NEW EFFICIENT SYNTHESIS OF 2-ARYLOXY-4(3*H*)-QUINAZOLINONES

Ming-Wu Ding*, Shang-Jun Yang, Bo-Qiao Fu

Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P. R. China

Abstract: 2-Aryloxy-4(3*H*)-quinazolinones **5** were synthesized from cyclization of carbodiimides **2** with various phenols in presence of catalytic solid potassium carbonate in satisfactory yields.

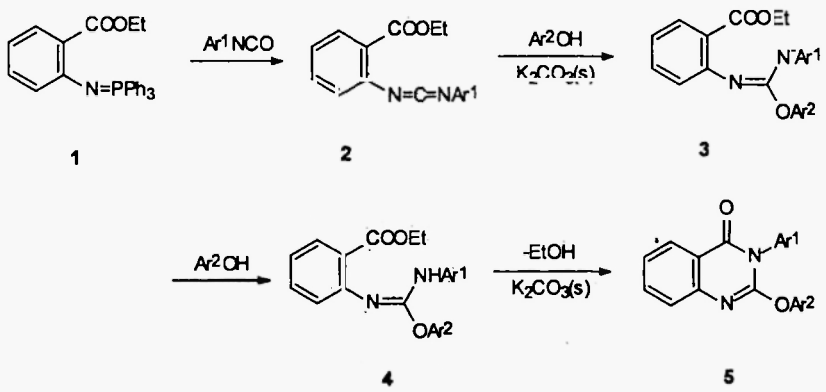
Introduction

4(3*H*)-Quinazolinones are important heterocycles exhibiting good biological and pharmaceutical activities. Some of these activities include antimicrobial(1,2), antiinflammotory(3,4), antifungal(5-7), anticancer(8) and AMPA receptor antagonistical properties(9,10). The range of biological activities and characteristic chemical structures have made synthetic studies of quinazolinones very attractive. However, 2-aryloxy substituted quinazolinones were seldom studied probably due to the fact that they were not easily accessible by currently existing routes. We have reported an efficient synthesis of 2-aryloxy-3,5-dihydro-4*H*-imidazol-4-ones *via* the base catalytic reaction of various phenols with functionalized carbodiimides under mild conditions(11). This method was further utilized to synthesis 2-aryloxy-4(3*H*)-quinazolinones **5**.

Results and Discussion

Iminophosphorane **1** reacted with aromatic isocyanates to give carbodiimides **2**. The direct reaction of carbodiimide **2** with phenols did not produce 2-aryloxy-4(3*H*)-quinazolinones **5**. However, when carried our in presence of catalytic potassium carbonate, the reaction took place to give **5** in good yields. The formation of **5** can be rationalized in terms of an initial nucleophilic addition of phenoxides to the carbodiimides **2** to give **3** , **3** are converted to the intermediates **4** which cyclize to give **5** (Scheme 1). No matter the substituents on the Ar^2 ring are electron-withdrawing or electron-releasing groups, the cyclization can be completed all at room temperature. The results are listed in Table 1.

*To receive any correspondence. E-mail: ding5229@yahoo.com.cn

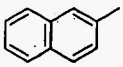
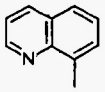


Scheme 1

The structure of the synthesized compounds **5** were confirmed by their spectral data. For example, the IR spectra of **5e** revealed C=O absorption bands at 1689 cm^{-1}. The ^1H NMR spectral data in **5e** show the signals of Ar-H at 8.20~6.96ppm as mutiple absorption and -CH_3 at 2.33 ppm as single absorption. The MS spectrum of **5e** shows obvious molecule ion peak at m/z 328 with 40% abundance.

In conclusion, we have developed an efficient synthesis of 2-aryloxy-4(3*H*)-quinazolinones via base catalytic reaction of functionalized carbodiimides with various phenols. This method has the advantage of easily accessible starting material, mild reaction condition and good yields.

Table 1. Preparation of 2-Aryloxy-4(3*H*)-quinazolinones **5**

Compound	Ar^1	Ar^2	Condition	Yield* (%)
5a	Ph	3-$NO_2C_6H_4$	r.t./12 hr	54
5b	Ph	4-ClC_6H_4	r.t./12 hr	85
5c	Ph	4-BrC_6H_4	r.t./12 hr	78
5d	Ph	Ph	r.t./12 hr	68
5e	Ph	4-MeC_6H_4	r.t./12 hr	82
5f	Ph	4-$MeOC_6H_4$	r.t./6 hr	85
5g	Ph		r.t./12 hr	65
5h	Ph		r.t./12 hr	68
5i	3-MeC_6H_4	Ph	r.t./12 hr	82
5j	4-ClC_6H_4	Ph	r.t./12 hr	89
5k	4-ClC_6H_4	4-$MeOC_6H_4$	r.t./6 hr	67

*Isolated yields based on iminophosphorane **1**.

Exeperimental

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ on a Varian XL-200 spectrometer and resonances are given in ppm (□) relative to TMS. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument.

General Preparation of 2-aryloxy-4(3H)-quinazolinones **5**-To a solution of iminophosphorane **1**(12) (2.12g, 5 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (5 mmol) under

nitrogen at room temperature. After the reaction mixture was stood for 6-12 hours at 0-5□, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was used directly without further purification. To the solution of **2** prepared above in CH_3CN (15 ml) was added substituted phenol (5mmol) and catalytic solid K_2CO_3 (0.07 g, 0.5 mmol). The mixture was stirred for 6-12 h at room temperature and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give 2-aryloxy-4(3*H*)-quinazolinones **5**.

5a: white crystals, m.p.153-155□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.22~7.22 (m, 13H, Ar-H); IR (*cm*$^{-1}$, KBr), 1697 (C=O), 1609, 1473, 1364, 1217; MS (*m/z*, %), 359 (M^+, 84), 240 (95), 221 (100), 194 (76), 166 (72), 90 (83); Anal. Calcd. for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69. Found: C, 66.67; H, 3.53; N, 11.73.

5b: white crystals, m.p.144-146□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.21~7.04 (m, 13H, Ar-H); IR (*cm*$^{-1}$, KBr), 1680 (C=O), 1619, 1473, 1356, 1211; MS (*m/z*, %), 350 (18), 348 (M^+, 51), 229 (100), 194 (68), 146 (25), 77 (80); Anal. Calcd. for $C_{20}H_{13}ClN_2O_2$: C, 68.87; H, 3.76; N, 8.03. Found: C, 68.94; H, 3.58; N, 8.07.

5c: white crystals, m.p.135-137□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.21~7.03 (m, 13H, Ar-H); IR (*cm*$^{-1}$, KBr), 1680 (C=O), 1618, 1473, 1358, 1210; MS (*m/z*, %), 394 (55), 392 (M^+, 58), 273 (39), 221 (74), 194 (100), 77 (77); Anal. Calcd. for $C_{20}H_{13}BrN_2O_2$: C, 61.09; H, 3.33; N, 7.12. Found: C, 61.24; H, 3.23; N, 7.02.

5d: white crystals, m.p.162-163□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.22~7.10 (m, 14H, Ar-H); IR (*cm*$^{-1}$, KBr), 1680 (C=O), 1618, 1473, 1358, 1210; MS (*m/z*, %), 314 (M^+, 18), 221 (16), 195 (100), 77 (79); Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.47; H, 4.34; N, 8.98.

5e: white crystals, m.p.161-162□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.20~6.96 (m, 13H, Ar-H), 2.33 (s, 3H, CH_3); IR (*cm*$^{-1}$, KBr), 1689 (C=O), 1621, 1471, 1358, 1199; MS (*m/z*, %), 328 (M^+, 40), 221 (20), 209 (100), 77 (79); Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.90; H, 4.95; N, 8.37.

5f: white crystals, m.p.151-152□. ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.20~6.82 (m, 13H, Ar-H), 3.77 (s, 3H, OCH_3); IR (*cm*$^{-1}$, KBr), 1689 (C=O), 1621, 1471, 1358, 1199; MS (*m/z*, %), 344 (M^+, 4), 225 (31), 210 (21), 182 (21), 77 (100); Anal. Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.17; H, 4.63; N, 8.21.

5g: white crystals, m.p.195-197□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.23~7.20 (m, 16H, Ar-H); IR (*cm*$^{-1}$, KBr), 1690 (C=O), 1614, 1474, 1361, 1213; MS (*m/z*, %), 364 (M^+, 3), 245 (42), 115 (41), 77 (100); Anal. Calcd. for $C_{24}H_{16}N_2O_2$: C, 79.11; H, 4.43; N, 7.69. Found: C, 79.34; H, 4.65; N, 7.67.

5h: white crystals, m.p.221-223□, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.72 (d, 1H, J=3.9 Hz, quinolyl-2-H), 8.23~7.10 (m, 14H, Ar-H); IR (*cm*$^{-1}$, KBr), 1680 (C=O), 1616, 1471, 1357; MS (*m/z*, %), 365 (M^+, 2), 246 (15), 218 (20), 77 (100); Anal. Calcd. for $C_{23}H_{15}N_3O_2$: C, 75.61; H, 4.14; N, 11.50. Found: C,

75.74; H, 4.04; N, 11.43.

5i: white crystals, m.p.142-143 □, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.21~6.91 (m, 13H, Ar-H), 2.34 (s, 3H, CH_3); IR (cm^{-1}, KBr), 1696 (C=O), 1620, 1473, 1359; MS (*m/z*, %), 328 (M^+, 37), 221 (17), 209 (100), 77 (36); Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.75; H, 4.88; N, 8.67.

5j: white crystals, m.p.180-182 □, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.20~7.09 (m, 13H, Ar-H); IR (cm^{-1}, KBr), 1697 (C=O), 1617, 1473, 1403, 1204; MS (*m/z*, %), 348 (M^+, 2), 255 (2), 195 (38), 146 (12), 45 (100); Anal. Calcd. for $C_{20}H_{13}ClN_2O_2$: C, 68.87; H, 3.76; N, 8.03. Found: C, 68.98; H, 3.85; N, 7.87.

5k: white crystals, m.p.153-155 □, ^{1}H NMR ($CDCl_3$, 200 MHz) □ 8.18~6.83 (m, 12H, Ar-H), 3.78 (s, 3H, OCH_3); IR (cm^{-1}, KBr), 1703 (C=O), 1620, 1474, 1362, 1199; MS (*m/z*, %), 378 (M^+, 7), 255 (8), 225 (79), 182 (43), 90 (100); Anal. Calcd. for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.75; H, 4.03; N, 7.23.

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