MICROWAVE-ASSISTED SOLVENT-FREE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES CATALYZED BY NH_4OBr

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Catalytic potential of ammonium hypobromite in the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from Biginelli-type condensation reaction between an aldehyde, β-keto ester and urea has been explored. The reaction proceeds under solvent-free conventional heating as well as microwave-irradiation conditions to afford the respective products in excellent yields.

Keywords: 3,4-Dihydropyrimidin-2(1*H*)-one; Biginelli-type condensation; Ammonium hypobromite; Aldehydes; β-Keto ester; Urea; Solvent-free; Aromaticity; Asymmetric synthesis; C–C coupling; Heterocycles; Heterogeneous catalysis.

Dihydropyrimidinones and their derivatives are of remarkable biological and pharmacological importance as antitumor, antiflammatory, antibiotics, antiviral, antibacterial, antifungal agents, and tyrosinase inhibitors[1]. In the last few decades, these compounds have also found applications as calcium channel blockers, antihypertensive, α_{1a}-antagonists, and neuropeptide Y (NDY) antagonists used for the treatment of prostatic hyperplasia[2]. Moreover, several dihydropyrimidine derivatives including dihydropyrimidin-5-carboxylate core have been discovered as marine-extracted alkaloids which show interesting biological activities, e.g. as potent HIV gp-120CD_4 inhibitors[3].

The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones was first reported by Biginelli in 1893 by a simple one-pot condensation of a β-keto ester, an aldehyde and urea under strongly acidic conditions[4]. However, this protocol often suffers from low yields of the more demanding products in the cases of aliphatic and certain substituted aromatic aldehydes. Owing to the extensive biological and pharmacological applications of 3,4-dihydro-

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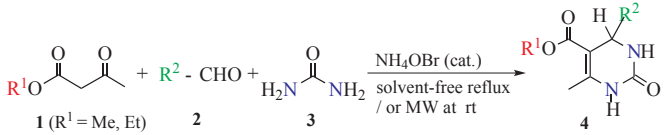
pyrimidin-2(1*H*)-ones[1c,5], many improved and more robust routes have been continuously reported for the synthesis of these compounds either by the classical one-pot Biginelli approach[4,6], or through the development of novel multistep procedures[7]. In recent years, a variety of catalytic methods for promoting the Biginelli reaction have been developed employing various metal salts as Lewis acid catalysts including LiBr [8], $NiCl_2 \cdot 6H_2O$ and $FeCl_3 \cdot 6H_2O$ [9], $CuCl_2 \cdot 2H_2O$ [10], $CeCl_3 \cdot 7H_2O$ [11], $Mn(OAc)_3 \cdot 2H_2O$ [12], $ZrCl_4$ [13], $InCl_3$ [3a], $InBr_3$ [14], $ZnCl_2$ [15], ZnI_2 [16], $CdCl_2$ [17], $BiCl_3$ [18], $LiClO_4$ [19], $Zn(OTf)_2$ [20], $Al(HSO_4)_3$ [21], $BiO(NO_3)$[22], $LnCl_3$ [5], and $Ln(OTf)_3$ (Ln = Yb, Sc, La)[23], trichloroisocyanuric acid[24], $Yb(PFO)_3$ [25], thiamine hydrochloride[26], silica-supported tin chloride and titanium tetrachloride[27], H_3PO_3 [28], hexaaquaaluminium(III) tetrafluoroborate[29]. In addition, several other methods have been reported to promote the Biginelli reaction including solid phase reactions[30], microwave irradiation[31], Biginelli reaction starting directly from alcohols[32], and other catalytic reactions such as the use of various ionic liquids, e.g. 1-butyl-3-methylimidazolium tetrafluroborate ($BMImBF_4$) to accelerate the Biginelli reaction[33].

RESULTS AND DISCUSSION

In continuation of our studies to explore new and more benign approaches towards one-pot synthesis of heterocyclic compounds[34], including dihydropyrimidinones[35], we are prompted to report herein a simple and practical method for the direct synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (**4**) by the Biginelli-type reaction using ammonium hypobromite as an effective and non-polluting catalyst. In the presence of a catalytic amount of NH_4OBr (10 mole %), the reaction of β-keto ester **1**, aldehyde **2** and urea **3** was carried out in a one-pot condensation under solvent-free conventional heating as well as microwave-irradiation conditions (Scheme 1).



1 (R^1 = Me, Et) **2** **3** **4**

SCHEME 1

To optimize the reaction conditions, we initially examined the condensation of urea with benzaldehyde and ethyl acetoacetate (excess) as test compounds (entry 1). The effect of solvent was studied by using different solvents such as AcOH, DMF, MeCN, H_2O, EtOH as well as solvent-free con-

TABLE I
NH_4OBr-Catalyzed solvent-free synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (**4**) both under refluxing and microwave-irradiation conditions[a,b]

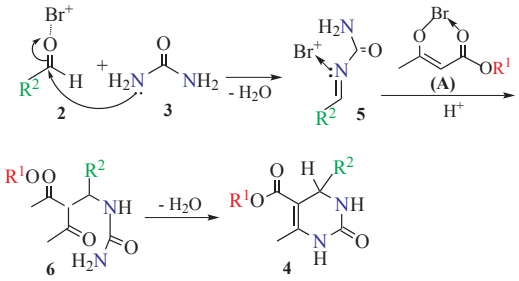
Entry	R^1	R^2	Reaction time min	Yield %[c]	M.p., °C	
					Found	Reported
1	Et	C_6H_5	180 (3)	83 (92)	205–207	204–206[36]
2	Et	4-FC_6H_4	200 (4)	75 (90)	181–182	182–184[36]
3	Et	2-$NO_2C_6H_4$	210 (3)	78 (85)	206–208	208–210[36]
4	Et	3-$NO_2C_6H_4$	240 (4)	75 (87)	223–225	227–229[36]
5	Et	4-$NO_2C_6H_4$	160 (3)	78 (90)	207–209	209–212[36]
6	Et	2-ClC_6H_4	195 (3)	80 (95)	220–223	222–224[36]
7	Et	4-ClC_6H_4	182 (3)	85 (95)	212–215	209–212[36]
8	Et	2-$MeOC_6H_4$	188 (3)	70 (82)	251–253	259–260[36]
9	Et	4-$MeOC_6H_4$	180 (2)	85 (90)	201–203	205–207[36]
10	Et	2-HOC_6H_4	190 (4)	70 (85)	200–202	201–203[9]
11	Et	4-HOC_6H_4	175 (2)	78 (96)	225–228	227–229[37]
12	Et	2-BrC_6H_4	220 (5)	65 (85)	207–209	206–208[23a]
13	Et	3-BrC_6H_4	210 (4)	70 (80)	186–188	185–186[9]
14	Et	4-BrC_6H_4	220 (5)	75 (92)	218–221	213–215[38]
15	Et	2,4-$Cl_2C_6H_3$	240 (6)	72 (94)	249–251	249–250[9]
16	Et	4-MeC_6H_4	185 (3)	80 (96)	211–213	215–216[39]
17	Et	1-Naphthyl	210 (4)	65 (90)	250–252	247–248[19]
18	Et	$PhCH_2CH_2$	190 (3)	80 (98)	183–185	182–184[36]
19	Et	n-C_7H_{15}	195 (4)	70 (85)	120–123	120–123[36]
20	Et	Thiophen-2-yl	190 (3)	75 (87)	219–221	215–217[14]
21	Et	C_2H_5	220 (6)	55 (75)	181–183	180–181[39]
22	Me	C_6H_5	170 (3)	70 (90)	210–212	210–212[23a]
23	Me	4-ClC_6H_4	180 (3)	66 (86)	203–205	203–205[23a]
24	Me	4-$MeOC_6H_4$	187 (4)	80 (90)	195–197	189–192[23a]
25	Me	2,4-$Cl_2C_6H_3$	185 (4)	65 (87)	250–253	252–253[23a]
26	Me	2-$NO_2C_6H_4$	197 (4)	70 (82)	284–286	280–282[40]
27	Me	4-$Me_2NC_6H_4$	180 (3)	67 (78)	210–213	213–215[11]
28	Me	4-FC_6H_4	198 (5)	70 (92)	190–192	192–194[23a]

[a] Conditions: β-keto ester **1** (30 mmol), aldehyde **2** (10 mmol), urea **3** (1.2 g, 20 mmol) and NH_4OBr (0.114 g, 1.0 mmol), reflux (or microwave irradiation at 50 °C). [b] The reaction times and yields obtained under microwave-irradiation condition are quoted in parentheses. [c] Isolated yields.

dition under various amounts of catalyst. The experimental results indicated that the highest yields of the reaction product obtained when the reaction was conducted under solvent- free condition using excess amount of ethyl acetoacetate under microwave irradiation at a power level of 60% or reflux conditions were 92 and 83%, respectively in the presence of NH_4OBr (10 mole %).

This achievement encouraged us to extend this reaction to a variety of aromatic aldehydes **4** and β-keto esters **1** under the optimized conditions (ethyl acetoacetate (twofold excess)/NH_4OBr (10 mole %)/refluxing or microwave irradiation), furnishing the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (**4**) and the experimental results are summarized in Table I. As shown in this Table, the reactions performed under microwave-irradiation condition (60% power level) were brought to completion in much shorter reaction times (2–6 min) and higher yields (80–98%) compared with those obtained under conventional heating condition. The structures of the products **4** were fully established by analysis of their spectral (^1H and ^{13}C NMR, IR) and physical data and compared with those reported (Table I).

In reliance on the mechanism previously proposed for the Biginelli reaction by Kappe[41], and others[5], we propose a mechanism for the ammonium hypobromite-promoted Biginelli reaction as shown in Scheme 2. In this mechanism, a Br^+ ion-coordinated and -stabilized acyl imine intermediate **5** is formed by Br^+ ion-catalyzed condensation of the aldehyde **2** with urea **3**. This intermediate subsequently undergoes reaction with Br^+ ion-activated β-keto ester (**A**) to yield the intermediate **6** followed by dehydrative cyclization to the product **4**.



SCHEME 2

CONCLUSION

In summary, the present work offers a simple and efficient procedure for the direct solvent-free synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones both under microwave irradiation and conventional heating conditions cata-

lyzed by NH_4OBr as non-toxic and inexpensive compound in good yields. The reactions occur in shorter times and higher yields when carried out under microwave-irradiation condition.

EXPERIMENTAL

Material and Instruments

All chemicals were purchased from Merck Company. Melting points were measured using the capillary tube method with an electrothermal 9200 apparatus. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90 MHz spectrometer in DMSO-d_6 solution. IR spectra were run from KBr disk on a Perkin–Elmer GX FT-IR spectrometer. Microwave-assisted reactions were conducted in a Milstone CombiChem Microwave Synthesizer. In all irradiation experiments, rotation of rotor, irradiation time, temperature, and power were monitored with the 'easy WAVE' software package.

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones **4**. General Procedure

A) *Thermal heating condition*. A mixture of threefold excess amount of β-keto ester **1** (30 mmol), the appropriate aldehyde **2** (10 mmol), urea **3** (1.2 g, 20 mmol) and NH_4OBr (0.114 g, 1.0 mmol) were let to stir under reflux for an appropriate time (Table I). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, poured onto crushed ice and stirring was continued for further few minutes. The resulting mixture was filtered, washed with cold water (2 × 50 ml) and crystallized from EtOH to yield the pure product. All products are known compounds which were characterized by their IR, ^1H and ^{13}C NMR spectral data and their melting points, and compared with those reported (Table I).

B) *Microwave-irradiation condition*. A mixture of urea **3** (0.12 g, 2 mmol), NH_4OBr (0.012 g, 0.1 mmol) and aldehyde **2** (1 mmol) was dissolved in two-fold excess amount of β-keto ester **1** (2 mmol), capped and irradiated in a Milstone CombiChem Microwave Synthesizer for an appropriate time at 50 °C (Table I). The progress of the reaction was monitored by intermittent rapid cooling of the mixture to room temperatuire every one minute and analyzed by TLC (hexane–ethyl acetate, 2:8). After the complete conversion of the substrate as indicated by TLC analysis, the reaction mixture was cooled and poured onto crushed ice and stirred for few minutes. The mixture was then filtered, washed with cold water (2 × 10 ml) and crystallized from EtOH to afford the pure product (Table I).

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