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Facile synthesis of 4-phenylquinolin-2(1*H*)-one derivatives from *N*-acyl-*o*-aminobenzophenones

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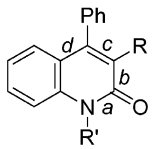
This paper is dedicated to Professor Dong H. Kim on the occasion of his retirement from the Department of Chemistry, Postech

Abstract—An efficient synthesis of 4-phenylquinolin-2(1*H*)-one derivatives has been achieved in a one-pot reaction from *N*-acyl-*o*-aminobenzophenones **1a**-**c** (**a**: acyl=acetyl; **b**: acyl=propanoyl; **c**: acyl=heptanoyl) using NaH as a base. Treatment of **1** with NaH provided the quinolones **2a**-**c** with 62–83% yields, whereas the reaction in the presence of alkyl iodide (alkyl=methyl, ethyl, *n*-octyl) gave the corresponding N-alkylated quinolones **3a**-**g** in 75–95% yields. The alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide gave a mixture of N-alkylated and O-alkylated products. Comparison of IR and NMR data of the N-alkylated and O-alkylated compounds with those of **2a**-**c** indicated that **2a**-**c** exist as the lactam form.

1. Introduction

Quinolines and their derivatives occur in numerous natural products and have interesting biological properties.[1] Their wide-ranging applicabilities such as pharmaceuticals, agrochemicals and synthetic building blocks have been discovered.[2] Thus, development of efficient methods for their syntheses is still attracting much interest of organic chemists,[3,4] even though the syntheses of quinolines have been known for more than a century. 4-Phenylquinolin-2(1*H*)-ones **2** and **3** are found to be useful intermediates in organic synthesis[5–7] and some of them show interesting biological profiles.[7–10]



2: R' = H
3: R' = alkyl

Quinolin-2(1*H*)-one skeletons usually have been prepared by acid-catalyzed cyclization of acylacetoanilides[9–11] forming bond *d* in the benzo-fused pyridine ring. The synthetic methods involving the final ring closure at bond *a*,[6,12] *b*[13] or *c*[7,8,14] and via cyclization/rearrangement[15] or desulfurization reaction[16] have also been reported. Most of these synthetic methods for 2-quinolones have their own drawbacks such as difficult accessibility of the starting materials, low yields, and/or harsh reaction conditions. Here, we wish to report a facile and efficient synthesis of 4-phenylquinolin-2(1*H*)-one derivatives **2** and **3** by forming the bond *c* from *N*-acyl-*o*-aminobenzophenones **1** using NaH as a base. It provides various 4-phenylquinolin-2(1*H*)-one derivatives in high yields from readily available starting materials by one-pot reaction. The tautomeric form of **2** was also clarified.

2. Results and discussions

2.1. Synthesis of 4-phenylquinolin-2(1*H*)-ones 2 from *N*-acyl-*o*-aminobenzophenones 1 and study on the alkylation reaction of 2

N-Acyl-*o*-aminobenzophenones **1a**-**c** were obtained in quantitative yields by reacting *o*-aminobenzophenone with the corresponding acyl chlorides in dichloromethane in the presence of pyridine. Treatment of **1a**-**c** with 6 equiv. of NaH in THF at refluxing temperature for 2.5–20 h provided 4-phenylquinolin-2(1*H*)-ones **2a**-**c** in 62–83% yields with the deacylated side product, *o*-aminobenzophenone in 16–23% yields (Scheme 1). There are scattered reports for the synthesis of **2a**[7–9,11b,12,13,15,16] and **2b**[13,14,17] by various methods, but the yields are low and/or the methodologies are rather too specific. We believe that the

Keywords: *N*-Acyl-*o*-aminobenzophenones; 4-Phenylquinolin-2(1*H*)-one; *N*-Alkyl-4-phenylquinolin-2(1*H*)-ones; 2-Alkoxy-4-phenylquinolines; Lactam–lactim tautomeric form.
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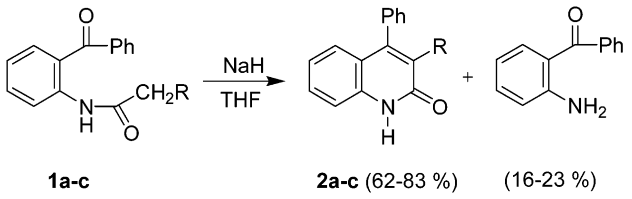


Scheme 1. Reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with NaH.

present method is very simple general route for the synthesis of 4-phenyl-quinoline-2(1*H*)-ones.

We studied the alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide. The reaction of **2a** with alkyl halide in DMF at 70 °C in the presence of various bases gave mixtures of the corresponding N-alkylated and O-alkylated products, **3** and **4** (Table 1). The reaction with methyl iodide in the presence of K_2CO_3 gave mostly N-alkylated product **3a**. However, with the alkyl halides of larger alkyl group, the proportion of the O-alkylated product **4** increases (see entries 1–3), presumably due to the steric interaction between the bulky *N*-alkyl group and the adjacent H atom in the 8-position of the quinoline ring. Using Cs_2CO_3 or NaH instead of K_2CO_3 as a base gave almost the same results. Changing the reaction medium from DMF to THF resulted in much slower reaction, but the yield of the N-alkylated product was higher (compare entries 2 and 4 vs. 5). This is reminiscent of the previous reports that pyridin-2-ones undergo alkylation at either nitrogen or oxygen.[18]

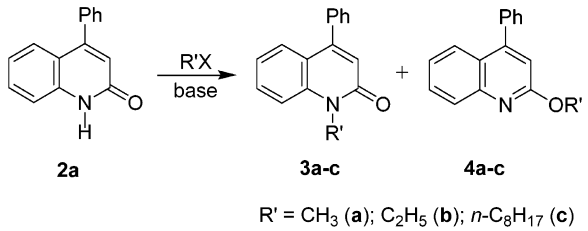
2.2. One-pot synthesis of *N*-alkyl-4-phenylquinolin-2(1*H*)-ones 3 from 1

The unsatisfactory yields of **2** from **1** and the formation of both N and O-alkylated products **3** and **4** in the alkylation reaction of **2** made us to search an alternative route for the synthesis of **3**. For the cyclization of the compounds **1** to the quinoline ring, the hydrogen atom attached to the alpha carbon to the carbonyl group needs to be removed. However, the hydrogen is less acidic than the hydrogen atom attached to the nitrogen of the amide group. We envisioned that N-alkylation of **1** prior to the treatment with the base would increase the yield of the cyclization reaction and also give the N-alkylated quinolones. Thus, we carried out the reaction of **1a-c** with NaH in the presence of alkyl iodide to achieve the alkylation and cyclization reactions in one pot. The product distributions obtained from the reactions of **1a** with NaH and methyl iodide under various conditions are listed in Table 2.

Table 2 shows that the yield of *N*-methyl-4-phenylquinolin-2(1*H*)-one **3a** is as high as 92% when 2.5 equiv. of CH_3I and 6 equiv. of NaH are used at the refluxing temperature of THF. Either lowering the reaction temperature or using less amount of NaH or CH_3I resulted in N-alkylated, but not-cyclized product, **5a**. The yields of *N*-alkyl-2-quinolone derivatives obtained from the reactions of *N*-acyl-*o*-aminobenzophenones **1a-c** with 6 equiv. of NaH in the presence of 2.5 equiv. of various alkyl iodides are summarized in Table 3. It shows that *N*-alkyl-4-phenylquinolin-2(1*H*)-ones **3a-g** can be efficiently prepared in the one-pot reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with alkyl iodide and NaH. Unlike the reaction of **2a** with alkyl halides, O-alkylated products **4** were not detected, suggesting that N-alkylation of **1** precedes the cyclization reaction.

Based on the data in Tables 2 and 3, we propose the mechanism for the reaction of *N*-acyl-*o*-aminobenzophenones **1a-c** with alkyl iodide and NaH as Scheme 2. To support the involvement of **5** as an intermediate, we prepared *N*-ethyl-*o*-benzoylacetanilide (**5b**: R=H; R′=Et) from the reaction of **1a** with ethyl iodide in the presence of cesium carbonate in acetone, and then it was reacted with 3 equiv. of NaH in refluxing THF. The yield of *N*-ethyl-4-phenylquinolin-2(1*H*)-one **3b** was higher in shorter reaction time (92% yield after 4 h) compared to the reaction of **1a** (85% yield after 7 h: see entry 2 of Table 3). The fact that the reaction of **2a** with alkyl iodide in THF is very slow and

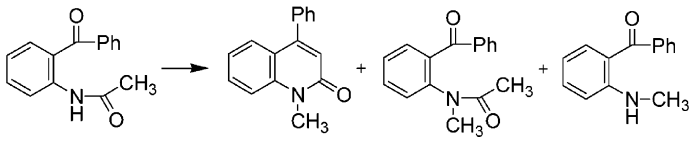
Table 1. Alkylation reaction of **2a** with alkyl halides



Entry	R′X	Base	Solvent	Temperature	Time (h)	Yields (%)	
						3	**4**
1	CH_3I	K_2CO_3	DMF	70 °C	0.5	84	8
2	C_2H_5I	K_2CO_3	DMF	70 °C	1	60	34
3	n-$C_8H_{17}Br$	K_2CO_3	DMF	70 °C	1.5	42	48
4	C_2H_5I	Cs_2CO_3	DMF	70 °C	0.5	59	31
5[a]	C_2H_5I	NaH	THF	Reflux	120	66 (72)[b]	13 (14)[b]
6	n-$C_8H_{17}I$	NaH	DMF	70 °C	0.5	43	52

[a] 8% of the starting material was remained unreacted.
[b] The yield in the parenthesis is the yield based on the consumed starting material.

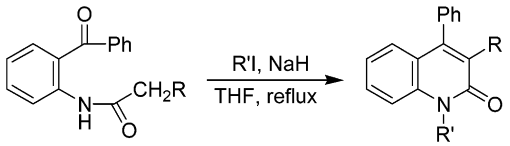
Table 2. Reaction of **1a** with methyl iodide and NaH in THF



1a **3a** **5a** **6a**

Entry	Equiv. of CH_3I	Equiv. of NaH	T (°C)	Time (h)	Yields (%)		
					3a	**5a**	**6a**
1	2.5	3	0	3	nd	100	nd
2	2.5	3	25	2	16	81	nd
3	2.5	6	0	2	13	77	8
4	2.5	6	25	1	60	31	8
5	2.5	6	40	1	67	24	7
6	2.5	3	Reflux	2	78	18	2
7	1.5	6	Reflux	2	85	9	nd
8	2.5	6	Reflux	2	92	nd	6

Table 3. The yields of *N*-alkyl-2-quinolones **3a-g** obtained from the reaction of **1a-c** with various alkyl iodide and NaH in THF



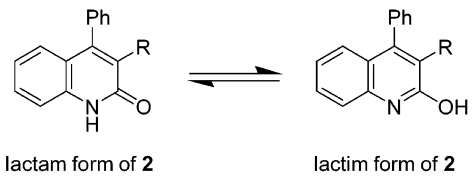
1a-c **3a-g**

Entry	Starting material	R	R′	Time (h)	Product	Yields (%)
1	**1a**	H	CH_3	2	**3a**	92
2	**1a**	H	C_2H_5	7	**3b**	85
3	**1a**	H	n-C_8H_{17}	40	**3c**	75
4	**1b**	CH_3	CH_3	4	**3d**	85
5	**1b**	CH_3	C_2H_5	5	**3e**	88
6	**1c**	n-C_5H_{11}	CH_3	4	**3f**	95
7	**1c**	n-C_5H_{11}	C_2H_5	8	**3g**	84

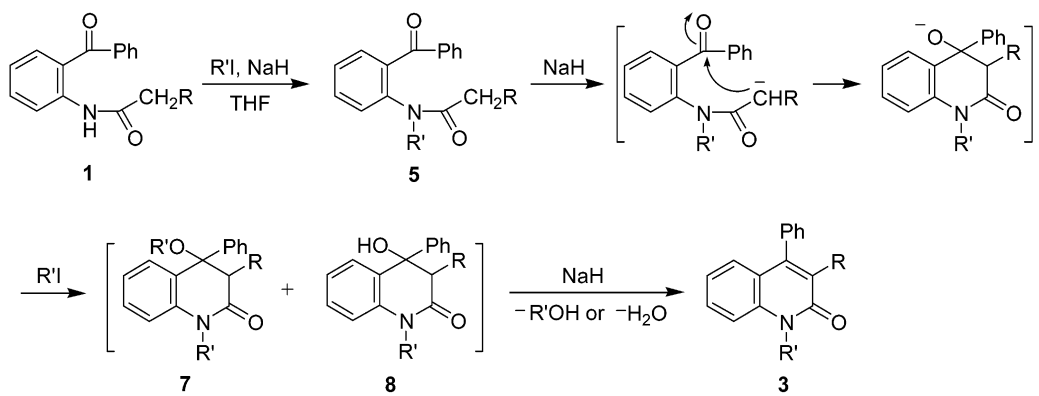
gives appreciable amount of O-alkylated product **4** (see entry 5 of Table 1) further supports the involvement of the intermediate **5** in the transformation of **1** to **3** in the presence of alkyl halide. We propose the involvement of the intermediate **7** in addition of **8** based on the following two facts. One is that the yield of **3a** becomes lower with less than 2 equiv. of alkyl iodide (compare entries 7 and 8 of Table 2). The other is that the yield of **3b** is increased from 92 to 99% in the reaction of **5b** with NaH when 1.5 equiv. of ethyl iodide is added to the reaction mixture.

2.3. Tautomeric form of 4-phenylquinolin-2(1*H*)-ones 2a-c

The tautomeric equilibrium of lactam–lactim continues to attract much attention owing to its chemical, biological, and theoretical importance.[19] Compounds **2a-c** can exist in either lactam or lactim forms. Of the two tautomers, the lactim form of **2a** (R=H) is reported to be more stable than the lactam by ca. 1 kJ/mol in the gas phase,[20] and the lactam is slightly more stable in solution, especially in polar solvent (ca. 20 kJ/mol in water).[21] It was also reported that both the lactam and lactim tautomers of **2a** exist in the supersonic jet expansion.[22] On the other hand, a paper suggested that the compound **2a** exists in the lactim form as 2-hydroxyquinoline, based on a singlet signal for one proton present at δ 12 in the ^{1}H NMR spectrum.[12b] The crystal structure of **2a** has recently been reported, showing that **2a** has the lactam structure.[23]



lactam form of **2** lactim form of **2**



Scheme 2. Proposed mechanism for the reaction of *N*-acyl-*o*-aminobenzophenones **1** with alkyl iodide and NaH.

Since both N-alkylated and O-alkylated compounds **3a-c** and **4a-c**, which correspond to the lactam and lactim forms, respectively, are at our hands, we compare the spectroscopic characteristics between the N-alkylated compounds **3** and the O-alkylated ones **4** and deduce the tautomeric structure of **2**. The NMR data of **3** are significantly different from those of **4** (see Section 4 for data): major differences are ^{1}H and ^{13}C peaks of CH_2 (or CH_3) bonded to the heteroatoms and ^{1}H peaks of the aromatic protons. The chemical shift of the carbon atom at the 2-position of the quinoline ring is almost same for both **3a-c** and **4a-c** as δ 161–162. As expected, ^{1}H and ^{13}C peaks of CH_2 (or CH_3) bonded to the oxygen atom in **4a-c** have larger δ values than those bonded to the nitrogen atom in **3a-c**: the O-alkylated compounds **4a-c** have the ^{1}H peaks at δ 4.11, 4.57, and 4.50, and the ^{13}C peaks at δ 53.39, 61.65, and 66.00, respectively, while **3a-c** have the corresponding ^{1}H peaks at 3.78, 4.43, and 4.34, and ^{13}C peaks at 29.45, 37.26, and 42.34, respectively.

^{1}H Peaks of the aromatic protons of **4a-c** are more downfield-shifted than those of **3a-c**: the singlet signal of the hydrogen atom at the 3-position of the quinoline ring appears at δ 6.84–6.85 for **4a-c**, but δ 6.66–6.68 for **3a-c**, and the protons at the 5-, 6-, 7-, and 8-positions of the quinoline ring of **4a-c** are well resolved as a doublet at δ 7.74–7.75, a triplet at δ 7.29–7.31, a triplet at δ 7.60–7.62, and a doublet at δ 7.89–7.91, respectively, while those of **3a-c** appear unresolved at higher field.

It is also seen that the characteristic IR peaks of **3a-c** and **4a-c** exhibit clear differences: N-alkylated compounds **3a-c** have a very strong peak around 1648–1665 cm^{-1}, while O-alkylated ones **4a-c** have a medium peak at 1608–1611 cm^{-1}. Comparison of the IR and NMR spectral data of **2a** with those of **3a-c** and **4a-c** indicates that the pattern and positions of the NMR peaks of the aromatic protons and the characteristic IR peak of **2a** are very much similar with those of N-alkylated compounds **3a-c**, but not with those of **4a-c**. Also, the spectroscopic characteristics of **2b** and **2c** are very alike with their N-alkylated products **3d** and **3e**, and **3f** and **3g**, respectively. Thus, we can conclude unequivocally that the compound **2a-c** exist as the lactam form in our experimental conditions, either in chloroform solution or in KBr pellet.

3. Conclusions

We have described an efficient synthesis of 4-phenylquinolin-2(1*H*)-ones **2** from *N*-acyl-*o*-aminobenzophenones **1** using NaH as a base. The alkylation reaction of 4-phenylquinolin-2(1*H*)-one **2a** with alkyl halide gave a mixture of N-alkylated and O-alkylated products **3** and **4**. The reaction of **1** with NaH in the presence of alkyl iodide gave the corresponding N-alkylated quinolones **3** in 75–95% yields, resulting from N-alkylation followed by cyclization reaction in one pot. Comparison of IR and NMR data of **3** and **4** with those of **2a-c** clearly indicates that **2a-c** exist as the lactam form.

4. Experimental

4.1. General

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

4.2. General procedure for the preparation of *N*-acyl-*o*-aminobenzophenones

To a mixture of 2-aminobenzophenone (5.00 g, 25.4 mmol) and pyridine (12.3 ml, 152 mmol) in dichloromethane (150 ml) was added slowly acyl chloride (30.4 mmol). After stirring at room temp for 0.5 h, the reaction mixture was concentrated to ca. 50 ml and washed with 10% aqeous HCl solution. Then the aqueous solution was extracted with dichloromethane 2–3 times. The combined organic layers were dried over sodium sulfate, filtered, and evaporated to afford a residue. Purification of the residue by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 3:1) provided the corresponding *N*-acyl-*o*-aminobenzophenones **1a-c** in 99–100% yields.

4.2.1. Compound 1a. R_f 0.49 (hexane–ethyl acetate, 2:1); mp 90–91 °C (lit.[24] 89–90 °C); ^{1}H NMR δ 10.82 (broad s, 1H), 8.63 (d, 1H, *J*=8 Hz), 7.70 (d, 2H, *J*=8 Hz), 7.60–7.46 (m, 5H), 7.08 (t, 1H, *J*=8 Hz), 2.23 (s, 3H). IR (KBr): 3161, 1668, 1645, 1603 cm^{-1}.

4.2.2. Compound 1b. R_f 0.56 (hexane–ethyl acetate, 2:1); mp 83–84 °C; ^{1}H NMR δ 10.89 (broad s, 1H), 8.67 (d, 1H, *J*=8 Hz), 7.69 (d, 2H, *J*=8 Hz), 7.62–7.53 (m, 3H), 7.48 (t, 2H, *J*=8 Hz), 7.07 (t, 1H, *J*=8 Hz), 2.48 (q, 2H, *J*=8 Hz), 1.28 (t, 3H, *J*=8 Hz). IR (KBr): 3223, 1667, 1647, 1601 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.49; H, 5.88; N, 5.35.

4.2.3. Compound 1c. R_f 0.78 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 10.87 (s, 1H), 8.67 (d, 1H, *J*=8 Hz), 7.69 (d, 2H, *J*=7 Hz), 7.62–7.52 (m, 3H), 7.48 (t, 2H, *J*=8 Hz), 7.06 (t, 1H, *J*=7 Hz), 2.43 (t, 2H, *J*=8 Hz), 1.75 (quintet, 2H, *J*=8 Hz), 1.43–1.25 (m, 6H), 0.87 (t, 3H, *J*=7 Hz). IR (KBr): 3309, 1699, 1635, 1603 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.74; H, 7.74; N, 4.66.

N-Alkylation of *N*-acyl-*o*-aminobenzophenone was carried out using cesium carbonate as a base. To a mixture of **1a** (0.10 g, 0.42 mmol) and cesium carbonate (0.82 g, 2.5 mmol) in acetone (10 ml) was added slowly ethyl iodide (67 μl, 0.84 mmol). After heating at reflux for 19 h, the reaction mixture was concentrated. Dichloromethane was added to the residue and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, concentrated, and then purified by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 1:1) to provide *N*-ethyl-*o*-benzoylacetanilide **5b** (0.105 g, 0.393 mmol) in 94% yield: R_f 0.30 (*n*-hexane–ethyl acetate, 1:1); mp 87–88 °C; ^{1}H NMR δ 7.80–7.76 (m, 2H), 7.63–7.42 (m, 6H), 7.28 (d, 1H, *J*=8 Hz), 4.05–3.95 (m, 1H), 3.08–2.98 (m, 1H), 1.86 (s, 3H), 1.03 (t, 3H, *J*=7 Hz). IR (KBr): 1659, 1594, 1577 cm^{-1}. Anal. Calcd for

$C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.22; H, 6.56; N, 5.14.

4.3. General procedure for the synthesis of 4-phenylquinolin-2(1*H*)-ones 2a-c

The mixture of *N*-acyl-*o*-aminobenzophenones **1a-c** (0.84 mmol) and sodium hydride (121 mg, 5.04 mmol) in THF (4 ml) was heated at reflux for 2.5 h for **1a**, 9 h for **1b**, and 20 h for **1c**. Dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and concentrated. Silica gel column chromatography of the residue (eluent: hexane–ethyl acetate, 2:1 for **2a**; hexane–ethyl acetate, 3:1 for **2b**; hexane–ethyl acetate, 5:1 and then 2:1 for **2c**) provided the corresponding **2a-c** in 83, 62, and 65% yields, together with the deacylated compound, *o*-aminobenzophenone with 16, 23, and 22% yields, respectively.

4.3.1. Compound 2a. R_f 0.10 (hexane–ethyl acetate, 2:1); mp 259–261 °C (lit.[16a] 260 °C; lit.[12b] 260–262 °C; lit.[15] 257–259 °C); ^{1}H NMR δ 12.87 (s, 1H), 7.58–7.45 (m, 8H), 7.16 (t, 1H, J=7 Hz), 6.71 (s, 1H); ^{13}C NMR δ 164.16, 153.33, 138.87, 137.05, 130.61, 128.78, 128.72, 128.53, 126.64, 122.46, 120.69, 119.52, 116.66. IR (KBr): $\nu_{C=O}$ 1663 cm^{-1}.

4.3.2. Compound 2b. R_f 0.13 (hexane–ethyl acetate, 2:1); mp 227–228 °C (lit[13] 227–230 °C); ^{1}H NMR δ 12.61 (s, 1H), 7.55–7.41 (m, 5H), 7.27–7.24 (m, 2H), 7.09–7.03 (m, 2H), 2.10 (s, 3H); ^{13}C NMR δ 164.46, 148.68, 137.02, 136.90, 129.17, 128.70, 128.57, 127.86, 127.37, 126.63, 122.07, 121.02, 115.85, 14.38. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}.

4.3.3. Compound 2c. R_f 0.28 (hexane–ethyl acetate, 2:1); mp 166–168 °C; ^{1}H NMR δ 12.47 (s, 1H), 7.53–7.39 (m, 5H), 7.28–7.22 (m, 2H), 7.07–6.98 (m, 2H), 2.49 (t, 2H, J=8 Hz), 1.54 (quintet, 2H, J=7 Hz), 1.28–1.17 (m, 4H), 0.83 (t, 3H, J=7 Hz); ^{13}C NMR δ 164.08, 148.50, 137.06, 136.70, 132.12, 129.11, 128.72, 128.37, 127.77, 126.82, 121.96, 121.27, 115.67, 31.97, 28.83, 28.19, 22.31, 14.00. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.72; H, 7.30; N, 5.04.

4.4. General procedure for the synthesis of *N*-alkyl-4-phenylquinolin-2(1*H*)-one derivatives 3a-g

The mixture of *N*-acyl-*o*-aminobenzophenones **1a-c** (0.84 mmol), alkyl iodide (2.10 mmol), and sodium hydride (121 mg, 5.04 mmol) in THF (4 ml) was heated at reflux. After the reaction, dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and evaporated to afford a residue. Silica gel column chromatography (eluent: hexane–ethyl acetate, 5:1 for **3c** and *n*-hexane–ethyl acetate, 2:1 for others) provided **3a-g**. The yields and reaction times are listed in Table 3.

4.4.1. Compound 3a. R_f 0.37 (hexane–ethyl acetate, 2:1); mp 146 °C (lit.[16a] 146 °C); ^{1}H NMR δ 7.60–7.40 (m, 8H), 7.16 (t, 1H, J=8 Hz), 6.68 (s, 1H), 3.78 (s, 3H); ^{13}C NMR δ 161.71, 150.73, 140.12, 136.90, 130.51, 128.76, 128.52, 128.40, 127.55, 121.77, 121.08, 120.32, 114.32, 29.45. IR (KBr): $\nu_{C=O}$ 1665 cm^{-1}.

4.4.2. Compound 3b. R_f 0.46 (hexane–ethyl acetate, 2:1); mp 99–100 °C (lit.[11c] 98–99 °C); ^{1}H NMR δ 7.59–7.39 (m, 8H), 7.14 (t, 1H, J=8 Hz), 6.67 (s, 1H), 4.43 (q, 2H, J=7 Hz), 1.42 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.27, 150.69, 139.10, 137.02, 130.47, 128.75, 128.49, 128.41, 127.80, 121.56, 121.21, 120.62, 114.21, 37.26, 12.80. IR (KBr): $\nu_{C=O}$ 1648 cm^{-1}.

4.4.3. Compound 3c. R_f 0.84 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 7.59–7.39 (m, 8H), 7.14 (t, 1H, J=8 Hz), 6.66 (s, 1H), 4.34 (t, 2H, J=8 Hz), 1.80 (quintet, 2H, J=8 Hz), 1.50 (quintet, 2H, J=7 Hz), 1.43–1.24 (m, 8H), 0.89 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.43, 150.60, 139.32, 137.02, 130.37, 128.74, 128.45, 128.38, 127.73, 121.49, 121.19, 120.57, 114.35, 42.34, 31.79, 29.36, 29.22, 27.54, 27.07, 22.63, 14.10. IR (KBr): $\nu_{C=O}$ 1652 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.87; H, 8.28; N, 4.32.

4.4.4. Compound 3d. R_f 0.31 (hexane–ethyl acetate, 2:1); mp 132–133 °C; ^{1}H NMR δ 7.53–7.42 (m, 4H), 7.39 (d, 1H, J=8 Hz), 7.23–7.19 (m, 2H), 7.12–7.05 (m, 2H), 3.82 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 162.50, 146.49, 138.47, 136.92, 129.17, 128.77, 128.53, 127.78, 127.54 (two overlapped C's), 121.63, 121.56, 113.75, 29.95, 15.33. IR (KBr): $\nu_{C=O}$ 1636 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.98; H, 6.05; N, 5.58.

4.4.5. Compound 3e. R_f 0.44 (hexane–ethyl acetate, 2:1); mp 111 °C (lit. 107–109 °C[25]); ^{1}H NMR δ 7.53–7.39 (m, 5H), 7.23–7.19 (m, 2H), 7.11 (dd, 1H, J=8, 2 Hz), 7.06 (t, 1H, J=8 Hz), 4.47 (q, 2H, J=7 Hz), 2.02 (s, 3H), 1.43 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.95, 146.47, 137.42, 137.03, 129.13, 128.74, 128.53, 127.78, 127.73, 127.54, 121.83, 121.39, 113.64, 37.77, 15.20, 12.80. IR (KBr): $\nu_{C=O}$ 1629 cm^{-1}.

4.4.6. Compound 3f. R_f 0.54 (hexane–ethyl acetate, 2:1); mp 78–79 °C; ^{1}H NMR δ 7.52–7.43 (m, 4H), 7.37 (d, 1H, J=8 Hz), 7.22 (d, 2H, J=8 Hz), 7.09–7.01 (m, 2H), 3.81 (s, 3H), 2.41 (t, 2H, J=8 Hz), 1.46 (quintet, 2H, J=8 Hz), 1.23–1.12 (m, 4H), 0.79 (t, 3H, J=7 Hz); ^{13}C NMR δ 162.05, 146.42, 138.53, 136.73, 132.16, 129.17, 128.77, 128.35, 127.72 (two overlapped C's), 121.78, 121.56, 113.69, 32.06, 29.86, 29.18, 28.79, 22.27, 13.98. IR (KBr): $\nu_{C=O}$ 1647 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.65; H, 7.64; N, 4.69.

4.4.7. Compound 3g. R_f 0.66 (hexane–ethyl acetate, 2:1); oil; ^{1}H NMR δ 7.52–7.37 (m, 5H), 7.27–7.17 (m, 2H), 7.08–6.99 (m, 2H), 4.45 (q, 2H, J=7 Hz), 2.40 (t, 2H, J=8 Hz), 1.51–1.37 (m, 5H), 1.23–1.13 (m, 4H), 0.79 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.47, 146.33, 137.49, 136.83, 132.16, 129.10, 128.75, 128.35, 127.95, 127.66, 122.02, 121.30, 113.55, 37.70, 32.08, 29.09, 28.76, 22.23, 13.98, 12.82. IR (KBr): $\nu_{C=O}$ 1637 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.80; H, 7.81; N, 4.39.

4.5. Alkylation reaction of 2a with alkyl halides

To a mixture of **2a** (100 mg, 0.47 mmol) and K_2CO_3 (393 mg, 2.84 mmol) in DMF (5 ml) was added slowly alkyl halide (0.95 mmol) and the reaction mixture was heated at 70 °C. After the reaction, dichloromethane was added to the concentrated reaction mixture and washed with distilled water. The organic layer was dried over sodium sulfate, filtered, and evaporated to afford a residue. Separation of the residue by silica gel column chromatography (eluents: *n*-hexane–ethyl acetate, 5:1 and then 2:1 or 1:1) provided the corresponding N-alkylated product (**3a-c**) and O-alkylated product (**4a-c**): O-alkylated product eluted first and then followed by N-alkylated product. The reactions using Cs_2CO_3 or NaH instead of K_2CO_3 as a base and THF instead of DMF as a solvent were carried out similarly. The product distributions and reaction times are listed in Table 1. The characterization data of **3a-c** are given in Section 4.4.

4.5.1. Compound 4a. R_f 0.76 (hexane–ethyl acetate, 5:1); mp 79–80 °C (lit.[26] 78–80 °C); ^{1}H NMR δ 7.91 (d, 1H, J=8 Hz), 7.75 (d, 1H, J=8 Hz), 7.62 (t, 1H, J=8 Hz), 7.53–7.44 (m, 5H), 7.31 (t, 1H, J=8 Hz), 6.85 (s, 1H), 4.11 (s, 3H); ^{13}C NMR δ 161.93, 151.03, 147.10, 137.89, 129.33, 129.27, 128.40, 128.26, 127.55, 125.72, 123.97, 123.88, 112.75, 53.39. IR (KBr): $\nu_{C=N}$ 1611 cm^{-1}.

4.5.2. Compound 4b. R_f 0.79 (hexane–ethyl acetate, 5:1); oil (lit.[27] 54–55 °C); ^{1}H NMR δ 7.89 (d, 1H, J=8 Hz), 7.74 (d, 1H, J=8 Hz), 7.60 (t, 1H, J=8 Hz), 7.52–7.43 (m, 5H), 7.29 (t, 1H, J=7 Hz), 6.84 (s, 1H), 4.57 (q, 2H, J=7 Hz), 1.46 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.64, 150.92, 147.19, 137.95, 129.26 (two overlapped C's), 128.38, 128.20, 127.55, 125.67, 123.90, 123.75, 112.98, 61.65, 14.72. IR (KBr): $\nu_{C=N}$ 1608 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.87; H, 6.04; N, 5.68.

4.5.3. Compound 4c. R_f 0.87 (hexane–ethyl acetate, 5:1); oil; ^{1}H NMR δ 7.89 (d, 1H, J=8 Hz), 7.74 (d, 1H, J=8 Hz), 7.60 (t, 1H, J=8 Hz), 7.52–7.43 (m, 5H), 7.29 (t, 1H, J=8 Hz), 6.85 (s, 1H), 4.50 (t, 2H, J=7 Hz), 1.84 (quintet, 2H, J=7 Hz), 1.49 (quintet, 2H, J=7 Hz), 1.43–1.24 (m, 8H), 0.88 (t, 3H, J=7 Hz); ^{13}C NMR δ 161.85, 150.89, 147.20, 137.96, 129.26, 129.23, 128.36, 128.20, 127.53, 125.66, 123.88, 123.72, 113.01, 66.00, 31.89, 29.46, 29.34, 29.12, 26.22, 22.74, 14.19. IR (KBr): $\nu_{C=N}$ 1608 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 83.06; H, 8.22; N, 4.00.

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