A Novel Synthesis of 2-Aryl-4-quinolones from 2-Aminobenzoic Acids

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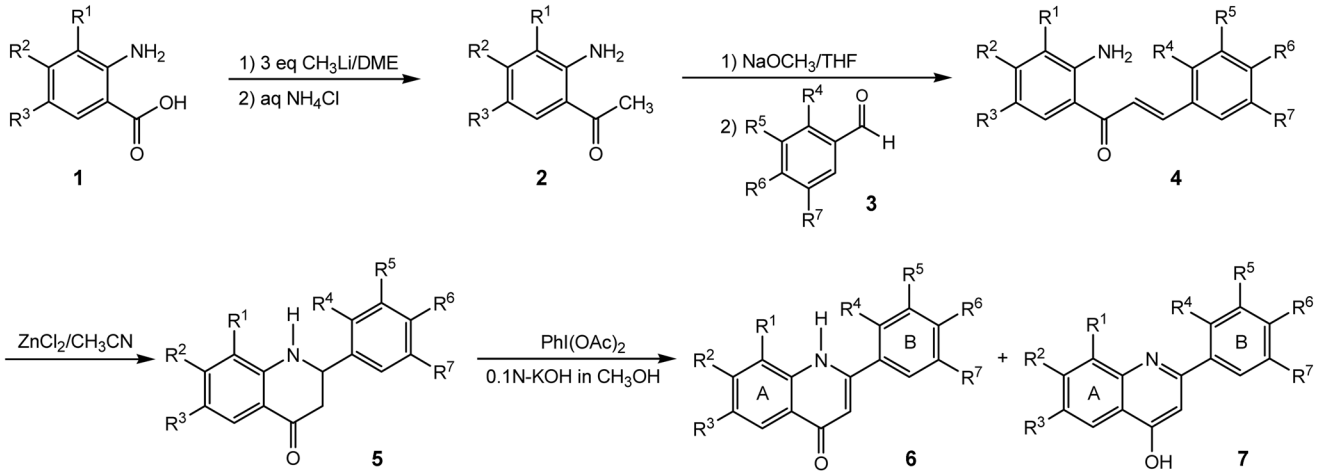
2-Aryl-4-quinolones, aza analogs of flavones, have played a central role in medicinal chemistry because they possess potent antimitotic antitumor effects through inhibition of tublin polymerization at the colchicine site.[1] The general method for preparing 2-aryl-4-quinolones is a condensation of anilines with ethyl benzoylacetates,[2] thioalkylidene-1,3-dioxane-4,6-diones,[3] and diethyl 2-(ethoxymethylene)malonate[4] in diphenyl ether at 240-250 °C. This process is amenable for scale-up and the starting material anilines are widely available, but it can lead to regioisomers depending on the structure of anilines. The cyclization of *N*-(2-acetylphenyl)benzamides, which are prepared from the benzoylation of 2'-aminoacetophenones with benzoyl chlorides[5] or Friedel-Crafts acylation of *N*-phenylbenzamides with acetyl chloride,[6] with potassium *t*-butoxide gives 2-aryl-4-quinolones. However, Friedel-Crafts acylation gives *N*-(2-acetylphenyl)benzamides in moderate yields together with its regioisomers. LDA-mediated cyclization of ketimines which are prepared by the condensation of anthranilides with acetophenones also gives 2-aryl-4-quinolones, but it fails when electron-withdrawing groups are present on the 2-phenyl ring.[7] The reaction of 2,3-dihydroquinolin-4(1*H*)-ones, which are prepared by the cyclization of 2'-aminochalcones with polyphosphoric acid[8] and micro-assisted K-10 clay[9] or $InCl_3$-SiO_2,[10] with thallium *p*-tolylsulphonate[11] results in dehydrogenation to give 2-aryl-4-quinolones. Alternatively, the reaction of succinimidyl esters derived from 2-aminobenzoic acids with anions of β-keto esters affords 2-aryl-4-quinolones *via* β-anilinoketo esters, but an excess of β-keto esters is used and yields are low.[12]

However, there are few reports on the preparation of 2-aryl-4-quinolones from 2'-aminoacetophenones. The use of 2'-aminoacetophenones for preparing 2-aryl-4-quinolones can avoid the undesirable reaction during the acetylation of *N*-phenylbenzamides. As part of our extending studies of flavonoids,[13] we report that 2-aryl-4-quinolones can be synthesized *via* 2'-aminoacetophenones derived newly from 2-aminobenzoic acids.

The preparation of 2'-aminoacetophenone was attempted by treating 2-aminobenzoic acid with 3 equiv of methyllithium in THF, Et_2O, and DME varying solvent at 0 °C. Under these conditions 2'-aminoacetophenone was obtained in 65%, 57%, and 80% yield, respectively, after 3 h, 2 h, and 1 h, respectively. Thus, the preparation of 2'-aminoacetophenones **2** was carried out by the slow addition of 3 equiv of methyllithium to a solution of 2-aminobenzoic acids **1** in DME at 0 °C (Scheme 1). After being stirred for 1 h, the resulting tan solution containing white precipitate was separated by usual acidic workup and the condensed residue was subjected to silica gel chromatography using 30% EtOAc/*n*-hexane or Kugelrohr vacuum distillation to give **2** (R^1=H, R^2=H, R^3=H; 80%, R^1=CH_3, R^2=H, R^3=H; 78%, R^1=H, R^2=Cl, R^3=H; 73%, R^1=H, R^2=H, R^3=Br; 74%).

The condensation of **2** was accomplished by the addition of sodium methoxide and benzaldehyes **3** to a solution of **2** in THF at 0 °C. The resulting greenish solution was stirred for 2 h between 0 °C and room temperature. After usual aqueous workup, the condensed residue was purified by silica gel chromatography to give 1-(2'-aminophenyl)-3-phenyl-2-propene-1-ones **4** in 76-95% yields as yellow solids. The condensation proceeded well toward various substituents (CH_3, OCH_3, Cl, Br) both on phenyl rings of **2** and **3**. The cyclization of **4** proceeded cleanly by heating with zinc chloride in acetonitrile at 80 °C for 24 h. The resulting light tan solution was separated by usual acidic workup and the subsequent recrystallization of the residue afforded 2,3-dihydro-2-aryl-4-quinolones **5** in 88-97% yields as pale yellow solids. The cyclization seems to proceed by the intramolecular conjugate addition of the amino group of **4** to the β-carbon of the α,β-unsaturated carbonyl group activated by zinc chloride.

The dehydrogenation of **5** was successfully accomplished by heating with (diacetoxyiodo)benzene[14] under basic condition. A solution of **5** and (diacetoxyiodo)benzene in 0.1 N-methanolic KOH was heated at 60 °C for 16 h. The volume of yellow mixture was reduced to a twentieth and the slow addition of 0.05 N-HCl resulted in the formation of precipitate, which was filtered and recrystallized in methanol to give 2-aryl-4-quinolones **6** in 84-90% yields. This dehydrogenation proceeded at C_2 and C_3 of hypervalent iodine intermediate of **5** to give **6** and was found to be general toward various substituents (CH_3, OCH_3, Cl, Br) both on the A-ring and B-ring of **5**. However, in the case of methoxy substituted **5** (**5c**, **5g**, **5h**) a mixture of **6** and 2-aryl-4-hydroxyquinolines **7** was obtained. The ratio of keto-enol tautomers was determined by ^{1}H NMR, which showed C_3 proton signal of keto form at the 6.12-6.33 ppm and C_3 proton signal of enol form at the 7.97-8.10 ppm. As shown in Table 1, various 2-aryl-4-quinolones were synthesized in overall high yields (44-64%) from the starting 2-amino-



Scheme 1

Table 1. Preparation of compounds **4**,**5** and 2-aryl-4-quinolones (**6**) from 2-aminobenzoic acids

Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Isolated yields, %		
								4	**5**	**6**
a	H	H	H	H	H	H	H	94	93	88
b	H	H	H	H	H	CH_3	H	89	93	85
c	H	H	H	H	H	OCH_3	H	95	94	90[a]
d	H	H	H	H	H	Cl	H	82	90	87
e	H	H	H	H	OCH_3	OCH_3	OCH_3	76	97	89
f	CH_3	H	H	OCH_3	H	H	H	87	91	85
g	H	Cl	H	OCH_3	H	H	H	82	88	84[a]
h	H	H	Br	H	H	OCH_3	H	84	92	90[a]

[a]A mixture of keto-enol tautomers.

benzoic acids. The reaction worked well with for the methyl (**6f**), chloro (**6g**), bromo (**6h**) substituents on the A-ring and methyl (**6b**), methoxy (**6c**, **6e**-**6g**), and chloro (**6d**) substituents on the B-ring.

Experimental Section

Preparation of 2'-aminoacetophenone 2a (General procedure). To a solution of 2-aminobenzoic acid (823 mg, 6.0 mmol) in DME (42 mL) was slowly added methyllithium (1.5 M in Et_2O, 13.2 mL, 19.8 mmol) under argon atmosphere at 0 °C. After being stirred for 1 h, the resulting tan solution containing white precipitate was quenched with saturated NH_4Cl (5 mL) and DME was evaporated *in vacuo*. The mixture was poured into saturated NH_4Cl (40 mL), extracted with methylene chloride (3 × 25 mL), and washed with saturated $NaHCO_3$ (40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by vacuum distillation using Kugelrohr apparatus to give **2a** (649 mg, 80%) as a liquid. bp 90-95 °C/1.0 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.70 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.22-7.28 (m, 1H), 6.61-6.66 (m, 2H), 6.28 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 150.3, 134.4, 132.0, 118.2, 117.2, 115.7, 27.8; FT-IR (film) 3467 & 3341 (NH_2), 3072, 2999, 1647 (C=O), 1615, 1450, 753 cm^{-1}; MS *m/z* (%) 135 (M^+, 72), 121 (8), 120 (100), 92 (47), 77 (3).

Preparation of 1-(2'-aminophenyl)-3-phenyl-2-propene-1-one 4a (General procedure). To a solution of **2a** (541 mg, 4.0 mmol) in THF (16 mL) was added sodium methoxide (25 wt.% in CH_3OH, 1.0 mL, 4.4 mmol) and benzaldehyde (424 mg, 4.0 mmol) at 0 °C. After being stirred for 2 h between 0 °C and room temperature, THF was evaporated *in vacuo*. The mixture was poured into saturated NH_4Cl (30 mL), extracted with methylene chloride (3 × 25 mL), and washed with saturated $NaHCO_3$ (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane to give **4a** (840 mg, 94%) as a yellow solid. mp 70-71 °C (lit.[8a] 71-72 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.74 (d, J = 15.6 Hz, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.60-7.64 (m, 2H), 7.37-7.43 (m, 3H), 7.25-7.31 (m, 1H), 6.67-6.72 (m, 2H), 6.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 151.0, 142.9, 135.3, 134.3, 131.0, 130.1, 128.9, 128.2, 123.1, 119.0, 117.3, 115.9; FT-IR (KBr) 3462 & 3334 (NH_2), 3021, 1645 (C=O), 1614, 1575, 1448, 1212, 1012, 746, 696 cm^{-1}; MS *m/z* (%) 223 (M^+, 34), 222 (51), 146 (100), 120 (9), 103 (11), 77 (11).

Preparation of 2,3-dihydro-2-phenyl-4-quinolone 5a (General procedure). A solution of **4a** (670 mg, 3.0 mmol) and zinc chloride (1.0 M in Et_2O, 3.3 mL, 3.3 mmol) in

CH_3CN (12 mL) was heated to 80 °C for 24 h. After evaporation of CH_3CN, the light tan mixture was poured into saturated NH_4Cl (30 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **5a** (623 mg, 93%) as a pale yellow solid. mp 150-151 °C (lit.[10] 149-150 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 7.32-7.48 (m, 6H), 6.75-6.81 (m, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.76 (dd, J_1 = 13.4 Hz, J_2 = 4.1 Hz, 1H), 4.51 (s, 1H), 2.90 (dd, J_1 = 16.2 Hz, J_2 = 13.4 Hz, 1H), 2.78 (dd, J_1 = 16.2 Hz, J_2 = 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 151.9, 141.4, 135.8, 129.4, 128.9, 128.0, 127.0, 119.4, 118.9, 116.3, 58.9, 46.9; FT-IR (KBr) 3330 (N-H), 1655 (C=O), 1608, 1328, 1154, 761, 700 cm^{-1}; MS *m/z* (%) 223 (M^+, 100), 222 (44), 146 (73), 145 (15), 119 (19), 77 (10).

Preparation of 2-phenyl-4-quinolone 6a (General procedure). To a **5a** (447 mg, 2.0 mmol) was added a solution of 0.1 N-KOH in CH_3OH (60 mL, 6.0 mmol) and (diacetoxyiodo)benzene (709 mg, 2.2 mmol) at room temperature. The mixture was heated to 60 °C for 16 h. After evaporation of CH_3OH, 0.05 N-HCl (50 mL) was slowly added to the mixture at 0 °C. The resulting precipitate was separated by filtration, washed with H_2O, and recrystallized twice in CH_3OH to give **6a** (389 mg, 88%) as a pale yellow solid. mp 252-253 °C (lit.[2b] 252-254 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.12 (dd, J_1 = 8.1 Hz, J_2 = 1.3 Hz, 1H), 7.77-7.87 (m, 3H), 7.61-7.71 (m, 1H), 7.57-7.62 (m, 3H), 7.33-7.38 (m, 1H), 6.36 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.8, 150.0, 140.5, 134.2, 131.7, 130.3, 128.9, 127.3, 124.7, 124.6, 123.2, 118.7, 107.2; FT-IR (KBr) 3260, 3067, 2967, 1635 (C=O), 1582, 1499, 1255, 771, 689 cm^{-1}; MS *m/z* (%) 221 (M^+, 100), 220 (26), 193 (63), 165 (20), 96 (8).

2-(4'-Methylphenyl)-4-quinolone (6b). mp 288-290 °C (lit.[11] 290-292 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.10 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.69-7.79 (m, 3H), 7.63-7.67 (m, 1H), 7.31-7.41 (m, 3H), 6.34 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.2, 150.4, 140.7, 140.6, 132.1, 131.6, 129.9, 127.6, 125.1, 125.0, 123.6, 119.1, 107.2, 21.2; FT-IR (KBr) 3263, 3056, 2898, 1633 (C=O), 1594, 1504, 1440, 1355, 1251, 813, 753 cm^{-1}; MS *m/z* (%) 235 (M^+, 100), 234 (18), 207 (59), 206 (18), 178 (9).

2-(4'-Methoxyphenyl)-4-quinolone (6c). mp 288-290 °C; ^{1}H NMR (300 MHz, DMSO-d_6) a mixture of keto-enol tautomer (4:6) δ 11.82 (br s, 1H), 8.20 & 8.09 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 8.10 (s, 0.6H), 7.81 & 7.67 (d, J = 8.8 Hz, 2H), 7.75-7.79 & 7.56-7.63 (m, 2H), 7.30-7.36 (m, 1H), 7.14 & 6.96 (d, J = 8.8 Hz, 2H), 6.33 (s, 0.4H), 3.85 & 3.78 (s, 3H); FT-IR (KBr) 3216, 3096, 2984, 1634 (C=O), 1594, 1505, 1246, 1029, 802, 753 cm^{-1}; MS *m/z* (%) 251 (M^+, 100), 250 (28), 236 (24), 208 (27), 152 (10).

2-(4'-Chlorophenyl)-4-quinolone (6d). mp 340-342 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.11 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.68-7.71 (m, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.33-7.38 (m, 1H), 6.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.3, 149.1, 140.9, 135.6, 133.4, 132.3, 129.6, 129.4, 128.1, 125.0, 123.8, 119.1, 107.8; FT-IR (KBr) 3264, 3059, 2876, 1633 (C=O), 1594, 1495, 1251, 1092, 835, 758 cm^{-1}; MS *m/z* (%) 257 (M^++2, 34), 255 (M^+, 100), 229 (16), 227 (48), 165 (15), 95 (10).

2-(3',4',5'-Trimethoxyphenyl)-4-quinolone (6e). mp 252-254 °C (lit.[7] 257-258 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.10 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.64-7.71 (m, 1H), 7.32-7.37 (m, 1H), 7.11 (s, 2H), 6.43 (s, 1H), 3.91 (s, 6H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.3, 153.5, 153.1, 150.3, 140.8, 139.5, 132.1, 130.0, 125.1, 123.6, 119.0, 107.6, 105.4, 60.5, 56.5; FT-IR (KBr) 3262, 2965, 1636 (C=O), 1586, 1508, 1450, 1250, 1136, 1003, 752 cm^{-1}; MS *m/z* (%) 311 (M^+, 100), 296 (25), 268 (9), 253 (8).

8-Methyl-2-(2'-methoxyphenyl)-4-quinolone (6f). mp 225-226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.49-7.58 (m, 3H), 7.20-7.26 (m, 2H), 7.09-7.14 (m, 1H), 6.16 (s, 1H), 3.88 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.5, 157.3, 148.7, 138.9, 132.9, 131.9, 130.6, 126.8, 125.3, 123.6, 123.1. 123.0, 121.1, 112.4, 109.6, 56.1, 17.7; FT-IR (KBr) 3204, 3071, 2965, 1623 (C=O), 1552, 1456, 1241, 1026, 754 cm^{-1}; MS *m/z* (%) 265 (M^+, 100), 250 (14), 234 (40), 233 (19).

7-Chloro-2-(2'-methoxyphenyl)-4-quinolone (6g). mp 265-267 °C; ^{1}H NMR (300 MHz, DMSO-d_6) a mixture of keto-enol tautomer (3:7) δ 11.76 (br s, 1H), 8.14 & 8.10 (d, J = 8.7 Hz, 1H), 7.97 (s, 0.7H), 7.67 & 7.62 (d, J = 2.0 Hz, 1H), 7.48-7.57 & 7.28-7.36 (m, 3H), 7.23 & 7.05 (d, J = 8.1 Hz, 1H), 7.09-7.14 & 6.94-6.99 (m, 1H), 6.12 (s, 0.3H), 3.84 & 3.71 (s, 3H); FT-IR (KBr) 3210, 3069, 2966, 1633 (C=O), 1598, 1544, 1458, 1238, 1024, 868, 756 cm^{-1}; MS *m/z* (%) 287 (M^++2, 34), 285 (M^+, 100), 270 (25), 256 (23), 254 (51), 179 (8).

6-Bromo-2-(4'-methoxyphenyl)-4-quinolone (6h). mp 350-352 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) a mixture of keto-enol tautomer (3:7) δ 12.07 (br s, 1H), 8.28 & 8.16 (d, J = 2.1 Hz, 1H), 8.17 (s, 0.7H), 7.78-7.83 (m, 1H), 7.83 & 7.67 (d, J = 8.7 Hz, 2H), 7.57 & 7.78 (d, J = 9.0 Hz, 1H), 7.15 & 6.97 (d, J = 8.7 Hz, 2H), 6.39 (s, 0.3H), 3.85 & 3.78 (s, 3H); FT-IR (KBr) 3260, 3078, 2990, 1634 (C=O), 1606, 1489, 1391, 1247, 1024, 820 cm^{-1}; MS *m/z* (%) 331 (M^++2, 97), 329 (M^+, 100), 316 (19), 314 (20), 250 (10), 178 (18).

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