HETEROCYCLES, Vol. 89, No. 1, 2014, pp. 171 - 182. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 17th Spetember, 2013, Accepted, 14th November, 2013, Published online, 19th November, 2013
DOI: 10.3987/COM-13-12844

MICROWAVE-IRRADIATED SYNTHESIS OF 1,2-DIHYDROPYRIDINES FROM *N*-FUNCTIONALIZED ENAMINONES AND ENALS THROUGH DOMINO CONDENSATION AND 6Π-AZAELECTROCYCLIZATION

Elkhabiry Shaban,[1] Md. Imran Hossain,[1] Ming-Yu Wu,[1] Yoshihiko Takemasa,[1] Sachie Nagae,[1] Wei Peng,[1] Hiroyuki Kawafuchi,[2] and Tsutomu Inokuchi[1]*

Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan, [2]Toyama National College of Technology, Hongo-machi, Toyama, 939-8630, Japan
E-mail*: inokuchi@cc.okayama-ac.jp

Abstract – *N*-Amino-substituted 1,2-dihydropyridine motifs are constructed using cyclohexane-1,3-diones via the Knoevenagel condensation with enals followed by 6π-electrocyclization using ethylenediammonium diacetate as a catalyst under MW irradiation. A survey of substituents on the N atom of the enaminones indicated that the phenylamino and benzoylamino groups are favorable for the reaction, while phenyl, benzyl, and no-substituent are not. The substituent at C2 of enals is crucial for smooth formation of the corresponding adducts and slightly higher yields are obtained with enals bearing an electron-withdrawing aromatic at C3.

Recently, 1,4-dihydropyridine-based systems have attracted considerable attention due to their wide spectra of biological activities.[1] For example, cardiovascular agents such as nifedipine (**I**), used for the treatment of hypertension, contain the dihydropyridyl motif (Figure 1).[2] NADH coenzymes are comprised of 1,4-dihydropyridine units, which have been explored for their calcium channel activity.[3] Accordingly, numerous methods have been reported for the synthesis and biological evaluation of 1,4-dihydropyridine derivatives, i.e. **IIa**, however, most of them have relied on the three-component coupling of 1,3-dicarbonyls (2 equiv.), aldehydes (1 equiv.), and amines (1 equiv.) by the Hantzsch reaction or its

modification.[4] Furthermore, the *N*-aminated derivatives **IIb** were recently prepared using enaminones derived from arylhydrazines for one component of the Hantzsch reaction,[5a,c,f] and their biological activities were evaluated.[5c]

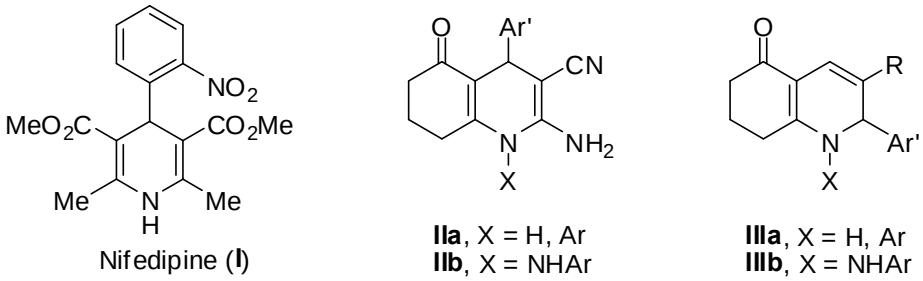


Figure 1. Structures of 1,4- and 1,2-dihydropyridines **I**–**III**

In contrast to the intensive synthetic and biological studies of 1,4-dihydropyridines,[5] little attention has been paid to the synthesis and biological evaluation of their double bond regioisomer, i.e., the 1,2-dihydropyridines **IIIa**.[6]

Until now, some synthetic access to the 1,2-dihydropyridines has been explored. The 6π-electron electrocyclic ring closures of the 1-azatriene systems are considered one of the most promising and useful means to form the 1,2-dihydropyridines. Key step to this strategy is the preparation of the functionalized 1-azatriene units. Currently, these units are assembled in situ and directly used to construct the nitrogen heterocycles. For example, the Knoevenagel condensation of iminium ions with enaminones has proven to be a successful strategy for the construction of the 1,2-dihydropyridines.[6] A more direct access to the 1-azatrienes has relied on the reaction of primary amines and 2,4-dienals.[7,8] Although the use of such cyclic enaminones in a formal [3+3] cycloaddition had already been described by Hsung et al.,[9] the reaction conditions were more severe (150 °C in a sealed tube) and the moisture sensitive α,β-unsaturated imminium salts have to be handled. Besides these procedures, Brønsted acid catalyzed procedures were developed for the formal [3+3] annulation to the cyclohexane-1,3-diones.[10] Therefore, an improved procedure to the 1,2-dihydropyridine structures with the increased choice of substituents and structural diversity by examination of the kind of amine component is still in needed.

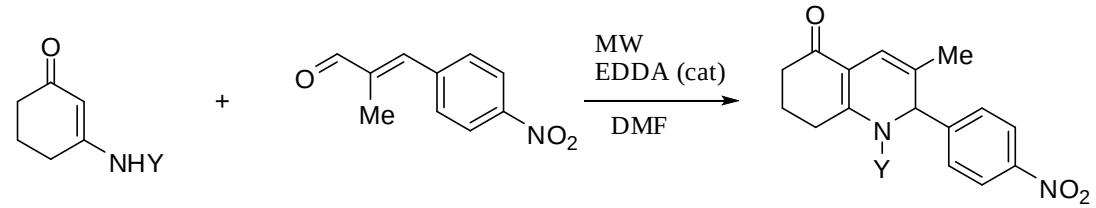
In this paper, we report the MW-assisted tandem Knoevenagel condensation of enaminone and enals **2** followed by 6π-azaelectrocyclization, which is affected by kind of substituent on the N atom of the enamines **1** and the substituent on the iminium intermediate from the enals **2**.

The Knoevenagel condensation of enaminones was performed under the iminium conditions using ethylenediammonium diacetate (EDDA) as a catalyst.[11] Microwave irradiation was used to enhance the

sequential condensation and 6π-electron electrocyclizaion in a short period. The effect of the substituent Y on the enaminones **1** was first examined using the eaminones **1a**–**1e**, prepared by the reaction of cyclohexane-1,3-dione **8a** and the respective phenylhydrazine (**9a**), benzohydrazide (**9b**), aniline, bnezylamine, and ammonia.

Results of the condensation and cyclization of these enaminones **1a**–**1e** with the enal **2g** are shown in Table 1. The reaction of the enaminone **1a** with **2g** smoothly proceeds to produce the corresponding **3g** in moderate yield (entry 1). Similarly, the enaminone **1b** reacts with **2g** under the same conditions in a slightly lesser yield (entry 2). On the other hand, the enaminones **1c** and **1d** lack the N-N group in the nucleophilic unit result in a decreased reactivity, and produce none of the desired products **5g** and **6g** (entries 3 and 4). The enamine **1e** formed the adduct **7g** in a small quantity by the reaction with **2g**, which changed to the starting enaminone **1e** and the enal **2g** during chromatographic purification.

Table1. MW-Assisted tandem condensation and 6π-azaelectrocyclization by reaction of **1a**–**1e** with **2g** using ethylenediammonium diacetate (EDDA)[a)]



1a, Y = NHPh
1b, Y = NHCOPh
1c, Y = Ph
1d, Y = CH_2Ph
1e, Y = H

2g

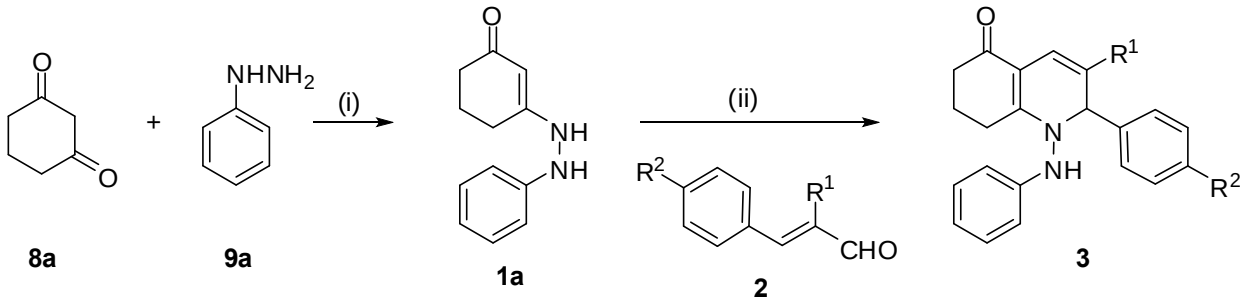
3g, Y = NHPh
4g, Y = NHCOPh
5g, Y = Ph
6g, Y = CH_2Ph
7g, Y = H

Entry	Enaminone	Product	Yield[b)] (%)
1	**1a**	**3g**	65
2	**1b**	**4g**	58
3	**1c**	**5g**	--
4	**1d**	**6g**	--
5	**1e**	**7g**	--

[a)]Carried out using the enaminones **1a**–**g** (1 mmol) and **2g** (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. [b)]Yield based on isolated products.

We then applied this domino condensation-cyclization sequence to the reaction of **1a** and **1b** with various α-substituted enals **2**, and the results are listed in Tables 2 and 3, respectively.

Table 2. Synthesis of 1-(phenylamino)-1,2-dihydropyridines **3** from enaminones **1a** and enals **2**[a)]

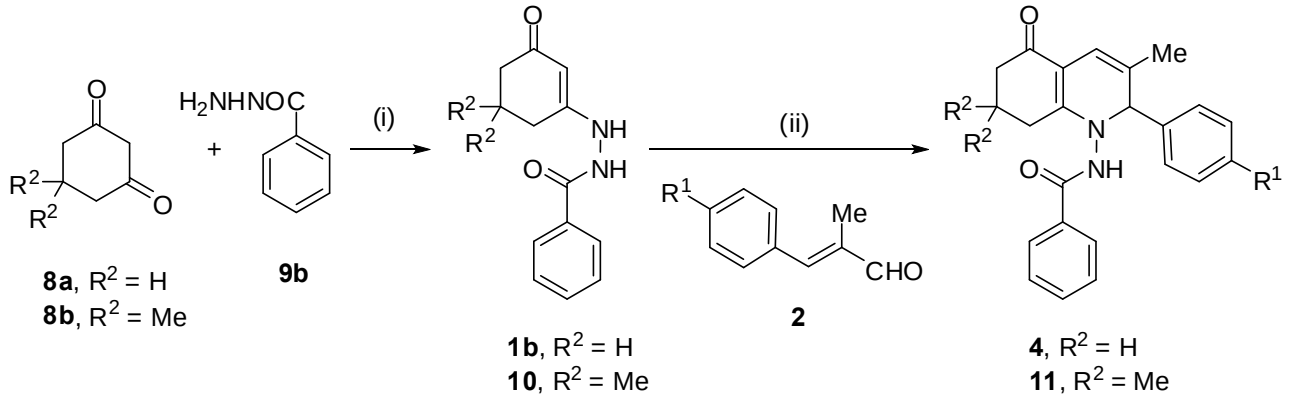


Reagents: (i) H_2O-AcOH (cat), reflux, 2 h. (ii) DMF, ethylenediammonium diacetate (EDDA, 5 mol%), MW irradiation.

Entry	Enaminone	**2**			Product	Yield, %[b)]
			R^1	R^2		
1	**1a**	**a**	Me	H	**3a**	50
2	**1a**	**b**	Me	MeO	**3b**	35
3	**1a**	**c**	Me	Cl	**3c**	55
4	**1a**	**g**	Me	NO_2	**3g**	65
5	**1a**	**h**	H	H	**3h**	22

[a)]Carried out using the enaminones **1a** (1 mmol) and **2** (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. [b)]Yield based on isolated products.

Table 3. Synthesis of 1-(benzoylamino)-1,2-dihydropyridines **4**, **11** from enaminones **1b**, **10** and enals **2**[a)]



Reagents: (i) H_2O-AcOH (cat), reflux, 2 h. (ii) DMF, EDDA (5 mol%), MW irradiation.

Entry	Enaminone	**2**		R^2	Product	Yield, %[b)]
			R^1			
1	**1b**	**a**	H	H	**4a**	22
2	**1b**	**b**	MeO	H	**4b**	33

3	**1b**	**c**	Cl	H	**4c**	45
4	**1b**	**d**	F	H	**4d**	54
5	**1b**	**e**	MeO_2C	H	**4e**	45
6	**1b**	**f**	CF_3	H	**4f**	56
7	**1b**	**g**	NO_2	H	**4g**	58
8	**10**	**a**	H	Me	**11a**	45
9	**10**	**c**	Cl	Me	**11b**	60
10	**10**	**g**	NO_2	Me	**11c**	70
11	**10**	**f**	CF_3	Me	**11d**	65
12	**10**	**d**	F	Me	**11e**	62
13	**10**	**e**	MeO_2C	Me	**11f**	57

[a)]Carried out using the enaminones **1b**, **10** (1 mmol) and **2** (1 mmol) in DMF (3 mL) with EDDA (5 mol%) at 115 °C under MW irradiation for 5 min. [b)]Yield based on isolated products.

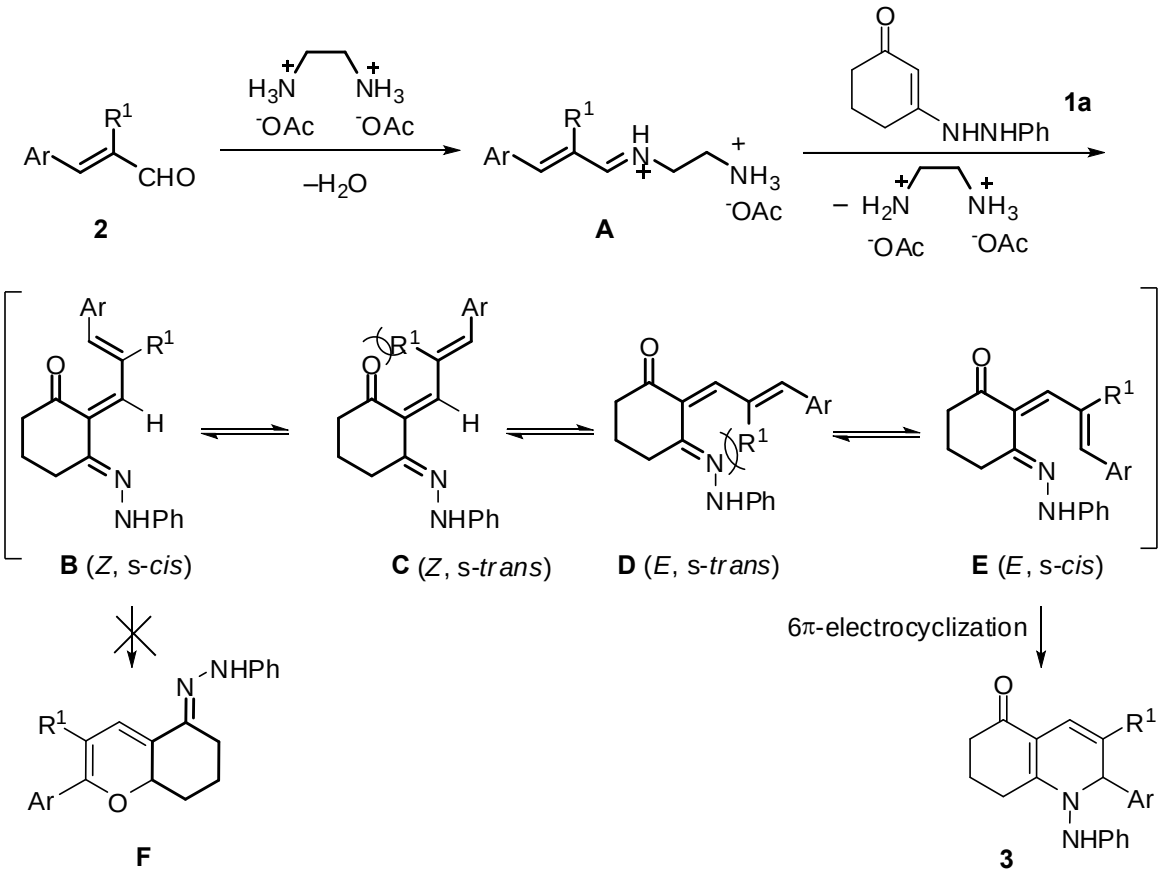
The effect of the kinds of aromatic rings at the β-carbon of the α,β-unsaturated aldehydes **2** was observed. Thus, slightly higher yields are obtained using the aromatic R^2 bearing electron-withdrawing groups (entries 3, 4 for **1a** in Table 2, and entries 3−7, 9−13 for **1b** in Table 3), compared to that of the donating group (entry 2 for **1a** in Table 2, and entry 2 for **1b** in Table 3).

We observed that the yield in Table 2 is better than that in Table 3. Thus, the electron-donating group (NH–NHPh) in the enaminones is more favorable for the formation of the corresponding 1,2-dihydropyridines than the enaminones with the NH–NHCOPh group bearing an electron-withdrawing group.

In spite of the smooth formation of the 2,3-disubstituted 1,2-dihyropyridine ring onto the cyclic 1,3-diketone monoimines **1a** and **1b** by the condensation-6π-electrocyclization sequence, the limitation of this method was encountered in the reaction of **1a** with cinnamaldehyde (**2h**) which lacks an α-substituent. The reaction of **1a** and cinnamaldehyde (**2h**) under the iminium conditions described above resulted in a decreased yield of the corresponding annulated adduct **3h** (about 22% yield) (Table 2, entry 5).

The reaction mechanism for the formation of **3** can be rationalized as described in Scheme 1 by taking the steric effect of R^1 substituent at the C2 of the enals **2** in account. The Knoevenagel condensation through the iminium **A** and enaminone **1a** would lead to the 1-azatrienes **B**–**E**, the stereochemical and conformational isomers at equilibrium. The equilibration between **B**–**E** would be catalyzed by the employed EDDA. Among them, **E** (*E*, s-*cis*), a sterically favorable configuration for the ensuing cyclization would lead to the desired **3** via spontaneous 6π-electrocyclization. On the other hand, in all our attempts, the 2H-pyran structure **F**, which can be available by the 6π-electrocyclization of the

favorable configuration **B** (*Z*, s-*cis*), was not detected. This preferable cyclization at the 1-azatriene moiety rather than the 1-oxatriene in the same molecule is good agreement with the results reported by Hsung.[9]



Scheme 1. Rationale for favorable formation of **3** by the condensation of **1** and **2** catalyzed by EDDA followed by 6π-electrocyclization

In conclusion, we described the convergent access to the poly-substituted 1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-ones **3** and *N*-(5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamides **4** and **11** by the reaction of the corresponding enaminones **1a** and **1b** with 2-enals **2**. This protocol involves the tandem Knoevenagel condensation, which was readily catalyzed using ethylenediammonium diacetate, and the subsequent 6π-electrocyclization. The reaction feasibility was dependent on the kind of *N*-substituents and the presence of a C2 substituent on the enals **2**. The enaminones **1a** from phenylhydrazine showed a slightly higher reactivity than the benzoyl analogues **1b** obtained from benzohydrazide. A further study of the biological activities of these products is currently underway.

EXPERIMENTAL

The ^{1}H NMR, ^{13}C NMR spectra were measured on the Varian INOVA-600 or Varian INOVA-400 spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard.

MW reaction was performed with μReactor EX, Shikoku Instrumentation Co. Ltd, operated at 2.46 GHz.

2-(4-Chlorophenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one, a general procedure for 3c. In a side-armed tube flask (10 mm diameter) were introduced *N*'-(3-oxocyclohex-1-enyl)benzohydrazide (**1a**, 202 mg, 1 mmol) and 3-(4-chlorophenyl)-2-methylacryladehyde (**2c**, 180 mg, 1 mmol) and EDDA (9 mg, 5% mole) in DMF (2 mL) and the tube was placed into the microwave cavity. The mixture was irradiated under constant microwave for about 5 min at controlled temperature of 115 °C. Heating was continued for 3 min under TLC monitoring. The mixture was diluted with cold water and extracted with EtOAc (20 mL, 3 times). Combined organic layer was dried ($MgSO_4$), and concentrated in vacuum. The crude products were purified by flash column chromatography on SiO_2 using a mixture of hexane and AcOEt with a gradient from 4:1 to 1: 4 to obtain the pure product.

3-Methyl-2-phenyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one (3a): Yield 165 mg (50%), brown solids; mp 203–205 °C; IR (KBr) ν_{max} = 3196, 3176, 3020, 2997, 2947,1593, 1545, 1516, 1496, 1433, 1400, 1377, 1269, 1246, 1188, 1143, 1026, 875, 752, 696 cm^{-1}; ^1H NMR (600MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (m, 2H), 6.98 (t, *J* = 7.20 Hz, 1H), 6.74 (d, *J* = 7.80 Hz, 2H), 6.59 (s, 1H), 5.49 (s, 1H), 4.99 (s, 1H), 2.63 (t, *J* = 6.6 Hz, 2H), 2.34 (t, *J* = 6.6 Hz, 2H), 1.92–1.96 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (151MHz, $CDCl_3$) δ 193.6, 161,4, 145.3, 139.5, 130.8 (2C), 130.1 (2C), 130.0, 128.9 (2C), 125.4, 122.7, 116.3, 114.4 (2C), 106.7, 68.2, 36.8, 25.9, 22.2, 21.0. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48%. Found: C, 79.29; H, 6.51; N, 8.44%.

2-(4-Methoxyphenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one (3b): Yield 125 mg (35%), brown solids; mp 170–173 °C; IR (KBr) ν_{max} = 3254, 2933, 1670, 1600, 1546, 1508, 1452, 1400, 1303,1249,1184, 1138, 1030, 835, 752, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.24–7.15 (m, 3H), 7.01 (s, 1H), 7.01–6.88 (m, 1H), 6.76 (d, *J* = 7.6 Hz, 2H), 6.60 (s, 1H), 5.46 (s, 1H), 4.96 (s, 1H), 3.81 (s, 3H), 2.65 (d, *J* = 4.0 Hz, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 1.93 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.8, 160.7, 160.4, 144.7, 130.8, 130.1 (2C), 129.8, 129.4 (2C), 124.9, 121.9, 115.5, 114.7 (2C),113.7 (2C), 66.7, 55.6, 36.0, 31.2, 25.2, 21.5. Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77%. Found: C, 76.84; H, 6.19; N, 7.79%.

2-(4-Chlorophenyl)-3-methyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one (3c): Yield 202 mg (55%), brown solids; mp 200–204 °C; IR (KBr) ν_{max} = 3257, 2947, 1599, 1548, 1494, 1427, 1398, 1259, 1186, 1138, 1087, 1014, 879, 829, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39–7.27 (m, 4H), 7.25-7.15 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.60 (s, 1H), 5.49 (s, 1H), 5.00 (s, 1H), 2.63 (t, *J* = 6.2 Hz, 2H), 2.36 (t, *J* = 6.5 Hz, 2H), 2.09–1.89 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.9, 160.5, 144.4, 137.4, 135.2, 130.1 (2C), 129.6 (2C), 129.5 (2C), 124.3, 122.0, 115.9, 113.5 (2C), 106.0, 66.8, 36.0, 25.2, 21.4, 20.2. Anal. Calcd for $C_{22}H_{21}ClN_2O$: C, 72.42; H, 5.80; N, 7.68%. Found: C, 71.82; H, 5.66; N, 7.73%.

3-Methyl-2-(4-nitrophenyl)-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one (3g): Yield 245 mg (65%), brown solids; mp 106–108 °C; IR (KBr) ν_{max} = 3240, 2945, 1670, 1599, 1548, 1519, 1398, 1346, 1271, 1247, 1188, 1139 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.66 (s, 1H), 5.46 (s, 1H), 5.17 (s, 1H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.41 (t, *J* = 6.5 Hz, 2H), 1.99-1.92 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (151 MHz $CDCl_3$) δ 194.5, 162.0, 150.0, 147.5, 145.6, 131.8 (2C), 131.7, 130.5 (2C), 126.1 (2C), 123.7, 118.1, 114.9 (2C), 107.9, 68.5, 37.5, 26.7, 22.9, 21.7. Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19%. Found: C, 69.87; H, 5.19; N, 10.82%.

2-Phenyl-1-(phenylamino)-1,2,7,8-tetrahydroquinolin-5(6*H*)-one (3h): Yield 70 mg (22%), brown solids; mp 180–183 °C; IR (KBr) ν_{max} = 3211, 3176, 3024, 2945, 1735, 1643, 1593, 1531, 1494, 1433, 1348, 1278, 1190, 1028 ,904 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2H), 7.29–7.25 (m, 5H), 6.99 (t, *J* = 12.1, Hz, 1H), 6.97 (m, 3H), 5.58 (s, 1H), 5.33 (m, 1H), 5.28 (d, *J* = 4.8 Hz, 1H), 2.86–2.62 (m, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 1.96–1.88 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5, 162.7, 144.2, 139.9, 129.8 (2C), 129.2 (2C), 129.0, 127.7 (2C), 121.7, 119.0, 116.6, 113.4 (2C), 105.4, 63.4, 35.7, 25.1, 21.1. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85%. Found: C, 78.97; H, 6.09; N, 9.01%.

***N*-(3-Methyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4a):** Yield 72.5 mg (22%), yellow solids; mp 130–133 °C; IR (KBr) ν_{max} = 3176, 2947, 2360, 1683, 1591, 1543, 1523, 1491, 1433, 1396, 1375, 1352, 1265, 1193, 1166, 1139, 1089,1028, 896, 806, 738, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.4 Hz, 2H), 7.54 (dd, *J* = 13.0, 4.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 3H), 7.34–7.28 (m, 5H), 6.51 (s, 1H), 5.26 (s, 1H), 2.49 (m, 2H), 2.28 (m, 2H), 1.88–1.79 (m, 2H), 1.45 (s, 3H). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82%. Found: C, 76.89; H, 5.76; N, 7.86%.

***N*-(2-(4-Methoxyphenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4b):** Yield 114 mg (33%), yellow solids; mp 116–118 °C; IR (KBr) ν_{max} = 3198, 2951, 1681, 1668, 1608, 1510, 1404, 1354, 1251, 1174, 1139, 1028, 895, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.53 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.24 (m, 3H), 6.82 (d, *J* = 3.9 Hz, 2H), 6.43 (s, 1H), 5.18 (s, 1H), 3.75 (s, 3H), 2.47 (m, 2H), 2.17 (t, *J* = 6.5 Hz, 2H), 1.87–1.80 (m, 2H), 1.44 (s, 3H). HRMS (ESI) calcd for $C_{24}H_{24}N_2O_3$ $[M+H]^+$ Exact Mass: 388.18, found 388.18.

***N*-(2-(4-Chlorophenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4c):** Yield 158.5 mg (45%), yellow solids; mp 143–146 °C; IR (KBr) ν_{max} = 3196, 2945, 2362, 1686, 1599, 1556, 1489, 1435, 1402, 1354, 1288, 1263, 1193, 1089, 1014, 895, 831 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2Hz, 2H), 7.28 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.33 (s, 1H), 5.25 (s, 1H), 2.47 (t, *J* = 6.5 Hz, 2H), 2.03 (t, *J* = 10.6 Hz, 2H), 1.81 (m, 2H), 1.42 (s, 3H). HRMS (ESI) calcd for $C_{23}H_{21}ClN_2O_2$ $[M+H]^+$ Exact Mass: 392.13, found 392.13.

***N*-(2-(4-Fluorophenyl)-3-methyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4d):** Yield

206 mg (54%), yellow solids; mp 140–142 °C; IR (KBr) ν_{max} = 3192, 2947, 1681, 1602, 1552, 1506, 1402, 1266, 1222, 1193, 1155, 1139, 1087, 1028, 896, 839, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.3 Hz, 2H), 7.54 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33–7.26 (m, 3H), 7.01 (s, 2H), 6.43 (s, 1H), 5.25 (s, 1H), 2.50 (m, 2H), 2.26 (t, *J* = 4.8 Hz, 2H), 2.00–1.83 (m, 2H), 1.46 (s, 3H). Anal. Calcd for $C_{23}H_{21}FN_2O_2$: C, 73.39; H, 5.62; N, 7.44 %. Found: C, 73.53; H, 5.43; N, 7.24%.

Methyl 4-(1-benzamido-3-methyl-5-oxo-1,2,5,6,7,8-hexahydroquinolin-2-yl)benzoate (4e): Yield 186 mg (45%), yellow solid; mp 131–133 °C (decomp.); IR (KBr) ν_{max} = 3192, 2947,1681, 1670, 1602, 1552, 1506, 1437,1402, 1354, 1265, 1222, 1139, 1087, 1028, 896, 839, 694 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.44–7.35 (m, 4H), 6.49 (s, 1H), 5.35 (s, 1H), 3.86 (s, 3H), 2.52 (dd, *J* = 9.6, 5.8 Hz, 2H), 2.25 (s, 2H), 1.90 (d, *J* = 5.3 Hz, 2H), 1.46 (s, 3H). HRMS (ESI) calcd for $C_{25}H_{24}N_2O_4$ $[M+H]^+$ Exact Mass: 416.17, found 416.17.

***N*-(3-Methyl-5-oxo-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4f):** Yield 241 mg (56%), yellow solids; mp 125–127 °C; IR (KBr) ν_{max} = 3176, 2947, 1681, 1591, 1543, 1433, 1396, 1265, 1253, 1193, 1139, 1091, 1028, 896, 698.cm^1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69–7.60 (d, *J* = 6 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 3H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 6Hz, 2H), 6.45 (s, 1H), 5.36 (s, 1H), 2.51 (dt, *J* = 15.3, 6.2 Hz, 2H), 2.16 (t, *J* = 6.5 Hz, 2H), 2.02–1.71 (m, 2H), 1.46 (s, 3H). Anal. Calcd for $C_{24}H_{21}F_3N_2O_2$: C, 67.60; H, 4.96; N, 6.57%. Found: C, 66.98; H, 4.82; N, 6.49%.

***N*-(3-Methyl-2-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (4g):** Yield 241 mg (58%), yellow solids; mp 125–127 °C; IR (KBr) νmax = 3182, 3026, 2945, 1645, 1595, 1552, 1516, 1491, 1437, 1400, 1344, 1290, 1193, 1149, 1107, 1084, 956, 920, 856 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.23 (d, *J* = 6.Hz, 2H), 7.88 (d, *J* = 6.Hz, 1H), 7.72 (d, *J* = 6.2 Hz, 2H), 7.60 (d, *J* = 6.2 Hz, 2H), 7.55–7.43 (m, 3H), 6.94 (s, 1H), 6.38 (s, 1H), 5.39 (s, 1H), 2.47 (m, 2 H), 2.16 (s,2 H), 1.81 (m, 2H), 1.44 (m, 3 H). HRMS (ESI) calcd for $C_{23}H_{21}N_3O_4$ $[M+H]^+$ Exact Mass: 403.15, found 403.17.

***N*-(3,7,7-Trimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (11a):** Yield 172 mg (45%), yellow solids; mp 198–201 °C; IR(KBr) ν_{max} = 3157, 2956, 2362, 1680, 1597, 1585, 1552, 1519, 1489,1437, 1404, 1301, 1292, 1251, 1186, 1151, 1089, 1070, 1028, 1001, 966, 927, 910,881, 806, 763, 694 cm^1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.0 Hz, 2H), 7.51 (d, *J* = 6 Hz, 1H), 7.39 (d, *J* = 6.1 Hz, 2H), 7.32 (s, 4H), 6.37 (s, 1H), 5.25 (s, 1H), 2.45 (dd, *J* = 18.0,18.0 Hz, 2H), 1.94 (s, 2H), 1.45 (s, 3H), 0.97 (d, *J* = 6.0 Hz, 6H). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25%. Found: C, 77.55; H, 6.05; N, 6.82%.

***N*-(2-(4-Chlorophenyl)-3,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (11b):** Yield 255 mg (60%), yellow solid; mp 125–127 °C; IR (KBr) ν_{max} = 3188, 2958, 2360, 1681, 1600, 1552, 1487, 1435, 1402, 1288, 1257, 1149, 1089, 1014, 883, 833, 694 cm^1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 6.0 Hz, 2H), 7.51 (d, *J* = 6 Hz, 1H), 7.38 (t, *J* = 12 Hz, 2H), 7.28–7.24 (m, 4H), 6.35 (s, 1H), 5.24

(s, 1H), 7 (dd, *J* = 18.0, 18.0 Hz, 2H), 1.93 (s, 2H), 1.43 (s, 3H), 0.95 (d, *J* = 4.2 Hz, 6H). Anal. Calcd for $C_{25}H_{25}ClN_2O_2$: C, 71.33; H, 5.99; N, 6.66%. Found: C, 70.93; H, 5.75; N, 6.67%.

***N*-(3,7,7-Trimethyl-2-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (11c):** Yield 305 mg (70%), yellow solids; mp 158–160 °C; IR (KBr) ν_{max} = 3192, 2958, 1685, 1600, 1554, 1519, 1437, 1346, 1247, 1182, 1149, 1070, 1028, 1014, 968, 922, 889, 812, 754, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.0 Hz, 2H), 7.77 (d, *J* = 6.0 Hz, 2H), 7.52 (m, 3H), 7.42 (t, *J* = 12.0 Hz, 2H), 6.38 (s, 1H), 5.37 (s, 1H), 27 (dd, *J* = 18.0, 18.0 Hz, 2H), 2.1 (s, 2H), 1.46 (s, 3H), 1.01 (d, *J* = 12.0 Hz, 6H). Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; N, 9.74%. Found: C, 68.86; H, 5.64; N, 9.54%.

***N*-(3,7,7-Trimethyl-5-oxo-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (11d):** Yield 297 mg (65%), yellow solids; mp 128–130 °C; IR (KBr) ν_{max} = 3201, 2960, 1681, 1600, 1556, 1435, 1325, 1249, 1165, 1126, 1066, 1018, 883, 844, 798, 761, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.64–7.51 (m, 2H), 7.47–7.41(m, 5H), 6.44 (s, 1H), 5.34 (s, 1H), 2.37 (dd, *J* = 18.0, 18.0 Hz, 2H), 2.05 (s, 2H), 1.46 (s, 3H), 0.99 (m, 6H). Anal. Calcd for $C_{26}H_{25}F_3N_2O_2$: C, 68.71; H, 5.54; N, 6.16%. Found: C, 68.76; H, 5.29; N, 5.86%.

***N*-(2-(4-Fluorophenyl)-3,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzamide (11e):** Yield 252 mg (62%), yellow solids; mp 204–206 °C; IR (KBr) ν_{max} = 3201, 2960, 1681, 1600, 1556, 1435, 1325, 1249, 1165, 1126, 1066, 1018, 883, 844, 798, 761, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 12.0, 6.0 Hz, 2H), 7.31–7.25 (m, 2H), 7.01 (s, 2H), 6.40 (s, 1H), 5.25 (s, 1H), 2.46–2.23 (dd, *J* = 18.0, 18.0 Hz, 2H), 2.01 (d, *J* = 3.6 Hz, 2H), 1.45 (s, 3H), 0.97 (d, *J* = 30.0 Hz, 6H). HRMS (ESI) calcd for $C_{25}H_{25}FN_2O_2$ $[M+H]^+$ Exact Mass: 404.19, found 404.19.

Methyl 4-(1-benzamido-3,7,7-trimethyl-5-oxo-1,2,5,6,7,8-hexahydroquinolin-2-yl)benzoate (11f): Yield 250 mg (57%), Yellow solids; mp 130–133 °C; IR (KBr) ν_{max} = 3209, 2955, 1724, 1681, 1600, 1554, 1435, 1413, 1402, 1280, 1261, 1149, 1105, 966 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.42 (dt, *J* = 15.8, 8.2 Hz, 1H), 7.33–7.20 (m, 4H), 6.38 (s, 1H), 5.34 (s, 1H), 3.81 (d, J = 6.3 Hz, 3H), 2.33 (dd, *J* = 18.0, 18.0 Hz, 2H), 1.97 (t, *J* = 6.0 Hz, 2H), 1.42 (s, 3H), 0.96 (d, *J* = 5.8 Hz, 6H). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30%. Found: C, 72.93; H, 6.30; N, 6.06%.

ACKNOWLEDGEMENTS

We are grateful to Okayama University for its support by Promotion of Graduate Course Students to E.S. and to the Advanced Science Research Center for the NMR experiments and EA by Ms. M. Kosaka and Mr. M. Kobayashi. This study was partially supported by the Adaptable and Seamless Technology Transfer Program of JST.

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