JOC The Journal of Organic Chemistry

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Solvent-Free and Catalyst-Free Biginelli Reaction To Synthesize Ferrocenoyl Dihydropyrimidine and Kinetic Method To Express Radical-Scavenging Ability

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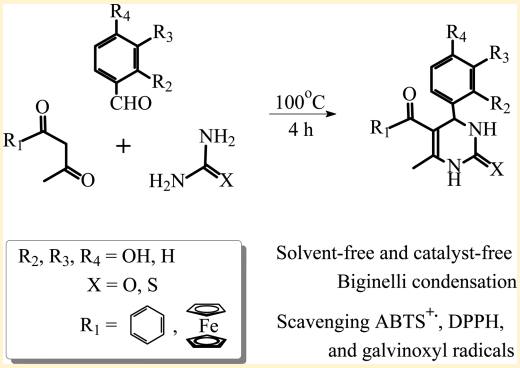
Supporting Information

ABSTRACT: Benzoyl and ferrocenoyl 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) (DHPMs) were synthesized in modest yields via catalyst-free and solvent-free Biginelli condensation of 1-phenylbutane-1,3-dione or 1-ferrocenylbutane-1,3-dione, hydroxyl benzaldehyde, and urea or thiourea. This synthetic protocol revealed that catalysts may not be necessary for the self-assembling Biginelli reaction. The radical-scavenging abilities of the obtained 11 DHPMs were carried out by reacting with 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\bullet}$), galvinoxyl radical, and 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH), respectively. The variation of the concentration of these radicals with the reaction time (t) followed exponential function, $[\text{radical}] = Ae^{-t/a} + Be^{-t/b} + C$. Then, the differential style of this equation led to the relationship between the reaction rate (r) and the reaction time (t), $-d[\text{radical}]/dt = (A/a)e^{-t/a} + (B/b)e^{-t/b}$, which can be used to calculate the reaction rate at any time point. On the basis of the concept of the reaction rate, $r = k[\text{radical}][\text{antioxidant}]$, the rate constant ($k$) can be calculated with the time point being $t = 0$. By the comparison of k of DHPMs, it can be concluded that phenolic *ortho*-dihydroxyl groups markedly enhanced the abilities of DHPMs to quench $ABTS^{+\bullet}$, but the introduction of ferrocenoyl group made DHPMs efficient $ABTS^{+\bullet}$ scavengers even in the absence of phenolic hydroxyl group. This phenomenon was also found in DHPM-scavenging galvinoxyl radical. In contrast, the ferrocenoyl group cannot enhance the abilities of DHPMs to scavenge DPPH, and phenolic *ortho*-dihydroxyl groups still played the key role in this case.



INTRODUCTION

The multicomponent condensation was an active field in the research of organic reactions because it can readily construct complicated heterocyclic scaffolds.[1,2] Dihydropyrimidine (DHPM) as a N-contained heterocycle attracted much attention due to activities of anticancer, anti-inflammatory, antibacterial, antifungal, anthelmintic, and antitopoisomerase[3−5] and functions of DHPM amidohydrolase, dihydropyrimidinase, and dehydrogenase.[6−8] Hence, the old Biginelli reaction for the synthesis of DHPMs became an attractive topic, and the investigation on this reaction mainly focused on the exploration of catalysts.[9−12] The original catalyst for the Biginelli reaction was Brønsted acid, thus, Lewis acids reasonably became the candidates for the selection of catalysts. A decade ago, the usage of BF_3 resulted in a modest yield of DHPMs by one-pot reaction of β-ketoester, aryl aldehyde, and urea.[13] Then, some transition metallic salts were found to catalyze the Biginelli reaction. For example, the applications of $Fe(NO_3)_3{\cdot}9H_2O$,[14] $TiCl_4$,[15] and $InCl_3$[16] lowered the temperature for the occurrence of the Biginelli reaction. Some non-acidic inorganic salts including CaF_2,[17] $CeCl_3{\cdot}7H_2O$,[18] iodotrimethylsilane/NaI,[19] NH_4Cl,[20] and even NaCl[21] were proved to be active toward the Biginelli reaction. Recently, basic compounds such as t-$(CH_3)_3COK$,[22] Ph_3P,[23] and L-proline[24] were found to be catalysts for the Biginelli condensation. The catalysts for the Biginelli condensation were well investigated in order to increase the yield and to expand to much more substrates. The chiral BINOL-phosphoric catalysts afforded chiral DHPMs with 88−97% ee and 40−86% yield.[25] In addition to the heating method, other experimental techniques have been explored. In the presence of polyphosphate ester or the polyaniline−bismoclite complex as catalysts, the Biginelli condensation can be finished within a few minutes under microwave irradiation[26] and ultrasound vibration[27] or in ionic liquids.[28] The microwave-assisted synthesis improved the yield when acetylacetone or acetylacetate acted as the reagent and $Yb(OTf)_3$ as the catalyst.[29]

The solvent-free reaction became a useful strategy for the formation of heterocycles.[30] Although some DHPMs can be prepared in the absence of catalyst and solvent,[31] the catalyst-free and solvent-free Biginelli reaction was not usually reported. The usage of solvent was beneficial for the reaction occurring in the same phase with high enantioselectivities.[32] The reaction can also take place on the surface of resin linked with urea via a N atom, leading to convenient isolation of DHPMs.[33] The

Received: February 14, 2012
Published: April 10, 2012

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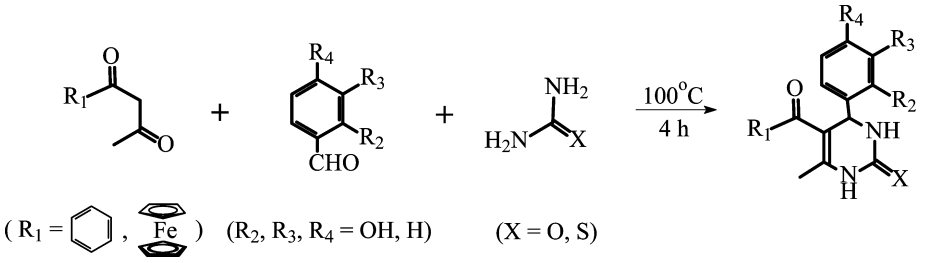
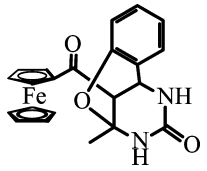
Table 1. Synthesis and Structures of DHPMs Employed Herein

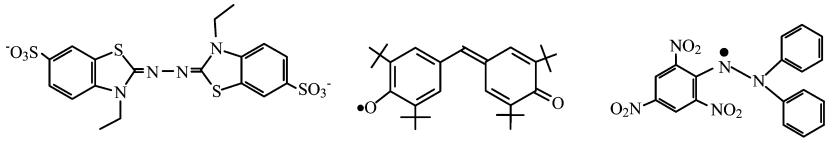


compound	R_1	R_2	R_3	R_4	X	yield (%)[a]
1	Ph	H	H	H	O	77
2	Ph	H	H	H	S	61
3	Ph	H	H	OH	O	60
4	Ph	H	H	OH	S	55
5	Ph	H	OH	OH	O	34
6	Ph	H	OH	OH	S	31
7	Fc[b]	H	H	H	O	50
8	Fc	H	H	H	S	43
9	Fc	H	H	OH	O	41
10	Fc	H	H	OH	S	37
11[c]	Fc	O–	H	H	O	25

[a]The isolation yields. [b]The ferrocenyl group. [c]The structure of **11** was



Scheme 1. Structures of ABTS Salt, Galvinoxyl Radical, and DPPH



ABTS salt galvinoxyl DPPH

substituents in benzaldehyde were electron-withdrawing groups or methyl and methoxyl group, but a hydroxyl group was not often found. This background motivated us to test whether the Biginelli reaction can take place in the absence of solvents and catalysts. Presented here was a study on the synthesis of benzoyl and ferrocenoyl DHPMs (structures in Table 1) in the absence of catalysts and solvents. The abilities of the obtained 11 DHPMs to scavenge 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\bullet}$), galvinoxyl radical, and 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH) (structures in Scheme 1) were investigated by calculating the rate constant (k) of DHPMs trapping these radicals.

RESULTS AND DISCUSSION

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones (-thiones) (DHPMs). DHPMs mentioned in this work were known compounds, but they were synthesized by directly heating the solid states of benzoylacetone or ferrocenoylacetone (1.0 equiv), hydroxyl benzaldehyde (1.0 equiv), and urea or thiourea (1.5 equiv). The absence of solvents increased the concentration of the reagents and was beneficial for shortening the reaction period. The hydroxyl benzaldehyde was not often used when Lewis acids acted as catalysts. This may be due to a phenolic hydroxyl group that was able to deactivate Lewis acids, but the catalyst-free method can avoid this shortcoming. The yields of DHPMs obtained by this method were not as high as that in the presence of a catalyst and a solvent because the reagents not diluted by a solvent were readily oxidized during heating. For example, the *ortho*-hydroxyl group in benzaldehyde adds to the C=C in DHPM via Michael addition, forming a tricyclic compound, **11** (yield, 25%). It was reported that compound **11** was formed by using $InBr_3$ (yield, 62%) and $InCl_3{\cdot}4H_2O$ (yield, 58%) as catalysts.[34] However, the benefit of the present method was to simplify the operation in the synthesis, and the *clean* reaction mixture resulted in a simple isolation procedure. The residual benzoylacetone and aldehyde were extracted by organic solvents because DHPMs were difficult to dissolve in usually used organic solvents. The excess of urea or thiourea was washed by ice water. Finally, the recrystallization from $DMSO/H_2O$ or DMF/C_2H_5OH afforded pure DHPMs.

Scavenging $ABTS^{+\bullet}$ Kinetics. $ABTS^{+\bullet}$ was usually used to test the ability of an antioxidant to reduce radicals.[35] A recent report provided a method for calculating the number of single electrons in $ABTS^{+\bullet}$ trapped by an antioxidant, in which the reaction between $ABTS^{+\bullet}$ and the antioxidant was artificially

dx.doi.org/10.1021/jo300282y | J. Org. Chem. 2012, 77, 3952−3958

divided into two period: $ABTS^{+\bullet}$ was trapped by *fresh* antioxidant and then by the oxidized products from the antioxidant.[36] However, it is difficult to divide these two periods completely because the reaction of the oxidized products from the antioxidant with $ABTS^{+\bullet}$ may take place before the whole antioxidant converts into the oxidized products, viz., the first period does not finish, and the second period may occur. The reaction rate between antioxidants and $ABTS^{+\bullet}$ is so fast that the absorbance of $ABTS^{+\bullet}$ decreases within a few seconds after the solution of antioxidant was mixed with $ABTS^{+\bullet}$. It is difficult to measure the decay of the absorbance of $ABTS^{+\bullet}$ at the first period in the case of artificial mixing of two solutions. Thus, some special apparatus were designed to measure the decay of the concentration of radicals during the first few seconds. For example, stopped-flow injection equipment was used to test the reaction rate of $ABTS^{+\bullet}$ with an antioxidant.[37] This equipment can measure the absorbance of $ABTS^{+\bullet}$ when *fresh* $ABTS^{+\bullet}$ just contacts with the fresh antioxidant, but the complicated apparatus and large exhaustion of solutions limit its application. On the other hand, the research interests focus on the improvement of experimental skills when the visible spectrometer was employed to follow the decay of the absorbance of $ABTS^{+\bullet}$. For example, the pseudo-first-order kinetic method can be used to test the ability of an antioxidant to quench radicals. In this method, the concentration of the antioxidant is much higher than that of $ABTS^{+\bullet}$, meaning the variation of the concentration of the antioxidant can be neglected. However, this method makes the measurement of the decay of the concentration of $ABTS^{+\bullet}$ more difficult because a low concentration of $ABTS^{+\bullet}$ can be depleted by the high concentration of the antioxidant within much shorter period. On the contrary, when the concentration of $ABTS^{+\bullet}$ is assigned to be a high value, the absorbance of $ABTS^{+\bullet}$ does not decrease, one cannot measure the decay of the concentration of radicals. In addition, the results from the pseudo-first-order kinetic method do not embody the influence of the reagent with high concentration on the reaction rate because the high concentration is composed of the value of the reaction rate. Hence, the measurement of the decay of the concentration of $ABTS^{+\bullet}$ should be carried out at appropriate concentrations of the antioxidant and $ABTS^{+\bullet}$, and the aim of this work is to find a suitable mathematical function to fit the obtained data from the measurement of the decay of the concentration of $ABTS^{+\bullet}$.

The most important index for a reaction is the rate constant ($\boldsymbol{k}$), which can be calculated by the relationship between the concentration of reagents and the reaction rate ($\boldsymbol{r}$), $\boldsymbol{k} = \boldsymbol{r}/([\text{antioxidant}]^{a}[\text{radical}]^{b})$. The calculation of $\boldsymbol{k}$ is based on the measurements of $\boldsymbol{r}$ and the reaction order for every reagent, a and b. For example, in the oxidation of γ-terpinene by 2,2′-azobis(isobutyronitrile) (AIBN), the reaction orders for γ-terpinene and AIBN (a and b) were first confirmed by measuring the formation rate of *p*-cymene in the case of fixing the concentration of one reagent and varying another one.[38] This method is a popular way to measure the reaction rate and then to calculate the rate constant, but the amount of the experimental operation of this method is very large. Previous reports revealed that the reaction between an antioxidant and a radical followed bimolecular kinetics, viz., first-order kinetics for the antioxidant and for the radical.[39] The kinetic equation for a second-order reaction with different concentrations of two reagents, $\ln([\text{antioxidant}]/[\text{radical}]) = \boldsymbol{k}t([\text{antioxidant}]_0 - [\text{radical}]_0) + \ln([\text{antioxidant}]_0/[\text{radical}]_0)$, can be applied to treat the reaction between the antioxidant and $ABTS^{+\bullet}$. In addition to the improvement of the synthetic operation, another aim of this work is to find a suitable function to fit the decrease of the concentration of $ABTS^{+\bullet}$ in the case of limit measured data employed, and this function is suitable not only for $ABTS^{+\bullet}$ but also for other radicals regardless of the reaction orders for the antioxidant and the radical. Although it is difficult to measure the decay of the concentration of $ABTS^{+\bullet}$ just after being mixed with an antioxidant, Figure 1 shows that the

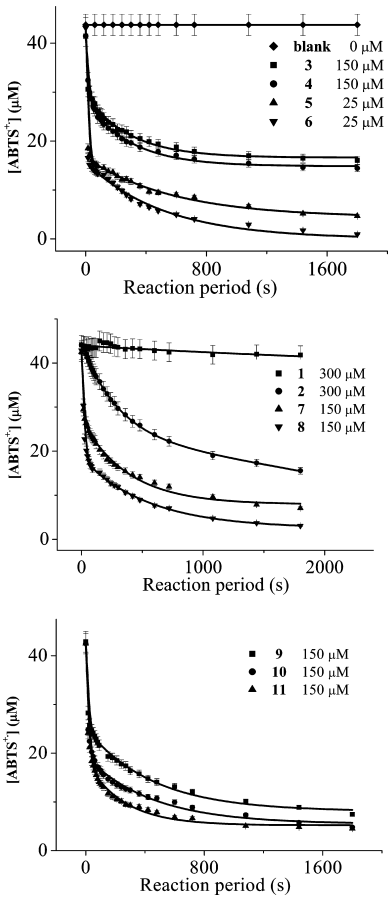


Figure 1. Decay of 42.96 μM $ABTS^{+\bullet}$ in the presence of various concentrations of DHPMs.

concentration of $ABTS^{+\bullet}$ decreases as the reaction time increases. One can observe the shape of the decay line and find that this kind of line is suitable for the exponential decay just in light of mathematics. In spite of the chemical kinetic meaning, the multiexponential function is applied to fit the decay line in Figure 1. The second order of exponential function can perfectly express the decrease of the concentration of $ABTS^{+\bullet}$ as shown in eq 1, and the coefficients in the third and much higher items of the exponential function are so low that the second order of exponential function is sufficient for mathematical fitting. Occasionally, one-order exponential function is capable of fitting the decrease of the concentration of the radical (see compound **5** and **6** in Table 3). Equation 1 is just a mathematical equation to express the variation of $[ABTS^{+\bullet}]$ versus reaction time (t).

$$[ABTS^{+\bullet}] = A\mathbf{e}^{-t/a} + B\mathbf{e}^{-t/b} + C \quad (1)$$

Figure 1 outlines that the concentration of $ABTS^{+\bullet}$ decreased with the reaction period (t) in the presence of DHPMs. The

dx.doi.org/10.1021/jo300282y | J. Org. Chem. 2012, 77, 3952−3958

Table 2. Equation of $[ABTS^{+\bullet}] \sim t$ and Its Differential Style $(-d[ABTS^{+\bullet}]/dt \sim t)$, Reaction Rate at $t = 0$ (r_0), and Rate Constant (k)[a]

compound	equation of $[ABTS^{+\bullet}]$ $(\mu M)] \sim t$ (s)	equation of $-d[ABTS^{+\bullet}]/dt \sim t$	r_0 $(\mu M \cdot s^{-1})$	k $(nM^{-1} \cdot s^{-1})$
2	$[ABTS^{+\bullet}] = 21.15e^{-t/164.48} + 13.06e^{-t/203.51} + 10.56$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 0.018e^{-t/164.48} + 0.06e^{-t/203.51}$	0.078	6.40×10^{-3}
3	$[ABTS^{+\bullet}] = 11.91e^{-t/8.99} + 12.68e^{-t/287.60} + 16.62$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.32e^{-t/8.99} + 0.05e^{-t/287.60}$	1.37	0.21
4	$[ABTS^{+\bullet}] = 13.11e^{-t/16.54} + 13.35e^{-t/293.26} + 14.85$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 0.79e^{-t/16.54} + 0.04e^{-t/293.26}$	0.83	0.13
5	$[ABTS^{+\bullet}] = 27.04e^{-t/6.10} + 12.01e^{-t/548.81} + 4.69$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 4.43e^{-t/6.10} + 0.02e^{-t/548.81}$	4.45	4.14
6	$[ABTS^{+\bullet}] = 27.42e^{-t/4.93} + 15.70e^{-t/515.67} + 0.00$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 5.56e^{-t/4.93} + 0.03e^{-t/515.67}$	5.59	5.20
7	$[ABTS^{+\bullet}] = 15.33e^{-t/10.00} + 19.19e^{-t/381.56} + 7.93$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.53e^{-t/10.00} + 0.05e^{-t/381.56}$	1.58	0.24
8	$[ABTS^{+\bullet}] = 24.67e^{-t/18.50} + 15.99e^{-t/554.44} + 2.46$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.13e^{-t/18.50} + 0.03e^{-t/554.44}$	1.36	0.21
9	$[ABTS^{+\bullet}] = 17.71e^{-t/10.02} + 17.07e^{-t/447.03} + 8.05$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.77e^{-t/10.02} + 0.04e^{-t/447.03}$	1.81	0.28
10	$[ABTS^{+\bullet}] = 22.80e^{-t/12.50} + 13.99e^{-t/434.25} + 5.53$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.82e^{-t/12.50} + 0.03e^{-t/434.25}$	1.85	0.29
11	$[ABTS^{+\bullet}] = 23.89e^{-t/12.88} + 13.24e^{-t/251.51} + 5.20$	$-\frac{d[ABTS^{+\bullet}]}{dt} = 1.85e^{-t/12.88} + 0.05e^{-t/251.51}$	1.90	0.30

[a]The concentration of **2** was 300 μM, and the concentrations of **5** and **6** were 25.0 μM. The concentrations of other compounds were 150 μM. The concentration of $ABTS^{+\bullet}$ was 42.96 μM.

data of $[ABTS^{+\bullet}]$ and reaction period (t) were input into statistical software, the coefficients, A, B, C, a, and b were given and listed in Table 2.

Equation 2, the differential style of eq 1, indicated the variation of the reaction rate $(r = -d[ABTS^{+\bullet}]/dt)$ with the reaction time (t). The obtained equations of $-d[ABTS^{+\bullet}]/dt \sim t$ are listed in Table 2.

$$\frac{d[ABTS^{+\bullet}]}{dt} = \frac{d(Ae^{-t/a} + Be^{-t/b} + C)}{dt} = \frac{d(Ae^{-t/a})}{dt} + \frac{d(Be^{-t/b})}{dt} + \frac{dC}{dt}$$

$$\text{viz.} -\frac{d[ABTS^{+\bullet}]}{dt} = r = \frac{A}{a}e^{-t/a} + \frac{B}{b}e^{-t/b} \quad (2)$$

The reaction rate at $t = 0$ (r_0) can be calculated by the equation of $-d[ABTS^{+\bullet}]/dt \sim t$ when t was assigned to be 0, as shown in eq 3, and the results were involved in Table 2, as well.

$$r_0 = \frac{A}{a}e^{-0/a} + \frac{B}{b}e^{-0/b} = \frac{A}{a} + \frac{B}{b} \quad (3)$$

According to the concept of the reaction rate, r was the product of the concentrations of $ABTS^{+\bullet}$ and the antioxidant as shown in eq 4.

$$r = k[ABTS^{+\bullet}][\text{antioxidant}] \quad (4)$$

Therefore, the rate constant, k $(nM^{-1} \cdot s^{-1})$, can be calculated by eq 5 when the value of every item was assigned at $t = 0$, and the results were collected in Table 2, as well.

$$k = \frac{r_0}{[ABTS^{+\bullet}]_0[\text{antioxidant}]_0} \quad (5)$$

The compound **1** was not able to quench $ABTS^{+\bullet}$, and compound **2** just possessed a very low value of k, indicating that the H in N−H of DHPMs cannot react with $ABTS^{+\bullet}$ in the absence of phenolic −OH. Contrarily, high values of k for **5** and **6** (4.14 and 5.20 $nM^{-1} \cdot s^{-1}$, respectively) indicated that **5** and **6** were able to quench $ABTS^{+\bullet}$ efficiently, owing to phenolic *ortho*-dihydroxyl groups. The k value of **6** was higher than that of **5**, revealing that C═S in the skeleton of DHPM was beneficial for the phenolic −OH to react with $ABTS^{+\bullet}$. This result also implicated that phenolic −OH existed in an intramolecular synergistic effect with C═S, although the distance between these two functional groups was long. Moreover, k values from compounds **7** to **11** ranged a narrow scale from 0.21 to 0.30 $nM^{-1} \cdot s^{-1}$, demonstrating that the introduction of the ferrocene moiety to modify DHPM led to an average effect on scavenging $ABTS^{+\bullet}$, but it was worthy to note that k values of compounds **7** and **8** (0.24 and 0.21 $nM^{-1} \cdot s^{-1}$, respectively) were much higher than that of compounds **1** and **2** (not detected and 6.40×10^{-3} $nM^{-1} \cdot s^{-1}$, respectively), indicating that the ferrocene moiety markedly enhanced the abilities of DHPMs to scavenge $ABTS^{+\bullet}$. This phenomenon was also found by comparing k values of compounds **9** and **10** with those of **3** and **4**. The structures of **3** and **4** were correspondingly similar to those of **9** and **10**. The phenyl group in **3** and **4** (k values were 0.21 and 0.13 $nM^{-1} \cdot s^{-1}$, respectively) was replaced by ferrocenyl group to form **9** and **10** (k values were 0.28 and 0.29 $nM^{-1} \cdot s^{-1}$, respectively), leading to high abilities of **9** and **10** to scavenge $ABTS^{+\bullet}$. Thus, the ferrocenoyl group also existed in an intramolecular synergistic effect with phenolic −OH on reducing $ABTS^{+\bullet}$. On the other hand, it can be found that k values of **9** and **10** were not remarkably higher than those of **7** and **8**, indicating that phenolic −OH did not increase the

dx.doi.org/10.1021/jo300282y | J. Org. Chem. 2012, 77, 3952−3958

abilities of ferrocenoyl DHPMs to scavenge $ABTS^{+\bullet}$. In particular, the high value of k of compound **11** (0.30 $nM^{-1}\cdot s^{-1}$) revealed that N−H in ferrocenoyl DHPMs can also reduce $ABTS^{+\bullet}$ even without the aid of phenolic −OH. Therefore, it can be concluded that the ferrocene moiety played the key role in scavenging $ABTS^{+\bullet}$ and even weakened the influence of phenolic −OH on scavenging $ABTS^{+\bullet}$.

Scavenging Galvinoxyl Radical Kinetics. Galvinoxyl radical was widely employed to evaluate the ability of an antioxidant to contribute the hydrogen atom to the oxygen radical.[40] Figure 2 showed the decrease of the concentration of galvinoxyl radical in the presence of compounds **5**−**11**. Other DHPMs cannot quench the galvinoxyl radical. The decay of the concentration of galvinoxyl radical with reaction time also fitted the exponential function, and then, the derivation operation was performed on the equations of [galvinoxyl] ∼ t to obtain $-d$[galvinoxyl]$/dt \sim t$. The following calculation was the same as DHPM-scavenging $ABTS^{+\bullet}$, and the results are listed in Table 3.

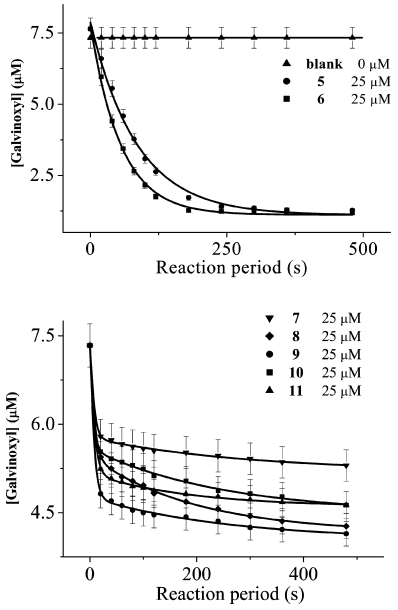


Figure 2. Decay of 7.49 μM galvinoxyl radical in the presence of various concentrations of DHPMs.

Among benzoyl DHPMs, only compounds **5** and **6** were active to quench the galvinoxyl radical with relatively low values of k, 0.43 and 0.64 $nM^{-1}\cdot s^{-1}$, respectively, due to *ortho*-dihydroxyl groups donating the H atom to the oxygen radical. In contrast, all of the ferrocenoyl DHPMs can quench the galvinoxyl radical and generate relative high k values ranging from 1.34 to 2.14 $nM^{-1}\cdot s^{-1}$. Hence, the introduction of the ferrocene moiety enhanced the abilities of DHPMs to contribute the H atom to the oxygen radical. In the absence of phenolic −OH, compounds **7**, **8**, and **11** still generated 1.34, 1.50, and 1.60 $nM^{-1}\cdot s^{-1}$ k values, respectively. The H atom in N−H of DHPMs can be donated to the oxygen radical, owing to the presence of the ferrocene moiety. Furthermore, only one phenolic −OH increased k values of compounds **9** and **10** to 1.90 and 2.14 $nM^{-1}\cdot s^{-1}$, respectively, demonstrating that the ferrocene moiety can also enhance the abilities of DHPMs to donate the H atom in phenolic −OH to the oxygen radical.

Scavenging DPPH Kinetics. DPPH was a nitrogen-centered radical. Figure 3 shows the decrease of the

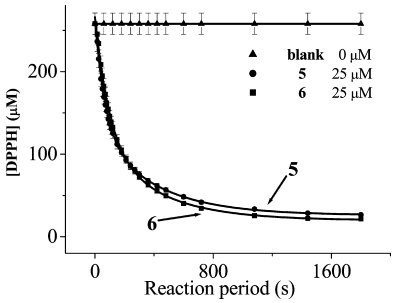


Figure 3. Decay of 258.20 μM DPPH in the presence of various concentrations of DHPMs.

Table 3. Equation of [Galvinoxyl] ∼ t and Its Differential Style ($-d$[Galvinoxyl]$/dt \sim t$), Reaction Rate at t = 0 (r_0), and Rate Constant (k)[a]

compound	equation of [galvinoxyl (μM)] ∼ t	equation of $-d$[galvinoxyl]$/dt \sim t$	r_0 (μM·s^{-1})	k ($nM^{-1}\cdot s^{-1}$)
5	$[\text{galvinoxyl}] = 6.76e^{-t/85.22} + 0.12$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.08e^{-t/85.22}$	0.08	0.43
6	$[\text{galvinoxyl}] = 6.66e^{-t/55.74} - 0.40$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.12e^{-t/55.74}$	0.12	0.64
7	$[\text{galvinoxyl}] = 1.56e^{-t/6.19} + 0.57e^{-t/288.06} + 5.20$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.25e^{-t/6.19} + 1.98 \times 10^{-3}e^{-t/288.06}$	0.25	1.34
8	$[\text{galvinoxyl}] = 1.86e^{-t/6.84} + 1.31e^{-t/194.10} + 4.16$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.27e^{-t/6.84} + 6.75 \times 10^{-3}e^{-t/194.10}$	0.28	1.50
9	$[\text{galvinoxyl}] = 1.74e^{-t/5.01} + 1.11e^{-t/249.63} + 4.48$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.35e^{-t/5.01} + 4.45 \times 10^{-3}e^{-t/249.63}$	0.35	1.90
10	$[\text{galvinoxyl}] = 2.57e^{-t/6.43} + 0.73e^{-t/255.63} + 4.04$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.40e^{-t/6.43} + 2.85 \times 10^{-3}e^{-t/255.63}$	0.40	2.14
11	$[\text{galvinoxyl}] = 2.17e^{-t/7.26} + 0.57e^{-t/186.53} + 4.60$	$-\frac{d[\text{galvinoxyl}]}{dt} = 0.30e^{-t/7.26} + 3.06 \times 10^{-3}e^{-t/186.53}$	0.30	1.60

[a]The concentration of DHPM was 25.0 μM, and the concentration of the galvinoxyl radical was 7.49 μM. The second items in the equation of [galvinoxyl (μM)] ∼ t of compounds **5** and **6** were omitted because the coefficients were very small.

dx.doi.org/10.1021/jo300282y | J. Org. Chem. 2012, 77, 3952−3958

Table 4. Equation of [DPPH] ~ t and Its Differential Style ($-d$[DPPH]/dt ~ t), Reaction Rate at t = 0 (r_0), and Rate Constant (k)[a]

compound	equation of [DPPH (μM)] ~ t	equation of $-d$[DPPH]/dt ~ t	r_0 (μM·s^{-1})	k (nM^{-1}·s^{-1})
5	$[\mathrm{DPPH}] = 104.34e^{-t/387.83} + 130.59e^{-t/68.16} + 26.08$	$-\frac{d[\mathrm{DPPH}]}{dt} = 0.27e^{-t/387.83} + 1.91e^{-t/68.16}$	2.18	0.34
6	$[\mathrm{DPPH}] = 147.29e^{-t/95.45} + 98.98e^{-t/389.25} + 19.83$	$-\frac{d[\mathrm{DPPH}]}{dt} = 1.54e^{-t/94.45} + 0.25e^{-t/389.25}$	1.79	0.28

[a]The concentration of DHPM was 25.0 μM, and the concentration of DPPH was 258.20 μM.

concentration of DPPH in the presence of compounds **5** and **6**. The decay of the concentration of DPPH with the reaction time also fitted the exponential function, and then, the derivation operation was performed on the equations of [DPPH] ~ t to obtain $-d$[DPPH]/dt ~ t as shown in eq 6.[39]

$$-\frac{d[\mathrm{DPPH}]}{dt} = r = k[\mathrm{DPPH}][\mathrm{antioxidant}] \quad (6)$$

The following calculation was the same as DHPM-scavenging ABTS$^{+\bullet}$, and the results are listed in Table 4.

The data for DPPH showed a completely different picture from that of either ABTS$^{+\bullet}$ or the galvinoxyl radical. Except for **5** and **6**, other DHPMs cannot trap DPPH, revealing that the H atom in N−H of DHPMs and in single phenolic −OH cannot be abstracted by the nitrogen radical, and the introduction of the ferrocene moiety cannot ameliorate the abilities of DHPMs to quench the nitrogen radical either. The phenolic *ortho*-dihydroxyl groups in DHPMs acted as the scavengers toward DPPH. The introduction of the ferrocenoyl group actually enhances the reactivity of DHPMs toward radicals, but the chemical mechanisms were different for a redox-active radical (ABTS$^{+\cdot}$) and for a H acceptor (galvinoxyl radical and DPPH). For example, ferrocene-appended chalcones without a phenolic hydroxyl group attached were still able to reduce ABTS$^{+\bullet}$ by Fe(II)/Fe(III) redox, but the abilities to quench the galvinoxyl radical and DPPH were lower than those chalcones with a phenolic hydroxyl group attached. Thus, the phenolic hydroxyl group played the main role in donating a H atom to the galvinoxyl and DPPH radical.[41]

CONCLUSION

The catalyst seemed unnecessary for the Biginelli condensation, which can take place under heating conditions in the absence of any solvents. Therefore, the formation of DHPMs was a self-assembling procedure occurring among aldehyde, β-diketone, and urea or thiourea. The benzoyl and ferrocenoyl DHPMs were able to quench ABTS$^{+\bullet}$, galvinoxyl radical, and DPPH. Although phenolic hydroxyl was of importance for DHPMs to quench ABTS$^{+\bullet}$, the presence of the ferrocene moiety converted DHPMs into ABTS$^{+\bullet}$ scavengers even without a phenolic hydroxyl attached. This rule was reinforced in the interaction between DHPMs and the galvinoxyl radical, but the ferrocene moiety did not enhance the abilities of DHPMs to scavenge DPPH, and phenolic *ortho*-dihydroxyl groups still played the key role in this case.

EXPERIMENTAL SECTION

Materials and Instrumentation. Diammonium 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) (ABTS), 2,2′-diphenyl-1- picrylhydrazyl radical (DPPH), and galvinoxyl radical were purchased from ACROS ORGANICS, Geel, Belgium. Other agents were of analytical grade and used directly. The structures of the obtained products were identified by ^{1}H NMR. DHPMs were detected by gas chromatography equipped with mass spectra (GC/MS).

General Procedure for the Synthesis of DHPMs (Compounds 1−11). 1-Phenylbutane-1,3-dione or 1-ferrocenylbutane-1,3-dione (2 mmol), the corresponding aldehyde (2 mmol), and urea or thiourea (3 mmol) were mixed at solid states and heated at 100 °C for 4 h under stirring. After the mixture was cooled to room temperature, it was washed with ether or ethyl acetate. The residual solid was washed with cold water (10 mL × 2) and dried to give crude DHPMs. Compound **1−6** were recrystallized from DMSO/H_2O, and compounds **7−11** were recrystallized from DMF/C_2H_5OH.

5-Benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1): Yield 77%; mp 226−228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (s, 3H), 5.30 (s, 1H), 7.18−7.53 (m, 10H), 7.80 (s, 1H), 9.17 (s, 1H); MS m/z 291.07 [M$^{+\bullet}$].

(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenylmethanone (2): Yield 61%; mp 242−244 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (s, 3H), 5.29 (s, 1H), 7.16−7.55 (m, 10H), 9.68 (s, 1H), 10.35 (s, 1H); MS m/z 307.98 [M$^{+\bullet}$].

5-Benzoyl-4-(4′-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3): Yield 60%; mp 234−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (s, 3H), 5.19 (d, J = 2.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 7.41−7.52 (m, 5H), 7.66 (s, 1H), 9.08 (s, 1H), 9.32 (s, 1H); MS m/z 307.99 [M$^{+\bullet}$].

(4-(4′-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenylmethanone (4): Yield 55%; mp 259−260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (s, 3H), 5.18 (s, 1H), 6.68 (d, J = 6.6 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 7.41−7.54 (m, 5H), 9.41 (s, 1H), 9.56 (s, 1H), 10.24 (s, 1H); MS m/z 323.98 [M$^{+\bullet}$].

5-Benzoyl-4-(3′,4′-dihydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (5): Yield 34%; mp >300 °C (decomp); ^{1}H NMR (300 MHz, DMSO- d_6) δ 1.66 (s, 3H), 5.14 (s, 1H), 6.40 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 9.6 Hz, 2H), 7.42−7.55 (m, 5H), 7.65 (d, 1H), 8.77 (s, 1H), 8.90 (s, 1H), 9.06 (s, 1H); MS m/z 323.07 [M$^{+\bullet}$].

(4-(3′,4′-Dihydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)phenylmethanone (6): Yield 31%; mp >300 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (s, 3H), 5.12 (s, 1H), 6.37−6.41 (dd, J = 1.8 Hz, J = 7.8 Hz, 1H), 6.59−6.65 (m, 2H), 7.42−7.58 (m, 5H), 8.88 (s, 1H), 8.98 (s, 1H), 9.54 (s, 1H), 10.23 (s, 1H); MS m/z 339.99 [M$^{+\bullet}$].

5-Ferrocenoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (7): Yield 50%; mp 270−274 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.82 (s, 5H), 4.42 (s, 1H), 4.53 (s, 2H), 4.77 (s, 1H), 5.43 (s, 1H), 7.27−7.43 (m, 5H), 7.66 (s, 1H); MS m/z 400.05 [M$^{+\bullet}$].

5-Ferrocenoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (8): Yield 43%; mp 262−265 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.89 (s, 3H), 3.83 (s, 5H), 4.46−4.79 (m, 4H), 5.44 (d, J = 3.3 Hz, 1H), 7.33−7.45 (m, 5H), 9.53 (s, 1H), 10.12 (s, 1H); MS m/z 415.96 [M$^{+\bullet}$].

5-Ferrocenoyl-6-methyl-4-(4′-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (9): Yield 41%; mp 240−246 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.83 (s, 5H), 4.41−4.75 (m, 4H), 5.33 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.54 (s, 1H); MS m/z 416.00 [M$^{+\bullet}$].

5-Ferrocenoyl-6-methyl-4-(4′-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (10): Yield 37%; mp 264−268 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.87 (s, 3H), 3.85 (s, 5H), 4.46 (s, 1H), 4.56 (s, 2H), 4.77 (s, 1H), 5.34 (s, 1H), 6.78 (d, J =

dx.doi.org/10.1021/jo300282y | J. Org. Chem. 2012, 77, 3952−3958

8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 9.41 (s, 1H), 9.46 (s, 1H), 10.01 (s, 1H); MS m/z 431.90 [$M^{+\bullet}$].

13-Ferrocenoyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6-triene (11): Yield 25%; mp 256−262 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (s, 3H), 3.74 (s, 1H), 4.31 (s, 5H), 4.47−4.90 (m, 5H), 6.81−7.25 (m, 5H), 7.57 (s, 1H); MS m/z 415.99 [$M^{+\bullet}$].

Scavenging DPPH, ABTS$^{+\bullet}$, and Galvinoxyl radicals. DPPH and galvinoxyl radical were dissolved in 50 mL of ethanol to make the absorbance around 1.00 at 517 nm (ε_{DPPH} = 4.09 × 10^3 M^{-1} cm^{-1}) and 428 nm ($\varepsilon_{galvinoxyl}$ = 1.4 × 10^5 M^{-1} cm^{-1}), respectively. ABTS$^{+\bullet}$ was produced from 2.0 mL of aqueous solution containing 4.0 mM ABTS and 1.41 mM $K_2S_2O_8$ after kept for 16 h and diluted by 100 mL of ethanol. The absorbance of ABTS$^{+\bullet}$ solution was around 0.70 at 734 nm ($\varepsilon_{ABTS^{+\bullet}}$ = 1.6 × 10^4 M^{-1} cm^{-1}). The DMSO solutions of DHPMs (0.1 mL) were added to 1.9 mL of DPPH or galvinoxyl radical solution with the final concentrations of DHPMs being 25.0 μM. The DMSO solutions of DHPMs (0.1 mL) were added to 1.9 mL of ABTS$^{+\bullet}$ with the final concentrations of DHPMs being 300.0 μM for compounds **1** and **2**, 150 μM for **3**, **4**, and **7**−**11**, and 25 μM for **5** and **6**. The decreases of the absorbance of these radicals were recorded at 20 °C with a certain time interval.

Statistical Analysis. All of the data were the average value from at least three independent measurements with the experimental error within 10%. The relationships between the concentrations of radicals and the reaction time were fitted by a second-order exponential function in Origin 7.5 professional software.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and MS spectra for compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Jilin Provincial Foundation for Natural Science, China (201115017), is acknowledged gratefully.

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