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

Jae In Lee* and Jung Suk Youn

Department of Chemistry and Plant Resources Research Institute, College of Natural Science, Duksum Women’s University, Seoul 132-714, Korea. *E-mail: jilee@duksung.ac.kr
Received July 1, 2008

Key Words : 2-Aryl-4-quinolones, Cyclization, Condensation, Dehydrogenation

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 tubulin polymerization at the colchicine site. The general method for preparing 2-aryl-4-quinolones is a condensation of anilines with ethyl benzoylacetates, thioalkylidene-1,3-dioxane-4,6-diones, and diethyl 2-(ethoxymethylene)malonate 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 or Friedel-Crafts acylation of N-phenylbenzamides with acetyl chloride, with potassium t-butoxide gives 2-aryl-4-quinolones. However, Friedel-Crafts acylation gives N-(2-acetylphenyl)benzamides in moderate yields together with its precipitate, which was filtered and recrystallized in methanol to give 1-(2’-amino phenyl)-3-β-anilinoketo esters, but an excess of β-keto esters is used and yields are low.

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, 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 methylolithium to a solution of 2-aminobenzoic acids 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 (R1=H, R2=H, R3=H; 80%, R1=CH3, R2=H, R3=H; 78%, R1=H, R2=Cl, R3=H; 73%, R1=H, R2=H, R3=Br; 74%).

The condensation of 2 was accomplished by the addition of sodium methoxide and benzaldehyes 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 (CH3, OCH3, 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 the intermediate of (R1=H, R2=Cl, R3=H; 73%, R1=H, R2=H, R3=Br; 74%).

The dehydrogenation of 5 was successfully accomplished by heating with (diacetoxyiodo)benzene 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 pre-cipitate, which was filtered and recrystallized in methanol to give 2-aryl-4-quinolones 6 in 84-90% yields. This dehydrogenation proceeded at C2 and C3 of hypervalent iodine intermediate of 5 to give 6 and was found to be general toward various substituents (CH3, OCH3, 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 1H NMR, which showed C3 proton signal of keto form at the 6.12-6.33 ppm and C3 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-aminoo-
benzoic acids. The reaction worked well with 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 methyl lithium (1.5 M in Et2O, 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 NH4Cl (5 mL) and DME was evaporated in vacuo. The mixture was poured into saturated NH4Cl (40 mL), extracted with methylene chloride (3 × 25 mL), and washed with saturated NaHCO3 (40 mL). The combined organic phases were dried over MgSO4, 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 oC/1.0 mmHg; 1H NMR (300 MHz, CDCl3) δ 7.70 (dd, J1 = 8.3 Hz, J2 = 1.5 Hz, 1H), 7.22-7.28 (m, 1H), 6.61-6.66 (m, 2H), 6.28 (s, 2H), 2.56 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 200.7, 150.3, 134.4, 132.0, 118.2, 117.2, 115.7, 27.8; FT-IR (film) 3467 & 3341 (NH2), 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 CH3OH, 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 NH4Cl (30 mL), extracted with methylene chloride (3 × 25 mL), and washed with saturated NaHCO3 (30 mL). The combined organic phases were dried over MgSO4, 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); 1H NMR (300 MHz, CDCl3) δ 7.86 (dd, J1 = 8.3 Hz, J2 = 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); 13C NMR (75 MHz, CDCl3) 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 (NH2), 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 Et2O, 3.3 mL, 3.3 mmol) in benzene (30 mL) was treated with 0.1N-KOH in CH3OH (2 mL), and the mixture was stirred for 8 h and then 2N-HCl (1 mL) was added. The mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic phases were dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 30% EtOAc/n-hexane to give 5a (510 mg, 94%) as a yellow solid. mp 90-95 °C; 1H NMR (300 MHz, CDCl3) δ 11.5 (s, 1H), 7.72-7.77 (m, 1H), 7.67-7.75 (m, 1H), 7.45-7.50 (m, 1H), 6.67-6.72 (m, 2H), 6.33 (s, 2H); 13C NMR (75 MHz, CDCl3) δ 190.7, 151.0, 142.9, 135.3, 131.0, 130.1, 128.9, 128.2, 123.1, 119.0, 117.3, 115.9; FT-IR (KBr) 3334 (NH2), 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).
CHCl₃ (12 mL) was heated to 80 °C for 24 h. After evaporation of CH₂CN, the light tan mixture was poured into saturated NH₄Cl (30 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was recrystallized twice from 10% EtOAc/hexane to give 5a (62 mg, 93%) as a pale yellow solid. mp 150-151 °C (lit.10 149-150 °C); ¹H NMR (300 MHz, CDCl₃) δ 7.87 (dd, J = 7.9 Hz, J₂ = 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, J₁ = 13.4 Hz, J₂ = 4.1 Hz, 1H), 4.51 (s, 1H), 2.90 (dd, J₁ = 16.2 Hz, J₂ = 13.4 Hz, 1H), 2.78 (dd, J₁ = 16.2 Hz, J₂ = 4.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) 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 CH₂OH (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 CH₂OH, 0.05 N-HCl (50 mL) was slowly added to the mixture at 0 °C. The resulting precipitate was separated by filtration, washed with H₂O, and recrystallized twice in CH₃OH to give 6a (389 mg, 88%) as a pale yellow solid. mp 252-253 °C (lit.20 252-254 °C); ¹H NMR (300 MHz, DMF-d₆) δ 11.75 (s, 1H), 8.12 (dd, J₁ = 8.1 Hz, J₂ = 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); ¹³C NMR (75 MHz, DMF-d₆) 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.21 290-292 °C); ¹H NMR (300 MHz, DMF-d₆) δ 11.69 (s, 1H), 8.10 (dd, J₁ = 8.1 Hz, J₂ = 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); ¹³C NMR (75 MHz, DMF-d₆) δ 177.2, 150.4, 140.0, 133.2, 132.1, 129.9, 127.6, 125.1, 125.0, 123.6, 119.1, 107.2, 21.2; FT-IR (KBr) 3263, 3056, 2988, 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'-Chlorophenyl)-4-quinolone (6c). mp 288-290 °C; ¹H NMR (300 MHz, DMF-d₆) δ 11.78 (br s, 1H), 8.18 & 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).

8-Methyl-2-(2'-methoxyphenyl)-4-quinolone (6d). mp 265-267 °C; ¹H NMR (300 MHz, DMF-d₆) 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); ¹³C NMR (75 MHz, DMF-d₆) δ 177.5, 153.7, 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'-methylphenyl)-4-quinolone (6g). mp 350-352 °C (dec.); ¹H NMR (300 MHz, DMF-d₆) 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, 756 cm⁻¹; MS m/z (%) 331 (M⁺+2, 97), 329 (M⁺, 100), 316 (19), 314 (20), 250 (10), 178 (18).

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by the Korea Government (MOEHRD), Basic Research Promotion Fund (KRF-2007-005-J13001).

References