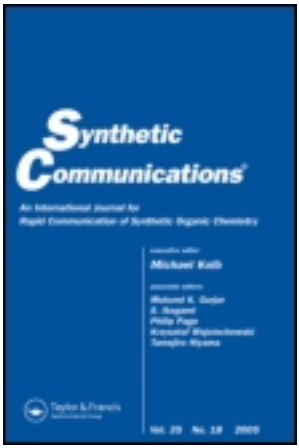

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Bismuth Subnitrate Catalyzed Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones: An Improved Protocol for the Biginelli Reaction

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Bismuth Subnitrate Catalyzed Efficient Synthesis of 3,4-Dihydropyrimidin-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 subnitrate as the catalyst for the first time from an aldehyde, β-ketoester, and urea in acetonitrile is described. This new method consistently has the advantage of excellent yields (88–96%) and short reaction times (1.5–4 h) than do classical Biginelli reaction conditions.

Key Words: Biginelli reaction; Bismuth subnitrate; Dihydropyrimidinones; One-pot condensation.

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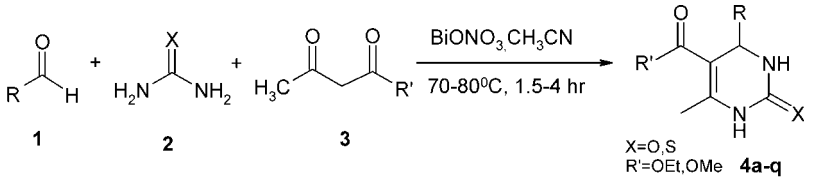
INTRODUCTION

Dihydropyrimidinones form an important class of compounds that are becoming increasingly considered due to their therapeutic and pharmacological properties as calcium channel blockers, antihypertensive agents and α-1a-antagonists, and neuropeptide Y (NPY) antagonists.[1]

The simple and direct procedure first recorded by Biginelli involving three-component condensation of a β-ketoester with an aldehyde and urea (or) thiourea in ethanol solution often suffers from low yields (25–60%).[2] Several improved procedures for the synthesis of dihydropyrimidinones have recently been reported. Hu[3] and Kappe[4] reported reagents involving the use of $BF_3 \cdot OEt_2$/CuCl and PPE (polyphosphate ester) mediated variation of the Biginelli reaction giving high yields of dihydropyrimidinones, but the reaction requires 15–18 h of reaction time. More recently, Lewis acids like $BiCl_3$, $Bi(OTf)_3$, $InCl_3$, $LiClO_4$, $ZrCl_4$, $La(OTf)_3$, $NiCl_2 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, and ionic liquids[5] have been employed for this transformation. Recently, acidic montmorillonite KSF and microwave irradiation were also reported to be effective for Biginelli reaction.[6] In this note, we describe a general and practical route for the Biginelli cyclocondensation reaction using bismuth subnitrate as the catalyst in solution conditions.

RESULTS AND DISCUSSION

As shown in Sch. 1, the one-pot reaction of benzaldehyde **1** (1 mmol) with urea **2** (1.5 mmol) and ethylacetoacetate **3** (1 mmol) in the presence of $BiONO_3$ (0.2 mmol) in acetonitrile as solvent at 70–80°C gave 4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4a** in 96% yield within 1.5 h. Many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. We noted that all aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted well, giving moderate to excellent yields (Table 1).



Scheme 1.

Table 1. $BiONO_3$-catalyzed efficient synthesis of dihydropyrimidin-2(1H)-ones.

Product	R	R^1	X	Time (h)	Yield (%)[a]
4a[5h]	C_6H_5	OEt	O	1.5	96
4b[5h]	3-(NO_2)-C_6H_4	OEt	O	3.0	90
4c[5h]	4-(NO_2)-C_6H_4	OEt	O	3.5	92
4d[5h]	4-(OCH_3)-C_6H_4	OEt	O	3.0	90
4e	3-(Cl)-C_6H_4	OEt	O	2.5	88
4f[5h]	4-(Cl)-C_6H_4	OEt	O	3.0	90
4g[5h]	4-(OH)-C_6H_4	OEt	O	3.0	92
4h[5k]	2-Furyl	OEt	O	4.0	90
4i[5h]	C_6H_5	OMe	O	2.5	92
4j[5h]	3-(NO_2)-C_6H_4	OMe	O	3.5	88
4k[5h]	4-(NO_2)-C_6H_4	OMe	O	3.5	89
4l[5h]	4-(OCH_3)-C_6H_4	OMe	O	3.0	92
4m	3-(Cl)-C_6H_4	OMe	O	3.0	90
4n[5h]	4-(Cl)-C_6H_4	OMe	O	3.0	89
4o[5h]	4-(OH)-C_6H_4	OMe	O	3.5	91
4p[5i]	4-(OH)-C_6H_4	OEt	S	4.0	90
4q[5i]	4-(OCH_3)-C_6H_4	OEt	S	3.5	92

[a]Yields refer to pure solid products; all products were characterized by comparison of their physical and spectral data with those of authentic samples.

In conclusion, we developed a simple modification of the Biginelli dihydropyrimidinone synthesis by using the inexpensive and commercially available $BiONO_3$ as an efficient Lewis acid catalyst. The method offers several advantages, including high yields, short reaction times and a simple experimental workup procedure and product isolation; hence, it is a useful addition to the existing methods.

EXPERIMENTAL

General Procedure

A solution of an appropriate β-keto ester (1 mmol), corresponding aldehyde (1 mmol), urea or thiourea (1.5 mmol), and $BiONO_3$ (0.2 mmol) in anhydrous acetonitrile (10 mL) was stirred at 40–50°C for a certain period of time as required to complete the reaction (TLC). The solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered, and recrystallized from ethanol to afford pure product.

4e: Mp 217–219°C; [1]H-NMR (200 MHz, DMSO-d_6): δ 1.12 (t, J = 7 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.88 (q, J = 5.22 Hz, 2H, OCH_2), 5.42 (s, 1H, CH), 7.55–7.78 (m, 2H, Ar), 7.88 (bs, 1H, NH), 8.06–8.18 (m, 2H, Ar), 9.38 (bs, 1H, NH). IR (KBr): 1585, 1640, 1688, 2965, 3102, 3218, 3352 cm^{-1}. Anal. calculated for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; Cl, 12.03; N, 9.50. Found: C, 57.10; H, 5.10; Cl, 12.08; N, 9.47.

4m: Mp 208–210°C; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 5.38 (s, 1H, CH), 7.60–7.75 (m, 2H, Ar), 7.91 (bs, 1H, NH), 8.01–8.12 (m, 2H, Ar), 9.41 (bs, 1H, NH). IR (KBr): 1578, 1646, 1692, 2962, 3102, 3222, 3348 cm^{-1}. Anal. calculated for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.63; H, 4.70; Cl, 12.68; N, 9.97.

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