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IBX promoted three component, one-pot, condensation reaction: An efficient synthesis of 4-substituted 3,4-dihydropyrimidin-2-ones

J.Venkateswara Rao[1]*, Ch.Subrahmanyam[1], N.Bramhananda Reddy[2]

[1]Department of Chemistry, Bapatla Engeneering College, Bapatla - 522 101, (INDIA)

[2]Escientia Bio Pharma (P) Ltd, IDA, Mallapur, Hyderabad - 500 076, (INDIA)

E-mail : jonnalagadda.bec@gmail.com

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ABSTRACT

o-Iodoxy Benzoic Acid (IBX) efficiently catalyzes the three component condensation reaction of aldehyde, β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones in excellent yields.

KEYWORDS

Biginelli reaction;
IBX;
Dihydropyrimidinones.

INTRODUCTION

Recently, dihydropyrimidinone derivatives[1] have been shown to exhibit important pharmacological activities as the integral backbone of several calcium channel blockers, antihypertensive agents, alpha-la-antagonists, and neuropeptide Y(NPY) antagonist[2], Moreover, several isolated marine alkaloids with interesting biological activities were also found to contain the dihydropyrimidinone-5-carboxylate moiety[3]. Most important among them, are the batzelladine alkaloids, which are potent HIV gp120-CD_4 inhibitors[4]. In addition, these compounds exhibit a broad range of biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory properties. The most simple and straight forward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions[5]. However, one serious drawback of Biginelli's reaction is the low yields obtained in the case of substituted aromatic and aliphatic aldehydes[6]. Then, has led to the development of multistep strategies that produce rather higher overall yields, but lack of the simplicity like one-pot, one-setp synthesis[7].

The art of performing an efficient chemical transformation, coupling of three or more components in a single operation by a catalytic process avoiding stoichometric toxic reagents, large amounts of solvents, and expensive purification techniques represents a fundamental target of the modern organic synthesis[8] of dihydropyrimidinone has received renewed interest. Recently BF_3-OEt_2, $InCl_3$[9], $FeCl_3$ and lanthanide triflates[10] are found to be effective for this transformation. However many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, inadequate yields and compatibility with other functional groups. Consequently, there is scope for further renovation of the substituents in all three components, and better yields.

Iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency, easy availability, mild reaction conditions, and its stability to moisture and air[11]. A wide functional group tolerance and high-yielding reactions, without over oxidation have made IBX very familiar for the oxidation of alcohols even in the presence of olefins, thioethers and amino groups[12]. In re-

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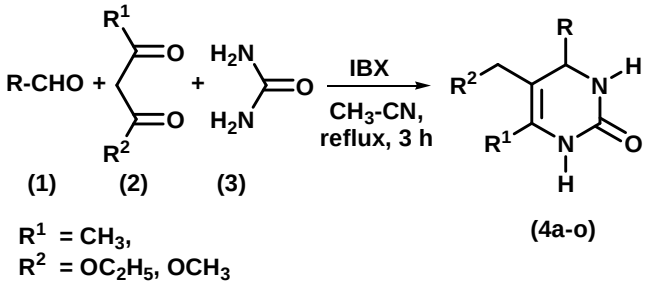

Scheme 1

cent reports, the use of IBX as a mild oxidant has been extended to many other elegant oxidative transformations[13].

EXPERIMENTAL

General remarks

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 using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a finnigan MAT 1020 Mass spectrometer operating at 70eV.

General procedure for the synthesis of dihydropyrimidin-2-one for representative compound 4(a)

A solution of β-keto ester **(2)**, (1mmol) and aldehyde **(1)**, (1mmol), urea **(3)**, (3mmol) and catalytic amount of IBX (195mg) in acetonitrile (5ml) was heated under reflux for 3 hrs. After completion of reaction as indicated by TLC analysis, IBX was removed by cinterred funnel under high vacuum. The reaction mixer poured into the crushed ice and the resulting solid was filtered and recrystallied from hot methanol to afford the pure product.

Spectroscopic data for the compounds

Ethyl-4(4-phenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4a)

m.p. 205-206°C. ^{1}H NMR($CDCl_3$/DMSO-d_6) : δ 8.89 (s, 1H, NH), 7,.01(S,1H, NH), 7.15-7.32 (m, 5H, Ar-CH), 5.27(s, 1H, CH), 4.03(q, *J*=7.1Hz, 2H, OCH_2), 2.31(s, 3H, CH_3) 1.15(t, *J*=7.1Hz, 3H). FABMS: m/z(%) = 261(M+1) (28), 183(10), 154(100), 136(76), 120(16), 107(28), 89(30), 77(32), 55(42). IR (KBr) : 3234, 3108, 1701, 1645, 1091, 758, 698 cm^{-1}.

Ethyl-4(4-fluorophenyl)-6-methyl-2-oxo-3,4-dihydroPyrimidine-5-carboxylate(4b)

m.p. 176-177°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 9.0 (brs, 1H, NM), 7.45(brs, 1H, NH), 7.25-7.30 (m, 2H, Ar-CH), 6.93-7.00 (m, 2H, Ar-CH), 5.20(s, 1H, CH), 3.98(q, 2H, *J*=7.1Hz, OCH_2), 2.28(s, 3H, CH_3), 1.13(t, *J*=7.1Hz, 3H). FABMS: m/z(%) = 278(M^+), 248(24), 232(10), 204(10), 189(8), 182(32), 154(58), 136(46), 124(12), 107(20), 89(20), 77(22). IR (KBr) : 3243, 3117, 2957, 1706, 1647, 1223, 1090, 781, 683 cm^{-1}.

Ethyl-4(4-chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate(4c)

m.p. 218-219°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 8.88 (brs, 1H, NH), 7.51 (brs, 1H, NH), 7.25(m, 4H, Ar), 5.19(d, *J*=3.57Hz, 1H), 3.98(q, J=7.1Hz, 2H, OCH_2), 2.24(s, 3H, CH_3), 1.12(t, *J*=7.152Hz, 3H). FABMS: m/z(%) = 294 (M^+), 182(12), 165(8), 153(100), 137(72), 120(14), 107 (26), 89(22), 77(24), 65(10). IR (KBr) : 3245, 3122, 2978, 1706, 1647, 1221, 1094, 846, 790 cm^{-1}.

Ethyl-4(2-nitrophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4d)

m.p. 206-207°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 9.32 (brs, 1H, NH), 7.84 (d, J=-8.176Hz, 1H, arom CH), 7.64 (t, 1H, *J*=7.433), 7.56 (d, 1H, *J*=8.176Hz, arom CH) 7.44 (t, *J*=4.33Hz, 1H), 6.82 (brs, 1H, NH), 5.82 (d, 1H, *J*=2.23Hz), 3.90 (q, 2H, *J*=7.4333, OCH_2), 2.38 (s, 3H, CH_3), 0.99(t, 3H, J=7.433Hz). FABMS: m/z (%) = 305(M^+) (100), 286(48), 270(4), 259(18), 228(24), 213(38), 197(12), 182(26), 154(14), 136(18), 120(8), 107(8), 65(6), 51(10). IR (KBr) : 3420, 3249, 3117, 2952, 1717, 1683, 1649, 1244, 1093, 1026, 823, 782 cm^{-1}.

Ethyl-4(4-nitrophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4e)

m.p. 206-208°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 9.08 (brs, 1H, NH), 8.08(d, *J*=8.76Hz, 2H, arom CH), 7.55 (brs, 1H, NH), 7.45 (d, J=8.69Hz, 2H, arom CH), 5.28 (d, *J*=2.230Hz, 1H, CH), 3.97(q, *J*=7.1Hz,

2H, OCH_2), 2.24(s, 3H, CH_3), 1.10 (t, *J*=7.1Hz, 3H, CH_3). EIMS: m/z(%) = 315 (M^+) (75), 278(40), 234(17), 184(90), 156(100), 138 (80), 111(20), 76(17), 42(40). IR (KBr) : 3236, 3119, 2982, 1729, 1703, 1644, 1521, 1218, 1092, 778, 698 cm^{-1}.

Ethyl-4(4-methylphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4f)

m.p. 175-176°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.93 (brs, 1H, NH), 7.15(brs, 1H, NH), 6.95-7.10 (m, 4H, ArCH), 5.15 (d, *J*=2.9Hz, 1H, CH), 3.95 (q, *J*=6.95Hz, 2H, OCH_2), 2.24 (s, 3H), 2.20 (s, 3H, CH_3), 1.11(t, J=7.3Hz, 3H, CH_3). FABMS: m/z(%) 275(M^+) (100), 245(20), 229(10), 201(10), 183(39), 154(68), 136(58), 120(14), 107(24), 85(36), 69(24), 55(34). IR (KBr): 3422, 3229, 3106, 2927, 1702, 1644, 1026, 1002, 824, 763 cm^{-1}.

Ethyl-4(4-dimethylamino)-6-methyl-2-oxo-3,4dihydropyrimidine-5-carboxylate (4g)

m.p. 200-202°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.89 (brs, 1H, NH), 7.28(brs, 1H, NH), 7.11 (d, *J*=8.176Hz, 2H, arom CH), 6.65(d, 2H, *J*=8.176Hz), 5.11 (d, *J*=2.23Hz, 1H, CH), 4.01 (q, *J*=4.33Hz, 2H), 2.92 (s, 6H, $N(CH_3)_2$), 2.27(s, 3H, CH_3), 1.18(t, *J*=7.433Hz, 3H, CH_3). FABMS: m/z(%) = 303 (M^+) (15), 289 (10), 238 (6), 176 (6), 165(8), 154 (100), 136 (80), 121(20), 107 (32), 89 (40), 77 (42), 63 (20). IR (KBr) : 3423, 2253, 1654, 1027, 1002, 1446, 1230, 824, 763 cm^{-1}.

Methyl-4(4-dimethylamino)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4h)

m.p. 214-216°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.88 (brs, 1H, NH), 7.09(brs, 1H, NH), 7.11 (d, *J*=8.176Hz, 2H, arom CH), 6.61(d, 2H, *J*=8.176Hz), 5.14 (d, *J*=2.23Hz, 1H, CH), 3.58 (s, 3H), 2.92 (s, 6H, $N(CH_3)_2$), 2.29 (s, 3H, CH_3). EIMS: m/z(%) = 290(M+1) (15), 275 (5), 231(8), 142 (10), 121(15), 85 (75), 66 (100), 46 (55). IR (KBr) : 3239, 3105, 2926, 1703, 1681, 1648, 1615, 1524, 1247, 1025, 1002, 821, 783 cm^{-1}.

Ethyl-4(4-hydroxyphenyl)-6-methyl-2-oxo-3,4dihydropyrimidine-5-carboxylate (4i)

m.p. 202-204°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.85 (brs, 1H, phenolic-OH), 8.76(brs, 1H, NH), 7.01-7.05 (m, 3H), 6.63 (d, 2H, *J*=8.76Hz), 5.11 (d, *J*=1.59Hz, 1H, CH), 3.97 (q, 3H, *J*=7.1Hz), 2.23 (s, 3H, CH_3), 1.12 (t, *J*=7.16 Hz, 3H, CH_3). FABMS: m/z (%) = 276(M^+) (100), 246(26), 230(16), 202(12), 182(50), 154(48), 136(42), 120 (10), 107(18), 89 (18), 77 (18). IR (KBr) : 3239, 3120, 2976, 1686, 1645, 1463, 1350, 1294, 1090, 755, 651 cm^{-1}.

Ethyl-4(4-methoxyphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4j)

m.p. 206-208°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.95 (brs, 1H, NH), 7.19 (d, 2H, *J*=8.6Hz, arom CH), 6.96 (brs, 1H, NH), 6.77 (d, *J*=8.5Hz, 2H, arom CH), 5.23 (s, 1H, CH), 4.03(q, *J*=7.0Hz, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3), 1.17 (t, *J*=7.0Hz, 3H, CH_3). EIMS: m/z(%) = 292(M+2) (30), 276(5), 263(100), 218(75), 184(65), 156(55), 138(20), 111(20), 78(30), 42(48). IR (KBr): 3243, 3112, 2956, 1705, 1650, 1221, 1087, 840, 791 cm^{-1}.

Ethyl-4(3,4,5-trimethoxyphenyl)-6-methyl-2-oxo-3,4dihydropyrimidine-5-carboxy late (4k)

m.p. 215-217°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 8.91 (brs, 1H, NH), 7.26 (brs, 1H, NH), 6.52 (s, 2H, arom CH), 5.20(d, *J*=2.23Hz, 1H, CH), 4.06(q, *J*=7.433Hz, 2H, OCH_2), 3.80(s, 6H, $OCH)_2$), 3.72(s, 3H, OCH_3), 2.30(s, 3H), 1.20 (t, *J*=7.433Hz, 3H, CH_3). EIMS: m/z(%) = 350 (M^+) (44), 320(10), 306(20), 288((12), 276(6), 221(4), 182(34), 153(100), 136(72), 120 (14), 107 (30), 77 (26). IR (KBr): 3442, 2927, 1702, 1646, 1581, 1220, 1121, 1084, 792, 773, 700 cm^{-1}.

Ethyl-4(2-napthyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxy late (4l)

m.p. 245-247°C. ^1H NMR : ($CDCl_3$/DMSO-d_6) δ 9.11 (brs, 1H, NH), 7.54 (brs, 1H, NH), 7.38-7.82 (m, 7H, arom CH), 5.43 (d, *J*=2.23 Hz, 1H, CH), 4.02 (q, *J*=7.433Hz, 2H, OCH_2), 2.23 (s, 3H), 1.16(t, *J*=7.433Hz, 3H, CH_3). EIMS: m/z(%) 312 (M+2) (50), 282 (55), 238(45), 184(100), 156(60), 128(62), 11(15), 78(15), 42(75). IR (KBr): 3422, 1699, 1646, 1225, 1049, 1026, 1002, 823, 761 cm^{-1}.

Ethyl-4(4-styrl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4m)

m.p. 237-239°C. ^1H NMR : ($CDCl_3$/DMSO-d_6)

δ 8.81 (brs, 1H, NH), 6.75 (brs, 1H, NH), 7.13-7.36 (m, 5H, arom CH), 6.42 (d, *J*=16.36 Hz, 1H CH), 6.17 (dd, *J*=16.353, 6.690 Hz, 1H), 4.87 (d, *J*=6.021Hz 1H), 4.15 (q, 2H, *J*=6.690), 2.26 (s, 3H), 1.29 (t, 3H, *J*=6.690Hz, 3H). EIMS: m/z(%) = 287 (M+1), (80), 258(90), 214(74), 184(64), 156(74), 138(50), 116(55), 77(74), 42 (100). IR (KBr) : 3244, 3113, 2976, 1721, 1651, 1463, 1289, 1227, 1094, 971, 780, 692 cm^{-1}.

Ethyl-4(4-ethylphenyl))-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (4n)

m.p. 186-187°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 8.8 (brs, 1H, NH), 7.09 (brs, 1H, NH), 7.14-7.23 (m, 5H, arom CH), 4.20 (m, 1H), 4.05 (m, 2H), 2.55-2.68(m, 2H), 2.25)(s, 3H), 1.80 (m, 2H), 1.20 (t, 3H, J=7.2Hz). EIMS: m/z(%) = 288 (M^+) (25), 184(100), 156(50), 138(40), 92(48), 42(35). IR (KBr) : 3423, 2976, 2253, 1710, 1652, 1027, 1003, 825, 765 cm^{-1}.

Ethyl-6-methyl-2-oxo-3-pentyl-3,4dihydropyrimidine-5-carboxylate (4o)

m.p. 155-157°C. ^{1}H NMR : ($CDCl_3$/DMSO-d_6) δ 8.78 (brs, 1H, NH), 7.09 (brs, 1H, NH), 4.42 (m, 1H), 4.25(m, 2H), 2.32 (s, 3H), 1.65(m, 2H), 1.32-1.47 (m, 9H), 0.95 (t, *J*=6.86Hz, 3H). EIMS: m/z(%) = 255 (M+1) (84), 231(36), 225(70), 183(100), 166(26), 153(28), 137 (36), 107 (22), 100 (66), 55 (90). IR (KBr) : 3245, 3118, 2930, 1702, 1648, 1236, 1085, 772, 744 cm^{-1}.

RESULTS AND DISCUSSION

In view of this we have utilized IBX as an efficient catalyst for the Biginelli three component one-pot synthesis. In this report we describe a simple and practical method for the biginelli reaction using catalytic amount of IBX in acetonitrile. The reaction of benzaldehyde, ethyl acetoacetate and urea in the presence IBX in refluxing acetronitrile for 3 h furnished the corresponding dihydropyrimidinone in 94% yield (Scheme 1). Thus, a series of dihydropyrimidinones were prepared in good yields as summarized in TABLE 1. Similarly, several aromatic, aliphatic aldehydes reacted well under these reaction conditions to give the corresponding dihydropyrimidinones in good to excellent yields.

TABLE 1 : IBX promoted synthesis of dihydropyrimidones

DHPM	R	R^1	R^2	Reaction time Hrs	Yield (%)[b]
4a	C_6H_5	Me	OEt	3.0	90
4b	4-(F)-C_6H_4	Me	OEt	3.2	92
4c	4-(Cl)-C_6H_4	Me	OEt	3.0	88
4d	2-(NO_2)-C_6H_4	Me	OEt	3.3	89
4e	4-(NO_2)-C_6H_4	Me	OEt	3.2	92
4f	4-(CH_3)-C_6H_4	Me	OEt	3.3	91
4g	4-(N Me_2)-C_6H_4	Me	OEt	3.2	94
4h	4-(N Me_2)-C_6H_4	Me	OMe	3.4	93
4i	4-(OH)-C_6H_4	Me	OEt	3.5	94
4j	4-(CH_3O)-C_6H_4	Me	OEt	3.6	92
4k	3,4,5-(CH_3O)$_3$-C_6H_2	Me	OEt	3.3	91
4l	2-Napthyl	Me	OEt	3.1	88
4m	Cinnamyl	Me	OEt	3.1	90
4n	Phenyl Propyl	Me	OEt	3.2	89
4o	n-Hexyl	Me	OEt	3.1	88

[a]**All Products were characterized by IR, ^{1}H NMR and Mass Spectroscopy and compared with literature reports, [b]All yields were isolated and unoptimized**

Many of the pharmacological relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded high yields of products in high purity. Another important feature of this procedure is the survival of variety functional groups such as olefins, esters, nitro, hydroxy and halides under the reaction conditions. The advantage of IBX for the reaction lies in its simplicity.

Interestingly, Bis-acetoxy Iodobenzene (BAIB) also catalyses Biginelli one-pot, three component condensation reaction giving less yields (35%-45%) and taking long reaction times (7-9 h) for the conversion. Thus IBX is more superior for Biginelli protocol in terms of conversion and time.

This procedure offers an easy access to substituted dihydropyrimidinones with a variety of substitution patterns. Among the various solvents such as acetonitrile, methanol, THF, ethanol and DMSO were used for this transformation, acetonitrile was found to be a best reveal the scope and generality of the reaction with respect to the various aldehydes, β-ketoesters and urea.

CONCLUSION

In conclusion, we have developed a simple and

general method for the synthesis of dihydropyrimidinones using the inexpensive and easily available IBX. The method offers several advantages including high yields, short reaction times and simple experimental workup procedure, which makes a useful process for the synthesis of dihydropyrimidinones.

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