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One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using boric acid as catalyst

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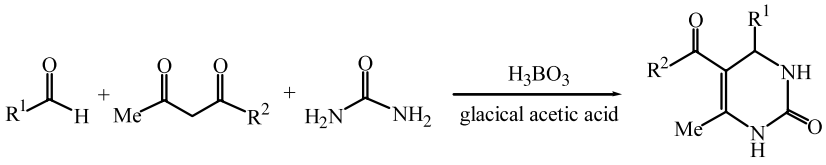
Abstract—A simple effective synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives, using boric acid as catalyst, from aromatic aldehydes, 1,3-dicarbonyl compounds and urea in glacial acetic acid is described. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (86–97%) and short reaction time (0.5–2 h).

Biginelli reaction is a three-component condensation of ethyl acetoacetate, benzaldehyde and urea for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 1).[1] The reaction can be carried out in a one-pot fashion in alcohol solution in the presence of a catalytic amount of hydrogen chloride. A major drawback of the classical Biginelli reaction is the poor to moderate yields, particularly when substituted aromatic aldehydes are employed. This reaction played an important role in organic and medicinal chemistry due to the importance of the resulting dihydropyrimidinone products. These compounds exhibit attractive pharmacological properties by serving as the integral backbones of several calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonists.[2] In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also show interesting biological activities.[3]

Due to the importance of the Biginelli reaction products, much work on improving the yield and reaction conditions has been actively pursued in several decades.[4–11] Among such developments the report of Hu and Sidler[12] using $BF_3{\cdot}OEt_2$ as promoter, Kappe and co-workers further improved this reaction by employing microwave irradiation in the presence of PPE to give higher chemical yields of dihydropyrimidinone products.[13] Recently, several other methods indicate the use of lanthanide compounds[14,15] and soluble polymer-supported[16] and several other Lewis acids[17–20] can overcome the drawback of the classical Biginelli reaction.

Very recently, we found that the Biginelli reaction can occur more smoothly under microwave irradiation in the presence of ferric chloride or TsOH as the catalyst.[21] In this letter, we would like to report a simple effective approach to the Biginelli reaction products by using boric acid as the catalyst in glacial acetic acid. The synthesis is usually complete within 0.5–2 h at 100°C to give very high yields. The preferred ratio of aldehydes, 1,3-dicarbonyl compounds, urea and H_3BO_3 is 1:1:1.2:0.20 (Scheme 1).



1 **2** **3** **4**

Scheme 1.

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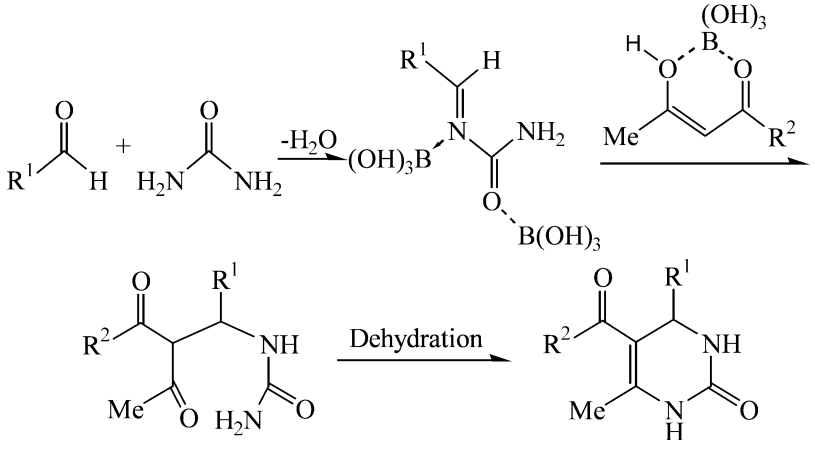
Table 1. Boric acid catalyzed synthesis of dihydropyrimidinones

Entry	R^1	R^2	Yield(%)			Mp(°C)	
			A[a]	B[b]	C[c]	Found	Reported
4a	C_6H_5	OEt	97	94	78	202–203	202–203[20]
4b	2-ClC_6H_4	OEt	93	–	51	215–217	215–218[13]
4c	3,4-$OCH_2OC_6H_3$	OEt	90	–	49	186–187	187–188[20]
4d	4-$NO_2C_6H_4$	OEt	89	91	58	207–208	207–208.5[20]
4e	4-$NMe_2C_6H_4$	OEt	86	–	–	257–258	256–257[20]
4f	2-OHC_6H_4	OEt	86	–	19	202–203	201–203[20]
4g	2,4-$(Cl)_2$-C_6H_3	OEt	94	–	69	248–250	249–250[20]
4h	4-ClC_6H_4	OEt	93	92	56	214–215	213–215[20]
4i	4-OHC_6H_4	OEt	89	–	67	228–230	227–229[20]
4j	4-$NO_2C_6H_4$	Me	92	–	–	227–229	230[15]
4k	4-$OCH_3C_6H_4$	Me	93	–	–	165–168	168–170[15]
4l	4-$NO_2C_6H_4$	OMe	92	92	41	237–238	235–237[12]
4m	4-$OCH_3C_6H_4$	OMe	94	87	28	193–196	192–194[12]
4n	4-ClC_6H_4	OMe	98	95	56	206–208	204–207[12]
4o	4-FC_6H_4	OMe	89	88	–	193–195	192–194[15]
4p	2-$NO_2C_6H_4$	OMe	95	–	–	280–282	–
4q	2-NO_2-5-Cl-C_6H_3	OMe	90	–	–	290–292	–

[a] Method A: cat. H_3BO_3 in glacial acetic acid at 100°C for 0.5–2 h.[22]
[b] Method B: 1.3 equiv. of $BF_3{\cdot}OEt_2$, 10 mol% CuCl, 10 mol% AcOH, in THF, reflux for 18 h.[12]
[c] Method C: cat. HCl in EtOH, reflux for 18 h.[14,24]



Scheme 2.

The results (Table 1) show a series of aromatic aldehydes that undergo the cyclocondensation to give excellent yields (86–97%) of the products.[22] This new procedure is also simple to operate. The work-up consists of simple filtration. All the products were characterized by IR and ^1H NMR analysis. Meanwhile, the structure of compounds **4b** and **4n** were further confirmed by X-ray diffraction study.[23]

The reaction may proceed through imine formation from the aldehyde and urea, which is stabilized by boric acid. Subsequent addition of the 1,3-diketone or β-keto ester to the imine followed by cyclodehydration afford dihydropyrimidin-2(1*H*)-one (Scheme 2).

Boric acid is supposed to increase the electrophilicity of the imine by coordinating with the nitrogen and oxygen lone pair and to promote the deprotonation of the enol tautomer of the 1,3-diketone via complexing with the two oxygen atoms. The catalytic role of boric acid is especially evident for the aldehyde with electron donating substituents. Thus, reaction of 4-(*N*,*N*-dimethylamino)benzaldehyde is complete within 1.7 h in the presence of boric acid, but it did not reach a complete conversion even after 5 h in its absence. These facts are in agreement with mechanistic Scheme 2.

In conclusion, a concise, high yielding and shortened procedure for Biginelli reaction was found. The method reported here is not only simple to operate but also efficient.

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22. The general procedure is represented as follows: A solution of the appropriate aldehyde **1** (3 mmol), 1,3-dicarbonyl compound **2** (3 mmol), urea **3** (3.6 mmol), H_3BO_3 (0.6 mmol), in glacial acetic acid (10 mL) is heated at 100°C, while stirring for 0.5–2 h. Then it is cooled to room temperature, and poured into 50 mL ice-water. The solid products are filtered, washed with ice-water and ethanol (95%), dried and recrystallized from ethanol to give the pure product. All products (except **4p** and **4q**) are known compounds, characterized by mp, IR and ^{1}H NMR spectral data. **4p**: mp 280–282°C; ν_{max} (KBr) 3359, 3232, 3108, 2954, 1702, 1644, 1530 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.38 (1H, br s, NH), 8.13–8.11 (2H, m, aromH), 7.91 (1H, br s, NH), 7.66–7.61 (2H, m, aromH), 5.29 (1H, d, J=3.1 Hz, CH), 3.53 (3H, s, CH_3OCO), 2.27 (3H, s, CH_3). Anal. $C_{13}H_{13}N_3O_5$. Calcd: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.56; H, 4.31; N, 14.40%. **4q**: mp 290–292°C; ν_{max} (KBr) 3359, 3233, 3119, 2953, 1703, 1644, 1572, 1530 cm^{-1}; δ_H (400 MHz, DMSO-d_6): 9.45 (1H, br s, NH), 7.95 (1H, s, aromH), 7.92 (1H, br s, NH), 7.62–7.45 (2H, m, aromH), 5.80 (1H, d, J=2.7 Hz, CH), 3.39 (3H, s, $OCOCH_3$), 2.26 (3H, s, CH_3). Anal. $C_{13}H_{12}ClN_3O_5$. Calcd: C, 47.94; H, 3.71; N, 12.90. Found: C, 47.80; H, 3.52; N, 12.76%.
23. The single-crystal growth was carried out in an ethanol at room temperature. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer (graphite monochromator, MoKα radiation λ=0.71073 Å). Crystal data for **4b**: $C_{14}H_{15}ClN_2O_3$, light yellow, crystal dimension 0.44×0.32×0.20 mm, triclinic, space group P-1, a=7.688(1), b=9.106(2), c=11.412(2) Å, α=102.963(3), β=105.957(2), γ=102.484(2)°, V=714.9(2) Å^3, Mr=294.73, Z=2, D_c=1.369 g/cm^3, λ=0.71073 Å, μ(MoKα)=0.276 mm^{-1}, F(000)=308, S=1.084, R_1=0.0845, wR_2=0.2092. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 202250. Crystal data for **4n**: $C_{13}H_{13}ClN_2O_3$, light yellow, crystal dimension 0.50×0.32×0.28 mm, triclinic, space group P-1, a=5.4513(4), b=7.619(1), c=16.118(4) Å; V=646.19(19) Å^3, α=80.42(1), β=83.42(1), γ=79.29(1)°, V=646.19(19) Å^3, Mr=280.70, Z=2, D_c=1.443 g/cm^3, λ=0.71073 Å, μ(MoKα)=0.301 mm^{-1}, F(000)=292, S=1.061, R_1=0.043, wR_2=0.1167. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 194807. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-3366-033; e-mail: deposit@ccdc.cam.ac.uk).
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