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BORAX: AN ECOFRIENDLY AND EFFICIENT CATALYST FOR ONE-POT SYNTHESIS OF 3,4-DIHYDROPYRIMIDINE-2(1H)-ONES UNDER SOLVENT-FREE CONDITIONS

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Borax in the presence of a very small amount of 5 M sulfuric acid efficiently catalyses the three-component condensation of an aldehyde, β-ketoester, and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1H)-ones or 3,4-dihydropyrimidin-2(1H)-thiones in good to excellent yields under solvent-free conditions at 80 °C. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield, short reaction time (1–2 h), easy workup, and no use of volatile organic solvent.

Keywords: Biginelli reaction; borax; 3,4-dihydropyrimidin-2(1H)-ones; solvent free

INTRODUCTION

3,4-Dihydropyrimidinones (DHPMs) are known to exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial, and anti-inflammatory properties. In addition, these compounds have emerged as potent calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists, and neuropeptide antagonists. Furthermore, the 2-oxodihydropyrimidine-5 carboxylate core unit is found in many marine natural products, including batzelladine alkaloids, which are potent HIV gp-120-CD_4 inhibitors.[1]

The classical synthesis of DHPMs was first reported by the Italian chemist Pietro Biginelli in 1983, involving a one-pot condensation of an aldehyde, β-ketoester, and urea under strongly acidic conditions. However, this method suffers from poor yields (20–40%) of the desired products.[2] Subsequent multistep syntheses produced somewhat better yields, but these lack the simplicity of the original one-pot Biginelli protocol. To improve the efficiency of the Biginelli reaction, many Lewis acid catalysts such as $Cu(OTf)_2$,[3] $LaCl_3 \cdot H_2O$,[4] $ZrCl_4$,[5] $Sr(OTf)_2$,[6] $In(OTf)_3$,[7]

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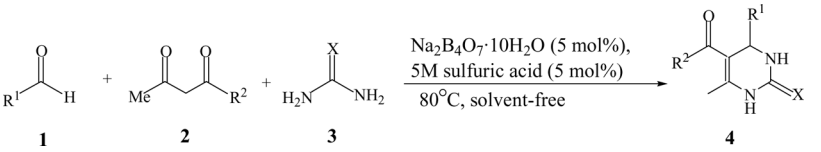


1 2 3 4

Scheme 1. Borax–5 M sulfuric acid catalyzed synthesis of 3,4-dihydropyrimidinones.

$ZnCl_2$,[8] $FeCl_3 \cdot 6H_2O$,[9] $RuCl_3$,[10] L-proline,[11] $Ce(NO_3)_3 \cdot 6H_2O$,[12] and CuI[13] were used. Some other methodologies were based on the use of ionic liquids,[14] microwave irradiation,[15] ultrasonication,[16] solid-phase reagents[17] and polymer-supported catalysts.[18] However, in spite of their potential utility, many of the existing procedures require strongly acidic conditions, longer reaction times, and use of organic solvents. Three boron compounds, Et_2OBF_3 in the presence of CuCl and acetic acid in refluxing tetrahydrofuran (THF) for 18 h,[19] boric acid in glacial acetic acid at 100 °C,[20] and phenyl boronic acid in acetonitrile under reflux for 18 h,[21] have also been used. Use of volatile organic solvent, concentrated acid, and longer reaction time makes the process unattractive both economically and ecologically. Two asymmetric syntheses using $CeCl_3/InCl_3$ or $Yb(OTf)_3$ in the presence of chiral ligands were recently investigated.[22,23] Notably, a Lewis acid or a protic acid is essential in bringing about Biginelli-type condensation reactions irrespective of whether the reaction is catalytic. Considering all these and in view of our interest in developing reactions that use a catalytic amount of a nontoxic or minimally toxic, readily available, and ecologically favorable agent, we opted for borax ($Na_2B_4O_7 \cdot 10H_2O$) as a catalyst of choice.

We recently found borax to be an efficient catalyst for hetero-Michael reactions in an aqueous medium.[24] We sought to explore the possibility of borax as a catalyst for Biginelli-type condensation reactions. In this letter, we report a simple, clean, and practical method for the synthesis of 3,4-dihydropyrimidinones using borax and a very small amount of 5 M sulfuric acid as catalysts under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

The efficacy of the catalyst was tested for benzaldehyde under different reaction conditions. The results are summarized in Table 1.

We started to study the reaction with 5 mol% of borax and 5 mol% 5 M sulfuric acid using varying amount of urea. There was a noticeable enhancement of yield when the amount of urea was increased from 1 equivalent to 1.5 equivalents (based on benzaldehyde), but the yield did not improve with further increment of urea up to 2 equivalents. Thereafter, the reaction was evaluated by changing the concentration of the catalyst. It was found that the combination of 5 mol% borax and 5 mol% 5 M sulfuric acid was sufficient to push the reaction into completion with excellent yield (Table 1, entry 6). On further increasing the concentration of catalyst from 5 mol% to 15 mol%, the reaction efficiency was not significantly influenced. When the amount was decreased from 5 mol% to 2.5 mol%, conversion significantly decreased so that only 75% yield was obtained (Table 1, entry 8). However, when the reaction

Table 1. Synthesis of 3,4-dihydropyrimidinones under different conditions[a]

Entry	Catalyst (mmol)	Urea (mmol)	Time (h)	Yield[b] (%)
1	—	1.5	12	0
2	Borax (0.05)	1.5	12	20
3	5 M H_2SO_4 (0.05)	1.5	1.5	60
4	Borax (0.05) and 5 M H_2SO_4 (0.05)	1	2	75
5	Borax (0.05) and 5 M H_2SO_4 (0.05)	1.2	1.5	78
6	Borax (0.05) and 5 M H_2SO_4 (0.05)	1.5	0.75	93
7	Borax (0.05) and 5 M H_2SO_4 (0.05)	2	0.75	85
8	Borax (0.025) and 5 M H_2SO_4 (0.025)	1.5	0.75	75
9	Borax (0.10) and 5 M H_2SO_4 (0.10)	1.5	0.75	93
10	Borax (0.15) and 5 M H_2SO_4 (0.15)	1.5	0.75	90

[a]Reaction conditions: benzaldehyde 1 mmol; ethyl acetoacetate 1 mmol; 80 °C.
[b]Isolated yield.

was performed in the absence of 5 mol% 5 M sulfuric acid, a decrease of yield (Table 1, entry 2) was observed. Hence, it is evident that an optimum of 0.05 equivalent (5 mol%) of borax with 0.05 equivalent (5 mol%) of 5 M sulfuric acid and 1.5 equivalents of urea (with respect to benzaldehyde) in the reaction mixture was ideal for achieving the best yield. However, in the absence of catalyst, the reaction did not yield the desired product even after 12 h (Table 1, entry 1).

After optimizing the reaction conditions, we extended the procedure to a variety of aromatic aldehydes. The results are summarized in Table 2.

Several aromatic aldehydes carrying either electron-releasing (Table 2, entries 2, 5, 7, and 12) or electron-withdrawing (Table 2, entries 3, 4, 6, 9, and 11) substituents afforded excellent yields of the products. An important feature of this procedure is the survival of a variety of functional groups such as ethers (Table 2, entries 10 and 13), nitro groups (Table 2, entries 4, 9, and 11), hydroxyl groups (Table 2, entries 2, 7, and 12), and halides (Table 2, entries 3 and 6) under the reaction conditions.

Table 2. Borax–5 M sulfuric acid–catalyzed synthesis of 3,4-dihydropyrimidinones

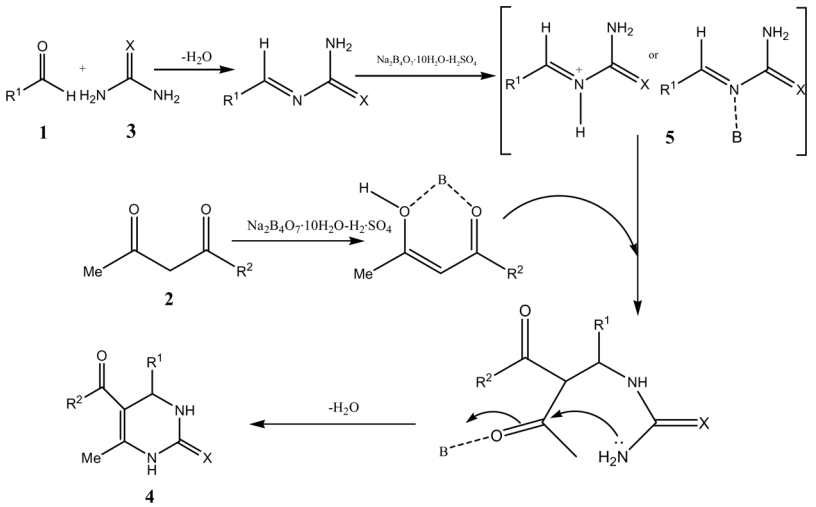
Entry	Product	R^1	R^2	X	Time (min)	Yield (%)	Mp (°C) [lit.]
1	**4a**	C_6H_5	OEt	O	60	93	202–203 (202–203)[31]
2	**4b**	2-OHC_6H_4	OEt	O	60	85	200–202 (201–203)[25]
3	**4c**	2-ClC_6H_4	OEt	O	90	85	214–216 (215–218)[15]
4	**4d**	4-NO_2 C_6H_4	OEt	O	105	82	207–208 (207–208.5)[25]
5	**4e**	4-$NMe_2C_6H_4$	OEt	O	60	90	255–256 (256–257)[25]
6	**4f**	4-ClC_6H_4	OEt	O	120	83	213–214 (213–215)[25]
7	**4g**	4-OHC_6H_4	OEt	O	90	88	227–228 (227–229)[25]
8	**4h**	C_6H_5	OMe	O	90	90	(212–213)[6]
9	**4i**	4-NO_2 C_6H_4	OMe	O	90	81	235–237 (235–237)[25]
10	**4j**	4-$OCH_3C_6H_4$	OMe	O	120	87	194–196 (192–194)[25]
11	**4k**	2-NO_2 C_6H_4	OMe	O	120	85	279–281 (280–282)[20]
12	**4l**	4-OHC_6H_4	OMe	O	120	87	230–231 [260 (dec)][8]
13	**4m**	4-$OCH_3C_6H_4$	OEt	S	120	70	150–152 (150–152)[21]
14	**4n**	C_6H_5	OEt	S	120	78	202–204 (206–207)[21]

Table 3. Comparisons of recent results on Biginelli reaction

Sl. no.	Catalyst (amount)	Reaction conditions: solvent/ temp. (°C)/time (h)	Yield (%)	Ref.
1	$Na_2B_4O_7 \cdot 10H_2O$ (5 mol%) and 5 M sulfuric acid (5 mol%)	—/80/1–2	85–93	Present work
2	H_3BO_3 (20 mol%)	AcOH/100/0.5–2	86–97	20
3	$PhB(OH)_3$ (10 mol%)	CH_3CN/reflux/18	60–91	21
4	Silica sulfuric acid (30 mol%)	C_2H_5OH/reflux/6	84–96	26
5	Propane phosphonic acid anhydride (1 equivalent)	CH_3COOEt/reflux/6	30–86	27
6	12-tungstophosphoric acid (2 mol%)	AcOH/117/6–7	40–75	28
7	Fluorapatite doped with metal halide (200 wt%)	AcOH/117/72	73–90	29
8	HAU zeolite (30 wt%)	AcOH/100/4–5	60–87	30

Likewise, thiourea was used with equal success to provide the corresponding 3,4-dihydropyrimidinethiones, which are also of interest with regard to their biological activities. In our experimental conditions, cyclization took place in moderate to good yields (Table 2, entries 13, 14). All the products were characterized by infrared (IR), ^{1}H NMR, ^{13}C NMR, and melting-point analysis. Lack of organic solvent, clean and mild reaction conditions, inexpensive and ecofriendly catalyst, very good yield, short reaction time, lack of contamination of product by heavy metals, and compatibility with various functional group are the main advantages of this procedure over many other recently reported catalytic systems for the synthesis of 3,4-dihydropyrimidinones (Table 3).

The mechanism for Biginelli condensation is well reported in the literature.[19] In the present procedure, the reaction probably proceeds through formation of an acylimine intermediate from aldehyde and urea. The acylimine intermediate is



Scheme 2. Probable mechanism of the reaction.

activated either by protonation or coordination with boron atom of borax, and subsequent addition of the iminium ion to carbanion derived from β-dicarbonyl compound followed by cyclodehydration affords 3,4-dihydropyrimidinones (Scheme 2).

CONCLUSION

In conclusion, we have developed a clean, efficient, facile, and environmentally acceptable synthetic methodology for the preparation of 3,4-dihydropyrimidinones using borax and a little dilute H_2SO_4 as catalyst under solventless conditions.

EXPERIMENTAL

A mixture of aldehyde (2 mmol), β-ketoester (2 mmol), urea (3 mmol), borax (0.05 mmol), and 5 M sulfuric acid (0.05 mmol) was stirred at 80 °C for the appropriate time (Table 2). After completion of the reaction as indicated by thin-layer chromatography, the mixture was poured into crushed ice. The solid product was filtered and washed with cold water and a mixture of $EtOH/H_2O$ (1:1). The solid was dried and recrystallized from hot ethanol to afford the pure product.

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