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ORIGINAL ARTICLE

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via Biginelli reaction promoted by bismuth(III)nitrate or PPh_3 without solvent

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KEYWORDS

Biginelli reaction;
3,4-Dihydropyrimidinones;
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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 PPh_3 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.

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: $BF_3(OEt)_2$ (Hu et al., 1998), $FeCl_3{\cdot}6H_2O$ (Lu and Ma, 2000), $FeCl_3$ immobilized in Al-MCM-41 (Oskooie et al., 2011), $InCl_3$ (Brindaban et al., 2000), $LaCl_3{\cdot}7H_2O$ (Lu et al., 2000), $ZrCl_4$ or $ZrOCl_2$ (Reddy et al., 2002; Dominguez et al., 2007), $BiCl_3$ (Ramalinga et al., 2001), $InBr_3$ (Fu et al., 2002), LiBr (Maiti et al., 2003), $CdCl_2$ (Chari and Syamasundar, 2004), $SnCl_2{\cdot}2H_2O$ (Russowsky et al., 2004), $CuCl_2{\cdot}2H_2O$ (Singh et al., 2008), $[Al(H_2O)_6](BF_4)_3$ (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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Table 1 Influence of the solvent on Biginelli reaction.

Product	CH_3CN	EtOH	CH_2Cl_2	Water	THF	Toluene
Yield (%)						
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); $Bi(NO_3)_3$ (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 $Bi(NO_3)_3$ (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 PPh_3 (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 ^{13}C (75 MHz) NMR spectra are recorded on a Bruker spectrometer in DMSO-d_6, with tetramethysilane as internal reference.

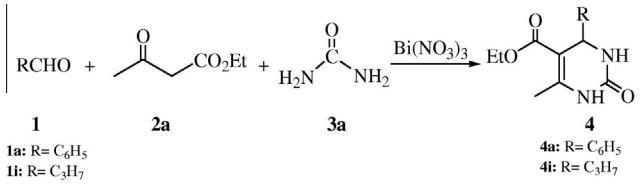

Figure 1 Bismuth(III)nitrate catalyzed Biginelli reaction.

Table 2 Synthesis of dihydropyrimidinones/thiones via Biginelli reaction using aliphatic and aromatic aldehydes.

Aldehyde	1,3-Dicarbonyl compound	3	Product	mp (°C)	Yield (%)	
					M_1	M_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); $Bi(NO_3)_3$ (5% mmol); Acetonitrile (20 mL); 2.5 h.

All the products were confirmed by comparing their melting points, ^1H NMR and ^{13}C 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 $Bi(NO_3)_3$ in acetonitrile

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

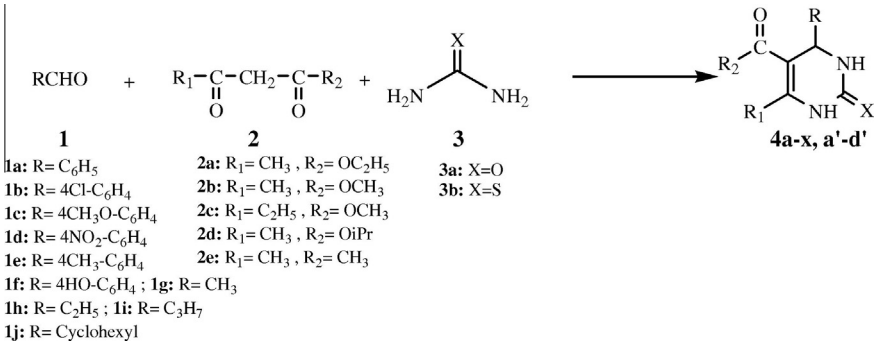

Figure 2 Synthesis of dihydropyrimidinones/thiones catalyzed by bismuth(III) nitrate in acetonitrile.

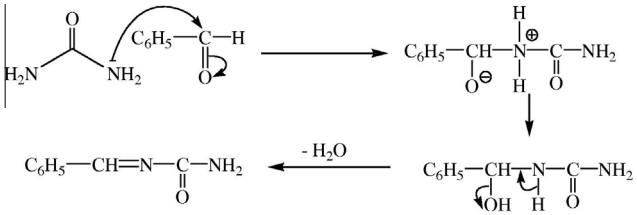

Figure 3 Formation of acylimine intermediate.

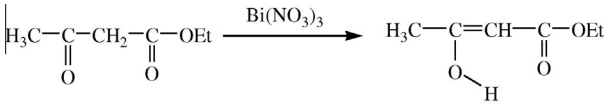

Figure 4 Enolization of dicarbonyl compound.

Table 2 shows that yields range from 42% to 95% under similar conditions as in Table 1. The results, at first sight, are surprising since an increase of the chain length of aliphatic aldehydes implies higher yields. Further analysis of the results reveals that aldehydes bearing donor or electron withdrawing groups react without exception to afford dihydropyrimidinones in excellent yields. Again, bismuth nitrate is revealed as an appropriate catalyst making the method attractive compared to Atwal's multistep procedure (O'Reilly and Atwal, 1987). Aldehydes substituted by various functional groups conferring interesting pharmacological properties can be used without altering the excellent yields. In this context, Banik et al. reported that Biginelli reaction occurs rapidly and gives quantitative yields in presence of $Bi(NO_3)_3$ under the influence of microwave irradiation in the absence of solvent (Banik et al., 2007).

Table 3 Synthesis of dihydropyrimidinones without solvent.

Aldehyde	1,3-Dicarbonyl compound	Product	Yield (%)	
			M_1	M_3
1a	2a	**4a**	74	70
1b	2a	**4b**	56	54
1c	2a	**4c**	61	59
1d	2a	**4d**	54	57
1e	2a	**4e**	55	60
1f	2a	**4f**	66	57
1a	2b	**4k**	52	58
1b	2b	**4l**	52	58
1c	2b	**4m**	54	60
1d	2b	**4n**	52	55
1a	2c	**4o**	44	46
1b	2c	**4p**	60	65
1c	2c	**4q**	30	35
1d	2c	**4r**	62	66

M_1: Aldehyde (4 mmol); urea (5 mmol); 1,3-dicarbonyl compound (5 mmol); EtOH (20 mL); HCl; reflux for 18 h. **M_3**: Aldehyde (4 mmol); β-dicarbonyl compound (4 mmol); urea (6 mmol); PPh_3; 100 °C; 12 h.

The reaction begins with the condensation of the aldehyde and urea yielding an intermediate of acylimine type. A further step follows by cyclization and dehydration to liberate the

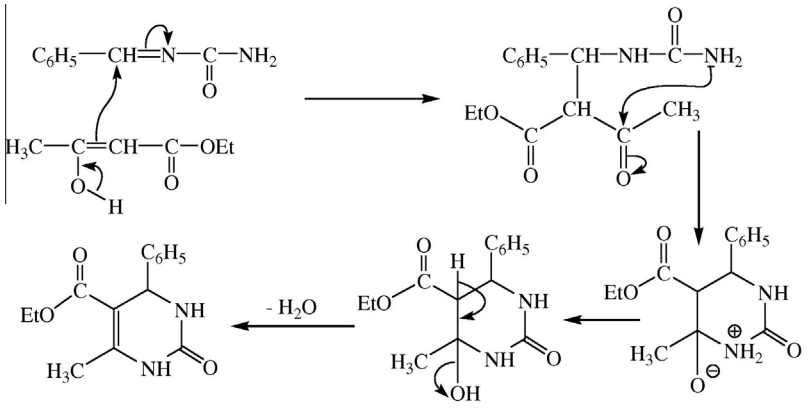

Figure 5 Formation of the dihydropyrimidinone.

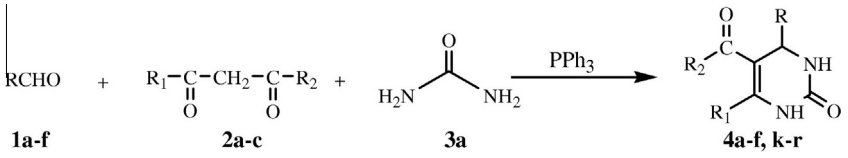

Figure 6 PPh_3 catalyzed Biginelli reaction under solvent free conditions.

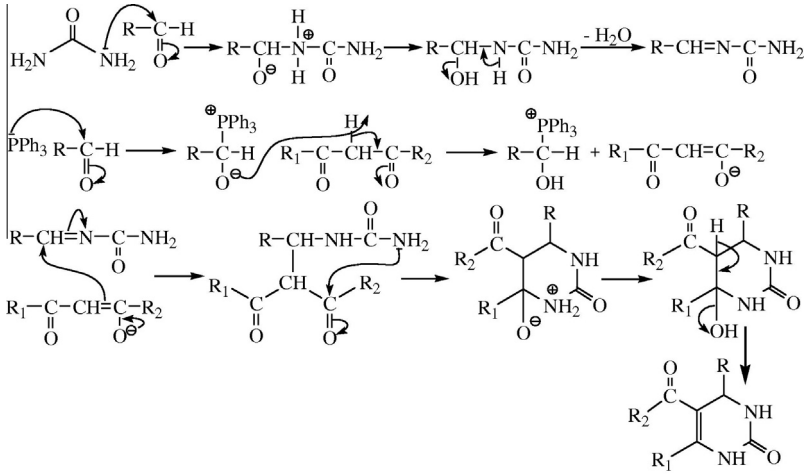

Figure 7 Suggested mechanism for the Biginelli reaction catalyzed by triphenylphosphine under solvent-free conditions.

Biginelli product. However, it seems that Bismuth salt may stabilize the acylimine intermediate due to the presence of vacant d-orbital. As an example, the mechanism of the reaction involving benzaldehyde, urea and ethylacetoacetate can be schematised as follows:

- formation of the acylimine (see Fig. 3),
- enolization of ethylacetoacetate (see Fig. 4),
- condensation of this enol with the acylimine to give an intermediate which undergoes cyclization followed by dehydration to eventually afford the corresponding dihydropyrimidinone (see Fig. 5).

3.3. Synthesis of dihydropyrimidinones without solvent

As we have been involved in reactions under solventless conditions, we have been prompted to examine the Biginelli reaction in the presence of triphenylphosphine. The reactions involve aromatic aldehydes, 1,3-dicarbonylated compounds and urea (Table 3) (see Fig. 6).

Table 3 shows that triphenylphosphine is an efficient catalyst for the synthesis of a variety of 3,4-dihydropyrimidinones by means of a three-component condensation of an aldehyde, β-ketoester and urea in one pot under solvent-free conditions. These results are in agreement with those reported by Debache et al. (2008).

The proposed mechanism includes formation of an acylimine as a first step. The second key intermediate is the 1,3-dicarbonylated compound in enolate form. Indeed, the triphenylphosphine plays the role of a Lewis base by interaction with electrophilic carbon of aldehyde, than a deprotonation of the 1,3-dicarbonylated compound which offers an enolate. A condensation between the enolate and the acylimine follow-up of a cyclization and dehydration to form the corresponding dihydropyrimidinone (Fig. 7).

4. Conclusions

The synthesis of 3,4-dihydropyrimidinones via Biginelli reactions leads to excellent yields in the presence of bismuth nitrate as catalyst in acetonitrile. The reaction occurs even with diversely substituted aromatic aldehydes. From a mechanistic point of view, the reaction begins with the condensation of the aldehyde and urea yielding an intermediate of acylimine type. A further step follows by cyclization and dehydration to liberate the corresponding dihydropyrimidinone. We have also showed that the reaction could be catalyzed by triphenylphosphine in the absence of solvent.

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