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Approach to Polysubstituted 4-Pyridones from *N*-Aryl Acetoacetamides via a *N* to *C* 1,3-Acyl Migration Mediated by Sodium Persulfate

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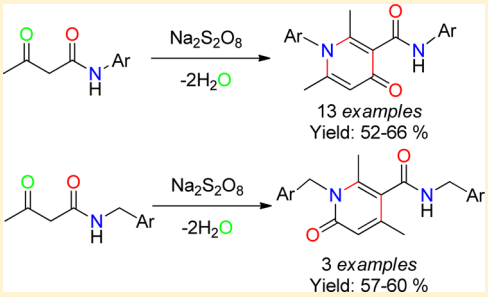
Supporting Information

ABSTRACT: Mediated by sodium persulfate ($Na_2S_2O_8$), a series of polysubstituted 4-pyridones were synthesized via self-condensation of *N*-aryl acetoacetamides, during which a novel *N* to *C* 1,3-acyl migration should be involved. The structure of 4-pyridone was unequivocally confirmed by X-ray diffraction analysis. However, the self-condensation of *N*-benzyl acetoacetamides under the same condition gave polysubstituted 2-pyridones instead of 4-pyridones.



4-Pyridone derivatives are identified as antibacterial activities,[1] antitumor activities,[2] antiviral activities,[3] antiinflammatory activities,[4] and other bioactivities.[5] They are also important intermediates in the organic synthesis[6] and the key structure of some natural products (Figure 1).[4,5b,7] A lot of reports can be found in the literature concerning the synthesis of *N*-alkyl- and *N*-aryl-2-/4-pyridones.[8] For example, the two well-known methods for preparing 4-pyridones involve the reaction of a pyrone with a primary amine[9] and the hetero Diels−Alder reaction.[10] In this paper, we disclose a direct and simpler approach to pyridone derivatives via dimerization of industrial acetoacetamides mediated by sodium persulfate.

Acetoacetamides or their derivatives are really very convenient and versatile building blocks in the synthesis of heterocyclic compounds.[4,11−17] Combining with our recent research for the direct synthesis of heterocyclic compounds from acyclic acetoacetamide derivatives precursors,[18] we made efforts to realize an intramolecular cyclization of **1a** to **3** catalyzed by transition metals (Scheme 1), but the results disappointed. Compound **3** was not observed after many attempts by using Pd, Fe, and Cu salts. During these attempts, it was observed that an unexpected product, which was subsequently characterized as a 4-pyridone derivate **2a** by ^{1}H NMR, ^{13}C NMR, HRMS and the X-ray diffraction (XRD) analysis, was formed in low yield by treatment of **1a** with sodium persulfate in the presence of $FeCl_3$ (Scheme 1). Further investigations revealed that $FeCl_3$ was unnecessary for the reaction and the yield was a little higher in the absence of $FeCl_3$. To the best of our knowledge, only one direct approach to polysubstituted 4-pyridones from *N*-aryl acetoacetamides was reported,[4] which was catalyzed by *p*-toluenesulfonic acid via the self-condensation of *N*-aryl acetoacetamides in moderate yields. Therefore, the unexpected finding is worthy of further evaluation as an alternative approach to 4-pyridones without using Brønsted acid as catalyst.

To optimize the reaction condition, we used *N*-(2-chlorophenyl)-3-oxobutanamide **1a** as a model for the dimerization. The screening of reaction conditions (Table 1) showed that the 4-pyridone **2a** can be obtained in 65% yield alone with some unidentified complex mixture by treating **1a** (1.0 mmol) with $Na_2S_2O_8$ (0.5 mmol) in dichloroethane (DCE, 6.0 mL) at reflux for 10 h (entry 3). It would result in a dramatically lower yield of **2a** when the reaction was performed at lower temperature at 75 °C (entry 4). The experiments also showed that the equivalent of sulfur was required, while increasing or decreasing the amount of $Na_2S_2O_8$ cannot improve the yield of dimerization (entries 1, 2, 5, 6). It exhibited uncoordinated yield effects in different halogenous solvents of 1,1,2,2-tetrachloroethane (1,1,2,2-TeCE) and 1,2-dibromoethane (1,2-DBE) (entries 7, 8). Other solvents such as DMF, THF, CH_2Cl_2, CH_3CN, EtOH, DMSO, and toluene were proved to be fundamentally ineffective, and the material **1a** in most of the reactions was recovered (entries 9−15). The dichloroethane dependent reaction was therefore tested by other catalysts in dichloroethane. The facts proved that $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were less effect for this condensation and only gave the desired product **2a** in yields of 18 and 43%, respectively, along with 75% **1a** was recovered in the case of $K_2S_2O_8$ (entries 16, 17 vs 3). Other oxidants like *tert*-butyl hydroperoxide (TBHP) and *m*-chloroperbenzoic acid (*m*-CPBA) were also fundamentally ineffective (entries 18, 19).

The optimal condition was finally identified as $Na_2S_2O_8$ (0.5 equiv) in DCE at reflux (Table 1, entry 3). Consequently, we

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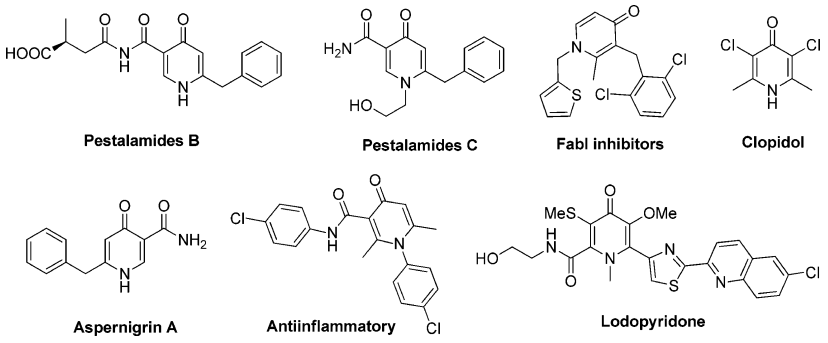


Figure 1. Representative 4-pyridones possessing bioactivities.

Scheme 1. Reactions of Acetoacetamide 1a in the Presence of Transition Metals

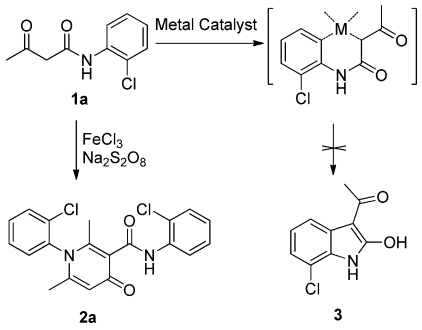
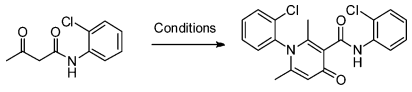


Table 1. Survey of Reaction Conditions[a]

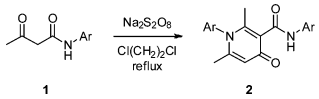


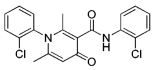
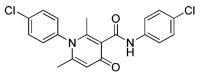
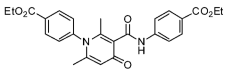
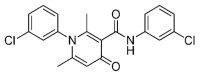
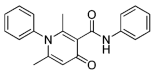
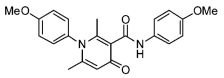
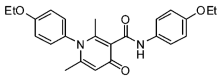
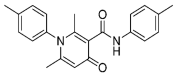
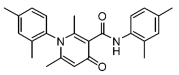
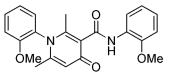
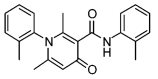
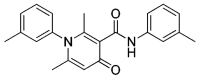
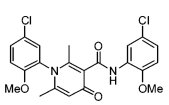
entry	cat. (equiv)	solvent	time (h)	yield (%)[b]
1	$Na_2S_2O_8$ (0.1)	DCE	24	46[c]
2	$Na_2S_2O_8$ (0.2)	DCE	24	50[d]
3	**$Na_2S_2O_8$ (0.5)**	**DCE**	**10**	**65**
4	$Na_2S_2O_8$ (0.5)	DCE	24	16[e]
5	$Na_2S_2O_8$ (1.0)	DCE	6	62
6	$Na_2S_2O_8$ (2.0)	DCE	5	45
7	$Na_2S_2O_8$ (0.5)	1,1,2,2-TeCE	24	42[f]
8	$Na_2S_2O_8$ (0.5)	1,2-DBE	23	30[f]
9	$Na_2S_2O_8$ (0.5)	DMF	30	0[g]
10	$Na_2S_2O_8$ (0.5)	THF	32	0
11	$Na_2S_2O_8$ (0.5)	CH_2Cl_2	40	0[h]
12	$Na_2S_2O_8$ (0.5)	CH_3CN	13	0
13	$Na_2S_2O_8$ (0.5)	EtOH	48	0[i]
14	$Na_2S_2O_8$ (0.5)	DMSO	36	0[j]
15	$Na_2S_2O_8$ (0.5)	Toluene	48	0[k]
16	$K_2S_2O_8$ (0.5)	DCE	12	18[l]
17	$(NH_4)_2S_2O_8$ (0.5)	DCE	24	43
18	TBHP (1.0)	DCE	12	0
19	*m*-CPBA (1.0)	DCE	24	0[m]

[a]Unless otherwise indicated, all reactions were carried out with **1a** (1.0 mmol) and solvent 6.0 mL at reflux. [b]Isolated yield. [c]48% **1a** was recovered. [d]30% **1a** was recovered. [e]75 °C was used and 71% **1a** was recovered. [f]100 °C was used. [g]120 °C was used and 85% **1a** was recovered. [h]95% **1a** was recovered. [i]85% **1a** was recovered. [j]120 °C was used and 70% **1a** was recovered. [k]80% **1a** was recovered. [l]75% **1a** was recovered. [m]90% **1a** was recovered.

tested the generality of this dimerization of *N*-aryl acetoacetamides under the optimal condition (Table 2). Notably, a variety of substituted *N*-aryl acetoacetamides **1a**–**1m** could easily be

Table 2. Self-condensation of *N*-Aryl Acetoacetamides 1[a]



Entry	Product		Time (h)	Yield (%)[b]
1		**2a**	10	65
2		**2b**	10	65
3		**2c**	10	62
4		**2d**	7.5	66
5		**2e**	10	63
6		**2f**	12	52
7		**2g**	11	52
8		**2h**	12	53
9		**2i**	11	62
10		**2j**	12	60
11		**2k**	7	62
12		**2l**	10	64
13		**2m**	11	58

[a]All reactions were carried out with **1** (1.0 mmol), $Na_2S_2O_8$ (0.5 equiv), in $Cl(CH_2)_2Cl$ (6.0 mL) at reflux. [b]Isolated yield.

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converted into the corresponding 4-pyridones **2a**–**2m** in moderate yields (52–66%) in 7–12 h. Various electron-withdrawing groups (EWG) (Cl, CO_2Et; entries 1–4) and electron-donating groups (EDG) (Me, OMe, OEt; entries 6–12) on the aryl ring were tolerated in current transformation, including without substituents on benzene ring (entry 5) and with both EWG and EDG substituents on benzene ring (Table 2, entry 13). Furthermore, the positions of the substituents on the aryl group (para-, meta- and ortho- positions) did not show any effects on the reaction.

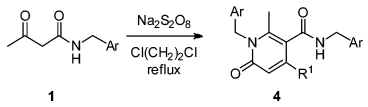
The scope of the new method was further examined in the context of *N*-nonaromatic acetoacetamides (Table 3). It is noteworthy that *N*-benzyl substituted acetoacetamides **1n**–**1p**, under the same conditions, gave eccentric series of 2-pyridones **4n**–**4p** instead of 4-pyridones in moderate yields of 57–60% (Table 3). Similarly, the EDG (Table 3, entry 3) and EWG (Table 3, entry 2) on benzyl ring did not show effect on the reaction. The structures of these compounds **4n**–**4p** were deduced from a comparison of their NMR spectra with those of 4-pyridones. The chemical shifts of *N*-H protons of the carboxanilide groups of 2-pyridones **4** were almost in normal positions (8.0–10.0 ppm), which were totally different from the 4-pyridones **2** series whose chemical shifts of *N*-H protons of the carboxanilide group absorbs unusually far downfield (>12.0 ppm) due to the intramolecular hydrogen bonding interaction between the *N*–H moiety and the carbonyl oxygen at 4-position of the pyridone ring.[4] But other *N*-non aromatic substituted acetoacetamides, such as *N*-(*tert*-butyl)-3-oxobutanamide **1q** and primary amine 3-oxobutanamide **1r**, failed to convert to either the corresponding **4q** and **4r** or **2q** and **2r** for the subsequent substrate expansion.

Any intermediate, as direct evidence for the mechanism of the self-condensation, was not isolated in the control experiments of quenching the reaction in 2.0 h (Table 1, entry 3) or performing the reaction at a slightly lower temperature (Table 1, entry 4). We deduced that it may be a radical pathway for the sole $Na_2S_2O_8$ to promote the direct self-condensation of acetoacetamides. As it is well-known that sodium persulfate is a strong oxidant capable of both electron transfer and free radical oxidation processes. Under thermally enhanced conditions (i.e., 30–100 °C) or UV irradiation conditions, there is considerable evidence[19] indicating that peroxodisulfate $S_2O_8^{2-}$ can be converted into sulfate free radical $SO_4^{\cdot-}$ with one unpaired electron, which is a powerful oxidant. The production of the highly reactive $SO_4^{\cdot-}$ by the thermal decomposition (as known "thermal activation") of the persulfate anion in an aqueous phase is: $S_2O_8^{2-}$ + heat → $2SO_4^{\cdot-}$. To gain insight into the details of the novel $Na_2S_2O_8$-catalyzed direct dimerization, radical scavenger, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), was employed in the reaction. Authentically, the reactions were shut off, which could indicate that this transformation involved radical process.

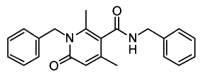
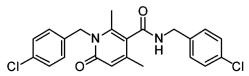
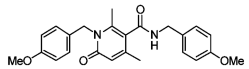
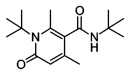
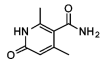
So far, the mechanism for the present self-condensation of acetoacetamides catalyzed by $Na_2S_2O_8$ has not been completely clear. The plausible mechanism was deduced according to the above control experiments together with some previous literature results (Scheme 2). Acetoacetamides **1** initially react with $Na_2S_2O_8$ to generate nitrogen radicals **A** via a single electron transfer (SET) process.[20] Next, **A** attacks the enol form of acetoacetamides **1** to form intermediate **B**.[20b] Then, **B** affords *β*-enaminone species **C** via back electron-transfer (BET) process and intramolecular dehydration reaction,[21] which is the reason why 0.5 equiv of $Na_2S_2O_8$ is needed in the dimerization. Subsequently, a 1,3-acyl migration from *N* to *C* of intermediate **C**,[22] when R^2 is aryl, gives imine **D** and its equilibrium **D′**, which undergoes intramolecular nucleophilic cyclization to give the final product 4-pyridones **2**.[4,11c,23] On the other hand, for intermediate **C**, when R^2 is alkyl, a direct ring-closing reaction takes place to produce 2-pyridone derivatives **4**.[4] *N*-Aliphatic-substituted intermediate **C** cannot form a stable aryl imine steady-state **D**, compared with *N*-aryl substituents, which should account for the emergence of terminal 2-pyridone derivatives **4**.

In summary, we have developed a convenient one-pot process for the synthesis of a variety of biologically potent polysubstituted 4-pyridones via self-condensation of industrialized *N*-aryl acetoacetamides in the presence of sole $Na_2S_2O_8$, during which, a novel *N* to *C* 1,3-acyl migration should be involved. All products were constructed efficiently in a single step from the readily available acyclic precursors. As a representative of a series of 4-pyridones, **2a** was characterized by the XRD analysis for the first time. Also, the simple

Table 3. Self-condensation of *N*-Nonaromatic Acetoacetamides 1[a]

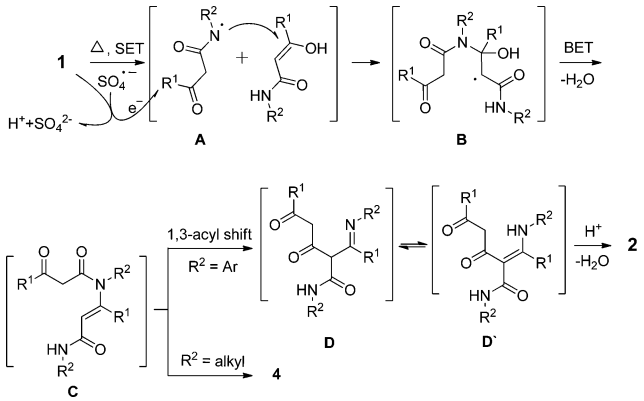


1 4

Entry	Product		Time (h)	Yield (%)[b]
1		**4n**	12	60
2		**4o**	48	57
3		**4p**	48	59
4		**4q**	24	0[c]
5		**4r**	26	0[c]

[a]All reactions were carried out with **1** (1.0 mmol), $Na_2S_2O_8$ (0.5 equiv), in $Cl(CH_2)_2Cl$ (6.0 mL) at reflux. [b]Isolated yield. [c]Very complex mixture.

Scheme 2. Plausible Mechanism



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operation with satisfactory yields, metal catalyst-free, a relative broad range of substrates, and readily availability of catalyst ($Na_2S_2O_8$) and substrates make this a valuable addition to existing methods.

EXPERIMENTAL SECTION

General Information. All reagents were obtained from commercial sources and used without further purification, unless otherwise noted. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash column chromatography was carried out by using 200−300 mesh silica gel at increased pressure. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in solutions of $CDCl_3$ using tetramethylsilane as the internal standard, δ values are given in ppm and coupling constants (J) in Hz. The high-resolution mass spectra were measured on a MicroTOF mass spectrometer. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. IR spectra were recorded on a FT-IR spectrophotometer as KBr pellets.

Typical Experimental Procedure for the Self-condensation of Acetoacetamides. A mixture of *N*-(2-chlorophenyl)-3-oxobutanamide **1a** (211 mg, 1.0 mmol) and $Na_2S_2O_8$ (119 mg, 0.5 mmol) in DCE (6.0 mL) in a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) was well stirred for 10 h at reflux. After cooling off, the mixture was washed with saturated sodium chloride solution (6.0 mL × 3). The organic solvent DCE was then removed under reduced pressure and the residue was purified through a short flash silica gel column chromatography to give compound **2a** (125 mg, 65%) (Eluent: diethyl ether/petroleum ether = 2/1).

*N,1-Bis(2-chlorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2a**).* Colorless crystal (125 mg, 65%); mp: 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.10 (s, 1H), 8.49 (dd, J = 1.2, 6.8 Hz, 1H), 7.62 (dd, J = 2.0, 6.0 Hz, 1H), 7.55−7.50 (m, 2H), 7.40 (dd, J = 1.2, 6.8 Hz, 1H), 7.35 (dd, J = 2.0, 5.6 Hz, 1H), 7.27−7.23 (m, 1H), 7.03−7.00 (m, 1H), 6.56 (s, 1H), 2.51 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 164.3, 156.5, 148.1, 137.1, 136.3, 132.6, 131.6, 131.2, 129.5, 129.2, 128.8, 127.0, 124.2, 124.0, 122.6, 119.2, 118.6, 20.9, 19.7. HRMS (ESI) m/z calcd for $C_{20}H_{16}Cl_2N_2O_2$: 386.0589, found 386.0584. IR (KBr, neat): ν 3658, 3072, 2389, 1674, 1526, 1440, 1193, 1035, 888, 758 cm^{-1}.

*N,1-Bis(4-chlorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2b**).*[4] Colorless crystal (125 mg, 65%); mp: 269−271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.82 (s, 1H), 7.64 (d, J 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.46, (s, 1H), 2.49 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 164.0, 156.2, 148.3, 137.8, 137.6, 136.3, 130.7, 129.1, 128.7, 128.3, 121.7, 119.0, 118.6, 21.7, 20.7. HRMS (ESI) m/z calcd for $C_{20}H_{16}Cl_2N_2O_2$: 386.0589, found 386.0584. IR (KBr, neat): ν 3663, 3069, 2390, 1676, 1528, 1443, 1195, 1037, 891, 756 cm^{-1}.

*Ethyl 4-(1-(4-(Ethoxycarbonyl)phenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamido)benzoate (**2c**).* Colorless crystal (143 mg, 62%); mp: 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 8.28 (d, J= 8.4 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.53 (s, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.52 (s, 3H), 1.92 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 166.4, 164.9, 164.3, 156.4, 148.1, 143.2, 143.0, 132.4, 131.8, 130.6, 128.0, 125.2, 119.7, 119.2, 118.5, 61.8, 60.7, 21. 8, 20.9, 14.4, 14.3. HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2O_6$: 462.1791, found 462.1786. IR (KBr, neat): ν 3662, 3058, 2401, 1678, 1518, 1442, 1198, 1040, 879 cm^{-1}.

*N,1-Bis(3-chlorophenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2d**).* Colorless crystal (127 mg, 66%); mp: 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.92 (s, 1H), 7.91 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.2 (t, J = 8.0 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 2.53 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 164.0, 156.3, 148.1, 140.3, 140.1, 136.2, 134.3, 131.4, 130.5, 129.6, 128.1, 126.1, 123.5, 120.5, 119.0, 118.5, 118.4, 21.7, 20.8. HRMS (ESI) m/z calcd for $C_{20}H_{16}Cl_2N_2O_2$: 386.0589, found 386.0584. IR (KBr, neat): ν 3679, 3056, 2340, 1676, 1591, 1457, 1250, 1106, 876 cm^{-1}.

*2,6-Dimethyl-4-oxo-N,1-diphenyl-1,4-dihydropyridine-3-carboxamide (**2e**).*[4] Colorless crystal (100 mg, 63%); mp: 209−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.53 (m, 3H), 7.31 (t, J = 8.0 Hz, 2H), 7.21 (dd, J = 2.0, 5.6 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 6.48 (s, 1H), 2.50 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 164.2, 156.2, 148.5, 139.5, 139.0, 130.4, 129.9, 128.7, 127.7, 123.5, 120.6, 118.8, 21.7, 20.7. HRMS (ESI) m/z calcd for $C_{20}H_{18}N_2O_2$: 318.1368, found 318.1363. IR (KBr, neat): ν 3603, 3054, 2842, 1680, 1485, 1277, 1191, 1003, 895 cm^{-1}.

*N,1-Bis(4-methoxyphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2f**).* Colorless crystal (198 mg, 52%); mp: 211−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.49 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.53 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 163.9, 160.2, 156.6, 155.8, 148.9, 132.3, 132.2, 128.7, 122.2, 118.8, 118.7, 115. 4, 113.9, 55.6, 55.4, 21.7, 20.7. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_4$: 378.1580, found 378.1574. IR (KBr, neat): ν 3621, 2931, 1726, 1600, 1439, 1341, 1181, 1030, 836 cm^{-1}.

*N,1-Bis(4-ethoxyphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2g**).* Colorless crystal (106 mg 52%); mp: 223−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H,), 7.61 (d, J = 9.2 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.48 (s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 4.01 (q, J = 6.8 Hz, 2H), 2.52 (s, 3H), 1.93 (s, 3H), 1.46 (t, J= 7.2 Hz, 3H), 1.39 (t, J= 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 163.9, 159.6, 156.6, 155.2, 148.9, 132.1, 131.9, 128.6, 122.1, 118.8, 118.6, 115.7, 114.5, 63.9, 63.5, 21.7, 20.7, 14.8, 14.6. HRMS (ESI) m/z calcd for $C_{24}H_{26}N_2O_4$: 406.1893, found 406.1887. IR (KBr, neat): ν 3646, 3027, 2879, 1668, 1473, 1243, 1117, 1042, 860 cm^{-1}.

*2,6-Dimethyl-4-oxo-N,1-di-p-tolyl-1,4-dihydropyridine-3-carboxamide (**2h**).* Colorless crystal (92 mg, 53%); mp: 241−243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 6.47 (s, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.31 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.81, 164.0, 156.3, 148.5, 140.1, 136.9, 136.4, 132.9, 130.8, 129.1, 127.3, 120.5, 118.78, 118.6, 21.6, 21.1, 20.8, 20.6. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_2$: 346.1681, found 346.1676. IR (KBr, neat): ν 3640, 3017, 2919, 1672, 1529, 1341, 1280, 1190, 1073, 853 cm^{-1}.

*N,1-Bis(2,4-dimethylphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2i**).* Colorless crystal (116 mg, 62%); mp: 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 12.0 Hz, 2H), 7.00 (t, J = 7.2 Hz, 3H), 6.55 (s, 1H), 2.51 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H), 2.00 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 164.1, 156.3, 148.2, 140. 3, 136.0, 134.8, 134.4, 133.1, 132.5, 130.8, 128.8, 128.6, 127.2, 126.6, 122.2, 118.9, 118.8, 21.1, 21.0, 20.7, 19.8 18.4, 16.8. HRMS (ESI) m/z calcd for $C_{24}H_{26}N_2O_2$: 374.1994, found 374.1989. IR (KBr, neat): ν 3641, 2929, 1673, 1597, 1451, 1341, 1195, 1038, 861 cm^{-1}.

*N,1-Bis(2-methoxyphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2j**).*[4] Colorless crystal (113 mg, 60%); mp: 239−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H), 8.51 (d, J = 7.6 Hz, 1H), 7.49 (m, 1H), 7.13−7.01 (m, 4H), 6.96−6.90 (m, 2H), 6.52 (s, 1H), 3.96 (s, 3H), 3.81 (s, 3H), 2.48 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 164.3, 156.5, 154.3, 149.3, 148.7, 131.6, 128.9, 128.8, 128.0, 123.2, 121.6, 120.8, 120.6, 119.3, 118.7, 112.4, 110.2, 55.9, 55.8, 20.9, 19.6. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_4$: 378.1580, found 378.1574. IR (KBr, neat): ν 3624, 2963, 1667, 1598, 1460, 1343, 1278, 1120, 1019, 864 cm^{-1}.

*2,6-Dimethyl-4-oxo-N,1-di-o-tolyl-1,4-dihydropyridine-3-carboxamide (**2k**).*[4] Colorless crystal (107 mg, 62%); mp: 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.7 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.45−7.39 (m, 3H), 7.20 (t, J = 6.8 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.57 (s, 1H), 2.52 (s, 3H), 2.46 (s, 3H), 2.05 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 164.1, 156.2, 148.0, 138.5, 137.4, 134.8, 131.9, 130.1, 130.1, 128.7, 128.00,

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127.5, 126.1, 123.7, 122.1, 119.1, 118.8, 21.1, 19.8, 18.5, 16.9. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_2$: 346.1681, found 346.1676. IR (KBr, neat): ν 3646, 3052, 2348, 1675, 1587, 1458, 1378, 1271, 1125, 1046, 872 cm^{-1}.

*2,6-Dimethyl-4-oxo-N,1-di-m-tolyl-1,4-dihydropyridine-3-carboxamide (**2l**).* Colorless crystal (111 mg, 64%); mp: 158−160 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H), 7.58 (s, 1H), 7.50−7.43 (m, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.50 (s, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 164.1, 156.3, 148.4, 140.8, 139.4, 138.8, 138.4, 130.6, 130.1, 128.1, 128.0, 124.1, 124.3, 121.2, 118.7, 118.6, 117.7, 21.7, 21.5, 21.3, 20.8. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_2$: 346.1681, found 346.1676. IR (KBr, neat): ν 3639, 2862, 1672, 1592, 1459, 1339, 1202, 1168, 858 cm^{-1}.

*N,1-Bis(5-chloro-2-methoxyphenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**2m**).*[4] Colorless crystal (129 mg, 58%); mp: 215−217 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.91 (s, 1H), 8.60 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 2.4, 6.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 9.2 Hz, 1H), 6.98 (dd, J = 2.4, 6.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.52 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 2.51 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 164.2, 156.6, 153.2, 148.4, 147.8, 131.6, 129.8, 128.8, 128.6, 126.3, 125.5, 122.6, 120.5, 118.9, 113.4, 110.8, 56.2, 56.2, 20.9, 19.7. HRMS (ESI) m/z calcd for $C_{22}H_{20}Cl_2N_2O_4$: 446.0800, found 446.0795. IR (KBr, neat): ν 3507, 2940, 1733, 1497, 1421, 1179, 1131, 1023, 882 cm^{-1}.

*N,1-Dibenzyl-2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4n**).*[4] Colorless crystal (104 mg, 60%); mp: 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.53 (d, J = 8.0 Hz, 5H), 7.33 (t, J = 8.0 Hz, 5H), 7.16 (t, J = 7.2 Hz, 2H), 5.48 (s, 1H), 5.35 (s, 1H), 2.43 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 162.6, 148.2, 143.2, 137.9, 135.5, 128.7, 128.6, 127.98, 127.5, 126.3, 119.3, 116.6, 46.9, 43.8, 19.5, 17.6. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2O_2$: 346.1681, found 346.1676. IR (KBr, neat): ν 3425, 3023, 1677, 1584, 1471, 1387, 1209, 1121, 879 cm^{-1}.

*N,1-Bis(4-chlorobenzyl)-2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4o**).*[4] Colorless crystal (118 mg, 57%); mp: 91−94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (br, 1H), 7.30−7.24 (m, 6H), 6.96 (d, J = 8.4 Hz, 2H), 6.19 (s, 1H), 5.05 (s, 2H), 4.51 (d, J = 6.0 Hz, 2H), 2.18 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 162.5, 148.4, 143.0, 136.4, 133.8, 133.5, 133.5, 129.5, 129.0, 128.8, 127.8, 119.3, 116.7, 46.4, 43.2, 19.6, 17.7. HRMS (ESI) m/z calcd for $C_{22}H_{20}Cl_2N_2O_2$: 414.0902, found 414.0897. IR (KBr, neat): ν 3363, 2974, 1657, 1563, 1403, 1376, 1236, 1185, 1074, 849 cm^{-1}.

*N,1-Bis(4-methoxybenzyl)-2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (**4p**).*[4] Colorless crystal (120 mg, 59%); mp: 151−153 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 7.09 (br, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.83−6.77 (m, 4H), 6.20 (s, 1H), 5.04 (s, 2H), 4.47 (d, J = 5.6 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.7, 158.8, 148.0, 143.2, 130.0, 129.4, 128.7, 127.9, 127.6, 119.2, 116.8, 114.1, 113.9, 55.2, 55.2, 46.5, 43.3, 19.5, 17.7. HRMS (ESI) m/z calcd for $C_{24}H_{26}N_2O_4$: 406.1893, found 406.1887. IR (KBr, neat): ν 3333, 2973, 1925, 1678, 1584, 1439, 1298, 1106, 873 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra, result of radical trapping experiments, and X-ray data and ORTEP drawing for compounds **2a** (CIF). 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.

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