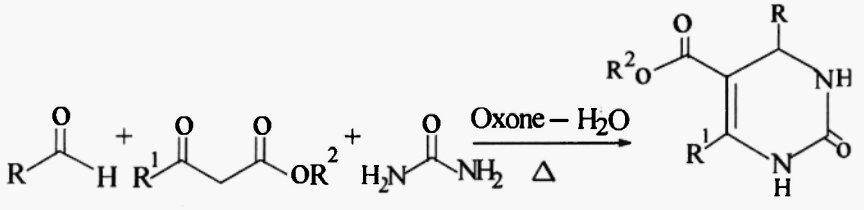
POTASSIUM MONOPEROXYSULFATE AN EFFICIENT CATALYST FOR BIGINELLI REACTION UNDER AQUEOUS CONDITIONS

S. Ramesh Kumar and P. Leelavathi *
Department of Chemistry, Osmania University College for Women, Koti, Hyderabad-500095, India, Phone No.91-40-27058177
email: rameshteja_2001@yahoo.co.in

Abstract: Biginelli reaction was carried out successfully in aqueous medium using potassium monoperoxysulfate as catalyst. This method can be applied for various aldehydes to get the desired product in very good yields with high purity.
Keywords: Aldehydes, Ethyl acetoacetate, Urea, Dihydropyrimidones, Oxone.

The reaction in which three or more reactants come together in a single reaction vessel to form a new product that contain portions of all the components is called a multi-component reaction. The Biginelli reaction[1] is very good example for multi-component reaction, which contain the combination of ethyl acetoacetate, aldehyde and urea. The Biginelli product of 3, 4-dihydropyrimidin-2 (*1H*)-ones (DHPMs) are pharmacologically important as calcium channel blockers, antihypertensive agents, α-adrenergic antagonists and neuropeptide Y (NPY) antagonists.[2] The dihydropyrimidone derivatives are found as core units in many marine alkaloids (Batzelladine and Crambine), which have been found to be potent HIVgp-120-CD_4 inhibitors.[3] Therefore, the synthesis of this heterocyclic nucleus has gained importance in organic synthesis. A simple and direct method, reported by Biginelli in 1893, involves one-pot condensation of an aldehyde, a β-ketoester and urea or thiourea under strongly acidic conditions. However, this protocol often suffers from low yields, particularly in case of substituted aromatic or aliphatic aldehydes. Hence, several attempts have been made to prepare DHPMs under mild reaction conditions and improved yields (**Scheme-1**).



1 2 3 4

Scheme-1

Recently many improved procedures have been reported, which includes metal halides,[4] metal triflates,[5] ionic liquid,[6] acidic montmorillonite-KSF[7] and microwave irradiation.[8] Some of them are really very fascinating from synthetic point of view. But many of these methods have drawbacks which involve strong Lewis acids (BF_3),[9] protic acids (HCl, Ac-OH, H_2SO_4),[10] additives, prolonged reaction times, vigorous reaction conditions (High temperature), unsatisfactory yields and incompatibility with other functional groups.

Environmental concerns in chemical research and industry are ever increasing. The challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvent or even better aqueous media. Potassium monoperoxysulfate (Oxone^R) is an unique catalyst that is currently of great research interest. The potassium salt of peroxysulfate is well known in the literature for a variety organic transformations[11] as an efficient catalyst. The oxone is moisture stable, white solid, very much soluble in water and insoluble in common organic solvents.

Herein, we disclose a novel procedure for the synthesis of 3, 4-dihydropyrimidinones using potassium monoperoxysulfate salt catalyzed Biginelli reaction applied to one-pot condensation under aqueous conditions, which is very simple and environmentally green protocol. In a typical general experimental procedure, a solution of β-dicarbonyl compound, an aldehyde and urea in tetrahydrofuran-water mixture was heated at 75-80 °C in the presence of a catalytic amount of potassium peroxymonosulfate (10 mol%) for a specified period (Table-1). The progress of the reaction was monitored by thin layer chromatography (TLC). After complete conversion of the starting material (aldehyde) as indicated by TLC, the reaction mixture was poured into crushed ice and stirred well. The solid obtained was separated by filtration and the crude product of dihydropyrimidone was recrystalized with methanol.

To study the generality of this method, using the optimized reaction conditions, a variety of substituted aromatic, aliphatic and heterocyclic aldehydes have been subjected to this condensation successfully. In all the cases the catalyst potassium monoperoxysulfate was used in catalytic amount (10 mol %) only. All the reactions were completed within 4-6 hours of time at 75-80 °C of reaction temperature. Whereas in the case of acid sensitive aldehyde, such as furfural (entry **f**) reacted very smoothly to obtain the corresponding dihydropyrimidone in excellent yield without, the formation of any side products. In a similar manner, α,β-unsaturated aldehyde (entry **h**) also

Table-1 : Potassiummonoperoxysulfate catalyzed Biginelli reaction under aqueous conditions:

Entry	R	R^1	R^2	Product[a]	Reaction Time (h)	Yield (%)[b]
a	4-MeO-C_6H_4	CH_3	C_2H_5	4a	4.5	87
b	4-Cl-C_6H_4	CH_3	C_2H_5	4b	5.0	86
c	4-NO_2-C_6H_4	CH_3	C_2H_5	4c	6.0	84
d	C_6H_5	CH_3	C_2H_5	4d	5.0	80
e	2-Naphthyl	CH_3	C_2H_5	4e	5.5	85
f	2-furyl	CH_3	C_2H_5	4f	4.0	90
g	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	C_2H_5	4g	4.5	89
h	(*E*)C_6H_4-CH=CH-	CH_3	C_2H_5	4h	4.0	80
i	2-Thienyl	CH_3	C_2H_5	4i	5.0	82
j	n-C_6H_{11}-	CH_3	C_2H_5	4j	6.0	81
k	4-CH_3-C_6H_5	CH_3	C_2H_5	4k	5.5	84
l	2,4-Cl_2-C_6H_3	CH_3	C_2H_5	4l	4.0	87
m	3-pyridyl	CH_3	C_2H_5	4m	4.0	80
n	n-$C_{10}H_{21}$-	CH_3	C_2H_5	4n	6.0	80
O	4-OH-C_6H_4	CH_3	C_2H_5	4o	5.5	85

a : All the products were characterized by ^{1}H NMR, IR and Mass spectra and comparison of their physical characteristics with those of the authentic compounds.

b : Isolated and unoptimized yields.

reacted very well to give the desired product in very good yield. The reaction of aliphatic aldehydes (entry **j, n**) needs little longer reaction time for complete conversion but the yields were very good. Furthermore, the aromatic aldehydes carrying either electron donating or electron withdrawing substituents afforded high yields of corresponding dihydropyrimidone derivatives in high yield and with high purity. The products thus obtained were characterized by ^{1}H NMR, IR and Mass spectra and by comparison of their physical characteristics with those of the authentic compounds in the literature.[5] The solvent system used for the reaction was tetrahydrofuran and water mixture. The above observation clearly indicates that this protocol can be applicable to a wide range of reactants.

In conclusion, the present methodology for the synthesis of dihydropyrimidin-2(*1H*)-ones catalyzed by potassium monoperoxysulfate, provides an efficient and improved procedure for Biginelli reaction. The simple experimental procedure, milder reaction conditions and inexpensive catalyst is the highlights of this method. The aqueous medium of the reaction makes this protocol as environmental friendly process.

Experimental Section

General Methods: All commercial reagents were used without purification and all solvents were reagent grade. All the reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel $60F_{254}$ precoated glass plates, which were visualized with UV light. Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT/IR-240 C spectrophotometer with KBr optics. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer recorded in DMSO-d6 using TMS as an internal standard. Mass spectra were recorded on finnigan-MAT 1020 Mass spectrum operating at 70 eV.

General procedure for the preparation of 3,4-dihydropyridine-2 (*1H*)-ones: A mixture of aldehyde (10 mmol), ethyl acetoacetate (12 mmol), urea (15 mmol) and potassium peroxymonosulfate (1mmol) in tetrahydrofuran and water mixture (7:3 ml) was heated at 75-80 °C for a specified time in Table 1. After complete conversion of the starting material (Aldehyde) as indicated by thin layer chromatography (TLC), the reaction mixture was poured in crushed ice and stirred for some time. The obtained solid was filtered and recrystalized with methanol.

Spectral data for selected compounds:

5-EthoxyCarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydrpyrimidin-2(*1H*)-one (4a) : M.P: 200-202 °C, I.R (KBr).ν 3421, 3197, 3068, 2931, 2847, 1693, 1651, 1597, 1408, 1321, 1241, 1163, 1049, 941, 864, 780, 736 cm^{-1}.; ^1H NMR (DMSO-d_6): δ 1.10 (t, 3H, J = 6.5Hz), 2.25 (s, 3H), 3.68 (s, 3H), 4.08 (q, 2H, J = 6.5Hz), 5.10 (s, 1H), 6.86 (d, 2H, J = 7.5 Hz), 7.18 (d, 2H, J = 7.5 Hz), 7.68 (brs, 1H), 9.16 (s, 1H). EIMS *m/z* (%). 290 (m^+ 28), 275 (47), 231 (39), 183 (23), 183 (100), 151 (71), 113 (22), 76 (41), 51(32).

5-EthoxyCarbonyl-4-(2-furyl)-6-methyl-3,4-dihydrpyrimidin-2(*1H*)-one (4f) : M.P: 209-211 °C, I.R (KBr).ν 3327, 3226, 3142, 3083, 2976, 2842, 1704, 1611, 1546, 1322, 1261, 1203, 1019, 874, 751 cm^{-1}.; ^1H NMR (DMSO-d_6): δ 1.22 (t, 3H, J = 6.0Hz), 2.35 (s, 3H), 4.20 (q, 2H, J = 6.0Hz), 5.18 (d, 1H, J=3.0 Hz), 6.06 (d, 1H, J = 3.5 Hz), 6.36 (d, 1HJ = 3.5 Hz), 7.58 (s, 1H), 7.83 (brs, 1H, NH), 9.22 (s, 1H, NH). EIMS *m/z* (%). 250 (m^+ 42), 221 (63), 177 (100), 110 (31), 71 (28), 57 (49), 42(12).

5-EthoxyCarbonyl-4-[(*E*)-2-phenylethenyl)-6-methyl-3, 4-dihydrpyrimidin-2(*1H*)-one (4h) : M.P: 225-227 °C, I.R (KBr).ν 3349, 3251, 3032, 2947, 2831, 1698, 1656, 1521, 1488, 1351, 1208, 1123, 1071, 953, 875, 822, 742 cm^{-1}.; ^1H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 7.0 Hz), 2.38 (s, 3H), 4.22 (q, 2H, J = 7.0 Hz), 4.82 (d, 1H, J=6.0 Hz), 6.30 (dd, 1H, J = 14.0 & 4.5 Hz), 6.42 (d, 1H, J = 14.0 Hz), 7.20-7.43 (m, 5H), 7.52 (s, 1H, NH), 9.13 (s, 1H, NH).; EIMS *m/z* (%). 286 (m^+ 22), 259 (100), 224 (38), 196 (60), 149 (20), 117 (15), 92 (20), 76 (52), 51(34).

5-EthoxyCarbonyl-4-(n-hexyl)-6-methyl-3,4-dihydrpyrimidin-2(*1H*)-one (4j) : M.P: 150-152 °C, I.R (KBr).ν 3346, 3291, 2847, 1708, 1691, 1614, 1583, 1458, 1326, 1235, 1131, 1069, 1012, 952, 866, 812, 791, 741 cm^{-1}.; ^1H NMR (DMSO-d_6): δ 0.92 (t, 3H, J = 6.5Hz), 1.22-1.42 (m, 9H), 1.52-1.58 (m, 2H), 2.30 (s, 3H), 4.18 (q, 2H, J = 6.5Hz), 4.30 (s, 1H), 6.10 (brs, 1H, NH), 9.10 (s, 1H, NH).; EIMS *m/z* (%). 253 (m^+ 20), 209 (27), 183 (33), 155 (100), 137 (41), 91 (28), 76 (11), 51(22), 40 (30).

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Received on June 23, 2006.