A New Biginelli Reaction Procedure Using Potassium Hydrogen Sulfate as the Promoter for an Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one

Shujiang Tu,* Fang Fang, Songlei Zhu, Tuanjie Li, Xiaojing Zhang, Qiya Zhuang

Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology on Medical Plant, Xuzhou; Jiangsu, 221009, P. R. China
Fax +86(516)3403164; E-mail: laotu2001@263.net
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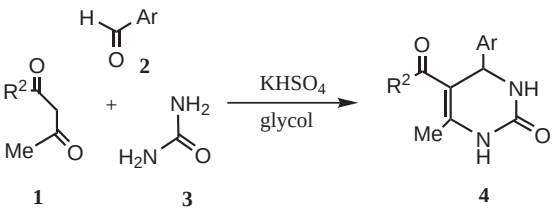
Abstract: Simple and improved conditions have been found to carry out the Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives. This synthesis was performed using potassium hydrogen sulfate as the promoter in glycol solution. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (85–99%) and short reaction time (0.5–2 h).

Key words: dihydropyrimidin-2(1*H*)-one, Biginelli reaction, potassium hydrogen sulfate, cyclic 1,3-dicarbonyl compounds

Dihydropyrimidinone derivatives have attracted considerable interest in recent years because these type of compounds exhibits attractive pharmacological profiles as calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonists.[1] In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological properties.[2]

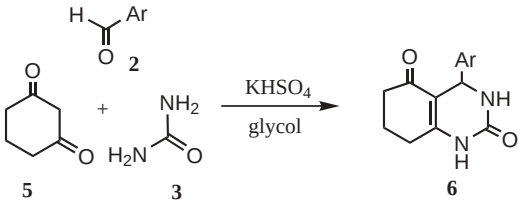
Biginelli synthesis involves reaction of ethyl acetoacetate, benzaldehyde and urea in alcohol solution in the presence of a catalytic amount of hydrogen chloride to give 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 1).[3] A major drawback of the classical Biginelli reaction is the poor to moderate yields, particularly when substituted aromatic aldehydes were employed. Therefore, several improved procedures for the preparation of DHPMs ('Biginelli compounds') have been reported during the last two decades.[4–11] Among the improved synthetic methods is to use $BF_3{\cdot}OEt_2$ as promoter as reported by Hu and Sidler.[12] Later on, 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, the use of lanthanide compounds,[14,15] Lewis acids,[16–20] silica sulfuric acid,[21] and $InBr_3$[22] also gave improved yield. In our previous communication,[23] we reported that boric acid can catalyze Beginelli reaction. All these improved procedures can overcome the drawback of the classical Biginelli reaction to some extent.

However, attention has so far been mainly paid to using open-chained 1,3-dicarbonyl compounds to afford dihydropyrimidinone derivatives, while the use of cyclic 1,3-dicarbonyl compounds has been seldom reported. Herein, we would like to report a new economic approach to the Beginelli reaction products using $KHSO_4$ as the promoter in glycol. This catalyst is efficient not only for open-chained 1,3-dicarbonyl compounds, but also for cyclic 1,3-dicarbonyl compounds. The synthesis can be finished within 2 hours at 100 °C to give very high yields (Scheme 1, Scheme 2).



1 **3** **4**

Scheme 1

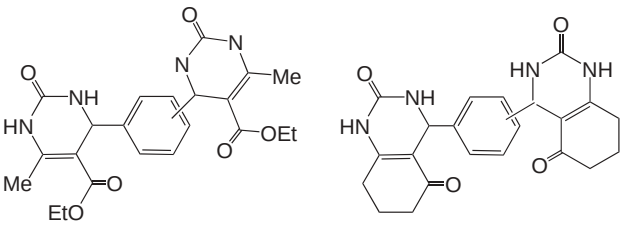


5 **3** **6**

Scheme 2

Furthermore, we have synthesized the bifunctional compounds containing two dihydropyrimidinone units (**8**, **9**), using *iso*-phthalicaldehyde and *tert*-phthalicaldehyde as precursor (Scheme 3).

The results (Table 1, Table 2) show that a wide range of aldehydes can take part in this reaction to give excellent yields (85–99%) of products. This new procedure is



8 **9**

Scheme 3

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Table 1 $KHSO_4$ Catalyzed Open-Chained 1,3-Dicarbonyl Compounds

Entry	ArCHO	R^2	Yield (%)			Mp (°C)	
			A[a]	B[b]	C[c]	Found	Reported
4a	C_6H_5CHO	OEt	95	94	78	202–203	202–203[20]
4b	2-ClC_6H_4CHO	OEt	91	–	51	215–217	215–218[13]
4c	3,4-OCH_2 °C_6H_3 CHO	OEt	90	–	49	186–187	187–188[20]
4d	4-$NO_2C_6H_4CHO$	OEt	92	91	58	207–208	207–208.5[20]
4e	4-$NMe_2C_6H_4CHO$	OEt	86	–	–	257–258	256–257[20]
4f	2-OHC_6H_4CHO	OEt	86	–	19	202–203	201–203[20]
4g	2,4-$(Cl)_2$-C_6H_3CHO	OEt	91	–	69	248–250	249–250[20]
4h	4-ClC_6H_4CHO	OEt	93	92	56	214–215	213–215[20]
4i	4-OHC_6H_4CHO	OEt	87	–	67	228–230	227–229[20]
4j	4-$NO_2C_6H_4CHO$	Me	91	–	–	227–229	230[15]
4k	4-$OCH_3C_6H_4CHO$	Me	91	–	–	165–168	168–170[15]
4l	4-$NO_2C_6H_4CHO$	OMe	93	92	41	237–238	235–237[12]
4m	4-$OCH_3C_6H_4CHO$	OMe	90	87	28	193–196	192–194[12]
4 n	4-ClC_6H_4CHO	OMe	95	95	56	206–208	204–207[12]
4o	4-FC_6H_4CHO	OMe	87	88	–	193–195	192–194[15]
4p	2-$NO_2C_6H_4CHO$	OMe	90	–	–	280–282	280–282[23]
4q	2-NO_2-5-Cl-C_6H_3CHO	OMe	89	–	–	290–292	290–292[23]
4r	$CH_3CH_2CH_2CHO$	OEt	85	–	15	152–153	152–154[20]
4s	$(CH_3)_2CHCHO$	OEt	86	–	10	172–174	170–172[20]
4t	Furfural	OEt	85	–	–	205	203–205[18]
8a	1,3-$CHOC_6H_4CHO$	OEt	96	–	–	>300	–
8b	1,4-$CHOC_6H_4CHO$	OEt	99	–	–	>300	–

[a] Method A: cat. $KHSO_4$ in glycol at 100 °C for 0.5–2 h.[25]
[b] Method B: 1.3 equiv of $BF_3{\cdot}OEt_2$, 10 mol% CuCl, 10 mol% HOAc, in THF, reflux for 18 h.[12]
[c] Method C: cat. HCl in EtOH, reflux for 18 h.[14,24]

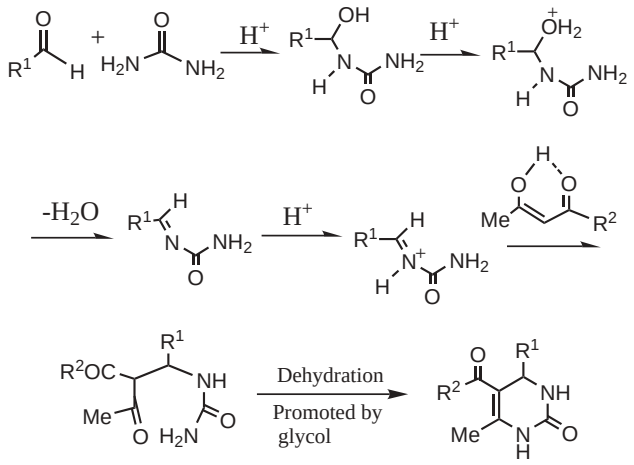
simple and the work-up consists of simple filtration. All the products were characterized by IR and ^1H NMR analysis, and their melting points are identical to those of the known compounds reported in the literature.

According to the mechanism suggested by Folkers, Johnson and Kappe, we think the reaction may proceed through imine formation from the aldehyde and urea, which is activated by protonation. Subsequent addition of the carbanion derived from 1,3-diketone or β-keto ester to the imine followed by cyclodehydration afford dihydropyrimidin-2(1*H*)-one (Scheme 4).

During the reaction process, the hydrogen ion, H^+, is donated by the potassium hydrogen sulfate. The hydrogen ion cannot only help the dehydration but also benefit the enolization of 1,3-diketone or β-keto ester to form the

Table 2 $KHSO_4$ Catalyzed Cyclic 1,3-Dicarbonyl Compounds

Entry	ArCHO	Yield (%)	Mp (°C)
6a	4-ClC_6H_4CHO	93	259.9–261.3
6b	2-ClC_6H_4CHO	91	>300
6c	2,4-$(Cl)_2$-C_6H_3CHO	95	226.8–227.7
6d	3,4-$(Cl)_2$-C_6H_3CHO	95	>300
6e	3-$NO_2C_6H_4CHO$	92	268.1–268.4
9a	1,3-$CHOC_6H_4CHO$	92	>300
9b	1,4-$CHOC_6H_4CHO$	95	>300



Scheme 4

enolate intermediate. The solvent glycol can particularly accelerate dehydration reaction of the last step.

In conclusion, $KHSO_4$ can be applied as an efficient catalyst not only for the open-chained 1,3-dicarbonyl compounds, but also for cyclic 1,3-dicarbonyl compounds. In addition, the catalyst is suitable for the aromatic, aliphatic and hetrocyclic aldehydes. The application of this novel catalyst resulted in decreased reaction time and increased yields of the potentially biologically active dihydropyrimidinone derivatives. This method also has the advantage of an easy work-up and being environmentally friendly because of the atomic economy.

Acknowledgment

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(25) The general procedure is as follows: A solution of the appropriate aldehyde (3 mmol) or dialdehyde (1.5 mmol), 1,3-dicarbonyl compound (3 mmol), urea (3.6 mmol), and $KHSO_4$ (0.75 mmol) in glycol (10 mL) was heated at 100 °C with stirring for 0.5–2 h before cooled down to r.t. The mixture was then poured into 50 mL of ice-water. The solid product was filtered, washed with ice-water and EtOH (95%), and subsequently dried and recrystallized from EtOH to give pure product. All products (except **8a**,**b**, **6a–e**, **9a**,**b**) are known compounds, which were characterized by mp, IR and ^{1}H NMR spectral data. Compound **4p**: mp 280–282 °C. IR (KBr): 3539, 3232, 3108, 2954, 1702, 1644, 1530 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 9.38 (s, 1 H, NH), 8.13–8.11 (m, 2 H, Ar-H), 7.91 (s, 1 H, NH), 7.66–7.61 (m, 2 H, Ar-H), 5.29 (d, *J* = 3.1 Hz, 1 H, CH), 3.53 (s, 3 H, OCH_3), 2.26 (s, 3 H, CH_3). Compound **4t**: mp 205 °C. IR (KBr): 3413, 3239, 3119, 2984, 1702, 1644, 1457 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 9.22 (s, 1 H, NH), 7.74 (s, 1 H, NH), 7.53 (s, 1 H, furanH), 6.33 (d, *J* = 2.8 Hz, 1 H, furanH), 6.07 (d, *J* = 2.8 Hz, 1 H, furanH), 5.20 (s, 1 H, CH), 3.98 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.22 (s, 3 H, CH_3), 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3). Compound **6d**: mp >300 °C. IR (KBr): 3283, 3258, 3065, 2962, 1706, 1676, 1617, 1442, 1371, 1243, 1189, 1132, 1021, 946, 758 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 9.59 (s, 1 H, NH), 7.83 (s, 1 H, NH), 7.59 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.43 (s, 1 H, Ar-H), 7.21 (d, *J* = 8.4 Hz, 1 H, Ar-H), 5.19 (s, 1 H, CH), 1.82–2.45 (m, 6 H, CH_2). Compound **8b**: mp >300 °C. IR (KBr): 3231, 3112, 2973, 1700, 1458, 1374, 1321, 1227, 1171, 1094, 808, 663 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 9.18 (s, 2 H, NH), 7.69 (s, 2 H, NH), 7.17 (s, 4 H, Ar-H), 5.09 (s, 2 H, CH), 3.97 (q, *J* = 7.2 Hz, 4 H, OCH_2), 2.22 (s, 6 H, CH_3), 1.09 (t, *J* = 7.2 Hz, 6 H, CH_3). Compound **9b**: mp >300 °C. IR (KBr): 3241, 2948, 1699, 1672, 1613, 1369, 1240, 1181, 806, 764 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 9.45 (s, 2 H, NH), 7.69 (s, 2 H, NH), 7.01–7.19 (m, 4 H, Ar-H), 5.05–5.11 (m, 2 H, CH), 1.93–2.49 (m, 12 H, CH_2).