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FACILE SYNTHESIS OF 3-SUBSTITUTED AND 1,3-DISUBSTITUTED QUINOLIN-2(1*H*)-ONES FROM 2-NITROBENZALDEHYDES

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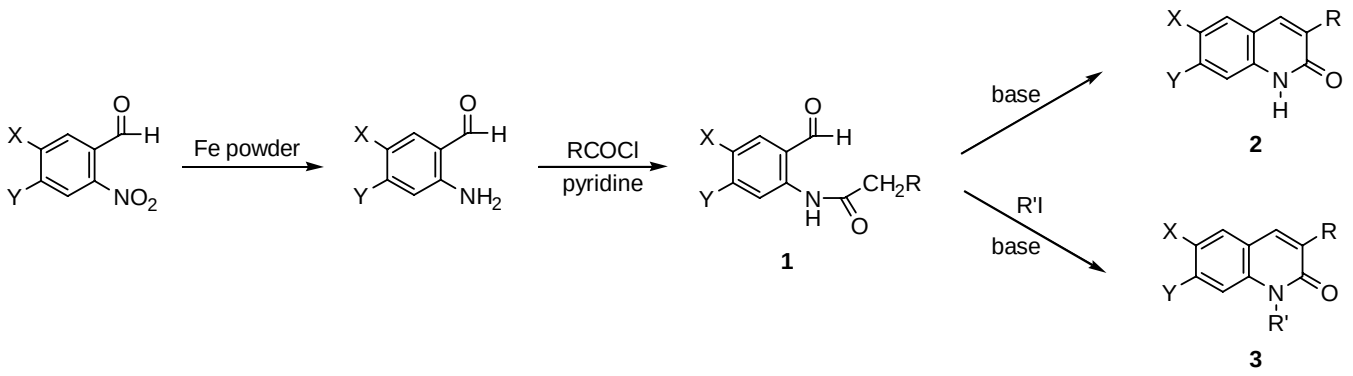
Abstract – 2-Nitrobenzaldehydes were reduced with iron powder to 2-aminobenzaldehydes, which were reacted immediately with acyl chlorides to provide 2-carboxamidobenzaldehydes (**1**) with overall yields of 71-90 %. Reaction of **1** with base provided 3-substituted quinolin-2(1*H*)-ones with 63-97 % yields. Treatment of **1** with methyl iodide and base gave 1-methyl-3-substituted quinolin-2(1*H*)-ones with 82-95 % yields, whereas the treatment with isopropyl iodide gave 1-isopropyl-3-substituted quinolin-2(1*H*)-ones with 7-42 % yields.

INTRODUCTION

Quinolin-2(1*H*)-one skeleton is frequently found in many pharmacologically useful compounds,[1-6] such as antitumor,[1,2] antiplatelet,[3] and antiviral agents,[4] and various types of receptor antagonists.[5,6] Extensive efforts have been made for the synthesis of quinolin-2(1*H*)-one derivatives.[1-17] Conventional method for the synthesis is the cyclization of β-ketoanilides or acrylanilides.[7] However, this method has two major limitations. One is that mixtures of 5- and 7-substituted quinolin-2(1*H*)-ones are obtained when *meta*-substituted anilides are cyclized and the other is that the necessary starting materials are not readily accessible.[7] A wide variety of other synthetic routes for quinolin-2(1*H*)-one derivatives have also been reported. These include intramolecular Wittig reaction of 2-pyruvoylaminobenzyltriphenylphosphonium halide,[1,8] palladium-catalyzed carbonylative annulation of alkyne by *o*-substituted aryl iodide,[9] electrocyclizations of *o*-vinylphenyl isocyanate,[10] palladium-catalyzed amidation of *o*-carbonyl-

substituted aryl halides,[11] conversion of Baylis-Hillman adducts of 2-nitrobenzaldehydes,[12] cyclization of 3-(2-aminophenyl)acrylic acid derivatives,[5,13] reaction of α–substituted acetanilides with Vilsmeier reagent,[2,14] tandem Ugi-Knoevenagel condensation,[15] free radical cyclization of alkylsulfonyl substituted anilides,[16] introduction of the desired substituent into the preformed quinoline ring system.[17] However, many of them suffer narrow scope, harsh reaction conditions, and/or low yields. Thus, the development of efficient and general synthetic methods for quinolin-2(1*H*)-one derivatives is still highly desired. Recently, we found that 4-phenylquinolin-2(1*H*)-ones can be efficiently prepared from *N*-acyl-*o*-aminobenzophenones.[18] Here, we wish to report a facile and efficient synthesis of 3-substituted quinolin-2(1*H*)-ones (**2**) and 1,3-disubstituted quinolin-2(1*H*)-ones (**3**) starting from 2-nitrobenzaldehydes *via* 2-carboxamidobenzaldehyde intermediates (**1**) (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

Preparation of 2-Carboxamidobenzaldehydes (1) From 2-Nitrobenzaldehydes

There are numerous methods for reduction of nitrobenzenes to anilines. As 2-aminobenzaldehyde is unstable and easily undergoes self-condensation reaction,[19] the reduction of 2-nitrobenzaldehydes to 2-aminobenzaldehydes should be carried out by a method requiring minimal work-up procedure and the product should be used immediately for the next step. We tested various reducing agents for the synthesis of 2-acetamidobenzaldehyde (**1a**) from 2-nitrobenzaldehyde and found that iron powder[20] is simple and facile agent for the reduction. The reduction reaction could be effectively coupled with the acylation reaction with a minimal work-up.[21]

Reduction of 2-nitrobenzaldehyde to 2-aminobenzaldehyde with iron powder was accomplished within 15 min, and the crude reduction product was immediately subjected to acylation reaction. The reaction with acetyl chloride in the presence of pyridine in benzene solvent for 10 min gave **1a** with overall yield of 80 %: the reaction in dichloromethane solvent for 6 h gave **1a** with only 40 % yield. We believe that this

procedure for the synthesis of **1a** is much better than the reported methods for **1a**. Meanwell *et al.* reported the synthesis of **1a** from 2-nitrobenzaldehyde by the lengthy sequence via protection of carbonyl group, reduction (10 % Pd on C), and acetylation (the yields were not mentioned),[23] while Dave *et al.* reported 58 % overall yield of **1a** from 2-nitrobenzaldehyde using $FeSO_4$/acetic anhydride after rather complicated work-up procedure.[19] This reduction/acylation procedure for **1a** was successfully applied for the synthesis of various other 2-carboxamidobenzaldehydes (**1**) with the overall yields of 71-90 %. The results are summarized in Table 1.

Table 1. Yields of 2-carboxamidobenzaldehydes (**1**) from 2-aminobenzaldehydes, and yields of 3-substituted quinolin-2(1*H*)-ones (**2**) from **1**

entry	X	Y	R	yields	
				1[a]	**2**[b,c]
1	H	H	H	**1a** (80%)	**2a** (83%)
2	H	H	Me	**1b** (73%)	**2b** (76%)
3	H	H	n-Pr	**1c** (71%)	**2c** (72%)
4	H	H	n-C_5H_{11}	**1d** (82%)	**2d** (63%)
5	H	H	Ph	**1e** (72%)	**2e** (92%)
6	H	H	CO_2Et	**1f**[d]	**2f** (75%)[e]
7	Cl	H	Ph	**1g** (90%)	**2g** (97%)
8	OMe	OMe	H	**1h** (89%)	**2h** (64%)
9	OMe	OMe	Ph	**1i** (74%)	**2i** (95%)

[a] Isolated yields from the corresponding 2-nitrobenzaldehydes. [b] Isolated yields from **1**. [c] Cs_2CO_3 was used as a base for **2a-d** and **2h**, and K_2CO_3 was used for **2e-g** and **2i**. [d] Crude product was used for the synthesis of **2f**. [e] The yield is the isolated overall yield from 2-nitrobenzaldehyde.

Synthesis of 3-substituted quinolin-2(1*H*)-ones (2) from 1

The facile access of 2-carboxamidobenzaldehydes (**1**) prompted us to try the synthesis of various 3-substituted quinolin-2(1*H*)-ones (**2**) via intramolecular Aldol-type condensation of **1**. Various bases such as NaH, K_2CO_3, and Cs_2CO_3 were tested for the cyclization reaction. When R is electron-withdrawing group such as phenyl or ethoxycarbonyl, K_2CO_3 was strong enough to induce cyclization and the yields of **2** were better than 90 % (Table 1, entries 5-7 and 9).[24] When R is H or alkyl group (Table 1, entries 1-4 and 8), NaH or Cs_2CO_3 was necessary for the cyclization reaction. The use of

Cs_2CO_3 gave 8-17 % better yields than NaH. Longer acyl moiety in **1** (compare entries 1-4 of Table 1) and electron-donating substituent in the benzene ring (entry 8) lowered the yield. The yields of **2** from **1** are included in Table 1.

Synthesis of 1,3-disubstituted quinolin-2(1*H*)-ones (3) from 2-carboxamidobenzaldehydes (1)

The alkylation reaction of the preformed quinolin-2(1*H*)-one ring with alkyl halide gives a mixture of *N*- and *O*-alkylated products.[5,18] Thus, to prepare 1,3-disubstituted quinolin-2(1*H*)-ones (**3**) from **1**, *N*-alkylation of **1** and subsequent cyclization of the resulting *N*-alkyl-2-carboxamidobenzaldehyde would be a desirable choice. We first tested the reaction of **1a** with methyl iodide in DMF in the presence of various bases. As hoped, *N*-alkylation to give *N*-methyl-2-acetamidobenzaldehyde preceded the cyclization and the one pot reactions provided 1-methyl-quinolin-2(1*H*)-ones (**3a**) without any noticeable amount of *O*-methylated isomer. *N*-Methylation reaction went into completion in the presence of either K_2CO_3 or Cs_2CO_3 at 40 ^oC, and Cs_2CO_3 required much less reaction time (2 h) than K_2CO_3 (18 h). For the subsequent cyclization reaction of *N*-methyl-2-acetamidobenzaldehyde, Cs_2CO_3 or NaH was effective at the reaction temperature of 60 ^oC. *N*-Methylation at 40 ^oC and then cyclization at 60 ^oC in the presence of ten molar excess of Cs_2CO_3 was found to give the highest yield (86 %) of **3a** from **1a**.

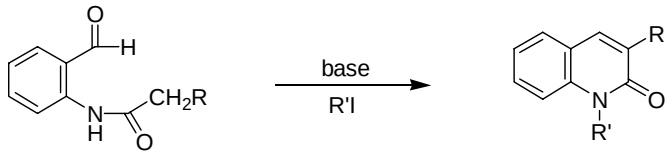
The similar reaction of **1a** with isopropyl iodide in the presence of Cs_2CO_3 provided 1-isopropylquinolin-2(1*H*)-one (**3b**) with 42 % yield (Table 2, entry 2). The yield is far better than the reported yield (6.5 %) of 1-isopropylated compound obtained from the alkylation reaction of a quinolin-2(1*H*)-one derivative with isopropyl iodide.[5] The corresponding reactions of **1b** with methyl or isopropyl iodide and the reaction of **1e** with methyl iodide gave the corresponding 1,3-disubstituted quinolin-2(1*H*)-ones with moderate to excellent yields (Table 2, entries 3-5).

The reaction of 2-phenylacetamidobenzaldehyde (**1e**) with isopropyl iodide in the presence of base gave a quite contrasting result (Table 2, entry 6). It gave both the *N*-isopropylated product, 1-isopropyl-3-phenylquinolin-2(1*H*)-one (**3f**) and the *O*-isopropylated product, 2-isopropoxy-3-phenylquinoline **(4f)** with 7 % and 81 % yields, respectively. We could not increase the yield of **3f** by changing the reaction conditions such as base and/or temperature. The similar yields of the *N*-alkylated and *O*-alkylated products were also obtained from the reaction of 3-phenylquinolin-2(1*H*)-one (**2e**) with isopropyl iodide. The result indicates that in the reaction of **1e** with isopropyl iodide in the presence of base, the cyclization reaction of **1e** proceed prior to the *N*-alkylation reaction of **1e**. This can be explained by the fact that the α-hydrogen atom to the carbonyl group is more acidic in **1e** than the one in **1a** or **1b**, and isopropyl iodide is much poorer alkylating agent than methyl iodide.

It is noteworthy that the yields of the consecutive reactions of *N*-methylation and cyclization of **1** to **3** are higher than the yields of the simple cyclization reactions of the corresponding **1** to **2** (compare the yields of **2** in entries 1, 2, and 5 of Table 1 with the respective yields of **3** in entries 1, 3, and 5 of Table 2). This

is reasonable as the removal of the α-hydrogen atom to the carbonyl group for the cyclization would be more feasible in *N*-methyl-2-carboxamidobenzaldehyde than in 2-carboxamidobenzaldehyde without *N*-methyl group: the former has only one kind of acidic hydrogens to be removed, while the latter has two kinds of them and N-H hydrogen is more acidic than the α-hydrogen atom.

Table 2. Yields of 1,3-disubstituted quinolin-2(1*H*)-ones (**3**) obtained from alkylation/cyclization reaction of **1**



1a,b,e **3a-f**

entry	starting material	base	product	R	R'	yield of **3**[a]
1	**1a**	Cs_2CO_3	**3a**	H	Me	86%
2	**1a**	Cs_2CO_3	**3b**	H	*i*-Pr	42%
3	**1b**	Cs_2CO_3	**3c**	CH_3	Me	82%
4	**1b**	Cs_2CO_3	**3d**	CH_3	*i*-Pr	40%
5	**1e**	K_2CO_3	**3e**	Ph	Me	95%
6	**1e**	K_2CO_3	**3f**	Ph	*i*-Pr	7%[b]

[a] Isolated yields. [b] *O*-Alkylated product (**4f**) was obtained in 81 % yield, together with **3f**.

In conclusion, facile synthetic routes for 3-substituted and 1,3-disubstituted quinolin-2(1*H*)-ones (**2** and **3**) from 2-nitrobenzaldehydes *via* 2-carboxamidobenzaldehydes (**1**) have been developed. The compounds (**1**) are efficiently prepared from 2-nitrobenzaldehydes *via* reduction with iron powder and then acylation reaction. Base-catalyzed cyclization of **1** affords various 3-substituted quinolin-2(*1H*)-ones (**2**). The reaction of **1** with alkyl iodide in the presence of base gives the corresponding 1-alkyl-3-substituted quinolin-2(*1H*)-ones (**3**), resulting from *N*-alkylation followed by cyclization reaction in one pot, except for the case of the reaction of 2-phenylacetamidobenzaldehyde (**1e**) with isopropyl iodide. In the reaction of **1e** with isopropyl iodide, *N*-alkylation occurs after the cyclization reaction, giving mostly *O*-alkylated product (**4f**).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using tetramethylsilane as an internal standard in $CDCl_3$ or DMSO-d_6. Melting points are uncorrected.

General procedure for the preparation of 2-carboxamidobenzaldehydes (1) from 2-nitrobenzaldehydes

2-Nitrobenzaldehyde (3.31 mmol) and iron powder (1.29 g, 23.2 mmol) were added to a mixture of ethanol (8 mL), acetic acid (8 mL), and water (4 mL), and the mixture was refluxed for 5 min and then stirred at rt for 10 min. The reaction mixture was filtered, and the filtrate was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and water, dried over anhydrous sodium sulfate, and concentrated to give crude 2-aminobenzaldehyde. The crude 2-aminobenzaldehyde was used for the synthesis of **1** without further purification.

To a mixture of crude 2-aminobenzaldehyde and pyridine (0.393 g, 4.96 mmol) in benzene (20 mL) was added slowly acyl chloride (4.96 mmol). After stirring at rt for 10 min, the reaction mixture was washed with 10 % aqueous HCl solution and then water. The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluents: *n*-hexane-ethyl acetate, 4:1) to afford the corresponding 2-carboxamidobenzaldehydes (**1**) in 71-90 % yields (see Table 1). In case of the reaction of 2-aminobenzaldehyde with ethyl malonyl chloride (Table 1, entry 6), the concentrated organic layer was used for the synthesis of **2f** without purification.

1a: mp 70-71 ^{o}C (lit.,[19] 70 ^{o}C); ^{1}H NMR ($CDCl_3$) δ 11.12 (br s, 1H), 9.91 (s, 1H), 8.73 (d, 1H, J = 8 Hz), 7.66 (dd, 1H, J = 8 and 2 Hz), 7.61 (dt, 1H, J = 8 and 2 Hz), 7.22 (dt, 1H, J = 8 and 1 Hz), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.4, 169.5, 140.8, 136.1, 135.9, 122.8, 121.4, 119.7, 25.4.

1b: oil (lit.,[25] mp 46 ^{o}C); ^{1}H NMR ($CDCl_3$) δ 11.14 (br s, 1H), 9.92 (s, 1H), 8.76 (d, 1H, J = 8 Hz), 7.66 (dd, 1H, J = 8 and 2 Hz), 7.61 (dt, 1H, J = 8 and 2 Hz), 7.21 (dt, 1H, J = 8 and 1 Hz), 2.50 (q, 2H, J = 8 Hz), 1.29 (t, 3H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 195.4, 173.3, 141.0, 136.1, 135.9, 122.6, 121.5, 119.8, 31.6, 9.5. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.88; H, 6.47; N, 7.76.

1c: oil; ^{1}H NMR ($CDCl_3$) δ 11.13 (br s, 1H), 9.91 (s, 1H), 8.76 (d, 1H, J = 8 Hz), 7.66 (dd, 1H, J = 8 and 2 Hz), 7.58 (dt, 1H, J = 8 and 2 Hz), 7.21 (t, 1H, J = 8 Hz), 2.46 (t, 2H, J = 7.5 Hz), 1.75 (quintet, 2H, J = 7.5 Hz), 1.43 (sextet, 2H, J = 7.5 Hz), 0.96 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 195.4, 172.7, 140.9, 136.1, 135.9, 122.6, 121.4, 119.7, 38.3, 27.5, 22.3, 13.8. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.39; H, 7.27; N, 6.86.

1d: oil; ^{1}H NMR ($CDCl_3$) δ 11.13 (br s, 1H), 9.92 (s, 1H), 8.76 (d, 1H, J = 9 Hz), 7.66 (dd, 1H, J = 8 and 2 Hz), 7.60 (dt, 1H, J = 8 and 2 Hz), 7.21 (dt, 1H, J = 8 and 1 Hz), 2.46 (t, 2H, J = 8 Hz), 1.76 (quintet, 2H, J = 8 Hz), 1.43-1.28 (m, 6H), 0.89 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 195.4, 172.7, 140.9, 136.1, 135.9, 122.6, 121.4, 119.8, 38.6, 31.5, 28.9, 25.4, 22.5, 14.1. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.09; H, 8.36; N, 5.99.

1e: mp 42-44 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 11.08 (br s, 1H), 9.80 (s, 1H), 8.74 (d, 1H, J = 8 Hz), 7.62-7.55 (m, 2H), 7.40-7.30 (m, 5H), 7.19 (dt, 1H, J = 8 and 1 Hz), 3.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 195.1, 170.6,

140.67, 136.0, 135.8, 133.9, 129.6, 128.9, 127.4, 122.9, 121.7, 119.8, 45.8. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.53; H, 5.65; N, 5.87.

1g: mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 10.95 (br s, 1H), 9.73 (s, 1H), 8.73 (d, 1H, J= 9 Hz), 7.56 (s, 1H), 7.52 (d, 1H, J = 9 Hz), 7.44-7.30 (m, 5H), 3.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 193.8, 170.5, 139.1, 135.7, 134.8, 133.6, 129.6, 129.10, 128.0, 127.5, 122.7, 121.5, 45.7. Anal. Calcd for $C_{15}H_{12}NO_2Cl$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.74; H, 4.74; N, 5.00.

1h: mp 181-183 °C (lit.,[26] 178-179 °C); ^{1}H NMR ($CDCl_3$) δ 11.32 (br s, 1H), 9.75 (s, 1H), 8.47 (s, 1H), 7.03 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.0, 169.5, 155.4, 144.2, 137.5, 116.3, 114.3, 102.8, 56.4, 56.2, 25.4.

1i: mp 132-134 °C; ^{1}H NMR ($CDCl_3$) δ 11.33 (br s, 1H), 9.67 (s, 1H), 8.48 (s, 1H), 7.43-7.30 (m, 5H), 7.00 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.77 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 192.9, 170.6, 155.2, 144.3, 137.3, 133.9, 129.5, 128.8, 127.4, 116.1, 114.5, 102.9, 56.4, 56.2, 45.7. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.33; H, 5.62; N, 4.65.

General procedure for the synthesis of 3-substituted quinolin-2(*1H*)-ones 2 from 1

A mixture of 2-carboxamidobenzaldehyde (**1**) (0.500 mmol) and base (2.50 mmol) in DMF (5 mL) was heated at 60 °C for 2-16 h. Dichloromethane was added to the reaction mixture and then washed with aqueous saturated NH_4Cl solution and water. The organic layer was dried over sodium sulfate and concentrated. Silica gel column chromatography of the residue (eluent: hexane-ethyl acetate, 1:1 or 2:1) provided the corresponding quinolin-2(*1H*)-ones (**2**) in 63-97 % yields (see Table 1).

2a: mp 197-199 °C (lit.,[27] 198-199 °C); ^{1}H and ^{13}C NMR were identical with those from Aldrich.

2b: mp 247-249 °C (lit. 250 °C[28]; 237-240 °C[17d]); ^{1}H NMR (DMSO-d_6) δ 11.72 (br s, 1H), 7.73 (s, 1H), 7.54 (dd, 1H, J = 8 and 1 Hz), 7.40 (ddd, 1H, J = 8, 7 and 1 Hz), 7.26 (d, 1H, J = 8 Hz), 7.12 (ddd, 1H, J = 8, 7 and 1 Hz), 2.07 (d, 3H, J = 1 Hz); ^{13}C NMR (DMSO-d_6) δ 162.3, 137.8, 136.3, 129.7, 129.0, 126.9, 121.6, 119.4, 114.7, 16.6.

2c: mp 142-143 °C; ^{1}H NMR ($CDCl_3$) δ 12.77 (br s, 1H), 7.57 (s, 1H), 7.49-7.39 (m, 3H), 7.15 (ddd, 1H, J = 8, 6 and 2 Hz), 2.67 (t, 2H, J = 7 Hz), 1.75 (sextet, 2H, J = 7 Hz), 1.04 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 164.5, 137.4, 136.4, 133.7, 129.0, 126.7, 122.1, 120.1, 115.7, 32.3, 21.6, 14.0. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.90; H, 7.12; N, 7.37.

2d: mp 140-142 °C; ^{1}H NMR ($CDCl_3$) δ 12.59 (br s, 1H), 7.59 (s, 1H), 7.49 (d, 1H, J = 8 Hz), 7.45-7.40 (m, 2H), 7.16 (ddd, 1H, J = 8, 5 and 3 Hz), 2.69 (t, 2H, J = 7 Hz), 1.72 (quintet, 2H, J = 7 Hz), 1.46-1.35 (m, 4H), 0.93 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 164.5, 137.4, 136.3, 134.1, 129.1, 126.8, 122.2, 120.2, 115.7, 31.7, 30.2, 28.1, 22.6, 14.1. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.11; H, 8.17; N, 6.30.

2e: mp 234-235 °C (lit.,[9a] 230-231 °C); ^{1}H NMR (DMSO-d_6) δ 11.95 (br s, 1H), 8.10 (s, 1H), 7.77-7.72 (m, 3H), 7.50 (t, 1H, J = 7 Hz), 7.44 (t, 2H, J = 7 Hz), 7.38 (d, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 7.20 (t, 1H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 160.9, 138.2, 137.5, 136.2, 131.4, 130.1, 128.6, 128.0, 127.8, 127.7, 121.8, 119.5, 114.6.

2f: mp 183-184 °C (lit.,[5] 175-179 °C); ^{1}H NMR ($CDCl_3$) δ 12.74 (br s, 1H), 8.56 (s, 1H), 7.65 (d, 1H, J = 8 Hz), 7.60 (t, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz), 4.46 (q, 2H, J = 7 Hz), 1.46 (t, 3H, J= 7 Hz); ^{13}C NMR ($CDCl_3$) δ 164.3, 161.3, 145.6, 140.0, 132.9, 129.0, 123.0, 122.0, 118.4, 116.3, 61.4, 14.4.

2g: mp 249-250 °C (lit.,[29] 234-235 °C); ^{1}H NMR (DMSO-d_6) δ 12.06 (br s, 1H), 8.11 (s, 1H), 7.86 (d, 1H, J = 2 Hz), 7.77 (d, 2H, J = 7 Hz), 7.56 (dd, 1H, J = 9 and 2 Hz), 7.50-7.42 (m, 3H), 7.38 (d, 1H, J = 9 Hz); ^{13}C NMR (DMSO-d_6) δ 160.7, 136.9, 136.4, 135.8, 132.7, 129.9, 128.6, 128.0, 127.9, 126.9, 125.6, 120.6, 116.5.

2h: mp 232-234 °C (lit.,[13a] 231 °C); ^{1}H NMR (DMSO-d_6) δ 11.53 (br s, 1H), 7.75 (d, 1H, J = 9 Hz), 7.15 (s, 1H), 6.84 (s, 1H), 6.30 (d, 1H, J = 9 Hz), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.7, 151.7, 144.6, 139.6, 134.4, 118.6, 112.2, 108.7, 97.6, 55.7, 55.5.

2i: mp 259-261 °C (lit. 260 °C;[13b] 242-244 °C[17e]); ^{1}H NMR (DMSO-d_6) δ 11.73 (br s, 1H), 7.98 (s, 1H), 7.73 (d, 2H, J = 7.5 Hz), 7.39 (t, 2H, J = 7.5 Hz), 7.31 (t, 1H, J = 7.5 Hz), 7.24 (s, 1H), 6.87 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.6, 151.8, 144.7, 137.1, 136.6, 134.0, 128.3, 128.2, 127.7, 127.2, 112.7, 108.9, 97.1, 55.7, 55.5.

General procedure for the synthesis of 1-alkyl-3-substituted quinolin-2(*1H*)-ones (3) from 1

To a stirred mixture of 2-carboxamidobenzaldehyde (**1a** or **1b**) (1.00 mmol) and Cs_2CO_3 (3.26 g, 10.0 mmol) in DMF (5 mL) at 40 °C, alkyl iodide (2.50 mmol) was added slowly and stirring was continued at 40 °C until TLC showed that 2-carboxamidobenzaldehyde disappeared almost completely. Then temperature was raised from 40 °C to 60 °C and the reaction mixture was stirred at 60 °C for 1-48 h. In case of **1e** (0.239 g, 1.00 mmol), K_2CO_3 (0.691 g, 5.00 mmol) was used as a base and the reaction went to completion at 40 °C. After the reaction, dichloromethane was added to the reaction mixture and then washed with aqueous saturated NH_4Cl solution and water. The organic layer was dried over sodium sulfate and concentrated. Silica gel column chromatography of the residue (eluent: hexane-ethyl acetate, 1:1 or 2:1) provided the corresponding 1-alkylquinolin-2(*1H*)-ones (**3a-e**) (see Table 2). In case of the reaction of **1e** with isopropyl iodide in the presence of K_2CO_3, purification by silica gel column chromatography (eluent: hexane-ethyl acetate, 9:1) afforded *N*-isopropylated product (**3f**) and

O-isopropylated product (**4f**) with 7 % and 81 % yields, respectively (Table 2, entry 6).

3a: mp 75-76 °C (lit.,[16] 74-75 °C); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 9 Hz), 7.56 (t, 1H, J = 8 Hz), 7.55 (d, 1H, J = 8 Hz), 7.36 (d, 1H, J = 8 Hz), 7.23 (t, 1H, J = 8 Hz), 6.71 (d, 1H, J = 9 Hz), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.2, 139.9, 138.8, 130.5, 128.6, 122.0, 121.6, 120.6, 114.0, 29.4.

3b: oil; ^{1}H NMR ($CDCl_3$, 70 °C) δ 7.55 (d, 2H, J = 9 Hz), 7.51-7.44 (m, 2H), 7.15 (t, 1H, J = 7 Hz), 6.60 (d, 1H, J = 9 Hz), 5.48 (br s, 1H), 1.64 (d, 6H, J = 7 Hz). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.92; H, 7.20; N, 7.29.

3c: mp 73-74 °C (lit.,[30] 64-65 °C) ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1H), 7.52-7.47 (m, 2H), 7.32 (d, 1H, J = 9 Hz), 7.20 (dt, 1H, J = 8 and 1 Hz), 3.74 (s, 3H), 2.26 (d, 3H, J = 1 Hz); ^{13}C NMR ($CDCl_3$) δ 162.7, 138.9, 135.5, 129.9, 129.1, 127.6, 121.8, 120.6, 113.7, 29.7, 17.8.

3d: oil; ^{1}H NMR ($CDCl_3$, 70 °C) δ 7.52 (d, 1H, J = 9 Hz), 7.46-7.38 (m, 3H), 7.12 (t, 1H, J = 7 Hz), 5.47 (br s, 1H), 2.22 (s, 3H), 1.64 (d, 6H, J = 7 Hz). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.64; H, 7.30; N, 6.88.

3e: mp 140-142 °C (lit.,[14] 137-138 °C); ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1H), 7.70 (d, 2H, J = 8 Hz), 7.59 (d, 1H, J = 8 Hz), 7.55 (t, 1H, J = 8 Hz), 7.43 (t, 2H, J = 8 Hz), 7.39-7.34 (m, 2H), 7.24 (t, 1H, J = 8 Hz), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.4, 139.5, 136.7, 132.4, 130.2, 128.9, 128.7, 128.0, 127.9, 122.1, 120.6, 113.9, 30.0 (one carbon is missing due to overlap).

3f: oil; ^{1}H NMR ($CDCl_3$, 70 °C) δ 7.70 (s, 1H), 7.69 (d, 2H, J = 8 Hz), 7.55 (d, 2H, J = 8 Hz), 7.47 (t, 1H, J = 8 Hz), 7.39 (t, 2H, J = 7 Hz), 7.32 (t, 1H, J = 7 Hz), 7.16 (t, 1H, J = 7 Hz), 5.47 (br s, 1H), 1.69 (d, 6H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 70 °C) δ 161.8,139.1, 137.0, 136.5, 133.3, 129.4, 129.2, 129.1, 128.0, 127.9, 121.7, 121.6, 114.6, 47.4, 19.9. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.15; H, 6.59; N, 5.24.

4f: oil; ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.82 (d, 1H, J = 8 Hz), 7.69 (dd, 1H, J = 8 and 2 Hz), 7.65-7.62 (m, 2H), 7.57 (ddd, 1H, J = 8, 7, and 2 Hz), 7.44-7.39 (m, 2H), 7.37-7.31 (m, 2H), 5.65 (heptet, 1H, J = 6 Hz), 1.39 (d, 6H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 158.8, 145.9, 137.8, 137.0, 129.4, 129.0, 127.9, 127.4, 127.3, 126.7, 126.6, 125.2, 123.8, 68.4, 22.0. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.14; H, 6.56; N, 5.16.

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REFERENCES AND NOTES

1. P. Ferrer, C. Avendano, and M. Sollhuber, *Liebigs Ann. Chem*., 1995, 1895.
2. B. Joseph, F. Darro, A. Behard, B. Lesur, F. Collignon, C. Decaestecker, A. Frydman, G. Guillaumet, and R. Kiss, *J. Med. Chem*., 2002, **45**, 2543.
3. L. Huang, M. Hsieh, C. Teng, K. Lee, and S. Kuo, *Biorg. Med. Chem*., 1998, **6**, 1657.
4. M. Patel, R. J. McHugh, Jr., B. C. Cordova, R. M. Klabe, L. T. Bacheler, S. Erickson-Viitanen, and J. D. Rodgers, *Bioorg. Med. Chem. Lett*., 2001, **11**, 1943.
5. M. Suzuki, Y. Ohuchi, H. Asanuma, T. Kaneko, S. Yokomori, C. Ito, Y. Isobe, and M. Muramatsu, *Chem. Pharm. Bull*., 2000, **48**, 2003.
6. W. W. K. R. Mederski, M. Osswald, D. Dorsch, M. Christadler, C.-J. Schmitges, and C. Wilm, *Bioorg. Med. Chem. Lett*., 1997, 1883.
7. (a) G. Jones, 'Comprehensive Heterocyclic Chemistry,' Vol. 2, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, New York, 1984, pp. 395-510. (b) P. A. Claret, 'Comprehensive Organic Chemistry,' Vol. 4, ed. by D. Barton and W. D. Ollis, Pergamon Press, New York, 1979, pp. 157-166.
8. (a) L. Capuano, A. Ahlhelm, and H. Hartmann, *Chem. Ber*., 1986, **119**, 2069. (b) K. Miyashita, K. Tsuchiya, K. Kondoh, H. Miyabe, and T. Imanishi, *Heterocycles*, 1996, **42**, 513.
9. (a) D. V. Kadnikov and R. C. Larock, *J. Organometallic Chem*., 2003, **687**, 425. (b) D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772.
10. L. Luo, M. D. Bartberger, and W. R. Dolbier, *J. Am. Chem. Soc*., 1997, **119**, 12366.
11. P. J. Manley and M. T. Bilodeau, *Org. Lett*., 2004, **6**, 2433.
12. (a) D. Basavaiah, R. M. Reddy, N. Kumaragurubaran, and D. S. Sharada, *Tetrahedron*, 2002, **58**, 3693. (b) K. Y. Lee, J. M. Kim, and J. N. Kim, *Bull. Korean Chem. Soc*., 2002, **23**, 1493. (c) O. B. Familoni, P. T. Kaye, and P. Klaas, *Chem. Commun*., 1998, 2563.
13. (a) G. R. Pettit, B. Stevenson, and G. Gever, *Org. Prep. Proced. Int*., 1971, **3**, 93. (b) N. Oda, *Yakugaku Zasshi*, 1962, **82**, 1115 (*Chem. Abstr*., 1963, **59**, 565).
14. J. P. Chupp and S. Metz, *J. Heterocycl. Chem*., 1979, **16**, 65.
15. S. Marcaccini, R. Pepino, M. C. Pozo, S. Basurto, M. Garcia-Valverde, and T. Torroba, *Tetrahedron Lett*., 2004, **45**, 3999.
16. Y.-L. Wu, C.-P. Chuang, and P.-Y. Lin, *Tetrahedron*, 2000, **56**, 6209.
17. (a) T. Kauffmann and J. Schulz, *Chem. Ber*., 1966, **99**, 1837. (b) C. E. Kaslow and B. Buchner, *J. Org. Chem*., 1958, **23**, 271. (c) Y. Miura, S. Takaku, Y. Nawata, and M. Hamana, *Heterocycles*, 1991, **32**, 1579. (d) R. E. Lyle and M. J. Kane, *J. Org. Chem*., 1973, **38**, 3740. (e) G. Uray, K. S. Niederreiter, F. Belaj, and W. M. F. Fabian, *Helv. Chim. Acta*, 1999, **82**, 1408. (f) O. Martin, E. de la Cuesta, and C. Avendano, *Tetrahedron*, 1995, **51**, 7547.

18. K. K. Park and J. J. Lee, *Tetrahedron*, 2004, **60**, 2993.
19. R. H. Dave and B. D. Hosangadi, *Tetrahedron*, 1999, **55**, 11295.
20. E. C. Riesgo, X. Jin, and R. P. Thummel, *J. Org. Chem.*, 1996, **61**, 3017.
21. There is a report that 2-nitrobenzaldehyde is reduced to 2-aminobenzaldehyde by $SnCl_2$, and the reduced product is effectively coupled with the condensation reaction with ketones.[22] We attempted the reduction of 2-nitrobenzaldehyde with $SnCl_2$ and then reaction of the reduced product with acetyl chloride, but it gave 2-acetylaminobenzaldehyde (**1a**) with poorly reproducible and low yield.
22. B. R. McNaughton and B. L. Miller, *Org. Lett.*, 2003, **5**, 4257.
23. N. A. Meanwell, B. C. Pearce, H. R. Roth, E. C. R. Smith, D. L. Wedding, J. J. K. Wright, J. O. Buchanan, U. M. Baryla, M. Gamberdella, E. Gillespie, D. C. Hayes, S. M. Seiler, H. C. Stanton, G. B. Zavoico, and J. S. Fleming, *J. Med. Chem.*, 1992, **35**, 2672.
24. The overall yield of **2f** from 2-nitrobenzaldehyde is 75 % (Table 1, entry 6). If one assumes the yield of **1f** as *ca.* 80 %, the yield of the cyclization step becomes more than 90 %.
25. W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*(C), 1966, 234.
26. M. Lempert-Sreter, K. Lempert, and J. Moeller, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2011.
27. Y.-J. Cherng, *Tetrahedron*, 2002, **58**, 1125.
28. A. Chibani, R. Hazard, M. Jubault, and A. Tallec, *Bull. Soc. Chim. Fr.*, 1987, 795.
29. M. Natarajan, T. Manimaran, and V. T. Ramakrishnan, *Indian J. Chem.*, 1984, **23B**, 529.
30. Y. Sato, H. Kojima, and H. Shirai, *J. Org. Chem.*, 1976, **41**, 195.