Note

One-pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one Using TsOH as a Catalyst under Microwave Irradiation

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A series of Biginelli compounds was synthesized using TsOH as a catalyst under microwave irradiation. This simple method provided the title compounds in 86%—98% yields by the reaction of aromatic aldehydes with 1, 3-carbonyl compound and urea. The structure of 4o was determined by single crystal X-ray diffraction analysis.

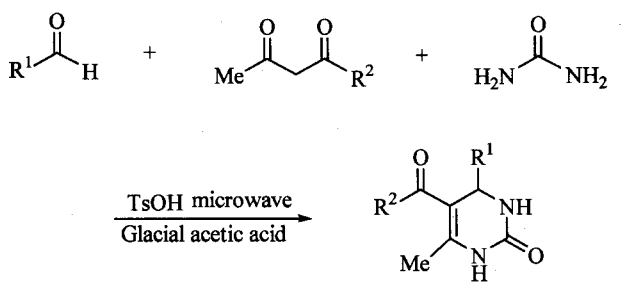
Keywords dihydropyrimidinones, Biginelli reaction, microwave, TsOH

Introduction

Over the past decade, dihydropyrimidinones and their derivatives have been shown to exhibit important pharmacological properties. They have emerged as the integral backbones of several calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y(NPY) antagonists.[1] Moreover, several alkaloids containing the dihydropyrimidin-one-5-carboxylate structure have been isolated from marine sources, which also have certain biological properties.[2] Therefore, synthesis of the dihydropyrimidinone nucleus has received much attention continuously.

Dihydropyrimidinone derivatives (DHPMs) were firstly synthesized by the reaction of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions.[3] The major drawback of this classical reaction is the moderate yield, particularly, when using substituted aromatic aldehyde. Several improved procedures for the preparation of DHPMs (Biginelli compounds) have been reported.[4-11] Hu[12] reported the use of Lewis acid $BF_3 \cdot OEt_2$, Kappe[13] improved this reaction by employing microwave irradiation in the presence of PPE, both the approaches can give high yields of dihydropyrimidinones. Xu *et al.*[14] also improved this reaction by microwave. Recently, some Lanthanide compounds[15,16] and Lewis acids[17,18] have been employed for the transformation. In addition, there are also some other methods using Iron(III),[19] Ni(II),[20] the methods which also can compensate the drawback of the classical Biginelli reaction to some extent. In our previous paper,[21] we reported that under microwave irradiation, Ferric chloride could catalyze Biginelli reaction. Here, we report the synthesis of the dihydropyrimidinones by using of new catalyst TsOH[22] under microwave irradiation (Scheme 1). A structure study of **4o** by X-ray analysis for the first time is described.

Scheme 1



All the products were characterized by IR and ^1H NMR spectra, their melting points are identical with those reported in the literatures (Table 1). Meanwhile, the structure of the compound **4o** was established on the basis of spectroscopic data and confirmed by X-ray diffraction study (Fig. 1). Its crystallographic data are listed in Table 2. X-Ray crystallographic analysis reveals that the pyrimidinone ring has a boat conformation in the structure of **4o**.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzn spectrometer. ^1H NMR spectra were measured on a

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spacer with EO number of 45.

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Table 1 Synthesis of dihydropyrimidinone derivatives

Entry	R^1	R^2	Time (min)	Yield (%)	M.p. (℃)	
					Found	Reported
4a	3,4-$OCH_2OC_6H_3$	OEt	5	93	186—187	187—188[23]
4b	2-ClC_6H_4	OEt	4	91	215—217	215—218[13]
4c	C_6H_5	OEt	5	97	202—203	202—204[20]
4d	4-$NO_2C_6H_4$	OEt	3	89	207—208	207—208.5[12]
4e	4-$NMe_2C_6H_4$	OEt	6	89	257—258	256—257[20]
4f	2-OHC_6H_4	OEt	7	86	202—203	201—203[20]
4g	2,4-$Cl_2C_6H_3$	OEt	3	92	248—250	249—250[20]
4h	4-ClC_6H_4	OEt	3	98	214—215	213—215[12]
4i	4-OHC_6H_4	OEt	6	89	228—210	227—229[22]
4j	4-$NO_2C_6H_4$	Me	3	92	227—229	230[16]
4k	4-$OCH_3C_6H_4$	Me	6	93	165—168	166—168[16]
4l	2-NO_2-5-ClC_6H_3	OMe	5	90	290—292	—
4m	4-$NO_2C_6H_4$	OMe	3	92	237—238	235—237[12]
4n	4-$OCH_3C_6H_4$	OMe	6	94	193—196	192—194[12]
4o	4-ClC_6H_4	OMe	3	98	206—208	204—207[12]
4p	4-FC_6H_4	OMe	3	92	193—195	192—194[16]

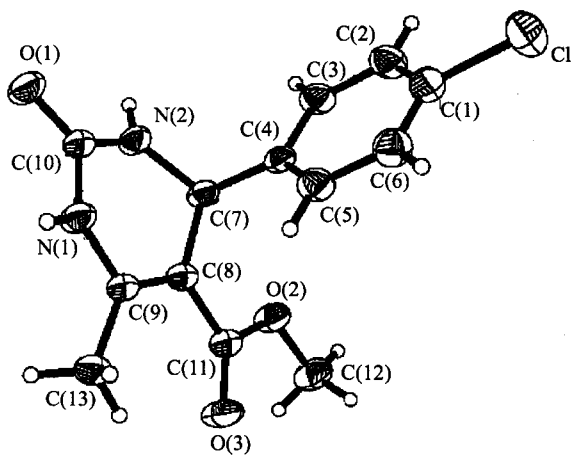

Fig. 1 Crystal structure of **4o**.

DPX 300 MHz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. X-Ray diffraction was measured on a Semens P4 diffractometer.

Typical experimental procedure

A dry flask (25 mL) was charged with the aromatic aldehyde (5 mmol), 1,3-dicarbonyl compound (5 mmol), urea (7.5 mmol), TsOH (1 mmol) and glacial acetic acid (1 mL). The flask was then connected with refluxing equipment. After microwave irradiation for 4—7 min, the reaction mixture was cooled and poured into water (50 mL), the solid products were filtered, washed with ethanol (95%), dried and recrystallized from hot ethanol.

Selected spectral data

4a ^{1}H NMR (DMSO-d_6) δ: 9.16 (s, 1H), 7.66 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 5.05 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3414, 3233, 2975, 1700, 1696, 1638, 1495 cm^{-1}.

4b ^{1}H NMR (DMSO-d_6) δ: 9.30 (s, 1H), 7.72 (s, 1H), 7.23—7.46 (m, 4H), 5.67 (d, J = 2.5 Hz, 1H), 3.91 (q, J = 7.5 Hz, 2H), 2.32 (s, 3H), 1.08 (t, J = 7.5 Hz, 3H); IR (KBr) ν: 3360, 3220, 3100, 1690, 1640 cm^{-1}.

4c ^{1}H NMR (DMSO-d_6) δ: 9.17 (s, 1H), 7.72 (s, 1H), 7.21—7.32 (m, 5H), 5.14 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3414, 3230, 3109, 2936, 1702, 1649, 1599 cm^{-1}.

4d ^{1}H NMR (DMSO-d_6) δ: 9.32 (s, 1H), 8.28 (d, J = 8.4 Hz, 2H), 7.89 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 2.2 Hz, 1H), 3.94 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3416, 3235, 3109, 2975, 1701, 1645, 1558 cm^{-1}.

4e ^{1}H NMR (DMSO-d_6) δ: 9.07 (s, 1H),

Table 2 Crystallographic data for **4o**

Empirical formula	$C_{13}H_{13}ClN_2O_3$
Color/shape	Colourless/prism
Formula weight	280.70
Temperature	296(2) K
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	$a = 0.5451(1)$ nm, $\alpha = 80.42(1)°$ $b = 0.7619(1)$ nm, $\beta = 83.43(1)°$ $c = 0.16118(4)$ nm, $\gamma = 79.29(1)°$
Volume	0.64619(19) nm^3
Z	2
D_c	1.443 Mg/m^3
Absorption coefficient	0.301 mm^{-1}
Diffractometer/scan	Siemens P4/$\omega - 2\theta$
$F(000)$	292
Crystal size	0.50 mm × 0.32 mm × 0.28 mm
θ Range for data collection	2.57° to 24.98°
Limiting indices	$0 \leqslant h \leqslant 6$, $-8 \leqslant k \leqslant 8$, $-19 \leqslant l \leqslant 19$
Reflections collected	2629
Independent reflections	2255 [R(int) = 0.0093]
Data/restraints/parameters	2255/0/175
Goodness-of-fit on F^2	1.061
Final R indices [$I > 2(\sigma(I))$]	$R_1 = 0.0432$, $wR_2 = 0.1167$
R indices (all data)	$R_1 = 0.0566$, $wR_2 = 0.1237$
Extinction coefficient	0.044(6)
Largest diff. peak and hole	259 and −212 e·nm^{-3}

7.57 (s, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 3.2 Hz, 1H), 3.96 (q, J = 7.2 Hz, 1H), 2.83 (s, 6H), 2.22 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3420, 3245, 3117, 2976, 1704, 1647, 1527 cm^{-1}.

4f ^{1}H NMR (DMSO-d_6) δ: 9.33 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.87 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3414, 3236, 3119, 2984, 1720, 1702, 1644, 1521 cm^{-1}.

4g ^{1}H NMR (DMSO-d_6) δ: 9.33 (s, 1H), 7.77 (s, 1H), 7.31—7.57 (m, 3H), 5.59 (d, J = 2.8 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3415, 3219, 3104, 2969, 1699, 1641 cm^{-1}.

4h ^{1}H NMR (DMSO-d_6) δ: 9.23 (s, 1H), 7.75 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.12 (d, J = 2.8 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.24 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); IR (KBr) ν: 3419, 3242, 3116, 2979, 1703, 1648 cm^{-1}.

4i ^{1}H NMR (DMSO-d_6) δ: 9.32 (s, 1H), 9.11 (s, 1H), 7.61 (s, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.04 (d, J = 3.2 Hz, 1H), 3.97 (q, J = 7.1 Hz), 2.23 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); IR (KBr) ν: 3417, 3241, 3120, 2984, 1687, 1649, 1512 cm^{-1}.

4j ^{1}H NMR (DMSO-d_6) δ: 9.40 (s, 1H), 8.21 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 5.39 (s, 1H), 2.32 (s, 3H), 2.19 (s, 3H); IR (KBr) ν: 3242, 3116, 2979, 1703, 1699, 1648 cm^{-1}.

4k ^{1}H NMR (DMSO-d_6) δ: 9.16 (s, 1H), 7.78 (s, 1H), 7.16 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.20 (d, J = 3.0 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H); IR (KBr) ν: 3242, 1714, 1624 cm^{-1}.

4l ^{1}H NMR (DMSO-d_6) δ: 9.45 (s, 1H), 7.94 (d, 2H), 7.58—7.62 (m, 1H), 7.45 (d, J = 2.7 Hz, 1H), 5.80 (d, J = 2.7 Hz, 1H), 3.39 (s, 3H), 2.26 (s, 3H); IR (KBr) ν: 3359, 3233, 3119, 2953, 1703, 1644, 1572, 1530 cm^{-1}.

4m ^{1}H NMR (DMSO-d_6) δ: 9.36 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 7.93 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 5.29 (d, J = 2.7 Hz, 1H), 3.54 (s, 3H), 2.27(s, 3H); IR (KBr) ν: 3362, 3221, 3113, 2949, 1711, 1635 cm^{-1}.

4n ^{1}H NMR (DMSO-d_6) δ: 9.19 (s, 1H), 7.69 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.09 (d, J = 2.7 Hz, 1H), 3.72 (s, 3H), 3.52 (s, 3H), 2.24 (s, 3H); IR (KBr) ν: 3415, 3247, 3111, 2953, 1719, 1682, 1512 cm^{-1}.

4o ^{1}H NMR (DMSO-d_6) δ: 9.30 (s, 1H), 7.82 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.14 (d, J = 2.8 Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H); IR (KBr) ν: 3364, 3221, 3103, 2947, 1712, 1636, 1494 cm^{-1}.

4p ^{1}H NMR (DMSO-d_6) δ: 9.27 (s, 1H), 7.79 (s, 1H), 7.29 (m, 4H), 7.23 (d, J = 8.4 Hz, 2H), 5.16 (d, J = 3.0 Hz, 1H), 3.54 (s, 3H), 2.26 (s, 3H); IR (KBr) ν: 3326, 1682, 1603 cm^{-1}.

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