

Bismuth (III) nitrate catalyzed one-pot synthesis of 3,4-dihydro-pyrimidin-2-(1H)-ones: an improved protocol for the Biginelli reaction

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Abstract

An efficient synthesis of 3,4-dihydropyrimidinones (DHPMs) using bismuth (III) nitrate as a catalyst for the first time from an aldehyde, β -keto ester and urea in acetonitrile is described. Compared to the classical Biginelli reaction conditions, this new method consistently has the advantage of excellent yields (80-93%) and short reaction time (1.5-2.5 hours) at room temperature.

Keywords: Dihydropyrimidinones, Biginelli reaction, bismuth (III) nitrate

Introduction

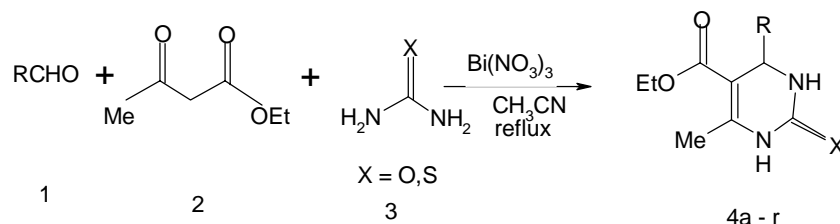
Dihydropyrimidinones (DHPMs) and their derivatives exhibit wide range of biological activities such as antibacterial, antiviral, antitumor and anti-inflammatory actions.¹ Biginelli compounds exhibit pharmacological activities as calcium channel blockers, antihypertensive agents, α -1a-antagonists, and neuropeptide Y(NPY) antagonists.² Several biologically active marine alkaloids were also found to contain the dihydropyrimidinone-5-carboxylate core.³ Most notable among them are batezelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.⁴ Consequently, syntheses of these compounds have gained importance. Biginelli (1893) reaction⁵ is a simple one pot condensation of an aldehyde, ketoester and urea or thiourea in the presence of a catalytic amount of acid to produce 3,4-dihydropyrimidin-2-(1H)-ones and which often suffer from low yields, especially in the 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 the original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract attention of researchers searching for a milder and more efficient procedure for the synthesis of dihydropyrimidinones.

In recent years, several synthetic procedures for the preparation of DHPMs have been reported including classical conditions with microwave irradiation⁸ and by using Lewis acids, as

well as protic acids, as promoters. Such promoters as conc. HCl,⁹ BF₃•OEt₂,^{10a} PPE,^{10b} KSF clay,^{10c} InCl₃,^{10d} LaCl₃,^{10e,f} lanthanide triflate,^{10g} H₂SO₄,^{10h} ceric ammonium nitrate (CAN),¹⁰ⁱ Mn(OAc)₃,^{10j} ion-exchange resin,^{10k} 1-n-butyl-3-methyl imidazolium tetrafluoroborate (BMImBF₄),^{10l} BiCl₃,^{10m} LiClO₄,¹⁰ⁿ InBr₃,^{10o} FeCl₃,^{10p} ZrCl₄,^{10q} Cu(OTf)₂,^{10r} Bi(OTf)₃,^{10s} LiBr,^{10t} ytterbium triflates,^{10u} NH₄Cl,^{10v} SiO₂/NaHSO₄,^{10x} CdCl₂,^{10y} etc. have been found to be effective. However, some of these methods require the use of toxic reagents in combination with Bronsted acids, such as hydrochloric acid and acetic acid, as additives. Many of these methods involve expensive reagents, stoichiometric 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 bismuth nitrate as an efficient catalyst for the Biginelli three-component one-pot synthesis in our laboratory. We are particularly interested in bismuth nitrate, because it is inexpensive and can be easily available in a laboratory. Bi(NO₃)₃ is an oxidizing agent which has a wide variety of utility in different chemical transformations, like bismuth nitrate catalyzed addition of amines, imidazoles and thiols to enones.¹¹ We wish to report here a simple and efficient method for the synthesis of DHPMs using Bi(NO₃)₃ as a catalyst.

Results and Discussion













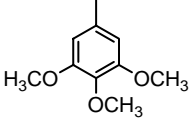




Initially, we have studied the Biginelli's one-pot condensation reaction of benzaldehyde (1.0 mmol) with urea (1.2 mmol) and ethyl acetoacetate (1.2 mmol) using 5-mol% of bismuth (III) nitrate in acetonitrile (5 ml) as solvent at ambient temperature (Scheme 1). The reaction is very fast and 90% conversion was observed in 1.5 h.



Scheme 1

Encouraged by these results, we examined several aromatic and aliphatic aldehydes under the optimized conditions (Table 1). It seems that acetonitrile is a much better solvent in terms of yields (93%) than all other tested solvents such as methanol (85%), dichloromethane (72%), tetrahydrofuran (55%), water (25%), H₂O-THF (50%), toluene (32%). Furthermore, the use of just 5-mol% of bismuth (III) nitrate in acetonitrile is sufficient to promote the reaction. There are no improvements in the reaction rates and yields by increasing the amount of the bismuth (III) nitrate from 5-mol% to 10-mol%.

Table 1. Bi(NO₃)₃ – catalyzed efficient synthesis of dihydropyrimidinones

Entry	R	X	Products	Time (h)	Yield ^a (%)
1		0	4a	1.5	92
2		0	4b	2.0	90
3		0	4c	2.0	90
4		0	4d	1.5	90
5		0	4e	1.5	88
6		0	4f	2.0	90
7		0	4g	2.5	86
8		0	4h	2.5	88
9		0	4i	2.0	85
10		0	4j	2.5	85
11		0	4k	2.5	80
12		0	4l	2.5	92
13		0	4m	2.5	84
14	2-Furfuryl	0	4n	2.5	84
15		S	4o	1.5	93
16		S	4p	2.0	90
17		S	4q	2.0	90
18		S	4r	2.0	90

^a yields refers to pure solid products, properly characterized by m.p. spectral (IR, ¹H NMR and Mass) data.

The best results were achieved when the reactions were carried out at room temperature for 1.5-2.5 h in the presence of catalytic amount $\text{Bi}(\text{NO}_3)_3$. The results are listed in Table 1. 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.

Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving excellent yields of products. Many of the pharmacologically relevant substitution patterns on the aromatic ring were introduced with high efficiency. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2-(1*H*)-thiones in high yields, which are also of much interest with regard to biological activity. An acid sensitive aldehyde worked well without formation of any side product. Especially noteworthy is the survival of a variety of functional groups, such as ether, hydroxy, halides, nitro, double bond, etc., under the reaction conditions.

Conclusions

In summary, we have developed a new methodology for the synthesis of DHPMs by a three-component condensation in one pot using a catalytic amount of $\text{Bi}(\text{NO}_3)_3$. By using $\text{Bi}(\text{NO}_3)_3$ as a catalyst at ambient temperature, the yields of the one-pot Biginelli reaction can be increased from 25-55% to 56-95% while the reaction time is shortened from 18 to 1-4 h. Thus, bismuth (III) nitrate mediated one-pot synthesis of DHPMs is a simple, high yielding, time saving, and eco-friendly process.

Experimental Section

General procedure for the $\text{Bi}(\text{NO}_3)_3$ catalyzed synthesis of pyrimidinones

A solution of an appropriate β -keto ester (1.2 mmol), corresponding aldehyde (1.0 mmol), urea or thiourea (1.2 mmol), and $\text{Bi}(\text{NO}_3)_3$ (5 mol%) in acetonitrile (5 ml) was heated under reflux in the presence of a catalytic amount of $\text{Bi}(\text{NO}_3)_3$ (5 mol%) for 3 h (completion of reaction was monitored by TLC). The reaction mixture was washed thoroughly with water, filtered and recrystallized from methanol to afford pure product. The spectral data of the some of the compounds are given below.

Entries 1,6 (4a, 4f). The spectroscopic data is in full agreement with the literature data.^{10w}

Entries 2-5 (4b-4e). The spectroscopic data is in full agreement with the literature data.¹⁰ⁿ

Entry 7 (4g). Solid, m.p. 247-248 °C. ^1H NMR (DMSO-d_6): δ 0.90 (t, 3H, $J = 7.0$ Hz), 2.40 (s, 3H), 3.91 (q, 2H, $J = 7.0$ Hz), 6.12 (s, 1H), 7.40 – 7.55 (m, 5H), 7.80 (t, 1H, $J = 8.2$ Hz), 7.85 (d, 1H, $J = 8.2$ Hz), 8.30 (d, 1H, $J = 8.2$ Hz), 9.10 (br s, NH). EIMS: m/z (%) 310 (M^+), 217, 176, 133, 119, 91, 69. IR (KBr): $\nu = 3244, 3120, 2960, 1690, 1647, 1430, 1230, 1088, 789$ cm^{-1} .

Entry 8 (4h). Solid, m.p. 214-216 °C, ¹H NMR (DMSO-d₆): δ 9.08 (s, 1H, NH), 7.75 (s, 1H, NH), 7.24 (m, 4H), 5.20 (d, 1H, J = 3.0 Hz), 4.08 (q, 2H, J = 7.5 Hz), 2.24 (s, 3H), 1.12 (t, 3H, J = 7.5 Hz). EIMS: m/z 274 (M⁺, 28), 245 (31), 229 (42), 201 (49), 183 (100), 155 (40), 138 (28), 91 (67). IR (KBr): ν 3325, 3152, 1691, 1655, 1560, 1232, 1050, 783, 784 cm⁻¹.

Entry 9 (4i). Solid, m.p. 205-207 °C. ¹H NMR (DMSO-d₆): δ 1.07 (t, 3H, J = 6.8 Hz), 2.26 (s, 3H), 5.27 (s, 1H), 7.5 (d, 2H, J = 7.3 Hz), 7.85 (s, 1H, NH), 8.2 (d, 2H, J = 7.2 Hz), 9.35 (s, 1H, NH). EIMS: m/z (%) 305 (M⁺, 25), 276 (92), 260 (20), 183 (100). IR (KBr): ν = 3215, 1731, 1702, 1640 cm⁻¹.

Entry 10 (4j). Solid, m.p. 237-238 °C. ¹H NMR (DMSO-d₆): δ 1.04 (m, 4H), 1.25 (t, 3H, J = 6.8 Hz), 1.44 (m, 3H), 1.75 (m, 4H), 2.3 (s, 3H), 4.15 (m, 3H), 6.15 (br s, 1H, NH), 8.44 (br s, 1H, NH). EIMS: m/z (%) 266 (M⁺), 183, 155, 40. IR (KBr): ν = 3236, 3118, 2920, 2850, 1726, 1702, 1647, 1450, 1230, 1095, 789 cm⁻¹.

Entry 11 (4k). Solid, m.p. 193-194 °C. ¹H NMR (DMSO-d₆): 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 (br s, NH), 6.85 (m, 1H), 7.05 (m, 5H), 7.45 (m, 3H), 8.40 (br s, NH). EIMS: m/z 352 (M⁺), 323, 279, 183, 155, 137, 91, 69. IR (KBr): ν = 3242, 3112, 2981, 1712, 1654, 1582, 1487, 1245, 1097, 786.

Entry 12 (4l). Solid, m.p. 229-231 °C, ¹H NMR (DMSO-d₆): 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), 7.25 (m, 5H), 7.45 (d, NH, J = 1.7 Hz), 8.95 (br s, NH). EIMS: m/z 286 (M⁺), 252, 224, 196, 149, 84. IR (KBr): ν = 3335, 3242, 3098, 2978, 1689, 1642, 1492, 1373, 1218, 1121, 785.

Entry 13 (4m). Solid, m.p. 180-182 °C, ¹H NMR (DMSO-d₆): δ 1.12 (t, 3H, J = 7.0 Hz), 2.25 (s, 3H), 3.72 (s, 9H), 4.0 (q, 2H, J = 6.6 Hz), 5.12 (s, 1H), 6.50 (s, 2H), 7.72 (s, 1H), 9.23 (s, 1H). EIMS: m/z 250 (M⁺, 80), 221 (97), 177 (100), 110 (34). IR (KBr): ν = 3227, 3100, 2910, 2840, 1700, 1642, 1610, 1580, 1510 cm⁻¹.

Entry 14 (4n). Solid, m.p. 210-212 °C, ¹H NMR (DMSO-d₆): δ 9.25 (s, 1H, NH), 7.8 (s, 1H, NH), 7.55 (s, 1H), 6.33 (d, 1H, J = 3.0 Hz), 6.05 (d, 1H, J = 3.0 Hz), 5.22 (d, 1H, J = 3.5 Hz), 4.25 (q, 2H, J = 6.5 Hz), 2.37 (s, 3H), 1.25 (t, 3H, J = 6.5 Hz). EIMS: m/z 250 (M⁺, 80), 221 (97), 177 (100), 110 (34). IR (KBr): ν = 3325, 3234, 3125, 2980, 1695, 1650, 1455, 1080, 874, 784 cm⁻¹.

Entry 15-18 (4o-4r). The spectroscopic data is in full agreement with the literature data.^{10w}

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