recent papers report that DDQ acts as a Lewis acid catalyst [27]. On the other hand we have developed DDQ as a coupling reagent in this reaction. In this paper, we wish to describe a simple and efficient procedure for the synthesis of DPHMS *via* condensation of aldehyde, β-ketoester and urea in refluxing acetonitrile in the presence of DDQ.

Scheme 1

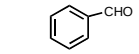
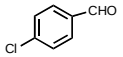
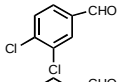
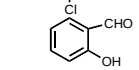
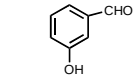
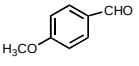
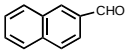
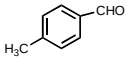
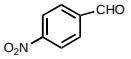
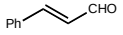
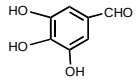
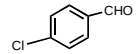


RESULTS AND DISCUSSION

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 DDQ as coupling reagent under reflux and acetonitrile solvent conditions (Scheme 1).

Table 1

DDQ catalysed synthesis of dihydropyrimidinones and thio derivaties.

Entry(1)	R	X	Time (h)	Yield(%)
a		O	1.5	92
b		O	2.0	89
c		O	2.0	91
d		O	1.5	90
e		O	1.5	88
f		O	2.0	90
g		O	2.5	84
h		O	2.5	88
i		O	2.0	85
j		O	2.5	85
k		O	2.5	80
l		O	2.5	91
m		O	2.5	85
n		O	2.5	85
o		S	1.5	92
p		S	2.0	90
q		S	2.0	90

Encouraged by these results, we examined several aromatic and aliphatic aldehydes under the optimized conditions. Furthermore, the use of just 5-mole% DDQ as coupling reagent is sufficient to promote the reaction. The three-component condensations proceeded smoothly in refluxing acetonitrile and also are complete with in 1-2.5 h of reaction time. There are no improvements in the reaction rates and yields by increasing the amount of the catalyst from 5-mol% to 10-mol%. The best results were achieved when the reactions were carried out at reflux temperature in an oil bath for 90 -150 minutes in the presence of catalytic amount of DDQ. 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 DHPMs in excellent yields. Thus this procedure offers an easy access to substituted DHPMs 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 dihydropyrimidinones that 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 DDQ. 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 DHPMs by using DDQ.

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 2.5 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 recrystallised from methanol. The spectral data of some of the compounds are given below.

Compound (l). Solid, m.p. 193-194°C. ^{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): υ 3242, 3112, 2981, 1712, 1654, 1582, 1487, 1245, 1097, 786. *Anal.* Calcd. for $C_{20}H_{22}N_2O_4$ (354.16): C, 67.78; H, 6.26; N, 7.90; O, 18.06. Found: C, 67.79; H, 6.26; N, 7.94; O, 18.10.

Compound (m). Solid, m.p. 229-231°C (lit. 232-235). ^{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): υ 3335, 3242, 3098, 2978, 1689, 1642, 1492, 1373, 1218, 1121, 785. *Anal.* Calcd. for $C_{16}H_{20}N_2O_3$ (288.15): C, 66.65; H, 6.99; N, 9.72; O, 16.65. Found: C, 66.68; H, 6.99; N, 9.75; O, 16.67.

All other products were characterized by spectral (NMR & IR) data and by comparison with those of authentic samples and

also by the melting points of the samples mixed with the authentic ones.

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