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Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via Biginelli reaction promoted by bismuth(III)nitrate or PPh₃ without solvent

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Received 9 March 2011; accepted 8 June 2011

KEYWORDS

Biginelli reaction;
3,4-Dihydropyrimidinones;
Solvent free conditions;
Bismuth(III) nitrate

Abstract 3,4-Dihydropyrimidinones/thiones and their derivatives are synthesized via Biginelli routes involving an aldehyde, 1,3-dicarbonyl compound and urea or thiourea. Use of catalysts such as bismuth nitrate in acetonitrile or PPh₃ without solvent lead to higher yields compared to the classic method using HCl in ethanol. In such way, 3,4-dihydropyrimidinones which are hardly prepared under classic conditions can be synthesized with fair yields.

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1. Introduction

Dihydropyrimidinones and their derivatives take an important place in pharmacology and organic synthesis due to their remarkable properties as calcium-blockers (Yu et al., 2007;

Jauk et al., 2000), antihypertensive (Kappe, 2000; Bahekar and Shinde, 2003), anti-inflammatory (Grover et al., 1995; Bahekar and Shinde, 2004), antibacterial (Brands et al., 2003; Tozkoparan et al., 1999), antioxidative (Stefani et al., 2006), anticancer (Haggarty et al., 2000; Holla et al., 2004), antiviral compounds (Kumar et al., 2006). The original method was reported by Biginelli (1893). It involves the condensation of an aldehyde, a ketoester and a urea or thiourea under acidic conditions. The method, however, requires harsh conditions leading often to low yields despite long reaction times. In order to circumvent these drawbacks several catalytic systems using various Lewis acids have been devised: BF₃(OEt)₂ (Hu et al., 1998), FeCl₃·6H₂O (Lu and Ma, 2000), FeCl₃ immobilized in Al-MCM-41 (Oskooie et al., 2011), InCl₃ (Brindaban et al., 2000), LaCl₃·7H₂O (Lu et al., 2000), ZrCl₄ or ZrOCl₂ (Reddy et al., 2002; Dominguez et al., 2007), BiCl₃ (Ramalinga et al., 2001), InBr₃ (Fu et al., 2002), LiBr (Maiti et al., 2003), CdCl₂ (Chari and Syamasundar, 2004), SnCl₂·2H₂O (Russowsky et al., 2004), CuCl₂·2H₂O (Singh et al., 2008), [Al(H₂O)₆](BF₄)₃ (Litvic et al., 2010). Triflates or lanthanides have also been tested In(OTf)₃ (Ghosh et al., 2004), Cu(OTf)₂ (Paraskar

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Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2011.06.010



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Table 1 Influence of the solvent on Biginelli reaction.

Product	CH ₃ CN	EtOH	CH ₂ Cl ₂	Water	THF	Toluene
<i>Yield (%)</i>						
4a	94	84	72	23	54	30
4i	76	72	61	18	46	22

Aldehyde (4 mmol); urea (5 mmol); 1,3-dicarbonyl compound (5 mmol); Bi(NO₃)₃ (5% mmol); solvent (20 mL); 2.5 h.

et al., 2003), Bi(OTf)₃ (Varala et al., 2003), Sr(OTf)₂ (Su et al., 2005), La(OTf)₃ (Ma et al., 2000), Fe(OTf)₃ (Adibi et al., 2007), Li(OTf) (Lusch and Tallarico, 2004).

We have been interested in the Biginelli synthesis of some dihydropyrimidinones by studying the effect of the solvent, the nature of the aldehyde and the catalytic system.

2. Experimental

2.1. Procedure (*M*₁)

Ethanol (20 mL) and concentrated HCl are introduced into a round-bottomed flask equipped with a cooling device. The aldehyde (4 mmol), urea or thiourea (5 mmol), the 1,3-dicarbonyl compound (5 mmol) are added and the solution is permitted to react for 18 h under reflux with magnetic stirring. The mixture is then washed with water and filtrated. The resulting product is recrystallized in ethanol.

2.2. Procedure (*M*₂)

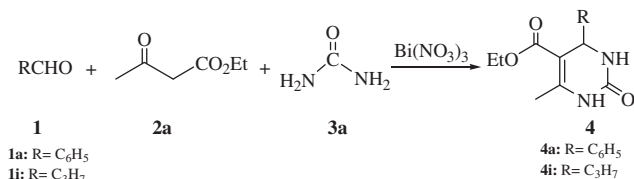
Acetonitrile (20 mL) and Bi(NO₃)₃ (0.2 mmol) are introduced into a round-bottomed flask equipped with a cooling device. The aldehyde (4 mmol), urea or thiourea (5 mmol), the 1,3-dicarbonyl compounds (5 mmol) are added and the solution is permitted to react for 2.5 h with magnetic stirring at room temperature. The mixture is then washed with water and filtrated. The resulting product is recrystallized in ethanol.

2.3. Procedure (*M*₃)

A mixture of aldehyde (4 mmol), 1,3-dicarbonyl compound (4 mmol), urea or thiourea (6 mmol) and catalytic amount of PPh₃ (0.4 mmol) are introduced into a round-bottomed flask equipped with a cooling device. The reaction mixture was heated with stirring at 100 °C for 3 h. The product was filtrated, washed with water. The solid crude products were recrystallized in ethanol.

2.4. Recording of spectra

¹H (300 MHz) and ¹³C (75 MHz) NMR spectra are recorded on a Bruker spectrometer in DMSO-d₆, with tetramethylsilane as internal reference.

**Figure 1** Bismuth(III)nitrate catalyzed Biginelli reaction.**Table 2** Synthesis of dihydropyrimidinones/thiones via Biginelli reaction using aliphatic and aromatic aldehydes.

Aldehyde	1,3-Dicarbonyl compound	3	Product	mp (°C)	Yield (%)	
					<i>M</i> ₁	<i>M</i> ₂
1a	2a	3a	4a	199–201	74	94
1b	2a	3a	4b	210–213	56	91
1c	2a	3a	4c	202–203	61	90
1d	2a	3a	4d	206–208	54	84
1e	2a	3a	4e	215–216	55	82
1f	2a	3a	4f	226–227	66	90
1g	2a	3a	4g	193–195	26	42
1h	2a	3a	4h	179–181	30	72
1i	2a	3a	4i	179–181	30	76
1j	2a	3a	4j	237–238	42	87
1a	2b	3a	4k	209–211	52	88
1b	2b	3a	4l	207–208	52	83
1c	2b	3a	4m	193–194	54	83
1d	2b	3a	4n	214–215	48	80
1a	2c	3a	4o	133–134	44	84
1b	2c	3a	4p	149–151	60	89
1c	2c	3a	4q	105–106	30	87
1d	2c	3a	4r	184–186	62	90
1a	2d	3a	4s	223–224	65	80
1b	2d	3a	4t	231–232	55	78
1d	2d	3a	4u	196–197	52	75
1e	2d	3a	4v	237–238	54	74
1e	2e	3a	4w	256–257	52	78
1d	2e	3a	4x	234–235	48	80
1a	2a	3b	4a'	203–205	67	95
1b	2a	3b	4b'	192–193	50	90
1c	2a	3b	4c'	139–141	48	88
1d	2a	3b	4d'	108–110	47	88

*M*₁: Aldehyde (4 mmol); urea or thiourea (5 mmol); 1,3-dicarbonyl compound (5 mmol); EtOH (20 mL); HCl; reflux for 18 h. *M*₂: Aldehyde (4 mmol); urea or thiourea (5 mmol); 1,3-dicarbonyl compound (5 mmol); Bi(NO₃)₃ (5% mmol); Acetonitrile (20 mL); 2.5 h.

All the products were confirmed by comparing their melting points, ¹H NMR and ¹³C NMR data with the literature data (Joseph et al., 2006; Kumar and Parmar, 2008; Shaabani et al., 2003; Chitra and Pandiarajen, 2009; Chari et al., 2005; Gholap et al., 2008; Kapadia et al., 2009; Falsone and Kappe, 2001).

3. Results and discussion

3.1. Solvent effect

The results of Table 1 reveal that bismuth nitrate is a suitable catalyst for Biginelli reactions. The nature of the solvent is not innocent as higher values of the dielectric constant induce higher yields. Water is a noticeable exception. This proves the ionic character of the reaction. Thus, the Biginelli reaction catalyzed by bismuth nitrate in acetonitrile at room temperature is an efficient synthetic procedure for the preparation of dihydropyrimidinones from benzaldehyde or butanal as aldehydes, ethyl acetoacetate and urea (see Fig. 1).

3.2. Biginelli reaction catalyzed by Bi(NO₃)₃ in acetonitrile

Generalization of the method leads to the results exposed in Table 2 (see Fig. 2).

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